1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD): Development of Synthetic Methodologies and Their Applications in Medicinal Chemistry

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Abstract

First utilized by polymer chemists some twenty years ago, 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) is a multifunctional organic reagent that has attracted growing attention over the years. Despite recent advancements in TBD-mediated organic transformations, there are still challenges to overcome. Even reactions that are known to be catalyzed by TBD, such as lactone aminolysis, are currently underdeveloped. Cascade reactions that utilize different functions of TBD are also needed to realize the full potential of TBD. In particular, discovery of new functions is anticipated to give new life to the catalytic ability of TBD. This thesis aims to tackle these issues by developing novel synthetic methodologies. Three synthetic methods, as well as an application of these methods in medicinal chemistry, are featured in this thesis.

Chapter 2 covers a TBD-catalyzed lactone aminolysis reaction. This work offers a practical and effective approach to perform catalytic lactone aminolysis. Despite the challenging nature of this transformation, it was successfully carried out at room temperature in the presence of TBD. Thanks to its catalytic character, this method requires a lower lactone loading compared to previous reports and eliminates the need for extra base, providing a more sustainable alternative. A closer look at the reaction mechanism, backed by detailed NMR studies, confirmed the occurrence of catalyst deactivation, product inhibition, as well as irregular orders of reaction for both catalyst and the amine substrate. The acyl-TBD intermediate was confirmed to be the reactive species during the aminolysis process.

Building upon the work of Chapter 2, Chapter 3 features a TBD-catalyzed synthesis of 3-hydroxyisoindolin-1-ones. 3-Alkylidenephthalides first undergo amidations, followed by intramolecular cyclizations to furnish 3-hydroxyisoindolin-1-ones. In addition to improved sustainability compared to other routes, extra beneficial factors, such as a 100% atom economy and chromatography-free purification process, further demonstrate the advantages of TBD catalysis.

Elaborating on the progress described in Chapter 3, Chapter 4 focuses on a TBD-catalyzed synthesis of cyclic imides via an amidation-cyclization-elimination cascade. In particular, the elimination process in this cascade is unprecedented, adding a new tool to the toolbox of TBD catalysis. On account of the effectiveness and the mild reaction conditions, this method is compatible with late stage functionalization of complex molecules. Mechanistic investigations by

both experimental and computational means explain the role of TBD in the reaction system as well as a plausible pathway for the original elimination step.

Chapter 5 takes a different turn and presents a medicinal chemistry study enabled by the methodology reported in Chapter 2. The incorporation of three-dimensional scaffolds into pantothenamides is explored to improve their bioactivity. Therefore, 17 molecules are each accessed through TBD-catalyzed lactone aminolysis. Evaluation of these compounds in antiplasmodial assays reveals 3 compounds with high nanomolar activity against *P. falciparum*. Computational studies are employed to tentatively explore the factors that contribute to the high potency of these molecules.

Résumé

Utilisé pour la première fois par des chimistes des polymères il y a une vingtaine d'années, le 1,5,7-triazabicyclo[4.4.0]déc-5-ène (TBD) est un réactif organique multifonctionnel qui a suscité une attention croissante au fil des années. Malgré les progrès récents dans les transformations organiques médiées par le TBD, il reste encore des défis à surmonter. Même les réactions catalysées par le TBD, comme l'aminolyse des lactones, sont actuellement sous-développées. Les réactions en cascade qui utilisent différentes fonctions du TBD sont également nécessaires pour réaliser tout le potentiel du TBD. En particulier, la découverte de nouvelles fonctions devrait revigorer la capacité catalytique du TBD. Cette thèse vise à aborder ces questions en développant de nouvelles méthodologies de synthèse. Trois méthodes de synthèse, ainsi qu'une application de ces méthodes en chimie médicinale, sont présentées dans cette thèse.

Le chapitre 2 couvre une réaction d'aminolyse de lactone catalysée par TBD. Ce travail offre une approche pratique et efficace pour effectuer l'aminolyse catalytique des lactones. Malgré la nature difficile de cette transformation, elle a été réalisée avec succès à température ambiante en présence de TBD. Grâce à son caractère catalytique, cette méthode nécessite moins d'équivalents de lactone que les méthodes rapportées précédemment et élimine le besoin d'une base supplémentaire, offrant ainsi une alternative plus durable. Un examen plus approfondi du mécanisme réactionnel, appuyé par des études détaillées par RMN, a confirmé une désactivation du catalyseur, une inhibition par le produit, ainsi que des ordres de réaction irréguliers pour le catalyseur et le substrat aminé. L'intermédiaire acyl-TBD est confirmé comme étant l'espèce réactive au cours du processus d'aminolyse.

S'appuyant sur les travaux du chapitre 2, le chapitre 3 présente une synthèse catalysée par TBD de 3-hydroxyisoindolin-1-ones. Les 3-alkylidènephtalides subissent d'abord une amidation, suivie d'une cyclisation intramoléculaire produisant des 3-hydroxyisoindolin-1-ones. En plus de la durabilité supérieure de cette méthode comparée aux autres synthèses de ces composés, des facteurs bénéfiques supplémentaires, tels qu'une économie atomique à 100 % et un processus de purification sans chromatographie, mettent encore plus en évidence les avantages de la catalyse par TBD.

Afin de bâtir sur les progrès du chapitre 3, le chapitre 4 se concentre sur une synthèse, toujours catalysée par TBD, d'imides cycliques via une cascade d'amidation-cyclisation-élimination.

Notamment, le processus d'élimination de cette cascade est sans précédent, ajoutant un nouvel outil à la boîte à outils de TBD. En raison de son efficacité et des conditions de réaction douces, cette méthode est compatible avec une fonctionnalisation tardive de molécules complexes. Des investigations mécanistiques expérimentales et informatiques ont permises de mieux définir le rôle de TBD dans la réaction et de proposer une voie plausible pour l'étape d'élimination initiale.

Le chapitre 5 prend une direction différente et présente les résultats d'une étude en chimie médicinale grandement facilitée par la méthodologie rapportée au chapitre 2. Une variété d'échafaudages tridimensionnels sont incorporés à la structure des pantothénamides pour en améliorer l'activité biologique. Ainsi, 17 molécules sont toutes générées en partie via une réaction d'aminolyse de lactone catalysée par TBD. L'évaluation de ces composés dans des tests antiplasmodiaux révèle 3 composés démontrant une habileté à diminuer la croissance de *P. falciparum* a des concentrations nanomolaires. Des études informatiques ont permis d'explorer provisoirement les facteurs qui pourraient contribuer à l'augmentation de l'activité de ces molécules.

Contributions of Authors

Four manuscripts are featured in this thesis. Chapter 2 is a published manuscript titled "1,5,7-Triazabicyclo[4.4.0]dec-5-ene: An Effective Catalyst for Amide Formation by Lactone Aminolysis" (Lan, C. B.; Auclair, K. *J. Org. Chem.* **2023**, *88*, 10086-10095). All of the experimental work was performed by Chunling Blue Lan. This chapter was adapted from the publication, originally written by Chunling Blue Lan and edited by Karine Auclair.

Chapter 3 features a published manuscript titled "1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD): An Organocatalyst for Rapid Access to 3-Hydroxyisoindolin-1-ones" (Lan, C. B.; Auclair, K. *Eur. J. Org. Chem.* **2024**, e202400071). All of the experimental work was performed by Chunling Blue Lan. This chapter was adapted from the publication, originally written by Chunling Blue Lan and edited by Karine Auclair.

Chapter 4 consists of a published manuscript titled "Organocatalytic Hat Trick: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)-Catalyzed Synthesis of Cyclic Imides via an Amidation-Cyclization-Elimination Cascade" (Lan, C. B.; Auclair, K. published by *J. Org. Chem.*). All of the experimental and computational work was performed by Chunling Blue Lan. This chapter was adapted from the accepted publication, originally written by Chunling Blue Lan and edited by Karine Auclair.

Chapter 5 contains a manuscript in preparation titled "Exodus from Flatland: Overcoming the Stability Issue of Antiplasmodial Pantothenamides with Three-Dimensional Scaffolds" (Lan, C. B.; Liu, X.; Saliba, K. J.; Auclair, K.). All of the synthetic and computational work was performed by Chunling Blue Lan. Xiangning Liu, supervised by Kevin J. Saliba at the Australian National University, performed all biological assays. This chapter was written by Chunling Blue Lan and edited by Karine Auclair.

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Torn down, full of aching
Somehow our youth would take the blame
Worn out, the way we let it stay
Taught how to celebrate it
All out, I'd replicate your pain
Climb down, if only for a taste

Hallowed, but hesitated
Shallow, but full in all your veins
Shadowed by every other weight
Hollow, a doubt can make it
Borrowed a love that never came
Followed in every other shade

Let it lead your love away
I never strayed
Let it bury you away
In all your blame, in all your pain
I will carry you always

Fade me away, I won't ever be the same
Fade me away, I won't ever be the same
Fade me away, I won't ever be the same

--Carry You by Novo Amor

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List of abbreviations

∴	ball milling
Ac	acetate
ACQ	aggregation-caused quenching
AIBN	2,2’-azobis(2-methylpropionitrile)
AIE	aggregated induced emission
AIEgen	luminogens that exhibit aggregated induced emission
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
Cbz	benzyloxycarbonyl
CDI	carbonyldiimidazole
conc.	concentrated
o-DCB	*ortho*-dichlorobenzene
DCE	1,2-dichloroethane
DCM	dichloromethane
DIPEA	*N*,*N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMP	Dess-Martin Periodinane
EA	ethyl acetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
EDG	electron donating groups
EDTA	ethylenediaminetetraacetic acid
EWG	electron withdrawing groups
GF	graphene foam
Hex	hexanes
HFIP	hexafluoroisopropanol
LC-MS	liquid chromatography-mass spectrometry

MOM	methoxymethyl
MTBD	7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene
Ms	mesyl
MW	microwave
NHC	*N*-heterocyclic carbene
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMP	*N*-methyl pyrrolidone
NMR	nuclear magnetic resonance
Ns	nosyl
PIDA	(diacetoxyiodo)benzene
PMB	*para*-methoxy benzyl
*p*TSA	*p*-toluenesulfonic acid
PPTS	pyridinium *p*-toluenesulfonate
rt	room temperature
SAR	structure-activity relationship
sat.	saturated
SEM	standard error of the mean
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDPS	*tert*-butyl diphenyl silyl
TBS	*tert*-butyl dimethyl silyl
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	trimethylsilyl
Tf	triflate
Tr	trityl
Ts	tosyl
UV	ultraviolet

Chapter 1

Organic Transformations Utilizing 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD): A Tale of Two Nitrogens

1.1 Introduction

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) is a bicyclic guanidine that has attracted significant attention over the years. As demonstrated in Figure 1.1, the number of Google scholar search results that contain keyword “triazabicyclodecene” or “1,5,7-triazabicyclo[4.4.0]dec-5-ene” has increased tremendously over the past two decades. Often referred to as a multifunctional reagent, TBD bears two functional types of nitrogens and exhibits ambiphilicity (Figure 1.2). The sp^2-hybridized nitrogen can serve as both an organic superbase and a strong nucleophile, while the N−H bond is Brønsted acidic and able to form adducts through hydrogen-bonding with various substrates. Although the core function of TBD originated from its sp^2 nitrogen, the presence of the adjacent N−H bond proved to be beneficial in multiple cases.

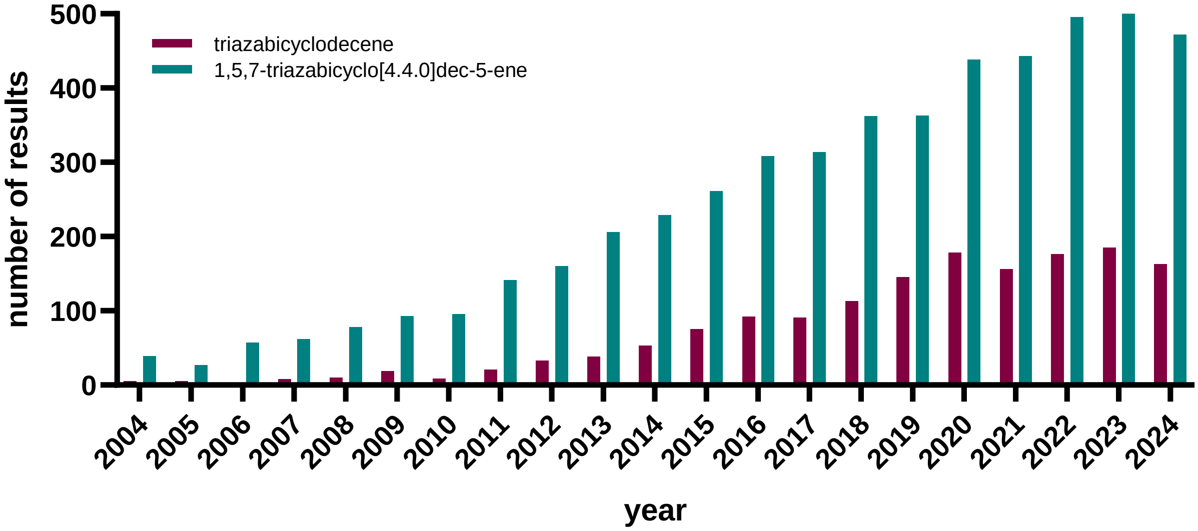


Figure 1.1. Google scholar search results about TBD over the past two decades. Results were obtained in October 2024.

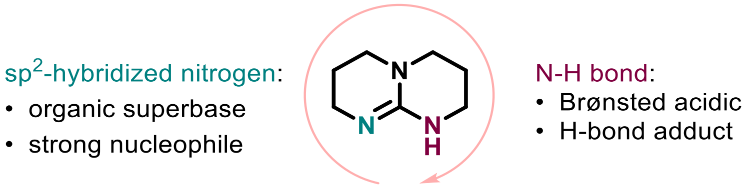


Figure 1.2. The molecular structure of TBD.

The use of TBD in organic transformations renders numerous advantages. Compared to other amidine and guanidine bases, TBD is superior in terms of both basicity[1] and nucleophilicity.[2]

Details of these will be discussed in the following sections. TBD also exhibits greater resistance towards hydrolysis.[3] Moreover, TBD proved to be harmless and relatively non-toxic in *in vitro* studies,[4] which is crucial for pharmaceutical and agrochemical manufacturing.

Initially reported as a highly efficient catalyst for ring-opening polymerization,[5] TBD has been extensively employed in the polymer field and beyond.[6-7] Due to the nature of this thesis, advances in polymerization/depolymerization with TBD are not covered. Instead, this chapter focuses on recent developments in small molecule transformations enabled/facilitated by TBD. An overview of each type of transformations is provided and classified based on the role played by TBD in the reaction. Applications of such transformations in other fields, such as medicinal chemistry and total synthesis, are provided when relevant. Since TBD often plays multiple roles in a reaction, most reactions are categorized by the primary role played.

1.2 TBD as a Base

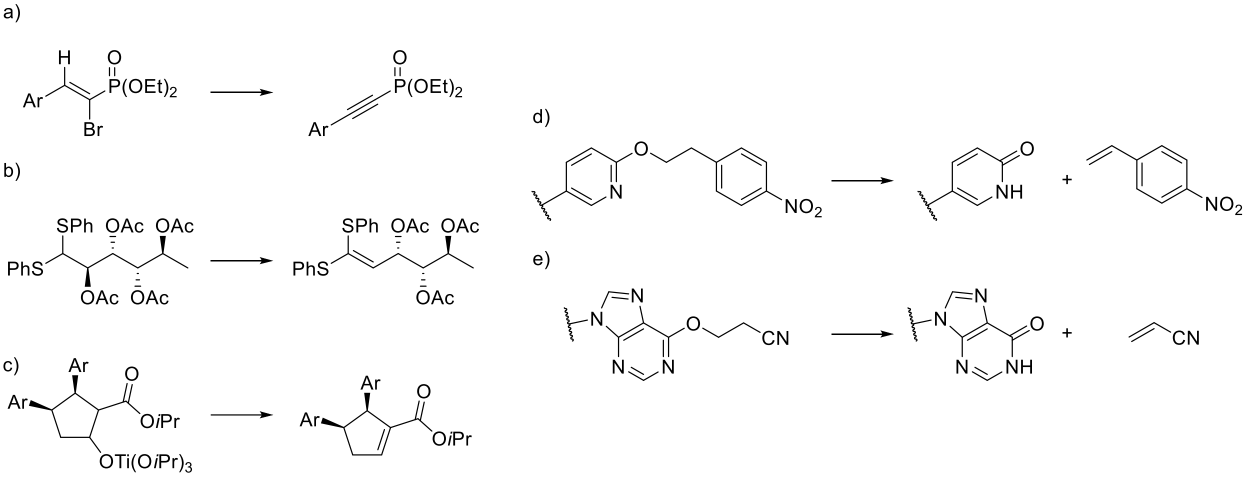
1.2.1 Basicity of TBD

TBD is considered a guanidine-based organic superbase. Organic superbases are defined as neutral organic compounds with basic functional groups that exhibit basicity greater than the Proton-sponge® ($pK_{aH} = 18.6$ in MeCN).[8] Being one of the strongest nitrogen-based organic superbase,[1] TBD ($pK_{aH} = 26.0$ in MeCN) is able to deprotonate or facilitate the deprotonation of various functionalities, such as phenol, thiol, amide, and acidic C–H bond. The following section covers reported methodologies in which TBD is used primarily as a base, as well as related diverse applications.

1.2.2 TBD as a Stoichiometric Deprotonation Reagent

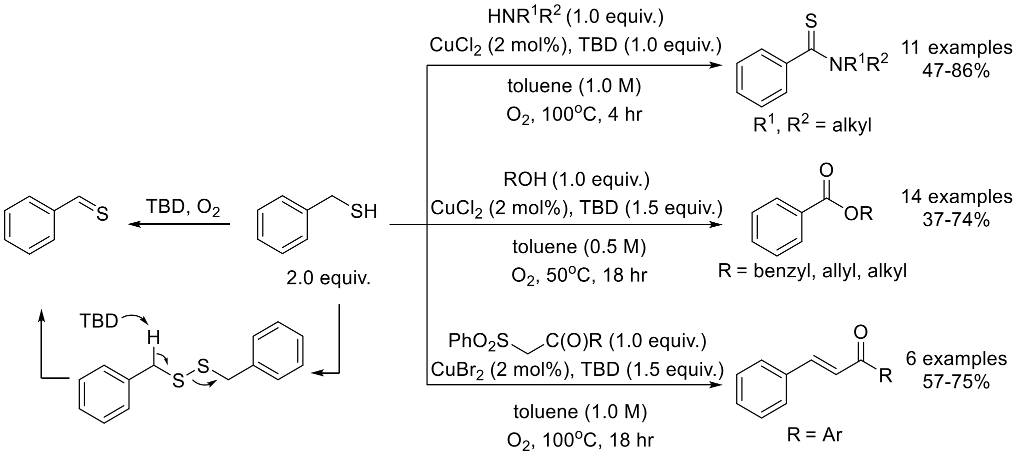
1.2.2.1 Elimination Reactions

Owing to its high basicity, TBD is able to trigger numerous elimination reactions. Alkynylphosphonates can be accessed from the corresponding vinyl bromide in the presence of TBD (Scheme 1.1a).[9] A selective dehydration was also reported for a sugar substrate (Scheme 1.1b).[10] Reaction intermediates such as titanium alkoxides were successfully transformed into the acrylate products by TBD-mediated elimination (Scheme 1.1c).[11] In DNA chemistry, the Leumann lab at the University of Bern demonstrated that TBD can remove the *p*-nitrophenethyl (NPE) group[12-13] (Scheme 1.1d) and the cyanoethyl group[14] (Scheme 1.1e) via elimination reactions, both of which were initiated by deprotonation at the α-carbon to the electron withdrawing groups.



Scheme 1.1. Elimination reactions enabled by TBD.

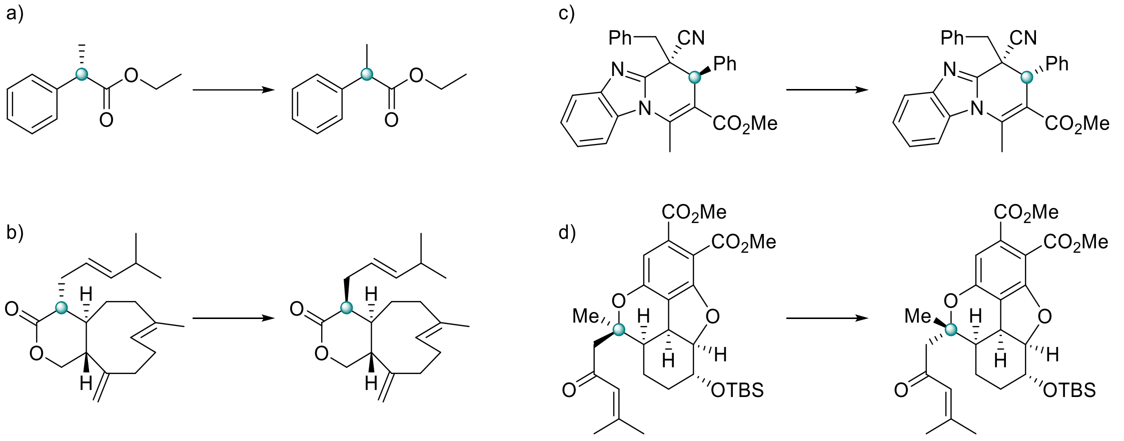
Jang and coworkers at Ajou University reported a series of copper-catalyzed oxidative reactions that utilized benzyl mercaptans under aerobic conditions (Scheme 1.2).[15-17] It was proposed that the thiols were first oxidized to the corresponding disulfides, which underwent elimination in the presence of stoichiometric TBD to generate the reactive species, benzothialdehydes.



Scheme 1.2. Copper-catalyzed oxidative reactions enabled by TBD-promoted elimination.

1.2.2.2 Racemizations/Epimerizations

Racemization/epimerization can be directly triggered by TBD when the stereocenter is acidic. Although catalytic in nature, stoichiometric or excess amount of TBD was employed to shift the equilibrium to the formation of the desired stereoisomer. This was demonstrated for the racemization of α-aryl propionates (Scheme 1.3a).[18] A similar approach was also utilized in conjunction with enzymes to achieve dynamic kinetic resolution.[19] For the synthesis of coraxeniolide-A, the unwanted product was epimerized back to the desired one in the presence of TBD (Scheme 1.3b).[20] Meanwhile, a ring opening-closing equilibrium was achieved upon the deprotonation of an acidic proton, making it possible to racemize/epimerize a stereocenter further away. This was exemplified with the synthesis of fused benzimidazoles[21] (Scheme 1.3c) as well as the total synthesis of (±)-bisabosqual A (Scheme 1.3d).[22]



Scheme 1.3. Racemization/epimerization of diverse scaffolds initiated by TBD. The scrambled stereocenters are highlighted in turquoise.

1.2.2.3 Generation of Active Catalysts

Some highly reactive catalysts, namely *N*-heterocyclic carbenes (NHCs), are usually employed in their precursor form. Upon the addition of a base, the acidic proton of the precursor is deprotonated and the active carbene form is generated *in situ*. TBD is an excellent base for the generation of NHCs. A variety of NHC precursors can be deprotonated by TBD, including triazolium-based and imidazolium-based compounds (Figure 1.3).[11, 23-27]

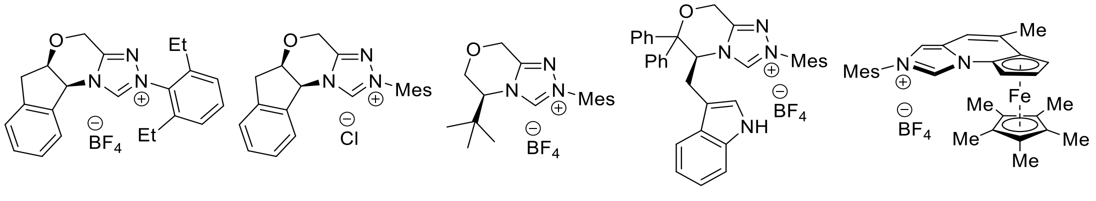
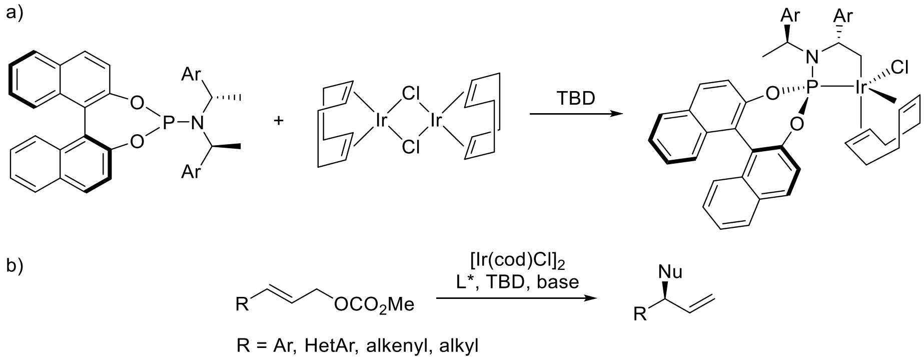


Figure 1.3. NHC precursors known to be deprotonated by TBD.

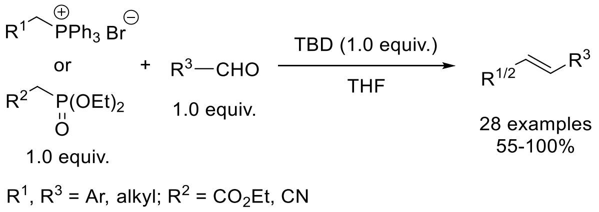
TBD also proved to be a superior base to generate the active catalyst in iridium-catalyzed asymmetric allylic substitutions. Initially reported by Helmchen and coworkers,[28] the iridium precatalyst [Ir(cod)Cl]$_2$ and the chiral ligand are first transformed to the active species in the presence of TBD (Scheme 1.4a). In this process, TBD serves as a base to deprotonate the phenethyl group and generate the active ligand, which then coordinates to [Ir(cod)Cl]$_2$ to form the active catalyst. This active species is able to catalyze asymmetric allylic substitutions with high enantioselectivity in the presence of various nucleophiles (Scheme 1.4b).[29] These transformations were also successfully adapted to access natural products and pharmaceuticals.[30]



Scheme 1.4. TBD-initiated generation of an active iridium catalyst. a) Activation mechanism for iridium catalyst. b) Iridium-catalyzed asymmetric allylic substitutions.

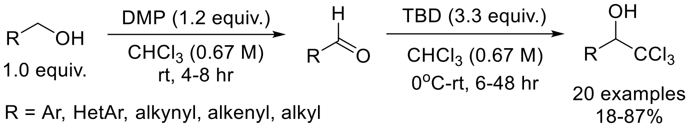
1.2.2.4 Generation of Active Nucleophiles

In general, pre-nucleophiles bearing acidic protons can be activated by TBD through deprotonation. In terms of carbon-based nucleophiles, Simoni *et al.* reported that TBD can generate ylides from the corresponding phosphonium salts or phosphonate carbanions from phosphonates, thus promoting Wittig and Horner-Wadsworth-Emmons reactions (Scheme 1.5).[31] Notably, TBD (pK_{aH} = 26.0 in MeCN) enabled the production of alkenes that MTBD (pK_{aH} = 25.4 in MeCN) failed to generate, despite their similar pK_{aH}. This suggests that the presence of the N-H bond in TBD is crucial to the reaction, possibly by activating the aldehydes. Similar transformations were also employed in the synthesis of biologically active compounds.[32-33]



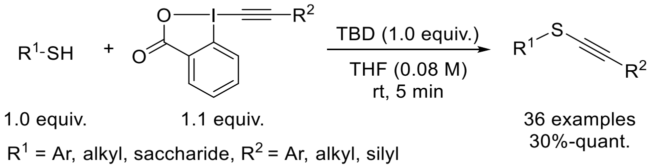
Scheme 1.5. TBD-promoted Wittig and Horner-Wadsworth-Emmons reactions.

Beside ylides, TBD can produce the trichlorocarbanion from chloroform, which reacts with aldehydes for the synthesis of trichloromethyl carbinols. In the method described by Snowden and coworkers, alcohols can be directly transformed into trichloromethyl carbinols in a one-pot oxidation-trichloromethylation cascade (Scheme 1.6).[34-35]

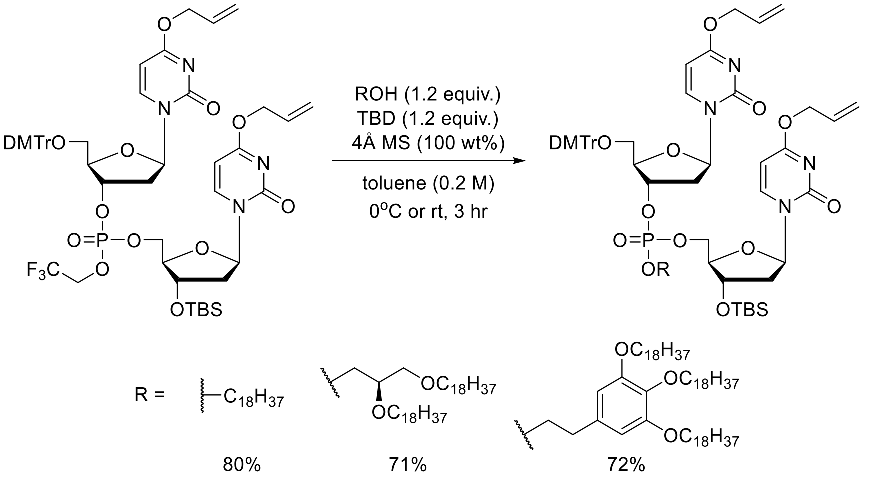


Scheme 1.6. TBD-promoted synthesis of trichloromethyl carbinols.

Due to their high acidity, thiols are readily deprotonated by TBD to generate thiolates that are much better nucleophiles. TBD-promoted alkynylations of thiols with hypervalent iodine reagents was reported by Frei *et al.* (Scheme 1.7).[36] This reaction was complete within five minutes at room temperature and tolerated diverse substrates, demonstrating the selectivity and effectiveness of TBD as a base in this system.



Scheme 1.7. TBD-promoted alkynylation of thiols.



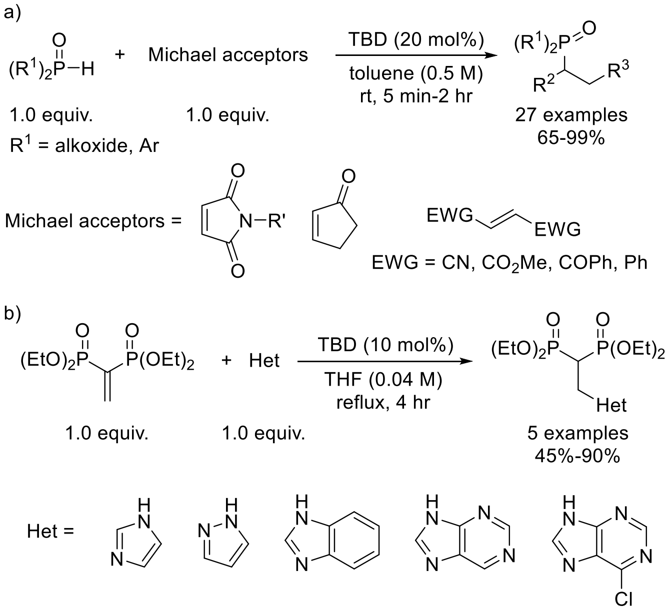
Scheme 1.8. TBD-promoted transesterification to access functionalized dinucleotides.

Similarly, alkoxides can be generated from alcohol in the presence of TBD. This was demonstrated by a TBD-promoted transesterification reaction on a dinucleotide substrate (Scheme 1.8).[37] These functionalized dinucleotides with different hydrophobic moieties were prepared in high yields under mild conditions, paving the way for their utilization in solid-phase RNA synthesis.

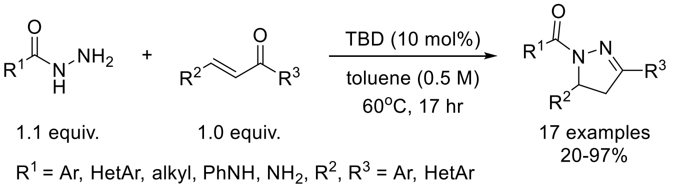
1.2.3 TBD as a Catalytic Proton Transfer Reagent

1.2.3.1 Phospha-, Aza-, and Oxa-Michael Additions

Traditional Michael additions will be covered in section 1.2.4.2. Pnictogen-based nucleophiles are appropriate substrates for aza- and phospha-Michael additions, respectively. Jiang *et al.* reported a TBD-catalyzed phospha-Michael addition with phosphites and phosphines (Scheme 1.9a).[38] This protocol is attractive due to its mild conditions, short reaction time, and broad scope. Similarly, an aza-Michael addition was utilized to synthesize a variety of aminobisphosphonates as potential antitumor reagents (Scheme 1.9b).[39]



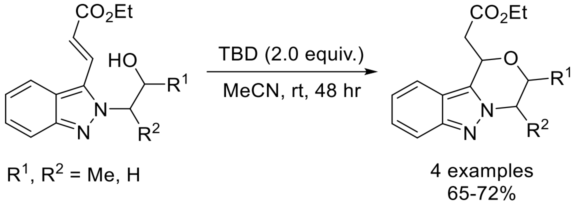
Scheme 1.9. TBD-catalyzed phospha- and aza-Michael additions.



Scheme 1.10. TBD-catalyzed synthesis of pyrazolines.

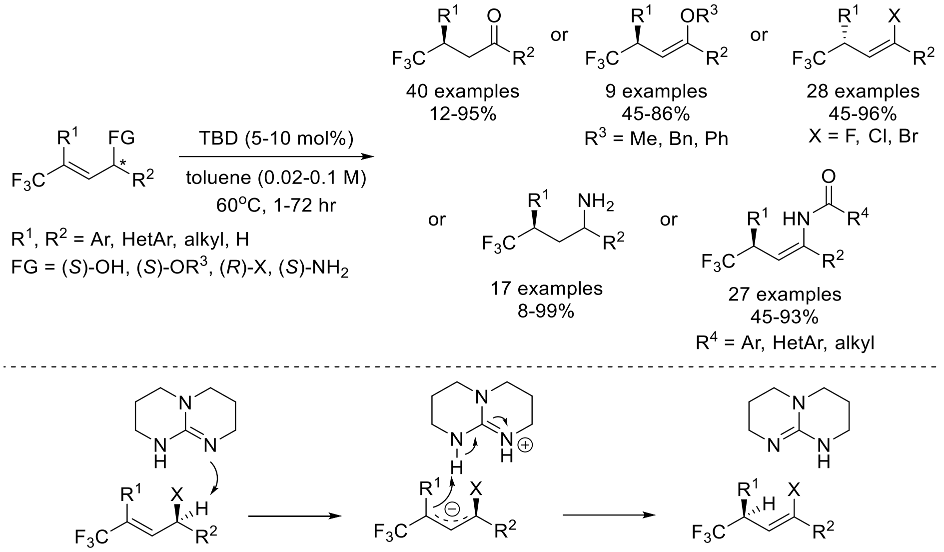
A TBD-catalyzed synthesis of pyrazolines was reported[40], which takes advantage of a regioselective aza-Michael addition (Scheme 1.10). Among all the nitrogen-containing bases tested, only TBD allowed selective aza-Michael addition of the acyl nitrogen in the hydrazide substrates. A subsequent condensation with the carbonyls afforded the final pyrazolines.

Finally, a TBD-mediated intramolecular oxa-Michael addition was reported to access indazole-fused morpholines (Scheme 1.11).[41] Despite its catalytic nature, this reaction required stoichiometric amount of TBD for satisfactory conversion at room temperature.



Scheme 1.11. TBD-mediated oxa-Michael additions.

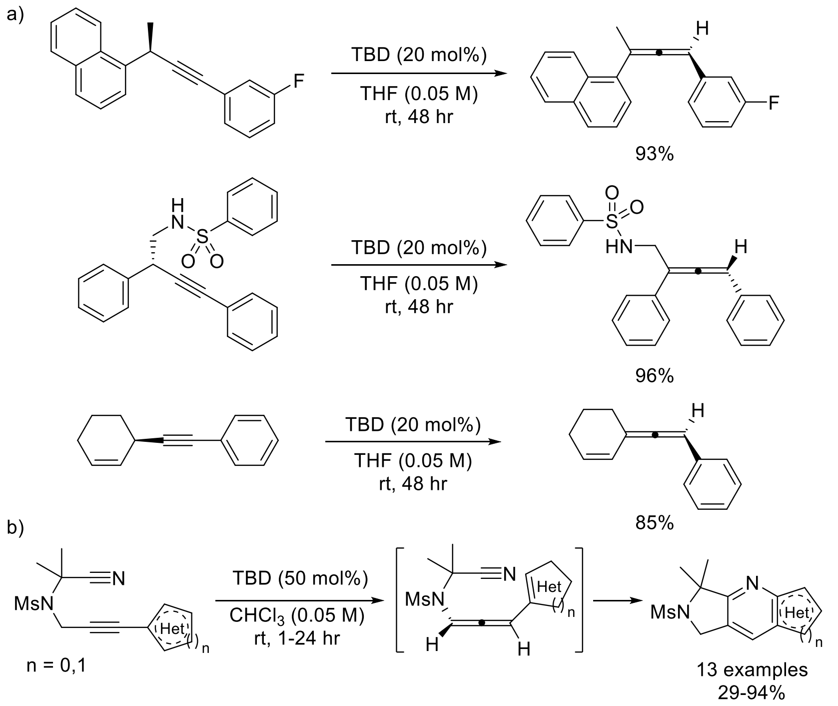
1.2.3.2 Alkene/Alkyne Isomerizations via 1,3-Proton Transfer



Scheme 1.12. TBD-catalyzed isomerization of allylic compounds and its mechanism

When the α position of an alkene or alkyne is acidic, TBD is capable of triggering isomerization via 1,3-proton transfer. Many reports of the alkene isomerization came from the Martín-Matute lab at Stockholm University. These involved assorted allylic substrates isomerized in a highly stereospecific fashion (Scheme 1.12).[42-47] Both the proton and the stereochemical information of the carbon were transferred at the same time by TBD. The isomerization proceeded through an ion-pair mechanism, where deprotonation and reprotonation happened on the same face of the molecule, allowing stereoselective isomerizations. A wide range of allylic substrates, including alcohols, ethers, halides, and amines, can be subjected to these conditions and generate the vinyl products. For alcoholic and amino substrates, tautomerization happened spontaneously to afford ketones and imines, respectively. In particular, the imines were further transformed into stable products, either through reduction to the amines or acylation to the enamides.

Likewise, TBD can catalyze the 1,3-proton transfer of alkyne substrates to afford allenes.[48-50] This process is stereoselective as well and undergoes identical mechanism, resulting in axially chiral allenes (Scheme 1.13a). It was also employed to generate allenes *in situ* to initiate downstream Diels-Alder reactions and construct fused heterocycles (Scheme 1.13b).[51]



Scheme 1.13. TBD-mediated isomerization of alkynes.

1.2.4 Reactions Involving Enolates Generated by TBD

1.2.4.1 Aldol Reactions

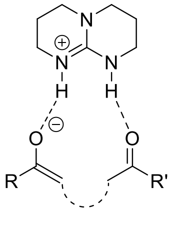
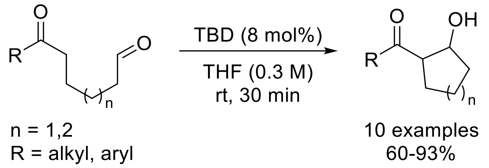


Figure 1.4. Key interaction proposed for TBD-catalyzed aldol reactions.

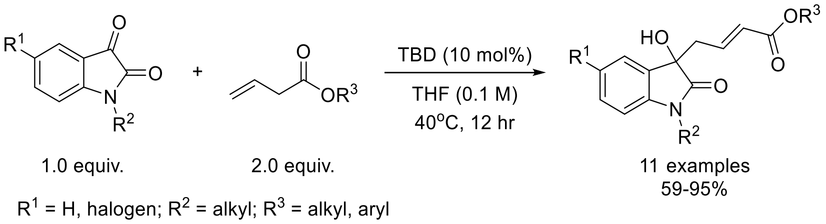
TBD was reported to be an excellent catalyst for aldol reactions, especially intramolecular aldolization. It was proposed that TBD was able to bring the enolate and the carbonyl into close proximity, thus greatly facilitating the reaction (Figure 1.4).

Although TBD-catalyzed intermolecular aldolizations were reported, they did not find broad applications due to their limited scope and poor chemoselectivity.[52-53] In 2008, Ghobril *et al.* reported the intramolecular aldolization of ketoaldehydes catalyzed by TBD (Scheme 1.14).[54] This method operated at room temperature and was complete within 30 minutes, allowing the aldolization of ketoaldehydes with appropriate carbon chain length to form five- or six-membered rings. Exclusive formation of the thermodynamic product was observed.



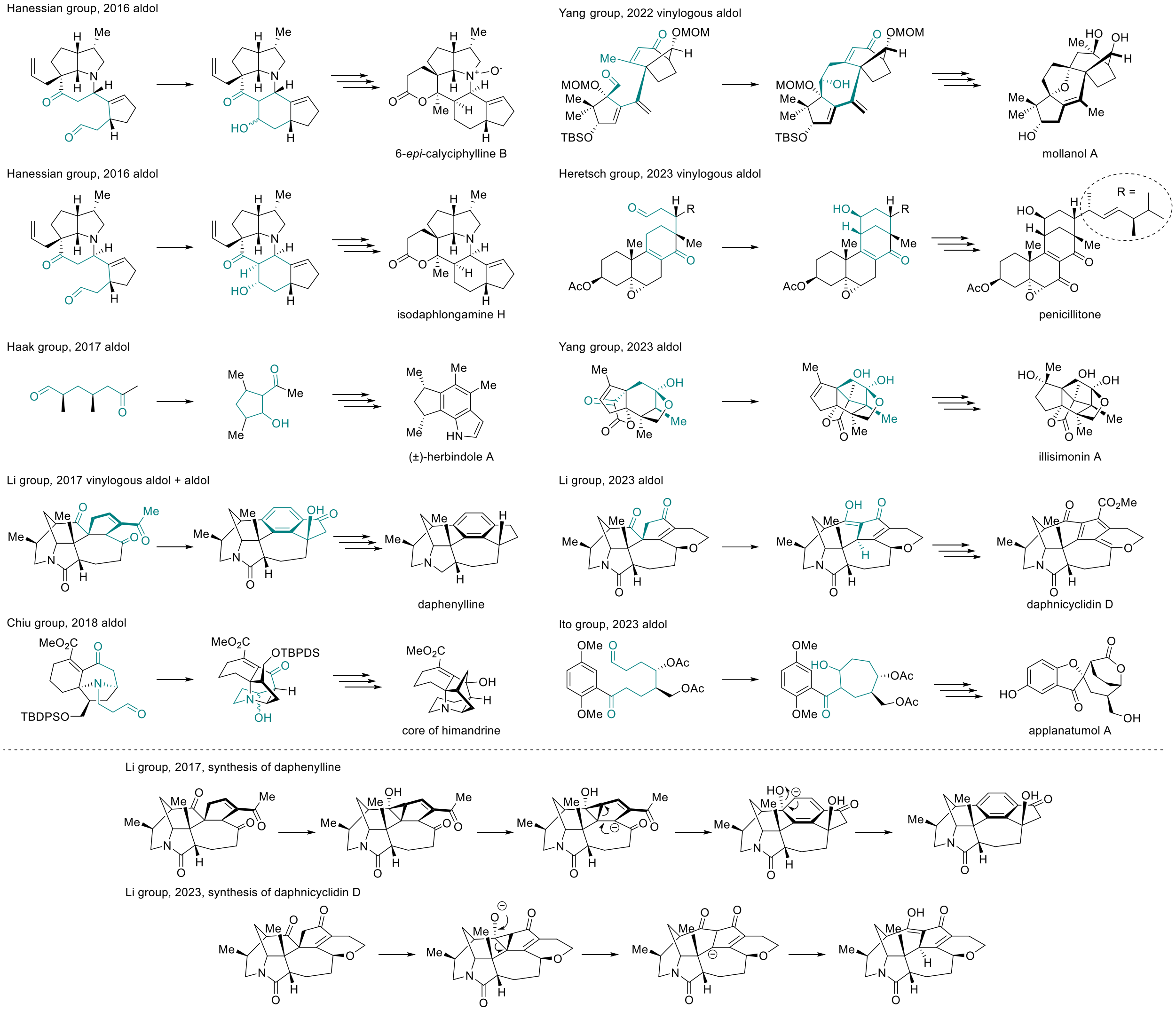
Scheme 1.14. TBD-catalyzed intramolecular aldolization of ketoaldehydes.

Apart from conventional aldol condensations, a vinylogous aldol reaction was also catalyzed by TBD. Wang and coworkers reported the TBD-catalyzed vinylogous aldol reaction of isatins for the synthesis of 3-hydroxy-2-oxoindoles (Scheme 1.15).[55] High chemoselectivity for the γ-adduct was achieved in most cases.



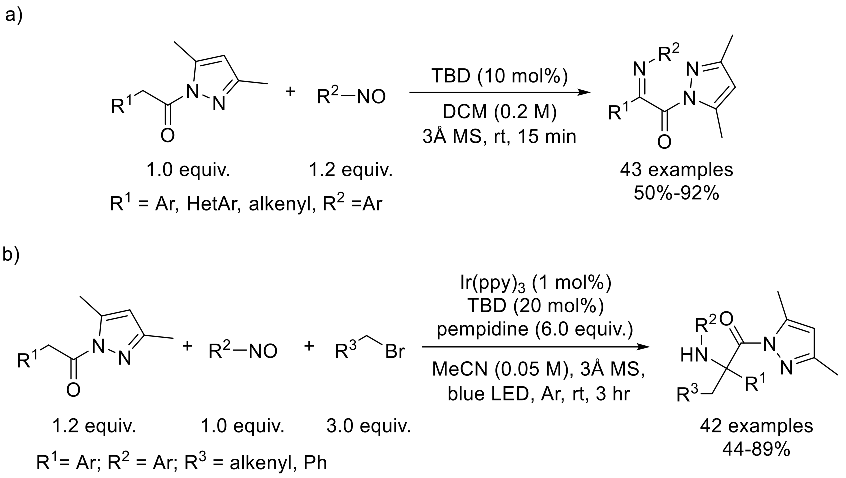
Scheme 1.15. TBD-catalyzed vinylogous aldol reaction for the synthesis of 3-hydroxy-2-oxoindoles.

Both regular aldol and vinylogous aldol reactions catalyzed by TBD have been extensively adopted in natural product synthesis to install fused aliphatic rings in a stereoselective manner.[56-65] Examples of such utilizations are showcased in Scheme 1.16. Specifically, two reports from the Li group at Shanghai Institute of Organic Chemistry describe the use of TBD for more than an aldol catalyst, demonstrating its multifunctionality. En route to daphenylline, an aromatic ring was creatively constructed through a vinylogous aldol−6π electrocyclic ring opening−β-hydroxide elimination sequence. In the synthesis of daphnicyclidin D, an aldol cyclization–retro-aldol fragmentation cascade was adopted to achieve a carbon scaffold rearrangement.



Scheme 1.16. TBD-catalyzed aldol and vinylogous aldol reactions involved in natural product synthesis. The fragments that participated in the intramolecular aldol reaction are highlighted in turquoise.

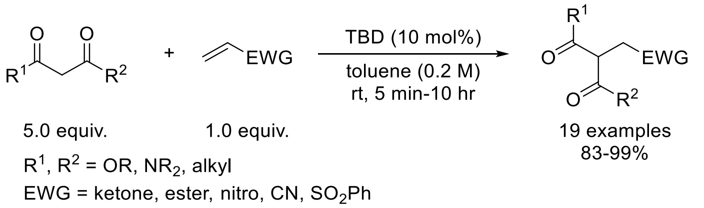
When a nitroso group replaces the carbonyl as the electrophile, an analogous reaction, coined nitroso aldol reaction, can take place. Nucleophilic attack on the nitrogen of the nitroso group, followed by rapid dehydration, results in imination at the α-position. TBD was reported as an appropriate catalyst for this process, either alone (Scheme 1.17a) or as one step of a reaction cascade (Scheme 1.17b).[66-67] TBD was proposed to promote the photosensitization process of pempidine (Scheme 1.17b), further demonstrating the multifunctionality of TBD.



Scheme 1.17. TBD-catalyzed nitroso aldol reactions.

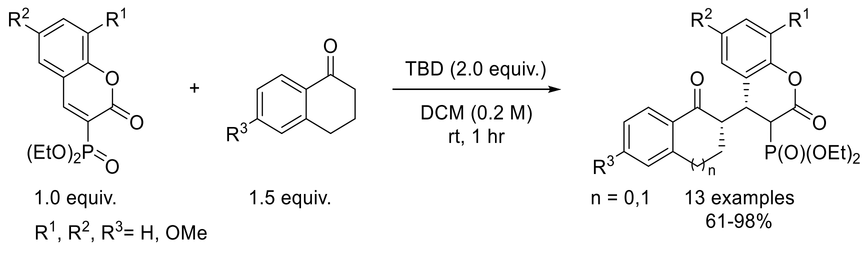
1.2.4.2 Michael Additions

The high efficiency of TBD as a catalyst for Michael additions was first reported by Ye *et al.* The reactions of β-dicarbonyl compounds with various Michael acceptors, including vinyl ketones, nitroalkenes, acrylates, acrylonitriles, and vinyl sulfones, were complete within two hours at room temperature (Scheme 1.18).[68]



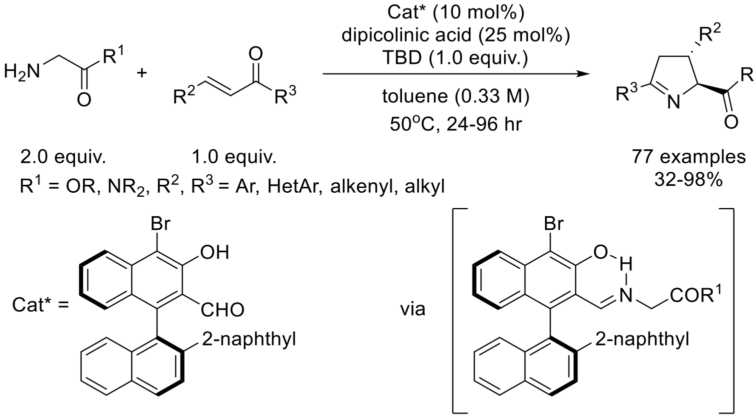
Scheme 1.18. TBD-catalyzed Michael additions between β-dicarbonyl compounds and various Michael acceptors.

Later, Krawczyk and coworkers reported that phosphorylcoumarin derivatives react as Michael acceptors with ketones in the presence of TBD (Scheme 1.19). [69-72] The phosphonate moiety in the products can be further derivatized by employing the Horner-Wadsworth-Emmons reaction.



Scheme 1.19. Michael additions between ketones and phosphorylcoumarin derivatives in the presence of TBD.

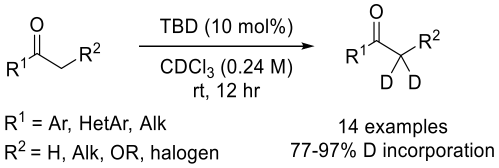
TBD-catalyzed Michael additions can also be incorporated into reaction cascades to construct complex scaffolds. A stereoselective pyrroline synthesis promoted by TBD and a chiral aldehyde was reported to proceed via an imination-Michael addition-imination cascade (Scheme 1.20).[73-74] The amino acid derivative substrates first formed an imine adduct with the chiral aldehyde. This not only introduced a chiral environment, but also increased the acidity at the α-position for the ease of deprotonation by TBD to trigger downstream Michael addition, which was followed by intramolecular imination to furnish the final products.



Scheme 1.20. Cascade reactions consisting of TBD-mediated Michael addition.

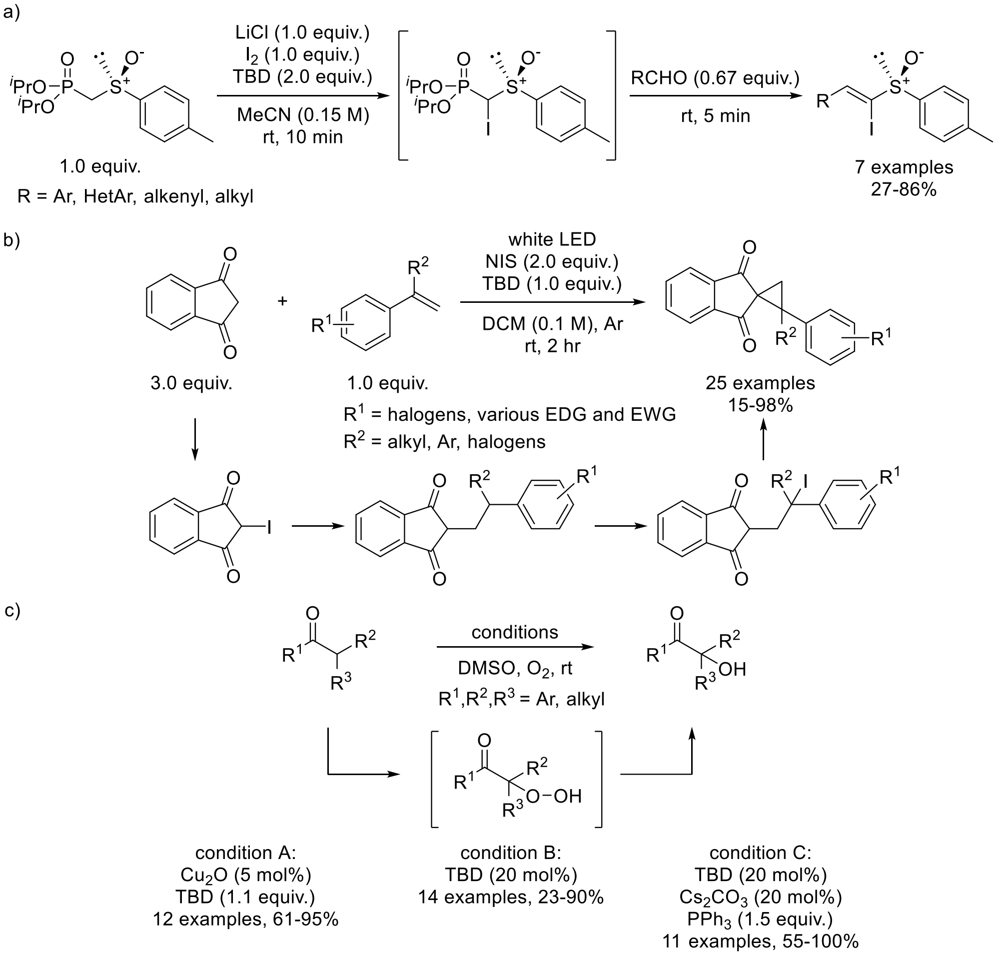
1.2.4.3 Functionalization at the Acidic α-Carbon Positions

The first reaction in this category was reported by Mioskowski and coworkers in 2007,[75] and involved deuteration at the α-position of ketones with a combination of TBD and $CDCl_3$ (Scheme 1.21). Using 10 mol% of TBD as a catalyst, multiple deuterium atoms were successfully incorporated into various ketones.



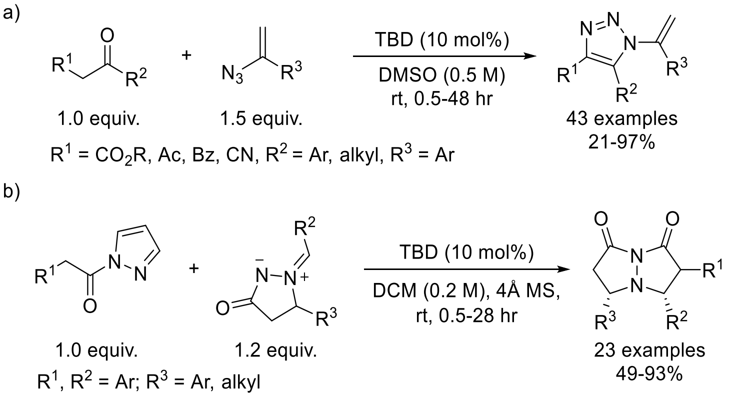
Scheme 1.21. Deuteration at the α-position of ketones catalyzed by TBD.

Different electrophiles can be employed to functionalize acidic α-carbon. Jung *et al.* successfully synthesized α-iodovinyl sulfoxides from the corresponding phosphonates via a one-pot iodination and Horner-Wadsworth-Emmons reaction cascade (Scheme 1.22a).[76] TBD was involved in both steps, and a good *Z* selectivity was observed. A photochemical synthesis of spirocyclopropanes reported by Pan and coworkers[77] adopted a similar approach (Scheme 1.22b). An initial TBD-mediated iodination initiated the radical coupling process. This intermediate was iodinated again, and a TBD-mediated intramolecular cyclization afforded the cyclopropane products. Conveniently, molecular oxygen can be used as an environmentally friendly oxidant for the TBD-promoted synthesis of α-hydroxy ketones (Scheme 1.22c).[78-82] This transformation proceeds through the hydroperoxide intermediate, and a variety of reagents were utilized to either promote the formation (Cu_2O) or the breakdown (PPh_3) of this intermediate. The key function of TBD to generate the enolates, however, remains the same.



Scheme 1.22. TBD-mediated functionalization of acidic α positions.

Last but not least, TBD can catalyze [3+2] cycloadditions involving enolates. Both vinyl azides[83] and azomethine imines[84] were suitable dipoles under these conditions (Scheme 1.23). Unlike traditional cycloadditions, elimination of a neutral molecule (water or pyrazole) was required to afford the final product.



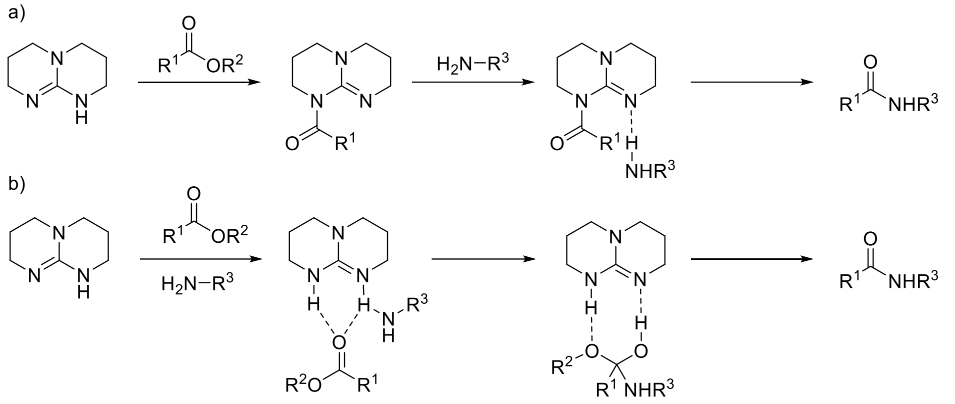
Scheme 1.23. TBD-catalyzed [3+2] cycloadditions.

1.3 TBD as a Nucleophile

1.3.1 TBD as an Acyl Transfer Reagent

TBD has arguably gained its popularity from its ability to promote acyl transfer reactions. In the polymer field, it has been predominantly employed as a powerful acyl transfer catalyst.[5] In the context of small molecules synthesis, TBD was found to be an excellent reagent to construct carboxylate derivatives, particularly amides. Evidently, the advantage of this process is the circumvention of the hydrolysis step and the direct access to esters and amides through transesterifications and amidations. Moreover, TBD is often introduced in catalytic amounts, providing a better alternative to traditional amide coupling reagents.

Two plausible mechanisms were proposed for TBD-mediated acyl transfer reactions.[85] One of them is termed the nucleophilic mechanism (Scheme 1.24a). In this one, TBD serves as a nucleophile to generate the reactive acyl-TBD species. This species is also able to bring the amine (in the case of amidation) in close proximity to the activated acyl group. A final nucleophilic addition affords the amide product. The other one is the hydrogen-bonding mechanism (Scheme 1.24b), where TBD activates the carbonyl and the amine at the same time. TBD is also able to actively participate in proton transfers, thus facilitating product formation before being regenerated. The nucleophilic mechanism is widely accepted, as the reactive acyl-TBD species has been isolated and fully characterized on many occasions.[85,93-94] The hydrogen-bonding mechanism, however, was only validated *in silico*.[85,106,109] This explains why TBD is catalogued as a nucleophile in the context of acyl transfer reactions in this chapter.



Scheme 1.24. Proposed mechanism for TBD-mediated acyl transfer reactions. a) Nucleophilic mechanism. b) Hydrogen-bonding mechanism.

1.3.1.1 Esters as Acyl Donors

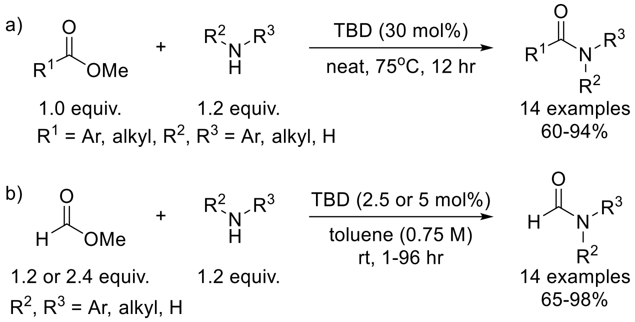
Esters are the most common acyl donors for TBD-mediated acyl transfer reactions. Apart from the advantages mentioned above, the versatility and robustness of TBD makes it an appealing reagent for the aminolysis of esters. Notably, TBD is able to facilitate acyl transfers in various solvents and neat conditions, and tolerates a wide range of temperatures. Moreover, no strictly anhydrous nor oxygen-free conditions are required, making it easy to set up such reactions.

1.3.1.1.1 Intermolecular Ester Aminolysis

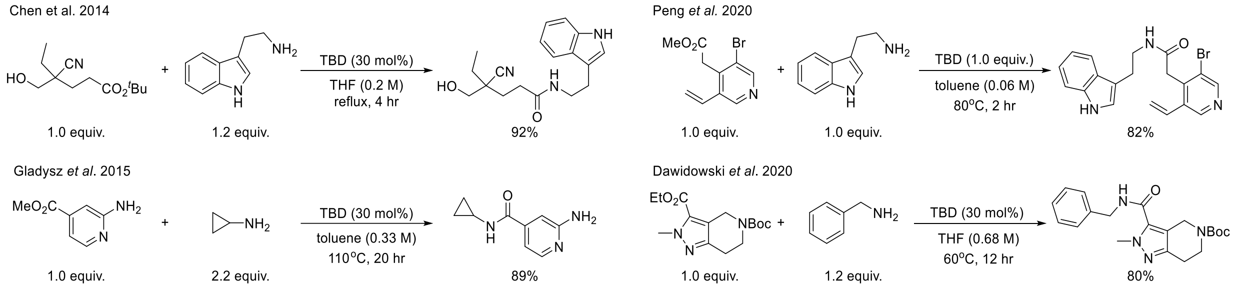
In 2005, Mioskowski and coworkers reported the first TBD-catalyzed ester aminolysis (Scheme 1.25a).[86] Assorted esters and amines led to product formation in high yields. Although the solvent-free conditions used in this method are a major benefit in terms of sustainability, they might not be applicable if both substrates remain solid at the reaction temperature. Later, Deutsch *et al.* described a formylation method with methyl formate and TBD (Scheme 1.25b).[87] Complementary to the reported reactions under neat conditions, this method features an in-solution reaction with low catalyst loading at room temperature. Notably, both primary and secondary amines are adequate substrates in these transformations.

Over the years, many applications of these reactions were reported, particularly in the synthesis of biologically active compounds. It is unfeasible to discuss them all here. Therefore, illustrative examples are provided to showcase the broad scope of these transformations.

The TBD-mediated intermolecular ester aminolysis has been extensively used in natural product synthesis and medicinal chemistry (Scheme 1.26).[88-91] These transformations show excellent tolerance for assorted functionalities, in particular heterocyclic compounds. Notably, deactivated substrates, such as aromatic carboxylates and *tert*-butyl esters, proved to be appropriate acyl donors, extending the scope of previously reported methodologies. Moreover, nucleophile selectivity was also observed, where alcohols, anilines, and nucleophilic aromatic nitrogens remained inert.

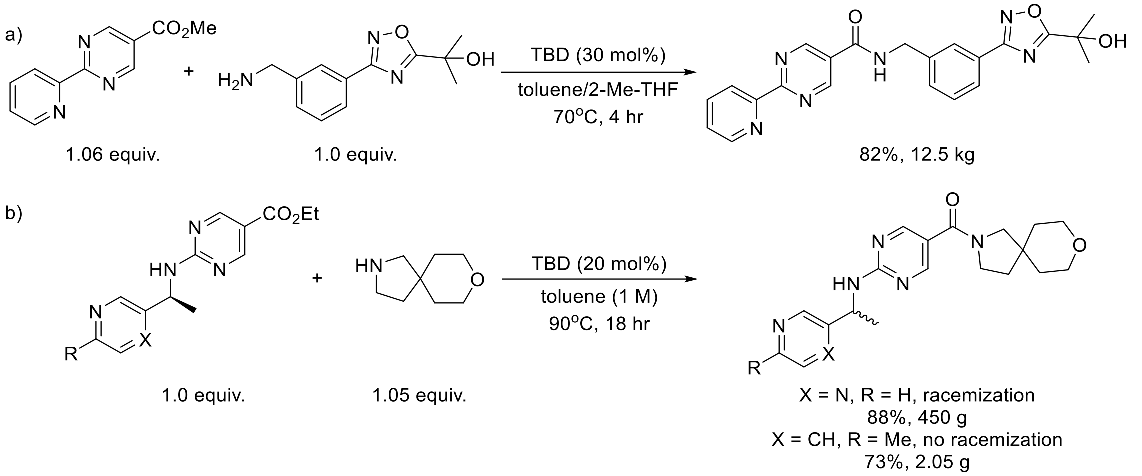


Scheme 1.25. TBD-catalyzed intermolecular ester aminolysis.



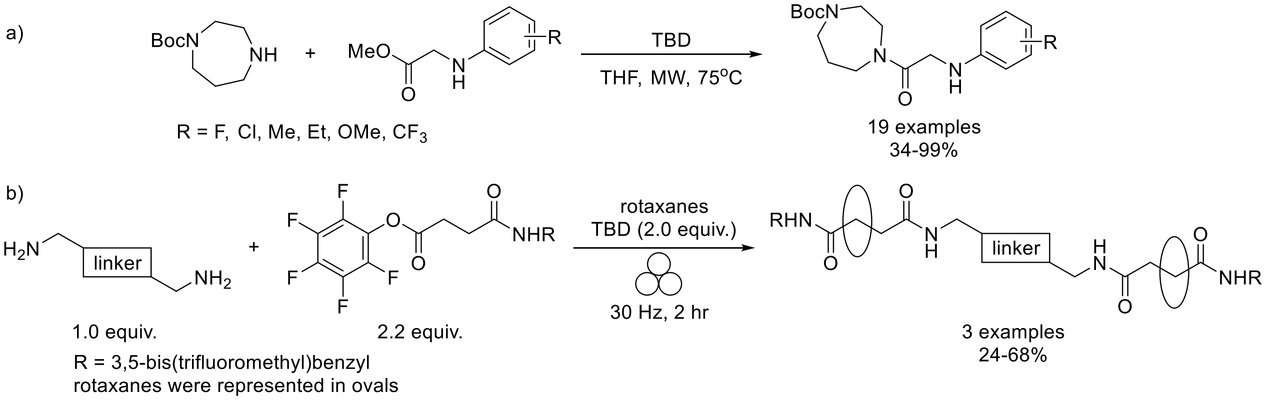
Scheme 1.26. Applications of TBD-mediated intermolecular ester aminolysis in natural product synthesis and medicinal chemistry.

TBD has also been employed at process scales. Weiberth and colleagues from Sanofi demonstrated that TBD is an efficient catalyst for the aminolysis of an unactivated ester (Scheme 1.27a).[92] This reaction was run on a kilogram scale with a heterogenous mixture. Later, Casimiro-Garcia *et al.* from Pfizer reported the early process development of a vanin-1 inhibitor (Scheme 1.27b).[93-94] The use of TBD allowed a direct conversion of an ester to an amide, avoiding the acid intermediate that was extremely difficult to handle due to its physical properties. Moreover, LC-MS analysis of the reaction mixture suggested that an acyl-TBD was indeed the intermediate. In addition, they encountered an unexpected racemization of the product. This phenomenon was studied via computational means and attributed to the presence of the adjacent pyrazine nitrogen and its ability for resonance stabilization of the carbanion, which was estimated to make the benzylic proton 6.9 pK_a units more acidic than the pyridine derivative.



Scheme 1.27. TBD-catalyzed intermolecular ester aminolysis reactions performed at process scales.

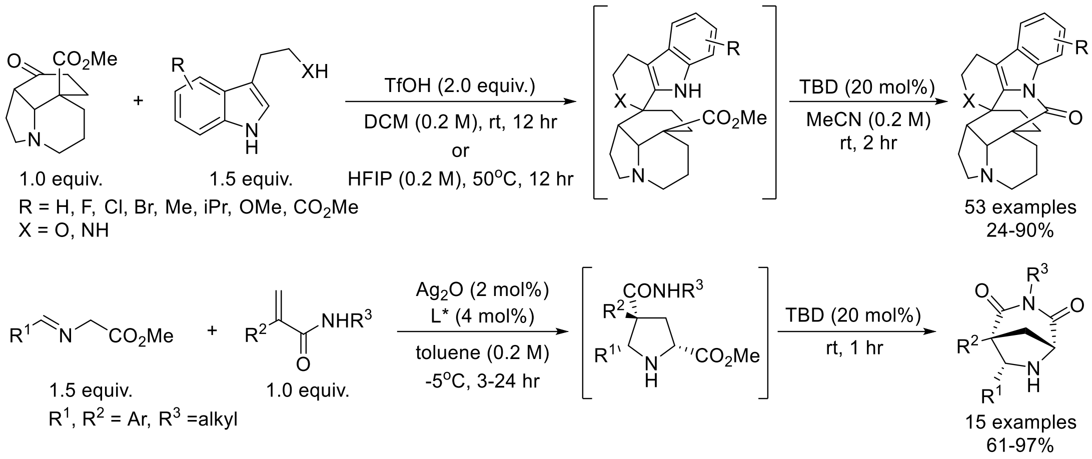
Finally, TBD can be used in conjunction with enabling technologies such as microwave and mechanochemistry. Gu *et al.* performed a series of intermolecular ester aminolysis under microwave irradiation to access 1,4-diazepane derivatives (Scheme 1.28a).[95] Nierengarten and coworkers reported the synthesis of rotaxanes, in which a key step was the mechanochemical TBD-mediated aminolysis of a pentafluorophenol ester (Scheme 1.28b).[96-97]



Scheme 1.28. TBD-promoted intermolecular ester aminolysis using enabling technologies.

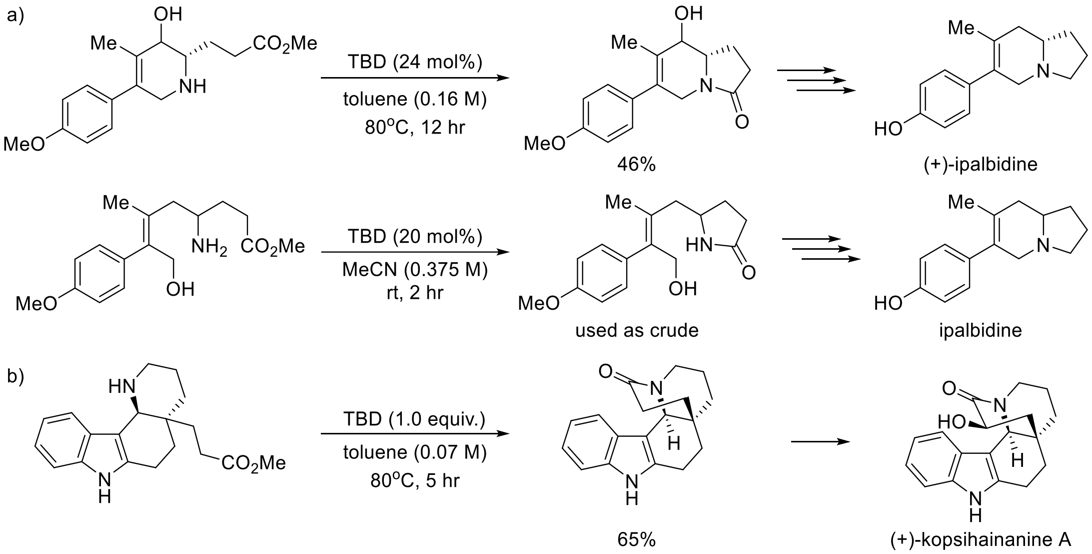
1.3.1.1.2 Intramolecular Ester Aminolysis

If the ester aminolysis takes place intramolecularly, lactams and imides can be synthesized efficiently in the presence of TBD. This has been adopted to construct complex scaffolds, including monoterpene indole alkaloids[98] and amidopyrrolidines (Scheme 1.29).[99] These reactions proceed catalytically at room temperature with broad scope and are complete within hours, further confirming the effectiveness of TBD catalysis.



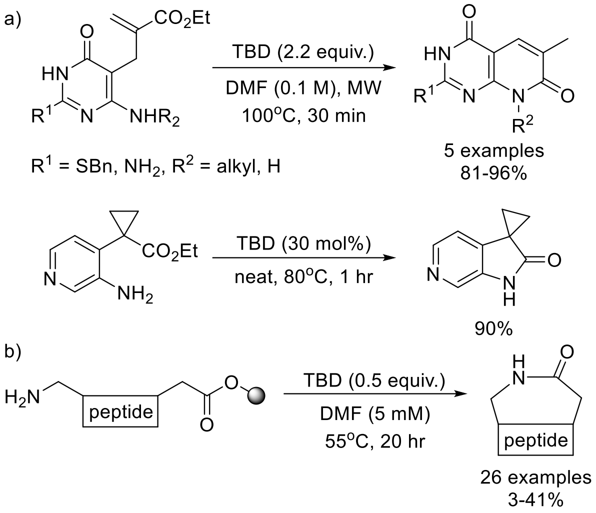
Scheme 1.29. TBD-catalyzed intramolecular ester aminolysis.

Consequently, this strategy was frequently adopted in natural product synthesis. Two reports of the synthesis of ipalbidine[100-101] took advantage of TBD-catalyzed intramolecular ester aminolysis as a key step to build the lactam ring (Scheme 1.30a), which led to the indolizidine core upon reduction. The lactam ring in kopsihainanine A was also constructed in a similar fashion (Scheme 1.30b).[102]



Scheme 1.30. TBD-catalyzed intramolecular ester aminolysis for the synthesis of natural products.

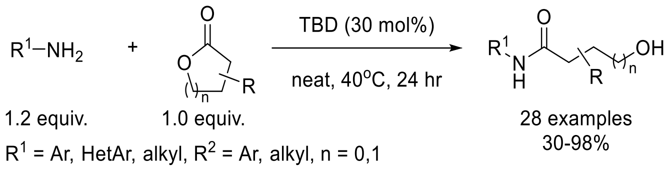
Interestingly, chemoselectivity for esters in the presence of other electrophilic groups has been reported. No conjugate addition was observed for substrates bearing Michael acceptors or homo-Michael acceptors, allowing the selective formation of lactams in high yields (Scheme 1.31a).[103-104] Although TBD has been reported as a catalyst for aza-Michael reactions,[39] we suppose that the absence of such reactions in this case is driven by the formation of aromatic products, which greatly favors ester aminolysis. Another fascinating protocol, developed by Hickey *et al*. at Merck, used TBD to achieve macrocyclization and peptide cleavage from the resin in one pot (Scheme 1.31b).[105] After solid-phase peptide synthesis, the short peptides, ranging from five to eight amino acids, were directly cleaved from the resin and underwent cyclization to form an amide bond between the *N*- and *C*-termini.



Scheme 1.31. Miscellaneous TBD-promoted intramolecular ester aminolysis. a) Chemoselective TBD-catalyzed intramolecular ester aminolysis. b) TBD-mediated one-pot peptide cleavage and macrocyclization.

1.3.1.2 Lactones as Acyl Donors

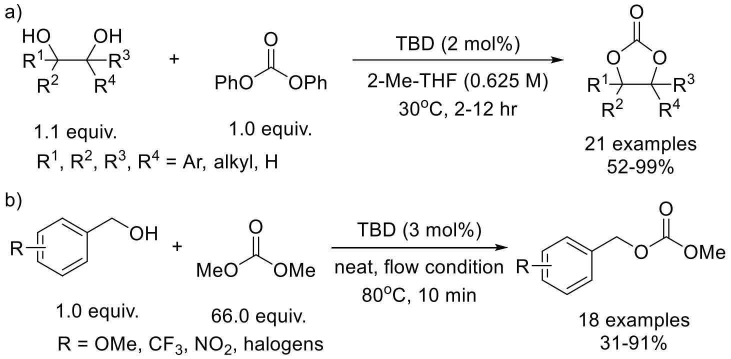
Although lactones are cyclic esters, lactones aminolysis is significantly harder to perform than ester aminolysis. The intrinsic stability of lactones, the tendency of self polymerization, as well as the lack of an entropic gain during aminolysis all make lactone aminolysis a challenging reaction. TBD-mediated acyl transfer reactions with lactones are underdeveloped. To our knowledge, only one practical ring-opening aminolysis of lactones was reported. Guo *et al*. successfully performed a series of lactone aminolysis reactions in the presence of TBD (Scheme 1.32).[106] This method was mild, catalytic, and easy to operate. The neat conditions, on one hand, successfully promoted the reaction of deactivated substrates such as anilines. On the other hand, it required at least one substrate to be liquid at the reaction temperature, which limited its scope.



Scheme 1.32. TBD-catalyzed lactone aminolysis.

1.3.1.3 Carbonates and Carbamates as Acyl Donors

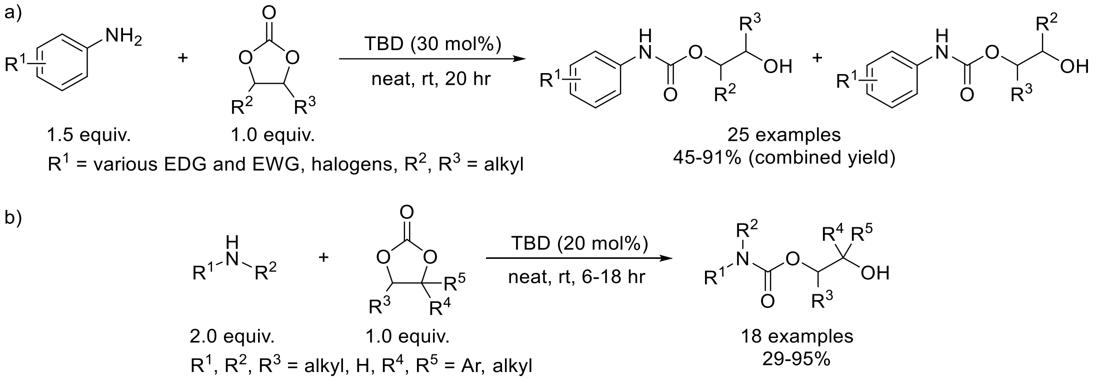
Although less reactive than esters, carbonates and carbamates are also suitable acyl donors for TBD-mediated acyl transfer reactions. Carbonates with better leaving groups attached can be used for transesterifications to afford other carbonates. Baral *et al.* achieved a TBD-catalyzed cyclic carbonate synthesis from diphenyl carbonate and diols (Scheme 1.33a).[107] This method required a low catalyst loading and proceeded at near-room temperature, making it a more sustainable choice for the synthesis of such scaffolds. A similar approach was adopted in flow chemistry to synthesize unsymmetrical carbonates from dimethylcarbonate (Scheme 1.33b).[108] With only 3% TBD loading and 10 minutes residence time, numerous benzyl alcohols were converted to the corresponding carbonates with satisfactory yields.



Scheme 1.33. TBD-catalyzed transesterifications of carbonates.

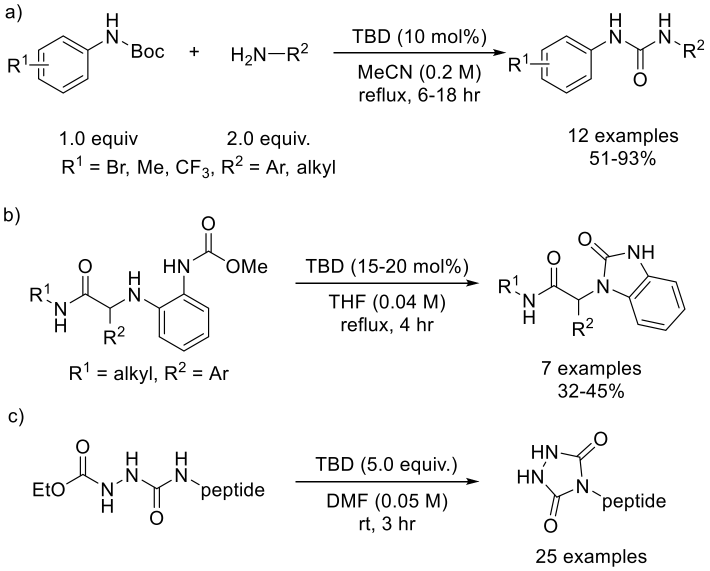
If amines are used as nucleophiles, carbamates can be accessed from carbonates. The Kleij group at the Institute of Chemical Research of Catalonia described the first TBD-catalyzed ring-opening aminolysis reaction of cyclic carbonates (Scheme 1.34a).[109] Despite the mild conditions, poor regioselectivity is the main issue of this method. Later, they discovered that the regioselectivity can be significantly improved by exploiting steric biases (Scheme 1.34b).[110] Disubstitution on one carbon in five-membered cyclic carbonates created ample steric hindrance to prevent nucleophilic addition from happening on the same side. Consequently, a regioselectivity of >99:1

was observed, favoring reaction at the less hindered side.



Scheme 1.34. TBD-catalyzed amidations with carbonates.

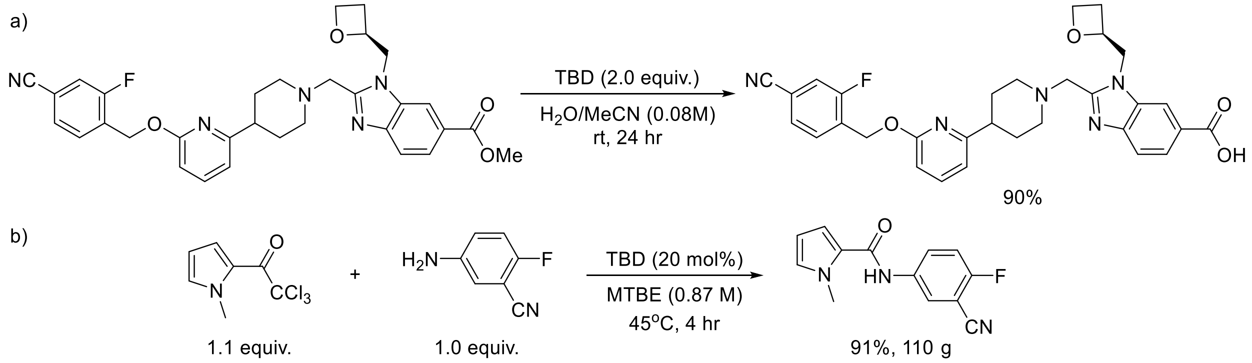
Furthermore, carbamates can be utilized to synthesize ureas in the presence of TBD. Wang *et al.* reported a method to convert Boc-protected anilines to unsymmetrical ureas (Scheme 1.35a).[111] Similar approaches were also explored for intramolecular transformations. Therefore, TBD proved to be an appropriate catalyst for the synthesis of benzimidazolone[112] derivatives (Scheme 1.35b). In addition, an on-resin peptide derivatization to access urazoles was reported (Scheme 1.35c).[113]



Scheme 1.35. TBD-catalyzed amidations with carbamates.

1.3.1.4 Unusual Applications of TBD as an Acyl Transfer Reagent

In 2022, Griffith *et al.* from Pfizer reported an atypical ester hydrolysis mediated by TBD (Scheme 1.36a).[114] According to the authors, all common methods failed to deliver the desired product, as the base-sensitive aromatic nitrile was hydrolyzed concomitantly. TBD, however, selectively attacked the ester group to generate the acyl-TBD species, which was then quenched by water to release the free acid. Another creative use of TBD came from the process team at Johnson & Johnson, who performed a haloform-type amidation in the presence of TBD (Scheme 1.36b).[115] The trichlorocarbanion served as a leaving group, allowing smooth construction of the amide product as a precursor to bersacapavir. This protocol significantly improved the process mass intensity, providing a more sustainable route.



Scheme 1.36. Unusual use of TBD as an acyl transfer reagent.

1.3.2 Utilization of CO_2

With the increasing threats created by climate change, CO_2 utilization/fixation is a topic that has attracted significant attentions in recent years. TBD is able to form stable adducts with CO_2 at ambient temperature, the crystal structures of which were reported by Ephritikhine and colleagues. (Figure 1.5).[116] Under strictly anhydrous conditions, the TBD−CO_2 complex is formed, whereas in the presence of moisture the [TBDH][HCO_3] dimer is observed.

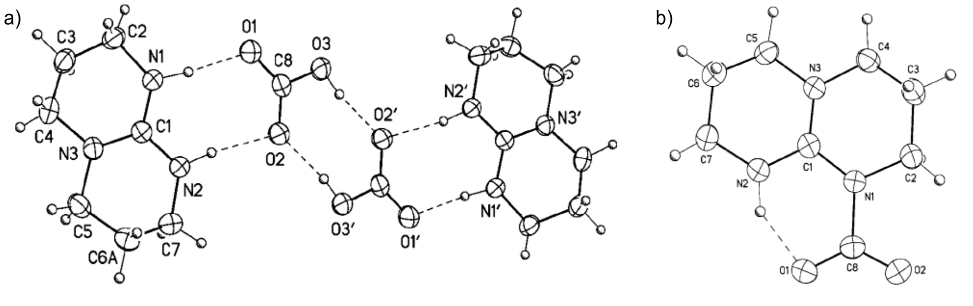


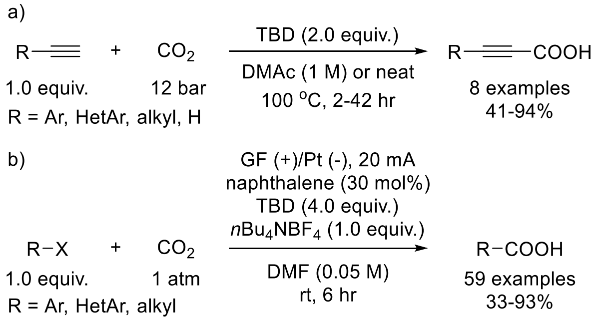
Figure 1.5. Crystal structures of a) the [TBDH][HCO_3] dimer and b) the TBD−CO_2 adduct. Figures reproduced from the original publication.[112] Reproduction permission was obtained from the publisher.

The feasibility of TBD participating in CO_2 chemical fixation has been evaluated. TBD−CO_2 complexes were successfully transformed to carbamates in the presence of amines and alkyl halides.[117] The thermal stability of TBD−CO_2 complexes in the solid state was also evaluated, revealing that it is stable at up to 80°C with slight decomposition observed after prolonged heating at 90°C.[117] This indicates that TBD can actively promote CO_2 fixation reactions under moderate heating. In another study, activation of CO_2 by TBD in solution was observed, implying that TBD−CO_2 complexation is important in TBD-mediated CO_2 utilization.[118] Notably, sensitivity of the TBD−CO_2 adduct towards water was observed in all cases, suggesting that nucleophilic attack of such an adduct should proceed smoothly.

Owing to its strong ability to trap CO_2, TBD has been extensively used to promote CO_2 utilization in organic synthesis. This offers several advantages, including easy operation, milder reaction conditions (avoiding cryogenic or intense heating), as well as allowing the use of safer and more accessible CO_2 sources (CO_2 balloon or ambient CO_2 instead of pressurized CO_2 or dry ice).

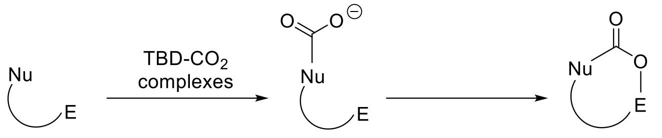
1.3.2.1 Redox-Neutral Utilization of CO_2

Redox-neutral utilization of CO_2 incorporates all atoms of this molecule into the product. The most straightforward of such transformations is the synthesis of carboxylic acids. Due to the acidity of the product, TBD must be employed in stoichiometric or excess amount. In 2013, Wang *et al.* successfully performed alkyne carboxylation in the presence of TBD (Scheme 1.37a).[119] However, this method required the use of an autoclave and highly pressurized CO_2, which significantly hampered its applications. Another method, reported by Qiu and coworkers, uses an electrochemical approach to synthesize carboxylic acids from aryl and alkyl halides (Scheme 1.37b).[120] This method is much safer to operate and only required a CO_2 balloon as the CO_2 source.



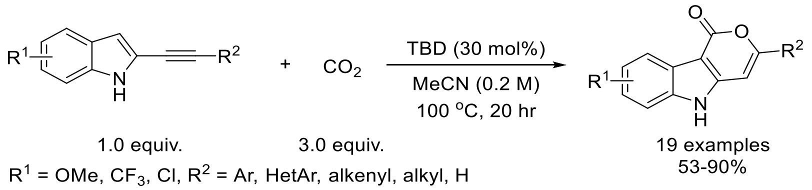
Scheme 1.37. TBD-mediated synthesis of carboxylic acids from CO_2.

A broadly adopted strategy to extract CO_2 from the TBD–CO_2 complexes exploits molecules containing both nucleophilic and electrophilic groups. As illustrated in Scheme 1.38, the nucleophilic groups could attack the TBD–CO_2 complexes, generating a nucleophile–CO_2 intermediate bearing a nucleophilic carboxylate. If electrophilic groups are positioned in vicinity, carboxylative cyclization could occur, resulting in final trapping of CO_2. Compounds bearing propargylic/allylic nucleophiles are perfect substrates for this type of transformation, allowing rapid cyclization to access five- or six-membered carboxylated rings.



Scheme 1.38. Strategy for TBD-mediated CO_2 trapping.

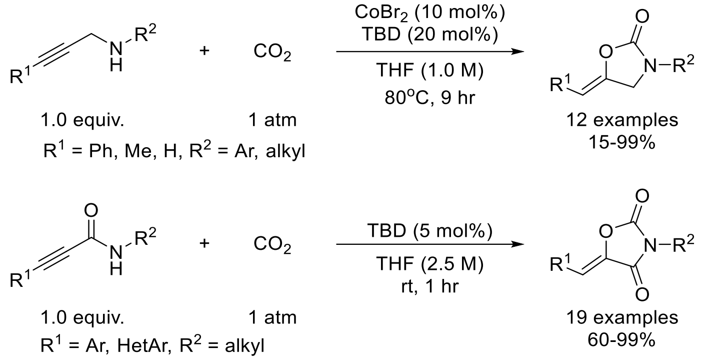
Although Della Ca *et al*. have reported a TBD-mediated CO_2 capture process using propargyl alcohols back in 2011,[121] this method was not particularly useful due to the need for supercritical CO_2 and the generation of a mixture of products. In 2015, the Skrydstrup group at Aarhus University reported the first synthetically advantageous CO_2 transformation involving TBD. In this method, CO_2 was trapped with alkynyl indoles in the presence of TBD (Scheme 1.39).[122] Since the final products are neutral compounds, the reaction proceeded with catalytic amounts of TBD. A fixed amount of CO_2 gas was injected into the reaction vessel, and no special measure was needed to maintain a CO_2 atmosphere.



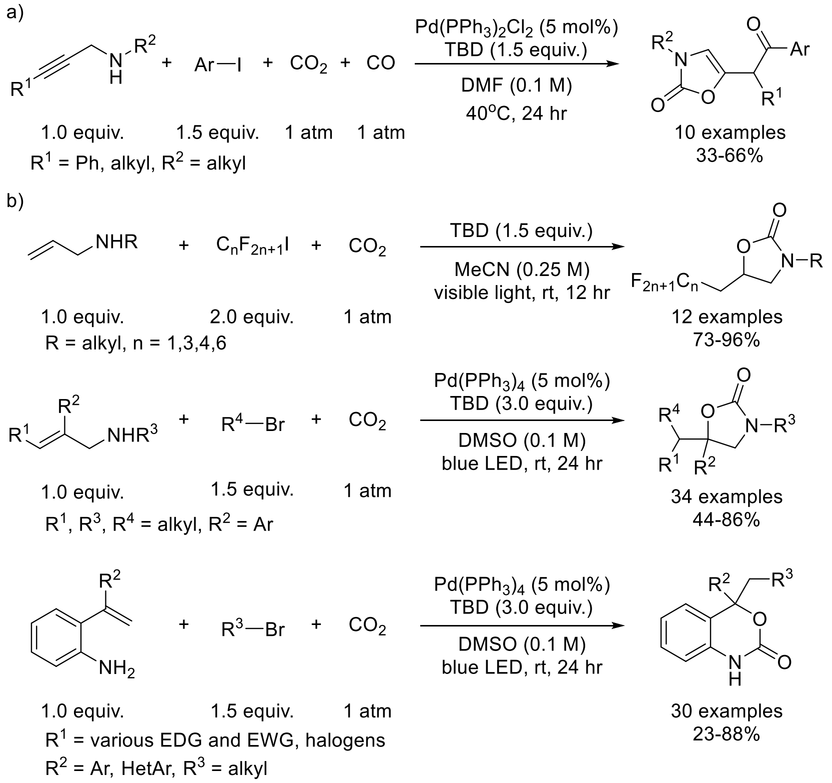
Scheme 1.39. TBD-catalyzed CO_2 utilization with alkynyl indoles.

Other compounds, such as propargyl amines and propiolamides, are suitable substrates for CO_2 utilizations and to access carbamate derivates (Scheme 1.40).[123-124] Similarly, these reactions only require catalytic amount of TBD and an atmospheric pressure of CO_2, highlighting more advantages of utilizing TBD.

In addition, this type of transformation can be coupled with other processes to access compounds of higher complexity. Both palladium-catalyzed couplings and photochemical reactions are compatible. For instance, in the presence of aryl iodides, CO, and a palladium catalyst, the carbamate obtained from propargyl amines and CO_2 were reported to undergo acylation (Scheme 1.41a).[125] Photochemical methods can also further decorate carbamates derived from allyl amines and CO_2 (Scheme 1.41b).[126-128]



Scheme 1.40. TBD-catalyzed CO_2 utilization with propargyl amines and propiolamides.

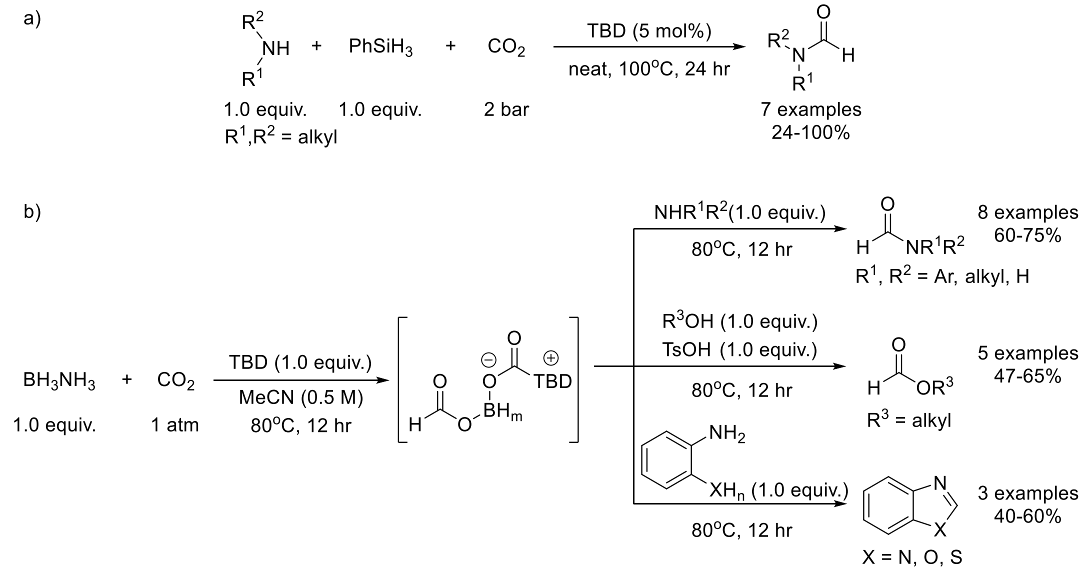


Scheme 1.41. TBD-promoted CO_2 utilizations coupled with palladium chemistry and photochemistry.

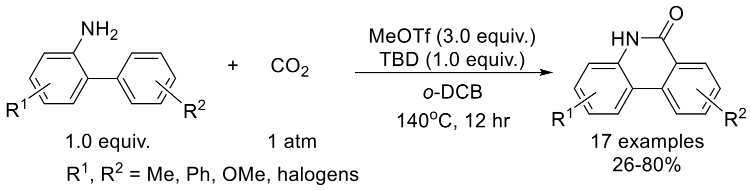
1.3.2.2 Reductive Utilization of CO_2

CO_2 can also be employed under reducing conditions, allowing it to serve as a one-carbon synthon.

When one oxygen atom is removed, CO_2 becomes a carbonylation reagent. As a proof of concept, Das Neves Gomes *et al.* reported a TBD-catalyzed formylation reaction of secondary amines with phenylsilane and CO_2 (Scheme 1.42a).[129] However, only a few aliphatic secondary amines were successfully transformed in reasonable yields. Later, the Xi group at Tsinghua University expanded this method to a one-pot two-step procedure, where CO_2 was first activated and reduced by an ammonia-borane complex, before addition of a nucleophile (Scheme 1.42b).[130] Primary amines, secondary amines, and primary alcohols were all suitable substrates for this formylation process. When ortho-substituted anilines were used, condensation occurred after formylation to afford various heterocyclic compounds.[131]



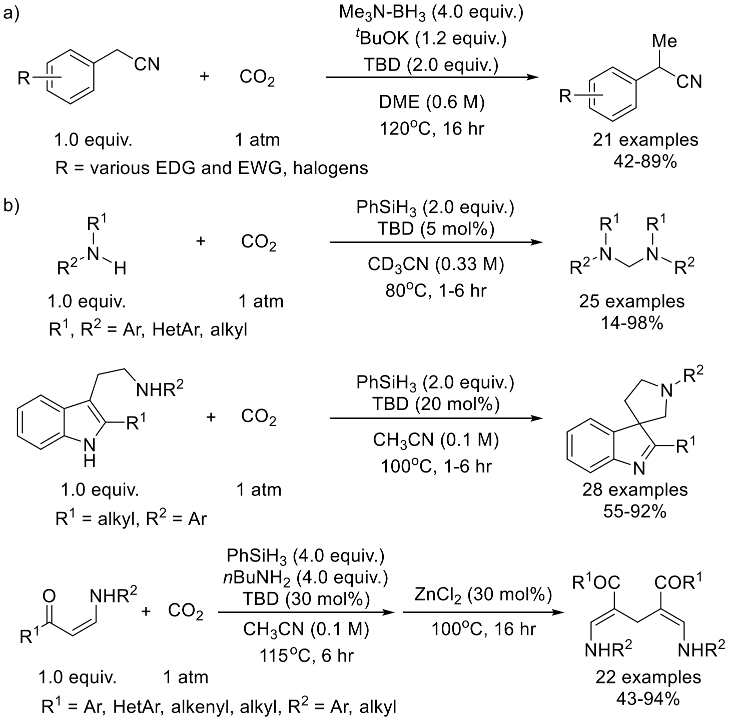
Scheme 1.42. CO_2 as a carbonyl equivalent in TBD-mediated reductive utilization of CO_2.



Scheme 1.43. TBD-mediated reductive utilization of CO_2 without a reductant.

Interestingly, the Xi group also described a method to access phenanthridinones from *ortho*-arylanilines, using CO_2 as a carbonyl source (Scheme 1.43).[132] This method removed the oxygen atom by converting it to a leaving group with methyl triflate, rather than by direct reduction. To our knowledge, this is the only example of reductive utilization of CO_2 without the involvement of a reductant.

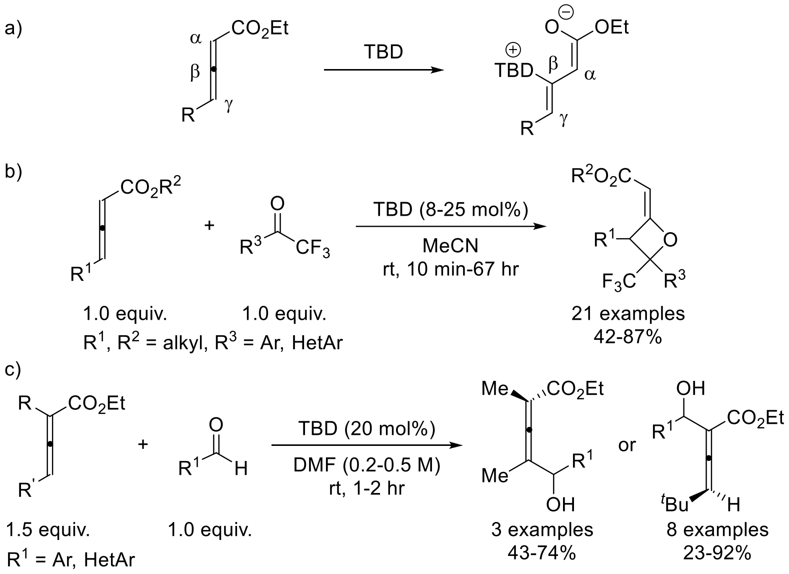
If more reductant is used, CO_2 can be further reduced to aliphatic carbon equivalents. Depending on the substrate, CO_2 can turn into a methyl or a methylene unit. The Xi group achieved the TBD-promoted α-methylation of 2-arylacetonitrile with trimethylamine-borane as the reductant (Scheme 1.44a).[133] CO_2 was directly reduced to a methyl before being transferred to the product. Likewise, reduction of CO_2 to a methylene unit was reported in the synthesis of numerous compounds, including aminals,[134] spiro-indolepyrrolidines,[135] and enaminones (Scheme 1.44b).[136]



Scheme 1.44. TBD-mediated reductive utilization of CO_2 as a) a methyl source and b) a methylene source.

1.3.3 Activation of Allenoates

Allenoates are allenes with carboxylates directly attached on them. This type of compound can be specifically activated by TBD through nucleophilic attack, generating an enolate-like zwitterion reactive species with nucleophilicity at both α- and γ-position (Scheme 1.45a). The Selig group at RWTH Aachen University have focused on TBD-catalyzed transformations involving alleonates. In 2013, the group reported the synthesis of highly substituted oxetanes from alleonates and trifluoroacetophenones (Scheme 1.45b).[137] No formation of tetrahydrofuran byproducts was detected during this process. Later, the group described a diastereoselective synthesis of Morita–Baylis–Hillman alcohols (Scheme 1.45c).[138] By altering the substituents on allenoates, both α- and γ- chemoselectivity were accomplished.



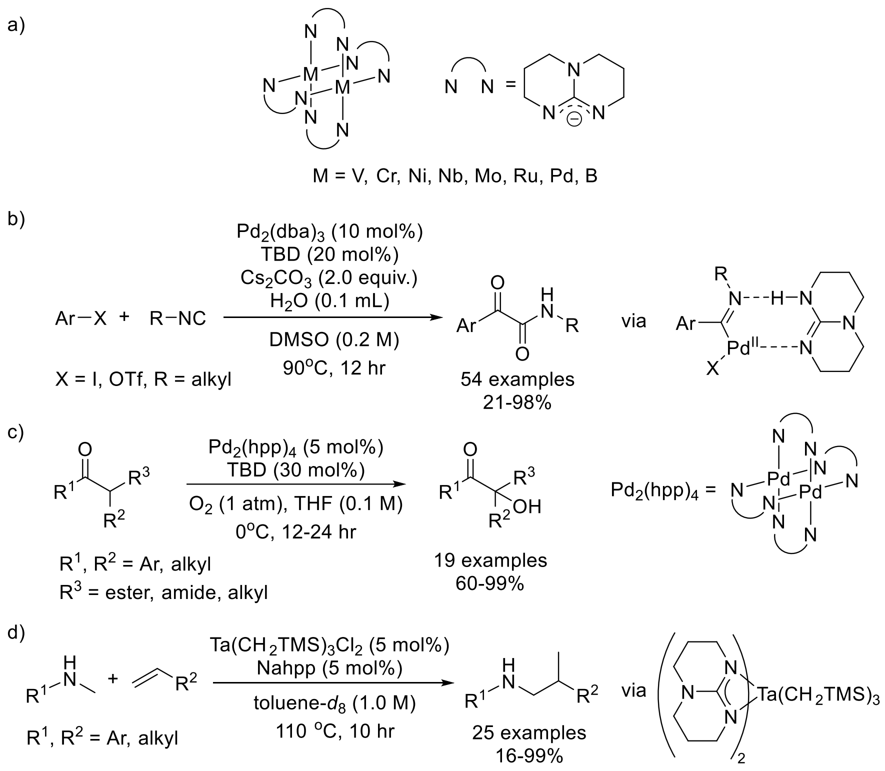
Scheme 1.45. Activation of allenoates by TBD. a) Mechanism of allenoate activation by TBD. b) TBD-catalyzed oxetane synthesis from allenoate and trifluoroacetophenone. c) TBD-catalyzed diastereoselective synthesis of Morita–Baylis–Hillman alcohols.

1.4 TBD as a Ligand

The deprotonated TBD anion can serve as an excellent bidentate ligand for various transition metals, including V,[139] Cr,[139] Ni,[140] Nb,[141] Mo,[139] Ru,[142] Pd,[143-145] and Ta,[146-147] as well as main group elements such as boron (Scheme 1.46a).[148] Except with Ta, the TBD anion formed a dinuclear complex with these atoms, which was of particular interest for organometallic chemistry. Although these complexes have not yet found broad applications in organic synthesis, some were reported to be catalysts for varying transformations, including isocyanide insertion (Scheme 1.46b),[145] oxidation (Scheme 1.46c),[144] and hydroaminoalkylation (Scheme 1.46d).[147]

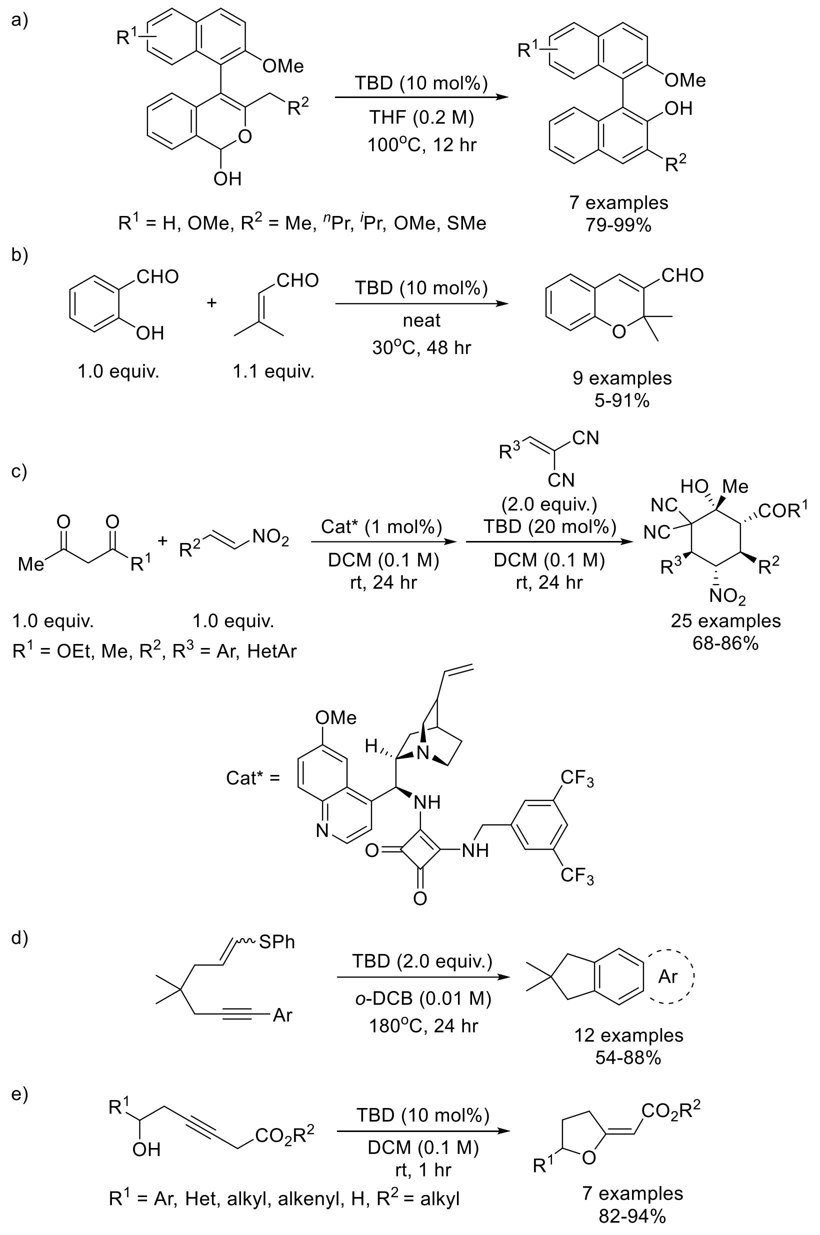
1.5 TBD as a Multifunctional Reagent

Although the multifunctionality of TBD was briefly introduced above, this section will showcase a few examples for which the multifunctional role of TBD is clearly demonstrated. For instance, the basicity of TBD allows it to promote multiple steps in the same transformation. Terada *et al.*



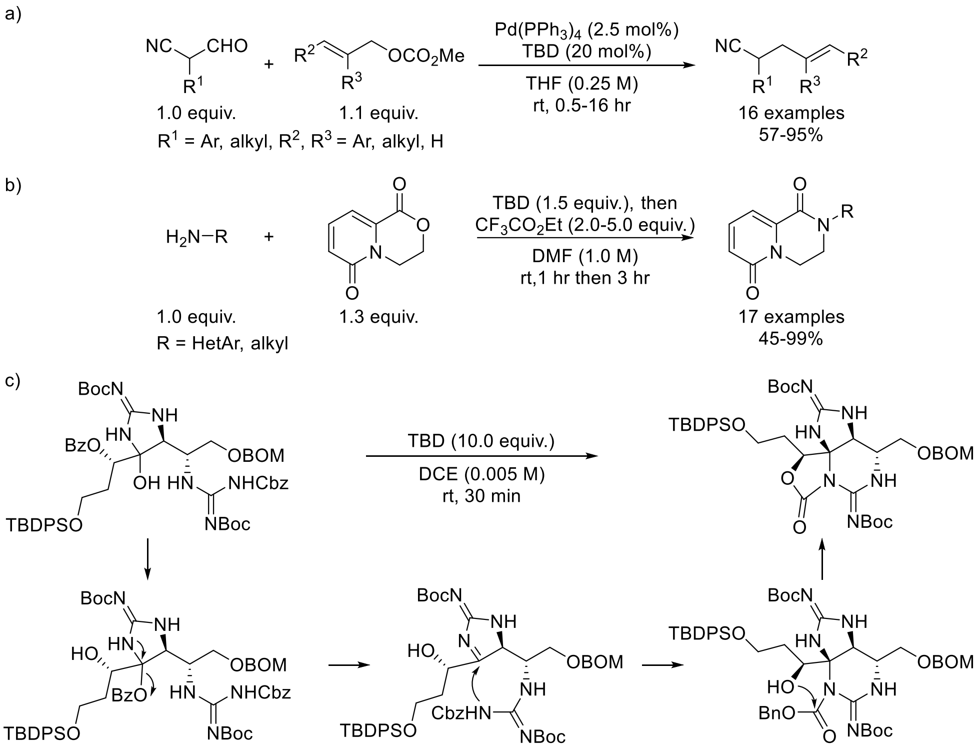
Scheme 1.46. Dinuclear organometallic compounds ligated by the TBD anion and their applications in organic synthesis and their applications in organic synthesis.

reported a TBD-catalyzed Ferrier-type rearrangement (Scheme 1.47a).[149] TBD first triggered ring-opening of the hemiacetal, generating a keto-aldehyde structure. Subsequent intramolecular aldolization, followed by dehydration and aromatization afforded substituted biaryl phenols. TBD was proposed to catalyze all steps in this transformation. Lanari *et al*. developed a domino reaction for the synthesis of chromenes (Scheme 1.47b),[150] where TBD catalyzed an intermolecular oxa-Michael addition and the following intramolecular aldol reaction. A Michael-Michael-1,2-addition cascade, facilitated by both a chiral squaramide and TBD, was employed by Chauhan *et al.* to access highly functionalized cyclohexanes (Scheme 1.47c).[151] Both the second Michael addition and the 1,2-addition to the ketone were catalyzed by TBD. Another method, described by Yang and coworkers,[152] took advantage of the 1,3-hydrogen transfer of alkynes to produce allenes, which permitted intramolecular Diels-Alder reactions (Scheme 1.47d). Elimination of the thiolate in the presence of TBD furnished the final polyaromatic product. Last but not least, tetrahydrofuran derivatives were accessed through a TBD-catalyzed tandem reaction. Alkynes were first isomerized to allenes, which then underwent intramolecular oxa-Michael reactions and [1,5]-proton shifts to afford the desired products (Scheme 1.47e).[153]

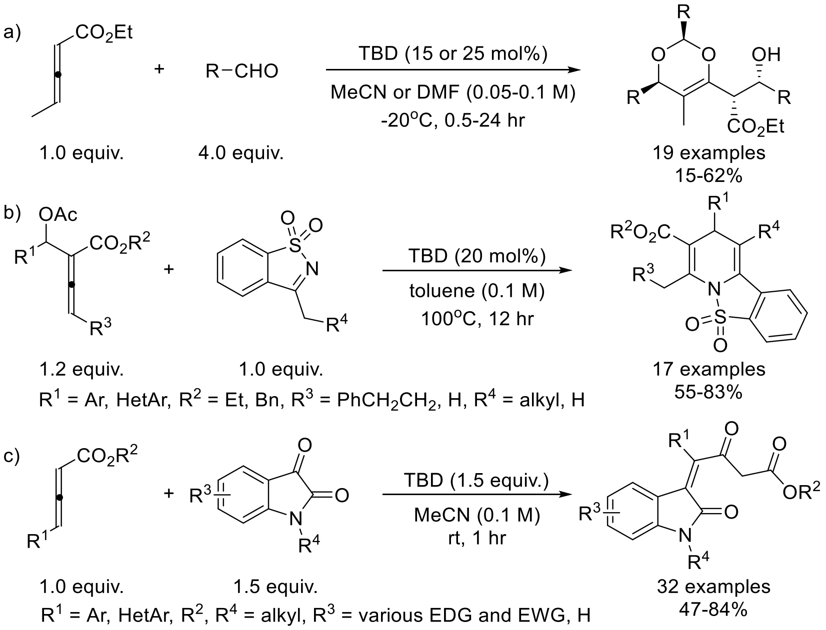


Scheme 1.47. Reactions utilizing TBD as a multifunctional base.

In addition, TBD can be employed as both an acyl transfer reagent and an organic superbase to enable cascade reactions. Maji *et al*. developed a catalytic α-allylation reaction of aryl acetonitriles (Scheme 1.48a).[154] TBD was proposed to generate the enolate first, thus enabling allylation. It then served as an acyl transfer reagent to remove the formyl group. Rankic and colleagues reported a simple lactone-to-lactam transformation (Scheme 1.48b).[155-156] TBD first mediated the aminolysis of the lactone, which released a free hydroxyl handle. This was then activated with ethyl trifluoroacetate to permit a subsequent intramolecular cyclization promoted by TBD. Another



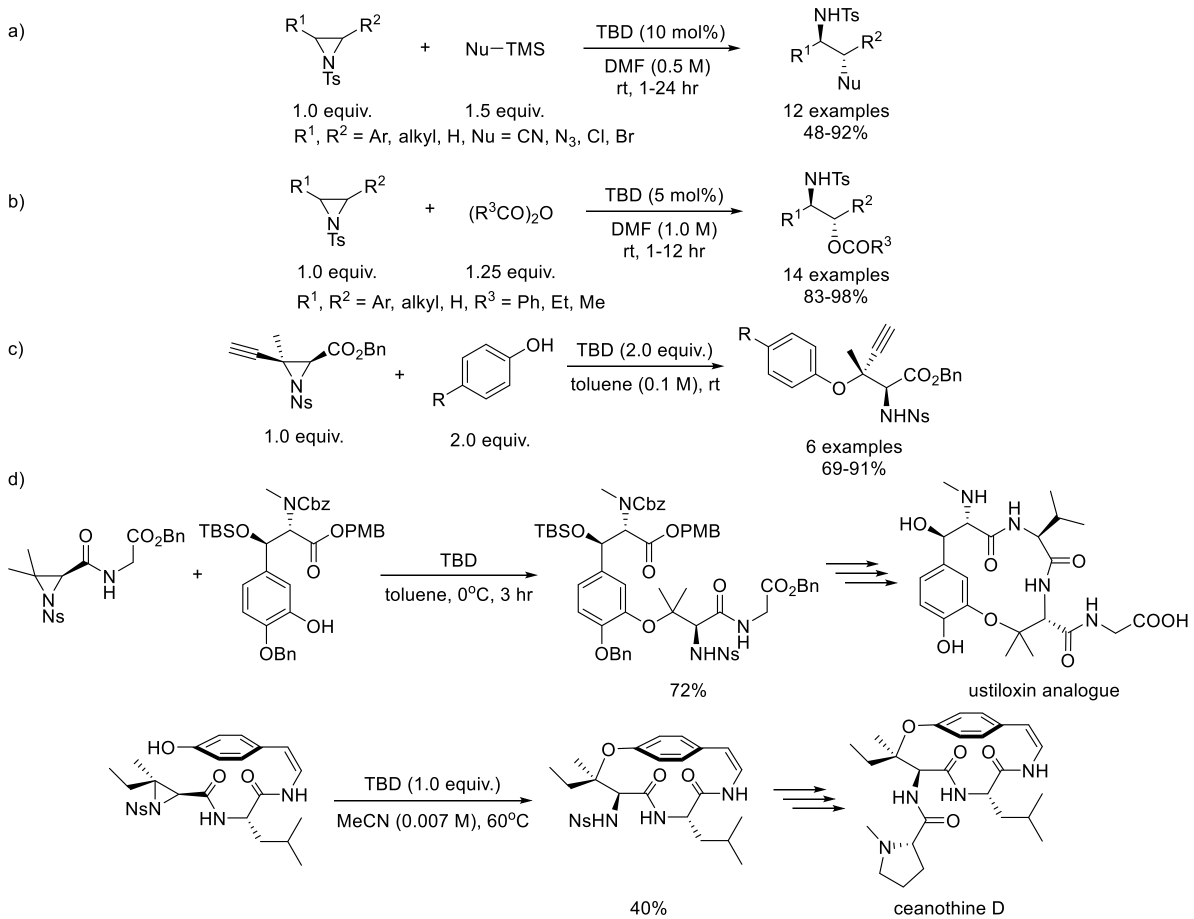
Scheme 1.48. Reactions utilizing TBD as an acyl transfer reagent and an organic superbase.



Scheme 1.49. Allenoate transformations utilizing TBD as a multifunctional reagent.

captivating transformation, this time for the synthesis of saxitoxin[157] took advantage of the multifunctionality of TBD to promote acyl migration, elimination, nucleophilic addition, and intramolecular transesterification (Scheme 1.48c). Notably, all of these steps proceeded at room temperature with remarkable tolerance for a variety of functionalities, demonstrating the mildness and effectiveness of TBD as a multifunctional reagent.

Likewise, TBD can exert its multifunctionality on cascade reactions involving allenoates. Selig and colleagues developed a triple functionalization of allenoates which employs TBD as a catalyst for two consecutive Morita-Baylis-Hillman reactions, an acetalization, and an oxa-Michael reaction (Scheme 1.49a).[158] Other reports by Qureshi *et al.*[159] (Scheme 1.49b) and Santhoshkumar *et al.*[160] (Scheme 1.49c) required TBD to deprotonate at key positions to initiate downstream processes.



Scheme 1.50. TBD-mediated ring-opening of aziridines.

The regio- and stereoselective ring-opening of aziridines can also benefit from TBD. The nucleophilic nitrogen plays an important role in activating the pre-nucleophile, be it silylated nucleophiles,[161] anhydrides,[162] or phenols,[163] while the electrophilic N-H bond is proposed to activate the aziridines by hydrogen-bonding (Scheme 1.50a-1.50c). Moreover, this forms a substrate-catalyst complex similar to that illustrated in section 1.2.4.1, bringing two components in close proximity to facilitate the reaction. The reactions with phenols were also used in the synthesis of natural products, including ustiloxin analogues[164] and ceanothine D (Scheme 1.50d).[165]

1.6 Objectives of the Research

Despite recent advances in the utilization of TBD in organic synthesis, there are still areas left uncharted. For example, as stated in section 1.3.1.2, there are very few reports concerning TBD-promoted lactone aminolysis, which is intrinsically more difficult to perform than ester aminolysis due to the high stability and facile polymerization of lactones. Furthermore, a majority of the reports only exploit one of many functions of TBD. Hence, it is sensible to believe that more sophisticated systems can be designed in which TBD operates as a multifunctional reagent. Lastly, the discovery of new functions to expand the utility of TBD is welcomed.

This thesis exploits TBD for the development of more sustainable synthetic methodologies. In particular, it aims to take advantage of the multifunctionality of TBD to enable useful organic transformations. Chapter 2 describes a TBD-catalyzed lactone aminolysis reaction. This method presents several major improvements over conventional approaches, which require prolonged heating, high lactone loading, as well as stoichiometric amounts of base to facilitate proton transfers. In contrast, the TBD-catalyzed aminolysis reaction proceeds at ambient temperature, requires a lower loading of lactone, and avoids the need for extra base. Furthermore, mechanistic studies via NMR experiments revealed the complex nature of this reaction and demonstrated that an acyl-TBD species is indeed a reactive intermediate. Overall, this method points to the right direction for more sustainable lactone aminolysis reactions. In addition, it is complementary to the reaction developed by the Kleij lab[106] because it uses a solvent rather than neat conditions, allowing a greater diversity of aminolysis partners, especially solid substrates, to react smoothly.

Following the successful method development in Chapter 2, Chapter 3 reports a rapid access to 3-hydroxyisoindolin-1-ones from 3-alkylidenephthalides and amines, enabled by the multifunctionality of TBD. In this transformation, TBD first serves as an acyl transfer reagent, enabling the aminolysis of the enol lactone moiety embedded in 3-alkylidenephthalides. Next, it facilitates the ring-closure process to afford the final products. This method inherits the sustainable conditions of the aminolysis reaction presented in Chapter 2, allowing rapid access to the products at room temperature. Moreover, toluene as the choice of solvent allowed many products to precipitate out of the reaction mixture, which greatly simplified the purification process. Given that 3-hydroxyisoindolin-1-one is a privileged core in numerous natural products and pharmaceuticals, this method provides a valuable alternative for the synthesis of such scaffolds.

During the development of the method reported in Chapter 3, we made the serendipitous discovery that TBD was able to catalyze a C–C bond cleavage, which is a novel mechanism for TBD. In Chapter 4, we elaborate on this exciting function and describe the TBD-catalyzed synthesis of cyclic imides *via* an amidation-cyclization-elimination cascade. The mild and efficient conditions employed in this methodology are compatible with late stage functionalization of complex molecules, as well as the synthesis of bioactive molecules. To further elucidate the mechanism of this unprecedented C–C bond cleavage, both experimental and computational approaches were utilized.

With all the newly developed methodologies that employ TBD as a catalyst, it is important to demonstrate the utility of such transformations. Chapter 5 showcases an application of the TBD-catalyzed lactone aminolysis in medicinal chemistry research. A total of 17 novel pantothenamide-mimicking compounds were synthesized and evaluated as potential antiplasmodials. These compounds are structurally diverse and accessed through the method reported in Chapter 2. Three of the compounds exhibit antiplasmodial activity at high nanomolar concentrations. Lastly, computational methods were adopted to tentatively explore the ability of these compounds to mimic pantothenamides. Together, these results further demonstrate the extraordinary potential of TBD as an organocatalyst.

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Preface for Chapter 2

Driven by challenges experienced with an aminolysis step that is central to our medicinal chemistry efforts, Chapter 2 presents a novel TBD-catalyzed lactone aminolysis reaction. As mentioned in Chapter 1 and later in Chapter 5, traditional lactone aminolysis suffers several drawbacks, which significantly hinder its further applications.

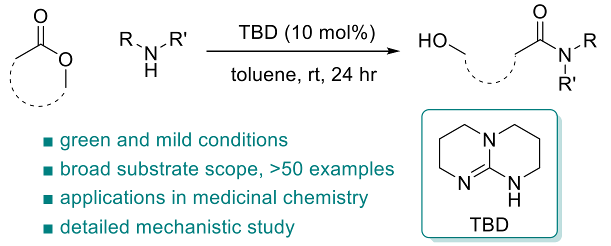
Herein, we report a catalytic lactone aminolysis reaction that utilizes TBD as a catalyst. This method is mild, efficient, and tolerates a broad range of functionalities. Applications in the synthesis of bioactive molecules are also demonstrated. Moreover, we conducted detailed mechanistic studies, revealing the complex mechanism of this seemingly simple reaction. This work has not only inspired several additional projects on TBD-catalyzed organic methodologies (Chapters 3-4), but also laid a solid foundation for Chapter 5, which employed TBD-catalyzed lactone aminolysis to access the target molecules.

All of the results presented in this chapter were acquired by the author of this thesis under the supervision of prof. Karine Auclair. This work is published as follows:

Lan, C. B.; Auclair, K.* 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD): An Effective Catalyst for Amide Formation by Lactone Aminolysis. *J. Org. Chem.* **2023**, *88*, 10086-10095.

Chapter 2

1,5,7-Triazabicyclo[4.4.0]dec-5-ene: An Effective Catalyst for Amide Formation by Lactone Aminolysis



Abstract: The amide is one of the most prevalent functional groups throughout natural and engineered chemical space. Among various methods of constructing amide bonds, lactone aminolysis remains one of the most atom economical. Herein, we report 1,5,7 triazabicyclo[4.4.0]-dec-5-ene (TBD) as an effective catalyst for lactone aminolysis under mild conditions. This methodology is compatible with a wide range of lactones and amines (>50 examples), including various natural products and pharmaceuticals, and applicable to the synthesis of bioactive molecules. Detailed mechanistic studies under synthetically relevant conditions, including reaction progress kinetic analysis and variable time normalization analysis, reveal a likely mechanism for this reaction involving acyl-TBD as the reactive intermediate.

2.1 Introduction

2.1.1 Amide Bond Formation

The amide bond is arguably the most important functional group in chemistry. It serves as the key connection in proteins and a variety of synthetic polymers[1] and also exists in countless natural products and biologically active molecules.[2] Amide bond formation is one of the most frequent reactions carried out in contemporary pharmaceutical synthesis.[3] Despite continuous efforts toward the development of new amide bond formation reactions, the existing methods typically suffer from poor atom economy and high waste generation.[3] Hence, it is crucial to discover more sustainable methods for amide assembly.

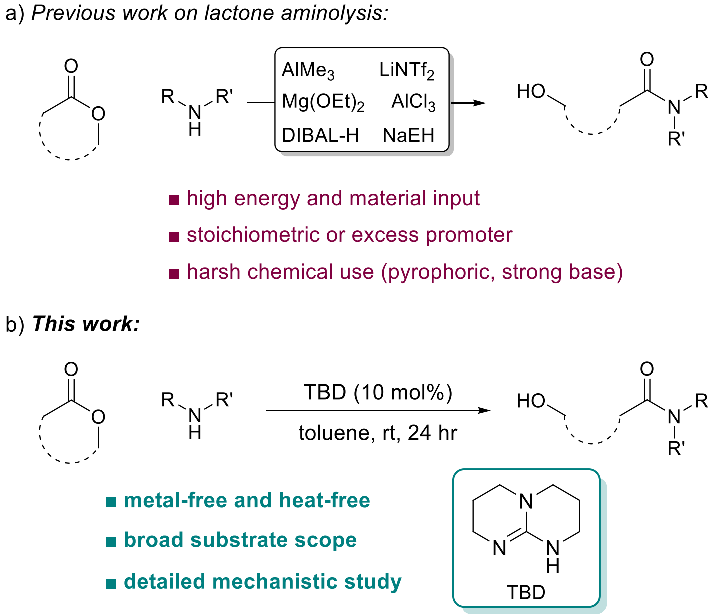
2.1.2 Lactone Aminolysis

Lactone aminolysis is a privileged approach to construct amide bonds. Its atom economy is 100%, making it intrinsically more sustainable. It also uncages a hydroxy handle that can be further elaborated. Despite the benefits, lactone aminolysis has long been overlooked for practical reasons; due to the high stability of most lactones, forcing conditions such as high pressure,[4a] high temperature,[4d,e] and largely excessive reagent use are typically employed,[4b-e] which offsets the benefits of lactone aminolysis. Although a few improvements[5] have been reported, they rely on additional energy input (constant heating or cooling),[5e,f,h,i] stoichiometric or excess promoters,[5a-d,f,g,i] moisture sensitive reagents,[5a,e,i] or pyrophoric reagents,[5b,d] which still limit the applications of lactone aminolysis (Scheme 2.1a). Therefore, novel, more sustainable methods that promote lactone aminolysis would have far reaching impacts in synthesis.

2.1.3 Acyl Transfer Catalyst

Acyl-transfer catalysts activate acyl groups and facilitate the formation of carboxylic acid derivatives. First studied as additives in amide coupling to prevent epimerization,[6] acyl-transfer catalysts nowadays fulfill many more purposes, notably as asymmetric esterification catalysts to achieve kinetic resolution.[7] Despite the variations, most acyl-transfer catalysts discovered fall into two mechanistic groups: activation of carbonyl, often in the presence of metals; or generation of reactive acyl species by nucleophilic attack. There have been a few successful attempts on nonclassical amide bond formation with acyl-transfer catalysts,[8] yet most of them work solely on the aminolysis of acyclic esters, which is intrinsically easier to perform than lactone aminolysis, because the low-molecular weight alcohol products (*e.g.*, methanol) can be distilled off by heating the reaction mixture, providing a driving force to product formation. To the best of our knowledge, there are only two reports that focused on lactone aminolysis;[5h,9] however, both elaborated on a specific type of lactones and did not explore functional group compatibility comprehensively, thus lacking universality. We therefore sought an acyl-transfer catalyst for general lactone aminolysis under benign conditions.

Herein, we report a mild, versatile, and catalytic lactone aminolysis method (Scheme 2.1b) to directly access amides. This 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD)-catalyzed reaction proceeds under ambient conditions in the absence of metals or harsh chemicals, offering a more sustainable option for amide formation. It exhibits high scalability and exceptional functional group tolerance. It also proved efficient with complex substrates such as natural products and pharmaceuticals and in the synthesis of biologically active molecules. Finally, a systematic study is presented, providing a better understanding of the reaction mechanism.



Scheme 2.1. Previous methods reported for lactone aminolysis in comparison to this report. DIBAL-H, diisobutylaluminium hydride; NaEH, sodium 2-ethylhexanoate; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; Tf, triflate.

2.2 Results and Discussion

2.2.1 Condition Screening

Considering the extensive application of D-pantolactone in medicinal chemistry and in the cosmetics industry,[10] we selected the ring-opening of D-pantolactone with piperonylamine (Figure 2.1) as a model reaction to explore lactone aminolysis. Various additives with potential acyl-transfer ability were tested, including aprotic nucleophiles (Figure 2.1a), protic nucleophiles (Figure 2.1b), and miscellaneous promoters, classified based on their potential mechanism of action (Figure 2.1c). TBD was the most promising additive and was therefore used for further optimization. Realizing that the initially selected reaction temperature of 80 °C was inadequate to identify the best solvent among aprotic ones (Figure 2.1d), we repeated the reaction at room temperature. This revealed toluene as the superior solvent under these conditions, with 92% yield (Figure 2.1e). It is worth noting that contrary to common belief, heat did not improve reaction yield. Next, altering substrate stoichiometry revealed that 1−2 equiv of lactone was sufficient to maintain very good yields (Figure 2.1f). Interestingly, changing the solvent volume/reactant concentration did not affect the reaction yield significantly (Figure 2.1g); hence, all subsequent reactions were performed with minimum solvent use (1.0 M amine, *i.e.*, 0.5 mmol amine in 0.5 mL of the solvent). Turning next to TBD loading, increasing it above 10 mol % did not have a considerable impact on the reaction yield (Figure 2.1h). Although the duration of the reaction was set to 18 h during optimization, we later observed that this parameter was substrate-dependent. As expanded upon below, substrates with minimal steric hindrance reacted faster (as fast as 4 h), whereas bulky substrates were required up to 24 h to achieve optimal yields. Therefore, subsequent reactions were allowed to proceed for 24 h.

2.2.2 Substrate Scope of the Amines

With optimized conditions in hand, we explored the amine scope for reactions with D-pantolactone (Figure 2.2). The presence of common functionalities (see **2.2a**−**2.2c**), protecting groups (acetonide, TBS, Boc, THP, and trityl, see **2.2d**−**2.2f**, **2.2p**−**2.2q**), or various heterocycles (furan, pyridine, tetrahydrofuran, tetrahydrothiophene, indole, and imidazole, see **2.2g**−**2.2j** and **2.2o**−**2.2p**) was well tolerated with good to excellent yields. Notably, acyclic esters, such as the aryl methyl ester of **2.2k**, were preserved, indicating that the intrinsic reactivity of lactones was differentiated by the catalyst, achieving the desired chemoselectivity. Other nucleophilic groups on the amine substrate, such as alcohol, aryl amine, and thiol (**2.2l**−**2.2n**), were inert under our conditions, resulting in the selective reaction of alkyl amines. Notably, late-stage acylation of diverse natural product derivatives and pharmaceuticals (**2.2n**−**2.2u**) proceeded with excellent

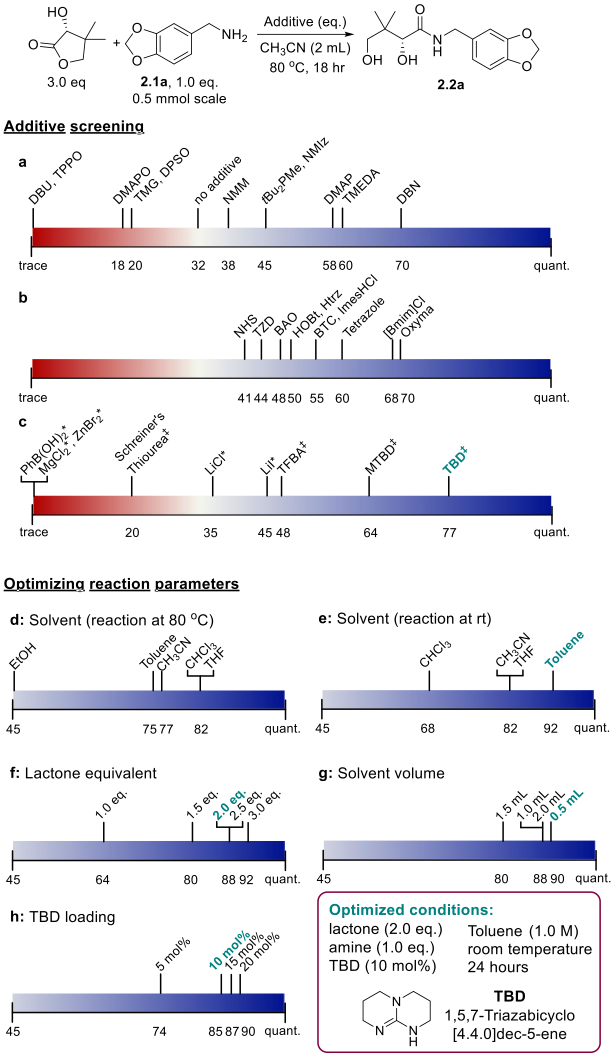


Figure 2.1. Condition screening and optimization. Yields are based on NMR analysis using DMSO as an internal standard. Various additives were first tested as promoters for the reaction (A-C), before optimizing the reaction parameters individually (D-H), with each newly optimized condition (shown in orange) maintained in subsequent optimization. A: 1.5 mmol (3 eq.) of additive was employed; B: 0.4 mmol (0.2 eq.) of additive was used together with 1.5 mmol of triethylamine (3 eq.); C: 1.5 mmol (3 eq.)* or 0.4 mmol (0.2 eq.)‡ of additive was used. Abbreviations: BAO, benzaldehyde oxime; [Bmim]Cl, 1-butyl-3-methylimidazolium chloride; BTC, 3-benzyl-5-(2-hydroxyethyl)-4-methylthiazolium chloride; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP, 4-dimethylaminopyridine; DMAPO, 4-dimethylaminopyridine N-oxide; DPSO, diphenylsulfoxide; HOBt, N-hydroxybenzotriazole; Htrz, 1H-1,2,4-triazole; ImesHCl, 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride; MTBD, 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene; NHS, N-hydroxysuccinimide; NMIz, N-methylimidazole; NMM, N-methylmorpholine; Oxyma, ethyl 2-cyano-2-(hydroxyimino)acetate; Schreiner's thiourea, N,N′-bis[3,5-bis(trifluoromethyl)phenyl]-thiourea; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TFBA, 3,4,5-trifluorophenylboronic acid; TMEDA, N,N,N′,N′-tetramethylethylenediamine; TMG, 1,1,3,3,-tetramethylguanidine; TPPO, triphenyl phosphine oxide; TZD, thiazolidine-2,4-dione.

efficiency. α-Tertiary amine, aniline, and N-containing nucleophiles such as hydrazide and hydroxylamine, however, reacted poorly, resulting in trace product formation. A hydrazine derivative (**2.2v**) was however obtained in 30% yield. Since no side reactions were observed, we believe that the low yields observed with these substrates are due to either steric hindrance (α-tertiary amine), electronic deactivation (aniline), or catalyst deactivation by strong hydrogen bonding interaction (hydrazide and hydroxylamine).

Since D-pantolactone is an enantiopure lactone, we examined whether the configuration of its stereocenter was retained during the process. Although TBD-mediated racemization/epimerization of acidic stereocenters has been reported,[11] chiral HPLC analysis of product **2.2a** demonstrated that no racemization had occurred under our reaction conditions (see the Supporting Information). This is consistent with other reports[11b] showing that chiral α-hydroxy acyl moieties retain their configuration in the presence of TBD. The absence of racemization was further corroborated by reactions with chiral amines, leading to a single stereoisomer in all cases (**2.2b**, **2.2i**, **2.2l**, **2.2r**, and **2.2s**). To determine whether the observed stereoretention was due to the free hydroxyl group of D-pantolactone, an O-benzylated D-pantolactone derivative was prepared and reacted with (*R*)-1-phenylethan-1-amine. This reaction yielded a product that was fully racemized at the ether carbon (see the Supporting Information), suggesting that the hydroxyl group of D-pantolactone precludes TBD from accessing the stereocenter, possibly as a hydrogen bond donor to the basic nitrogen of TBD.

The reactivity of secondary amines in this reaction was next studied. The results (Figure 2.3) imply that steric hindrance is a key determinant of the amine reactivity in this context. Azetidine (**2.4a**), pyrrolidine (**2.4b**), and azepane (**2.4d**) were excellent aminolysis reaction partners. Piperidine (**2.4c**) and norbornane (**2.4e**) skeletons were also tolerated amine reactants, whereas nortropane (**2.4f**) and *N*-methylbenzylamine (**2.4g**) reacted poorly.

2.2.3 Substrate Scope of the Lactones

Subsequently, the reaction was evaluated for its tolerance to assorted lactones. Encouraged by the lack of reactivity of acyclic esters (**2.2k**) in the amine substrate, we investigated the effect of their presence in the lactone substrate (Figure 2.4). Gratifyingly, benzoylated and pivaloylated D-pantolactone (**2.5a** and **2.5b**, respectively) underwent selective lactone ring opening to afford **2.6aa**/**2.6ab** and **2.6ba**/**2.6bb**, respectively, in excellent yields. 1,3-Acyl migration was however observed, likely *via* a six-membered ring transition state, with TBD potentially facilitating proton transfers. The benzoyl group had a much higher tendency to migrate than the pivaloyl group, indicating that the migration was sensitive to steric effects.

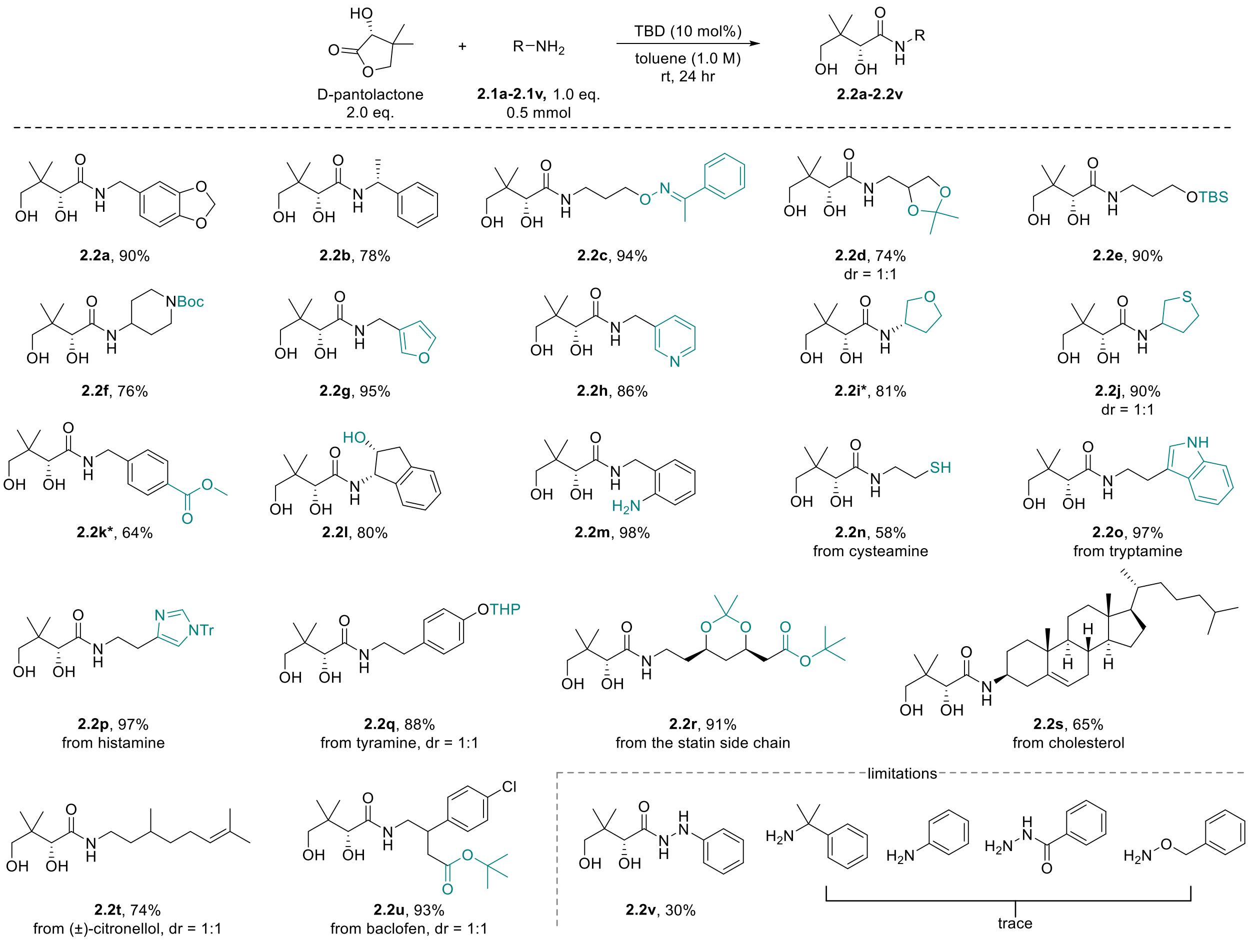


Figure 2.2. Substrate scope for the aminolysis of D-pantolactone. Isolated yields are presented. *The free amine was obtained from its hydrochloride salt. The corresponding amine hydrochloride salt was dissolved in a saturated solution of sodium carbonate before extraction of the free amine in dichloromethane. The solvent was evaporated, and the free amine was dried under vacuum for 2 h prior to use. Abbreviations: TBS, *tert*-butyldimethylsilyl; Boc, *tert*-butyloxycarbonyl; THP, tetrahydropyranyl; and Tr, trityl.

To further establish the general nature of this method, various lactones were next reacted with *para*-methoxybenzyl amine in the presence of TBD (Figure 2.5). When possible, conditions and yields were compared to published methods with identical or similar substrates (see the Supporting Information). Electronically deactivated lactones (**2.8a** and **2.8c**) were found to require higher catalyst loading (30 mol %) to reach reasonable yields, whereas activated lactones (**2.8b** and **2.8d**)

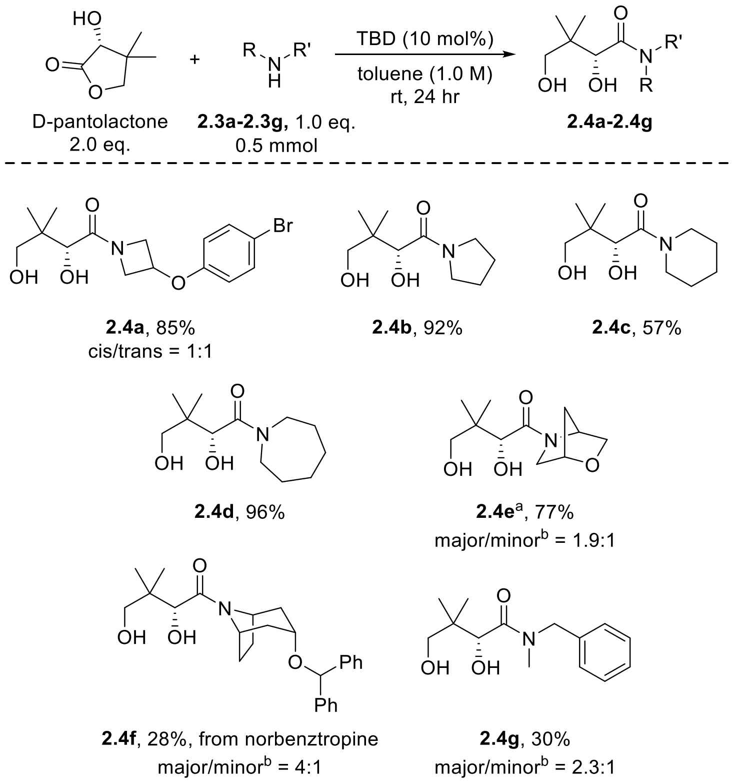


Figure 2.3. Scope of D-pantolactone aminolysis with secondary amines. Isolated yields are presented. [a] The free amine was obtained from its hydrochloride salt. [b] Amide rotamer ratio.

reacted smoothly under the standard catalyst loading with reduced lactone use (1.2 equiv). Lactones containing fused or separate rings were well tolerated (**2.8e**−**2.8g**). Remarkably, sensitive groups such as a donor−acceptor cyclopropane and bromohydrin were preserved (as in products **2.8e** and **2.8g**, respectively). No conjugate addition was observed with substrates bearing conjugated carbonyl groups (**2.8j**, **2.8k**). An amino acid derivative was also tolerated, albeit with slight racemization observed in the product (**2.8h**). Chiral HPLC analysis of **2.8h** after 4 or 24 h of the reaction resulted in a similar product enantiomeric ratio (see the Supporting Information), suggesting that racemization is likely to occur directly on the lactone substrate during activation, rather than on the amide product. To our delight, late-stage aminolysis of various natural products and pharmaceuticals proceeded in high yields (**2.8h**−**2.8l**). Unfortunately, the reaction of artemisinin and ribonolactone led to the formation of multiple products, while the reaction of cyclopentadecanolide favored polymerization over aminolysis. Lastly, several lactones were tested with pyrrolidine as a model secondary amine. Compared to primary amines (as in **2.8a**, **2.8b**, **2.8e**, **2.8f**, **2.8h**, **2.8i**, **2.8j**, and **2.8k**), pyrrolidine reacted in similar or improved yields (**2.8m**−**2.8t**).

