Multicomponent Synthesis of Indolizines via Palladium Catalyzed Carbonylation Chemistry

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Abstract

Indolizines are a valuable target in medicinal chemistry and materials science, and as such, multiple routes to access this framework have been developed. However, most existing methods either require pre-functionalized substrates or offer limited product substitution. Therefore, there is still a need for efficient syntheses that can rapidly generate diversely substituted indolizines from simple building blocks.

To address this issue, the research in Chapter 2 describes the synthesis of indolizines through a palladium catalyzed, multicomponent pathway using 2-bromopyridines, imines, CO and alkynes. Mechanistic studies suggest that this reaction proceeds via the catalytic in situ build-up of 2-pyridyl acid chlorides followed by reaction with the imine to form a mesoionic 1,3-dipole. The subsequent cycloaddition of this 1,3-dipole with an alkyne leads to the formation of indolizines. By modulating the 2-bromopyridine, imine and alkyne employed in the reaction, a wide variety of substituted indolizines can be generated in one pot reactions with independent control of each substituent.

Résumé

Les indolizines sont une cible de choix en chimie médicinale. À ce titre, plusieurs approches permettant de générer cette structure ont été développées. Toutefois, la plupart des méthodes existantes soit requièrent la préfonctionnalisation des réactifs de départ, soit permettent peu de variations dans la position et l'identité des substituants du produit. Ainsi, une synthèse efficace qui générerait rapidement des indolizines aux structures variées à partir de réactifs simples reste élusive.

Pour pallier ce problème, le chapitre 2 décrit la synthèse d'indolizines via une réaction multicomposants et monotope catalysée au palladium à partir de 2-bromopyridines, d'imines, de monoxyde de carbone et d'alcynes. Des études mécanistiques pointent vers la formation catalytique de chlorures d'acyles de 2-pyridine, qui réagissent ensuite avec l'imine et forment un dipole mésoionique antérieurement étudié. Dans une étape subséquente, ce dipole génère ensuite le squelette de l'indolizine par le bais d'une cycloaddition avec l'alcyne. Les substituants des 2-bromopyridines, imines et alcynes employés dans cette réaction peuvent être modifiés de façon indépendante, permettant d'obtenir une grande variété d'indolizines, substituées à la fois dans l'anneau pyridinique et l'anneau pyrrolique.

Acknowledgements

First and foremost, I would like to thank my supervisor, Bruce Arndtsen, for his guidance throughout my degree. These have been very formatives years and I am thankful I could spend them in his laboratory.

Thanks to past and present group members for making this experience enjoyable are also in order. The lively discussions we’ve had, the experiences we’ve shared and the assistance you’ve provided have shaped my experience for the better and I couldn’t be more thankful. Special thanks to Gerardo Martin-Torres for his guidance at the start of my degree, and to Huseyin Erguven for his willingness to assist me with his cycloaddition expertise.

I would also like to use this opportunity to thank the support staff at the university, especially Dr. Robin Stein who worked tirelessly to maintain the NMR equipment and was always reachable would a problem arise, as well as all administrative officers who worked behind the scenes to make the experience as smooth as possible.

Finally, I must acknowledge the support I have received from my family and would like to thank my parents for being so understanding.

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List of Abbreviations

Δ: heating

1,10-Phen: 1,10-Phenanthroline

Å: Angstrom

Ac: Acetyl

Alk: Alkyl

Ar: Aryl

atm: Atmosphere

[B]: Boron reagent

Boc: tert-Butyloxycarbonyl

Bn: Benzyl

HB_{pin}: Pinacolborane

Bu: Butyl

Bz: Benzoyl

ºC: Degrees Celcius

Cp*: 1,2,3,4,5-pentamethylcyclopentadienyl

Cy: Cyclohexyl

δ : Chemical Shift

d: Doublet/day

dba: trans,trans-dibenzalacetone

DBU: 1,8-Diazabicyclo[4.4.0]undec-7-ene

DCE: 1,2-Dichloroethane

dig: Digonal (cyclization)

DMAD: Dimethylacetylene Dicarboxylate

DMF: Dimethylfuran

DMSO: Dimethylsufoxide

dpe-phos: Bis(2-diphenylphosphinophenyl)ether

dppp : 1,3-bis(diphenylphosphino)propane

dppe: 1,2-bis(diphenylphosphino)ethane

E: Electrophile

e-poor: Electron-poor

Eq., equiv.: Equivalent

ESI: Electrospray Ionization

Et: Ethyl

EWG: Electron Withdrawing Group

Fig.: Figure

h: Hour

hept: Heptet (Septet)

Het: Heteroatom/heterocycle

HIV: Human Immunodeficiency Virus

HRMS: High-Resolution Mass Spectrometry

Hz: Hertz

^{i}Pr: Isopropyl

μL: Microliter

L: Ligand

LDA : Lithium diisopropylamide

[M]: Metal (where M=Au, Pd)

m: Multiplet

min: Minute

mg: Milligram

MHz: Megahertz

mL: Milliliter

mM: Millimole per liter

mol: Mole

mmol: Millimole

Me: Methyl

MeCN: Acetonitrile

n: Unspecified number

NHC: N-Heterocyclic Carbene

NIS: N-Iodosuccinimide

NMR: Nuclear Magnetic Resonance

Nu: Nucleophile

OAc: Acetyl

$Rh_2(oct)_4$: Dirhodium tetraoctanoate

Rh_2esp_2: Dirhodium α,α,α’,α’-tetramethyl-1,3-benzene dipropanoate

OTf: Triflate (Trifluoromethanesulfonyl)

PEt_3: Triethylphosphine

Pd/C: Palladium on carbon

Ph: Phenyl

PIDA: (diacetyloxyiodo)benzene

PPh_3: Triphenylphosphine

ppm: Parts per Million

Pr: Propyl

p-tol: *para*-Tolyl

py : Pyridine

q: Quadruplet

R: Substituent

rt: Room Temperature

s: Singlet

S-DOSP: 1-[[4-alkyl(C_{11}-C_{13})phenyl]sulfonyl]-(2S)-pyrrolidinecarboxylate

t: Triplet

TBDMS or TBS: *tert*-butyldimethylsilyl

^{t}Bu: *tert*-Butyl

TBD: 1,5,7-triazabicyclo[4.4.0]dec-5-ene

Tf: Triflyl

TFA: Trifluoroacetic Acid

THF: Tetrahydrofuran

TMS: Trimethylsilane

Ts: Tosyl

X: Halogen atom

Xantphos: 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Contributions of Co-Authors

This thesis is made up of three chapters. Chapter 1 is a summary of the main routes to synthesize indolizines. Chapter 2 is a published manuscript (*Chem. Sci.*, **2021**, *12*, 2251-2256) and describes a palladium-catalyzed synthesis of indolizines from bromopyridines, imines, CO and alkynes. All experiments detailed in Chapter 2 were performed by me under the supervision of Dr. Bruce Arndtsen for the completion of the degree of Master of Science in chemistry, apart from the catalytic reaction with tetrabutylammonium bromide instead of chloride (Fig 2.3.2. a), the one-pot synthesis of **2m** (Fig 2.5.2.1) and the synthesis of **2o** (Table 2.3.3), which were performed by other labmates, Jose Zgheib and Cuihan Zhou. My supervisor throughout my degree, Dr. Arndtsen, assisted in the editing of this thesis. Chapter 3 is a brief conclusion to the work described in this thesis.

1. Introduction

1.1. Perspective

Heterocycles, which are cyclic organic compounds that contain one or more non-carbon atom in the ring, have long attracted the attention of organic chemists. One intriguing variant of these are indolizines. Indolizines are a 6,5 fused heteroaromatic ring system in which the nitrogen atom is at the bridgehead position (Figure 1.1a). These heterocycles were first discovered by Angeli in 1890 during the study of the reaction of diethyl oxalate and 2-acetylpyrrole and named pyrrocoline.[1] Over the years, and in their quality of indole isosteres, substituted indolizines have been identified as important compounds for a range of applications, including most notably as biologically active compounds. The pharmaceutical relevance of indolizine derivatives has been covered in reviews in multiple occasions.[2] Examples of their uses include as HIV inhibitors,[3] anticancer agents,[4] and antioxidants (Figure 1.1b).[5] Fully or partially hydrogenated analogs to indolizines are also present in many natural products (e.g. Figure 1.1c).[6] In addition, indolizines have been heavily exploited in materials science, where their extended conjugation make them often highly fluorescent.[7]

Given their utility, the development of efficient syntheses of indolizines is of importance. This chapter will provide an overview of the main routes to their preparation. These are separated into four general categories: nucleophilic cyclization reactions (section 1.2); metal catalyzed methods (section 1.3), and 1,3-dipolar cycloadditions (section 1.4). Chapter 2 will describe a new, palladium catalyzed multicomponent synthesis of indolizines starting from bromopyridines, imines, CO and alkynes that was developed during my master studies.

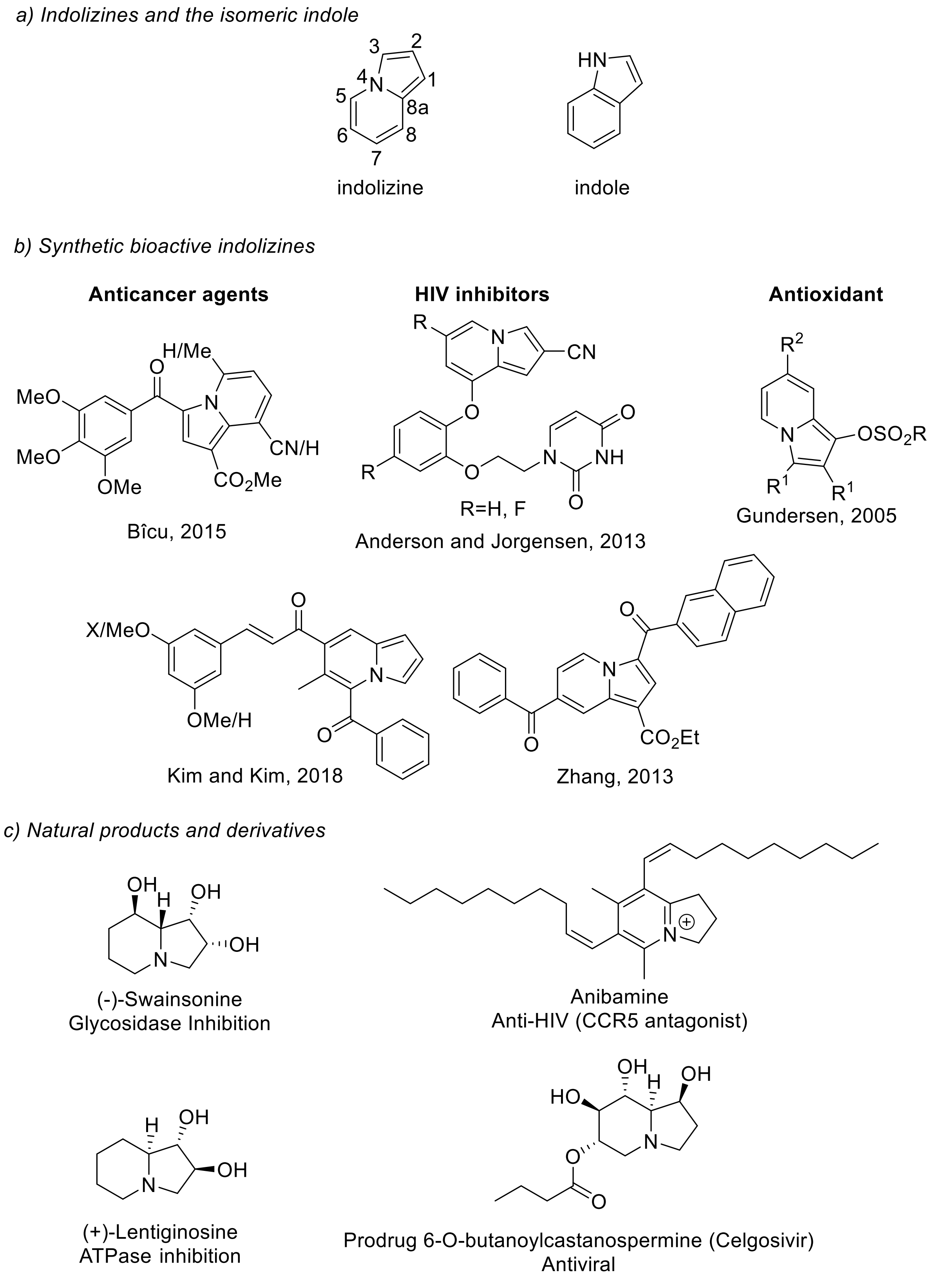
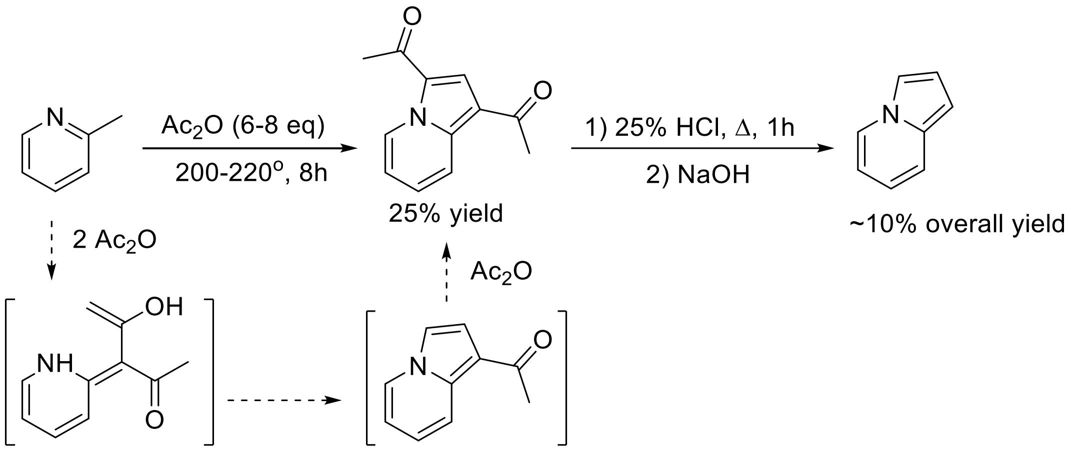