Overall, the herein reported methodology not only affords similar or better yields than previous methods (see Section S6 of the Supporting Information) but also proceeds without the need for heat, metals, stoichiometric promoters, or pyrophoric reagents.

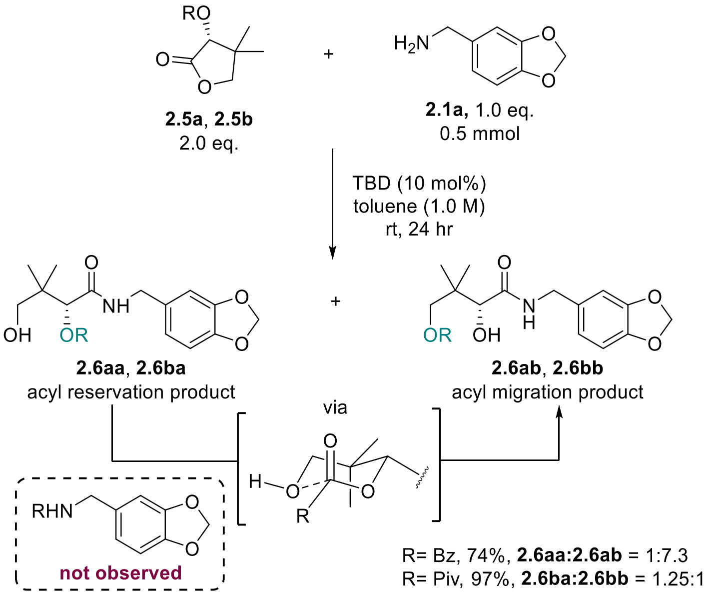


Figure 2.4. Aminolysis of acylated D-pantolactone. Isolated yields are presented. The product ratio was determined by ^{1}H NMR.

2.2.4 Applications of the Methodology

To illustrate the applicability of our method, three known biologically relevant D-pantothenate derivatives were synthesized (Figure 2.6A, see the Supporting Information for detailed reaction schemes and comparisons). The antiplasmodial compound **2.10a**[4e] was produced from D-pantolactone and the corresponding amine in excellent yield (96%). This transformation was also used to demonstrate the scalability of the method, where a 10 mmol scale reaction proceeded in 92% yield. Next, compound **2.10b**, an important intermediate in the synthesis of the preclinical antiplasmodial drug MMV693183,[10a] was successfully prepared at gram scale in 96% yield. Lastly, our method enabled the synthesis of the antibacterial compound **2.10c**,[10c] *via* a new route that resulted in 86% yield over three steps. Conveniently, the final product precipitated out, making it a chromatography-free process with an overall 62% yield.

With a growing demand for more sustainable chemical transformations, catalyst immobilization has gained popularity.[12] Therefore, we examined the possibility of employing immobilized TBD as a catalyst (Figure 2.6B). Although immobilization slightly alters the catalyst structure (loss of the N−H bond), the reaction of D-pantolactone and pyrrolidine progressed to a similar yield. Reusability was next tested, revealing that the immobilized catalyst can be recovered and reused for at least three cycles without a decrease in the reaction yield.

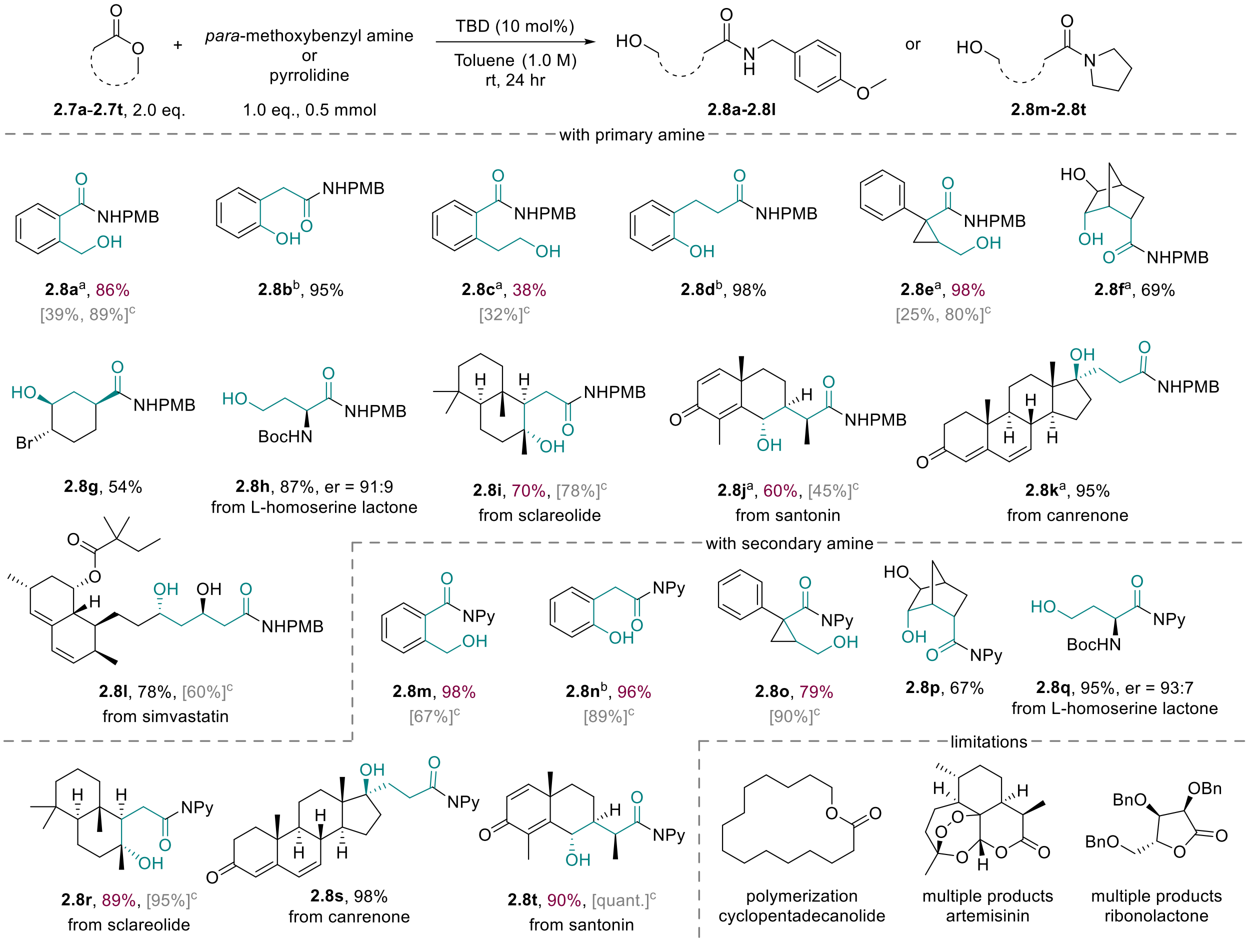
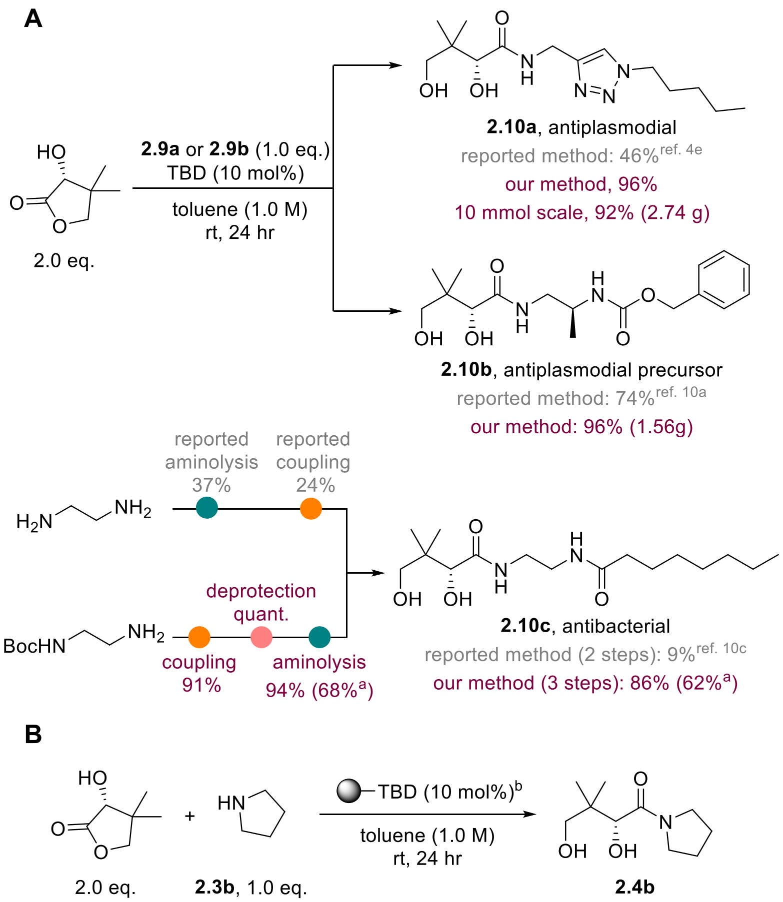


Figure 2.5. Scope of aminolysis of various lactones. Isolated yields are presented. Original lactone scaffolds are highlighted in teal in the product structure. Yields of previously published methods are given in brackets for comparison. PMB, *para*-methoxybenzyl, NPy, pyrrolidinyl. [a] 30 mol % TBD was used. [b] 1.2 equiv of lactone was used. [c] See the Supporting Information for detailed comparison.

2.2.5 Mechanistic Studies

To gain a better understanding of the reaction mechanism, we first performed a comprehensive kinetic study using reaction progress kinetic analysis (RPKA) as developed by Blackmond[13] and variable time normalization analysis (VTNA) as developed by Burés.[14] These kinetic methods have the advantage of providing mechanistic insights under synthetically relevant conditions, which has not been achieved before on similar reactions. TBD-catalyzed aminolysis of D-pantolactone with *para*-methoxybenzyl amine was used as the model reaction for the kinetic studies presented here (see Section S7A of the Supporting Information). D-Pantolactone was strategically chosen as its *α*-chiral center allows chemical shift distinction between substrates and product, and the *gem*-dimethyl group provides accurate integrations. Analysis of the kinetic data using VTNA (Figure 2.7a,b) revealed that TBD exhibits an overall reaction order of 0.6, suggesting the formation of inactive off-cycle TBD species. This was further confirmed by the same excess experiment (Figure 2.7c). Time adjustment of the data *via* RPKA revealed a lack of overlay



Reaction Cycle	Catalyst/mg	Reaction scale on **2.3b**/mmol	Yield
0 (prewash)	200.0	---	---
1	192.1	5.00	92%
2	181.4	4.72	91%
3	173.3	4.50	92%

Figure 2.6. Synthetic applications of TBD-catalyzed lactone aminolysis (A) and suitability of an immobilized catalyst (B). Isolated yields are presented. [a] Yield after filtration only, *i.e.*, from a chromatography-free process. [b] TBD was immobilized on cross-linked divinylbenzene polymer beads with a loading of 2.6 mmol/g.

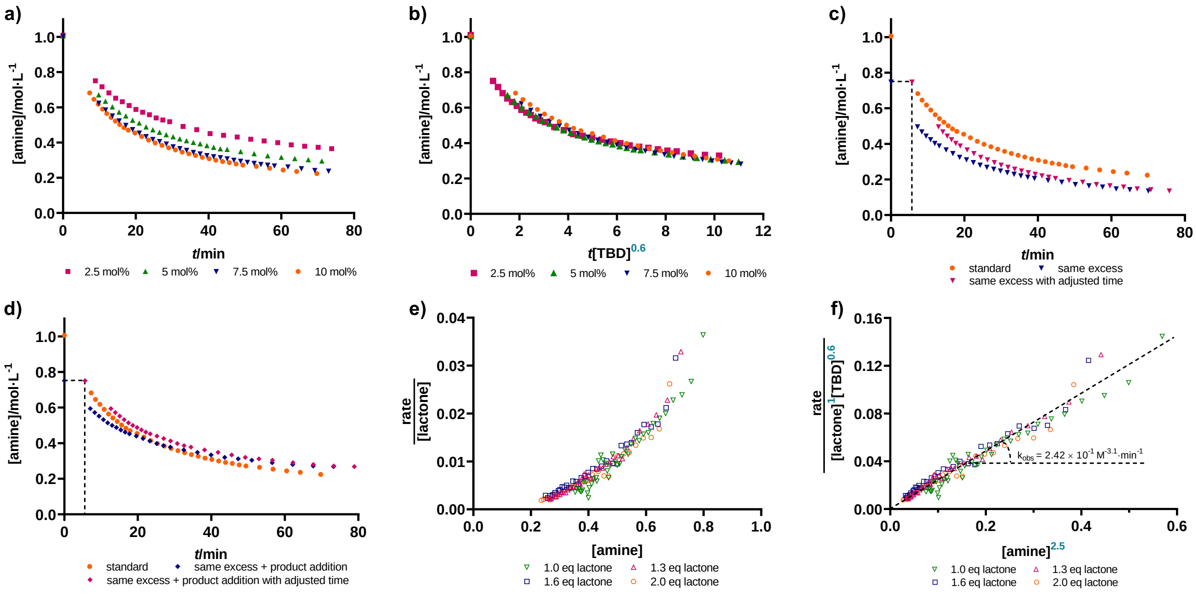


Figure 2.7. Results of kinetic studies. (a) Original VTNA data for the aminolysis of D-pantolactone with *p*-methoxybenzyl amine at different catalyst loadings. (b) Processed VTNA data with time normalization by multiplying the time with 0.6 power of TBD concentration. (c) Same excess experiment. (d) Same excess experiment with product addition. (e) Different excess experiments without adjustment of kinetic driving forces. (f) Different excess experiments with adjustment of kinetic driving forces.

between the reaction curves, as expected for catalyst deactivation. To distinguish product inhibition from other catalyst deactivation pathways, the same excess experiment was conducted with product addition (Figure 2.7d). After time adjustment, this experiment exhibited a similar reaction progress as that observed under standard conditions, albeit slower. This result implies product inhibition, likely *via* hydrogen bonding, although TBD dimerization and formation of non-covalent TBD/lactone adducts are also plausible. Finally, substrate reaction orders were determined by different excess experiments. Plotting rate/[lactone] over [amine], as instructed by RPKA, displayed an overlay of curves, revealing that the lactone exhibits an order of 1 (Figure 2.7e). After raising all kinetic driving forces to their correct powers, the overlayed curves were found to linearize in a way that is consistent with the amine exhibiting an order of 2.5 (Figure 2.7f). A non-integer reaction order for the amine substrate implies its participation in more than one pathway. Conveniently, this experiment allowed us to extrapolate an observed rate constant of 2.42 × 10^{-1} M$^{-3.1}$ · min^{-1}.

Another important aspect of the reaction mechanism is the interaction between the catalyst and the substrate. Previous studies[11b] have shown that TBD activates esters primarily *via* nucleophilic attack to generate a reactive acyl-TBD species. NMR was used here to investigate the possible formation of such an adduct (Figure 2.8). First, ^{1}H NMR analysis of a TBD solution in toluene-d_8 revealed significant TBD dimer formation (87% of all molecules), implying that catalyst

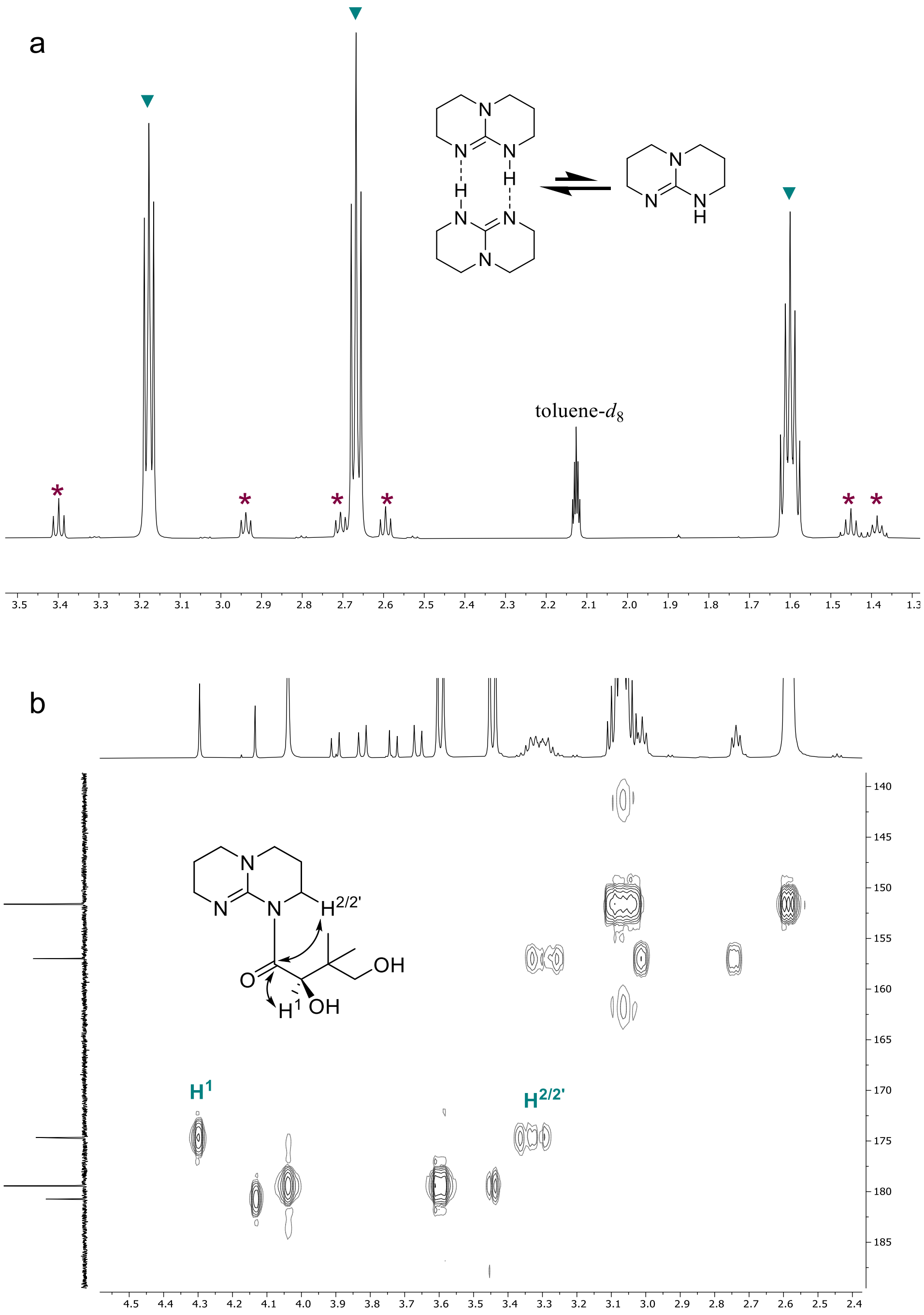


Figure 2.8. Results of NMR studies. (a) ^{1}H NMR spectrum of TBD in toluene-d_8. TBD monomer peaks are denoted with asterisks and TBD dimer peaks with down-pointed triangles. (b) HMBC NMR spectrum of a 1:1 mixture of TBD and D-pantolactone (0.4 M) in toluene-d_8. Signals confirming the formation of the acyl-TBD product are labeled.

deactivation may be caused by TBD dimerization (Figure 2.8a). Next, a detailed NMR study (^{1}H, ^{13}C, HSQC, and HMBC) of a 1:1 mixture of TBD and D-pantolactone in toluene-d_8 allowed the detection of an acyl-TBD adduct. The chemical structure of this product was fully assigned by HSQC and HMBC (see Section S7B of the Supporting Information). This confirmed the formation of an acyl-TBD intermediate under our reaction conditions (Figure 2.8b). Supplementary studies further demonstrate that the nucleophilic nitrogen of TBD is crucial to its catalytic activity (see Section S7C of the Supporting Information). A minor non-covalent species was also detected by NMR, as indicated by the lack of cross peaks between TBD and the lactone. Although the latter might contribute to catalyst deactivation, it is not of great significance, considering the low population of this species and the difference between the reaction conditions (lactone/TBD = 20:1) and the NMR studies (lactone/TBD = 1:1).

Based on these mechanistic studies, we propose the following mechanism for the TBD-catalyzed aminolysis of lactones (Figure 2.9). First, the active TBD monomer, which is in equilibrium with its dimer, proceeds to react with the lactone *via* nucleophilic attack (Figure 2.9A), before rearrangement to a reactive acyl-TBD species (Figure 2.9B). A first amine molecule (Figure 2.9C, in maroon) next attacks the activated carbonyl to generate a tetrahedral intermediate. This intermediate is stabilized by one (in teal) or two (in orange) additional amine molecules *via* hydrogen bonding, akin to the effect of the oxyanion hole of enzymes.[15] Similar stabilization of an acyl intermediate has been proposed in several previous studies.[16] It has been suggested that such a hydrogen bonding network is beneficial to transition-state stabilization by dissipating the charges. Next, a proton is transferred to the hydrogen bond donor nitrogen of TBD (Figure 2.9D). The resulting species might still associate with additional amine molecules for stabilization. It eventually collapses to afford the desired product and TBD. The product is expected to engage in hydrogen bonding with TBD to form a product−catalyst adduct, causing some product inhibition.

2.3 Conclusions

In summary, we have reported that TBD is a highly efficient, versatile catalyst for the aminolysis of lactones. This new method is simple to operate, scalable, proceeds at room temperature, and shows excellent functional group tolerance. The organocatalytic nature of this process overcomes the drawbacks of traditional lactone aminolysis, including the use of stoichiometric promoters, metals, and pyrophoric reagents. Notably, TBD selectively activates lactones over acyclic esters, while enabling the reactions of alkyl amines in the presence of other nucleophilic groups. We believe that with its demonstrated ability to selectively derivatize unprotected natural products and pharmaceuticals, it will find broad application.

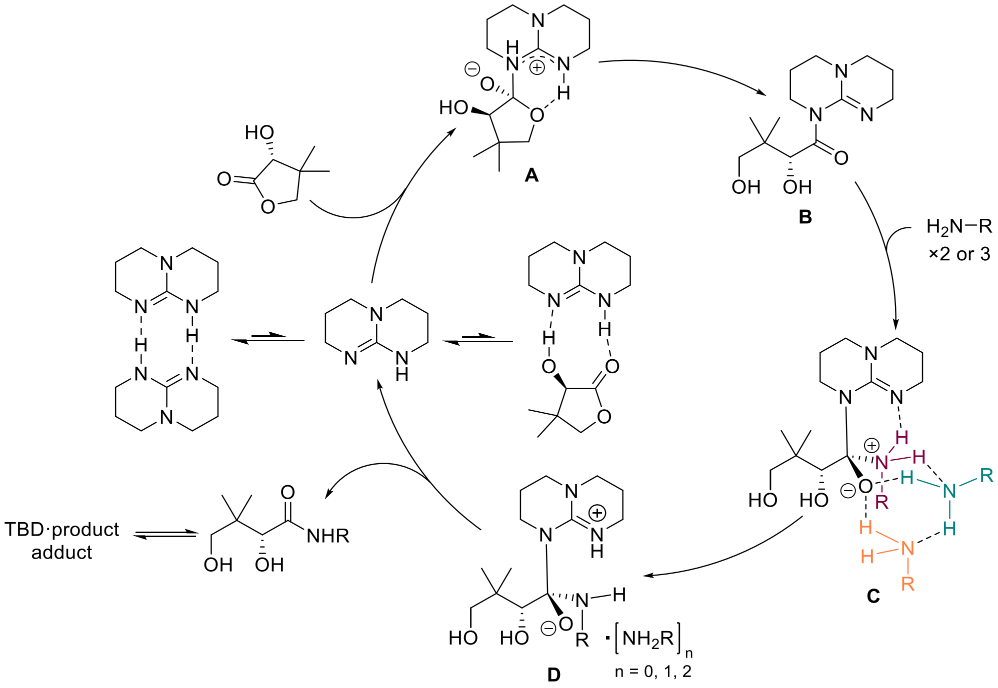


Figure 2.9. Proposed mechanism.

2.4 Author Contributions

C.B.L. performed all the experiments reported, wrote the first draft of the manuscript, and contributed to its editing. K.A. oversaw the project and was highly involved in manuscript editing. All authors have given approval to submission of the final version of the manuscript.

2.5 Acknowledgements

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2.6 Experimental Section

For experimental procedures and characterization of starting materials and products, see section 7.2. For kinetic study data, see Appendix III-I. For other related information, including comparisons of synthetic routes and copies of NMR spectra, see the published document at https://pubs.acs.org/doi/suppl/10.1021/acs.joc.3c00913/suppl_file/jo3c00913_si_001.pdf.

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Preface for Chapter 3

In Chapter 3, we describe a TBD-catalyzed synthesis of 3-hydroxyisoindolin-1-ones. This work builds on Chapter 2 and takes advantage of the multifunctional properties of TBD that are combined into one reaction.

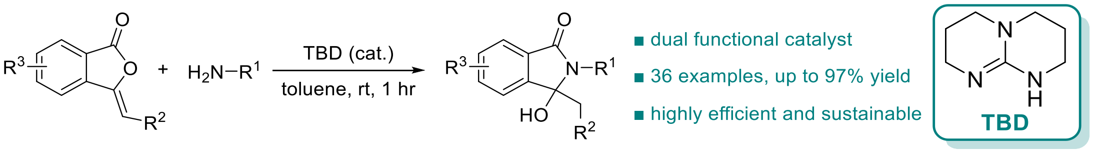
Herein, a rapid synthesis of 3-hydroxyisoindolin-1-ones from 3-alkylidenephthalidies is reported. As a valuable core for various natural products and pharmaceuticals, 3-hydroxyisoindolin-1-ones can be accessed catalytically in the presence of TBD *via* an amidation-cyclization reaction. This transformation is complete in only 1 hour at room temperature, which is a major improvement compared to existing methods. Diverse applications, including decagram-scale synthesis, secondary transformations of the products, as well as the synthesis of biologically active compounds are included to demonstrate the utility of the reaction. A brief mechanistic study also revealed that TBD is the superior choice of catalyst.

All of the results presented in this chapter were acquired by the author of this thesis under the supervision of prof. Karine Auclair. This work is published as follows:

Lan, C. B.; Auclair, K.* 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD): An Organocatalyst for Rapid Access to 3-Hydroxyisoindolin-1-ones. *Eur. J. Org. Chem.* **2024**, *27*, e202400071.

Chapter 3

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD): An Organocatalyst for Rapid Access to 3-Hydroxyisoindolin-1-ones



Abstract: The readily available organocatalyst 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) was used for the rapid synthesis of 3-hydroxyisoindolin-1-ones from 3-alkylidenephthalides. The transformation occurs at room temperature and requires less solvent than traditional methods, providing a more sustainable synthetic option to access 3-hydroxyisoindolin-1-ones with broad scope. Elaboration of the products to diverse scaffolds as well as synthesis of biologically active compounds are demonstrated.

3.1 Introduction

3.1.1 3-Hydroxyisoindolin-1-ones

The 3-hydroxyisoindolin-1-one is an important scaffold with numerous utilities. It is present in various natural products and pharmaceuticals,[1] such as isoindolobenzazepine alkaloids and the diuretic drug chlortalidone (Figure 3.1). Furthermore, it serves as a useful building block to access compounds with various biological activities (Figure 3.1). For example, 3-hydroxyisoindolin-1-one can be used to synthesize 3-alkylideneisoindolin-1-one derivatives with potent vasodilator (AKS-186) or analgesic (AL-12) effect.[2] It can also lead to phthalazin-1(2*H*)-one containing pharmaceuticals such as azelastine, which is used as an H_1 blocker.[2] Hence, efforts have been made to seek efficient synthetic approaches to 3-hydroxyisoindolin-1-ones.

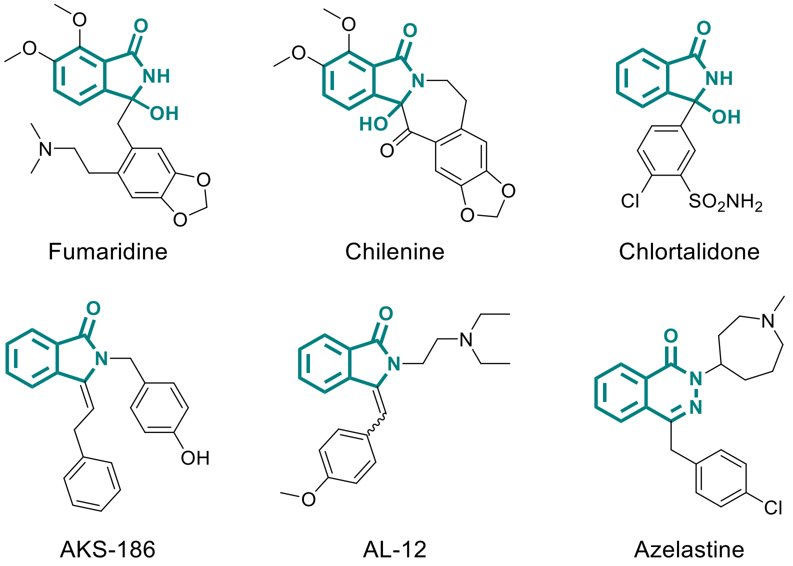
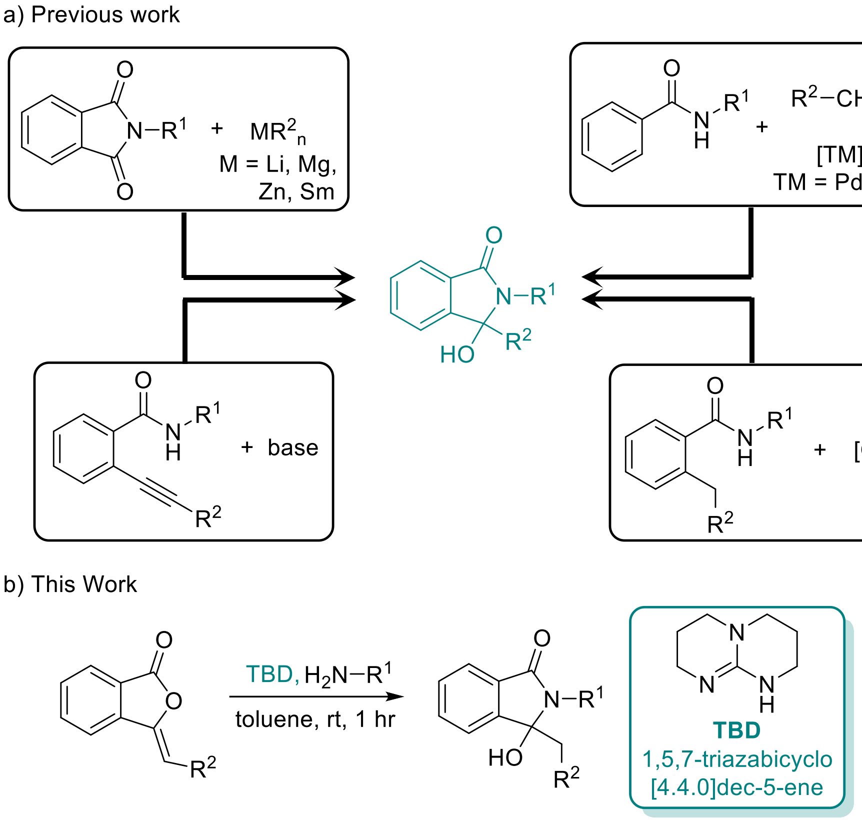


Figure 3.1. Biologically active compounds containing 3-hydroxyisoindolin-1-ones or related scaffolds.

3.1.2 Previously Reported Synthesis of 3-Hydroxyisoindolin-1-ones

Traditionally, 3-hydroxyisoindolin-1-ones were accessed via nucleophilic addition of phthalimides with organometallic reagents (Scheme 3.1a).[3] This method, however, requires stoichiometric amounts of metal, exhibits low functional group tolerance, and lacks regioselectivity. In recent years, different strategies have been employed to synthesize 3-hydroxyisoindolin-1-ones, including benzylic C–H oxidation/annulation,[4] C–H acylation/annulation,[5] and annulation of *ortho*-alkynyl amides (Scheme 3.1a).[6] However, these methods oftentimes require prolonged heating, a strong base, or precious transition metals, which limit their use, especially at industrial scale. In comparison, amidation of 3-alkylidenephthalides followed by annulation is a privileged yet underdeveloped approach.[7] It appeals to modern organic synthesis as its atom economy is 100%, making it a more sustainable reaction. However, forcing conditions, such as lengthy heating, ultrasonic irradiation, and/or excess amine use are necessary for satisfactory product formation, which offset the intrinsic benefits of this reaction. We envisioned that this approach could be greatly improved with a suitable organocatalyst, thus offering a sustainable option for the synthesis of 3-hydroxyisoindolin-1-ones.



Scheme 3.1. Past and present synthesis of 3-hydroxyisoindolin-1-ones.

3.1.3 This Work

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) is a bicyclic guanidine that has found extensive application in organic chemistry, notably as a powerful catalyst for polymer synthesis and recycling,[8] CO2 utilization,[9] and carboxylic acid derivative synthesis.[10] Bearing both a nucleophilic nitrogen and an electrophilic N–H group, TBD is a multifunctional reagent. It can serve as an organic superbase, an acyl transfer reagent, and a hydrogen bonding activator.[11] With the prior success of a TBD-catalyzed lactone aminolysis reaction at room temperature,[10f] we envisaged that TBD could be a suitable catalyst for the synthesis of 3-hydroxyisoindolin-1-ones from 3-alkylidenephthalides. Considering the reactivity of 3-alkylidenephthalides, we hypothesize that TBD could activate the enol lactone moiety rapidly to facilitate amidation, while also potentially promoting annulation.

Herein, we report the rapid TBD-catalyzed synthesis of 3- hydroxyisoindolin-1-ones. This method exhibits a broad substrate scope, high scalability, and applicability to the synthesis of biologically active compounds. Moreover, this organocatalytic process operates at room temperature with reduced solvent use, providing a more sustainable synthetic approach.

3.2 Results and Discussion

3.2.1 Method Development

Method development was initiated using benzalphthalide and 4-methoxybenzylamine, under conditions similar to those reported for a lactone aminolysis method.[10f] Optimization revealed that substrates used in a 1:1 ratio were rapidly transformed into the desired 3-hydroxyisoindolin-1-one in the presence of 10 mol% TBD. A significant amount of precipitate was observed in the final reaction mixture, prompting us to explore a chromatography-free process. Precipitation was later confirmed to be an additional driving force for the reaction, as products that remained in solution required higher substrate input and catalyst loading to reach full conversion within the same time frame. Notably, amines of high purity were crucial for precipitation to occur. Therefore, amine substrates were purified before use when contamination was suspected (*e. g.* brown color, high viscosity, precipitate found in liquid amines).

3.2.2 Substrate Scope of the Amines

We first examined the scope of amines (Figure 3.2). Chromatography-free yields are reported in brackets when they are available. Common functional groups and protecting groups were well tolerated (methoxy, ester, acetal, Boc, TBS, trityl, acetonide, and *tert*-butyl; see **3.2a-3.2f**, **3.2p**) in the amine substrate. In particular, an ester group (**3.2b**) remained untouched, demonstrating that TBD was able to selectively activate the enol lactone moiety. A variety of heterocycle-containing amines afforded the desired products with good to excellent yields (imidazole, furan, thiophene, pyridine, and indole; see **3.2f-3.2j**). When other nucleophiles were present (alcohol, phenol, aniline; see **3.2k-3.2m**), the reaction proceeded selectively at the alkyl amines, without detection of the

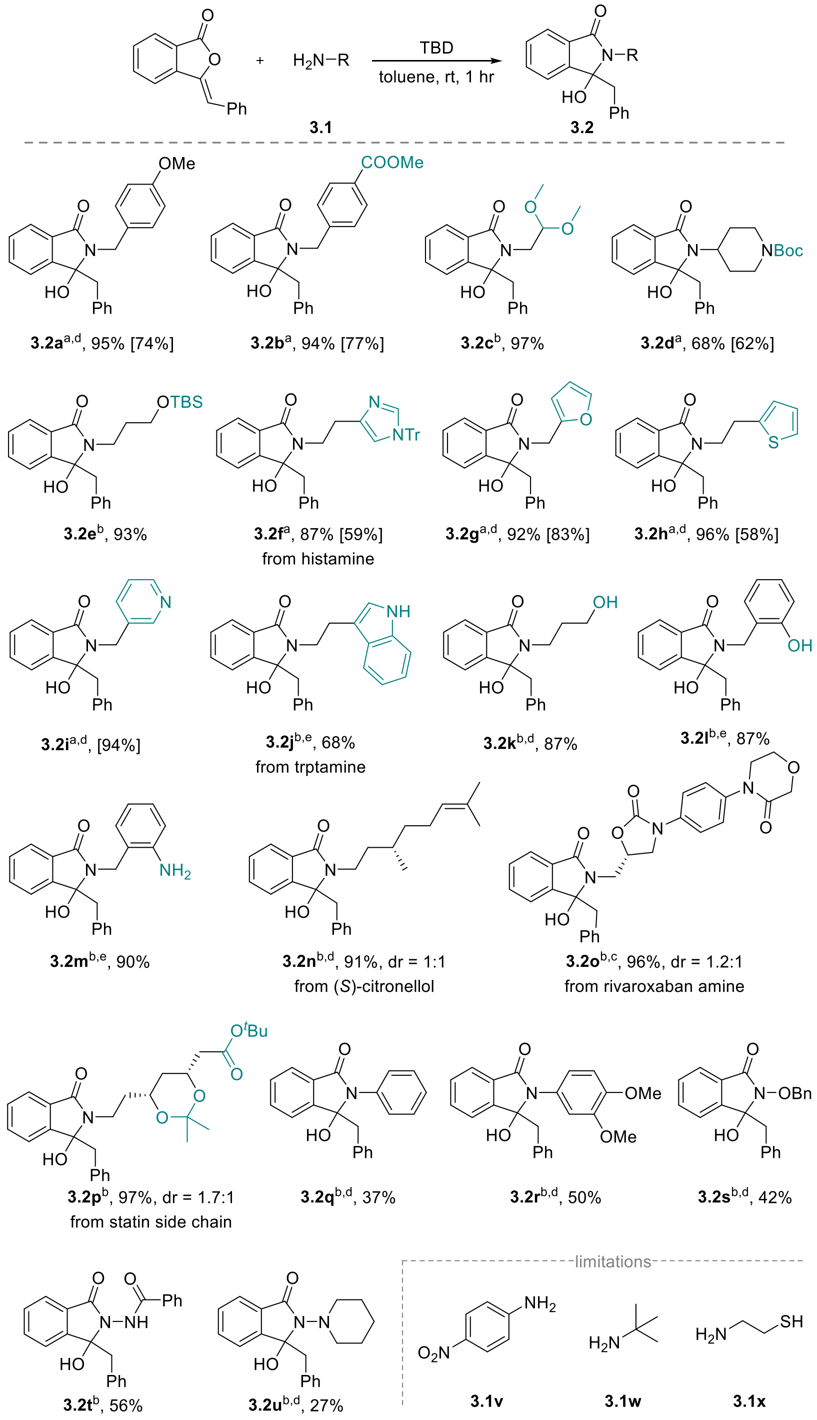


Figure 3.2. Scope of amines. [a] Reaction conditions: benzalphthalide (0.5 mmol, 1.0 equiv.), amine (0.5 mmol, 1.0 equiv.), TBD (0.05 mmol, 10 mol%), and toluene (0.5 mL). Yields obtained from chromatography-free processes are indicated in brackets. [b] Reaction conditions: benzalphthalide (0.5 mmol, 1.0 equiv.), amine (0.75 mmol, 1.5 equiv.), TBD (0.15 mmol, 30 mol%), and toluene (0.5 mL). [c] Reaction was carried out in DMSO instead of toluene. [d] Amine starting materials were purified before use by distillation (liquid) or recrystallization (solid). [e] No satisfactory purification of the amine starting materials could be achieved.

byproduct(s). One natural product and two pharmaceutical derivatives containing an amine were also excellent substrates (see **3.2n**-**3.2p**), making our conditions suitable for late-stage functionalization of complex molecules. The unequal value of diastereomeric ratio observed in certain cases (**3.2o**-**3.2p**) demonstrates that chiral amines can affect the stereo outcome of the reactions. Despite being inert under our previously reported conditions for lactone aminolysis,[10f] amino compounds other than alkyl amines (anilines, hydroxylamine, hydrazine, hydrazide, see **3.2q**-**3.2u**) were successfully transformed into 3-hydroxyisoindolin-1-ones, albeit with diminished yields. Strongly deactivated substrate, either by electronics (**3.1v**) or sterics (**3.1w**), as well as thiol-containing amine (**3.1x**), were unreactive under our conditions.

3.2.3 Substrate Scope of the 3-Alkylidenephthalides

The scope of 3-alkylidenephthalides was next explored (Figure 3.3). Assorted substituents attached to the alkylidene ring were well tolerated (see **3.4a**-**3.4g**). Electronic properties of these substituents did not seem to have a significant effect on reactivity, as both electron donating and withdrawing groups resulted in similar yields. A very strong electron withdrawing group at the *para* position, however, was unproductive (**3.3p**). Decomposition of **3.3p** was observed in the presence of TBD, as indicated by a rapidly blackening reaction mixture. Allyl (**3.4h**), alkyl (**3.4i**), and diphenyl substitution (**3.4j**) all led to the corresponding 3-hydroxyisoindolin-1-ones smoothly. Notably, the presence of a Michael acceptor was not detrimental to the reaction (**3.4k**). Meanwhile, similar chemoselectivity was observed, where the ester group remained intact during the reaction (**3.4d**, **3.4k**). Modifications on the phthalide ring were also tolerated (**3.4l**-**3.4o**), following the same trend as substituents on the alkylidene moiety did. Unfused enol lactone rings, however, were unfruitful under our conditions (**3.3q**-**3.3r**).

3.2.4 Investigation on the Superiority of TBD in Our System

Next, we investigated the advantages of TBD compared to other catalysts for this reaction. Since precipitation proved to be an additional driving force, we chose the formation of **3.2c** as a model reaction to eliminate the effect of precipitation. Both the reaction yield after one hour and the time required to reach full conversion of benzalphthalide were evaluated for five common nitrogen-containing bases (Figure 3.4a). Even though all bases showed improvement over the uncatalyzed reaction, only TBD afforded an almost quantitative yield at the one-hour reaction time point. A similar trend was observed for the time required for the full conversion of benzalphthalide; the

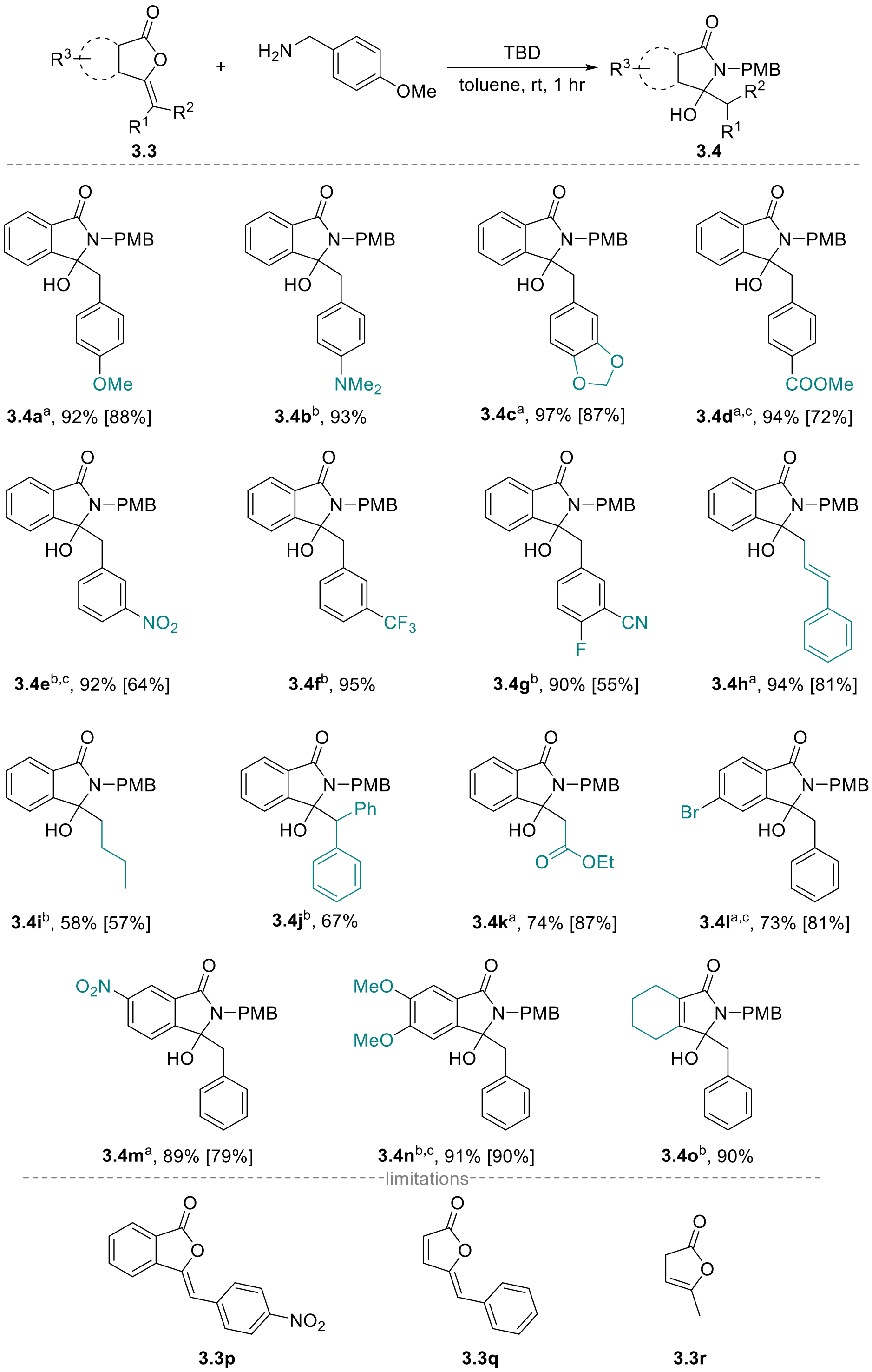


Figure 3.3. Scope of 3-alkylidenephthalides. PMB, *para*-methoxy benzyl; [a] Reaction conditions: 3-alkylidenephthalide (0.5 mmol, 1.0 equiv.), 4-methoxybenzylamine (0.5 mmol, 1.0 equiv.), TBD (0.05 mmol, 10 mol%), and toluene (0.5 mL). Yields obtained from chromatography-free process are indicated in brackets. [b] Reaction conditions: 3-alkylidenephthalide (0.5 mmol, 1.0 equiv.), 4-methoxybenzylamine (0.75 mmol, 1.5 equiv.), TBD (0.15 mmol, 30 mol%), and toluene (0.5 mL). [c] 1.0 mL of toluene was used.

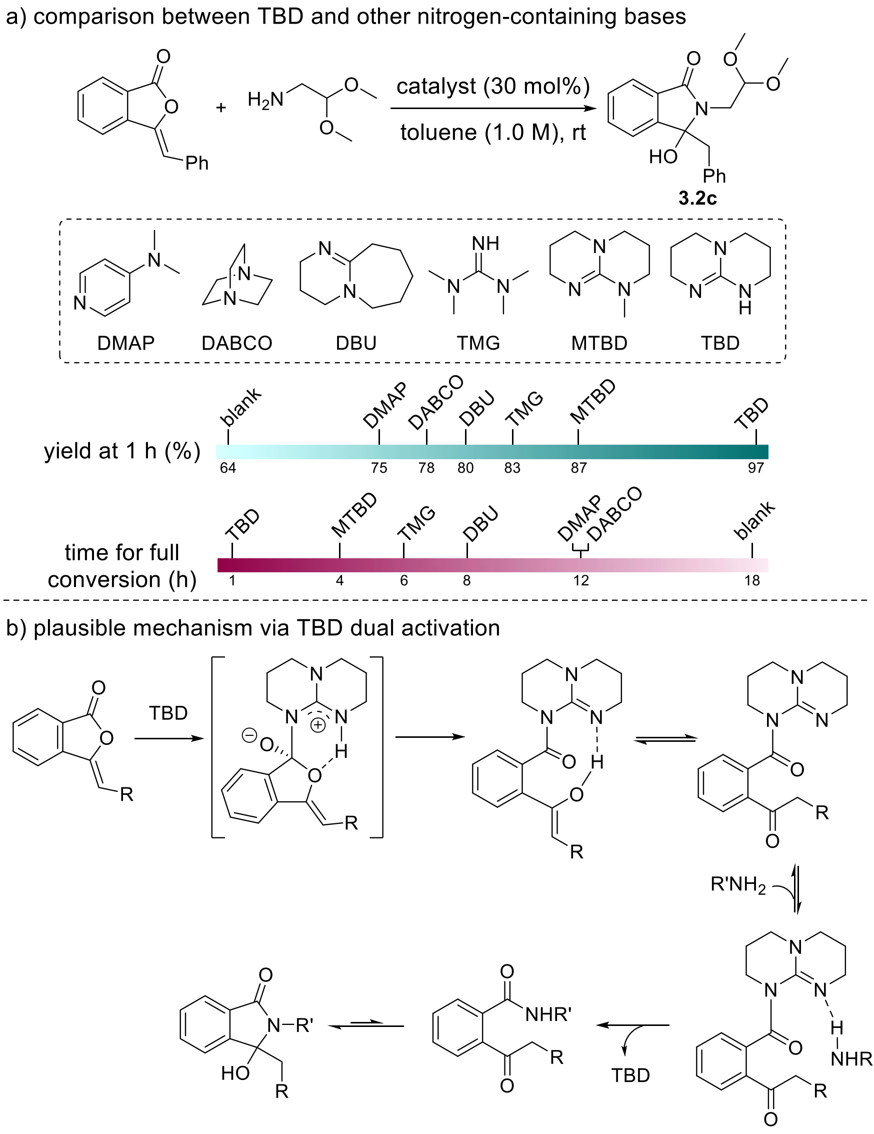


Figure 3.4. Comparison of TBD with other catalysts and proposed mechanism. Reaction conditions: benzalphthalide (0.5 mmol, 1.0 equiv.), amine (0.75 mmol, 1.5 equiv.), catalyst (0.15 mmol, 0.3 equiv.), and toluene (0.5 mL). DMAP, 4-dimethylaminopyridine; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; TMG, 1,1,3,3-tetramethylguanidine; MTBD, 7-methyl-1,5,7-triazabicyclo [4.4.0]dec-5-ene; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

reaction with a higher yield after one hour required less time to reach full conversion. These results indicate that TBD is superior to the other catalysts for this reaction. Notably, even though only the nucleophilic nitrogen is required for its catalytic activity, the presence of N–H proved to be beneficial, as TBD was more efficient than its structural analog 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD). These results were consistent with those from TBD-catalyzed ring-opening polymerization, implying a dual activation mechanism (Figure 3.4b).[8a]

During the nucleophilic activation of 3-alkylidenephthalide, the adjacent N–H is positioned for rapid proton transfer, generating the reactive acyl-TBD species after tautomerization. The same nitrogen has now been converted to a Lewis basic one, thus being able to activate the incoming amine nucleophile through hydrogen-bonding. Amide bond formation, followed by tautomerization, eventually leads to 3-hydroxyisoindolin-1-one.

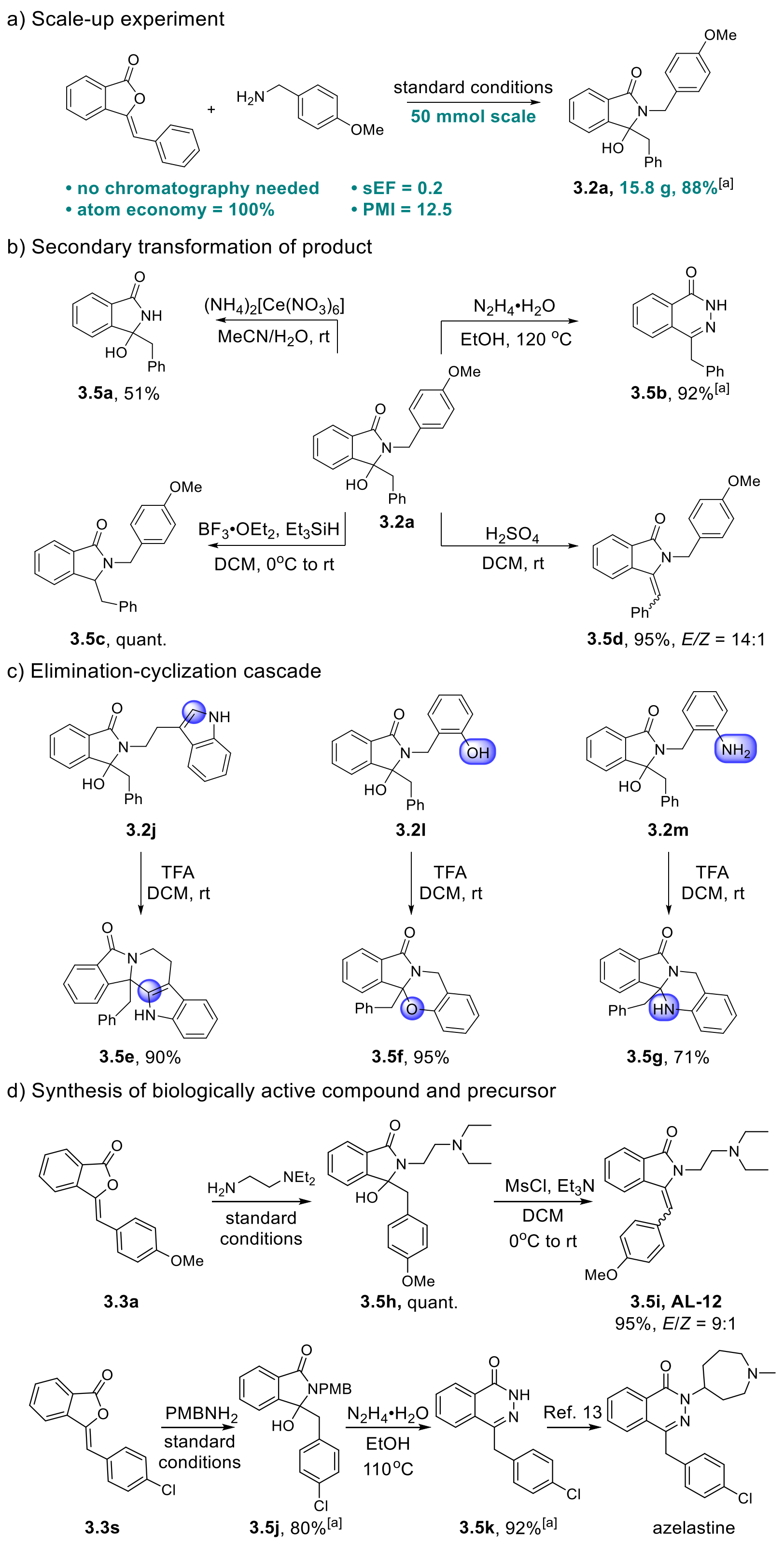
3.2.5 Applications of the Methodology

To demonstrate the synthetic utility of our method, we next tested its scalability (Scheme 3.2a). A 50 mmol scale reaction was successfully performed and decagrams of the product were isolated by filtration and recrystallization. Some green chemistry metrics were employed to evaluate the sustainability of this process. Apart from an ideal atom economy (100%) and a very good yield (88%), this process only has a simple *E* factor (sEF) of 0.2, which is optimal for early-stage development use. The calculated process mass intensity (PMI) of 12.5 is also below the range for typical pharmaceutical manufacturing (~25-100).[12] This can be further improved if solvent recycling is in place in a process plant setting.

Secondary transformation of the product was next explored (Scheme 3.2b). The *para*-methoxybenzyl moiety of **3.2a** can be removed under oxidative conditions to afford **3.5a**. Hydrazinolysis of **3.2a** led to the formation of phthalazine-1(2*H*)-one (**3.5b**), which is a valuable scaffold in drug discovery.[2c] The presence of a labile tertiary alcohol in **3.2a** allowed us to easily obtain 3-alkyl (**3.5c**) and alkylidene (**3.5d**) substituted isoindolinones, under ionic hydrogenation and acidic elimination conditions, respectively. Alternatively, polyheterocyclic compounds can be accessed via an elimination-cyclization cascade (Scheme 3.2c) if an adjacent aromatic ring containing a nucleophile is present (**3.5e**-**3.5g**). Finally, the applicability of our methodology in the synthesis of a biologically active compound and of a drug precursor was demonstrated. The potent analgesic compound AL-12 (**3.5i**) was synthesized with excellent yield using our method. Phthalazine-1(2*H*)-one (**3.5k**), a precursor in the synthesis of the antihistamine azelastine[13] was also easily accessed without the need for chromatography.

3.3 Conclusions

In summary, we have developed a rapid and efficient method for the synthesis of 3-hydroxyisoindolin-1-ones. Using TBD as a simple and readily available catalyst, this method is in line with sustainable chemistry principles and demonstrates broad synthetic utility.



Scheme 3.2. Synthetic applications. sEF, simple *E* factor; PMI, process mass intensity; PMB, *para* methoxy benzyl; TFA, trifluoroacetic acid. [a] Isolated yield from a chromatography-free process.

3.4 Author Contributions

C.B.L. performed all the experiments reported, wrote the first draft of the manuscript, and contributed to its editing. K.A. oversaw the project and was highly involved in manuscript editing. All authors have given approval to submission of the final version of the manuscript.

3.5 Acknowledgements

This work was supported by the research grants PJT-166175 to K.A. from the Canadian Institute of Health Research (CIHR). We also thank the Fonds de Recherche du Québec FRQNT (scholarship to C.B.L.) for financial support. We thank Dr. Kirill Levin for help with NMR, as well as Dr. Alexander S. Wahba and Mr. Nadim K. Saadeh for HRMS analyses.

3.6 Experimental Section

For experimental procedures and characterization of starting materials and products, see section 7.3. For copies of NMR spectra, see the published document at https://chemistry-europe.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1002%2Fejoc.202400071&file=ejoc202400071-sup-0001-misc_information.pdf.

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Preface for Chapter 4

During the development of the methodology featured in Chapter 3, it was serendipitously discovered that TBD could catalyze a C–C cleavage step. The work introduced in Chapter 4 built upon this discovery. It further elaborates it into a full methodology and reveals an unprecedented reaction mechanism catalyzed by TBD.

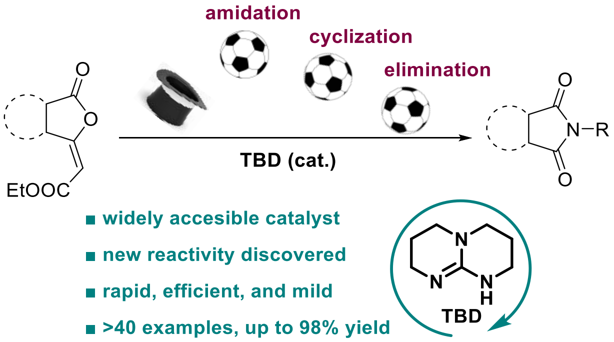
In Chapter 4, we report a unique synthesis of cyclic imides that involves an amidation-cyclization-elimination cascade. The cyclic imide is a privileged scaffold that is prevalent in various molecules, such as natural products, pharmaceuticals, agrochemicals, and polymers. The work described herein provides an organocatalytic alternative to previously reported methods, which often resort to prolonged heating or precious metal catalysts. In particular, late stage functionalization of complex molecules was performed to demonstrate the mildness and effectiveness of this methodology. Both experimental and computational studies were employed to better understand the TBD-catalyzed C–C cleavage step.

All of the results presented in this chapter were acquired by the author of this thesis under the supervision of prof. Karine Auclair. This work is published as follows:

Lan, C. B.; Auclair, K.* Organocatalytic Hat Trick: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)-Catalyzed Synthesis of Cyclic Imides via an Amidation−Cyclization−Elimination Cascade. *J. Org. Chem.* **2025**, *90*, 700-708.

Chapter 4

Organocatalytic Hat Trick: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD)-Catalyzed Synthesis of Cyclic Imides via an Amidation-Cyclization-Elimination Cascade

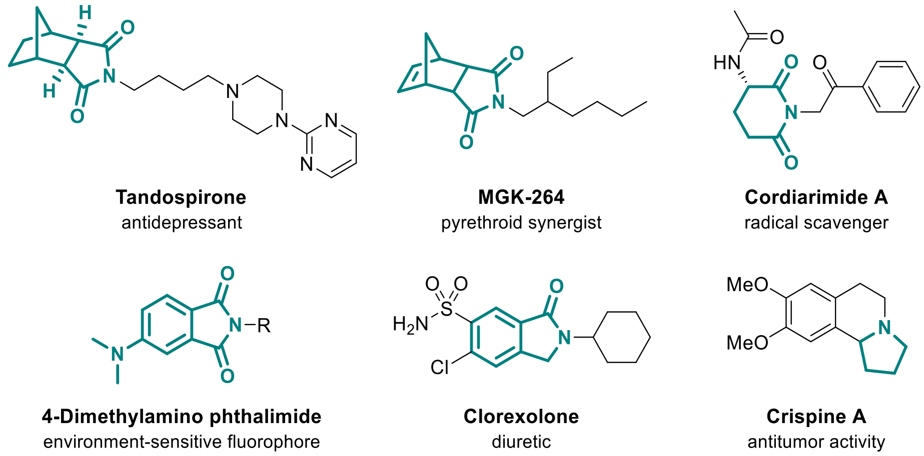


Abstract: 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) was used for the synthesis of cyclic imides via an amidation−cyclization−elimination cascade. This organocatalytic transformation features both the traditional reactivity of TBD and its unprecedented C−C bond cleavage capability, allowing rapid and efficient access to cyclic imides. This method is compatible with the late stage functionalization of complex molecules and the synthesis of bioactive molecules. Both experimental and computational approaches were employed to gain a better understanding of the reaction mechanism.

4.1 Introduction

4.1.1 Cyclic Imides

The cyclic imide is an important and versatile scaffold. It is widely present in various chemical entities, including pharmaceuticals, agrochemicals, natural products, and fluorescent materials (Figure 4.1).[1] It is also utilized to access other valuable moieties, such as the lactam in clorexolone[2] and the pyrrolidine in crispine A.[3] Hence, the development of novel methods for cyclic imide synthesis remains a research focus in organic chemistry.


Tandospirone
antidepressant

MGK-264
pyrethroid synergist

Cordiarimide A
radical scavenger

4-Dimethylamino phthalimide
environment-sensitive fluorophore

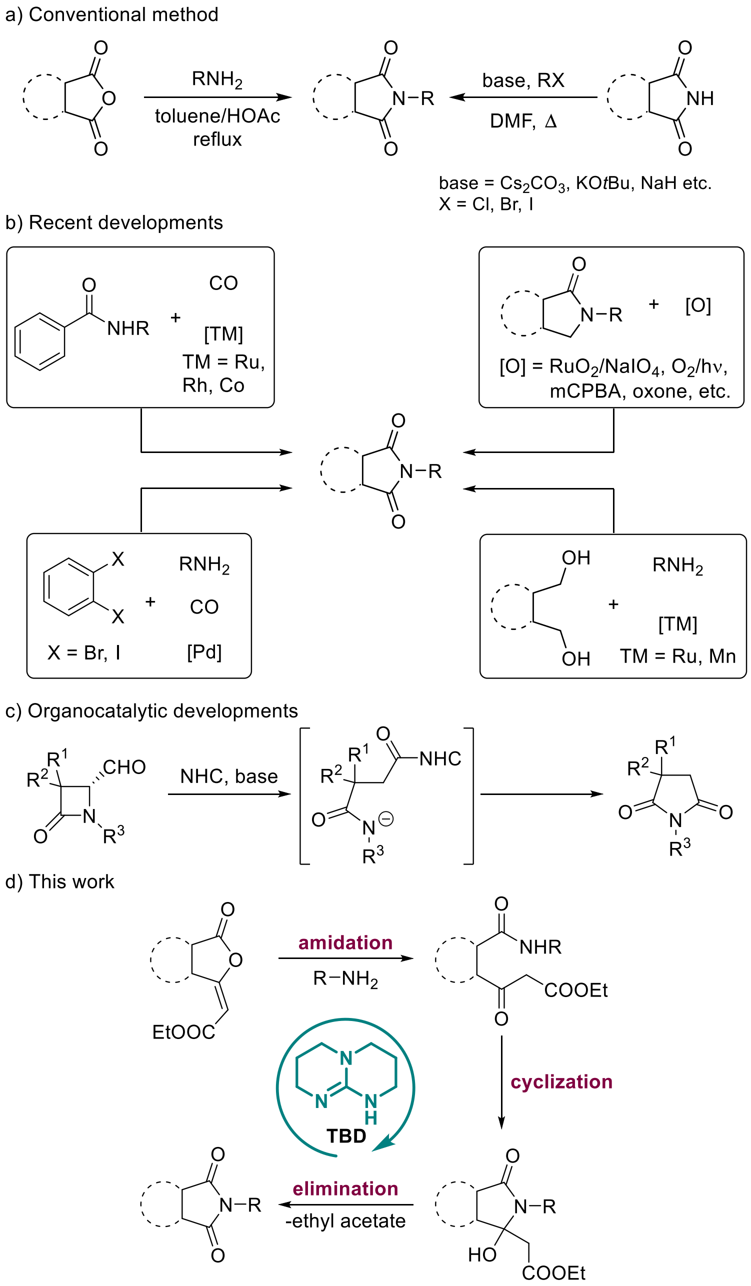
Clorexolone
diuretic

Crispine A
antitumor activity

Figure 4.1. Examples of molecules containing a cyclic imide or accessed from a cyclic imide.

4.1.2 Previously Reported Synthesis of Cyclic Imides

Traditionally, two approaches are employed to access cyclic imides (Scheme 4.1a).[4] Condensation between cyclic anhydrides and amines is one of the most common methods. Reflux conditions are typically necessary to achieve satisfactory yields, together with the use of stoichiometric promoters or a Dean−Stark apparatus to facilitate proton transfer or water elimination. Nucleophilic substitution between phthalimide derivatives and alkyl halides, although less universal, is also utilized to access cyclic imides. An excess amount of base is required, and these reactions are primarily run in *N*,*N*-dimethylformamide, which is a hazardous solvent that has been restricted in countries of the European Union.[4] Beyond conventional methods, numerous strategies, in particular, transition-metal-catalyzed/mediated reactions, have been developed to construct cyclic imides (Scheme 4.1b). For instance, organometallic carbonylation has been extensively applied. Various substrates, including benzamides[5] and aromatic dihalides,[6] can be readily transformed into cyclic imides in the presence of transition metals and CO. The use of precious metals and



Scheme 4.1. Past and present methodologies to access cyclic imides. DMF, *N*,*N*-dimethylformamide; DMSO, dimethylsulfoxide; mCPBA, *meta*-chloroperoxybenzoic acid; NHC, *N*-heterocyclic carbene; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

highly toxic reagents such as pressurized CO gas and metal carbonyls, however, does not appeal to modern sustainable synthesis. Besides, these methods are incompatible with the synthesis of nonaromatic cyclic imides. Another common strategy takes advantage of redox chemistry, converting lactams[7] and diols[8] into the corresponding cyclic imides. Apart from the usage of precious metals and costly ligands, chemoselectivity and functional group tolerance are the main issues. In contrast, organocatalysis has seldom been employed. To date, ring expansion of 4-formyl-*β*-lactams to succinimides is the only organocatalytic method reported for the synthesis of cyclic imides (Scheme 4.1c).[9] Hence, we were motivated to seek novel organocatalytic routes to access cyclic imides.

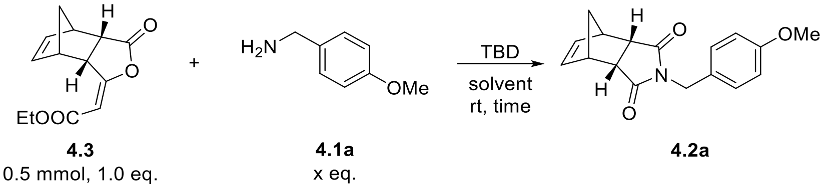
4.1.3 This Work

1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD) is a bicyclic guanidine frequently utilized in organic synthesis. Its principal function originates from a combination of the nucleophilic nitrogen serving as both an organic superbase and an acyl transfer reagent and the presence of the electrophilic N−H group beneficial for H-bonding.[10] Owing to its multifunctionality, TBD has proven to be an excellent catalyst for various reactions involving C−C or C−X (X = N, O, P, S) bond formation, such as Michael addition, Henry reaction, and ring-opening polymerization.[10] In our efforts to develop TBD-catalyzed reactions,[11] a serendipitous, yet unique reactivity of TBD, its promotion of C−C bond cleavage, was unveiled. We envisioned that this novel mode of reaction, if incorporated fittingly, could expand the chemical space accessed via TBD catalysis. Herein, we report the TBD-catalyzed synthesis of cyclic imides via an amidation−cyclization−elimination cascade (Scheme 4.1d). This method exploits the properties of TBD to access an unprecedented C−C bond cleavage capability. Moreover, it proceeds catalytically under mild conditions, allowing for the rapid construction of diverse cyclic imides.

4.2 Results and Discussion

4.2.1 Condition Screening

We initially observed the C−C bond cleavage ability of TBD under our previously reported conditions for isoindolinone synthesis (Table 4.1, entry 1).[11b] We noticed that an enol lactone derived from carbic anhydride was successfully converted into the corresponding imide. Altering the equivalents of amine did not affect the yield (Table 4.1, entries 2 and 3); hence, 1.2 equiv of amine was selected for further optimization. In the attempt to lower the catalyst loading (Table 4.1, entries 4−8), we detected a sudden halt of product formation at 10 mol % TBD (Table 4.1, entry 5), with concomitant precipitate formation. This precipitate was later confirmed to be the isoindolinone intermediate. We supposed that TBD was unable to access this intermediate for further transformation due to its low solubility in toluene; thus, it was anticipated that switching to a better solvent could solve this problem. This strategy worked exceptionally well with DMSO, improving the yield to 88% (Table 4.1, entry 6). Although catalyst loadings as low as 5% performed well for the model reaction (Table 4.1, entry 7), it was not a universal condition. Therefore, a catalyst loading of 10 mol % was maintained for further exploration. Notably, no product formation occurred if the catalyst loading was dropped to 2.5 mol % (Table 1, entry 8); this was a crucial finding to generate aromatic imides (vide infra). Further elaboration on amine loading and reaction duration (Table 4.1, entries 9 and 10) revealed that 1.05 equiv of the amine and 30 min of reaction were sufficient.



entry	amine (eq.)	TBD loading (mol%)	solvent (0.5 mL)	duration (hr)	yield (%)
1	1.5	30	toluene	1	75
2	2.0	30	toluene	1	72
3	1.2	30	toluene	1	71
4	1.2	20	toluene	1	72
5	1.2	10	toluene	1	trace[a]
6	1.2	10	DMSO	1	88
7	1.2	5	DMSO	1	90
8	1.2	2.5	DMSO	1	trace[a]
9	1.05	10	DMSO	1	89
10	1.05	10	DMSO	0.5	88

Table 4.1. Screening of reaction conditions. [a] The elimination reaction did not occur, yielding the hydroxyisoindolinone intermediate instead. DMSO, dimethyl sulfoxide; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

4.2.2 Substrate Scope of the Amines

With the optimized conditions in hand, we proceeded to investigate the substrate scope and functional group tolerance for the amine reactant. Gratifyingly, this method demonstrated a broad

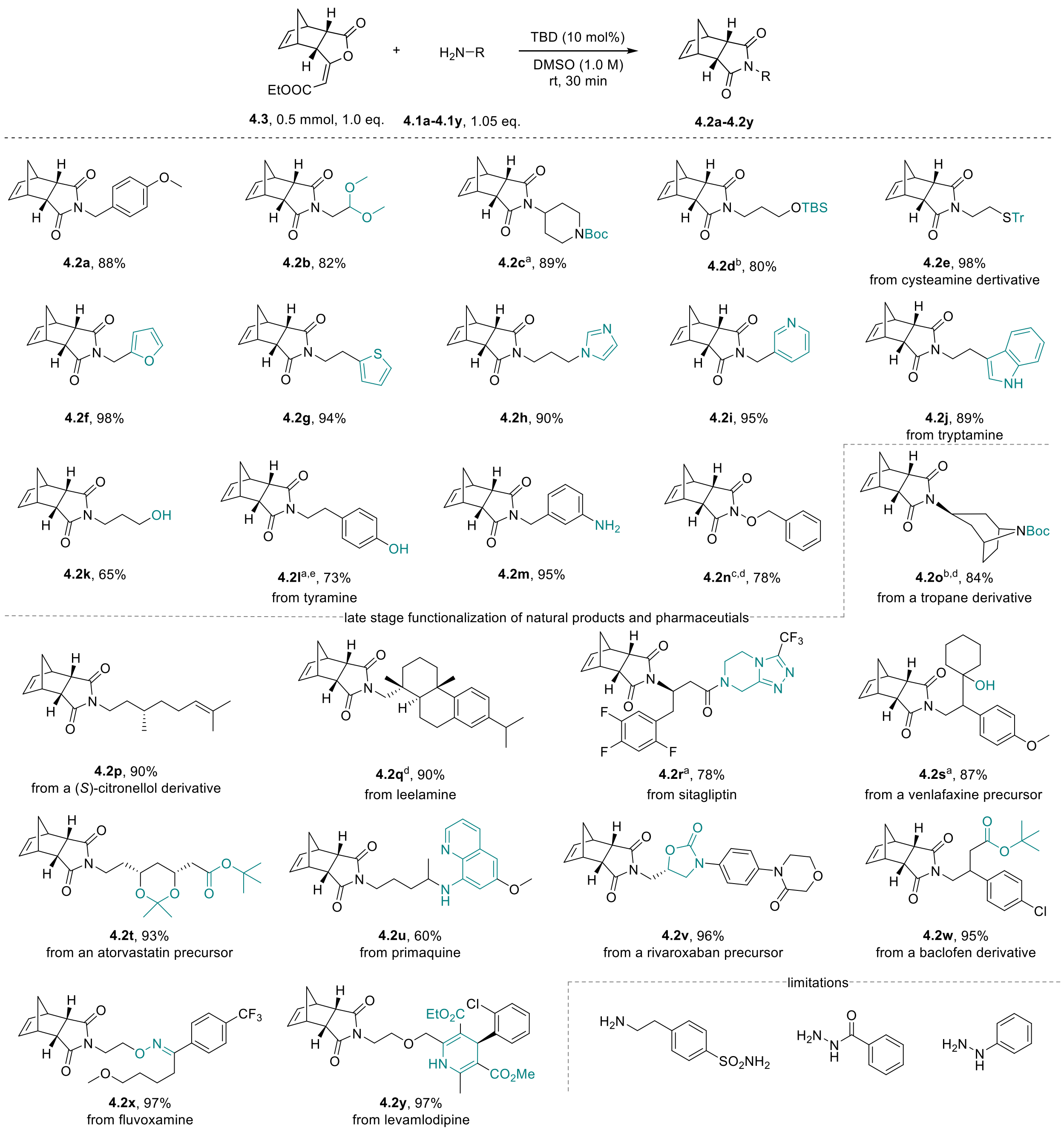


Figure 4.2. Substrate scope of the amine substrates. Isolated yields are presented. Many amine starting materials were purified before use (see details in the Supporting Information). DMSO, dimethyl sulfoxide; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [a] Reaction time was 2 h. [b] Reaction time was 1 h. [c] Reaction time was 4 h [d] 20 mol % TBD was used. [e] 30 mol % TBD was used.

substrate scope, and remarkable tolerance was observed for a variety of functional groups (Figure 4.2). Briefly, common functional and protecting groups (methoxy, acetal, Boc, TBS, and trityl; see **4.2a**–**4.2e**) remained intact under these conditions. Various heterocycles (furan, thiophene,

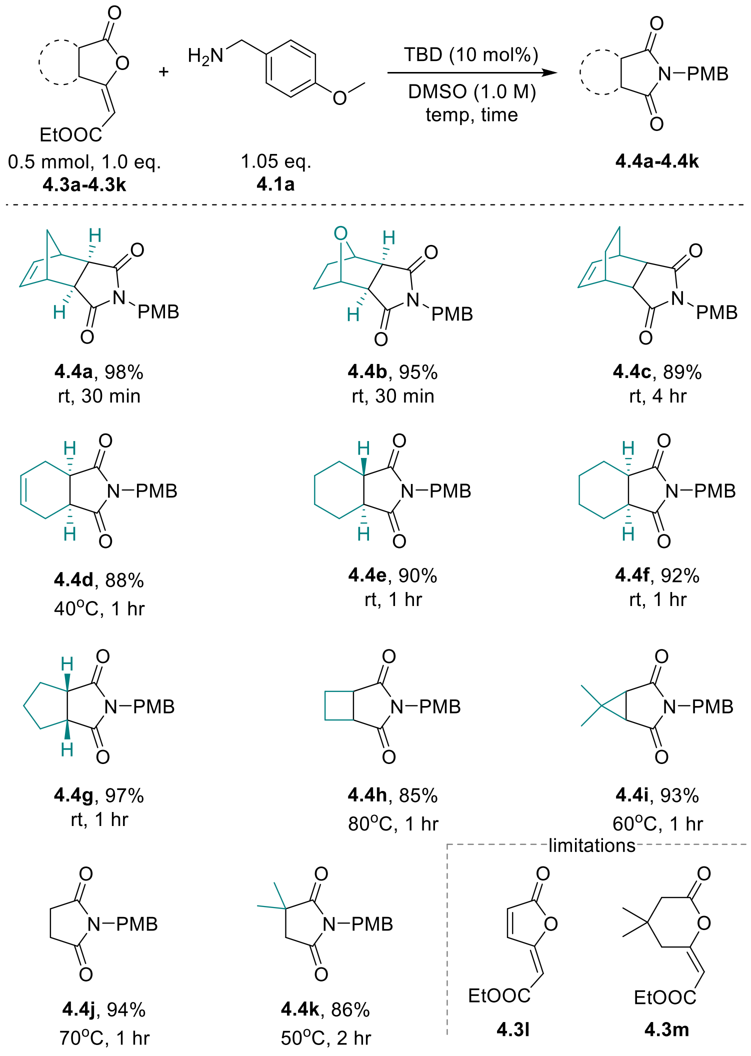


Figure 4.3. Substrate scope for nonaromatic enol lactones. PMB, *para*-methoxy benzyl. DMSO, dimethyl sulfoxide; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

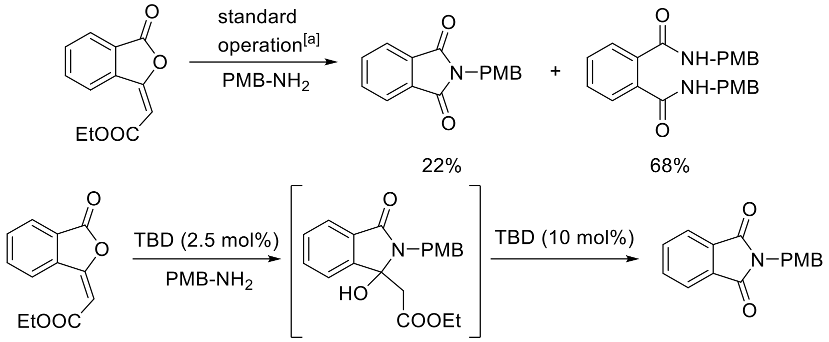
imidazole, pyridine, and indole; see **4.2f–4.2j**) were also well tolerated. A sulfonamide-containing amine, however, failed to transform into the desired product. As previously observed with other TBD-catalyzed reactions,[11] chemoselectivity toward alkyl amines was achieved in the presence of other nucleophilic groups (alcohol, phenol, and aniline; see **4.2k–4.2m**). In terms of amino-containing compounds beyond alkyl amines, hydroxylamine was a suitable candidate (**4.2n**), whereas the use of hydrazine and hydrazide did not lead to product formation. Remarkably, three natural product derivatives (**4.2o–4.2q**) and eight pharmaceutical derivatives (**4.2r–4.2y**) were successfully transformed into their corresponding carbic imides, making this method suitable for the late-stage functionalization of complex molecules. These derivatives also pave the way for novel bioactive and therapeutic polymers as the norbornene moiety is one of the optimal candidates for ring-opening metathesis polymerization.[12]

4.2.3 Substrate Scope of the Non-Aromatic Enol Lactones

We then examined the behavior of other enol lactones using 4-methoxybenzylamine (PMB-NH_2) as the amine substrate (Figure 4.3). Substrates containing a bridged bicyclic system reacted smoothly in excellent yields (**4.4a**–**4.4c**). Optimal conditions started to deviate from the standard ones when the ring size and shape changed. Cyclohexane and cyclopentane were well tolerated, and full conversion was achieved at room temperature (**4.4e**–**4.4g**), whereas cyclohexene required a slightly higher temperature for the desired transformation to occur (see **4.4d**). Highly strained rings, such as cyclobutane and cyclopropane, necessitated moderate heating for satisfactory conversion (**4.4h**–**4.4i**). A similar phenomenon was observed for nonfused substrates (**4.4j**–**4.4k**). Notably, the presence of a gem-dimethyl group in **4.4k** allowed the transformation to occur at a lower temperature than **4.4j**, suggesting that the Thorpe–Ingold effect could have a positive impact on our reaction system. In particular, the size and shape of the fused rings were found to be predominant factors affecting the reactivity, regardless of stereochemical configurations. Both the *endo* (**4.2a**) and the *exo* (**4.4a**) isomers of the norbornene reactant reached similar yields under identical conditions. Likewise, the *cis* (**4.4f**) and the *trans* (**4.4e**) configuration of the cyclohexane derivatives had no impact on the reaction outcome. Unfortunately, maleic and glutaric derivatives **4.3l** and **4.3m** did not lead to product formation.

4.2.4 Substrate Scope of the Aromatic Enol Lactones

Despite previous efforts, the synthesis of aromatic imides remains uncharted. An initial attempt revealed that the standard one-pot operation employed above did not render the desirable result. Even though imide formation was observed, it rapidly reacted with residual amine to form the unwanted diamide in the presence of TBD (Scheme 4.2). This is consistent with a previous report demonstrating that phthalimides undergo ring-opening aminolysis in the presence of DBU.[13] As long as extra amine was present in the solution, a one-pot regime was unfruitful, as it was inadequate to suppress diamide formation. As mentioned above, one result from our initial optimization attempts (Table 4.1, entry 8) provided a solution to this issue. Indeed, we took advantage of the fact that a low TBD loading stopped the reaction progress at the isoindolinone stage. This enabled us to introduce a wash step for the removal of excess amine (and possibly other side products), followed by subsequent reaction with 10 mol % of TBD for imide formation. Alternatively, when the amine had been mostly consumed in the intermediate stage, directly adding more TBD into the system was a reasonable alternative.



Scheme 4.2. Strategies for phthalimide synthesis. PMB, *para*-methoxy benzyl; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene. [a] standard operation refers to a one-pot mixture of enol lactone (0.5 mmol, 1.0 eq.), amine (1.5 eq.), TBD (30 mol%), and DMSO (0.5 mL), reacted at rt for 1 hr.

With these two solutions available, we began to investigate the scope of aromatic enol lactones. As expected, the two-step procedure granted access to aromatic cyclic imides with excellent yields in most cases (Figure 4.4). Although one-pot reactions were viable, implementing a wash between the two steps proved to be beneficial in most cases. The initial success with a phthalic derivative (**4.6a**) encouraged us to explore other related substrates. Halogens at various positions (**4.6b**−**4.6e**) were well tolerated. Groups with various electron-donating strengths (**4.6f**−**4.6i**) did not have an impact on reactivity. In particular, the 4,7-disubstituted substrate **4.5f** required even less time for the full transformation to **4.6f**, suggesting that sterics may exert a positive effect in the phthalic series. A substrate with a mild electron-withdrawing group (**4.5j**) reacted smoothly, whereas others with strong electron-withdrawing groups (**4.5k**−**4.5l**) required gentle heating to enable the transformation. The polycyclic derivative **4.5m** was also an appropriate substrate. Lastly, since 3-nitrophthalic anhydride and 1,8-naphthalic anhydride failed to be derivatized to the corresponding enol lactones, they could not be tested in the reaction.

4.2.5 Applications of the Methodology

To further demonstrate the synthetic value of this method, we next conducted a gram-scale experiment. A reaction on the 10 mmol scale proceeded successfully without a decrease in yield (Scheme 4.3a). Monitoring the temperature of the reaction mixture in real time revealed an exothermic process. A peak temperature of 39.2 °C was recorded after 100 s of reaction. This was

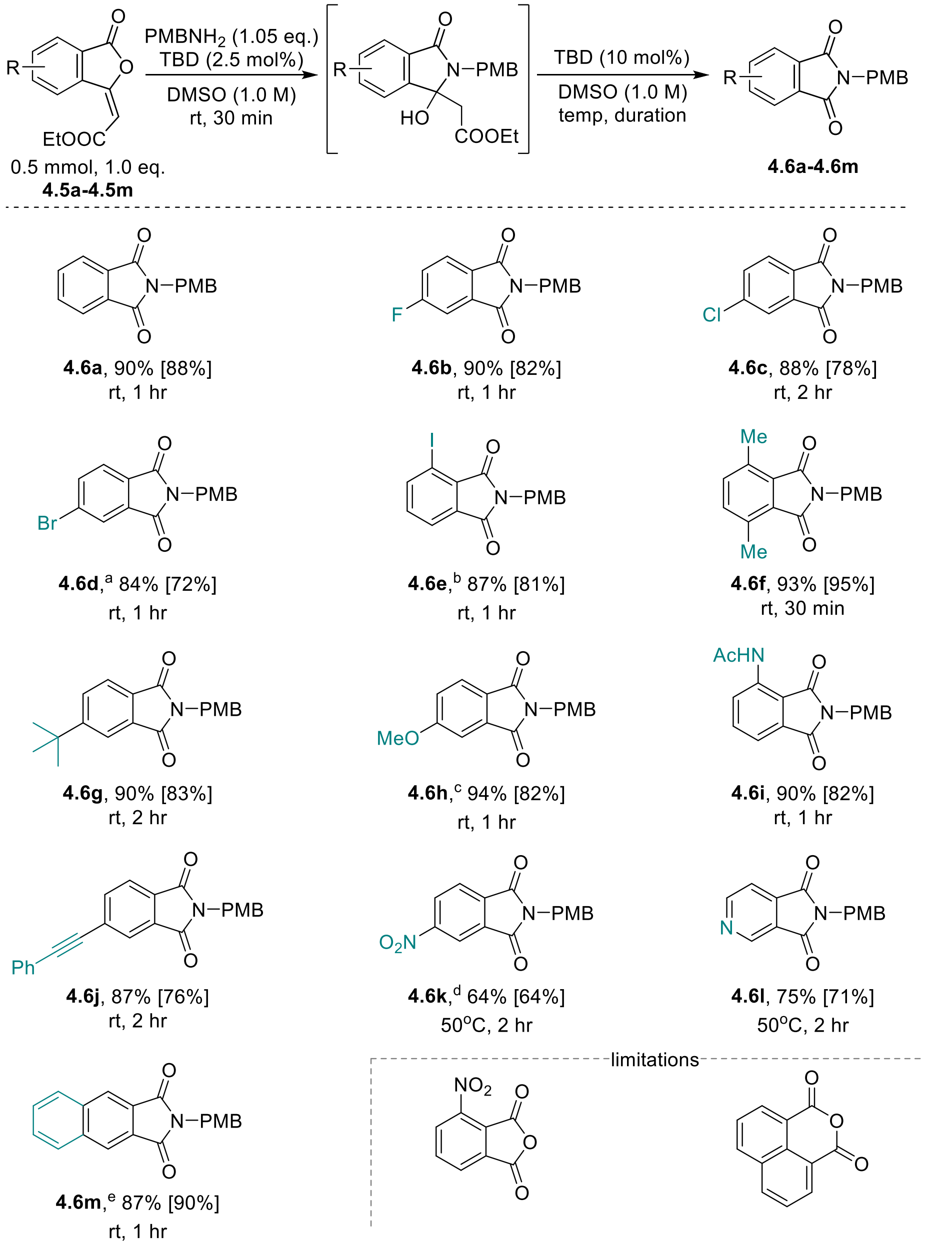
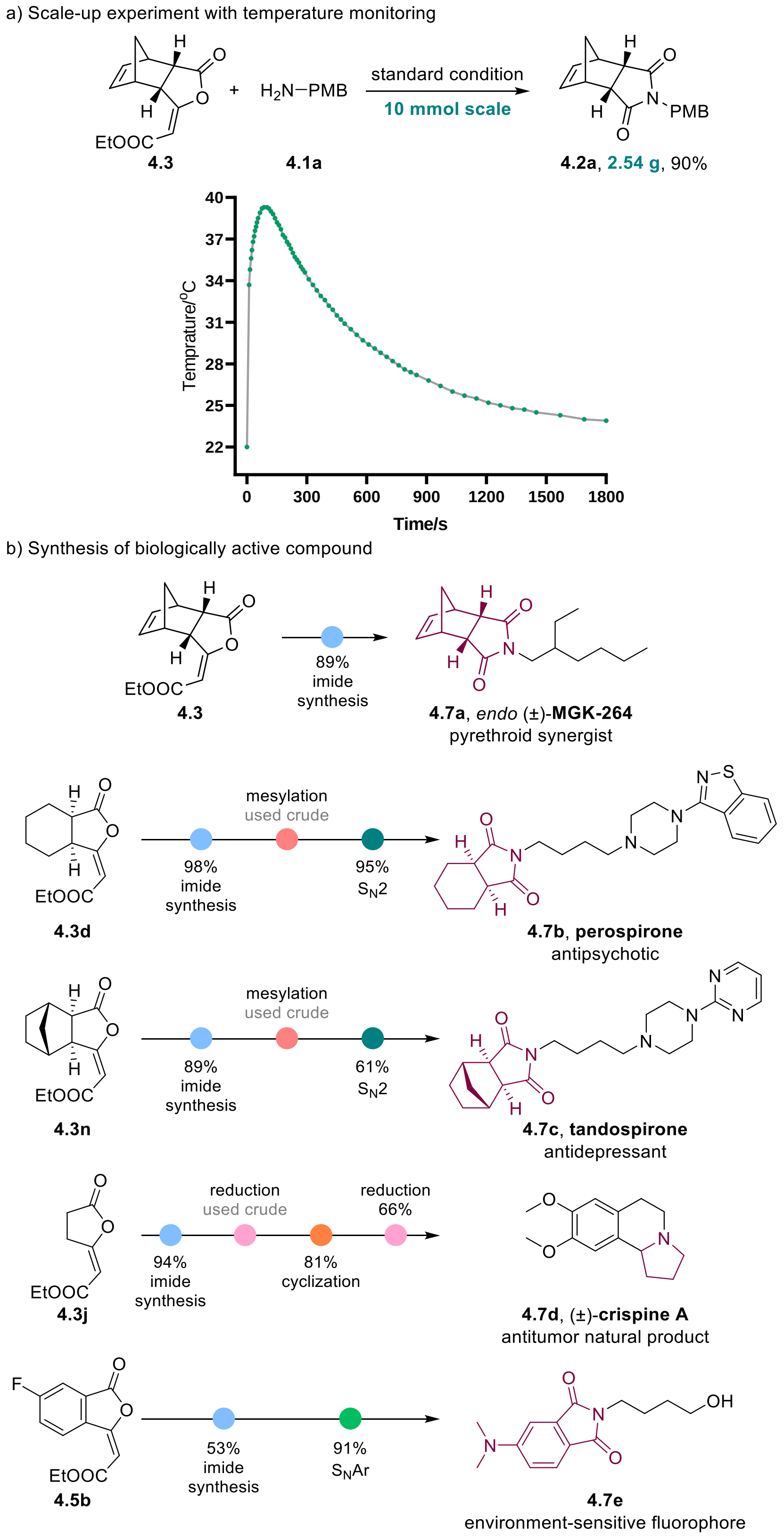


Figure 4.4. Substrate scope of aromatic enol lactones. Reaction yields in the absence of washing are indicated in brackets. See the Supporting Information for more details. The reaction temperatures and durations indicated above are for the second half of the process. PMB, *para*-methoxy benzyl. DMSO, dimethyl sulfoxide; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene. Solvent variations are indicated for both half reactions. [a] 0.75 mL DMSO was used. [b] 1.5 mL DMSO was used. [c] 1.25 mL DMSO was used. [d] 20 mol % TBD was used. [e] 1 mL DMSO was used.

followed by a slow return toward room temperature. Next, our methodology was applied to the synthesis of diverse biologically active compounds (Scheme 4.3b). The endo isomer of MGK-264 **4.7a**), a pyrethroid insecticide synergist,[14] was rapidly accessed as a racemate in high yield. Two


a) Scale-up experiment with temperature monitoring

b) Synthesis of biologically active compound

Scheme 4.3. Synthetic applications. See the Supporting Information for detailed reaction schemes.

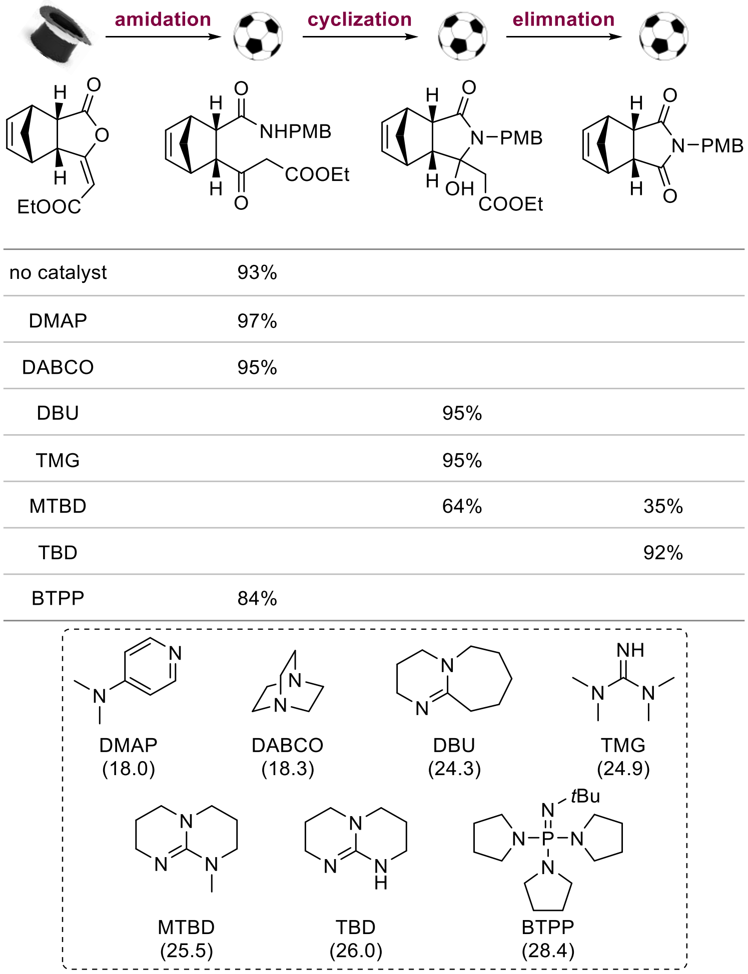
imide-containing pharmaceuticals, perospirone (**4.7b**) and tandospirone (**4.7c**),[1c] were also obtained from the corresponding enol lactones. Crispine A (**4.7d**) is a natural product with antitumor activity.[15] (±)-Crispine A was constructed from the corresponding succinimide via imide formation followed by a reduction− cyclization−reduction cascade. Last but not least, a 4-fluorophthalimide derivative containing a hydroxy handle was synthesized with our method, leading to the corresponding environmentally sensitive fluorophore 4-dimethylamino phthalimide (**4.7e**). This scaffold has been widely employed for the development of biocompatible fluorescent ligands for cell imaging.[16]

4.2.6 Experimental Mechanistic Studies

Given the lack of precedent for this transformation, we decided to probe the reaction mechanism, in particular, the function of TBD in the amidation−cyclization−elimination cascade. Briefly, our results establish that both the nucleophilic nitrogen and the electrophilic N−H bond of TBD, in this unique bicyclic guanidine moiety, contribute to catalysis in all three steps. As presented in Figure 4.5, only the amidation step was found to proceed in a system with no catalyst or when using traditional nitrogen-containing bases (DMAP and DABCO), suggesting that a stronger base is necessary for the cascade to proceed. Nevertheless, the amidation step was clearly accelerated by TBD, consistent with the total consumption of the starting material that took less than 1 min in the presence of TBD, compared to 15 min with no catalyst. Utilizing nitrogen-based organic superbases (DBU, TMG, MTBD, and TBD) allowed cyclization to take place, yet only bicyclic guanidines (MTBD and TBD) were able to initiate the elimination. The partial elimination observed with MTBD is consistent with the electrophilic N−H bond of TBD enhancing this step. A phosphazene base (BTPP) stronger than TBD was also tested, but neither cyclization nor elimination products were detected in this case. This implies that the catalytic activity of TBD is not solely the result of basicity; nucleophilicity is an integral part of its catalytic ability, as well.

4.2.7 Computational Mechanistic Studies

A surprising feature of this cascade is the elimination of ethyl acetate instead of water. Under the reaction conditions, the elimination of water was not detected. Since no scenario of water elimination could be created by experimentation, we decided to seek aid from computational approaches. DFT calculations were performed at the ωB97M-D4/def2-QZVP/CPCM(DMSO)// B3LYP-D4/def2-SVP/CPCM(DMSO) level of theory with the ORCA 5.0.4 version.[18] The results



pK_{aH}[a]	amidation	cyclization	elimnation
no catalyst	93%		
DMAP	97%		
DABCO	95%		
DBU		95%	
TMG		95%	
MTBD		64%	35%
TBD			92%
BTPP	84%		

Figure 4.5. Results of mechanistic studies. [a] The pK_{aH} value refers to basicity measured in acetonitrile. See ref 17 for more details. BTPP, *tert*-butylimino-tri(pyrrolidino)phosphorane; DABCO, 1,4-diazabicyclo[2.2. 2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DMAP, 4-dimethylaminopyridine; MTBD, 7-methyl-1,5,7-triazabicyclo[4.4.0]-dec-5-ene; TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene; TMG, 1,1,3,3-tetramethylguanidine.

were visualized in ChimeraX[19] with SEQCROW[20] (see the Supporting Information for computational details). A methyl group was used instead of the *para*-methoxy benzyl moiety to expedite the calculations. Given that TBD is an organic superbase and that the enolate/hydroxide is a relatively poor leaving group, we adopted the E1cB mechanism to model the elimination. Overall, for this system, our calculations correctly predicted that elimination of ethyl acetate is favored over that of water (Figure 4.6). The energy profiles computed for ethyl acetate elimination suggest that the barrier height of O−H deprotonation is inconsequential, whereas that of C−C bond breaking is significant. For the alternative water elimination pathway, the barrier heights for both steps are of significance. In particular, the considerably large barrier difference ($\Delta\Delta G$ = 19.9

kcal/mol) dictates that deprotonation at the α-carbon of the ester is highly unlikely, thus preventing the elimination of water. Furthermore, the calculations consistently indicate that the substrate should form a double hydrogen-bonded species with TBD (Figure 4.6, rxt), the geometry of which greatly benefits deprotonation at the oxygen atom.

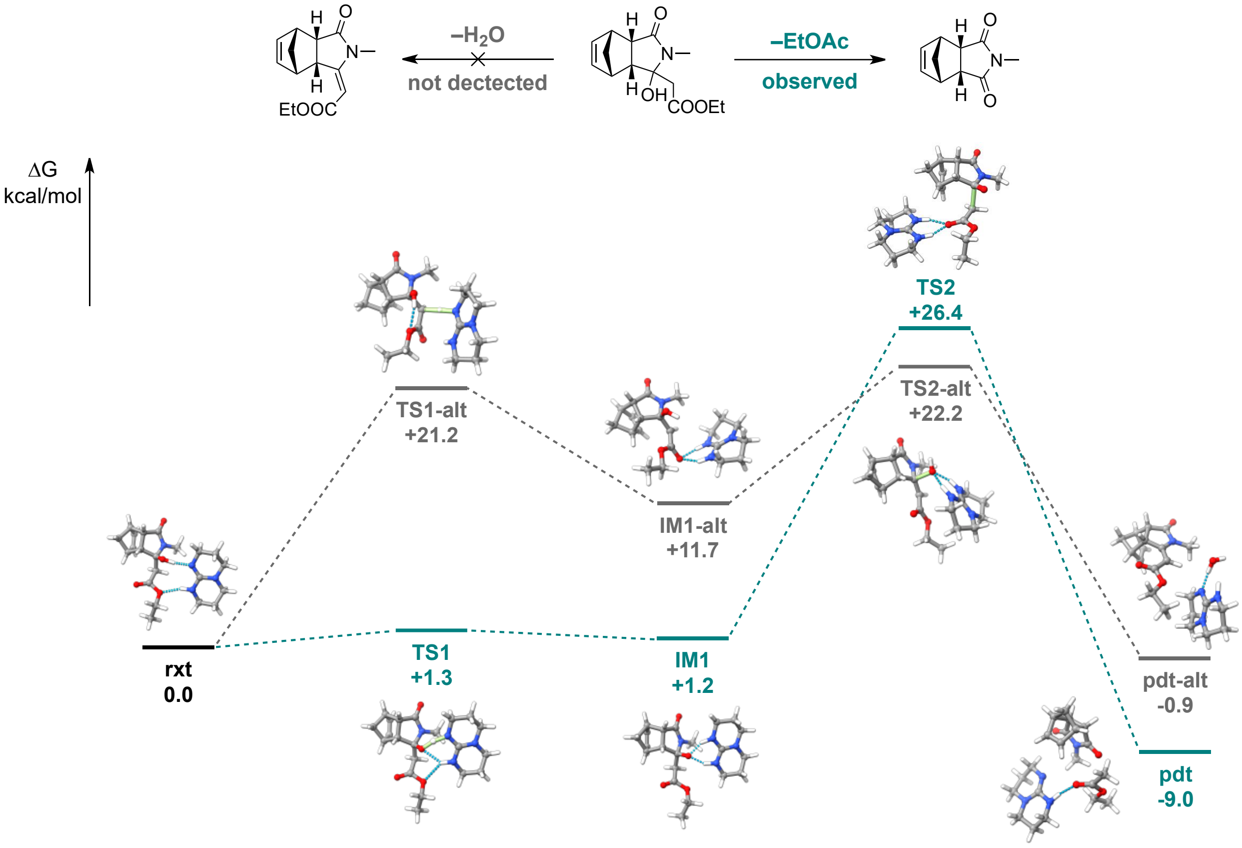


Figure 4.6. Results from the DFT investigation on the elimination step. Calculations were performed at the ωB97M-D4/def2-QZVP/CPCM(DMSO)//B3LYP-D4/def2-SVP/CPCM(DMSO) level of theory. Free energies were calculated based on Grimme's quasi-RRHO model with a 100 cm^{-1} cutoff frequency.[21] See the upporting Information for computational details. The pathway for the elimination of ethyl acetate is indicated in turquoise and that of elimination of water is in gray. Hydrogen bonding interactions are indicated as blue dashed lines, and transition state bonds are highlighted as green hollow bonds. alt, alternative; IM, intermediate; pdt, product; rxt, reactant; TS, transition state.

Considering the C−C bond cleavage step as the highest barrier to overcome for the elimination of ethyl acetate, we attempted to search for a better optimized transition state for this step. The initial transition state had been designed based on previous reports,[22] which proposed that TBD forms a double hydrogen-bonded structure with the leaving group to facilitate its departure (Figure 4.7). However, our results suggest that TBD is likely to form hydrogen bonds with both the imide and ester carbonyl. Such a scheme was found to lower the barrier height by 2.5 kcal/mol, which is a significant improvement over the initially proposed interactions. This is also consistent with the principle of least motion,[23] where the geometry with a lower barrier requires the slightest change in nuclear positions from its precursor (Figure 4.6, IM1).

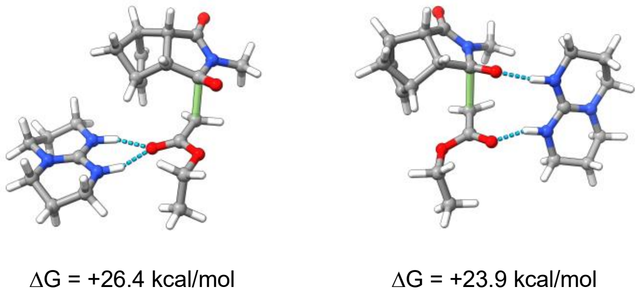


Figure 4.7. Initial and optimized calculated geometry for transition state of C–C bond cleavage.

4.3 Conclusions

In summary, we have established a TBD-catalyzed method for the construction of cyclic imides that involves an amidation-cyclization-elimination cascade. Both experimental and computational studies have provided a deeper understanding of the reaction mechanism. Notably, this transformation features an unprecedented C–C bond cleavage catalyzed by TBD. Mild and efficient, the method is compatible with late stage functionalization of complex molecules and synthesis of bioactive molecules.

In summary, we have established a TBD-catalyzed method for the construction of cyclic imides, which involves an amidation−cyclization−elimination cascade. Both experimental and computational studies have provided a deeper understanding of the reaction mechanism. Notably, this transformation features an unprecedented C−C bond cleavage catalyzed by TBD. Mild and efficient, the method is compatible with the late-stage functionalization of complex molecules and synthesis of bioactive molecules.

4.4 Author Contributions

C.B.L. performed all the experiments reported, wrote the first draft of the manuscript, and contributed to its editing. K.A. oversaw the project and was highly involved in manuscript editing. All authors have given approval to submission of the final version of the manuscript.

4.5 Acknowledgements

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4.6 Experimental Section

For experimental procedures and characterization of starting materials and products, see section 7.4. For computational data, see Appendix II-I. For copies of NMR spectra, see the published document at pubs.acs.org/doi/suppl/10.1021/acs.joc.4c02649/suppl_file/jo4c02649_si_001.pdf.

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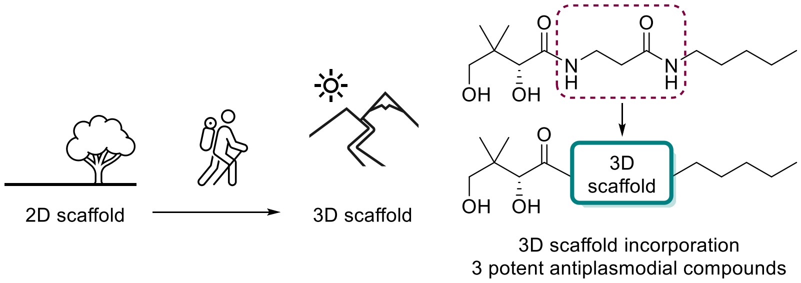
Preface for Chapter 5

Unlike previous chapters, Chapter 5 focuses on the applications of TBD-catalyzed organic transformations. This work utilizes the TBD-catalyzed lactone aminolysis reported in Chapter 2 to successfully generate 17 novel pantothenamide derivatives as potential antiplasmodial compounds. Two strategies are adopted to improve the efficacy and stability of these compounds, namely hetero non-aromatic bioisosteres and steric bulk enhancements, both of which exploit the incorporation of three-dimensional scaffolds. Among all compounds synthesized, 3 demonstrate high potency against *Plasmodium falciparum*, with high nanomolar antiplasmodial activity. Lastly, tentative computational studies are performed to help us understand the origins of the high potency of these compounds.

All of the results related to chemistry (synthesis of target molecules and computational studies) presented in this chapter were acquired by the author of this thesis under the supervision of prof. Karine Auclair. This work will be submitted for publication in the near future.

Chapter 5

Exodus from Flatland: Overcoming the Stability Issue of Antiplasmodial Pantothenamides with Three-Dimensional Scaffolds



Abstract: The incorporation of three-dimensional scaffolds into pantothenamides is presented in this study. The results demonstrate that replacement of either the labile amide or the carbon linker are viable strategies, yielding serum-stable pantothenamide-mimicking compounds that reduce the proliferation of intraerythrocytic *Plasmodium falciparum* at high nanomolar concentrations. Computational analysis of the molecular structures provides a better understanding of the mimicking abilities of various moieties.

5.1 Introduction

5.1.1 Malaria

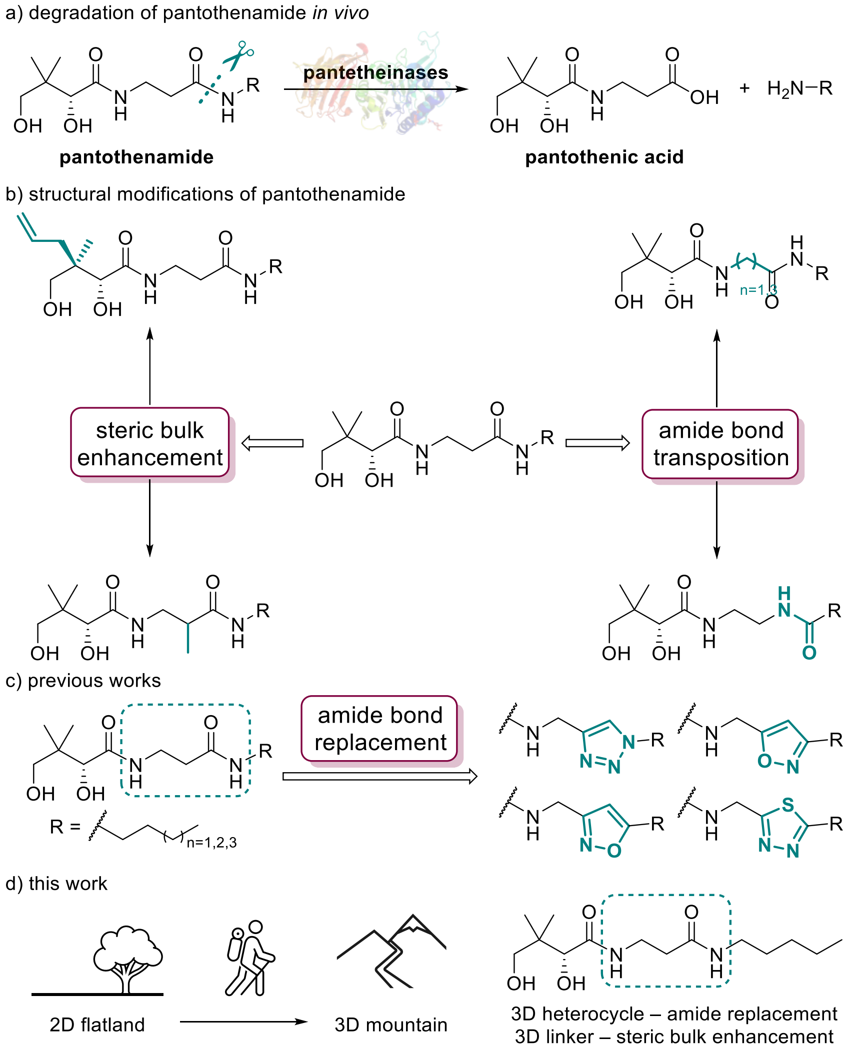
Malaria is a serious parasitic disease that affects tropical and subtropical countries. It is caused by parasites of the genus *Plasmodium*. With climate change and consistent increase in global travelling, malaria is expected to affect more areas around the world.[1] Compounding this problem is the fact that significant resistance to front-line antimalarials has developed over the years,[2] making it urgent to search for novel therapeutics against *Plasmodium* species. In particular, molecules that exhibit new mechanisms of action are attractive to minimize cross-resistance.

5.1.2 Pantothenamides

Pantothenamides are amide derivatives of pantothenic acid, many of which exhibit potent antimalarial activity.[3] The benchmark pantothenamide has been *N*-pentylpantothenamide (N5-Pan, Table 5.1). These compounds are transformed into active antimetabolites by the coenzyme A (CoA) biosynthetic pathway of plasmodial parasites.[4] As such, they target the CoA biosynthetic pathway and/or downstream CoA-utilizing enzymes, which is highly detrimental to parasite proliferation.[5,6] Despite the promising outlook, pantothenamides are inadequate clinical candidates due to their instability in blood.[3] The pantetheinase enzymes present in human serum readily hydrolyze the amide bond connecting pantothenic acid and the decorated amines, rendering pantothenamides ineffective (Figure 5.1a). Consequently, various structural modifications of pantothenamides have been reported to overcome this issue (Figure 5.1b). One effective approach is to enhance the steric bulk of the molecule. This was successful with modifications either at the *gem*-dimethyl group[7] or the α-carbon to the labile amide.[8] Another fruitful means is to alter the position of the labile amide by either changing the chain length[9] or using a reverse amide.[10] Combining these strategies together has also proven to be a viable option, as showcased in a preclinical compound with both a reverse amide and an α-methyl group.[5f] Although these approaches mitigate enzyme degradations, they often result in diminished potency. Moreover, synthesis of these molecules suffers from long routes and high waste generation, which limits their further development.

5.1.3 Previous Reports

In order to address these issues, our group has recently focused on installing aromatic heterocycles as potential amide bioisosteres in pantothenamide derivatives (Figure 5.1c).[11] With an initial hit on triazole analogs,[11a] we conducted a thorough examination on the structure-activity relationships (SARs) which revealed that the 1-alkyl-4-aminomethyl triazoles with 4- to 6-carbon chains were the best motifs to achieve high serum stability and antiplasmodial activity at nanomolar concentrations.[11b] It was proposed that the triazole ring could mimic the reverse amide group. Following up, a comprehensive investigation on diverse aromatic heterocycles was performed.[11c] Several scaffolds, including the isoxazole[11d] and the thiadiazole, proved to be adequate replacement for the labile amide.


a) degradation of pantothenamide *in vivo*

b) structural modifications of pantothenamide

c) previous works

d) this work

Figure 5.1. Background, previous reports, and current work.

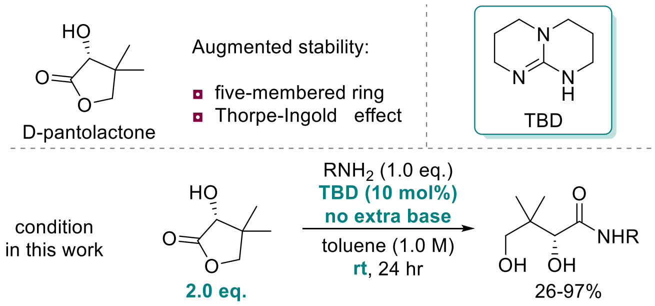
5.1.4 Current Work

With the recent trend of decreasing molecular planarity in drug discovery,[12] we are intrigued to explore the effect of incorporating three-dimensional scaffolds into pantothenamide derivatives. Such scaffolds are reported to offer many benefits, such as increased shape diversity, improved metabolic stability, and enhanced target selectivity.[13] Herein, we report the synthesis and antiplasmodial activity of pantothenamide derivatives containing various three-dimensional scaffolds (Figure 5.1d). Incorporated as labile amide replacement or for steric bulk enhancement, some of these groups led to increased potency against intraerythrocytic *Plasmodium falciparum* even in the presence of pantetheinases.

5.2 Results and Discussion

5.2.1 Aminolysis of D-Pantolactone

A crucial yet challenging reaction to stereoselectively access pantothenamide derivatives is the aminolysis of D-pantolactone. The difficulty of performing this reaction lies in the high stability of the five-membered lactone ring, further enhanced by the *gem*-dimethyl group due to the Thorpe-Ingold effect (Scheme 5.1).[14] As a result, extremely forcing conditions are typically employed to achieve such transformations, which suffer from poor functional group tolerance and low yield, while posing a safety concern.[11,15] We recently reported that 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD) is an exceptional catalyst for D-pantolactone aminolysis (Scheme 5.1).[16] This novel method allows aminolysis to proceed at room temperature with low catalyst loading, reduced lactone loading, and no excess base. Herein, this enabled the production of pantothenamide analogs with various three-dimensional scaffolds, thus allowing us to move from the "2D flatland" of our previous bioisosteres to the "3D mountain".



Scheme 5.1. Conditions employed for D-pantolactone aminolysis. TBD, 1,5,7-triazabicyclo[4.4.0]dec-5-ene.

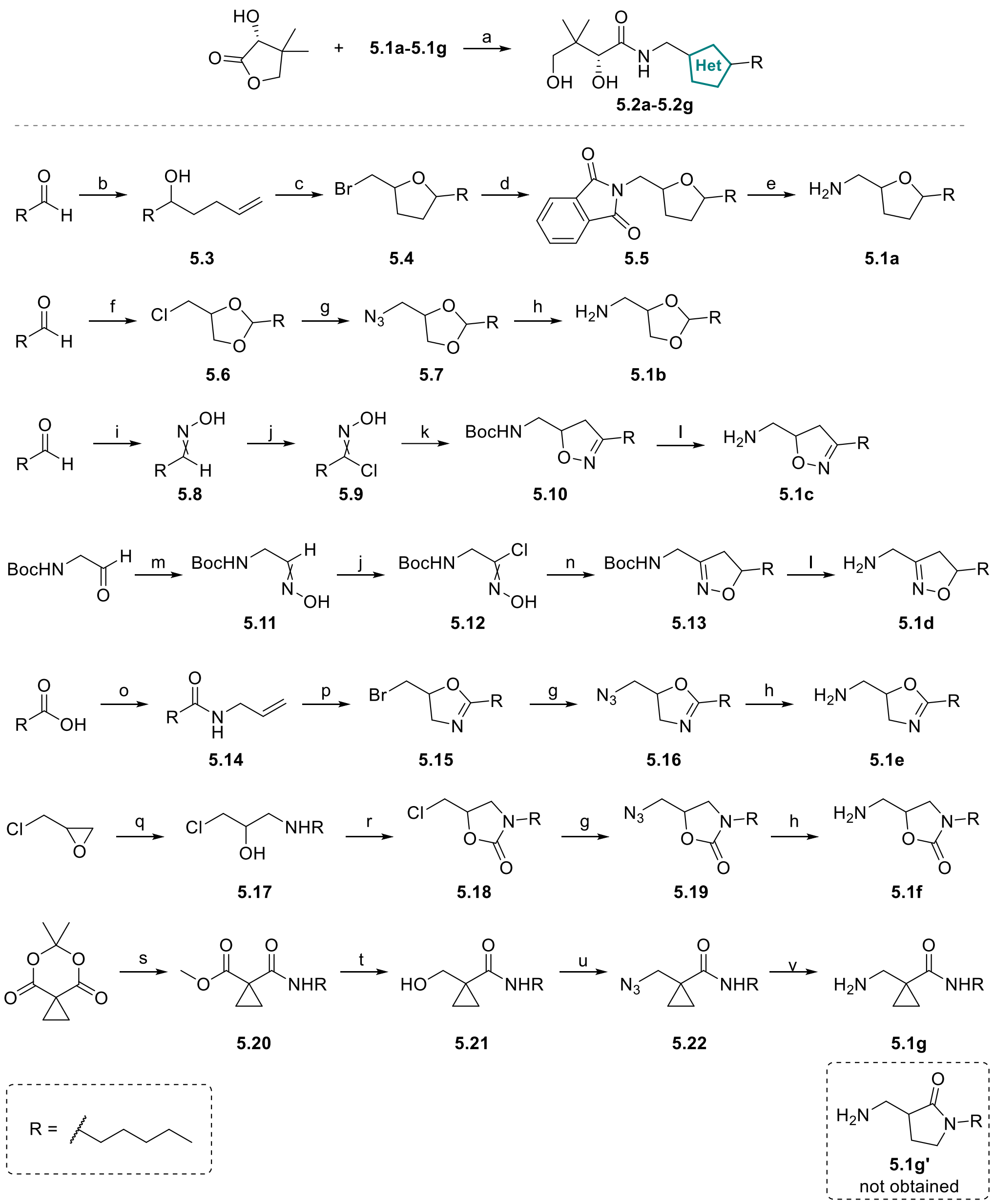
5.2.2 Labile Amide Replacement with Non-Aromatic Heterocycles

We first explored the possibility of using non-aromatic heterocycles as a replacement for the labile amide. Seven derivatives were synthesized as shown in Scheme 5.2. Considering the SARs for previously reported pantothenamides and their analogs, we chose a linear 5-carbon chain (*n*-pentyl) as a benchmark to evaluate the efficacy of our modifications.

Overall, a series of amines (**5.1a-5.1g**) were assembled and used in an aminolysis reaction with D-pantolactone to afford **5.2a-5.2g**. Fragment **5.1a** containing a tetrahydrofuran ring was accessed through a Grignard reaction, followed by an intramolecular oxybromination[17] and a Gabriel synthesis. The 1,3-dioxolane fragment **5.1b** was synthesized from traditional acetal formation between α-chlorohydrin and 1-hexanal, followed by azidation and reduction. Moving on to partially unsaturated heterocycles, the isoxazoline-containing **5.1c** and **5.1d** were both produced with a similar route. The corresponding aldehydes were first transformed into the oxime chlorides as nitrile oxide precursors, followed by [3+2] cycloadditions with the alkenes. Deprotection of the *tert*-butyloxycarbonyl (Boc) group eventually furnished **5.1c** and **5.1d**. For fragment **5.1e**, the *N*-allyl amide was first synthesized, before intramolecular oxybromination to generate an oxazoline ring with a bromide handle.[18] This was then transformed into the corresponding azide, and Staudinger reduction of the azide afforded **5.1e**. Carbonyl-containing non-aromatic heterocycles were next explored. For the preparation of **5.1f**, amination of epichlorohydrin, followed by carbonylation with carbonyldiimidazole delivered the oxazolidinone ring. Azidation and subsequent Staudinger reduction afforded the amine **5.1f**. Following Danishefsky's homoconjugate addition-cyclization protocol,[19] we had originally planned to access pyrrolidone derivative **5.1g'**.[19] However, this reported procedure furnished the simple amidation product **5.20** instead. Nevertheless, **5.20** was further elaborated to the corresponding pantothenamide-mimic because it can serve to probe the effect of increased steric bulk next to the labile amide group. Thus, reduction of the ester, followed by mesylation and substitution afforded the azide intermediate, which was then subjected to heterogenous hydrogenation to afford **5.1g**. Notably, Staudinger reduction of the azide failed to afford the desired product here. All amine fragments were converted to the final pantothenamide derivatives **5.2a-5.2g** with the TBD-catalyzed protocol mentioned above.

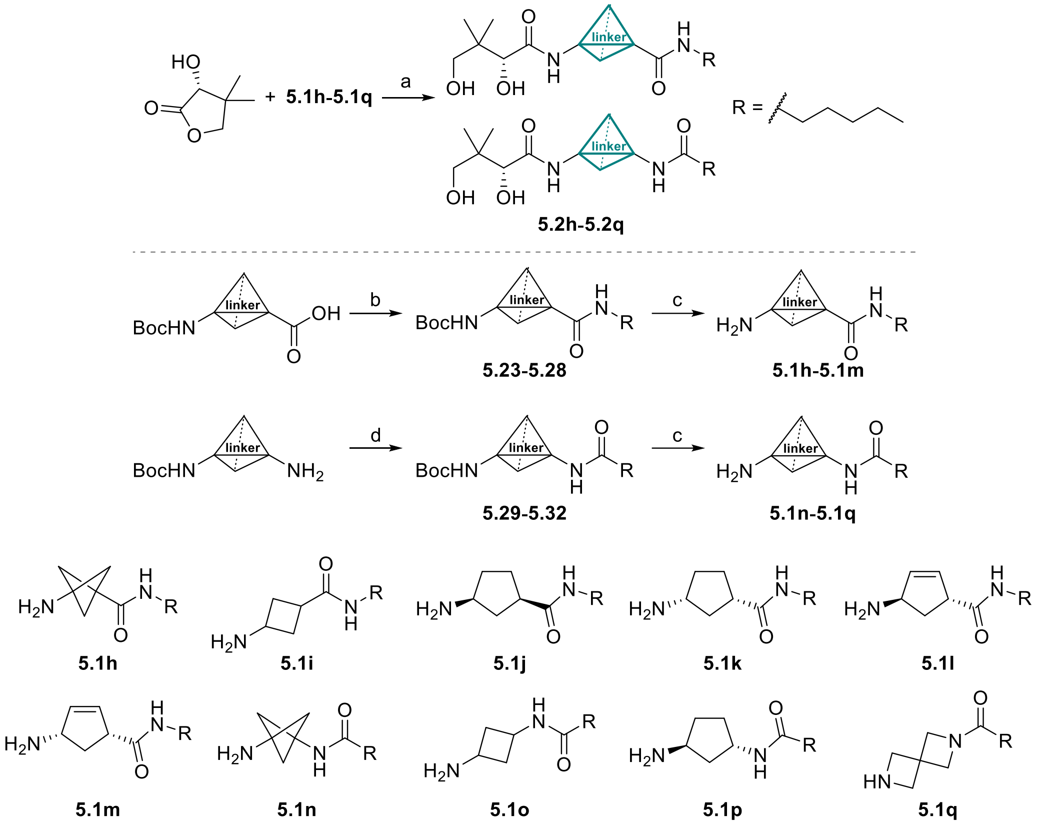
5.2.3 Steric Bulk Enhancement with Three-Dimensional Scaffolds

The syntheses of pantothenamide derivatives with three-dimensional linkers were facilitated by recent synthetic developments on similar scaffolds (Scheme 5.3).[20] Starting from commercially



Scheme 5.2. Synthetic schemes for the synthesis of pantothenamide derivatives containing non-aromatic heterocycles. a) TBD, toluene, rt, 24 hr. b) 3-Butenylmagnesium bromide, THF, 0ºC to rt, overnight. c) NBS, L-proline, THF, rt, 10 min. d) Potassium phthalimide, DMF, 80ºC, overnight. e) $N_2H_4 \cdot H_2O$, EtOH, reflux, 2 hr. f) α-Chlorohydrin, *p*TSA·H_2O, toluene, Dean-Stark, reflux, overnight. g) NaN_3, DMSO, MW, 100ºC, 1 hr. h) PPh_3, THF/H_2O=10:1, rt, overnight. i) $NH_2OH \cdot HCl$, NaOAc, EtOH:H_2O = 2:1, 0ºC to rt, overnight. j) NCS, DMF, rt, 3 hr. k) *N*-Boc-allylamine, TEA, EA, 0ºC to rt, overnight. l) TFA, DCM, rt, 2 hr. m) $NH_2OH \cdot HCl$, $NaHCO_3$, MeOH:H_2O = 2:1, rt, overnight. n) 1-Heptene, TEA, EA, 0ºC to rt, overnight. o) Allyl amine, EDCI, DMAP, DCM, 0ºC to rt, overnight. p) PIDA, TMSBr, DCM, rt, overnight. q) Amylamine, *i*PrOH, 0ºC to rt, overnight. r) CDI, THF, 50ºC, overnight. s) Amylamine, neat, rt, overnight; then H_2SO_4, MeOH, reflux, 2 hr. t) $NaBH_4$, MeOH, 0ºC to rt, overnight. u) MsCl, TEA, DCM, 0ºC, 1.5 hr; then NaN_3, DMF, 80ºC, overnight. v) Pd/C, H_2, MeOH, rt, overnight.

available Boc-protected amino acids or diamines, traditional amide coupling with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) gave the corresponding amides. Deprotection of the Boc group afforded the desired fragments which were each reacted with D-pantolactone as before. Among the ten derivatives synthesized, six (**5.2h-5.2m**) maintained the normal amide bond and four (**5.2n-5.2q**) contained a reverse amide bond.



Scheme 5.3. Synthetic schemes for the synthesis of pantothenamide derivatives containing three-dimensional linkers. a) TBD, toluene, rt, 24 hr. b) Amylamine, EDCI, DMAP, DCM, 0°C to rt, overnight. c) TFA, DCM, rt, 2 hr. d) Caproic acid, EDCI, DMAP, DCM, 0°C to rt, overnight.

5.2.4 Evaluation of Antiplasmodial Activities

With the successful delivery of these compounds, *in vitro* antiplasmodial activity was evaluated against intraerythrocytic *P. falciparum* in the *presence of pantetheinases* as previously reported.[11a] The results are summarized in Table 5.1. Antiplasmodial activity of both N5-Pan and reverse N5-Pan in the *absence of pantetheinases* are included for reference.[3,10a] The saturated heterocycles found in **5.2a** and **5.2b** were decent replacements for the labile amide, with 50% inhibition of parasite proliferation (IC_{50}) values in the low micromolar range. A strong dependence

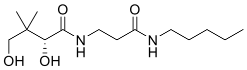
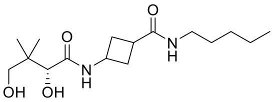
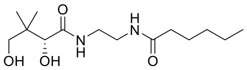
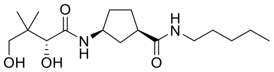
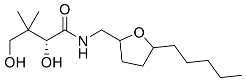
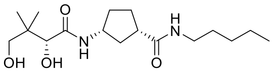
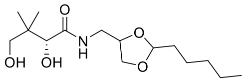
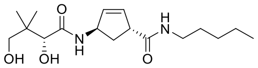
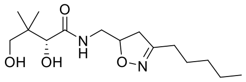
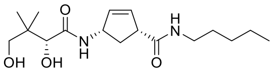
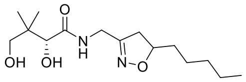
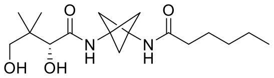
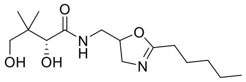
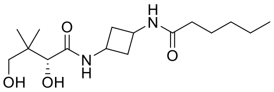
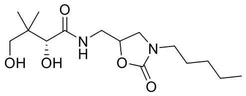
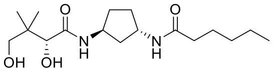
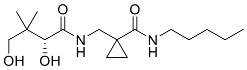
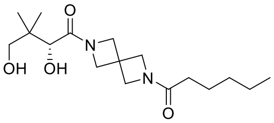
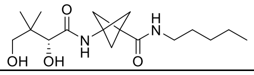
No.	Structure	IC$_{50}$ against *P. falciparum* with 1 μM pantothenate (μM)[a]	No.	Structure	IC$_{50}$ against *P. falciparum* with 1 μM pantothenate (μM)[a]
N5-Pan		2.0 ± 0.2[3]	**5.2i**		7.0 ± 0.6
reverse N5-Pan		0.63[10a]	**5.2j**		>200
5.2a		4.1 ± 0.2	**5.2k**		27 ± 3
5.2b		8.7 ± 0.6	**5.2l**		11 ± 1
5.2c		21 ± 2	**5.2m**		0.27 ± 0.04 (>3.1)[b]
5.2d		0.9 ± 0.1 (>12.5)[b]	**5.2n**		90 ± 10
5.2e		120 ± 10	**5.2o**		120 ± 10
5.2f		55 ± 2	**5.2p**		44 ± 2
5.2g		0.11 ± 0.01 (>1.6)[b]	**5.2q**		>200
5.2h		170 ± 20			

Table 5.1. Antiplasmodial activity of N5-Pan and of reverse N5-Pan in the absence of pantetheinases, and activity of compound **5.2a-5.2q** in the presence of pantetheinases. a) IC$_{50}$ values are averages from three or more independent experiments, each performed in triplicate, and errors represent SEM. Entries within the nanomolar range are highlighted in red. b) IC$_{50}$ values from experiments performed in the presence of 100 μM pantothenate are indicated in parentheses.

on the position of the double bond and of the heteroatoms was observed for the partially unsaturated heterocycles. Isoxazoline derivatives **5.2c** and **5.2d** were more potent than the oxazoline **5.2e**. Positioning of the double bond on the amide side rather than the alkyl chain side was preferred. Indeed, compound **5.2d** exhibited submicromolar activity against *P. falciparum.* A carbonyl positioned away from the original amide was detrimental, likely due to improper location and/or orientation (**5.2f**). The serendipitous production of **5.2g** further confirmed that steric bulk enhancement at the α-position of the amide is an effective strategy, leading to a compound with antiplasmodial activity in the high nanomolar range.

In terms of linker modifications, these tended to be more successful in compounds with normal amide orientation rather than the reverse amide. In terms of linker replacement with normal amide orientation, bicyclo[1.1.0]pentane was not a suitable scaffold (**5.2h**). Cyclobutane was an adequate linker that led to a compound with low micromolar activity (**5.2i**). A cyclopentane ring with the (1*R*,3*S*) configuration (**5.2j**) gave an inactive compound, while the (1*S*,3*R*) configuration (**5.2k**) afforded a compound with weak activity. Surprisingly, cyclopentene linkers were significantly better than cyclopentanes. Even though a cyclopentene linker with the (1*R*,4*R*) configuration was only moderately tolerated, the (1*R*,4*S*) configuration (**5.2m**) was highly beneficial, with antiplasmodial activity in the high nanomolar range. Unfortunately, none of the three-dimensional linkers used in the context of the reverse amide were well tolerated (**5.2n**-**5.2q**). For the three most potent compounds, antiplasmodial assay was also performed in the presence of 100 μM pantothenate to verify if the compounds are on target. Pantothenate competes with pantothenamides for transformation by the CoA biosynthetic pathway. The IC_{50} values shifted to significantly higher concentrations in all cases, consistent with the proposed mode of action of pantothenamides. Cytotoxicity of these three compounds were also studied using human foreskin fibroblasts and no obvious cytotoxicity was observed up to a concentration of 200 μM.

5.2.5 Discussion of the Results

In this study, we demonstrated that incorporating three-dimensional scaffolds was a feasible strategy to generate serum-stable pantothenamide derivatives. Replacement of either the labile amide or the linker led to compounds with excellent potency against *P. falciparum* even in the presence of pantetheinases. In the transition from two-dimensional to three-dimensional scaffolds, new stereocenters were inevitably introduced, which resulted in the formation of diastereomers in certain cases. Although a few target molecules (**5.2g**, **5.2h**, **5.2j**-**5.2n**, **5.2p**,) are enantiopure, the rest are mixtures of diastereomers as a result of non-stereospecific syntheses. Given the importance of chirality in medicinal chemistry,[21] it would be beneficial to access the pure diastereomers for compounds with high potency and investigate them individually in future studies. It is difficult to access **5.2d** in a stereoselective manner due to the spontaneous nature of [3+2] cycloadditions.[22] Hence, chiral separation via chromatography may be a more desirable approach.

The most active compound, **5.2g**, is particularly interesting. It is an exemplary case in the category of steric bulk enhancement at the α-position, contradicting previous reports suggesting that a methyl group was the only modification tolerated at this position.[8] The high potency of **5.2g** demonstrates that a cyclopropane ring is an excellent substituent for steric enhancement. On the other hand, the pyrrolidone derivative **5.2g'** remains an attractive target molecule that combines a three-dimensional scaffold with α-alkylation through ring-chain transformation.[23] In the original report from Danishefsky *et al.*,[19] aniline was used as the nucleophile and the pyrrolidone scaffold was accessed via a homoconjugate addition-cyclization sequence. However, the formation of **5.20** observed with amylamine suggests that amidation is preferred over homoconjugate addition for aliphatic amines. This could be tentatively explained by the hard-soft acid-base (HSAB) theory.[24] Aliphatic amines are harder nucleophiles than aniline, resulting in the preferential attack at the hard carbonyl carbon. We speculate that once amidation has taken place, the amide generated is not nucleophilic enough to proceed to homoconjugate addition at room temperature. A few reports[25] on similar transformations all adopted heating, hinting that elevated temperature is necessary for the homoconjugation addition to occur.

5.2.6 Computational Studies

As the structures of these derivatives drift further away from original pantothenamides, it is unclear how these compounds mimic pantothenamides. Previously, we have conducted qualitative analysis and proposed that the replacement of the labile amide with aromatic heterocycles more closely resembled the reverse amide bond.[11] To this end, modern computational chemistry was next utilized to gain a more quantitative understanding on this matter, where both conformational sampling and electronic charge calculations were examined. All calculations were performed with ORCA version 6.0[26] and the results were visualized in ChimeraX[27] with SEQCROW.[28] Conformational sampling was performed with the semiempirical tight binding (GFN2-xTB) method[29] and the analytical linearized Poisson-Boltzmann (ALPB) model as an implicit solvent model of water.[30] Electronic charge distribution was calculated based on charges from electrostatic potentials using a grid-based method (CHELPG)[31] at the B3LYP/def2-TZVPPD level of theory.

We initially performed several trial runs with the full structures of pantothenamides for conformational samplings. This proved to be inadequate as these compounds contain many sp^3 carbons, resulting in extremely flexible molecules without a predominant conformation. Since the pantoyl group and the *N*-substituted carbon chain are the same for these derivatives, we decided to simplify these sections and focus on the parts where modifications were made. Hence, the pantoyl group was reduced to an acetyl group and the *n*-pentyl chain to an ethyl chain for these studies.

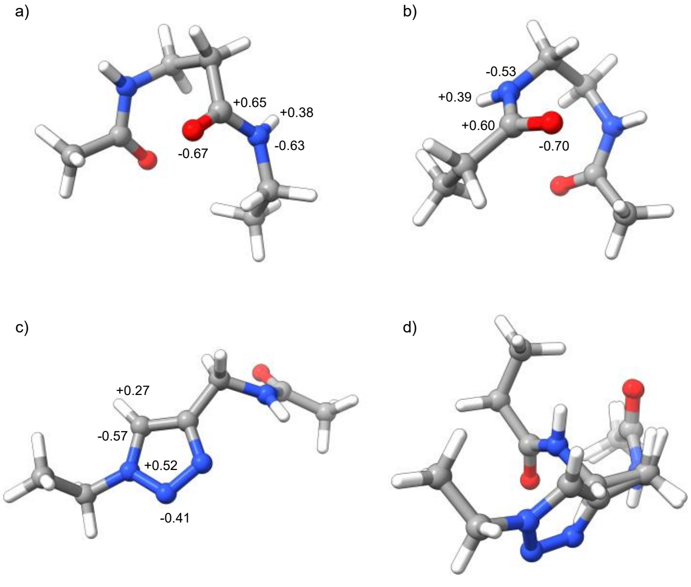


Figure 5.2. Conformational sampling and charge distribution analysis of truncated derivatives. a) Global minimum of N5-Pan. b) Global minimum of reverse N5-Pan. c) The truncated triazole derivative in a conformation that mimics reverse N5-Pan. d) Superposition of (b) and (c).

Conformational sampling of the truncated version of N5-Pan and reverse-N5-Pan (Figure 5.2a and 5.2b) reveals that both exhibit a U-shaped geometry at their global minimum, yet the two methylene groups linking the two amides bend in different directions. These conformations maximize the interactions between the two amide carbonyls, either through $n \rightarrow \pi^*$ interactions or dipole-dipole interactions.[32] Notably, these two scaffolds display a strong conformational bias that is not observed in heterocyclic mimics, suggesting that interactions between the two amides play a key role in conformational stability. Next, we conducted the same calculations on the truncated triazole derivative to test if the triazole can mimic the reverse amide as previously suggested.[11b] Indeed, the triazole was found to adequately mimic the reverse amide bond. Despite being less polarized, the charge distribution of the triazole matches that of the amide bond (Figure 5.2c). The overall geometry of the triazole derivative is less bent compared to that of the reverse N5-Pan due to the lack of amide-amide interaction, yet the indicated atomic positions directly match those of the reverse amide bond (Figure 5.2d). Notably, the first triazole conformer in the ensemble that resembles the reverse amide most is not at global minimum (+0.4 kcal/mol). This is consistent with the observation that bound ligands are often not in a minimum conformation, globally or locally.[33]

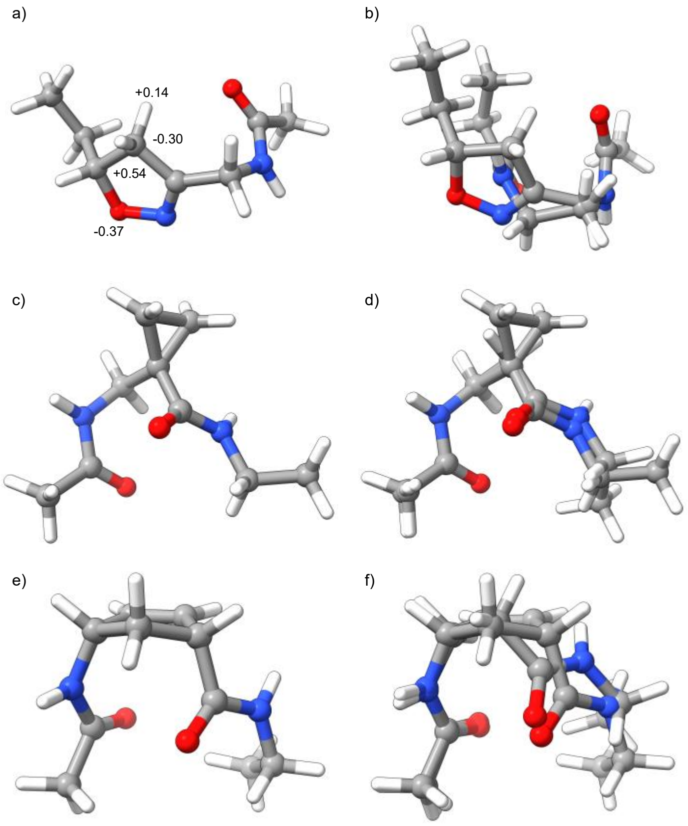


Figure 5.3. Conformational sampling and charge distribution analysis of truncated derivatives. a) Reverse N5-Pan-mimicking conformer of the (*R*)-isoxazoline derivative (truncated (*R*)-isomer of compound **5.2d**). b) Superposition of figure 5.2b and figure 5.3a. c) N5-Pan-mimicking conformer of the cyclopropane derivative (truncated compound **5.2g**). d) Superposition of figure 5.2a and figure 5.3c. e) N5-Pan-mimicking conformer of the cyclopentene derivative (truncated compound **5.2j**). f) Superposition of figure 5.2a and figure 5.3e.

Moving on to pantothenamide-mimics with a three-dimensional scaffold, we investigated our top three molecules. Despite being non-aromatic, the isoxazoline core in compound **5.2d** exhibits a primarily planar geometry (Figure 5.3a). Although not as polarized, the charge distribution of the isoxazoline loosely mimics that of the reverse amide bond. The stereocenter of this isoxazoline does not alter the orientation of the amide, but rather changes the geometry of the alkyl chain. Because of the flexibility of the alkyl chain, it is difficult to predict which isomer would give a better mimic of reverse N5-Pan. Hence, a representative superposition of the (*R*)-isomer on reverse

N5-Pan is depicted (Figure 5.3b). Expectedly, compound **5.2g** largely resembles N5-Pan, despite being 1.4 kcal/mol higher than the global minimum (Figures 5.3c and 5.3d). As a result of the rigidification at the α-carbon center, conformers of **5.2g** with lower energies favor intramolecular hydrogen bonding over amide carbonyl interactions. Moving on to compound **5.2j**, conformational sampling unveiled its ability to mimic N5-Pan (Figures 5.3e and 5.3f). Despite being 2.1 kcal/mol higher than the global minimum, one conformer of **5.2j** exhibits both the U-shape geometry and the orientation of the amide carbonyls of N5-Pan. These computational results offer a better understanding of how these compounds may mimic the original pantothenamides, and potentially point to directions for further optimization.

5.3 Conclusions

In summary, we have explored the incorporation of three-dimensional scaffolds as a means to generate serum-stable pantothenamide derivatives with nanomolar activity against *P. falciparum*. Two strategies, amide replacement and linker modification, were adopted, both of which proved to be effective. Overall, we secured three novel pantothenamide derivatives with antiplasmodial activity at nanomolar concentrations in the presence of pantetheinases. With the aid of computational chemistry, conformational sampling and charge distribution analyses were conducted for some of the compounds to strengthen our understanding of their ability to imitate pantothenamides. This study provides a stepping stone for further development of novel antimalarial treatments.

5.4 Author Contributions

C.B.L. synthesized all molecules and performed all computational studies. X.L. performed all biological testing. K.A. and K.J.S. oversaw the project. C.B.L. wrote the first draft of the manuscript and contributed to its editing. K. A. was highly involved in manuscript editing. All authors have given approval to the final version of the manuscript.

5.5 Acknowledgements

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for providing a platform for computational study. Free academic use of ORCA and ChimeraX is greatly appreciated.

5.6 Experimental Section

For experimental procedures and characterization of starting materials and products, see section 7.5. For copies of NMR spectra, see Appendix I-II. For computational data, see Appendix II-II. For antiplasmodial assay and cytotoxicity study data, see Appendix III-II.

5.7 References

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Chapter 6

Conclusion, Contribution to Knowledge, and Future Work: D'où Venons-Nous? Que Sommes-Nous? Où Allons-Nous?

6.1 Conclusion and Contribution to Knowledge

With rising awareness of sustainability in organic synthesis, the demand for sustainable yet affordable synthetic methodologies is growing rapidly. TBD has attracted significant attention as a versatile reagent with numerous advantages, such as high stability,[1] low toxicity,[2] easy accessibility,[3] low cost,[3] and most importantly, multifunctionality. Although a series of reactions have been reported, further development is still required to reach the full potential of TBD, including lactone aminolysis and multistep cascade reactions. This thesis aims to enrich the portfolio of TBD by reporting novel synthetic methodologies and medicinal chemistry applications thereof.

Chapter 2 utilized TBD to perform a seemingly simple reaction — lactone aminolysis. This work fills an important void in lactone aminolysis and is complementary to the reported methods. The results in this chapter demonstrate that TBD-catalysis enables the mild, effective, and more sustainable aminolysis of a broad range of lactones by diverse amines. Detailed mechanistic studies, conducted for the first time for this reaction, revealed the complex nature of this transformation. This has not only deepened our understanding of the catalytic behaviour of TBD in lactone aminolysis, but also provided valuable information for future catalyst optimization and reaction development.