Figure 1.1. Indolizine heterocycle and select examples of bioactive molecules

1.2. Synthesis of indolizines by nucleophilic cyclization

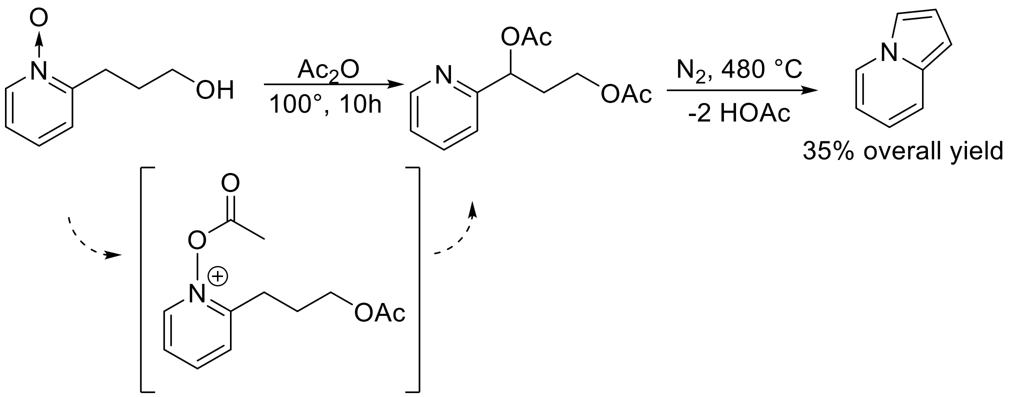
1.2.1. Unsubstituted indolizine

The first laboratory synthesis of unsubstituted indolizine was described in 1910 by Scholtz via the reaction of α-picoline (2-methylpyridine) with acetic anhydride and then acid (Scheme 1.2.1.1).[8] The now accepted mechanism of this reaction was only proposed in 1929 by Stepanow and Tschitschibabin.[9] This involve the initial diacetylation of picoline, which is followed by cyclization of the pyridine nitrogen on its enol tautomer to give, after loss of water and a third acylation, a 1,3-diacetylated indolizine. In a subsequent acidic catalyzed reaction, the acetyl groups are removed to generate the unsubstituted indolizine, albeit in low yield (10%).



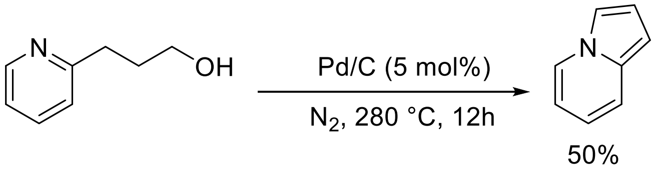
Scheme 1.2.1.1. Scholtz synthesis of indolizines

The synthesis of unsubstituted indolizine was only achieved in reasonable yields in the late 1950s. Boekelheide reported in 1957 a 2-step procedure in which 3-(2-pyridyl)-propanol N-oxide was reacted with acetic anhydride yielding an intermediate with acetyl esters at the 1- and 3-position of the alkyl side chain. Subsequent thermal cyclization and aromatization affords the unsubstituted indolizine in 35% overall yield (Scheme 1.2.1.2).[10]



Scheme 1.2.1.2. Boekelheide synthesis of indolizine starting from 3-(2-pyridyl)-propanol N-oxide

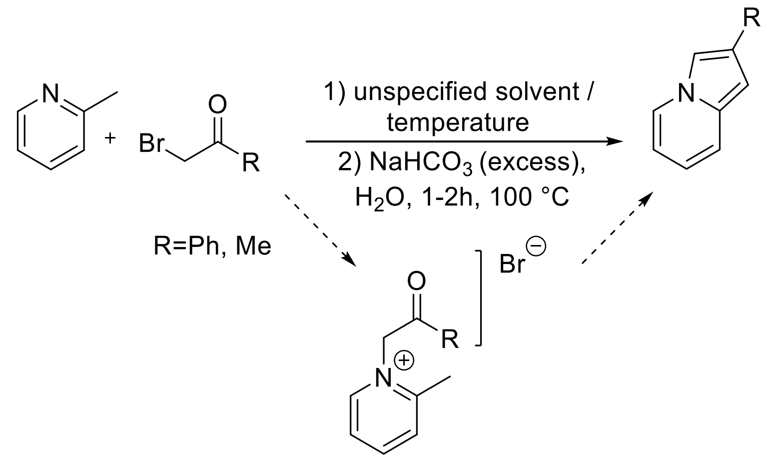
In 1959, Boekelheide reported a one-step synthesis to unsubstituted indolizine.[11] In this, 3-(2-pyridyl)propanol is oxidized over palladium on carbon, presumably generating first an aldehyde for cyclocondensation to ultimately form indolizine in 50% yield (Scheme 1.2.1.3).



Scheme 1.2.1.3. One-step synthesis of indolizines from 3-(2-pyridyl)propanol

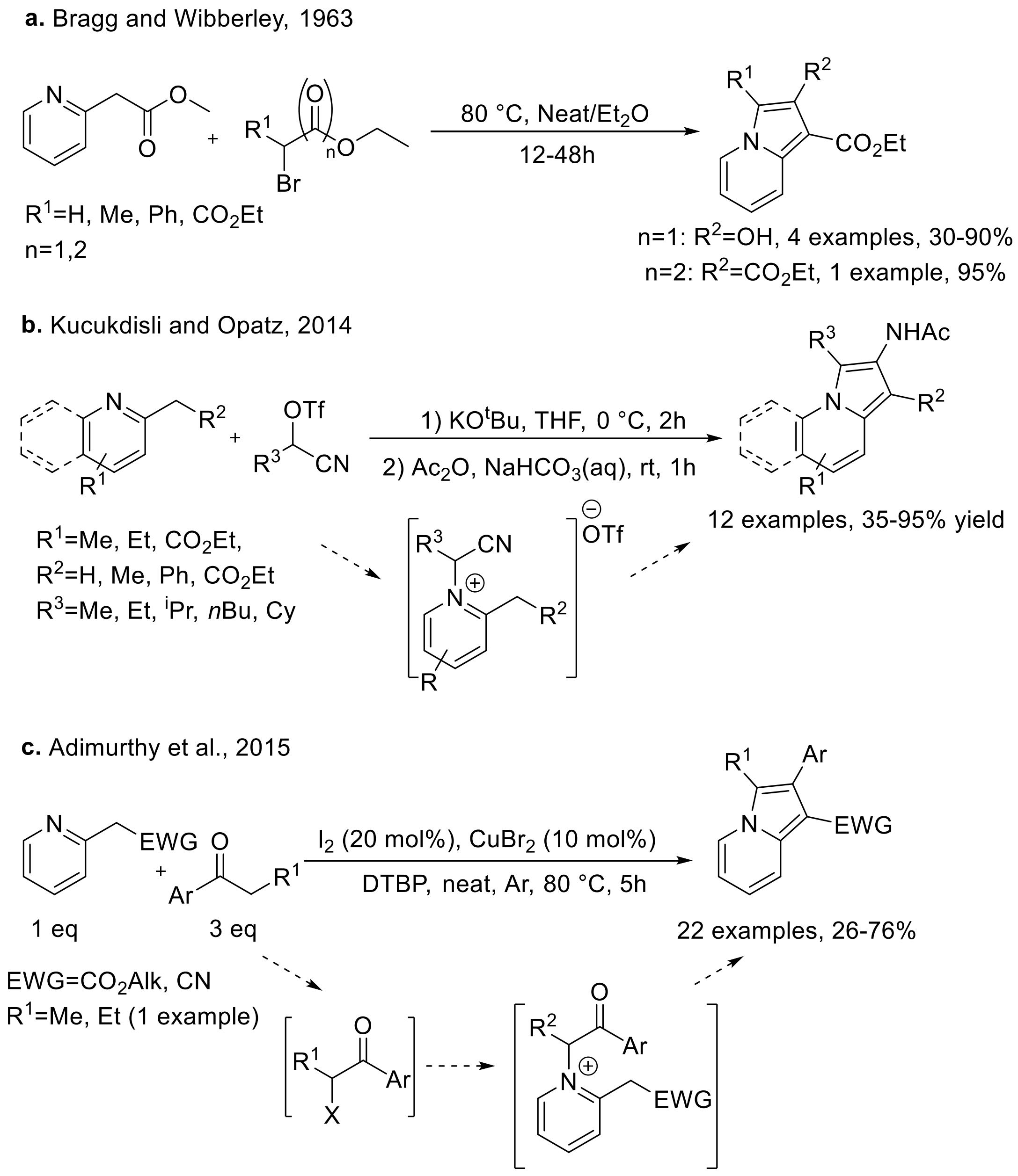
1.2.2. Substituted indolizines

One of the earliest, widely adopted approaches to substituted indolizines was reported by Tschitschibabin in 1927, and involves the reaction of α-halo ketones with 2-alkyl pyridines.[12,13] The transformation, now known as the Tschitschibabin (or Chichibabin) reaction, proceeds by an initial alkylation of the pyridine nitrogen, followed by a spontaneous base catalyzed cyclization of the α-methyl group on the ketone and aromatization (Scheme 1.2.2.1).



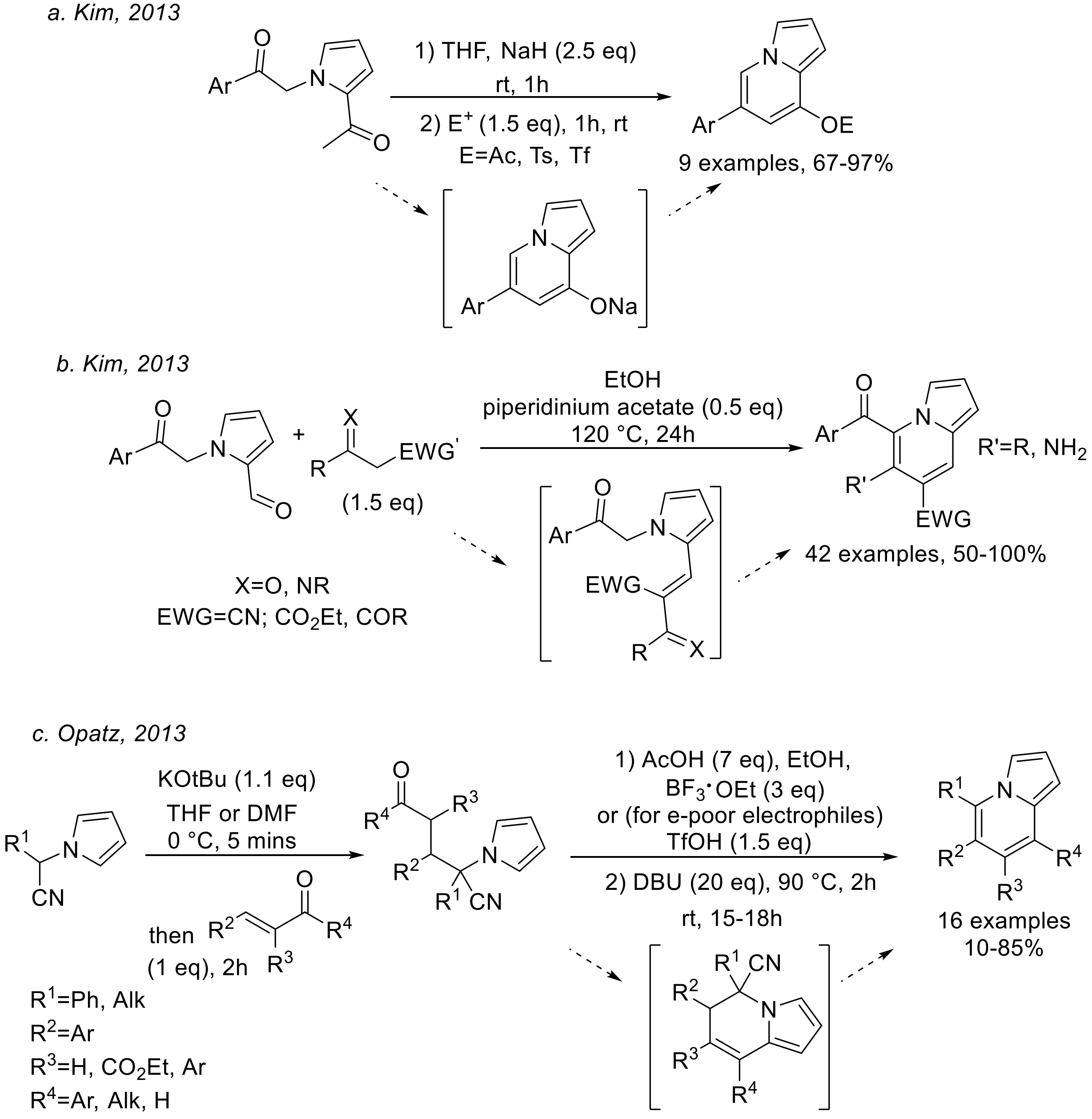
Scheme 1.2.2.1. Tschitschibabin reaction for the synthesis of indolizines

The Tschitschibabin reaction is still heavily used today for the synthesis of diversely substituted indolizines. A number of notable improvements have been made since its development. For example, Bragg and Wibberley extended this transformation to the use of α-halo esters or α-halo ketoesters to give 2-hydroxyl or 2-ester-substituted products, respectively (Scheme 1.2.2.2a).[14] α-Cyano triflates have also been used to yield 2-aminoindolizines (Scheme 1.2.2.2b).[15] Other substrates include organoboron-[16] and sydnone-[17] substituted α-halo ketones or the use of 2-sulfanyl or 2-selenyl pyridines.[18] King reported the formation of pyridinium salts using iodine and alkyl ketones as an α-haloketone equivalent,[19] which has been extended to the synthesis of indolizines by a number of groups (Scheme 1.2.2.2c).[20,21]



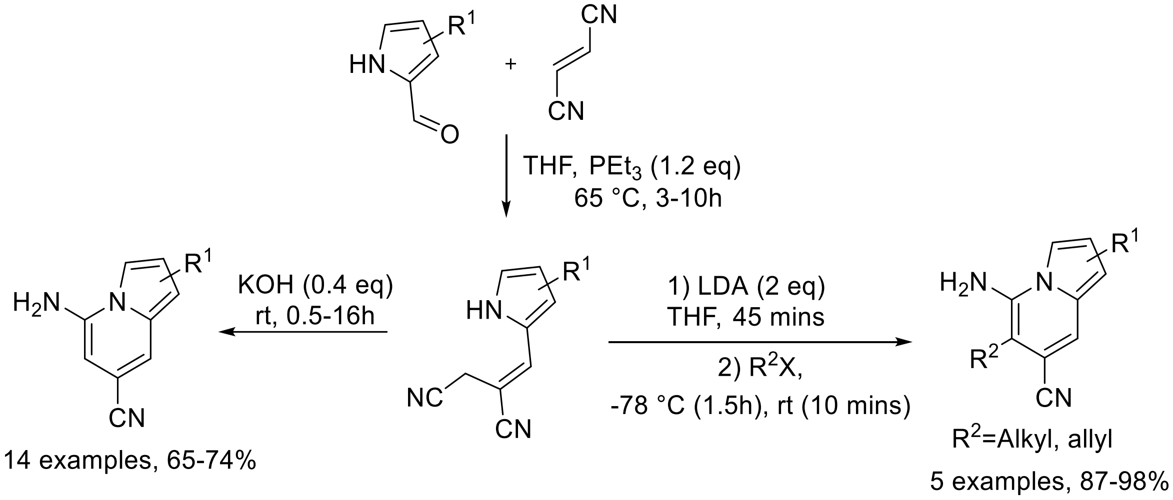
Scheme 1.2.2.2. Select improvements on the Tschitschibabin indolizine synthesis

A variety of other cyclocondensation reactions have been developed for indolizine synthesis. One general approach involves the cyclization of substituted pyrrole derivatives. For example, Kim reported that N-(2-oxoalkyl)-2-acetylpyrroles can undergo an intramolecular aldol condensation to give an aromatic indolizin-8-olate that is then trapped by an electrophile (Scheme 1.2.2.3a).[22] Kim also showed that an intermolecular aldol condensation between 2-formyl pyrroles and ketones (or imines), followed by spontaneous cyclization, can afford indolizines (Scheme 1.2.2.3b).[23,24] Alternatively, the reaction between N-substituted pyrroles and α,β-unsaturated aldehydes or ketones has been shown to afford indolizines by Opatz (Scheme 1.2.2.3c). In this, an initial Michael addition of the deprotonated pyrrole generates a tethered ketone. Subsequent acid catalyzed condensation reaction of the carbonyl on the 2-pyrrole position is followed by dehydrocyanation under basic conditions.[25]



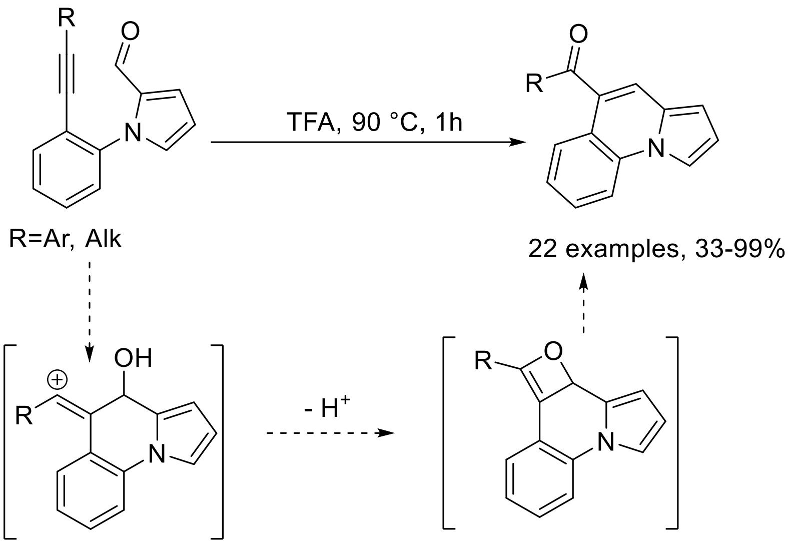
Scheme 1.2.2.3. Intramolecular condensation approaches to indolizine from N-(oxoalkyl)pyrroles

Cyano groups can be suitable alternatives to carbonyls in condensation reactions to form indolizines. This has been exploited by Townsend to generate 5-aminoindolizines from 2-cyano-tethered pyrroles by intramolecular nucleophilic attack of the pyrrole nitrogen on the cyano group. When the reaction was performed in the presence of superstoichiometric amounts of base, the 6-position of the indolizine was deprotonated and could be functionalized by an electrophile (Scheme 1.2.2.4).[26]



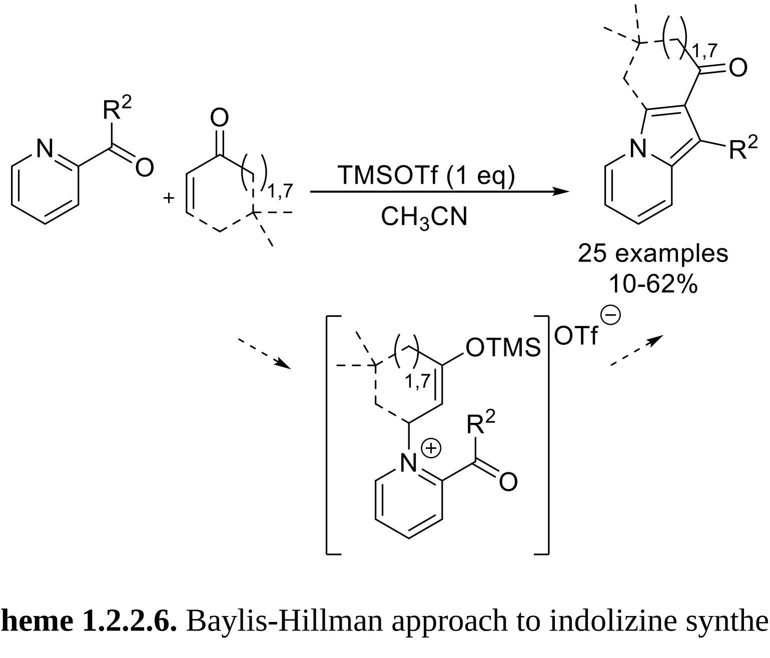
Scheme 1.2.2.4. Nucleophilic attack on nitriles to generate 5-amino substituted indolizines

Kim reported an alternative cyclization approach to indolizines via the intramolecular carbonyl-olefin metathesis reaction catalyzed by trifluoroacetic acid.[27] A proposed mechanism involves an acid catalyzed formal 2+2 cycloaddition followed by ring opening to afford the carbonyl substituted product (Scheme 1.2.2.5).



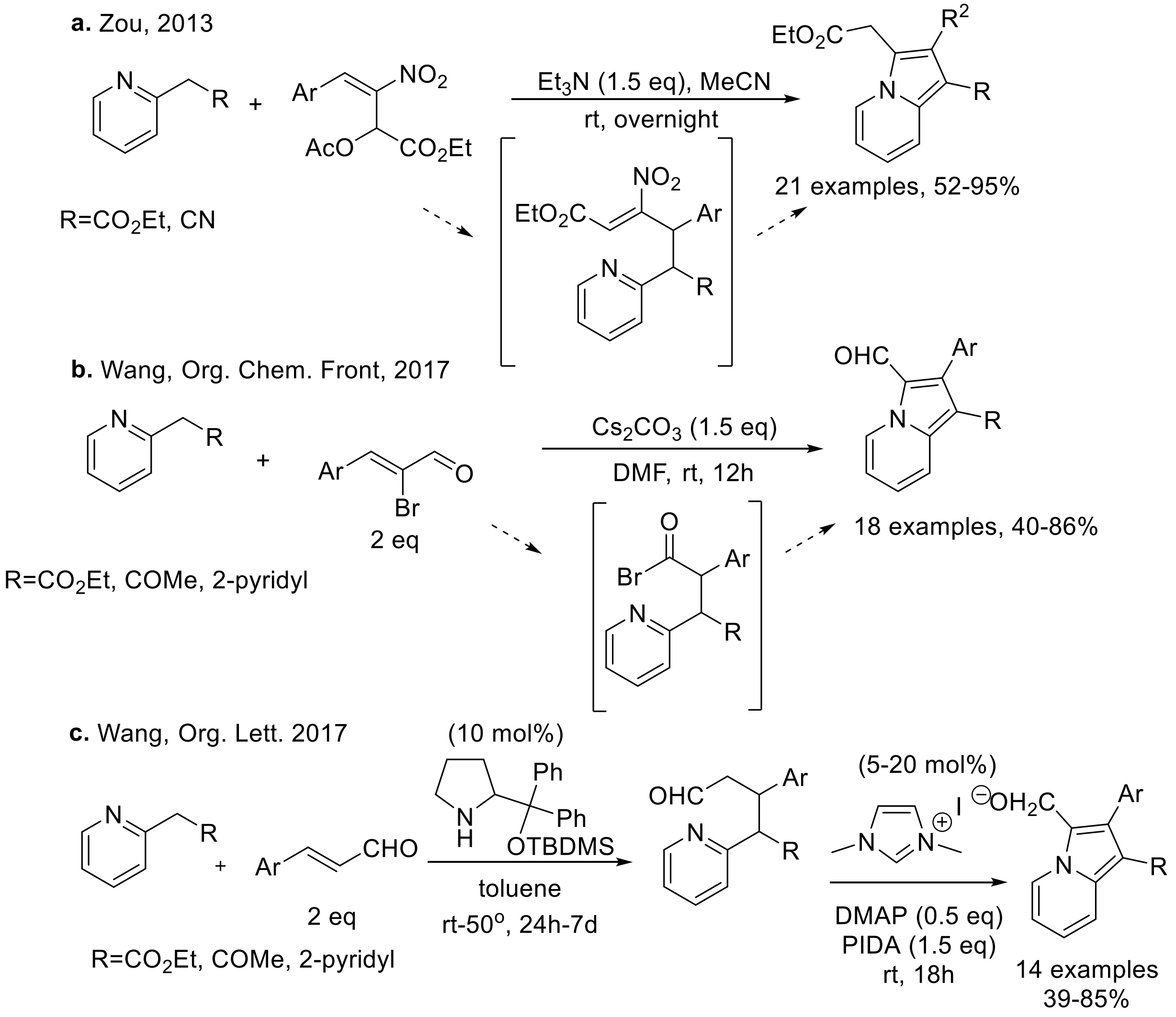
Scheme 1.2.2.5. TFA-catalyzed alkyne-carbonyl metathesis