Chapter 3 demonstrated that more sophisticated transformations can be built upon this lactone aminolysis. Taking advantage of both the nucleophilicity and the basicity of TBD, 3-alkylidenephthalides were successfully transformed into 3-hydroxyisoindolin-1-ones. Remarkably, this reaction proceeds at ambient temperature within 1 hour. Many products also precipitate out of solution, which greatly simplifies the purification process. Gratifyingly, the level of sustainability of this method was quantified using a few important green chemistry metrics for both academic laboratories as well as industrial settings.

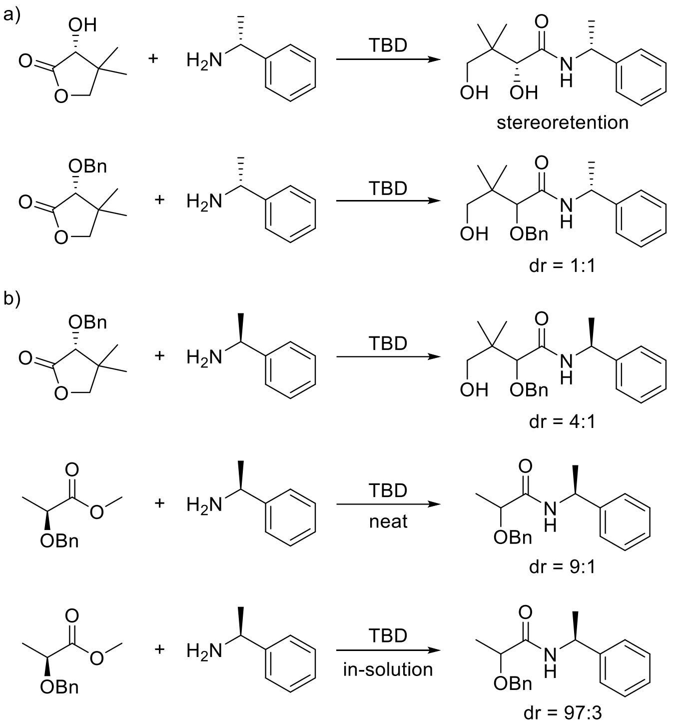
Following on the work described in Chapter 3, Chapter 4 introduced a novel method for the synthesis of cyclic imides via an amidation-cyclization-elimination cascade. By incorporating an unprecedented C–C bond cleavage, this method paved a new path to access cyclic imides. Owing to the efficiency and mildness of TBD, late stage functionalization of complex molecules is explicitly demonstrated here. As a new transformation catalyzed by TBD, the C–C bond cleavage step was of particular interest. Hence, both experimental and computational approaches were employed to understand this step which favors the elimination of ethyl acetate instead of water.

Chapter 5 employed the lactone aminolysis methodology reported in Chapter 2 to build a series of pantothenamide derivatives with potential antiplasmodial activity. The TBD-catalyzed lactone aminolysis enabled the access to the target molecules, some of which would not tolerate traditional aminolysis conditions such as prolonged heating or microwave irradiation. Two original strategies, both using three-dimensional scaffold incorporation, were explored to obtain serum-stable molecules, namely non-aromatic heterocycles for amide replacement and cyclic structures for steric bulk enhancement. Both approaches proved to be adequate to afford potent antiplasmodial compounds. For the first time in this context, computational studies were conducted to help us better understand the mimicking ability of several selected derivatives.

6.2 Future Work

6.2.1 TBD-Triggered Racemization/Epimerization Reactions

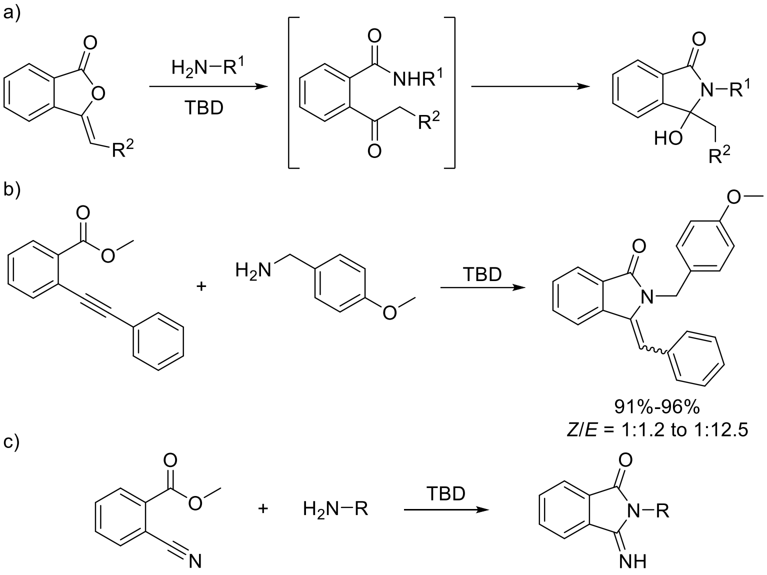
While developing the lactone aminolysis reaction described in Chapter 2, one aspect that we paid special attention to was the retention of stereochemistry, since this is of utter importance for the synthesis of biologically active compounds.[4] An unexpected phenomenon was observed: the stereocenter of D-pantolactone was retained under the reaction conditions, while that of *O*-benzylated D-pantolactone was completely scrambled (Scheme 6.1a).[5] Although TBD has been reported to trigger the loss of stereochemical information of the α-position to the carbonyls during aminolysis,[6] such a strong substituent effect had never been reported. In addition, there was no clear information about what combinations of substrates and reaction conditions would lead to racemization/epimerization. Hence, a detailed study of TBD-triggered racemization/epimerization during the aminolysis reaction under synthetically relevant conditions is clearly needed. Results of this study would provide valuable information to users and serve as a future reference. Preliminary results from one of the group members (Ahmed Bahaa-Eddin Abdelaal) have demonstrated that it is a complicated matter (Scheme 6.1b). Many factors, including the type of lactone/ester substrates, the stereo compatibility between lactones/esters and amines, solvent, reaction temperature, and TBD loading, could influence the stereochemical outcome of the reaction.



Scheme 6.1. Reported and preliminary results on TBD-triggered racemization/epimerization reactions.

6.2.2 TBD-Catalyzed Amidation-Cyclization Reactions with *ortho*-Substituted Benzoate Derivatives

In Chapter 3, we demonstrated that TBD is an efficient catalyst for the synthesis of 3-hydroxyisoindolin-1-ones from 3-alkylidenephthalides via an amidation-cyclization reaction (Scheme 6.2a).[7] The enol lactone moiety embedded in the starting material, on one hand, provided a reactive carboxyl group for the amidation reaction to occur. On the other hand, an *ortho*-carbonyl was unmasked upon amidation, providing the necessary electrophilic group for the cyclization reaction. This inspired us to design a substrate bearing a carboxyl group and an *ortho*-electrophilic group, which could undergo a similar TBD-catalyzed amidation-cyclization reactions. *ortho*-Alkynyl benzoates are candidates that perfectly fit the description above (Scheme 6.2b). Preliminary results by the author of this thesis showed that methyl 2-(phenylethynyl)benzoate and *para*-methoxybenzyl amine were converted to the corresponding isoindolinone product smoothly in the presence of TBD. A *Z*/*E* mixture was observed on the benzylidene moiety and the ratio was highly dependent on the reaction conditions employed. This protocol is advantageous compared to other reported methods[8] as transition metals are typically required to activate the alkyne. The pre-formation of the amides is also necessary for the cyclization to occur in certain cases. Our preliminary results demonstrated that this transformation could proceed smoothly in the absence of metals and no pre-formation of amide was required. Likewise, we propose that methyl 2-cyanobenzoate could undergo a similar transformation to afford iminoisoindolinone (Scheme 6.2c).



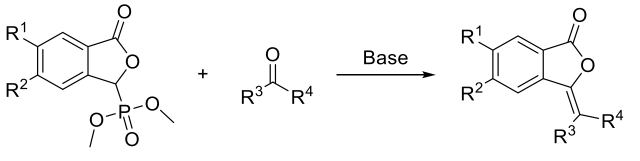
91%-96%
Z/*E* = 1:1.2 to 1:12.5

Scheme 6.2. Reported and proposed reactions involving TBD-catalyzed amidation-cyclization reactions.

6.2.3 Aggregation Induced Emission Materials

Aggregation induced emission (AIE) refers to the phenomenon where fluorophores are non-emissive in solution but highly emissive in their aggregated forms.[9] Since most in-solution fluorophores suffer from aggregation-caused quenching (ACQ),[9] the phenomenon of AIE is of great importance to offer complementary fluorescent systems when traditional fluorophores fail. Through the course of Chapter 3, we serendipitously discovered that one of the 3-alkylidenephthalide starting materials exhibited strong AIE properties (Scheme 6.3). Preliminary results by the author of this thesis showed that this AIE luminogen (AIEgen) scaffold has several originalities. Contrary to most carbon-based AIEgens, this alkylidenephthalide incorporates two heteroatoms. In terms of the synthetic feasibility, this scaffold is directly accessed via Horner–Wadsworth–Emmons from the corresponding phthalide phosphonate and ketone. This is much simpler compared to the synthesis of traditional AIEgens, which requires multistep synthesis and heavily relies on Pd-catalyzed cross couplings.[10] Moreover, the fluorescent properties can be easily tuned with different substituents. Several test molecules synthesized were subjected to 365 nm UV light and AIE emission colors ranging from purple to yellow were observed (Figure 6.1).

Notably, unlike other AIEgens, the carboxyl group in 3-alkylidenephthalides presents a chemical liability towards strong base, which can be utilized to develop base-quenched AIE systems or AIE-based *p*H probes.



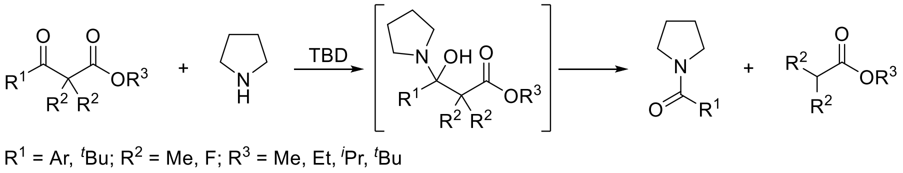
AIE active molecules
emission color under 365nm UV:
purple to yellow

Scheme 6.3. 3-Alkylidenephthalide-based AIEgens.

Figure 6.1. Photos of different AIEgens under 365 nm UV light.

6.2.4 TBD-Catalyzed Acylation of Secondary Amines

One of the fascinating features of the methodology reported in Chapter 4 is the TBD-catalyzed C−C cleavage. The key intermediate in this process comprises an hemiaminal at the β-position of the ester. We reckon that if we can recreate the same pattern from different reactions, we should be able to utilize the TBD-catalyzed C−C cleavage in a broader context. We propose that β-keto esters would be plausible candidates for such transformations (Scheme 6.4). The core issue is to prevent the formation of the enamine/imine, which not only is a favored pathway, but also causes the removal of the hydroxyl handle required for the C−C cleavage to occur. This can be achieved by using ketones that lack α-protons. For example, aromatic or *tert*-butyl (R^1) ketones harboring a dimethyl/difluoro (R^2) group at the other α-position meet these requirements. Secondary amines (pyrrolidine as an example) could also be used to avoid the possibility of imine formation. Once the hemiaminal intermediate is captured by TBD, it can potentially undergo the same C−C cleavage process observed in Chapter 4 to afford the amide with elimination of the ester. If unwanted reactions at the carboxyl site were observed with methyl/ethyl esters, bulkier groups such as isopropyl and *tert*-butyl groups could be utilized to block this site.



Scheme 6.4. Proposed TBD-catalyzed acylation of secondary amines.

6.2.5 New Strategies of Pantothenamide Derivatization for Better Antimicrobials

Chapter 5 reported two novel strategies for the derivatization of pantothenamides and both proved to be viable options to obtain antiplasmodial compounds with high nanomolar activities. It would be interesting to explore the structure-activity relationships (SARs) for the three most potent compounds. As shown in previous studies,[12] the alkyl chain is the group with the highest tolerance to variations. Relevant research is currently conducted by Alec McAlpine, another group member.

In terms of the successful strategy of steric bulk enhancement at the α-position that was stumbled upon, previous studies only reported the methyl group as a viable modification to prevent enzymatic hydrolysis.[13] However, the results from Chapter 5 demonstrate that a cyclopropane group is also appropriate. Encouraged by this, we propose to expand this strategy and test different substituents, including cyclopropane, cyclobutane, and fluorine atoms in diverse pantothenamide contexts, both with the amide group in its normal and reverse orientation (Figure 6.2a).

Another promising strategy is to utilize linear groups as potential amide bioisosteres in pantothenamide derivatives. Although this strategy was briefly explored previously,[14] it was used to primarily increase the *in vivo* stability of pantothenamides and no potent antimicrobial molecules were secured. Preliminary results by the author of this thesis revealed that this is indeed a feasible strategy for antiplasmodial pantothenamide derivatization (Figure 6.2b). We propose that other groups, including fluoroalkene, trifluoroethylamine, cyclopropane, and amidine, could be effective replacements of the labile amide of pantothenamides.

Interestingly, many pantothenamide derivatives are also reported that show antibacterial activity.[11] Thus, it would be interesting to test the compounds reported in Chapter 5 for their effect on the growth of pathogenic bacteria. These studies are currently underway in our laboratory by another group member, Suzana Diaconescu-Grabari.

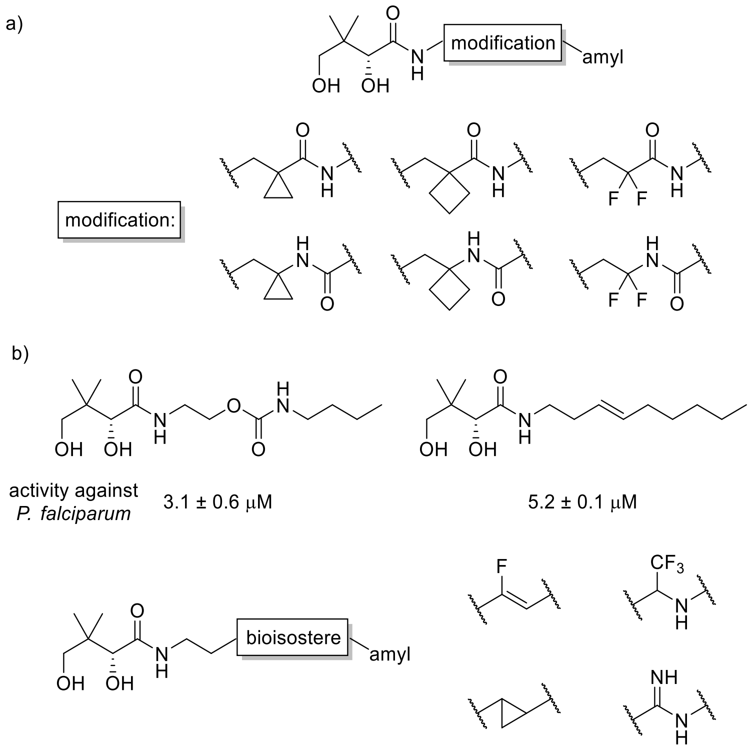


Figure 6.2. New strategies for pantothenamide derivatization.

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Chapter 7

Synthetic Procedures and Characterization of the Products:

The TBD Cookbook

7.1 General Considerations

Reactions that require heating were heated in an oil bath with digital temperature control. Room temperature in this thesis is between 22 and 23°C. Analytical thin-layer chromatography (TLC) was carried out using 200 mm aluminum backed silica gel plates with F-254 indicator, purchased from Silicycle (TLA-R10011B-323). Visualization of the compounds on TLCs was accomplished under UV light (254 nm) and/or potassium permanganate stain. Reaction product purification was achieved by flash column chromatography on Biotage Isolera One using 40-63 μm silica gel purchased from Silicycle (R12030B). All flash column chromatography was run in an isocratic or step gradient fashion. Anhydrous DMSO used as NMR internal standard was purchased from Sigma-Aldrich. Anhydrous solvents (THF, DMF, DCM) were obtained from a Mbraun MB SPS-7 solvent purification system. Anhydrous ethyl acetate was obtained by distillation from anhydrous potassium carbonate. Triethylamine was distilled from potassium hydroxide before use. Toluene was treated by azeotropic water removal (distill for 5 minutes and discard all distillate, then cool down to rt and filter) without using extra drying reagent. Unless otherwise noted, reagents were purchased from commercial sources (Sigma-Aldrich, Thermo Scientific, Oakwood, Combi-Blocks, Ambeed), and used as received. Microwave reactions were run in a Biotage® Initiator microwave synthesizer. Uncorrected melting points were measured on a Thiele block equipped with a digital thermometer and reported in degree Celsius. Specific rotation was measured on a Jasco DIP-140 digital polarimeter. Infrared spectra were recorded on a PerkinElmer Spectrum One FT-IR spectrometer and reported in wavenumbers. FT-IR absorptions are reported as weak (w), medium (m), strong (s), and/or broad (br). Proton nuclear magnetic resonance (^{1}H-NMR) and carbon nuclear magnetic resonance (^{13}C-NMR) spectra, proton-decoupled fluorine nuclear magnetic resonance (^{19}F{^{1}H}-NMR) spectra, and proton-decoupled phosphorus nuclear magnetic resonance (^{31}P{^{1}H}-NMR) spectra were recorded on a Bruker AVIIIHD 500 MHz NMR Spectrometer and a Bruker AVIIIHD 400 MHz NMR at 298K. Chemical shifts (δ) for ^{1}H-NMR are reported in parts per million (ppm) and referenced to residual protons in the solvent; $CDCl_3$ (δ = 7.26 ppm), DMSO-d_6 (δ = 2.50 ppm), CD_3OD (δ = 3.31 ppm), D_2O (δ = 4.79 ppm). Chemical shifts (δ) for ^{13}C-NMR are reported in ppm and referenced to the carbon signal of the solvent; $CDCl_3$ (δ = 77.16 ppm), DMSO-d_6 (δ = 39.52 ppm), CD_3OD (δ = 49.00 ppm). NMR splitting patterns are reported as singlet (s), broad singlet (bs), doublet (d), triplet (t), quartet (q), and quintet (p). High resolution mass spectra (HR-MS) were obtained by electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Bruker Maxis atmospheric pressure ionization (API) Quadruple Time-of-Flight (QTOF) mass spectrometer. Purity of all final compounds was determined on an Agilent 1100 series HPLC system using a Phenomenex Luna® LC column (C18, 200 × 4.6 mm, 100 Å, 5 μm), with water as mobile phase A and acetonitrile as mobile phase B. The detector was set to 214 nm and the flow rate was 1 mL/min. All changes in solvent ratio during elution were linear. Elution method A: 0-3 min: 1% B in A, 3-5 min: 1% to 10% B, 5-10 min: 10% to 15% B, 10-13 min: 15% to 30% B, 13-26 min: 30% B, 26-30 min: 30% to 99% B, 30-32 min: 99% B, 32-35 min: 99% B to 1% B, 35-38 min: 1% B. Elution method B: 0-8 min: 1% B in A, 8-15 min: 1% to 50% B, 15-25 min: 50% B, 25-30 min: 50% to 99% B, 30-38 min: 99% B, 38-40 min: 99% to 1% B, 40-43 min: 1% B.

7.2 Experimental Details for Chapter 2

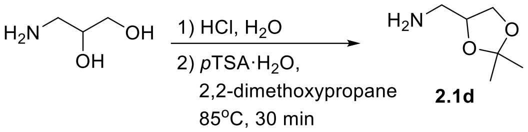
7.2.1 Synthesis and Characterization of Starting Materials and Intermediates

2.1ca **2.1c**

(*E*)-1-Phenylethan-1-one *O*-(3-aminopropyl) oxime (**2.1c**)

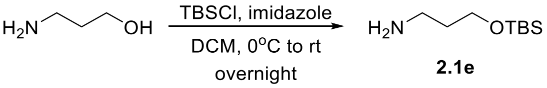
To a 100 mL round bottom flask were added acetophenone (2.92 mL, 25 mmol, 1.0 equiv.), hydroxylamine hydrochloride (4.34 g, 62.5 mmol, 2.5 equiv.), sodium acetate (6.15 g, 75 mmol, 3.0 equiv.) and EtOH (30 mL). The mixture was heated to reflux overnight. The reaction mixture was cooled to rt and poured into ice water (60 mL). The precipitate was collected by filtration and washed with cold water to give the product **2.1ca** as a white solid (2.56 g, 76%). This compound was previously reported.[1] It was directly used in the next step without further purification.

To a 50 mL round bottom flask were added **2.1ca** (676 mg, 5.0 mmol, 1.0 equiv.) and anhydrous DMSO (10 mL). KOH (pre-ground powder, 1.40 g, 25 mmol, 5.0 equiv.) was added in one portion and the mixture was stirred at rt for 20 minutes. The reaction mixture was then cooled to 0°C and a solution of 3-bromopropylamine hydrobromide (1.64 g, 7.5 mmol, 1.5 equiv.) in DMSO (2.5 mL) was added dropwise. The reaction mixture was warmed to rt and stirred overnight. Upon completion, the reaction was quenched with water (20 mL), and the product was extracted in EA (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified by flash chromatography (SiO_2, DCM/MeOH/TEA = 100:4:1) to give the product **2.1c** as a light yellow oil (515 mg, 54%). R_f = 0.43 (DCM/MeOH/TEA = 100:10:1); IR (neat, cm^{-1}): 3365 (w, br), 2932 (w), 2869 (w), 1444 (w), 1369 (w), 1042 (m), 759 (s), 691 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.63 (m, 2H), 7.37-7.33 (m, 3H), 4.28 (t, J = 6.2 Hz, 2H), 2.86 (t, J = 6.9 Hz, 2H), 2.22 (s, 3H), 1.88 (m, 2H), 1.69 (bs, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 154.6, 136.8, 129.1, 128.5, 126.1, 72.0, 39.4, 33.2, 12.8; HRMS (ESI$^+$) *m/z* $[C_{11}H_{17}N_2O]^+$ cacld: 193.1335; found: 193.1332. Characterization matched reported data.[1]



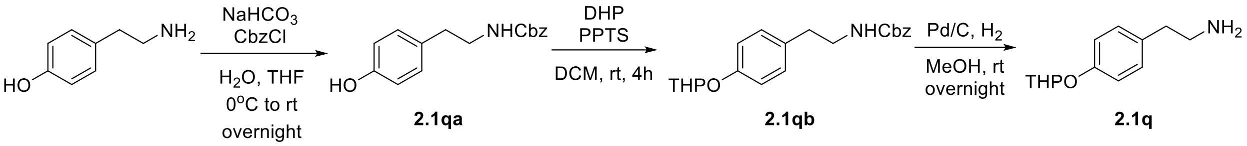
(2,2-Dimethyl-1,3-dioxolan-4-yl)methanamine (**2.1d**)

To a 50 mL round bottom flask were added 1-amino-2,3-propanediol (1.37 g, 15 mmol, 1.0 equiv.) and water (5 mL). Conc. HCl was added until the *p*H was adjusted to 1. This mixture was concentrated under vacuum, redissolved in MeOH (30 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. *p*TSA·H_2O (142.7 mg, 0.75 mmol, 0.05 equiv.) and 2,2-dimethoxypropane (9 mL) were then added, and the mixture was stirred at 85°C for 30 minutes. A white precipitate formed. After cooling down to rt, the mixture was filtered and washed with acetone to afford a white solid. This was dissolved in 2 M NaOH (40 mL) and the product extracted in DCM (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give the product **2.1d** (1.66 g, 84%) as a colorless oil. IR (neat, cm^{-1}): 3370 (w, br), 2982 (w), 2872 (w), 1371 (m), 1059 (s), 826 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 4.06 (m, 1H), 3.97 (m, 1H), 3.61 (m, 1H), 2.78 (m, 1H), 2.72 (m, 1H), 1.37 (s, 3H), 1.30 (s, 3H), 1.17 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 109.2, 77.5, 67.1, 44.9, 27.0, 25.5; HRMS (ESI$^+$) *m/z* $[C_6H_{14}NO_2]^+$ cacld: 132.1019; found: 132.1021. Characterization matched reported data.[2]



(2,2-Dimethyl-1,3-dioxolan-4-yl)methanamine (**2.1e**)

To a 50 mL round bottom flask were added 3-aminopropanol (0.38 mL, 5 mmol, 1.0 equiv.), imidazole (1.02 g, 15 mmol, 3.0 equiv.), and anhydrous DCM (5 mL). The mixture was stirred at rt for 10 min, then cooled down to 0°C. TBSCl (904.3 mg, 6 mmol, 1.2 equiv.) was added in small portions and the mixture was stirred at rt overnight. Upon completion, the mixture was diluted in DCM (40 mL), washed with water (2×30 mL) and brine (1×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give **2.1e** (779 mg, 82%) as a colorless oil. IR (neat, cm^{-1}): 3362 (w, br), 2952 (m), 2854 (m), 1254 (m), 1096 (s), 833 (s), 772 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.68 (t, J = 6.1 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 1.64 (m, 2H), 1.22 (bs, 2H), 0.87 (s, 9H), 0.03 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 61.4, 39.6, 36.6, 26.1, 18.4, -5.2. HRMS (ESI$^+$) *m/z* $[C_9H_{24}NOSi]^+$ cacld: 190.1622; found: 190.1617. Characterization matched reported data.[3]



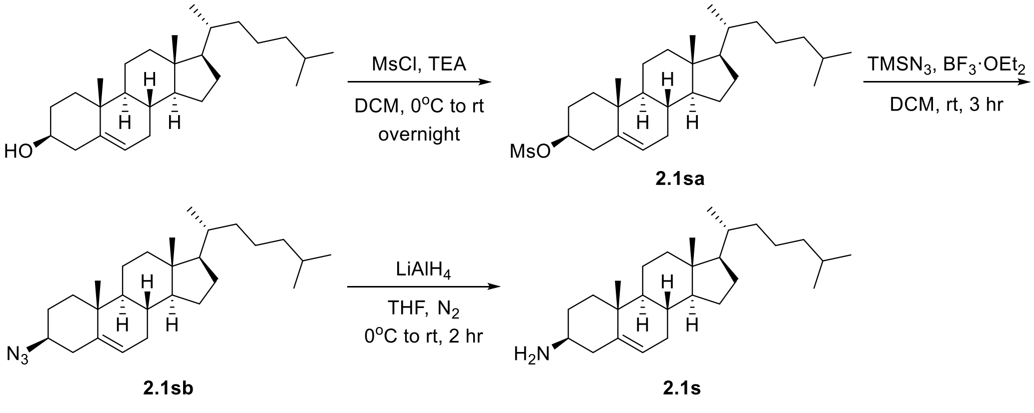
2-(4-((Tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-amine **(2.1q)**

To a 50 mL round bottom flask were added tyramine (1.37 g, 10 mmol, 1.0 equiv.), $NaHCO_3$ (1.09 g, 13 mmol, 1.3 equiv.), water (10 mL), and THF (10 mL). The mixture was cooled to 0°C and benzyl chloroformate (1.55 mL, 11 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was kept at 0°C for 1 hour, warmed to rt and stirred overnight. The reaction was quenched with 1 M KH_2PO_4 (20 mL), and the product was extracted in EA (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) to give the product **2.1qa** as a white solid (1.72 g, 63%). R_f = 0.30 (Hex/EA = 5:1); Mp: 99-100°C; IR (neat, cm^{-1}): 3329 (m, br), 3029 (w), 2637 (w), 1685 (s), 1512 (s), 1242 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.31 (m, 5H), 7.00 (d, J = 8.2 Hz, 2H), 6.77 (d, J = 8.3 Hz, 2H), 6.52 (bs, 1H), 5.11 (s, 2H), 4.91 (t, J = 6.1 Hz, 1H), 3.42 (m, 2H), 2.72 (t, J = 7.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.8, 154.9, 136.4, 130.2, 129.9, 128.7, 128.3, 128.2, 115.7, 67.0, 42.6, 35.2. HRMS (ESI$^+$) *m/z* $[C_{16}H_{17}NO_3Na]^+$ cacld: 294.1101; found: 294.1096. Characterization matched reported data.[4]

To a 50 mL round bottom flask were added **2.1qa** (1.72 g, 6.3 mmol, 1.0 equiv.), anhydrous DCM (6 mL), PPTS (158 mg, 0.63 mmol, 0.1 equiv.) and dihydropyran (1.15 mL, 12.6 mmol, 2.0 equiv.).

The mixture was stirred at rt for 4 hours, and diluted in DCM (30 mL). The mixture was washed with sat. $NaHCO_3$ (2×25 mL) and 1 M KH_2PO_4 (2×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give a sticky oil. This oil was placed on ice, and white crystals subsequently formed. A 1:1 mixture of ether and hexanes (30 mL) was slowly added, and the precipitate was collected by filtration and washed with hexanes to give the product **2.1qb** as a white solid (1.75 g, 78%). The product was previously reported.[1] It was directly used in the next step without further purification.

To a 50 mL round bottom flask were added **2.1qb** (1.75 g, 4.9 mmol), 10% Pd/C (100 mg), and MeOH (10 mL). The flask was sealed under an atmosphere of hydrogen (using a balloon). The mixture was stirred at rt overnight. The mixture was filtered through Celite, and the filter cake was washed with MeOH (the filter cake containing Pd/C was subsequently quenched with water). The combined filtrates were evaporated under vacuum to give the desired product **2.1q** (937 mg, 86%) as a light yellow oil, which partially solidified upon standing. IR (neat, cm^{-1}): 3329 (m, br), 3029 (w), 2937 (w), 1685 (s), 1512 (s), 1242 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.07 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 5.35 (m, 1H), 3.89 (m, 1H), 3.55 (m, 1H), 2.89 (q, J = 7.0 Hz, 2H), 2.66 (q, J = 6.9 Hz, 2H), 1.97 (m, 1H), 1.83-1.78 (m, 4H), 1.67-1.53 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 155.5, 132.7, 129.7, 116.5, 96.5, 62.0, 43.5, 38.9, 30.4, 25.2, 18.9. HRMS (ESI$^+$) *m/z* $[C_{13}H_{20}NO_2]^+$ cacld: 222.1489; found: 222.1498. Characterization matched reported data.[1]

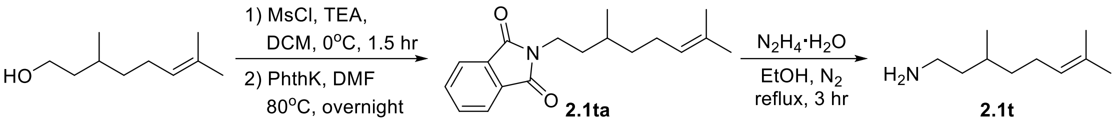


Cholesterylamine (**2.1s**)

To a 100 mL round bottom flask were added cholesterol (3.86 g, 10 mmol, 1.0 equiv), anhydrous DCM (40 mL), and TEA (2.10 mL, 15 mmol, 1.5 equiv.). The mixture was cooled to 0°C before MsCl (0.85 mL, 11 mmol, 1.1 equiv.) was added dropwise. The reaction mixture was stirred at rt overnight. The mixture was next washed with water (2×50 mL) and brine (1×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum. The solid residue was triturated with MeOH, filtered, washed with MeOH, and dried to give the product **2.1sa** (4.28 g, 92%) as a white solid. This compound was previously reported.[5] It was used without further purification.

To a 50 mL round bottom flask were added **2.1sa** (2.09 g, 4.5 mmol, 1.0 equiv.), anhydrous DCM (15 mL), $TMSN_3$ (0.66 mL, 5.0 mmol, 1.1 equiv.), and $BF3{\cdot}OEt_2$ (1.11 mL, 9.0 mmol, 2.0 equiv.). The reaction mixture was stirred at rt for 3 hours, and quenched with 2 M NaOH solution (20 mL). The mixture was stirred for 5 minutes, and the organic layer was separated. The aqueous layer was extracted with DCM (2×25 mL), and the combined organic layers were washed with brine (2×25 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum. The residue was eluted through a short silica pad using hexanes (200 mL) followed by hexanes/EA = 50:1 (150 mL). The combined organic layers were evaporated under vacuum to afford **2.1sb** (1.06 g, 58%) as an off-white solid. This compound was previously reported.[5] It was used directly into next step without further purification.

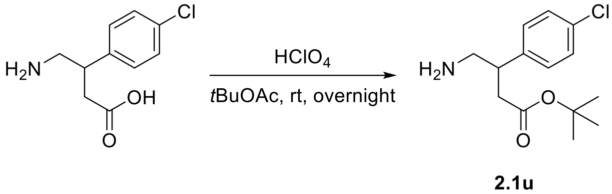
To a 50 mL round bottom flask were added **2.1sb** (1.06 g, 2.57 mmol, 1.0 equiv.) and anhydrous THF (10 mL). The mixture was cooled to 0°C and the atmosphere was exchanged with a N_2 balloon. A $LiAlH_4$ solution (2.0 M in THF, 1.9 mL, 3.86 mmol, 1.5 equiv.) was added dropwise and the mixture was stirred at rt for 2 hours. Upon completion, the mixture was cooled to 0°C and carefully quenched (caution: exothermic and violent gas evolution) with water (2 mL), 1 M NaOH (2 mL), and water (6 mL). A white suspension formed which was filtered off by vacuum through Celite, then washed with diethyl ether. The filtrate was extracted with diethyl ether (3×25 mL). The combined organic layers were washed with brine (1×25 mL), dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum to give **2.1s** (946 mg, 95%) as an off-white solid. $[\alpha]_D^{23}$ = −31.2 (c = 1.00, $CHCl_3$); Mp: 101-103°C; IR (neat, cm^{-1}): 3350 (w), 2931 (m), 2866 (m), 1465 (w), 1382 (s);); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.28 (m, 1H), 2.57 (m, 1H), 2.12 (m, 1H), 2.05-1.93 (m, 3H), 1.81-1.77 (m, 2H), 1.67 (m, 1H), 1.60-0.83 (m, 35H), 0.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.9, 120.7, 56.9, 56.3, 52.1, 50.3, 43.5, 42.4, 39.9, 39.6, 38.3, 36.6, 36.3, 35.9, 32.8, 32.00, 31.98, 28.3, 28.1, 24.4, 23.9, 22.9, 22.7, 21.1, 19.5, 18.8, 12.0; HRMS (ESI$^+$) *m/z* $[C_{27}H_{48}N]^+$ cacld: 386.3781; found: 386.3772. Characterization matched reported data.[5]



3,7-Dimethyloct-6-en-1-amine (**2.1t**)

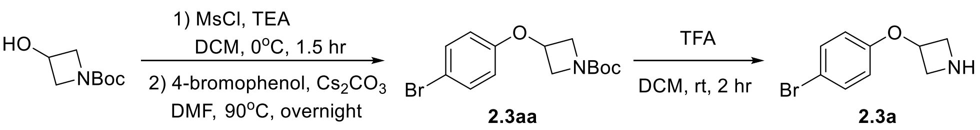
To a 50 mL round bottom flask were added (±)-citronellol (707 mg, 4.52 mmol, 1.0 equiv.), TEA (0.95 mL, 6.78 mmol, 1.5 equiv.), and anhydrous DCM (10 mL). The mixture was cooled to 0°C and MsCl (0.42 mL, 5.43 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred at 0°C for 1.5 hours, then diluted in DCM (30 mL), washed with water (1×30 mL) and brine (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give the mesylate intermediate. Potassium phthalimide (1.26 g, 6.78 mmol, 1.5 equiv.) and anhydrous DMF (10 mL) were then added, and the mixture was stirred at 80°C overnight. After cooling down to rt, the mixture was diluted in EA (75 mL), washed with water (2×40 mL), sat. Na_2CO_3 (2×30 mL), and brine (1×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, Hex/EA = 20:1) to afford the desired product **2.1ta** (1.05 g, 81% over two steps) as a colorless oil. $R_f = 0.36$ (Hex/EA = 10:1); IR (neat, cm^{-1}): 2964 (s), 2854 (s), 1771(m), 1708 (s), 1395 (m), 1368 (m), 1057 (m), 718 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.80 (m, 2H), 7.67 (m, 2H), 5.04 (m, 1H), 3.67 (m, 2H), 2.02-1.89 (m, 2H), 1.70 (m, 1H), 1.62 (m, 3H), 1.57 (m, 3H), 1.50-1.40 (m, 2H), 1.37 (m, 1H), 1.18 (m, 1H), 0.96 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.5, 133.9, 132.3, 131.4, 124.7, 123.2, 36.9, 36.4, 35.5, 30.4, 25.8, 25.4, 19.4, 17.7; HRMS (ESI^+) *m/z* $[C_{18}H_{24}NO_2]^+$ cacld: 286.1802; found: 286.1797.

To a 50 mL round bottom flask were added **2.1ta** (1.05 g, 3.68 mmol), EtOH (25 mL), and $N_2H_4 \cdot H_2O$ (0.71 mL, 14.7 mmol, 4.0 equiv.). The system was purged with nitrogen and refluxed for 3 hours (maintaining a nitrogen atmosphere was essential to prevent diimide formation). After cooling down to rt, the mixture was filtered, and the filtrate was concentrated under vacuum. The residue was dissolved in 2 M KOH (40 mL) and the product was extracted in diethyl ether (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give **2.1t** (480 mg, 84%) as a light yellow oil. IR (neat, cm^{-1}): 3296 (w, br), 2964 (m), 2913 (m), 2854 (m), 1571 (m), 1456 (m), 1312 (m), 820 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.05 (m, 1H), 2.68 (m, 2H), 1.91 (m, 2H), 1.63 (m, 3H), 1.55 (m, 3H), 1.43 (m, 2H), 1.30-1.08 (m, 5H), 0.84 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.2, 124.9, 41.2, 40.2, 37.3, 30.2, 25.8, 25.6, 19.6, 17.7. HRMS (ESI$^+$) *m/z* [$C_{10}H_{22}N$]$^+$ cacld: 156.1747; found: 156.1750. Characterization matched reported data.[6]



tert-Butyl 4-amino-3-(4-chlorophenyl)butanoate (**2.1u**)

To a 50 mL round bottom flask were added baclofen (1.60 g, 7.5 mmol, 1.0 equiv.) and *t*BuOAc (20 mL). Perchloric acid (70% aq.) was added dropwise and the mixture was stirred at rt overnight. The reaction was quenched with water (20 mL), and layers were separated. The product was extracted in 1 M HCl (2×20 mL), and the combined aqueous layers were neutralized with solid K_2CO_3, before product extraction in diethyl ether (4×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give **2.1u** (329 mg, 16%) as a white solid. Mp: 35-36°C; IR (neat, cm^{-1}): 3261 (w, br), 2973 (w), 2925 (w), 2860 (w), 1715 (s), 1490 (m), 1133 (s), 866 (m), 823 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.27 (d, J = 8.4 Hz, 2H), 7.14 (d, J = 8.5 Hz, 2H), 3.07 (m, 1H), 2.90 (dd, J = 12.8, 5.5 Hz, 1H), 2.83 (dd, J = 12.7, 8.4 Hz, 1H), 2.60 (dd, J = 15.1, 6.7 Hz, 1H), 2.44 (dd, J = 15.1, 8.6 Hz, 1H), 1.31 (s, 9H), 1.06 (bs, 2H); ^{13}C NMR ($CDCl_3$, 500 MHz): δ 171.3, 140.7, 132.5, 129.3, 128.7, 80.6, 47.6, 45.4, 39.8, 28.0; HRMS (ESI$^+$) *m/z* [$C_{14}H_{21}NO_2Cl$]$^+$ cacld: 270.1255; found: 270.1252. Characterization matched reported data.[7]

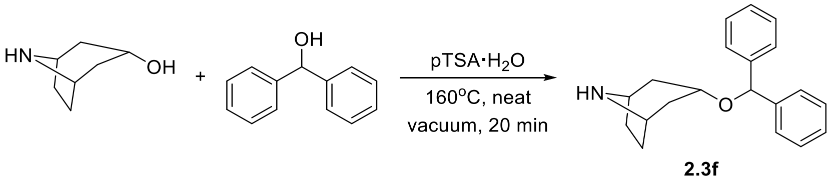


3-(4-Bromophenoxy)azetidine (**2.3a**)

To a 100 mL round bottom flask was added *N*-Boc-3-hydroxyazetidine (1.67 g, 9.6 mmol, 1.0 equiv.), anhydrous DCM (20 mL), and TEA (2.01 mL, 14.4 mmol, 1.5 equiv.). The mixture was cooled to 0°C and MsCl (0.89 mL, 11.5 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred at 0°C for 1.5 hours and diluted in DCM (40 mL), washed with water (1×40 mL) and brine (2×40 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to afford the mesylate intermediate. 4-Bromophenol (2.49 g, 14.4 mmol, 1.5 equiv.),

Cs_2CO_3 (6.26 g, 19.2 mmol, 2.0 equiv.), and anhydrous DMF (20 mL) were then added and the mixture was stirred at 90°C overnight. After cooling down to rt, the mixture was diluted in EA (100 mL), washed with water (2×50 mL), sat. Na_2CO_3 (2×50 mL), and brine (1×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) to afford **2.3aa** (1.83 g, 58% over two steps) as a white solid. $R_f = 0.58$ (Hex/acetone = 5:1); Mp: 102-103°C; IR (neat, cm^{-1}): 2979 (w), 2884 (w), 1685 (s), 1392 (s), 1239 (s), 1150 (s), 818 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 9.0 Hz, 2H), 4.79 (tt, J = 6.4, 4.1 Hz, 1H), 4.25 (ddd, J = 9.7, 6.4, 1.1 Hz, 2H), 3.94 (ddd, J = 9.6, 4.1, 1.1 Hz, 2H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.1, 155.7, 132.60, 116.4, 113.9, 79.9, 65.9, 56.3, 28.4; HRMS (ESI^+) *m/z* $[C_{14}H_{18}NO_3BrNa]^+$ cacld: 350.0362; found: 350.0370.

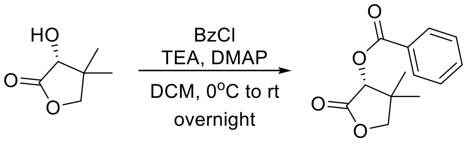
To a 50 mL round bottom flask were added **2.3aa** (1.83 g, 5.58 mmol, 1.0 equiv.), anhydrous DCM (5 mL), and TFA (5 mL). The mixture was stirred at rt for 2 hours and then the solvent was evaporated under vacuum. Sat. Na_2CO_3 (25 mL) was added and the product was extracted in DCM (3×25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give **2.3a** (912 mg, 72%) as a light yellow oil, which solidifies upon standing to afford an off-white solid. Mp: 43-45°C; IR (neat, cm^{-1}): 3284 (w, br), 2943 (w), 2860 (w), 1485 (s), 1233 (s), 823 (s), 795 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.29 (d, J = 9.0 Hz, 2H), 6.57 (d, J = 9.0 Hz, 2H), 4.87 (p, J = 6.0 Hz, 1H), 3.86 (m, 2H), 3.71 (m, 2H), 2.43 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.0, 132.4, 116.4, 113.3, 70.6, 54.5; HRMS (ESI^+) *m/z*: $[C_9H_{11}NOBr]^+$ cacld: 228.0019; found 228.0019.



Norbenztropine (**2.3f**)

To a 50 mL round bottom flask were added nortropine (636.0 mg, 5.0 mmol, 1.0 equiv.), benzhydrol (1.11 g, 6.0 mmol, 1.2 equiv.), and *p*TSA·H_2O (1.05 g, 5.5 mmol, 1.1 equiv.). The flask was connected to vacuum and put into an oil bath pre-heated to 160°C. The mixture was stirred for 20 minutes until water ceased to generate. The mixture was then cooled to rt and dissolved in 2 M

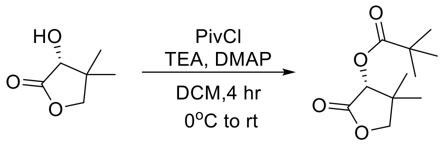
NaOH (50 mL). The aqueous solution was extracted with diethyl ether (3×30 mL). The combined organic layers were washed with water (2×30 mL) and brine (1×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified by flash chromatography (SiO_2, DCM/EA = 1:1, then DCM/MeOH/TEA = 100:2:1 to 100:20:1) to afford **2.3f** (1.24 g, 85%) as an orange oil. $R_f = 0.15$ (DCM/MeOH/TEA = 100:5:1); $[\alpha]_D^{23} = +2.7$ (c = 1.00, MeOH); IR (neat, cm^{-1}): 3222 (w, br), 2931 (w), 1493 (w), 1081 (m), 1056 (s), 738 (s), 694 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36 (m, 4H), 7.31 (t, J = 7.5 Hz, 4H), 7.23 (t, J = 7.4 Hz, 2H), 5.43 (s, 1H), 3.65 (t, J = 5.1 Hz, 1H), 3.49 (m, 2H), 2.27 (m, 2H), 2.00-1.91 (m, 2H), 1.88 (bs, 1H), 1.82 (m, 2H), 1.77-1.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 143.1, 128.3, 127.2, 126.9, 80.8, 69.9, 53.7, 37.3, 29.6; HRMS (ESI^+) *m/z* $[C_{20}H_{24}NO]^+$ cacld: 294.1852; found: 294.1852. Characterization matched reported data.[8]



2.5a

(R)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl benzoate (**2.5a**)

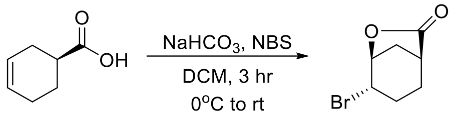
To a 50 mL round bottom flask were added D-pantolactone (650.7 mg, 5.0 mmol, 1.0 equiv.), DMAP (61.1 mg, 0.5 mmol, 0.1 equiv.), TEA (1.40 mL, 10.0 mmol, 2.0 equiv.), and anhydrous DCM (10 mL). The mixture was cooled to 0°C and BzCl (0.70 mL, 6.0 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at rt overnight. The mixture was next diluted in DCM (50 mL), washed with sat. $NaHCO_3$ (2×30 mL) and 1 M KH_2PO_4 (1×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified by flash chromatography (SiO_2, Hex/EA = 10:1 to 5:1) to afford **2.5a** (1.14 g, 97%) as a yellow oil, which solidifies upon standing. $R_f = 0.44$ (Hex/EA = 2:1); $[\alpha]_D^{23} = +22.0$ (c = 1.00, MeOH); Mp: 45-46°C; IR (neat, cm^{-1}): 2973 (w), 2878 (w), 1786 (s), 1724 (s), 1264 (s), 1116 (s), 701 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.07 (m, 2H), 7.57 (m, 1H), 7.43 (m, 2H), 5.60 (s, 1H), 4.07 (s, 2H), 1.23 (s, 3H), 1.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.4, 165.2, 133.7, 129.9, 128.7, 128.5, 76.2, 75.4, 40.4, 22.9, 19.9; HRMS (ESI^+) *m/z* $[C_{13}H_{14}O_4Na]^+$ cacld: 257.0784; found: 257.0777. Characterization matched reported data.[9]



2.5b

(*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl pivalate (**2.5b**)

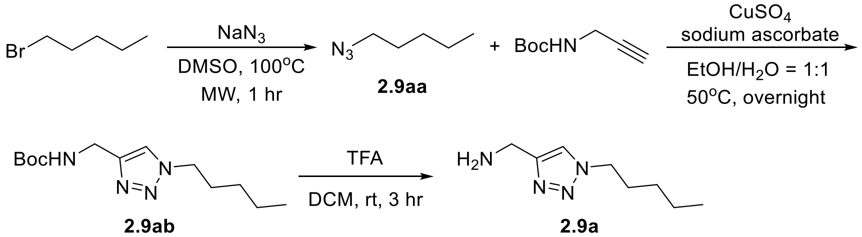
To a 50 mL round bottom flask were added D-pantolactone (650.7 mg, 5.0 mmol, 1.0 equiv.), DMAP (61.1 mg, 0.5 mmol, 0.1 equiv.), TEA (1.05 mL, 7.5 mmol, 1.5 equiv.), and anhydrous DCM (10 mL). The mixture was cooled to 0°C, and PivCl (0.74 mL, 6.0 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at rt for 4 hours. The mixture was next diluted in DCM (50 mL), washed with sat. $NaHCO_3$ (2×30 mL) and 1 M KH_2PO_4 (1×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The product was purified by flash chromatography (SiO_2, Hex/EA = 10:1 to 5:1) to afford **2.5b** (992 mg, 93%) as a colorless oil, which solidifies upon standing. R_f = 0.58 (Hex/EA = 2:1); $[\alpha]_D^{23} = -8.7$ (c = 1.00, MeOH); Mp: 45-46°C; IR (neat, cm^{-1}): 2973 (w), 2878 (w), 1774 (s), 1739 (s), 1136 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.32 (s, 1H), 4.04 (d, J = 9.0 Hz, 1H), 4.01 (d, J = 9.0 Hz, 1H), 1.27 (s, 9H), 1.18 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.4, 172.5, 76.2, 74.7, 40.3, 39.2, 27.2, 23.2, 20.0; HRMS (ESI$^+$) *m/z* $[C_{11}H_{18}O_4Na]^+$ cacld: 237.1097; found: 237.1088.



2.7g

(1*S*,4*S*,5*S*)-4-Bromo-6-oxabicyclo[3.2.1]octan-7-one (**2.7g**)

To a 50 mL round bottom flask were added (*S*)-cyclohex-3-ene-1-carboxylic acid (946.5 mg, 7.5 mmol, 1.0 equiv.), $NaHCO_3$ (661.9 mg, 7.88 mmol, 1.05 equiv.), and anhydrous DCM (5 mL). The mixture was cooled to 0°C before adding recrystallized NBS (1.40 g, 7.88 mmol, 1.05 equiv.) in one portion. The reaction mixture was stirred at rt for 2 hours. TLC monitoring indicated that the reaction was incomplete and additional NBS (267.0 mg, 1.5 mmol, 0.2 equiv.) was added. The mixture was stirred for an additional hour and the reaction was quenched with sat. $Na_2S_2O_3$ (5 mL). DCM (20 mL) was added and the organic layer was washed with sat. $Na_2S_2O_3$ (2×25 mL) and sat. NH_4Cl (1×25 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. Hot water (25 mL) was added to the residue before collection of the product by filtration and washing it with hot water. The solid obtained was treated again with hot water (25 mL), filtered, washed with hot water, and dried under vacuum to give the desired product **2.7g** (956 mg, 62%) as an off-white solid, which was used without further purification. $[\alpha]_D^{23}$ = −22.3 (c = 1.00, MeOH); Mp: 130-131°C; IR (neat, cm^{-1}): 2872 (w), 1782 (s), 1141 (s), 904 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.77 (m, 1H), 4.38 (m, 1H), 2.69-2.56 (m, 2H), 2.52-2.22 (m, 2H), 2.13 (m, 1H), 1.91 (m, 1H), 1.84 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.6, 79.1, 45.4, 38.3, 32.8, 28.3, 22.6; HRMS (APCI$^+$) *m/z* $[C_7H_{10}O_2Br]^+$ cacld: 204.9859; found: 204.9856. Characterization matched reported data.[10]

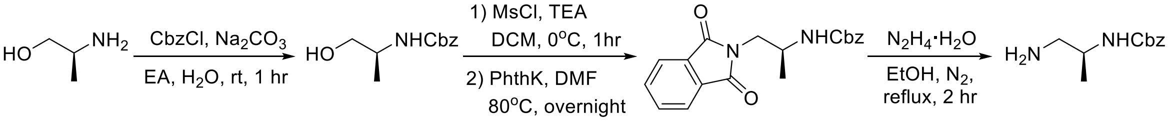


(1-Pentyl-1*H*-1,2,3-triazol-4-yl)methanamine (**2.9a**)

To a Biotage® 20 mL microwave vial were added 1-bromopentane (1.86 mL, 15 mmol, 1.0 equiv.), NaN_3 (1.95 g, 30 mmol, 2.0 equiv.), and DMSO (15 mL). The vial was sealed, and the mixture was subject to microwave irradiation for 1 hour at 100°C. After cooling down to rt, the mixture was diluted in water (40 mL) and the product was extracted in diethyl ether (3×25 mL). The combined organic layers were washed with water (3×25 mL), dried over anhydrous Na_2SO_4 and the solvent was carefully evaporated under vacuum (no heating water bath) to afford **2.9aa** (1.18 g, 69%) as a volatile yellow oil, which was directly used in the next step without purification.

To a 50 mL round bottom flask were added **2.9aa** (1.18 g, 10.4 mmol, 1.0 equiv.), *N*-Boc-propagylamine (1.61 g, 10.4 mmol, 1.0 equiv.), $CuSO_4$ (167.6 mg, 1.05 mmol, 0.1 equiv.), sodium ascorbate (2.06 g, 10.4 mmol, 1.0 equiv.), and EtOH/H_2O = 1:1 (20 mL). The mixture was stirred at 50°C overnight. The mixture was next cooled to rt, and EDTA (306.9 mg, 1.05 mmol, 0.1 equiv., dissolved in 5 mL sat. Na_2CO_3) was added. This mixture was stirred at rt for 10 minutes before extraction of the product in EA (3×30 mL). The combined organic layers were washed with 0.05 M EDTA·2Na (2×30 mL) and brine (1×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was eluted through a short silica pad (DCM/EA = 1:1). The filtrate was collected, and the solvent was evaporated under vacuum. The residue was left into a freezer for 2 hours before dilution in hexanes and collection of the product by filtration. The solid was washed with hexanes and dried under vacuum to afford **2.9ab** (2.40 g, 86%) as a white solid. This compound was previously reported.[11] It was used in the next step without further purification.

To a 50 mL round bottom flask were added **2.9ab** (2.40 g, 8.94 mmol, 1.0 equiv.), anhydrous DCM (5 mL), and TFA (5 mL). The mixture was stirred at rt for 3 hours. Upon completion, volatiles were evaporated under vacuum, and the residue was diluted in water (20 mL). The *p*H of this solution was adjusted to 14 with 4 M NaOH, and the product was extracted in DCM (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to give **2.9a** (1.46 g, 97%) as a light yellow solid. Mp: 37-39°C; IR (neat, cm^{-1}): 3353 (w, br), 2955 (m), 2857 (s), 1054 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37 (s, 1H), 4.24 (m, 2H), 3.90 (bs, 2H), 1.79 (m, 2H), 1.55 (bs, 2H), 1.33-1.15 (m, 4H), 0.81 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 149.4, 120.4, 50.2, 37.6, 29.9, 28.5, 22.0, 13.8; HRMS (ESI^+) *m/z* $[C_8H_{17}N_4]^+$ cacld: 169.1448; found: 169.1445.



2.9ba **2.9bb** **2.9b**

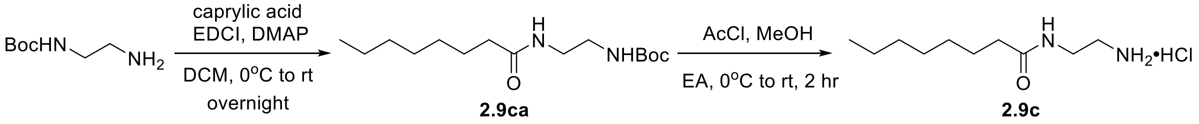
Benzyl (*S*)-(1-aminopropan-2-yl)carbamate (**2.9b**)

To a 100 mL round bottom flask were added L-alaninol (2.25 g, 30 mmol, 1.0 equiv.), EA (10 mL), H_2O (20 mL), and Na_2CO_3 (9.54 g, 90 mmol, 3.0 equiv.). Benzyl chloroformate (4.50 mL, 31.5 mmol, 1.05 equiv.) was then added dropwise and the mixture was stirred at rt for 1 hour. Water (70 mL) was added, and the product was extracted in EA (3×30 mL). The combined organic layers were washed with brine (1×30 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum. The residue was recrystallized (Hex/EA), collected by filtration, and washed with hexanes to give **2.9ba** (4.44g, 71%) as a white solid. This compound was previously reported.[12] It was used in the next step without further purification.

To a 50 mL round bottom flask were added **2.9ba** (2.09g, 10 mmol, 1.0 equiv.), TEA (2.10 mL, 15 mmol, 1.5 equiv.), and anhydrous DCM (20 mL). The mixture was cooled to 0°C, and MsCl (0.92

mL, 12 mmol, 1.2 equiv.) was added dropwise. The mixture was stirred at 0°C for 1 hour and diluted in DCM (20 mL). The mixture was washed with water (1×40 mL) and 1 M KH_2PO_4 (1×40 mL). The organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to afford the mesylate intermediate as a beige solid. To this solid were added potassium phthalimide (2.78g, 15 mmol, 1.5 equiv.) and anhydrous DMF (20 mL). The mixture was stirred at 80°C overnight. Upon completion, the mixture was diluted in EA (80 mL), washed with water (2×40 mL), sat. $NaHCO_3$ (2×40 mL), and brine (1×40 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was recrystallized (Hex/EA), collected by filtration, and washed with hexanes to give **2.9bb** (2.35 g, 69% over two steps) as a white solid. This compound was previously reported[12] and was used in the next step without further purification.

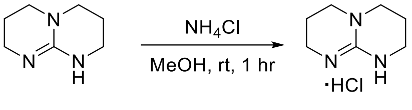
To a 250 mL round bottom flask were added **2.9bb** (2.35 g, 6.94 mmol, 1.0 equiv.), EtOH (70 mL), and $N_2H_4 \cdot H_2O$ (1.68 mL, 34.7 mmol, 5.0 equiv.). The system was purged with N_2 and the mixture was refluxed for 2 hours, before cooling to rt and filtration over Celite. The filtrate was evaporated under vacuum and the residue was dissolved in 2 M KOH (50 mL). The product was extracted in diethyl ether (4×25 mL), the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum to afford **2.9b** (1.00 g, 69%) as a light yellow oil. $[\alpha]_D^{23}$ = +11.4 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3308 (w, br), 2967 (w), 1694 (s), 1530 (m), 1248 (s), 695 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.27 (m, 5H), 5.09 (s, 2H), 4.98 (bs, 1H), 3.71 (m, 1H), 2.74 (dd, J = 13.1, 4.7 Hz, 1H), 2.64 (dd, J = 13.1, 6.5 Hz, 1H), 1.36 (bs, 2H), 1.12 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 156.3, 136.7, 128.6, 128.2, 127.0, 66.7, 49.3, 47.4, 18.6; HRMS (ESI)$^+$ m/z $[C_{11}H_{17}N_2O_2]^+$ cacld: 209.1285; found: 209.1288.



<u>*N*-(2-Aminoethyl)octanamide hydrochloride (**2.9c**)</u>

To a 100 mL round bottom flask were added *N*-Boc-ethylenediamine (1.60 g, 10 mmol, 1.0 equiv.), caprylic acid (1.74 mL, 11 mmol, 1.1 equiv.), DMAP (122.2 mg, 1 mmol, 0.1 equiv.), and anhydrous DCM (20 mL). The mixture was cooled to rt and EDCI (2.11 g, 11 mmol, 1.1 equiv.) was added in a few portions. The reaction mixture was warmed to rt and stirred overnight. The mixture was next diluted in DCM (40 mL), washed with sat. $NaHCO_3$ (2×50 mL), 1 M KH_2PO_4 (2×50 mL), and brine (1×50 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was dissolved in a mixture of hexanes and EA (Hex/EA = 100:1, 20 mL) and left in a freezer for 1 hour. The product was collected by filtration and washed with hexanes to afford **2.9ca** (2.62 g, 91%) as a white solid. This compound was previously reported.[13] It was used in the next step without further purification.

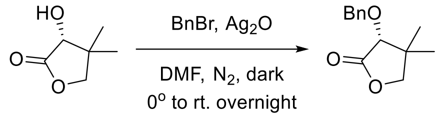
To a 100 mL round bottom flask were added **2.9ca** (2.62 g, 9.1 mmol, 1.0 equiv.), anhydrous EA (15 mL), and anhydrous MeOH (2.43 mL, 60 mmol). The mixture was cooled to 0°C and AcCl (4.28 mL, 60 mmol) was added dropwise. The mixture was stirred at rt for 2 hours. The product was collected by filtration and washed with EA to afford **2.9c** (2.09 g, quant.) as a very hygroscopic white solid. Mp: 111°C (decomp.); IR (neat, cm^{-1}): 3359 (w, br), 2922 (m), 2854 (m), 1665 (m), 1601 (m), 1521 (m); ^1H NMR (DMSO-d_6, 500 MHz): δ 8.74 (bs, 1H), 8.27 (bs, 3H), 3.24 (m, 2H), 2.76 (m, 2H), 2.00 (m, 2H), 1.38 (m, 2H), 1.14-1.11 (m, 8H), 0.74 (m, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 173.6, 39.0, 36.8, 35.8, 31.6, 29.1, 28.9, 25.5, 22.5, 14.3; HRMS (ESI$^-$) *m/z*: $[C_{10}H_{22}N_2OCl]^-$ cacld: 221.1426; found: 221.1425.



TBD·HCl

1,5,7-Triazabicyclo[4.4.0]dec-5-ene hydrochloride **(TBD·HCl)**

To a 25 mL round bottom flask were added TBD (278.2 mg, 2.0 mmol, 1.0 equiv.), NH_4Cl (117.7 mg, 2.2 mmol, 1.1 equiv.), and anhydrous MeOH (5 mL). The mixture was stirred at rt for 1 hr and the solvent was evaporated under vacuum. The residue was dissolved in DCM (10 mL) and solids were filtered off. The solvent was evaporated under vacuum to afford **TBD·HCl** (247 mg, 70%) as a white solid. Mp: 171-173°C; IR (neat, cm^{-1}): 3335 (m, br), 3195 (m, br), 2973 (w), 2875 (w), 1625 (s), 1316 (m), 1063 (m); ^1H NMR (DMSO-d_6, 500 MHz): δ 8.12 (s, 2H), 3.27 (t, J = 6.0 Hz, 4H), 3.18 (t, J = 6.0 Hz, 4H), 1.86 (p, J = 5.9 Hz, 4H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 150.9, 46.1, 37.4, 20.3; HRMS (ESI$^+$) *m/z* $[C_7H_{14}N_3]^+$ cacld: 140.1182; found: 140.1180. Characterization matched reported data.[14]



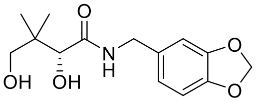
***O*-Bn D-pan**

(*R*)-3-(Benzyloxy)-4,4-dimethyldihydrofuran-2(3*H*)-one (***O*-Bn D-pan**)

To a 100 mL round bottom flask were added D-pantolactone (650.7 mg, 5 mmol, 1.0 equiv.), silver oxide (2.31 g, 10 mmol, 2.0 equiv.), and anhydrous DMF (20 mL). The round bottom flask was wrapped up in aluminum foil to protect the reaction from light. The mixture was cooled to 0ºC and the system was purged with N_2. Benzyl bromide (0.65 mL, 5.5 mmol, 1.1 equiv.) was added and the mixture was stirred at 0ºC for 2 hours, then stirred at rt overnight. DCM (50 mL) was then added and the mixture was filtered over Celite. The filter cake was washed with DCM. The filtrate was evaporated under vacuum and the residue was dissolved in EA (80 mL). The solution was washed with 0.5 M HCl (2×40 mL), water (2×30 mL), and brine (2×30 mL). The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) to afford ***O*-Bn D-pan** (701 mg, 64%) as a colorless oil, which solidifies upon standing. R_f = 0.34 (Hex/EA = 5:1); $[\alpha]_D^{23}$ = +85.7 (c = 1.00, MeOH); Mp: 42-44ºC; IR (neat, cm^{-1}): 2982 (w), 2961 (w), 2872 (w), 1764 (s), 1121 (s), 987 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39-7.35 (m, 4H), 7.32 (m, 1H), 5.04 (d, J = 12.1 Hz, 1H), 4.75 (d, J = 12.1 Hz, 1H), 3.99 (d, J = 8.8 Hz, 1H), 3.86 (d, J = 8.8 Hz, 1H), 3.74 (s, 1H), 1.13 (s, 3H), 1.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.4, 137.4, 128.5, 128.1, 128.0, 80.5, 76.4, 72.4, 40.4, 23.3, 19.4; HRMS (ESI$^+$) *m/z* $[C_{13}H_{16}O_3Na]^+$ cacld: 243.0992; found: 243.0988. Characterization matched reported data.[15]

7.2.2 Synthesis and Characterization of Reaction Products

Unless specified, amine (0.5 mmol, 1.0 equiv.), lactone (1.0 mmol, 2.0 equiv.), TBD (7.0 mg, 0.05 mmol, 0.1 equiv.), and toluene (0.5 mL) were added to reaction vial and sealed with a Teflon septum and an aluminum cap. The mixture was stirred at rt for 24 hours, and volatiles were evaporated under vacuum. The product was purified by flash chromatography. Note: If a reaction needs to be diluted, one cannot use ethyl acetate, or any ester-based solvent, as this will acylate the hydroxyl group in the final product.

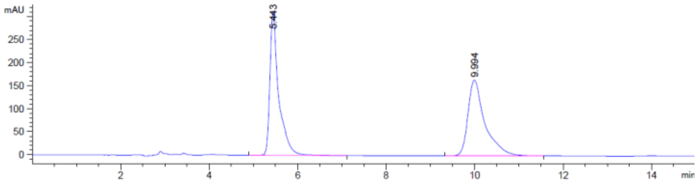


<u>(*R*)-*N*-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2a**)</u>

Piperonylamine (62 μL, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2a** (126 mg, 90%) as a yellow oil, which solidifies upon standing. R_f = 0.48 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +40.5 (c = 1.00, MeOH); Mp: 73-75°C; IR (neat, cm^{-1}): 3369 (m, br), 3333 (m, br), 2873 (w), 1623 (s), 1488 (s), 1246 (s), 1056 (s), 1036 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.22 (t, *J* = 6.1 Hz, 1H), 6.75-6.66 (m, 3H), 5.90 (s, 2H), 4.57 (m, 1H), 4.34 (dd, *J* = 14.6, 6.0 Hz, 1H), 4.28 (dd, *J* = 14.6, 6.0 Hz, 1H), 4.02 (d, *J* = 3.7 Hz, 1H), 3.95 (bs, 1H), 3.45 (s, 2H), 0.96 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.6, 148.1, 147.2, 131.9, 121.2, 108.51, 108.48, 101.3, 77.7, 71.4, 43.1, 39.6, 21.4, 20.5; HRMS (ESI^+) *m/z* $[C_{14}H_{19}NO_5Na]^+$ cacld: 304.1155; found 304.1165.

Chiral HPLC analysis indicated no racemization. HPLC (Lux Cellulose-1, isopropanol/hexanes = 25/75, flow rate = 1.0 mL/min, l = 214 nm) t_R = 5.44 min (*R*), t_S = 9.99 min (*S*).

Chromatogram of racemic standard:



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Signal 2: DAD1 C, Sig=214,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   5.443 BB    0.2009 4361.10645  312.31918  49.8991
   2   9.994 BB    0.3888 4378.74023  164.36884  50.1009

Totals :                  8739.84668  476.68802
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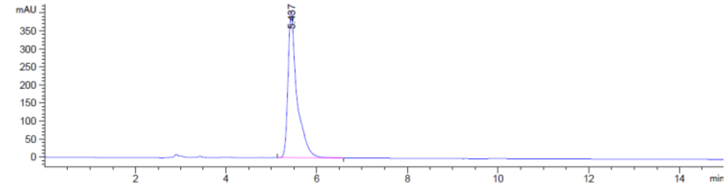
Chromatogram of **2.2a**



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Signal 2: DAD1 C, Sig=214,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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Totals :                  5616.76660  405.66763
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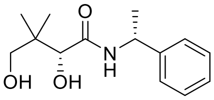
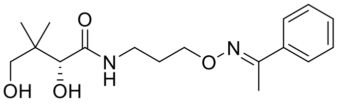


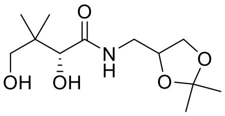
<u>(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-((*R*)-1-phenylethyl)butanamide (**2.2b**)</u>

(*R*)-1-Phenylethan-1-amine (64 μL, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2b** (98 mg, 78%) as a colorless oil. $R_f = 0.54$ (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +124.5 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3373 (w, br), 3281 (w, br), 2980 (w), 1623 (s), 1573 (s), 1032 (s), 1012 (s), 700 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34-7.24 (m, 5H), 7.10 (bs, 1H), 5.11 (m, 1H), 4.00-3.89 (m, 2H), 3.65-3.34 (m, 3H), 1.49 (d, J = 7.0 Hz, 3H), 1.00 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.3, 142.9, 128.9, 127.6, 126.3, 77.6, 71.5, 48.7, 39.6, 22.1, 21.6, 20.1; HRMS (ESI^+) *m/z* $[C_{14}H_{21}NO_3Na]^+$ cacld: 274.1414; found: 274.1417.



(*R*,*E*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(3-(((1-phenylethylidene)amino)oxy)propyl)butanamide (**2.2c**)

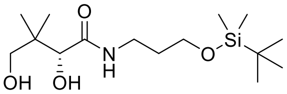
(*E*)-1-Phenylethan-1-one *O*-(3-aminopropyl) oxime (96.2 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2c** (151 mg, 94%) as a light yellow oil. $R_f = 0.60$ (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +16.7 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3341 (m, br), 2932 (m), 2873 (w), 1645 (s), 1528 (s), 1044 (s), 759 (s), 691 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.62 (m, 2H), 7.39-7.31 (m, 3H), 7.18 (bs, 1H), 4.50 (bs, 1H), 4.25 (t, J = 6.0 Hz, 2H), 4.04 (bs, 1H), 3.98 (d, J = 4.1 Hz, 1H), 3.61-3.24 (m, 4H), 2.23 (s, 3H), 1.93 (p, J = 6.1 Hz, 2H), 0.96 (s, 3H), 0.88 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 155.2, 136.6, 129.2, 128.5, 126.1, 77.5, 72.0, 71.3, 39.4, 36.7, 29.2, 21.4, 20.3, 13.8; HRMS (ESI^+) *m/z* $[C_{17}H_{26}N_2O_4Na]^+$ cacld: 345.1785; found: 345.1791.



(2*R*)-*N*-((2,2-Dimethyl-1,3-dioxolan-4-yl)methyl)-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2d**)

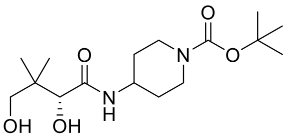
(2,2-Dimethyl-1,3-dioxolan-4-yl)methanamine (65.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2d** (97 mg, 74%, dr = 1:1) as a light yellow oil. $R_f = 0.51$ (DCM/MeOH = 10:1); IR (neat, cm^{-1}): 3361 (m, br), 2984 (w), 2936 (w), 2876 (w), 1647 (s), 1528 (s), 1072 (s), 1042 (s);

^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.16 (bs, 1H), 4.34-4.20 (m, 2H), 4.05-4.01 (m, 2H), 3.65-3.61 (m, 2H), 3.49-3.39 (m, 4H), 1.43 (s, 3H), 1.32 (s, 3H), 1.00 (m, 3H), 0.92 (m, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ (173.9, 173.8), 109.6, (77.8, 77.6), (74.5, 74.4), (71.32, 71.26), (66.74, 66.66), (41.05, 41.03), (39.42, 39.40), (26.74, 26.72), 25.1, (21.5, 21.3), (20.6, 20.4); HRMS (ESI$^+$) *m/z* [$C_{12}H_{23}NO_5Na$]$^+$ cacld: 284.1468; found: 284.1469.



(*R*)-*N*-(3-((*tert*-Butyldimethylsilyl)oxy)propyl)-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2e**)

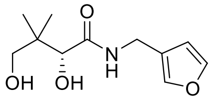
3-((*tert*-Butyldimethylsilyl)oxy)propan-1-amine (68.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2e** (144 mg, 90%) as a colorless oil. R$_f$ = 0.47 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +39.3 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3349 (m, br), 2956 (m), 2928 (m), 2857 (m), 1645 (m), 1530 (m), 1254 (m), 1094 (s), 832 (s), 774 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.23 (t, J = 5.8 Hz, 1H), 4.46 (bs, 1H), 4.09 (bs, 1H), 3.95 (d, J = 4.7 Hz, 1H), 3.68 (t, J = 5.8 Hz, 2H), 3.45 (s, 2H), 3.42-3.19 (m, 2H), 1.71 (p, J = 6.2 Hz, 2H), 0.96 (s, 3H), 0.88 (s, 3H), 0.87 (s, 9H), 0.04 (s, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.5, 77.7, 71.4, 61.8, 39.4, 37.2, 32.0, 26.1, 21.4, 20.4, 18.4, -5.3; HRMS (ESI$^+$) *m/z* [$C_{15}H_{33}NO_4SiNa$]$^+$ cacld: 342.2071; found: 342.2061.



tert-Butyl (*R*)-4-(2,4-dihydroxy-3,3-dimethylbutanamido)piperidine-1-carboxylate (**2.2f**)

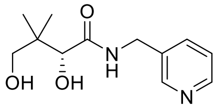
tert-Butyl 4-aminopiperidine-1-carboxylate (100.2 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2f** (126 mg, 76%) as a sticky white solid. R$_f$ = 0.46 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +24.2 (c = 1.00, MeOH); Mp: 152-154°C; IR (neat, cm^{-1}): 3384 (w, br), 3329 (m, br), 2968 (w), 2928 (w), 2869 (w), 1688 (s), 1643 (s), 1526 (s), 1425 (s), 1145 (s), 1082 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.84 (bs, 1H), 4.44 (bs, 1H), 3.98-3.74 (m, 5H), 3.47 (m, 2H), 2.87 (m, 2H), 1.85 (m, 2H), 1.43

(s, 9H), 1.34 (m, 2H), 0.98 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 172.7, 154.9, 80.0, 71.5, 46.4, 42.6, 39.4, 32.1, 31.8, 28.5, 21.4, 20.2; HRMS (ESI$^+$) *m/z*: [$C_{16}H_{30}N_2O_5Na$]$^+$ Cacld: 353.2047; found: 353.2038.



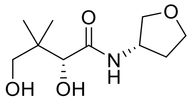
(*R*)-*N*-(Furan-3-ylmethyl)-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2g**)

3-Aminomethylfuran (44 μL, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2g** (108 mg, 95%) as a yellow oil. R$_f$ = 0.45 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +43.7 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3329 (m, br), 2964 (w), 2876 (w), 1647 (s), 1526 (s), 1072 (s), 1042 (s), 735 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.32 (m, 1H), 7.25 (bs, 1H), 6.29 (m, 1H), 6.21 (m, 1H), 4.55 (bs, 1H), 4.43 (m, 2H), 4.03 (s, 1H), 3.88 (bs, 1H), 3.45 (s, 2H), 0.96 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.5, 151.1, 142.4, 110.5, 107.6, 77.5, 71.3, 39.4, 36.1, 21.1, 20.4; HRMS (ESI$^+$) *m/z* [$C_{11}H_{17}NO_4Na$]$^+$ cacld: 250.1050; found: 250.1055.



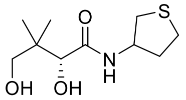
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(pyridin-3-ylmethyl)butanamide (**2.2h**)

3-Picolylamine (51 μL, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 15:1 to 10:1) gave the desired product **2.2h** (115 mg, 86%) as a light yellow oil, which solidifies upon standing to an off-white solid. R$_f$ = 0.27 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +39.3 (c = 1.00, MeOH); Mp: 102-103°C; IR (neat, cm^{-1}): 3329 (m), 3099 (w, br), 2857 (w), 2817 (w), 1651 (s), 1528 (m), 1084 (s), 1032 (s), 711 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.45-8.41 (m, 2H), 7.66-7.63 (m, 2H), 7.26 (bs, 1H), 4.45 (m, 2H), 4.09 (m, 1H), 3.48 (m, 2H), 0.99 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 174.1, 148.6, 148.3, 136.2, 134.5, 123.9, 77.7, 71.2, 40.5, 39.4, 21.3, 20.7; HRMS (ESI$^+$) *m/z* [$C_{12}H_{19}N_2O_3$]$^+$ cacld: 239.1390; found: 239.1386.



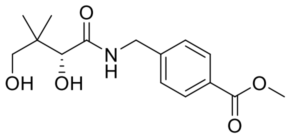
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-((*S*)-tetrahydrofuran-3-yl)butanamide (**2.2i**)

(*S*)-Tetrahydrofuran-3-amine (43.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 15:1) gave the desired product **2.2i** (88 mg, 81%) as a white solid. R_f = 0.40 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +24.4 (c = 1.00, MeOH); Mp: 111-112°C; IR (neat, cm^{-1}): 3480 (m), 3301 (m), 2976 (w), 2920 (w), 2888 (w), 2571 (w), 1637 (s), 1542 (m), 1060 (s), 1042 (s); ^1H NMR (D_2O, 500 MHz): δ 4.45 (m, 1H), 3.99 (s, 1H), 3.96 (dt, *J* = 8.5, 7.3 Hz, 1H), 3.92 (dd, *J* = 9.5, 5.8 Hz, 1H), 3.87 (td, *J* = 8.5, 5.6 Hz, 1H), 3.72 (dd, *J* = 9.4, 3.4 Hz, 1H), 3.52 (d, *J* = 11.2 Hz, 1H), 3.41 (d, *J* = 11.3 Hz, 1H), 2.29 (ddt, *J* = 13.1, 8.4, 7.4 Hz, 1H), 1.95 (dddd, *J* = 13.1, 7.5, 5.5, 3.5 Hz, 1H), 0.94 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (D_2O, 125 MHz): δ 174.9, 75.7, 72.3, 68.3, 66.9, 50.0, 38.7, 31.5, 20.6, 19.1; HRMS (ESI^+) *m/z* $[C_{10}H_{19}NO_4Na]^+$ cacld: 240.1206; found 240.1203.



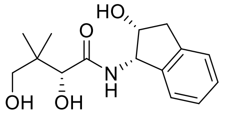
(2*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(tetrahydrothiophen-3-yl)butanamide (**2.2j**)

Tetrahydrothiophen-3-amine (51.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2j** (105 mg, 90%, dr = 1:1) as an off-white solid. R_f = 0.55 (DCM/MeOH = 10:1); Mp: 77-79°C; IR (neat, cm^{-1}): 3500 (w, br), 3376 (m, br), 3309 (m, br), 2964 (m), 2932 (w), 2873 (w), 1633 (s), 1518 (s), 1052 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.09 (bs, 1H), 4.65 (m, 1H), 4.41 (bs, 1H), 3.99 (s, 1H), 3.78 (bs, 1H), 3.47 (s, 2H), 3.06 (m, 1H), 2.91 (m, 1H), 2.86 (m, 1H), 2.70 (m, 1H), 2.12-1.98 (m, 2H), 0.98 (m, 3H), 0.90 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 77.6, 71.4, 53.3, (39.43, 39.39), (37.1, 36.9), (35.9, 35.6), 28.4, (21.3, 21.2), (20.4, 20.3); HRMS (ESI^+) *m/z* $[C_{10}H_{19}NO_3SNa]^+$ cacld: 256.0978; found: 256.0975.



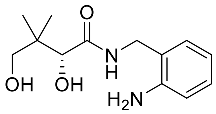
Methyl (*R*)-4-((2,4-dihydroxy-3,3-dimethylbutanamido)methyl)benzoate (**2.2k**)

Methyl 4-(aminomethyl)benzoate (82.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2k** (95 mg, 64%) as a sticky colorless oil. R$_f$ = 0.26 (DCM/MeOH = 20:1); $[\alpha]_D^{23}$ = +32.2 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3349 (m, br), 2956 (w), 2876 (w), 1716 (s), 1647 (s), 1276 (s), 1107 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): *δ* 7.97 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 7.31 (bs, 1H), 4.53 (dd, *J* = 15.2, 6.1 Hz, 1H), 4.46 (dd, *J* = 15.3, 6.0 Hz, 1H), 4.09 (s, 1H), 3.89 (s, 3H), 3.48 (m, 2H), 1.00 (s, 3H), 0.91 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 173.4, 167.0, 143.4, 130.1, 129.4, 127.6, 77.9, 71.5, 52.3, 42.8, 39.5, 21.4, 20.4; HRMS (ESI$^+$) *m/z* [C$_{15}$H$_{21}$NO$_5$Na]$^+$ cacld: 318.1312; found: 318.1304.



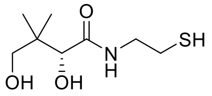
(*R*)-2,4-Dihydroxy-*N*-((1*S*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)-3,3-dimethylbutanamide (**2.2l**)

(1*S*,2*R*)-(-)-*cis*-1-Amino-2-indanol (74.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Upon reaction completion, DCM (2 mL) was added and the product was collected by filtration. The filter cake was washed with DCM and diethyl ether to give the desired product **2.2l** (112 mg, 80%) as a white solid. R$_f$ = 0.49 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +75.6 (c = 1.00, MeOH); Mp: 156-157°C; IR (neat, cm^{-1}): 3464 (m, br), 3404 (m, br), 1621 (s), 1534 (s), 1068 (s), 1032 (s), 729 (s); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): *δ* 7.62 (d, *J* = 8.6 Hz, 1H), 7.24-7.17 (m, 4H), 5.54 (bs, 1H), 5.22 (bs, 1H), 5.18 (dd, *J* = 8.6, 5.1 Hz, 1H), 4.58 (bs, 1H), 4.41 (s, 1H), 3.91 (s, 1H), 3.34 (d, *J* = 10.3 Hz, 1H), 3.29 (d, *J* = 10.4 Hz, 1H), 3.07 (dd, *J* = 16.3, 4.9 Hz, 1H), 2.81 (d, *J* = 16.3 Hz, 1H), 0.89 (s, 6H); ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): *δ* 173.0, 142.4, 140.6, 127.3, 126.3, 125.0, 124.1, 75.1, 72.1, 68.0, 56.1, 39.2, 21.1, 20.7; HRMS (ESI$^+$) *m/z* [C$_{15}$H$_{21}$NO$_4$Na]$^+$ cacld: 302.1363; found: 302.1372.



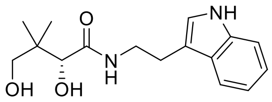
(*R*)-*N*-(2-Aminobenzyl)-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2m**)

2-Aminobenzylamine (61.1 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2m** (125 mg, 98%) as a sticky light brown oil. R$_f$ = 0.56 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +42.0 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3412 (m, br), 3345 (m, br), 3285 (m, br), 2960 (w), 1635 (s), 1536 (s), 1080 (s), 1038 (s), 759 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.23 (bs, 1H), 7.09 (td, *J* = 7.6, 1.7 Hz, 1H), 7.04 (dd, *J* = 7.6, 1.8 Hz, 1H), 6.68 (td, *J* = 7.6, 1.2 Hz, 1H), 6.63 (dd, *J* = 7.7, 1.2 Hz, 1H), 4.52 (bs, 2H), 4.35 (dd, *J* = 14.6, 6.4 Hz, 1H), 4.30 (dd, *J* = 14.6, 6.3 Hz, 1H), 4.16 (bs, 2H), 4.00 (s, 1H), 3.41 (s, 2H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.9, 145.2, 130.7, 129.3, 121.9, 118.3, 116.1, 77.2, 70.9, 40.3, 39.4, 21.2, 20.6; HRMS (ESI$^+$) *m/z* [C$_{13}$H$_{20}$N$_2$O$_3$Na]$^+$ cacld: 275.1366; found: 275.1378.



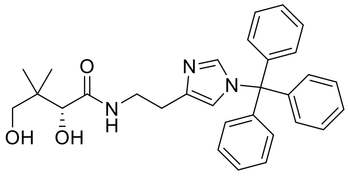
(*R*)-2,4-Dihydroxy-*N*-(2-mercaptoethyl)-3,3-dimethylbutanamide (**2.2n**)

Cysteamine (38.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 15:1) gave the desired product **2.2n** (60 mg, 58%) as a light yellow oil. R$_f$ = 0.45 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +56.2 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3329 (m, br), 2961 (w), 2931 (w), 2875 (w), 1641 (s), 1527 (s), 1073 (m), 1038 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.29 (t, *J* = 6.9 Hz, 1H), 4.04 (s, 1H), 3.78 (bs, 2H), 3.53-3.40 (m, 4H), 2.67 (dt, *J* = 8.5, 6.5 Hz, 2H), 1.43 (t, *J* = 8.4 Hz, 1H), 1.00 (s, 3H), 0.92 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.7, 77.6, 71.3, 42.1, 39.4, 24.6, 21.3, 20.5; HRMS (ESI$^+$) *m/z* [C$_8$H$_{17}$NO$_3$SNa]$^+$ cacld: 230.0821; found: 230.0824.



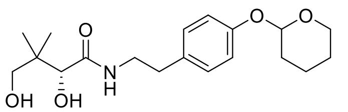
(*R*)-*N*-(2-(1*H*-Indol-3-yl)ethyl)-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2o**)

Tryptamine (80.1 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2o** (140 mg, 97%) as a yellow semi-solid. R_f = 0.49 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +38.1 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3329 (m, br), 2960 (w), 2928 (w), 2873 (w), 1635 (s), 1530 (s), 1034 (s), 737 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.48 (bs, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.32 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.99 (bs, 1H), 6.94 (s, 1H), 4.38 (bs, 1H), 3.97 (bs, 1H), 3.93 (d, *J* = 5.0, 1H), 3.57 (m, 2H), 3.41 (s, 2H), 2.93 (m, 2H), 0.92 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 136.5, 127.3, 122.4, 122.2, 119.4, 118.7, 112.5, 111.5, 77.4, 71.1, 39.4, 39.3, 25.3, 21.4, 20.3; HRMS (ESI^+) *m/z* $[C_{16}H_{22}N_2O_3Na]^+$ cacld: 313.1523; found: 313.1514.



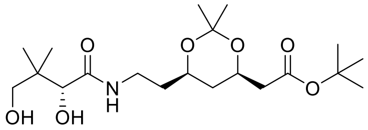
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)butanamide (**2.2p**)

2-(1-Trityl-1*H*-imidazol-4-yl)-ethylamine (176.7 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1 to 10:1) gave the desired product **2.2p** (235 mg, 97%) as a white solid. R_f = 0.40 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +14.7 (c = 1.00, MeOH); Mp: 55-57°C; IR (neat, cm^{-1}): 3317 (w, br), 2960 (w), 2869 (w), 1645 (m), 1442 (m), 1036 (m), 745 (s), 700 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37-7.32 (m, 11H), 7.11-7.09 (m, 6H), 6.61 (s, 1H), 5.91 (bs, 1H), 4.94 (bs, 1H), 3.94 (s, 1H), 3.65 (m, 1H), 3.55 (d, *J* = 11.1 Hz, 1H), 3.41 (d, *J* = 11.1 Hz, 1H), 3.37 (m, 1H), 2.69 (m, 2H), 1.04 (s, 3H), 0.99 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 142.2, 139.0, 138.7, 129.8, 128.31, 128.26, 119.1, 78.6, 75.6, 70.0, 39.4, 39.2, 28.3, 22.7, 21.4; HRMS (ESI^+) *m/z*: $[C_{30}H_{34}N_3O_3]^+$ cacld: 484.2595; found: 484.2588.



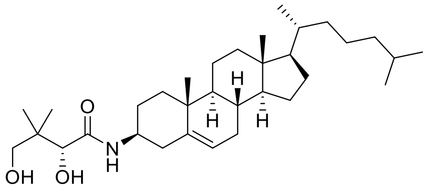
(2*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-(4-((tetrahydro-2*H*-pyran-2-yl)oxy)phenethyl)butanamide (**2.2q**)

2-(4-((Tetrahydro-2*H*-pyran-2-yl)oxy)phenyl)ethan-1-amine (110.7 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2q** (154 mg, 88%, dr = 1:1) as a sticky white solid. R_f = 0.60 (DCM/MeOH = 10:1); Mp: 88-90°C; IR (neat, cm^{-1}): 3373 (m, br), 2940 (m), 2869 (w), 1629 (s), 1617 (s), 1508 (s), 1234 (s), 1034 (s), 959 (s), 919 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.09 (d, J = 8.5 Hz, 2H), 6.96 (d, J = 8.6 Hz, 2H), 6.92 (bs, 1H), 5.35 (t, J = 4.2 Hz, 1H), 4.34 (bs, 1H), 3.94 (s, 1H), 3.89 (m, 1H), 3.79 (bs, 1H), 3.59-3.50 (m, 2H), 3.44 (m, 1H), 3.40 (s, 2H), 2.75 (m, 2H), 1.96 (m, 1H), 1.87-1.79 (m, 2H), 1.70-1.55 (m, 3H), 0.94 (s, 3H), 0.84 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, (155.80, 155.79), (131.79, 131.78), 129.7, (116.83, 116.80), (96.69, 96.67), 77.6, 71.3, 62.3, 40.4, 39.3, 34.9, 30.5, 25.3, 21.5, 20.2, 19.0; HRMS (ESI$^+$) *m/z* $[C_{19}H_{29}NO_5Na]^+$ cacld: 374.1938; found: 374.1948.



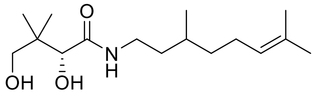
tert-Butyl 2-((4*R*,6*R*)-6-(2-((*R*)-2,4-dihydroxy-3,3-dimethylbutanamido)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**2.2r**)

tert-Butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (136.7 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2r** (184 mg, 91%) as a light yellow oil. R_f = 0.50 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +20.4 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3369 (m, br), 2980 (m), 2940 (m), 2873 (w), 1726 (m), 1647 (m), 1532 (m), 1151 (s), 1046 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.37 (bs, 1H), 4.44-4.21 (m, 2H), 3.95-3.81 (m, 3H), 3.51-3.44 (m, 3H), 3.21 (m, 1H), 2.38 (m, 1H), 2.26 (m, 1H), 1.69 (m, 1H), 1.59 (m, 1H), 1.51 (m, 1H), 1.41 (m, 12H), 1.34 (s, 3H), 1.20 (m, 1H), 0.96 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 170.4, 98.9, 80.9, 77.8, 71.4, 68.5, 66.2, 42.7, 39.3, 36.5, 36.2, 35.2, 30.1, 28.2, 21.4, 20.4, 19.8; HRMS (ESI$^+$) *m/z* $[C_{20}H_{37}NO_7Na]^+$ cacld: 426.2462; found: 426.2457.



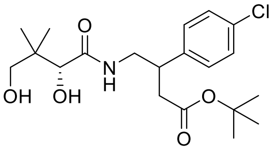
(*R*)-*N*-Cholesteryl-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2s**)

Cholesterylamine (192.8 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 10:1, then DCM/MeOH = 20:1) gave the desired product **2.2s** (168 mg, 65%) as an off-white solid. R_f = 0.50 (DCM/MeOH = 10:1); $[\alpha]_D^{23} = -2.5$ (c = 1.00, $CHCl_3$); Mp: 215ºC (decomp.); IR (neat, cm^{-1}): 3277 (w, br), 2928 (s), 2869 (s), 1617 (s), 1536 (s), 1050 (s); ^1H NMR ($CDCl_3$, 500 MHz): *δ* 6.70 (d, *J* = 8.3 Hz, 1H), 5.37 (m, 1H), 4.13 (d, *J* = 4.1 Hz, 1H), 3.97 (d, *J* = 4.1 Hz, 1H), 3.69 (m, 1H), 3.63 (bs, 1H), 3.50 (m, 2H), 2.27 (m, 1H), 2.13 (m, 1H), 2.02-1.95 (m, 2H), 1.87-1.80 (m, 3H), 1.58-0.90 (m, 33H), 0.87 (d, *J* = 2.3 Hz, 3H), 0.85 (d, *J* = 2.3 Hz, 3H), 0.67 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 172.6, 140.2, 122.4, 77.5, 71.5, 57.0, 56.5, 50.4, 49.7, 42.6, 40.0, 39.8, 39.6, 39.5, 38.1, 36.8, 36.4, 36.1, 32.08, 32.06, 29.2, 28.5, 28.3, 24.5, 24.1, 23.1, 22.8, 21.8, 21.2, 20.3, 19.6, 19.0, 12.1; HRMS (ESI$^+$) *m/z* $[C_{33}H_{57}NO_3Na]^+$ cacld: 538.4231; found: 538.4228.



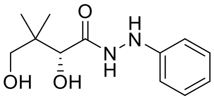
(2*R*)-*N*-(3,7-Dimethyloct-6-en-1-yl)-2,4-dihydroxy-3,3-dimethylbutanamide (**2.2t**)

3,7-Dimethyloct-6-en-1-amine (77.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 15:1) gave the desired product **2.2t** (105 mg, 74%, dr = 1:1) as a colorless oil. R_f = 0.58 (DCM/MeOH = 10:1); IR (neat, cm^{-1}): 3307 (m, br), 2960 (m), 2916 (m), 2873 (m), 1643 (s), 1532 (s), 1072 (s), 1044 (s); ^1H NMR ($CDCl_3$, 500 MHz): *δ* 6.80 (bs, 1H), 5.07 (m, 1H), 4.11 (bs, 1H), 4.00 (m, 1H), 3.71 (bs, 1H), 3.50 (m, 2H), 3.28 (m, 2H), 1.95 (m, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.49 (m, 2H), 1.32 (m, 2H), 1.16 (m, 1H), 1.00 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* (173.2, 173.1), 131.6, 124.6, (77.69, 77.67), 71.5, 39.5, 37.3, (37.1, 37.0), 36.7, 30.4, 25.8, 25.5, (21.59, 21.57), (20.2, 20.1), (19.44, 19.38), 17.8; HRMS (ESI$^+$) *m/z* [$C_{16}H_{32}NO_3$]$^+$ cacld: $C_{16}H_{32}NO_3$ 286.2377; found: 286.2372.



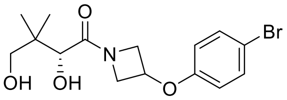
<u>*tert*-Butyl 3-(4-chlorophenyl)-4-((*R*)-2,4-dihydroxy-3,3-dimethylbutanamido)butanoate (**2.2u**)</u>

tert-Butyl 4-amino-3-(4-chlorophenyl)butanoate (134.9 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.2u** (186 mg, 93%, dr = 1:1) as a white solid. R_f = 0.48 (DCM/MeOH = 10:1); Mp: 108-110°C; IR (neat, cm^{-1}): 3391 (m, br), 3293 (m, br), 2982 (w), 2872 (w), 1712 (s), 1616 (s), 1144 (s), 1054 (s), 826 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (7.26, 7.25) (d, J = 8.5 Hz, 2H), (7.14, 7.13) (d, J = 8.4 Hz, 2H), (6.90, 6.89) (d, J = 6.1 Hz, 1H), (4.29, 4.26) (d, J = 4.9 Hz, 1H), 3.92 (t, J = 5.0 Hz, 1H), 3.71 (m, 1H), 3.61-3.22 (m, 5H), (2.59, 2.56) (dd, J = 6.2, 1.6 Hz, 1H), (2.48, 2.45) (dd, J = 8.9, 4.7 Hz, 1H), (1.29, 1.28) (s, 9H), (0.90, 0.84) (s, 3H), (0.81, 0.74) (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (173.5, 173.4), (171.1, 171.0), (139.66, 139.64), 133.0, (129.23, 129.21), (128.89, 128.86), 81.2, (77.6, 77.5), (71.27, 71.25), (44.0, 43.6), (41.87, 41.85), (39.91, 39.88), (39.3, 39.2), (28.01, 27.99), (21.3, 21.2), (20.3, 20.1); HRMS (ESI$^+$) *m/z* [$C_{20}H_{30}NO_5ClNa$]$^+$ cacld: 422.1705; found: 422.1708.



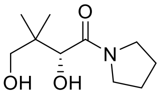
<u>(*R*)-2,4-Dihydroxy-3,3-dimethyl-N'-phenylbutanehydrazide (**2.2v**)</u>

Phenylhydrazine (54.1 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 15:1) gave the desired product **2.2v** (37 mg, 30%) as a yellow oil, which solidifies upon standing. R_f = 0.45 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +32.0 (c = 1.00, MeOH); Mp: 116-117°C; IR (neat, cm^{-1}): 3297 (m, br), 2964 (w), 1659 (s), 1601 (s), 1496 (s), 1038 (s), 691 (s); ^{1}H NMR (CD_3OD, 500 MHz): δ 7.17 (dd, J = 8.7, 7.3 Hz, 2H), 6.85 (m, 2H), 6.80 (tt, J = 7.3, 1.1 Hz, 1H), 4.05 (s, 1H), 3.53 (d, J = 10.9 Hz, 1H), 3.44 (d, J = 10.8 Hz, 1H), 1.01 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (CD_3OD, 125 MHz): δ 175.7, 150.0, 129.9, 121.1, 114.4, 77.1, 70.2, 40.6, 21.6, 20.8; HRMS (ESI$^+$) *m/z* $[C_{12}H_{18}N_2O_3Na]^+$ cacld: 261.1210; found: 261.1204.



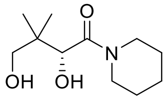
(*R*)-1-(3-(4-Bromophenoxy)azetidin-1-yl)-2,4-dihydroxy-3,3-dimethylbutan-1-one (**2.4a**)

3-(4-Bromophenoxy)azetidine (114.0, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (DCM/EA = 4:1, then DCM/MeOH = 15:1) gave the desired product **2.4a** (153 mg, 85%, cis/trans = 1:1) as a white solid. R_f = 0.38 (DCM/MeOH = 10:1); Mp: 123-124ºC; IR (neat, cm^{-1}): 3421 (w, br), 2952 (w), 2875 (w), 1616 (s), 1487 (m), 1239 (s), 826 (s), 808 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (7.39, 7.38) (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.9 Hz, 2H), 4.92 (m, 1H), (4.64, 4.63) (d, J = 10.1, 1H), (4.50, 4.36) (dd, J = 11.1, 6.5 Hz, 1H), (4.29, 4.28) (d, J = 10.1, Hz, 1H), (4.14, 4.05) (dd, J = 11.5, 4.0 Hz, 1H), (4.03, 4.02) (s, 1H), 3.59-3.46 (m, 3H), 3.01 (bs, 1H), 0.97 (s, 3H), (0.94, 0.93) (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (174.0, 173.5), (155.5, 155.4), (132.84, 132.82), (116.49, 116.46), (114.41, 114.39), (74.1, 74.0), 70.0, (66.2, 66.1), (58.8, 58.5), (55.7, 55.6), (40.11, 40.09), (22.0, 21.9), (20.1, 20.0); HRMS (ESI$^+$) *m/z* $[C_{15}H_{20}NO_4BrNa]^+$ cacld: 380.0468; found: 380.0456.



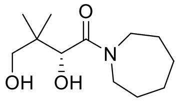
(*R*)-2,4-Dihydroxy-3,3-dimethyl-1-(pyrrolidin-1-yl)butan-1-one (**2.4b**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.4b** (93 mg, 92%) as an off-white solid. For the catalyst immobilization reaction, A pre-wash of the commercially available immobilized TBD was introduced to estimate transfer loss. Reaction scale was adjusted to recovered immobilized catalyst. General procedure for reaction with immobilized TBD: Pyrrolidine (1.0 equiv.), D-pantolactone (2.0 equiv.), and immobilized TBD (10 mol%) were reacted at rt for 24 hours. The catalyst was then filtered off using a Whatman grade 5 filter paper, washed with DCM, and dried under vacuum for 2 hours. The filtrate was concentrated and the mixture was purified by flash chromatography to afford the desired product. R_f = 0.43 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = -47.5 (c = 1.00, MeOH); Mp: 88-90°C; IR (neat, cm^{-1}): 3384 (m, br), 2972 (w), 2869 (w), 1607 (s), 1454 (s), 1327 (m), 1050 (s), 713 (w); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 4.16 (d, *J* = 9.2 Hz, 1H), 3.61-3.54 (m, 3H), 3.51-3.35 (m, 4H), 3.31 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.98-1.80 (m, 4H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 172.9, 74.8, 69.3, 47.5, 46.4, 40.4, 26.2, 24.1, 22.9, 20.1; HRMS (ESI$^+$) *m/z* [$C_{10}H_{19}NO_3Na$]$^+$ cacld: 224.1257; found: 224.1250.



(*R*)-2,4-Dihydroxy-3,3-dimethyl-1-(piperidin-1-yl)butan-1-one (**2.4c**)

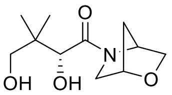
Piperidine (50 µL, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.4c** (61 mg, 57%) as a white solid. R_f = 0.58 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = -67.7 (c = 1.00, MeOH); Mp: 65-67°C; IR (neat, cm^{-1}): 3388 (w, br), 2940 (w), 2851 (w), 1619 (s), 1254 (m), 1041 (s), 1016 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 4.44 (s, 1H), 3.77 (m, 1H), 3.63 (bs, 1H), 3.56-3.49 (m, 2H), 3.44-3.36 (m, 3H), 3.04 (bs, 1H), 1.68-1.51 (m, 6H), 0.93 (s, 3H), 0.88 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 172.7, 71.5, 69.6, 47.6, 43.9, 40.5, 26.3, 25.6, 24.5, 22.6, 19.8; HRMS (ESI$^+$) *m/z* [$C_{11}H_{22}NO_3$]$^+$ cacld: 216.1594; found: 216.1598.



(*R*)-1-(Azepan-1-yl)-2,4-dihydroxy-3,3-dimethylbutan-1-one (**2.4d**)

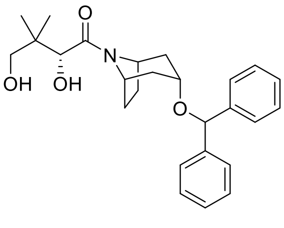
Azepane (49.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.4d** (110 mg, 96%) as a light yellow solid. R_f = 0.55 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = -76.2 (c = 1.00, MeOH); Mp: 63-64°C; IR (neat, cm^{-1}): 3454 (w, br), 3222 (w, br), 2922 (w), 2869 (w), 1614 (s), 1073 (m), 1047 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 4.35 (s, 1H), 3.91 (ddd, *J* = 13.7, 6.4, 4.8 Hz, 1H), 3.75 (ddd, *J* = 14.4, 5.5, 5.4 Hz, 1H), 3.53 (d, *J* = 11.3 Hz, 1H), 3.38 (d, *J* = 11.3 Hz, 1H), 3.33 (bs, 2H), 3.26 (ddd, *J*

= 14.5, 8.5, 5.0 Hz, 1H), 3.13 (ddd, *J* = 13.7, 8.9, 4.1 Hz, 1H), 1.85-1.46 (m, 8H), 0.94 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 174.2, 72.4, 69.3, 48.6, 47.0, 40.4, 29.3, 27.3, 27.0, 26.4, 22.9, 20.1; HRMS (ESI$^+$) *m/z*: [$C_{12}H_{23}NO_3Na$]$^+$ cacld: 252.1570; found: 252.1570.



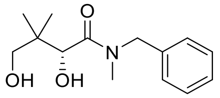
(*R*)-1-((1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptan-5-yl)-2,4-dihydroxy-3,3-dimethylbutan-1-one (**2.4e**)

(1*S*,4*S*)-2-Oxa-5-azabicyclo[2.2.1]heptane (49.6 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.4e** (88 mg, 77%, amide rotamer major:minor = 1.9:1) as an off-white solid. R$_f$ = 0.36 (DCM/MeOH = 10:1); Mp: 119-121°C; IR (neat, cm^{-1}): 3436 (w, br), 3344 (w, br), 2961 (w), 2872 (w), 1599 (s), 1051 (m), 1039 (m), 850 (m); major isomer: ^{1}H NMR (CDCl$_3$, 500 MHz): *δ* 4.86 (m, 1H), 4.62 (m, 1H), 4.05 (s, 1H), 3.88 (t, *J* = 7.2 Hz, 1H), 3.79 (dd, *J* = 7.8, 1.6 Hz, 1H), 3.64-3.33 (m, 6H), 1.90 (m, 1H), 1.79 (m, 1H), 0.93 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 172.6, 76.0, 74.5, 74.0, 69.4, 56.7, 56.3, 40.3, 35.8, 22.4, 19.9; minor isomer: ^{1}H NMR (CDCl$_3$, 500 MHz): *δ* 4.84 (m, 1H), 4.63 (m, 1H), 4.28 (s, 1H), 3.88 (t, *J* = 7.2 Hz, 1H), 3.81 (dd, *J* = 7.8, 1.8 Hz, 1H), 3.64-3.33 (m, 6H), 1.93 (m, 1H), 1.79 (m, 1H), 0.95 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 171.5, 75.4, 75.3, 73.6, 69.6, 59.2, 54.5, 40.1, 37.4, 22.1, 20.7; HRMS (ESI$^+$) *m/z* [$C_{11}H_{20}NO_4$]$^+$ cacld: 230.1387; found: 230.1385.



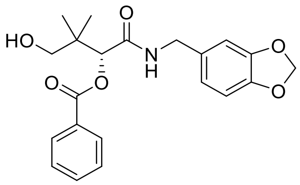
(*R*)-1-((1*R*,3*R*,5*S*)-3-(Benzhydryloxy)-8-azabicyclo[3.2.1]octan-8-yl)-2,4-dihydroxy-3,3-dimethylbutan-1-one (**2.4f**)

Norbenztropine (146.7 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 15:1) gave the desired product **2.4f** (60 mg, 28%, amide rotamer major:minor = 4:1) as a beige solid. $R_f = 0.48$ (DCM/MeOH = 10:1); IR (neat, cm^{-1}): 3373 (m, br), 2944 (w), 2876 (w), 1615 (s), 1454 (m), 1056 (s), 703 (s); Mp: 135-137°C; major isomer: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.29 (m, 8H), 7.25-7.22 (m, 2H), 5.43 (s, 1H), 4.61 (m, 1H), 4.25 (m, 1H), 4.19 (d, J = 8.7 Hz, 1H), 3.72 (m, 1H), 3.59-3.38 (m, 3H), 3.00 (bs, 1H), 2.40-2.34 (m, 2H), 2.09-1.88 (m, 6H), 0.94 (s, 3H), 0.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.5, 142.6, 142.6, 128.6, 128.5, 127.6, 127.5, 126.9, 126.8, 81.5, 73.7, 69.8, 69.6, 55.2, 52.2, 40.0, 38.0, 35.3, 28.3, 27.4, 22.3, 19.7; minor isomer: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.29 (m, 8H), 7.25-7.22 (m, 2H), 5.44 (s, 1H), 4.86 (m, 1H), 4.36 (m, 1H), 4.17 (d, J = 8.5 Hz, 1H), 3.72 (m, 1H), 3.59-3.38 (m, 3H), 3.35 (bs, 1H), 2.32-2.26 (m, 2H), 1.97-1.77 (m, 6H), 0.96 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.1, 142.6, 142.6, 128.6, 128.5, 127.6, 127.5, 126.9, 126.8, 81.4, 74.1, 69.4, 69.3, 54.6, 51.1, 39.7, 36.9, 36.0, 29.3, 26.3, 23.1, 20.7; HRMS (ESI^+) *m/z* $[C_{26}H_{33}NO_4Na]^+$ cacld: 446.2302; found: 446.2312.

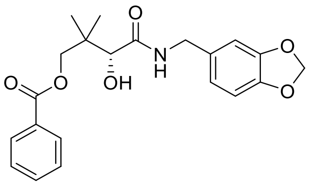


(*R*)-*N*-Benzyl-2,4-dihydroxy-*N*,3,3-trimethylbutanamide (**2.4g**)

N-Benzyl methylamine (65 μL, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.4g** (37 mg, 30%, amide rotamer major:minor = 2.3:1) as an off-white solid. $R_f = 0.53$ (DCM/MeOH = 10:1); Mp: 78-79°C; IR (neat, cm^{-1}): 3349 (m, br), 3297 (m, br), 2964 (w), 2920 (w), 2869 (w), 1621 (s), 1076 (s), 1046 (s), 701 (s); major isomer: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.16 (m, 5H), 4.77 (d, J = 14.0 Hz, 1H), 4.51-4.47 (m, 2H), 3.63 (bs, 1H), 3.52-3.45 (m, 2H), 3.10 (bs, 1H), 2.97 (s, 3H), 0.96 (s, 3H), 0.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.6, 136.4, 129.1, 128.9, 128.4, 72.2, 69.6, 51.8, 40.8, 35.5, 22.7, 20.0; minor isomer: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.36-7.16 (m, 5H), 5.00 (d, J = 16.2 Hz, 1H), 4.53 (d, J = 8.7 Hz, 1H), 4.21 (d, J = 16.2 Hz, 1H), 3.63 (bs, 1H), 3.52-3.45 (m, 2H), 3.10 (bs, 1H), 2.91 (s, 3H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.8, 135.7, 128.1, 127.9, 126.9, 72.3, 69.5, 53.8, 40.6, 34.1, 22.6, 20.2; HRMS (ESI^+) *m/z* $[C_{14}H_{21}NO_3Na]^+$ cacld: 274.1414; found: 274.1418.



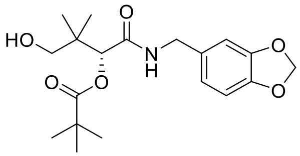
2.6aa



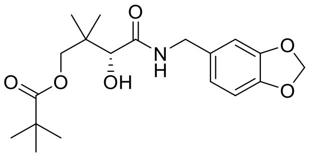
2.6ab

(*R*)-1-((Benzo[*d*][1,3]dioxol-5-ylmethyl)amino)-4-hydroxy-3,3-dimethyl-1-oxobutan-2-yl benzoate (**2.6aa**) and (*R*)-4-((Benzo[*d*][1,3]dioxol-5-ylmethyl)amino)-3-hydroxy-2,2-dimethyl-4-oxobutyl benzoate (**2.6ab**)

Piperonylamine (62 μL, 0.5 mmol, 1.0 equiv.) and (*R*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl benzoate (234.3 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, Hex/EA = 4:1 to 1:1) gave a mixture of **2.6aa** and **2.6ab** (142 mg, 74%, **2.6aa**:**2.6ab** = 1:7.3) as a sticky yellow oil. R_f = 0.30 (Hex/EA = 1:1); IR (neat, cm^{-1}): 3369 (w, br), 2964 (w), 2876 (w), 1714 (m), 1649 (m), 1270 (s), 1248 (s), 1036 (s), 709 (s); **2.6aa**: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.05 (m, 2H), 7.60 (m, 1H), 7.46 (m, 2H), 7.02 (t, J = 5.9 Hz, 1H), 6.74-6.65 (m, 3H), 6.53 (t, J = 5.7 Hz, 1H), 5.91 (s, 2H), 4.39 (d, J = 5.9 Hz, 1H), 4.32 (d, J = 5.8 Hz, 1H), 4.03-3.92 (m, 1H), 3.60 (d, J = 11.6 Hz, 1H), 3.46 (d, J = 11.7 Hz, 1H), 1.08 (s, 3H), 1.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.6, 165.6, 148.0, 147.2, 133.8, 131.4, 129.9, 129.2, 128.8, 121.1, 108.4, 108.4, 101.2, 78.8, 69.6, 43.3, 39.8, 22.7, 20.6; **2.6ab**: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.01 (m, 2H), 7.55 (m, 1H), 7.42 (m, 2H), 7.02 (t, J = 5.9 Hz, 1H), 6.74-6.65 (m, 3H), 5.91 (s, 2H), 4.43 (d, J = 11.0 Hz, 1H), 4.29 (d, J = 5.9 Hz, 2H), 4.03-3.92 (m, 3H), 1.17 (s, 3H), 1.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.9, 167.3, 148.0, 147.0, 133.4, 132.0, 129.9, 129.8, 128.6, 121.2, 108.5, 108.4, 101.1, 74.9, 71.0, 43.0, 39.3, 21.9, 19.8; HRMS (ESI^+) *m/z* $[C_{21}H_{23}NO_6Na]^+$ cacld: 408.1415; found: 408.1416.



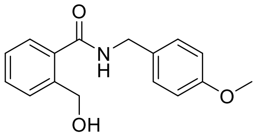
2.6ba



2.6bb

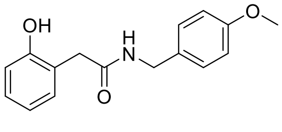
(*R*)-1-((Benzo[*d*][1,3]dioxol-5-ylmethyl)amino)-4-hydroxy-3,3-dimethyl-1-oxobutan-2-yl pivalate (**2.6ba**) and (*R*)-4-((Benzo[*d*][1,3]dioxol-5-ylmethyl)amino)-3-hydroxy-2,2-dimethyl-4-oxobutyl pivalate (**2.6bb**)

Piperonylamine (62 μL, 0.5 mmol, 1.0 equiv.) and (*R*)-4,4-dimethyl-2-oxotetrahydrofuran-3-yl pivalate (214.3 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, Hex/EA = 4:1 to 1:1) gave a mixture of **2.6ba** and **2.6bb** (177 mg, 97%, **2.6ba**:**2.6bb** = 1.25:1) as a sticky yellow oil. R_f = 0.30 (Hex/EA = 1:1); IR (neat, cm^{-1}): 3365 (m, br), 2968 (w), 1726 (s), 1653 (s), 1250 (s), 1155 (s), 1038 (s); **2.6ba**: ^1H NMR ($CDCl_3$, 500 MHz): δ 6.76-6.75 (m, 3H), 6.26 (m, 1H), 5.93 (s, 2H), 5.04 (s, 1H), 4.41 (dd, *J* = 14.6, 6.2 Hz, 1H), 4.28 (dd, *J* = 14.7, 5.3 Hz, 1H), 3.52 (d, *J* = 11.5 Hz, 1H), 3.37 (d, *J* = 11.6 Hz, 1H), 3.31 (bs, 1H), 1.21 (s, 9H), 1.00 (s, 3H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.2, 169.7, 148.1, 147.3, 131.4, 121.2, 108.5, 108.4, 101.3, 78.0, 69.5, 43.4, 39.6, 39.1, 27.2, 22.6, 20.5; **2.6bb**: ^1H NMR ($CDCl_3$, 500 MHz): δ 6.98 (m, 1H), 6.73-6.66 (m, 3H), 5.92 (s, 2H), 4.37-4.31 (m, 2H), 4.24 (d, *J* = 11.1 Hz, 1H), 3.81-3.82 (m, 2H), 3.71 (d, *J* = 11.1 Hz, 1H), 1.20 (s, 9H), 1.09 (s, 3H), 0.92 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.6, 171.6, 148.0, 147.1, 132.1, 121.3, 108.5, 108.4, 101.2, 74.9, 70.8, 43.1, 39.3, 39.2, 27.3, 21.5, 19.7; HRMS (ESI^+) *m/z*: $[C_{19}H_{27}NO_6Na]^+$ cacld: 388.1731; found: 388.1729.



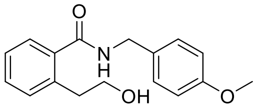
2-(Hydroxymethyl)-*N*-(4-methoxybenzyl)benzamide (**2.8a**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.), phthalide (134.1 mg, 1.0 mmol, 2.0 equiv.), and TBD (21.0 mg, 0.15 mmol, 0.3 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 2:1) gave the desired product **2.8a** (116 mg, 86%) as an off-white solid. R_f = 0.50 (DCM/EA = 1:1); Mp: 120-122°C; IR (neat, cm^{-1}): 3345 (w, br), 3285 (m), 2936 (w), 1623 (s), 1514 (s), 1248 (s), 1024 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.52 (dd, *J* = 7.6, 1.0 Hz, 1H), 7.43 (td, *J* = 7.5, 1.3 Hz, 1H), 7.37 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.33 (td, *J* = 7.5, 1.4 Hz, 1H), 7.28 (d, *J* = 8.7 Hz, 2H), 6.89 (d, *J* = 8.7 Hz, 2H), 6.67 (bs, 1H), 4.60 (d, *J* = 6.7 Hz, 2H), 4.56 (d, *J* = 5.7 Hz, 2H), 4.44 (t, *J* = 6.8 Hz, 1H), 3.80 (s, 3H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 169.9, 159.3, 140.4, 135.6, 131.4, 131.0, 130.0, 129.3, 128.3, 127.6, 114.4, 64.9, 55.5, 43.9; HRMS (ESI^+) *m/z* $[C_{16}H_{18}NO_3]^+$ cacld: 272.1281; found: 272.1279.



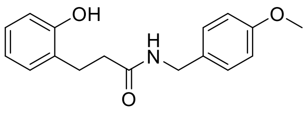
2-(2-Hydroxyphenyl)-*N*-(4-methoxybenzyl)acetamide (**2.8b**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.) and 2-coumaranone (80.5 mg, 0.6 mmol, 1.2 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 50:1 to 10:1) gave the desired product **2.8b** (129 mg, 95%) as an off-white solid. R_f = 0.63 (DCM/EA = 5:1); Mp: 108-110ºC; IR (neat, cm^{-1}): 3313 (m), 3194 (w, br), 2829 (w), 1619 (s), 1512 (s), 1244 (s), 749 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.77 (bs, 1H), 7.18-7.13 (m, 3H), 7.00 (m, 1H), 6.94 (m, 1H), 6.83-6.81 (m, 3H), 6.54 (bs, 1H), 4.31 (d, *J* = 5.6 Hz, 2H), 3.77 (s, 3H), 3.56 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 159.3, 156.1, 130.7, 129.32, 129.26, 121.6, 120.5, 117.93, 117.90, 114.3, 55.4, 43.7, 40.9; HRMS (ESI^+) *m/z* $[C_{16}H_{17}NO_3Na]^+$ cacld: 294.1101; found: 294.1105.



2-(2-Hydroxyethyl)-*N*-(4-methoxybenzyl)benzamide (**2.8c**)

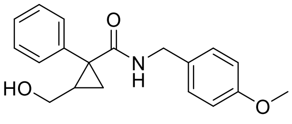
4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.), 1-isochromanone (148.2 mg, 1.0 mmol, 2.0 equiv.), and TBD (21.0 mg, 0.15 mmol, 0.3 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 2:1) gave the desired product **2.8c** (54 mg, 38%) as a yellow oil. R_f = 0.37 (DCM/EA = 1:1); IR (neat, cm^{-1}): 3261 (m, br), 3063 (w), 2928 (w), 1629 (s), 1510 (s), 1244 (s), 1030 (s), 751 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41 (dd, *J* = 7.6, 1.5 Hz, 1H), 7.39 (td, *J* = 7.6, 1.4 Hz, 1H), 7.28-7.26 (m, 3H), 7.23 (td, *J* = 7.5, 1.3 Hz, 1H), 6.88 (d, *J* = 8.6 Hz, 2H), 6.72 (bs, 1H), 4.53 (d, *J* = 5.7 Hz, 2H), 4.05 (bs, 1H), 3.89 (m, 2H), 3.80 (s, 3H), 2.96 (t, *J* = 5.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 159.3, 138.6, 136.5, 130.84, 130.80, 130.1, 129.4, 127.2, 126.6, 114.3, 64.0, 55.4, 43.8, 36.1; HRMS (ESI^+) *m/z* $[C_{17}H_{19}NO_3Na]^+$ cacld: 308.1257; found: 308.1269.



3-(2-Hydroxyphenyl)-*N*-(4-methoxybenzyl)propenamide (**2.8d**)

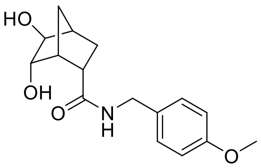
4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.) and 2-chromanone (88.9 mg, 0.6 mmol, 1.2 equiv.) were reacted following the general procedure. Purification by flash chromatography

(SiO_2, DCM/EA = 20:1 to 4:1) gave the desired product **2.8d** (140 mg, 98%) as an off-white solid. R_f = 0.63 (DCM/EA = 2:1); Mp: 106-107°C; IR (neat, cm^{-1}): 3269 (m, br), 2932 (w), 1619 (s), 1607 (s), 1567 (s), 1244 (s), 1032 (m), 816 (s), 768 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.80 (s, 1H), 7.12 (td, J = 7.6, 1.8 Hz, 1H), 7.08 (d, J = 8.6 Hz, 2H), 7.04 (dd, J = 7.5, 1.7 Hz, 1H), 6.90 (m, 1H), 6.83 (td, J = 7.5, 1.7 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 5.90 (bs, 1H), 4.31 (d, J = 5.6 Hz, 2H), 3.78 (s, 3H), 2.92 (m, 2H), 2.60 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.1, 159.2, 155.1, 130.7, 129.7, 129.3, 128.2, 128.0, 120.5, 118.0, 114.2, 55.4, 43.6, 37.2, 24.9; HRMS (ESI$^+$) *m/z* $[C_{17}H_{19}NO_3Na]^+$ cacld: 308.1257; found: 308.1251.



2-(Hydroxymethyl)-*N*-(4-methoxybenzyl)-1-phenylcyclopropane-1-carboxamide (**2.8e**)

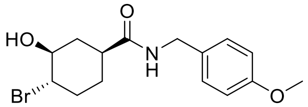
4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.), 1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (174.2 mg, 1.0 mmol, 2.0 equiv.), and TBD (21.0 mg, 0.15 mmol, 0.3 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 1:1) gave the desired product **2.8e** (154 mg, 98%) as an orange solid. R_f = 0.40 (DCM/EA = 1:1); Mp: 100-101°C; IR (neat, cm^{-1}): 3416 (m), 2865 (w), 1649 (s), 1508 (s), 1244 (m), 1030 (m), 709 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.39 (m, 2H), 7.34 (m, 2H), 7.28 (m, 1H), 7.06 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.85 (bs, 1H), 4.34 (dd, J = 14.9, 5.9 Hz, 1H), 4.28 (dd, J = 14.8, 5.8 Hz, 1H), 4.10 (m, 1H), 3.80 (s, 1H), 3.77 (s, 3H), 3.21 (bs, 1H), 1.81 (m, 1H), 1.73 (dd, J = 6.9, 4.6 Hz, 1H), 1.32 (dd, J = 9.2, 4.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 159.0, 140.6, 130.3, 130.1, 129.2, 128.7, 128.0, 114.2, 61.2, 55.4, 43.5, 36.0, 30.7, 17.9; HRMS (ESI$^+$) *m/z* $[C_{19}H_{21}NO_3Na]^+$ cacld: 334.1414; found: 334.1410.



(±)-5,6-Dihydroxy-*N*-(4-methoxybenzyl)bicyclo[2.2.1]heptane-2-carboxamide (**2.8f**)

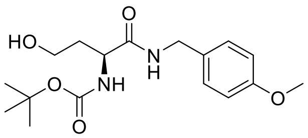
4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.), 5-hydroxynorbornane-2,6-lactone (154.2 mg, 1.0 mmol, 2.0 equiv.), and TBD (21.0 mg, 0.15 mmol, 0.3 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/MeOH = 50:1

to 20:1) gave the desired product **2.8f** (100 mg, 69%) as a yellow solid. $R_f = 0.31$ (DCM/MeOH = 10:1); Mp: 137-138°C; IR (neat, cm^{-1}): 3361 (w, br), 3269 (m, br), 2958 (w), 2928 (w), 1639 (s), 1561 (s), 1250 (s), 1044 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.48 (t, $J = 5.9$ Hz, 1H), 7.18 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.6$ Hz, 2H), 5.24 (d, $J = 8.7$ Hz, 1H), 4.77 (d, $J = 3.9$ Hz, 1H), 4.21 (m, 2H), 3.72 (s, 3H), 3.63 (s, 1H), 3.22 (s, 1H), 2.66 (m, 1H), 2.42 (m, 1H), 1.98 (d, $J = 5.4$ Hz, 1H), 1.80 (td, $J = 12.1$, 5.5 Hz, 1H), 1.67 (d, $J = 9.6$ Hz, 1H), 1.40 (ddd, $J = 12.2$, 6.4, 2.2 Hz, 1H), 1.17 (dd, $J = 9.8$, 2.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 175.8, 158.2, 131.2, 128.6, 113.7, 83.5, 81.2, 55.1, 44.6, 44.2, 43.7, 41.9, 35.7, 29.0; HRMS (ESI$^+$) *m/z* $[C_{16}H_{21}NO_4Na]^+$ cacld: 314.1363; found: 314.1354.



(1*S*,3*S*,4*S*)-4-Bromo-3-hydroxy-*N*-(4-methoxybenzyl)cyclohexane-1-carboxamide (**2.8g**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.) and (1*S*,4*S*,5*S*)-4-bromo-6-oxabicyclo[3.2.1]octan-7-one (205.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Upon completion, DCM (2 mL) was added, and the product was collected by filtration. The filter cake was washed with DCM and diethyl ether to give the desired product **2.8g** (93 mg, 54%) as a white solid. $R_f = 0.35$ (DCM/EA = 1:1); $[\alpha]_D^{23} = +12.5$ (c = 1.00, MeOH); Mp: 165-167°C; IR (neat, cm^{-1}): 3309 (w), 3183 (w, br), 1631 (s), 1532 (m), 1254 (m), 828 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.22 (t, $J = 5.9$ Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 2H), 6.87 (d, $J = 8.7$ Hz, 2H), 5.24 (d, $J = 6.0$ Hz, 1H), 4.16 (d, $J = 5.8$ Hz, 2H), 3.86 (ddd, $J = 12.2$, 9.6, 4.5 Hz, 1H), 3.72 (s, 3H), 3.43 (m, 1H), 2.33 (tt, $J = 12.3$, 3.6 Hz, 1H), 2.27 (dq, $J = 13.2$, 3.6 Hz, 1H), 1.98 (m, 1H), 1.77 (qd, $J = 13.3$, 4.0 Hz, 1H), 1.65 (m, 1H), 1.48-1.35 (m, 2H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 173.3, 158.1, 131.6, 128.3, 113.7, 73.2, 60.2, 55.0, 42.0, 41.3, 38.5, 35.5, 29.5; HRMS (ESI$^+$) *m/z* $[C_{15}H_{20}NO_3BrNa]^+$ cacld: 364.0519; found: 364.0515.

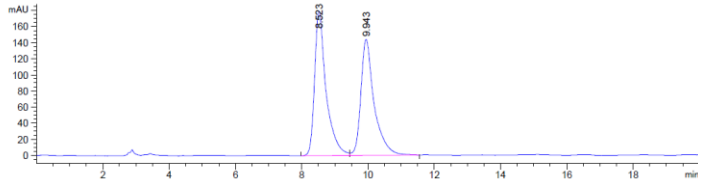


tert-Butyl (*S*)-(4-hydroxy-1-((4-methoxybenzyl)amino)-1-oxobutan-2-yl)carbamate (**2.8h**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.) and *N*-Boc homoserine lactone (201.2 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/MeOH = 50:1 to 20:1) gave the desired product **2.8h** (148 mg, 87%, er = 91:9) as a colorless semi-solid, which solidifies upon standing to a white solid. R_f = 0.45 (DCM/MeOH = 10:1); $[\alpha]_D^{23} = -20.8$ (c = 1.00, MeOH); Mp: 83-85°C; IR (neat, cm^{-1}): 3373 (m), 3234 (w, br), 3224 (w, br), 2972 (w), 1692 (s), 1666 (s), 1510 (s), 1252 (s), 1163 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.15 (d, J = 8.4 Hz, 2H), 7.05 (bs, 1H), 6.82 (d, J = 8.5 Hz, 2H), 5.68 (bs, 1H), 4.36-4.26 (m, 3H), 3.76 (s, 3H), 3.66-3.61 (m, 3H), 1.98 (m, 1H), 1.72 (bs, 1H), 1.40 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.0, 159.1, 156.7, 130.1, 129.1, 114.1, 80.4, 58.6, 55.4, 51.6, 43.1, 36.5, 28.4; HRMS (ESI$^+$) *m/z* $[C_{17}H_{27}N_2O_5]^+$ cacld: 339.1914; found: 339.1909.

Chiral HPLC analysis indicated that a slight racemization had occurred. HPLC (Lux Cellulose-1, isopropanol/hexanes = 10/90, flow rate = 1.0 mL/min, l = 214 nm) t_R = 8.53 min (minor, *R*); t_S = 9.91 min (major, *S*).