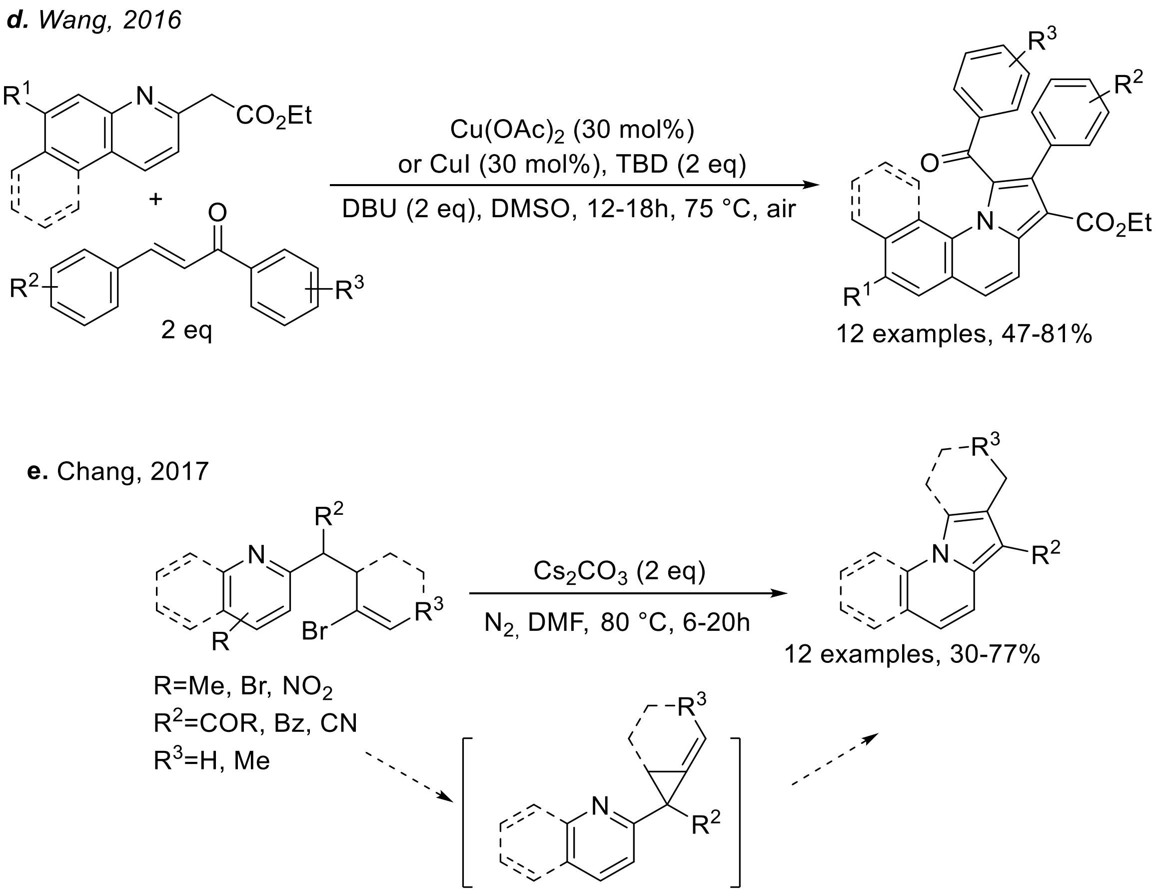
Substituted pyridines have also been heavily exploited in cyclizations to afford indolizines. Basavaiah and Rao described a Baylis-Hillman-type reaction involving α,β-unsaturated ketones and 2-formyl or 2-keto pyridines (Scheme 1.2.2.6).[28,29] In this, the pyridine undergoes an initial Michael addition to the enone, followed by an aldol reaction and aromatization.



Scheme 1.2.2.6. Baylis-Hillman approach to indolizine synthesis

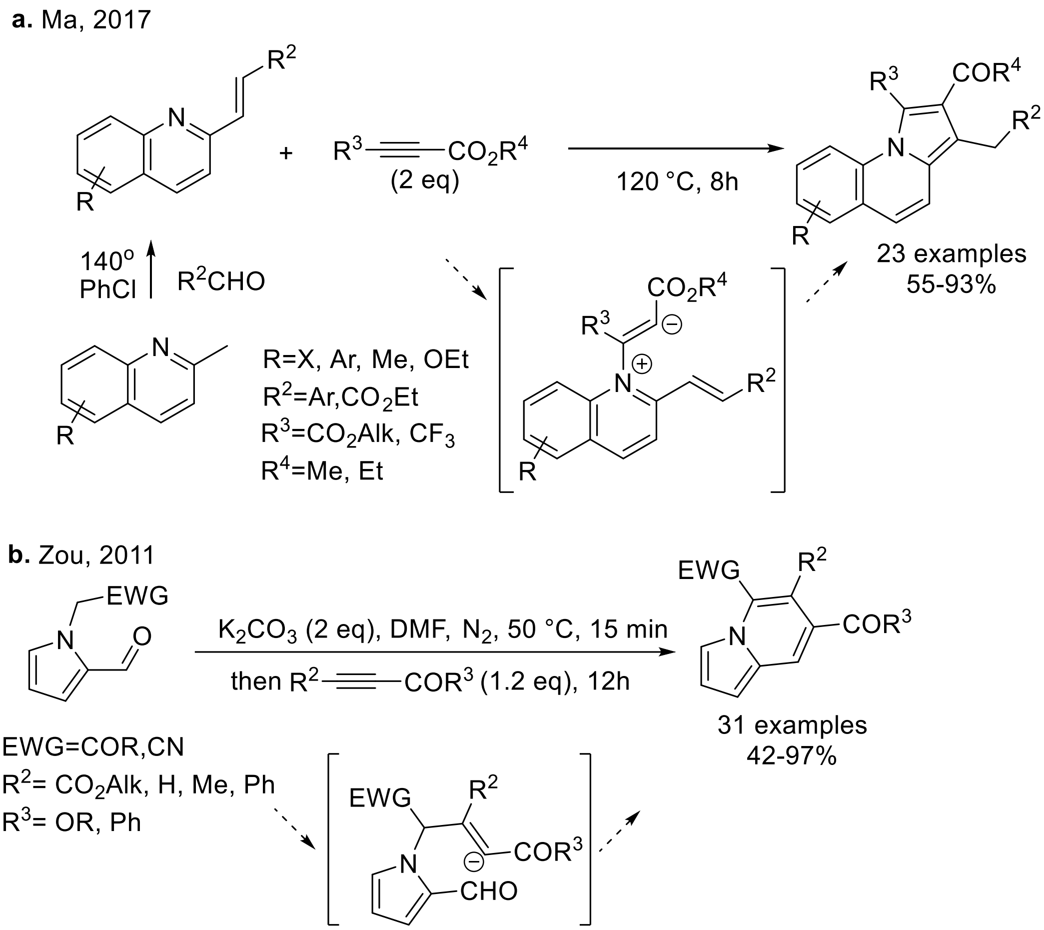
Many cyclization routes to indolizines start from 2-alkylpyridines containing an α-electron withdrawing group. These can be readily deprotonated at the α-position for reaction with an unsaturated electrophile. For example, one approach involves the reaction of 2-alkylpyridines with electron poor nitro-alkenes under basic conditions (Scheme 1.2.2.7a).[30] In this, initial Michael addition of the deprotonated pyridine is followed by nucleophilic cyclization on the pyridine nitrogen and HNO_2 loss. Lei and Roy have reported related reactions.[31] The reaction of 2-substituted pyridines and α-bromoenals can also access the indolizine scaffold via a similar series of steps (Scheme 1.2.2.7b).[32] Li and Wang have reported two different approaches to indolizines from 2-substituted pyridines and α,β-unsaturated carbonyl derivatives. One exploits a two-step pathway involving an initial amine catalyzed Michael addition to unsaturated aldehydes, followed by an NHC-catalyzed cyclization (Scheme 1.2.2.7c).[33] Alternatively, the reaction can be performed in one pot under copper catalysis with α,β-unsaturated ketones, wherein the copper catalyzed oxidation of the intermediate Michael addition product initiates cyclization (Scheme 1.2.2.7d).[34] Chang has reported an interesting cyclization of vinyl bromide substituted pyridines, which is postulated to proceed via an initial base mediated formation of cyclopropanes and ring expansion (Scheme 1.2.2.7e).[35]


a. Zou, 2013
R=CO2Et, CN
Et3N (1.5 eq), MeCN
rt, overnight
21 examples, 52-95%
b. Wang, Org. Chem. Front, 2017
R=CO2Et, COMe, 2-pyridyl
2 eq
Cs2CO3 (1.5 eq)
DMF, rt, 12h
18 examples, 40-86%
c. Wang, Org. Lett. 2017
(10 mol%)
2 eq
toluene
rt-50o, 24h-7d
R=CO2Et, COMe, 2-pyridyl
(5-20 mol%)
DMAP (0.5 eq)
PIDA (1.5 eq)
rt, 18h
14 examples
39-85%



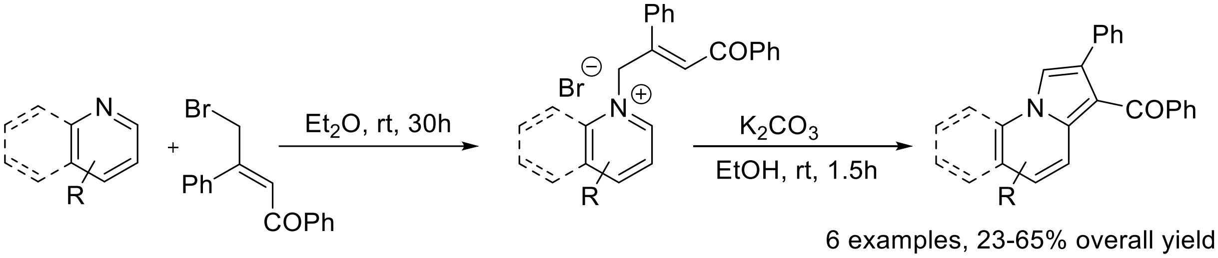
Scheme 1.2.2.7. Synthesis of indolizines by Michael addition

Another strategy for indolizine synthesis involves the coupling of electron-poor alkynes with substituted pyridines or pyrroles. As an example, Ma et al. showed the reaction of alkynyl esters and ketones with 2-vinyl quinolines (generated in-situ from 2-methylquinolines and aldehydes) can generate indolizines via an initial Michael addition by the quinoline nitrogen followed by cyclization on the 2-vinyl substituent and tautomerization (Scheme 1.2.2.8a).[36] An alternative use of alkynes in indolizine synthesis involves reactions with N-substituted 2-formyl pyrroles in the presence of base. In this, deprotonation of the acidic α-hydrogen on the pyrrole N-substituent initiates reaction with electron poor alkynes and followed by cyclization onto the aldehyde (Scheme 1.2.2.8b).[37]