Chromatogram of racemic standard:



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Signal 2: DAD1 C, Sig=214,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|--------|
   1   8.523 BV    0.3504 4305.44434  179.15810  51.7955
   2   9.943 VB    0.4029 4006.95337  143.90527  48.2045
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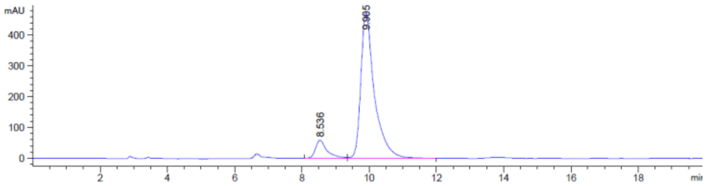
Chromatogram of **2.8h**



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Signal 2: DAD1 C, Sig=214,4 Ref=360,100

Peak RetTime Type  Width     Area      Height     Area
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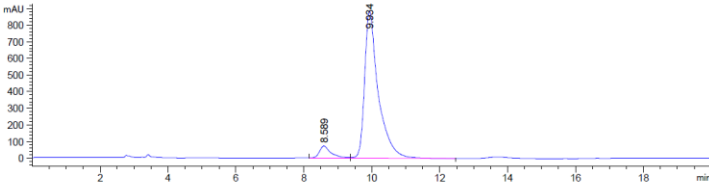
----|-------|----|-------|----------|----------|--------|
   1   8.536 BV    0.3417 1370.08154   58.40961   9.4185
   2   9.905 VB    0.4046 1.31766e4   473.62708  90.5815
```

Chiral HPLC analysis at the 4-hour reaction time point is shown below (the reaction was worked up and purified after 4 hours of reaction). A similar er value (93:7) on this 4-hour reaction product suggests that racemization likely happened during the reaction (lactone activation), and not on the amide product.

Chromatogram of **2.8h** (4-hour reaction time point)



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Signal 2: DAD1 C, Sig=214,4 Ref=360,100

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   2   9.934 VB    0.4026 2.45838e4   883.67944  93.4686
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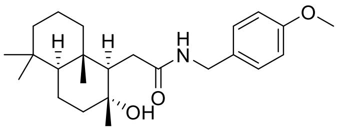
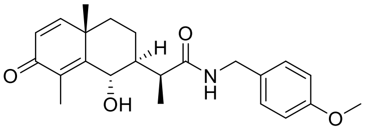


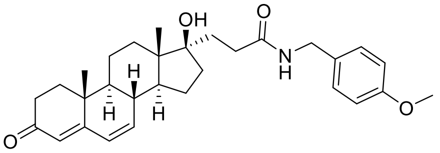
2-((1*R*,2*R*,4a*S*,8a*S*)-2-Hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)-*N*-(4-methoxybenzyl)acetamide (**2.8i**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.) and sclareolide (250.4 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 1:1) gave the desired product **2.8i** (136 mg, 70%) as an off-white solid. R_f = 0.35 (DCM/EA = 1:1); $[\alpha]_D^{23}$ = +24.6 (c = 1.00, MeOH); Mp: 48-49°C; IR (neat, cm^{-1}): 3285 (w, br), 2920 (m), 1633 (m), 1510 (s), 1246 (s), 1173 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.17 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 6.33 (bs, 1H), 4.34 (dd, *J* = 14.8, 5.5 Hz, 1H), 4.29 (dd, *J* = 14.7, 5.5 Hz, 1H), 3.77 (s, 3H), 2.94 (bs, 1H), 2.39 (dd, *J* = 15.4, 5.2 Hz, 1H), 2.13 (dd, *J* = 15.4, 4.2 Hz, 1H), 1.90 (m, 1H), 1.78 (m, 1H), 1.67-1.34 (m, 6H), 1.24 (qd, *J* = 13.5, 3.3 Hz, 1H), 1.14 (dd, *J* = 13.4, 3.5 Hz, 1H), 1.11 (s, 3H), 0.98-0.89 (m, 2H), 0.86 (s, 3H), 0.77 (s, 3H), 0.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.2, 159.0, 130.7, 129.2, 114.1, 73.1, 57.9, 56.0, 55.4, 44.4, 43.3, 41.9, 39.4, 38.8, 33.4, 33.3, 32.7, 23.8, 21.5, 20.6, 18.5, 15.6; HRMS (ESI$^+$) *m/z* $[C_{24}H_{37}NO_3Na]^+$ cacld: 410.2666; found: 410.2657.



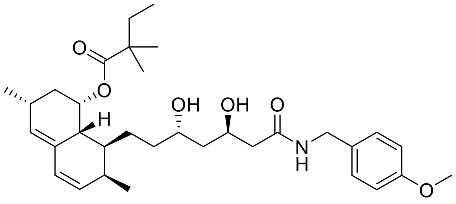
(*S*)-2-((1*S*,2*S*,4a*S*)-1-Hydroxy-4a,8-dimethyl-7-oxo-1,2,3,4,4a,7-hexahydronaphthalen-2-yl)-*N*-(4-methoxybenzyl)propenamide (**2.8j**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.), santonin (246.3 mg, 1.0 mmol, 2.0 equiv.), and TBD (21.0 mg, 0.15 mmol, 0.3 equiv.) were reacted following the general procedure. Upon completion, toluene (2 mL) was added, and the product was collected by filtration. The filter cake was washed with diethyl ether to give the desired product **2.8j** (116 mg, 60%) as a white solid. R_f = 0.20 (DCM/EA = 1:1); $[\alpha]_D^{23}$ = −10.5 (c = 1.00, MeOH); Mp: 153°C (decomp.); IR (neat, cm^{-1}): 3285 (w, br), 2936 (w), 1651 (s), 1609 (s), 1508 (s), 1242 (s), 1167 (m), 832 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.15 (t, *J* = 5.7 Hz, 1H), 7.14 (d, *J* = 8.6 Hz, 2H), 6.86 (m, 1H), 6.85 (d, *J* = 8.5 Hz, 2H), 6.11 (d, *J* = 9.7 Hz, 1H), 5.27 (bs, 1H), 4.39 (d, *J* = 11.2, 1H), 4.22 (dd, *J* = 14.7, 4.8 Hz, 1H), 4.12 (dd, *J* = 14.6, 4.7 Hz, 1H), 3.70 (s, 3H), 2.94 (m, 1H), 2.16 (s, 3H), 1.88 (tt, *J* = 12.1, 4.0 Hz, 1H), 1.79 (m, 1H), 1.56 (qd, *J* = 13.4, 4.2 Hz, 1H), 1.47 (m, 1H), 1.19 (s, 3H), 1.06 (m, 1H), 1.03 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 186.4, 174.9, 161.0, 158.1, 157.1, 132.0, 128.4, 128.1, 124.7, 113.6, 71.3, 55.0, 48.5, 41.8, 41.5, 38.5, 37.6, 23.0, 20.1, 11.2, 10.2; HRMS (ESI$^+$) *m/z* $[C_{23}H_{29}NO_4Na]^+$ cacld: 406.1989; found: 406.1989.



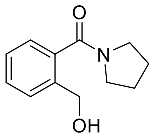
3-((8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Hydroxy-10,13-dimethyl-3-oxo-2,3,8,9,10,11,12,13,14,15,16,17-dodecahydro-1*H*-cyclopenta[*a*]phenanthren-17-yl)-*N*-(4-methoxybenzyl)propenamide (**2.8k**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.), canrenone (340.5 mg, 1.0 mmol, 2.0 equiv.) and TBD (21.0 mg, 0.15 mmol, 0.3 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1 to 1:1, then DCM/MeOH = 20:1) gave the desired product **2.8k** (228 mg, 95%) as a golden solid. R$_f$ = 0.52 (DCM/MeOH = 10:1); $[\alpha]_D^{23} = -68.2$ (c = 1.00, MeOH); Mp: 161-163°C; IR (neat, cm^{-1}): 3297 (w, br), 2940 (w), 2869 (w), 1641 (s), 1613 (s), 1512 (s), 1246 (s), 1030 (m), 751 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.17 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.3 Hz, 2H), 6.11-6.06 (m, 3H), 5.63 (s, 1H), 4.32 (m, 2H), 3.77 (s, 3H), 3.03 (bs, 1H), 2.52 (m, 1H), 2.47-2.38 (m, 2H), 2.34 (dt, *J* = 15.4, 6.6 Hz, 1H), 2.28 (t, *J* = 10.5 Hz, 1H), 2.03-1.93 (m, 2H), 1.82 (m, 1H), 1.75-1.51 (m, 6H), 1.51-1.33 (m, 4H), 1.14 (m, 1H), 1.11 (s, 3H), 0.95 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 199.8, 174.3, 163.9, 159.1, 140.8, 130.3, 129.3, 128.0, 123.7, 114.2, 82.5, 55.4, 50.8, 47.8, 47.5, 43.4, 38.5, 36.2, 34.57, 34.56, 34.0, 31.6, 31.5, 31.1, 23.2, 20.5, 16.4, 14.4; HRMS (ESI$^+$) *m/z*: $[C_{30}H_{39}NO_4Na]^+$ cacld: 500.2771; found: 500.2763.



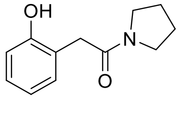
(1*S*,3*R*,7*S*,8*S*,8a*R*)-8-((3*S*,5*R*)-3,5-Dihydroxy-7-((4-methoxybenzyl)amino)-7-oxoheptyl)-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl 2,2-dimethylbutanoate (**2.8l**)

4-Methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.) and simvastatin (418.6 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1 to 2:1, then DCM/MeOH = 20:1) gave the desired product **2.8l** (218 mg, 78%) as an off-white solid. R_f = 0.20 (DCM/EA = 1:1); $[\alpha]_D^{23}$ = +57.3 (c = 1.00, MeOH); Mp: 56-58°C; IR (neat, cm^{-1}): 3341 (w, br), 2964 (w), 2928 (w), 2873 (w), 1716 (m), 1643 (m), 1514 (s), 1248 (s), 1161 (s), 1032 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.19 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.6 Hz, 2H), 6.51 (bs, 1H), 5.97 (d, J = 9.7 Hz, 1H), 5.76 (dd, J = 9.6, 6.1 Hz, 1H), 5.48 (t, J = 3.3 Hz, 1H), 5.39 (q, J = 3.2 Hz, 1H), 4.74 (s, 1H), 4.36 (d, J = 5.7 Hz, 2H), 4.22 (m, 1H), 3.78 (s, 3H), 3.76 (m, 1H), 3.70 (s, 1H), 2.44 (m, 1H), 2.38-2.31 (m, 3H), 2.21 (dq, J = 12.1, 2.8 Hz, 1H), 1.95 (ddd, J = 15.1, 8.2, 2.7 Hz, 1H), 1.88 (dd, J = 15.0, 3.6 Hz, 1H), 1.59-1.49 (m, 7H), 1.21-1.17 (m, 2H), 1.10 (s, 3H), 1.09 (s, 3H), 1.08 (d, J = 7.4 Hz, 3H), 0.85 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 178.4, 171.8, 159.1, 133.2, 131.6, 130.3, 129.7, 129.2, 128.4, 114.2, 72.4, 69.7, 68.3, 55.4, 43.2, 43.1, 43.0, 42.5, 37.9, 36.1, 34.8, 33.3, 33.1, 30.5, 27.4, 24.9, 24.8, 24.1, 23.2, 14.0, 9.4; HRMS (ESI$^+$) *m/z* $[C_{33}H_{49}NO_6Na]^+$ cacld: 578.3452; found: 578.3442.



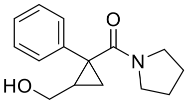
(2-(Hydroxymethyl)phenyl)(pyrrolidin-1-yl)methanone (**2.8m**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and phthalide (134.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.8m** (100 mg, 98%) as a light yellow oil. R_f = 0.50 (DCM/MeOH = 10:1); IR (neat, cm^{-1}): 3369 (w, br), 2972 (w), 2873 (w), 1609 (s), 1595 (s), 1431 (s), 1046 (m), 747 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.40 (m, 1H), 7.36 (m, 1H), 7.31-7.28 (m, 2H), 4.50 (s, 2H), 4.13 (bs, 1H), 3.64 (t, J = 6.8 Hz, 2H), 3.28 (t, J = 6.7 Hz, 2H), 1.95 (p, J = 6.9 Hz, 2H), 1.85 (p, J = 6.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 139.1, 136.6, 129.9, 127.5, 126.7, 64.2, 49.5, 45.9, 26.3, 24.5; HRMS (ESI$^+$) *m/z*: $[C_{12}H_{16}NO_2]^+$ cacld: 206.1176; found: 206.1169.



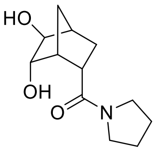
2-(2-Hydroxyphenyl)-1-(pyrrolidin-1-yl)ethan-1-one (**2.8n**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and 2-coumaranone (80.5 mg, 0.6 mmol, 1.2 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 5:1) gave the desired product **2.8n** (99 mg, 96%) as a pink solid. R_f = 0.65 (DCM/EA = 1:1); Mp: 110-111ºC; IR (neat, cm^{-1}): 3134 (w, br), 2964 (w), 2876 (w), 1617 (s), 1591 (s), 1454 (s), 1260 (m), 753 (s); H NMR ($CDCl_3$, 500 MHz): δ 10.35 (s, 1H), 7.17 (td, J = 7.8, 1.7 Hz, 1H), 7.02 (dd, J = 7.4, 1.7 Hz, 1H), 6.98 (dd, J = 7.9, 1.2 Hz, 1H), 6.81 (td, J = 7.4, 1.3 Hz, 1H), 3.69 (s, 2H), 3.67 (t, J = 6.9 Hz, 2H), 3.46 (t, J = 6.9 Hz, 2H), 2.00 (p, J = 6.8 Hz, 2H), 1.88 (p, J = 6.8 Hz, 2H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz): δ 171.6, 157.4, 130.6, 129.1, 121.1, 120.0, 118.4, 47.7, 46.3, 39.0, 26.1, 24.5; HRMS (ESI^+) *m/z* $[C_{12}H_{15}NO_2Na]^+$ cacld: 228.0995; found: 228.0990.



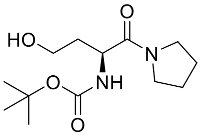
(2-(Hydroxymethyl)-1-phenylcyclopropyl)(pyrrolidin-1-yl)methanone (**2.8o**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and 1-phenyl-3-oxabicyclo[3.1.0]hexan-2-one (174.2 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/acetone = 20:1 to 2:1) gave the desired product **2.8o** (97 mg, 79%) as a yellow oil. R_f = 0.62 (DCM/acetone = 1:1); IR (neat, cm^{-1}): 3391 (m, br), 2970 (w), 2872 (w), 1602 (s), 1429 (s), 1042 (m), 698 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.32-7.14 (m, 5H), 4.75 (bs, 1H), 4.04 (d, J = 12.4 Hz, 1H), 3.53-3.43 (m, 3H), 3.27-3.16 (m, 2H), 1.87-1.72 (m, 4H), 1.59-1.52 (m, 2H), 1.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 139.7, 128.8, 126.7, 126.2, 65.0, 46.9, 46.3, 35.5, 32.1, 26.0, 24.1, 16.8; HRMS ($APCI^+$) *m/z* $[C_{15}H_{20}NO_2]^+$ cacld: 246.1489; found: 246.1490.



(±)-(5,6-Dihydroxybicyclo[2.2.1]heptan-2-yl)(pyrrolidin-1-yl)methanone (**2.8p**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and 5-hydroxynorbornane-2,6-lactone (154.2 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 3:1, then DCM/MeOH = 15:1) gave the desired product **2.8p** (75 mg, 67%) as a yellow oil. $R_f = 0.43$ (DCM/MeOH = 10:1); IR (neat, cm^{-1}): 3347 (m, br), 2958 (m), 2878 (m), 1770 (m), 1592 (s), 1450 (s), 1081 (m), 1011 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.78 (m, 1H), 3.84 (m, 1H), 3.60-3.26 (m, 6H), 2.83 (m, 1H), 2.55 (m, 1H), 2.19 (m, 1H), 1.97-1.90 (m, 3H), 1.87-1.78 (m, 3H), 1.60 (m, 1H), 1.26 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.5, 85.1, 81.9, 47.2, 46.5, 44.4, 44.3, 42.8, 36.4, 30.0, 26.2, 24.3; HRMS (ESI^+) *m/z* $[C_{12}H_{19}NO_3Na]^+$ cacld: 248.1257; found: 248.1255.

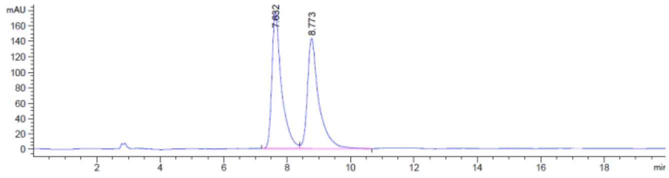


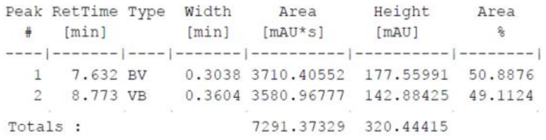
<u>*tert*-Butyl (*S*)-(4-hydroxy-1-oxo-1-(pyrrolidin-1-yl)butan-2-yl)carbamate (**2.8q**)</u>

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and *N*-Boc homoserine lactone (201.2 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then EA) gave the desired product **2.8q** (130 mg, 95%, er = 93:7) as a sticky colorless oil, which solidifies upon standing to a white solid. $R_f = 0.19$ (EA); $[\alpha]_D^{23} = -15.6$ (c = 1.00, MeOH); Mp: 68-70°C; IR (neat, cm^{-1}): 3427 (w, br), 3267 (w, br), 2976 (w), 2878 (w), 1671 (s), 1632 (s), 1168 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.68 (d, $J = 8.1$ Hz, 1H), 4.54 (m, 1H), 3.70-3.37 (m, 7H), 1.98-1.83 (m, 5H), 1.52 (m, 1H), 1.42 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.5, 156.9, 80.3, 58.1, 49.0, 46.6, 46.2, 36.2, 28.4, 26.1, 24.2; HRMS (ESI^+) *m/z* $[C_{13}H_{24}N_2O_4Na]^+$ cacld: 295.1628; found: 295.1630.

Chiral HPLC analysis indicated that a slight racemization had occurred. HPLC (Lux Cellulose-1, isopropanol/hexanes = 10/90, flow rate = 1.0 mL/min, l = 214 nm) $t_R = 7.63$ min (minor, *R*); t_S = 8.77 min (major, *S*).

Chromatogram of racemic standard





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Totals :                  7291.37329  320.44415
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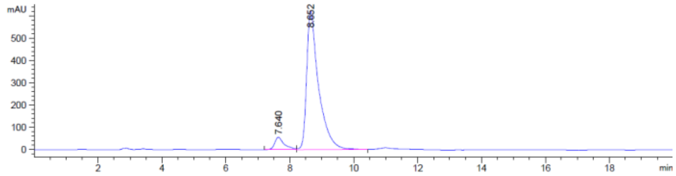
Chromatogram of **2.8q**



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   2   8.652 VB    0.3691 1.60523e4   621.96704  93.2795

Totals :                  1.72088e4   677.63428
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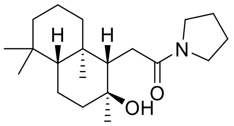
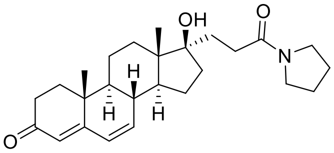


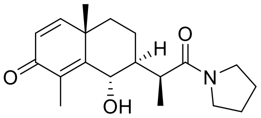
2-((1*S*,2*S*,4a*R*,8a*R*)-2-Hydroxy-2,5,5,8a-tetramethyldecahydronaphthalen-1-yl)-1-(pyrrolidin-1-yl)ethan-1-one (**2.8r**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and sclareolide (250.4 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 25:1) gave the desired product **2.8r** (143 mg, 89%) as a white solid. R_f = 0.57 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +9.9 (c = 1.00, MeOH); Mp: 175°C (decomp.); IR (neat, cm^{-1}): 3471 (w, br), 2928 (w), 2866 (w), 1617 (s), 1430 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.65 (bs, 1H), 3.47-3.39 (m, 4H), 2.28-2.27 (m, 2H), 1.97-1.87 (m, 4H), 1.83-1.77 (m, 2H), 1.65-1.29 (m, 6H), 1.21 (qd, J = 13.6, 3.3 Hz, 1H), 1.09 (m, 1H), 1.10 (s, 3H), 0.98 (dd, J = 12.4, 2.4 Hz, 1H), 0.93 (dd, J = 12.6, 4.0 Hz, 1H), 0.82 (s, 3H), 0.76 (s, 3H), 0.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.3, 72.5, 56.0, 55.9, 46.7, 46.2, 44.5, 41.8, 39.4, 38.6, 33.4, 33.3, 30.0, 26.1, 24.4, 23.5, 21.4, 20.6, 18.5, 16.0; HRMS (ESI$^+$) m/z $[C_{20}H_{35}NO_2Na]^+$ cacld: 344.2560; found: 344.2558.



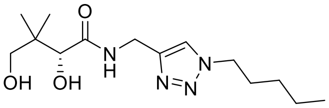
(8*R*,9*S*,10*R*,13*S*,14*S*,17*R*)-17-Hydroxy-10,13-dimethyl-17-(3-oxo-3-(pyrrolidin-1-yl)propyl)-1,2,8,9,10,11,12,13,14,15,16,17-dodecahydro-3*H*-cyclopenta[*a*]phenanthren-3-one (**2.8s**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and canrenone (340.5 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.8s** (204 mg, 98%) as a yellow solid. R_f = 0.57 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = −73.2 (c = 1.00, MeOH); Mp: 162°C (decomp.); IR (neat, cm^{-1}): 3367 (w, br), 2937 (w), 2872 (s), 1656 (m), 1610 (m), 1453 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.06-6.00 (m, 2H), 5.58 (m, 1H), 3.69 (bs, 1H), 3.38-3.32 (m, 4H), 2.53-2.33 (m, 4H), 2.22 (m, 1H), 2.03-1.86 (m, 4H), 1.80-1.73 (m, 3H), 1.66-1.55 (m, 6H), 1.44-1.30 (m, 4H), 1.10 (m, 1H), 1.05 (s, 3H), 0.89 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 199.5, 172.9, 163.9, 140.9, 127.7, 123.5, 82.0, 50.7, 47.6, 47.3, 46.6, 45.9, 38.4, 36.1, 34.3, 33.9, 31.3, 30.2, 29.2, 26.0, 24.3, 23.0, 20.3, 16.3, 14.3; HRMS (ESI$^+$) *m/z* $[C_{26}H_{37}NO_3Na]^+$ cacld: 434.2666; found: 434.2681.



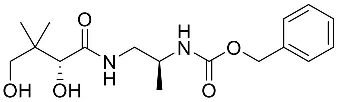
(4a*S*,7*S*,8*S*)-8-Hydroxy-1,4a-dimethyl-7-((*S*)-1-oxo-1-(pyrrolidin-1-yl)propan-2-yl)-5,6,7,8-tetrahydronaphthalen-2(4a*H*)-one (**2.8t**)

Pyrrolidine (35.6 mg, 0.5 mmol, 1.0 equiv.) and santonin (246.3 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.8t** (143 mg, 90%) as a white solid. R_f = 0.55 (DCM/MeOH = 10:1); $[\alpha]_D^{23} = -40.4$ (c = 1.00, MeOH); Mp: 142°C (decomp.); IR (neat, cm^{-1}): 3347 (w, br), 2970 (w), 2875 (w), 1659 (m), 1620 (s), 1447 (m), 1165 (m), 830 (w); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.63 (d, *J* = 9.8 Hz, 1H), 6.17 (d, *J* = 9.8 Hz, 1H), 4.47 (dd, *J* = 11.1, 6.0 Hz, 1H), 3.64 (m, 1H), 3.58-3.39 (m, 4H), 2.93 (m, 1H), 2.19 (s, 3H), 1.98-1.91 (m, 3H), 1.85-1.81 (m, 2H), 1.76-1.72 (m, 2H), 1.55 (qd, *J* = 13.5, 4.3 Hz, 1H), 1.23 (m, 1H), 1.20 (s, 3H), 1.19-1.16 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 187.6, 175.4, 159.3 (bs), 156.3, 129.4, 125.7, 75.1 (bs), 48.9 (bs), 46.8, 46.1, 42.0, 39.8 (bs), 38.3, 26.2, 24.4, 23.6, 23.4 (bs), 14.5 (bs), 11.4; HRMS (ESI$^+$) *m/z* $[C_{19}H_{27}NO_3Na]^+$ cacld: 340.1883; found: 340.1891.



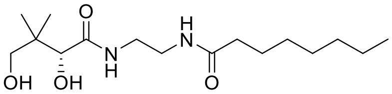
(*R*)-2,4-Dihydroxy-3,3-dimethyl-*N*-((1-pentyl-1*H*-1,2,3-triazol-4-yl)methyl)butanamide (**2.10a**)

(1-Pentyl-1*H*-1,2,3-triazol-4-yl)methanamine (84.2 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) gave the desired product **2.10a** (143 mg, 96%) as a light yellow oil. For reactions performed at 10 mmol scale, the following protocol applied: To a 50 mL round bottom flask were added (1-pentyl-1*H*-1,2,3-triazol-4-yl)methanamine (1.38 g, 10 mmol, 1.0 equiv.), D-pantolactone (2.60 g, 20 mmol, 2.0 equiv.), TBD (139.2 mg, 1 mmol, 0.1 equiv.), and toluene (10 mL). The flask was capped with a glass stopper and the mixture was stirred at rt for 24 hours. Upon completion, solvent was removed under vacuum and the residue was purified by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) to give the desired product **2.10a** (2.74 g, 92%) as a light yellow oil. R_f = 0.45 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +29.0 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3325 (m, br), 2956 (m), 2932 (m), 2869 (w), 1647 (s), 1524 (s), 1048 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.74 (t, J = 5.6 Hz, 1H), 7.53 (s, 1H), 5.18 (bs, 1H), 4.47 (d, J = 5.7 Hz, 2H), 4.39 (bs, 1H), 4.27 (m, 2H), 4.04 (s, 1H), 3.47 (d, J = 11.1 Hz, 1H), 3.40 (d, J = 11.1 Hz, 1H), 1.84 (m, 2H), 1.33-1.22 (m, 4H), 0.92 (s, 3H), 0.89-0.81 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.0, 144.6, 122.3, 77.4, 70.9, 50.5, 39.5, 34.3, 29.9, 28.6, 22.1, 21.3, 20.6, 13.9; HRMS (ESI^+) *m/z* $[C_{14}H_{26}N_4O_3Na]^+$ cacld: 321.1897; found: 321.1890.



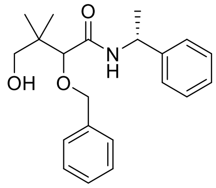
Benzyl ((*S*)-1-((*R*)-2,4-dihydroxy-3,3-dimethylbutanamido)propan-2-yl)carbamate (**2.10b**)

To a 50 mL round bottom flask were added benzyl (*S*)-(1-aminopropan-2-yl)carbamate (1.00 g, 4.8 mmol, 1.0 equiv.), D-pantolactone (1.25 g, 9.6 mmol, 2.0 equiv.), TBD (66.7 mg, 0.48 mmol, 0.1 equiv.), and toluene (5 mL). The flask was capped with a glass stopper and the mixture was stirred at rt for 24 hours. Next, the solvent was removed under vacuum and the residue was purified by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) to give the desired product **2.10b** (1.56 g, 96%) as a sticky light yellow oil. R_f = 0.53 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +24.0 (c = 1.00, MeOH); IR (neat, cm^{-1}): 3321 (m, br), 2964 (w), 2876 (w), 1692 (s), 1645 (s), 1526 (s), 1248 (s), 1060 (s) 695 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.35-7.28 (m, 6H), 5.37 (d, J = 8.0 Hz, 1H), 5.05 (d, J = 12.4 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 4.38 (d, J = 4.4 Hz, 1H), 3.99 (d, J = 4.5 Hz, 1H), 3.83 (m, 1H), 3.75 (t, J = 5.3 Hz, 1H), 3.42 (d, J = 5.3 Hz, 2H), 3.32 (m, 1H), 3.25 (m, 1H), 1.15 (d, J = 6.7 Hz, 3H), 0.94 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.4, 156.7, 136.4, 128.6, 128.3, 128.2, 77.9, 71.2, 66.9, 47.9, 44.7, 39.2, 21.3, 20.5, 18.9; HRMS (ESI^+) *m/z* $[C_{17}H_{26}N_2O_5Na]^+$ cacld: 361.1734; found: 361.1732.



(*R*)-*N*-(2-(2,4-Dihydroxy-3,3-dimethylbutanamido)ethyl)octanamide (**2.10c**)

N-(2-Aminoethyl)octanamide (93.1 mg, 0.5 mmol, 1.0 equiv.) and D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 15:1) gave the desired product **2.10c** (148 mg, 94%) as a white solid. Alternatively, upon completion, the mixture was diluted in toluene (2 mL) and the product was collected by filtration. The filter cake was washed with toluene and hexanes to give the desired product **2.10c** (107 mg, 68%) as a white solid. R_f = 0.37 (DCM/MeOH = 10:1); $[\alpha]_D^{23}$ = +30.3 (c = 1.00, MeOH); Mp: 95-97°C; IR (neat, cm^{-1}): 3329 (m, br), 3287 (m, br), 2925 (w), 2854 (w), 1642 (s), 1558 (m), 1032 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.52 (t, J = 5.7 Hz, 1H), 6.97 (t, J = 5.3 Hz, 1H), 5.05 (d, J = 5.0 Hz, 1H), 4.37 (t, J = 5.4 Hz, 1H), 3.97 (d, J = 4.9 Hz, 1H), 3.46 (dd, J = 11.1, 5.4 Hz, 1H), 3.40 (dd, J = 11.1, 5.5 Hz, 1H), 3.38-3.26 (m, 4H), 2.13 (t, J = 7.7 Hz, 2H), 1.54 (m, 2H), 1.27-1.17 (m, 8H), 0.92 (s, 3H), 0.90 (s, 3H), 0.83 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.9, 77.5, 70.8, 40.0, 39.3, 39.1, 36.7, 31.7, 29.3, 29.1, 25.8, 22.7, 21.1, 20.9, 14.1; HRMS (ESI^+) *m/z* $[C_{16}H_{32}N_2O_4Na]^+$ cacld: 339.2254; found: 339.2259.

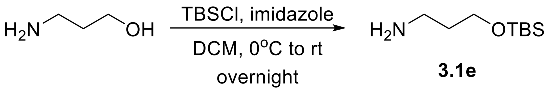


Chiral derivatization experiment on *O*-benzylated D-pantolactone: 2-(Benzyloxy)-4-hydroxy-3,3-dimethyl-*N*-((*R*)-1-phenylethyl)butanamide (***O*-Bn 2.2b**)

(*R*)-1-Phenylethan-1-amine (64 μL, 0.5 mmol, 1.0 equiv.) and *O*-benzylated D-pantolactone (220.3 mg, 1.0 mmol, 2.0 equiv.) were reacted following the general procedure. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 2:1) gave the desired product ***O*-Bn 2.2b** (40 mg, 23%) as a colorless oil. R_f = 0.53 (DCM/EA = 2:1); IR (neat, cm^{-1}): 3406 (w, br), 3305 (w, br), 2970 (w), 2869 (w), 1648 (s), 1510 (m), 1072 (m), 697 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.41-7.15 (m, 10H), (6.91, 6.85) (d, J = 8.7 Hz, 1H), 5.24-5.18 (m, 1H), (4.57, 4.53) (d, J = 11.3 Hz, 1H), (4.41, 4.39) (d, J = 11.2 Hz, 1H), (3.81, 3.78) (s, 1H), (3.47, 3.40) (d, J = 11.7 Hz, 1H), (3.35, 3.32) (d, J = 11.8 Hz, 1H), 3.04 (bs, 1H), (1.51, 1.46) (d, J = 7.0 Hz, 3H), (1.08, 1.03) (s, 3H), (0.89, 0.77) (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (171.44, 171.37), (142.82, 142.82), (137.1, 136.9), (129.0, 128.9), (128.8, 128.7), (128.5, 128.4), (128.34, 128.30), (127.8, 127.6), (126.3, 126.2), (85.6, 85.5), (74.5, 74.4), (70.7, 70.6), (48.54, 48.45), (40.6, 40.4), (23.2, 23.1), (21.9, 21.8), (19.53, 19.51); HRMS (ESI$^+$) *m/z* [$C_{21}H_{27}NO_3Na$]$^+$ cacld: 364.1883; found: 364.1879.

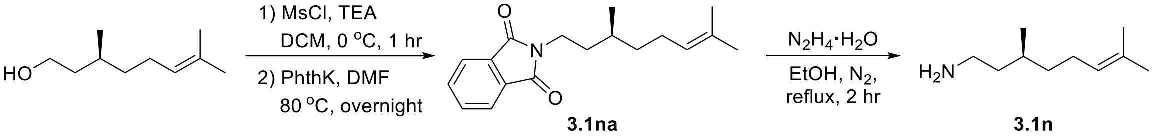
7.3 Experimental Details for Chapter 3

7.3.1 Synthesis and Characterization of Starting Materials and Intermediates



(2,2-Dimethyl-1,3-dioxolan-4-yl)methanamine (**3.1e**)

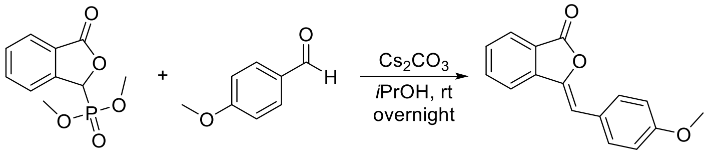
The same procedure reported for compound **2.1e** was followed.



(*S*)-3,7-Dimethyloct-6-en-1-amine (**3.1n**)

To a 100 mL round bottom flask were added (*S*)-citronellol (2.74 mL, 15 mmol, 1.0 equiv.), TEA (3.14 mL, 22.5 mmol, 1.5 equiv.), and DCM (30 mL). The mixture was cooled to 0°C and methanesulfonyl chloride (1.40 mL, 18 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at 0°C for 1 hour. The mixture was then washed with 1 M KH_2PO_4 (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to afford the crude mesylate intermediate. To this intermediate were added potassium phthalimide (4.17 g, 22.5 mmol, 1.5 equiv.) and anhydrous DMF (40 mL). The reaction mixture was stirred at 80°C overnight. The mixture was then diluted in EA (75 mL), washed with H_2O (2 × 50 mL), sat. Na_2CO_3 (1 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, Hex/EA = 10:1 to 5:1) to afford **3.1na** (3.75 g, 87% over two steps) as a colorless oil. $R_f = 0.80$ (Hex/EA = 2:1); IR (neat, cm^{-1}): 2960 (s), 2855 (s), 1774 (m), 1702 (s), 1395 (m), 1050 (m), 720 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (dd, J = 5.5, 3.0 Hz, 2H), 7.68 (dd, J = 5.5, 3.0 Hz, 2H), 5.05 (m, 1H), 3.68 (m, 2H), 1.94 (m, 2H), 1.67 (m, 1H), 1.62 (d, J = 1.4 Hz, 3H), 1.56 (d, J = 1.4 Hz, 3H), 1.49-1.33 (m, 3H), 1.18 (dddd, J = 13.4, 9.5, 7.5, 6.0 Hz, 1H), 0.96 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.4, 133.9, 132.3, 131.4, 124.7, 123.2, 36.9, 36.3, 35.5, 30.3, 25.8, 25.4, 19.4, 17.7; HRMS (ESI$^+$) *m/z* [$C_{18}H_{23}NO_2Na$]$^+$ calcd: 308.1621; found: 308.1608.

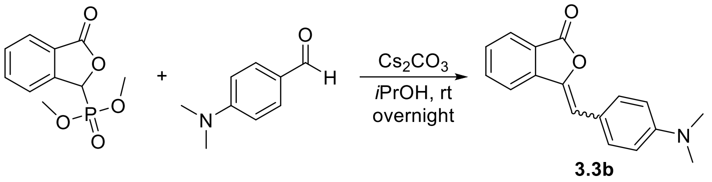
To a 250 mL round bottom flask were added **3.1na** (3.75 g, 13.1 mmol, 1.0 equiv.), EtOH (130 mL), and $N_2H_4 \cdot H_2O$ (2.55 mL, 52.5 mmol, 4.0 equiv.). The atmosphere was changed to N_2 (crucial to prevent diimide formation) and the mixture was refluxed for 2 hours under N_2. The mixture was then cooled to rt, and the flask was put into ice for 30 min. The mixture was filtered over Celite® under vacuum, and the filter cake was washed with cold EtOH. The filtrate was evaporated under vacuum and the residue was dissolved in 2 M KOH (40 mL). The product was extracted in diethyl ether (3 × 25 mL), and the combined organic layers were washed with H_2O (2 × 20 mL) and brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to give a light yellow oil. Vacuum distillation on the crude product afforded **3.1n** (1.59 g, 78%) as a colorless oil. IR (neat, cm^{-1}): 3370 (w), 2961 (m), 2913 (s), 2851 (m), 1453 (m), 1376 (m), 821 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.05 (m, 1H), 2.67 (m, 2H), 1.93 (m, 2H), 1.63 (d, J = 1.5 Hz, 3H), 1.56 (d, J = 1.5 Hz, 3H), 1.41 (m, 2H), 1.26 (m, 2H), 1.11 (dddd, J = 13.4, 9.5, 7.6, 5.9 Hz, 1H), 1.05 (bs, 2H), 0.84 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 131.2, 124.9, 41.3, 40.2, 37.3, 30.2, 25.8, 25.5, 19.6, 17.7; HRMS (ESI$^+$) *m/z* $[C_{10}H_{22}N]^+$ calcd: 156.1747; found: 156.1743.



3.3a

<u>(*Z*)-3-(4-Methoxybenzylidene)isobenzofuran-1(3*H*)-one (**3.3a**)</u>

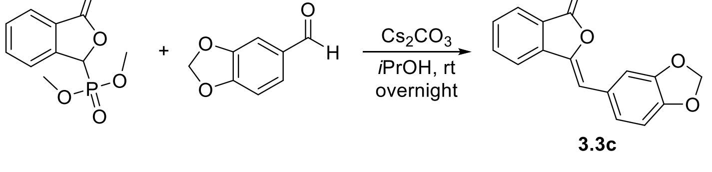
To a 100 mL round bottom flask were added freshly distilled 4-methoxybenzaldehyde (0.30 mL, 2.5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (666.0 mg, 2.75 mmol, 1.1 equiv.), and anhydrous *i*PrOH (15 mL). Cs_2CO_3 (977.5 mg, 3.0 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned dark red. The solvent was evaporated under vacuum, then H_2O (40 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O, diethyl ether, and hexanes. The collected solid was dried under vacuum to afford **3.3a** (196 mg, 31%) as a yellow solid. Mp: 143-144°C; IR (neat, cm^{-1}): 3062 (w), 2934 (w), 2842 (w), 1782 (s), 1767 (s), 1259 (s), 976 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.92 (dt, J = 7.8, 1.0 Hz, 1H), 7.80 (d, J = 8.8 Hz, 2H), 7.73 (dt, J = 7.8, 1.1 Hz, 1H), 7.69 (td, J = 7.8, 1.1 Hz, 1H), 7.51 (td, J = 7.9, 1.1 Hz, 1H), 6.94 (d, J = 8.8 Hz, 2H), 6.38 (s, 1H), 3.85 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.4, 159.9, 143.2, 140.9, 134.5, 131.8, 129.4, 126.0, 125.6, 123.2, 119.6, 114.4, 107.1, 55.5; HRMS (ESI$^+$) *m/z* [$C_{16}H_{13}O_3$]$^+$ calcd: 253.0859; found: 253.0855. Characterization matched reported data.[16]



3.3b

3-(4-(Dimethylamino)benzylidene)isobenzofuran-1(3*H*)-one (**3.3b**)

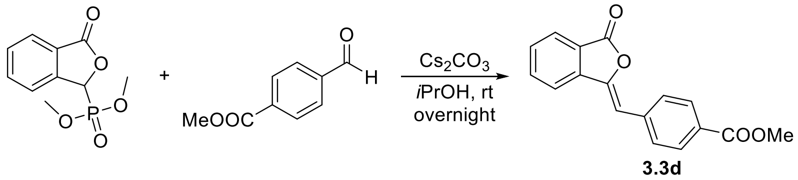
To a 100 mL round bottom flask were added 4-dimethylaminobenzaldehyde (746.0 mg, 5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.33 g, 5.5 mmol, 1.1 equiv.), and anhydrous *i*PrOH (30 mL). Cs_2CO_3 (1.95 g, 6 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned brown. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O. The collected solid was resuspended in H_2O (30 mL) and sonicated for 30 seconds. The slurry was filtered under vacuum and the filter cake was washed with H_2O. The collected solid was dried under vacuum to afford **3.3b** (1.10 g, 83%, *Z*/*E* = 6.4:1) as a yellow solid. Mp: 170°C (decomp.); IR (neat, cm^{-1}): 2902 (w), 2810 (w), 1755 (s), 1599 (s), 974 (s), 761 (s), 687 (s); (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (dt, J = 7.7, 1.0 Hz, 1H), 7.74 (d, J = 8.9 Hz, 2H), 7.67 (dt, J = 7.9, 1.1 Hz, 1H), 7.64 (td, J = 7.6, 1.0 Hz, 1H), 7.43 (td, J = 7.9, 1.2 Hz, 1H), 6.69 (d, J = 9.0 Hz, 2H), 6.33 (s, 1H), 3.00 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.7, 150.3, 141.6, 141.1, 134.2, 131.7, 128.6, 125.4, 122.7, 121.2, 119.3, 112.1, 108.19, 40.2; (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (dt, J = 7.5, 1.1 Hz, 1H), 7.79 (dt, J = 7.6, 1.0 Hz, 1H), 7.52 (td, J = 7.6, 1.2 Hz, 1H), 7.47 (td, J = 7.4, 1.1 Hz, 1H), 7.35 (d, J = 8.7 Hz, 2H), 6.84 (s, 1H), 6.74 (d, J = 8.8 Hz, 2H), 3.01 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1, 150.4, 144.9, 138.0, 133.94, 130.4, 129.7, 125.9, 125.3, 122.6, 120.1, 114.4, 108.2, 40.3; HRMS (ESI$^+$) *m/z* [$C_{17}H_{15}NO_2$]$^+$ calcd: 265.1097; found: 265.1094.



3.3c

(*Z*)-3-(Benzo[*d*][1,3]dioxol-5-ylmethylene)isobenzofuran-1(3*H*)-one (**3.3c**)

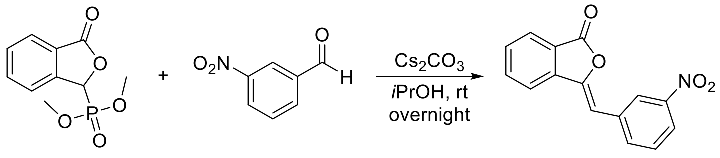
To a 100 mL round bottom flask were added piperonal (750.7 mg, 5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.33 g, 5.5 mmol, 1.1 equiv.), and anhydrous *i*PrOH (30 mL). Cs_2CO_3 (1.95 g, 6 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned orange. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O, diethyl ether, and hexanes. The collected solid was dried under vacuum to afford **3.3c** (1.12 g, 84%) as a yellow solid. Mp: 198ºC (decomp.); IR (neat, cm^{-1}): 2893 (w), 2789 (w), 1758 (s), 1266 (s), 974 (s), 762 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.92 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.73 (m, 1H), 7.70 (m, 1H), 7.54-7.50 (m, 2H), 7.22 (m, 1H), 6.84 (d, *J* = 8.1 Hz, 1H), 6.34 (s, 1H), 6.01 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.2, 148.3, 148.1, 143.4, 140.8, 134.5, 129.6, 127.5, 125.7, 125.2, 123.3, 119.7, 110.0, 108.7, 107.2, 101.5; HRMS (ESI$^+$) *m/z* $[C_{16}H_{10}O_4Na]^+$ calcd: 289.0471; found: 289.0460.



Methyl (*Z*)-4-((3-oxoisobenzofuran-1(3*H*)-ylidene)methyl)benzoate (**3.3d**)

To a 100 mL round bottom flask were added methyl 4-formylbenzoate (820.8 mg, 5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.33 g, 5.5 mmol, 1.1 equiv.), and anhydrous *i*PrOH (30 mL). Cs_2CO_3 (1.95 g, 6 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned orange. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O, diethyl ether, and hexanes. The collected solid was dried under vacuum to afford **3.3d** (1.02 g, 73%) as an off-white solid. Mp: 176-177ºC; IR (neat, cm^{-1}): 1791 (s), 1719 (s), 1281 (s), 971 (s), 685 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04 (d, *J* = 8.5 Hz, 2H), 7.94 (dt, *J* = 7.6, 1.0 Hz, 1H), 7.88 (d, *J* = 8.4 Hz, 2H), 7.78 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.74 (td, *J* = 7.5, 1.1 Hz, 1H), 7.58 (td, *J* = 7.5, 1.1 Hz, 1H), 6.43 (s, 1H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.80, 166.78, 146.2, 140.4, 137.6, 134.8, 130.5, 130.1, 130.0, 129.5, 125.9, 123.7, 120.2, 105.9, 52.3;

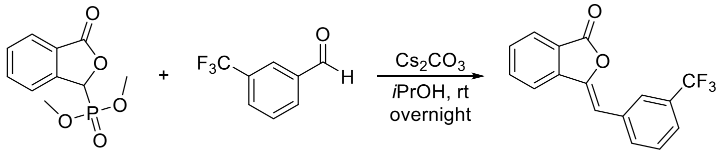
HRMS (ESI$^+$) *m/z* [$C_{17}H_{12}O_4Na$]$^+$ calcd: 303.0628; found: 303.0622. Characterization matched reported data.[17]



3.3e

(*Z*)-3-(3-Nitrobenzylidene)isobenzofuran-1(3*H*)-one (**3.3e**)

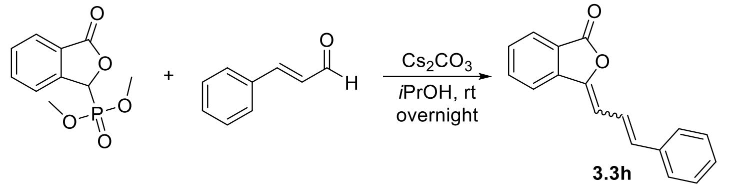
To a 100 mL round bottom flask were added 3-nitrobenzaldehyde (755.6 mg, 5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.33 g, 5.5 mmol, 1.1 equiv.), and anhydrous *i*PrOH (30 mL). Cs_2CO_3 (1.95 g, 6 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned brown. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O. The collected solid was resuspended in H_2O (30 mL) and sonicated for 30 seconds. The slurry was filtered under vacuum and the filter cake was washed with H_2O. The collected solid was recrystallized ($CHCl_3$) to afford **3.3e** (761 mg, 57%) as a yellow solid. Mp: 238-239ºC; IR (neat, cm^{-1}): 1779 (s), 1527 (s), 1347 (s), 977 (s), 759 (s), 687 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.54 (t, J = 2.0 Hz, 1H), 8.32 (dt, J = 7.7, 1.3 Hz, 1H), 8.16 (ddd, J = 8.2, 2.5, 0.9 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.83-7.77 (m, 2H), 7.65-7.59 (m, 2H), 6.48 (s, 1H); HRMS (ESI$^+$) *m/z* [$C_{15}H_9NO_4Na$]$^+$ calcd: 290.0424; found: 290.0411. This compound has a significantly low solubility in all common NMR solvents, hence ^{13}C-NMR was not obtained.



3.3f

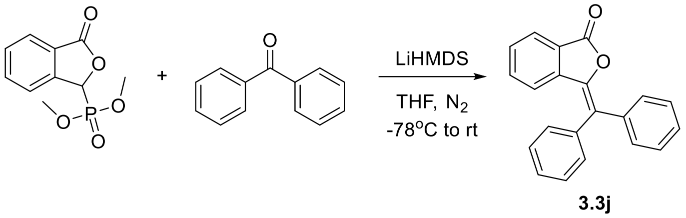
(*Z*)-3-(3-(Trifluoromethyl)benzylidene)isobenzofuran-1(3*H*)-one (**3.3f**)

To a 100 mL round bottom flask were added freshly distilled 3-trifluoromethylbenzaldehyde (870.5 mg, 5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.33 g, 5.5 mmol, 1.1 equiv.), and anhydrous *i*PrOH (30 mL). Cs_2CO_3 (1.95 g, 6 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned brown. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O. The collected solid was resuspended in H_2O (30 mL) and sonicated for 30 seconds. The slurry was filtered under vacuum and the filter cake was washed with H_2O. The collected solid was recrystallized (Hex/EA) to afford **3.3f** (642 mg, 44%) as a light pink solid. Mp: 142-144°C; IR (neat, cm^{-1}): 3068 (w), 1768 (s), 1324 (s), 1112 (s), 974 (s), 695 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.04 (m, 1H), 7.94 (m, 1H), 7.89 (m, 1H), 7.74 (m, 1H), 7.72 (m, 1H), 7.56-7.47 (m, 3H), 6.37 (s, 1H); ^{19}F NMR ($CDCl_3$, 471 MHz): δ -62.7; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.6, 145.8, 140.2, 134.8, 134.0, 133.0, 131.2 (q, J = 32.4 Hz), 130.4, 129.3, 126.6 (q, J = 3.8 Hz), 125.7, 124.8 (q, J = 3.8 Hz), 124.1 (q, J = 272.5 Hz), 123.5, 120.1, 105.3; HRMS (ESI$^+$) *m/z* $[C_{16}H_9F_3O_2Na]^+$ calcd: 313.0447; found: 313.0441.



3-(3-Phenylallylidene)isobenzofuran-1(3*H*)-one (**3.3h**)

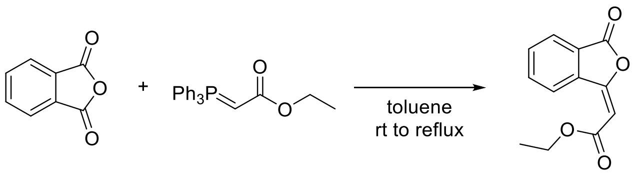
To a 100 mL round bottom flask were added freshly distilled cinnamaldehyde (0.63 mL, 5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.33 g, 5.5 mmol, 1.1 equiv.), and anhydrous *i*PrOH (30 mL). Cs_2CO_3 (1.95 g, 6 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned beige. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O, diethyl ether, and hexanes. The collected solid was recrystallized (Hex/$CHCl_3$) twice to afford **3.3h** (570 mg, 46%, *Z*/*E* = 5.4:1) as a yellow solid. Mp: 132-135°C; IR (neat, cm^{-1}): 1770 (m), 959 (m), 746 (s), 684 (s); (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.90 (dt, J = 7.8, 1.1 Hz, 1H), 7.69-7.68 (m, 2H), 7.53-7.49 (m, 3H), 7.42-7.34 (m, 3H), 7.29 (m, 1H), 6.79 (d, J = 15.7 Hz, 1H), 6.35 (dd, J = 11.3, 0.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.6, 145.2, 139.4, 136.9, 135.8, 134.45, 129.8, 128.9, 128.6, 127.0, 125.7, 124.3, 121.5, 120.0, 108.4; (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.00 (m, 1H), 7.95 (dt, J = 7.6, 1.1 Hz, 1H), 7.78 (td, J = 7.6, 1.1 Hz, 1H), 7.70-7.66 (m, 2H), 7.57 (m, 1H), 7.53-7.30 (m, 4H), 6.85 (d, J = 15.3 Hz, 1H), 6.60 (dd, J = 12.1, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.7, 146.2, 137.81, 137.75, 136.7, 134.52, 129.9, 129.0, 128.7, 126.9, 125.90, 125.85, 123.3, 121.1, 114.1; HRMS (ESI$^+$) *m/z* $[C_{17}H_{12}O_2Na]^+$ calcd: 271.0730; found: 271.0732.



3.3j

3-(Diphenylmethylene)isobenzofuran-1(3*H*)-one (**3.3j**)

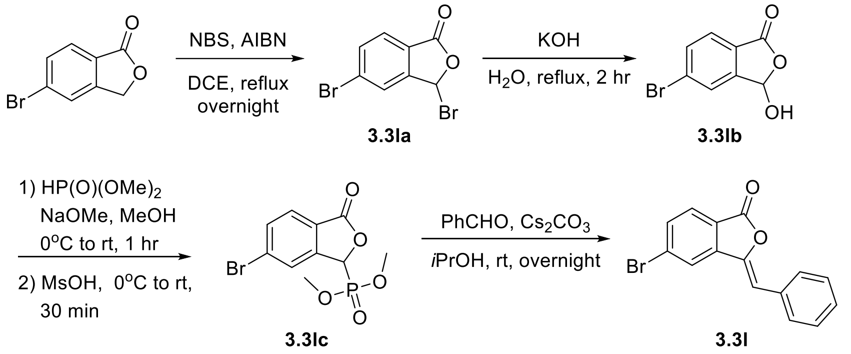
A reported procedure was followed.[18] To a 250 mL round bottom flask was added dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.21 g, 5 mmol, 1.0 equiv.). The atmosphere was changed to N_2 before anhydrous THF (100 mL) was added. The mixture was cooled to -78°C (acetone/dry ice) and LiHMDS (5 mL, 1.0 M in THF, 5 mmol, 1.0 equiv.) was added dropwise. The reaction mixture was stirred at -78°C for 1 hour and benzophenone (911.1 mg, 5 mmol, 1.0 equiv.) in THF (10 mL) was added dropwise. The reaction mixture was stirred at -78°C for 1 hour, then stirred at rt overnight. The solvent was evaporated under vacuum and sat. NH_4Cl (25 mL) was added. The product was extracted in EA (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was recrystallized (Hex/EA) to afford **3.3j** (1.03 g, 70%) as a golden solid. Mp: 142-143°C; IR (neat, cm^{-1}): 3068 (w), 1764 (s), 1004 (s), 756 (s), 691 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.91 (dt, J = 7.7, 1.1 Hz, 1H), 7.58-7.56 (m, 2H), 7.55-7.52 (m, 3H), 7.43 (td, J = 7.5, 1.0 Hz, 1H), 7.40-7.33 (m, 5H), 7.31 (m, 1H), 6.33 (dt, J = 8.0, 1.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.2, 142.6, 139.6, 137.6, 137.5, 134.0, 130.6, 130.5, 129.5, 129.4, 128.9, 128.3, 128.2, 125.3, 125.0, 124.9, 123.7; HRMS (ESI$^+$) *m/z* $[C_{21}H_{15}O_2]^+$ calcd: 299.1067; found: 299.1063. Characterization matched reported data.[19]



3.3k

Ethyl (*E*)-2-(3-oxoisobenzofuran-1(3*H*)-ylidene)acetate (**3.3k**)

A reported procedure was followed.[20] To a 250 mL round bottom flask were added phthalic anhydride (1.48 g, 10 mmol, 1.0 equiv.) and toluene (60 mL). Ethyl (triphenylphosphoranylidene)-acetate (3.83 g, 11 mmol, 1.1 equiv.) was added portion wise. The mixture was stirred at rt for 3 hours, then brought to reflux for 30 minutes. The resulting dark red solution was cooled to rt and the solvent was evaporated under vacuum. The residue was suspended in diethyl ether (50 mL) and filtered. The solvent was evaporated under vacuum and the product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) to afford **3.3k** (1.55 g, 71%) as a white solid. R_f = 0.50 (Hex/EA = 5:1); Mp: 68-69°C; IR (neat, cm^{-1}): 2991 (w), 1786 (s), 1711 (m), 1653 (m), 1044 (s), 772 (s), 690 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.01 (dt, J = 7.6, 1.0 Hz, 1H), 7.93 (dt, J = 7.6, 1.0 Hz, 1H), 7.78 (td, J = 7.6, 1.1 Hz, 1H), 7.67 (td, J = 7.6, 1.0 Hz, 1H), 6.10 (s, 1H), 4.27 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.7, 165.6, 157.9, 136.2, 135.3, 132.6, 128.3, 126.6, 125.4, 102.5, 61.0, 14.3; HRMS (ESI$^+$) *m/z* $[C_{12}H_{10}O_4Na]^+$ calcd: 241.0471; found: 241.0464. Characterization matched reported data.[20]

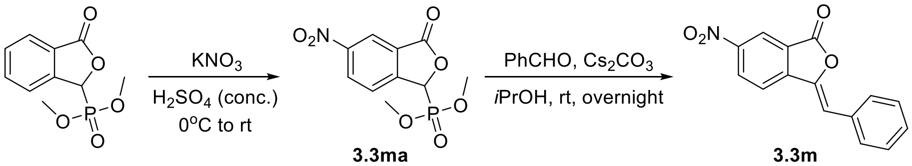


<u>(*Z*)-3-Benzylidene-5-bromoisobenzofuran-1(3*H*)-one (**3.3l**)</u>

A reported procedure was followed.[21] To a 250 mL round bottom flask were added 5-bromophthalide (3.19 g, 15 mmol, 1.0 equiv.), recrystallized NBS (2.94 g, 1.1 equiv.), and AIBN (246.3 mg, 1.5 mmol, 0.1 equiv.). The mixture was refluxed overnight. An extra amount of NBS (801.8 mg, 4.5 mmol, 0.3 equiv.) was added and the mixture was refluxed for additional 2 hours. The mixture was then cooled to rt and the solvent was evaporated under vacuum. DCM (25 mL) was added and the mixture was filtered. The filtrate was evaporated under vacuum and the residue was purified by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) to afford **3.3la** (3.73 g, 85%) as a white solid. R_f = 0.30 (Hex/EA= 5:1) To a 250 mL round bottom flask were added **3.3la** (3.73 g, 12.75 mmol, 1.0 equiv.), KOH (1.43 g, 25.5 mmol, 2.0 equiv.), and H_2O (150 mL). The reaction mixture was refluxed for 2 hours. The mixture was cooled to rt and filtered. The pH of the filtrate was adjusted to 1 using conc. HCl. The mixture was cooled in an ice bath for 2 hours and filtered. The solid obtained was dried under vacuum to afford **3.3lb** (2.69 g, 92%) as an off-white solid.

A reported procedure was followed.[21] To a 100 mL round bottom flask were added MeOH (25 mL) and NaOMe (3.8 mL, 25% wt. in MeOH, 16.4 mmol, 1.4 equiv.). The mixture was cooled to 0°C and dimethyl phosphite (2.14 mL, 23.5 mmol, 2.0 equiv.) was added dropwise. The mixture was stirred at 0°C for 10 minutes. A suspension of **3.3lb** (2.69 g, 11.74 mmol, 1.0 equiv.) in MeOH (15 mL) was added dropwise. The reaction mixture was slowly returned to rt over 1 hour. The mixture was then cooled to 0°C before methanesulfonic acid (1.68 mL, 25.8 mmol, 2.2 equiv.) was added dropwise. An off-white thick suspension was generated. It was stirred at rt for 20 minutes and the solvent was evaporated under vacuum. The residue was dissolved in H_2O (50 mL) and the product was extracted in DCM (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was triturated with diethyl ether and filtered under vacuum. The filter cake was washed with diethyl ether and dried under vacuum to afford **3.3lc** (3.29 g, 87%) as a white solid. Mp: 150-152°C; IR (neat, cm^{-1}): 3068 (w), 2964 (w), 1771 (s), 1262 (m), 10454 (s), 1026 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.88 (m, 1H), 7.77 (m, 1H), 7.71 (m, 1H), 5.66 (d, J = 11.4 Hz, 1H), 3.90 (d, J = 10.8 Hz, 3H), 3.66 (d, J = 10.7 Hz, 3H); ^{31}P NMR ($CDCl_3$, 203 MHz): δ 15.0; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.7 (d, J = 2.6 Hz), 145.4 (d, J = 4.1 Hz), 133.7 (d, J = 2.6 Hz), 130.0 (d, J = 3.2 Hz), 127.3 (d, J = 1.9 Hz), 126.9 (d, J = 2.9 Hz), 124.1 (d, J = 4.2 Hz), 74.6 (d, J = 165.8 Hz), 54.8 (d, J = 6.9 Hz), 54.4 (d, J = 7.0 Hz); HRMS (ESI^+) *m/z* $[C_{10}H_{10}O_5BrPNa]^+$ calcd: 342.9341; found: 342.9331.

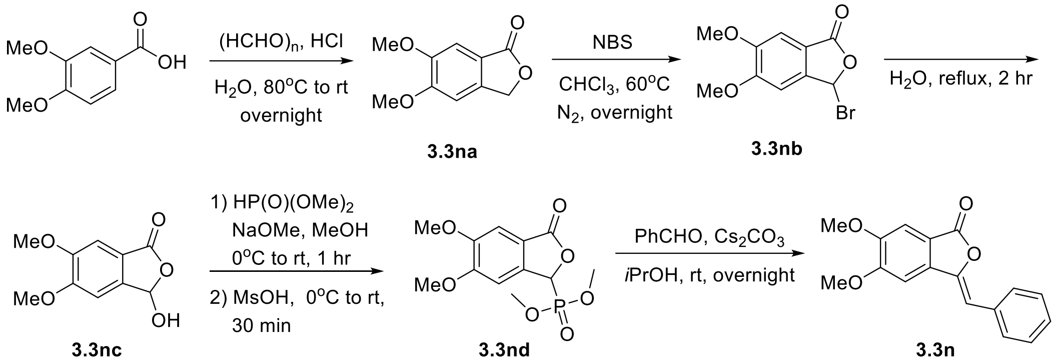
To a 100 mL round bottom flask were added freshly distilled benzaldehyde (0.40 mL, 4 mmol, 1.0 equiv.), **3.3lc** (1.41 g, 4.4 mmol, 1.1 equiv.), and anhydrous *i*PrOH (25 mL). Cs_2CO_3 (1.56 g, 4.8 mmol, 1.2 equiv.) was added in one portion and the reaction mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned pink. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O, diethyl ether, and hexanes. The collected solid was dried under vacuum to afford **3.3l** (923 mg, 61%) as a light yellow solid. Mp: 194-195°C; IR (neat, cm^{-1}): 3062 (w), 1756 (s), 986 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.92 (d, J = 1.5 Hz, 1H), 7.83-7.79 (m, 2H), 7.78 (d, J = 8.1 Hz, 1H), 7.65 (dd, J = 8.1, 1.5 Hz, 1H), 7.43-7.40 (m, 2H), 7.34 (m, 1H), 6.40 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 166.2, 143.3, 142.3, 133.3, 132.8, 130.4, 129.9, 129.0, 127.0, 123.2, 122.2, 108.5; HRMS (ESI$^+$) *m/z* [$C_{15}H_9O_2BrNa$]$^+$ calcd: 322.9678; found: 322.9670. Characterization matched reported data.[16]



(*Z*)-3-Benzylidene-6-nitroisobenzofuran-1(3*H*)-one (**3.3m**)

To a 50 mL round bottom flask were added dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.94 g, 8 mmol, 1.0 equiv.) and conc. H_2SO_4 (5 mL). The mixture was cooled to 0°C. A solution of KNO_3 (1.05 g, 10.4 mmol, 1.3 equiv.) in conc. H_2SO_4 (8 mL) was added dropwise at 0°C. The reaction mixture was stirred at rt for 6 hours. The mixture was then poured into ice water, and the product was extracted in DCM (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was triturated with diethyl ether and filtered under vacuum to obtain a light yellow solid. Recrystallization (Hex/EA) of the crude afforded **3.3ma** (1.71 g, 74%) as a white solid. Mp: 112-113°C; IR (neat, cm^{-1}): 2964 (w), 2899 (w), 1770 (s), 1350 (m), 1014 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.64 (m, 1H), 8.52 (m, 1H), 7.90 (m, 1H), 5.82 (d, J = 13.0 Hz, 1H), 3.88 (d, J = 11.0 Hz, 3H), 3.64 (d, J = 10.9 Hz, 3H); ^{31}P NMR (CDCl$_3$, 203 MHz): δ 14.2; ^{13}C NMR (CDCl$_3$, 125 MHz): δ 167.2 (d, J = 2.5 Hz), 149.3 (d, J = 2.7 Hz), 149.1 (d, J = 4.0 Hz), 129.2 (d, J = 2.4 Hz), 126.7 (d, J = 4.2 Hz), 125.1 (d, J = 2.5 Hz), 121.4 (d, J = 1.8 Hz), 75.4 (d, J = 164.6 Hz), 54.7 (d, J = 6.9 Hz), 54.5 (d, J = 6.9 Hz); HRMS (ESI$^+$) *m/z* [$C_{10}H_{10}NO_7PNa$]$^+$ calcd: 310.0087; found: 310.0086.

To a 100 mL round bottom flask were added freshly distilled benzaldehyde (0.40 mL, 4 mmol, 1.0 equiv.), **3.3ma** (1.26 g, 4.4 mmol, 1.1 equiv.), and anhydrous *i*PrOH (25 mL). Cs_2CO_3 (1.56 g, 4.8 mmol, 1.2 equiv.) was added in one portion and the mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned brown. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O. The collected solid was recrystallized (CHCl$_3$) to afford **3.3m** (532 mg, 50%) as a golden solid. Mp: 232°C (decomp.); IR (neat, cm^{-1}): 3053 (w), 1777 (s), 1522 (s), 1337 (s), 981 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.79 (dd, J = 2.0, 0.6 Hz, 1H), 8.59 (dd, *J* = 8.6, 2.0 Hz, 1H), 7.94 (dd, *J* = 8.5, 0.6 Hz, 1H), 7.8.8 (m, 2H), 7.46 (m, 2H), 7.40 (m, 1H), 6.64 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.9, 148.8, 145.0, 143.1, 132.3, 130.9, 129.9, 129.5, 129.2, 124.5, 121.9, 121.0, 111.8; HRMS (ESI$^+$) *m/z* $[C_{15}H_9NO_4Na]^+$ calcd: 290.0424; found: 290.0428.



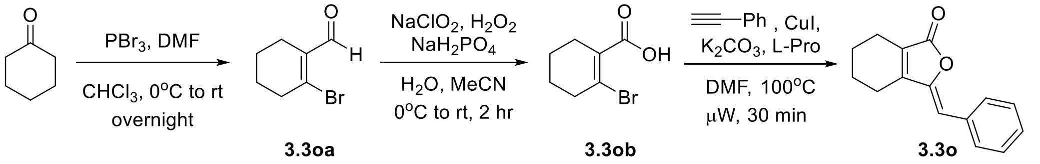
<u>(*Z*)-3-Benzylidene-5,6-dimethoxyisobenzofuran-1(3*H*)-one (**3.3n**)</u>

A reported procedure was followed with modifications.[22] To a 250 mL round bottom flask were added 3,4-dimethoxybenzoic acid (9.11 g, 50 mmol, 1.0 equiv.), paraformaldehyde (15.0 g, 500 mmol, 10.0 equiv.), and conc. HCl (70 mL). The reaction mixture was heated at 80°C for 6 hours, then stirred at rt overnight. The mixture was then diluted in H_2O (50 mL) and NH_3 (aq.) was added to adjust the pH to 2. The precipitate was filtered and dried under vacuum. The collected solid was recrystallized (Hex/$CHCl_3$) twice, dissolved in DCM, and passed through a short silica pad (DCM/EA = 1:1, 400 mL). The solvent was evaporated under vacuum to afford **3.3na** (3.35 g, 35%) as a white solid. Mp: 150-151°C; IR (neat, cm^{-1}): 1752 (s), 1294 (s), 1044 (s), 765 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (s, 1H), 6.91 (s, 1H), 5.21 (s, 2H), 3.97 (s, 3H), 3.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.5, 155.0, 150.5, 141.2, 117.7, 106.2, 103.6, 69.2, 56.5, 56.4; HRMS (ESI$^+$) *m/z* $[C_{10}H_{10}O_4Na]^+$ calcd: 217.0471; found: 217.0479.

A reported procedure was followed with modifications.[23] To a 100 mL round bottom flask were added **3.3na** (2.91 g, 15 mmol, 1.0 equiv.), recrystallized NBS (4.27 g, 24 mmol, 1.6 equiv.), and $CHCl_3$ (25 mL). The atmosphere was changed to N_2 and the reaction mixture was stirred at 60°C overnight under N_2 atmosphere. The mixture was then cooled to rt, left in a freezer for 30 minutes, and filtered. The solvent was evaporated under vacuum and the product was purified from the residue by flash chromatography (SiO_2, Hex/EA/DCM= 10:1:1 to 4:1:1) to afford **3.3nb** (1.93 g, 47%) as an off-white solid. R_f = 0.50 (Hex/EA/DCM = 4:1:1) To a 100 mL round bottom flask were added **3.3nb** (1.93 g, 7.1 mmol) and H_2O (40 mL). The solution was refluxed for 2 hours. The mixture was cooled to rt, left in a fridge overnight, and filtered under vacuum. The filter cake was washed with cold water and dried under vacuum to afford **3.3nc** (1.18 g, 79%) as a beige solid.

A reported procedure was followed.[21] To a 100 mL round bottom flask were added MeOH (12 mL) and NaOMe (1.82 mL, 25% wt. in MeOH, 7.84 mmol, 1.4 equiv.). The mixture was cooled to 0ºC and dimethyl phosphite (1.02 mL, 11.2 mmol, 2.0 equiv.) was added dropwise. The mixture was stirred at 0ºC for 10 minutes. A suspension of **3.3nc** (1.18 g, 5.6 mmol, 1.0 equiv.) in MeOH (6 mL) was added dropwise. The reaction mixture was slowly returned to rt over 1 hour. The mixture was then cooled to 0ºC before methanesulfonic acid (0.80 mL, 12.32 mmol, 2.2 equiv.) was added dropwise. An off-white thick suspension was generated. This suspension was stirred at rt for 20 minutes and the solvent was evaporated under vacuum. The residue was dissolved in H_2O (20 mL) and the product was extracted in DCM (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was triturated with diethyl ether and filtered under vacuum. The filter cake was washed with diethyl ether and dried under vacuum to afford **3.3nd** (1.52 g, 90%) as a white solid. Mp: 125-126ºC; IR (neat, cm^{-1}): 2973 (w), 2913 (w), 1762 (s), 1313 (m), 1032 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (s, 1H), 7.10 (bs, 1H), 5.57 (dd, J = 10.2, 0.8 Hz, 1H), 3.94 (s, 3H), 3.88 (s, 3H), 3.87 (d, J = 10.7 Hz, 3H), 3.53 (d, J = 10.6 Hz, 3H); ^{31}P NMR ($CDCl_3$, 203 MHz): δ 15.9; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.9 (d, J = 2.7 Hz), 155.2 (d, J = 2.8 Hz), 151.2 (d, J = 2.0 Hz), 138.1 (d, J = 4.2 Hz), 117.1 (d, J = 4.5 Hz), 106.2 (d, J = 1.6 Hz), 104.7 (d, J = 2.7 Hz), 74.4 (d, J = 164.8 Hz), 56.7, 56.3, 54.7 (d, J = 7.1 Hz), 54.2 (d, J = 7.1 Hz); HRMS (ESI^+) *m/z* $[C_{12}H_{15}O_7PNa]^+$ calcd: 325.0448; found: 325.0442.

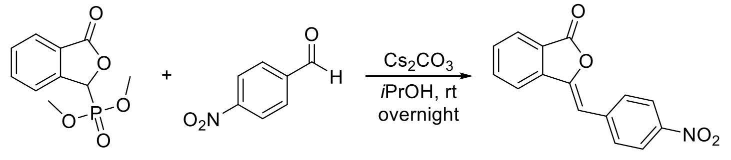
To a 100 mL round bottom flask were added freshly distilled benzaldehyde (0.40 mL, 4 mmol, 1.0 equiv.), **3.3nd** (1.33 g, 4.4 mmol, 1.1 equiv.), and anhydrous *i*PrOH (25 mL). Cs_2CO_3 (1.56 g, 4.8 mmol, 1.2 equiv.) was added in one portion and the reaction mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned pink. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O, diethyl ether, and hexanes. The collected solid was dried under vacuum to afford **3.3n** (1.04 g, 92%) as an off-white solid. Mp: 182-184ºC; IR (neat, cm^{-1}): 3008 (w), 2833 (w), 1756 (s), 1002 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.81-7.79 (m, 2H), 7.40-7.36 (m, 2H), 7.29 (m, 1H), 7.26 (s, 1H), 7.10 (s, 1H), 6.26 (s, 1H), 4.04 (s, 3H), 3.94 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.4, 155.4, 151.7, 144.8, 135.4, 133.5, 130.0, 128.8, 128.2, 116.2, 105.8, 105.6, 100.9, 56.6, 56.5; HRMS (ESI$^+$) *m/z* $[C_{17}H_{14}O_4Na]^+$ calcd: 305.0784; found: 305.0786. Characterization matched reported data.[24]



<u>(*Z*)-3-Benzylidene-4,5,6,7-tetrahydroisobenzofuran-1(3*H*)-one (**3.3o**)</u>

A reported procedure was followed.[24] To a 50 mL round bottom flask were added $CHCl_3$ (10 mL) and DMF (2.32 mL, 30 mmol, 3.0 equiv.). The mixture was cooled to 0°C and PBr_3 (2.54 mL, 27 mmol, 2.7 equiv.) was added dropwise. The mixture was stirred at 0°C for 1 hour. Freshly distilled cyclohexanone (1.04 mL, 10 mmol, 1.0 equiv.) was added and the mixture was stirred at rt overnight. The mixture was poured into H_2O (100 mL) and neutralized with solid $NaHCO_3$. The product was extracted in DCM (3 × 20 mL). The combined organic layers were washed with H_2O (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 20:1) to afford **3.3oa** (670 mg, 35%) as a light yellow oil. $R_f = 0.55$ (Hex/EA = 5:1); To a 50 mL round bottom flask were added **3.3oa** (1.18 g, 6.27 mmol, 1.0 equiv.), MeCN (6 mL), NaH_2PO_4 (255.7 mg, 1.88 mmol, 0.3 equiv.), H_2O (3 mL), and H_2O_2 (0.78 mL, 30% aq., 7.52 mmol, 1.2 equiv.). The mixture was cooled to 0°C. A solution of $NaClO_2$ (992.3 mg, 80%, 8.78 mmol, 1.4 equiv.) in H_2O (9 mL) was added dropwise at 0°C over 30 minutes. The reaction mixture was slowly returned to rt over 1.5 hours, and then quenched with sat. Na_2CO_3 (20 mL). The aqueous solution was washed with diethyl ether (2 × 15 mL), then acidified to pH = 2 with conc. HCl. The product was extracted in diethyl ether (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to afford **3.3ob** (1.09 g, 85%) as a white solid. Mp: 96-98°C; IR (neat, cm^{-1}): 2928 (w), 2869 (w), 2802 (m, br), 1690 (s), 1619 (m), 1267 (s), 719 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.77 (bs, 1H), 2.63 (m, 2H), 2.42 (m, 2H), 1.74-1.70 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.0, 129.8, 129.6, 38.2, 28.8, 24.0, 21.5; HRMS (ESI$^-$) *m/z* $[C_7H_8O_2Br]^-$ calcd: 202.9713; found: 202.9705. Characterization matched reported data.[25]

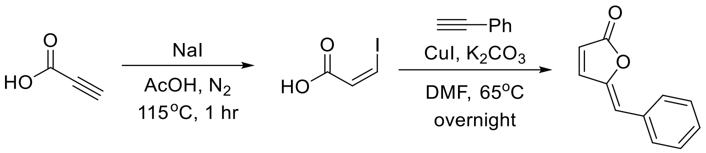
A reported procedure was followed.[10] To a Biotage® microwave vial (capacity 10-20 mL) were added **3.3ob** (205.1 mg, 1 mmol, 1.0 equiv.), freshly distilled phenylacetylene (0.16 mL, 1.5 mmol, 1.5 equiv.), CuI (19.0 mg, 0.1 mmol, 0.1 equiv.), K_2CO_3 (276.4 mg, 2 mmol, 2.0 equiv.), L-proline (34.5 mg, 0.3 mmol, 0.3 equiv.), and DMF (10 mL). The mixture was subject to microwave irradiation at 100°C for 30 minutes. The mixture was then cooled to rt, diluted in EA (25 mL), washed with H_2O (2 × 25 mL), and brine (1 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) to afford **3.3o** (196 mg, 87%) as an off-white solid. $R_f = 0.48$ (Hex/EA = 5:1); Mp: 109-110°C; IR (neat, cm^{-1}): 2940 (w), 2860 (w), 1749 (s), 971 (s), 761 (s), 694 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.77-7.75 (m, 2H), 7.38-7.35 (m, 2H), 7.29 (tt, J = 7.4, 1.3 Hz, 1H), 5.85 (s, 1H), 2.48 (m, 2H), 2.34 (m, 2H), 1.84-1.74 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0, 152.7, 148.1, 133.3, 130.4, 128.8, 128.6, 126.7, 107.9, 21.7, 21.6, 21.3, 20.3; HRMS (ESI$^+$) *m/z* $[C_{15}H_{15}O_2]^+$ calcd: 227.1067; found: 227.1060. Characterization matched reported data.[25]



3.3p

(*Z*)-3-(4-Nitrobenzylidene)isobenzofuran-1(3*H*)-one (**3.3p**)

To a 100 mL round bottom flask were added 4-nitrobenzaldehyde (755.6 mg, 5 mmol, 1.0 equiv.), dimethyl (3-oxo-1,3-dihydroisobenzofuran-1-yl)phosphonate (1.33 g, 5.5 mmol, 1.1 equiv.), and anhydrous *i*PrOH (30 mL). Cs_2CO_3 (1.95 g, 6 mmol, 1.2 equiv.) was added in one portion and the reaction mixture was stirred at rt overnight. A thick precipitate appeared and the solution turned dark green. The solvent was evaporated under vacuum, then H_2O (80 mL) was added. The mixture was stirred vigorously at rt for 30 min, then filtered under vacuum. The filter cake was washed with H_2O. The collected solid was resuspended in H_2O (30 mL) and sonicated for 30 seconds. The slurry was filtered under vacuum and the filter cake was washed with H_2O. The collected solid was recrystallized ($CHCl_3$) to afford **3.3p** (411 mg, 31%,) as a golden solid. Mp: 219-221°C; IR (neat, cm^{-1}): 1785 (s), 1774 (s), 1333 (s), 967 (s), 685 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.25 (d, J = 8.9 Hz, 2H), 8.00-7.98 (m, 3H), 7.83 (dt, J = 7.9, 1.2 Hz, 1H), 7.79 (td, J = 7.2, 1.2 Hz, 1H), 7.64 (td, J = 7.2, 1.2 Hz, 1H), 6.47 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.4, 147.5, 147.0, 140.0, 139.8, 135.1, 131.1, 130.6, 126.1, 124.2, 123.8, 120.5, 104.4; HRMS (ESI$^+$) *m/z* $[C_{15}H_9NO_4Na]^+$ calcd: 290.0424; found: 290.0426.



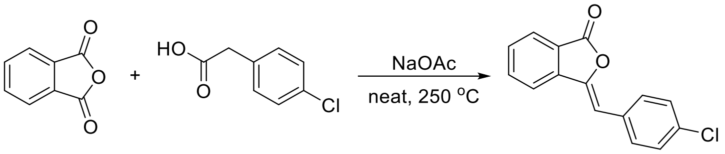
3.3qa **3.3q**

(*Z*)-5-Benzylidenefuran-2(5*H*)-one (**3.3q**)

A reported procedure was followed.[26] To a 50 mL round bottom flask were added propiolic acid (1.42 g, 20 mmol, 1.0 equiv.), NaI (4.80 g, 32 mmol, 1.6 equiv.), and AcOH (8 mL). The atmosphere was changed to N_2 and the reaction mixture was stirred at 115°C under N_2 atmosphere for 1 hour. The mixture was then cool to rt, diluted in H_2O (30 mL), and the product was extracted in diethyl ether (3 × 25 mL). The combined organic layers were washed with sat. $Na_2S_2O_3$ (2 × 20 mL) and brine (1 × 20 mL), dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was dissolved in minimum amount of boiling hexanes, and cooled to rt. The flask was left in the freezer overnight and the precipitate was collected by vacuum filtration. The filter cake was washed with cold hexanes and dried under vacuum to afford **3.3qa** (2.48 g, 55%) as an off-white solid. Mp: 64-65°C; IR (neat, cm^{-1}): 2816 (m, br), 1693 (s), 1596 (s), 1227 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 11.70 (bs, 1H), 7.68 (d, J = 9.0 Hz, 1H), 6.98 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.2, 129.7, 98.5; HRMS (ESI$^-$) *m/z* $[C_3H_2O_2I]^-$ calcd: 196.9105; found: 196.9099. Characterization matched reported data.[26]

A reported procedure was followed.[27] To a 100 mL round bottom flask were added **3.3qa** (989.8, 5 mmol, 1.0 equiv.), freshly distilled phenylacetylene (1.07 mL, 10 mmol, 2.0 equiv.), CuI (952.3 mg, 5 mmol, 1.0 equiv.), K_2CO_3 (1.38 g, 10 mmol, 2.0 equiv.), and DMF (20 mL). The reaction mixture was stirred at 65°C overnight. The mixture was then cooled to rt, diluted in diethyl ether (40 mL), and filtered through Celite® under vacuum. The filter cake was washed with diethyl ether. The filtrate was washed with H_2O (2 × 25 mL) and sat. NH_4Cl (1 × 25 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 50:1 to 5:1) to afford **3.3q** (505 mg, 59%) as a yellow solid. R_f = 0.20 (Hex/EA = 5:1); Mp: 84-85°C; IR (neat, cm^{-1}): 3103 (w), 3023 (w), 1743 (s), 1113 (m), 756 (s), 681 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.77-7.75 (m, 2H), 7.47 (d, J = 5.3 Hz, 1H), 7.39-7.35 (m, 2H), 7.32 (m, 1H), 6.17 (dd, J = 5.3, 0.9 Hz, 1H), 6.01 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 148.4, 145.4, 132.9, 130.7, 129.3, 128.8, 118.0, 114.3;

HRMS (ESI$^+$) *m/z* [$C_{11}H_8O_2Na$]$^+$ calcd: 195.0417; found: 195.0413. Characterization matched reported data.[27]



3.3s

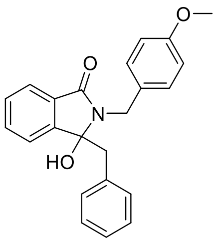
(*Z*)-3-(4-Chlorobenzylidene)isobenzofuran-1(3*H*)-one (**3.3s**)

To a 50 mL round bottom flask were added phthalic anhydride (3.70 g, 25 mmol, 1.0 equiv.), 4-chlorophenylacetic acid (4.69 g, 26.5 mmol, 1.1 equiv.), and anhydrous sodium acetate (205.1 mg, 2.5 mmol, 0.1 equiv.). The solids were heated at 250°C in a sand bath to a yellow melt, with a Dean-Stark apparatus attached. The mixture was stirred at 250°C for 3 hours and it became an orange melt. The mixture was then cooled to 120°C before ethanol (30 mL) was added, which caused rapid precipitation. The solid was collected by filtration and washed with cold ethanol to afford the light orange crude product. The obtained crude product was triturated in ethanol (20 mL) with mortar and pestle. The mixture was filtered, washed with cold ethanol, and dried under vacuum to afford **3.3s** (4.70 g, 73%) as a light yellow solid. Mp: 149-150°C; IR (neat, cm^{-1}): 3068 (w), 3029 (w), 1792 (s), 1076 (m), 968 (s), 759 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.95 (dt, J = 7.8, 1.1 Hz, 1H), 7.78 (d, J = 8.5 Hz, 2H), 7.77 (m, 1H), 7.74 (m, 1H), 7.57 (m, 1H), 7.37 (d, J = 8.7 Hz, 2H), 6.37 (s, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 167.0, 145.1, 140.5, 134.7, 134.4, 131.8, 131.4, 130.2, 129.1, 125.8, 123.6, 120.0, 105.9; HRMS (ESI$^+$) *m/z* [$C_{15}H_9O_2ClNa$]$^+$ calcd: 279.0183; found: 279.0190. Characterization matched reported data.[16]

7.3.2 Synthesis and Characterization of Reaction Products

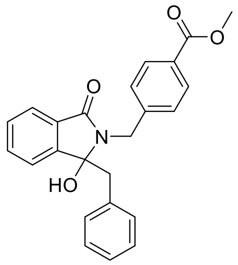
General procedure A for the synthesis of 3-hydroxyisoindolin-1-ones (conditions for when a precipitate forms): To a reaction vial were added the desired amine (0.5 mmol, 1.0 equiv.) and TBD (7.0 mg, 0.05 mmol, 10 mol%). The 3-alkylidenephthalide (0.5 mmol, 1.0 equiv.) was then added, followed by toluene (0.5 mL). The vial was sealed with a septum and the mixture was stirred at room temperature for 1 hour. The volatiles were evaporated under vacuum and the product was purified from the residue by flash chromatography. Alternatively, the product can be accessed through filtration. Upon reaction completion, the mixture was diluted in toluene and filtered under vacuum. The collected solid was washed with toluene, then hexanes, and dried under vacuum to afford the desired product.

General procedure B for the synthesis of 3-hydroxyisoindolin-1-ones (conditions used in the absence of a precipitate): To a reaction vial were added the desired amine (0.75 mmol, 1.5 equiv.) and TBD (20.9 mg, 0.15 mmol, 30 mol%). The 3-alkylidenephthalide (0.5 mmol, 1.0 equiv.) was then added, followed by toluene (0.5 mL). The vial was sealed with a septum and the reaction mixture was stirred at room temperature for 1 hour. The volatiles were evaporated under vacuum and the product was purified from the residue by flash chromatography.



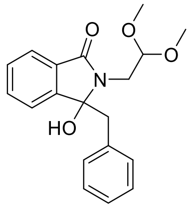
3-Benzyl-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.2a**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2a** (171 mg, 95%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.2a** (133 mg, 74%). $R_f = 0.23$ (Hex/EA = 2:1); Mp: 149-150°C; IR (neat, cm^{-1}): 3225 (w, br), 3023 (w), 2836 (w), 1659 (s), 1510 (m), 1239 (s), 694 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.51 (m, 1H), 7.37-7.33 (m, 2H), 7.31 (d, J = 8.9 Hz, 2H), 7.16-7.10 (m, 3H), 6.93 (m, 1H), 6.89-6.87 (m, 2H), 6.72 (d, J = 8.9 Hz, 2H), 4.59 (d, J = 15.1 Hz, 1H), 4.42 (d, J = 15.1 Hz, 1H), 3.97 (s, 1H), 3.69 (s, 3H), 3.43 (d, J = 13.9 Hz, 1H), 2.84 (d, J = 13.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.3, 158.7, 146.3, 134.9, 131.7, 131.0, 130.9, 130.5, 130.0, 129.5, 127.9, 127.0, 123.24, 123.22, 113.9, 91.5, 55.3, 44.1, 41.9; HRMS (ESI$^+$) *m/z* $[C_{23}H_{21}NO_3Na]^+$ calcd: 382.1414; found: 382.1416.



Methyl 4-((1-benzyl-1-hydroxy-3-oxoisoindolin-2-yl)methyl)benzoate (**3.2b**)

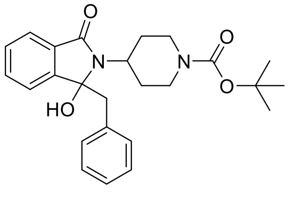
Following general procedure A, methyl 4-aminomethylbenzoate (82.6 mg, 0.5 mmol, 1.0 equiv.; colorless sticky oil) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2b** (182 mg, 94%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.2b** (150 mg, 77%). R_f = 0.20 (Hex/EA = 2:1); Mp: 168-169°C; IR (neat, cm^{-1}): 3237 (w, br), 3023 (w), 2955 (w), 1712 (s), 1685 (s), 1673 (s), 1275 (s), 1072 (s), 755 (s), 698 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, J = 8.5 Hz, 2H), 7.48 (m, 1H), 7.38- 7.36 (m, 3H), 7.33 (td, J = 7.4, 1.3 Hz, 1H), 7.14 (m, 1H), 7.12-7.09 (m, 2H), 6.98 (m, 1H), 6.87-6.86 (m, 2H), 4.74 (d, J = 15.5 Hz, 1H), 4.50 (d, J = 15.5 Hz, 1H), 4.29 (s, 1H), 3.79 (s, 3H), 3.40 (d, J = 13.9 Hz, 1H), 2.90 (d, J = 13.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.4, 167.2, 146.3, 143.8, 134.7, 131.9, 130.8, 130.5, 129.8, 129.6, 128.8, 128.4, 128.0, 127.1, 123.3, 123.2, 91.5, 52.2, 44.1, 42.4; HRMS (ESI^+) *m/z* $[C_{24}H_{21}NO_4Na]^+$ calcd: 410.1363; found: 410.1374.



3-Benzyl-2-(2,2-dimethoxyethyl)-3-hydroxyisoindolin-1-one (**3.2c**)

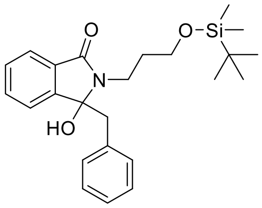
Following general procedure B, freshly distilled aminoacetaldehyde dimethyl acetal (78.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2c** (158 mg, 97%) as a colorless oil. R_f = 0.38 (Hex/EA = 1:1); IR (neat, cm^{-1}): 3364 (w, br), 2934 (w), 2833 (w), 1699 (s), 1395 (m), 1122 (m), 695 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ

7.59 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.51 (td, *J* = 7.5, 1.0 Hz, 1H), 7.39 (td, *J* = 7.5, 1.0 Hz, 1H), 7.35 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.12-7.06 (m, 3H), 6.85-6.83 (m, 2H), 4.77 (dd, *J* = 7.3, 3.7 Hz, 1H), 4.55 (s, 1H), 4.03 (dd, *J* = 14.6, 3.7 Hz, 1H), 3.48 (s, 3H), 3.45 (d, *J* = 14.0 Hz, 1H), 3.40 (s, 3H), 3.37 (dd, *J* = 14.6, 7.3 Hz, 1H), 3.19 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.6, 147.1, 134.5, 132.1, 130.6, 130.1, 129.3, 128.1, 127.0, 123.2, 122.6, 102.0, 90.5, 55.9, 54.9, 43.9, 41.7; HRMS (ESI$^+$) *m/z* $[C_{19}H_{21}NO_4Na]^+$ calcd: 350.1363; found: 350.1355.



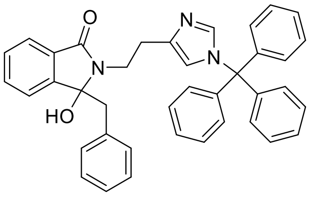
tert-Butyl 4-(1-benzyl-1-hydroxy-3-oxoisoindolin-2-yl)piperidine-1-carboxylate (**3.2d**)

Following general procedure A, 4-amino-1-Boc piperidine (100.1 mg, 0.5 mmol, 1.0 equiv.; white solid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 2:1) gave **3.2d** (143 mg, 68%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.2d** (130 mg, 62%). $R_f = 0.34$ (DCM/EA = 2:1); Mp: 192°C (decomp.); IR (neat, cm^{-1}): 3169 (w, br), 2970 (w), 2848 (w), 1694 (s), 1669 (s), 1657 (s), 1242 (s), 1088 (s), 700 (s); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 7.51-7.47 (m, 2H), 7.44 (m, 1H), 7.16-7.14 (m, 3H), 7.09 (m, 1H), 7.00-6.98 (m, 2H), 6.58 (s, 1H), 4.03 (bs, 2H), 3.65 (tt, *J* = 12.1, 4.0 Hz, 1H), 3.53 (d, *J* = 13.9 Hz, 1H), 3.07 (d, *J* = 13.9 Hz, 1H), 2.78 (bs, 2H), 2.40 (qd, *J* = 12.6, 4.4 Hz, 1H), 2.24 (qd, *J* = 12.6, 4.5 Hz, 1H), 1.71 (m, 1H), 1.58 (m, 1H), 1.42 (s, 9H); ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ 166.0, 153.8, 146.7, 135.8, 132.0, 131.3, 130.2, 129.1, 127.6, 126.6, 123.1, 121.9, 91.1, 78.6, 49.3, 43.1, 29.1 (bs), 28.8 (bs), 28.1; HRMS (ESI$^+$) *m/z* $[C_{25}H_{30}N_2O_4Na]^+$ calcd: 445.2098; found: 445.2089.



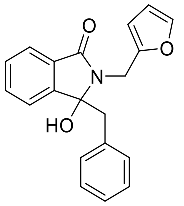
3-Benzyl-2-(3-((*tert*-butyldimethylsilyl)oxy)propyl)-3-hydroxyisoindolin-1-one (**3.2e**)

Following general procedure B, freshly distilled 3-((isopropyldimethylsilyl)oxy)propan-1-amine (78.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 2:1) gave **3.2e** (191 mg, 93%) as a colorless oil, which solidifies upon standing. $R_f = 0.46$ (Hex/EA = 2:1); Mp: 99-100°C; IR (neat, cm^{-1}): 3281 (w, br), 2949 (w), 2854 (w), 1678 (s), 1093 (s), 833 (s), 774 (s), 704 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.53 (m, 1H), 7.44 (m, 1H), 7.35-7.31 (m, 2H), 7.10-7.04 (m, 3H), 6.85-6.83 (m, 2H), 5.21 (s, 1H), 3.97 (dt, J = 14.1, 6.1 Hz, 1H), 3.81 (t, J = 5.3 Hz, 2H), 3.45-3.41 (m, 2H), 3.21 (d, J = 13.8 Hz, 1H), 2.16 (m, 1H), 1.94 (m, 1H), 0.72 (s, 9H), -0.05 (s, 3H), -0.21 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.3, 147.2, 134.8, 131.63, 131.55, 130.1, 129.1, 128.0, 126.9, 122.9, 122.6, 91.3, 62.8, 43.5, 37.6, 30.6, 25.8, 18.2, -5.57, -5.61; HRMS (ESI$^+$) *m/z* $[C_{24}H_{34}NO_3Si]^+$ calcd: 412.2303; found: 412.2315.



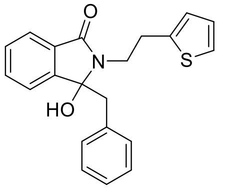
3-Benzyl-3-hydroxy-2-(2-(1-trityl-1*H*-imidazol-4-yl)ethyl)isoindolin-1-one (**3.2f**)

Following general procedure A, 2-(1-trityl-1*H*-imidazol-4-yl)ethan-1-amine (176.7 mg, 0.5 mmol, 1.0 equiv.; off-white solid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, DCM/EA = 20:1 to 1:1) gave **3.2f** (250 mg, 87%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.2f** (170 mg, 59%). $R_f = 0.43$ (DCM/EA = 2:1); Mp: 84-86°C; IR (neat, cm^{-1}): 3056 (w), 2925 (w), 1693 (m), 746 (s), 698 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.50 (d, J = 7.4 Hz, 1H), 7.41 (td, J = 7.5, 1.1 Hz, 1H), 7.35 (d, J = 7.5 Hz, 1H), 7.32-7.30 (m, 10H), 7.07-7.03 (m, 9H), 6.99 (d, J = 1.5 Hz, 1H), 6.89-6.87 (m, 2H), 6.61 (d, J = 1.5 Hz, 1H), 4.18 (m, 1H), 3.68 (dt, J = 13.9, 5.9 Hz, 1H), 3.51 (d, J = 13.7 Hz, 1H), 3.30 (d, J = 13.8 Hz, 1H), 3.17-3.08 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.3, 148.0, 142.3, 138.2, 137.4, 135.3, 131.40, 131.38, 130.2, 129.9, 128.7, 128.14, 128.12, 127.9, 126.7, 122.6, 122.5, 119.0, 91.6, 75.4, 44.0, 38.4, 26.2; HRMS (ESI$^+$) *m/z* $[C_{39}H_{34}N_2O_3]^+$ calcd: 576.2645; found: 576.2638.



3-Benzyl-2-(furan-2-ylmethyl)-3-hydroxyisoindolin-1-one (**3.2g**)

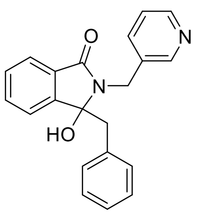
Following general procedure A, freshly distilled furfurylamine (48.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 1:1) gave **3.2g** (147 mg, 92%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.2g** (133 mg, 83%). $R_f = 0.33$ (Hex/EA = 2:1); Mp: 171°C (decomp.); IR (neat, cm^{-1}): 3272 (w, br), 3026 (w), 2928 (w), 1675 (s), 1423 (m), 756 (s), 713 (s); ^1H NMR (DMSO-d_6, 500 MHz): δ 7.58 (m, 1H), 7.54 (td, J = 7.4, 1.1 Hz, 1H), 7.47 (dt, J = 7.5, 1.0 Hz, 1H), 7.41 (td, J = 7.5, 1.0 Hz, 1H), 7.37 (dt, J = 7.4, 1.1 Hz, 1H), 7.07-7.00 (m, 3H), 6.73-6.71 (m, 2H), 6.69 (s, 1H), 6.41-6.40 (m, 2H), 4.75 (d, J = 16.0 Hz, 1H), 4.62 (d, J = 16.0 Hz, 1H), 3.41 (d, J = 13.8 Hz, 1H), 3.20 (d, J = 13.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.0, 151.7, 146.9, 141.8, 135.2, 131.6, 131.0, 129.9, 129.0, 127.5, 126.4, 123.2, 122.1, 110.6, 108.0, 90.7, 42.8, 35.0; HRMS (ESI$^+$) m/z $[C_{20}H_{17}NO_3Na]^+$ calcd: 342.1101; found: 342.1109.



3-Benzyl-3-hydroxy-2-(2-(thiophen-2-yl)ethyl)isoindolin-1-one (**3.2h**)

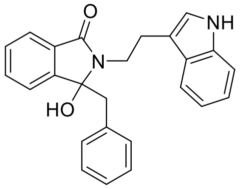
Following general procedure A, freshly distilled 2-(2-aminoethyl)thiophene (63.6 mg, 0.5 mmol, 1.0 equiv.; faintly yellow liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2h** (168 mg, 96%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.2h** (102 mg, 58%). $R_f = 0.33$ (Hex/EA = 2:1); Mp: 156-157°C; IR (neat, cm^{-1}): 3219 (w, br), 3026 (w), 2925 (w), 1684 (s), 1669 (s), 1069 (s), 688 (s); ^1H NMR ($CDCl_3$, 500

MHz): δ 7.53 (m, 1H), 7.41 (m, 1H), 7.37 (m, 1H), 7.15-7.09 (m, 5H), 6.92 (dd, *J* = 5.1, 3.4 Hz, 1H), 6.89-6.87 (m, 2H), 6.83 (m, 1H), 3.92 (m, 1H), 3.51 (m, 1H), 3.45 (d, *J* = 13.9 Hz, 1H), 3.35 (m, 1H), 3.21 (m, 1H), 3.05 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.2, 146.2, 141.8, 134.6, 131.8, 131.3, 130.3, 129.6, 128.1, 127.13, 127.11, 125.6, 124.0, 123.1, 122.9, 91.2, 43.2, 41.6, 29.0; HRMS (ESI$^+$) *m/z* $[C_{21}H_{19}NO_2SNa]^+$ calcd: 372.1029; found: 372.1041.