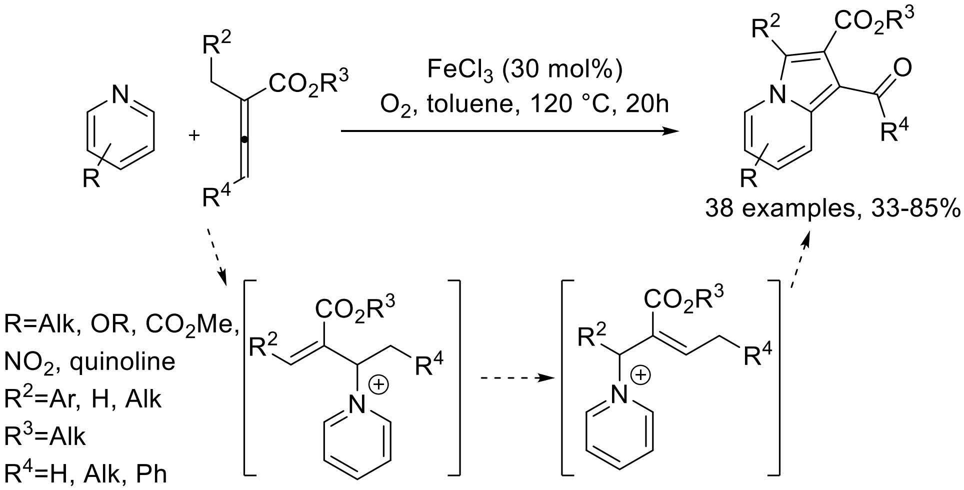
Scheme 1.2.2.8. Synthesis of indolizine and pyrrolo[1,2-a]quinoline by Michael addition on activated alkynes

Unsubstituted pyridines can also serve as precursors to indolizines. Ikeda showed the reaction of pyridine and electron poor allyl halide derivatives leads to N-allylated pyridinium salts. Under basic conditions, these undergo cyclization at the electrophilic 2-pyridinium position (Scheme 1.2.2.9).[38]



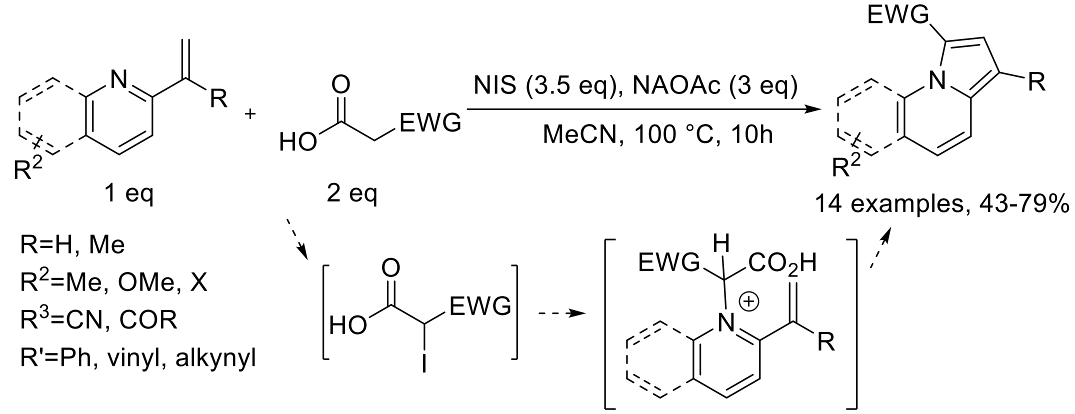
Scheme 1.2.2.9. 1,5-cycloaddition approach to indolizines

Jia and Li showed that electron poor allenes can undergo reaction with pyridine in the presence of Lewis acid and under oxidative conditions to form polysubstituted indolizines (Scheme 1.2.2.10).[39] In this case, an initial Michael addition of the pyridine forms an N-substituted pyridinium salt, which undergoes an allylic rearrangement. The latter is then cyclized to indolizine and oxidized in the presence of oxygen to 1-acylindolizine.



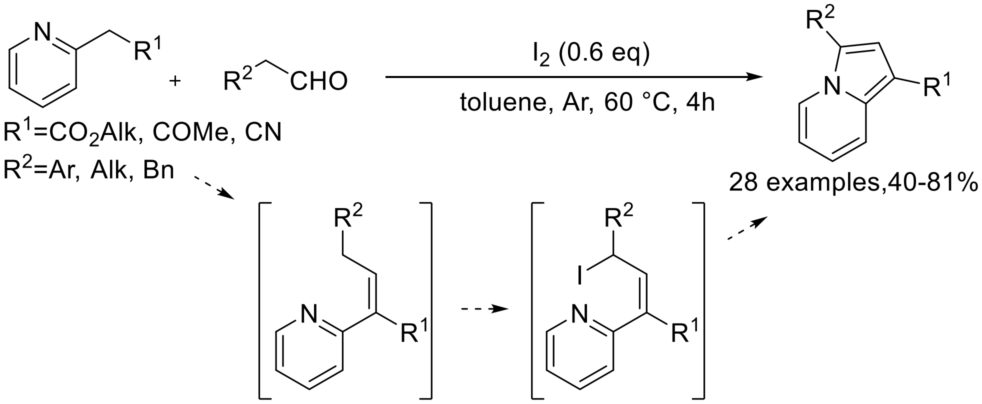
Scheme 1.2.2.10. Synthesis of indolizine from allenoates derivatives

Indolizines can be formed by the reaction of 2-vinyl pyridines and malonate derivatives. In this, in situ iodination of the malonate derivative allows N-alkylation of the pyridine, which is followed by deprotonation of the acidic hydrogen for cyclization of the vinyl unit. The latter undergoes decarboxylation to afford the product (Scheme 1.2.2.11).[40]



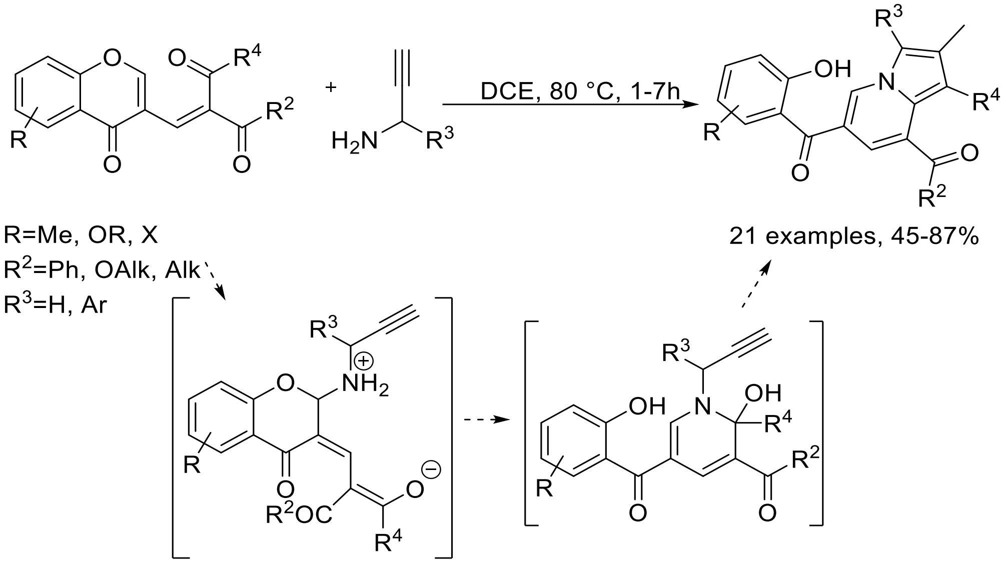
Scheme 1.2.2.11. Cyclization of 2-vinylpyridines and carboxylic acids by α-iodination and decarboxylation

In another iodination-driven synthesis of indolizines by Yan, condensation of the methylene of a 2-Pyridylacetate on an aldehyde is followed by iodination at the resulting vinylic carbon and cyclization by nucleophilic substitution (Scheme 1.2.2.12).[41]



Scheme 1.2.2.12. In-situ iodination and nucleophilic substitution at the vinylic position

Finally, the Daich group has reported one of the few syntheses of indolizines that does not start from pyrroles or pyridines derivatives (Scheme 1.2.2.13).[42] In this, 1,6-addition of propargyl amines to the enol ether position of chromones is followed by ring-opening of the chromone to generate an enaminone intermediate. Subsequent amine cyclization onto the ketone moiety generates the 6-membered ring. The 5-membered ring is then formed by 5-endo-dig cyclization between the alkyne and enamine.

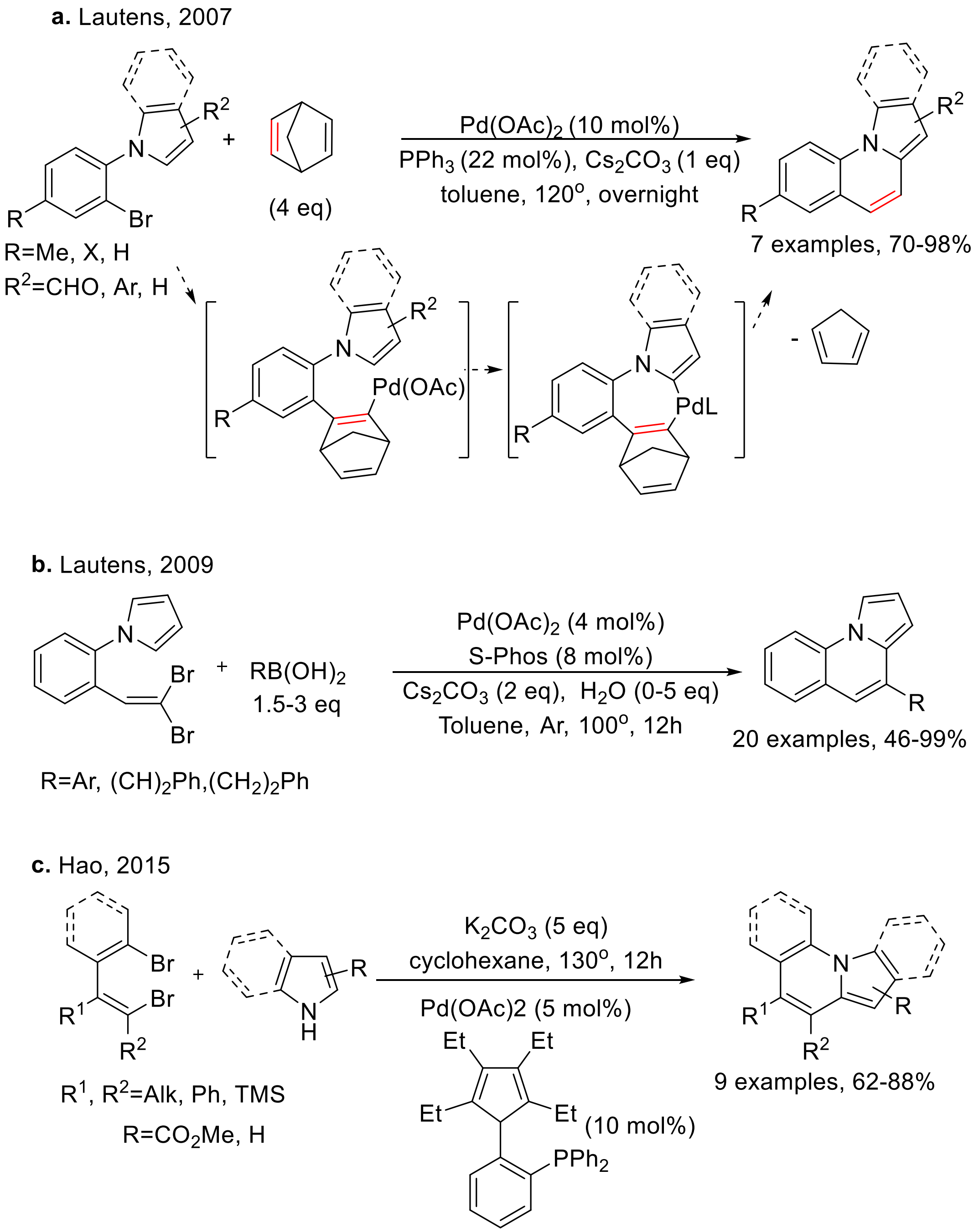


Scheme 1.2.2.13. Chromone-based synthesis of indolizines

1.3. Metal-catalyzed syntheses

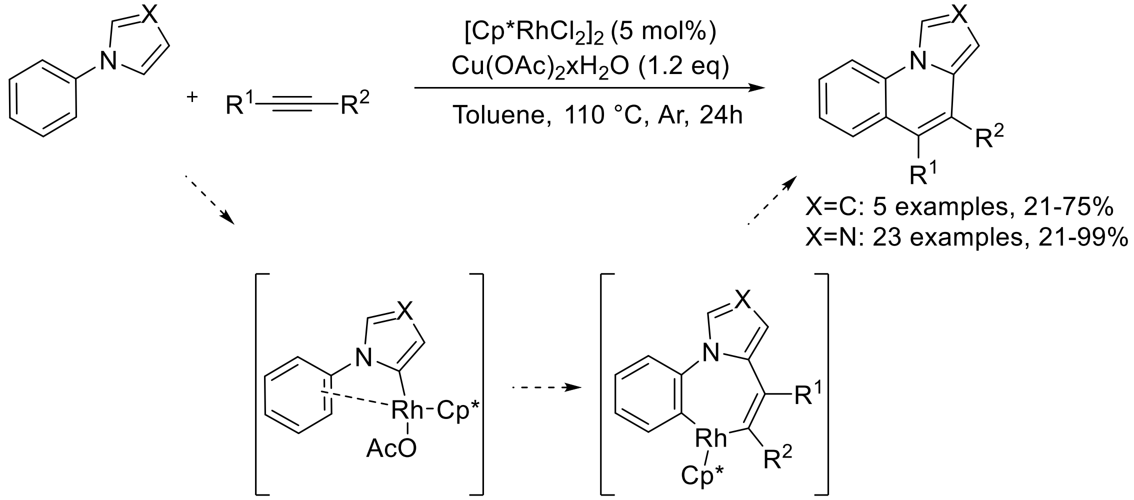
1.3.1. C-H functionalization approaches to indolizines