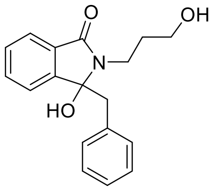
3-Benzyl-3-hydroxy-2-(pyridin-3-ylmethyl)isoindolin-1-one (**3.2i**)

Following general procedure A, freshly distilled 3-picolylamine (54.1 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. After reaction, the mixture was diluted with DCM, filtered under vacuum, washed with DCM and hexanes, dried under vacuum to give **3.2i** (155 mg, 94%) as a pink solid. R_f = 0.19 (EA); Mp: 202-204°C; IR (neat, cm^{-1}): 3053 (w, br), 1697 (s), 1066 (m), 703 (s); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 8.66 (dd, *J* = 2.4, 0.9 Hz, 1H), 8.43 (dd, *J* = 4.8, 1.9 Hz, 1H), 7.81 (dt, *J* = 7.9, 1.9 Hz, 1H), 7.59 (ddd, *J* = 7.6, 6.2, 2.4 Hz, 1H), 7.51 (dt, *J* = 7.5, 0.8 Hz, 1H), 7.45-7.42 (m, 2H), 7.31 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 7.07-7.02 (m, 3H), 6.80-6.78 (m, 3H), 4.77 (d, *J* = 15.7 Hz, 1H), 4.71 (d, *J* = 15.7 Hz, 1H), 3.44 (d, *J* = 13.7 Hz, 1H), 3.35 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ 166.1, 149.4, 147.9, 146.9, 135.8, 135.0, 134.3, 131.7, 131.1, 129.9, 129.1, 127.5, 126.5, 123.2, 123.1, 122.0, 91.1, 42.8, 40.0; HRMS (ESI$^+$) *m/z* $[C_{21}H_{19}N_2O_2]^+$ calcd: 331.1441; found: 331.1434.



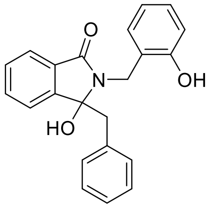
2-(2-(1*H*-Indol-3-yl)ethyl)-3-benzyl-3-hydroxyisoindolin-1-one (**3.2j**)

Following general procedure B, tryptamine (120.2 mg, 0.75 mmol, 1.5 equiv.; beige solid, could not be purified further) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2j** (130 mg, 68%) as a beige solid. $R_f = 0.20$ (Hex/EA = 1:1); Mp: 149-151°C; IR (neat, cm^{-1}): 3302 (w, br), 3056 (w), 2928 (w), 1685 (s), 1666 (m), 1060 (m), 747 (s), 700 (s); ^1H NMR (DMSO-d_6, 500 MHz): δ 10.87 (s, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.58 (m, 1H), 7.54 (dt, J = 7.5, 1.1 Hz, 1H), 7.46 (dt, J = 7.5, 1.4 Hz, 1H), 7.43 (td, J = 7.2, 1.1 Hz, 1H), 7.37 (dt, J = 8.1, 1.1 Hz, 1H), 7.28 (d, J = 2.3 Hz, 1H), 7.10 (ddd, J = 8.2, 6.9, 1.2 Hz, 1H), 7.05-7.00 (m, 4H), 6.80-6.78 (m, 2H), 6.73 (s, 1H), 3.82 (ddd, J = 13.5, 11.5, 5.3 Hz, 1H), 3.62 (ddd, J = 13.6, 11.4, 5.3 Hz, 1H), 3.45 (d, J = 13.7 Hz, 1H), 3.32 (d, J = 13.8 Hz, 1H), 3.14 (ddd, J = 13.9, 11.2, 4.9 Hz, 1H), 3.07 (ddd, J = 13.9, 11.3, 5.0 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 165.9, 147.1, 136.3, 135.2, 131.6, 131.5, 129.8, 129.0, 127.5, 127.2, 126.4, 122.9, 122.7, 121.8, 121.0, 118.4, 118.3, 111.9, 111.4, 91.0, 42.5, 39.9, 25.0; HRMS (ESI$^+$) m/z $[C_{25}H_{22}N_2O_2Na]^+$ calcd: 405.1574; found: 405.1566.



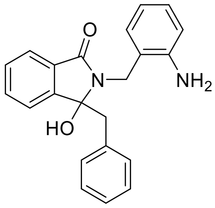
3-Benzyl-3-hydroxy-2-(3-hydroxypropyl)isoindolin-1-one (**3.2k**)

Following general procedure B, freshly distilled 3-amino-1-propanol (56.3 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 1:1 to EA) gave **3.2k** (130 mg, 87%) as a white hygroscopic semi-solid. $R_f = 0.37$ (EA); IR (neat, cm^{-1}): 3281 (w, br), 3029 (w), 2872 (w), 1672 (s), 1064 (m), 697 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.43-7.38 (m, 2H), 7.30 (m, 1H), 7.15 (d, J = 7.5 Hz, 1H), 7.11-7.05 (m, 3H), 6.82-6.80 (m, 2H), 5.69 (bs, 1H), 4.20 (bs, 1H), 3.69 (m, 1H), 3.45-3.38 (m, 4H), 3.07 (d, J = 13.8 Hz, 1H), 1.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.2, 146.7, 134.5, 131.9, 130.9, 130.1, 129.4, 128.0, 127.0, 122.84, 122.82, 91.8, 59.6, 43.4, 36.0, 31.5; HRMS (ESI$^+$) m/z $[C_{18}H_{19}NO_3Na]^+$ calcd: 320.1257; found: 320.1265.



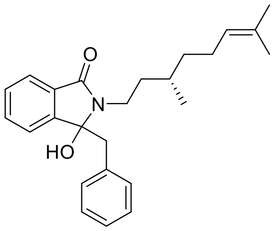
3-Benzyl-3-hydroxy-2-(2-hydroxybenzyl)isoindolin-1-one (**3.2l**)

Following general procedure B, 2-(aminomethyl)phenol (92.4 mg, 0.75 mmol, 1.5 equiv.; beige solid, could not be further purified) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2l** (151 mg, 87%) as a yellow solid. $R_f = 0.52$ (Hex/EA = 2:1); Mp: 161-163°C; IR (neat, cm^{-1}): 3222 (w, br), 2925 (w), 1669 (s), 1232 (m), 1063 (m), 755 (s), 700 (s); ^1H NMR (DMSO-d_6, 500 MHz): δ 9.70 (bs, 1H), 7.56 (td, J = 7.5, 1.2 Hz, 1H), 7.50 (dt, J = 7.4, 1.1 Hz, 1H), 7.44 (td, J = 7.4, 1.0 Hz, 1H), 7.38 (dt, J = 7.5, 1.1 Hz, 1H), 7.25 (dd, J = 7.5, 1.7 Hz, 1H), 7.10-7.02 (m, 4H), 6.86 (dd, J = 8.1, 1.2 Hz, 1H), 6.78-6.76 (m, 3H), 6.73 (td, J = 7.4, 1.2 Hz, 1H), 4.75 (d, J = 16.2 Hz, 1H), 4.61 (d, J = 16.2 Hz, 1H), 3.42 (d, J = 13.7 Hz, 1H), 3.23 (d, J = 13.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.8, 154.7, 147.1, 135.2, 131.6, 131.0, 130.0, 129.2, 129.1, 127.8, 127.5, 126.4, 124.5, 123.2, 122.1, 118.9, 115.2, 91.2, 43.1, 37.1; HRMS (ESI$^+$) *m/z* $[C_{22}H_{19}NO_3Na]^+$ calcd: 368.1257; found: 368.1251.



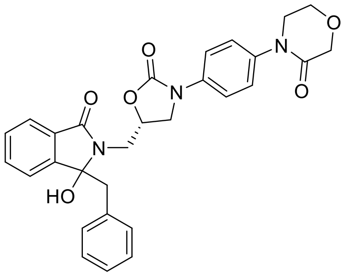
2-(2-Aminobenzyl)-3-benzyl-3-hydroxyisoindolin-1-one (**3.2m**)

Following general procedure B, 2-aminobenzylamine (91.7 mg, 0.75 mmol, 1.5 equiv.; black solid, could not be purified further) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2m** (155 mg, 90%) as a yellow solid. $R_f = 0.45$ (Hex/EA = 2:1); Mp: 155-156°C; IR (neat, cm^{-1}): 3448 (w, br), 3364 (w, br), 3005 (w), 2925 (w), 1650 (s), 1410 (m), 755 (s), 704 (s); ^1H NMR (DMSO-d_6, 500 MHz): δ 7.56 (td, J = 7.4, 1.3 Hz, 1H), 7.45-7.40 (m, 3H), 7.19 (dd, J = 7.6, 1.7 Hz, 1H), 7.02 (m, 1H), 6.99-6.96 (m, 3H), 6.84 (s, 1H), 6.69-6.66 (m, 3H), 6.51 (td, J = 7.4, 1.0 Hz, 1H), 5.39 (s, 2H), 4.60 (d, J = 15.6 Hz, 1H), 4.52 (d, J = 15.6 Hz, 1H), 3.36 (d, J = 13.6 Hz, 1H), 3.23 (d, J = 13.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.8, 147.1, 146.7, 135.0, 131.6, 131.0, 130.3, 130.0, 129.0, 127.9, 127.3, 126.3, 123.1, 122.0, 120.9, 115.7, 114.8, 91.5, 43.0, 39.2; HRMS (ESI$^+$) *m/z* $[C_{22}H_{20}N_2O_2Na]^+$ calcd: 367.1417; found: 367.1414.



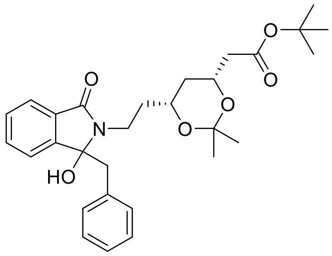
3-Benzyl-2-((*S*)-3,7-dimethyloct-6-en-1-yl)-3-hydroxyisoindolin-1-one (**3.2n**)

Following general procedure B, freshly distilled (*S*)-citronellyl amine (116.5 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1) gave **3.2n** (173 mg, 91%, dr = 1:1) as a colorless oil, which solidifies upon standing. $R_f = 0.60$ (Hex/EA = 2:1); Mp: 80-81°C; IR (neat, cm^{-1}): 3302 (w, br), 2961 (w), 1678 (s), 1663 (m), 1420 (m), 707 (s), 694 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.48 (m, 1H), 7.35-7.31 (m, 2H), 7.20-7.14 (m, 3H), 7.01-6.98 (m, 2H), 6.91 (m, 1H), 5.09 (m, 1H), (3.88, 3.84) (d, *J* = 1.2 Hz, 1H), 3.54-3.45 (m, 2H), 3.06 (m, 1H), (2.96, 2.94) (dd, *J* = 8.1, 1.3 Hz, 1H), 2.00 (m, 2H), 1.69 (m, 1H), (1.69, 1.67) (d, *J* = 1.3 Hz, 3H), 1.61 (d, *J* = 1.3 Hz, 3H), 1.57-1.42 (m, 2H), 1.35 (m, 1H), 1.18 (m, 1H), (0.94, 0.92) (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1, (146.29, 146.27), (135.05, 135.02), 131.44, (131.42, 131.41), 131.35, (130.55, 130.53), 129.4, 128.0, 127.1, (124.87, 124.85), (123.18, 123.14), (123.03, 123.02), (91.27, 91.23), (43.7, 43.6), (37.69, 37.61), (37.0, 36.9), (36.2, 36.1), (31.2, 31.1), (25.84, 25.82), 25.5, (19.5, 19.4), 17.8; HRMS (ESI$^+$) *m/z* $[C_{25}H_{31}NO_2Na]^+$ calcd: 400.2247; found: 400.2233.



4-(4-((5*S*)-5-((1-Benzyl-1-hydroxy-3-oxoisoindolin-2-yl)methyl)-2-oxooxazolidin-3-yl)phenyl)-morpholin-3-one (**3.2o**)

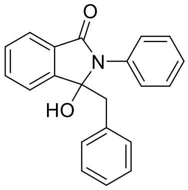
Following general procedure B with modification, (*S*)-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morph-olin-3-one (218.5 mg, 0.75 mmol, 1.5 equiv.; off-white solid), benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.), and DMSO (0.5 mL) were used. Upon reaction completion, the mixture was diluted with DCM (10 mL), washed with H_2O (1 × 5 mL) and 1 M KH_2PO_4 (2 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/MeOH = 100:1 to 20:1) gave **3.2o** (246 mg, 96%, dr = 1.2:1) as a white foam. R_f = 0.55 (DCM/MeOH = 20:1); Mp: 102-104°C; IR (neat, cm^{-1}): 3281 (w, br), 2930 (w), 2866 (w), 1748 (m), 1694 (m), 1660 (m), 1515 (m), 1406 (m), 1125 (m), 751 (s), 698 (s); major diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.52 (dt, J = 7.3, 1.0 Hz, 1H), 7.49 (dd, J = 7.6, 1.3 Hz, 1H), 7.42-7.36 (m, 3H), 7.31 (dt, J = 7.5, 1.0 Hz, 1H), 7.16 (d, J = 9.0 Hz, 2H), 7.09-7.05 (m, 3H), 6.76-6.74 (m, 2H), 5.58 (s, 1H), 4.97 (m, 1H), 3.99 (dd, J = 14.3, 8.8 Hz, 1H), 3.93-3.88 (m, 3H), 3.82 (dd, J = 9.2, 6.0 Hz, 1H), 3.65 (dd, J = 9.3, 4.9 Hz, 1H), 3.62 (m, 2H), 3.46 (d, J = 3.7 Hz, 1H), 3.18 (d, J = 14.0 Hz, 1H), 2.44 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.65, 167.23, 154.4, 146.69, 137.11, 136.6, 134.2, 132.2, 130.7, 129.9, 129.41, 128.0, 127.00, 126.1, 122.98, 122.8, 118.9, 91.4, 70.8, 67.9, 63.90, 48.8, 43.0, 42.1, 40.6; minor diastereomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.54 (dt, J = 7.5, 0.9 Hz, 1H), 7.46 (dd, J = 7.5, 1.2 Hz, 1H), 7.43-7.36 (m, 3H), 7.20 (dt, J = 7.6, 1.0 Hz, 1H), 7.13 (d, J = 8.9 Hz, 2H), 7.05-7.02 (m, 3H), 6.80-6.78 (m, 2H), 5.76 (s, 1H), 4.98 (m, 1H), 4.04 (dd, J = 14.3, 5.4 Hz, 1H), 3.93-3.86 (m, 3H), 3.74 (dd, J = 10.0, 8.9 Hz, 1H), 3.64-3.58 (m, 2H), 3.54 (dd, J = 14.3, 7.4 Hz, 1H), 3.48 (d, J = 3.6 Hz, 1H), 3.10 (d, J = 14.0 Hz, 1H), 2.43 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.63, 167.18, 154.5, 146.70, 137.16, 136.5, 134.3, 132.1, 130.8, 130.0, 129.45, 128.0, 127.03, 126.1, 123.02, 122.9, 118.7, 91.0, 70.4, 68.0, 63.92, 49.7, 48.7, 43.4, 42.7,; HRMS (ESI$^+$) *m/z* $[C_{29}H_{27}N_3O_6Na]^+$ calcd: 536.1792; found: 536.1780.



<u>*tert*-Butyl 2-((4*R*,6*R*)-6-(2-(1-benzyl-1-hydroxy-3-oxoisoindolin-2-yl)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (**3.2p**)</u>

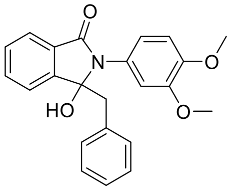
Following general procedure B, *tert*-butyl 2-((4*R*,6*R*)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate (205.1 mg, 0.75 mmol, 1.5 equiv.; colorless sticky oil) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to

1:1) gave **3.2p** (242 mg, 91%, dr = 1.7:1) as a white solid. R_f = 0.68 and 0.60 (Hex/EA = 2:1); Mp: 49-50°C; IR (neat, cm^{-1}): 3335 (w, br), 2979 (w), 2934 (w), 1727 (m), 1679 (s), 1152 (s), 698 (s); major: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.53 (dt, J = 7.4, 1.0 Hz, 1H), 7.44 (td, J = 7.5, 1.0 Hz, 1H), 7.35 (td, J = 7.4, 1.0 Hz, 1H), 7.30 (dt, J = 7.5, 1.0 Hz, 1H), 7.09-7.04 (m, 3H), 6.87-6.84 (m, 2H), 4.91 (s, 1H), 4.25-3.80 (m, 3H), 3.44 (t, J = 14.1 Hz, 1H), 3.31 (ddd, J = 14.1, 6.0, 2.4 Hz, 1H), 3.20 (d, J = 14.0 Hz, 1H), 2.31 (dd, J = 15.1, 7.2 Hz, 1H), 2.20 (dd, J = 15.0, 6.0 Hz, 1H), 2.18 (m, 1H), 1.94 (m, 1H), 1.68 (ddt, J = 14.8, 6.0, 2.4 Hz, 1H), 1.47 (dt, J = 12.8, 2.5 Hz, 1H), 1.39 (s, 9H), 1.06 (s, 3H), 0.73 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0, 167.7, 147.4, 134.7, 131.7, 131.5, 130.1, 129.1, 128.0, 126.8, 122.8, 122.5, 98.88, 91.7, 80.69, 68.9, 66.0, 42.64, 42.5, 36.8, 35.8, 35.6, 29.2, 28.1, 19.4; minor: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.53 (dt, J = 7.4, 1.0 Hz, 1H), 7.40 (td, J = 7.5, 1.0 Hz, 1H), 7.32 (td, J = 7.4, 1.0 Hz, 1H), 7.15 (dt, J = 7.5, 1.0 Hz, 1H), 7.09-7.04 (m, 3H), 6.87-6.84 (m, 2H), 4.57 (s, 1H), 4.25-3.80 (m, 3H), 3.43 (t, J = 14.0 Hz, 1H), 3.14 (d, J = 13.9 Hz, 1H), 2.37 (dd, J = 15.3, 7.2 Hz, 1H), 2.25 (dd, J = 15.3, 6.0 Hz, 1H), 2.18 (m, 1H), 1.53 (dt, J = 12.7, 2.4 Hz, 1H), 1.43 (s, 3H), 1.41 (s, 9H), 1.30-1.13 (m, 3H), 1.20 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.3, 167.0, 146.7, 134.8, 131.6, 131.3, 130.2, 129.3, 128.0, 126.9, 122.9, 122.6, 98.94, 91.3, 80.68, 68.6, 66.1, 43.5, 42.62, 36.1, 36.0, 35.2, 29.9, 28.2, 19.9; HRMS (ESI^+) *m/z* $[C_{29}H_{37}NO_6Na]^+$ calcd: 518.2513; found: 518.2529.



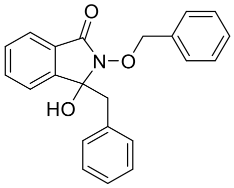
3-Benzyl-3-hydroxy-2-phenylisoindolin-1-one (**3.2q**)

Following general procedure B, freshly distilled aniline (69.8 mg, 0.75 mmol, 1.5 equiv.; light yellow liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 2:1) gave **3.2q** (59 mg, 37%) as an off-white solid. R_f = 0.10 (Hex/EA = 5:1); Mp: 159-160°C; IR (neat, cm^{-1}): 3160 (w, br), 2955 (w), 2916 (w), 1666 (s), 1103 (m), 695 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.58-7.56 (m, 2H), 7.46 (td, J = 7.5, 1.4 Hz, 1H), 7.38 (m, 1H), 7.36-7.33 (m, 2H), 7.31-7.26 (m, 2H), 7.16 (m, 1H), 7.10 (m, 1H), 7.05-7.02 (m, 2H), 6.66 (m, 2H), 4.03 (s, 1H), 3.43 (d, J = 14.1 Hz, 1H), 3.07 (d, J = 14.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 146.0, 136.0, 134.4, 132.4, 130.7, 130.6, 129.8, 128.8, 127.8, 127.0, 126.6, 126.1, 123.7, 123.1, 93.0, 43.0; HRMS (ESI$^+$) *m/z* [$C_{21}H_{17}NO_2Na$]$^+$ calcd: 338.1151; found: 338.1154.



3-Benzyl-2-(3,4-dimethoxyphenyl)-3-hydroxyisoindolin-1-one (**3.2r**)

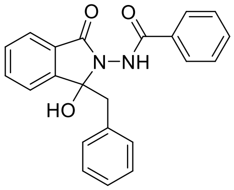
Following general procedure B with modification, freshly recrystallized 4-aminoveratrole (114.9 mg, 0.75 mmol, 1.5 equiv.; orange solid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Upon reaction completion, the mixture was diluted in DCM (10 mL) and washed with 1% AcOH (2 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 20:1 to 5:1) gave **3.2r** (95 mg, 50%) as an off-white solid. R_f = 0.12 (DCM/EA = 10:1); Mp: 152-154°C; IR (neat, cm^{-1}): 3329 (w, br), 3005 (w), 2833 (w), 1688 (s), 1676 (s), 1513 (s), 1239 (s), 1027 (s), 703 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.45 (td, *J* = 7.5, 1.2 Hz, 1H), 7.23-7.20 (m, 2H), 7.13 (m, 1H), 7.08-7.05 (m, 2H), 7.01-6.97 (m, 3H), 6.73 (d, *J* = 8.7 Hz, 1H), 6.61-6.59 (m, 2H), 4.64 (s, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 3.40 (d, *J* = 14.1 Hz, 1H), 3.02 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.9, 148.4, 147.5, 146.1, 134.4, 132.2, 130.6, 130.5, 129.7, 128.7, 127.7, 126.9, 123.2, 122.9, 118.4, 110.6, 110.2, 93.0, 56.0, 55.8, 42.9; HRMS (ESI$^+$) *m/z* [$C_{23}H_{21}NO_4Na$]$^+$ calcd: 398.1363; found: 398.1356.



3-Benzyl-2-(benzyloxy)-3-hydroxyisoindolin-1-one (**3.2s**)

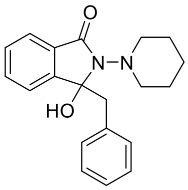
Following general procedure B, freshly distilled *O*-benzyl hydroxylamine (92.4 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.2s** (72 mg, 42%) as a white solid. R_f = 0.25 (Hex/EA = 2:1); Mp: 152-154°C; IR (neat, cm^{-1}): 3267 (w, br), 3032 (w), 2922 (w), 1700 (s), 1072 (m), 695 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ

7.57-7.55 (m, 2H), 7.51-7.47 (m, 2H), 7.43-7.33 (m, 4H), 7.26 (m, 1H), 7.08-7.04 (m, 3H), 6.95-6.93 (m, 2H), 5.34 (d, *J* = 10.6 Hz, 1H), 5.26 (d, *J* = 10.6 Hz, 1H), 3.44 (d, *J* = 13.6 Hz, 1H), 3.36 (d, *J* = 13.6 Hz, 1H), 2.90 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.3, 143.3, 135.9, 134.1, 132.6, 130.6, 129.8, 129.7, 129.0, 128.7, 128.0, 127.0, 123.3, 122.7, 91.5, 79.7, 42.5; HRMS (ESI$^+$) *m/z* $[C_{22}H_{19}NO_3Na]^+$ calcd: 368.1257; found: 368.1246.



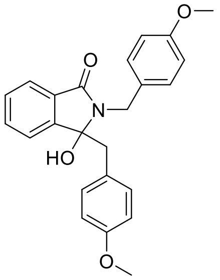
<u>*N*-(1-Benzyl-1-hydroxy-3-oxoisoindolin-2-yl)benzamide (**3.2t**)</u>

Following general procedure B, benzhydrazide (102.1 mg, 0.75 mmol, 1.5 equiv.; off-white solid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, DCM/EA = 20:1 to 2:1) gave **3.2t** (100 mg, 56%) as a white solid. R_f = 0.63 (DCM/EA = 1:1); Mp: 179-180°C; IR (neat, cm^{-1}): 3261 (w, br), 3002 (w), 1713 (m), 1702 (s), 1659 (s), 1291 (m), 691 (s); ^{1}H NMR (CD_3OD, 500 MHz): δ 7.99-7.97 (m, 2H), 7.74 (m, 1H), 7.61 (m, 1H), 7.54-7.50 (m, 2H), 7.49-7.46 (m, 2H), 7.26-7.21 (m, 5H), 6.86 (m, 1H), 3.54 (d, *J* = 13.8 Hz, 1H), 3.10 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz): δ 170.2, 166.8, 146.8, 136.7, 133.6, 133.50, 133.47, 132.2, 130.6, 130.2, 129.6, 129.1, 128.8, 127.9, 125.3, 124.2, 92.5, 44.2; HRMS (ESI$^+$) *m/z* $[C_{22}H_{18}N_2O_3Na]^+$ calcd: 381.1210; found: 381.1196.



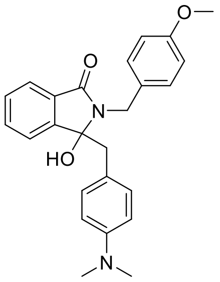
<u>3-Benzyl-3-hydroxy-2-(piperidin-1-yl)isoindolin-1-one (**3.2u**)</u>

Following general procedure B, freshly distilled 1-aminopiperidine (75.1 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and benzalphthalide (111.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 4:1) gave **3.2u** (44 mg, 27%) as an off-white solid. R_f = 0.41 (Hex/EA = 2:1); Mp: 152-153°C; IR (neat, cm^{-1}): 3201 (w, br), 2940 (w), 2854 (w), 1665 (s), 698 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.41 (td, *J* = 7.5, 1.1 Hz, 1H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 7.26-7.24 (m, 3H), 7.16-7.13 (m, 2H), 6.75 (dt, *J* = 7.5, 1.0 Hz, 1H), 3.71 (d, *J* = 13.9 Hz, 1H), 3.41 (bs, 3H), 3.18 (s, 1H), 2.89 (d, *J* = 13.9 Hz, 1H), 1.72-1.51 (m, 7H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 166.1, 144.0, 135.6, 131.8, 131.0, 130.8, 129.6, 128.1, 127.1, 123.7, 123.1, 90.1, 54.4, 43.9, 26.9, 23.6; HRMS (ESI$^+$) *m/z* $[C_{20}H_{22}N_2O_2Na]^+$ calcd: 345.1573; found: 345.1571.



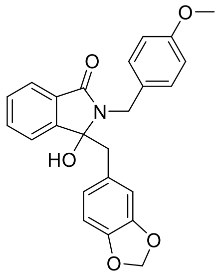
3-Hydroxy-2,3-bis(4-methoxybenzyl)isoindolin-1-one (**3.4a**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and **3.3a** (126.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO$_2$, Hex/EA = 5:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.4a** (180 mg, 92%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4a** (172 mg, 88%). R$_f$ = 0.20 (Hex/EA = 2:1); Mp: 143-144°C; IR (neat, cm^{-1}): 3272 (w, br), 2946 (w), 2830 (w), 1687 (s), 1672 (s), 1509 (s), 1075 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): *δ* 7.54 (m, 1H), 7.40-7.32 (m, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 6.99 (m, 1H), 6.77 (d, *J* = 8.7 Hz, 2H), 6.74 (d, *J* = 8.9 Hz, 2H), 6.64 (d, *J* = 8.9 Hz, 2H), 4.64 (d, *J* = 15.1 Hz, 1H), 4.43 (d, *J* = 15.1 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.55 (s, 1H), 3.37 (d, *J* = 14.1 Hz, 1H), 2.84 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 167.2, 158.7, 158.5, 146.3, 131.7, 131.4, 131.1, 130.9, 129.9, 129.4, 126.9, 123.2, 123.1, 113.8, 113.3, 91.6, 55.3, 55.2, 43.0, 41.9; HRMS (ESI$^+$) *m/z* $[C_{24}H_{24}NO_4]^+$ calcd: 390.1700; found: 390.1691.



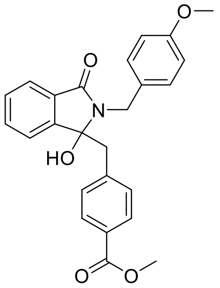
3-(4-(Dimethylamino)benzyl)-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.4b**)

Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and **3.3b** (133.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 1:1) gave **3.4b** (188 mg, 93%) as a light yellow solid. R_f = 0.38 (Hex/EA = 1:1); Mp: 167-169°C; IR (neat, cm^{-1}): 3290 (w, br), 2913 (w), 2804 (w), 1668 (s), 1512 (m), 1247 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.55 (td, J = 7.4, 1.4 Hz, 1H), 7.46 (dt, J = 7.4, 1.2 Hz, 1H), 7.44-7.40 (m, 2H), 7.39 (d, J = 8.7 Hz, 2H), 6.86 (d, J = 8.7 Hz, 2H), 6.61 (s, 1H), 6.56 (d, J = 8.7 Hz, 2H), 6.37 (d, J = 8.8 Hz, 2H), 4.66 (d, J = 15.4 Hz, 1H), 4.56 (d, J = 15.3 Hz, 1H), 3.72 (s, 3H), 3.27 (d, J = 13.9 Hz, 1H), 3.08 (d, J = 13.9 Hz, 1H), 2.76 (s, 6H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.2, 158.1, 148.8, 147.3, 131.42, 131.40, 131.0, 130.5, 129.5, 128.9, 123.1, 122.4, 121.9, 113.4, 111.4, 91.2, 55.0, 42.4, 41.7, 40.0; HRMS (ESI$^+$) *m/z* $[C_{25}H_{27}N_2O_3]^+$ calcd: 403.2016; found: 403.2012.



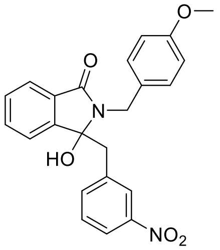
3-(Benzo[*d*][1,3]dioxol-5-ylmethyl)-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.4c**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and **3.3c** (133.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1, then DCM/EA = 4:1) gave **3.4c** (195 mg, 97%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4c** (175 mg, 87%). R_f = 0.20 (Hex/EA = 2:1); Mp: 161-163°C; IR (neat, cm^{-1}): 3287 (w, br), 2882 (w), 2835 (w), 1686 (s), 1672 (s), 1243 (s), 1072 (s), 1033 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.56 (td, J = 7.4, 1.3 Hz, 1H), 7.51 (dt, J = 7.5, 1.0 Hz, 1H), 7.45 (dd, J = 7.4, 1.0 Hz, 1H), 7.43-7.39 (m, 3H), 6.87 (d, J = 8.7 Hz, 2H), 6.72 (s, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.27 (d, J = 1.7 Hz, 1H), 6.23 (dd, J = 8.0, 1.7 Hz, 1H), 5.87 (s, 2H), 4.69 (d, J = 15.3 Hz, 1H), 4.56 (d, J = 15.3 Hz, 1H), 3.73 (s, 3H), 3.32 (d, J = 13.9 Hz, 1H), 3.12 (d, J = 13.9 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.2, 158.2, 147.0, 146.4, 145.6, 131.5, 131.4, 130.9, 129.5, 129.1, 128.9, 123.3, 123.2, 122.1, 113.5, 110.2, 107.4, 100.6, 91.0, 55.0, 42.8, 41.6; HRMS (APCI$^+$) *m/z* $[C_{24}H_{22}NO_5]^+$ calcd: 404.1493; found: 404.1487.



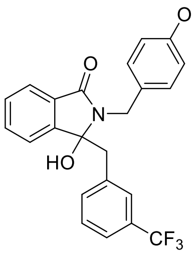
Methyl 4-((1-hydroxy-2-(4-methoxybenzyl)-3-oxoisoindolin-1-yl)methyl)benzoate (**3.4d**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid), **3.3d** (140.1 mg, 0.5 mmol, 1.0 equiv.), and toluene (1.0 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 4:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.4d** (196 mg, 94%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4d** (157 mg, 75%). $R_f = 0.43$ (Hex/EA = 1:1); Mp: 166-167°C; IR (neat, cm^{-1}): 3302 (w, br), 2952 (w), 2833 (w), 1718 (s), 1665 (s), 1284 (s), 1063 (s), 710 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.62 (d, J = 8.3 Hz, 2H), 7.56 (td, J = 7.3, 1.4 Hz, 1H), 7.48 (m, 1H), 7.44-7.37 (m, 4H), 6.90 (d, J = 8.3 Hz, 2H), 6.88 (d, J = 8.7 Hz, 2H), 6.84 (s, 1H), 4.74 (d, J = 15.3 Hz, 1H), 4.60 (d, J = 15.3 Hz, 1H), 3.78 (s, 3H), 3.73 (s, 3H), 3.48 (d, J = 13.5 Hz, 1H), 3.28 (d, J = 13.5 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.1, 166.0, 158.2, 146.7, 141.0, 131.6, 131.2, 130.9, 130.4, 129.6, 129.2, 128.3, 127.8, 123.1, 122.1, 113.5, 90.8, 55.0, 52.0, 43.2, 41.6; HRMS (ESI$^+$) *m/z* $[C_{25}H_{23}NO_5Na]^+$ calcd: 440.1468; found: 440.1457.



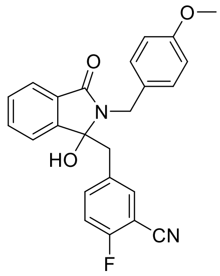
3-Hydroxy-2-(4-methoxybenzyl)-3-(3-nitrobenzyl)isoindolin-1-one (**3.4e**)

Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid), **3.3e** (133.6 mg, 0.5 mmol, 1.0 equiv.), and toluene (1.0 mL) were used. Purification by flash chromatography (SiO_2, DCM/EA = 50:1 to 5:1) gave **3.4e** (186 mg, 92%) as an off-white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4e** (129 mg, 64%). R_f = 0.58 (DCM/EA = 4:1); Mp: 170-172°C; IR (neat, cm^{-1}): 3225 (w, br), 3011 (w), 2931 (w), 2836 (w), 1675 (s), 1522 (s), 1346 (s), 1238 (s), 719 (s), 697 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.94 (ddd, J = 8.3, 2.4, 1.0 Hz, 1H), 7.60-7.56 (m, 2H), 7.50 (dt, J = 7.5, 1.1 Hz, 1H), 7.45 (td, J = 7.4, 1.0 Hz, 1H), 7.40 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 8.7 Hz, 2H), 7.33 (t, J = 7.9 Hz, 1H), 7.17 (dt, J = 7.7, 1.4 Hz, 1H), 6.91 (s, 1H), 6.85 (d, J = 8.7 Hz, 2H), 4.76 (d, J = 15.3 Hz, 1H), 4.55 (d, J = 15.3 Hz, 1H), 3.72 (s, 3H), 3.55 (d, J = 13.8 Hz, 1H), 3.34 (d, J = 13.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.2, 158.2, 147.0, 146.5, 137.6, 136.7, 131.8, 131.2, 130.7, 129.5, 129.4, 129.0, 124.6, 123.2, 122.3, 121.6, 113.5, 90.6, 55.0, 42.6, 41.5; HRMS (ESI$^+$) *m/z* $[C_{23}H_{20}N_2O_5Na]^+$ calcd: 427.1264; found: 427.1265.



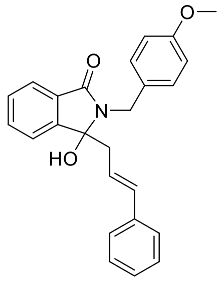
3-Hydroxy-2-(4-methoxybenzyl)-3-(3-(trifluoromethyl)benzyl)isoindolin-1-one (**3.4f**)

Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and **3.3f** (145.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 1:1) gave **3.4f** (203 mg, 95%) as a white solid. R_f = 0.25 (Hex/EA = 2:1); Mp: 129-130°C; IR (neat, cm^{-1}): 3329 (w, br), 3005 (w), 2842 (w), 1685 (s), 1673 (s), 1124 (s), 1069 (s), 703 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.49 (m, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.38-7.33 (m, 2H), 7.28 (d, J = 8.7 Hz, 2H), 7.23 (t, J = 7.8 Hz, 1H), 7.12 (s, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.84 (m, 1H), 6.73 (d, J = 8.7 Hz, 2H), 4.48 (d, J = 15.3 Hz, 1H), 4.38 (d, J = 15.2 Hz, 1H), 4.28 (s, 1H), 3.70 (s, 3H), 3.44 (d, J = 14.0 Hz, 1H), 2.80 (d, J = 13.9 Hz, 1H); ^{19}F NMR ($CDCl_3$, 471 MHz): δ -62.6; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.4, 158.8, 146.0, 136.0, 134.0, 131.9, 130.8, 130.6, 130.3 (q, J = 32.1 Hz), 129.9, 129.8, 128.3, 127.5 (q, J = 3.7 Hz), 124.1 (q, J = 272.3 Hz), 123.8 (q, J = 3.7 Hz), 123.4, 123.2, 114.0, 91.2, 55.3, 44.0, 41.7; HRMS (ESI$^+$) *m/z* $[C_{24}H_{21}NO_3F_3]^+$ calcd: 428.1468; found: 428.1463.



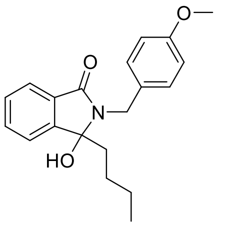
2-Fluoro-5-((1-hydroxy-2-(4-methoxybenzyl)-3-oxoisoindolin-1-yl)methyl)benzonitrile (**3.4g**)

Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and 2-fluoro-5-((3-oxoisobenzofuran-1(3*H*)-ylidene)methyl)-benzonitrile (132.6 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.4g** (181 mg, 90%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4g** (111 mg, 55%). $R_f = 0.45$ (Hex/EA = 1:1); Mp: 181-183°C; IR (neat, cm^{-1}): 3237 (w, br), 3029 (w), 2908 (w), 2839 (w), 2240 (w), 1682 (s), 1671 (s), 1505 (s), 1245 (s), 1073 (s), 771 (s); ^1H NMR (DMSO-d_6, 500 MHz): δ 7.60 (td, J = 7.4, 1.3 Hz, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.47 (td, J = 7.4, 1.0 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 7.40 (d, J = 8.7 Hz, 2H), 7.19 (t, J = 9.0 Hz, 1H), 7.11 (ddd, J = 8.5, 5.4, 2.2 Hz, 1H), 7.02 (dd, J = 6.4, 2.3 Hz, 1H), 6.90 (s, 1H), 6.88 (d, J = 8.7 Hz, 2H), 4.74 (d, J = 15.3 Hz, 1H), 4.53 (d, J = 15.3 Hz, 1H), 3.74 (s, 3H), 3.44 (d, J = 13.8 Hz, 1H), 3.23 (d, J = 13.8 Hz, 1H); ^{19}F NMR (DMSO-d_6, 471 MHz): δ -111.6; ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.3, 162.1, 160.1, 158.3, 146.4, 137.4 (d, J = 8.5 Hz), 134.8, 133.1 (d, J = 3.6 Hz), 131.8, 131.1, 130.8, 129.6, 129.4, 122.7 (d, J = 120.0 Hz), 115.6 (d, J = 19.2 Hz), 113.8, 113.6, 99.1 (d, J = 15.1 Hz), 90.5, 55.0, 41.6, 41.4; HRMS (ESI^+) *m/z* $[C_{24}H_{19}N_2O_3FNa]^+$ calcd: 425.1272; found: 425.1263.



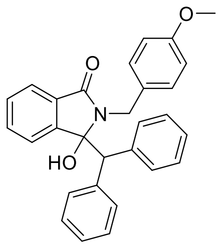
3-Cinnamyl-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.4h**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and **3.3h** (124.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.4h** (181 mg, 94%) as an off-white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4h** (157 mg, 81%). R_f = 0.22 (Hex/EA = 2:1); Mp: 163-164°C; IR (neat, cm^{-1}): 3231 (w, br), 3002 (w), 2833 (w), 1672 (s), 1239 (s), 755 (s), 692 (s); ^1H NMR (DMSO-d_6, 500 MHz): δ 7.66-7.60 (m, 3H), 7.49 (m, 1H), 7.44 (d, J = 8.7 Hz, 2H), 7.21-7.17 (m, 2H), 7.14 (m, 1H), 6.96-6.94 (m, 2H), 6.89 (d, J = 8.7 Hz, 2H), 6.70 (s, 1H), 5.90 (d, J = 15.8 Hz, 1H), 5.33 (dt, J = 15.8, 7.3 Hz, 1H), 4.78 (d, J = 15.2 Hz, 1H), 4.42 (d, J = 15.2 Hz, 1H), 3.72 (s, 3H), 2.95 (dd, J = 14.4, 7.2 Hz, 1H), 2.76 (dd, J = 14.3, 7.3 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.6, 158.3, 147.3, 136.7, 133.0, 132.0, 131.1, 129.7, 129.1, 128.4, 127.2, 125.6, 123.0, 122.6, 122.3, 113.6, 90.4, 55.0, 40.8, 40.5; HRMS (ESI$^+$) *m/z* $[C_{25}H_{23}NO_3Na]^+$ calcd: 408.1570; found: 408.1577.



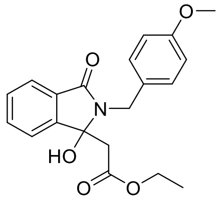
3-Butyl-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.4i**)

Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and 3-butylideneisobenzofuran-1(3*H*)-one (94.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.4i** (95 mg, 58%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4i** (93 mg, 57%). R_f = 0.30 (Hex/EA = 2:1); Mp: 164-165°C; IR (neat, cm^{-1}): 3281 (w, br), 2955 (w), 2857 (w), 1665 (s), 1250 (m), 1030 (m), 765 (s), 701 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.62 (d, J = 7.5 Hz, 1H), 7.52 (td, J = 7.4, 1.1 Hz, 1H), 7.46 (d, J = 7.5 Hz, 1H), 7.40 (td, J = 7.5, 1.1 Hz, 1H), 7.33 (d, J = 8.7 Hz, 2H), 6.76 (d, J = 8.7 Hz, 2H), 4.39 (d, J = 15.0 Hz, 1H), 4.34 (d, J = 15.0 Hz, 1H), 3.74 (bs, 1H), 3.72 (s, 3H), 2.02 (ddd, J = 13.9, 11.8, 5.4 Hz, 1H), 1.91 (ddd, J = 14.0, 11.7, 4.7 Hz, 1H), 0.88 (m, 1H), 0.74 (m, 1H), 0.52 (t, J = 7.3 Hz, 3H), 0.42-0.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.9, 158.9, 147.1, 132.5, 131.1, 130.6, 130.2, 129.5, 123.4, 121.8, 113.8, 92.0, 55.4, 41.4, 36.2, 25.4, 22.3, 13.7; HRMS (ESI$^+$) *m/z* [$C_{20}H_{23}NO_3Na$]$^+$ calcd: 348.1570; found: 348.1570.



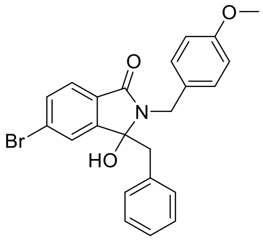
3-Benzhydryl-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.4j**)

Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and **3.3j** (149.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1) gave **3.4j** (145 mg, 67%) as a white solid. R_f = 0.29 (Hex/EA = 2:1); Mp: 168-169°C; IR (neat, cm^{-1}): 3309 (w, br), 3026 (w), 2907 (w), 2835 (w), 1686 (s), 1672 (m), 1511 (s), 1252 (s), 723 (s), 698 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.68 (m, 1H), 7.43 (td, *J* = 7.5, 1.0 Hz, 1H), 7.41-7.38 (m, 2H), 7.29-7.25 (m, 4H), 7.17 (d, *J* = 8.7 Hz, 2H), 7.13 (m, 1H), 7.09-7.06 (m, 2H), 6.69-6.67 (m, 2H), 6.65 (d, *J* = 8.7 Hz, 2H), 6.46 (dt, *J* = 7.6, 0.9 Hz, 1H), 4.78 (s, 1H), 4.48 (d, *J* = 15.2 Hz, 1H), 4.16 (d, *J* = 15.2 Hz, 1H), 3.70 (s, 3H), 3.30 (bs, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 158.6, 145.8, 139.0, 138.3, 132.3, 131.5, 131.0, 130.5, 129.9, 129.8, 129.1, 128.4, 127.9, 127.2, 127.0, 124.4, 123.4, 113.7, 92.7, 58.6, 55.3, 42.5; HRMS (ESI$^+$) *m/z* [$C_{29}H_{26}NO_3$]$^+$ calcd: 436.1907; found: 436.1906.



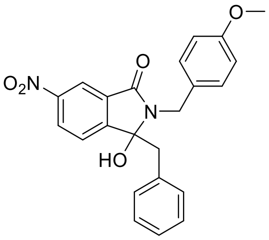
Ethyl 2-(1-hydroxy-2-(4-methoxybenzyl)-3-oxoisoindolin-1-yl)acetate (**3.4k**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and **3.3k** (109.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 4:1) gave **3.4k** (132 mg, 74%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4k** (155 mg, 87%). R_f = 0.21 (DCM/EA = 2:1); Mp: 147-149°C; IR (neat, cm^{-1}): 3264 (w, br), 2979 (w), 2902 (w), 1736 (m), 1660 (s), 1250 (s), 1069 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.72 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.54 (td, *J* = 7.4, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.46 (td, *J* = 7.3, 1.2 Hz, 1H), 7.27 (d, *J* = 8.8 Hz, 2H), 6.78 (d, *J* = 8.7 Hz, 2H), 4.91 (s, 1H), 4.70 (d, *J* = 15.5 Hz, 1H), 4.43 (d, *J* = 15.5 Hz, 1H), 3.84 (m, 2H), 3.74 (s, 3H), 2.93 (d, *J* = 16.3 Hz, 1H), 2.84 (d, *J* = 16.3 Hz, 1H), 1.00 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0, 167.8, 158.9, 146.7, 132.5, 130.9, 130.2, 129.9, 129.6, 123.6, 121.8, 113.9, 88.3, 61.2, 55.3, 41.6, 41.5, 13.8; HRMS (ESI$^+$) *m/z* $[C_{20}H_{22}NO_5]^+$ calcd: 356.1493; found: 356.1482.



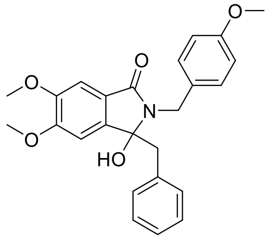
3-Benzyl-5-bromo-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.4l**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid), **3.3l** (150.6 mg, 0.5 mmol, 1.0 equiv.) and toluene (1.0 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1, then Hex/EA/DCM = 1:1:1) gave **3.4l** (161 mg, 73%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4l** (178 mg, 81%). R_f = 0.18 (Hex/EA = 2:1); Mp: 175-176°C; IR (neat, cm^{-1}): 3311 (w, br), 3002 (w), 2830 (w), 1685 (m), 1675 (m), 1244 (m), 1073 (m), 697 (s); ^{1}H NMR (CD_3OD, 500 MHz): δ 7.59 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.44 (d, *J* = 8.1 Hz, 1H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 1.7 Hz, 1H), 7.12-7.05 (m, 3H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.82-6.80 (m, 2H), 4.76 (d, *J* = 15.2 Hz, 1H), 4.69 (d, *J* = 15.2 Hz, 1H), 3.76 (s, 3H), 3.42 (d, *J* = 13.8 Hz, 1H), 3.14 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (CD_3OD, 125 MHz): δ 168.3, 160.4, 150.3, 136.0, 133.7, 131.60, 131.55, 131.4, 130.9, 128.8, 127.91, 127.87, 127.4, 125.2, 114.7, 92.7, 55.7, 44.7, 43.4; HRMS (ESI$^+$) *m/z* $[C_{23}H_{20}NO_3BrNa]^+$ calcd: 460.0519; found: 460.0519.



3-Benzyl-3-hydroxy-2-(4-methoxybenzyl)-6-nitroisoindolin-1-one (**3.4m**)

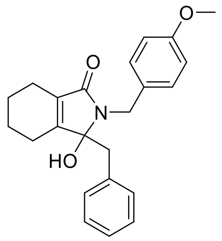
Following general procedure A, freshly distilled 4-methoxybenzyl amine (68.6 mg, 0.5 mmol, 1.0 equiv.; colorless liquid) and **3.3m** (133.6 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 4:1, then Hex/EA/DCM = 1:1:1) gave **3.4m** (180 mg, 89%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4m** (160 mg, 79%). $R_f = 0.33$ (Hex/EA = 2:1); Mp: 182-183°C; IR (neat, cm^{-1}): 3329 (w, br), 2931 (w), 2836 (w), 1690 (s), 1675 (s), 1536 (s), 1345 (s), 1248 (s), 703 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 8.43 (dd, J = 8.3, 2.1 Hz, 1H), 8.12 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 8.3 Hz, 1H), 7.42 (d, J = 8.7 Hz, 2H), 7.09-7.04 (m, 4H), 6.88 (d, J = 8.7 Hz, 2H), 6.81-6.79 (m, 2H), 4.76 (d, J = 15.3 Hz, 1H), 4.66 (d, J = 15.3 Hz, 1H), 3.72 (s, 3H), 3.48 (d, J = 13.8 Hz, 1H), 3.32 (d, J = 13.8 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 163.9, 158.3, 152.8, 148.5, 134.5, 132.7, 130.3, 130.0, 129.7, 127.7, 126.8, 126.7, 124.9, 116.9, 113.5, 91.2, 55.0, 42.7, 42.0; HRMS (ESI$^+$) *m/z* $[C_{23}H_{20}N_2O_5Na]^+$ calcd: 427.1264; found: 427.1272.



3-Benzyl-3-hydroxy-5,6-dimethoxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.4n**)

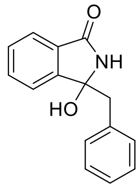
Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid), **3.3n** (141.1 mg, 0.5 mmol, 1.0 equiv.), and toluene (1.0 mL) were used. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 2:1) gave **3.4n** (190 mg, 91%) as a white solid. Alternatively, the mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.4n** (188 mg, 90%). $R_f = 0.33$ (DCM/EA = 4:1); Mp: 212-214°C; IR (neat, cm^{-1}): 3356 (w, br), 2931 (w), 2836 (w), 1679 (s), 1668 (m), 1250 (m), 1094 (m), 704 (m); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.38 (d, J = 8.7 Hz, 2H), 7.09-7.06 (m, 3H), 6.98 (s, 1H), 6.86 (d, J = 8.7 Hz, 2H), 6.85-6.83 (m, 2H), 6.79 (s, 1H), 6.58 (s, 1H), 4.69 (d, J = 15.5 Hz, 1H), 4.54 (d, J = 15.4 Hz, 1H), 3.76 (s, 3H), 3.72 (s, 6H), 3.40 (d, J = 13.6 Hz, 1H), 3.04 (d, J = 13.6 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz):

δ 166.4, 158.1, 151.7, 149.7, 140.3, 135.6, 131.3, 130.2, 129.3, 127.5, 126.4, 123.4, 113.4, 106.2, 104.3, 90.4, 55.7, 55.0, 43.6, 41.6; HRMS (ESI$^+$) *m/z* [$C_{25}H_{25}NO_5Na$]$^+$ calcd: 442.1625; found: 442.1615.



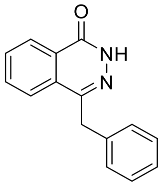
3-Benzyl-3-hydroxy-2-(4-methoxybenzyl)-2,3,4,5,6,7-hexahydro-1*H*-isoindol-1-one (**3.4o**)

Following general procedure B, freshly distilled 4-methoxybenzyl amine (102.9 mg, 0.75 mmol, 1.5 equiv.; colorless liquid) and **3.3o** (113.1 mg, 0.5 mmol, 1.0 equiv.) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1) gave **3.4o** (163 mg, 90%) as a white solid. R_f = 0.13 (Hex/EA = 2:1); Mp: 133-134°C; IR (neat, cm^{-1}): 3270 (w, br), 2937 (w), 2857 (w), 1673 (s), 1654 (s), 1239 (s), 1024 (s), 700 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.34 (d, *J* = 8.6 Hz, 2H), 7.20-7.16 (m, 3H), 6.98-6.96 (m, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 4.73 (d, *J* = 15.0 Hz, 1H), 4.34 (d, *J* = 15.0 Hz, 1H), 3.75 (s, 3H), 3.15 (d, *J* = 14.1 Hz, 1H), 3.09 (d, *J* = 14.1 Hz, 1H), 2.75 (s, 1H), 2.18 (m, 1H), 2.10-2.00 (m, 2H), 1.94 (m, 1H), 1.64-1.53 (m, 3H), 1.44 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 170.1, 158.7, 154.3, 134.8, 132.7, 131.3, 130.1, 129.6, 128.2, 127.1, 113.9, 92.4, 55.4, 42.1, 41.1, 22.0, 21.8, 21.7, 19.8; HRMS (ESI$^+$) *m/z* [$C_{23}H_{25}NO_3Na$]$^+$ calcd: 386.1727; found: 386.1736.



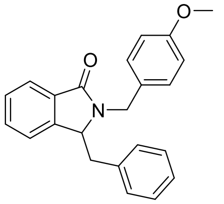
3-Benzyl-3-hydroxyisoindolin-1-one (**3.5a**)

To a 50 mL round bottom flask was added **3.2a** (359.4 mg, 1 mmol, 1.0 equiv.) and MeCN (15 mL). A solution of cerium ammonium nitrate (1.64 g, 3 mmol, 3.0 equiv.) in H_2O (8 mL) was added dropwise. The reaction mixture was stirred at rt for 45 minutes. The mixture was then quenched with sat. $NaHCO_3$ (caution: violent gas evolution) and stirred at rt for 10 minutes. The product was extracted in diethyl ether (4 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 3:1 to 1:3) to afford **3.5a** (123 mg, 51%) as a beige solid. $R_f = 0.10$ (Hex/EA = 2:1); Mp: 134-136ºC; IR (neat, cm^{-1}): 3341 (w, br), 3201 (w, br), 3026 (w), 1673 (s), 698 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.54 (td, J = 7.5, 1.2 Hz, 1H), 7.46-7.43 (m, 2H), 7.35 (td, J = 7.4, 1.1 Hz, 1H), 7.24-7.22 (m, 3H), 7.18-7.16 (m, 2H), 6.80 (bs, 1H), 3.98 (s, 1H), 3.36 (d, J = 13.6 Hz, 1H), 3.12 (d, J = 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.0, 148.5, 135.0, 132.8, 130.7, 130.5, 129.7, 128.4, 127.3, 123.6, 122.5, 87.8, 45.1; HRMS (ESI^+) m/z $[C_{15}H_{13}NO_2Na]^+$ calcd: 262.0838; found: 262.0841. Characterization matched reported data.[28]



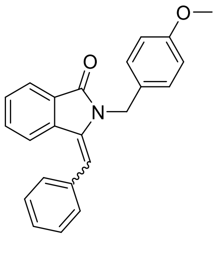
4-Benzylphthalazin-1(2*H*)-one (**3.5b**)

To a pressure vial were added **3.2a** (359.4 mg, 1 mmol, 1.0 equiv.), $N_2H_4 \cdot H_2O$ (0.73 mL, 15 mmol, 15.0 equiv.), and EtOH (1 mL). The reaction mixture was stirred at 120ºC over the weekend (about 65 hours). The mixture was then cooled to rt, and a yellow precipitate formed. The suspension was further cooled to 0ºC before adding H_2O (4 mL) dropwise while the mixture was stirred gently. The mixture was vacuum filtered and the filter cake was washed with H_2O and dried under vacuum to afford **3.5b** (219 mg, 92%) as a yellow solid. $R_f = 0.15$ (Hex/EA = 2:1); Mp: 192-194ºC; IR (neat, cm^{-1}): 3164 (w), 3007 (w), 2904 (w), 1655 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 11.45 (bs, 1H), 8.49 (m, 1H), 7.77-7.71 (m, 3H), 7.30-7.27 (m, 4H), 7.22 (m, 1H), 4.33 (s, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.1, 146.5, 137.8, 133.6, 131.4, 130.0, 128.9, 128.6, 128.4, 127.1, 126.9, 125.5, 39.0; HRMS (ESI^+) m/z $[C_{15}H_{13}N_2O]^+$ calcd: 237.1022; found: 237.1019. Characterization matched reported data.[29]



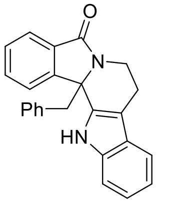
3-Benzyl-2-(4-methoxybenzyl)isoindolin-1-one (**3.5c**)

To a 50 mL round bottom flask was added **3.2a** (359.4 mg, 1 mmol, 1.0 equiv.) and DCM (10 mL). The atmosphere was changed to N_2. The mixture was cooled to 0°C and $BF_3 \cdot Et_2O$ (0.37 mL, 3 mmol, 3.0 equiv.) was added dropwise, followed by triethylsilane (0.48 mL, 3 mmol, 3.0 equiv.) also dropwise. The mixture was stirred at 0°C for 2 hours, then at rt overnight. The mixture was diluted in DCM (10 mL), washed with H_2O (1 × 10 mL) and sat. $NaHCO_3$ (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 5:1 to 3:1) to afford **3.5c** (342 mg, quant.) as a colorless oil, which solidifies upon standing. $R_f = 0.33$ (Hex/EA = 2:1); Mp: 86-88°C; IR (neat, cm^{-1}): 3026 (w), 2932 (w), 2835 (w), 1682 (s), 1511 (s), 1244 (s), 751 (s), 693 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.83 (m, 1H), 7.40 (td, J = 7.4, 0.8 Hz, 1H), 7.37 (td, J = 7.4, 1.6 Hz 1H), 7.26-7.22 (m, 3H), 7.17 (d, J = 8.7 Hz, 2H), 7.01-6.99 (m, 2H), 6.86 (m, 1H), 6.85 (d, J = 8.7 Hz, 2H), 5.41 (d, J = 15.0 Hz, 1H), 4.56 (dd, J = 7.9, 4.8 Hz, 1H), 4.16 (d, J = 15.0 Hz, 1H), 3.78 (s, 3H), 3.37 (dd, J = 13.8, 4.9 Hz, 1H), 2.82 (dd, J = 13.8, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.3, 159.1, 145.1, 136.2, 132.1, 131.1, 129.5, 129.2, 128.5, 128.2, 127.0, 123.8, 123.0, 114.2, 59.5, 55.3, 43.6, 38.4; HRMS (ESI$^+$) *m/z* $[C_{23}H_{22}NO_2]^+$ calcd: 344.1645; found: 344.1639.



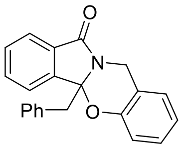
3-Benzylidene-2-(4-methoxybenzyl)isoindolin-1-one (**3.5d**)

To a 50 mL round bottom flask were added **3.2a** (359.4 mg, 1 mmol) and DCM (5 mL). Conc. H_2SO_4 (2 drops) was added and the reaction mixture was stirred at rt overnight. The mixture was diluted in DCM (5 mL) and washed with sat. $NaHCO_3$ (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 5:1) to afford **3.5d** (325 mg, 95%, *E*/*Z* = 14:1) as a white solid. $R_f = 0.43$ (Hex/EA = 2:1); Mp: 117-118°C; IR (neat, cm^{-1}): 2995 (w), 2838 (w), 1703 (s), 1511 (m), 1243 (m), 770 (s), 690 (s); (*E*)-isomer: ^1H NMR ($CDCl_3$, 500 MHz): δ 7.91 (dt, J = 7.5, 1.0 Hz, 1H), 7.45-7.36 (m, 8H), 7.26 (d, J = 8.7 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 6.51 (s, 1H), 5.07 (s, 2H), 3.78 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): 166.8, 158.9, 136.0, 135.2, 135.2, 131.7, 130.3, 129.6, 129.3, 129.0, 128.6, 128.4, 127.8, 123.4, 123.2, 114.2, 111.6, 55.3, 42.8; (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.93 (dt, *J* = 7.4, 1.1, 1H), 7.72 (dt, *J* = 7.7, 1.0 Hz, 1H), 7.60 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51 (td, *J* = 7.5, 0.9 Hz, 1H), 7.41-7.32 (m, 3H), 7.14-7.12 (m, 2H), 6.72 (s, 1H), 6.60 (d, *J* = 8.7 Hz, 2H), 6.47 (d, *J* = 8.7 Hz, 2H), 4.90 (s, 2H), 3.71 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.1, 158.5, 138.6, 134.8, 134.4, 132.1, 129.8, 129.1, 128.9, 128.2, 128.0, 127.9, 127.5, 123.5, 119.3, 113.5, 107.1, 55.2, 44.3; HRMS (ESI$^+$) *m/z* $[C_{23}H_{20}NO_2]^+$ calcd: 342.1489; found: 342.1481. Characterization matched reported data.[30]



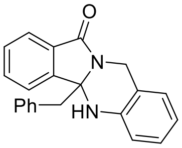
13b-Benzyl-7,8,13,13b-tetrahydro-5*H*-benzo[1,2]indolizino[8,7-*b*]indol-5-one (**3.5e**)

To a 25 mL round bottom flask were added **3.2j** (261.0 mg, 0.68 mmol, 1.0 equiv.) and DCM (4 mL). TFA (104 µL, 1.36 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at rt for 1 hour. The mixture was diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA/DCM= 5:1:1 to 1:1:1) to afford **3.5e** (224 mg, 90%) as a light yellow solid. R_f = 0.43 (Hex/EA = 1:1); Mp: 271°C (decomp.); IR (neat, cm^{-1}): 3329 (w), 3278 (w), 3029 (w), 2908 (w), 1659 (s), 737 (m), 700 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.53 (s, 1H), 8.47 (d, *J* = 7.7 Hz, 1H), 7.70 (td, *J* = 7.5, 1.2 Hz, 1H), 7.49 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.45 (m, 1H), 7.43-7.39 (m, 2H), 7.13 (m, 1H), 7.05-7.02 (m, 3H), 7.01 (m, 1H), 6.83-6.81 (m, 2H), 4.54 (dd, *J* = 13.1, 5.6 Hz, 1H), 3.65 (d, *J* = 13.8 Hz, 1H), 3.62 (d, *J* = 13.8 Hz, 1H), 3.43 (ddd, *J* = 13.1, 11.6, 4.7 Hz, 1H), 2.80 (dd, *J* = 15.3, 4.0 Hz, 1H), 2.68 (ddd, *J* = 15.3, 11.6, 6.1 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 167.6, 146.9, 136.3, 135.0, 134.5, 131.7, 131.1, 129.8, 128.5, 127.5, 126.5, 126.0, 123.4, 122.8, 121.7, 119.0, 118.4, 111.3, 107.0, 65.6, 43.0, 35.7, 21.5; HRMS (APCI$^+$) *m/z* $[C_{25}H_{21}N_2O]^+$ calcd: 365.1648; found: 365.1664. Characterization matched reported data.[31]



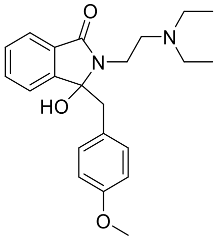
4b-Benzyl-10*H*-benzo[5,6][1,3]oxazino[2,3-*a*]isoindol-12(4b*H*)-one (**3.5f**)

To a 25 mL round bottom flask were added **3.2l** (314.0 mg, 0.9 mmol, 1.0 equiv.) and DCM (5 mL). TFA (138 μL, 1.8 mmol, 2.0 equiv.) was added and the reaction mixture was stirred at rt for 30 minutes. The mixture was diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1) to afford **3.5f** (280 mg, 95%) as a light yellow semi-solid. $R_f = 0.50$ (Hex/EA = 2:1); IR (neat, cm^{-1}): 3026 (w), 2854 (w), 1705 (s), 1403 (s), 1221 (s), 754 (s), 699 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.77 (dt, J = 7.3, 1.0 Hz, 1H), 7.55 (td, J = 7.5, 1.2 Hz, 1H), 7.48 (td, J = 7.5, 1.1 Hz, 1H), 7.40 (dt, J = 7.4, 1.0 Hz, 1H), 7.28-7.23 (m, 2H), 7.19-7.14 (m, 3H), 7.06-7.02 (m, 2H), 6.95-6.93 (m, 2H), 5.34 (d, J = 17.1 Hz, 1H), 4.58 (d, J = 17.0 Hz, 1H), 3.66 (d, J = 14.1 Hz, 1H), 3.21 (d, J = 14.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.3, 150.9, 143.7, 133.7, 131.9, 131.6, 130.1, 130.0, 128.7, 128.2, 127.21, 127.17, 123.7, 123.2, 122.0, 118.1, 117.7, 90.0, 40.2, 37.3; HRMS ($APCI^+$) m/z $[C_{22}H_{18}NO_2]^+$ calcd: 328.1332; found: 328.1338. Characterization matched reported data.[32]



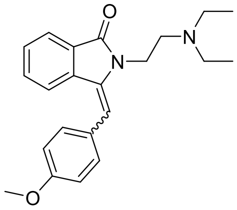
4b-Benzyl-5,10-dihydroisoindolo[1,2-*b*]quinazolin-12(4b*H*)-one (**3.5g**)

To a 25 mL round bottom flask were added **3.2m** (302.0 mg, 0.88 mmol, 1.0 equiv.) and DCM (5 mL). TFA (270 μL, 3.52 mmol, 4.0 equiv.) was added and the reaction mixture was stirred at rt for 30 minutes. The mixture was diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The product was purified from the residue by flash chromatography (SiO_2, Hex/EA = 10:1 to 3:1) to afford **3.5g** (205 mg, 71%) as a yellow solid. $R_f = 0.30$ (Hex/EA = 2:1); Mp: 152-154°C; IR (neat, cm^{-1}): 3318 (w), 3032 (w), 2841 (w), 1685 (s), 1484 (m), 739 (m), 687 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.76 (m, 1H), 7.49-7.43 (m, 2H), 7.20-7.14 (m, 6H), 6.92-6.89 (m, 3H), 6.76 (dd, J = 8.0, 1.2 Hz, 1H), 5.33 (d, J = 17.2 Hz, 1H), 4.68 (bs, 1H), 4.57 (d, J = 17.1 Hz, 1H), 3.49 (d, J = 13.6 Hz, 1H), 3.05 (d, J = 13.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.2, 145.9, 140.0, 134.6, 131.8, 131.5, 130.4, 129.4, 128.2, 128.1, 127.3, 127.2, 124.1, 122.0, 120.1, 118.2, 117.5, 73.8, 42.3, 38.6; HRMS (APCI$^+$) *m/z* $[C_{22}H_{19}N_2O]^+$ calcd: 327.1492; found: 327.1502. Characterization matched reported data.[32]



2-(2-(Diethylamino)ethyl)-3-hydroxy-3-(4-methoxybenzyl)isoindolin-1-one (**3.5h**)

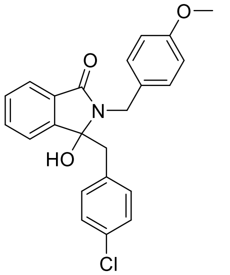
Following general procedure A, freshly distilled *N*,*N*-diethylethylenediamine (116.2 mg, 1.0 mmol, 1.0 equiv.; colorless liquid), **3.3a** (252.3 mg, 1.0 mmol, 1.0 equiv.), and TBD (13.9 mg, 0.1 mmol, 0.1 equiv.) were used. Purification by flash chromatography (SiO_2, DCM/EA = 4:1 + 1% TEA) gave **3.5h** (367 mg, quant.) as a yellow oil. $R_f = 0.23$ (Hex/EA = 1:1 + 1% TEA); IR (neat, cm^{-1}): 2973 (w), 2934 (w), 2833 (w), 2750 (w, br), 1690 (s), 1510 (s), 1247 (s), 1032 (m), 700 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.59 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.50 (td, *J* = 7.4, 1.1 Hz, 1H), 7.41 (dt, *J* = 7.5, 0.9 Hz, 1H), 7.35 (td, *J* = 7.3, 1.1 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 2H), 6.62 (d, *J* = 8.7 Hz, 2H), 4.02 (dt, *J* = 14.8, 2.6 Hz, 1H), 3.70 (s, 3H), 3.32 (d, *J* = 14.0 Hz, 1H), 3.29 (m, 1H), 3.14 (d, *J* = 14.0 Hz, 1H), 2.87 (ddd, *J* = 13.9, 12.1, 2.9 Hz, 1H), 2.68 (dq, *J* = 12.8, 7.2 Hz, 2H), 2.44 (dq, *J* = 12.8, 7.2 Hz, 2H), 2.39 (m, 1H), 0.98 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.7, 158.4, 148.7, 131.9, 131.1, 130.8, 128.7, 127.4, 123.0, 122.3, 113.4, 89.2, 55.2, 51.9, 47.1, 44.2, 38.4, 10.9; HRMS (ESI$^+$) *m/z* $[C_{22}H_{29}N_2O_3]^+$ calcd: 369.2173; found: 369.2177.



2-(2-(Diethylamino)ethyl)-3-(4-methoxybenzylidene)isoindolin-1-one (**3.5i**, **AL-12**)

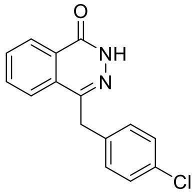
To a 25 mL round bottom flask were added **3.5h** (367.0 mg, 1.0 mmol, 1.0 equiv.), TEA (0.56 mL, 4.0 mmol, 4.0 equiv.), and DCM (2 mL). The mixture was cooled to 0°C before dropwise addition of methanesulfonyl chloride (93 μL, 1.2 mmol, 1.2 equiv.). The reaction mixture was stirred at room temperature overnight. The mixture was diluted in DCM (10 mL), washed with sat. Na_2CO_3

(2 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 + 1% TEA) gave **3.5i** (333 mg, 95%, *E*/*Z* = 9:1) as a light brown oil. R_f = 0.30 (DCM/EA = 4:1 + 1% TEA); IR (neat, cm^{-1}): 2964 (w), 2931 (w), 2804 (s), 1696 (s), 1510 (s), 1245 (s), 1030 (m), 755 (s); (*E*)-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.82 (dt, *J* = 7.6, 1.1 Hz, 1H), 7.40 (td, *J* = 7.4, 1.1 Hz, 1H), 7.38-7.36 (m, 3H), 7.31 (td, *J* = 7.5, 1.0 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 2H), 6.57 (s, 1H), 3.97 (m, 2H), 3.88 (s, 3H), 2.76 (m, 2H), 2.65 (q, *J* = 7.1 Hz, 4H), 1.08 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.6, 159.4, 135.9, 135.3, 131.4, 131.1, 131.0, 130.5, 129.1, 127.5, 123.2, 114.2, 110.3, 55.5, 50.7, 47.7, 38.2, 12.3; (*Z*)-isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84 (dt, *J* = 7.8, 1.1 Hz, 1H), 7.72 (dt, *J* = 7.9, 1.0 Hz, 1H), 7.57 (td, *J* = 7.6, 1.1 Hz, 1H), 7.47 (td, *J* = 7.5, 1.0 Hz, 1H), 7.29 (m, 2H), 6.93 (d, *J* = 8.9 Hz, 2H), 6.71 (s, 1H), 3.85 (m, 2H), 3.83 (s, 3H), 2.25 (m, 2H), 2.21 (q, *J* = 7.1 Hz, 4H), 0.78 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.1, 159.3, 138.8, 134.5, 131.9, 131.1, 128.8, 128.5, 127.1, 123.3, 119.2, 114.0, 106.5, 55.5, 50.4, 47.3, 39.5, 12.3; HRMS (ESI$^+$) *m/z* $[C_{22}H_{27}N_2O_2]^+$ calcd: 351.2067; found: 351.2078.



3-(4-Chlorobenzyl)-3-hydroxy-2-(4-methoxybenzyl)isoindolin-1-one (**3.5j**)

Following general procedure A, freshly distilled 4-methoxybenzyl amine (685.9 mg, 5.0 mmol, 1.0 equiv.; colorless liquid), **3.3s** (1.28 g, 5.0 mmol, 1.0 equiv.), and TBD (69.6 mg, 0.5 mmol, 0.1 equiv.) were used. The mixture was diluted in toluene, the product was collected by vacuum filtration, washed with toluene and hexanes, and dried under vacuum to give **3.5j** (1.57 g, 80%) as a white solid. R_f = 0.25 (Hex/EA = 2:1); Mp: 202-204°C; IR (neat, cm^{-1}): 3219 (m, br), 2940 (w), 2830 (w), 1671 (s), 1239 (s), 735 (s); ^{1}H NMR (DMSO-d_6, 500 MHz): δ 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.43 (t, *J* = 7.3 Hz, 1H), 7.41-7.39 (m, 3H), 7.09 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.9 Hz, 2H), 6.81 (bs, 1H), 6.76 (d, *J* = 8.5 Hz, 2H), 4.71 (d, *J* = 15.3 Hz, 1H), 4.57 (d, *J* = 15.4 Hz, 1H), 3.73 (s, 3H), 3.39 (d, *J* = 13.7 Hz, 1H), 3.21 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (DMSO-d_6, 125 MHz): δ 166.1, 158.2, 146.7, 134.3, 131.8, 131.6, 131.3, 131.2, 130.8, 129.5, 129.1, 127.4, 123.1, 122.0, 113.4, 90.8, 55.0, 42.4, 41.6; HRMS (ESI$^+$) *m/z* [$C_{23}H_{20}NO_3ClNa$]$^+$ calcd: 416.1024; found: 416.1015.

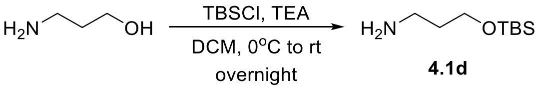


4-(4-Chlorobenzyl)phthalazin-1(2*H*)-one (**3.5k**)

To a 20 mL reaction tube were added **3.5j** (787.7 mg, 2 mmol, 1.0 equiv.), ethanol (4 mL), and N_2H_4•H_2O (1.46 mL, 30 mmol, 15.0 equiv.). The reaction mixture was stirred at 110°C over the weekend (about 60 hours). The mixture was then cooled to rt, and a yellow precipitate formed. The mixture was further cooled to 0°C, and water (30 mL) was added dropwise while the mixture was stirred gently. The solid was collected by vacuum filtration, washed with water, diethyl ether, and hexanes, and dried under vacuum to afford **3.5k** (500 mg, 92%) as a yellow solid. R_f = 0.45 (Hex/EA = 1:1); Mp: 209-210°C; IR (neat, cm^{-1}): 3163 (w), 3008 (w), 2902 (w, br), 1662 (s), 1485 (m), 798 (s); ^{1}H NMR (DMSO-*d*$_6$, 500 MHz): δ 12.58 (bs, 1H), 8.25 (dd, *J* = 7.8, 1.0 Hz, 1H), 7.91 (m, 1H), 7.85 (td, *J* = 7.6, 1.4 Hz, 1H), 7.80 (m, 1H), 7.33 (s, 4H), 4.29 (s, 2H); ^{13}C NMR (DMSO-*d*$_6$, 125 MHz): δ 159.4, 144.9, 137.2, 133.5, 131.5, 131.1, 130.5, 129.1, 128.4, 127.9, 126.0, 125.5, 36.8; HRMS (ESI$^+$) *m/z* [$C_{15}H_{11}N_2OClNa$]$^+$ calcd: 293.0452; found: 293.0463.

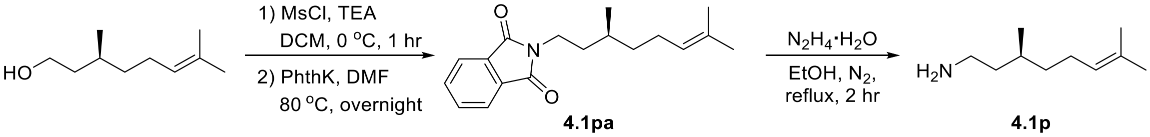
7.4 Experimental Details for Chapter 4

7.4.1 Synthesis and Characterization of Starting Materials and Intermediates



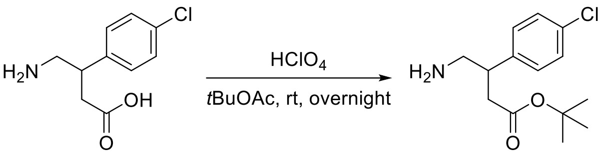
(2,2-Dimethyl-1,3-dioxolan-4-yl)methanamine (**4.1d**)

The same procedure reported for compound **2.1e** was followed.



(*S*)-3,7-Dimethyloct-6-en-1-amine (**4.1p**)

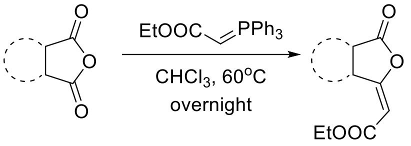
The same procedure reported for compound **3.1n** was followed.



4.1w

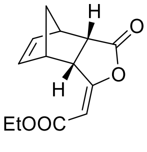
tert-Butyl 4-amino-3-(4-chlorophenyl)butanoate (**4.1w**)

The same procedure reported for compound **2.1u** was followed.



General procedure for the synthesis of enol lactones from non-aromatic cyclic anhydrides: To a round bottom flask were added the desired cyclic anhydride (1.0 equiv.), ethyl (triphenylphosphoranylidene) acetate (1.1 equiv.), and ethanol-free chloroform (15 mL/5 mmol anhydride). The reaction was stirred at 60°C overnight. The mixture was then cooled to rt, and the solvent was evaporated under vacuum. The residue was dissolved in a 1:1 mixture of hexanes and diethyl ether (15 mL/5 mmol anhydride). A white precipitate appeared and the mixture was put into a freezer for 30 minutes. The solid was filtered off, and the solvent was evaporated under vacuum. The residue was purified by flash chromatography to afford the product.

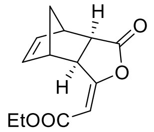
Note: The enol lactone products are very sensitive to nucleophiles. Ethanol-free chloroform must be used for the synthesis of such compounds. Alternatively, toluene can be used as a solvent. For the characterization of these compounds by mass spectrometry, even trace amount of methanol should be avoided in the system. Otherwise, only the methanol adduct is detected.



Enol lactone from carbic anhydride (**4.3**)

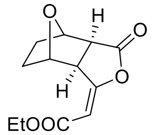
Following the general procedure, carbic anhydride (1.64 g, 10 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (3.83 g, 11 mmol, 1.1 equiv.), and ethanol-free chloroform (30 mL) were used. Purification by flash chromatography (SiO$_2$, Hex/EA = 20:1 to 10:1) gave **4.3**

(1.83 g, 78%) as a light yellow sticky oil, which solidifies to a white solid in freezer. This solidification process can take up to a week. R_f = 0.68 (Hex/EA = 2:1); Mp: 57-58°C; IR (neat, cm^{-1}): 2982 (w), 2875 (w), 1805 (m), 1709 (m), 1651 (s), 1091 (s), 1036 (m), 912 (m), 728 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.20 (dd, J = 5.8, 2.9 Hz, 1H), 6.14 (dd, J = 5.7, 3.0 Hz, 1H), 5.49 (d, J = 1.8 Hz, 1H), 4.18 (qd, J = 7.2, 3.2 Hz, 2H), 4.10 (ddd, J = 8.5, 4.3, 1.8 Hz, 1H), 3.73 (m, 1H), 3.39 (m, 1H), 3.33 (dd, J = 8.5, 4.6 Hz, 1H), 1.62 (dt, J = 8.9, 1.7 Hz, 1H), 1.53 (dt, J = 8.8, 1.6 Hz, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.8, 168.6, 166.5, 135.8, 135.2, 97.1, 60.2, 51.8, 47.0, 46.2, 45.52, 45.45, 14.4; HRMS (ESI$^+$) *m/z* [$C_{13}H_{14}O_4Na$]$^+$ calcd: 257.0784; found: 257.0775.



Enol lactone from *cis*-*exo*-5-norbornene-2,3-dicarboxylic anhydride (**4.3a**)

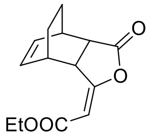
Following the general procedure, *cis*-*exo*-5-norbornene-2,3-dicarboxylic anhydride (821.0 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO$_2$, Hex/EA = 50:1 to 10:1) gave **4.3a** (541 mg, 46%) as a white solid. R_f = 0.58 (Hex/EA = 5:1); Mp: 32-33°C; IR (neat, cm^{-1}): 2985 (w), 2910 (w), 1811 (s), 1706 (s), 1647 (s), 1093 (s), 1039 (s), 841 (s), 719 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.37 (dd, J = 5.7, 3.1 Hz, 1H), 6.26 (dd, J = 5.7, 3.1 Hz, 1H), 5.63 (d, J = 1.8 Hz, 1H), 4.20 (qd, J = 7.2, 2.2 Hz, 2H), 3.60 (dq, J = 7.7, 1.4 Hz, 1H), 3.41 (m, 1H), 3.34 (m, 1H), 2.77 (dt, J = 7.7, 1.4 Hz, 1H), 1.52 (dp, J = 10.1, 1.6 Hz, 1H), 1.33 (dt, J = 10.1, 1.6 Hz, 1H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 174.0, 169.3, 166.4, 139.0, 137.3, 97.5, 60.3, 48.8, 47.4, 47.2, 46.6, 43.8, 14.4; HRMS (ESI$^+$) *m/z* [$C_{13}H_{14}O_4Na$]$^+$ calcd: 257.0784; found: 257.0794.



Enol lactone from norcantharidin (**4.3b**)

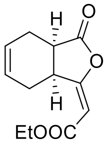
Following the general procedure, norcantharidin (840.8 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform

(15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.3b** (271 mg, 23%) as a white solid. $R_f = 0.18$ (Hex/EA = 5:1); Mp: 101-102°C; IR (neat, cm^{-1}): 3002 (w), 2955 (w), 1814 (m). 1705 (m), 1657 (s), 1106 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.67 (d, J = 1.7 Hz, 1H), 4.90 (dd, J = 15.2, 4.8 Hz, 2H), 4.18 (q, J = 7.2 Hz, 2H), 3.75 (dd, J = 7.9, 1.8 Hz, 1H), 2.92 (d, J = 7.8 Hz, 1H), 1.89-1.56 (m, 4H), 1.28 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.8, 168.9, 166.8, 97.4, 83.1, 80.1, 60.4, 48.7, 48.5, 28.5, 28.2, 14.4; HRMS (ESI$^+$) *m/z* $[C_{12}H_{14}O_5Na]^+$ calcd: 261.0733; found: 261.0733.



Enol lactone from bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (**4.3c**)

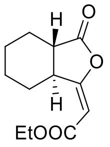
Following the general procedure, bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (891.0 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 10:1) gave **4.3c** (896 mg, 72%) as a colorless oil, which solidifies upon standing. R_f = 0.50 (Hex/EA = 5:1); Mp: 58-60°C; IR (neat, cm^{-1}): 2982 (w), 2937 (w), 2863 (s), 1810 (m), 1705 (m), 1650 (s), 1093 (s), 1035 (s), 730 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.25-6.18 (m, 2H), 5.56 (m, 1H), 4.16 (m, 2H), 3.72 (m, 1H), 3.36 (m, 1H), 3.11 (m, 1H), 2.93 (ddd, J = 9.2, 3.7, 1.8 Hz, 1H), 1.65 (m, 1H), 1.58 (m, 1H), 1.36 (m, 1H), 1.30-1.24 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.3, 170.7, 166.5, 133.6, 133.1, 97.2, 60.2, 43.7, 42.5, 32.5, 31.7, 24.0, 22.5, 14.3; HRMS (ESI$^+$) *m/z* $[C_{14}H_{16}O_4Na]^+$ calcd: 271.0941; found: 271.0933.



Enol lactone from *cis*-1,2,3,6-tetrahydrophthalic anhydride (**4.3d**)

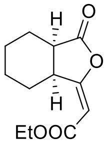
Following the general procedure, *cis*-1,2,3,6-tetrahydrophthalic anhydride (760.8 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) gave **4.3d** (485 mg, 44%) as a white solid. R_f = 0.54 (Hex/EA = 5:1); Mp: 31-32°C; IR (neat, cm^{-1}): 3041 (w), 2979 (w), 2851 (w), 1805 (s), 1703 (s), 1656 (s), 1096 (s), 841 (s); ^1H NMR

($CDCl_3$, 500 MHz): δ 5.83 (m, 2H), 5.62 (d, J = 1.1 Hz, 1H), 4.17 (qd, J = 7.1, 1.5 Hz, 2H), 3.98 (m, 1H), 3.06 (td, J = 8.6, 2.5 Hz, 1H), 2.58 (m, 2H), 2.33 (m, 1H), 2.04 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 175.7, 171.3, 166.3, 126.3, 126.0, 97.4, 60.3, 37.5, 36.0, 25.7, 21.8, 14.4; HRMS (APCI$^+$) m/z $[C_{12}H_{15}O_4]^+$ calcd: 223.0965; found: 223.0962.



Enol lactone from *trans*-1,2-cyclohexanedicarboxylic anhydride (**4.3e**)

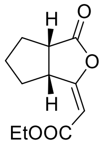
Following the general procedure, *trans*-1,2-cyclohexanedicarboxylic anhydride (770.8 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 15:1) gave **4.3e** (276 mg, 25%) as a white solid. R_f = 0.67 (Hex/EA = 5:1); Mp: 40-41°C; IR (neat, cm^{-1}): 2979 (w), 2907 (w), 2855 (w), 1800 (m), 1710 (m), 1665 (s), 1105 (s), 1037 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.57 (d, J = 0.9 Hz, 1H), 4.16 (qd, J = 7.2, 1.9 Hz, 2H), 3.85 (dt, J = 11.4, 6.9 Hz, 1H), 2.87 (m, 1H), 2.29-2.20 (m, 2H), 1.73-1.65 (m, 2H), 1.58 (m, 1H), 1.27 (t, J = 7.1 Hz, 3H), 1.24-1.14 (m, 2H), 1.04 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.5, 170.4, 166.3, 97.2, 60.3, 38.9, 38.5, 28.0, 23.2, 22.4, 21.9, 14.4; HRMS (APCI$^+$) m/z $[C_{12}H_{17}O_4]^+$ calcd: 225.1121; found: 225.1117.



Enol lactone from *cis*-1,2-cyclohexanedicarboxylic anhydride (**4.3f**)

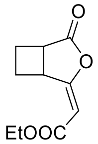
Following the general procedure, *cis*-1,2-cyclohexanedicarboxylic anhydride (770.8 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 15:1) gave **4.3f** (940 mg, 84%) as a white solid. R_f = 0.55 (Hex/EA = 5:1); Mp: 41-42°C; IR (neat, cm^{-1}): 2955 (w), 2857 (w), 1801 (m), 1713 (m), 1668 (s), 1107 (s), 1061 (s), 1038 (s), 918 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.52 (d, J = 0.9 Hz, 1H), 4.12 (qd, J = 7.1, 1.8 Hz, 2H), 3.81 (dt, J = 11.8, 6.9 Hz, 1H), 2.84 (m, 1H), 2.22 (m, 2H), 1.66 (m, 2H), 1.55 (m, 1H), 1.23 (t, J = 7.1

Hz, 3H), 1.21-1.07 (m, 2H), 1.00 (m, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 174.4, 170.4, 166.2, 97.0, 60.1, 38.8, 38.4, 27.9, 23.2, 22.3, 21.8, 14.3; HRMS (ESI$^+$) *m/z* [$C_{12}H_{16}O_4Na$]$^+$ calcd: 247.0941; found: 247.0935.



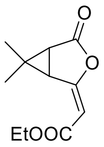
Enol lactone from *cis*-1,2-cyclopentanedicarboxylic anhydride (**4.3g**)

Following the general procedure, *cis*-1,2-cyclopentanedicarboxylic anhydride (700.7 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO$_2$, Hex/EA = 50:1 to 10:1) gave **4.3g** (591 mg, 56%) as a colorless oil. R$_f$ = 0.45 (Hex/EA = 5:1); IR (neat, cm^{-1}): 2975 (w), 2872 (w), 1807 (m), 1708 (m), 1651 (s), 1129 (m), 1068 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.62 (d, J = 1.7 Hz, 1H), 4.17 (qd, J = 7.2, 2.3 Hz, 2H), 4.06 (tdd, J = 9.2, 3.4, 1.7 Hz, 1H), 3.17 (td, J = 9.0, 2.3 Hz, 1H), 2.20 (m, 2H), 1.95 (m, 2H), 1.78 (m, 1H), 1.44 (m, 1H), 1.28 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 177.3, 172.1, 166.5, 96.8, 60.2, 43.8, 43.4, 35.0, 31.5, 25.6, 14.4; HRMS (ESI$^+$) *m/z* [$C_{11}H_{14}O_4Na$]$^+$ calcd: 233.0784; found: 233.0782.



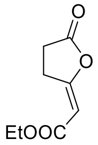
Enol lactone from 1,2-cyclobutanedicarboxylic anhydride (**4.3h**)

Following the general procedure, 1,2-cyclobutanedicarboxylic anhydride (630.6 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO$_2$, Hex/EA = 50:1 to 10:1) gave **4.3h** (378 mg, 39%) as a white solid. R$_f$ = 0.35 (Hex/EA = 5:1); Mp: 48-49°C; IR (neat, cm^{-1}): 3075 (w), 2984 (w), 2871 (w), 1806 (m), 1697 (m), 1650 (s), 1099 (s), 1034 (s), 855 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.60 (d, J = 1.5 Hz, 1H), 4.18 (m, 1H), 4.13 (qd, J = 7.2, 2.2 Hz, 2H), 3.28 (m, 1H), 2.82 (m, 1H), 2.64 (m, 1H), 2.26 (m, 1H), 2.15 (m, 1H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 176.4, 171.7, 166.3, 96.3, 60.2, 37.9, 36.0, 26.7, 23.1, 14.3; HRMS (ESI$^+$) *m/z* [$C_{10}H_{12}O_4Na$]$^+$ calcd: 219.0628; found: 219.0633.



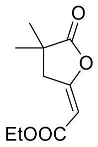
Enol lactone from caronic anhydride (**4.3i**)

Following the general procedure, caronic anhydride (700.7 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) gave **4.3i** (652 mg, 62%) as a colorless oil, which solidifies upon standing. $R_f = 0.16$ (Hex/EA = 5:1); Mp: 33-34°C; IR (neat, cm^{-1}): 2985 (w), 2902 (w), 1819 (m), 1711 (s), 1653 (s), 1248 (s), 1100 (s), 832 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.63 (s, 1H), 4.16 (qd, J = 7.2, 2.5 Hz, 2H), 3.49 (d, J = 5.0 Hz, 1H), 2.29 (d, J = 5.1 Hz, 1H), 1.28 (s, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.2, 166.7, 164.1, 98.4, 60.2, 35.2, 31.9, 29.7, 25.4, 16.0, 14.3; HRMS ($APCI^+$) m/z $[C_{11}H_{15}O_4]^+$ calcd: 211.0965; found: 211.0961.



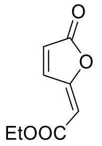
Enol lactone from succinic anhydride (**4.3j**)

Following the general procedure with modifications, succinic anhydride (1.00 g, 10 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (3.83 g, 11 mmol, 1.1 equiv.), and ethanol-free chloroform (30 mL) were used. The reaction was stirred at 60°C for 96 hours. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.3j** (735 mg, 43%) as a white solid. $R_f = 0.30$ (Hex/EA = 5:1); Mp: 95-97°C; IR (neat, cm^{-1}): 2985 (w), 1813 (m), 1691 (m), 1666 (s), 1093 (m), 869 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.67 (t, J = 2.2 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.36 (m, 2H), 2.72 (m, 2H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 167.5, 166.7, 97.5, 60.2, 26.21, 26.17, 14.4; HRMS (ESI^+) m/z $[C_8H_{10}O_4Na]^+$ calcd: 193.0471; found: 193.0472.



Enol lactone from 2,2-dimethylsuccinic anhydride (**4.3k**)

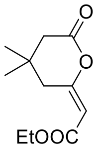
Following the general procedure with modifications, 2,2-dimethylsuccinic anhydride (1.28 g, 10 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (3.83 g, 11 mmol, 1.1 equiv.), and ethanol-free chloroform (30 mL) were used. The reaction was stirred at 60°C for 72 hours. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 10:1) gave **4.3k** (1.47 g, 74%) as a colorless oil. $R_f = 0.55$ (Hex/EA = 5:1); IR (neat, cm^{-1}): 2979 (w), 2937 (w), 1814 (m), 1709 (m), 1660 (s), 1045 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.68 (t, J = 2.1 Hz, 1H), 4.15 (q, J = 7.2 Hz, 2H), 3.20 (d, J = 2.1 Hz, 2H), 1.32 (s, 6H), 1.26 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.1, 166.7, 165.3, 98.0, 60.2, 41.5, 38.7, 25.4, 14.4; HRMS (ESI^+) *m/z* $[C_{10}H_{15}O_4]^+$ calcd: 199.0965; found: 199.0963.



<u>Enol lactone from maleic anhydride (**4.3l**)</u>

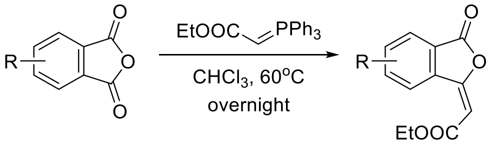
Note: Direct derivatization of maleic anhydride failed. An indirect approach from *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride derivatization, followed by retro Diels-Alder was used instead.

Following the general procedure with modifications, *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (1.66 g, 10 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (3.83 g, 11 mmol, 1.1 equiv.), and ethanol-free chloroform (30 mL) were used. The reaction was stirred at rt overnight, then at 60°C for 24 hours. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 15:1) gave **4.3l** (1.15 g, 68%) as a white solid. $R_f = 0.50$ (Hex/EA = 5:1); Mp: 79-80°C; IR (neat, cm^{-1}): 3157 (w), 3121 (w), 2988 (w), 1791 (m), 1702 (m), 1644 (m), 1262 (m), 1087 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.35 (dd, J = 5.6, 0.9 Hz, 1H), 6.44 (dd, J = 5.6, 1.8 Hz, 1H), 5.89 (dd, J = 1.8, 0.9 Hz, 1H), 4.23 (q, J = 7.1 Hz, 2H), 1.30 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.9, 164.9, 160.3, 142.1, 124.4, 102.7, 61.2, 14.2; HRMS (ESI^+) *m/z* $[C_8H_8O_4Na]^+$ calcd: 191.0315; found: 191.0314.



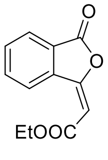
Enol lactone from 3,3-dimethylglutaric anhydride (**4.3m**)

Following the general procedure with modifications, 3,3-dimethylglutaric anhydride (1.42 g, 10 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (3.83 g, 11 mmol, 1.1 equiv.), and ethanol-free chloroform (30 mL) were used. The reaction was stirred at 60°C for 72 hours. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 10:1) gave **4.3m** (689 mg, 32%) as a white solid. $R_f = 0.45$ (Hex/EA = 5:1); Mp: 46-47°C; IR (neat, cm^{-1}): 2964 (w), 2875 (w), 1771 (m), 1709 (m), 1641 (s), 1094 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.63 (t, J = 1.4 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 2.99 (m, 2H), 2.47 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H), 1.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 166.6, 165.1, 102.9, 60.2, 44.4, 37.5, 29.6, 27.7, 14.3; HRMS (ESI^+) *m/z* $[C_{11}H_{16}O_4Na]^+$ calcd: 235.0941; found: 235.0941.



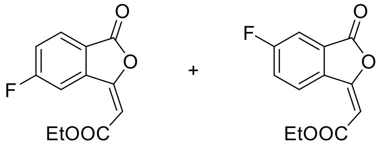
General procedure for the synthesis of enol lactones from phthalic anhydride derivatives: To a round bottom flask were added the desired phthalic anhydride derivative (1.0 equiv.), ethyl (triphenylphosphoranylidene) acetate (1.1 equiv.), and ethanol-free chloroform (15 mL/5 mmol anhydride). The reaction mixture was stirred at 60°C overnight. The mixture was then cooled to rt, and the solvent was evaporated under vacuum. The residue was purified by flash chromatography to afford the product. These reactions typically produce a small amount of (*Z*)-isomer (< 5%) that is significantly more polar than the major (*E*)-isomer product. The (*Z*)-isomer was not isolated.

Note: The enol lactone products are very sensitive to nucleophiles. Ethanol-free chloroform must be used for the synthesis of such compounds. Alternatively, toluene can be used as a solvent. For the characterization of these compounds by mass spectrometry, even trace amount of methanol should be avoided in the system. Otherwise, only the methanol adduct is detected.



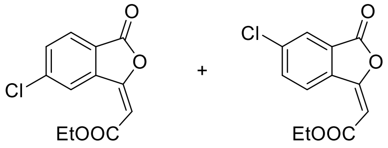
Enol lactone from phthalic anhydride (**4.5a**)

The same procedure reported for compound **3.3k** was followed.



Enol lactone from 4-fluorophthalic anhydride (**4.5b**)

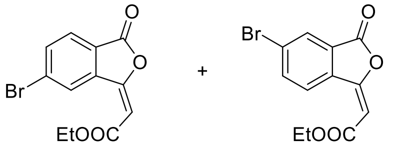
Following the general procedure, 4-fluorophthalic anhydride (830.6 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 15:1) gave **4.5b** (831 mg, 70%, regioisomers, major/minor = 2.7:1) as a white solid. $R_f = 0.63$ (Hex/EA = 5:1); Mp: 82-84°C; IR (neat, cm^{-1}): 3115 (w), 2985 (w), 1788 (m), 1705 (m), 1650 (m), 1244 (s), 1047 (s); major: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.78 (dd, J = 9.3, 2.3 Hz, 1H), 7.94 (dd, J = 8.4, 4.9 Hz, 1H), 7.38 (td, J = 8.4, 2.4 Hz, 1H), 6.14 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{19}F NMR ($CDCl_3$, 471 MHz): δ -99.9; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1 (d, J = 255.9 Hz), 165.4, 164.6, 156.7 (d, J = 3.7 Hz), 138.7 (d, J = 12.4 Hz), 130.9 (d, J = 9.2 Hz), 127.6 (d, J = 10.5 Hz), 120.7 (d, J = 24.7 Hz), 115.6 (d, J = 27.5 Hz), 103.6, 61.2, 14.3; minor: ^1H NMR ($CDCl_3$, 500 MHz): δ 9.08 (dd, J = 8.8, 4.6 Hz, 1H), 7.58 (dd, J = 6.9, 2.4 Hz, 1H), 7.48 (td, J = 8.7, 2.5 Hz, 1H), 6.10 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{19}F NMR ($CDCl_3$, 471 MHz): δ -104.0; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.9, 165.6, 164.3 (d, J = 91.6 Hz), 157.1, 132.3 (d, J = 2.3 Hz), 129.2 (d, J = 9.2 Hz), 123.1 (d, J = 23.3 Hz), 122.7 (d, J = 1.8 Hz), 112.1 (d, J = 24.3 Hz), 102.4 (d, J = 2.3 Hz), 61.1, 14.3; HRMS (ESI$^+$) *m/z* $[C_{12}H_9O_4FNa]^+$ calcd: 259.0377; found: 259.0372.



Enol lactone from 4-chlorophthalic anhydride (**4.5c**)

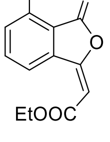
Following the general procedure, 4-chlorophthalic anhydride (1.82 g, 10 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (3.83 g, 11 mmol, 1.1 equiv.), and ethanol-free chloroform (30 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) gave **4.5c** (1.31 g, 52%, regioisomers, major/minor = 1.5:1) as a white solid. $R_f = 0.72$ (Hex/EA = 5:1); Mp: 90-100°C; IR (neat, cm^{-1}): 3120 (w), 2999 (w), 1795 (s), 1711 (m), 1649 (s), 1237 (s), 1040 (s), 855 (s); major: ^1H NMR ($CDCl_3$, 500 MHz): δ 9.06 (d, J = 1.8 Hz, 1H), 7.87 (d, J = 8.2 Hz, 1H), 7.65 (dd, J = 8.2, 1.8 Hz, 1H), 6.15 (s, 1H), 4.29 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.2 Hz, 3H); ^{13}C

NMR ($CDCl_3$, 125 MHz): δ 165.4, 164.7, 156.6, 142.3, 135.5, 133.1, 128.5, 126.4, 125.4, 103.7, 61.3, 14.3; minor: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.99 (d, J = 8.5 Hz, 1H), 7.89 (d, J = 1.8 Hz, 1H), 7.73 (dd, J = 8.5, 1.9 Hz, 1H), 6.13 (s, 1H), 4.28 (q, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.5, 164.5, 157.1, 139.1, 137.6, 134.4, 129.6, 128.3, 124.9, 103.1, 61.2, 14.3; HRMS (ESI$^+$) *m/z* $[C_{12}H_9O_4ClNa]^+$ calcd: 275.0082; found: 275.0088.



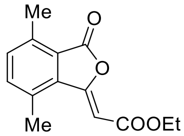
Enol lactone from 4-bromophthalic anhydride (**4.5d**)

Following the general procedure, 4-bromophthalic anhydride (1.14 g, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 10:1) gave **4.5d** (975 mg, 66%, regioisomers, major/minor = 1.3:1) as a white solid. R_f = 0.64 (Hex/EA = 5:1); Mp: 109-113°C; IR (neat, cm^{-1}): 3115 (w), 3073 (w), 2984 (w), 1783 (s), 1704 (m), 1647 (s), 1235 (s), 1041 (s), 839 (s); major: ^1H NMR ($CDCl_3$, 500 MHz): δ 9.23 (d, J = 1.7 Hz, 1H), 7.82 (dd, J = 8.1, 1.6 Hz, 1H), 7.79 (d, J = 8.0 Hz, 1H), 4.30 (q, J = 7.2 Hz, 2H), 1.36 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.3, 164.9, 156.5, 138.4, 136.0, 131.4, 129.7, 128.4, 126.5, 103.7, 61.3, 14.3; minor: ^1H NMR ($CDCl_3$, 500 MHz): δ 8.92 (d, J = 8.5 Hz, 1H), 8.05 (d, J = 2.0 Hz, 1H), 7.89 (dd, J = 8.5, 1.9 Hz, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.5, 164.3, 157.1, 137.7, 134.9, 130.8, 128.4, 127.2, 125.3, 103.2, 61.2, 14.3; HRMS (ESI$^+$) *m/z* $[C_{12}H_9O_4BrNa]^+$ calcd: 318.9576; found: 318.9576.



Enol lactone from 3-iodophthalic anhydride (**4.5e**)

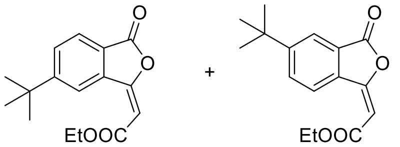
Following the general procedure, 3-iodophthalic anhydride (1.37 g, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) gave **4.5e** (705 mg, 41%) as a white solid. R_f = 0.48 (Hex/EA = 5:1); Mp: 101-102°C; IR (neat, cm^{-1}): 3109 (w), 2982 (w), 1786 (m), 1706 (m), 1642 (m), 1041 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 9.08 (dd, *J* = 8.0, 0.8 Hz, 1H), 8.10 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.44 (t, *J* = 7.9 Hz, 1H), 6.14 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.34 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 165.5, 164.0, 155.5, 143.8, 138.2, 135.8, 128.1, 127.7, 102.8, 91.7, 61.2, 14.3; HRMS (ESI$^+$) *m/z* $[C_{12}H_9O_4INa]^+$ calcd: 366.9438; found: 366.9441.



Enol lactone from 3,6-dimethylphthalic anhydride (**4.5f**)

Note: Unusual (*Z*)-isomer selectivity was observed due to sterics from the adjacent methyl groups.

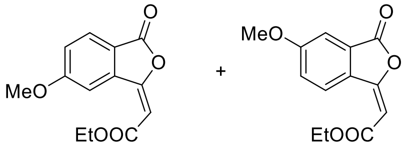
Following the general procedure with modifications, 3,6-dimethylphthalic anhydride (880.9 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. The reaction was stirred at 60°C for 72 hours. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 4:1) gave **4.5f** (1.03 g, 84%) as a white solid. R_f = 0.25 (Hex/EA = 5:1); Mp: 94-96°C; IR (neat, cm^{-1}): 2982 (w), 2908 (w), 1780 (s), 1721 (s), 1650 (s), 1162 (s), 1137 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.36 (m, 1H), 7.26 (m, 1H), 5.80 (m, 1H), 4.25 (m, 2H), 2.60 (m, 3H), 2.50 (m, 3H), 1.31 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 165.8, 163.8, 154.8, 137.9, 137.2, 136.3, 133.8, 132.4, 122.8, 99.0, 60.7, 20.2, 17.0, 14.3; HRMS (ESI$^+$) *m/z* $[C_{14}H_{14}O_4Na]^+$ calcd: 269.0784; found: 269.0780.



Enol lactone from 4-*tert*-butylphthalic anhydride (**4.5g**)

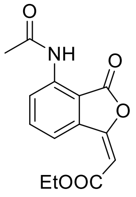
Following the general procedure, 4-*tert*-butylphthalic anhydride (1.02 g, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 4:1) gave **4.5g** (933 mg, 68%, regioisomers, major/minor = 1.6:1) as a white solid. R_f = 0.68 (Hex/EA = 5:1); Mp: 60-62°C; IR (neat, cm^{-1}): 2966 (w), 2871 (w), 1788 (s), 1650 (m), 1229 (s), 1039 (s); major isomer: ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 8.91 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 1.9, 0.6 Hz, 1H), 7.82 (dd,

J = 8.4, 1.8 Hz, 1H), 6.06 (s, 1H), 4.28 (m, 2H), 1.37 (s, 9H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.3, 165.72, 158.1, 157.1, 133.7, 133.0, 128.0, 126.8, 122.0, 101.7, 60.88, 35.6, 31.2, 14.35; minor: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.14 (d, J = 1.6 Hz, 1H), 7.85 (dd, J = 8.1, 0.8 Hz, 1H), 7.72 (dd, J = 8.1, 1.7 Hz, 1H), 6.09 (s, 1H), 4.28 m, 2H), 1.40 (s, 9H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.8, 165.68, 156.0, 158.3, 136.5, 130.2, 125.2, 125.0, 124.0, 102.1, 60.91, 36.1, 31.3, 14.38; HRMS (APCI$^+$) *m/z* $[C_{16}H_{19}O_4]^+$ calcd: 275.1278; found: 275.1270.



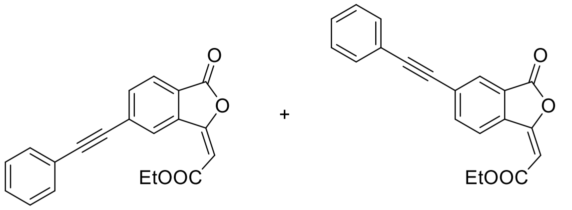
Enol lactone from 4-methoxyphthalic anhydride (**4.5h**)

Following the general procedure, 4-methoxyphthalic anhydride (890.7 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1) gave **4.5h** (926 mg, 75%, regioisomers, major/minor = 3.1:1) as a white solid. R_f = 0.43 (Hex/EA = 5:1); Mp: 96-98°C; IR (neat, cm^{-1}): 3136 (w), 3000 (w), 2910 (w), 2842 (w), 1796 (m), 1788 (m), 1647 (m), 1259 (s), 1044 (s); major: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.60 (d, J = 2.3 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.16 (dd, J = 8.5, 2.4 Hz, 1H), 6.08 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.95 (s, 3H), 1.34 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.8, 165.7, 165.5, 157.96, 138.8, 129.8, 126.7, 120.7, 111.3, 102.4, 61.0, 56.2, 14.4; minor: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.91 (d, J = 8.7 Hz, 1H), 7.32 (d, J = 2.4 Hz, 1H), 7.27 (dd, J = 8.8, 2.5 Hz, 1H), 5.99 (s, 1H), 4.26 (q, J = 7.1 Hz, 2H), 3.91 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.9, 165.9, 163.2, 158.04, 128.91, 128.86, 123.2, 118.8, 107.8, 100.6, 60.8, 56.1, 14.4; HRMS (ESI$^+$) *m/z* $[C_{13}H_{12}O_5Na]^+$ calcd: 271.0577; found: 271.0569.



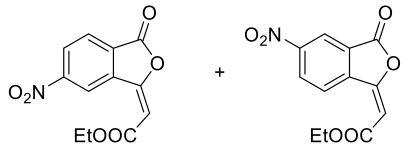
Enol lactone from 3-acetylaminophthalic anhydride (**4.5i**)

Following the general procedure, 3-acetylaminophthalic anhydride (1.02 g, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA/DCM = 10:1:1 to 4:1:1) gave **4.5i** (735 mg, 53%) as a white solid. $R_f = 0.45$ (Hex/EA/DCM = 4:1:1); Mp: 160-161°C; IR (neat, cm^{-1}): 3552 (w), 3114 (w), 2993 (w), 1765 (m), 1698 (m), 1611 (m), 1483 (m), 1242 (s), 1188 (s), 1043 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.33 (bs, 1H), 8.67 (d, J = 8.2 Hz, 1H), 8.60 (d, J = 8.0 Hz, 1H), 7.71 (t, J = 8.1 Hz, 1H), 6.11 (s, 1H), 4.27 (q, J = 7.2 Hz, 2H), 2.26 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.3, 167.1, 165.2, 157.2, 138.5, 137.6, 135.8, 122.5, 122.3, 111.4, 103.6, 61.1, 25.1, 14.3; HRMS (ESI$^+$) *m/z* $[C_{14}H_{13}NO_5Na]^+$ calcd: 298.0686; found: 298.0682.



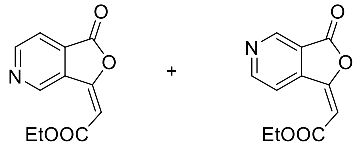
Enol lactone from 4-phenylethynylphthalic anhydride (**4.5j**)

Following the general procedure, 4-phenylethynylphthalic anhydride (1.02 g, 4.1 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.57 g, 4.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 15:1) gave **4.5j** (978 mg, 61%, regioisomers, major/minor = 1.2:1) as a yellow solid. $R_f = 0.61$ (Hex/EA = 5:1); Mp: 96-98°C; IR (neat, cm^{-1}): 3074 (w), 2973 (w), 2866 (w), 1788 (s), 1712 (m), 1651 (m), 1233 (s), 1051 (s); major: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.14 (dd, J = 1.2, 0.8 Hz, 1H), 7.89 (dd, J = 7.9, 0.8 Hz, 1H), 7.78 (dd, J = 7.9, 1.3 Hz, 1H), 7.57-7.53 (m, 2H), 7.39-7.34 (m, 3H), 6.14 (s, 1H), 4.31 (q, J = 7.1 Hz, 2H), 1.37 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.49, 165.1, 157.3, 138.0, 135.6, 132.0, 130.96, 129.27, 128.56, 128.2, 128.08, 125.28, 122.3, 103.1, 94.2, 88.3, 61.14, 14.3; minor: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.00 (dd, J = 8.2, 0.8 Hz, 1H), 8.03 (dd, J = 1.5, 0.8 Hz, 1H), 7.87 (dd, J = 8.2, 1.5 Hz, 1H), 7.57-7.53 (m, 2H), 7.39-7.34 (m, 3H), 6.11 (s, 1H), 4.28 (q, J = 7.2 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.52, 165.0, 157.5, 136.3, 134.9, 131.9, 130.99, 129.29, 128.59, 128.14, 127.0, 125.34, 122.2, 102.9, 93.9, 87.7, 61.08, 14.3; HRMS (ESI$^+$) *m/z* $[C_{20}H_{14}O_4Na]^+$ calcd: 341.0784; found: 341.0781.



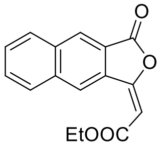
Enol lactone from 4-nitrophthalic anhydride (**4.5k**)

Following the general procedure, 4-nitrophthalic anhydride (965.6 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) gave **4.5k** (684 mg, 52%, regioisomers, major/minor = 1.5:1) as a light yellow solid. R_f = 0.62 (Hex/EA = 5:1); Mp: 89-90ºC; IR (neat, cm^{-1}): 3117 (w), 3090 (w), 2988 (w), 1805 (m), 1794 (m), 1705 (m), 1656 (m), 1533 (s), 1235 (s), 1044 (s); major: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.29 (d, *J* = 8.7 Hz, 1H), 8.74 (dd, *J* = 2.2, 0.7 Hz, 1H), 8.62 (dd, *J* = 8.7, 2.1 Hz, 1H), 6.30 (s, 1H), 4.31 (q, *J* = 7.2 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.00, 163.5, 155.8, 150.2, 140.5, 129.9, 127.5, 126.6, 120.8, 106.0, 61.6, 14.27; minor: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.91 (d, *J* = 1.9 Hz, 1H), 8.53 (dd, *J* = 8.4, 2.0 Hz, 1H), 8.13 (dd, *J* = 8.3, 0.7 Hz, 1H), 6.26 (s, 1H), 4.34 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 165.02, 163.6, 155.7, 152.5, 137.3, 130.9, 129.8, 128.1, 124.0, 105.1, 61.7, 14.29; HRMS (ESI^+) *m/z* $[C_{12}H_9NO_6Na]^+$ calcd: 286.0322; found: 286.0317.



Enol lactone from 3,4-pyridinedicarboxylic anhydride (**4.5l**)

Following the general procedure, 3,4-pyridinedicarboxylic anhydride (745.5 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (15 mL) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 4:1) gave **4.5l** (500 mg, 46%, regioisomers, major/minor = 4:1) as an off-white solid. R_f = 0.25 (Hex/EA = 5:1); Mp: 74-75ºC; IR (neat, cm^{-1}): 3124 (w), 2988 (w), 1792 (s), 1703 (m), 1659 (m), 1220 (m), 1041 (s); major: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.23 (d, *J* = 1.2 Hz, 1H), 9.00 (d, *J* = 5.3 Hz, 1H), 8.84 (dd, *J* = 5.3, 1.2 Hz, 1H), 6.26 (s, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 164.9, 164.2, 156.0, 155.6, 147.8, 143.0, 121.3, 121.2, 106.2, 61.5, 14.2; minor: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 10.23 (d, *J* = 1.4 Hz, 1H), 8.97 (d, *J* = 5.0 Hz, 1H), 7.81 (dd, *J* = 5.0, 1.3 Hz, 1H), 6.20 (s, 1H), 4.29 (q, *J* = 7.2 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 165.0, 164.3, 155.9, 152.7, 150.5, 133.5, 130.7, 118.0, 104.3, 61.4, 14.3; HRMS (ESI$^+$) *m/z* $[C_{11}H_{10}NO_4]^+$ calcd: 220.0604; found: 220.0603.



Enol lactone from 2,3-naphthalenedicarboxylic anhydride (**4.5m**)

Following the general procedure with modifications, 2,3-naphthalenedicarboxylic anhydride (990.9 mg, 5 mmol, 1.0 equiv.), ethyl (triphenylphosphoranylidene)acetate (1.92 g, 5.5 mmol, 1.1 equiv.), and ethanol-free chloroform (30 mL) were used. Purification by flash chromatography (SiO$_2$, Hex/EA = 20:1 to 10:1) gave **4.5m** (537 mg, 40%) as a white solid. R$_f$ = 0.58 (Hex/EA = 5:1); Mp: 146-148°C; IR (neat, cm^{-1}): 3097 (w), 2976 (w), 1794 (s), 1647 (s), 1242 (s), 1050 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 9.55 (s, 1H), 8.42 (s, 1H), 8.07 (m, 1H), 8.00 (m, 1H), 7.70-7.64 (m, 2H), 6.12 (s, 1H), 4.32 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 166.1, 165.8, 158.6, 136.6, 134.3, 130.5, 130.1, 129.9, 129.8, 129.6, 129.1, 127.1, 123.0, 101.3, 60.9, 14.4; HRMS (ESI$^+$) *m/z* $[C_{16}H_{12}O_4Na]^+$ calcd: 291.0628; found: 291.0624.

7.4.2 Synthesis and Characterization of Reaction Products

General procedure A for the synthesis of carbic imides: To a reaction vial were added the corresponding amine (0.525 mmol, 1.05 equiv.) and TBD (7.0 mg, 0.05 mmol, 10 mol%). Compound **3** (117.1 mg, 0.5 mmol, 1.0 equiv.) was then added, followed by DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred at rt for 30 minutes. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH$_2$PO$_4$ (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered, and evaporated under vacuum. Purification by flash chromatography afforded the desired product.

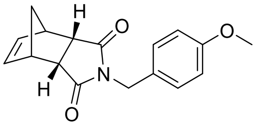
General procedure B for the synthesis of non-aromatic cyclic imides: To a reaction vial were added *para*-methoxybenzyl amine (72.0 mg, 0.525 mmol, 1.05 equiv.) and TBD (7.0 mg, 0.05 mmol, 10 mol%). The corresponding enol lactone (0.5 mmol, 1.0 equiv.) was then added, followed by DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred under the indicated conditions. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography afforded the desired product.

General procedure C for the synthesis of phthalic imide derivatives: To a reaction vial were added *para*-methoxybenzyl amine (72.0 mg, 0.525 mmol, 1.05 equiv.) and TBD (1.7 mg, 0.0125 mmol, 2.5 mol%). The corresponding enol lactone (0.5 mmol, 1.0 equiv.) was then added, followed by DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred at rt for 30 minutes. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. To the residue were added TBD (7.0 mg, 0.05 mmol, 10 mol%) and DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred under the indicated conditions. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography afforded the desired product.

General procedure D for the synthesis of phthalic imide derivatives: General procedure C was followed with modifications. Instead, no washing process was introduced after the first half reaction and TBD was directly added into the reaction vial. No additional DMSO was used.

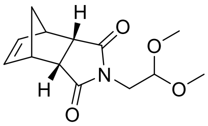
To a reaction vial were added *para*-methoxybenzyl amine (72.0 mg, 0.525 mmol, 1.05 equiv.) and TBD (1.7 mg, 0.0125 mmol, 2.5 mol%). The corresponding enol lactone (0.5 mmol, 1.0 equiv.) was then added, followed by DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred at rt for 30 minutes. TBD (7.0 mg, 0.05 mmol, 10 mol%) was then added and the reaction was stirred under the same conditions as for general procedure C. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography afforded the desired product.

General procedure E to obtain the amine free base from its salt: The commercially available amine salt was dissolved in excess sat. Na_2CO_3. The free base was extracted in DCM, and the organic solvent was evaporated under vacuum. The amine free base was dried under vacuum for 2 hours before use.



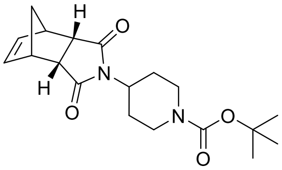
Carbic imide from *para*-methoxybenzyl amine (**4.2a**)

Following the general procedure A, freshly distilled *para*-methoxybenzyl amine (72.0 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 3:1) gave **4.2a** (125 mg, 88%) as a white solid. A 10 mmol scale reaction was performed as followed: To a 50 mL round bottom flask were added freshly distilled *para*-methoxybenzyl amine (1.44 g, 10.5 mmol, 1.05 equiv.) and TBD (139.2 mg, 1 mmol, 10 mol%). Compound **4.3** (2.34 g, 10 mmol, 1.0 equiv.) was then added, followed by DMSO (10 mL). The reaction was stirred at rt for 30 minutes. The mixture was diluted in DCM (40 mL), washed with 1 M KH_2PO_4 (2 × 30 mL), water (1 × 30 mL), and brine (1 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to give a light yellow oil. A hexanes and diethyl ether mixture (1:1, 5 mL) was slowly added and a white precipitate began to occur. The mixture was put into freezer for 20 minutes and filtered. The solid was washed with hexanes and dried under vacuum to give **4.2a** (2.54 g, 90%). R_f = 0.41 (Hex/EA = 2:1); Mp: 102-103°C; IR (neat, cm^{-1}): 2997 (w), 2934 (w), 2836 (w), 1694 (s), 1245 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.7 Hz, 2H), 5.86 (t, J = 2.0 Hz, 2H), 4.40 (s, 2H), 3.76 (s, 3H), 3.33 (m, 2H), 3.21 (dd, J = 2.9, 1.5 Hz, 2H), 1.66 (dt, J = 8.8, 1.6 Hz, 1H), 1.48 (dt, J = 8.7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.5, 159.2, 134.4, 130.4, 128.5, 113.7, 55.3, 52.2, 45.8, 45.1, 41.5; HRMS (ESI$^+$) *m/z* $[C_{17}H_{17}NO_3Na]^+$ calcd: 306.1100; found: 306.1097.



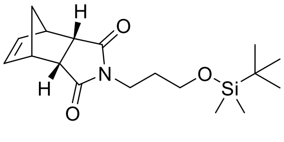
Carbic imide from aminoacetaldehyde dimethyl acetal (**4.2b**)

Following the general procedure A, freshly distilled aminoacetaldehyde dimethyl acetal (55.2 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1) gave **4.2b** (103 mg, 82%) as a white solid. R_f = 0.38 (Hex/EA = 1:1); Mp: 77-78°C; IR (neat, cm^{-1}): 2985 (w), 2839 (w), 1768 (w), 1694 (s), 1059 (s), 737 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.05 (t, J = 1.9 Hz, 2H), 4.50 (t, J = 5.8 Hz, 1H), 3.43 (d, J = 5.9 Hz, 2H), 3.35 (m, 2H), 3.26 (s, 6H), 3.23 (dd, J = 3.0, 1.5 Hz, 2H), 1.68 (dt, J = 8.8, 1.7 Hz, 1H), 1.50 (dt, J = 8.7, 1.6 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 177.5, 134.4, 99.3, 52.9, 52.2, 45.8, 45.0, 39.0; HRMS (ESI$^+$) *m/z* [$C_{13}H_{17}NO_4Na$]$^+$ calcd: 274.1050; found: 274.1044.



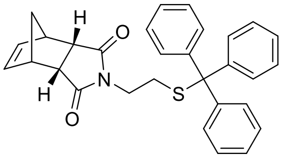
Carbic imide from 1-Boc-4-amino-piperidine (**4.2c**)

Following the general procedure A with modifications, 1-Boc-4-amino-piperidine (55.2 mg, 0.525 mmol, 1.05 equiv.) was used. The reaction was stirred for 2 hours. Purification by flash chromatography (SiO$_2$, Hex/EA = 5:1 to 2:1) gave **4.2c** (154 mg, 89%) as a white solid. R$_f$ = 0.49 (Hex/EA = 1:1); Mp: 119-120ºC; IR (neat, cm^{-1}): 2973 (w), 2827 (w), 1768 (w), 1685 (s), 1365 (m), 1167 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.05 (t, J = 2.0 Hz, 2H), 4.14 (bs, 2H), 3.90 (tt, J = 12.3, 4.0 Hz, 1H), 3.35 (m, 2H), 3.16 (dd, J = 3.0, 1.5 Hz, 2H), 2.62 (bs, 2H), 2.23 (dd, J = 12.6, 4.5 Hz, 1H), 2.18 (dd, J = 12.6, 4.6 Hz, 1H), 1.68 (dt, J = 8.9, 1.7 Hz, 1H), 1.48 (dt, J = 8.8, 1.6 Hz, 1H), 1.41 (s, 9H), 1.37 (m, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 177.8, 154.6, 134.4, 79.7, 52.1, 49.5, 45.3, 45.2, 43.5 (bs), 28.5, 28.0; HRMS (ESI$^+$) *m/z* [$C_{19}H_{26}N_2O_4Na$]$^+$ calcd: 369.1785; found: 369.1772.



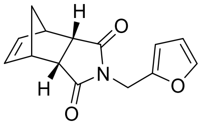
Carbic imide from 3-(*tert*-butyldimethylsiloxyl)propylamine (**4.2d**)

Following the general procedure A with modifications, freshly distilled 3-(*tert*-butyldimethylsiloxyl) propylamine (94.7 mg, 0.525 mmol, 1.05 equiv.) was used. The reaction was stirred for 1 hour. Purification by flash chromatography (SiO$_2$, Hex/EA = 10:1 to 5:1) gave **4.2d** (134 mg, 80%) as a sticky colorless oil. R$_f$ = 0.53 (Hex/EA = 2:1); IR (neat, cm^{-1}): 2928 (m), 2854 (w), 1768 (w), 1697 (s), 1173 (m), 1094 (m), 833 (s), 772 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.08 (t, J = 1.9 Hz, 2H), 3.56 (t, J = 6.3 Hz, 2H), 3.40 (m, 2H), 3.37 (m, 2H), 3.22 (dd, J = 3.0, 1.6 Hz, 2H), 1.71 (dt, *J* = 9.1, 1.9 Hz, 1H), 1.64 (m, 2H), 1.52 (m, 2H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 177.8, 134.5, 60.9, 52.3, 45.8, 45.0, 35.9, 31.1, 26.0, 18.4, -5.3; HRMS (ESI$^+$) *m/z* $[C_{18}H_{30}NO_3Si]^+$ calcd: 336.1989; found: 336.1978.



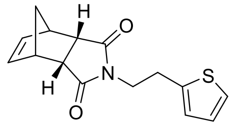
Carbic imide from *S*-trityl cysteamine (**4.2e**)

Following the general procedure A, *S*-trityl cysteamine (167.7 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 3:1) gave **4.2e** (227 mg, 98%) as a white solid. R_f = 0.35 (Hex/EA = 2:1); Mp: 161°C (decomp.); IR (neat, cm^{-1}): 2996 (w), 2942 (w), 1699 (s), 1390 (m), 1150 (m), 743 (m), 700 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.39 (m, 6H), 7.27 (m, 6H), 7.21 (m, 3H), 5.95 (t, *J* = 2.0 Hz, 2H), 3.32 (m, 2H), 3.27 (t, *J* = 7.3 Hz, 2H), 3.16 (dd, *J* = 3.0, 1.6 Hz, 2H), 2.25 (t, *J* = 7.3 Hz, 2H), 1.67 (dt, *J* = 8.7, 1.7 Hz, 1H), 1.48 (dt, *J* = 8.7, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 177.2, 144.7, 134.5, 129.7, 128.0, 126.8, 66.9, 52.1, 45.7, 45.0, 37.3, 29.6; HRMS (ESI$^+$) *m/z* $[C_{30}H_{27}NO_2SNa]^+$ calcd: 488.1655; found: 488.1653.



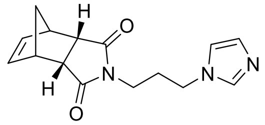
Carbic imide from furfurylamine (**4.2f**)

Following the general procedure A, freshly distilled furfuryl amine (60.0 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 3:1) gave **4.2f** (120 mg, 98%) as a white solid. R_f = 0.35 (Hex/EA = 2:1); Mp: 104-105°C; IR (neat, cm^{-1}): 3115 (w), 3000 (w), 1758 (w), 1697 (s), 1319 (m), 1159 (m), 1011 (m), 767 (s), 716 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.28 (dd, *J* = 1.9, 1.0 Hz, 1H), 6.25 (dd, *J* = 3.4, 1.8 Hz, 1H), 6.22 (dd, *J* = 3.3, 0.9 Hz, 1H), 5.92 (t, *J* = 1.9 Hz, 2H), 4.47 (s, 2H), 3.35-3.33 (m, 2H), 3.24 (dd, *J* = 3.1, 1.5 Hz, 2H), 1.67 (dt, *J* = 8.9, 1.7 Hz, 1H), 1.49 (dt, *J* = 8.9, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 177.0, 149.0, 142.2, 134.3, 110.4, 108.9, 52.1, 45.8, 45.0, 34.6; HRMS (ESI$^+$) *m/z* $[C_{14}H_{13}NO_3Na]^+$ calcd: 266.0788; found: 266.0795.



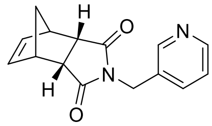
Carbic imide from thiophene-2-ethylamine (**4.2g**)

Following the general procedure A, freshly distilled thiophene-2-ethylamine (66.8 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 1:1) gave **4.2g** (129 mg, 94%) as a white solid. $R_f = 0.48$ (Hex/EA = 2:1); Mp: 107-108ºC; IR (neat, cm^{-1}): 3011 (w), 2946 (w), 1771 (w), 1693 (s), 1395 (m), 1176 (m), 706 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.12 (dd, J = 5.2, 1.2 Hz, 1H), 6.90 (dd, J = 5.1, 3.4 Hz, 1H), 6.82 (m, 1H), 5.97 (t, J = 1.9 Hz, 2H), 3.62 (m, 2H), 3.34 (m, 2H), 3.22 (dd, J = 3.0, 1.6 Hz, 2H), 2.97 (m, 2H), 1.69 (dt, J = 8.8, 1.7 Hz, 1H), 1.50 (dt, J = 8.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.5, 140.1, 134.4, 126.9, 125.6, 124.0, 52.2, 45.8, 45.0, 39.4, 27.7; HRMS (ESI$^+$) *m/z* $[C_{15}H_{15}NO_2SNa]^+$ calcd: 296.0716; found: 296.0722.



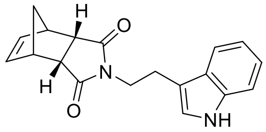
Carbic imide from 1-(3-aminopropyl)imidazole (**4.2h**)

Following the general procedure A, freshly distilled 1-(3-aminopropyl)imidazole (65.7 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, DCM/MeOH = 20:1) gave **4.2h** (122 mg, 90%) as a white solid. $R_f = 0.60$ (DCM/MeOH = 10:1); Mp: 144-145ºC; IR (neat, cm^{-1}): 3103 (w), 2952 (w), 1759 (w), 1687 (s), 1164 (m), 725 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.45 (bs, 1H), 7.01 (bs, 1H), 6.90 (bs, 1H), 6.06 (t, J = 2.0 Hz, 2H), 3.85 (m, 2H), 3.35-3.32 (m, 4H), 3.20 (dd, J = 3.0, 1.6 Hz, 2H), 1.90 (m, 2H), 1.70 (dt, J = 8.7, 1.8 Hz, 1H), 1.51 (dt, J = 8.8, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.7, 137.2 (bs), 134.5, 129.7 (bs), 118.7 (bs), 52.4, 45.8, 44.9, 44.6, 35.6, 29.3; HRMS (ESI$^+$) *m/z* $[C_{15}H_{18}N_3O_2]^+$ calcd: 272.1394; found: 272.1389.



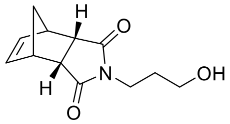
Carbic imide from 3-picolylamine (**4.2i**)

Following the general procedure A, freshly distilled 3-picolylamine (56.8 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, DCM/MeOH = 50:1 to 20:1) gave **4.2i** (120 mg, 95%) as a light pink oil. $R_f = 0.50$ (DCM/MeOH = 20:1); IR (neat, cm^{-1}): 2989 (w), 2944 (w), 2871 (w), 1765 (w), 1691 (s), 1390 (m), 1164 (m), 711 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.55-8.50 (m, 2H), 7.61 (dt, J = 7.9, 1.8 Hz, 1H), 7.19 (m, 1H), 5.84 (t, J = 2.0 Hz, 2H), 4.46 (s, 2H), 3.33 (m, 2H), 3.24 (dd, J = 3.0, 1.6 Hz, 2H), 1.66 (dt, J = 8.9, 1.7 Hz, 1H), 1.48 (dt, J = 8.9, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.2, 150.2, 149.2, 136.7, 134.4, 131.8 (bs), 123.5 (bs), 52.3, 45.8, 45.1, 39.6; HRMS (ESI$^+$) *m/z* $[C_{15}H_{14}N_2O_2Na]^+$ calcd: 277.0947; found: 277.0944.



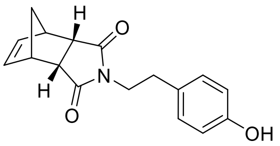
Carbic imide from tryptamine (**4.2j**)

Following the general procedure A, tryptamine (84.1 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1) gave **4.2j** (136 mg, 89%) as a beige solid. $R_f = 0.40$ (Hex/EA = 1:1); Mp: 176-178°C; IR (neat, cm^{-1}): 3344 (w, br), 3059 (w), 2964 (w), 2860 (w), 1761 (w), 1687 (s), 1159 (m), 725 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.13 (bs, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.34 (dt, J = 8.1, 1.0 Hz, 1H), 7.19 (m, 1H), 7.13 (m, 1H), 7.02 (d, J = 2.4 Hz, 1H), 5.98 (t, J = 1.9 Hz, 2H), 3.57 (m, 2H), 3.36 (m, 2H), 3.21 (dd, J = 3.0, 1.5 Hz, 2H), 2.91 (m, 2H), 1.70 (dt, J = 8.7, 1.6 Hz, 1H), 1.51 (dt, J = 8.7, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.9, 136.3, 134.4, 127.5, 122.2 (×2), 119.5, 119.0, 112.4, 111.2, 52.3, 45.9, 45.0, 38.9, 23.6; HRMS (ESI$^+$) *m/z* $[C_{19}H_{18}N_2O_2Na]^+$ calcd: 329.1261; found: 329.1256.



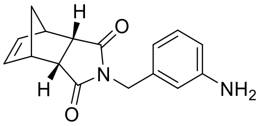
Carbic imide from 3-amino-1-propanol (**4.2k**)

Following the general procedure A, freshly distilled 3-amino-1-propanol (39.4 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, DCM/EA = 5:1 to 1:1) gave **4.2k** (72 mg, 65%) as an off-white solid. $R_f = 0.23$ (DCM/EA = 1:1); Mp: 52-53°C; IR (neat, cm^{-1}): 3454 (m, br), 2991 (w), 2958 (w), 2869 (w), 1754 (w), 1675 (s), 1042 (s), 718 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.10 (t, J = 1.9 Hz, 2H), 3.49-3.46 (m, 4H), 3.38 (m, 2H), 3.27 (dd, J = 3.0, 1.5 Hz, 2H), 2.67 (bs, 1H), 1.74 (dt, *J* = 8.8, 1.7 Hz, 1H), 1.64 (p, *J* = 6.0 Hz, 2H), 1.55 (dt, *J* = 8.7, 1.6 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 178.5, 134.7, 58.8, 52.5, 46.0, 45.0, 34.7, 30.7; HRMS (ESI$^+$) *m/z* [$C_{12}H_{16}NO_3$]$^+$ calcd: 222.1125; found: 222.1126.



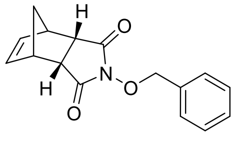
Carbic imide from tyramine (**4.2l**)

Following the general procedure A with modifications, tyramine (72.0 mg, 0.525 mmol, 1.05 equiv.) and TBD (20.9 mg, 0.15 mmol, 30 mol%) were used. The reaction was stirred for 2 hours. Purification by flash chromatography (SiO$_2$, Hex/EA = 10:1 to 2:1) gave **4.2l** (103 mg, 73%) as a white solid. R$_f$ = 0.37 (Hex/EA = 1:1); Mp: 176°C (decomp.); IR (neat, cm^{-1}): 3427 (m), 3000 (w), 2961 (w), 2869 (w), 1761 (w), 1675 (s), 1513 (m), 1155 (s), 732 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): *δ* 7.06 (d, *J* = 8.5 Hz, 2H), 6.75 (d, *J* = 8.5 Hz, 2H), 5.96 (t, *J* = 1.9 Hz, 2H), 5.48 (s, 1H), 3.56 (m, 2H), 3.35 (m, 2H), 3.21 (dd, *J* = 3.0, 1.6 Hz, 2H), 2.69 (m, 2H), 1.69 (dt, *J* = 8.9, 1.8 Hz, 1H), 1.50 (dt, *J* = 8.8, 1.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 178.0, 154.7, 134.5, 130.1, 129.9, 115.4, 52.3, 45.9, 45.0, 39.7, 32.9; HRMS (ESI$^+$) *m/z* [$C_{17}H_{17}NO_3Na$]$^+$ calcd: 306.1101; found: 306.1100.



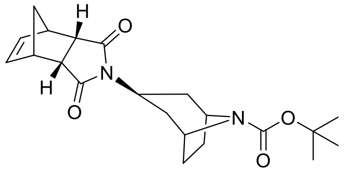
Carbic imide from 3-aminobenzylamine (**4.2m**)

Following the general procedure A, 3-aminobenzylamine (64.1 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO$_2$, Hex/EA = 5:1 to 1:1) gave **4.2m** (127 mg, 95%) as a brown oil. R$_f$ = 0.20 (Hex/EA = 1:1); IR (neat, cm^{-1}): 3448 (w, br), 3362 (w, br), 2988 (w), 2869 (w), 1762 (w), 1687 (s), 1605 (m), 1393 (m), 1336 (m), 1168 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): *δ* 7.04 (t, *J* = 7.8 Hz, 1H), 6.68 (dt, *J* = 7.7, 1.2 Hz, 1H), 6.62 (t, *J* = 2.3 Hz, 1H), 6.55 (ddd, *J* = 7.9, 2.4, 1.1 Hz, 1H), 5.93 (t, *J* = 2.0 Hz, 2H), 4.37 (s, 2H), 3.64 (bs, 2H), 3.36 (m, 2H), 3.23 (dd, *J* = 3.1, 1.5 Hz, 2H), 1.68 (dt, *J* = 8.7, 1.7 Hz, 1H), 1.50 (dt, *J* = 8.7, 1.7 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): *δ* 177.5, 146.6, 137.3, 134.5, 129.4, 119.1, 115.5, 114.5, 52.2, 45.9, 45.1, 42.1; HRMS (ESI$^+$) *m/z* [$C_{16}H_{16}N_2O_2Na$]$^+$ calcd: 291.1104; found: 291.1098.



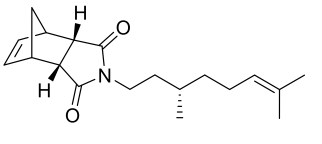
Carbic imide from *O*-benzylhydroxylamine (**4.2n**)

Following the general procedure E, the free base was obtained from its hydrochloride salt. Following the general procedure A with modifications, freshly distilled *O*-benzylhydroxylamine (64.6 mg, 0.525 mmol, 1.05 equiv.) and TBD (13.9 mg, 0.1 mmol, 20 mol%) were used. The reaction was stirred for 4 hours. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 3:1) gave **4.2n** (105 mg, 78%) as a white solid. R_f = 0.39 (Hex/EA = 2:1); Mp: 105-106ºC; IR (neat, cm^{-1}): 2991 (w), 2952 (w), 2887 (w), 1779 (w), 1715 (s), 1377 (m), 1210 (s), 719 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.45 (m, 2H), 7.37-7.34 (m, 3H), 6.00 (t, J = 2.0 Hz, 2H), 4.98 (s, 2H), 3.37 (m, 2H), 3.14 (dd, J = 2.8, 1.4 Hz, 2H), 1.71 (dt, J = 9.0, 1.8 Hz, 1H), 1.46 (dt, J = 8.9, 1.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.2, 134.6, 133.7, 129.8, 129.3, 128.5, 78.7, 51.4, 44.8, 42.8; HRMS (ESI^+) *m/z* $[C_{16}H_{15}NO_3Na]^+$ calcd: 292.0944; found: 292.0946.



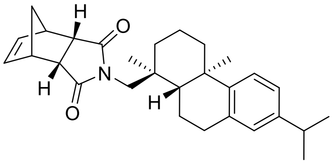
Carbic imide from *N*-Boc-*exo*-3-aminotropane (**2o**)

Following the general procedure A with modifications, *N*-Boc-*exo*-3-aminotropane (118.8 mg, 0.525 mmol, 1.05 equiv.) and TBD (13.9 mg, 0.1 mmol, 20 mol%) were used. The reaction was stirred for 1 hour. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 3:1) gave **2o** (156 mg, 84%) as a white solid. R_f = 0.46 (DCM/EA = 2:1); Mp: 172-173ºC; IR (neat, cm^{-1}): 2967 (w), 2929 (w), 2870 (w), 1684 (s), 1407 (m), 1170 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.02 (m, 2H), 4.32 (m, 1H), 4.22 (m, 1H), 4.12 (m, 1H), 3.33 (m, 2H), 3.13 (d, J = 2.7 Hz, 2H), 2.38 (m, 2H), 1.93 (m, 2H), 1.70-1.64 (m, 3H), 1.47 (s, 9H), 1.45 (m, 1H), 1.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.65, 153.60, 134.43, 134.25, 79.52, 53.37, 52.72, 52.00, 45.28, 45.17, 43.05, 32.49, 32.33, 28.60, 28.12, 27.30; HRMS (ESI^+) *m/z* $[C_{21}H_{28}N_2O_4Na]^+$ calcd: 395.1941; found: 395.1951.



Carbic imide from (*S*)-citronellyl amine (**4.2p**)

Following the general procedure A, freshly distilled (*S*)-citronellyl amine (81.5 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 5:1) gave **4.2p** (135 mg, 90%) as a colorless oil. $R_f = 0.55$ (Hex/EA = 2:1); $[\alpha]_D^{23} = +5.6$ (c = 1.00, $CHCl_3$); IR (neat, cm^{-1}): 2964 (w), 2869 (w), 1768 (w), 1690 (s). 1395 (m), 724 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.06 (t, J = 1.9 Hz, 2H), 5.04 (m, 1H), 3.36 (m, 2H), 3.32 (m, 2H), 3.20 (dd, J = 3.0, 1.5 Hz, 2H), 1.94 (m, 2H), 1.70 (dt, J = 8.7, 1.8 Hz, 1H), 1.65 (d, J = 1.4 Hz, 3H), 1.57 (d, J = 1.4 Hz, 3H), 1.51 (dt, J = 8.7, 1.4 Hz, 1H), 1.44-1.26 (m, 3H), 1.23-1.08 (m, 2H), 0.87 (d, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.8 (×2), 134.48, 134.46, 131.4, 124.7, 52.3, 45.79, 45.78, 45.00, 44.99, 36.8, 36.7, 34.8, 30.3, 25.8, 25.4, 19.2, 17.7; HRMS (ESI$^+$) *m/z* $[C_{19}H_{27}NO_2Na]^+$ calcd: 324.1934; found: 324.1923.

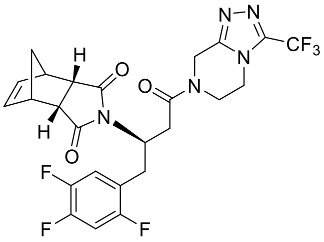


Carbic imide from leelamine (**4.2q**)

Leelamine was purified following a reported procedure.[33] Commercially available 90% pure leelamine (20.0 g) was dissolved in toluene (50 mL) with gentle heat and acetic acid (6.7 g) in toluene (20 mL) was added dropwise. The mixture was cooled to rt, then put into freezer overnight. The white precipitate was filtered and washed with hexane. This solid (the leelamine acetate salt) was recrystallized from MeOH. The recrystallized salt (15.0 g) was dissolved in hot water and 10% NaOH (20 mL) was slowly added. The free amine was extracted in diethyl ether (5 × 20 mL), and the combined organic layers were washed with water (4 × 15 mL), dried over anhydrous Na_2SO_4, and evaporated under vacuum to afford the pure leelamine as a white solid.

Following the general procedure A with modifications, leelamine (149.9 mg, 0.525 mmol, 1.05 equiv.) and TBD (13.9 mg, 0.1 mmol, 20 mol%) were used. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.2q** (193 mg, 90%) as a white solid. $R_f = 0.23$ (Hex/EA = 5:1);

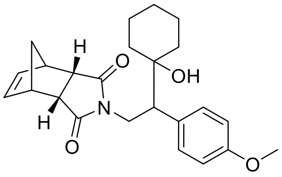
$[\alpha]_D^{23}$ = -18.6 (c = 1.00, $CHCl_3$); Mp: 156-157°C; IR (neat, cm^{-1}): 2988 (w), 2925 (m), 2863 (w), 1776 (w), 1700 (s), 1346 (m), 1143 (m), 741 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.13 (d, J = 8.1 Hz, 1H), 6.97 (dd, J = 8.2, 2.0 Hz, 1H), 6.90 (d, J = 2.0 Hz, 1H), 6.09 (dd, J = 5.8, 2.9 Hz, 1H), 5.97 (dd, J = 5.7, 2.9 Hz, 1H), 3.37-3.35 (m, 2H), 3.33 (d, J = 13.4 Hz, 1H), 3.27-3.22 (m, 3H), 2.92-2.89 (m, 2H), 2.82 (p, J = 6.9 Hz, 1H), 2.25 (m, 1H), 2.10 (m, 1H), 1.77-1.59 (m, 4H), 1.53 (dt, J = 8.6, 1.5 Hz, 1H), 1.36-1.31 (m, 2H), 1.28 (dd, J = 12.4, 2.0 Hz, 1H), 1.23 (d, J = 6.9 Hz, 6H), 1.19 (s, 3H), 1.18 (m, 1H), 0.93 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 178.6 (×2), 147.3, 145.6, 135.04, 134.95, 134.8, 127.0, 123.8, 123.7, 52.4, 49.3, 45.8 (×2), 45.3, 45.04, 44.99, 39.5, 38.3, 37.6, 36.9, 33.5, 30.1, 25.8, 24.1, 24.0, 19.5, 19.1, 18.6; HRMS (ESI$^+$) *m/z* $[C_{29}H_{37}NO_2Na]^+$ calcd: 454.2717; found: 454.2701.



Carbic imide from sitagliptin (**4.2r**)

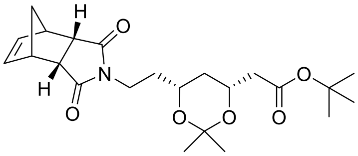
Note: The rotamers from the imide structure, amide structure, and the presence of fluorine atoms in 4 different environments make the ^{13}C spectrum impossible to decipher. Tentative peak picking was shown for reference.

Following the general procedure A with modifications, sitagliptin (213.8 mg, 0.525 mmol, 1.05 equiv.) was used. The reaction was stirred for 2 hours. Purification by flash chromatography (SiO_2, Hex/acetone = 5:1 to 1:1) gave **4.2r** (216 mg, 78%) as a white solid. R_f = 0.25 (Hex/acetone = 2:1); $[\alpha]_D^{23}$ = +17.8 (c = 1.00, $CHCl_3$); Mp: 86-88°C; IR (neat, cm^{-1}): 2997 (w), 2943 (w), 2866 (w), 1765 (w), 1696 (s), 1656 (m), 1516 (m), 1152 (m), 1011 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.01 (m, 1H), 6.85 (m, 1H), 5.93 (dd, J = 5.7, 3.1 Hz, 1H), 5.68 (m, 1H), 5.01-4.84 (m, 2H), 4.72 (m, 1H), 4.23-3.92 (m, 4H), 3.28-2.76 (m, 8H), 1.65 (dt, J = 8.8, 1.7 Hz, 1H), 1.45 (dt, J = 8.7, 1.6 Hz, 1H); ^{19}F NMR ($CDCl_3$, 377 MHz): δ -62.9 (minor), -63.1 (major), -118.5 (d, J = 14.6 Hz, major), -118.8 (d, J = 14.0 Hz, minor), -134.7 (d, J = 21.1 Hz, minor), -135.0 (d, J = 21.5 Hz, major), -142.4 (dd, J = 22.1, 15.0 Hz, minor), -142.6 (dd, J = 21.8, 15.3 Hz, major); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (177.6, 177.5), (168.8, 168.4), 156.2 (m), 150.0 (m), 147.8 (m), 145.6 (m), 143.7 (m), 134.6, (134.0, 133.9), 119.8 (m), 118.2 (m), 105.5 (dd, *J* = 28.5, 20.8 Hz), 52.3, (47.9, 47.8), (45.5, 45.4), (44.9, 44.8), (43.6, 43.2), (42.3, 41.7), (39.3, 38.1), (34.5, 34.2), (30.5, 30.3); HRMS (ESI$^+$) *m/z* $[C_{25}H_{22}N_5O_3F_6]^+$ calcd: 554.1621; found: 554.1615.



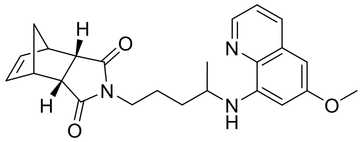
Carbic imide from *N*,*N*-didesmethylvenlafaxine (**4.2s**)

Following the general procedure E, the free base was obtained from its hydrochloride salt. Following the general procedure A with modifications, *N*,*N*-didesmethylvenlafaxine (130.9 mg, 0.525 mmol, 1.05 equiv.) was used. The reaction was stirred for 2 hours. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 4:1) gave **4.2s** (173 mg, 87%) as a white solid. R_f = 0.30 (Hex/EA = 1:1); Mp: 155-156°C; IR (neat, cm^{-1}): 3410 (w), 2980 (w), 2922 (w), 2852 (w), 1764 (w), 1687 (s), 1240 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 7.08 (broad d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 8.9 Hz, 2H), 5.65 (dd, *J* = 5.7, 3.0 Hz, 1H), 5.10 (dd, *J* = 5.6, 2.9 Hz, 1H), 4.12 (dd, *J* = 13.4, 12.1 Hz, 1H), 3.75 (s, 3H), 3.58 (dd, *J* = 13.5, 4.4 Hz, 1H), 3.19-3.15 (m, 2H), 3.10 (m, 1H), 2.98 (m, 2H), 1.68 (m, 1H), 1.59-1.33 (m, 9H), 1.27-1.09 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): *δ* 178.1, 177.4, 158.8, 134.0, 133.9, 131.2 (br), 129.8, 113.2, 72.6, 55.3, 52.1, 51.3 (br), 45.64, 45.59, 44.6, 38.3, 35.9, 35.8, 25.7, 22.0, 21.8; HRMS (ESI$^+$) *m/z* $[C_{24}H_{29}NO_4Na]^+$ calcd: 418.1989; found: 418.1988.



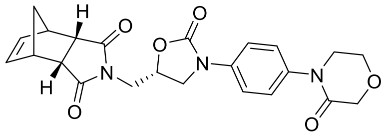
Carbic imide from 1,1-dimethylethyl (4*R*-*cis*)-6-aminoethyl-2,2-dimethyl-1,3-dioxane-4-acetate (**4.2t**)

Following the general procedure A, 1,1-dimethylethyl (4*R*-*cis*)-6-aminoethyl-2,2-dimethyl-1,3-dioxane-4-acetate (143.5 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1) gave **4.2t** (195 mg, 93%) as a colorless oil. R_f = 0.55 (Hex/EA = 1:1); $[\alpha]_D^{23}$ = +10.0 (c = 1.00, $CHCl_3$); IR (neat, cm^{-1}): 2991 (w), 2940 (w), 2869 (w), 1767 (w), 1725 (m), 1696 (s), 1150 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): *δ* 6.05 (t, *J* = 1.9 Hz, 2H), 4.18 (m, 1H), 3.75 (m, 1H), 3.44-3.35 (m, 4H), 3.20 (m, 2H), 2.37 (dd, *J* = 15.1, 7.0 Hz, 1H), 2.25 (dd, *J* = 15.1, 6.1 Hz, 1H), 1.70 (dt, *J* = 8.7, 1.7 Hz, 1H), 1.58 (m, 1H), 1.53-1.46 (m, 3H), 1.41 (s, 9H), 1.38 (s, 3H), 1.31 (s, 3H), 1.12 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.71, 177.67, 170.3, 134.48, 134.47, 98.8, 80.7, 66.9, 66.2, 52.3, 45.8, 45.8, 45.0 (×2), 42.7, 36.3, 34.9, 34.3, 30.1, 28.2, 19.7; HRMS (ESI$^+$) *m/z* $[C_{23}H_{33}NO_6Na]^+$ calcd: 442.2200; found: 442.2196.



Carbic imide from primaquine (**4.2u**)

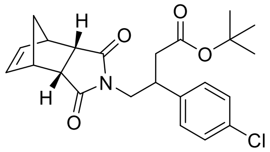
Following the general procedure E with modifications, the free base was obtained from its phosphate salt using 1 M NaOH instead. Following the general procedure A, primaquine (136.2 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1) gave **4.2u** (122 mg, 60%) as a sticky yellow oil that is light sensitive. $R_f = 0.56$ (Hex/EA = 1:1); IR (neat, cm^{-1}): 3385 (w, br), 2940 (w), 2869 (w), 1765 (w), 1691 (s), 1515 (s), 1158 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.51 (dd, *J* = 4.2, 1.7 Hz, 1H), 7.90 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.28 (dd, *J* = 8.2, 4.2 Hz, 1H), 6.31 (d, *J* = 2.5 Hz, 1H), 6.25 (d, *J* = 2.5 Hz, 1H), 6.09 (dd, *J* = 5.7, 3.3 Hz, 1H), 6.02 (dd, *J* = 5.7, 3.3 Hz, 1H), 5.96 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 3.57 (m, 1H), 3.39-3.33 (m, 4H), 3.21 (m, 2H), 1.69 (dt, *J* = 8.8, 1.7 Hz, 1H), 1.67-1.49 (m, 5H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.8 (×2), 159.5, 145.0, 144.4, 135.4, 134.8, 134.6, 134.5, 130.0, 121.9, 96.8, 91.8, 55.3, 52.4, 47.8, 45.8 (×2), 45.0 (×2), 38.4, 34.1, 24.8, 20.6; HRMS (ESI$^+$) *m/z* $[C_{24}H_{28}N_3O_3]^+$ calcd: 406.2125; found: 406.2113.



Carbic imide from (*S*)-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one (**4.2v**)

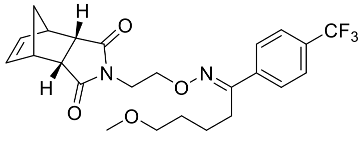
Following the general procedure A, (*S*)-4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl) morpholin-3-one (152.9 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, DCM/MeOH = 100:1 to 20:1) gave **4.2v** (211 mg, 96%) as a white solid. $R_f = 0.45$ (DCM/MeOH = 20:1); $[\alpha]_D^{23} = -37.5$ (c = 1.00, $CHCl_3$); Mp: 207-208ºC; IR (neat, cm$^-$

^{1}): 3000 (w), 2940 (w), 2872 (w), 1745 (s), 1696 (w), 1663 (w), 1309 (s), 1121 (s), 841 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.51 (d, J = 9.0 Hz, 2H), 7.31 (d, J = 9.0 Hz, 2H), 6.10 (dd, J = 5.7, 2.9 Hz, 1H), 6.04 (dd, J = 5.7, 2.9 Hz, 1H), 4.73 (dq, J = 8.8, 6.0 Hz, 1H), 4.29 (s, 2H), 4.01-3.95 (m, 3H), 3.77-3.71 (m, 4H), 3.62 (dd, J = 13.9, 5.5 Hz, 1H), 3.37 (m, 2H), 3.29 (dd, J = 2.9, 1.5 Hz, 2H), 1.71 (dt, J = 8.9, 1.7 Hz, 1H), 1.53 (dt, J = 8.8, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.6, 177.4, 166.8, 153.9, 137.3, 136.7, 134.64, 134.55, 126.2, 119.0, 69.4, 68.6, 64.2, 52.4, 49.7, 48.3, 46.0, 45.9, 45.13, 45.12, 40.8; HRMS (ESI^{+}) *m/z* $[C_{23}H_{23}N_3O_6Na]^+$ calcd: 460.1479; found: 460.1464.



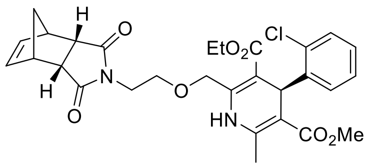
Carbic imide from baclofen *tert*-butyl ester (**4.2w**)

Following the general procedure A, baclofen *tert*-butyl ester (141.6 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1) gave **4.2w** (197 mg, 95%) as a white solid. R_f = 0.33 (Hex/EA = 2:1); Mp: 136-137°C; IR (neat, cm^{-1}): 3000 (w), 2967 (w), 2934 (w), 1722 (m), 1690 (s), 1155 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, J = 8.5 Hz, 2H), 7.13 (d, J = 8.5 Hz, 2H), 5.91 (dd, J = 5.6, 3.1 Hz, 1H), 5.64 (dd, J = 5.7, 3.0 Hz, 1H), 3.58 (m, 1H), 3.47-3.43 (m, 2H), 3.30-3.24 (m, 2H), 3.16-3.12 (m, 2H), 2.45 (m, 1H), 2.40 (m, 1H), 1.64 (dt, J = 8.7, 1.8 Hz, 1H), 1.46 (dt, J = 8.7, 1.7 Hz, 1H), 1.27 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.6, 177.4, 170.4, 139.0, 134.6, 134.4, 133.0, 129.6, 128.5, 80.8, 52.4, 45.80, 45.77, 44.88, 44.85, 43.0, 40.3, 39.7, 28.0; HRMS (ESI^{+}) *m/z* $[C_{23}H_{26}NO_4ClNa]^+$ calcd: 438.1443; found: 438.1449.



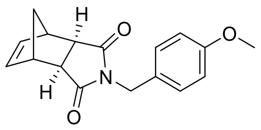
Carbic imide from fluvoxamine (**4.2x**)

Following the general procedure E, the free base was obtained from its hydrochloride salt. Following the general procedure A, fluvoxamine (167.1 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1) gave **4.2x** (225 mg, 97%) as a colorless oil. R_f = 0.50 (Hex/EA = 1:1); IR (neat, cm^{-1}): 2940 (w), 2872 (w), 1771 (w), 1697 (s), 1322 (s), 1112 (s), 844 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.73 (d, J = 8.1 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H), 6.08 (t, J = 1.9 Hz, 2H), 4.20 (t, J = 5.6 Hz, 2H), 3.70 (t, J = 5.6 Hz, 2H), 3.37-3.35 (m, 4H), 3.30 (s, 3H), 3.22 (dd, J = 3.1, 1.5 Hz, 2H), 2.71 (m, 2H), 1.71 (dt, J = 8.9, 1.8 Hz, 1H), 1.63-1.50 (m, 5H); ^{19}F NMR ($CDCl_3$, 471 MHz): δ -62.7; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.5, 157.8, 139.0, 134.4, 130.9 (q, J = 32.5 Hz), 126.6, 125.4 (q, J = 3.9 Hz), 124.0 (q, J = 270.0 Hz), 72.3, 70.5, 58.6, 52.2, 45.8, 44.9, 37.8, 29.6, 26.2, 23.0; HRMS (ESI$^+$) *m/z* $[C_{24}H_{27}N_2O_4F_3Na]^+$ calcd: 487.1815; found: 487.1830.



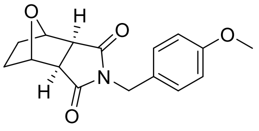
Carbic imide from levamlodipine (**4.2y**)

Following the general procedure A, levamlodipine (214.7 mg, 0.525 mmol, 1.05 equiv.) was used. Purification by flash chromatography (SiO_2, Hex/EA = 4:1 to 1:1) gave **4.2y** (270 mg, 97%) as a yellow semi-solid, which solidifies upon standing to a yellow solid. R_f = 0.32 (Hex/EA = 1:1); $[\alpha]_D^{23}$ = -22.0 (c = 1.00, $CHCl_3$); Mp: 86-88°C; IR (neat, cm^{-1}): 3332 (w, br), 2982 (w), 2869 (w), 1767 (w), 1691 (s), 1250 (m), 1096 (s), 741 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.33 (bs, 1H), 7.32 (dd, J = 7.8, 1.8 Hz, 1H), 7.18 (dd, J = 7.9, 1.3 Hz, 1H), 7.07 (td, J = 7.5, 1.4 Hz, 1H), 6.98 (td, J = 7.6, 1.7 Hz, 1H), 6.05 (dd, J = 5.7, 2.9 Hz, 1H), 5.98 (dd, J = 5.8, 2.9 Hz, 1H), 5.36 (s, 1H), 4.61 (d, J = 15.7 Hz, 1H), 4.54 (d, J = 15.7 Hz, 1H), 3.98 (m, 2H), 3.62 (m, 1H), 3.57 (s, 3H), 3.55-3.52 (m, 2H), 3.47 (m, 1H), 3.36 (m, 2H), 3.27 (m, 2H), 2.42 (s, 3H), 1.71 (dt, J = 8.8, 1.7 Hz, 1H), 1.53 (dt, J = 8.8, 1.6 Hz, 1H), 1.13 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 178.1, 178.0, 168.1, 167.2, 145.9, 145.0, 144.7, 134.3, 134.2, 132.3, 131.5, 129.2, 127.3, 126.8, 103.7, 101.0, 68.6, 68.0, 59.7, 52.3, 50.7, 45.9 (×2), 45.04, 45.02, 38.4, 37.0, 19.1, 14.3; HRMS (ESI$^+$) *m/z* $[C_{29}H_{31}N_2O_7ClNa]^+$ calcd: 577.1712; found: 577.1688.



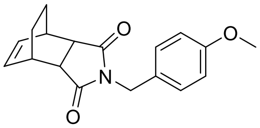
N-PMB imide with *cis*-*exo*-5-norbornene-2,3-dicarboxylic scaffold (**4.4a**)

Following general procedure B, **4.3a** (117.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 30 minutes. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 5:1) gave **4.4a** (139 mg, 98%) as a colorless oil. $R_f = 0.58$ (Hex/EA = 2:1); IR (neat, cm^{-1}): 2985 (w), 2836 (w), 1767 (w), 1690 (s), 1512 (m), 1245 (s), 1170 (m), 888 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.31 (d, J = 8.9 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 6.26 (t, J = 1.9 Hz, 2H), 4.55 (s, 2H), 3.77 (s, 3H), 3.23 (p, J = 1.7 Hz, 2H), 2.65 (d, J = 1.6 Hz, 2H), 1.39 (dp, J = 9.8, 1.5 Hz, 1H), 1.03 (dp, J = 9.9, 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.9, 159.3, 138.1, 130.5, 128.3, 114.1, 55.3, 47.9, 45.4, 42.7, 41.9; HRMS (ESI$^+$) *m/z* $[C_{17}H_{17}NO_3Na]^+$ calcd: 306.1101; found: 306.1111.



<u>*N*-PMB imide with norcantharidin scaffold (**4.4b**)</u>

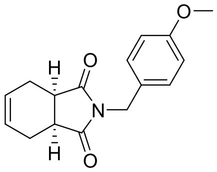
Following the general procedure B, **4.3b** (119.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 30 minutes. Purification by flash chromatography (SiO_2, Hex/EA = 5:1 to 2:1) gave **4.4b** (137 mg, 95%) as colorless oil, which solidifies upon standing to a white solid. R_f = 0.23 (Hex/EA = 2:1); Mp: 107-108°C; IR (neat, cm^{-1}): 2994 (w), 1767 (w), 1694 (s), 1513 (m), 1176 (s), 890 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.26 (d, J = 8.8 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.87 (dd, J = 3.4, 2.1 Hz, 2H), 4.55 (s, 2H), 3.76 (s, 3H), 2.84 (s, 2H), 1.84 (m, 2H), 1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.0, 159.3, 129.8, 127.9, 114.1, 79.2, 55.3, 50.1, 42.1, 28.7; HRMS (ESI$^+$) *m/z* $[C_{16}H_{17}NO_4Na]^+$ calcd: 310.1050; found: 310.1056.



<u>*N*-PMB imide with bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic scaffold (**4.4c**)</u>

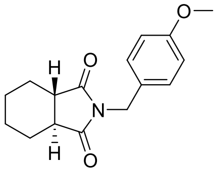
Following the general procedure B, **4.3c** (124.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 4 hours. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 5:1) gave **4.4c** (133 mg, 89%) as a white solid. R_f = 0.55 (Hex/EA = 2:1); Mp: 90-91°C; IR (neat, cm^{-1}): 3041 (w), 2946 (w), 2872 (w),1685 (s), 1513 (m), 1173 (s), 793 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.23 (d, J = 8.9 Hz, 2H), 6.79 (d, J = 8.9 Hz, 2H), 6.04 (dd, J = 4.6, 3.1 Hz, 2H), 4.48 (s, 2H), 3.77 (s, 3H), 3.12 (m, 2H), 2.80 (t, J = 1.7 Hz, 2H), 1.56 (m, 2H), 1.35 (m, 2H); ^{13}C NMR

(CDCl$_3$, 125 MHz): δ 178.8, 159.2, 132.3, 130.2, 128.4, 113.8, 55.3, 44.3, 41.7, 31.8, 23.8; HRMS (ESI$^+$) *m/z* [$C_{18}H_{19}NO_3Na$]$^+$ calcd: 320.1257; found: 320.1257.



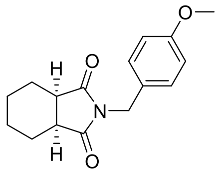
<u>*N*-PMB imide with *cis*-1,2,3,6-tetrahydrophthalic scaffold (**4.4d**)</u>

Following the general procedure B, **4.3d** (111.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at 40°C for 1 hour. Purification by flash chromatography (SiO$_2$, Hex/EA = 5:1 to 2:1) gave **4.4d** (119 mg, 88%) as a light yellow oil, which solidifies upon standing to a white solid. R$_f$ = 0.43 (Hex/EA = 2:1); Mp: 63-65°C; IR (neat, cm^{-1}): 3044 (w), 2946 (w), 2836 (w), 1767 (w), 1690 (s), 1244 (s), 912 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.25 (d, J = 8.7 Hz, 2H), 6.80 (d, J = 8.7 Hz, 2H), 5.85 (m, 2H), 4.55 (s, 2H), 3.77 (s, 3H), 3.05 (m, 2H), 2.58 (m, 2H), 2.21 (m, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 180.0, 159.3, 130.0, 128.3, 127.9, 114.0, 55.3, 42.1, 39.2, 23.6; HRMS (ESI$^+$) *m/z* [$C_{16}H_{17}NO_3Na$]$^+$ calcd: 294.1101; found: 294.1097.



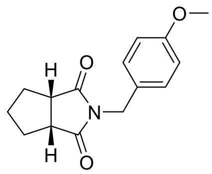
<u>*N*-PMB imide with *trans*-1,2-cyclohexanedicarboxylic scaffold (**4.4e**)</u>

Following the general procedure B, **4.3e** (112.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO$_2$, Hex/EA = 10:1 to 4:1) gave **4.4e** (123 mg, 90%) as a white solid. R$_f$ = 0.45 (Hex/EA = 2:1); Mp: 77-78°C; IR (neat, cm^{-1}): 3001 (w), 2933 (w), 2864 (w), 1766 (w), 1692 (s), 1243 (m), 1172 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.29 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.81 (m, 2H), 1.81 (m, 2H), 1.67 (m, 2H), 1.41 (m, 2H), 1.34 (m, 2H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 179.5, 159.3, 130.2, 128.5, 114.0, 55.3, 41.6, 39.8, 23.7, 21.6; HRMS (ESI$^+$) *m/z* [$C_{16}H_{19}NO_3Na$]$^+$ calcd: 296.1257; found: 296.1254.



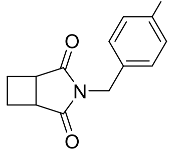
<u>*N*-PMB imide with *cis*-1,2-cyclohexanedicarboxylic scaffold (**4.4f**)</u>

Following the general procedure B, **4.3f** (112.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 5:1) gave **4.4f** (126 mg, 92%) as a colorless oil, which solidifies upon standing to a white solid. R_f = 0.43 (Hex/EA = 2:1); Mp: 77-78°C; IR (neat, cm^{-1}): 3002 (w), 2934 (w), 2866 (w), 1765 (w), 1691 (s), 1510 (m), 1245 (s), 1171 (s), 808 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.7 Hz, 2H), 4.56 (s, 2H), 3.77 (s, 3H), 2.82 (td, J = 4.5, 2.3 Hz, 2H), 1.80 (m, 2H), 1.68 (m, 2H), 1.41 (m, 2H), 1.34 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.5, 159.3, 130.2, 128.5, 114.0, 55.3, 41.7, 39.9, 23.7, 21.6; HRMS (ESI$^+$) *m/z* $[C_{16}H_{20}NO_3]^+$ calcd: 274.1438; found: 274.1440.



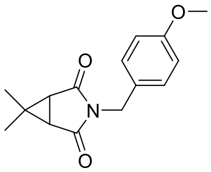
<u>*N*-PMB imide with *cis*-1,2-cyclopentanedicarboxylic scaffold (**4.4g**)</u>

Following the general procedure B, **4.3g** (105.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 4:1) gave **4.4g** (126 mg, 97%) as a light yellow oil. R_f = 0.34 (Hex/EA = 2:1); IR (neat, cm^{-1}): 2959 (w), 2871 (w), 2836 (w), 1774 (w), 1693 (s), 1512 (m), 1244 (m), 1176 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.28 (d, J = 8.7 Hz, 2H), 6.81 (d, J = 8.8 Hz, 2H), 4.54 (s, 2H), 3.77 (s, 3H), 3.11 (m, 2H), 2.10 (m, 2H), 1.83 (m, 2H), 1.69 (m, 1H), 1.16 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.2, 159.3, 130.1, 128.5, 114.0, 55.3, 45.3, 42.0, 30.6, 24.9; HRMS (ESI$^+$) *m/z* $[C_{15}H_{17}NO_3Na]^+$ calcd: 282.1101; found: 282.1103.



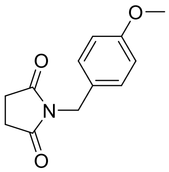
N-PMB imide with 1,2-cyclobutanedicarboxylic scaffold (**4.4h**)

Following the general procedure B, **4.3h** (98.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at 80ºC for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 4:1 to 2:1) gave **4.4h** (105 mg, 85%) as an off-white solid. R_f = 0.43 (Hex/EA = 1:1); Mp: 102-103ºC; IR (neat, cm^{-1}): 2992 (w), 2950 (w), 1764 (w), 1690 (s), 1169 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.34 (d, J = 8.8 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 4.63 (s, 2H), 3.77 (s, 3H), 3.24 (m, 2H), 2.61 (m, 2H), 2.09 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.6, 159.4, 130.2, 128.4, 114.1, 55.3, 42.0, 38.5, 23.0; HRMS (ESI^+) *m/z* $[C_{14}H_{15}NO_3Na]^+$ calcd: 268.0944; found: 268.0948.



N-PMB imide with caronic scaffold (**4.4i**)

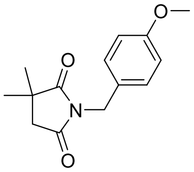
Following the general procedure B, **4.3i** (105.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at 60ºC for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 4:1) gave **4.4i** (121 mg, 93%) as a white solid. R_f = 0.40 (Hex/EA = 2:1); Mp: 80-81ºC; IR (neat, cm^{-1}): 3050 (w), 2943 (w), 2836 (w), 1759 (w), 1693 (s), 1515 (m), 1242 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.30 (d, J = 8.7 Hz, 2H), 6.79 (d, J = 8.7 Hz, 2H), 4.45 (s, 2H), 3.75 (s, 3H), 2.27 (s, 2H), 1.17 (s, 3H), 0.98 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 159.3, 130.7, 128.3, 113.9, 55.3, 41.2, 35.7, 33.5, 26.4, 15.4; HRMS (ESI^+) *m/z* $[C_{15}H_{17}NO_3Na]^+$ calcd: 282.1101; found: 282.1093.



N-PMB imide with succinic scaffold (**4.4j**)

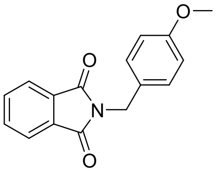
Following the general procedure B, **4.3j** (85.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at 70ºC for 1 hour. Purification by flash chromatography (SiO_2, DCM/EA = 10:1) gave **4.4j** (103 mg, 94%) as a white solid. R_f = 0.58 (Hex/EA = 1:2); Mp: 124-126ºC; IR (neat, cm^{-1}): 2961 (w), 2837 (w), 1758 (w), 1687 (s), 1512 (m), 1399 (m), 1244 (m), 1169 (s), 1025 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.33 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 4.58 (s, 2H), 3.76

(s, 3H), 2.66 (s, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 177.0, 159.4, 130.5, 128.2, 114.0, 55.3, 41.9, 28.3; HRMS (ESI$^+$) *m/z* [$C_{12}H_{13}NO_3Na$]$^+$ calcd: 242.0788; found: 242.0785.



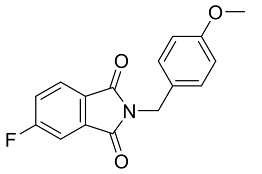
<u>*N*-PMB imide with succinic scaffold (**4.4k**)</u>

Following the general procedure B, **4.3k** (99.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at 50°C for 2 hours. Purification by flash chromatography (SiO$_2$, Hex/EA = 10:1 to 4:1) gave **4.4k** (107 mg, 86%) as a white solid. R$_f$ = 0.42 (Hex/EA = 2:1); Mp: 87-88°C; IR (neat, cm^{-1}): 2958 (w), 2928 (w), 1696 (s), 1513 (m), 1247 (m), 1107 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.8 Hz, 2H), 4.56 (s, 2H), 3.76 (s, 3H), 2.51 (s, 2H), 1.27 (s, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 183.0, 175.6, 159.3, 130.1, 128.3, 114.1, 55.3, 43.7, 41.9, 40.1, 25.6; HRMS (ESI$^+$) *m/z* [$C_{14}H_{17}NO_3Na$]$^+$ calcd: 270.1101; found: 270.1096.



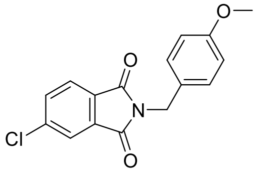
<u>*N*-PMB phthalimide (**4.6a**)</u>

Following the general procedure C, **4.5a** (109.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO$_2$, Hex/EA = 20:1 to 5:1) gave **4.6a** (121 mg, 90%) as an off-white solid. Alternatively, following the general procedure D gave **4.6a** (118 mg, 88%). R$_f$ = 0.65 (Hex/EA = 2:1); Mp: 127-129°C; IR (neat, cm^{-1}): 3065 (w), 2940 (w), 2845 (w), 1762 (w), 1716 (s), 1510 (m), 1390 (s), 1251 (s), 716 (s); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.82 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.68 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.38 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.78 (s, 2H), 3.76 (s, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 168.2, 159.3, 134.0, 132.3, 130.3, 128.8, 123.4, 114.1, 55.4, 41.2; HRMS (ESI$^+$) *m/z* [$C_{16}H_{13}NO_3Na$]$^+$ calcd: 290.0788; found: 290.0784.



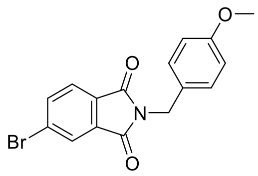
<u>*N*-PMB 4-fluorophthalimide (**4.6b**)</u>

Following the general procedure C, **4.5b** (118.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.6b** (128 mg, 90%) as a white solid. Alternatively, following general procedure D gave **4.6b** (117 mg, 82%). Product precipitation was observed during the course of the reaction. R_f = 0.63 (Hex/EA = 2:1); Mp: 132-134°C; IR (neat, cm^{-1}): 3032 (w), 2940 (w), 1767 (w), 1709 (s), 1614 (w), 1393 (s), 1251 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.84 (dd, *J* = 8.2, 4.4 Hz, 1H), 7.51 (dd, *J* = 7.0, 2.3 Hz, 1H), 7.39 (d, *J* = 8.7 Hz, 2H), 7.37 (m, 1H), 6.85 (d, *J* = 8.8 Hz, 2H), 4.78 (s, 2H), 3.78 (s, 3H); ^{19}F NMR ($CDCl_3$, 471 MHz): δ -102.0; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.1, 166.7 (d, *J* = 2.7 Hz), 166.4 (d, *J* = 256.8 Hz), 159.4, 135.1 (d, *J* = 9.2 Hz), 130.3, 128.5, 128.0 (d, *J* = 2.7 Hz), 125.7 (d, *J* = 9.2 Hz), 121.0 (d, *J* = 23.8 Hz), 114.1, 111.2 (d, *J* = 24.7 Hz), 55.3, 41.4; HRMS (ESI^+) *m/z* $[C_{16}H_{12}NO_3FNa]^+$ calcd: 308.0693; found: 308.0691.



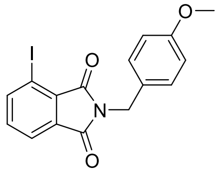
<u>*N*-PMB 4-chlorophthalimide (**4.6c**)</u>

Following the general procedure C, **4.5c** (126.3 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 2 hours. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.6c** (133 mg, 88%) as an off-white solid. Alternatively, following the general procedure D gave **4.6c** (118 mg, 78%). Product precipitation was observed during the course of the reaction. R_f = 0.70 (Hex/EA = 2:1); Mp: 114-115°C; IR (neat, cm^{-1}): 3069 (w), 2995 (w), 2841 (w), 1768 (w), 1714 (s), 1609 (m), 1514 (m), 1390 (s), 1248 (s), 1003 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.77 (d, *J* = 1.8 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.64 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 4.76 (s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.2, 166.8, 159.4, 140.7, 134.0, 133.9, 130.30, 130.26, 128.4, 124.6, 123.8, 114.1, 55.3, 41.4; HRMS (ESI^+) *m/z* $[C_{16}H_{12}NO_3ClNa]^+$ calcd: 324.0398; found: 324.0393.



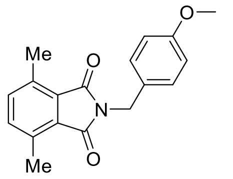
<u>*N*-PMB 4-bromophthalimide (**4.6d**)</u>

Following the general procedure C with modifications, **4.5d** (148.6 mg, 0.5 mmol, 1.0 equiv.) and DMSO (0.75 mL) were used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.6d** (145 mg, 84%) as a yellow solid. Alternatively, following the general procedure D gave **4.6d** (124 mg, 72%). R_f = 0.43 (Hex/EA = 5:1); Mp: 115-117°C; IR (neat, cm^{-1}): 3081 (w), 3003 (w), 2840 (w), 1771 (w), 1699 (s), 1511 (m), 1242 (m), 815 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.94 (d, J = 1.7 Hz, 1H), 7.81 (dd, J = 7.9, 1.8 Hz, 1H), 7.68 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.8 Hz, 2H), 4.76 (s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.3, 166.8, 159.4, 137.0, 133.9, 130.8, 130.3, 128.9, 128.4, 126.8, 124.8, 114.1, 55.4, 41.4; HRMS (APCI$^+$) m/z $[C_{16}H_{13}NO_3Br]^+$ calcd: 346.0073; found: 346.0075.



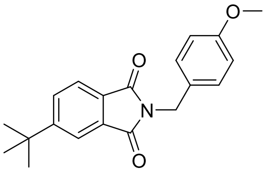
<u>*N*-PMB 3-iodophthalimide (**4.6e**)</u>

Following the general procedure C with modifications, **4.5e** (172.1 mg, 0.5 mmol, 1.0 equiv.) and DMSO (1.5 mL) were used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 4:1) gave **4.6e** (171 mg, 87%) as a yellow solid. Alternatively, following the general procedure D gave **4.6e** (160 mg, 81%). R_f = 0.65 (Hex/EA = 2:1); Mp: 124-125°C; IR (neat, cm^{-1}): 2994 (w), 2937 (w), 2830 (w), 1764 (w), 1699 (s), 1510 (m), 1393 (s), 1242 (s), 1097 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.04 (dd, J = 7.9, 1.1 Hz, 1H), 7.79 (dd, J = 7.4, 1.0 Hz, 1H), 7.39 (d, J = 8.9 Hz, 2H), 7.33 (m, 1H), 6.82 (d, J = 8.9 Hz, 2H), 4.77 (s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.8, 166.2, 159.4, 145.2, 134.7, 134.1, 132.7, 130.5, 128.4, 123.2, 114.1, 88.7, 55.4, 41.5; HRMS (ESI$^+$) m/z $[C_{16}H_{12}NO_3INa]^+$ calcd: 415.9754; found: 415.9744.



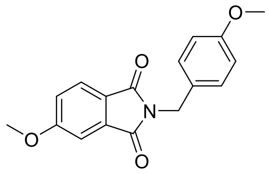
N-PMB 3,6-dimethylphthalimide (**4.6f**)

Following the general procedure C, **4.5f** (123.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 30 minutes. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) gave **4.6f** (137 mg, 93%) as a light yellow solid. Alternatively, following the general procedure D gave **4.6f** (141 mg, 95%). Product precipitation was observed during the course of the reaction. $R_f = 0.60$ (Hex/EA = 5:1); Mp: 144-145°C; IR (neat, cm^{-1}): 2934 (w), 2833 (w), 1755 (w), 1699 (s), 1510 (m), 1244 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.39 (d, $J = 8.7$ Hz, 2H), 7.27 (s, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 4.73 (s, 2H), 3.77 (s, 3H), 2.63 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.0, 159.2, 136.1, 135.5, 130.2, 129.2, 129.1, 114.1, 55.4, 40.8, 17.4; HRMS (ESI^+) *m/z* $[C_{18}H_{17}NO_3Na]^+$ calcd: 318.1101; found: 318.1096.



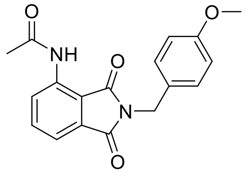
N-PMB 4-*tert*-butylphthalimide (**4.6g**)

Following the general procedure C, **4.5g** (137.2 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 2 hours. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.6g** (144 mg, 90%) as a light yellow solid. Alternatively, following the general procedure D gave **4.6g** (135 mg, 83%). $R_f = 0.52$ (Hex/EA = 5:1); Mp: 97-99°C; IR (neat, cm^{-1}): 2966 (w), 2874 (w), 1765 (w), 1701 (s), 1385 (s), 1241 (s), 1088 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.86 (dd, $J = 1.8, 0.7$ Hz, 1H), 7.74 (dd, $J = 7.9, 0.8$ Hz, 1H), 7.70 (dd, $J = 7.9, 1.7$ Hz, 1H), 7.37 (d, $J = 8.7$ Hz, 2H), 6.82 (d, $J = 8.8$ Hz, 2H), 4.77 (s, 2H), 3.76 (s, 3H), 1.36 (s, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.6, 168.2, 159.3, 158.6, 132.5, 131.0, 130.2, 129.6, 128.9, 123.2, 120.6, 114.1, 55.4, 41.1, 35.8, 31.2; HRMS ($APCI^+$) *m/z* $[C_{20}H_{22}NO_3]^+$ calcd: 324.1594; found: 324.1588.



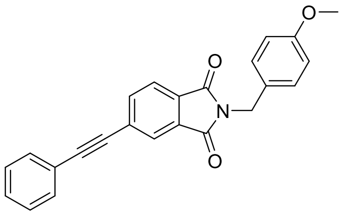
<u>*N*-PMB 4-methoxyphthalimide (**4.6h**)</u>

Following the general procedure C with modifications, **4.5h** (124.1 mg, 0.5 mmol, 1.0 equiv.) and DMSO (1.25 mL) were used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 3:1) gave **4.6h** (140 mg, 94%) as a light yellow solid. Alternatively, following the general procedure D gave **4.6h** (122 mg, 82%). Product precipitation was observed during the course of the reaction. R_f = 0.50 (Hex/EA = 2:1); Mp: 147-148ºC; IR (neat, cm^{-1}): 2922 (w), 2842 (w), 1765 (w), 1693 (s), 1238 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.72 (d, J = 8.2 Hz, 1H), 7.36 (d, J = 8.7 Hz, 2H), 7.29 (d, J = 2.3 Hz, 1H), 7.12 (dd, J = 8.2, 2.3 Hz, 1H), 6.83 (d, J = 8.8 Hz, 2H), 4.75 (s, 2H), 3.90 (s, 3H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.99, 167.96, 164.7, 159.3, 134.9, 130.2, 128.9, 125.1, 124.2, 119.7, 114.1, 108.2, 56.2, 55.4, 41.1; HRMS (ESI^+) m/z $[C_{17}H_{16}NO_4]^+$ calcd: 298.1074; found: 298.1069.



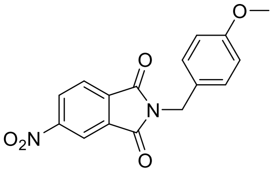
<u>*N*-PMB 3-acetylaminophthalimide (**4.6i**)</u>

Following the general procedure C, **4.5i** (124.1 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, Hex/EA = 2:1) gave **4.6i** (146 mg, 90%) as a light yellow solid. Alternatively, following the general procedure D gave **4.6i** (133 mg, 82%). Product precipitation was observed during the course of the reaction. R_f = 0.60 (Hex/EA = 1:1); Mp: 145-146ºC; IR (neat, cm^{-1}): 3346 (w), 3006 (w), 2947 (w), 2837 (w), 1768 (w), 1695 (s), 1619 (m), 1509 (m), 1242 (s), 736 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.48 (bs, 1H), 8.72 (dd, J = 8.5, 0.8 Hz, 1H), 7.62 (dd, J = 8.5, 7.2 Hz, 1H), 7.47 (dd, J = 7.3, 0.9 Hz, 1H), 7.34 (d, J = 8.9 Hz, 2H), 6.84 (d, J = 8.9 Hz, 2H), 4.73 (s, 2H), 3.76 (s, 3H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.0, 169.3, 167.6, 159.4, 137.5, 135.9, 131.6, 130.1, 128.4, 124.8, 118.1, 115.7, 114.2, 55.4, 41.1, 25.0; HRMS (ESI^+) m/z $[C_{18}H_{16}N_2O_4Na]^+$ calcd: 347.1002; found: 347.1006.



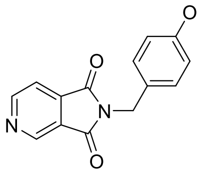
<u>*N*-PMB 4-phenylethynylphthalimide (**4.6j**)</u>

Following the general procedure C, **4.5j** (159.2 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at rt for 2 hours. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 4:1) gave **4.6j** (160 mg, 87%) as a yellow solid. Alternatively, following the general procedure D gave **4.6j** (140 mg, 76%). R_f = 0.48 (Hex/EA = 5:1); Mp: 134-135°C; IR (neat, cm^{-1}): 2940 (w), 2836 (w), 1764 (w), 1700 (s), 1614 (w), 1387 (m), 1244 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.94 (m, 1H), 7.82-7.78 (m, 2H), 7.56-7.54 (m, 2H), 7.41-7.35 (m, 5H), 6.85 (d, J = 8.7 Hz, 2H), 4.78 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.6, 167.5, 159.4, 136.9, 132.6, 132.0, 130.9, 130.3, 129.6, 129.3, 128.6, 126.2, 123.4, 122.2, 114.1, 94.0, 87.9, 55.4, 41.3; HRMS (ESI$^+$) *m/z* $[C_{24}H_{17}NO_3Na]^+$ calcd: 390.1101; found: 390.1093.



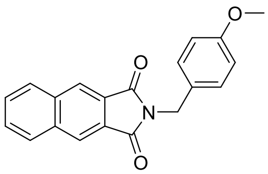
<u>*N*-PMB 4-nitrophthalimide (**4.6k**)</u>

Following the general procedure C with modifications, **4.5k** (131.6 mg, 0.5 mmol, 1.0 equiv.) and TBD (13.9 mg, 0.1 mmol, 20 mol%) were used. The reaction was stirred at 50°C for 2 hours. Purification by flash chromatography (SiO_2, Hex/EA/DCM = 8:1:1) gave **4.6k** (101 mg, 64%) as a yellow solid. Alternatively, following the general procedure D gave **4.6k** (100 mg, 64%). R_f = 0.55 (Hex/EA = 2:1); Mp: 150-152°C; IR (neat, cm^{-1}): 3114 (w), 2961 (w), 2836 (w), 1765 (w), 1704 (s), 1535 (m), 1345 (s), 1097 (m), 718 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.63 (dd, J = 2.0, 0.6 Hz, 1H), 8.57 (dd, J = 8.2, 2.1 Hz, 1H), 8.02 (dd, J = 8.1, 0.6 Hz, 1H), 7.37 (d, J = 8.9 Hz, 2H), 6.83 (d, J = 8.9 Hz, 2H), 4.82 (s, 2H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.0, 165.7, 159.6, 151.8, 136.7, 133.7, 130.4, 129.3, 127.9, 124.6, 118.8, 114.2, 55.4, 41.9; HRMS (APCI$^+$) *m/z* $[C_{16}H_{13}N_2O_5]^+$ calcd: 313.0819; found: 313.0812.



N-PMB pyridine-3,4-dicarboximide (**4.6l**)

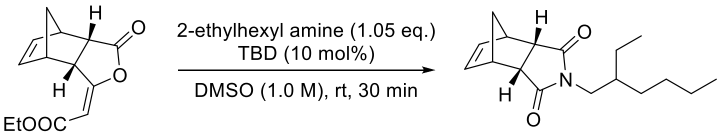
Following the general procedure C, **4.5l** (109.6 mg, 0.5 mmol, 1.0 equiv.) was used. The reaction was stirred at 50°C for 2 hours. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 4:1) gave **4.6l** (100 mg, 75%) as a white solid. Alternatively, following the general procedure D gave **4.6l** (95 mg, 71%). $R_f = 0.68$ (DCM/EA = 1:2); Mp: 132-134°C; IR (neat, cm^{-1}): 3062 (w), 2943 (w), 2845 (w), 1768 (w), 1711 (s), 1513 (m), 1389 (s), 1250 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 9.12 (s, 1H), 9.03 (d, J = 4.9 Hz, 1H), 7.72 (dd, J = 4.8, 1.1 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.9 Hz, 2H), 4.78 (s, 2H), 3.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.0, 166.6, 159.5, 155.7, 144.9, 139.6, 130.4, 128.0, 126.1, 116.9, 114.2, 55.4, 41.5; HRMS (ESI$^+$) *m/z* $[C_{15}H_{12}N_2O_3Na]^+$ calcd: 291.0740; found: 291.0740.



N-PMB 2,3-naphthalimide (**4.6m**)

Following the general procedure C with modifications, **4.5m** (134.1 mg, 0.5 mmol, 1.0 equiv.) and DMSO (1.0 mL) were used. The reaction was stirred at rt for 1 hour. Purification by flash chromatography (SiO_2, DCM) gave **4.6m** (138 mg, 87%) as a light yellow solid. Alternatively, following the general procedure D gave **4.6m** (143 mg, 90%). $R_f = 0.58$ (DCM); Mp: 172-173°C; IR (neat, cm^{-1}): 2937 (w), 2839 (w), 1758 (w), 1699 (s), 1512 (m), 1247 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.30 (s, 2H), 8.02 (dd, J = 6.2, 3.3 Hz, 2H), 7.66 (dd, J = 6.3, 3.2 Hz, 2H), 7.43 (d, J = 8.9 Hz, 2H), 6.85 (d, J = 8.9 Hz, 2H), 4.85 (s, 2H), 3.77 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.9, 159.4, 135.5, 130.38, 130.37, 129.3, 128.8, 128.0, 124.8, 114.1, 55.4, 41.4; HRMS (ESI$^+$) *m/z* $[C_{20}H_{16}NO_3]^+$ calcd: 318.1125; found: 318.1122.

7.4.3 Synthesis and Characterization of Biologically Active Compounds

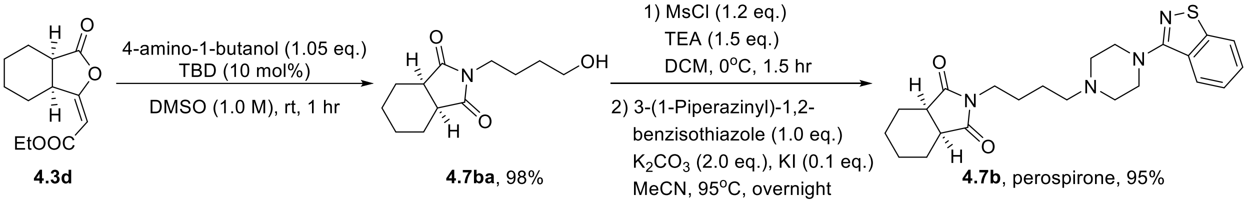


4.3

4.7a, **(±)-*endo*** MGK-264, 89%

endo (±)-MGK-264 (**4.7a**)

To a reaction vial were added 2-ethylhexyl amine (67.9 mg, 0.525 mmol, 1.05 equiv.) and TBD (7.0 mg, 0.05 mmol, 10 mol%). Compound **4.3** (117.1 mg, 0.5 mmol, 1.0 equiv.) was then added, followed by DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred at rt for 30 minutes. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 5:1) gave **4.7a** (122 mg, 89%) as a colorless oil. R_f = 0.38 (Hex/EA = 5:1); IR (neat, cm^{-1}): 2961 (m), 2866 (w), 1768 (w), 1693 (s), 1396 (m), 1177 (m), 724 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.08 (t, J = 1.9 Hz, 2H), 3.36 (m, 2H), 3.22 (dd, J = 3.0, 1.5 Hz, 2H), 3.20 (dd, J = 7.2, 1.4 Hz, 2H), 1.71 (dt, J = 8.7, 1.9 Hz, 1H), 1.56 (m, 1H), 1.52 (m, 1H), 1.27-1.10 (m, 8H), 0.87 (t, J = 7.0 Hz, 3H), 0.83 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 178.2, 134.6, 52.5, 45.8, 45.0, 42.4, 37.8, 30.5, 28.6, 23.8, 23.1, 14.2, 10.4; HRMS (ESI^+) *m/z* $[C_{17}H_{26}NO_2]^+$ calcd: 276.1958; found: 276.1950.



4.3d

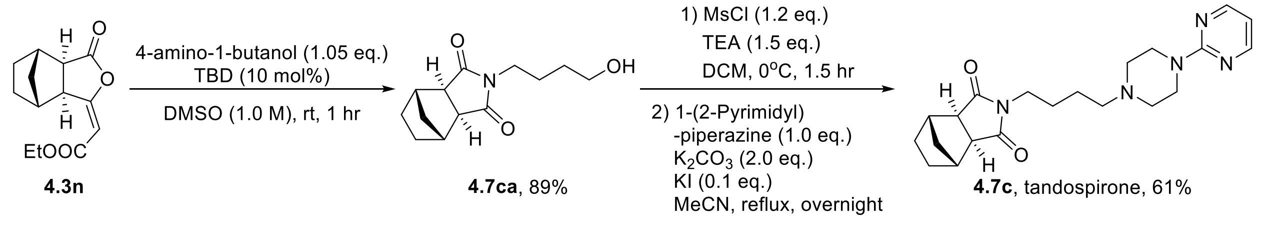
4.7ba, 98%

4.7b, perospirone, 95%

Perospirone (**7b**)