A number of metal catalyzed C-H bond functionalization approaches to indolizines have been developed. For example, Lautens reported the synthesis of substituted indolizines via the palladium catalyzed coupling of 1-(2-bromophenyl)-pyrrole and norbornadiene (Scheme 1.3.1.1a). In this, oxidative addition of the aryl bromide to palladium followed by norbornadiene insertion leads to a palladium intermediate that can undergo spontaneous intramolecular C-H functionalization of the pyrrole to afford indolizine (after cyclopentadiene elimination).[43] Lautens also reported the palladium catalyzed sequential cross-coupling/C-H functionalization with a dibromovinyl-substituted pyrrole.[44] An initial Suzuki cross-coupling with a boronic acid is believed to be followed by the annulation of the 2-position of the pyrrole ring (Scheme 1.3.1.1b). The latter likely proceeds via oxidative addition of the vinyl bromide to palladium, followed by C-H functionalization of the pyrrole for reductive elimination. Xi described a related intermolecular synthesis of indolizines from 1,4-dibromobuta-1,3-diene and pyrroles in which sequential N-H and then C-H functionalization affords an array of indolizine derivatives (Scheme 1.3.1.1c).[45]



Scheme 1.3.1.1. C-H functionalization in indolizine synthesis

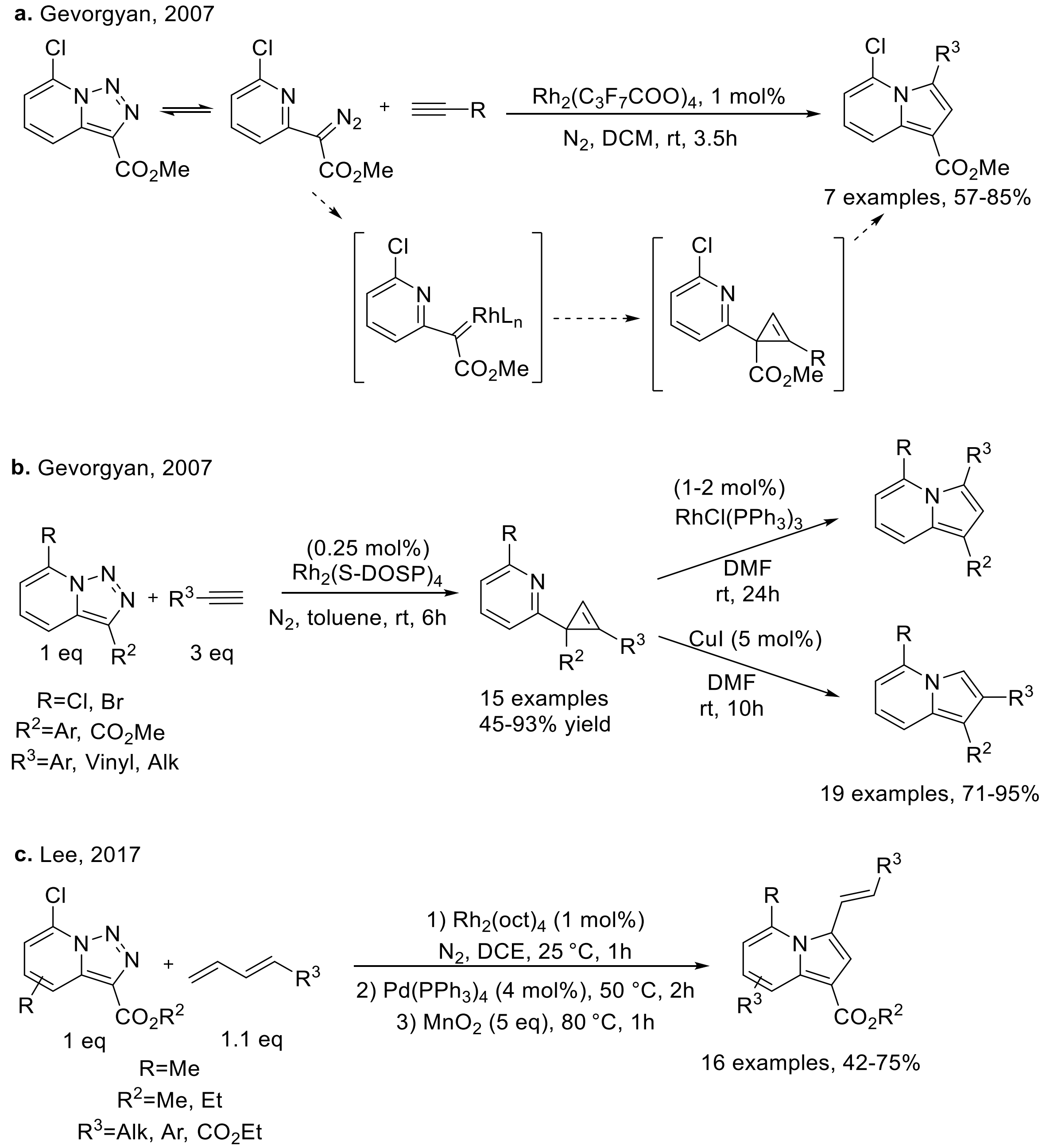
A rhodium catalyzed double C-H functionalization of simple N-phenylpyrroles with alkynes was reported by Dong and Cheng to afford indolizines (Scheme 1.3.1.2).[46] In this, a rhodium catalyzed C-H functionalization of the pyrrole is followed by alkyne insertion and then a second C-H functionalization for closing the ring. The overall reaction is oxidative, and uses stoichiometric $CuOAc_2$ to regenerate the Rh(III) catalyst. While efficient, the use of unsymmetrical alkyne substrates often resulted in poor regioselectivity, and the scope focused heavily on diphenylacetylene.

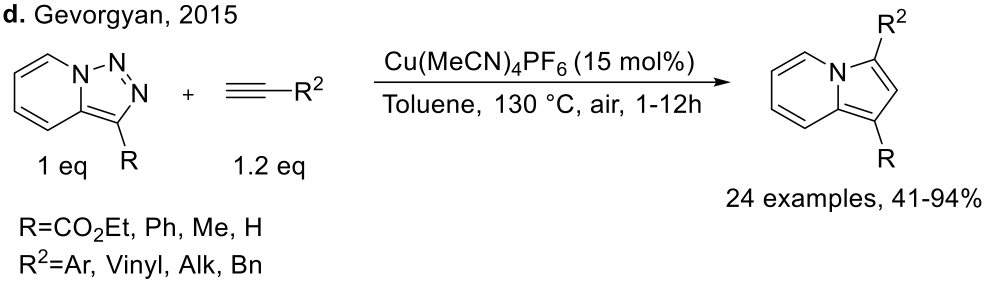


Scheme 1.3.1.2. Double C-H functionalization

1.3.2. Metal-Carbenoid Intermediates

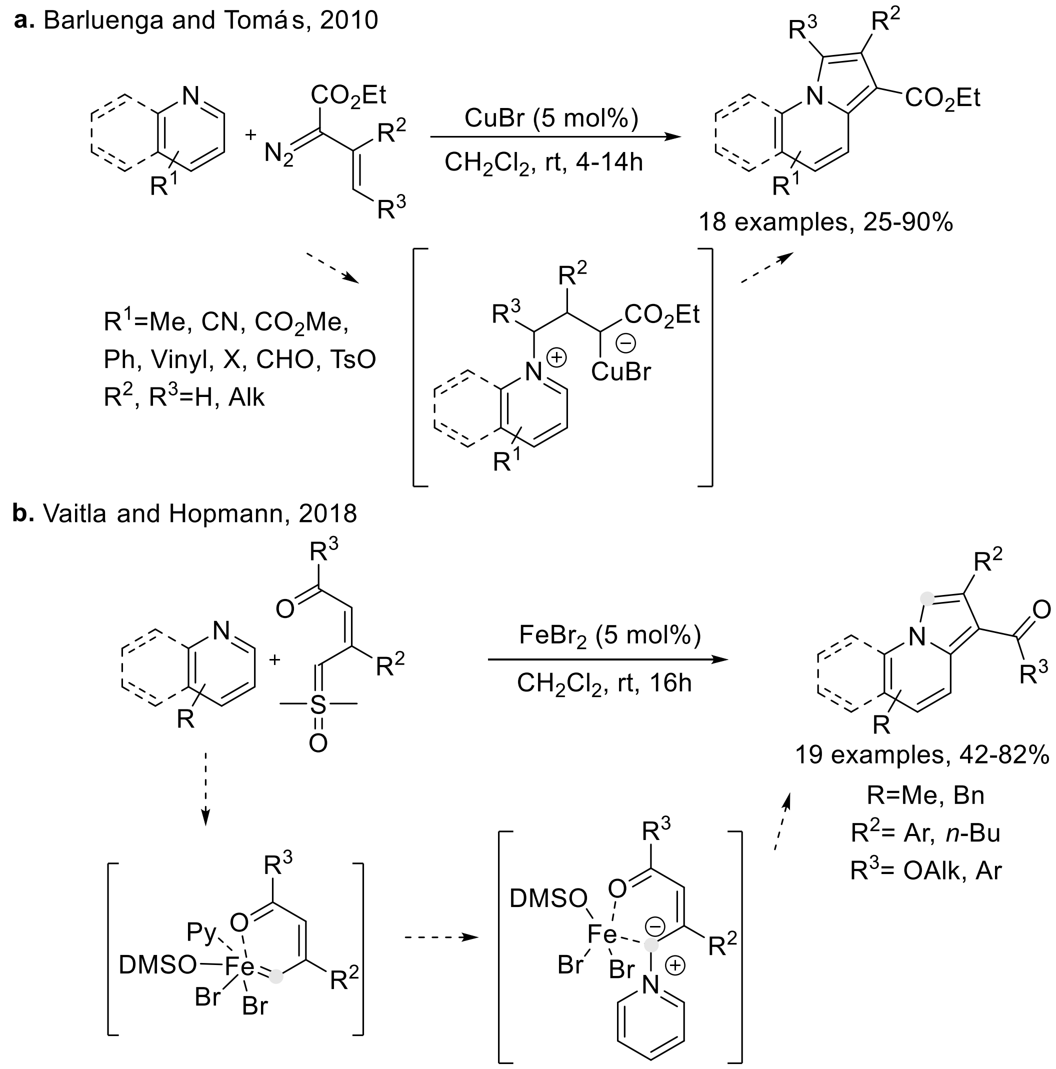
Various approaches to indolizines by metal catalyzed intramolecular ring-expansion have also been developed. One important method involves the transannulation of [1,2,3]triazolo[1,5-a]pyridines described by the Gevorgyan group. The triazole in these substrates can be considered as a tautomer of a ring-opened diazo-compound, and, as such, can serve as a carbene precursor. Gevorgyan first exploited this in indolizine synthesis in the rhodium catalyzed coupling of [1,2,3]triazolo[1,5-a]pyridines and terminal alkynes (Scheme 1.3.2.1a). While several mechanisms are plausible, the reaction can be considered to proceed via the cyclopropenation of the alkyne followed by a rhodium catalyzed ring opening to afford the cyclized product. Subsequent studies showed the use of a modified rhodium catalyst can stop the reaction at the cyclopropene. From here, the addition of either copper iodide or $RhCl(PPh_3)_3$ catalyst allows the selective generation of 1,3- or 1,2-disubstituted indolizines, respectively (Scheme 1.3.2.1b).[47] A similar sequence was described by Lee using 1,3-dienes instead of alkynes (Scheme 1.3.2.1c).[48,49] While these systems employ triazoles with 7-halo and 3-methyl ester substituents to favor its ring-opened isomer,[50] subsequent studies showed that the use of a $Cu(MeCN)_4PF_6$ catalyst at elevated temperature can allow these reactions to proceed with a range of pyridotriazoles (Scheme 1.3.2.1d).[51]