To a 25 mL round bottom flask were added freshly distilled 4-amino-1-butanol (468.0 mg, 5.25 mmol, 1.05 equiv.) and TBD (69.6 mg, 0.5 mmol, 10 mol%). Compound **4.3d** (1.12 g, 5 mmol, 1.0 equiv.) was added, followed by DMSO (5 mL). The reaction was stirred at rt for 1 hour. Upon completion, DCM (20 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 15 mL), water (1 × 15 mL), and brine (1 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, DCM/EA = 10:1 to 1:1) to give **4.7ba** (1.10 g, 98%) as a colorless oil, which solidifies to a white solid. R_f = 0.35 (DCM/EA = 1:1); Mp: 45-47°C; IR (neat, cm^{-1}): 3456 (w, br), 2937 (m), 2857 (w), 1770 (w), 1690 (s), 1398 (m), 1048 (m); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.64 (t, J = 6.3 Hz, 2H), 3.51 (t, J = 7.2 Hz, 2H), 2.82 (m, 2H), 1.93 (bs, 1H), 1.83 (m, 2H), 1.71 (m, 2H), 1.63 (m, 2H), 1.54 (m, 2H), 1.44-1.36 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.1, 62.3, 39.8, 38.3, 29.8, 24.4, 23.9, 21.7; HRMS (ESI$^+$) *m/z* $[C_{12}H_{19}NO_3Na]^+$ calcd: 248.1257; found: 248.1260.

To a 25 mL round bottom flask were added **4.7ba** (225.3 mg, 1 mmol, 1.0 equiv.), TEA (0.21 mL, 1.5 mmol, 1.5 equiv.), and DCM (2 mL). The mixture was cooled to 0°C and MsCl (93 μL, 1.2 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred at 0°C for 1.5 hours. The mixture was then diluted in DCM (10 mL) and washed with 1 M KH_2PO_4 (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was transferred to a reaction vial, and 3-(1-piperazinyl)-1,2-benzisothiazole (219.3 mg, 1 mmol, 1.0 equiv.), K_2CO_3 (276.4 mg, 2 mmol, 2.0 equiv.), KI (16.6 mg, 0.1 mmol, 0.1 equiv.), and MeCN (2 mL) were added. The vial was sealed with a PTFE septum and aluminum cap, and the reaction was stirred at 95°C overnight. Upon completion, the mixture was cooled to rt, and EA (10 mL) was added. The mixture was washed with water (2 × 10 mL), 10% $Na_2S_2O_3$ (1 × 10 mL), and brine (1 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, DCM/MeOH = 100:1 to 25:1) to give **4.7b** (405 mg, 95%) as a yellow oil. R_f = 0.38 (DCM/MeOH = 20:1); IR (neat, cm^{-1}): 2937 (m), 2857 (w), 2810 (w), 1770 (m), 1696 (s), 1493 (m), 1137 (m), 743 (s); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.87 (dt, J = 8.1, 1.0 Hz, 1H), 7.77 (dt, J = 8.1, 1.0 Hz, 1H), 7.43 (m, 1H), 7.32 (m, 1H), 3.54-3.49 (m, 6H), 2.82 (m, 2H), 2.64-2.62 (m, 4H), 2.42 (m, 2H), 1.83 (m, 2H), 1.72 (m, 2H), 1.59 (m, 2H), 1.50 (m, 2H), 1.46-1.35 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.9, 164.0, 152.8, 128.1, 127.6, 124.0, 123.9, 120.6, 58.1, 53.1, 50.1, 39.8, 38.4, 25.9, 24.2, 23.8, 21.7; HRMS (ESI$^+$) *m/z* $[C_{23}H_{31}N_4O_2S]^+$ calcd: 427.2162; found: 427.2169.

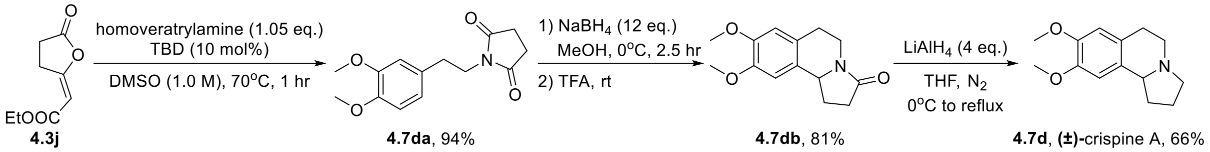


Tandospirone (**4.7c**)

To a 25 mL round bottom flask were added freshly distilled 4-amino-1-butanol (468.0 mg, 5.25 mmol, 1.05 equiv.) and TBD (69.6 mg, 0.5 mmol, 10 mol%). Compound **4.3n** (1.18 g, 5 mmol, 1.0 equiv.) was added, followed by DMSO (5 mL). The reaction was stirred at rt for 1 hour. Upon completion, DCM (20 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 15 mL), water (1 × 15 mL), and brine (1 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, DCM/EA = 10:1 to 1:1) to give **4.7ca** (1.05 g, 89%) as a colorless oil. $R_f = 0.25$ (DCM/EA = 1:1); IR (neat, cm^{-1}): 3446 (w, br), 2949 (w), 2875 (w), 1768 (w), 1682 (s), 1397 (m), 1164 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 3.62 (t, J = 6.3 Hz, 2H), 3.46 (t, J = 7.4 Hz, 2H), 2.66 (m, 2H), 2.56 (d, J = 1.5 Hz, 2H), 2.09 (bs, 1H), 1.66-1.57 (m, 4H), 1.52 (m, 2H), 1.32 (dd, J = 6.4, 2.3 Hz, 1H), 1.29 (dd, J = 6.5, 2.3 Hz, 1H), 1.18 (dp, J = 11.0, 1.6 Hz, 1H), 1.06 (dp, J = 11.0, 1.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 179.2, 62.2, 48.7, 39.8, 38.5, 33.2, 29.9, 28.1, 24.4; HRMS (ESI$^+$) *m/z* $[C_{13}H_{19}NO_3Na]^+$ calcd: 260.1257; found: 260.1257.

To a 25 mL round bottom flask were added **4.7ca** (237.3 mg, 1 mmol, 1.0 equiv.), TEA (0.21 mL, 1.5 mmol, 1.5 equiv.), and DCM (2 mL). The mixture was cooled to 0°C and MsCl (93 μL, 1.2 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred at 0°C for 1.5 hours. The mixture was then diluted in DCM (10 mL) and washed with 1 M KH_2PO_4 (2 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was transferred to a reaction vial, and 1-(2-pyrimidyl)piperazine (164.2 mg, 1 mmol, 1.0 equiv.), K_2CO_3 (276.4 mg, 2 mmol, 2.0 equiv.), KI (16.6 mg, 0.1 mmol, 0.1 equiv.), and MeCN (2 mL) were added. The vial was sealed with a PTFE septum and aluminum cap, and the reaction was stirred at 95°C overnight. Upon completion, the mixture was cooled to rt, and EA (10 mL) was added. The mixture was washed with water (2 × 10 mL), 10% aqueous $Na_2S_2O_3$ (1 × 10 mL), and brine (1 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, DCM/MeOH = 100:1 to 20:1) to give **4.7c** (234 mg, 61%) as a golden oil, which solidifies upon standing to a beige solid. $R_f = 0.45$ (DCM/MeOH = 20:1); Mp: 108-110°C; IR (neat, cm^{-1}): 2940 (w), 2852 (w), 1691 (s), 1580 (m), 1484 (m), 1352 (m), 1254 (m), 795 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.23 (d, J = 4.7 Hz, 2H), 6.40 (t, J = 4.7 Hz, 1H), 3.75 (m, 4H), 3.42 (t, J = 7.2 Hz, 2H), 2.63 (m, 2H), 2.53 (m, 2H), 2.41 (m, 4H), 2.32 (t, J = 7.4 Hz, 2H), 1.60 (m, 2H), 1.52 (m, 2H), 1.46 (m, 2H), 1.29 (dd, J = 6.3, 2.4 Hz, 1H), 1.26 (dd, J = 6.4, 2.3 Hz, 1H), 1.15 (dp, J = 11.1, 1.6 Hz, 1H), 1.03 (dp, J =

11.0, 1.8 Hz, 1H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 178.9, 161.6, 157.7, 109.8, 58.1, 53.1, 48.6, 43.6, 39.7, 38.5, 33.1, 28.0, 25.8, 24.2; HRMS (ESI$^+$) *m/z* [$C_{21}H_{30}N_5O_2$]$^+$ calcd: 384.2394; found: 384.2401.

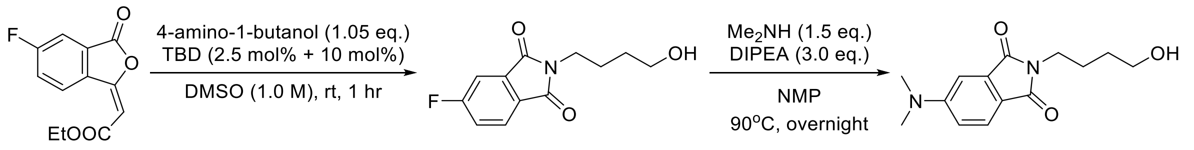


(±)-Crispine A (**4.7d**)

To a reaction vial were added freshly distilled homoveratrylamine (190.3 mg, 1.05 mmol, 1.05 equiv.) and TBD (13.9 mg, 0.1 mmol, 10 mol%). Compound **4.3j** (170.2 mg, 1 mmol, 1.0 equiv.) was added, followed by DMSO (1 mL). The reaction was stirred at 70°C for 1 hour. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, DCM/EA = 20:1 to 5:1) to give **4.7da** (247 mg, 94%) as a white solid. $R_f = 0.35$ (DCM/EA = 4:1); Mp: 126-128°C; IR (neat, cm^{-1}): 2961 (w), 2835 (w), 1772 (w), 1693 (s), 1510 (m), 1162 (s), 1025 (m), 816 (m); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 6.75-6.69 (m, 3H), 3.82 (s, 3H), 3.79 (s, 3H), 3.66 (m, 2H), 2.77 (m, 2H), 2.60 (s, 4H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 177.0, 148.9, 147.7, 130.2, 120.8, 111.9, 111.2, 55.9, 55.8, 39.9, 33.0, 28.1; HRMS (ESI$^+$) *m/z* [$C_{14}H_{17}NO_4Na$]$^+$ calcd: 286.1050; found: 286.1041.

To a 25 mL round bottom flask were added **4.7da** (263.3 mg, 1 mmol, 1.0 equiv.) and MeOH (5 mL). The mixture was cooled to 0°C and $NaBH_4$ (113.5 mg, 3 mmol, 3.0 equiv.) was added. The reaction was stirred at 0°C for 1 hour. TLC indicated that reaction was not complete. Therefore, $NaBH_4$ (113.5 mg, 3 mmol, 3.0 equiv.) was added every 30 minutes until the starting material was consumed (a total of 12 equiv. of $NaBH_4$ were used). Upon completion, the reaction was carefully quenched with sat. $NaHCO_3$ (15 mL), and the product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum to give a white solid. TFA (1.5 mL) was added to this solid and the reaction mixture was stirred at rt for 1 hour. Upon completion, the solvent was evaporated under vacuum and the residue was neutralized with sat. Na_2CO_3. The product was exacted in DCM (3 × 10 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, EA/acetone = 10:1 to 4:1) to give **4.7db** (201 mg, 81% over two steps) as a golden solid. $R_f = 0.31$ (EA/acetone = 2:1); Mp: 100-102°C; IR (neat, cm^{-1}): 2964 (w), 2854 (w), 1705 (s), 1515 (m), 1230 (s), 1118 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.58 (s, 1H), 6.54 (s, 1H), 4.69 (t, J = 7.8 Hz, 1H), 4.26 (ddd, J = 12.8, 6.2, 2.1 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 3H), 2.97 (tdd, J = 12.8, 4.4, 1.4 Hz, 1H), 2.85 (m, 1H), 2.66-2.57 (m, 2H), 2.53 (m, 1H), 2.42 (ddd, J = 16.5, 9.5, 1.4 Hz, 1H), 1.81 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.1, 148.1, 147.9, 129.4, 125.6, 111.7, 107.7, 56.6, 56.1, 55.9, 37.1, 31.8, 28.1, 27.8; HRMS (ESI^+) *m/z* $[C_{14}H_{17}NO_3Na]^+$ calcd: 270.1101; found: 270.1111.

To a 25 mL round bottom flask were added **4.7db** (123.6 mg, 0.5 mmol, 1.0 equiv.) and anhydrous THF (4 mL). The atmosphere was changed to N_2 and a nitrogen ballon was attached to maintain the atmosphere. The mixture was cooled to 0°C and $LiAlH_4$ (1 mL, 2 M in THF, 4.0 equiv.) was added dropwise. The reaction was stirred for 5 minutes at rt, then refluxed for 3 hours. The reaction was then cooled to 0°C, and carefully quenched with water (2 mL), 1 M NaOH (2 mL), and water (6 mL). The mixture was filtered over celite, and the product was extracted in EA (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, DCM/MeOH = 10:1) to give **4.7d** (77 mg, 66%) as a beige solid. $R_f = 0.30$ (DCM/MeOH = 10:1); Mp: 82-84°C; IR (neat, cm^{-1}): 2931 (w), 2792 (w), 1518 (m), 1213 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.59 (s, 1H), 6.55 (s, 1H), 3.83 (s, 3H), 3.83 (s, 3H), 3.53 (t, J = 8.2 Hz, 1H), 3.16 (ddd, J = 11.4, 6.0, 3.1 Hz, 1H), 3.06 (ddd, J = 9.2, 7.9, 4.3 Hz, 1H), 2.99 (m, 1H), 2.78-2.64 (m, 3H), 2.33 (m, 1H), 1.98-1.83 (m, 2H), 1.73 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 147.6, 147.5, 130.4, 126.1, 111.4, 109.0, 62.8, 56.1, 56.0, 53.2, 48.3, 30.8, 27.8, 22.4; HRMS (ESI^+) *m/z* $[C_{14}H_{20}NO_2]^+$ calcd: 234.1489; found: 234.1487.



4.5b **4.7ea**, 53% **4.7e**, 91%

<u>5-(Dimethylamino)-2-(4-hydroxybutyl)isoindoline-1,3-dione (**4.7e**)</u>

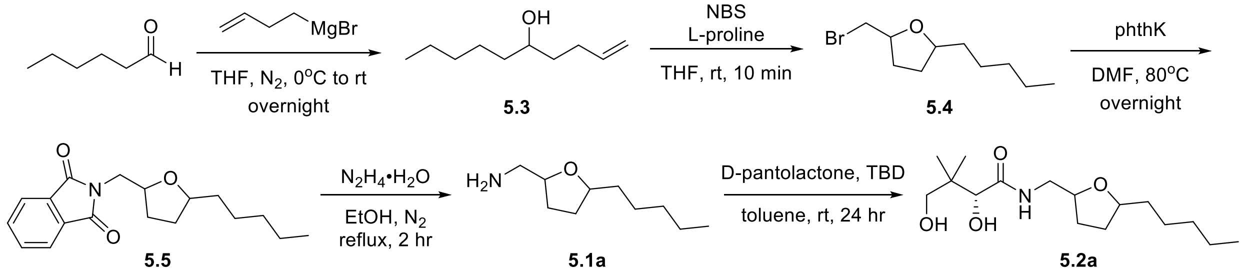
To a reaction vial were added freshly distilled 4-amino-1-butanol (46.8 mg, 0.525 mmol, 1.05 equiv.) and TBD (1.7 mg, 0.0125 mmol, 2.5 mol%). Compound **4.5b** (118.1 mg, 0.5 mmol, 1.0

equiv.) was then added, followed by DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred at rt for 30 minutes. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. To the residue were added TBD (7.0 mg, 0.05 mmol, 10 mol%) and DMSO (0.5 mL). The vial was stoppered with a rubber septum and the reaction was stirred at rt for 1 hour. Upon completion, DCM (5 mL) was added, and the mixture was washed with 1 M KH_2PO_4 (2 × 5 mL), water (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 2:1) gave **7ea** (63 mg, 53%) as a white solid. $R_f = 0.50$ (DCM/EA = 1:1); Mp: 75-76°C; IR (neat, cm^{-1}): 3267 (w, br), 2943 (w), 2869 (w), 1770 (w), 1697 (s), 1401 (m), 1050 (m); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.82 (dd, J = 8.2, 4.4 Hz, 1H), 7.49 (dd, J = 7.0, 2.3 Hz, 1H), 7.36 (td, J = 8.5, 2.3 Hz, 1H), 3.70 (t, J = 7.2 Hz, 2H), 3.66 (t, J = 6.3 Hz, 2H), 1.90 (bs, 1H), 1.75 (m, 2H), 1.58 (m, 2H); ^{19}F NMR ($CDCl_3$, 471 MHz): δ -102.0; ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.5, 167.2 (d, J = 2.7 Hz), 166.5 (d, J = 257.3 Hz), 135.0 (d, J = 9.6 Hz), 127.9 (d, J = 2.7 Hz), 125.7 (d, J = 9.6 Hz), 121.0 (d, J = 23.8 Hz), 111.2 (d, J = 24.7 Hz), 62.3, 38.1, 29.8, 25.2; HRMS (ESI^+) *m/z* $[C_{12}H_{12}NO_3FNa]^+$ calcd: 260.0693; found: 260.0690.

To a reaction vial were added **4.7ea** (118.6 mg, 0.5 mmol, 1.0 equiv.), Me_2NH (40% in H_2O, 95 μL, 0.75 mmol, 1.5 equiv.), DIPEA (0.26 mL, 1.5 mmol, 3.0 equiv.), and NMP (2 mL). The vial was sealed with a PTFE septum and aluminum cap, and the reaction was stirred at 90°C overnight. The mixture was then diluted in EA (10 mL), and the organic layer was washed with $NaHCO_3$ (2 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 1:1) gave **4.7e** (120 mg, 91%) as a yellow solid. $R_f = 0.48$ (DCM/EA = 1:2); Mp: 108-109°C; IR (neat, cm^{-1}): 3278 (w, br), 2937 (w), 2963 (w), 1758 (m), 1703 (s), 1617 (m), 1390 (s), 1026 (s); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.60 (d, J = 8.5 Hz, 1H), 7.03 (d, J = 2.4 Hz, 1H), 6.75 (dd, J = 8.5, 2.5 Hz, 1H), 3.68-3.64 (m, 4H), 3.09 (s, 6H), 1.93 (bs, 1H), 1.72 (m, 2H), 1.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.4, 169.1, 154.4, 134.8, 124.8, 117.7, 114.6, 105.8, 62.5, 40.6, 37.5, 29.9, 25.3; HRMS (ESI^+) *m/z* $[C_{14}H_{18}N_2O_3Na]^+$ calcd: 285.1210; found: 285.1210.

7.5 Experimental Details for Chapter 5

7.5.1 Synthesis and Characterization of Reaction Intermediates and Products



tetrahydrofuran derivative (**5.2a**)

To a 50 mL three-neck flask were added pre-treated Mg turnings (535.0 mg, 22 mmol, 1.1 equiv.) and a tiny piece of I_2 crystal. A reflux condenser and a pressure-equalizing dropping funnel were attached. The flask was sealed, and the atmosphere was exchanged to N_2. A nitrogen balloon was placed on top to maintain the atmosphere. Anhydrous THF (2.5 mL) was added and the mixture was heated to 70°C. 4-Bromo-1-butene (2.03 mL, 20 mmol, 1.0 equiv.) was dissolved in anhydrous THF (22.5 mL), and then transferred to the dropping funnel. A few drops of the bromobutene solution were added to initiate the reaction until the color of I_2 disappeared. The rest of the THF solution was added dropwise over 30 minutes to maintain a gentle reflux, then the solution was refluxed for another 30 minutes. The grey solution was cooled down to rt and the Grignard solution was ready to use.

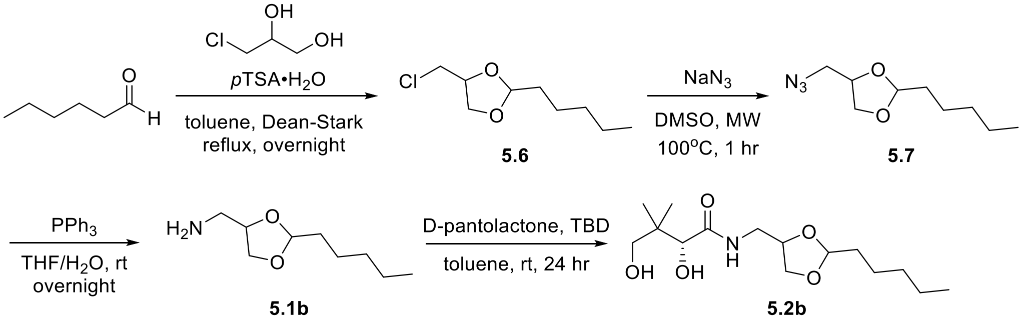
To a 100 mL round bottom flask were added freshly distilled hexanal (2.06 mL, 16.7 mmol, 1.0 equiv.) and anhydrous THF (20 mL). The flask was sealed, and the atmosphere was exchanged to N_2. A nitrogen balloon was placed on top to maintain the atmosphere. The mixture was cooled to 0°C and the prepared Grignard solution was added dropwise. The reaction mixture was stirred at rt for 1 hour, then carefully quenched with sat. NH_4Cl (25 mL). The layers were separated and the organic layer was collected, dried over Na_2SO_4, filtered, and the solvent was evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 50:1 to 20:1) afforded **5.3** (1.90 g, 73%) as a colorless oil. $R_f = 0.60$ (Hex/EA = 5:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.84 (ddt, J = 17.0, 10.2, 6.6 Hz, 1H), 5.04 (dq, J = 17.1, 1.7 Hz, 1H), 4.96 (m, 1H), 3.60 (m, 1H), 2.21-2.10 (m, 2H), 1.58-1.41 (m, 5H), 1.31-1.23 (m, 5H), 0.88 (t, J = 7.0, 3H). The characterization matched the reported data.[34]

Following a reported procedure,[35] to a 50 mL round bottom flask were added **5.3** (781.4 mg, 5 mmol, 1.0 equiv.), THF (25 mL), an aqueous solution of L-proline (2 M, 0.5 mL, 1 mmol, 0.2 equiv.), and recrystallized NBS (978.9 mg, 5.5 mmol, 1.1 equiv.). The reaction mixture was stirred at rt for 10 minutes. The mixture was then diluted in EA (50 mL), then washed with 10% aqueous $Na_2S_2O_3$ (1 × 50 mL) and brine (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 50:1) afforded **5.4** (918 mg, 78%, cis/trans = 26:74) as a yellow oil. $R_f = 0.47$ (Hex/EA = 20:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.21 (qd, J = 6.9, 4.7 Hz, 1H, trans), 4.12 (qd, J = 6.9, 4.7 Hz, 1H, cis), 4.00 (dq, J = 8.2, 6.0 Hz, 1H, trans), 3.89 (dq, J = 8.1, 6.2 Hz, 1H, cis), 3.42 (td, J = 10.3, 4.8 Hz, 1H, trans), 3.32 (td, J = 10.2, 6.8 Hz, 1H, cis), 2.22-1.87 (m, 2H), 1.74 (m, 1H), 1.69-1.48 (m, 2H), 1.50-1.33 (m, 2H), 1.28 (m, 5H), 0.87 (t, J = 6.9 Hz, 3H). The characterization matched the reported data.[35]

To a 50 mL round bottom flask were added **5.4** (918.0 mg, 3.9 mmol, 1.0 equiv.), potassium phthalimide (1.08 g, 5.85 mmol, 1.5 equiv.), and anhydrous DMF (10 mL). The reaction mixture was stirred at 80°C overnight. The mixture was then diluted in EA (50 mL) and washed with water (3 × 30 mL) and brine (1 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 20:1 to 10:1) afforded **5.5** (921 mg, 78%, cis/trans = 26:74) as a white solid. $R_f = 0.30/0.29$ (Hex/EA = 5:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.84-7.78 (m, 2H), 7.72-7.64 (m, 2H), 4.34 (m, 1H, trans), 4.21 (m, 1H, cis), 3.99-3.80 (m, 2H), 3.66 (dd, J = 13.6, 5.7 Hz, 1H, cis), 3.57 (dd, J = 13.7, 5.1 Hz, 1H, trans), 2.15-1.87 (m, 2H), 1.76-1.63 (m, 1H), 1.54-1.39 (m, 2H), 1.38-1.26 (m, 2H), 1.25-1.17 (m, 5H), 0.85-0.82 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 168.4, 133.9, (132.3, 132.2), 123.3, (80.4, 78.9), (76.0, 75.6), (42.8, 42.1), (36.2, 35.7), (31.99, 31.97), (31.4, 30.9), (29.5, 29.3), (25.93, 25.87), 22.7, 14.1; HRMS (ESI$^+$) *m/z* $[C_{18}H_{23}NO_3Na]^+$ calcd: 324.1570; found: 324.1567.

To a 100 mL round bottom flask were added **5.5** (921 mg, 3.05 mmol, 1.0 equiv.), $N_2H_4{\bullet}H_2O$ (0.74 mL, 15.3 mmol, 5.0 equiv.), and EtOH (30 mL). The atmosphere was exchanged to N_2 and a nitrogen balloon was placed on top to maintain the atmosphere. The reaction mixture was refluxed for 2 hours. The mixture was then cooled to rt and filtered over celite. The filtrate was evaporated under vacuum, and the residue was dissolved in 2 M KOH (50 mL). The product was extracted in diethyl ether (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford the crude **5.1a** (494 mg, 95%) as a yellow oil, which was used without further purification.

To a reaction vial was added **5.1a** (85.6 mg, 0.5 mmol, 1.0 equiv.), D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.), TBD (7.0 mg, 0.05 mmol, 0.1 equiv.), and toluene (0.5 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2a** (147 mg, 97%, 4 diastereomers) as a light-yellow oil. R_f = 0.49 (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.13 (bs, 1H), 4.30 (bs, 1H), 4.06-3.76 (m, 4H), 3.51-3.44 (m, 3H), 3.24-3.16 (m, 1H), 2.05-1.92 (m, 2H), 1.62-1.44 (m, 3H), 1.39-1.29 (m, 2H), 1.27-1.22 (m, 5H), 1.05-0.80 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, (80.37, 80.35, 79.7, 79.6), (77.8, 77.7, 77.6), (77.53, 77.52, 77.3), (71.2, 71.1), (43.4, 43.3, 43.1, 43.0), (39.5, 39.4), (36.0, 35.8), 32.0, (31.94, 31.87, 31.2), (29.4, 29.3, 28.6, 28.5), (26.0, 25.93, 25.91, 25.88), 22.7, (21.7, 21.5), (20.49, 20.45, 20.23, 20.20), 14.1; HRMS (ESI$^+$) *m/z* $[C_{16}H_{32}NO_4]^+$ calcd: 302.2326; found: 302.2322. HPLC: method A t_R = 31.66 min (>99%); method B t_R = 21.93 min (88%) and 22.17 min (11%).



dioxolane derivative (5.**2b**)

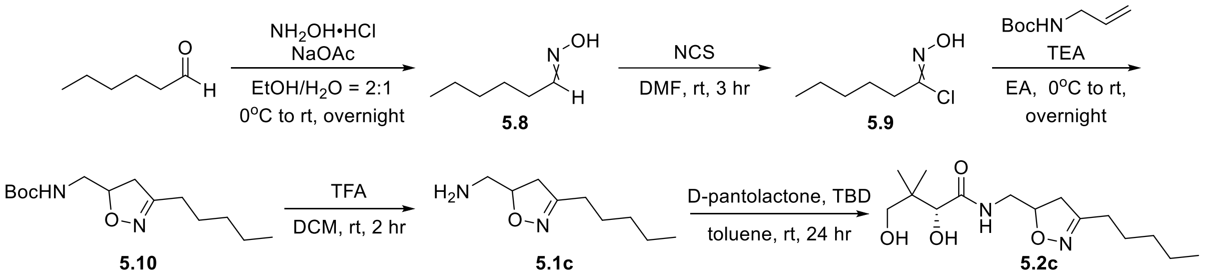
To a 100 mL round bottom flask were added α-chlorohydrin (2.51 mL, 30 mmol, 3.0 equiv.), freshly distilled hexanal (1.23 mL, 10 mmol, 1.0 equiv.), *p*TSA•H_2O (190.2 mg, 1 mmol, 0.1 equiv.), and toluene (40 mL). A Dean-Stark apparatus was connected to the flask and the reaction mixture was refluxed overnight. The mixture was then cooled to rt, washed with 10% aqueous $NaHSO_3$ (3 × 25 mL) and sat. aqueous $NaHCO_3$ (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 20:1) afforded **5.6** (1.84 g, 95%, cis/trans isomer, major/minor = 56:44) as a colorless oil. R_f = 0.52 (Hex/EA = 5:1); major: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.90 (t, J = 4.8 Hz, 1H), 4.23 (m, 1H), 3.95 (dd, J = 8.7, 3.9 Hz, 1H), 3.91 (dd, J = 8.8, 6.5 Hz, 1H), 3.54 (dd, J = 10.9, 4.8 Hz, 1H), 3.41 (dd, *J* = 10.9, 8.0 Hz, 1H), 1.64 (m, 2H), 1.39 (m, 2H), 1.30 (m, 4H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 105.9, 75.4, 68.3, 44.6, 34.1, 31.8, 23.65, 22.67, 14.1; minor: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.01 (t, *J* = 4.8 Hz, 1H), 4.29 (m, 1H), 4.19 (dd, *J* = 8.6, 6.3 Hz, 1H), 3.71 (dd, *J* = 8.6, 6.4 Hz, 1H), 3.63 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.49 (dd, *J* = 11.0, 7.4 Hz, 1H), 1.64 (m, 2H), 1.39 (m, 2H), 1.30 (m, 4H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 105.4, 75.0, 68.9, 44.4, 34.0, 31.8, 23.67, 22.68, 14.1; HRMS (ESI$^+$) *m/z* $[C_9H_{17}O_2ClNa]^+$ calcd: 215.0809; found: 215.0813.

To a microwave vial were added **5.6** (356.0 mg, 1.85 mmol, 1.0 equiv.), NaN_3 (300.3 mg, 4.62 mmol, 2.5 equiv.), and DMSO (3 mL). The vial was sealed with a PTFE septum and an aluminum cap, and the reaction mixture was subjected to microwave irradiation at 100°C for 1 hour. The mixture was cooled to rt, and TLC indicated that the reaction was incomplete. An additional amount of NaN_3 (300.3 mg, 4.62 mmol, 2.5 equiv.) was added and the reaction mixture was subjected to microwave irradiation at 120°C for 1 hour. The mixture was then cooled to rt, diluted in EA (20 mL), and washed with water (3 × 20 mL) and brine (1 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.7** (306 mg, 83%) as a light yellow oil, which was used without further purification.

To a 25 mL round bottom flask were added **5.7** (306.0 mg, 1.54 mmol, 1.0 equiv.) and THF/H_2O = 10:1 (3 mL). PPh_3 (485.2 mg, 1.85 mmol, 1.2 equiv.) was added in one portion and the reaction mixture was stirred at rt overnight. The solvent was then evaporated under vacuum. The product was purified from the residue using flash chromatography (SiO_2, DCM/MeOH = 100:1 to 5:1) to afford **5.1b** (263 mg, 98% cis/trans isomer, major/minor = 56:44) as a light yellow oil. R_f = 0.10 (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (4.95, 4.87) (t, *J* = 4.8 Hz, 1H), 4.11-3.86 (m, 2H), 3.68-3.51 (m, 1H), 2.86-2.74 (m, 2H), 1.61 (m, 2H), 1.57 (bs, 2H), 1.39 (m, 2H), 1.32-1.27 (m, 4H), 0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (105.1, 104.4), (77.51, 77.49), (68.0, 67.5), (44.9, 44.3), (34.2, 34.0), 31.8, 23.8, (22.68, 22.67), 14.1; HRMS (ESI$^+$) *m/z* $[C_9H_{20}NO_2]^+$ calcd: 174.1489; found: 174.1494.

To a reaction vial was added **5.1b** (86.6 mg, 0.5 mmol, 1.0 equiv.), D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.), TBD (7.0 mg, 0.05 mmol, 0.1 equiv.), and toluene (0.5 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2b** (148 mg, 98%, 4 diastereomers) as a colorless oil. R_f =

0.52 (DCM/MeOH = 10:1); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.22-7.14 (m, 1H), 4.99-4.81 (m, 1H), 4.58-4.47 (m, 1H), 4.21-4.16 (m, 1H), 4.09-3.32 (m, 8H), 1.67-1.56 (m, 2H), 1.38-1.32 (m, 2H), 1.30-1.25 (m, 4H), 0.98-0.97 (m, 3H), 0.91-0.85 (m, 6H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ (174.1, 174.0, 173.92, 173.88), (105.28, 105.26, 104.78, 104.76), (77.7, 77.44, 77.36, 77.33), (74.7, 74.6, 74.5, 74.4), (71.20, 71.17, 71.11), (67.8, 67.4, 67.3), (41.34, 41.31, 40.72, 40.67), (39.40, 39.38, 39.34), (34.08, 34.05, 33.74, 33.71), 31.8, (23.8, 23.74, 23.70, 23.69), 22.6, (21.4, 21.3, 21.2, 21.1), (20.6, 20.49, 20.47, 20.38), 14.1; HRMS (ESI$^+$) *m/z* [C$_{15}$H$_{29}$NO$_5$Na]$^+$ calcd: 326.1938; found: 326.1938. HPLC: method A t_R = 31.28 min (25%) and 31.34 min (71%); method B t_R = 20.53 min (48%) and 20.65 min (50%).



isoxazoline derivative (**5.2c**)

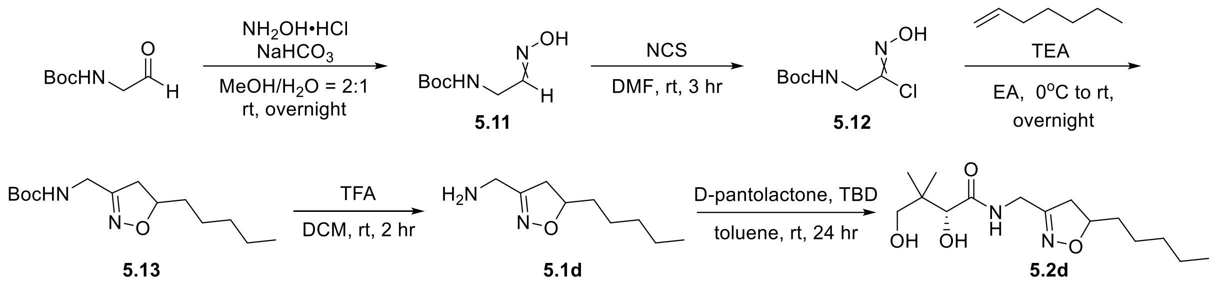
To a 100 mL round bottom flask were added freshly distilled hexanal (1.85 mL, 15 mmol, 1.0 equiv.), hydroxylamine hydrochloride (2.08 g, 30 mmol, 2.0 equiv.), and EtOH/H$_2$O = 2:1 (30 mL). The mixture was cooled to 0°C and sodium acetate (3.69 g, 45 mmol, 3.0 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The ethanol was then evaporated under vacuum, and the product was extracted in EA (3 × 25 mL). The combined organic layers were washed with sat. NaHCO$_3$ (2 × 25 mL), dried over Na$_2$SO$_4$, filtered, and evaporated under vacuum to afford crude **5.8** (1.47 g, 85%) as a colorless semi-solid, which was used without further purification.

To a 50 mL round bottom flask were added **5.8** (775.9 mg, 6.73 mmol, 1.0 equiv.) and anhydrous DMF (10 mL). NCS (1.08 g, 8.08 mmol, 1.3 equiv.) was added in one portion and the reaction mixture was stirred at rt for 3 hours. The mixture was then diluted in EA (50 mL), washed with water (3 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated under vacuum to afford crude **5.9** (1.00 g, quant.) as a green-yellow oil, which was used without further purification. This reactive intermediate is not stable and should be used immediately upon generation.

To a 100 mL round bottom flask were added *N*-Boc allylamine (1.05 g, 6.7 mmol, 1.0 equiv.), **5.9** (1.00 g, 6.7 mmol, 1.0 equiv.), and anhydrous EA (25 mL). The mixture was cooled to 0°C, then TEA (1.12 mL, 8.04 mmol, 1.2 equiv.) was added dropwise over 1 hour. The reaction mixture was slowly returned to rt and stirred at rt overnight. The mixture was then washed with water (1 × 30 mL) and brine (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 5:1) afforded **5.10** (774 mg, 43%, mixture of enantiomers) as a yellow oil, which solidifies upon standing. $R_f = 0.27$ (Hex/EA = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.91 (bs, 1H), 4.60 (m, 1H), 3.33 (m, 1H), 3.22 (m, 1H), 2.94 (dd, J = 17.2, 10.6 Hz, 1H), 2.66 (dd, J = 17.2, 7.1 Hz, 1H), 2.29 (m, 2H), 1.52 (p, J = 7.4 Hz, 2H), 1.41 (s, 9H), 1.32-1.28 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 159.6, 156.3, 79.6, 78.7, 43.7, 39.6, 31.5, 28.4, 27.7, 26.1, 22.4, 14.0; HRMS (ESI$^+$) *m/z* $[C_{14}H_{26}N_2O_3Na]^+$ calcd: 293.1835; found: 293.1834.

To a 25 mL round bottom flask were added **5.10** (774.0 mg, 2.88 mmol, 1.0 equiv.), DCM (2.5 mL), and TFA (2.5 mL). The reaction mixture was stirred at rt for 2 hours, then the solvent was evaporated under vacuum. Water (20 mL) was added to the residue and the *p*H was adjusted to 14 with 4 M NaOH. The product was extracted in DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1c** (480 mg, 98%) as a light brown oil, which was used without further purification.

To a reaction vial was added **5.1c** (85.2 mg, 0.5 mmol, 1.0 equiv.), D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.), TBD (7.0 mg, 0.05 mmol, 0.1 equiv.), and toluene (0.5 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2c** (145 mg, 97%, diastereomers) as a yellow oil. $R_f = 0.50$ (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.30 (bs, 1H), 4.64 (m, 1H), 4.44 (bs, 1H), (4.03, 4.02) (s, 1H), 3.80 (bs, 1H), 3.55 (m, 1H), 3.47 (s, 2H), 3.32 (m, 1H), (3.02, 2.99) (d, J = 10.4 Hz, 1H), (2.65, 2.62) (dd, J = 7.3, 3.2 Hz, 1H), 2.35-2.26 (m, 2H), 1.52 (p, J = 7.6 Hz, 2H), 1.36-1.23 (m, 4H), (0.98, 0.97) (s, 3H), 0.93-0.84 (m, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (174.1, 173.9), (159.76, 159.74), (78.3, 78.1), 77.6, (71.1, 71.0), (42.2, 42.0), (40.10, 40.06), (39.3, 39.2), (31.38, 31.36), (27.63, 27.58), 25.6, 22.3, (21.4, 21.2), (20.5, 20.2), 13.9; HRMS (ESI$^+$) *m/z* $[C_{15}H_{28}N_2O_4Na]^+$ calcd: 323.1941; found: 323.1938. HPLC: method A t_R = 23.53 min (49%) and 24.23 min (48%); method B t_R = 18.05 min (50%) and 18.15 min (47%).



isoxazoline derivative (**5.2d**)

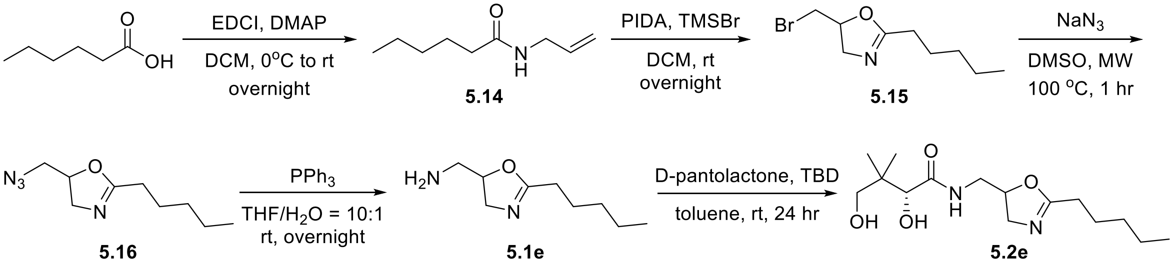
To a 100 mL round bottom flask were added *N*-Boc-2-aminoacetaldehyde (1.59 g, 10 mmol, 1.0 equiv.), hydroxylamine hydrochloride (763.5 mg, 11 mmol, 1.1 equiv.), and MeOH/H_2O = 2:1 (15 mL). $NaHCO_3$ (1.26 g, 15 mmol, 1.5 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The methanol was then evaporated under vacuum, and water (20 mL) was added. The product was extracted in EA (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.11** (1.67 g, 96%) as a yellow oil, which was used without further purification. This compound is not stable and should be used immediately upon generation.

To a 50 mL round bottom flask were added **5.11** (836.2 mg, 4.8 mmol, 1.0 equiv.) and anhydrous DMF (10 mL). NCS (854.6 mg, 6.4 mmol, 1.3 equiv.) was added in one portion and the reaction mixture was stirred at rt for 3 hours. The mixture was then diluted in EA (50 mL), washed with water (3 × 20 mL) and brine (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.12** (1.00 g, quant.) as a green-yellow oil, which was used without further purification. This reactive intermediate is not stable and should be used immediately upon generation.

To a 100 mL round bottom flask were added 1-heptene (0.56 mL, 4 mmol, 1.0 equiv.), **5.12** (1.00 g, 4.8 mmol, 1.0 equiv.), and anhydrous EA (20 mL). The mixture was cooled at 0°C, then TEA (0.67 mL, 4.8 mmol, 1.2 equiv.) was added dropwise over 40 minutes. The reaction was slowly returned to rt and stirred at rt overnight. The mixture was diluted in EA (30 mL), then washed with sat. $NaHCO_3$ (2 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/acetone = 50:1 to 20:1) afforded **5.13** (310 mg, 29%, mixture of enantiomers) as a light yellow oil. R_f = 0.30 (Hex/acetone = 5:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.97 (bs, 1H), 4.56 (m, 1H), 4.02 (m, 2H), 3.01 (dd, J = 17.0, 10.3 Hz, 1H), 2.59 (dd, J = 17.1, 8.3 Hz, 1H), 1.67 (m, 1H), 1.51 (m, 1H), 1.44 (s, 9H), 1.33-1.24 (m, 6H), 0.87 (m, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 156.4, 155.9, 81.3, 80.1, 40.8, 38.3, 35.2, 31.7, 28.4, 25.2, 22.6, 14.1; HRMS (ESI$^+$) *m/z* $[C_{14}H_{26}N_2O_3Na]^+$ calcd: 293.1836; found: 293.1840.

To a 25 mL round bottom flask were added **5.13** (310.0 mg, 1.14 mmol, 1.0 equiv.), DCM (1.5 mL), and TFA (1.5 mL). The reaction was stirred at rt for 2 hours, then the solvent was evaporated under vacuum. Water (20 mL) was added to the residue and the *p*H was adjusted to 14 with 4 M NaOH. The product was extracted in DCM (3 × 20 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and evaporated under vacuum to afford crude **5.1d** (160 mg, 83%) as a light yellow semi-solid, which was used without further purification.

To a reaction vial was added **5.1d** (85.2 mg, 0.5 mmol, 1.0 equiv.), D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.), TBD (7.0 mg, 0.05 mmol, 0.1 equiv.), and toluene (0.5 mL). The reaction was stirred at rt for 24 hours. Purification by flash chromatography (SiO$_2$, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2d** (128 mg, 85%, diastereomers) as a yellow oil. R$_f$ = 0.41 (DCM/MeOH = 10:1); ^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.44 (bs, 1H), 4.64 (bs, 1H), 4.58 (m, 1H), 4.20-4.12 (m, 2H), 4.03 (s, 1H), 3.88 (bs, 1H), 3.47-3.43 (m, 2H), (3.00, 2.99) (dd, *J* = 16.9, 10.2) Hz, 1H), (2.58, 2.57) (dd, *J* = 17.0, 8.4 Hz, 1H), 1.65 (m, 1H), 1.49 (m, 1H), 1.42-1.20 (m, 6H), (0.97,0.96) (s, 3H), (0.92, 0.91) (s, 3H), 0.86 (m, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 174.0, (156.4, 156.3), 81.5, 77.6, 71.0, 41.0, 39.4, (36.6, 36.5), (35.11, 35.09), 31.6, (25.23, 25.20), 22.6, (21.22, 21.19), (20.8, 20.7), 14.0; HRMS (ESI$^+$) *m/z* $[C_{15}H_{28}N_2O_4Na]^+$ calcd: 323.1941; found: 323.1944. HPLC: method A t_R = 25.57 min (52%) and 25.88 min (47%); method B t_R = 19.20 (>99%).



oxazoline derivative (**5.2e**)

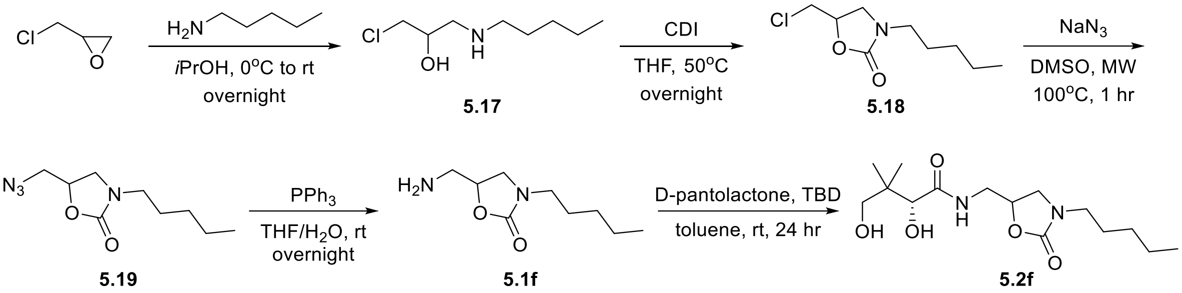
To a 100 mL round bottom flask were added freshly distilled allylamine (0.75 mL, 10 mmol, 1.0 equiv.), hexanoic acid (1.38 mL, 11 mmol, 1.1 equiv.), DMAP (122.2 mg, 1 mmol, 0.1 equiv.), and DCM (20 mL). The mixture was cooled to 0°C, and EDCI (2.11 g, 11 mmol, 1.1 equiv.) was added in small portions. The reaction was stirred at rt overnight. The mixture was then diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (2 × 30 mL), 1 M KH_2PO_4 (2 × 30 mL), and brine (1 × 30 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.14** (1.55 g, quant.) as a colorless oil, which was used without further purification.

Following a reported procedure,[35] to a 100 mL round bottom flask were added **5.14** (776.2 mg, 5 mmol, 1.0 equiv.), PIDA (1.77 g, 5.5 mmol, 1.1 equiv.), anhydrous DCM (20 mL) and TMSBr (0.73 mL, 5.5 mmol, 1.1 equiv.). The reaction was stirred at rt overnight. The mixture was then washed with 10% $Na_2S_2O_3$ (3 × 25 mL) and sat. $NaHCO_3$ (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 3:1) afforded **5.15** (716 mg, 61%, mixture of enantiomers) as a colorless oil. $R_f = 0.18$ (Hex/EA = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.70 (m, 1H), 3.93 (dd, J = 14.5, 9.7 Hz, 1H), 3.65 (dd, J = 14.5, 6.5 Hz, 1H), 3.41 (m, 2H), 2.25 (t, J = 7.7 Hz, 2H), 1.62 (p, J = 7.5 Hz, 2H), 1.31 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 167.9, 77.4, 58.9, 34.0, 31.5, 28.1, 25.7, 22.4, 14.0; HRMS (ESI$^+$) *m/z* $[C_9H_{17}NOBr]^+$ calcd: 234.0488; found: 234.0489.

To a microwave vial were added **5.15** (351.2 mg, 1.5 mmol, 1.0 equiv.), NaN_3 (243.7 mg, 3.75 mmol, 2.5 equiv.), and DMSO (2 mL). The vial was sealed with a PTFE septum and an aluminum cap, and the reaction mixture was subjected to microwave irradiation at 100°C for 1 hour. The mixture was then cooled to rt, diluted in EA (50 mL), and washed with water (2 × 25 mL) and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.16** (240 mg, 81%, mixture of enantiomers) as a yellow oil, which was used without further purification.

To a 25 mL round bottom flask were added **5.16** (240.0 mg, 1.22 mmol, 1.0 equiv.) and THF/H_2O = 10:1 (2 mL). PPh_3 (383.0 mg, 1.46 mmol, 1.2 equiv.) was added in one portion and the reaction was stirred at rt overnight. The solvent was then evaporated under vacuum. The residue was purified by flash chromatography (SiO_2, DCM/MeOH = 500:1 to 5:1) to afford **5.1e** (140 mg, 67%, mixture of enantiomers) as a light yellow oil. $R_f = 0.12$ (DCM/MeOH = 10:1). This compound is not stable and should be used immediately upon purification.

To a reaction vial was added **5.1e** (85.1 mg, 0.5 mmol, 1.0 equiv.), D-pantolactone (130.1 mg, 1.0 mmol, 2.0 equiv.), TBD (7.0 mg, 0.05 mmol, 0.1 equiv.), and toluene (0.5 mL). The reaction was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2e** (79 mg, 53%, diastereomers) as a colorless oil. R_f = 0.33 (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.16 (bs, 1H), 5.21 (bs, 1H), 4.63 (m, 1H), 4.19-3.99 (m, 2H), 3.85 (m, 1H), 3.55-3.37 (m, 5H), 2.25 (m, 2H), 1.59 (m, 2H), 1.31-1.26 (m, 4H), 0.99-0.87 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (174.3, 174.1), (168.9, 168.7), (78.2, 78.0), (77.4, 77.3), (71.3, 71.4), (56.8, 56.6), (42.1, 42.0), (39.4, 39.2), 31.5, 28.1, 25.7, 22.4, (21.32, 21.28), (20.8, 20.4), 14.0; HRMS (ESI$^+$) *m/z* $[C_{15}H_{28}N_2O_4Na]^+$ calcd: 323.1941; found: 323.1932. HPLC: method A t_R = 11.21 min (46%) and 11.81 min (52%); method B t_R = 14.94 min (46%) and 15.24 min (52%).



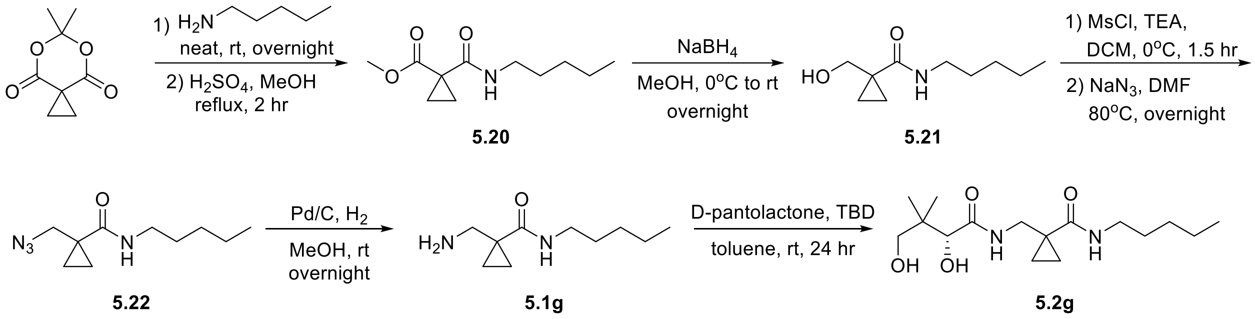
To a 100 mL round bottom flask were added amylamine (5.80 mL, 50 mmol, 1.0 equiv.) and isopropanol (25 mL). The mixture was cooled to 0°C and epichlorohydrin (4.05 mL, 50 mmol, 1.0 equiv.) was added dropwise. The reaction was stirred at rt overnight. The solvent was then evaporated under vacuum and hexanes (40 mL) was added. The mixture was put into a -20 °C freezer overnight and a white solid precipitated out. The solid was collected by filtration under vacuum and the filter cake was washed with hexanes to give **5.17** (3.84 g, 43%, mixture of enantiomers) as a highly hygroscopic white solid. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 3.86 (dtd, J = 8.1, 5.5, 3.9 Hz, 1H), 3.54 (d, J = 5.5 Hz, 2H), 2.78 (dd, J = 12.2, 3.8 Hz, 1H), 2.73-2.52 (m, 5H), 1.47 (p, J = 7.3 Hz, 2H), 1.37-1.22 (m, 4H), 0.88 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 69.4, 52.3, 50.0, 47.6, 29.9, 29.5, 22.7, 14.2; HRMS (ESI$^+$) *m/z* $[C_8H_{19}NOCl]^+$ calcd: 180.1150; found: 180.1153.

To a 50 mL round bottom flask were added **5.17** (898.4 mg, 5 mmol, 1.0 equiv.), anhydrous THF (10 mL), and CDI (972.9 mg, 6 mmol, 1.2 equiv.). The reaction was stirred at 50°C overnight. The mixture was then cooled to rt, diluted in EA (50 mL), and washed with 1 M KH_2PO_4 (2 × 50 mL), water (1 × 50 mL), and brine (1 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 20:1 to 10:1) afforded **5.18** (720 mg, 70%, mixture of enantiomers) as a yellow oil. $R_f = 0.65$ (DCM/EA = 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.70 (m, 1H), 3.71-3.62 (m, 2H), 3.63 (m, 1H), 3.44 (m, 1H), 3.25 (m, 2H), 1.54 (m, 2H), 1.39-1.22 (m, 4H), 0.89 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 157.1, 71.3, 47.5, 44.9, 44.2, 28.8, 27.0, 22.4, 14.1; HRMS (ESI$^+$) *m/z* $[C_9H_{16}NO_2ClNa]^+$ calcd: 228.0762; found: 228.0765.

To a microwave vial were added **5.18** (205.7 mg, 1.0 mmol, 1.0 equiv.), NaN_3 (162.5 mg, 2.5 mmol, 2.5 equiv.), and DMSO (2 mL). The vial was sealed with a PTFE septum and an aluminum cap, and the reaction mixture was subjected to microwave irradiation at 100°C for 1 hour. The mixture was then cooled to rt, diluted in EA (30 mL), and washed with water (2 × 10 mL) and brine (1 × 10 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. The residue was filtered through a short pipette filled with silica (DCM/EA = 20:1 to 10:1) to afford **5.19** (197 mg, 93%, mixture of enantiomers) as a light yellow oil. The compound was directly used in the next step without further purification.

To a 25 mL round bottom flask were added **5.19** (197.0 mg, 0.93 mmol, 1.0 equiv.) and THF/H_2O = 10:1 (2 mL). PPh_3 (293.8 mg, 1.12 mmol, 1.2 equiv.) was added in one portion and the reaction was stirred at rt overnight. The solvent was then evaporated under vacuum. The residue was diluted in water (10 mL), and the *p*H was adjusted to 2 with 1 M HCl. The mixture was washed with EA (3 × 15 mL), then the *p*H of the aqueous layer was adjusted to 12 with sat. Na_2CO_3. The product was extracted in EA (3 × 15 mL). The combined organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to afford **5.1f** (109 mg, 63%, mixture of enantiomers) as a colorless oil, which solidifies upon standing. The compound was directly used in the next step without further purification.

To a reaction vial was added **5.1f** (109.0 mg, 0.59 mmol, 1.0 equiv.), D-pantolactone (156.2 mg, 1.2 mmol, 2.0 equiv.), TBD (8.4 mg, 0.06 mmol, 0.1 equiv.), and toluene (0.6 mL). The reaction was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 15:1) afforded **5.2f** (182 mg, 97%, mixture of diastereomers) as a colorless oil. R_f = 0.46 (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.50 (bs, 1H), 4.80 (m, 1H), 4.63 (m, 1H), 4.03-3.95 (m, 2H), 3.63-3.58 (m, 2H), 3.46-3.38 (m, 3H), 3.30-3.02 (m, 3H), 1.52-1.46 (m, 2H), 1.33-1.23 (m, 4H), 0.94-0.86 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (174.6, 174.4), (157.90, 157.86), (77.6, 77.4), (72.4, 72.2), 71.1, (47.2, 47.1), (44.21, 44.17), (42.1, 41.9), (39.3, 39.2), (28.77, 28.75), (26.93, 26.91), 22.3, (21.2, 21.0), (20.7, 20.5), 14.0; HRMS (ESI$^+$) *m/z* $[C_{15}H_{29}N_2O_5]^+$ calcd: 317.2071; found: 317.2065. HPLC: method A t_R = 12.43 min (47%) and 12.78 min (52%); method B t_R = 15.05 min (53%) and 15.43 min (46%).



α-cyclopropane derivative (**5.2g**)

To a 50 mL round bottom flask was added 6,6-dimethyl-5,7-dioxaspiro[2.5]octane-4,8-dione (1.70 g, 10 mmol, 1.0 equiv.). Amylamine (3.45 mL, 30 mmol, 3.0 equiv.) was added rapidly (caution: extremely exothermic process) and the reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (30 mL), and the product was extracted in 1 M NaOH (3 × 25 mL). The combined aqueous layers were acidified to *p*H = 2 with 6 M HCl and the product was extracted in DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was evaporated under vacuum. To the resulting residue were added MeOH (10 mL) and conc. H_2SO_4 (0.1 mL). The mixture was refluxed for 2 hours. It was then diluted in EA (25 mL) and washed with sat. $NaHCO_3$ (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 4:1) afforded **5.20** (1.17 g, 55% over two steps) as a yellow oil. R_f = 0.76 (Hex/EA = 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.66 (bs, 1H), 3.64 (s, 3H), 3.25 (td, J = 7.2, 5.6 Hz, 2H), 1.65 (m, 2H), 1.54-1.48 (m, 4H), 1.34-1.27 (m, 4H), 0.88 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.3, 168.5, 52.2, 39.9, 29.3, 29.2, 26.0, 22.4, 19.9, 14.1; HRMS (ESI$^+$) *m/z* $[C_{11}H_{20}NO_3]^+$ calcd: 214.1438; found: 214.1434.

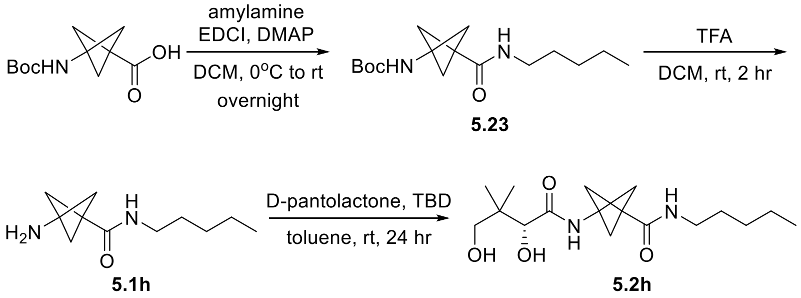
To a 250 mL round bottom flask were added **5.20** (1.17 g, 5.5 mmol, 1.0 equiv.) and MeOH (50 mL). The mixture was cooled to 0°C and $NaBH_4$ (1.04 g, 27.5 mmol, 5.0 equiv.) was added in small portions (caution: gas evolution). The reaction mixture was stirred at rt overnight. TLC indicated that the reaction was not complete, and therefore another portion of $NaBH_4$ (1.04 g, 27.5 mmol, 5.0 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight.

The reaction was quenched with water (5 mL), and the solvent was evaporated under vacuum. The residue was diluted in brine (40 mL) and the product was extracted in EA (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and the solvent was evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 2:1 to 1:2) afforded **5.21** (790 mg, 78%) as a colorless oil. $R_f = 0.18$ (Hex/EA = 1:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.24 (bs, 1H), 3.61 (s, 2H), 3.52 (bs, 1H), 3.21 (td, J = 7.3, 5.6 Hz, 2H), 1.48 (m, 2H), 1.33-1.25 (m, 4H), 1.15 (m, 2H), 0.87 (t, J = 6.9 Hz, 3H), 0.62 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.2, 66.8, 39.8, 29.3, 29.2, 25.7, 22.4, 14.1, 12.3; HRMS (ESI^+) *m/z* $[C_{10}H_{20}NO_2]^+$ calcd: 186.1489; found: 186.1487.

To a 100 mL round bottom flask were added **5.21** (790.0 mg, 4.26 mmol, 1.0 equiv.), TEA (0.89 mL, 6.40 mmol, 1.5 equiv.), and DCM (20 mL). The mixture was cooled to 0°C and MsCl (0.40 mL, 5.12 mmol, 1.2 equiv.) was added dropwise. The reaction mixture was stirred at 0°C for 1.5 hours. The mixture was then diluted in DCM (10 mL), washed with water (1 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum to afford the mesylate intermediate. To this intermediate were added NaN_3 (832.0 mg, 12.8 mmol, 3.0 equiv.) and anhydrous DMF (20 mL). The reaction mixture was stirred at 80°C overnight. The mixture was then cooled to rt, diluted in EA (30 mL), and washed with water (2 × 25 mL) and brine (1 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and the solvent was evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 3:1) afforded **5.22** (700 mg, 78%) as a colorless oil. $R_f = 0.63$ (Hex/EA = 1:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 6.27 (bs, 1H), 3.38 (s, 2H), 3.22 (m, 2H), 1.49 (p, J = 7.4 Hz, 2H), 1.33-1.26 (m, 4H), 1.24 (m, 2H), 0.87 (t, J = 7.0 Hz, 3H), 0.73 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 171.9, 55.7, 40.0, 29.2, 29.1, 24.0, 22.4, 14.0, 13.1; HRMS (ESI^+) *m/z* $[C_{10}H_{19}N_4O]^+$ calcd: 211.1553; found: 211.1550.

To a 50 mL round bottom flask were added **5.22** (700.0 mg, 3.32 mmol, 1.0 equiv.), Pd/C (10% wt., 100 mg), and MeOH (10 mL). The flask was sealed with a rubber septum and H_2 was bubbled into the solution for 5 minutes, then a H_2 balloon was attached to maintain the atmosphere. The reaction mixture was stirred overnight. The mixture was then filtered over celite (Caution: celite needs to remain wet all the time to prevent combustion. Quenching the filter cake with water after filtration is highly recommended). The filtrate was evaporated under vacuum to afford crude **5.1g** (612.0 mg, quant.), which was used without further purification.

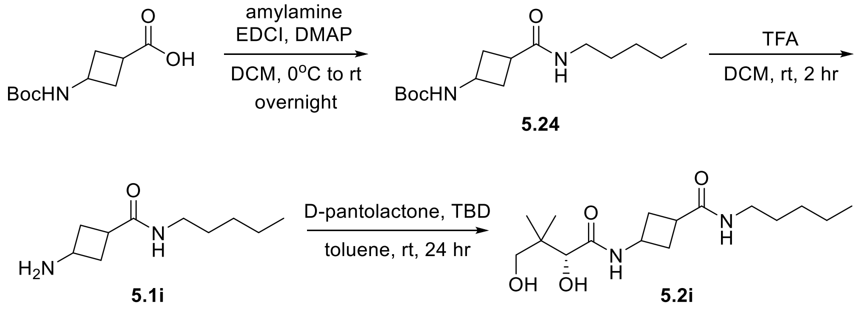
To a reaction vial was added **5.1g** (612.0 mg, 3.32 mmol, 1.0 equiv.), D-pantolactone (864.1 mg, 6.64 mmol, 2.0 equiv.), TBD (46.2 mg, 0.33 mmol, 0.1 equiv.), and toluene (3.5 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 50:1 to 20:1) afforded **5.2g** (510 mg, 49%) as a sticky colorless oil. $R_f = 0.54$ (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.63 (t, $J = 5.3$ Hz, 1H), 7.47 (t, $J = 6.8$ Hz, 1H), 5.18 (d, $J = 4.7$ Hz, 1H), 4.35 (t, $J = 5.6$ Hz, 1H), 3.96 (d, $J = 4.6$ Hz, 1H), 3.48 (dd, $J = 15.3$, 6.9 Hz, 1H), 3.41 (dd, $J = 12.4$, 6.3 Hz, 1H), 3.37 (dd, $J = 12.4$, 6.4 Hz, 1H), 3.29 (dd, $J = 15.3$, 6.7 Hz, 1H), 3.10 (m, 1H), 3.03 (m, 1H), 1.43 (p, $J = 7.4$ Hz, 2H), 1.27-1.20 (m, 4H), 1.13 (m, 2H), 0.88 (s, 3H), 0.87 (s, 3H), 0.83 (t, $J = 7.0$ Hz, 3H), 0.67 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.6, 173.1, 77.5, 71.3, 42.8, 40.4, 39.3, 29.2, 29.0, 25.5, 22.4, 20.8, 20.7, 14.6, 14.3, 14.1; HRMS (ESI$^+$) *m/z* $[C_{16}H_{31}N_2O_4]^+$ calcd: 315.2278; found: 315.2272. HPLC: method A $t_R = 23.52$ min (99%); method B $t_R = 18.48$ min (>99%).



<u>bicyclopentane derivative with normal amide (**5.2h**)</u>

To a 50 mL round bottom flask were added amylamine (115 μL, 1 mmol, 1.0 equiv.), 3-(Boc-amino)-bicyclo[1.1.1]pentane-1-carboxylic acid (250.0 mg, 1.1 mmol, 1.1 equiv.), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.), and DCM (5 mL). The mixture was cooled to 0°C and EDCI (210.9 mg, 1.1 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL), then washed with sat. $NaHCO_3$ (2 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 1:1 + 1% MeOH) afforded **5.23** (281 mg, 95%) as a white solid. $R_f = 0.37$ (DCM/EA = 2:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.47 (t, $J = 6.2$ Hz, 1H), 4.98 (bs, 1H), 3.22 (m, 2H), 2.23 (s, 6H), 1.50 (m, 2H), 1.44 (s, 9H), 1.34-1.24 (m, 4H), 0.89 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.3, 53.6, 45.2, 39.6, 29.4, 29.1, 28.5, 22.5, 14.1; HRMS (ESI$^+$) *m/z* [$C_{16}H_{28}N_2O_3Na$]$^+$ calcd: 319.1992; found: 319.2000.

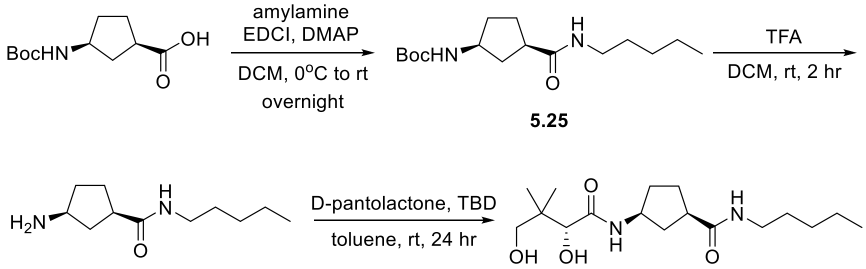
To a 25 mL round bottom flask were added **5.23** (281.0 mg, 0.95 mmol, 1.0 equiv.), DCM (1.5 mL), and TFA (1.5 mL). The reaction mixture was stirred at rt for 2 hours, then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (25 mL) and the product was extracted in DCM (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1h**. To this crude were added D-pantolactone (247.3 mg, 1.9 mmol, 2.0 equiv.), TBD (13.2 mg, 0.095 mmol, 0.1 equiv.), and toluene (1 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2h** (46 mg, 15% over two steps) as a white solid. $R_f = 0.50$ (DCM/MeOH = 10:1); ^{1}H NMR (CD_3OD, 500 MHz): δ 3.83 (s, 1H), 3.47 (d, J = 11.0 Hz, 1H), 3.37 (d, J = 11.0 Hz, 1H), 3.15 (t, J = 7.2 Hz, 2H), 2.29 (s, 6H), 1.50 (m, 2H), 1.38-1.26 (m, 4H), 0.93-0.90 (m, 9H); ^{13}C NMR (CD_3OD, 125 MHz): δ 176.8, 172.1, 77.4, 70.3, 54.7, 45.7, 40.4, 40.3, 38.8, 30.2, 30.1, 23.4, 21.5, 20.7, 14.3; HRMS (ESI$^+$) *m/z* [$C_{17}H_{30}N_2O_4Na$]$^+$ calcd: 349.2098; found: 349.2089. HPLC: method A t_R = 21.35 min (>99%); method B t_R = 17.99 min (>99%).



<u>cyclobutane derivative with normal amide (**5.2i**)</u>

To a 50 mL round bottom flask were added amylamine (0.23 mL, 2 mmol, 1.0 equiv.), 3-(Boc-amino)cyclobutane-1-carboxylic acid (cis/trans mixture, 473.4 mg, 2.2 mmol, 1.1 equiv.), DMAP (24.4 mg, 0.2 mmol, 0.1 equiv.), and DCM (10 mL). The mixture was cooled to 0°C, and EDCI (421.7 mg, 2.2 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL), then washed with sat. $NaHCO_3$ (2 × 20 mL) and 1 M KH_2PO_4 (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 2:1 to 1:1) afforded **5.24** (579 mg, quant., cis/trans isomers) as a white solid. R_f = 0.50 (Hex/EA = 1:2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (6.04, 5.93) (bs, 1H), (5.20, 5.09) (bs, 1H), (4.26, 4.04) (m, 1H), 3.18 (m, 2H), 2.92-2.45 (m, 3H), 2.12 (m, 2H), 1.45 (m, 2H), (1.39, 1.39) (s, 9H), 1.30-1.22 (m, 4H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (174.8, 174.1), 155.1, 79.3, 44.3, 41.8, 39.6, 34.4, 34.2, 33.6, 33.1, (29.4, 29.3), (29.09, 29.08), (28.43, 28.41), 22.37, 14.0; HRMS (ESI$^+$) *m/z* $[C_{15}H_{28}N_2O_3Na]^+$ calcd: 307.1992; found: 307.1990.

To a 25 mL round bottom flask were added **5.24** (579.0 mg, 2 mmol, 1.0 equiv.), DCM (2 mL), and TFA (2 mL). The reaction mixture was stirred at rt for 2 hours, then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (25 mL) and the product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1i**. To this crude were added D-pantolactone (520.6 mg, 4 mmol, 2.0 equiv.), TBD (27.8 mg, 0.2 mmol, 0.1 equiv.), and toluene (2 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2i** (265 mg, 42% over two steps, mixture of diastereomers) as a sticky white solid. R_f = 0.50/0.42 (DCM/MeOH = 10:1); ^{1}H NMR (CD_3OD, 500 MHz): δ 4.57-4.26 (m, 1H), 3.95-3.93 (m, 1H), 3.47-3.45 (m, 1H), 3.39-3.35 (m, 1H), 3.19-3.12 (m, 2H), 3.05-2.74 (m, 1H), 2.48 (m, 2H), 2.34-2.15 (m, 2H), 1.47 (m, 2H), 1.36-1.27 (m, 4H), 0.94-0.89 (m, 9H); ^{13}C NMR (CD_3OD, 125 MHz): δ (177.6, 177.5, 176.4, 176.3), (175.4, 175.2), (77.1, 70.2), 44.1, 44.0, (41.4, 41.2), (40.6, 40.5), (40.44, 40.41, 40.3), 35.2, (34.3, 34.2), (34.0, 33.91, 33.85), 33.6, (30.15, 30.13, 30.10, 30.0), (23.36, 23.35), (21.4, 21.1), (14.34, 14.33); HRMS (ESI$^+$) *m/z* $[C_{16}H_{30}N_2O_4Na]^+$ calcd: 337.2098; found: 337.2110. HPLC: method A t_R = 21.04 min (>99%); method B t_R = 17.93 min (97%).

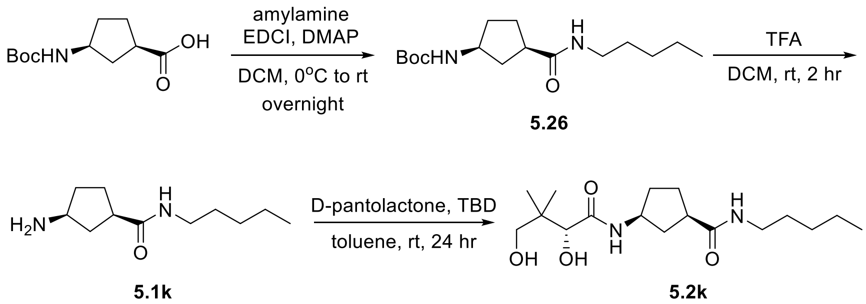


5.1j **5.2j**

(1*R*,3*S*)-cyclopentane derivative with normal amide (**5.2j**)

To a 50 mL round bottom flask were added amylamine (115 µL, 1 mmol, 1.0 equiv.), (1*R*,3*S*)-3-(Boc-amino)cyclopentane-1-carboxylic acid (252.2 mg, 1.1 mmol, 1.1 equiv.), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.), and DCM (5 mL). The mixture was cooled to 0ºC and EDCI (210.9 mg, 1.1 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL), then washed with sat. $NaHCO_3$ (2 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1) afforded **5.25** (282 mg, 94%) as a white solid. $R_f = 0.65$ (Hex/EA = 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.03 (bs, 1H), 5.80 (d, $J = 7.2$ Hz, 1H), 4.02 (bs, 1H), 3.17 (m, 2H), 2.60 (m, 1H), 2.00 (m, 1H), 1.83 (m, 2H), 1.76-1.66 (m, 3H), 1.45 (m, 2H), 1.38 (s, 9H), 1.30-1.19 (m, 4H), 0.84 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.9, 155.6, 78.8, 52.3, 43.8, 39.8, 36.6, 34.1, 29.4, 29.1, 28.8, 28.5, 22.4, 14.0; HRMS (ESI$^+$) *m/z* $[C_{16}H_{30}N_2O_3Na]^+$ calcd: 321.2149; found: 321.2156.

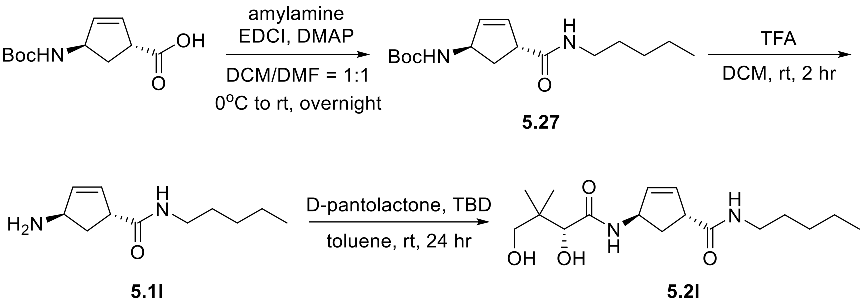
To a 25 mL round bottom flask were added **5.25** (282.0 mg, 0.94 mmol, 1.0 equiv.), DCM (1.5 mL), and TFA (1.5 mL). The reaction mixture was stirred at rt for 2 hours and then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (25 mL). The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1j**. To this crude were added D-pantolactone (244.7 mg, 1.88 mmol, 2.0 equiv.), TBD (13.1 mg, 0.09 mmol, 0.1 equiv.), and toluene (1 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2j** (268 mg, 87% over two steps) as a sticky light brown oil. $R_f = 0.53$ (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.81 (d, $J = 8.1$ Hz, 1H), 6.26 (t, $J = 5.8$ Hz, 1H), 4.51 (d, $J = 6.0$ Hz, 1H), 4.32 (m, 1H), 4.25 (t, $J = 5.6$ Hz, 1H), 3.94 (d, $J = 5.8$ Hz, 1H), 3.43 (m, 2H), 3.16 (m, 2H), 2.68 (m, 1H), 2.06 (ddd, $J = 13.7, 9.4, 6.7$ Hz, 1H), 1.95 (m, 1H), 1.82 (m, 2H), 1.73 (m, 2H), 1.45 (m, 2H), 1.31-1.20 (m, 4H), 0.95 (s, 3H), 0.89 (s, 3H), 0.85 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.2, 172.8, 77.4, 70.7, 50.9, 43.7, 39.9, 39.4, 36.6, 33.7, 29.2, 29.1, 29.0, 22.4, 21.5, 20.6, 14.0; HRMS (ESI$^+$) *m/z* $[C_{17}H_{32}N_2O_4Na]^+$ calcd: 351.2254; found: 351.2253. HPLC: method A $t_R = 23.83$ min (95%); method B $t_R = 18.45$ min (98%).



(1*S*,3*R*)-cyclopentane derivative with normal amide (**5.2k**)

To a 50 mL round bottom flask were added amylamine (115 μL, 1 mmol, 1.0 equiv.), (1*S*,3*R*)-3-(Boc-amino)cyclopentane-1-carboxylic acid (252.2 mg, 1.1 mmol, 1.1 equiv.), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.), and DCM (5 mL). The mixture was cooled to 0°C and EDCI (210.9 mg, 1.1 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL), then washed with sat. $NaHCO_3$ (2 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 10:1 to 2:1) afforded **5.26** (291 mg, 98%) as a white solid. $R_f = 0.60$ (Hex/EA = 1:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 5.87 (bs, 1H), 5.78 (bs, 1H), 4.04 (bs, 1H), 3.19 (m, 2H), 2.59 (m, 1H), 2.02 (ddd, J = 13.6, 9.3, 6.8 Hz, 1H), 1.87 (m, 2H), 1.78-1.68 (m, 3H), 1.47 (m, 2H), 1.39 (s, 9H), 1.31-1.22 (m, 4H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 176.9, 155.6, 78.8, 52.3, 43.9, 39.8, 36.7, 34.1, 29.4, 29.1, 28.9, 28.6, 22.4, 14.1; HRMS (ESI^+) *m/z* $[C_{16}H_{30}N_2O_3Na]^+$ calcd: 321.2149; found: 321.2147.

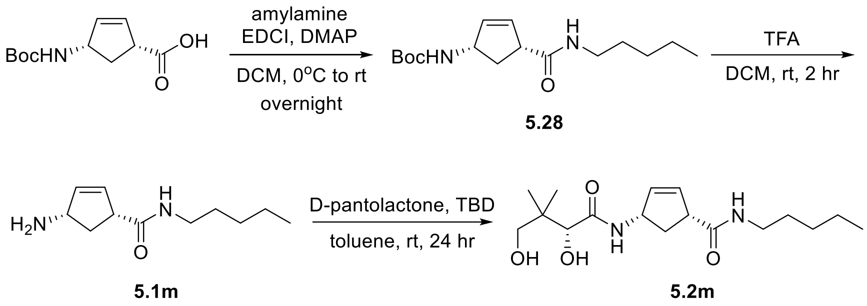
To a 25 mL round bottom flask were added **5.26** (291.0 mg, 0.98 mmol, 1.0 equiv.), DCM (1.5 mL), and TFA (1.5 mL). The reaction mixture was stirred at rt for 2 hours and then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (25 mL). The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1k**. To this crude were added D-pantolactone (255.1 mg, 1.96 mmol, 2.0 equiv.), TBD (13.9 mg, 0.1 mmol, 0.1 equiv.), and toluene (1 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2k** (286 mg, 88% over two steps) as a colorless sticky oil. $R_f = 0.56$ (DCM/MeOH = 10:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.87 (d, J = 7.9 Hz, 1H), 6.24 (t, J = 5.7 Hz, 1H), 4.55 (d, J = 5.6 Hz, 1H), 4.31 (m, 1H), 4.24 (bs, 1H), 3.94 (d, J = 4.9 Hz, 1H), 3.43 (s, 2H), 3.18 (m, 2H), 2.68 (m, 1H), 2.04 (ddd, J = 13.7, 9.4, 6.6 Hz, 1H), 1.93 (m, 1H), 1.81-1.72 (m, 4H), 1.45 (m, 2H), 1.30-1.21 (m, 4H), 0.95 (s, 3H), 0.88 (s, 3H), 0.85 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 177.1, 173.0, 77.4, 70.9, 50.9, 43.8, 39.9, 39.5, 36.2, 33.9, 29.2, 29.07, 29.05, 22.4, 21.5, 20.4, 14.0; HRMS (ESI$^+$) *m/z* $[C_{17}H_{32}N_2O_4Na]^+$ calcd: 351.2254; found: 351.2256. HPLC: method A t_R = 24.23 min (98%); method B t_R = 18.47 min (>99%).



<u>(1*R*,4*R*)-cyclopentene derivative with normal amide (**5.2l**)</u>

To a 50 mL round bottom flask were added amylamine (115 µL, 1 mmol, 1.0 equiv.), (1*R*,4*R*)-4-(Boc-amino)cyclopent-2-ene-1-carboxylic acid (250.0 mg, 1.1 mmol, 1.1 equiv.), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.), and DCM/DMF = 1:1 (5 mL). The mixture was cooled to 0°C and EDCI (210.9 mg, 1.1 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (20 mL), and then washed with sat. $NaHCO_3$ (2 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 2:1 to 1:2) afforded **5.27** (158 mg, 53%) as a white solid. R_f = 0.28 (Hex/EA = 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.91 (m, 1H), 5.84 (m, 1H), 5.64 (bs, 1H), 4.81 (bs, 1H), 4.60 (m, 1H), 3.51 (m, 1H), 3.18 (m, 2H), 2.45 (ddd, *J* = 13.3, 8.1, 4.7 Hz, 1H), 1.90 (m, 1H), 1.44 (m, 2H), 1.41 (s, 9H), 1.31-1.21 (m, 4H), 0.86 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.4, 155.3, 135.7, 132.6, 79.6, 56.6, 51.5, 39.7, 36.6, 29.4, 29.1, 28.5, 22.4, 14.1; HRMS (ESI$^+$) *m/z* $[C_{16}H_{28}N_2O_3Na]^+$ calcd: 319.1992; found: 319.1988.

To a 25 mL round bottom flask were added **5.27** (158.0 mg, 0.53 mmol, 1.0 equiv.), DCM (1 mL), and TFA (1 mL). The reaction mixture was stirred at rt for 2 hours, then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (20 mL). The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1l**. To this crude product were added D-pantolactone (138.0 mg, 1.06 mmol, 2.0 equiv.) and TBD (7.0 mg, 0.05 mmol, 0.1 equiv.), and toluene (0.5 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2l** (72 mg, 42% over two steps) as a beige sticky solid. R_f = 0.55 (DCM/MeOH = 10:1) ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.04 (d, *J* = 8.1 Hz, 1H), 6.13 (t, *J* = 5.8 Hz, 1H), 5.89 (s, 2H), 5.07 (m, 1H), 4.74 (bs, 1H), 4.11 (bs, 1H), 3.97 (s, 1H), 3.58 (m, 1H), 3.47 (d, *J* = 11.3 Hz, 1H), 3.44 (d, *J* = 11.3 Hz, 1H), 3.18 (m, 2H), 2.49 (ddd, *J* = 13.4, 8.2, 4.9 Hz, 1H), 1.90 (ddd, *J* = 13.5, 8.8, 4.4 Hz, 1H), 1.47 (m, 2H), 1.34-1.24 (m, 4H), 0.96 (s, 3H), 0.90 (s, 3H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 173.2, 134.7, 133.5, 71.2, 55.1, 51.5, 39.9, 39.4, 36.1, 29.3, 29.2, 22.4, 21.3, 20.6, 14.1; HRMS (ESI$^+$) *m/z* $[C_{17}H_{30}N_2O_4Na]^+$ calcd: 349.2098; found: 349.2094. HPLC: method A t_R = 21.39 min (98%); method B t_R = 18.00 min (97%).

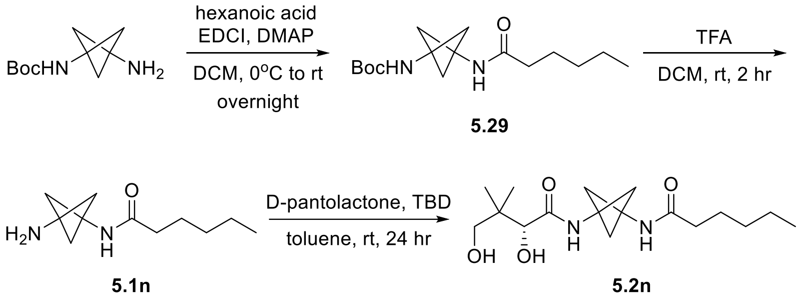


(1*R*,4*S*)-cyclopentene derivative with normal amide (**5.2m**)

To a 50 mL round bottom flask were added amylamine (115 μL, 1 mmol, 1.0 equiv.), (1*R*,4*S*)-4-(Boc-amino)cyclopent-2-ene-1-carboxylic acid (250.0 mg, 1.1 mmol, 1.1 equiv.), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.), and DCM (5 mL). The mixture was cooled to 0°C and EDCI (210.9 mg, 1.1 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL), and then washed with sat. $NaHCO_3$ (2 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 2:1) afforded **5.28** (117 mg, 40%) as an off-white solid. R_f = 0.58 (DCM/EA = 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.03 (bs, 1H), 5.89 (dt, *J* = 5.5, 2.1 Hz, 1H), 5.76 (ddd, *J* = 5.6, 2.5, 1.6 Hz, 1H), 5.42 (d, *J* = 8.9 Hz, 1H), 4.69 (t, *J* = 9.1 Hz, 1H), 3.25-3.19 (m, 3H), 2.38 (dt, *J* = 13.9, 8.5 Hz, 1H), 1.81 (dt, *J* = 13.8, 3.1 Hz, 1H), 1.49 (m, 2H), 1.41 (s, 9H), 1.34-1.25 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR

($CDCl_3$, 125 MHz): δ 174.1, 155.4, 135.3, 131.8, 79.2, 55.9, 51.6, 39.9, 35.2, 29.4, 29.2, 28.5, 22.4, 14.1; HRMS (ESI$^+$) *m/z* $[C_{16}H_{28}N_2O_3Na]^+$ calcd: 319.1992; found: 319.1979.

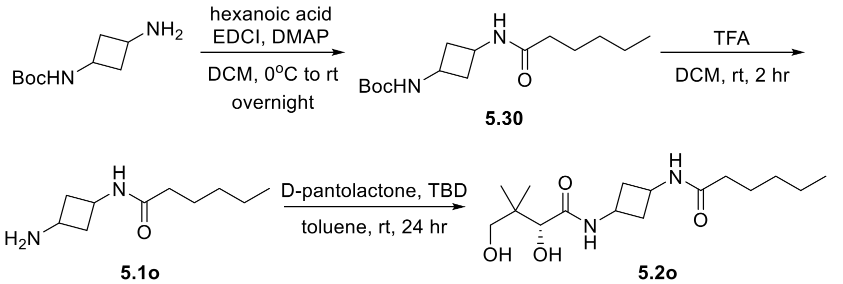
To a 25 mL round bottom flask were added **5.28** (117.0 mg, 0.4 mmol, 1.0 equiv.), DCM (1 mL), and TFA (1 mL). The reaction mixture was stirred at rt for 2 hours, then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (20 mL). The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1m**. To this crude product were added D-pantolactone (104.1 mg, 0.8 mmol, 2.0 equiv.) and TBD (5.6 mg, 0.04 mmol, 0.1 equiv.), and toluene (0.4 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2m** (74 mg, 57% over two steps) as a sticky light yellow oil. $R_f = 0.55$ (DCM/MeOH = 10:1); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.47 (d, $J = 9.2$ Hz, 1H), 6.02 (t, $J = 5.7$ Hz, 1H), 5.89 (dt, $J = 5.5$, 2.1 Hz, 1H), 5.82 (ddd, $J = 5.4$, 2.6, 1.4 Hz, 1H), 5.07 (m, 1H), 4.05 (d, $J = 6.0$ Hz, 1H), 4.00 (d, $J = 5.9$ Hz, 1H), 3.81 (bs, 1H), 3.50 (d, $J = 10.9$ Hz, 1H), 3.44 (d, $J = 11.0$ Hz, 1H), 3.29 (m, 1H), 3.22 (m, 2H), 2.40 (dt, $J = 13.9$, 8.4 Hz, 1H), 1.86 (dt, $J = 13.9$, 2.9 Hz, 1H), 1.49 (m, 2H), 1.36-1.23 (m, 4H), 1.01 (s, 3H), 0.89 (s, 3H), 0.88 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 174.2, 172.4, 134.7, 132.6, 77.2, 70.8, 54.2, 51.7, 40.1, 39.7, 35.0, 29.3, 29.1, 22.4, 21.9, 20.2, 14.1; HRMS (ESI$^+$) *m/z* $[C_{17}H_{30}N_2O_4Na]^+$ calcd: 349.2098; found: 349.2108. HPLC: method A $t_R = 23.75$ min (>99%); method B $t_R = 18.47$ min (>99%).



bicyclopentane derivative with reverse amide (**5.2n**)

To a 50 mL round bottom flask were added *tert*-butyl (3-aminobicyclo[1.1.1]pentan-1-yl)carbamate (396.6 mg, 2 mmol, 1.0 equiv.), hexanoic acid (0.28 mL, 2.2 mmol, 1.1 equiv.), DMAP (24.4 mg, 0.2 mmol, 0.1 equiv.), and DCM (10 mL). The mixture was cooled to 0°C and EDCI (421.7 mg, 2.2 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL) and MeOH (2 mL), and then washed with sat. $NaHCO_3$ (2 × 20 mL) and 1 M KH_2PO_4 (2 × 20 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/DCM/EA = 1:1:1, then DCM/EA = 1:1) afforded **5.29** (572 mg, 96%) as a white solid. R_f = 0.38 (Hex/DCM/EA = 1:1:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.99 (bs, 1H), 5.03 (bs, 1H), 2.28 (s, 6H), 2.10 (m, 2H), 1.58 (m, 2H), 1.42 (s, 9H), 1.31-1.22 (m, 4H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.7, 54.9, 44.9, 44.5, 36.8, 31.6, 28.5, 25.2, 22.5, 14.0; HRMS (ESI$^+$) m/z $[C_{16}H_{28}N_2O_3Na]^+$ calcd: 319.1992; found: 319.1999.

To a 25 mL round bottom flask were added **5.29** (572.0 mg, 1.92 mmol, 1.0 equiv.), DCM (2 mL), and TFA (2 mL). The reaction mixture was stirred at rt for 2 hours and the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (20 mL). The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1n**. To this crude product were added D-pantolactone (499.7 mg, 3.84 mmol, 2.0 equiv.), TBD (26.7 mg, 0.19 mmol, 0.1 equiv.), and toluene (2 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2n** (203 mg, 32% over two steps) as a white solid. R_f = 0.42 (DCM/MeOH = 10:1); ^{1}H NMR (CD_3OD, 500 MHz): δ 3.83 (s, 1H), 3.47 (d, J = 10.9 Hz, 1H), 3.37 (d, J = 10.9 Hz, 1H), 2.34 (s, 6H), 2.12 (t, J = 7.6 Hz, 2H), 1.58 (m, 2H), 1.37-1.25 (m, 4H), 0.92-0.89 (m, 9H); ^{13}C NMR (CD_3OD, 125 MHz): δ 176.7, 176.5, 77.4, 70.3, 55.7, 45.7, 45.5, 40.3, 37.1, 32.5, 26.5, 23.4, 21.5, 20.7, 14.3; HRMS (ESI$^+$) m/z $[C_{17}H_{30}N_2O_4Na]^+$ calcd: 349.2098; found: 349.2106. HPLC: method A t_R = 22.40 min (>99%); method B t_R = 18.20 min (>99%).

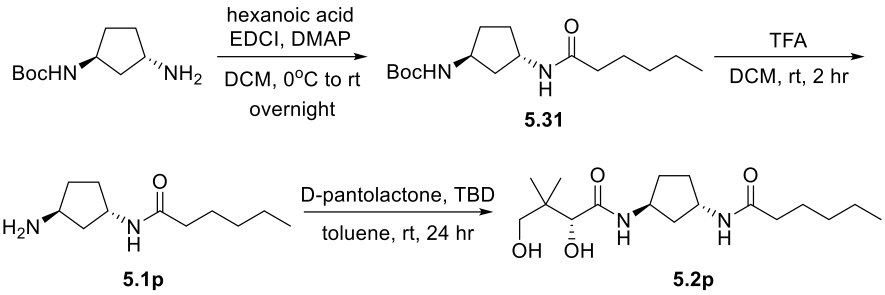


cyclobutane derivative with reverse amide (**5.2o**)

To a 50 mL round bottom flask were added *tert*-butyl (3-aminocyclobutyl)carbamate (cis/trans mixture, 250.0 mg, 1.34 mmol, 1.0 equiv.), hexanoic acid (0.19 mL, 1.48 mmol, 1.1 equiv.), DMAP (15.9 mg, 0.13 mmol, 0.1 equiv.), and DCM (8 mL). The mixture was cooled to 0°C and EDCI

(283.7 mg, 1.48 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (2 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, Hex/EA = 1:1 to 1:3) afforded **5.30** (368 mg, 97%, cis/trans isomers) as a white solid. $R_f = 0.34$ (Hex/EA = 1:2); ^{1}H NMR ($CDCl_3$, 500 MHz): δ (6.23, 6.00) (m, 1H), (5.03, 4.85) (m, 1H), (4.36, 4.01) (m, 1H), (4.16, 3.74) (m, 1H), (2.75-2.70, 2.28-2.20) (m, 3H), 2.16-2.07 (m, 2H), 1.82 (m, 1H), 1.58 (m, 2H), 1.39 (s, 9H), 1.29-1.21 (m, 4H), 0.85 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (173.2, 172.7), (155.3, 155.1), 79.5, (42.9, 41.6), (39.7, 39.2), 38.2, 37.9, (36.71, 36.68), 31.5, 28.5, (25.51, 25.45), 22.5, 14.0; HRMS (ESI$^+$) m/z $[C_{15}H_{28}N_2O_3Na]^+$ calcd: 307.1992; found: 307.1997.

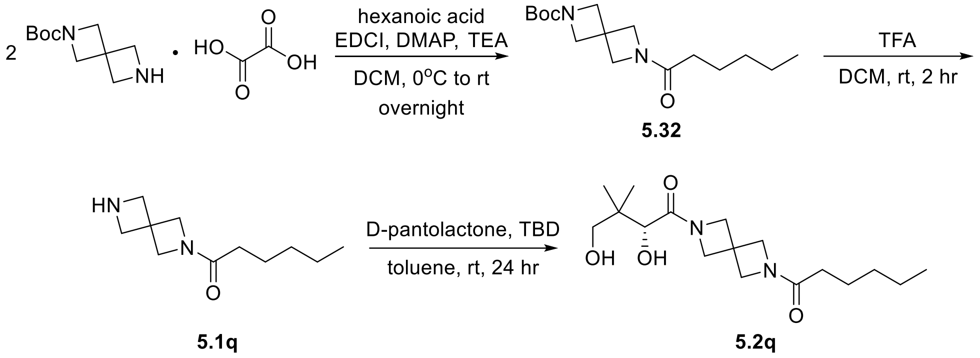
To a 25 mL round bottom flask were added **5.30** (368.0 mg, 1.3 mmol, 1.0 equiv.), DCM (1.5 mL), and TFA (1.5 mL). The reaction mixture was stirred at rt for 2 hours, and then the solvent was evaporated under vacuum. Water (20 mL) was added to the residue and the *p*H was adjusted to 14 with 4 M NaOH. The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1o**. To this crude product were added D-pantolactone (338.4 mg, 2.6 mmol, 2.0 equiv.), TBD (18.1 mg, 0.13 mmol, 0.1 equiv.), and toluene (1.5 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1 to 10:1) afforded **5.2o** (358 mg, 87% over two steps, mixture of diastereomers) as a colorless semi-solid. $R_f = 0.50$ (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ [7.44 (d, J = 7.0 Hz), 7.28 (d, J = 7.8 Hz), 1H], [6.92 (d, J = 6.9 Hz), 6.89 (d, J = 7.6 Hz), 1H], [5.21 (d, J = 5.0 Hz), 5.15 (d, J = 5.2 Hz), 1H], 4.47 (m, 1H), (4.40-4.34, 4.09-3.94) (m, 3H), 3.49-3.39 (m, 2H), (2.75-2.70, 2.32-2.29) (m, 3H), 2.15-2.09 (m, 2H), 1.91 (m, 1H), 1.55 (m, 2H), 1.30-1.21 (m, 4H), 0.94-0.84 (m, 9H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (173.91, 173.86), (173.5, 173.4), 77.1, (71.0, 70.9), (42.0, 41.5), (39.5, 39.4), (38.7, 38.6), (38.6, 38.3), (37.4, 37.3), (36.61, 36.58), 31.52, (25.6, 25.5), 22.5, (21.2, 21.0), (20.64, 20.60), 14.0; HRMS (APCI$^+$) m/z $[C_{16}H_{31}N_2O_4]^+$ calcd: 315.2278; found: 315.2290. HPLC: method A t_R = 19.65 min (42%) and 19.83 min (57%); method B t_R = 17.65 min (98%).



<u>(1*S*,3*S*)-cyclopentane derivative with reverse amide (**5.2p**)</u>

To a 50 mL round bottom flask were added *tert*-butyl ((1*S*,3*S*)-3-aminocyclopentyl)carbamate (200.3 mg, 1 mmol, 1.0 equiv.), hexanoic acid (0.14 mL, 1.1 mmol, 1.1 equiv.), DMAP (12.2 mg, 0.1 mmol, 0.1 equiv.), and DCM (5 mL). The mixture was cooled to 0°C and EDCI (210.9 mg, 1.1 mmol, 1.1 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL) and washed with sat. $NaHCO_3$ (2 × 15 mL) and 1 M KH_2PO_4 (2 × 15 mL). The organic layer was dried over Na_2SO_4, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO_2, DCM/EA = 10:1 to 1:1) afforded **5.31** (276 mg, 92%) as a white solid. R_f = 0.30 (Hex/EA = 1:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 5.68 (bs, 1H), 4.62 (bs, 1H), 4.31 (m, 1H), 4.03 (m, 1H), 2.18-2.08 (m, 4H), 1.79 (m, 2H), 1.58 (m, 2H), 1.41 (s, 9H), 1.37 (m, 2H), 1.35-1.22 (m, 4H), 0.86 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 172.9, 155.6, 79.4, 50.5, 49.0, 40.4, 36.9, 32.0, 31.8, 31.6, 28.5, 25.6, 22.5, 14.0; HRMS (ESI$^+$) *m/z* $[C_{16}H_{30}N_2O_3Na]^+$ calcd: 321.2149; found: 321.2141.

To a 25 mL round bottom flask were added **5.31** (276.0 mg, 0.92 mmol, 1.0 equiv.), DCM (1.5 mL), and TFA (1.5 mL). The reaction mixture was stirred at rt for 2 hours, and then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na_2CO_3 (20 mL). The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated under vacuum to afford crude **5.1p**. To this crude product were added D-pantolactone (239.4 mg, 1.84 mmol, 2.0 equiv.), TBD (12.8 mg, 0.09 mmol, 0.1 equiv.), and toluene (1 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1) afforded **5.2p** (80 mg, 26% over two steps) as a sticky colorless oil. R_f = 0.45 (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.09 (d, J = 7.8 Hz, 1H), 6.09 (d, J = 7.5 Hz, 1H), 4.79 (d, J = 5.2 Hz, 1H), 4.30 (m, 2H), 4.23 (bs, 1H), 3.98 (d, J = 5.0 Hz, 1H), 3.49 (d, J = 11.1 Hz, 1H), 3.45 (d, J = 11.1 Hz, 1H), 2.19-2.11 (m, 4H), 1.83 (m, 2H), 1.58 (m, 2H), 1.46 (m, 2H), 1.34-1.23 (m, 4H), 0.97 (s, 3H), 0.91 (s, 3H), 0.87 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl$_3$, 125 MHz): δ 173.6, 173.3, 77.5, 71.2, 49.2, 48.9, 40.0, 39.4, 36.8, 31.7, 31.5, 25.6, 22.5, 21.3, 20.7, 14.1; HRMS (ESI$^+$) *m/z* $[C_{17}H_{32}N_2O_4Na]^+$ calcd: 351.2254; found: 351.2246. HPLC: method A $t_R = 20.70$ min (99%); method B $t_R = 17.88$ min (99%).



spirocyclobutane derivative with reverse amide (**5.2q**)

To a 50 mL round bottom flask were added 2,6-diazaspiro[3.3]heptane-2-carboxylic acid tert-butyl ester hemioxalate (486.6 mg, 1 mmol, 1.0 equiv.), hexanoic acid (0.28 mL, 2.2 mmol, 2.2 equiv.), DMAP (24.4 mg, 0.2 mmol, 0.2 equiv.), and DCM (10 mL). The mixture was cooled to 0°C and EDCI (421.7 mg, 2.2 mmol, 2.2 equiv.) was added in small portions. The reaction mixture was stirred at rt overnight. The mixture was then diluted in DCM (10 mL), then washed with sat. NaHCO$_3$ (2 × 20 mL) and 1 M KH$_2$PO$_4$ (2 × 20 mL). The organic layer was dried over Na$_2$SO$_4$, filtered, and evaporated under vacuum. Purification by flash chromatography (SiO$_2$, DCM/MeOH = 20:1) afforded **5.32** (505 mg, 85%) as a white solid. $R_f = 0.40$ (DCM/MeOH = 20:1); ^{1}H NMR (CD$_3$OD, 500 MHz): δ 4.32 (bs, 2H), 4.08 (bs, 2H), 4.07 (bs, 4H), 2.11 (t, $J = 7.6$ Hz, 2H), 1.57 (m, 2H), 1.43 (s, 9H), 1.38-1.28 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (CD$_3$OD, 125 MHz): δ 175.5, 157.8, 81.1, 79.5, 61.4, 60.3 (bs), 58.9, 33.2, 32.6, 32.1, 28.6, 25.6, 23.5, 14.3; HRMS (ESI$^+$) *m/z* $[C_{16}H_{29}N_2O_3]^+$ calcd: 297.2173; found: 297.2178.

To a 25 mL round bottom flask were added **5.32** (505.0 mg, 1.7 mmol, 1.0 equiv.), DCM (1.5 mL), and TFA (1.5 mL). The reaction mixture was stirred at rt for 2 hours, and then the solvent was evaporated under vacuum. The residue was dissolved in sat. Na$_2$CO$_3$ (20 mL). The product was extracted in DCM (3 × 10 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and evaporated under vacuum to afford crude **5.1q**. To this crude product were added D-pantolactone (442.5 mg, 3.4 mmol, 2.0 equiv.), TBD (23.7 mg, 0.17 mmol, 0.1 equiv.), and toluene