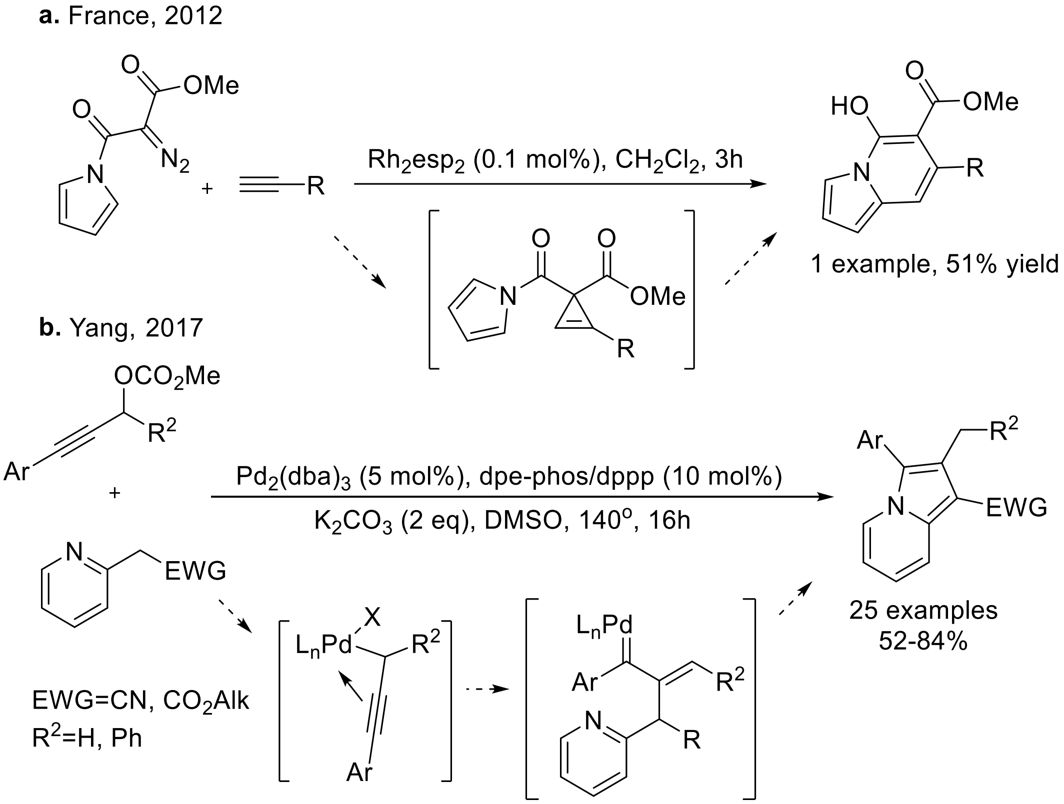
Scheme 1.3.2.1. Approaches to indolizines by transannulation of [1,2,3]triazolo[1,5-a]pyridines

Other carbene precursors have been employed as substrates in indolizine synthesis. Barluenga reported a copper-catalyzed coupling of simple pyridines and α,β-unsaturated diazo compounds to afford indolizines (Scheme 1.3.2.2a).[52] In this, an in situ formed α,β-unsaturated metal carbenoid undergoes Michael-type 1,4-addition to the pyridine nitrogen, followed by carbene C-H insertion. The $FeBr_2$ catalyzed reaction of sulfoxonium ylides and pyridines can also generate indolizines, wherein pyridine attack on a catalytically generated iron-carbenoid initiates nucleophilic cyclization on the 2-pyridine position (Scheme 1.3.2.2b).[53]



Scheme 1.3.2.2. Synthesis of indolizine through metal carbonyl conjugate addition to pyridine

The rhodium catalyzed coupling of alkynes with diazo-substituted pyrroles can also form indolizines.[54] France showed this reaction proceeds via the initial formation of a cyclopropene, followed by rearrangement to the fused 6,5-ring (Scheme 1.3.2.3a). An alternative approach to indolizines via metal carbenoids involves the palladium catalyzed coupling of propargyl alcohol derivatives and 2-substituted pyridines (Scheme 1.3.2.3b).[55] Similar to the reactions above, the palladium catalyzed activation of the propargyl reagent followed by nucleophilic attack of the deprotonated pyridine generates a palladium-carbene that, in this case, adds to the pyridine nitrogen to afford the aromatic product.

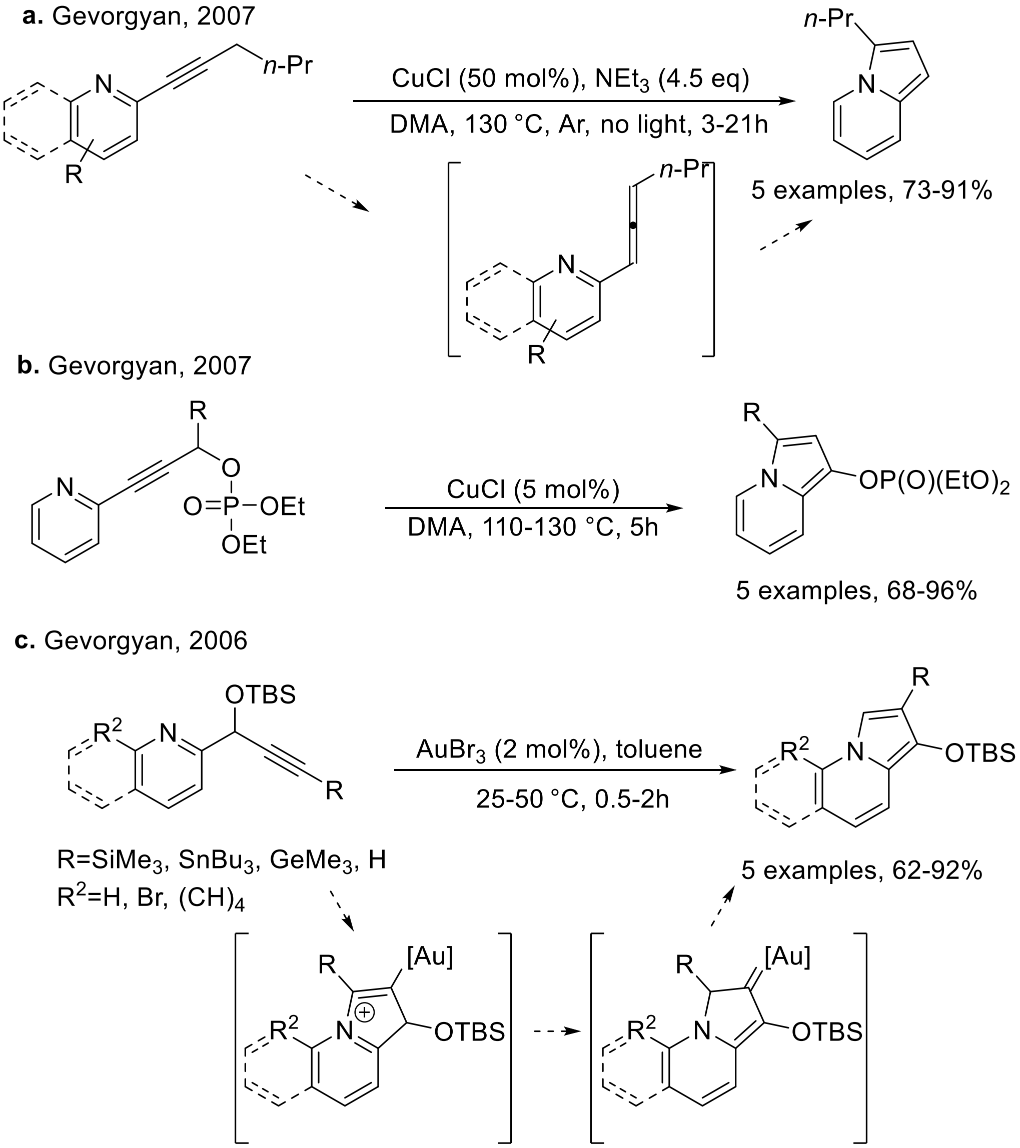


Scheme 1.3.2.3. Metal catalyzed indolizine synthesis via metal-carbenoids.

1.3.3. Cycloisomerizations to indolizines

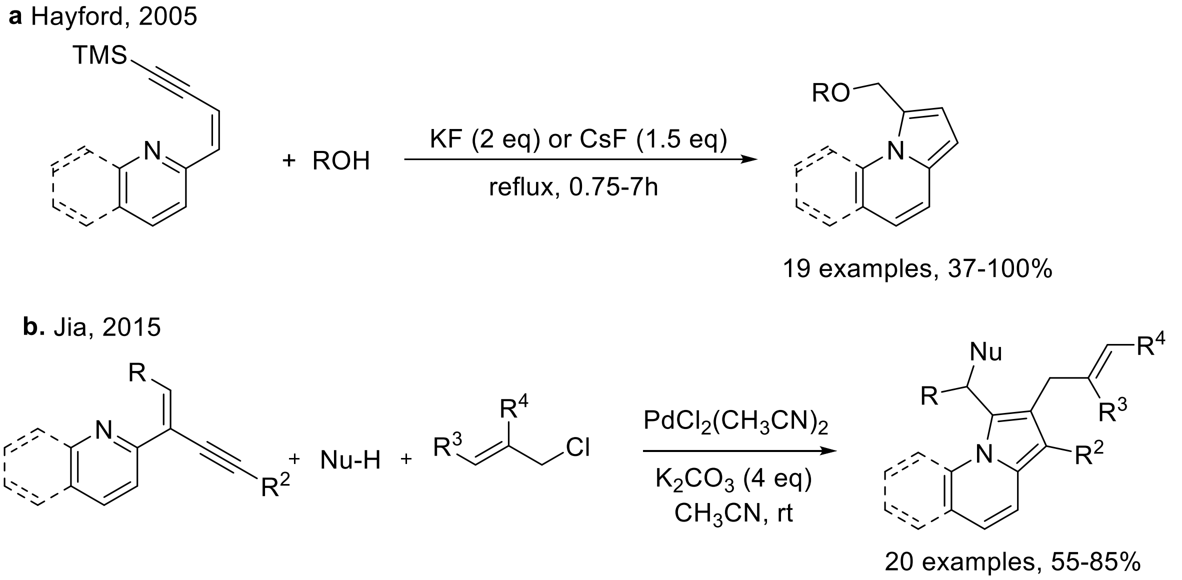
The metal catalyzed cycloisomerization to indolizines has emerged in the recent years as a valuable approach to indolizine synthesis.[56] These typically exploit alkynyl-tethered pyridine or pyrrole substrates, where a Lewis acidic catalyst can mediate either nucleophilic attack on the alkyne or rearrangement to an allenyl intermediate for cyclization. As representative examples, Gevorgyan showed that triethylamine and CuCl can catalyze the rearrangement of 2-alkynylpyridines to form indolizines in good overall yield via isomerization to allenes (Scheme 1.3.3.1a).[57] The cycloisomerization to indolizines can also be triggered by [1,3]-phosphatyloxy migration (Scheme 1.3.3.1b).[58] A range of related reactions have been described by Liu, Igeta, Kim, Lee and others.[59] The transformation can also occur with 2-propargylpyridines (Scheme 1.3.3.1c).[60] In these cases, computational and experimental results[61] have indicated that the reaction is more likely to proceed through 5-endo-dig-cyclization, followed by carbene formation and [1,2]-

migration of the terminal group rather than the initially proposed gold-vinylidene intermediate.