(2 mL). The reaction mixture was stirred at rt for 24 hours. Purification by flash chromatography (SiO_2, DCM/EA = 4:1, then DCM/MeOH = 20:1 to 10:1) afforded **5.2q** (90 mg, 16% over two steps, mixture of isomers) as a light yellow oil. $R_f = 0.33$ (DCM/MeOH = 10:1); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 4.42 (m, 2H), 4.28-4.20 (m, 3H), 4.14-4.11 (m, 3H), 3.98 (s, 1H), 3.64 (bs, 1H), 3.47 (m, 2H), 3.10 (bs, 1H), 2.04 (t, J = 7.6 Hz, 2H), 1.58 (m, 2H), 1.28-1.23 (m, 4H), 0.95 (s, 3H), 0.91 (s, 3H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (173.6, 173.5), 173.5, (74.2, 74.1), (70.0, 69.9), 61.9, (60.4, 60.3), 58.5, (58.0, 57.8), 40.0, (32.79, 32.75), 31.64, 31.55, 24.5, 22.5, (21.9, 21.8), (20.21, 20.15), 14.0; HRMS (ESI$^+$) *m/z* $[C_{17}H_{31}N_2O_4]^+$ calcd: 327.2278; found: 327.2286. HPLC: method A t_R = 19.31 min (>99%); method B t_R = 17.43 min (96%).

7.6 References

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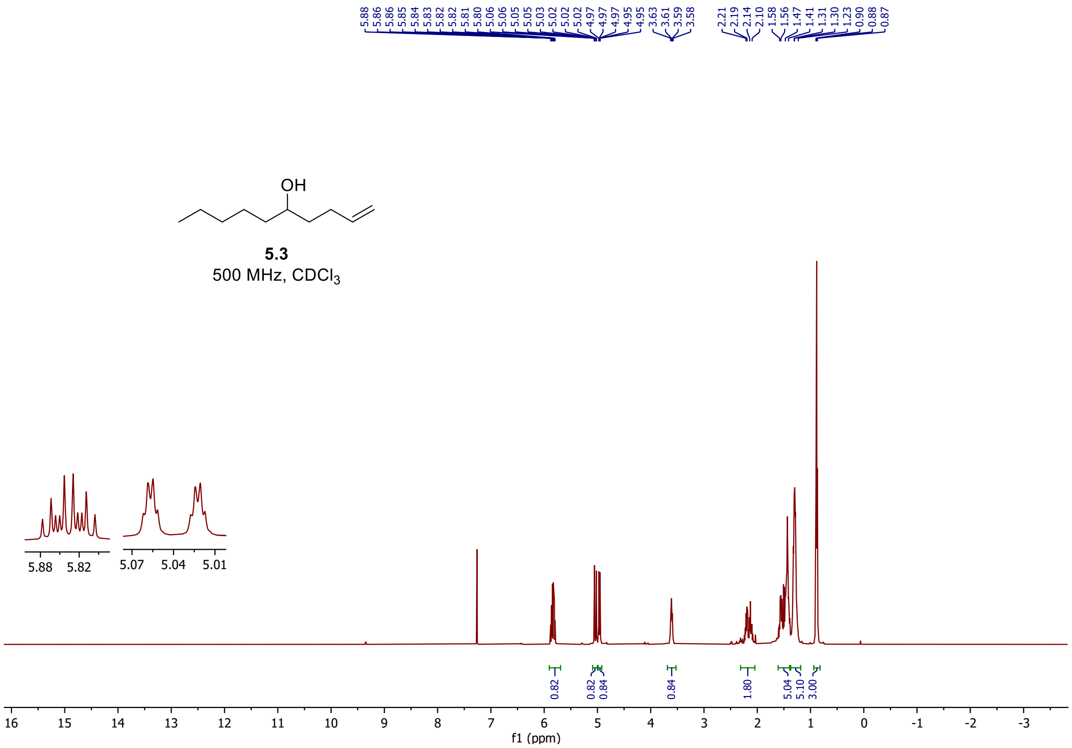
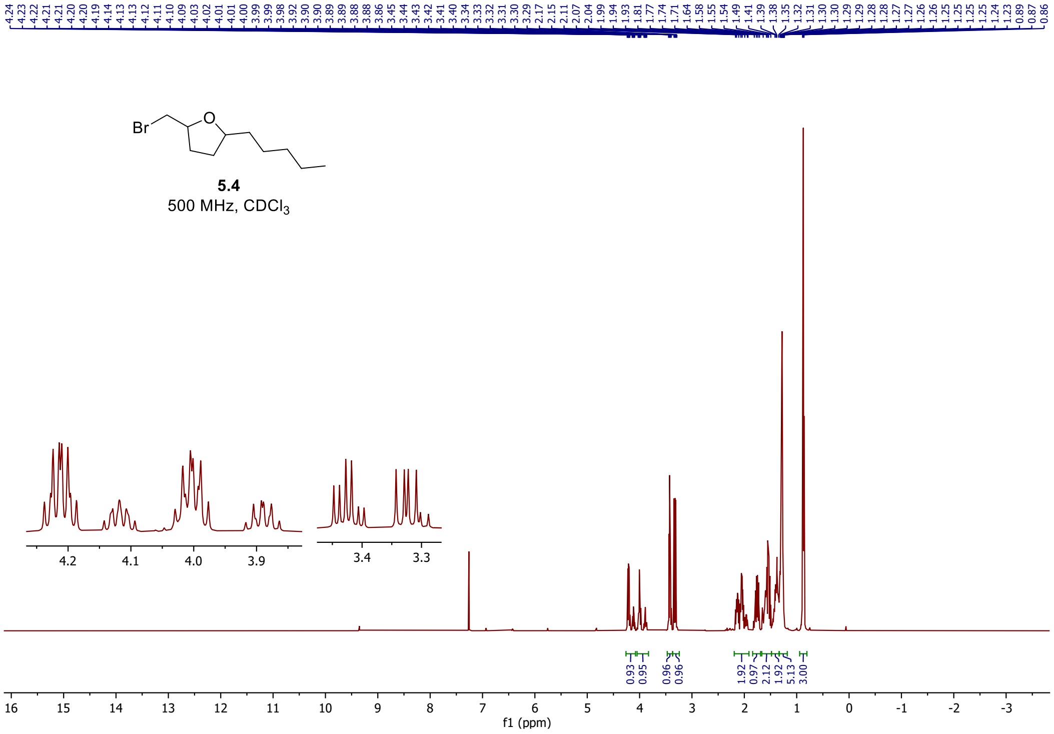
Appendix I. Copies of NMR Spectra for Chapter 5

^{1}H spectrum of **5.3**


5.3
500 MHz, $CDCl_3$

^{1}H spectra of **5.4**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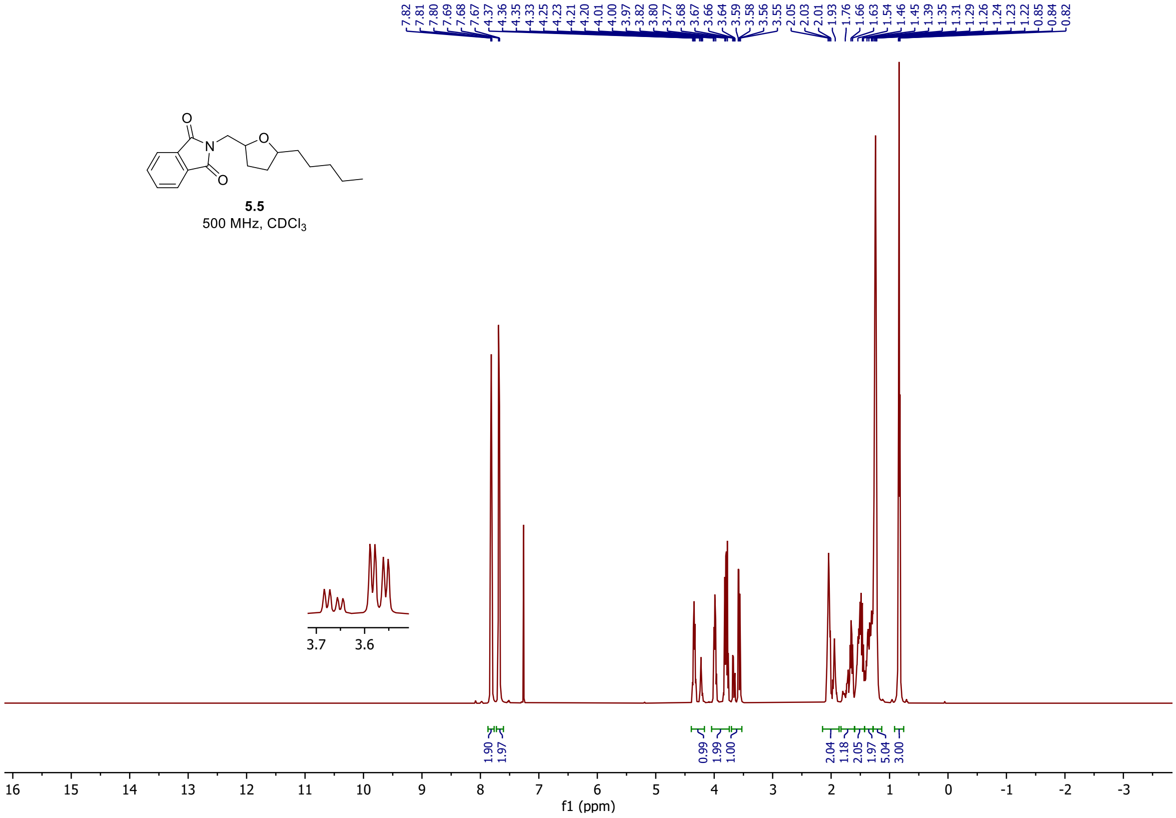
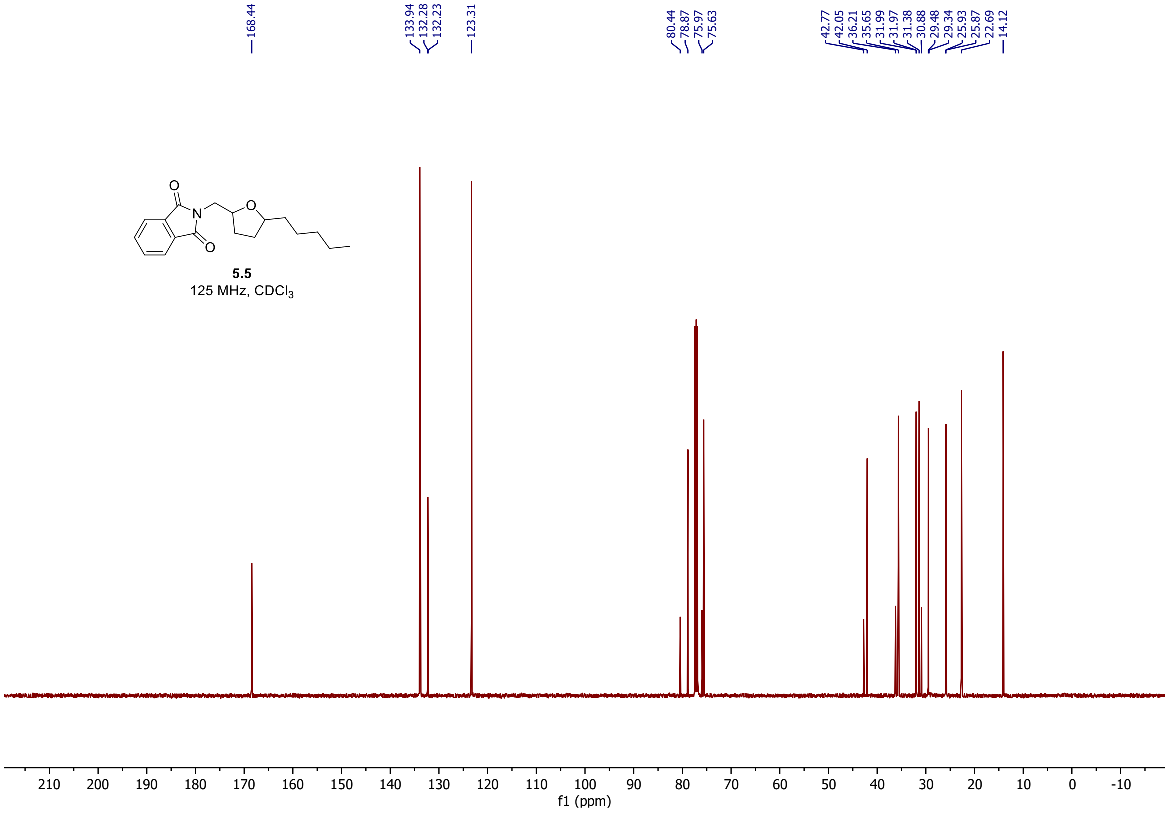
^{1}H and ^{13}C spectra of **5.5**





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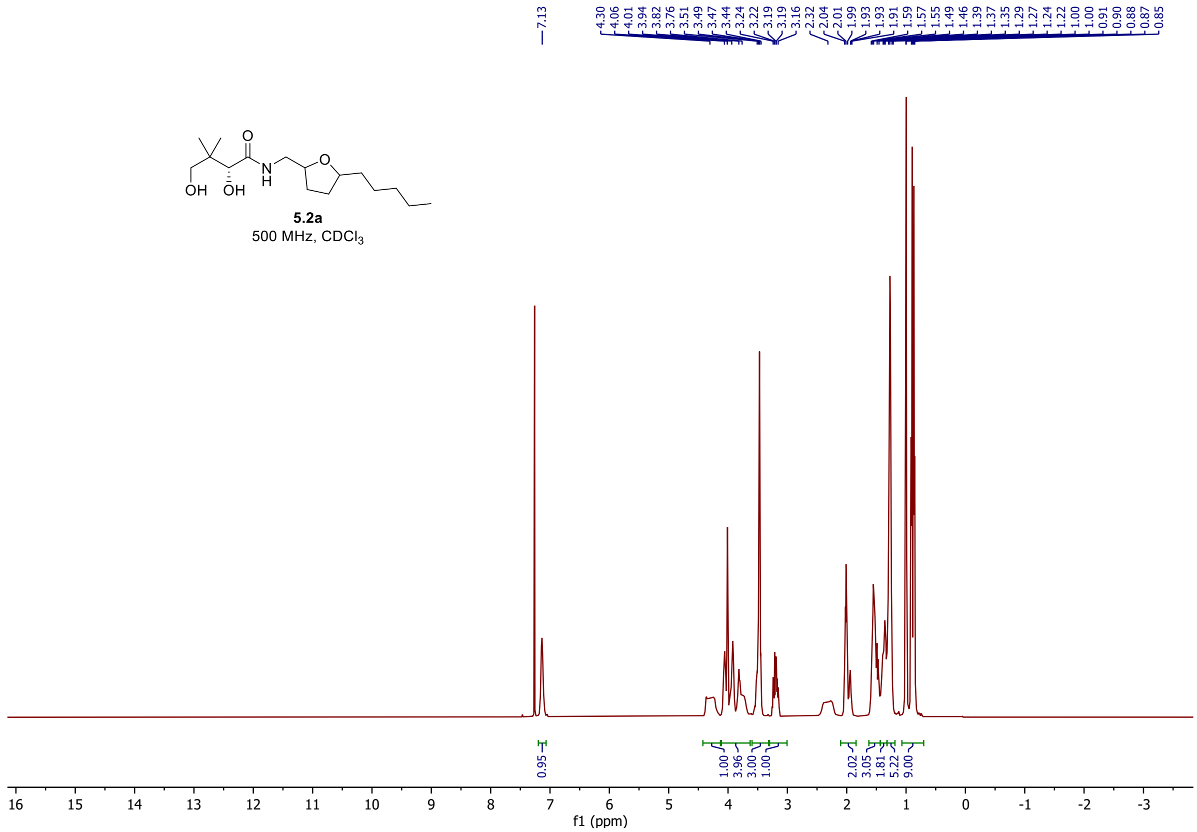

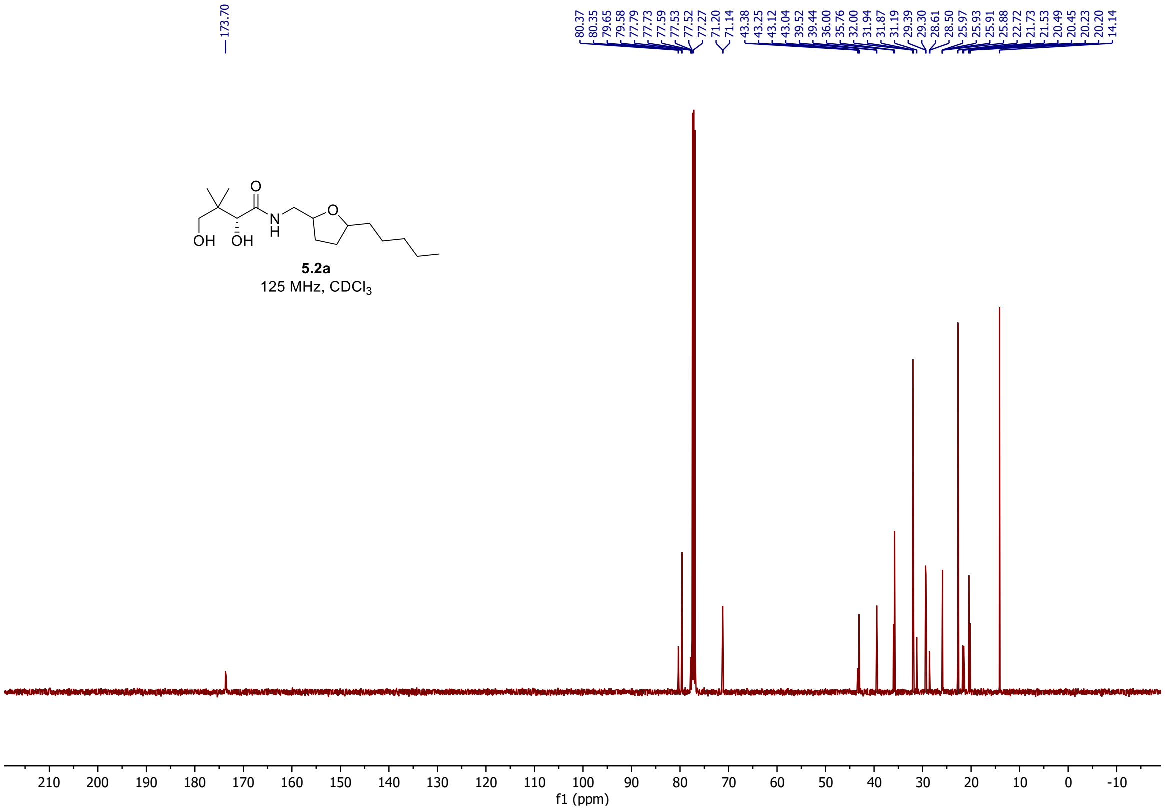

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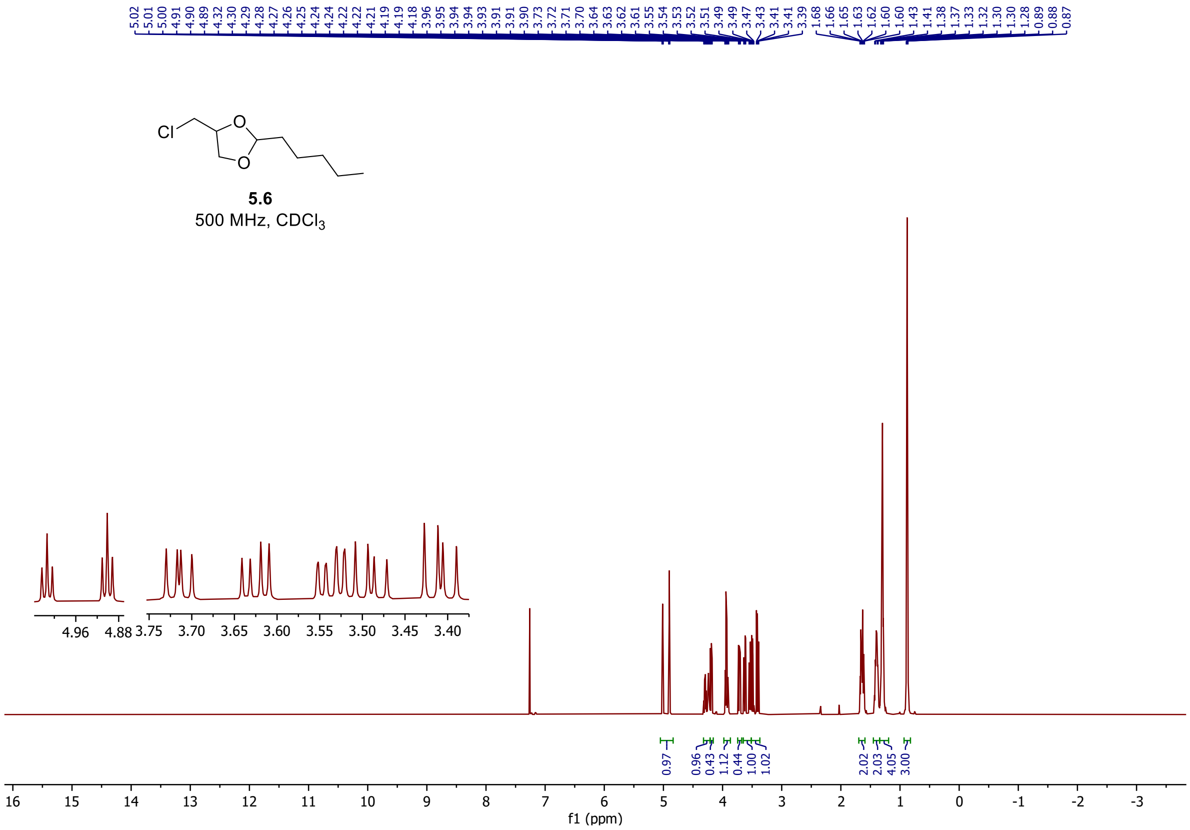

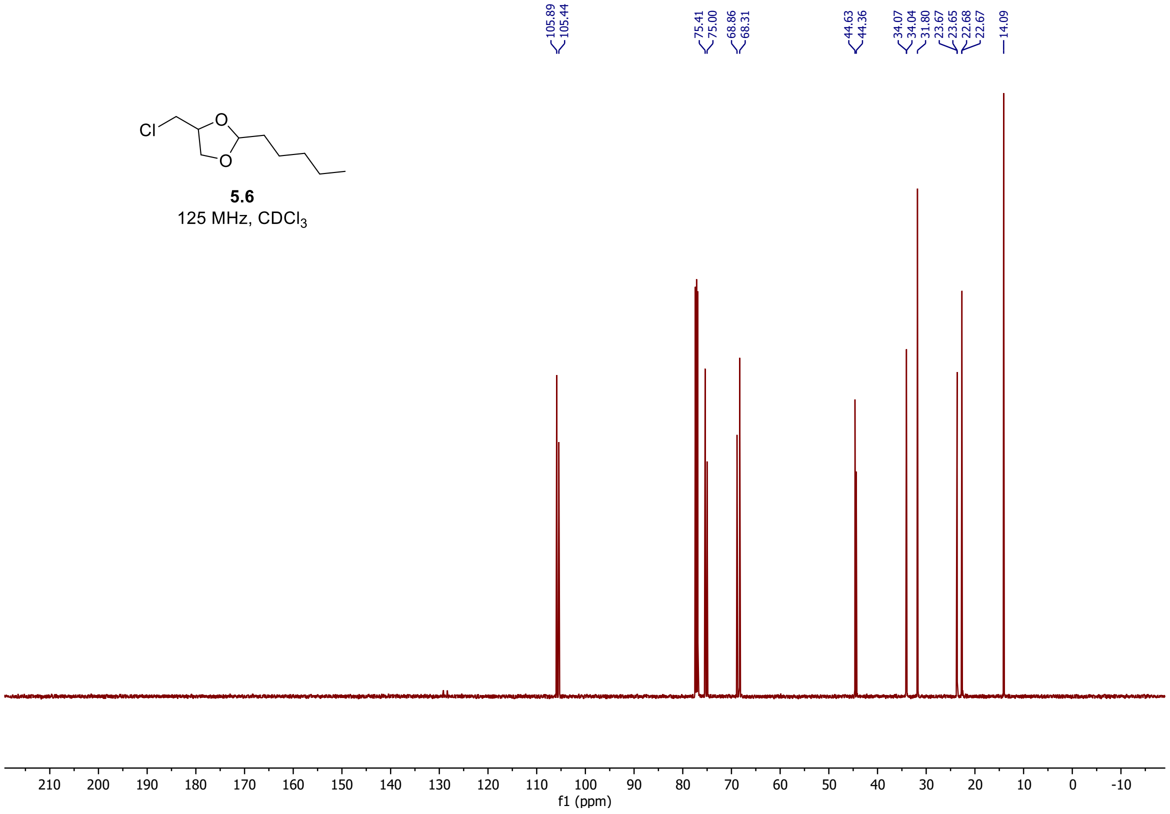

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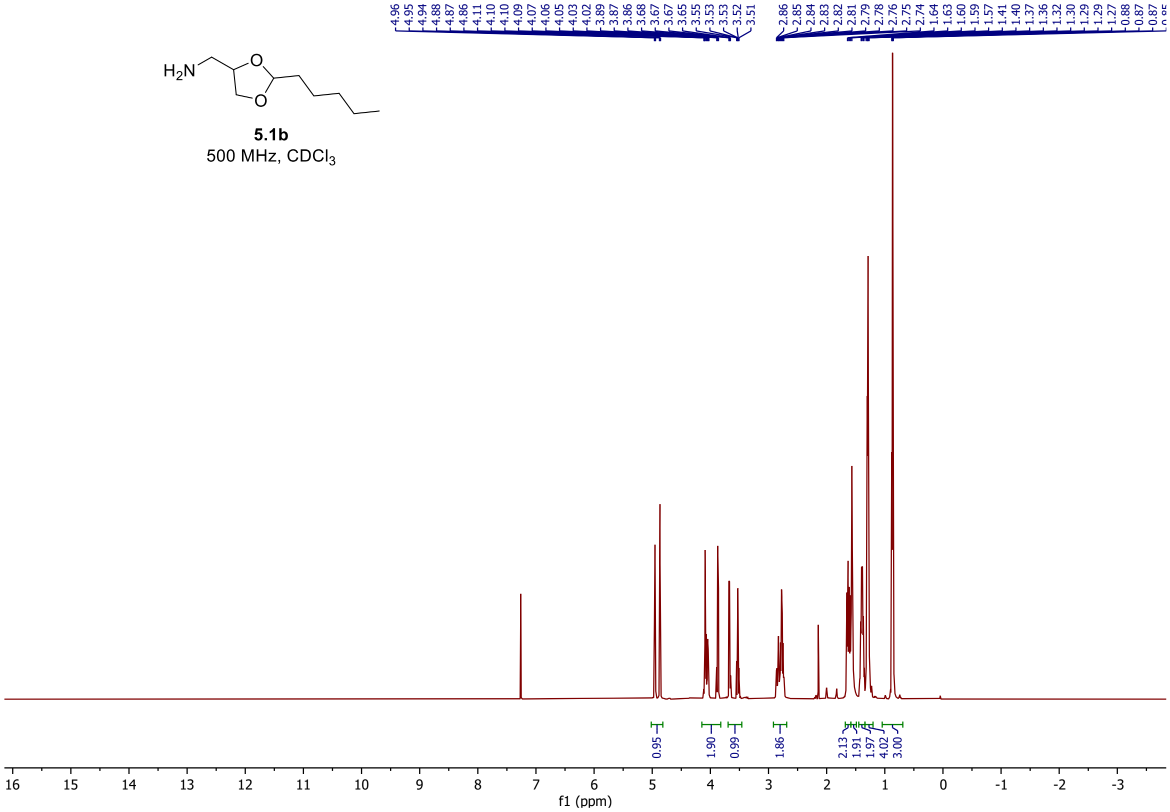

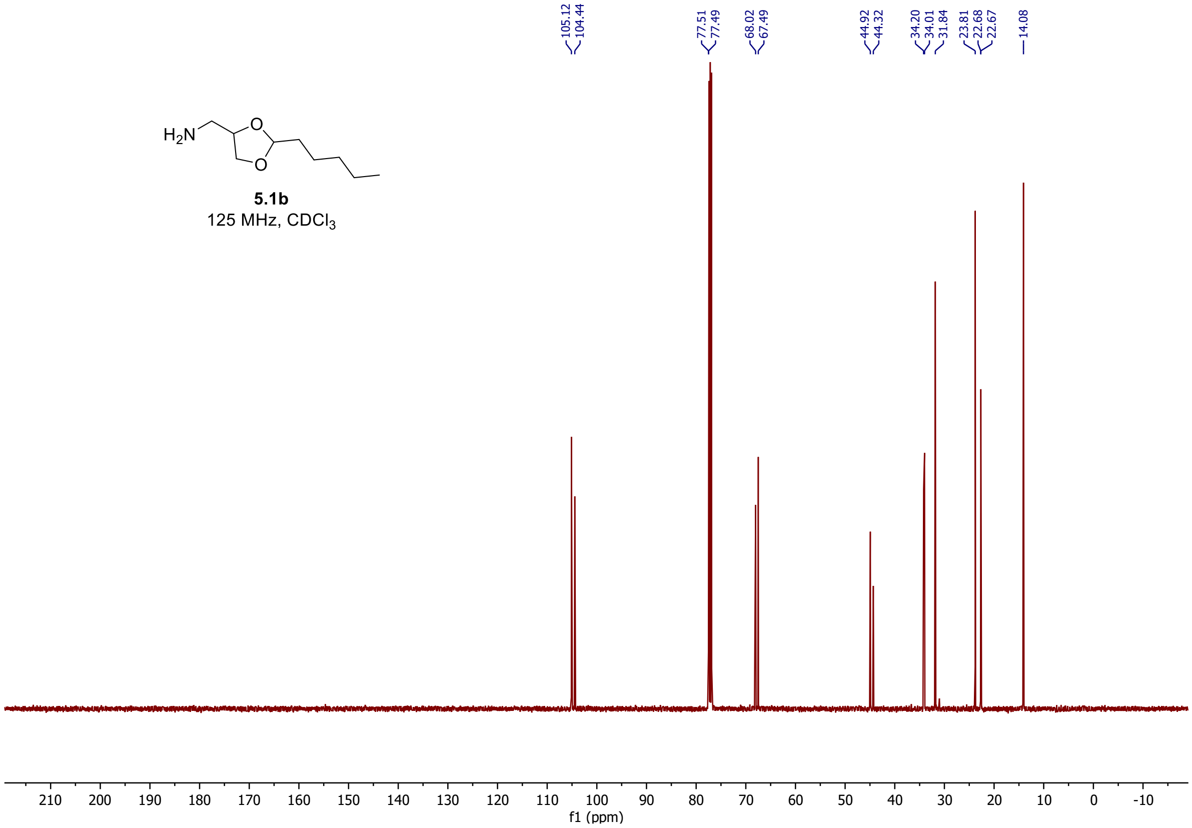

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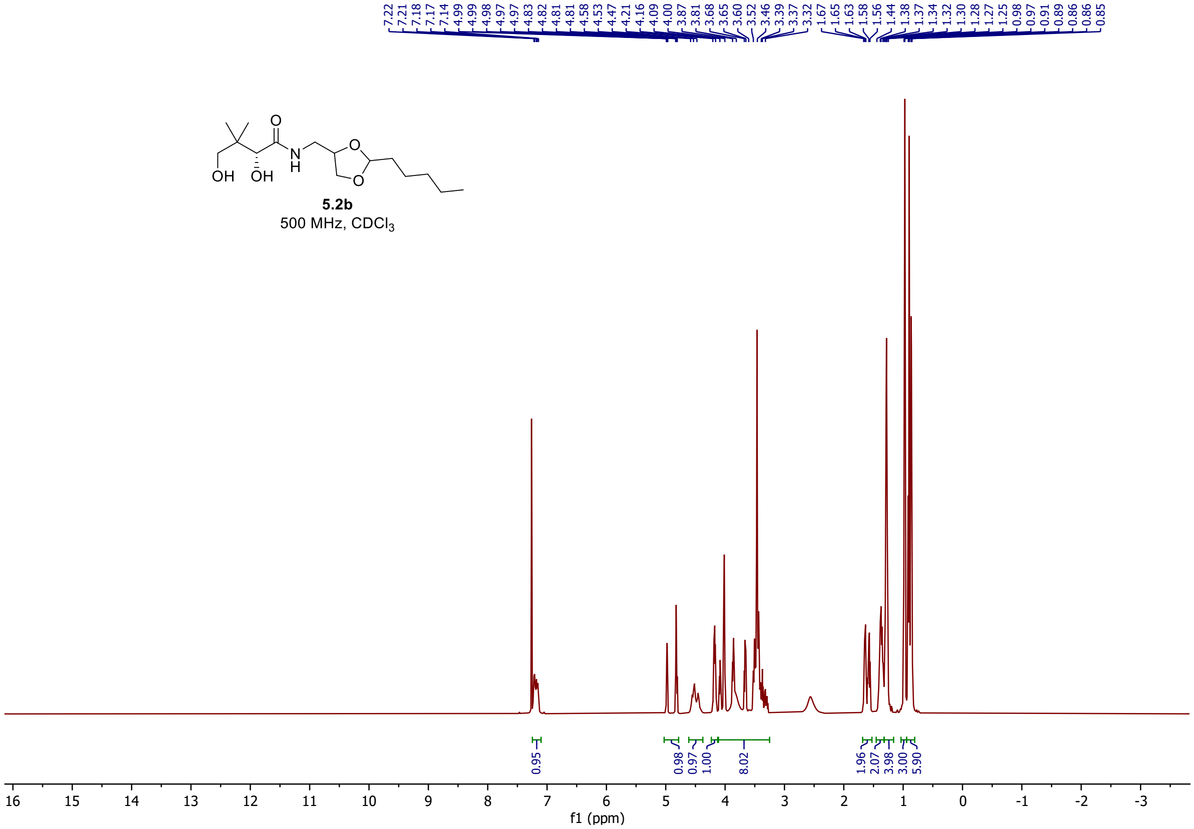

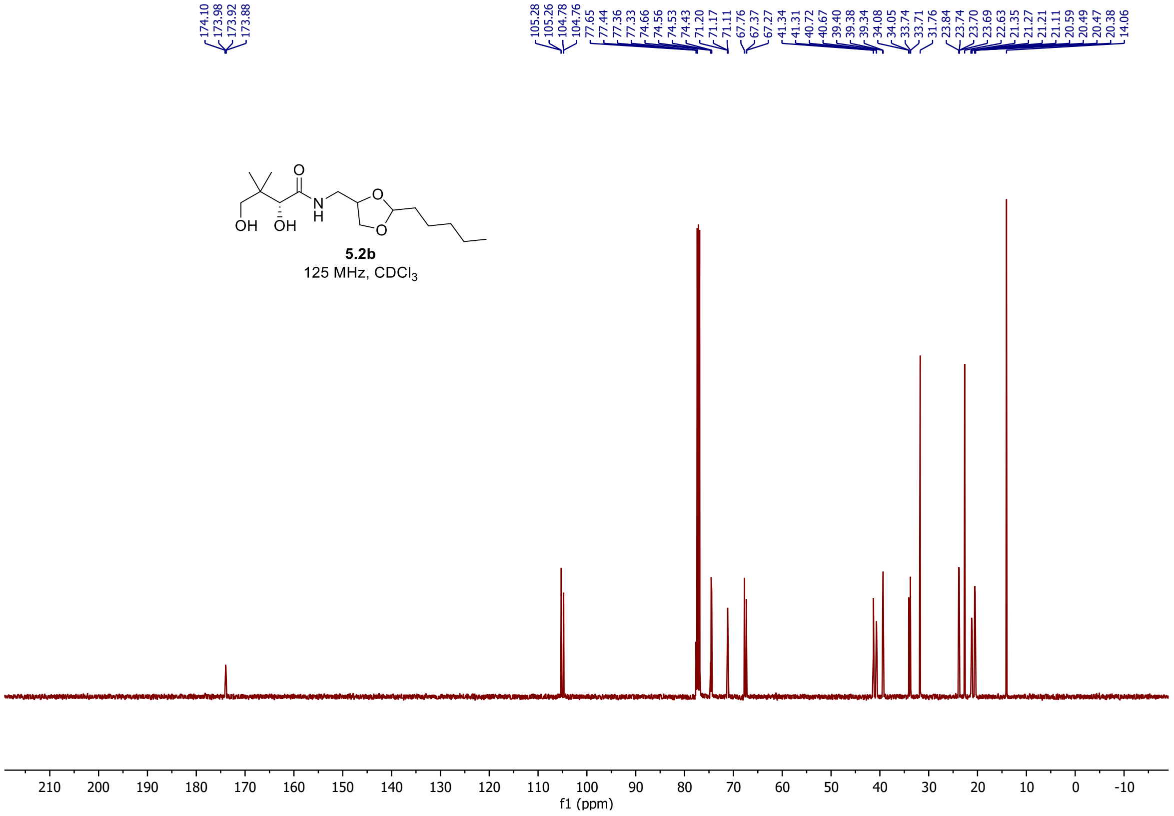

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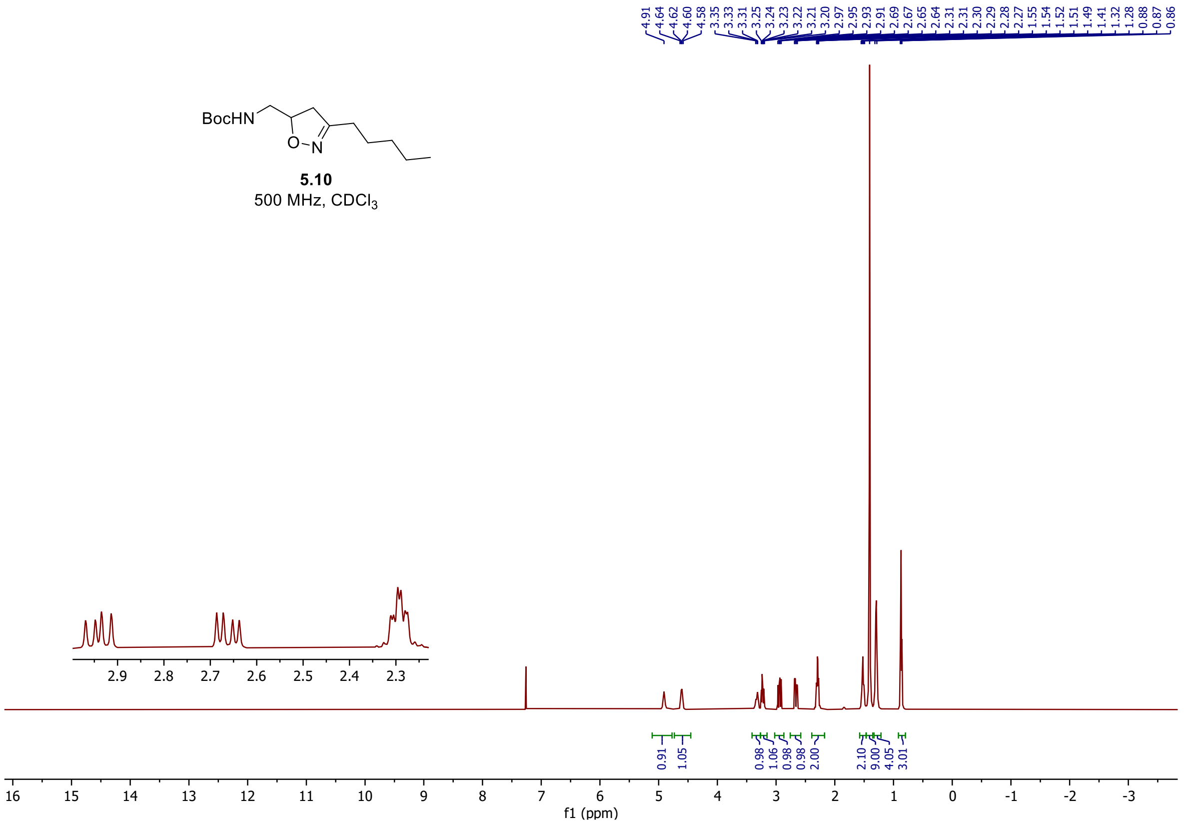

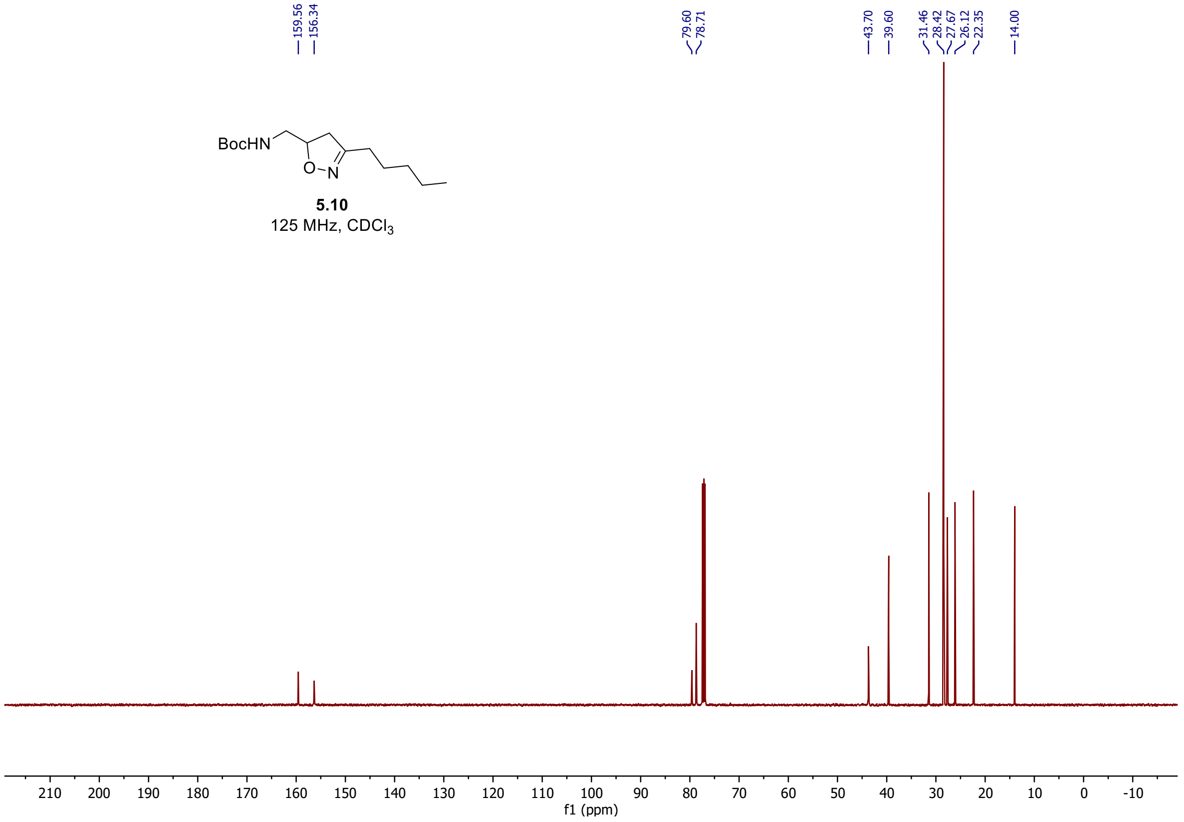

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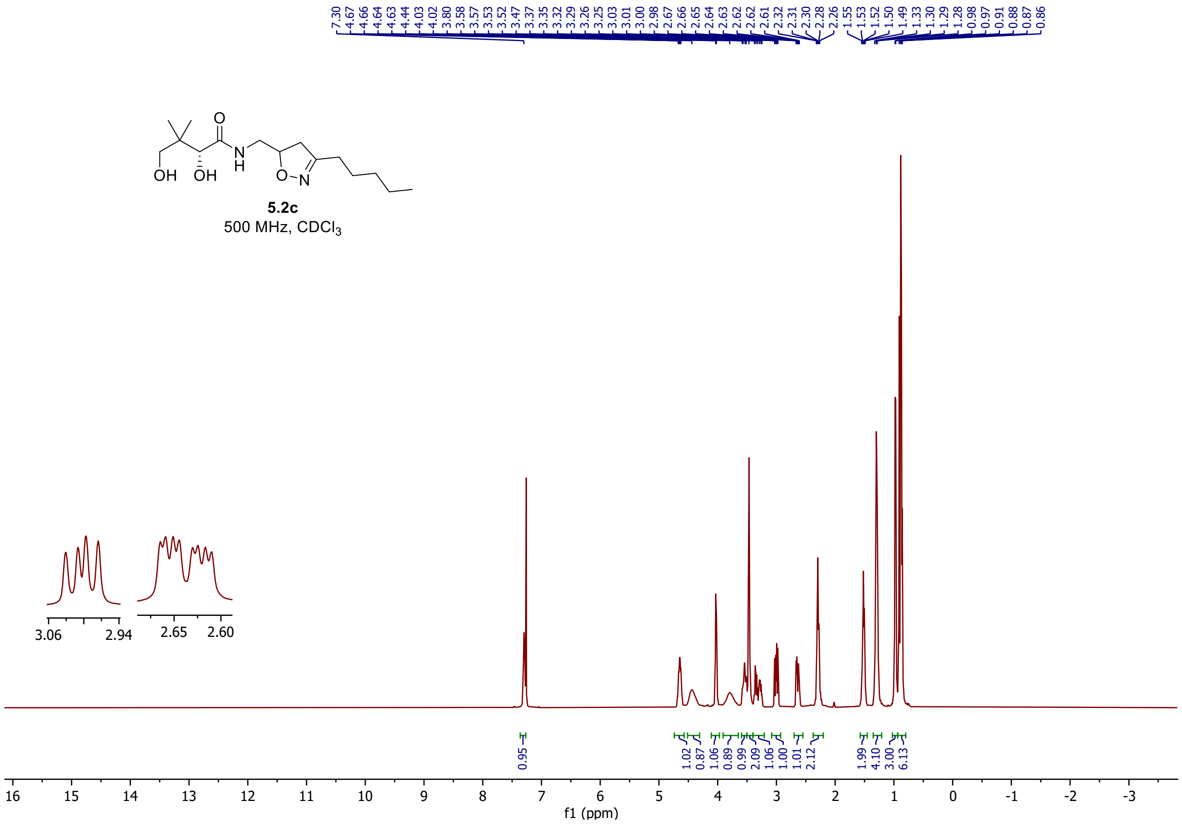

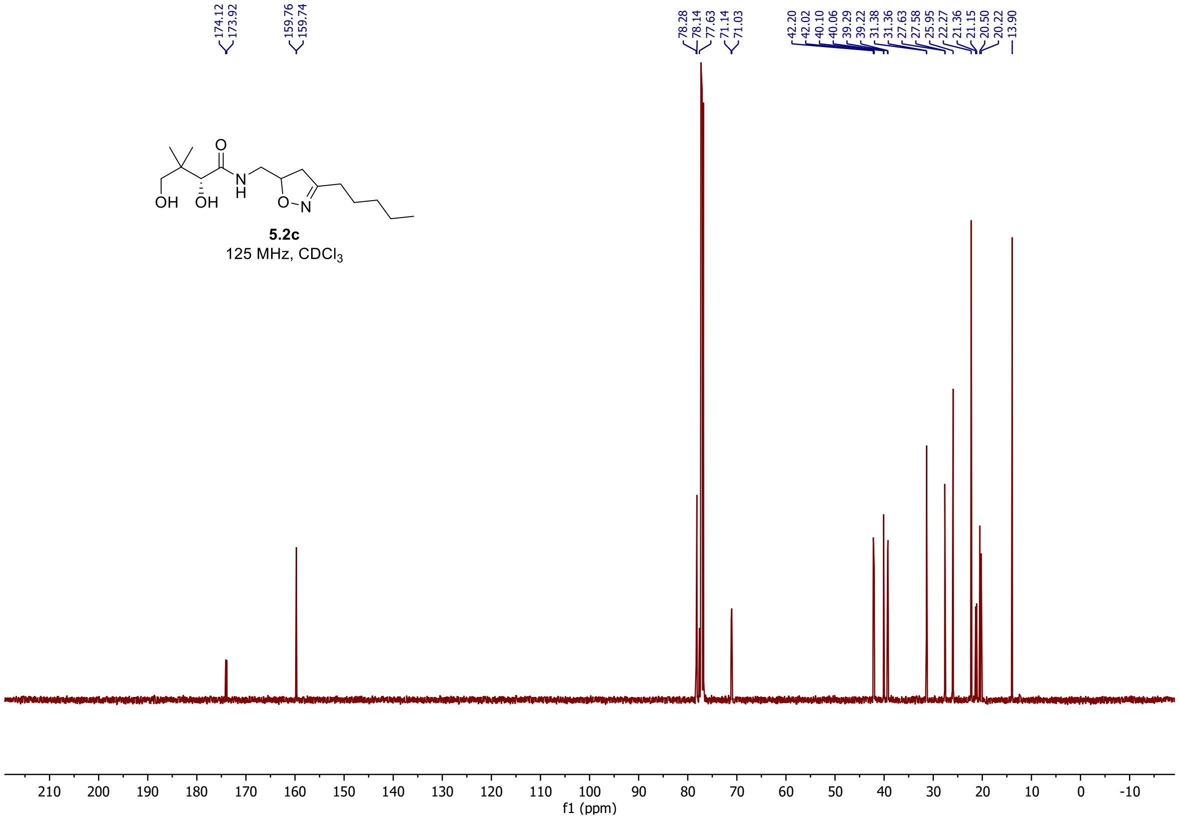

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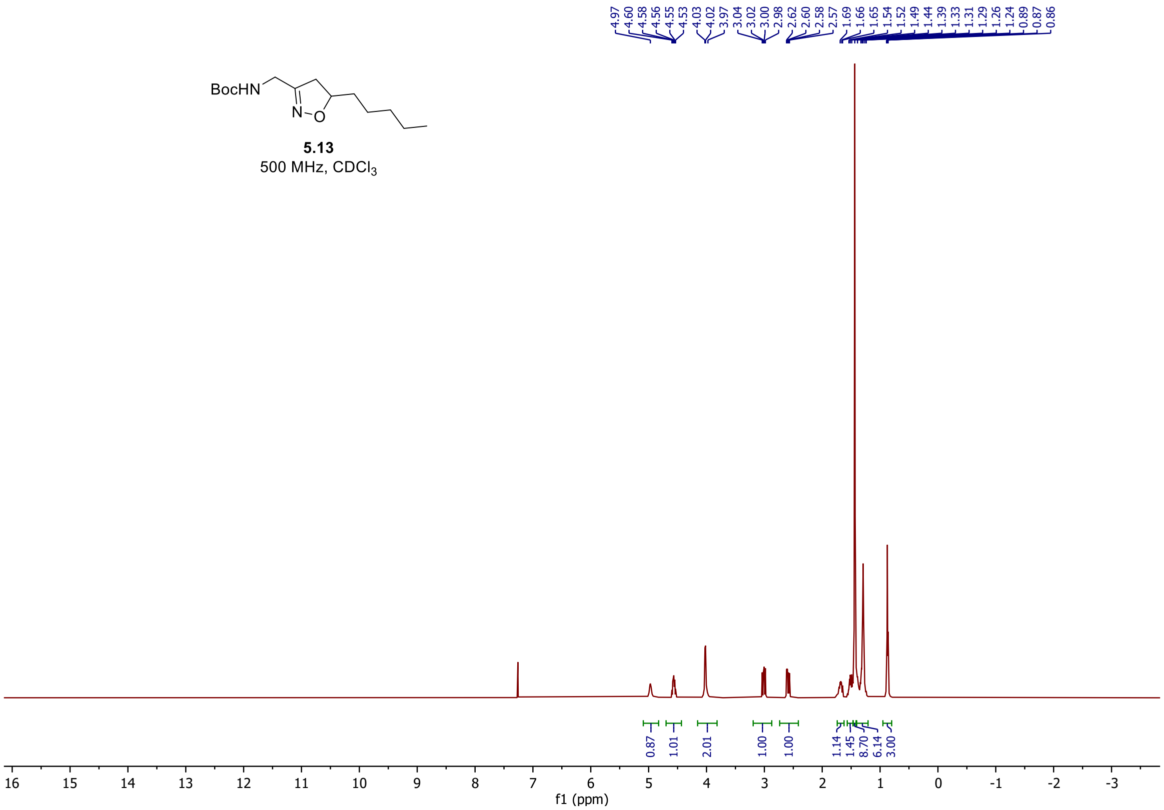

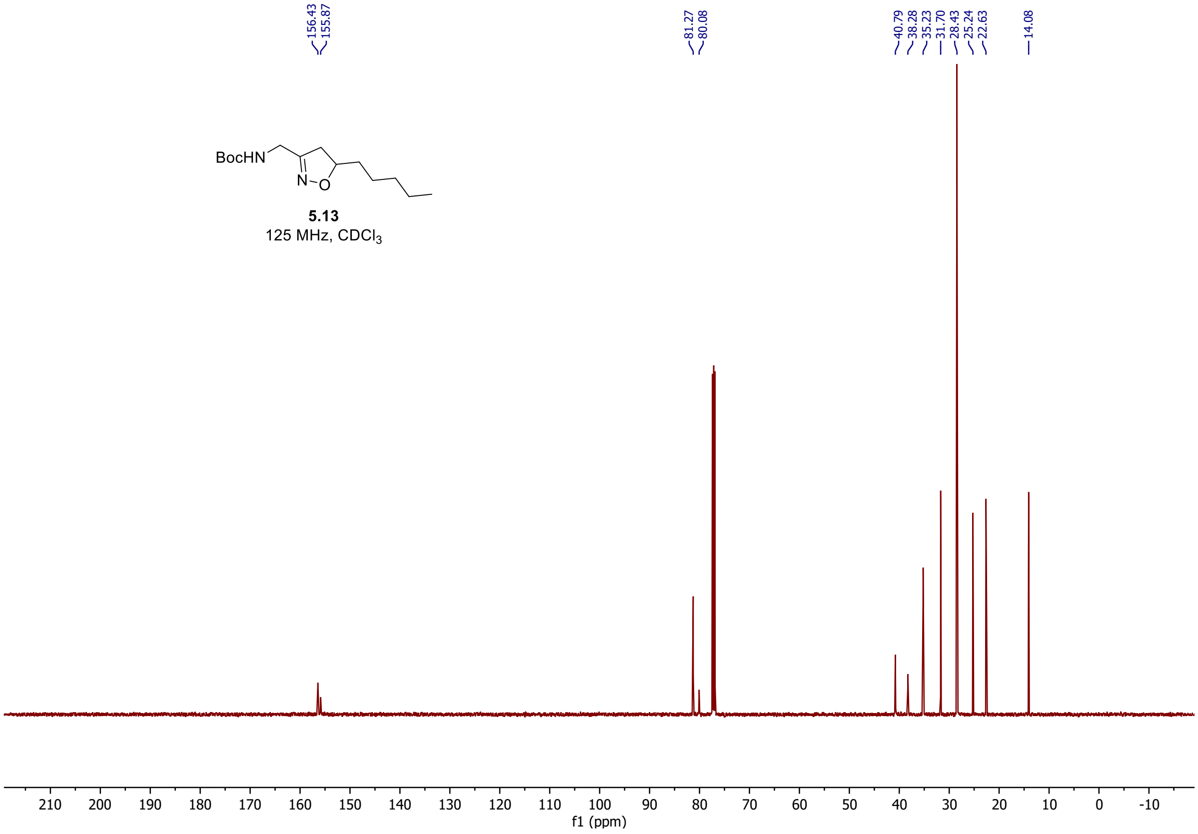

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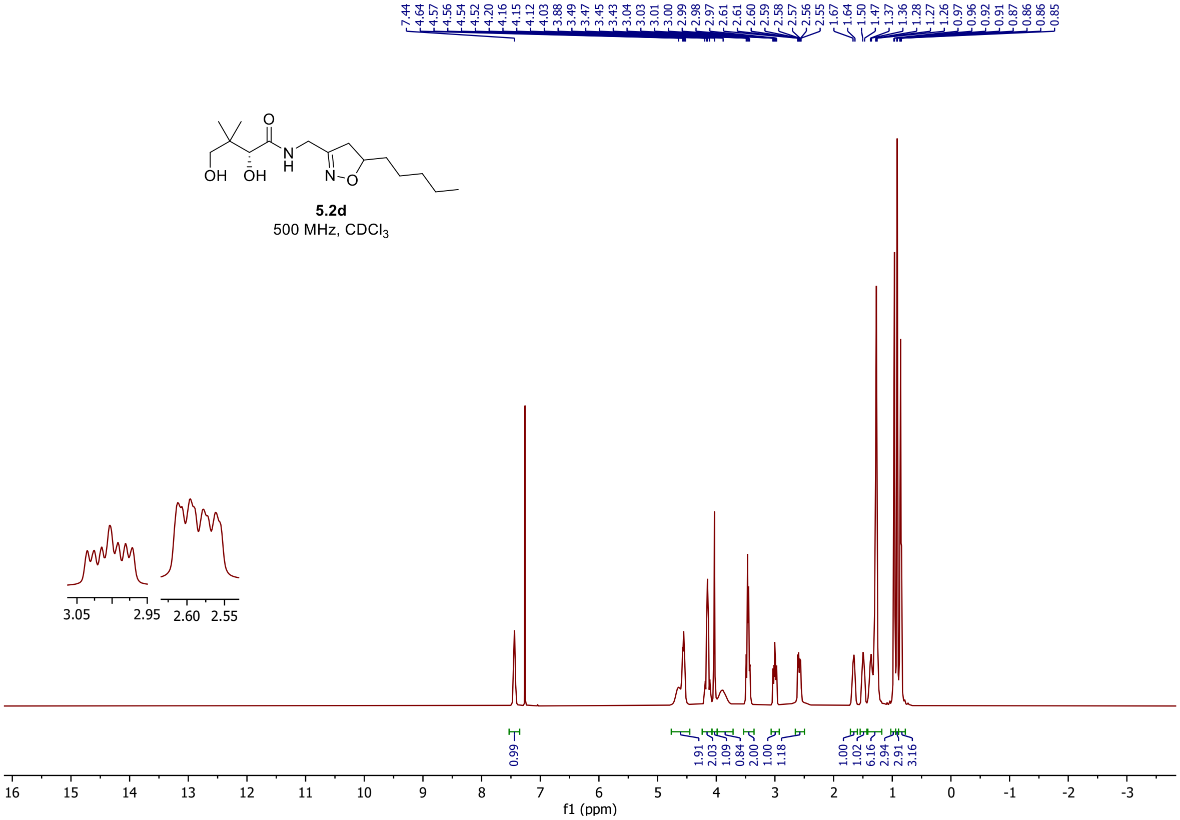

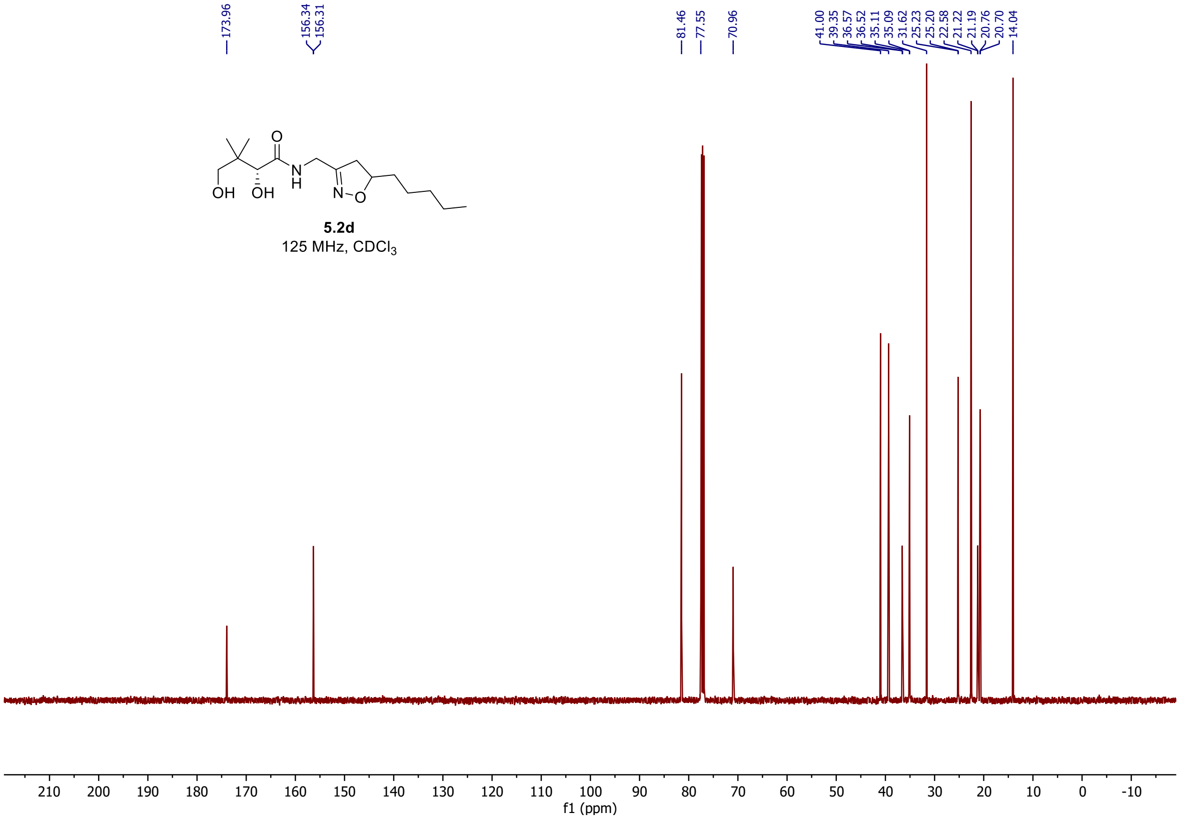

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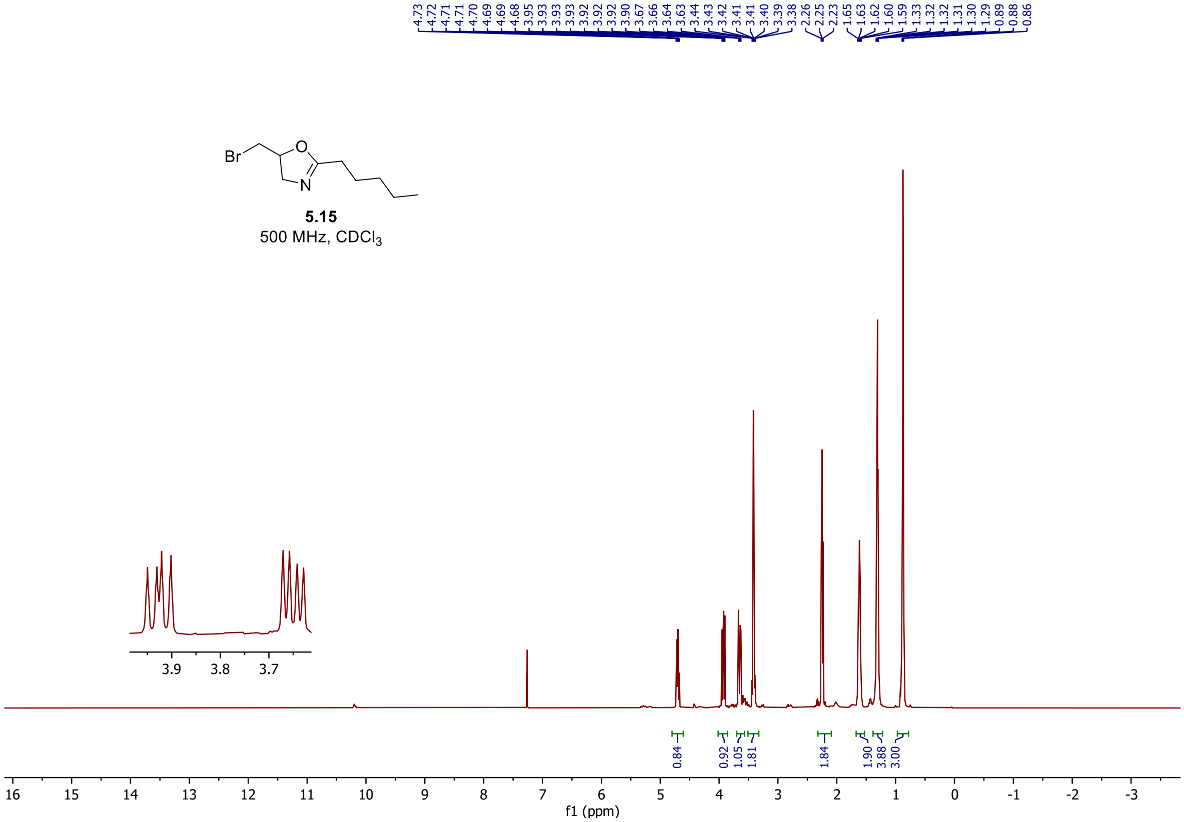

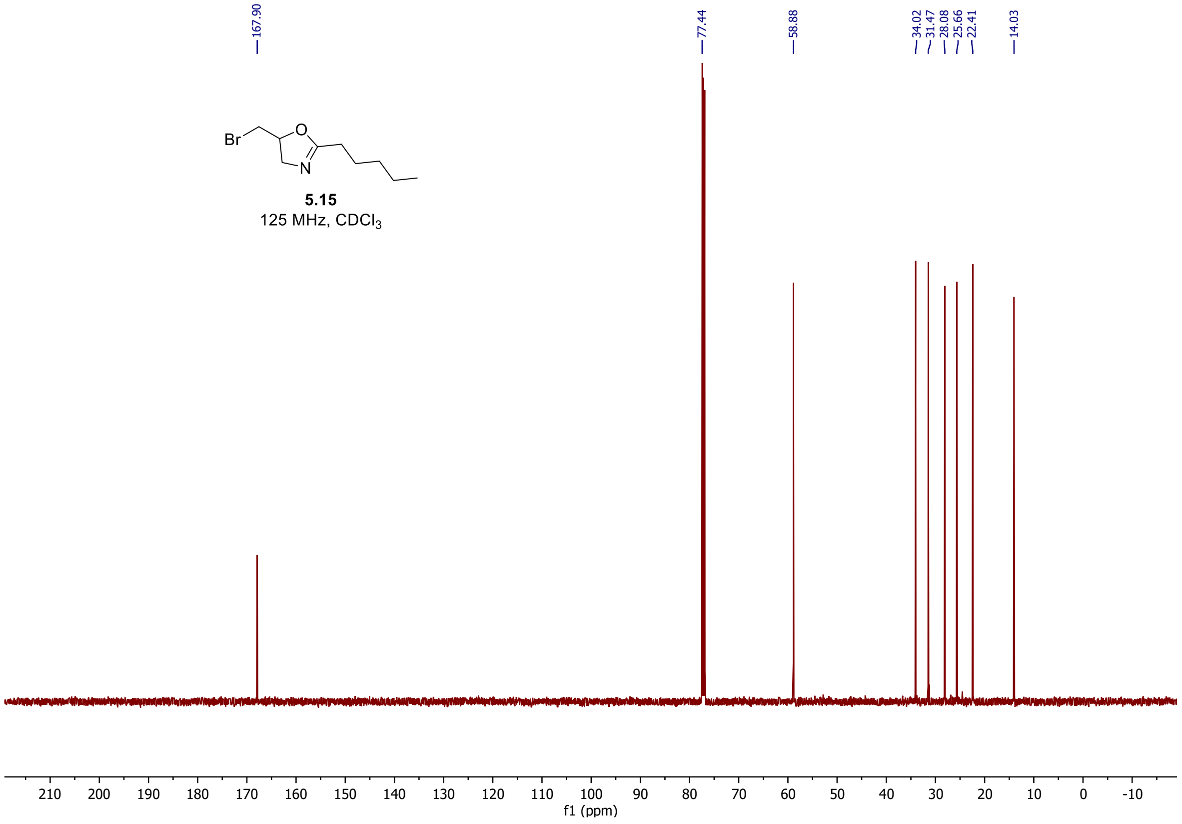

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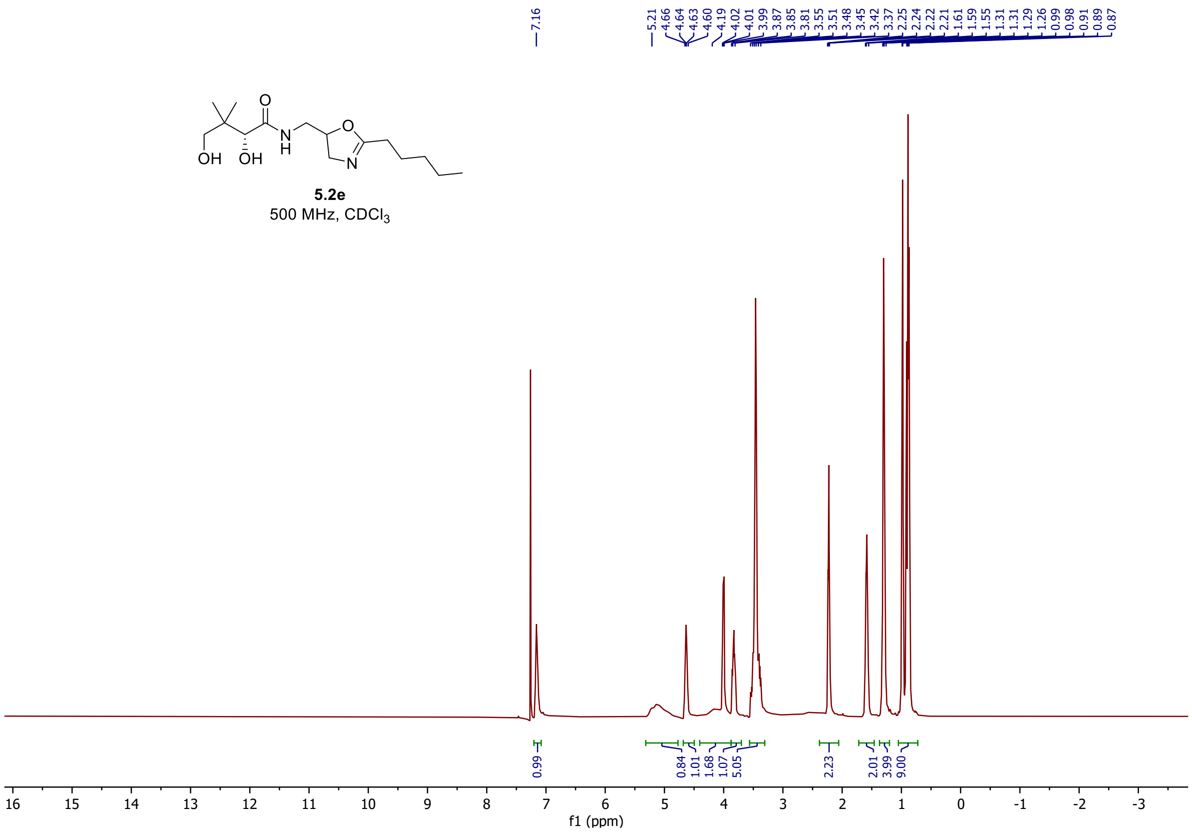

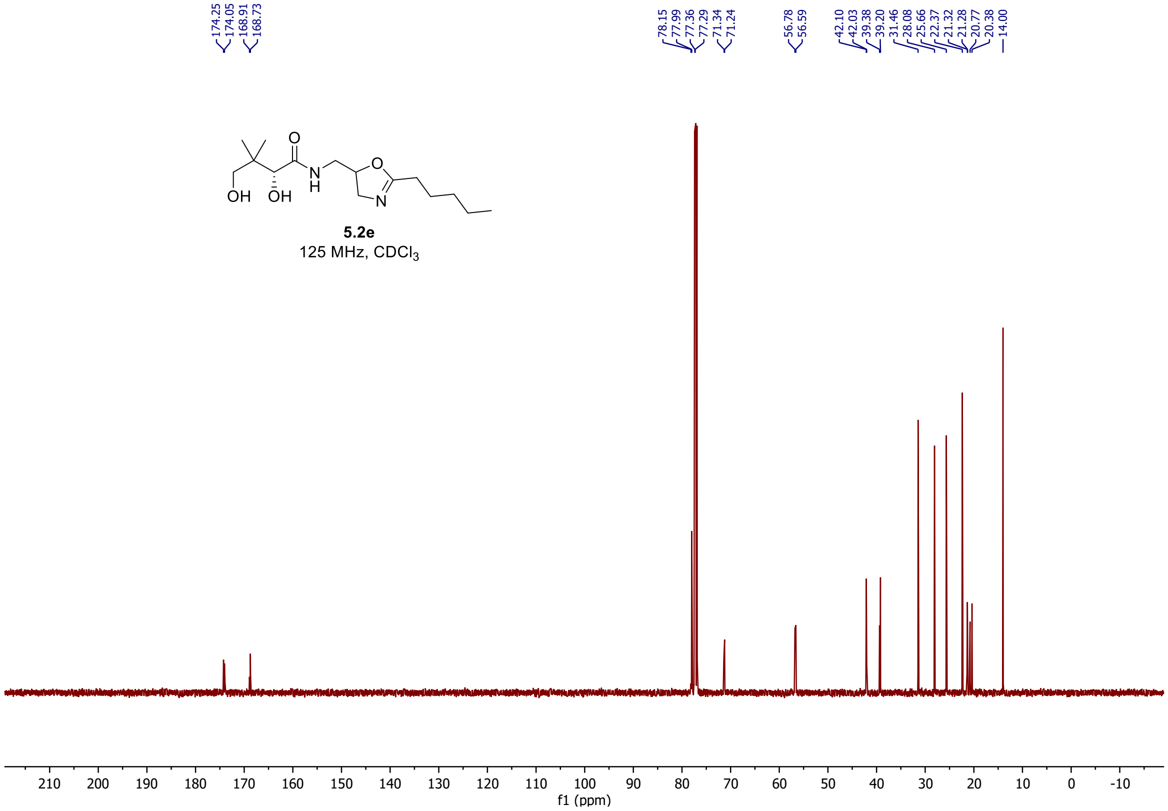

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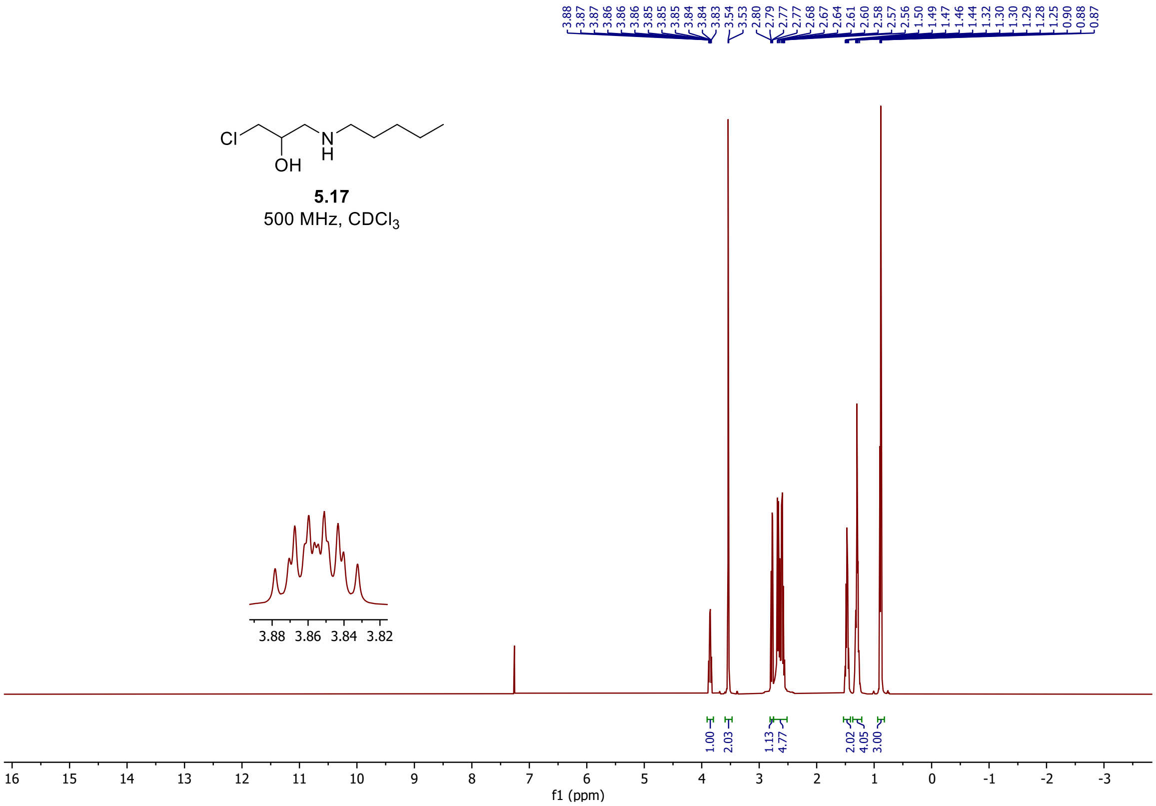

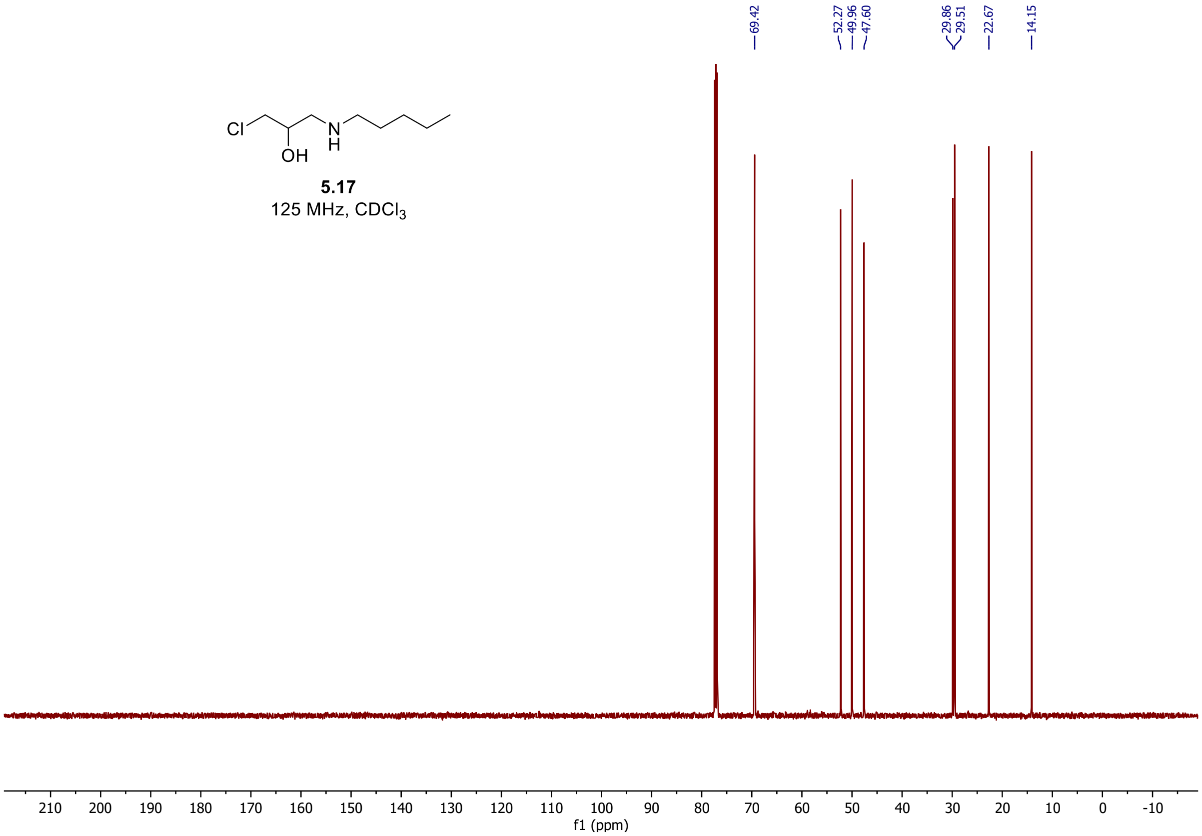

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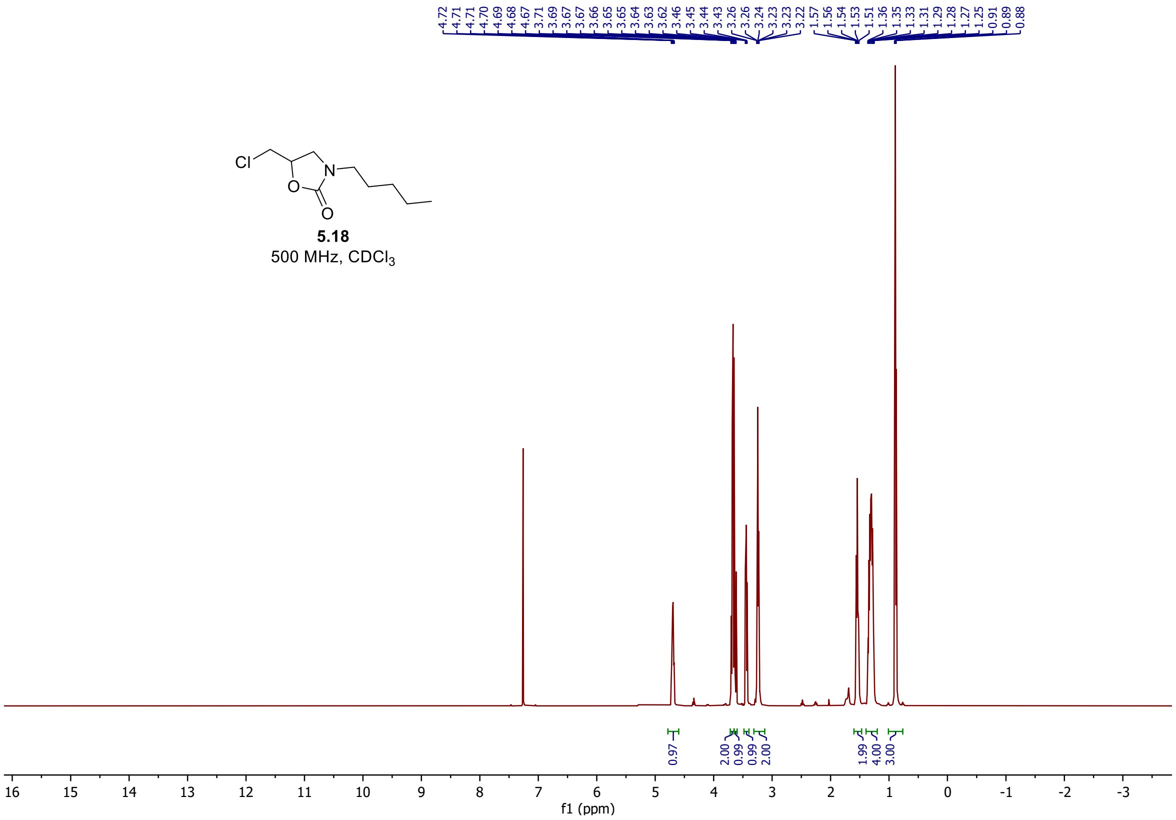

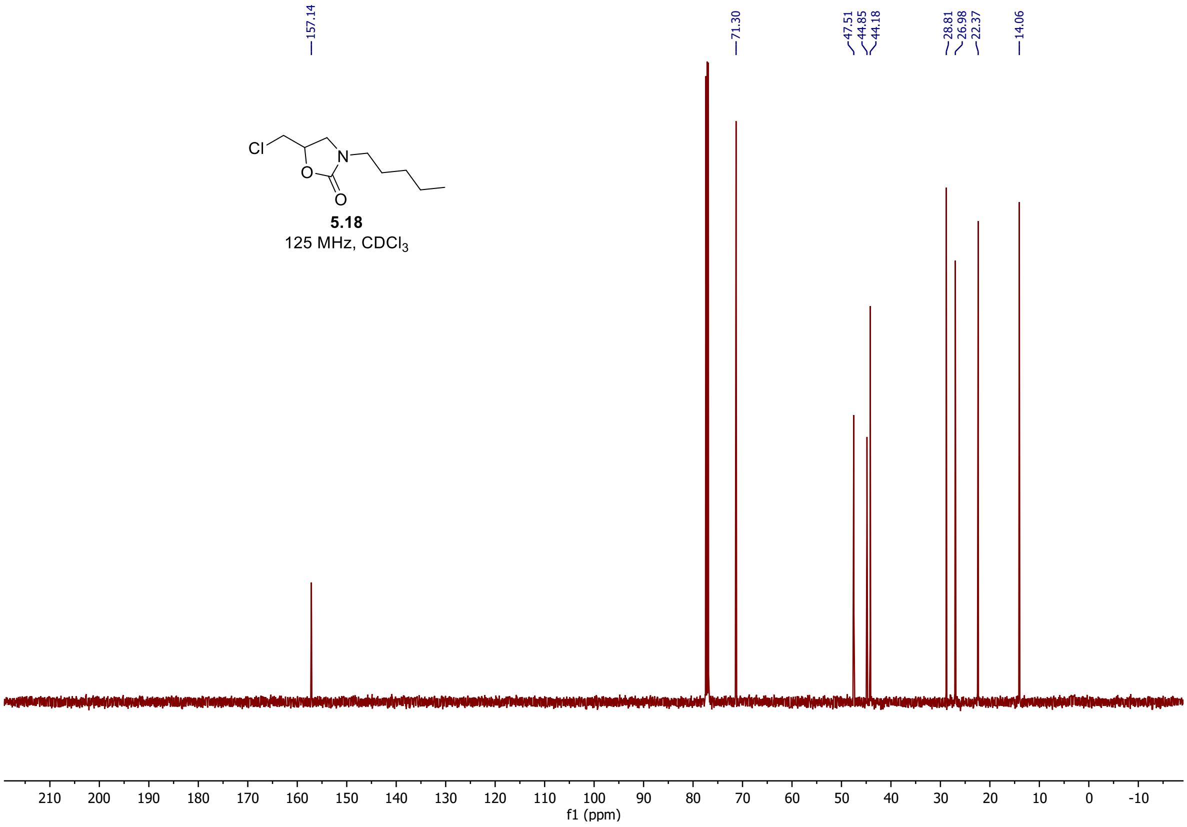

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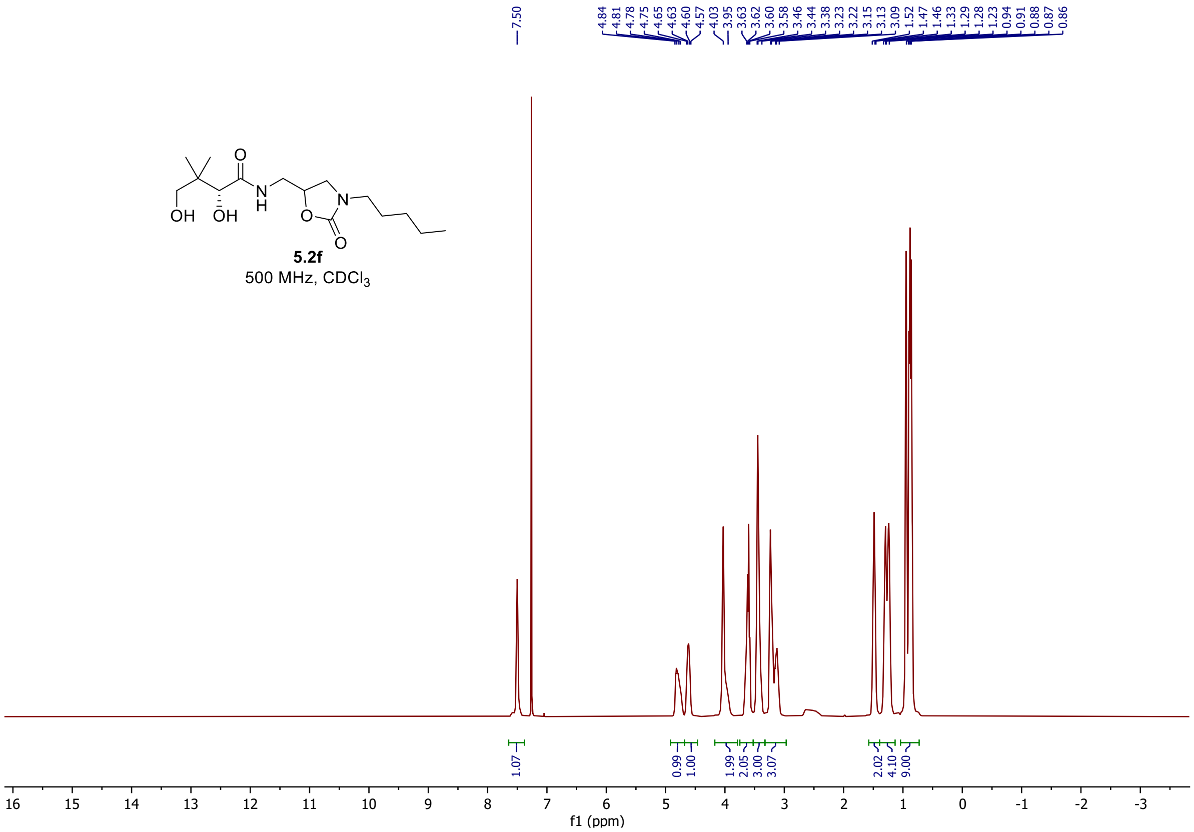

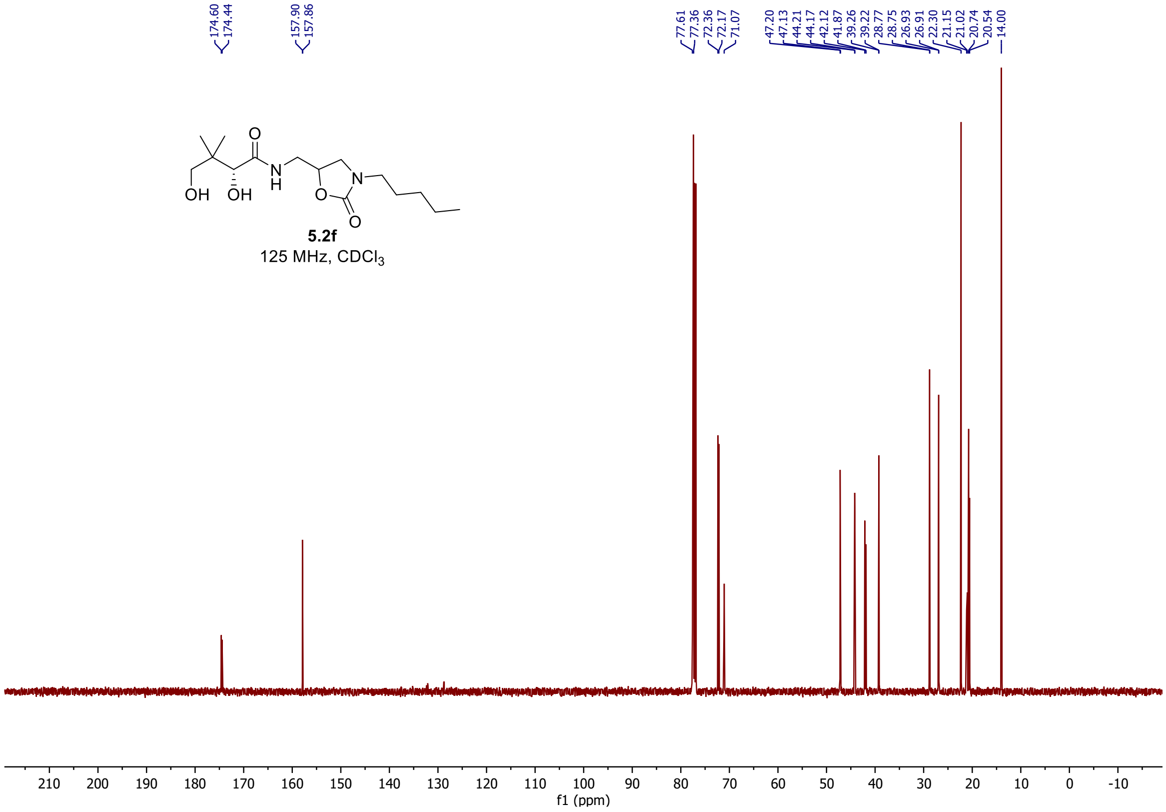

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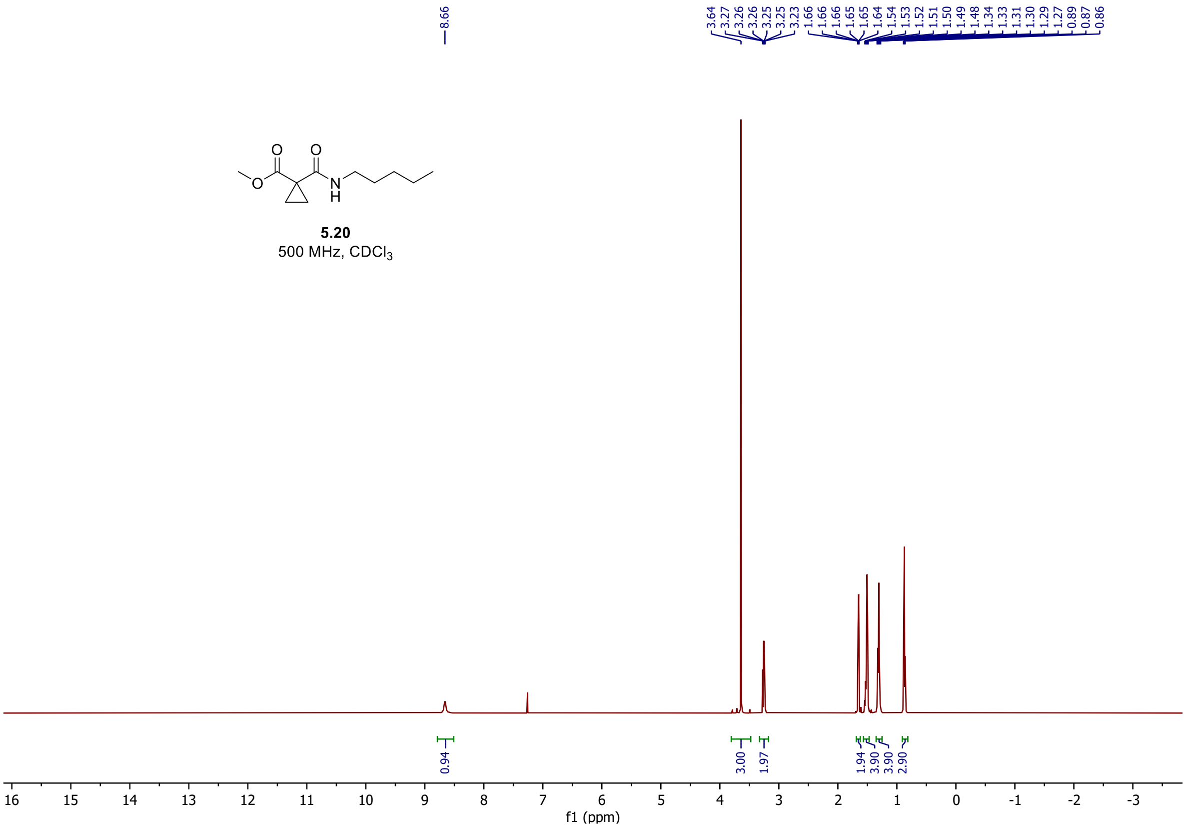
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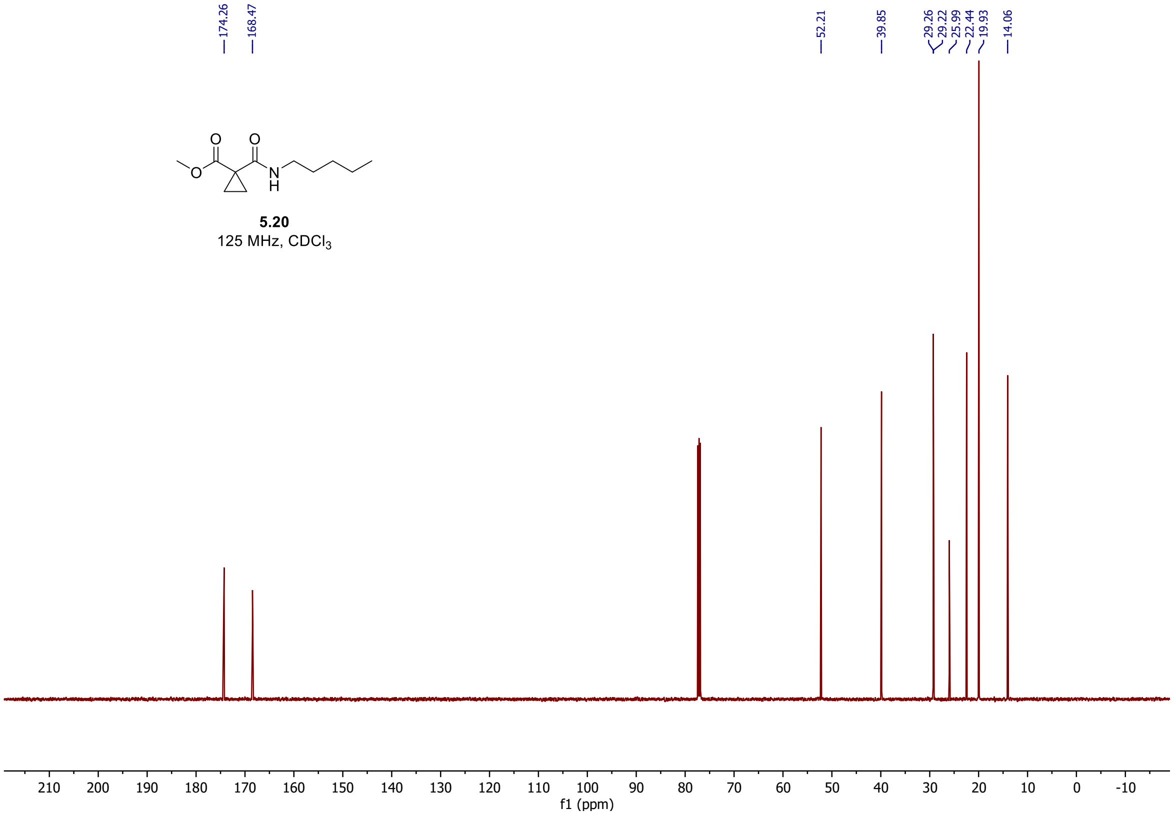
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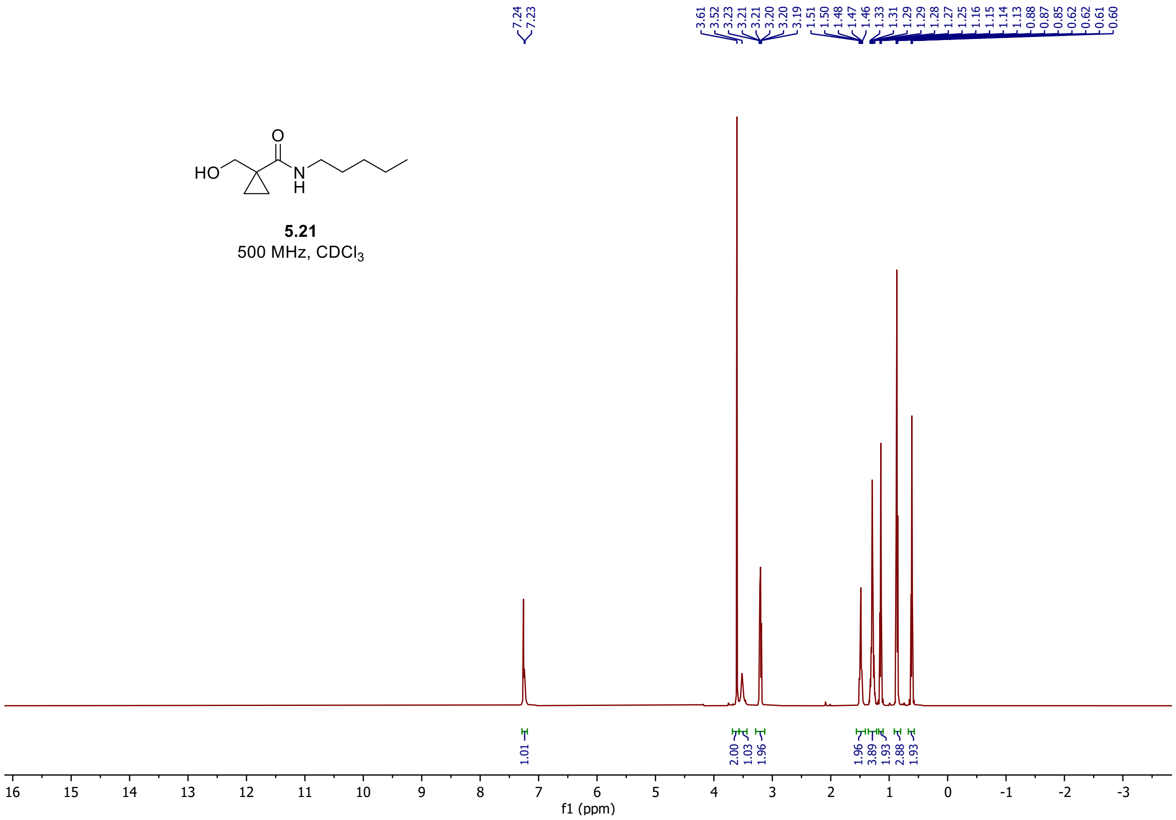

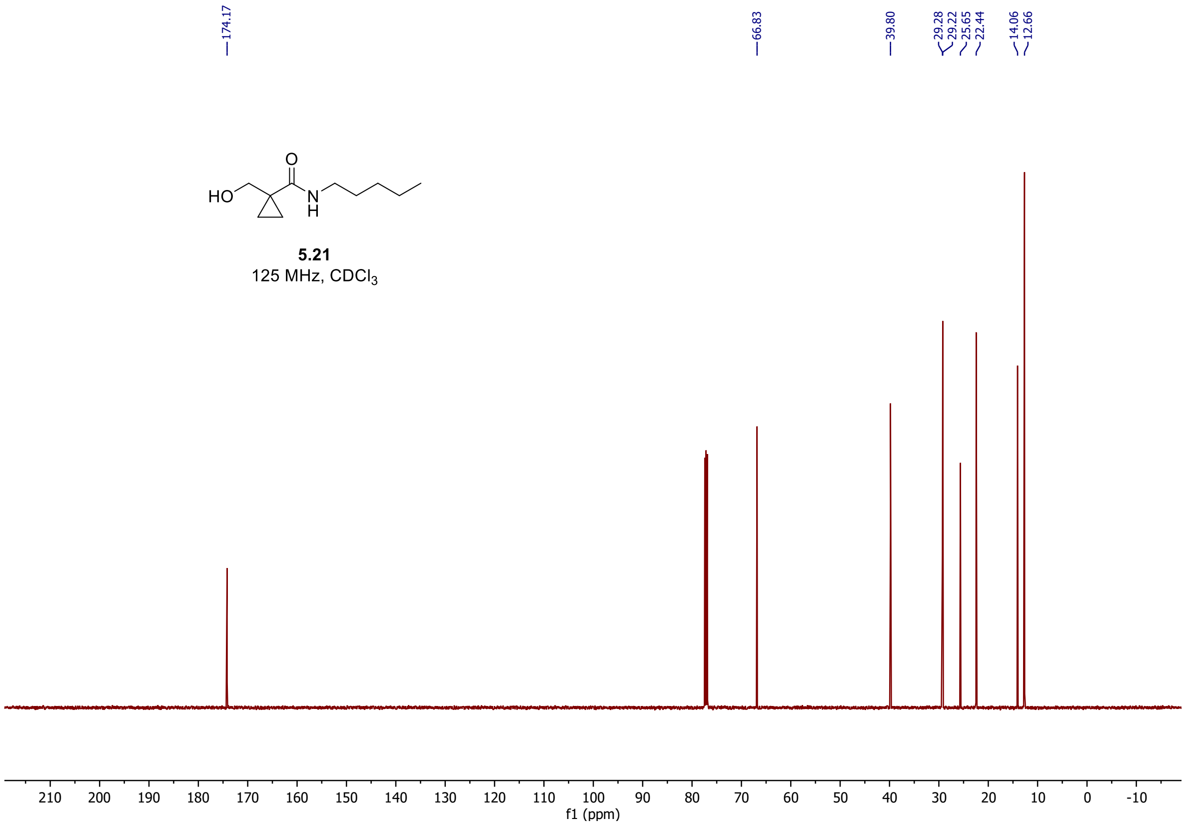

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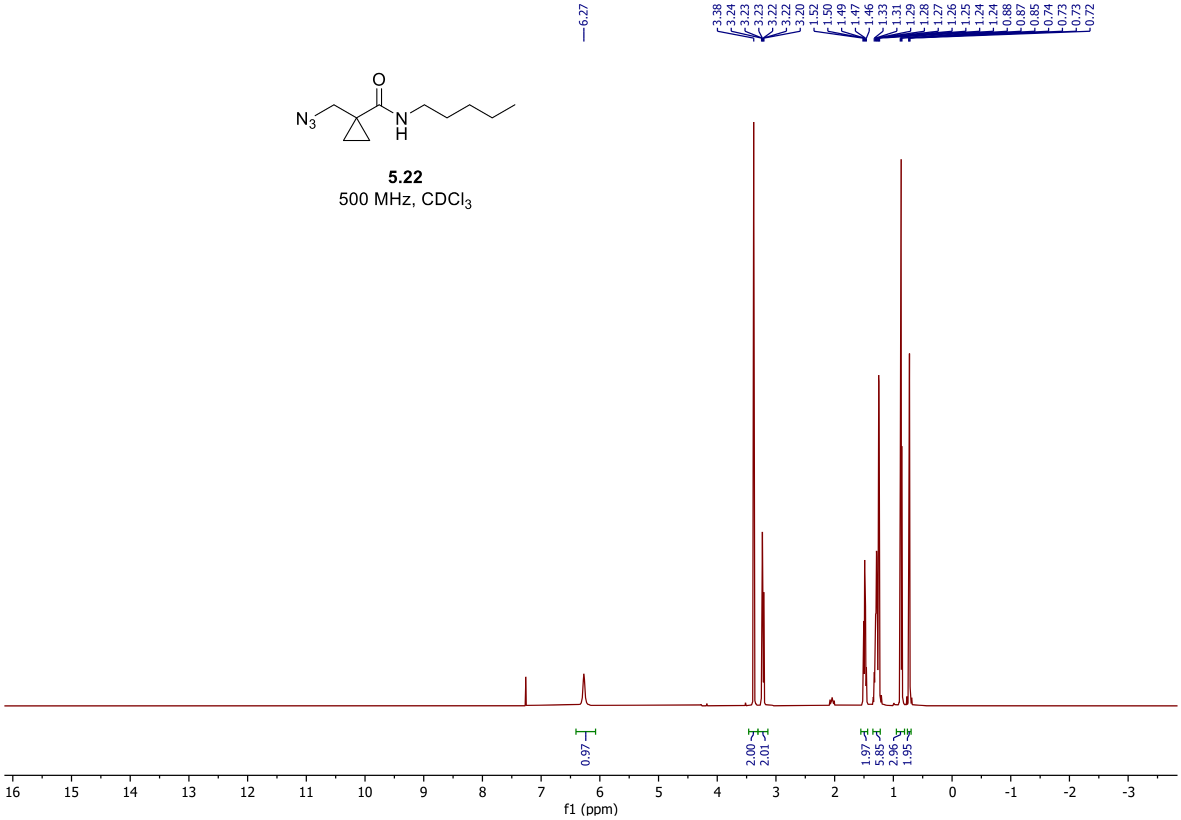

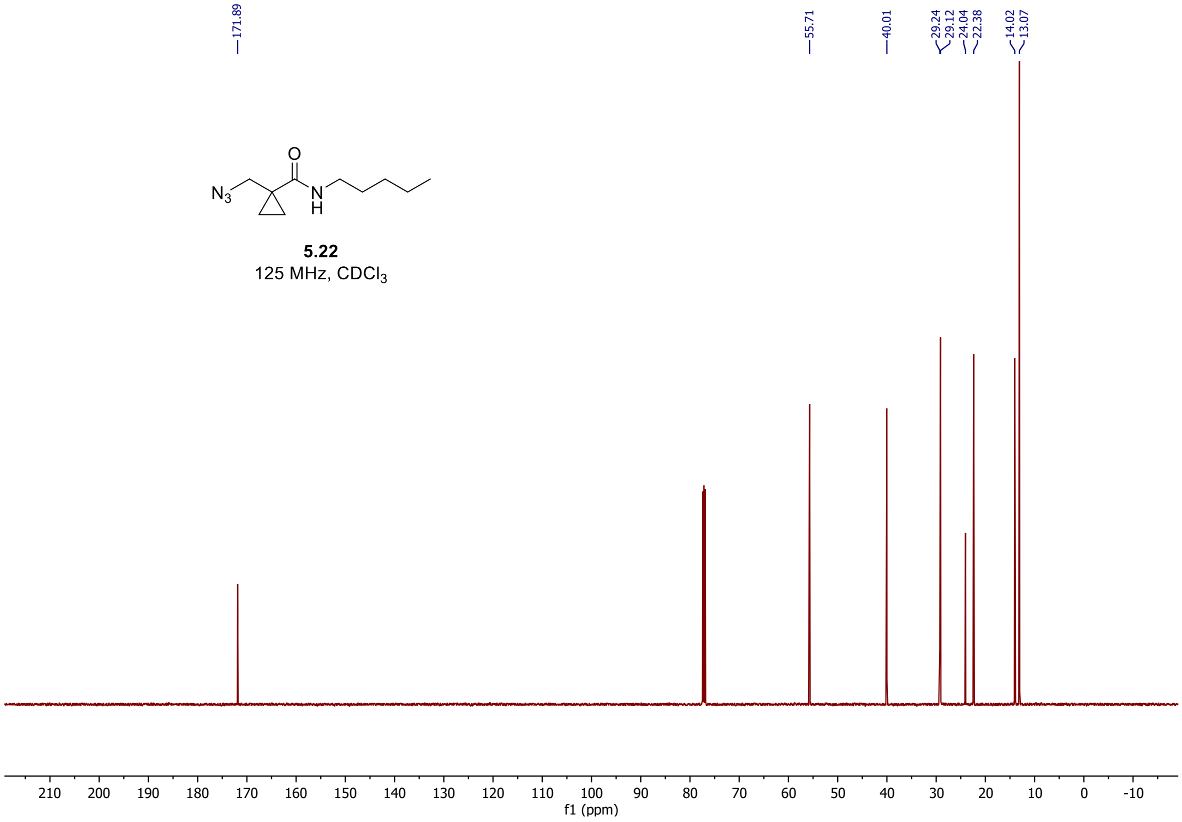

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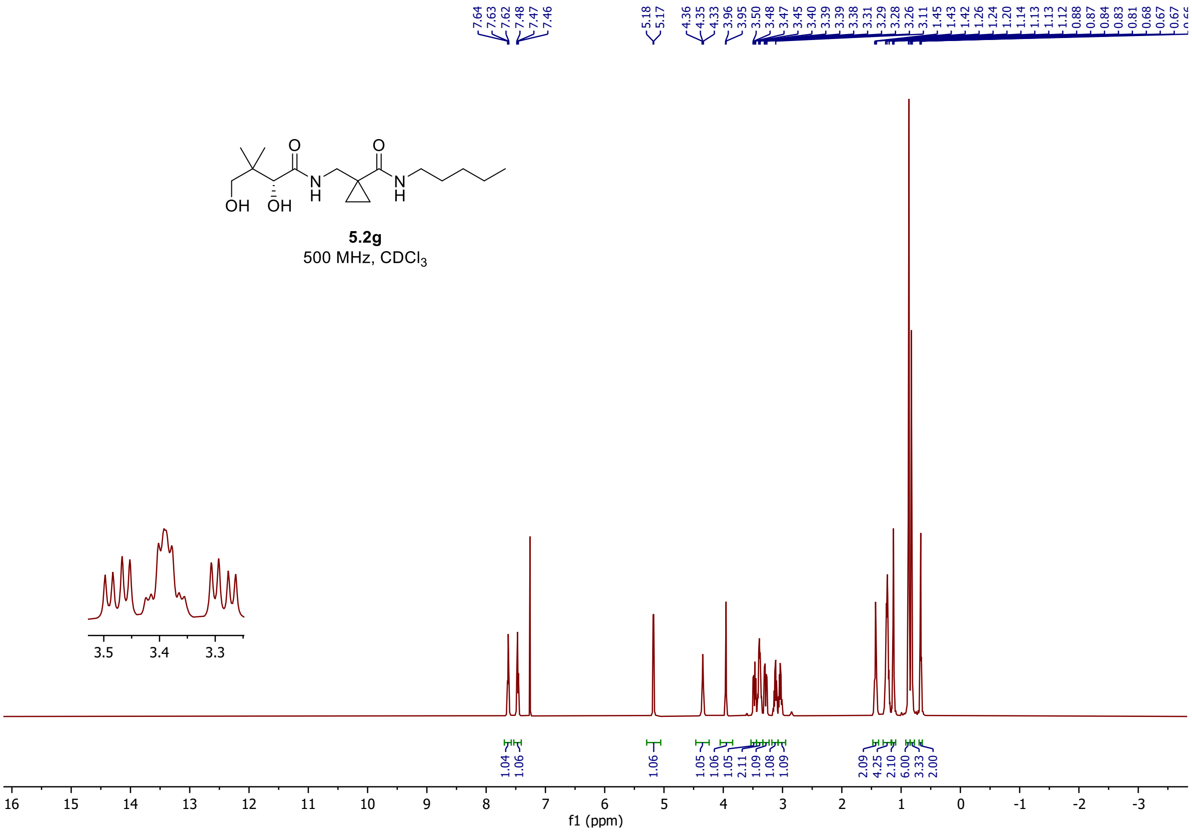

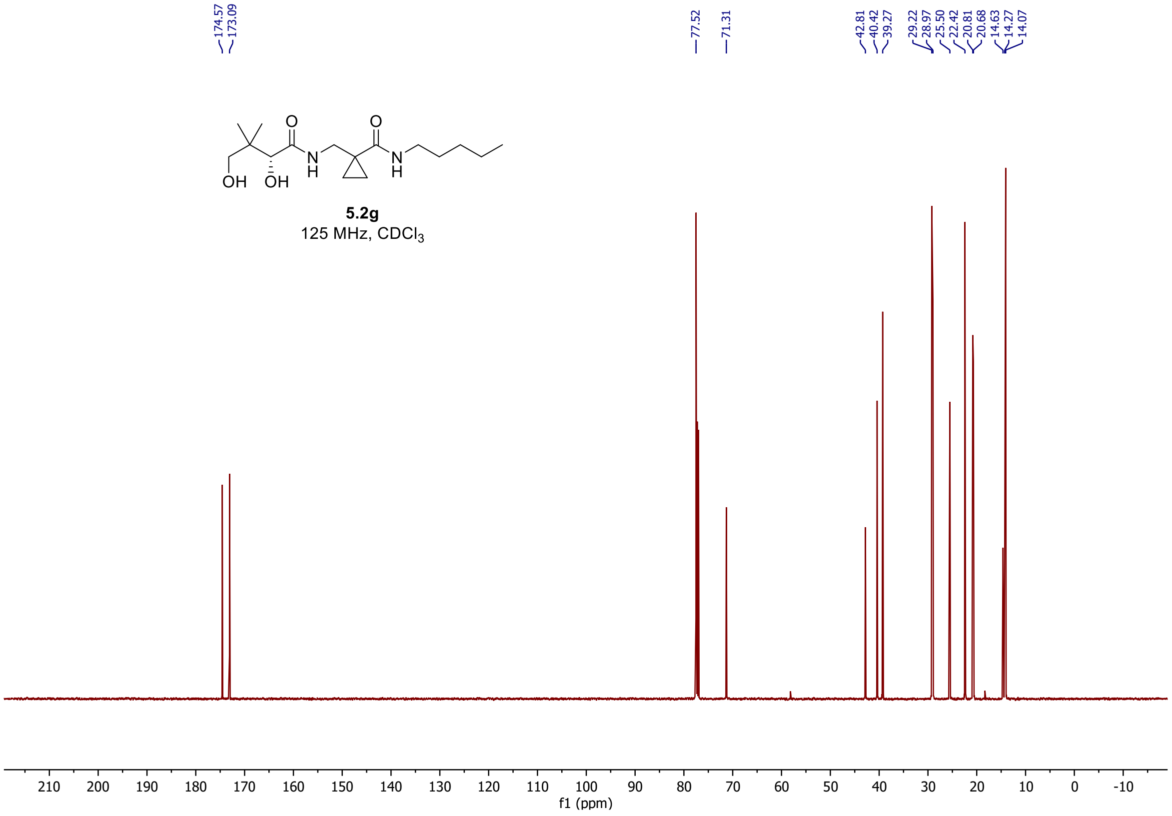

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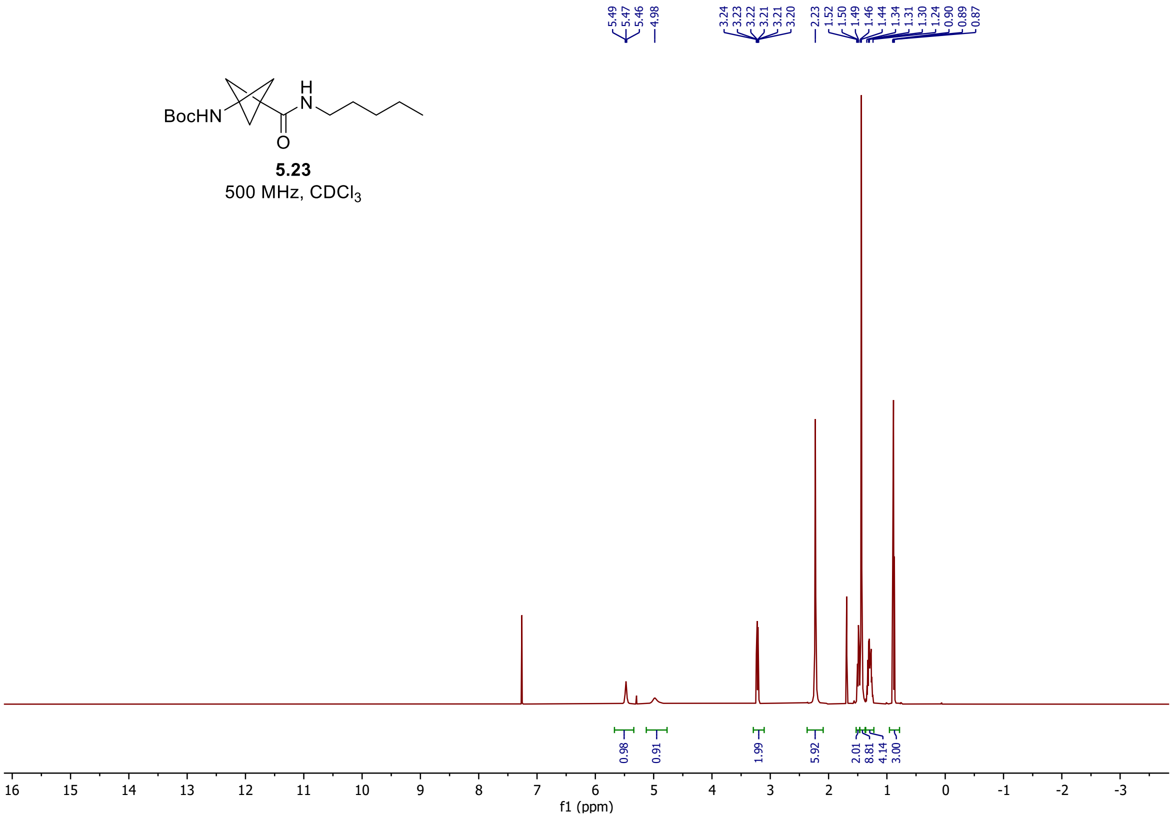

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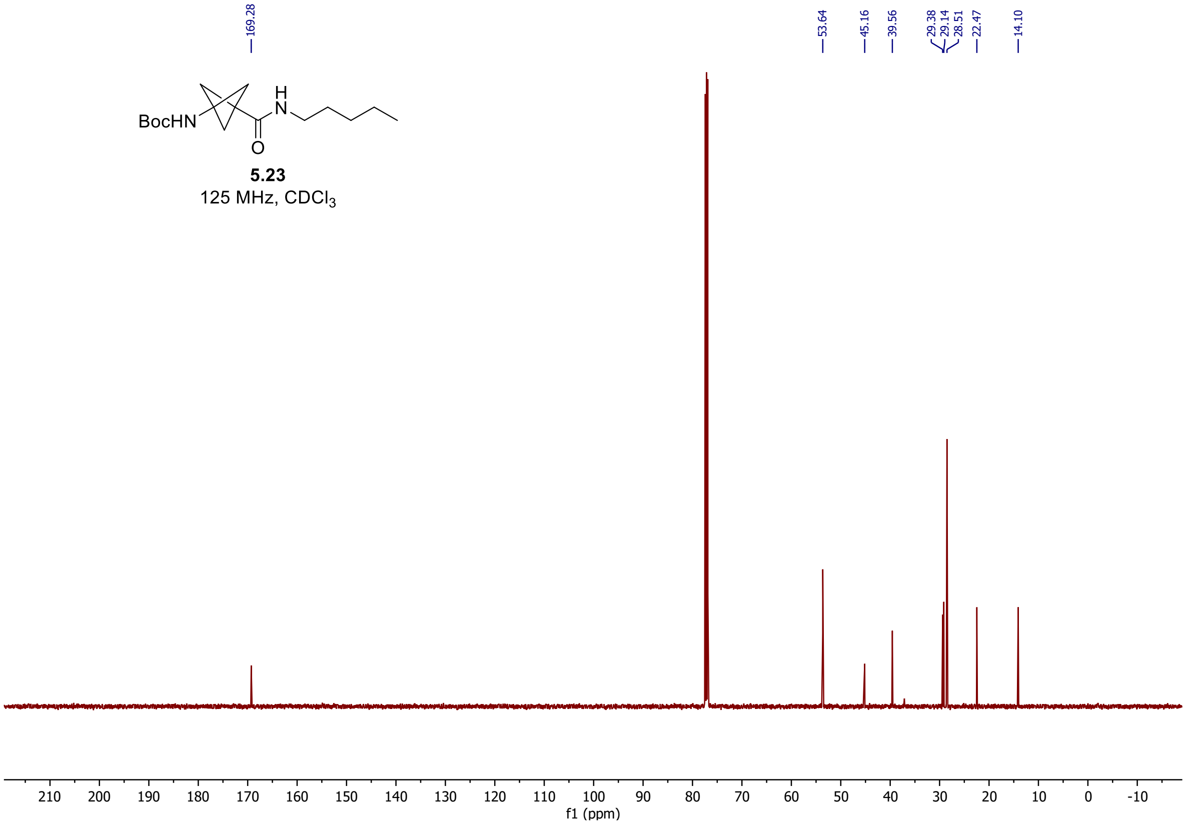

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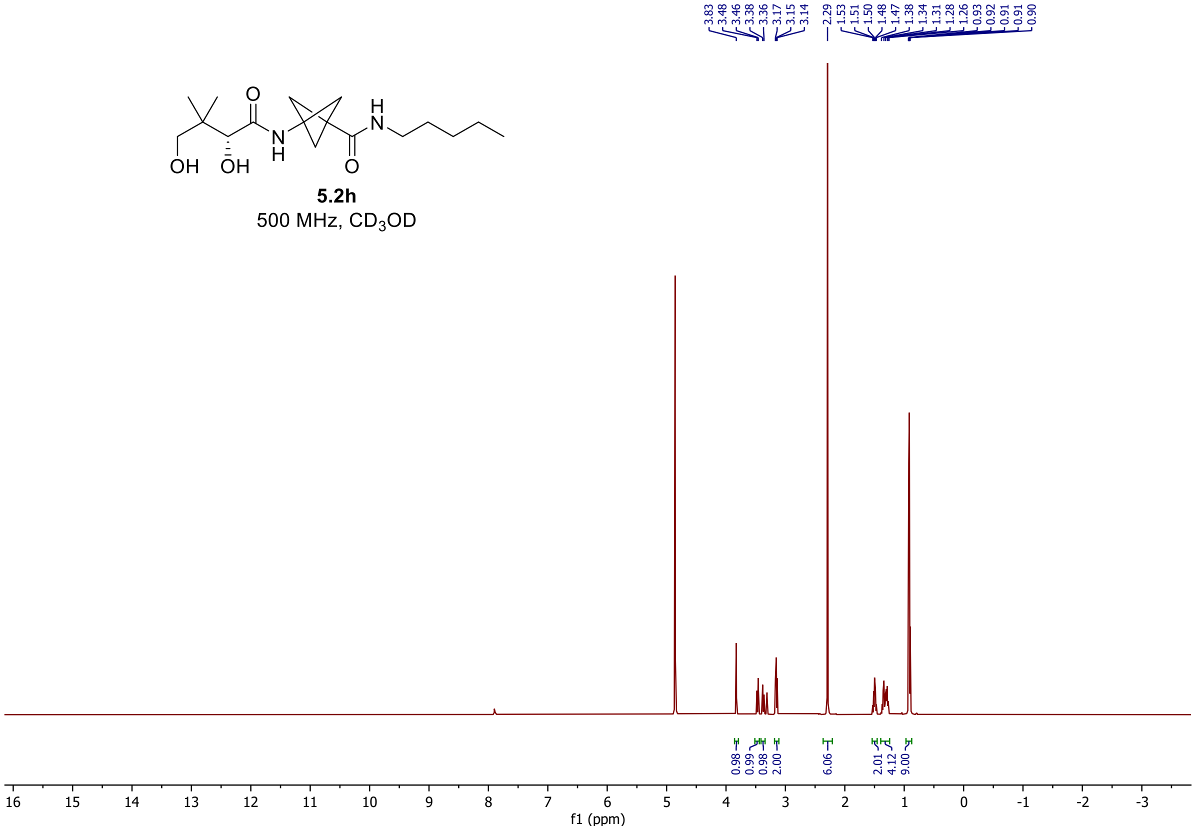

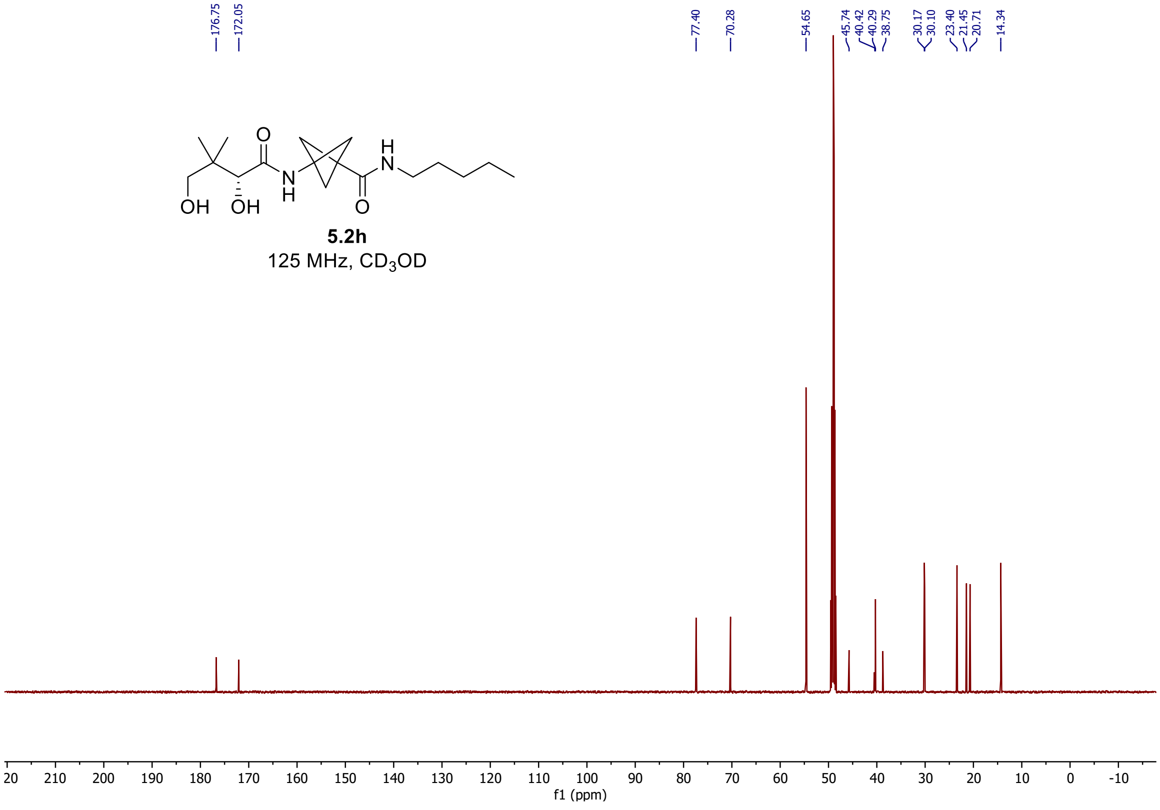

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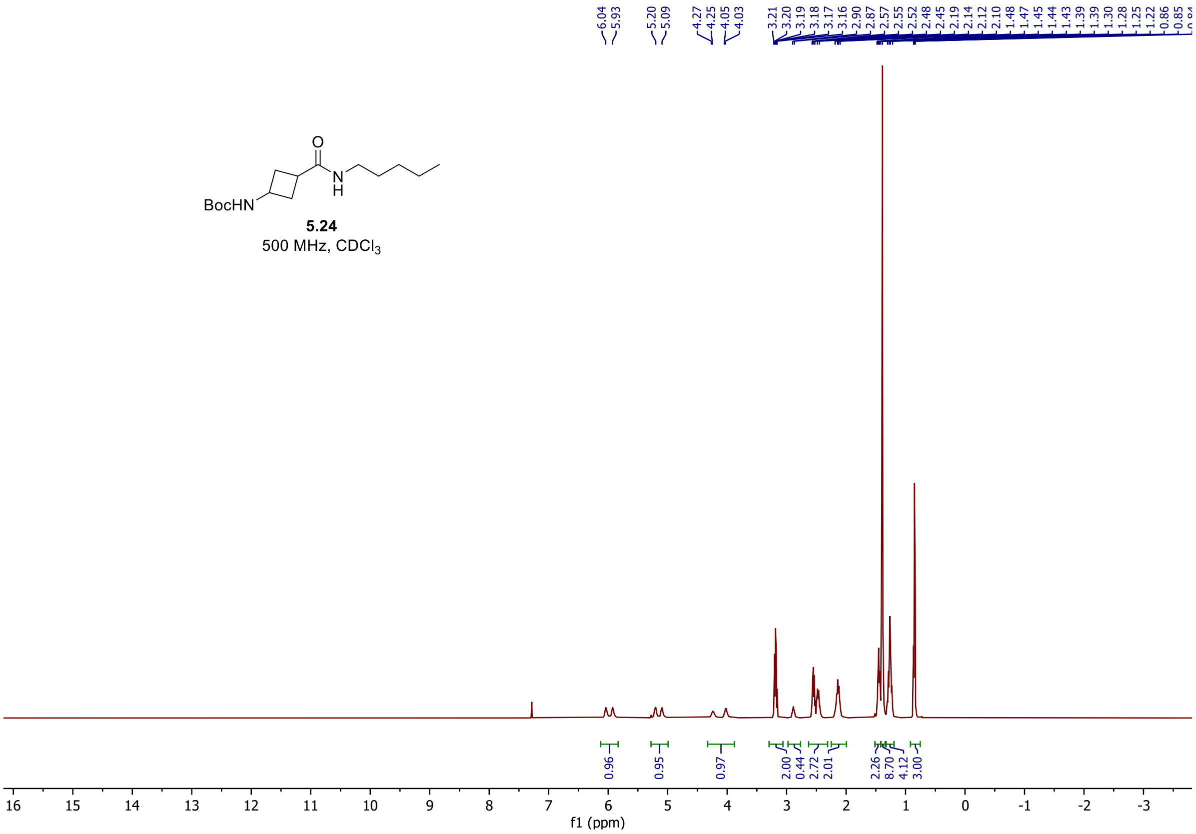
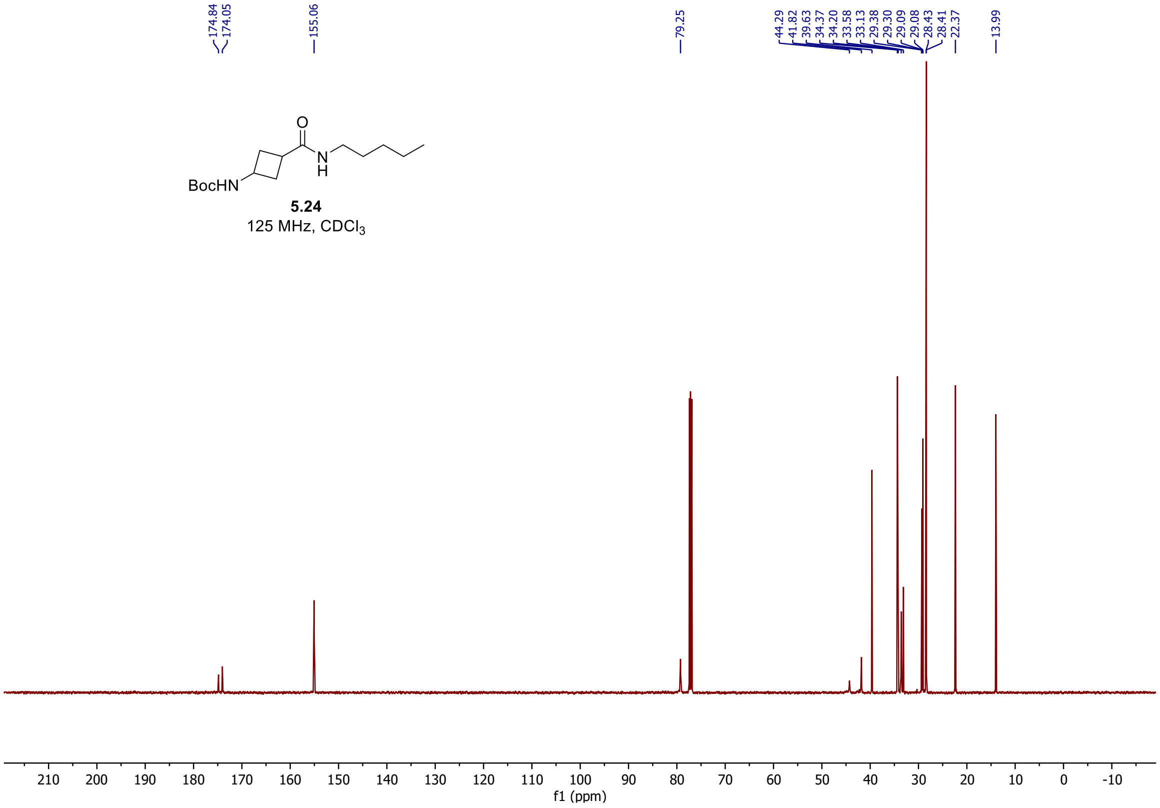
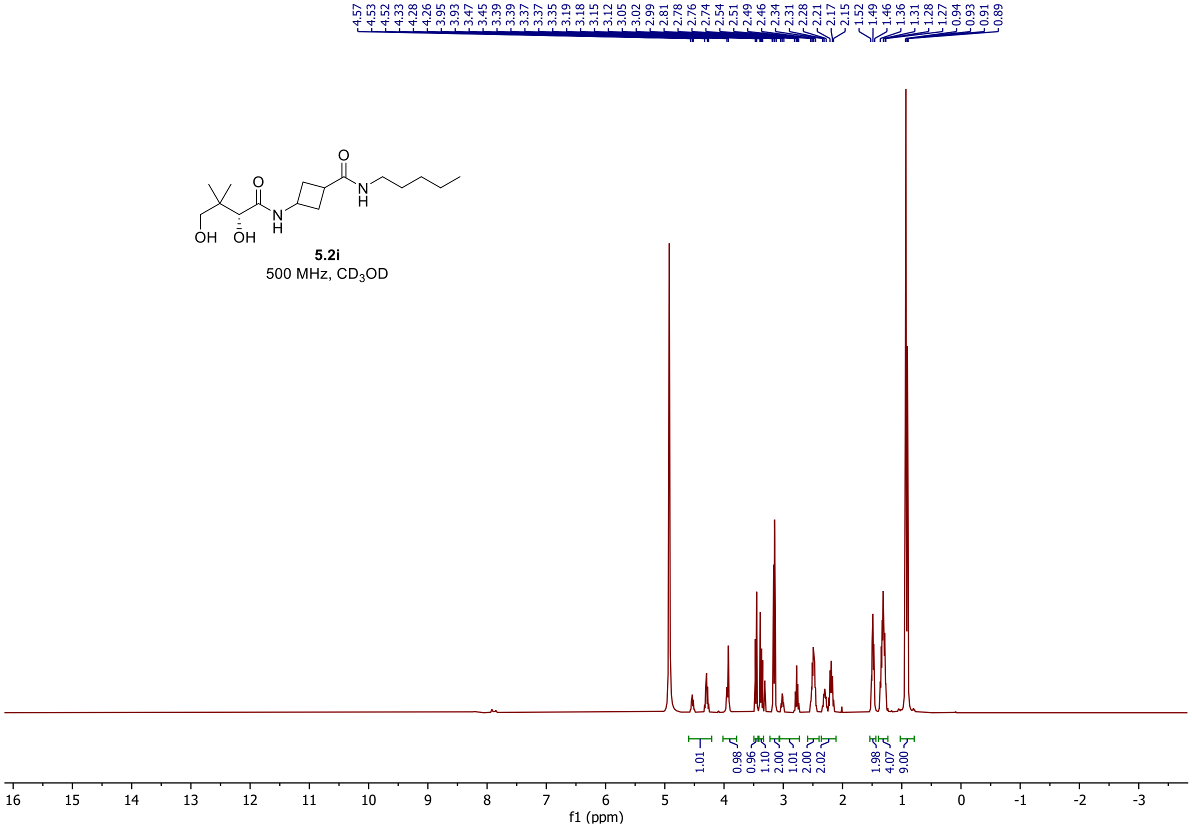
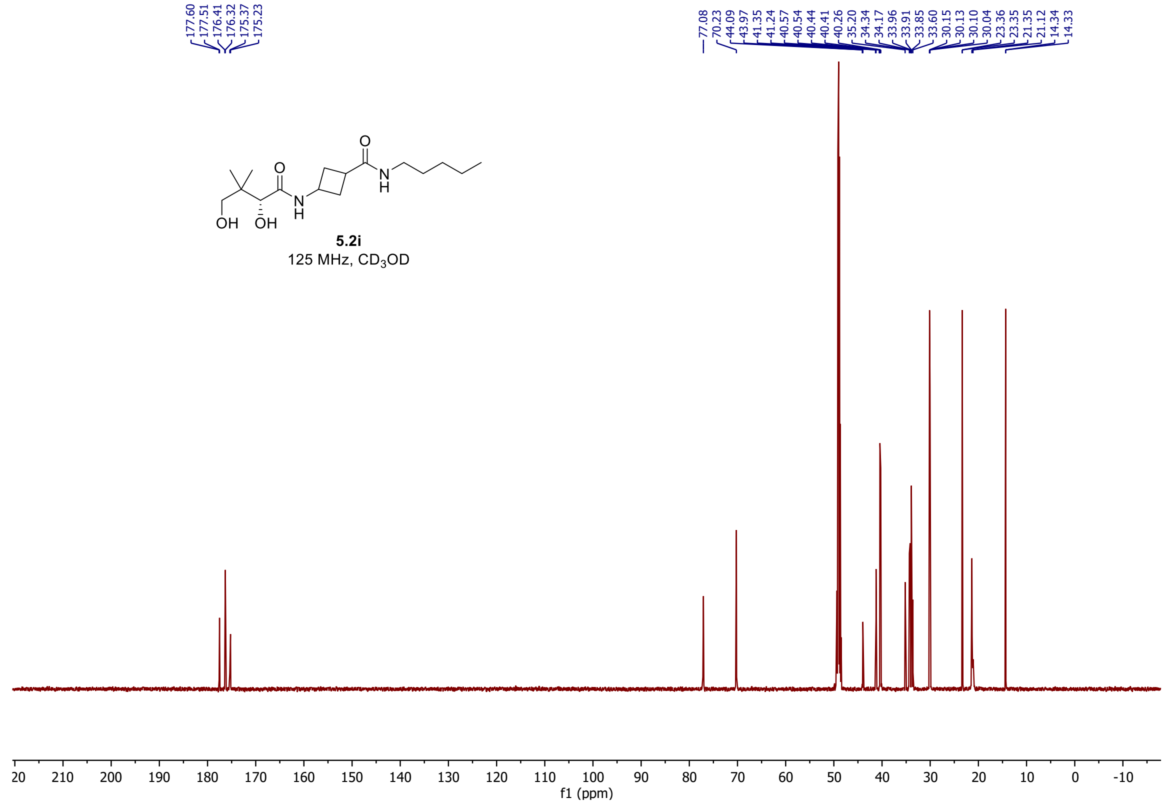


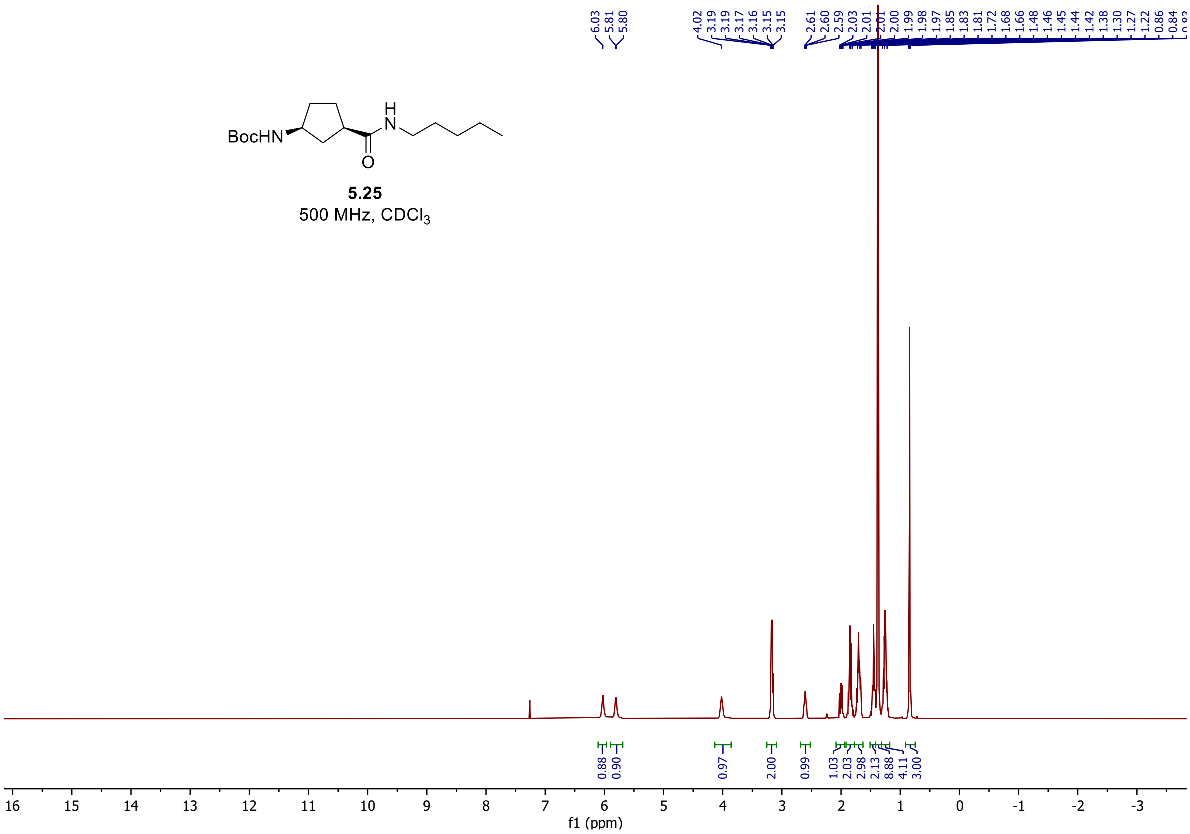


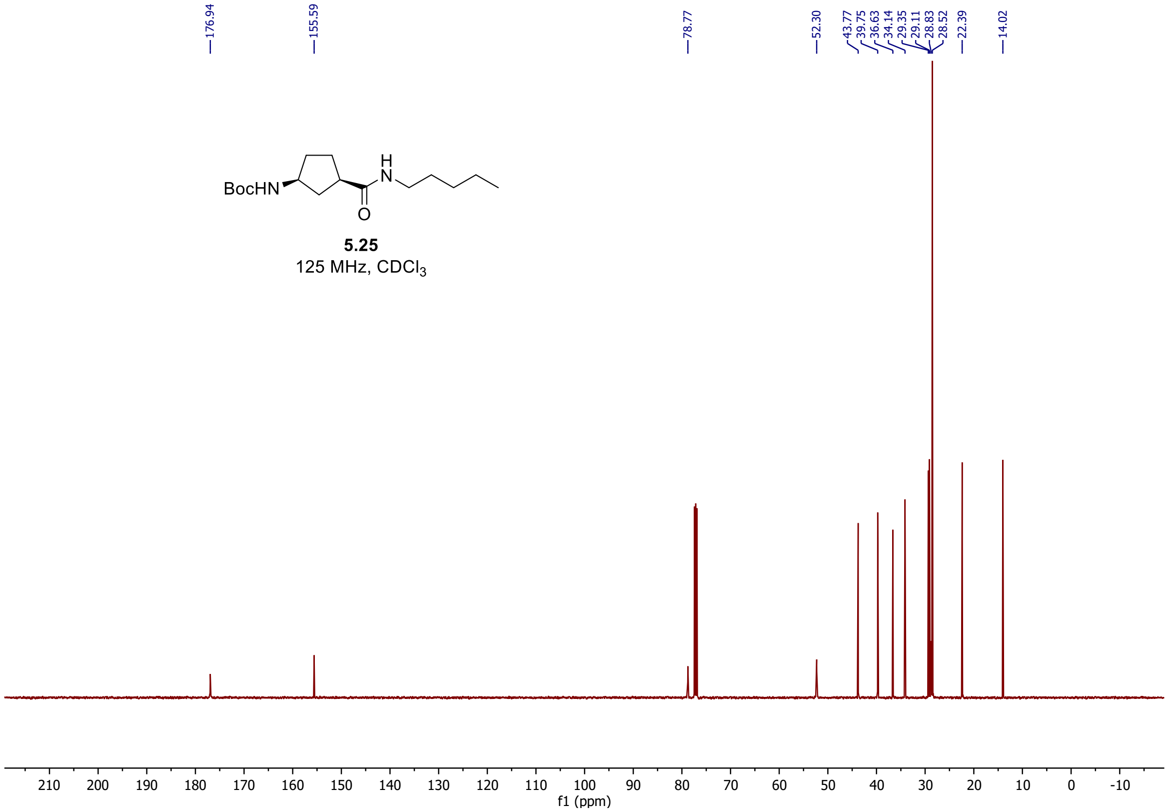
^{1}H and ^{13}C spectra of **5.2i**



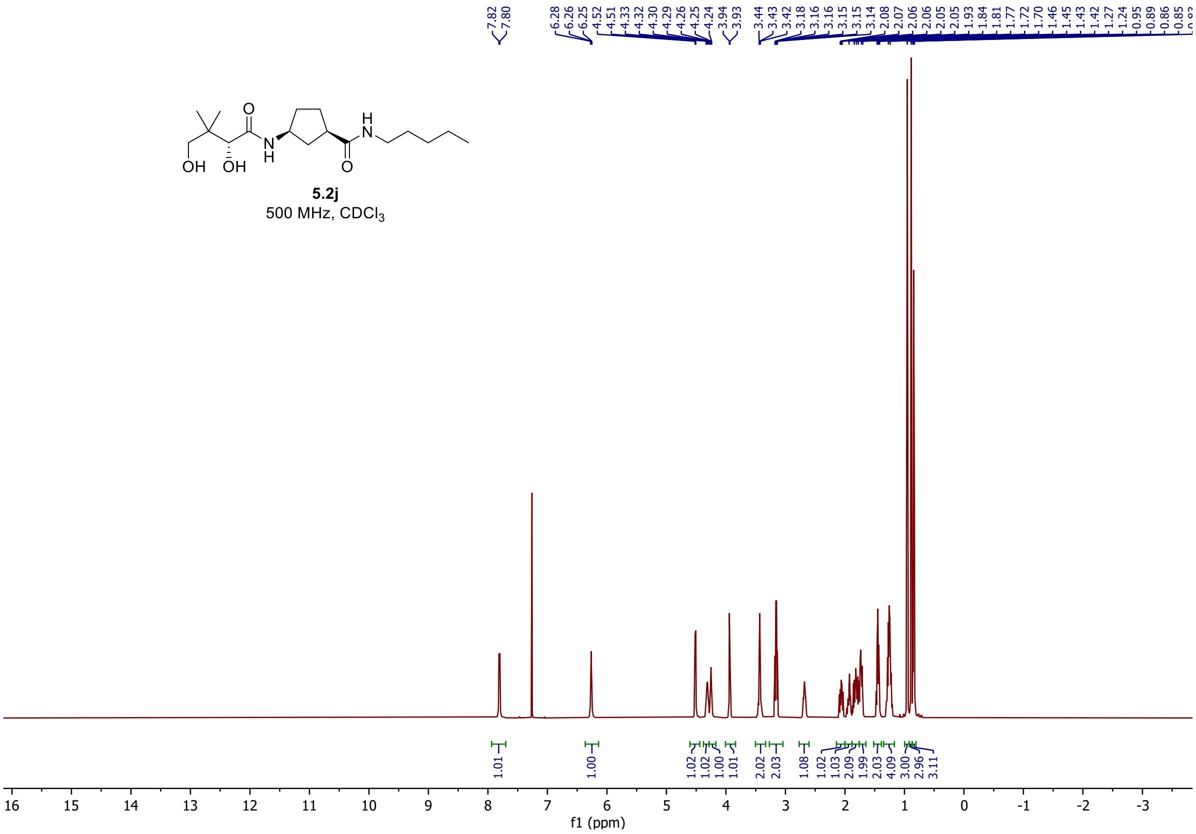


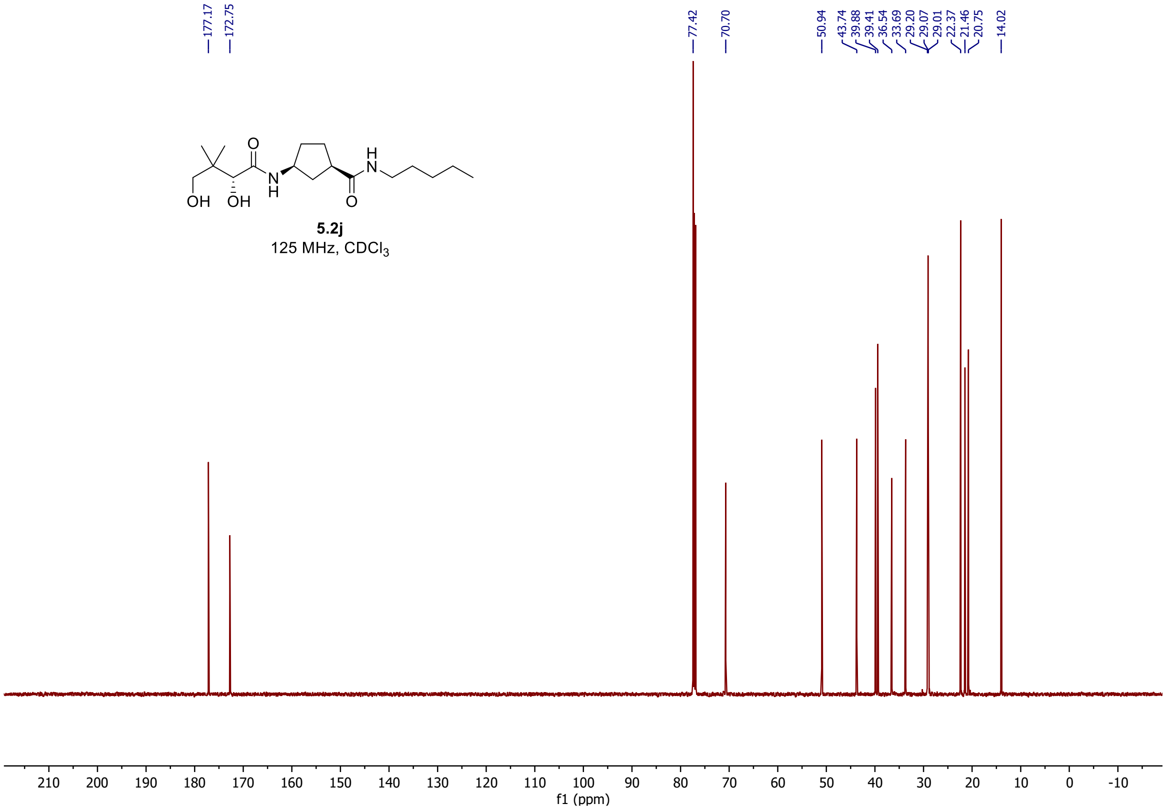
^{1}H and ^{13}C spectra of **5.25**



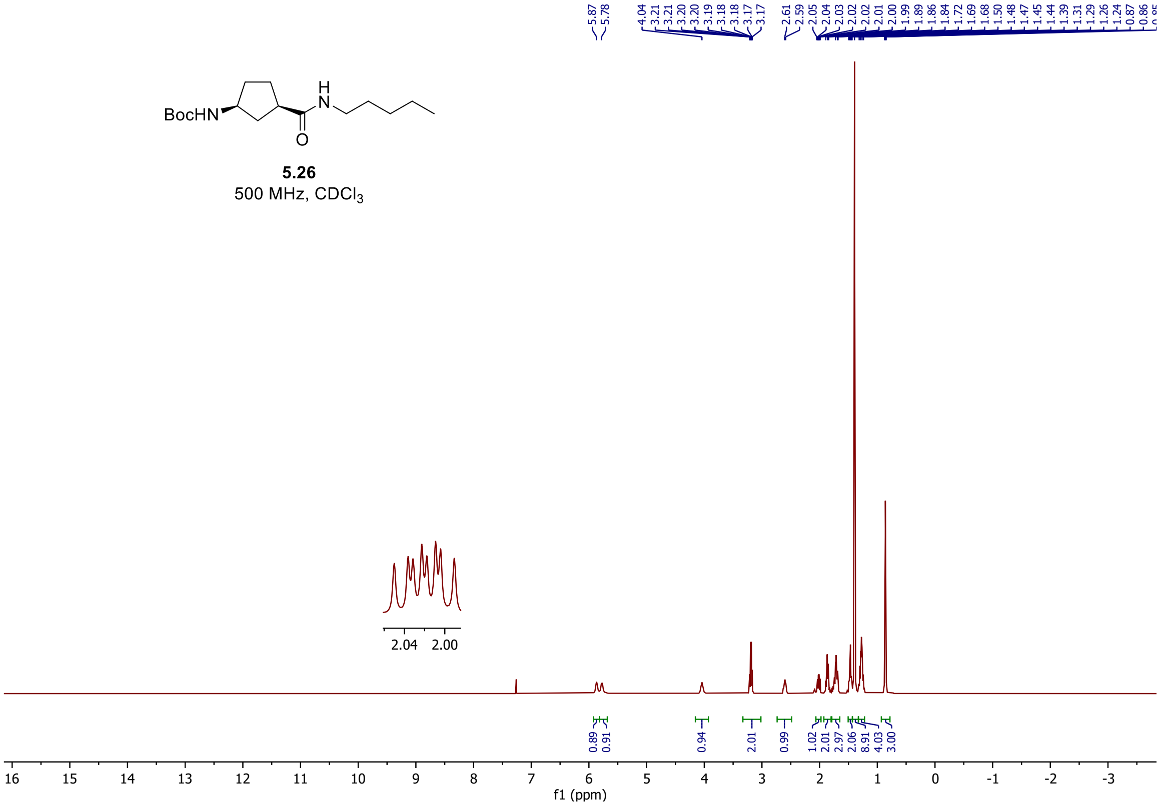


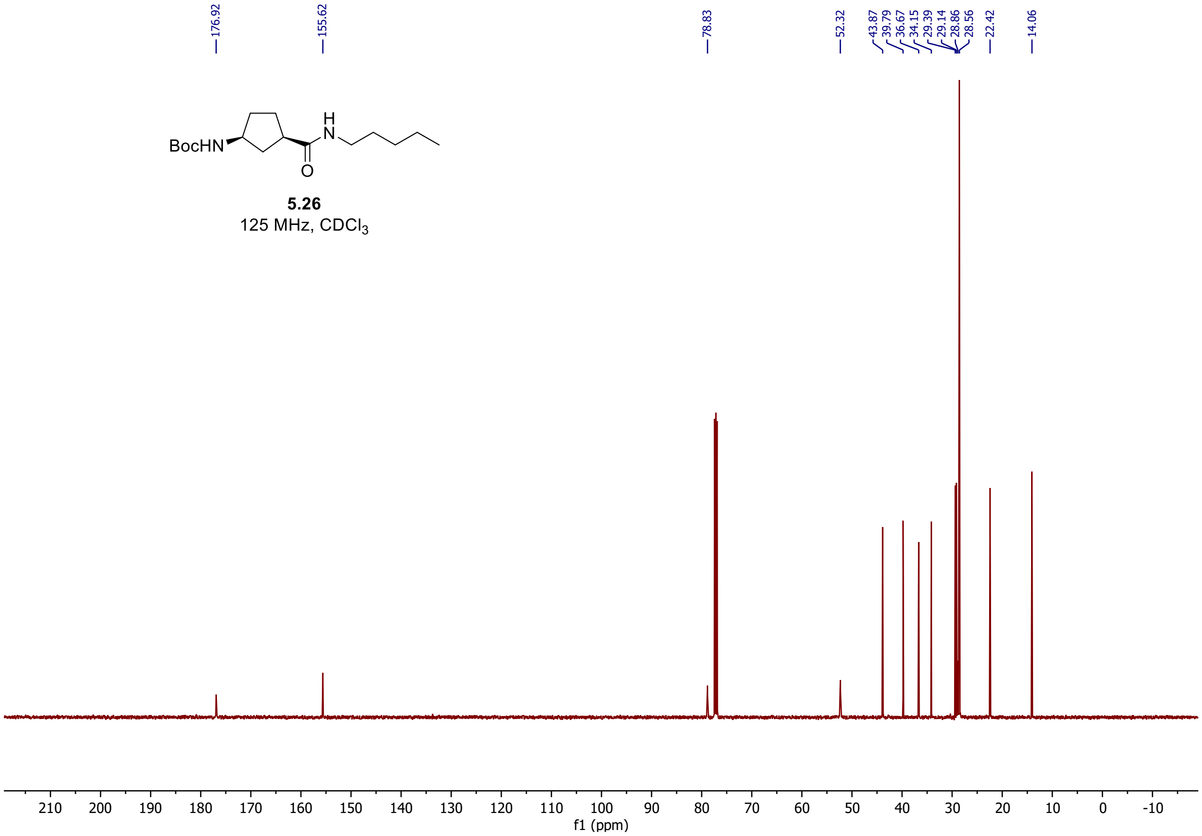
^{1}H and ^{13}C spectra of **5.2j**



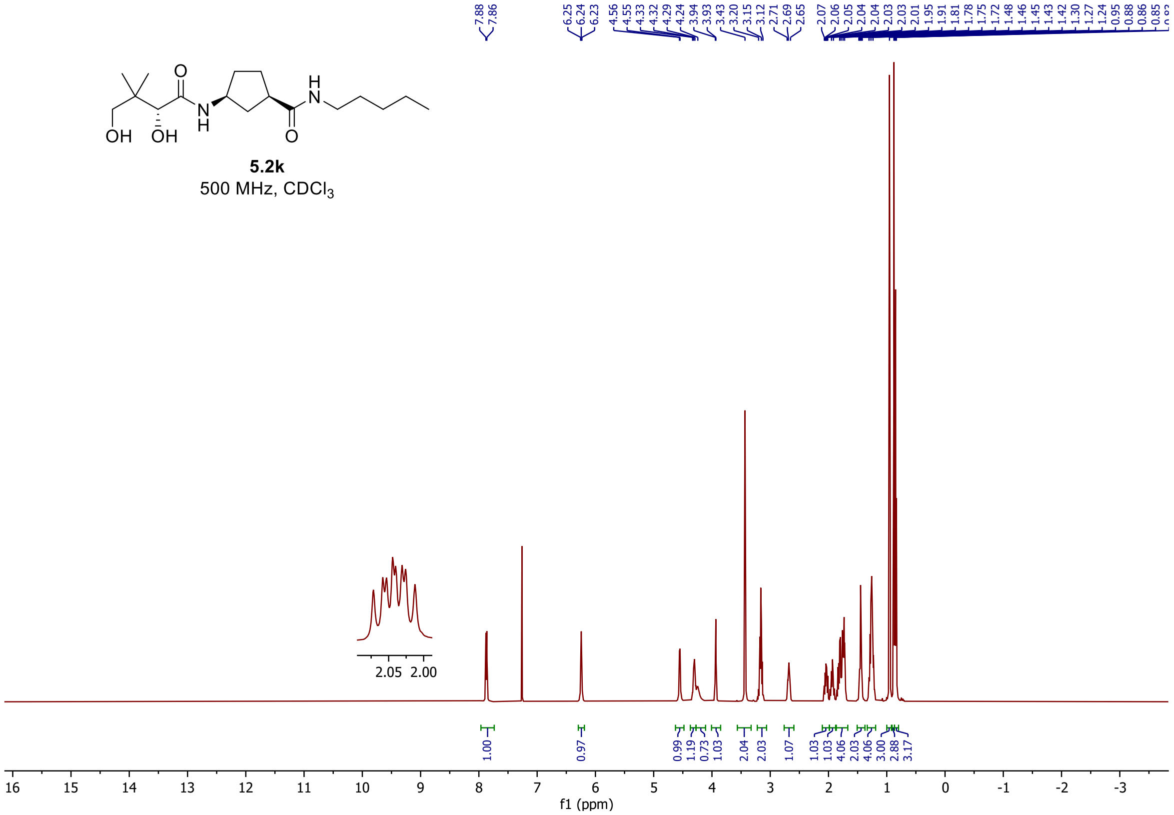


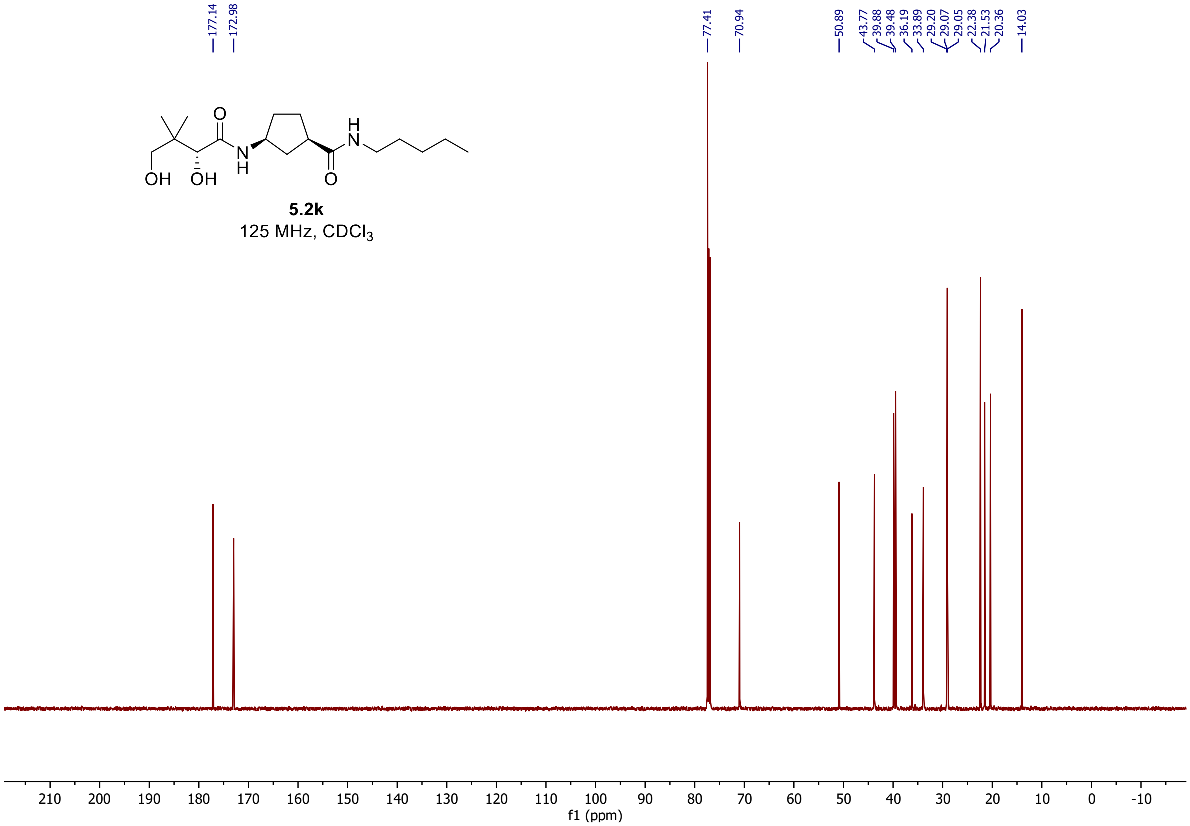
^{1}H and ^{13}C spectra of **5.26**



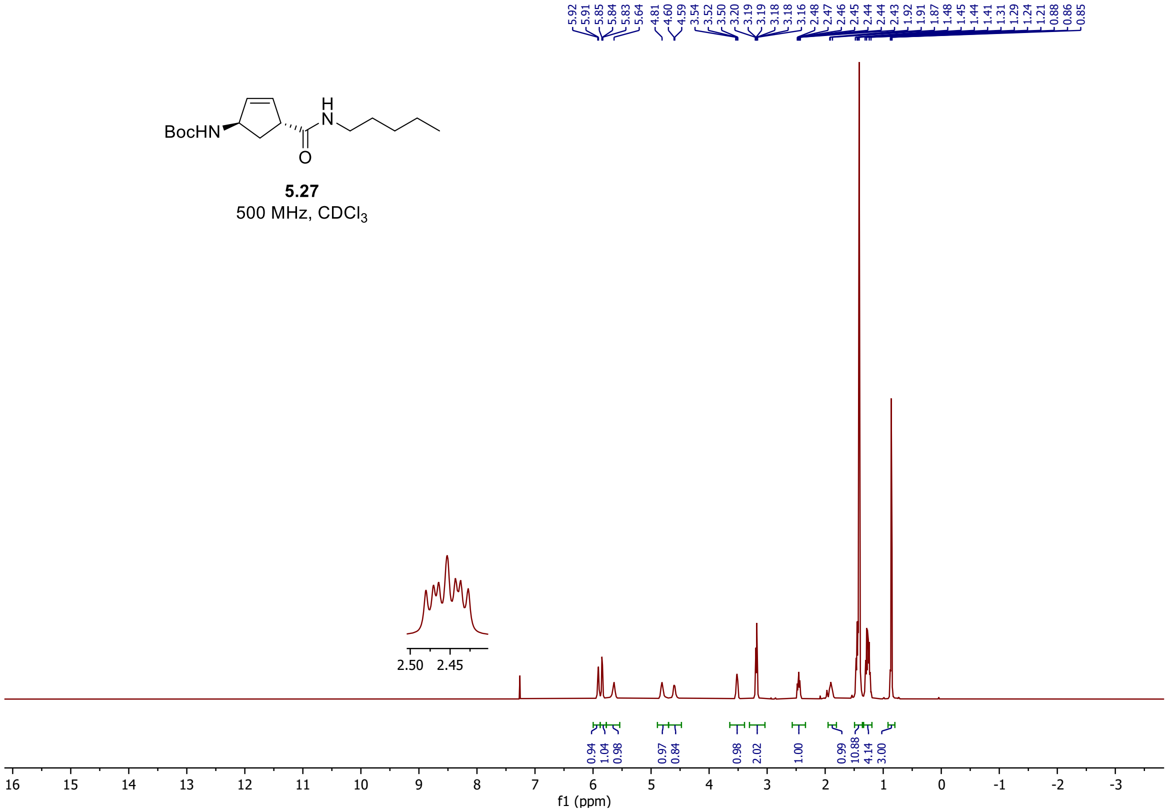


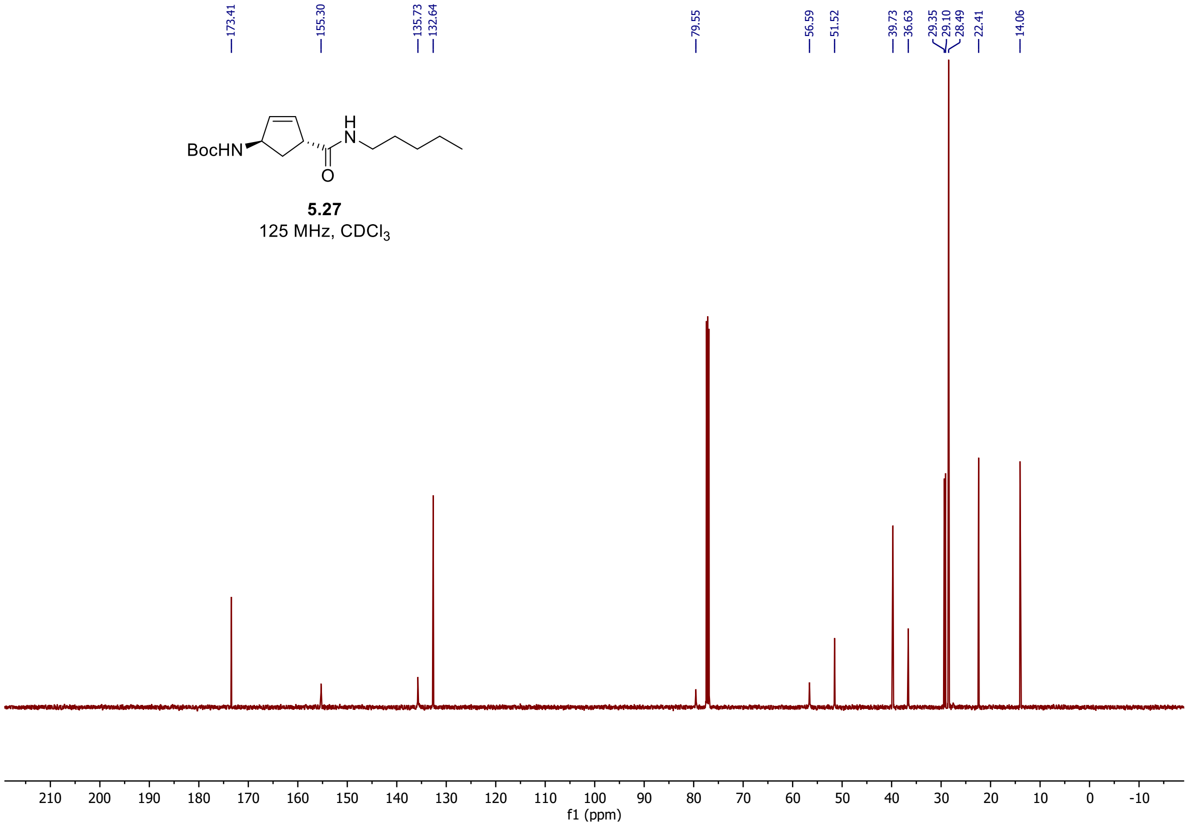
^{1}H and ^{13}C spectra of **5.2k**



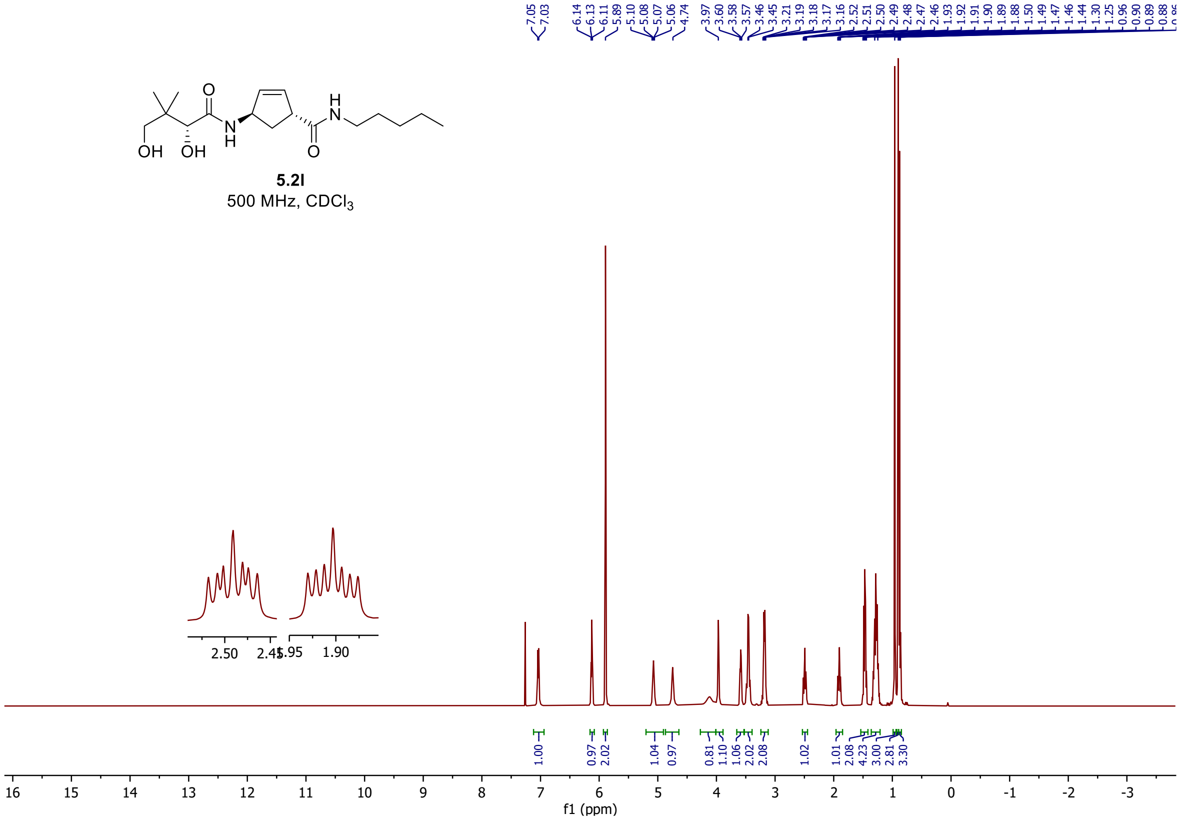


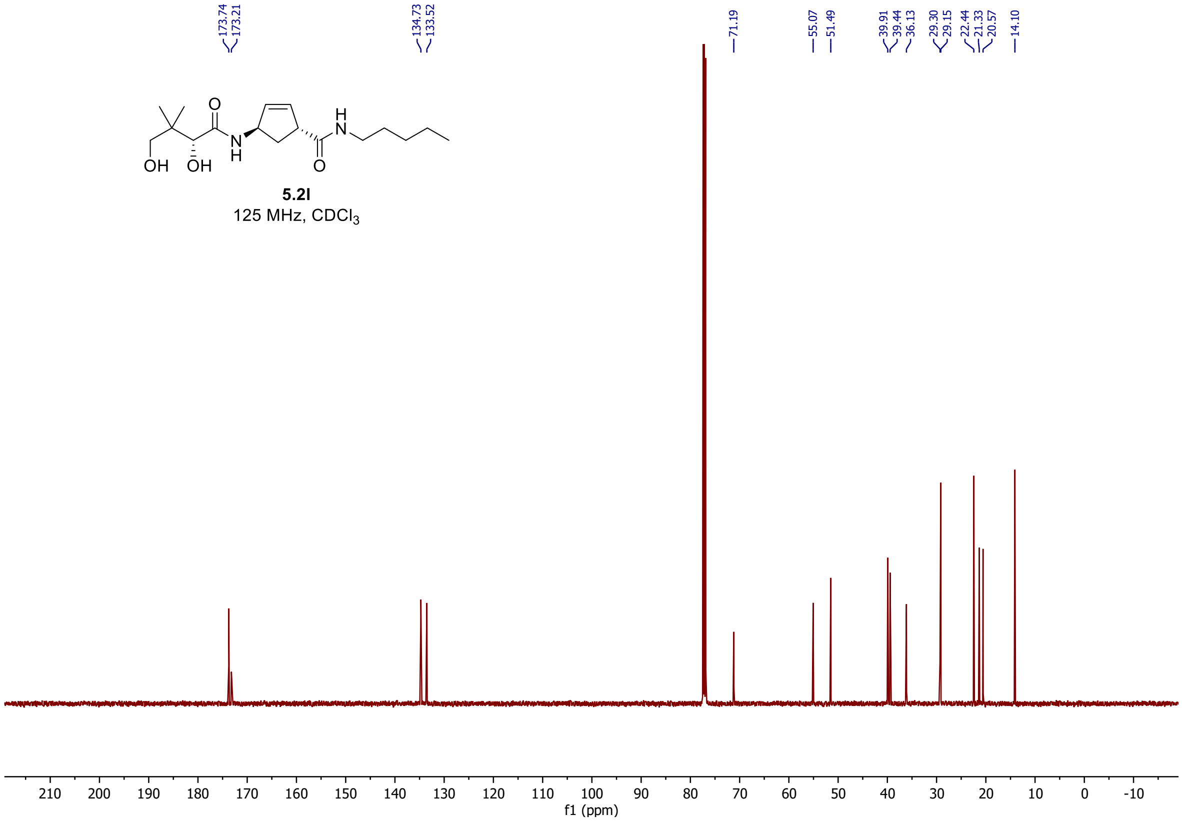
^{1}H and ^{13}C spectra of **5.27**



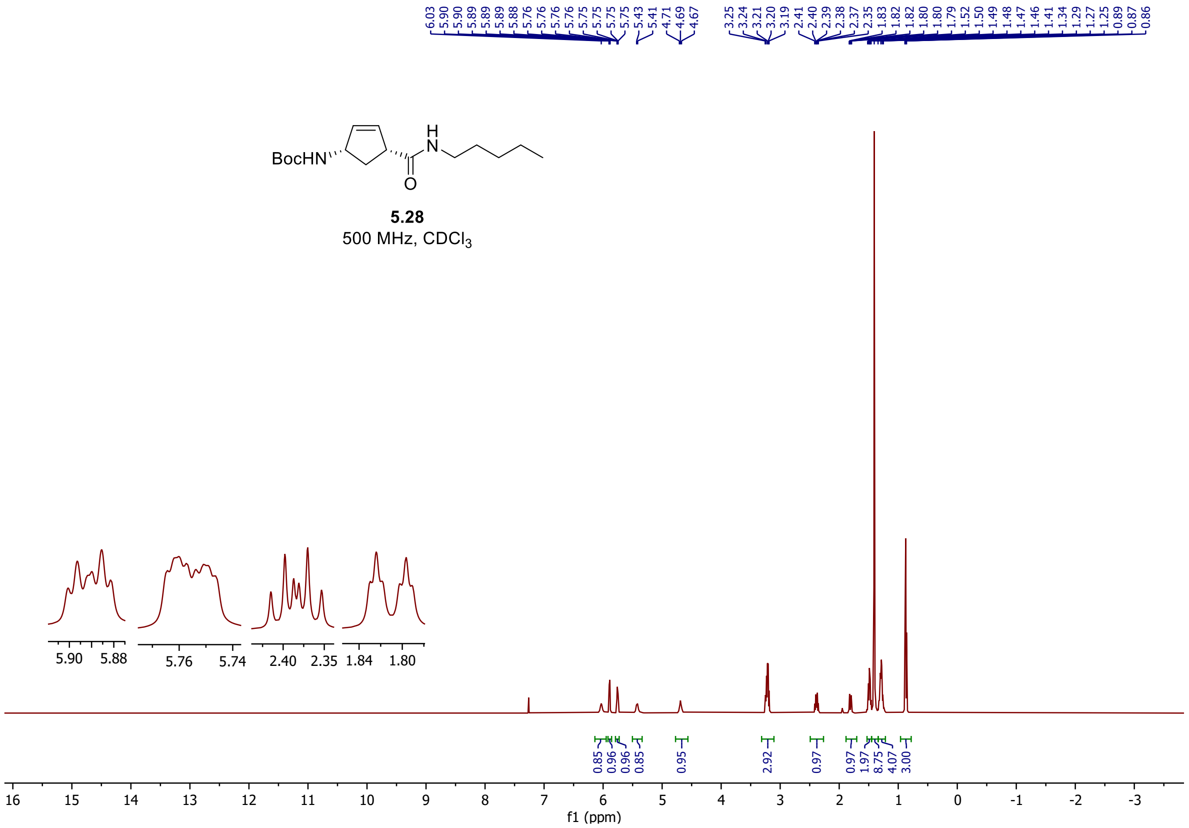


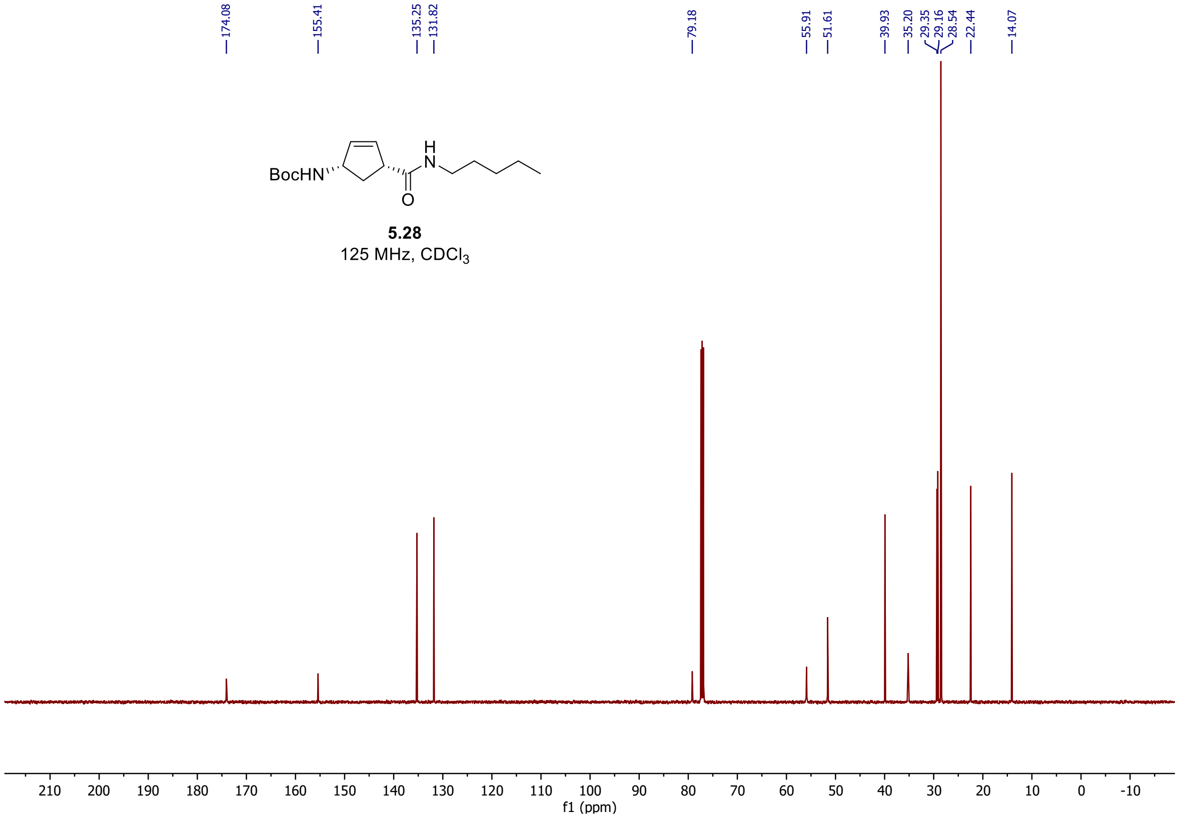
^{1}H and ^{13}C spectra of **5.2l**



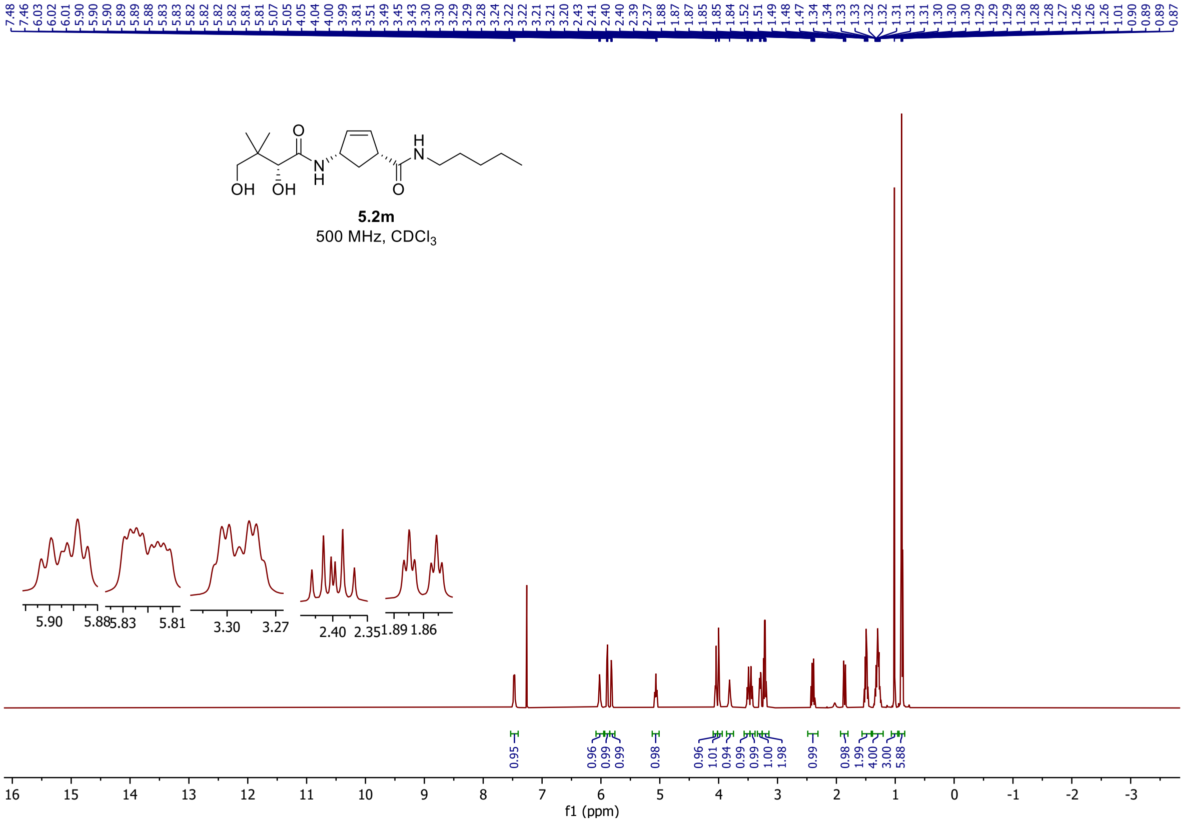


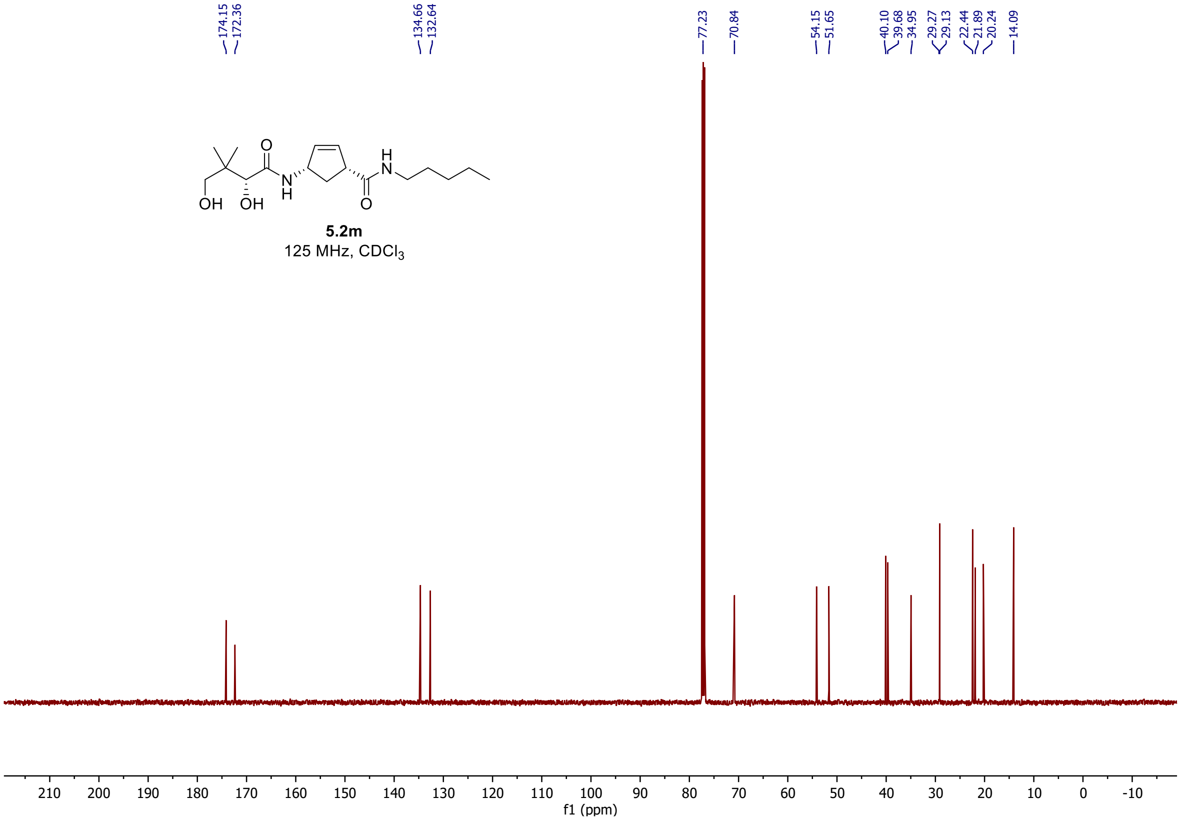
^{1}H and ^{13}C spectra of **5.28**



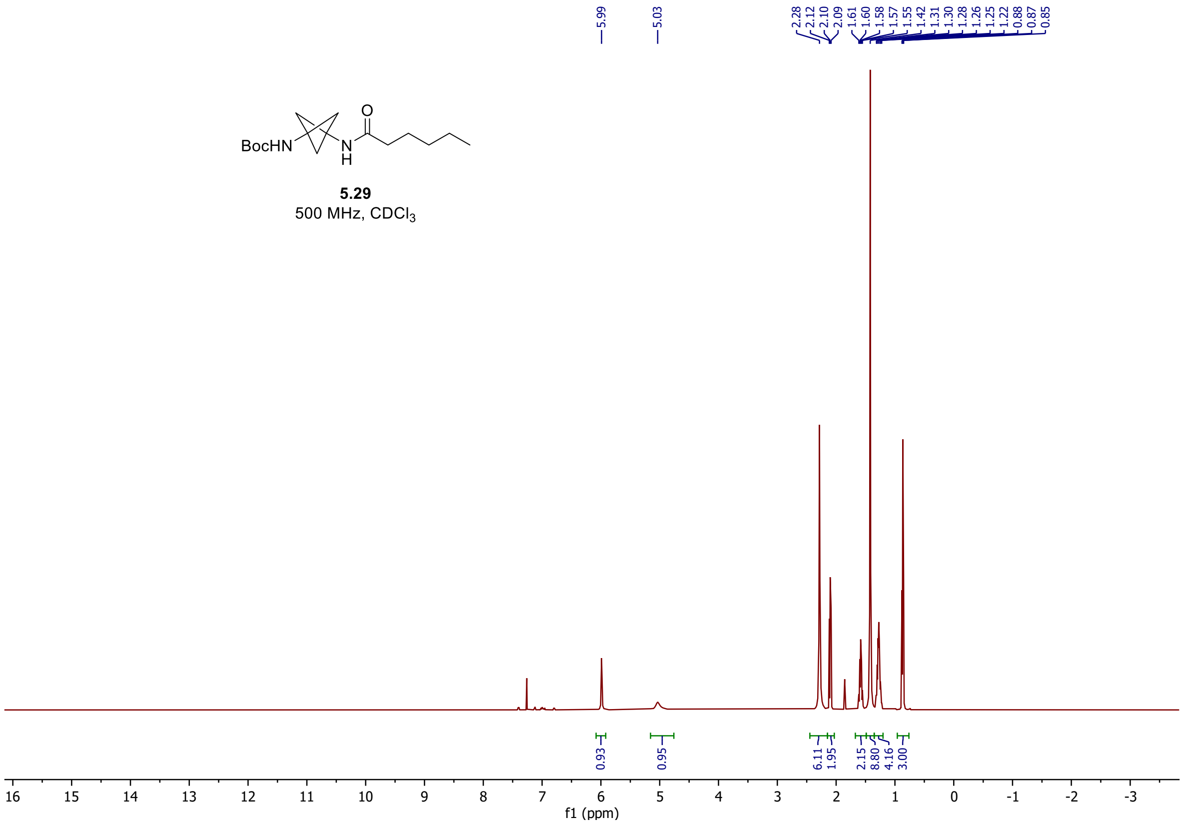


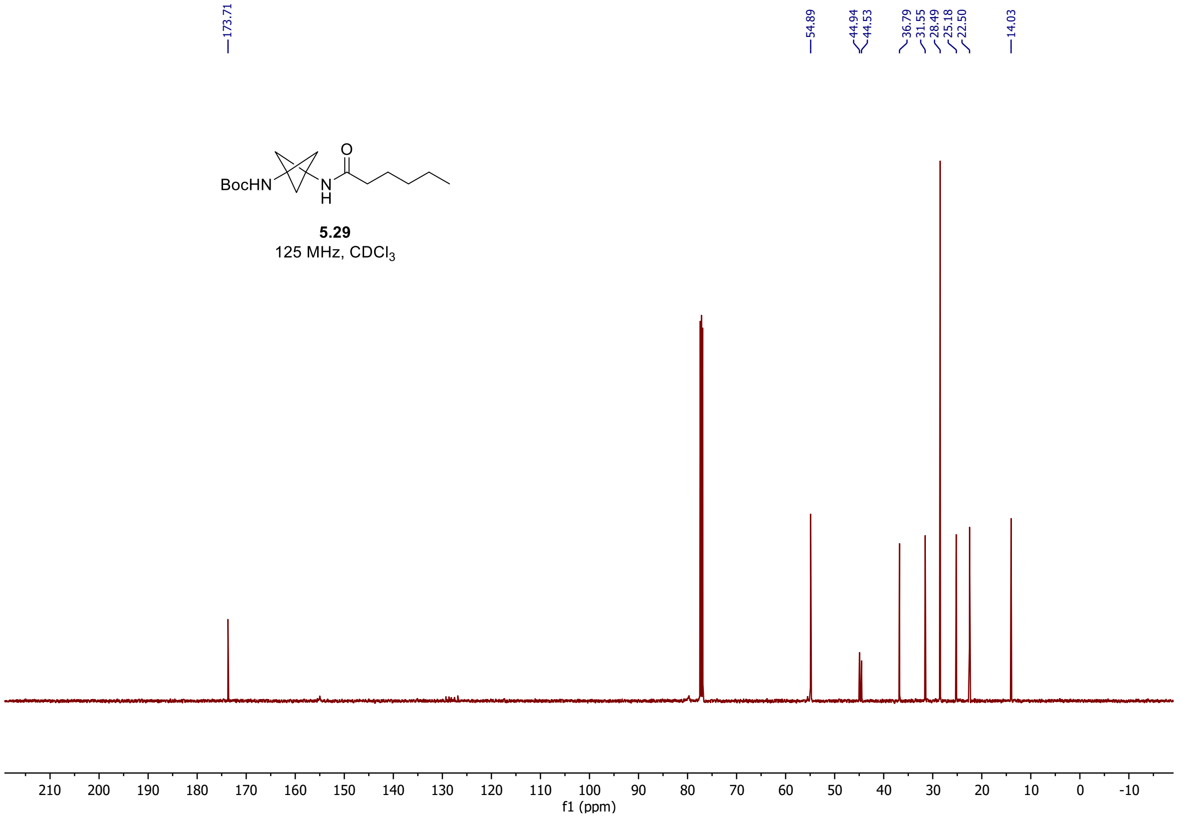
^{1}H and ^{13}C spectra of **5.2m**



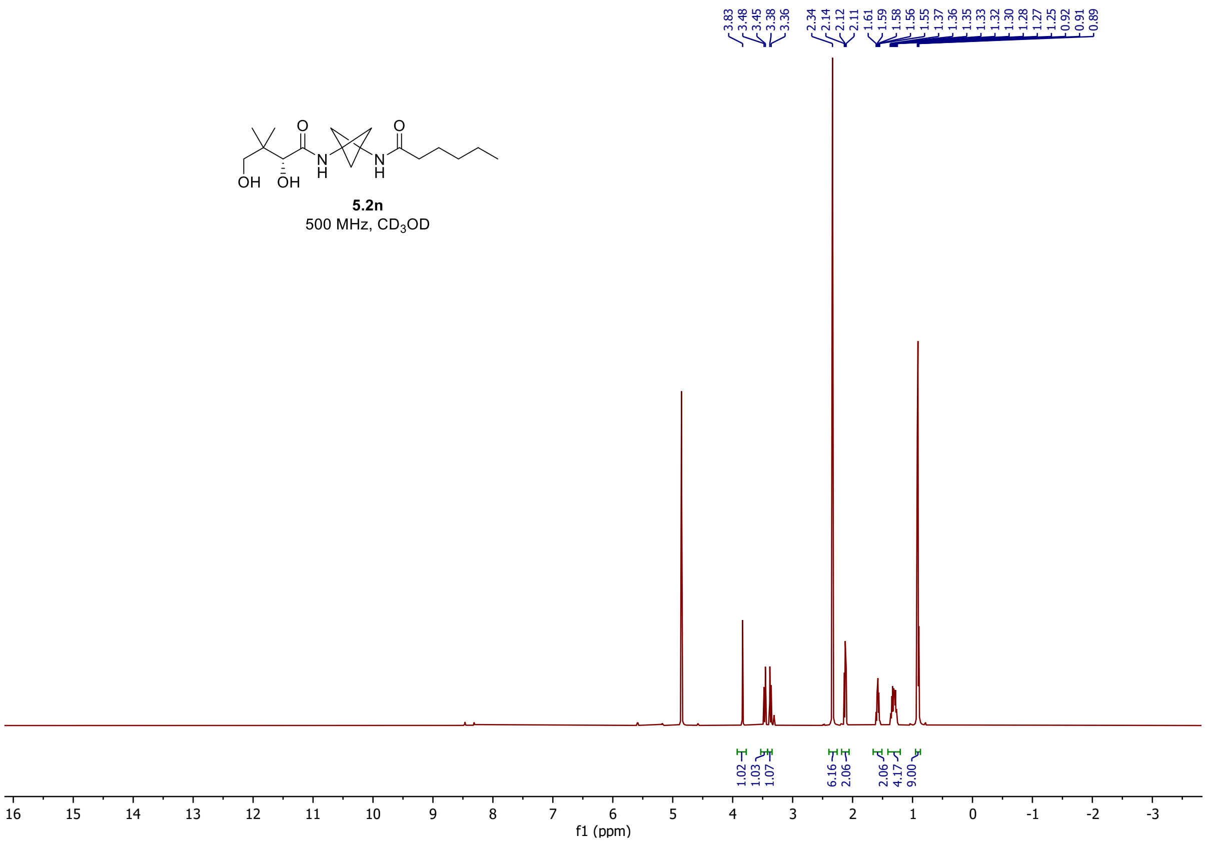


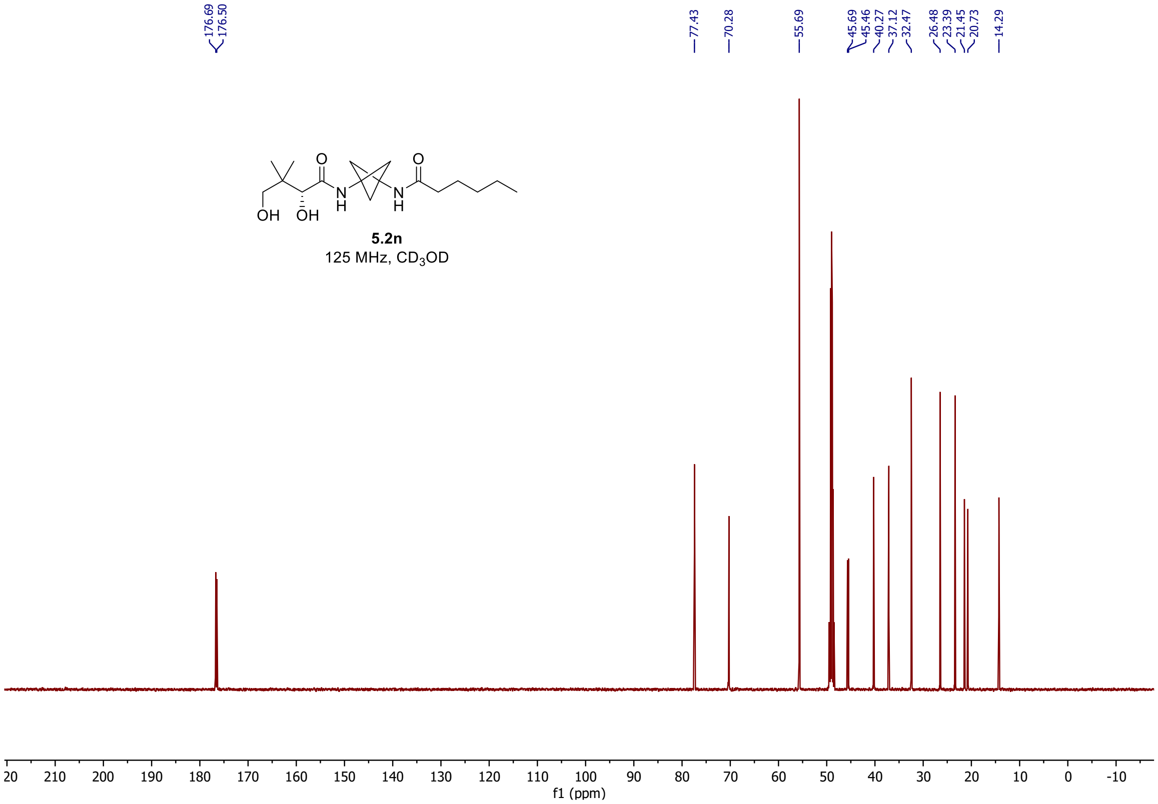
^{1}H and ^{13}C spectra of **5.29**



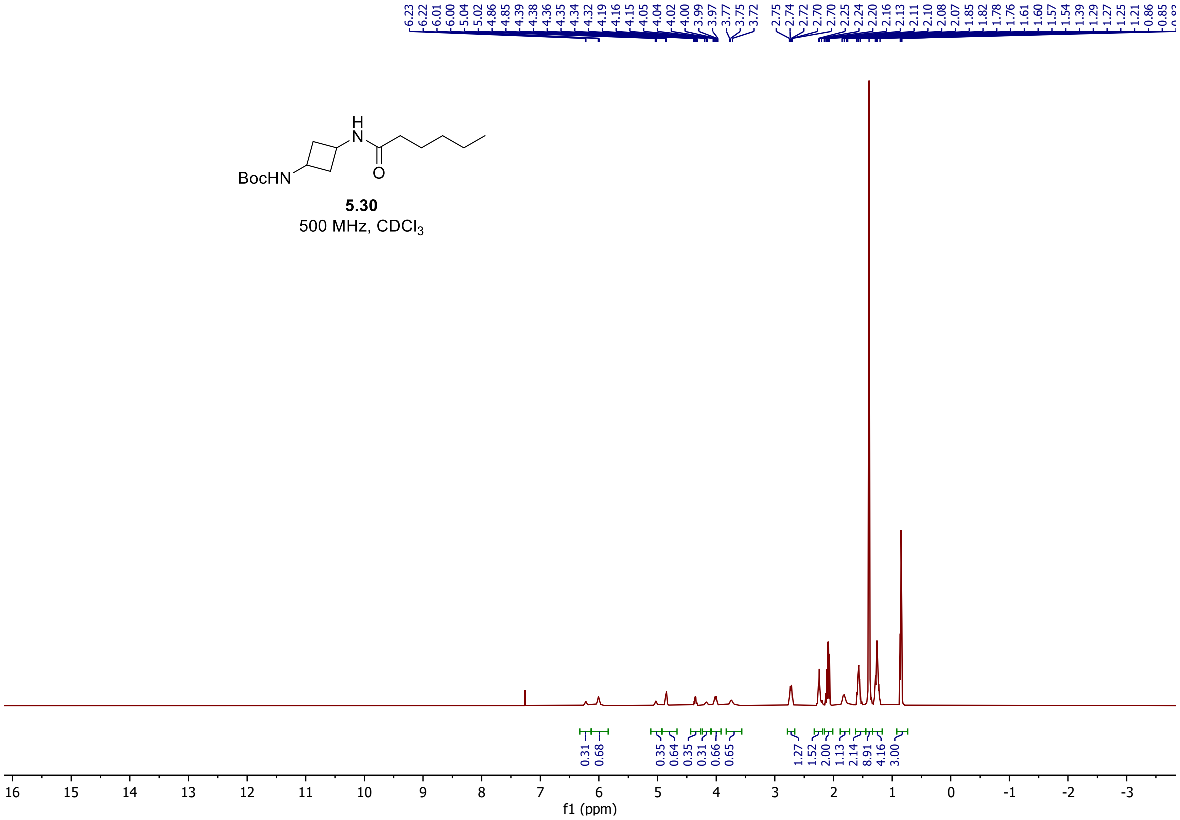


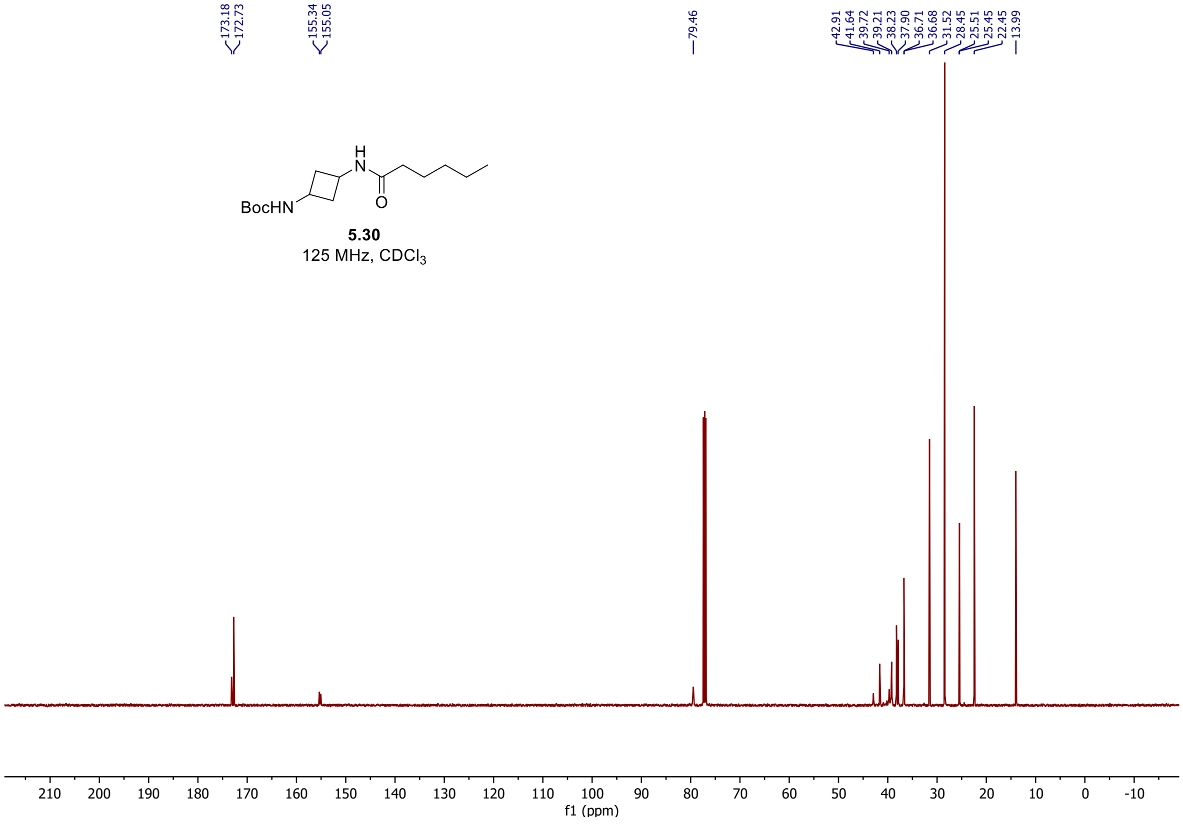
^{1}H and ^{13}C spectra of **5.2n**



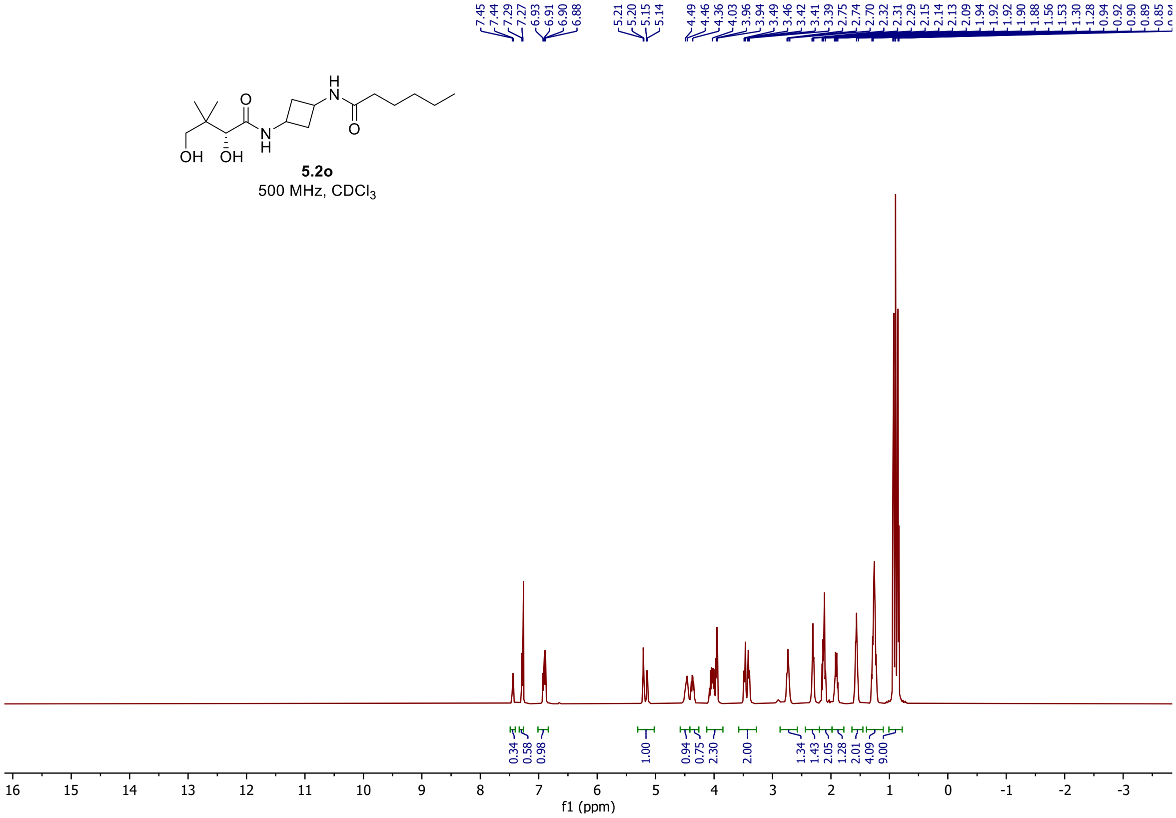


^{1}H and ^{13}C spectra of **5.30**

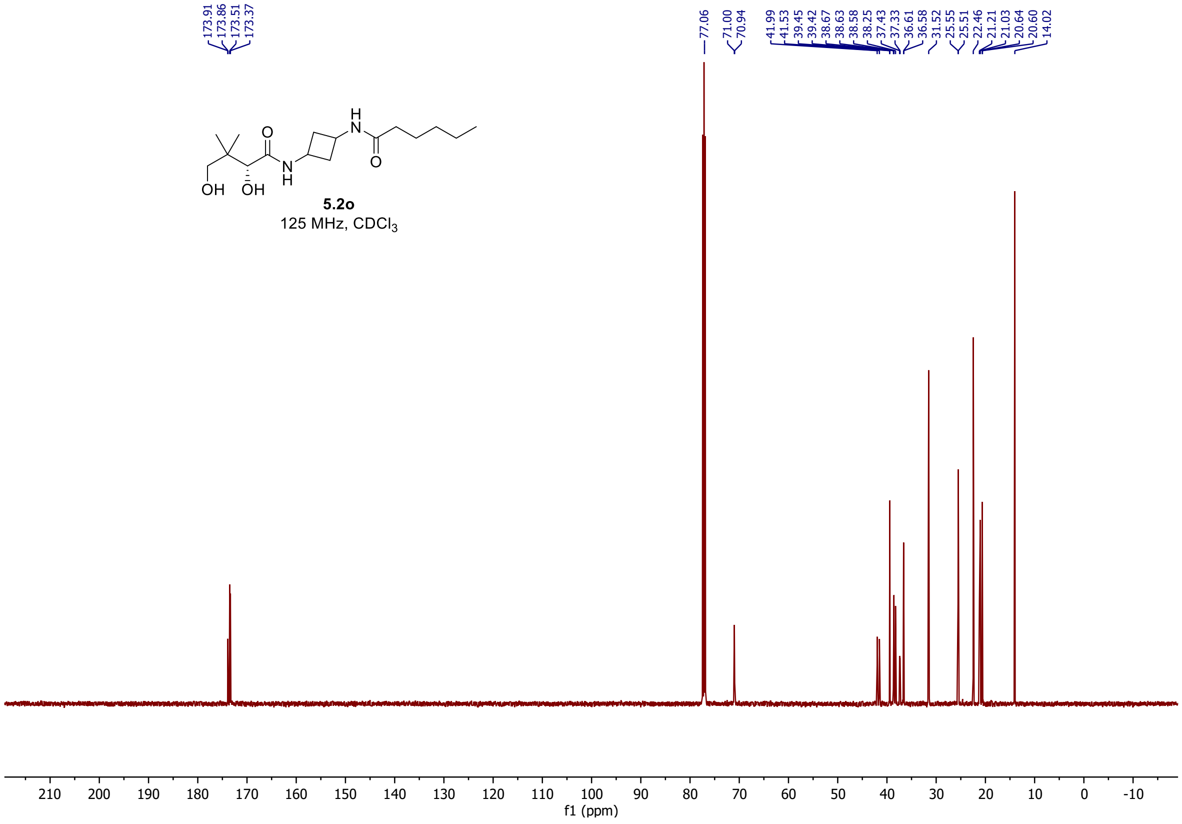




^1H and ^{13}C spectra of **5.2o**

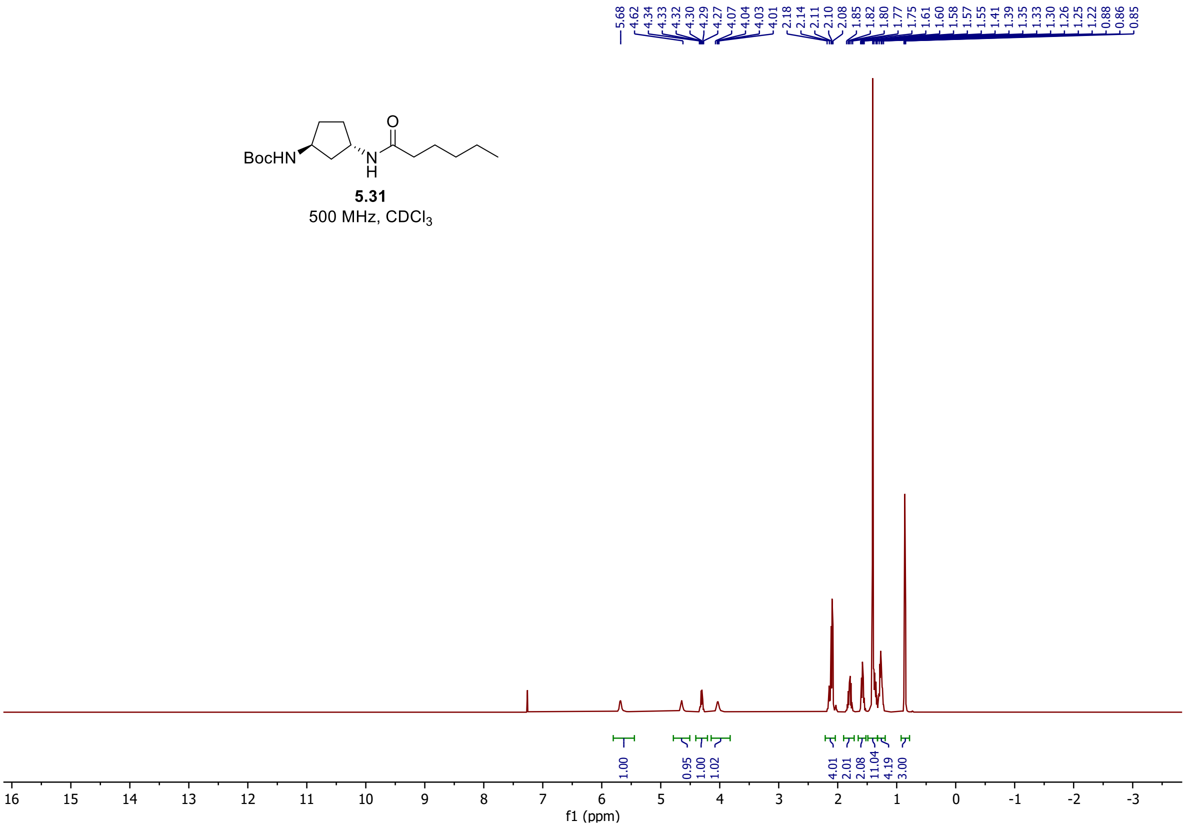

5.2o

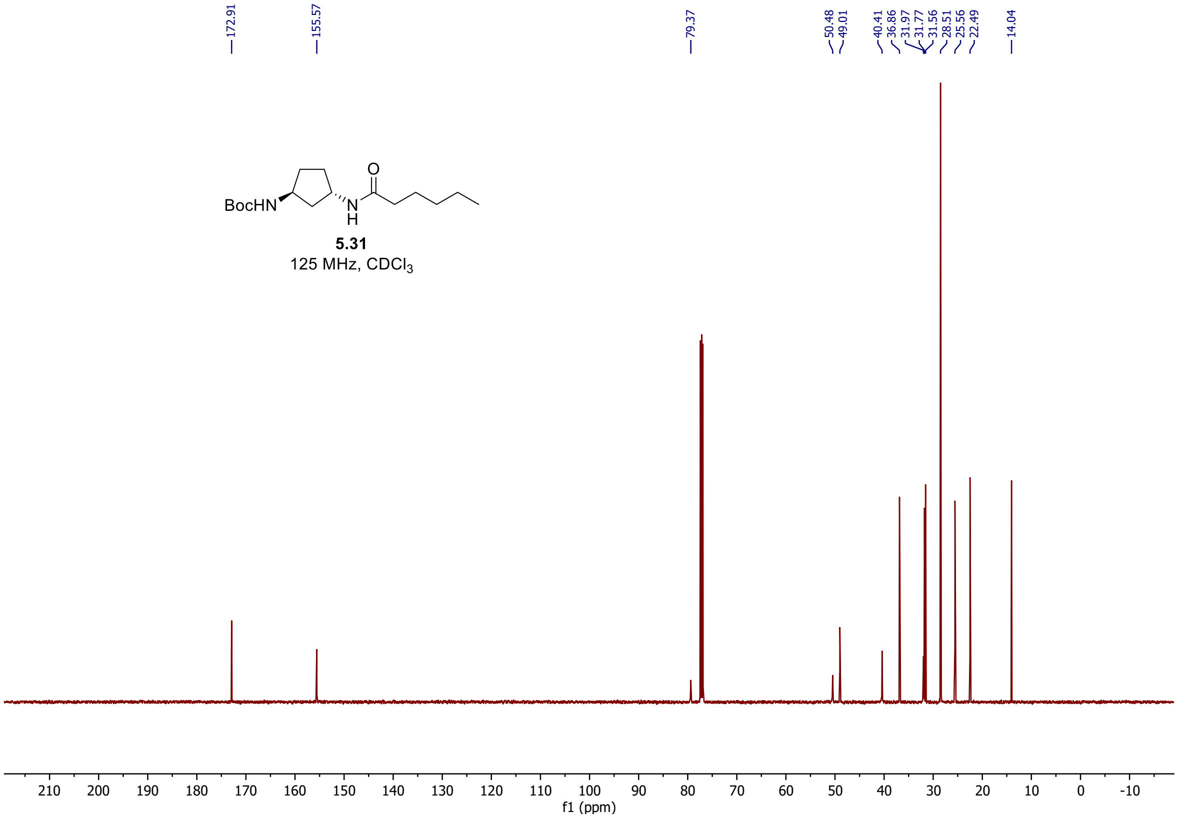
500 MHz, $CDCl_3$


5.2o

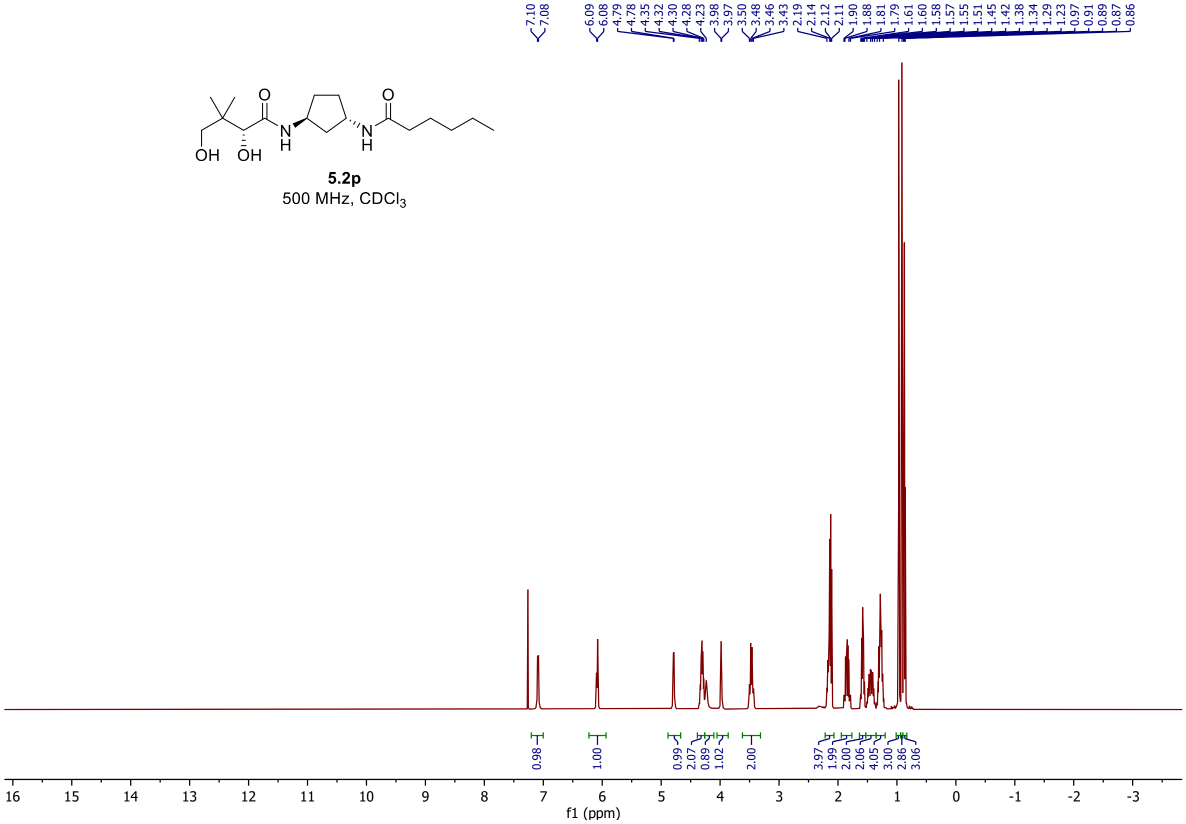
125 MHz, $CDCl_3$

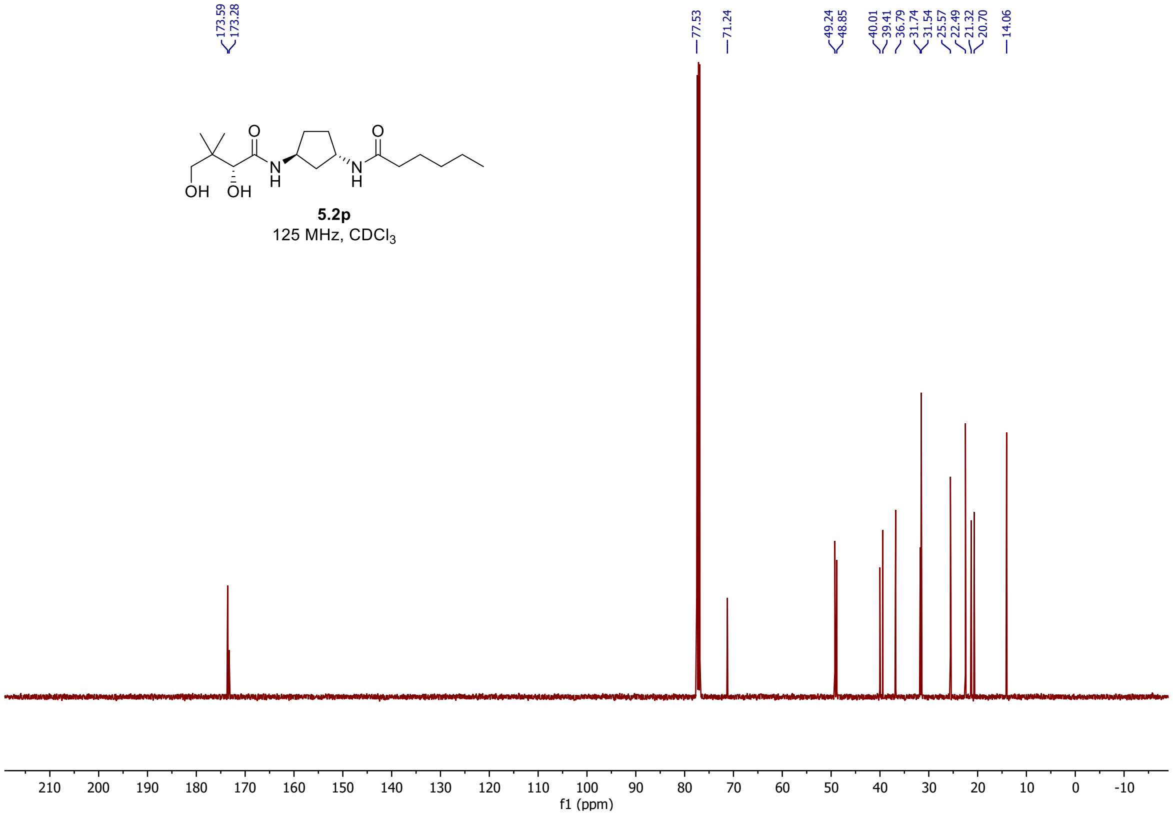
^{1}H and ^{13}C spectra of **5.31**



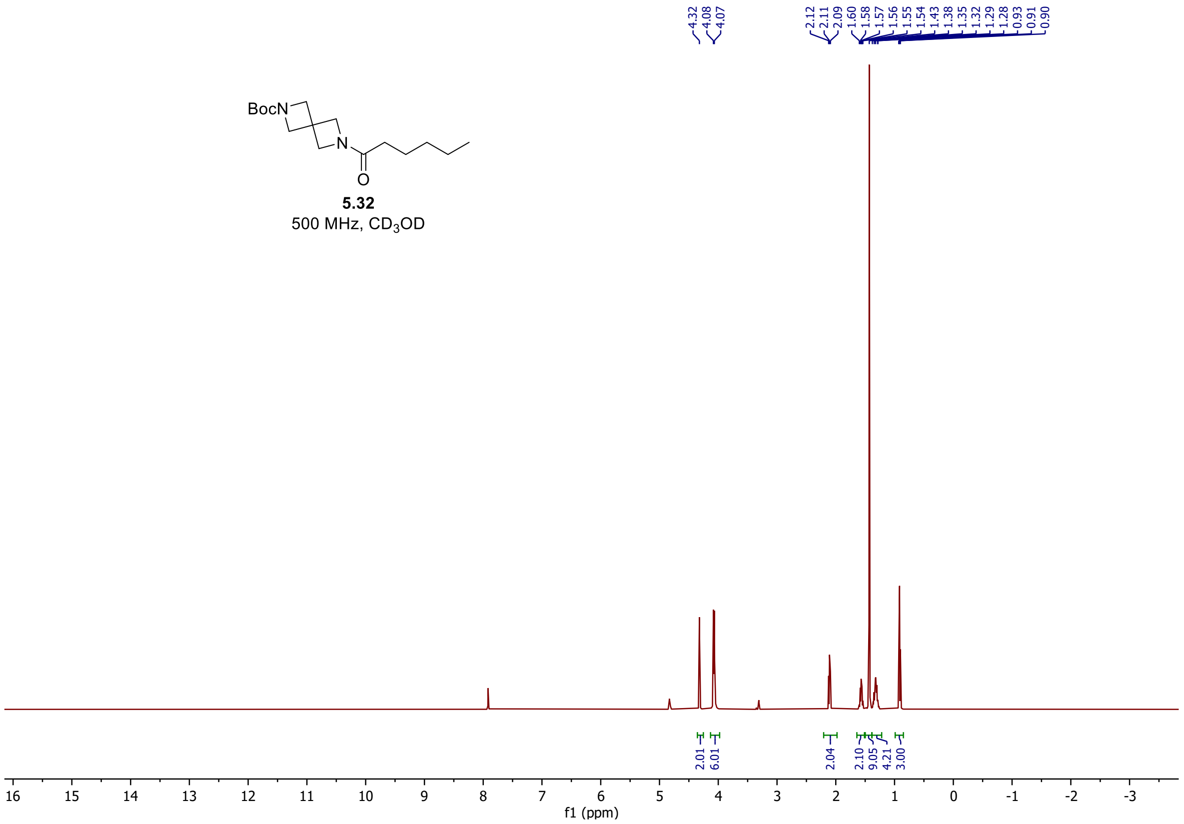


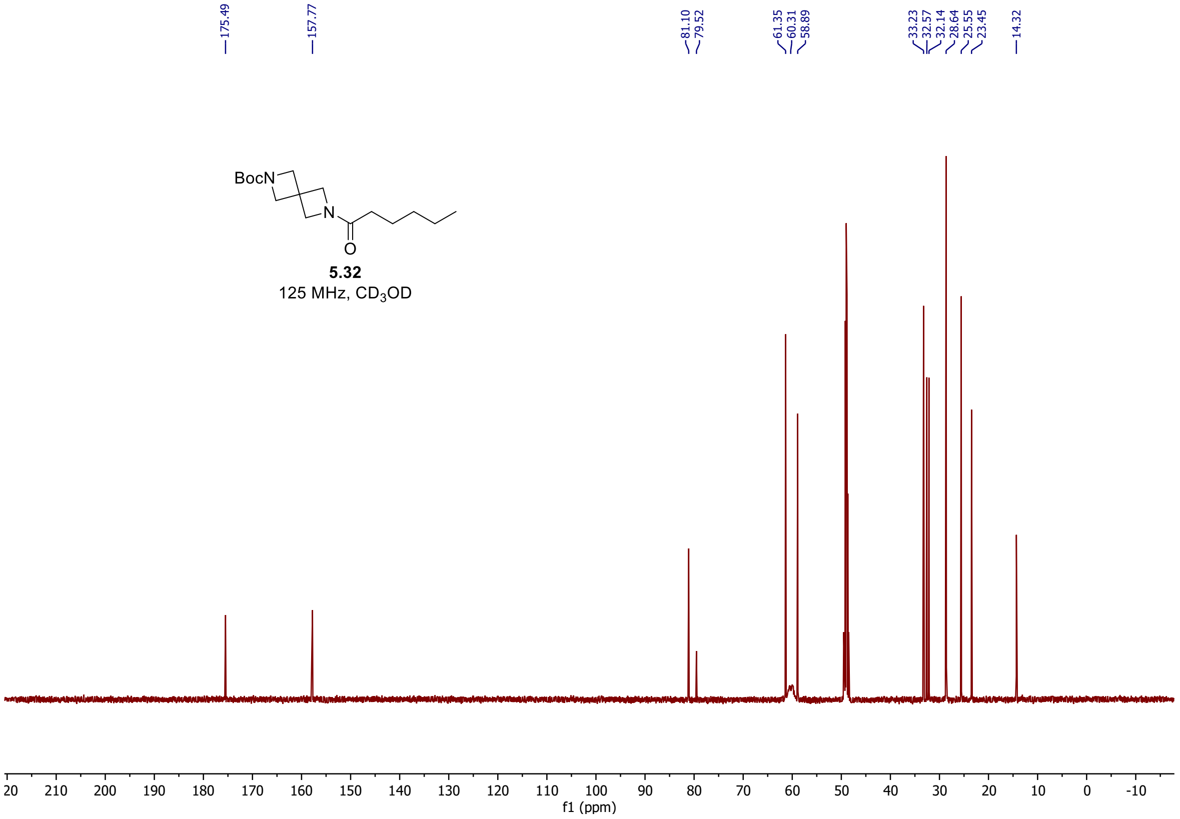
^{1}H and ^{13}C spectra of **5.2p**



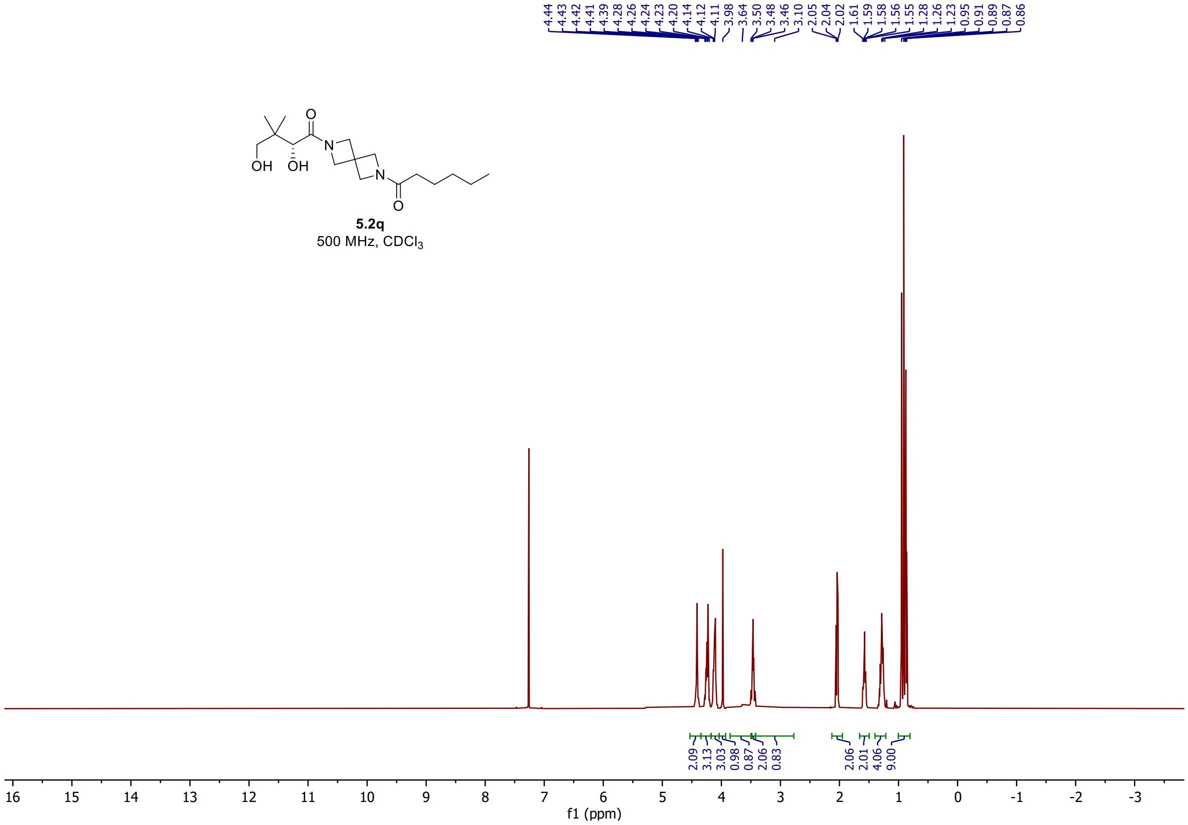


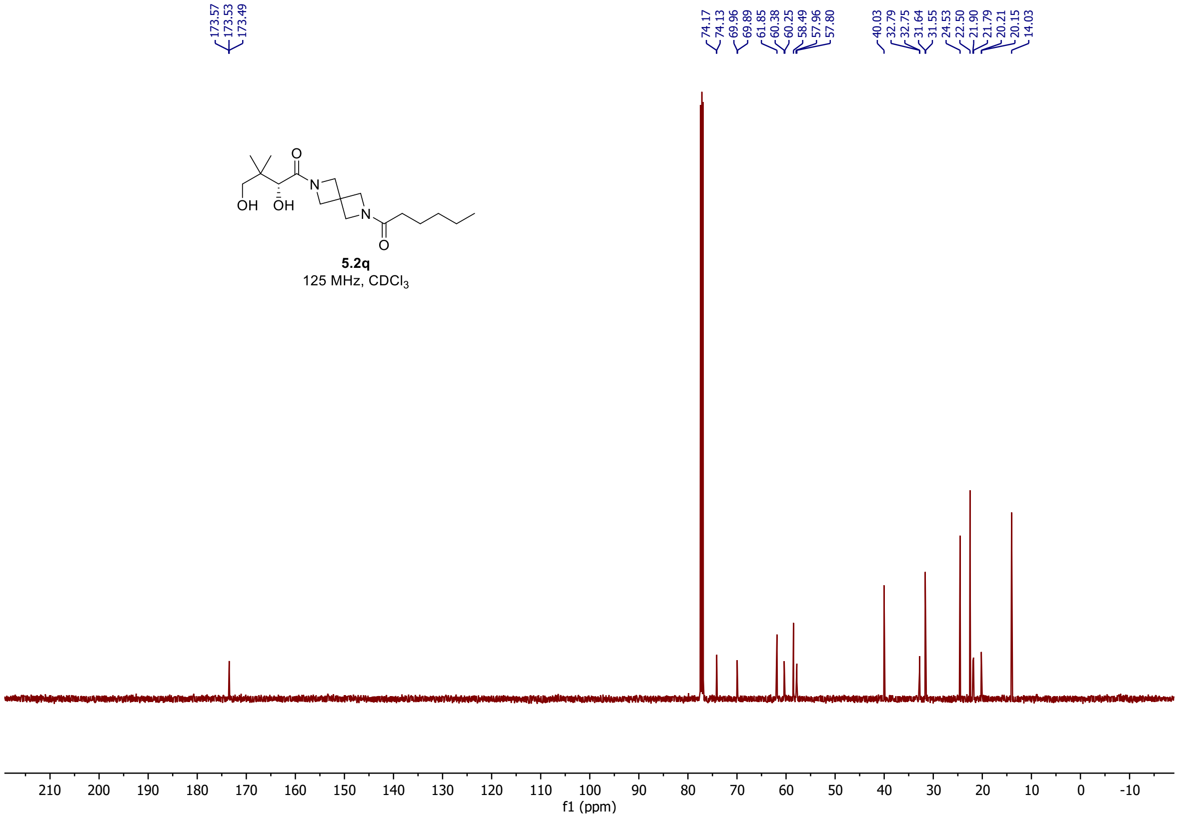
^{1}H and ^{13}C spectra of **5.32**





^{1}H and ^{13}C spectra of **5.2q**



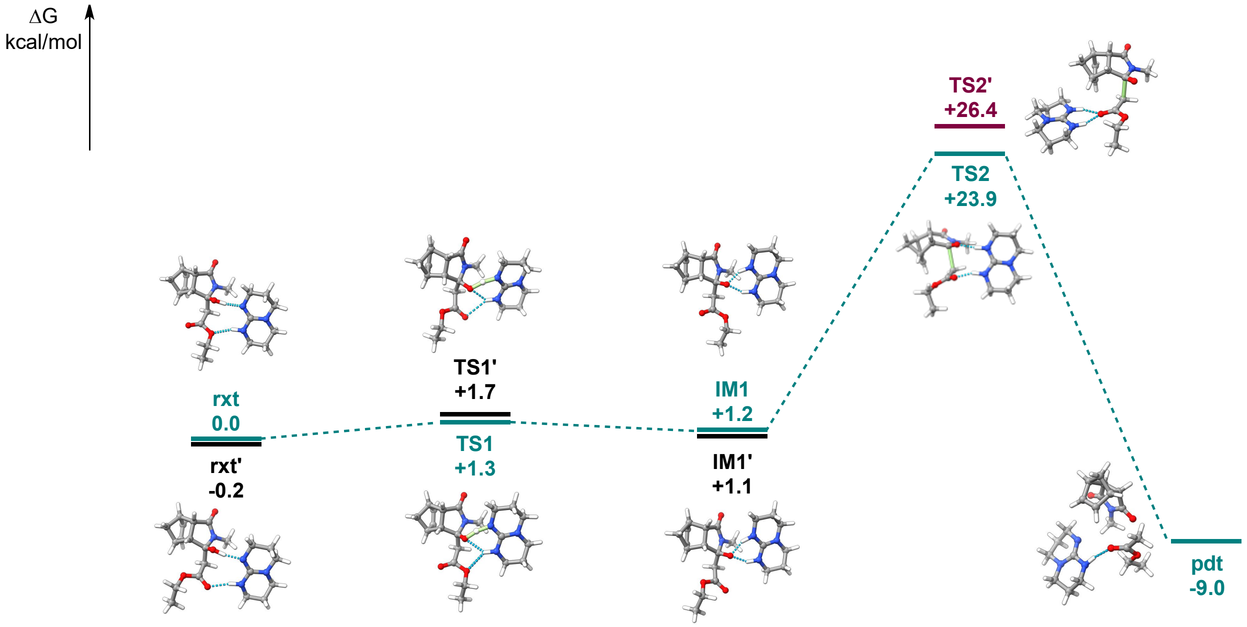


Appendix II. Computational Data

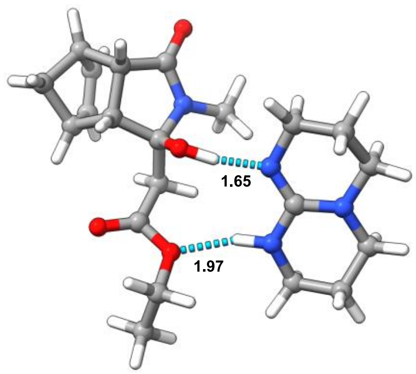
II-I Computational Data for Chapter 4

All calculations were performed with ORCA 5.0.4 version.[1] Results were visualized in ChimeraX[2] with SEQCROW.[3] Geometry optimization was performed at the B3LYP level of theory with the def2-SVP basis set[4] and D4 dispersion correction.[5] Conductor-like polarizable continuum model (CPCM)[6] was used as an implicit solvent model with default setting for DMSO. Frequency calculation was carried out at the same level of theory as geometry optimization. All stable structures were optimized to the local minimum with 0 imaginary frequency and all transition state structures were optimized to the saddle point with 1 imaginary frequency. Transition state search and optimization was achieved with the NEB-TS program[7] built in ORCA. Single-point energy was calculated at the ωB97M-V[8] level of theory with the def2-QZVP basis set[4] and D4 dispersion correction.[5] Free energy calculation was based on the Grimme's quasiRRHO model with a 100 cm^{-1} cut-off frequency[9] and performed by the SEQCROW thermochemistry function. Hydrogen bonds are indicated with blue dotted lines. Transition state bonds are indicated with green translucent lines. All bond lengths and atom distances are measured in Angstrom. All single point energies were given in Hartree.

<u>1. Elimination of ethyl acetate pathway</u>



In addition to what has been documented in the manuscript, an alternative pathway with different starting geometry for the deprotonation step was also calculated. Indicated in black in the above diagram, the alternative starting geometry features a hydrogen bond located on the carbonyl oxygen instead. All relative energies are referenced to the initial reactant structure (**rxt**). The two deprotonation pathways are essentially identical in terms of energy, thus the one with the lower barrier height was included in the main manuscript.

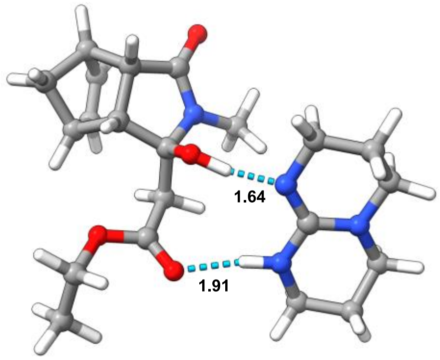


Substrate-TBD complex with hydrogen-bonding on the sp^3 oxygen atom (**rxt**)

single point energy: -1340.438841033339

C	3.086618	1.725232	-0.080782
C	2.575900	0.548961	0.837402
C	1.043210	0.755835	0.873914
C	0.836775	1.916362	-0.160806
C	1.315622	1.474677	-1.537068
C	2.655024	1.379890	-1.497236
C	2.034553	2.803806	0.264126
C	2.766537	-0.819780	0.215000
N	1.541136	-1.380328	0.010988
C	0.436023	-0.649078	0.649255
H	3.057566	0.582463	1.826165
H	0.691947	1.101899	1.853318
O	3.840355	-1.324438	-0.099367
O	0.142055	-1.162370	1.920470
C	-0.831889	-0.697735	-0.235119
C	-2.002470	-0.099427	0.505813
O	-2.857653	-1.047008	0.930326
O	-2.168369	1.080883	0.721453
C	-4.005852	-0.644282	1.714256
C	-5.182268	-0.296448	0.822828
C	1.385817	-2.675571	-0.620399
H	4.145550	1.974798	0.062819
H	-0.165462	2.355842	-0.116479
H	0.666077	1.215055	-2.375503
H	3.316821	1.004705	-2.280262
H	2.017978	3.079965	1.330764
H	2.136476	3.709088	-0.353284
H	-0.140962	-2.140111	1.888780
H	-0.679861	-0.145415	-1.170975
H	-1.064768	-1.741101	-0.482192
H	-4.220966	-1.516121	2.347993
H	-3.714578	0.201495	2.352856
H	-6.060966	-0.064538	1.445631

H	-4.959282	0.583176	0.199926
H	-5.438753	-1.141964	0.165160
H	2.377255	-3.143712	-0.680234
H	0.715162	-3.315078	-0.028360
H	0.982352	-2.580153	-1.642925
C	-0.230346	-6.545076	2.637973
N	-1.446801	-5.866888	2.205846
C	-1.392317	-4.524897	1.907924
N	-0.342705	-3.765027	2.088869
C	0.879442	-4.329786	2.636958
C	0.635599	-5.594968	3.453033
C	-2.546973	-6.714618	1.755453
C	-3.861309	-5.946913	1.726341
C	-3.675757	-4.671087	0.918568
N	-2.538369	-3.938138	1.442765
H	-0.527349	-7.420684	3.237005
H	0.335727	-6.927985	1.764869
H	1.592754	-4.557907	1.818947
H	1.374321	-3.559725	3.254534
H	0.113921	-5.344036	4.392816
H	1.586731	-6.082515	3.719050
H	-2.328407	-7.129088	0.750306
H	-2.615465	-7.571001	2.445031
H	-4.649568	-6.574252	1.283164
H	-4.166744	-5.693524	2.755479
H	-3.539366	-4.924889	-0.152296
H	-4.565932	-4.026485	0.986336
H	-2.446755	-2.958509	1.186983



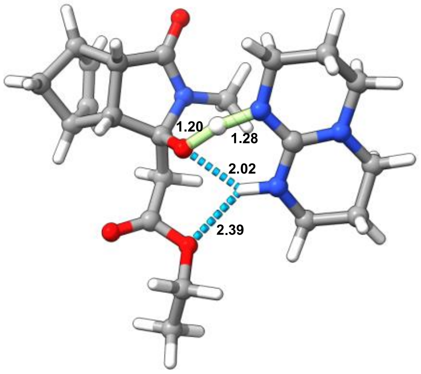
Substrate-TBD complex with hydrogen-bonding on the sp^2 oxygen atom (**rxt'**)

single point energy: -1340.439134371247

C	3.003966	1.511020	-0.186754
C	2.408216	0.400119	0.761853
C	0.888150	0.690146	0.753231
C	0.770412	1.816306	-0.332110
C	1.257136	1.294334	-1.677127

C	2.588467	1.132876	-1.599618
C	2.003437	2.655969	0.089186
C	2.537790	-0.999081	0.194525
N	1.288708	-1.497222	-0.025854
C	0.212365	-0.689758	0.571410
H	2.868421	0.445212	1.760252
H	0.534817	1.095650	1.708561
O	3.589319	-1.574231	-0.070038
O	-0.117511	-1.142951	1.855634
C	-1.047872	-0.719995	-0.326455
C	-2.244688	-0.177728	0.413032
O	-2.213540	1.147011	0.547176
O	-3.144118	-0.866828	0.860604
C	-3.284805	1.790730	1.277478
C	-4.477371	2.066317	0.381202
C	1.080450	-2.811400	-0.599775
H	4.070993	1.709412	-0.024671
H	-0.204284	2.315598	-0.333248
H	0.613813	1.032139	-2.519604
H	3.247872	0.692169	-2.349808
H	1.975773	2.973931	1.143813
H	2.167460	3.529697	-0.559462
H	-0.506781	-2.086242	1.845651
H	-0.886511	-0.157863	-1.255160
H	-1.284603	-1.759362	-0.584976
H	-3.559256	1.155227	2.131354
H	-2.838238	2.722293	1.650983
H	-5.240877	2.623703	0.947124
H	-4.182210	2.672661	-0.489537
H	-4.930051	1.128941	0.024614
H	2.053874	-3.317114	-0.646107
H	0.392340	-3.400976	0.022513
H	0.671340	-2.745654	-1.622079
C	-0.713045	-6.492809	2.162708
N	-1.867524	-5.780355	1.628670
C	-1.831010	-4.405412	1.562667
N	-0.879032	-3.664301	2.072969
C	0.242874	-4.285302	2.756922
C	-0.074180	-5.682432	3.281092
C	-2.824168	-6.563317	0.853584
C	-4.153578	-5.833630	0.722702
C	-3.902077	-4.438780	0.169034
N	-2.885237	-3.777463	0.963877
H	-1.062606	-7.469624	2.533059
H	0.027698	-6.696737	1.363064
H	1.115746	-4.345451	2.074369

H	0.561685	-3.628309	3.585486
H	-0.777804	-5.617080	4.129006
H	0.838047	-6.183630	3.641526
H	-2.415271	-6.790509	-0.152204
H	-2.962003	-7.528531	1.366224
H	-4.826203	-6.397991	0.058966
H	-4.634696	-5.761309	1.712662
H	-3.600032	-4.511578	-0.895429
H	-4.818354	-3.828778	0.200492
H	-2.865044	-2.757222	0.964001



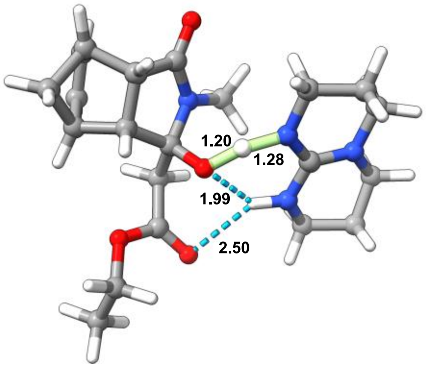
<u>Transition state for the deprotonation step starting from the **rxt** geometry (**TS1**)</u>

single point energy: -1340.433048666667

imaginary frequency: -944.05 cm^{-1}

C	3.608815	3.184290	-0.793049
C	2.832291	2.096065	0.044727
C	1.358855	2.559911	-0.037160
C	1.439344	3.760552	-1.043086
C	1.948860	3.271635	-2.392192
C	3.244268	2.945602	-2.249532
C	2.730555	4.421936	-0.496841
C	2.842811	0.722639	-0.598585
N	1.568033	0.382381	-0.923116
C	0.538009	1.277240	-0.347026
H	3.230182	2.033054	1.068875
H	0.988835	2.942270	0.921833
O	3.840082	0.041214	-0.828944
O	0.014184	0.768490	0.825785
C	-0.627658	1.472096	-1.354625
C	-1.795128	2.082475	-0.626719
O	-2.721102	1.159717	-0.313649
O	-1.893407	3.254046	-0.324971
C	-3.851983	1.572567	0.482669
C	-4.977562	2.101392	-0.386905

C	1.262551	-0.861887	-1.596208
H	4.679486	3.246691	-0.559775
H	0.524982	4.366015	-1.061579
H	1.337951	3.145143	-3.288318
H	3.895378	2.476559	-2.989917
H	2.672391	4.676120	0.573835
H	3.037340	5.307795	-1.073806
H	0.429968	-0.292956	1.197091
H	-0.342636	2.115106	-2.195716
H	-0.932227	0.493947	-1.745986
H	-4.155138	0.664945	1.023912
H	-3.517068	2.326396	1.209885
H	-5.853841	2.332560	0.239736
H	-4.673201	3.021919	-0.907753
H	-5.277320	1.351931	-1.136410
H	2.067074	-1.582865	-1.395933
H	0.314590	-1.274516	-1.230431
H	1.186266	-0.722602	-2.688857
C	0.820769	-4.333812	1.509570
N	-0.425015	-3.630688	1.212291
C	-0.428834	-2.268513	1.164842
N	0.603790	-1.521597	1.507726
C	1.872491	-2.110536	1.891444
C	1.684683	-3.513611	2.458845
C	-1.510941	-4.419078	0.631851
C	-2.839673	-3.681766	0.727769
C	-2.688794	-2.284840	0.142498
N	-1.563411	-1.622927	0.777416
H	0.558569	-5.304306	1.959232
H	1.370114	-4.547858	0.571883
H	2.557920	-2.146132	1.021974
H	2.355114	-1.454328	2.635000
H	1.189534	-3.455377	3.443119
H	2.656392	-4.010416	2.602962
H	-1.281696	-4.658722	-0.425135
H	-1.557821	-5.375527	1.175769
H	-3.615248	-4.244239	0.186544
H	-3.148853	-3.610258	1.784090
H	-2.548880	-2.348554	-0.954384
H	-3.593270	-1.683426	0.318366
H	-1.441767	-0.613364	0.655065



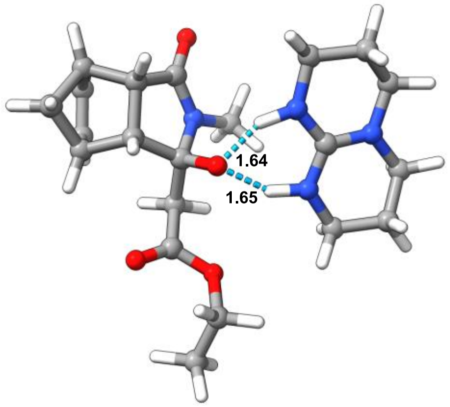
Transition state for the deprotonation step starting from the **rxt’** geometry (**TS1’**)

single point energy: -1340.432230803681

imaginary frequency: -952.06 cm^{-1}

C	3.677962	2.766961	-0.446930
C	2.774804	1.706714	0.294377
C	1.340640	2.253806	0.101835
C	1.572188	3.471875	-0.858702
C	2.164821	2.984606	-2.174081
C	3.423696	2.581647	-1.934094
C	2.847709	4.045399	-0.190209
C	2.766441	0.349397	-0.380468
N	1.510164	0.092357	-0.830315
C	0.482561	1.027126	-0.314972
H	3.080975	1.600252	1.346059
H	0.910117	2.632703	1.036510
O	3.740162	-0.385073	-0.536511
O	-0.160428	0.511289	0.796562
C	-0.588276	1.305654	-1.406861
C	-1.852943	1.787914	-0.748198
O	-1.745661	3.051939	-0.315948
O	-2.851177	1.112805	-0.592281
C	-2.846728	3.601846	0.439743
C	-3.937337	4.145615	-0.465240
C	1.200030	-1.130009	-1.541836
H	4.727010	2.762312	-0.124356
H	0.700552	4.133309	-0.936410
H	1.623318	2.909238	-3.119279
H	4.106574	2.091039	-2.630605
H	2.714620	4.278488	0.878560
H	3.249222	4.925275	-0.715791
H	0.192314	-0.565581	1.179202
H	-0.240087	2.030994	-2.152674
H	-0.841487	0.370557	-1.920376
H	-3.234784	2.821099	1.110580
H	-2.394069	4.400162	1.044434

H	-4.715869	4.630597	0.145370
H	-3.531192	4.894797	-1.163301
H	-4.407748	3.338248	-1.045894
H	1.930948	-1.901471	-1.262457
H	0.194495	-1.481415	-1.281928
H	1.250510	-0.985830	-2.635301
C	0.390036	-4.621743	1.466428
N	-0.787717	-3.866324	1.046904
C	-0.730037	-2.504557	1.021536
N	0.283560	-1.805401	1.496854
C	1.468756	-2.449958	2.029676
C	1.160325	-3.856032	2.534647
C	-1.831903	-4.599131	0.333249
C	-3.132818	-3.807694	0.293977
C	-2.860818	-2.412125	-0.249442
N	-1.782642	-1.808872	0.511558
H	0.044380	-5.593006	1.853184
H	1.040933	-4.831100	0.595014
H	2.260672	-2.492598	1.256204
H	1.872485	-1.827542	2.846100
H	0.549563	-3.798149	3.451675
H	2.088003	-4.393311	2.785018
H	-1.495407	-4.832401	-0.696168
H	-1.979017	-5.560751	0.849484
H	-3.865777	-4.331440	-0.337886
H	-3.553216	-3.735251	1.311076
H	-2.606380	-2.470251	-1.326038
H	-3.748674	-1.768504	-0.162559
H	-1.618355	-0.800499	0.441293



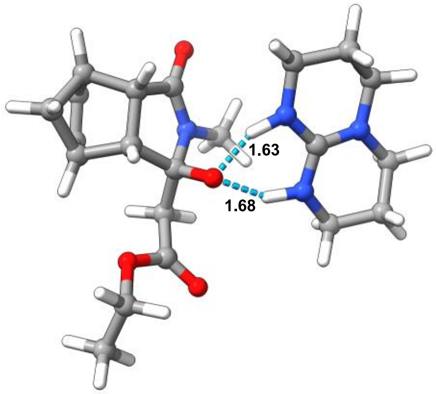
Deprotonated substrate-TBD complex starting from the **rxt** geometry (**IM1**)

single point energy: -1340.432230803681

C	3.152514	1.075014	-0.333691
C	2.542835	0.267053	0.876513
C	1.060816	0.709478	0.899854

C	0.954962	1.592131	-0.393318
C	1.267578	0.748821	-1.621235
C	2.578214	0.454926	-1.596858
C	2.294916	2.359010	-0.252165
C	2.502601	-1.231178	0.644340
N	1.209122	-1.630516	0.598059
C	0.236854	-0.597980	1.095701
H	3.094147	0.483963	1.804195
H	0.831787	1.343439	1.765284
O	3.486731	-1.957513	0.489822
O	-0.056563	-0.782366	2.408485
C	-1.069554	-0.681523	0.252102
C	-2.127694	0.143341	0.930805
O	-3.019601	-0.621200	1.584201
O	-2.177255	1.357510	0.922398
C	-4.046169	0.043866	2.349424
C	-5.231450	0.428549	1.482215
C	0.847071	-3.016473	0.407058
H	4.244148	1.183430	-0.293342
H	0.031454	2.182147	-0.436016
H	0.530759	0.388525	-2.342061
H	3.121039	-0.210375	-2.271440
H	2.393420	2.894416	0.706099
H	2.486508	3.051524	-1.086415
H	0.893264	-1.823828	3.252907
H	-0.930026	-0.320851	-0.775140
H	-1.407043	-1.724835	0.216415
H	-4.334822	-0.685942	3.119274
H	-3.608143	0.925123	2.840943
H	-6.026703	0.860665	2.110801
H	-4.941756	1.177559	0.730009
H	-5.641531	-0.453576	0.965159
H	1.738367	-3.640391	0.562002
H	0.069817	-3.314707	1.123717
H	0.467739	-3.202565	-0.613081
C	1.283466	-5.343612	4.744891
N	0.002295	-4.723193	4.404778
C	-0.032755	-3.486229	3.860265
N	1.068307	-2.727457	3.773162
C	2.398832	-3.207140	4.097796
C	2.304352	-4.292175	5.163674
C	-1.183824	-5.579898	4.369827
C	-2.458113	-4.745765	4.428557
C	-2.429608	-3.679920	3.340323
N	-1.175643	-2.951904	3.405290
H	1.101490	-6.055607	5.564032

H	1.658460	-5.925710	3.881699
H	2.902662	-3.596578	3.192909
H	2.998558	-2.356491	4.456697
H	1.996755	-3.844170	6.123215
H	3.284319	-4.768930	5.314459
H	-1.170084	-6.204453	3.456380
H	-1.126642	-6.262049	5.231669
H	-3.334155	-5.399118	4.302556
H	-2.535988	-4.264824	5.417921
H	-2.555590	-4.148174	2.345629
H	-3.256300	-2.964538	3.465368
H	-1.019336	-2.030187	2.910199

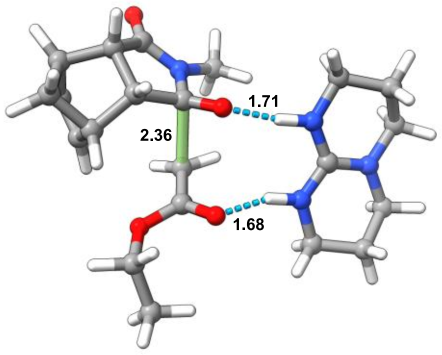


Deprotonated substrate-TBD complex starting from the **rxt'** geometry (**IM1'**)

single point energy: -1340.436754365581

C	3.049256	1.137098	0.262396
C	2.206022	0.056270	1.043058
C	0.746057	0.539458	0.874981
C	0.907882	1.744968	-0.117605
C	1.493141	1.255856	-1.435100
C	2.772813	0.911126	-1.215018
C	2.172184	2.385599	0.510568
C	2.242122	-1.316857	0.401860
N	0.996553	-1.633846	-0.023237
C	-0.081244	-0.735515	0.523744
H	2.541265	-0.015315	2.089173
H	0.327076	0.925711	1.812440
O	3.249029	-2.016098	0.264864
O	-0.645089	-1.265018	1.639500
C	-1.172237	-0.531260	-0.567995
C	-2.427335	-0.004872	0.072803
O	-2.301036	1.277850	0.452560
O	-3.440586	-0.650182	0.249899
C	-3.407318	1.890485	1.145616
C	-4.445300	2.431747	0.178406

C	0.710404	-2.912173	-0.633939
H	4.104268	1.182206	0.562265
H	0.008389	2.367645	-0.192050
H	0.936257	1.138871	-2.367078
H	3.460812	0.433824	-1.915890
H	2.051435	2.635463	1.577154
H	2.526410	3.270346	-0.040784
H	-0.838524	0.139889	-1.370315
H	-1.431231	-1.502348	-1.007831
H	-3.848246	1.152804	1.832300
H	-2.952249	2.699056	1.735218
H	-5.231614	2.964133	0.737437
H	-3.988243	3.139395	-0.531507
H	-4.918030	1.616318	-0.389353
H	1.541364	-3.600583	-0.425518
H	-0.215318	-3.336019	-0.221802
H	0.597655	-2.827769	-1.729062
C	1.016068	-6.058533	3.167345
N	-0.281309	-5.540273	2.730089
C	-0.433191	-4.222971	2.469753
N	0.526046	-3.335243	2.756125
C	1.847593	-3.705814	3.229396
C	1.766157	-5.021005	3.994484
C	-1.289664	-6.506128	2.290743
C	-2.676936	-5.875096	2.269101
C	-2.644915	-4.586128	1.457111
N	-1.567576	-3.739789	1.937265
H	0.829179	-6.965982	3.761130
H	1.614511	-6.360571	2.286901
H	2.551066	-3.791076	2.380937
H	2.224368	-2.898595	3.876579
H	1.238166	-4.863219	4.949723
H	2.775186	-5.393215	4.226216
H	-1.024831	-6.894820	1.289116
H	-1.261615	-7.357160	2.988078
H	-3.397806	-6.584327	1.836096
H	-2.998549	-5.656632	3.301111
H	-2.510120	-4.816852	0.382927
H	-3.591332	-4.032227	1.552261
H	-1.486876	-2.722611	1.677262
H	0.284120	-2.360187	2.418526



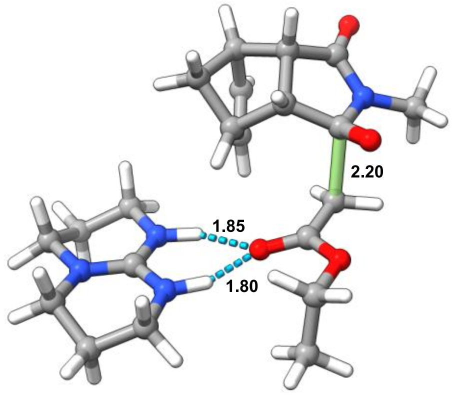
Transition state for the C–C bond cleavage with stabilization on both the product and leaving group (**TS2**)

single point energy: -1340.397335334514

imaginary frequency: -273.96 cm^{-1}

C	3.515145	3.798857	-0.936335
C	3.464166	2.476352	-0.101538
C	1.998468	2.403842	0.400476
C	1.341802	3.627554	-0.332117
C	1.420661	3.442495	-1.838023
C	2.709177	3.549403	-2.201438
C	2.498346	4.644499	-0.132472
C	3.674183	1.190200	-0.875718
N	2.610394	0.361175	-0.635580
C	1.598862	0.935370	0.206516
H	4.196058	2.501714	0.722414
H	1.918710	2.582067	1.481912
O	4.642926	0.901080	-1.565742
O	1.051594	0.282863	1.109657
C	-0.116168	0.730653	-1.401605
C	-1.183121	1.353577	-0.735137
O	-1.525464	2.594934	-1.226891
O	-1.788240	0.921144	0.275344
C	-2.493160	3.359920	-0.507859
C	-3.914969	3.030058	-0.936577
C	2.579149	-1.004211	-1.107941
H	4.526002	4.204912	-1.069891
H	0.358543	3.897694	0.067676
H	0.563494	3.219258	-2.468337
H	3.135372	3.392202	-3.194355
H	2.781479	4.789345	0.922868
H	2.292635	5.619397	-0.599727
H	0.383879	-1.283645	1.292435
H	0.205271	1.114725	-2.369066
H	-0.031694	-0.344332	-1.250111
H	-2.366498	3.196401	0.573139

H	-2.255427	4.412266	-0.730802
H	-4.631573	3.696516	-0.428692
H	-4.034640	3.161035	-2.024440
H	-4.166898	1.990174	-0.678753
H	3.605796	-1.391821	-1.163809
H	1.990229	-1.614170	-0.412425
H	2.123733	-1.071877	-2.109341
C	-0.491293	-4.989534	1.473684
N	-1.465758	-3.969156	1.083714
C	-1.100534	-2.668467	1.006427
N	0.112548	-2.276115	1.421184
C	1.126730	-3.172732	1.960135
C	0.475747	-4.433005	2.508679
C	-2.755685	-4.425176	0.561570
C	-3.801583	-3.323983	0.660414
C	-3.264620	-2.059925	0.006553
N	-1.947012	-1.745444	0.539362
H	-1.052810	-5.841736	1.882665
H	0.056602	-5.351748	0.583567
H	1.857755	-3.435923	1.173532
H	1.677165	-2.633852	2.746550
H	-0.072647	-4.204719	3.437677
H	1.243589	-5.183850	2.746316
H	-2.639678	-4.757855	-0.487013
H	-3.058228	-5.303286	1.151397
H	-4.729542	-3.648425	0.166813
H	-4.032509	-3.127355	1.720619
H	-3.214768	-2.188802	-1.090697
H	-3.919083	-1.197835	0.202159
H	-1.682607	-0.732701	0.526976



Transition state for the C–C bond cleavage with stabilization on the leaving group only (**TS2’**)

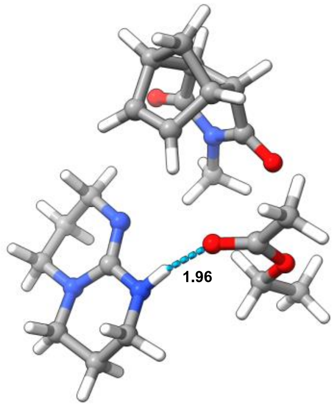
single point energy: -1340.394342742087

imaginary frequency: -287.77 cm^{-1}

C	4.046264	-0.586240	-0.064155

C	3.763108	-1.201545	1.349166
C	2.290395	-0.811665	1.642518
C	1.854256	-0.153734	0.286626
C	1.956282	-1.162599	-0.847119
C	3.257105	-1.414893	-1.064213
C	3.142595	0.667359	0.014986
C	3.795551	-2.716874	1.428571
N	2.606929	-3.151595	1.929704
C	1.669435	-2.078029	2.272033
H	4.469983	-0.806329	2.096946
H	2.215279	-0.042056	2.423418
O	4.747784	-3.433230	1.130519
O	1.145158	-2.061827	3.394551
C	0.026243	-2.798081	0.993621
C	-0.975842	-1.811448	1.094400
O	-1.669713	-1.862871	2.270060
O	-1.230308	-0.894224	0.273118
C	-2.588585	-0.813273	2.579723
C	-3.944140	-1.005846	1.915229
C	2.383765	-4.518490	2.335719
H	5.111519	-0.437302	-0.282616
H	0.909581	0.392514	0.352902
H	1.108608	-1.630064	-1.345372
H	3.686195	-2.149981	-1.747980
H	3.409192	1.352956	0.835741
H	3.101184	1.223096	-0.934276
H	-0.688104	0.013056	-1.247577
H	0.421736	-3.002349	0.000546
H	-0.100197	-3.661314	1.646022
H	-2.691692	-0.843997	3.675182
H	-2.148809	0.161457	2.313763
H	-4.645531	-0.227274	2.257271
H	-3.863571	-0.941610	0.819852
H	-4.366747	-1.989098	2.177717
H	3.353047	-5.024531	2.443035
H	1.852359	-4.520213	3.298788
H	1.778628	-5.070895	1.597516
C	-0.763948	3.276050	-3.227758
N	-1.648101	2.983954	-2.096150
C	-1.538154	1.824339	-1.419479
N	-0.706593	0.856436	-1.834097
C	0.199320	0.995139	-2.965147
C	-0.376757	1.996150	-3.956553
C	-2.489676	4.067141	-1.581018
C	-3.683731	3.506116	-0.820107
C	-3.199330	2.548243	0.259299

N	-2.270214	1.589933	-0.321472
H	-1.304295	3.958174	-3.900320
H	0.136428	3.808420	-2.869385
H	1.195418	1.324627	-2.619100
H	0.326387	0.005428	-3.426862
H	-1.266405	1.567726	-4.447213
H	0.362566	2.225052	-4.737868
H	-1.889995	4.731491	-0.931762
H	-2.823185	4.663047	-2.443011
H	-4.256131	4.329637	-0.368724
H	-4.349932	2.975426	-1.520380
H	-2.709994	3.107840	1.077156
H	-4.038162	1.989905	0.700461
H	-2.094458	0.682765	0.133556



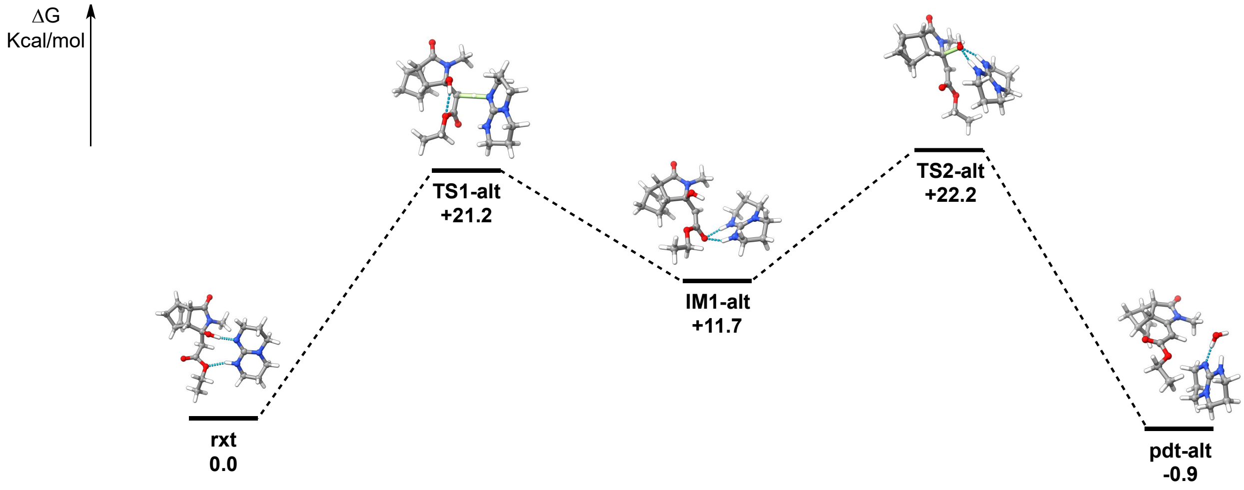
Product-TBD complex (**pdt**)

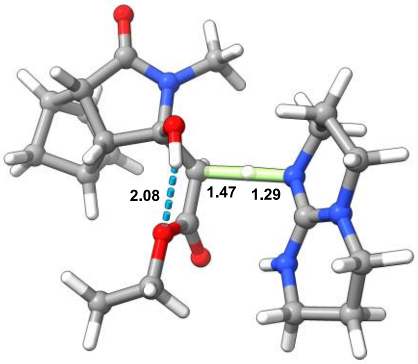
single point energy: -1340.446039896638

C	0.455525	0.738241	1.644215
C	-0.148361	0.593472	0.196697
C	0.380314	-0.780031	-0.271665
C	1.219478	-1.279426	0.963832
C	0.235291	-1.520882	2.098630
C	-0.214947	-0.321656	2.504846
C	-1.656332	0.470112	0.139471
N	-1.972347	-0.801201	-0.328320
C	-0.858970	-1.589761	-0.583954
O	-2.481703	1.305764	0.450655
O	-0.914556	-2.737638	-0.982702
C	-3.336658	-1.281884	-0.460481
H	0.171247	1.430611	-0.441411
H	1.013891	-0.728280	-1.169324
C	1.830772	0.071986	1.403633
H	0.443462	1.766783	2.025306
H	1.907661	-2.099938	0.726452
H	-0.119690	-2.504624	2.408449

H	-1.010335	-0.130041	3.226950
H	-3.360188	-2.065865	-1.227919
H	-3.676661	-1.689560	0.506397
H	-3.981483	-0.444178	-0.756420
H	2.425300	0.562593	0.616479
H	2.427397	-0.013306	2.323994
C	-5.681018	-1.360405	4.828090
N	-5.203784	-2.688121	4.463850
C	-4.179911	-2.798007	3.537147
N	-3.662848	-1.814162	2.862675
C	-4.140104	-0.464645	3.105659
C	-5.570144	-0.417869	3.638817
C	-5.499587	-3.753914	5.415051
C	-5.285529	-5.127035	4.794132
C	-3.893762	-5.182032	4.183342
N	-3.736163	-4.075358	3.256913
H	-6.727423	-1.455897	5.162970
H	-5.105825	-0.959266	5.688300
H	-3.471222	0.051867	3.826126
H	-4.060566	0.116133	2.171030
H	-6.273933	-0.740465	2.851526
H	-5.852199	0.604680	3.937235
H	-4.869910	-3.649926	6.323460
H	-6.545701	-3.634507	5.741107
H	-5.404578	-5.906642	5.562261
H	-6.041326	-5.303428	4.010093
H	-3.134103	-5.155859	4.992886
H	-3.740754	-6.123315	3.631812
H	-2.883942	-4.087514	2.697251
C	0.678037	-5.269867	0.498534
C	-0.768610	-5.079883	0.855016
O	-1.585377	-5.545487	-0.086029
O	-1.161340	-4.536550	1.873387
C	-2.996637	-5.272942	0.050714
C	-3.666241	-5.642146	-1.253964
H	0.948806	-4.467121	-0.205905
H	1.302627	-5.189773	1.396856
H	0.837677	-6.233934	-0.004361
H	-3.390405	-5.856145	0.898385
H	-3.125526	-4.207337	0.286297
H	-4.747661	-5.446722	-1.184196
H	-3.257138	-5.041235	-2.081500
H	-3.521271	-6.708517	-1.488812

2. Elimination of water pathway





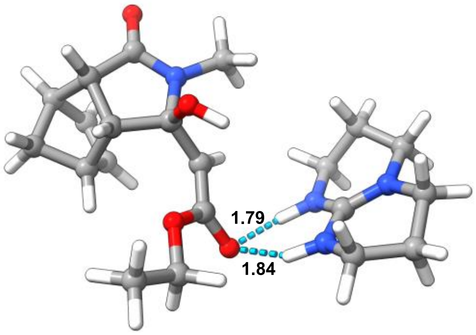
Transition state for the deprotonation step in the water elimination pathway (**TS1-alt**)

single point energy: -1340.401127635924

imaginary frequency: -1070.31 cm^{-1}

C	2.629148	4.285318	-0.855081
C	2.627180	3.114173	0.199617
C	1.200359	2.532631	0.098086
C	0.584640	3.356189	-1.085133
C	1.367601	3.067699	-2.356715
C	2.580034	3.631727	-2.227582
C	1.160576	4.748428	-0.723952
C	3.538505	1.966254	-0.167699
N	2.779791	0.853278	-0.387839
C	1.372544	0.985647	-0.027536
H	2.890657	3.489916	1.199998
H	0.609907	2.728547	0.999999
O	4.757672	2.027244	-0.294481
O	1.238165	0.410102	1.283808
C	0.445762	0.283692	-1.015953
C	-0.955348	0.600949	-0.948009

O	-1.346201	0.988213	0.312264
O	-1.792337	0.427051	-1.837036
C	-2.728598	1.297949	0.540712
C	-3.042558	2.746172	0.205951
C	3.396603	-0.409355	-0.723871
H	3.419621	5.029315	-0.693514
H	-0.505275	3.277169	-1.161582
H	1.016639	2.439057	-3.176481
H	3.429512	3.539783	-2.907483
H	0.892688	5.083344	0.291302
H	0.892277	5.525575	-1.455691
H	0.280715	0.367425	1.444160
H	0.802442	0.290300	-2.051541
H	0.261446	-1.141869	-0.730192
H	-3.355188	0.617329	-0.051497
H	-2.895414	1.091416	1.608007
H	-4.089377	2.972868	0.465643
H	-2.391086	3.432535	0.769815
H	-2.907354	2.937849	-0.869575
H	4.440304	-0.209614	-0.998820
H	3.385642	-1.101565	0.133378
H	2.883537	-0.885390	-1.572109
C	-0.036101	-4.145462	1.815647
N	-1.216389	-3.634020	1.110773
C	-1.119531	-2.702141	0.124273
N	0.034229	-2.383424	-0.451084
C	1.194224	-3.181468	-0.091209
C	1.230797	-3.403223	1.417229
C	-2.495032	-4.093580	1.656277
C	-3.664571	-3.747226	0.747913
C	-3.546967	-2.288065	0.329828
N	-2.251382	-2.088120	-0.296256
H	-0.222833	-4.054508	2.899614
H	0.063774	-5.224025	1.596013
H	1.169530	-4.158562	-0.612296
H	2.092503	-2.659259	-0.438610
H	1.279567	-2.417964	1.909505
H	2.112038	-3.985426	1.727852
H	-2.426529	-5.184156	1.806908
H	-2.641423	-3.640539	2.655001
H	-3.655674	-4.386850	-0.150321
H	-4.608843	-3.928278	1.282694
H	-4.322982	-2.013835	-0.398704
H	-3.672263	-1.629363	1.209945
H	-2.171375	-1.447857	-1.084361

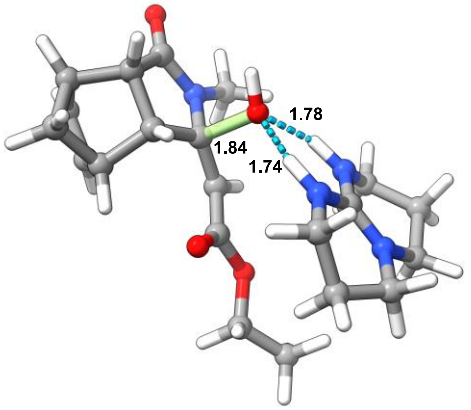


Deprotonated substrate-TBD complex in the water elimination pathway (**IM1-alt**)

single point energy: -1340.416217286328

C	1.395754	-0.336435	1.276053
N	0.157497	0.359952	0.913107
C	0.148838	1.300343	-0.048973
N	1.241362	1.561028	-0.778963
C	2.536815	0.950914	-0.525198
C	2.616410	0.505475	0.929517
C	-1.049999	0.029450	1.676852
C	-2.311332	0.421845	0.918707
C	-2.194635	1.861317	0.433218
N	-0.962279	2.002699	-0.323193
H	1.144813	2.391495	-1.394174
H	1.358051	-0.533538	2.358098
H	1.434171	-1.314864	0.763497
H	2.694437	0.087409	-1.196902
H	3.316122	1.692579	-0.754403
H	2.654359	1.391657	1.584685
H	3.530840	-0.080981	1.101492
H	-1.036875	-1.054877	1.867265
H	-1.009750	0.536294	2.658191
H	-2.449122	-0.247290	0.053182
H	-3.185307	0.306440	1.576231
H	-3.035065	2.128554	-0.224085
H	-2.211678	2.558715	1.291636
H	-0.824096	2.771659	-0.997777
C	4.383050	8.580576	-0.611735
C	3.731314	7.915525	0.658513
C	2.395936	7.346602	0.123826
C	2.474257	7.670819	-1.404323
C	3.637660	6.899487	-2.008890
C	4.774749	7.446660	-1.546290
C	4.486715	6.718042	1.192418
N	3.712746	5.611932	1.043570
C	2.334155	5.859032	0.579652
H	3.613959	8.657294	1.464095

H	1.526622	7.859093	0.551996
C	3.103383	9.084204	-1.318438
O	5.622713	6.735008	1.663960
C	4.120667	4.318990	1.545265
O	1.468556	5.820430	1.730308
C	1.932014	4.827638	-0.429656
C	0.713779	4.782997	-1.073975
O	-0.162023	5.810836	-0.770067
C	-1.475271	5.759123	-1.314151
C	-2.177588	7.054388	-0.952975
O	0.321240	3.892204	-1.903463
H	5.164352	9.315575	-0.378245
H	1.510671	7.573526	-1.917348
H	3.538631	6.009598	-2.630729
H	5.794044	7.083361	-1.694586
H	2.514903	9.790266	-0.709950
H	3.308107	9.525233	-2.306192
H	5.019655	4.455363	2.161641
H	3.317501	3.883219	2.159832
H	4.358052	3.613108	0.731891
H	0.993926	4.979119	1.662341
H	2.668962	4.080317	-0.717827
H	-1.430900	5.618000	-2.406968
H	-2.026220	4.894079	-0.900294
H	-3.210258	7.048645	-1.336565
H	-2.215394	7.187050	0.140505
H	-1.652481	7.921105	-1.386196



Transition state for the C–O bond cleavage in the water elimination pathway (**TS2-alt**)

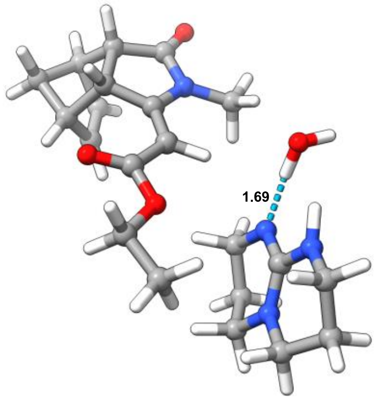
single point energy: -1340.401218565017

imaginary frequency: -238.62 cm^{-1}

C	2.977024	4.288824	0.592941
C	2.988115	2.760561	0.981797
C	1.512079	2.329000	0.788488

C	0.849911	3.631020	0.213532
C	1.481007	3.944419	-1.132862
C	2.742740	4.349946	-0.909534
C	3.776543	1.902110	0.015286
N	2.901654	1.063939	-0.628573
C	1.576933	1.092594	-0.109128
C	1.570303	4.673169	1.103447
H	3.371121	2.619024	2.003972
H	1.011660	2.072833	1.726927
O	4.980891	1.958888	-0.197360
C	3.342284	0.107666	-1.619773
C	0.519802	0.697220	-0.977690
C	-0.841778	0.819004	-0.632239
O	-1.363098	1.432310	0.310776
O	-1.648611	0.114937	-1.523344
C	-3.050190	0.357345	-1.490492
C	-3.766112	-0.852380	-2.058916
H	3.837405	4.850014	0.979639
H	-0.242931	3.588885	0.245437
H	1.006671	3.764060	-2.098856
H	3.514795	4.557959	-1.653406
H	1.431449	4.499093	2.182975
H	1.298127	5.710764	0.856316
H	4.436112	0.169582	-1.684971
H	3.048142	-0.912686	-1.328627
H	2.910845	0.331587	-2.608407
H	0.752244	0.035190	-1.811082
H	-3.369349	0.564962	-0.458395
H	-3.279072	1.262908	-2.085504
H	-4.854207	-0.680353	-2.076255
H	-3.434017	-1.062308	-3.088582
H	-3.566494	-1.744472	-1.445451
C	-3.002830	-2.867178	1.456162
N	-1.790389	-3.036440	0.651524
C	-0.703972	-2.270594	0.869875
N	-0.682100	-1.351956	1.841301
C	-1.815097	-1.055155	2.699567
C	-3.110024	-1.449381	2.000676
C	-1.816876	-4.078650	-0.380505
C	-0.416078	-4.469302	-0.835488
C	0.414198	-3.215152	-1.081211
N	0.406437	-2.417150	0.129260
H	-3.863798	-3.094608	0.809409
H	-3.004939	-3.606168	2.278753
H	-1.721107	-1.589545	3.663144
H	-1.802736	0.023015	2.914702

H	-3.302447	-0.749083	1.174461
H	-3.957015	-1.387022	2.699624
H	-2.342734	-4.951741	0.037326
H	-2.414268	-3.716010	-1.236004
H	0.075214	-5.081533	-0.061315
H	-0.488428	-5.076797	-1.749673
H	1.456521	-3.467647	-1.323460
H	0.002070	-2.641516	-1.933379
O	1.684181	-0.213544	1.139379
H	0.163198	-0.747130	1.825547
H	2.467515	-0.065172	1.693751
H	1.133426	-1.705156	0.320013



<u>Product-TBD complex in the water elimination pathway (**TS2-alt**)</u>

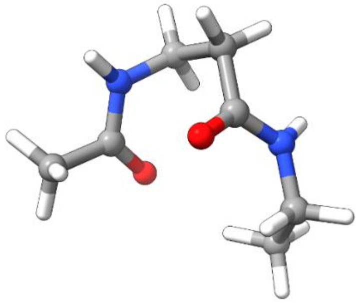
single point energy: -1340.434960516597

C	3.216086	1.215078	-0.221691
C	2.426955	0.442587	0.900324
C	0.948421	0.580797	0.463553
C	1.061230	1.401141	-0.878541
C	1.772414	0.514097	-1.887199
C	3.055187	0.406785	-1.501292
C	2.689289	-1.044601	0.933272
N	1.509773	-1.695964	0.591526
C	0.450860	-0.839128	0.344305
C	2.210380	2.358424	-0.486531
H	2.638340	0.875891	1.889251
H	0.329783	1.141075	1.176093
O	3.735757	-1.610702	1.188308
C	-0.798933	-1.275373	0.037559
C	-1.922254	-0.375804	-0.199871
O	-1.930989	0.843792	-0.120561
O	-3.028953	-1.076976	-0.535050
C	-4.225342	-0.331956	-0.809097
C	-5.291693	-1.317276	-1.235196
C	1.435157	-3.139005	0.464444

H	4.239892	1.485222	0.065579
H	0.108203	1.839502	-1.189873
H	1.282328	-0.015728	-2.706488
H	3.827882	-0.229391	-1.937938
H	1.990396	2.964625	0.406782
H	2.519802	3.013750	-1.314587
H	-1.022434	-2.339335	-0.009174
H	-4.518476	0.224813	0.096679
H	-4.015314	0.411463	-1.595500
H	-6.229817	-0.784507	-1.455052
H	-4.981094	-1.861740	-2.139868
H	-5.488798	-2.052806	-0.439821
H	2.394325	-3.553168	0.798031
H	0.612642	-3.547557	1.069057
H	1.261730	-3.418945	-0.587336
O	-1.510209	-4.586824	1.241824
H	-1.091370	-5.444927	1.403978
H	-1.537699	-4.514195	0.231414
C	-3.387660	-4.099731	-3.865417
N	-4.008291	-4.664390	-2.672563
C	-3.294252	-4.698759	-1.497370
N	-2.030976	-4.377779	-1.379351
C	-1.308715	-3.868336	-2.529432
C	-1.887379	-4.358383	-3.854150
C	-5.450471	-4.885859	-2.723316
C	-5.909706	-5.824122	-1.616069
C	-5.376237	-5.326229	-0.280557
N	-3.939136	-5.165160	-0.378847
H	-3.860275	-4.565961	-4.744859
H	-3.589794	-3.011789	-3.930654
H	-1.312005	-2.759396	-2.518872
H	-0.247863	-4.163075	-2.444601
H	-1.703324	-5.440876	-3.966717
H	-1.411338	-3.848832	-4.706908
H	-5.992216	-3.922088	-2.652344
H	-5.689845	-5.311262	-3.711467
H	-7.009279	-5.870064	-1.601196
H	-5.529948	-6.841821	-1.807790
H	-5.880709	-4.376509	-0.009511
H	-5.593947	-6.046840	0.523159
H	-3.395779	-5.048550	0.475783

II-II Computational Data for Chapter 5

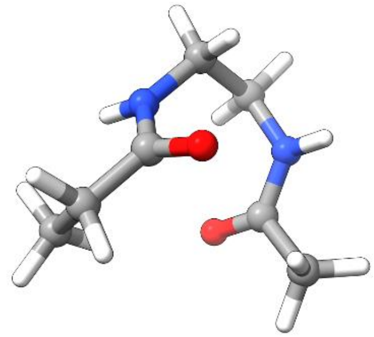
All calculations were performed with ORCA version 6.[1] Results were visualized in ChimeraX[2] with SEQCROW.[3] Conformational Sampling was performed with the semiempirical tight binding (GFN2-xTB) method[10] using the ORCA built-in global optimizer algorithm (GOAT). The analytical linearized Poisson-Boltzmann (ALPB) model was used as an implicit solvent model with default setting for water.[11] Electronic charge distribution was calculated based on charges from electrostatic potentials using a grid-based method (CHELPG)[12] at the B3LYP/def2-TZVPPD level of theory. Hydrogen bonds are indicated with blue dotted lines. All bond lengths and atom distances are measured in Angstrom. All energies are given in Hartree.



Global minimum of truncated *N*5-Pan (Figure **5.2a**)

Eh = -36.1605793405

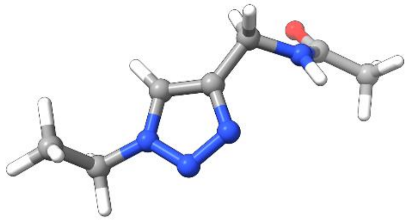
C	2.64611147628250797936	-1.36202200085954716613	0.92809328744409780310
C	1.69911909581169107142	-0.19059122564635533337	0.88664746172675945601
N	2.02078219243124124205	0.75723466184525500822	-0.01528509315795051338
O	0.73022820885510608679	-0.08536460765627655600	1.63287866141591209157
C	1.09748274777599319485	1.80970860730156535290	-0.37417803950922440270
C	0.23890798348815850405	1.41280977813436781076	-1.58884936610879257124
C	-0.47263662388299243489	0.10613218836309840087	-1.28193513679847859166
N	-1.70061637097194351398	0.23545480586476433271	-0.76688562114175162776
O	0.05873400277832279553	-0.98111106510064316488	-1.50073972576926895073
C	-2.45681771377432323078	-0.87544479610236458633	-0.22530771647662600765
C	-2.56170950546939435455	-0.77869679292974258722	1.29245258673116203418
H	2.41881855680071655712	-2.00449081589398714343	0.07890705289161958902
H	3.67789785262589186132	-1.03163552908838562772	0.86256826359153571104
H	2.49033958176508463112	-1.92364711729783577354	1.84420751633909918432
H	2.73654778180439661739	0.53638639049601011255	-0.69157639117164293463
H	0.46214654299552232475	1.98069989762652909349	0.49810453118241360126
H	1.66297084725132782168	2.71516146593854257318	-0.59912402632157280014
H	-0.47256680953390139965	2.20542128575635887344	-1.80913629685901700128
H	0.88592068445710814295	1.25185235444205433808	-2.45188325272591134407
H	-2.02926236302968998615	1.15701082858131898412	-0.51930009983176428356
H	-3.45137649468089025007	-0.88020516314101759914	-0.67987047273038281325
H	-1.92705543656928224294	-1.78555257792746857604	-0.51487360127737180626
H	-3.13607638356710172189	0.09798319273691963316	1.58122901322193332163
H	-3.05164252453541573473	-1.66311285724694712940	1.68744965884717101900
H	-1.56624730794104527476	-0.70398090819621239600	1.72640680119627920597



Global minimum of truncated reverse *N*5-Pan (Figure **5.2b**)

Eh = -36.1603275400

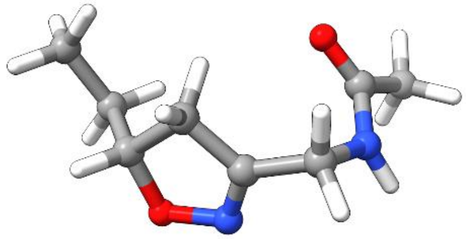
C	1.96764043568183910615	1.95427091340130099084	0.27646218248101139814
C	1.43943287666753594323	0.65898076432330454644	0.83880987775593374156
N	1.94892809232946095932	-0.44198714126318700002	0.25855613749504008370
O	0.63057264777983967896	0.60861556929430560281	1.76270303425924046437
C	1.40233557922542528829	-1.76177072577207383119	0.47977745445046054984
C	0.33661964176703057516	-2.10037767516708395732	-0.57565427434081550828
N	-0.80710364361919162413	-1.22187720896434637297	-0.47138909636928555402
C	-0.87460463487793393966	-0.04362552034853523636	-1.10851637011510328890
C	-2.07403310752888092594	0.82490495433114607859	-0.78350237807806633050
O	-0.04948751772841975677	0.29760678423025260786	-1.95648695663524918587
C	-2.52984730776477917402	0.77737112922067774790	0.67243111089568463612
H	1.59349005805550136827	2.06099871535726064664	-0.74105775118892291964
H	1.61399966539801398291	2.78562617620639141336	0.87868391620819730203
H	3.05319755523753677551	1.94860160305372320799	0.25539463720359317778
H	2.48407111339363151359	-0.31551262228308502023	-0.58797253275202798761
H	2.20969409820460604976	-2.49323559119244908544	0.43716271297040643073
H	0.95555479684452582223	-1.76054848718651890671	1.47681655643482123708
H	0.75528350019326540021	-1.96871959389254880257	-1.57644680684208138288
H	0.00183840468105367989	-3.12946508722415028814	-0.44745333185536950715
H	-1.42460174849372123163	-1.37391342677004346662	0.31089686243675329624
H	-1.80022479496839227231	1.84456699333257523321	-1.06063574117080694492
H	-2.88749434331349119631	0.51699652833902198790	-1.44538262705708375755
H	-3.05711975542135139250	-0.14599099950955629623	0.89872867009009804740
H	-1.67727251896302198553	0.87661907273418804287	1.34250761173871335785
H	-3.21086910336362674201	1.60186485987411386667	0.86556710727663044302



Reverse-*N*5-Pan-mimicking truncated triazole derivative (Figure **5.2c**)

Eh = -36.8861489685

C	-4.33111373306383118376	0.77278876931738837985	-0.80247912647646368889
C	-3.29980550895450353011	-0.29695780004702254651	-0.54071738357902687788
N	-2.48311173450949240760	-0.03404409432399446711	0.49282485822752741811
O	-3.22797301865266605958	-1.33515904296377563298	-1.19427383907684170339
C	-1.34444263179214451576	-0.86181779752046761001	0.82424011870116931089
C	-0.06032196399520307895	-0.18333074616939132317	0.47432636363810115609
C	1.11962273015628133166	-0.70939377171735018557	-0.01250848681644088287
N	1.93797312612934358178	0.35551577210044965627	-0.13955953231749457233
N	1.31003318009663116683	1.45644824132710581921	0.23846020480472651659
N	0.11613234315394681262	1.15066941968902436422	0.60803539903181336168
C	3.31018391417880053496	0.37469453581596229297	-0.57625368491590112097
C	4.23426279360321267120	-0.22182027113293964482	0.48101166822277430235
H	-4.87824501328117854371	0.99683117240919882907	0.10833487322818971532
H	-3.83480041531022930457	1.67640250729539830310	-1.14736581458201980510
H	-5.01954184743638442967	0.42797814432710573618	-1.56806773114613751119
H	-2.49511132878307995142	0.88270882094080704849	0.91462255737150111035
H	-1.36557360318160281309	-1.08415686617879236664	1.89688767966752247496
H	-1.43825693096229789703	-1.79473864468549693107	0.26269453826761290927
H	1.40757393030251920507	-1.70573769904082683802	-0.26791894482145400813
H	3.38579876556968262236	-0.18855524515442276257	-1.50931241458140052991
H	3.56267645913620611964	1.41970252492703297165	-0.75925011218791083056
H	5.26007477541443169144	-0.17806883671323420204	0.12962623804291192875
H	4.15798557629668330549	0.33925250108472915223	1.40865818321629454601
H	3.97597215589257224622	-1.25920359771887069300	0.67798038220948009247

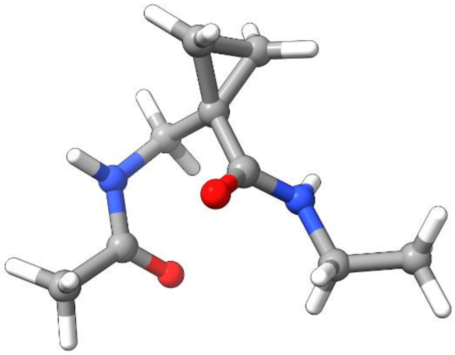


Reverse-*N*5-Pan-mimicking truncated (*R*)-isoxazoline derivative (Figure **5.3a**)

Eh = -38.2410753545

C	-3.26270235796038532428	-1.65298863270972451467	1.12763099589191750916
C	-2.47333909856020905949	-0.47182293358668364602	0.62313149705812354018
N	-2.54445846052740032306	-0.28239117986569894914	-0.70853505207946176903
O	-1.83626972321012482681	0.27703462551182350682	1.35743799936098485936
C	-1.75750593605823324239	0.74315614535290674958	-1.36965126499456735232
C	-0.29959932399443905959	0.39951418346219597089	-1.34700918706140981840
C	0.71632241744720537291	1.14974807027736858345	-0.52892832028735725647
C	1.96692748977154518997	0.29907113405803126271	-0.78369363554472515343
O	1.52225753215134096408	-0.73651713664556572869	-1.70623095864195528648
N	0.17950538709871113885	-0.60842284570810134525	-1.95202925426839235534
C	2.54331459797948955526	-0.35897560789481253174	0.46804413958121360295
C	3.26571823780025916051	0.65014134867893391689	1.35115223556582919606

H	-4.28185007663988947968	-1.61125111947284938019	0.75520552823522357766
H	-2.79767799395370575510	-2.57317344769865297138	0.78240040131867272244
H	-3.26849742098900453158	-1.64376494890127244908	2.21343249460351243485
H	-2.94309583045931022482	-1.00730249939420279937	-1.28404650028960332087
H	-2.11086722982932784021	0.83841494148813566767	-2.39528082421220522846
H	-1.90028223732195788998	1.68371291397112909927	-0.83188899603368393620
H	0.81617395710947393539	2.17966062253278547445	-0.86919825553939689122
H	0.41132476009534163497	1.15116958138460345751	0.51958039274116574191
H	2.75209485937682529766	0.85403686373210363492	-1.30860272712216918478
H	1.73011230640796820346	-0.83325354956389996453	1.02259290835468719116
H	3.23349957284975975114	-1.14187326313248571630	0.14888674445659377810
H	4.08233373628079831974	1.11570266734871781367	0.80510652871354859705
H	2.58355623487532914950	1.42809452985728313479	1.68425564644590752827
H	3.67299459881070111678	0.15228154249955236366	2.22622545671669280765

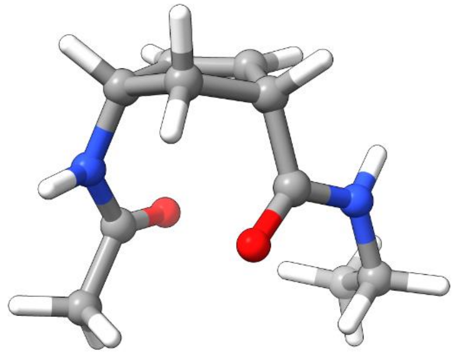


*N*5-Pan-mimicking truncated cyclopropane derivative (Figure **5.3c**)

Eh = -41.4418216156

N	2.12045452641180842690	-0.93916580962155660206	0.26689197069807524265
C	1.33530104377853287012	-1.14735205387000438471	-0.93225718652979061574
C	2.27302598347002771106	0.29276597358898548418	0.79420960047728283993
C	2.86189681116581828846	0.31245287412109373770	2.18070228160735668510
O	1.98214024372974861876	1.31125349624693243733	0.17381075260638012558
C	-0.14026305088404453225	-1.31934501009587479281	-0.59613819631643860664
C	-0.64662552933208761186	-0.17404549227119309185	0.25245989303037447149
C	-1.05936073011865095062	-1.97023182846108779742	-1.58674447282475661325
C	-0.67843367583391778197	-2.69409221907742857383	-0.32876329472372073370
N	-1.08801376783212688792	0.87431065163648979954	-0.44739880693763178776
O	-0.63816194106814161380	-0.22033743277544673433	1.48160571462920453989
C	-1.47803911722141645413	2.13173496123145955750	0.15562259102491493579
C	-2.72179517973736917469	2.69407574765292334718	-0.51646403671886831344
H	2.21029967957233486331	-1.72862755351968866435	0.88899992799744753658
H	1.48026773702445169079	-0.26197773901867371649	-1.55828871158363613247
H	1.70974611837519474555	-2.03010496180435406899	-1.45235052969070022044
H	3.22637459343599841688	1.30992228013222544725	2.40651979081384803649
H	2.06868306803018553452	0.06132366976185798374	2.88313657317588001305
H	3.66536954057489783310	-0.41128433161803484852	2.27345146476557680160

H	-2.06651089685989797218	-1.59321574739826110623	-1.67237206164024909683
H	-0.63446702217231909504	-2.31092083005045800803	-2.51825811939322141697
H	-0.00135956319336171709	-3.53092269541090608698	-0.40371938508349330954
H	-1.41826175767614581780	-2.79766710547093744310	0.45036655119645274681
H	-0.98005937784369434596	0.86694592612035603629	-1.45102273892513689013
H	-1.65746383047647172226	1.92945215056834529221	1.21414542616339748982
H	-0.64260127588260362863	2.83736947157747465553	0.07906084533209956078
H	-3.00589365300320254804	3.62495671675366981646	-0.03587577445899806788
H	-2.52927584857476750457	2.89085851996504938910	-1.56782928030014634402
H	-3.54696714815632807571	1.99185535334772012561	-0.43350977382050348563



*N*5-Pan-mimicking truncated cyclopentene derivative (Figure **5.3e**)

Eh = -43.5879430246

C	-2.13480480742378642134	2.21473212624216442279	0.47494726676850596014
C	-1.58552331403647150943	0.85211885107103868542	0.83284987114644071227
N	-2.30066263481545174585	-0.16492908701832778573	0.32090152461731458189
O	-0.60043433922797539992	0.71293139451365850068	1.55037061944648302259
C	-1.89059182938571601618	-1.56248698231396310199	0.21409027779621711551
C	-0.80056637371099281797	-1.92062820660497934888	1.18680781266540202878
C	0.36920893873776411409	-2.04857749727282278940	0.58259449169620147746
C	0.27111689538115846254	-1.74203056105669085163	-0.88851688502750836296
C	-1.23491833380262905351	-1.85759482659043984043	-1.15345251166614137794
C	0.75809510383643263776	-0.30522230457856558417	-1.12527777421054220319
N	2.03519237735244873377	-0.09597394850088931950	-0.78099081181355767267
O	0.04428119123634650933	0.56123795559038758274	-1.61766908601920689215
C	2.61322292353020202427	1.22932285763139970136	-0.67992620092993294456
C	2.69086038831846474650	1.67837230139195714429	0.77570011035609842676
H	-1.84275955325992724099	2.43025065707736098730	-0.55148479816124573727
H	-3.21694939494715193007	2.23705155497765018069	0.55538497618655613408
H	-1.69731748941765725469	2.96347383352867632667	1.12857270603697346090
H	-3.03673201459025721149	0.08895813037451570648	-0.32241171864710682637
H	-2.79250155557445500776	-2.16316541903765235944	0.36990479650202445772
H	-0.99573625828281531192	-2.02932630214242726296	2.23757896510360465570
H	1.29917620033930591994	-2.29255049127094912009	1.06348240944694794052
H	0.86519898948772977487	-2.41549912446135905952	-1.50915795514724715431
H	-1.48311580334446424523	-2.86847593550562240949	-1.47055425783066917589

H	-1.55310894331016169367	-1.14817028126937326071	-1.91599785263079436248
H	2.52647265384277908140	-0.83012523357661727186	-0.29365887431072656977
H	3.60713680238422229607	1.21449669896808409852	-1.13347187500409551930
H	1.96718243892133348716	1.89871763857024755673	-1.25126322174868342962
H	1.70692341790549839686	1.60300097029541799287	1.23652590826018737857
H	3.38249630321391592247	1.05172801377932501055	1.33328309016027013456
H	3.02914801390130117298	2.70835322103133258054	0.83083899695823182352

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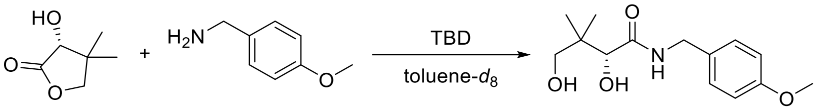
Appendix III. Miscellaneous Data

III-I Kinetic Study Data for Chapter 2

A. RPKA and VTNA kinetic studies

General procedure: D-Pantolactone was weighed and transferred into a vial, while 4-methoxybenzyl amine was weighed into a separate vial. Toluene-d_8 (0.50 mL), measured by a 1 mL syringe with 0.01 mL gauge, was then added into the vial containing the amine and the solution was gently mixed 3 times with a glass Pasteur pipette, before being transferred into the vial containing the lactone. This was recorded as the time zero data point of the experiment. The mixture was rapidly mixed for 3-5 times until the lactone was completely dissolved, before transferring the solution into a 5 mm × 20.3 cm NMR tube. Data collection was achieved on a Bruker AVIIIHD 400 MHz NMR spectrometer at 298 K.

General information: 4-Methoxybenzyl amine , D-pantolactone, and toluene-d_8 were purchased from Sigma-Aldrich. TBD was purchased from Combi-blocks. 4-Methoxybenzyl amine was distilled under reduced pressure before the first use and stored under nitrogen atmosphere at room temperature. D-Pantolactone was grinded to a powder using a mortar and pestle before the first use and stored in a desiccator at room temperature. Toluene-d_8 was used without any pre-treatment and stored in a desiccator at room temperature. The following reaction was used in kinetic studies.

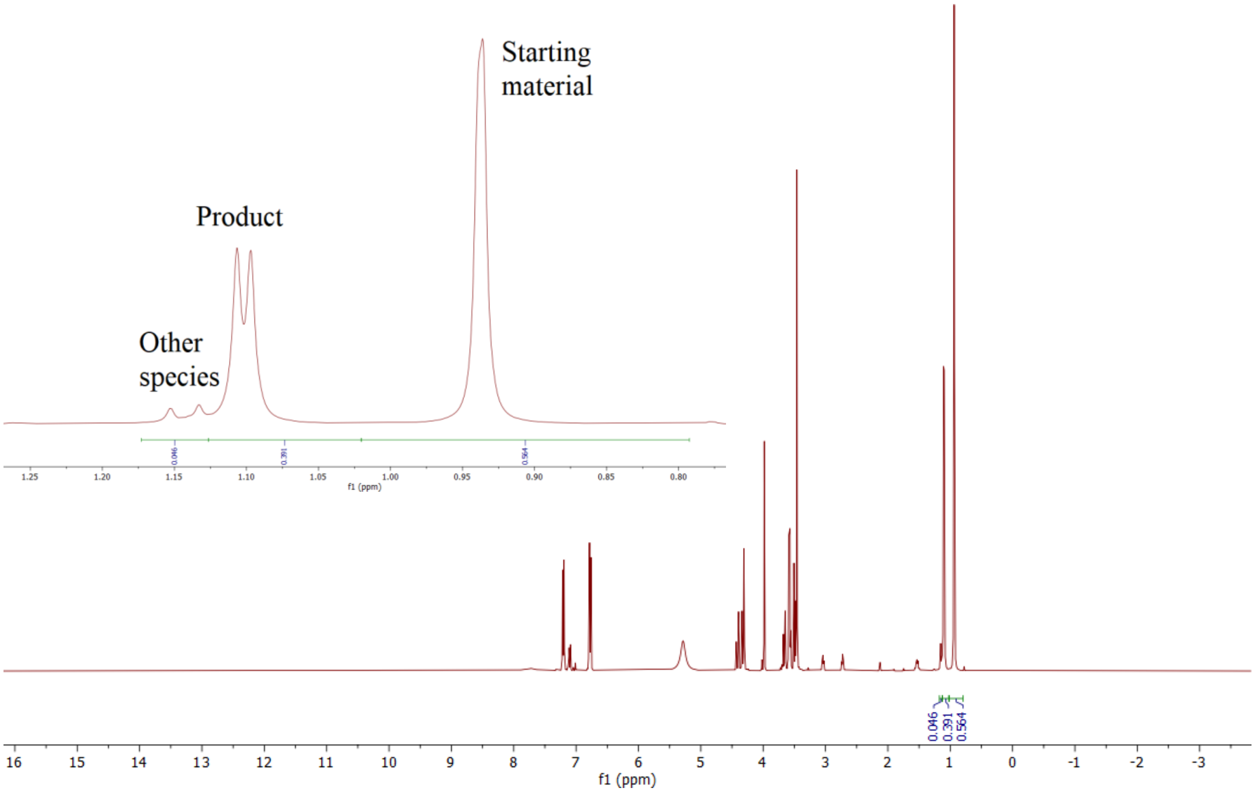


Consumption of the amine starting material was used to monitor the reaction throughout the kinetic studies. However, due to signal overlap of the proton signals on the phenyl ring with those of toluene-d_8, the amine concentration was calculated from integration of the *gem*-dimethyl groups according to the following equation:

$$[amine] = \frac{n_{amine} - \dfrac{\int_{GDM,P}}{\int_{GDM,P} + \int_{GDM,NP}} \times n_{lactone}}{V}$$

where $[amine]$ is the amine concentration; n_{amine} is the total number of moles of amine added to the mixture; $n_{lactone}$ is the total number of moles of lactone added to the mixture; V is the volume of solvent used; $\int_{GDM,P}$ is the integration of the NMR signal for the *gem*-dimethyl group of the product, $\int_{GDM,NP}$ is the integration of the NMR signal for the *gem*-dimethyl groups of non-products (starting materials + other species).

For example, in the experiment run with standard reaction conditions, n_{amine} = 0.503 mmol; $n_{lactone}$ = 1.000 mmol; V = 0.50 mL; $\int_{GDM,P}$ = 0.391; $\int_{GDM,NP}$ = 0.609, $[amine]$ was calculated to be 0.224 mol·L^{-1}. The NMR integration of this example is shown below.



For rate analysis, 3-point rates were used in this study. To obtain a 3-point rate, three adjacent time-concentration points were used in Excel to generate a linear regression. The absolute value of the slope was extrapolated as the rate of the middle time point of the three selected time points. As an example, in the experiment run with standard reaction conditions, using the three time-concentration points: (7.3, 0.682), (8.5, 0.646), (9.7, 0.618). A linear regression on Excel gave the result $[amine] = -0.0269t + 0.8768$. From this equation, the rate at *t* = 8.5 min was determined to be 0.0269 mol·L^{-1}·min^{-1}.

<u>Experimental kinetic data</u>:

<u>Experiment I</u> (standard conditions: 10 mol% TBD, 2.0 equiv. lactone)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	68.6	69.0	0.503	1.0	1.006
lactone	130.1	130.2	1.000	2.0	2.001
TBD	7.0	7.0	0.050	0.1	0.101

Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}	Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}
0	1.006	---	30.90	0.358	0.0065
7.30	0.682	0.0431	32.75	0.346	0.0060
8.48	0.646	0.0269	34.58	0.336	0.0054

9.68	0.618	0.0236	36.43	0.326	0.0054
10.85	0.590	0.0230	38.30	0.316	0.0048
12.03	0.564	0.0203	40.15	0.308	0.0043
13.22	0.542	0.0177	42.00	0.300	0.0043
14.40	0.522	0.0170	43.87	0.292	0.0038
15.57	0.502	0.0162	45.72	0.286	0.0038
16.75	0.484	0.0136	47.57	0.278	0.0038
17.93	0.470	0.0098	49.42	0.272	0.0025
19.78	0.454	0.0097	53.12	0.264	0.0024
21.63	0.434	0.0108	56.80	0.254	0.0027
23.50	0.414	0.0097	60.52	0.244	0.0024
25.35	0.398	0.0081	64.22	0.236	0.0022
27.20	0.384	0.0076	69.77	0.224	---
29.05	0.370	0.0070			

<u>Experiment II</u> (2.5 mol% TBD)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	68.6	69.3	0.505	1.0	1.010
lactone	130.1	130.8	1.005	2.0	2.010
TBD	1.7	1.6	0.012	0.025	0.023

Time/min	[amine] /mol·L^{-1}	Time/min	[amine] /mol·L^{-1}	Time/min	[amine] /mol·L^{-1}
0	1.010	25.59	0.540	59.01	0.399
8.88	0.751	27.44	0.528	62.73	0.387
10.73	0.717	29.31	0.518	66.43	0.379
12.60	0.682	33.01	0.491	70.13	0.373
14.45	0.652	36.73	0.473	73.85	0.365
16.30	0.632	40.43	0.451	77.57	0.357
18.17	0.610	44.15	0.441	81.27	0.353
20.04	0.588	47.87	0.431	86.84	0.341
21.89	0.572	51.59	0.419	92.39	0.333
23.74	0.558	55.29	0.409	97.97	0.329

<u>Experiment III</u> (5 mol% TBD)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	68.6	68.9	0.502	1.0	1.004
lactone	130.1	130.2	1.000	2.0	2.001
TBD	3.5	3.1	0.022	0.05	0.045

Time/min	[amine]	Time/min	[amine]	Time/min	[amine]

	/mol·L^{-1}		/mol·L^{-1}		/mol·L^{-1}
0	1.004	26.53	0.458	45.11	0.360
9.80	0.670	28.38	0.444	48.83	0.348
11.67	0.634	30.25	0.432	52.55	0.336
13.54	0.602	32.10	0.420	56.27	0.324
15.41	0.572	33.95	0.410	59.99	0.316
17.26	0.550	35.82	0.400	63.71	0.308
19.11	0.526	37.69	0.392	67.43	0.302
20.96	0.510	39.54	0.382	71.15	0.294
22.83	0.488	41.39	0.372		
24.68	0.472	43.24	0.364		

Experiment IV (7.5 mol% TBD)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	68.6	68.9	0.502	1.0	1.004
lactone	130.1	130.2	1.000	2.0	2.001
TBD	5.2	5.2	0.037	0.075	0.075

Time/min	[amine] /mol·L^{-1}	Time/min	[amine] /mol·L^{-1}	Time/min	[amine] /mol·L^{-1}
0	1.004	28.42	0.392	48.82	0.294
9.85	0.624	30.27	0.376	50.67	0.288
11.72	0.586	32.12	0.366	52.53	0.282
13.57	0.552	33.97	0.356	54.38	0.276
15.43	0.524	35.83	0.344	56.25	0.272
17.28	0.498	37.68	0.336	58.10	0.268
19.13	0.474	39.53	0.326	61.82	0.262
20.98	0.454	41.40	0.320	65.52	0.252
22.85	0.434	43.25	0.314	69.23	0.242
24.70	0.418	45.10	0.308	73.00	0.238
26.55	0.406	46.97	0.300		

Experiment V (1.0 equiv. lactone)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	68.6	68.8	0.502	1.0	1.003
lactone	65.1	65.6	0.504	1.0	1.008
TBD	7.0	7.0	0.050	0.1	0.101

Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}	Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}

0	1.003	---	45.95	0.465	0.0032
6.93	0.798	0.0284	47.80	0.458	0.0038
8.80	0.757	0.0196	49.65	0.451	0.0040
10.65	0.725	0.0167	51.52	0.443	0.0043
12.57	0.694	0.0151	53.37	0.435	0.0038
14.42	0.668	0.0127	55.22	0.429	0.0022
16.27	0.647	0.0116	57.07	0.427	0.0024
18.13	0.625	0.0105	60.78	0.416	0.0022
20.00	0.608	0.0091	64.48	0.411	0.0018
21.85	0.591	0.0086	68.18	0.403	0.0015
23.70	0.576	0.0076	71.88	0.400	0.0008
25.55	0.563	0.0076	75.60	0.397	0.0011
27.40	0.548	0.0068	79.30	0.392	0.0018
29.25	0.538	0.0056	83.00	0.384	0.0018
31.12	0.527	0.0059	86.72	0.379	0.0012
32.97	0.516	0.0051	90.42	0.375	0.0011
34.82	0.508	0.0043	94.12	0.371	0.0011
36.67	0.500	0.0041	97.83	0.367	0.0012
38.52	0.493	0.0043	103.38	0.360	0.0012
40.38	0.484	0.0049	108.95	0.354	0.0010
42.23	0.475	0.0038	114.58	0.349	---
44.10	0.470	0.0027			

Experiment VI (1.3 equiv. lactone)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	68.6	69.0	0.503	1.0	1.006
lactone	84.6	85.6	0.658	1.3	1.316
TBD	7.0	7.1	0.051	0.1	0.102

Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}	Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}
0	1.006	---	43.65	0.385	0.0046
8.22	0.721	0.0330	45.52	0.376	0.0039
10.25	0.674	0.0217	47.37	0.371	0.0032
12.10	0.636	0.0180	49.22	0.364	0.0035
13.97	0.607	0.0156	51.08	0.357	0.0028
15.82	0.578	0.0139	54.78	0.348	0.0027
17.67	0.556	0.0121	58.50	0.338	0.0027
19.53	0.534	0.0103	62.22	0.328	0.0023
21.38	0.518	0.0082	65.93	0.321	0.0019
23.23	0.503	0.0085	69.65	0.314	0.0019
25.10	0.486	0.0081	73.37	0.306	0.0019
26.95	0.473	0.0071	77.08	0.300	0.0016
28.80	0.460	0.0067	80.78	0.294	0.0016

30.67	0.448	0.0060	84.50	0.288	0.0014
32.52	0.438	0.0060	88.22	0.284	0.0013
34.38	0.426	0.0057	93.78	0.276	0.0013
36.23	0.417	0.0043	99.35	0.269	0.0011
38.08	0.410	0.0042	104.92	0.264	0.0011
39.95	0.401	0.0046	110.48	0.257	0.0011
41.80	0.393	0.0043	117.92	0.250	---

Experiment VII (1.6 equiv. lactone)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	68.6	68.5	0.499	1.0	0.999
lactone	104.1	104.2	0.801	1.6	1.601
TBD	7.0	7.1	0.051	0.1	0.102

Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}	Time/min	[amine] /mol·L^{-1}	3-point rate /mol·L^{-1}·min^{-1}
0	0.999	---	32.52	0.375	0.0061
7.05	0.703	0.0406	34.37	0.365	0.0047
8.23	0.670	0.0264	36.23	0.357	0.0052
9.42	0.641	0.0216	38.08	0.346	0.0052
10.60	0.618	0.0204	39.93	0.338	0.0039
11.78	0.593	0.0205	41.80	0.332	0.0039
12.95	0.570	0.0182	43.65	0.324	0.0043
14.15	0.549	0.0155	45.50	0.316	0.0039
15.33	0.533	0.0149	47.35	0.309	0.0039
16.52	0.514	0.0143	49.22	0.301	0.0034
17.68	0.500	0.0100	51.07	0.296	0.0032
19.53	0.484	0.0100	54.78	0.284	0.0028
21.38	0.463	0.0103	58.48	0.275	0.0024
23.25	0.445	0.0090	62.20	0.266	0.0022
25.10	0.429	0.0082	65.90	0.259	0.0019
26.95	0.415	0.0082	69.62	0.251	0.0022
28.82	0.399	0.0073	73.33	0.243	---
30.67	0.388	0.0065			

Experiment VIII (0.375 mmol amine, same excess)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	51.4	51.3	0.374	1.0	0.748
lactone	113.9	113.9	0.875	2.3	1.750
TBD	7.0	7.0	0.050	0.1	0.101

Time/min	Adjusted time/min	[amine] /mol·L^{-1}	Time/min	Adjusted time/min	[amine] /mol·L^{-1}
0	5.72	0.748	29.82	35.54	0.248
7.22	12.94	0.496	31.68	37.40	0.239
8.40	14.12	0.468	33.53	39.25	0.230
9.58	15.30	0.444	35.37	41.09	0.221
10.77	16.49	0.424	37.22	42.94	0.213
11.95	17.67	0.403	39.07	44.79	0.206
13.13	18.85	0.389	42.78	48.50	0.195
15.00	20.72	0.367	46.48	52.20	0.185
16.85	22.57	0.346	50.20	55.92	0.172
18.70	24.42	0.325	53.90	59.62	0.165
20.55	26.27	0.311	57.60	63.32	0.158
22.42	28.14	0.295	61.30	67.02	0.148
24.27	29.99	0.281	65.02	70.74	0.143
26.12	31.84	0.269	70.07	75.79	0.136
27.97	33.69	0.258			

<u>Experiment IX</u> (0.375 mmol amine + 0.125 mmol product, same excess)

Compound	Theoretical weight/mg	Actual weight/mg	n/mmol	Equiv.	Concentration /mol·L^{-1}
amine	51.4	51.5	0.375	1.0	0.751
lactone	113.9	114.1	0.877	2.3	1.753
product	33.4	33.3	0.125	0.13	0.249
TBD	7.0	7.0	0.050	0.1	0.101

Time/min	Adjusted time/min	[amine] /mol·L^{-1}	Time/min	Adjusted time/min	[amine] /mol·L^{-1}
0	5.62	0.751	25.13	30.75	0.398
7.07	12.69	0.594	26.98	32.60	0.386
8.27	13.89	0.572	28.83	34.45	0.378
9.45	15.07	0.552	32.53	38.15	0.362
10.65	16.27	0.532	36.23	41.85	0.348
11.82	17.44	0.514	39.93	45.55	0.334
13.00	18.62	0.500	43.63	49.25	0.320
14.18	19.80	0.488	47.33	52.95	0.312
15.37	20.99	0.474	51.03	56.65	0.304
16.55	22.17	0.462	56.58	62.20	0.290
17.73	23.35	0.452	62.15	67.77	0.280
19.58	25.20	0.440	67.72	73.34	0.272
21.43	27.05	0.426	73.28	78.90	0.268
23.28	28.90	0.412			

Data plotting

Determination of catalyst order (VTNA): Data from experiments I, II, III, and IV were used. Time was normalized with parameter $[TBD]^n$, where n is an arbitrary power. Amine concentrations were then plotted against $t[TBD]^n$ with various n values until curves overlayed and the corresponding n is the order of TBD, which was determined to be 0.6.

Determination of catalyst deactivation (RPKA, same excess): Data from experiments I and VIII were used. Amine concentrations were plotted over time. Time of the same excess reaction profile (experiment VIII) was then adjusted as follows. The amine concentration at the starting point of experiment VIII was used to extract a time from the curve of experiment I, and this time was added to all points of experiment VIII to achieve the adjustment. A non-overlay result indicated that catalyst deactivation occurred.

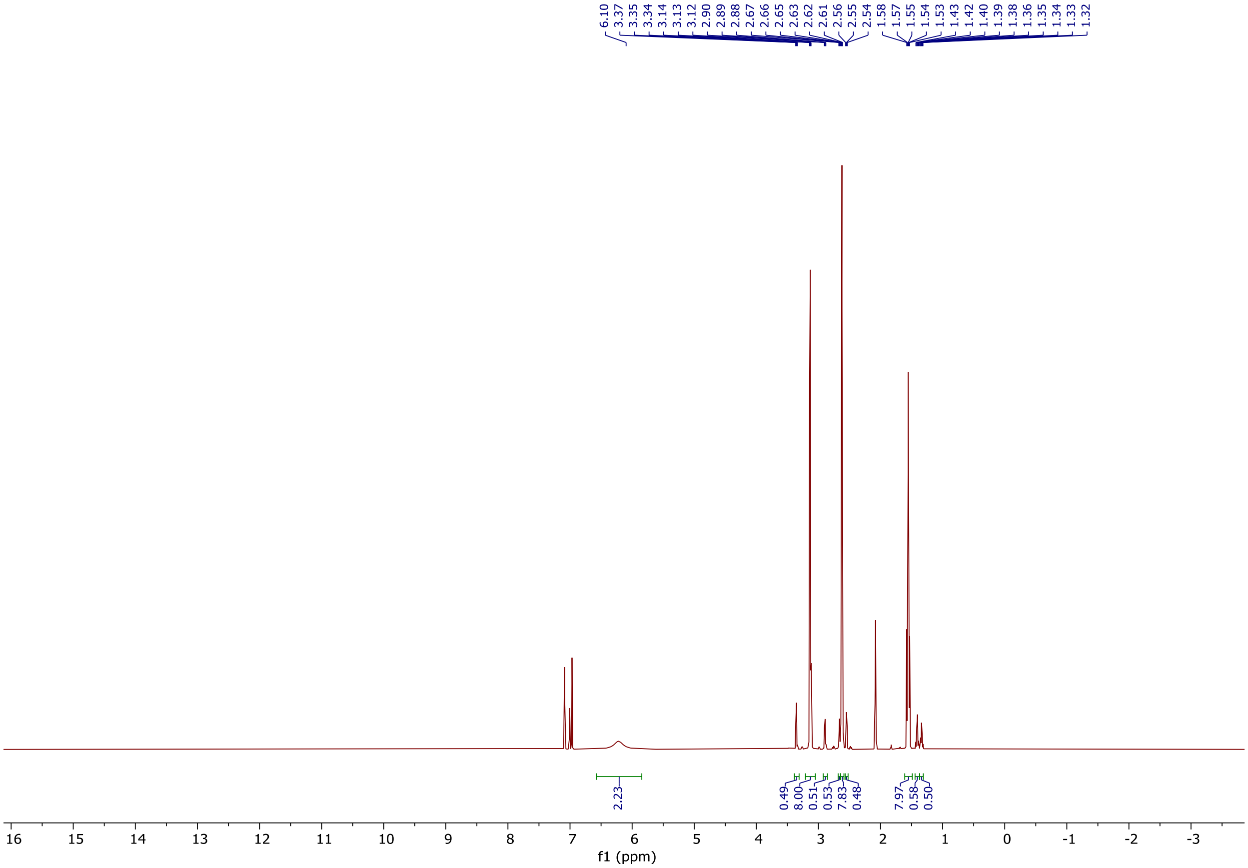
Determination of product inhibition (RPKA, same excess): Data from experiment I and IX were used. Amine concentrations were plotted against time. Time of the same excess reaction profile (experiment IX) was then adjusted. The concentration of the starting point of experiment IX was used to extract a time from the curve of experiment I, and this time was added to all points of experiment IX to achieve the adjustment. A near-overlay result indicated that product inhibition was one, but not the only reason for catalyst deactivation.

Determination of substrate order (RPKA, different excess): Data from experiments I, V, VI, and VII were used. 3-Point rates were extracted from the original data and used as follows. $\frac{rate}{[lactone]^1}$ were plotted over $[amine]^1$ and an overlay occurred. This indicated that the reaction is 1st order relative to the lactone. Next, to balance out the influence of other reaction driving forces, $\frac{rate}{[TBD]^{0.6}[lactone]^1}$ were plotted over $[amine]^n$, where n is an arbitrary power. A linear overlay occurred when n was 2.5, indicating the reaction is 2.5 order relative to the amine.

B. NMR studies

1) TBD in toluene-*d*$_8$

TBD (13.9 mg, 0.1 mmol) was dissolved in toluene-*d*$_8$ (0.5 mL, 0.2 M) and the ^{1}H NMR spectrum was acquired. Note that the solubility of TBD alone is poor in toluene, hence we expect the final solution concentration to be below 0.2 M. Judging from signal integration, 87% of the molecules in solution exist as TBD dimer.

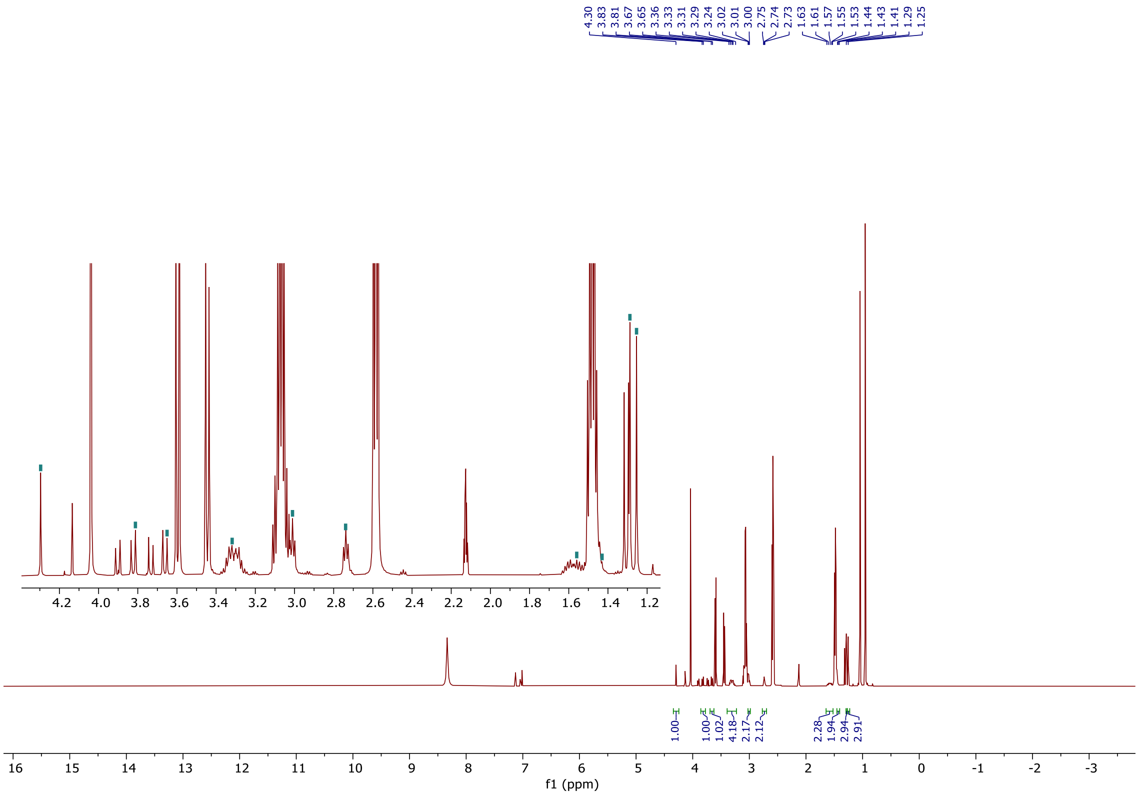


Dimer: ^{1}H NMR (toluene-*d*$_8$, 500 MHz): δ 6.22 (bs, 2H), 3.13 (t, $J = 6.0$ Hz, 8H), 2.62 (t, $J = 6.0$ Hz, 8H), 1.55 (p, $J = 5.9$ Hz, 8H). Monomer: ^{1}H NMR (toluene-*d*$_8$, 500 MHz): δ 3.35 (t, $J = 6.5$ Hz, 2H), 2.89 (t, $J = 5.8$ Hz, 2H), 2.66 (t, $J = 5.8$ Hz, 2H), 2.55 (t, $J = 6.3$ Hz, 2H), 1.40 (p, $J = 6.4$ Hz, 2H), 1.34 (p, $J = 5.8$ Hz, 2H).

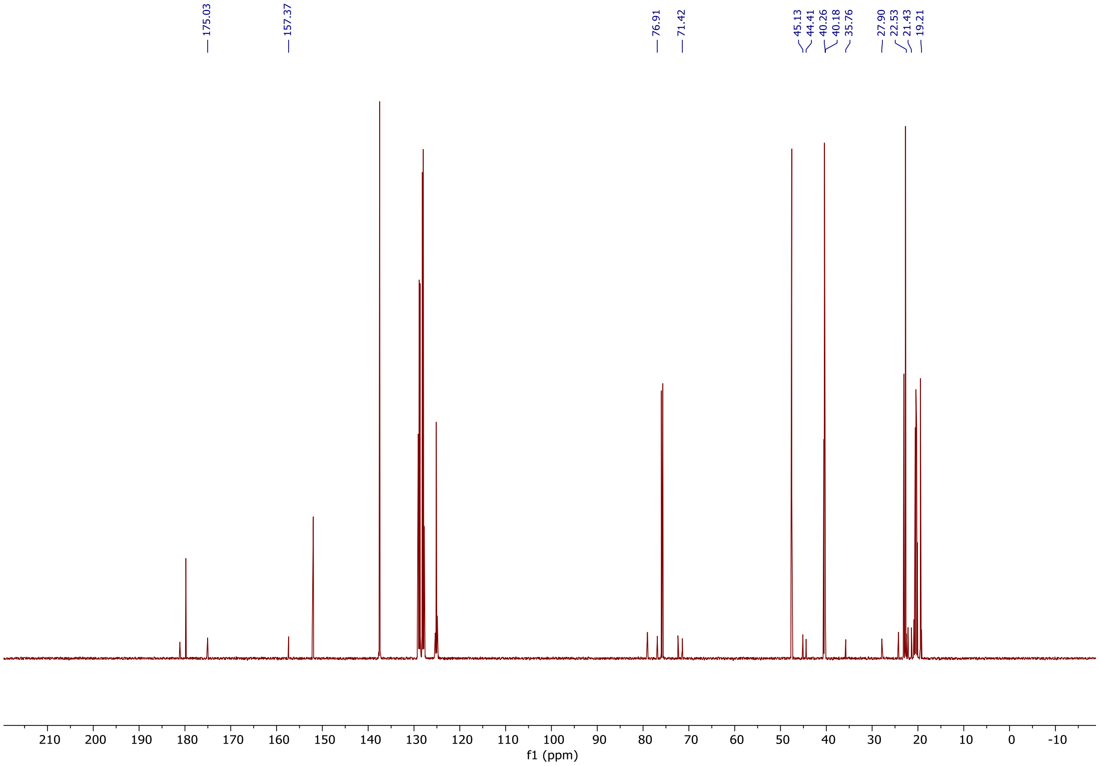
2) Mixture of TBD and D-pantolactone in toluene-*d*$_8$

TBD (27.8 mg, 0.2 mmol) and D-pantolactone (26.0 mg, 0.2 mmol) were dissolved in toluene-*d*$_8$ (0.5 mL, 0.4 M) before acquisition of ^{1}H, ^{13}C{^{1}H}, HSQC, HMBC spectra. Two new species were detected on both ^{1}H and ^{13}C{^{1}H} spectra. HSQC and HMBC spectra were used to identify the molecules and assign signals. The presence of the acyl-TBD derivative was confirmed by HMBC cross peaks between TBD and D-pantolactone. HSQC and HMBC spectra were processed with t$_1$ noise reduction before analysis.

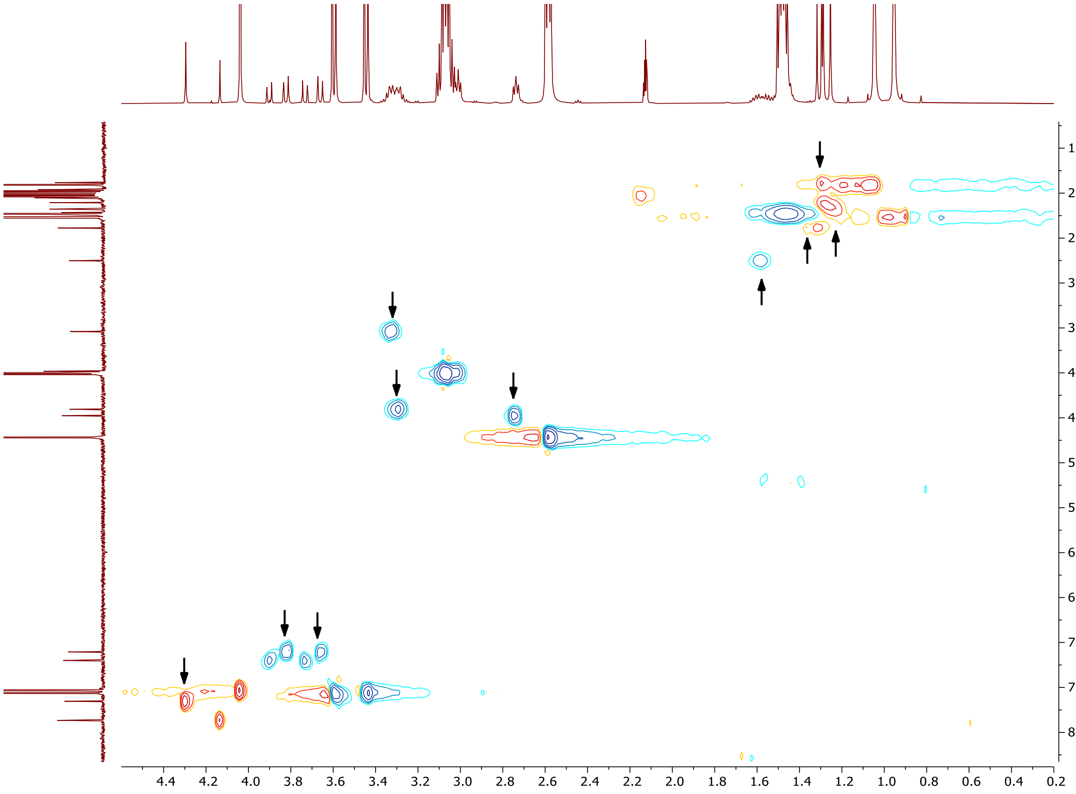
^{1}H NMR spectrum (integration is given only for the acyl-TBD species)



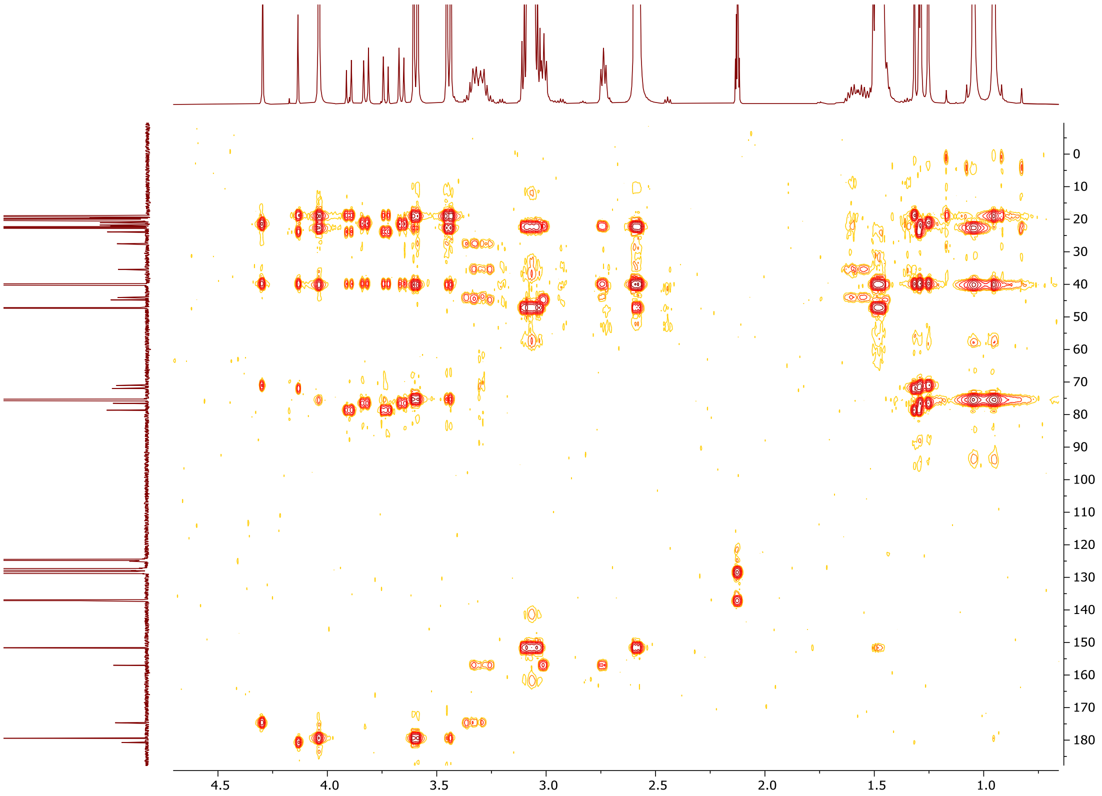
^{13}C{^{1}H} NMR spectrum (exact chemical shifts are given only for the acyl-TBD species)

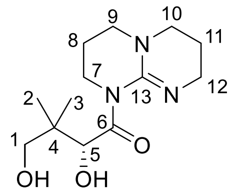


HSQC NMR spectrum (arrows point to signal from the acyl-TBD species)



HMBC NMR spectrum



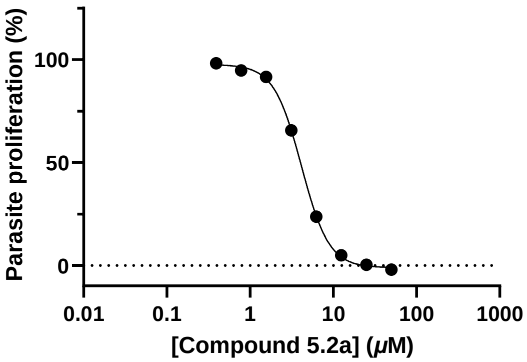


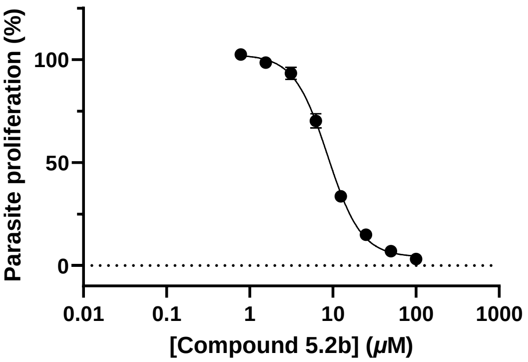
Characterization of the acyl-TBD intermediate: ^{1}H NMR (toluene-d_8, 500 MHz): δ 4.30 (s, 1H, H-5), 3.82 (d, J = 11.0 Hz, 1H, H-1a), 3.66 (d, J = 11.0 Hz, 1H, H-1b), 3.36-3.24 (m, 4H, H-7 and H-12), 3.01 (t, J = 6.1 Hz, 2H, H-8 or H-11), 2.74 (t, J = 6.0 Hz, 2H, H-8 or H-11), 1.56 (m, 2H, H-9 or H-10), 1.44 (m, 2H, H-9 or H-10), 1.29 (s, 3H, H-2 or H-3), 1.25 (s, 3H, H-2 or H-3); ^{13}C{^{1}H} NMR (toluene-d_8, 125 MHz): 175.03 (C-6), 157.37 (C-13), 76.91 (C-5), 71.42 (C-1), 45.13 (C-8 or C-11), 44.41 (C-12), 40.26 (C-4), 40.18 (C-8 or C-11), 35.76 (C-7), 27.90 (C-9 or C-10), 22.53 (C-9 or C-10), 21.43 (C-2 or C-3), 19.21 (C-2 or C-3).

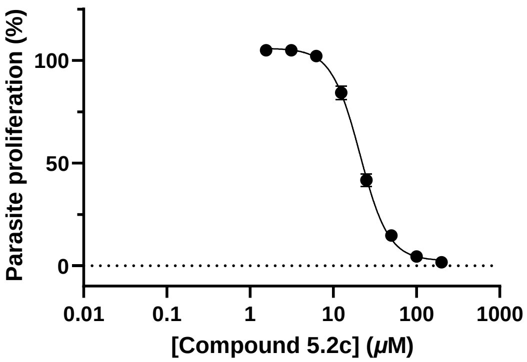
III-II Biological Assay Data for Chapter 5

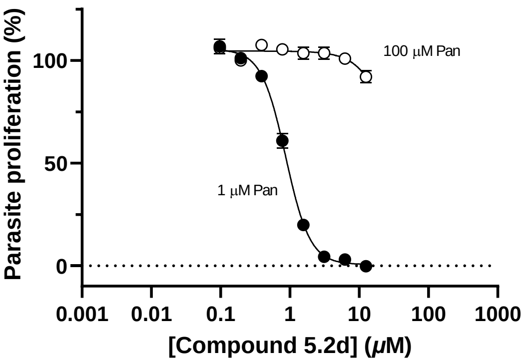
1) Antiplasmodial assays

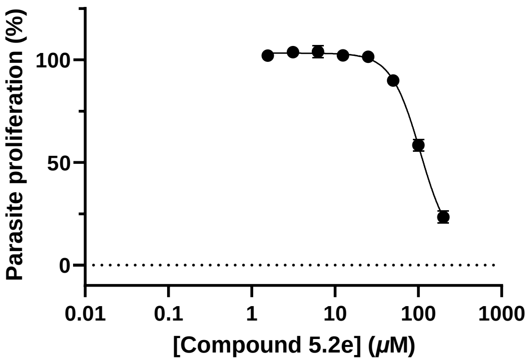
Results of antiplasmodial activity assays for compound **5.2a**-**5.2n** against *P. falciparum in vitro* in the presence of 1 μM or 100 μM pantothenate are shown below. The growth medium is fresh and should therefore contain pantetheinases. Data generated in the presence of 1 μM pantothenate are averages from three or more independent experiments and error bars represent SEM. Data generated in the presence of 100 μM pantothenate are averages from two independent experiments and error bars represent range/2. Where not visible, error bars are smaller than the symbol.

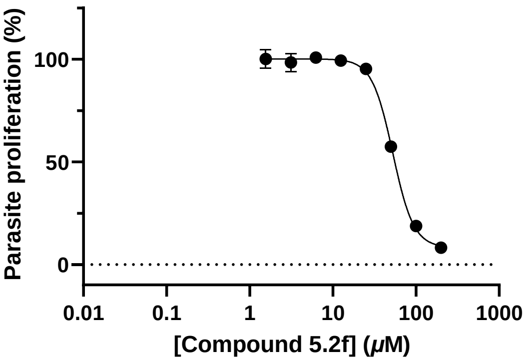


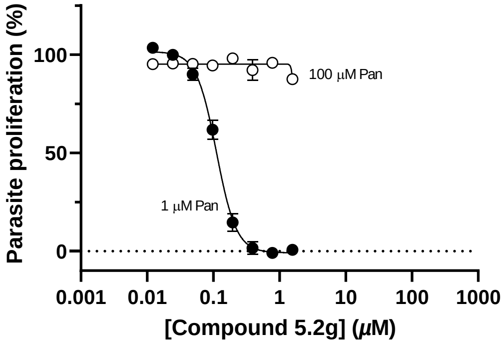











Parasite proliferation (%)
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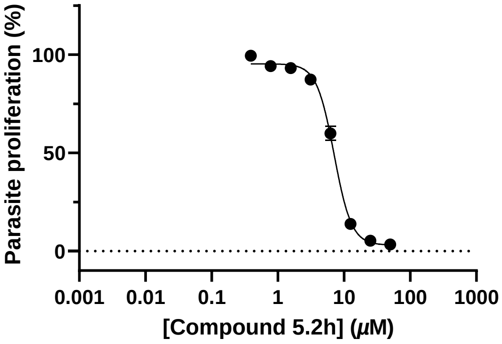
50
0
100 μM Pan
1 μM Pan
0.001
0.01
0.1
1
10
100
1000
[Compound 5.2g] (μM)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100
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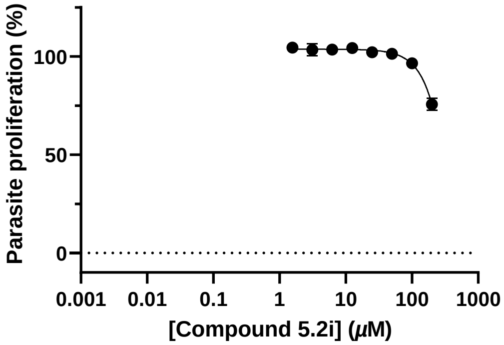
[Compound 5.2h] (μM)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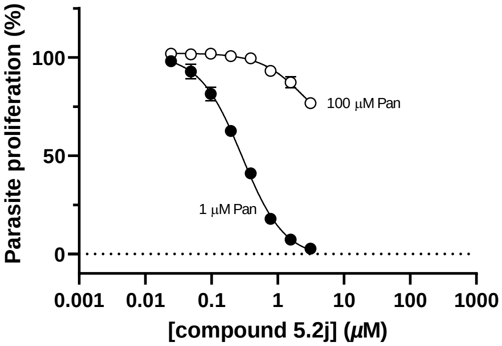
[Compound 5.2i] (μM)


Parasite proliferation (%)
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100 μM Pan
1 μM Pan
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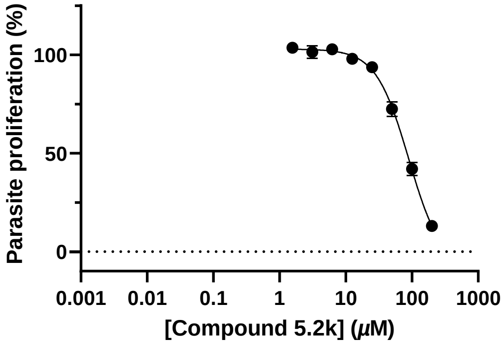
0.01
0.1
1
10
100
1000
[compound 5.2j] (μM)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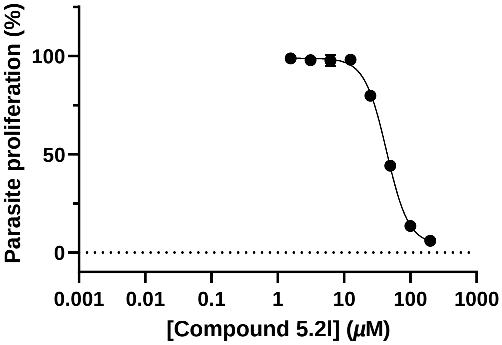
0.001
0.01
0.1
1
10
100
1000
[Compound 5.2k] (μM)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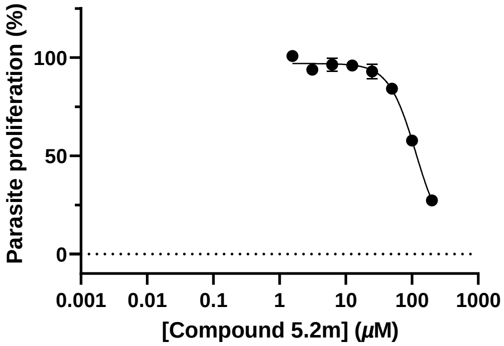
0.001
0.01
0.1
1
10
100
1000
[Compound 5.2l] (μM)


Parasite proliferation (%)
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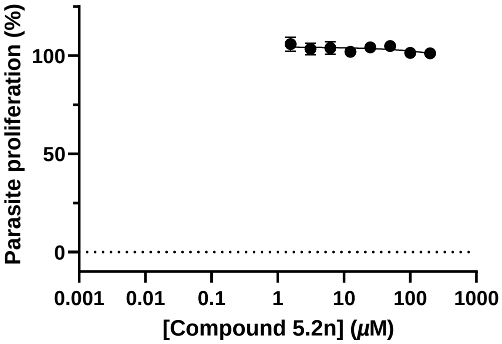
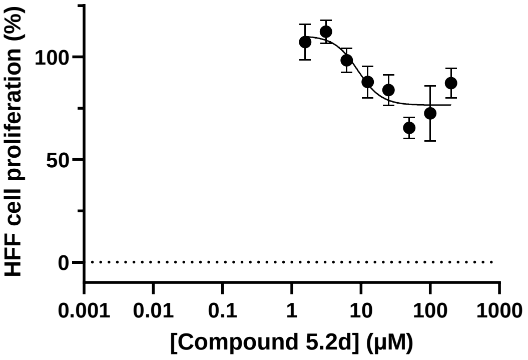
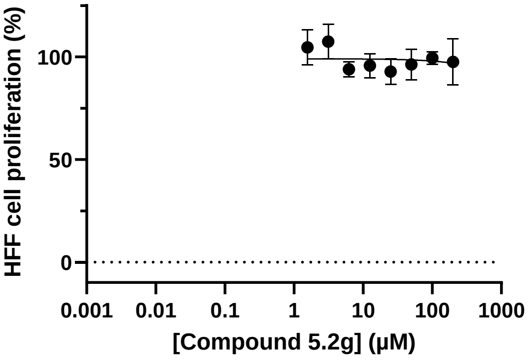
0
0.001
0.01
0.1
1
10
100
1000
[Compound 5.2m] (μM)

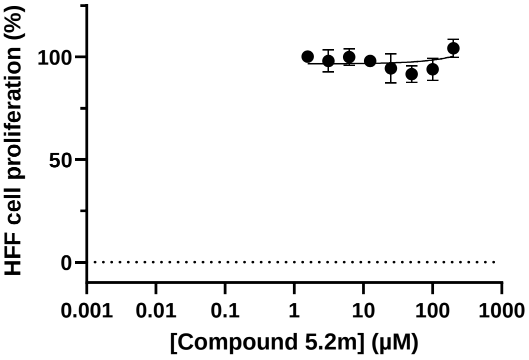

Parasite proliferation (%)
100
50
0
0.001
0.01
0.1
1
10
100
1000
[Compound 5.2n] (μM)

2) Cytotoxicity assays

Cytotoxicity was investigated by measuring proliferation of human foreskin fibroblast (HFF) cells in the presence of each compound. Up to 200 μM concentration was tested and no significant cytotoxicity was observed.







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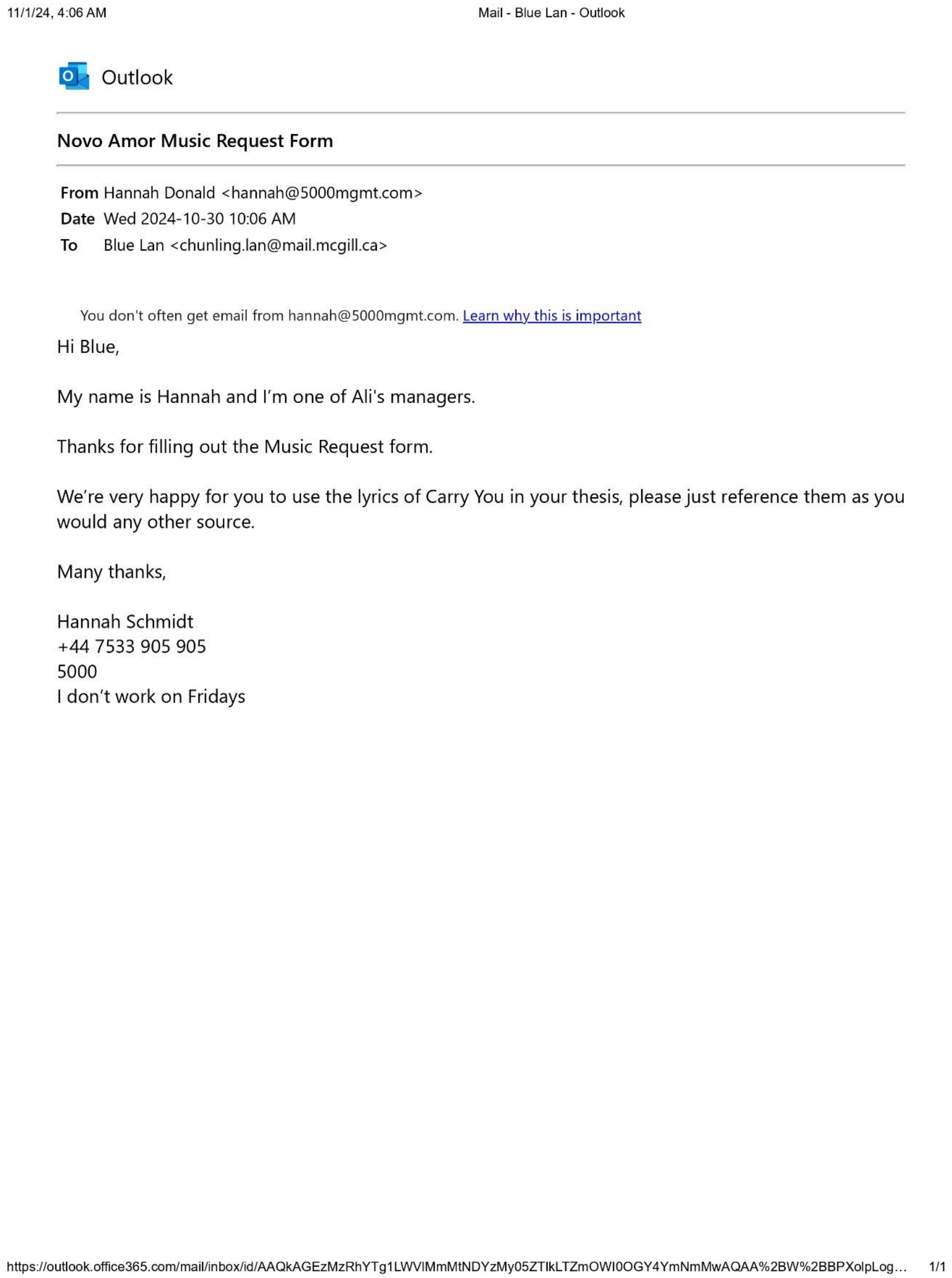

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Date Wed 2024-10-30 10:06 AM
To Blue Lan <chunling.lan@mail.mcgill.ca>

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Thanks for filling out the Music Request form.

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Many thanks,

Hannah Schmidt
+44 7533 905 905
5000
I don’t work on Fridays

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1,5,7-Triazabicyclo[4.4.0]dec-5-ene: An Effective Catalyst for Amide Formation by Lactone Aminolysis

Author: Chunling Blue Lan, Karine Auclair
Publication: The Journal of Organic Chemistry
Publisher: American Chemical Society
Date: Jul 1, 2023

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		End Page	n/a
		Issue	12
		Volume	27
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Author: Chunling Blue Lan, Karine Auclair
Publication: The Journal of Organic Chemistry
Publisher: American Chemical Society
Date: Jan 1, 2025

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