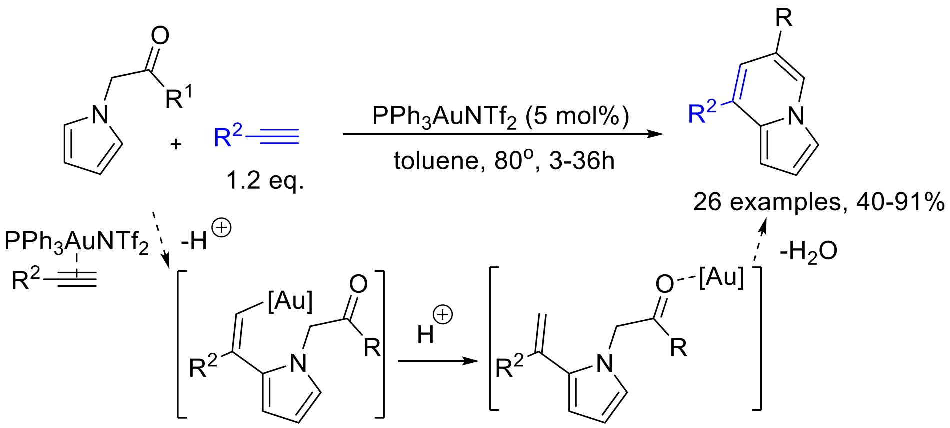
Scheme 1.3.3.1. Approaches to indolizines by cycloisomerization

2-Enyne substituted pyridines have also been shown to undergo cycloisomerization to indolizines. A version of this reaction was reported by Hayford, where protodesilylation of the TMS-protected alkyne moiety is followed by attack by alkoxide anion and electrocyclization (Scheme 1.3.3.2a).[62] Jia has recently described a multicomponent variant of this isomerization that allows the combination of nucleophiles, allyl chlorides and the substituted pyridine derivative to form a number of indolizines (Scheme 1.3.3.2b).[63,64]

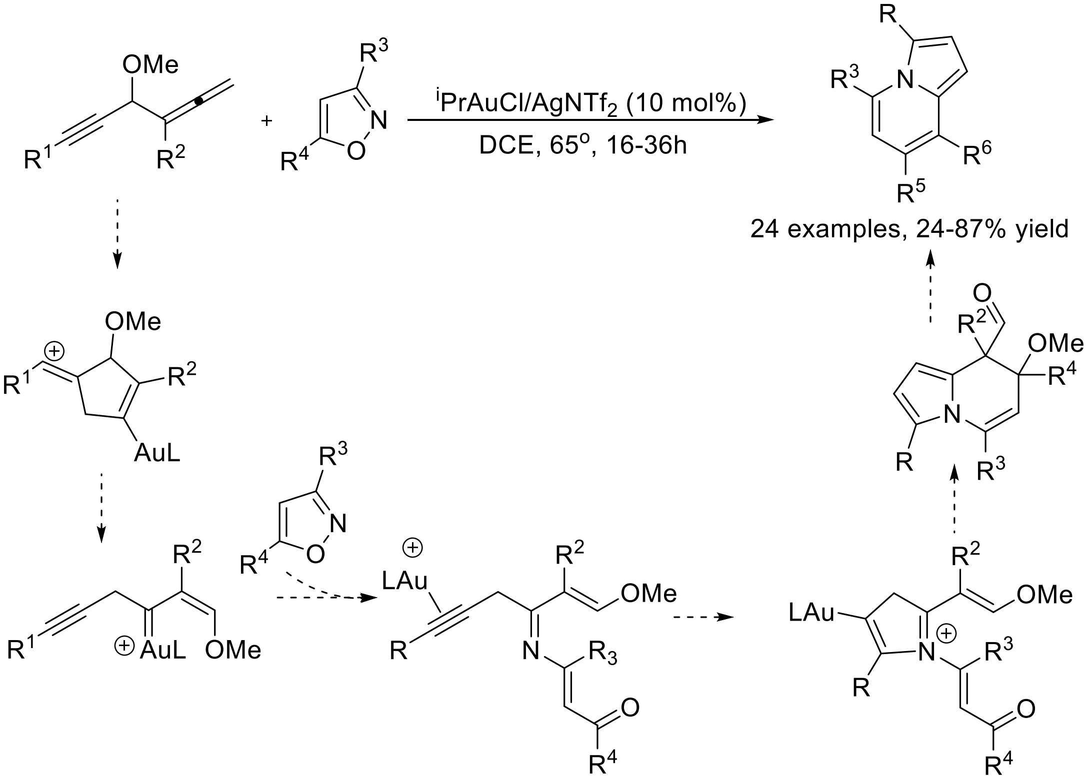


Scheme 1.3.3.2. Nucleophilic attack on an enyne moiety to synthesize indolizines

Related intermolecular reactions are also known. For example, Liu showed that gold(I) can catalyze the coupling of keto-substituted pyrroles with terminal alkynes to form indolizines (Scheme 1.3.3.3).[65,66] In this, gold coordination of the alkyne templates functionalization of the 2-position of the pyrrole, and is followed by cyclization on the ketone. Cheng, Liu et al. reported an unusual gold-catalyzed rearrangement of alkynyl allenes with isoxazoles (Scheme 1.3.3.4).[67] The reaction proceeds via a complex pathway involving several ring closing and ring opening isomerizations catalyzed by the gold complex to ultimately afford indolizines with various substituents around the ring.



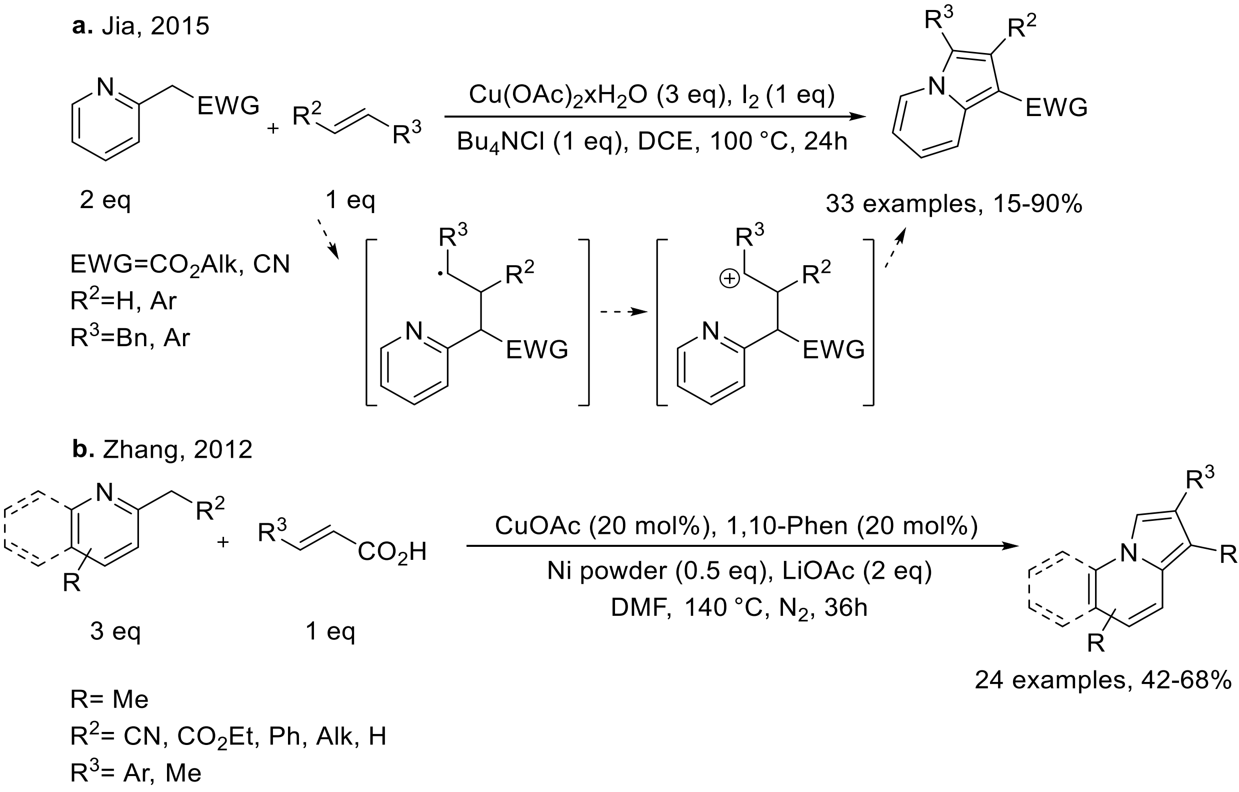
Scheme 1.3.3.3. Synthesis of indolizines under tandem gold catalysis



Scheme 1.3.3.4. Synthesis of indolizines by rearrangement of 1,2-dienyl-5-ynes and isoxazoles

1.3.4. Radical-mediated annulations

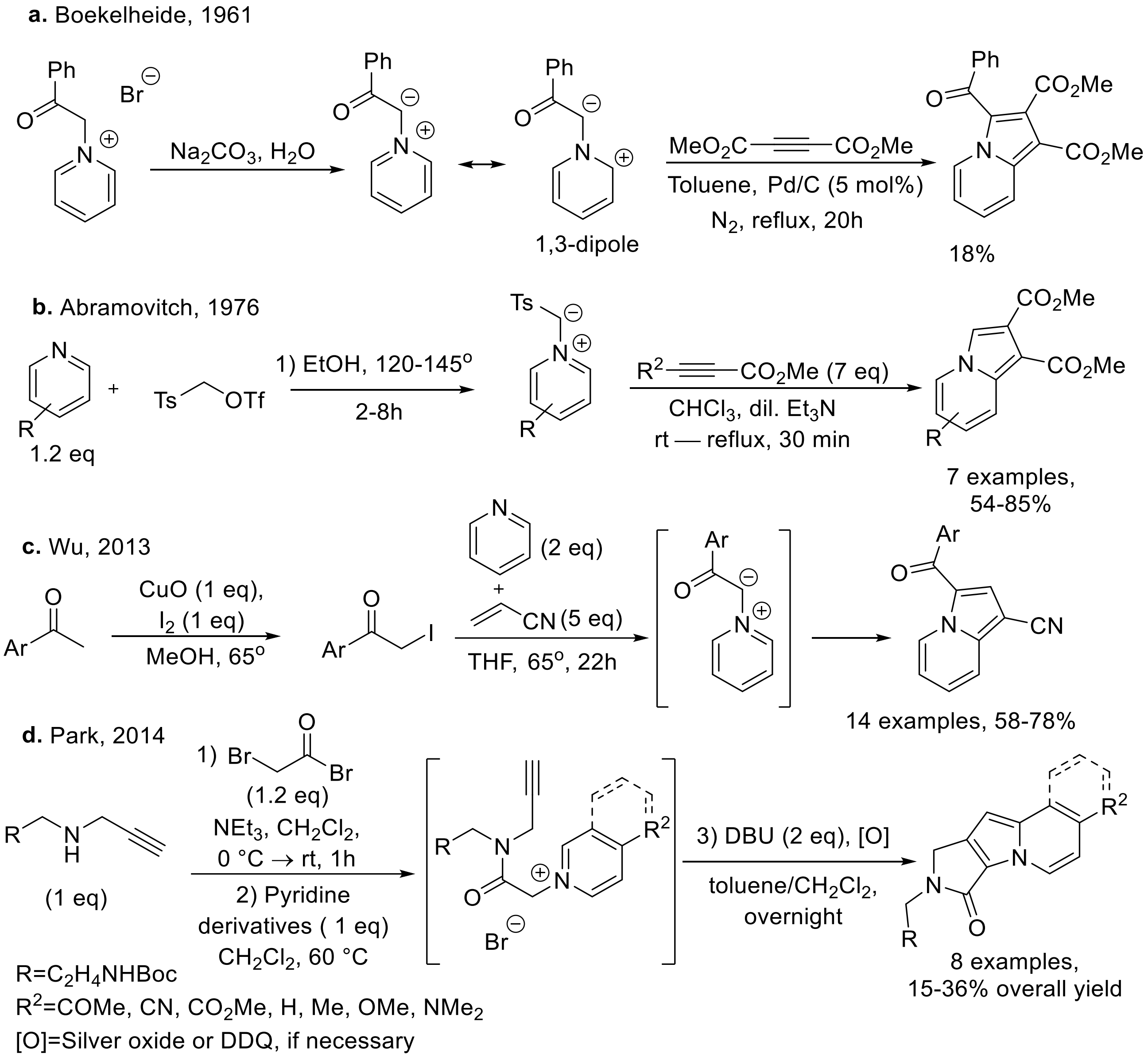
Metal catalyzed radical cyclizations have also seen use in indolizine synthesis. Jia reported a copper-generated radical at the α-position of the 2-substituted pyridines can add to alkenes, which, after oxidation to the carbocation, undergoes cyclization with the pyridine and aromatization under oxidative conditions (Scheme 1.3.4.1a).[68] Subsequent reports showed that iodine itself can mediate this reaction,[69] as can a combination of catalytic iodine and stoichiometric peroxide oxidant.[70,71] A copper-catalyzed decarboxylative coupling of α,β-unsaturated carboxylic acids and 2-alkylpyridines was also developed by Zhang under reductive conditions (Scheme 1.3.4.1b).[72] While the authors didn't propose a mechanism, the reaction likely involves C-H-olefination between the 2-alkyl substituent of the pyridine and the β-carbon of the carboxylic acid and decarboxylative amination between the nitrogen of the pyridine and the α-carbon of the carboxylic acid.



Scheme 1.3.4.1. Copper-mediated stepwise radical addition and annulation of 2-alkylpyridine

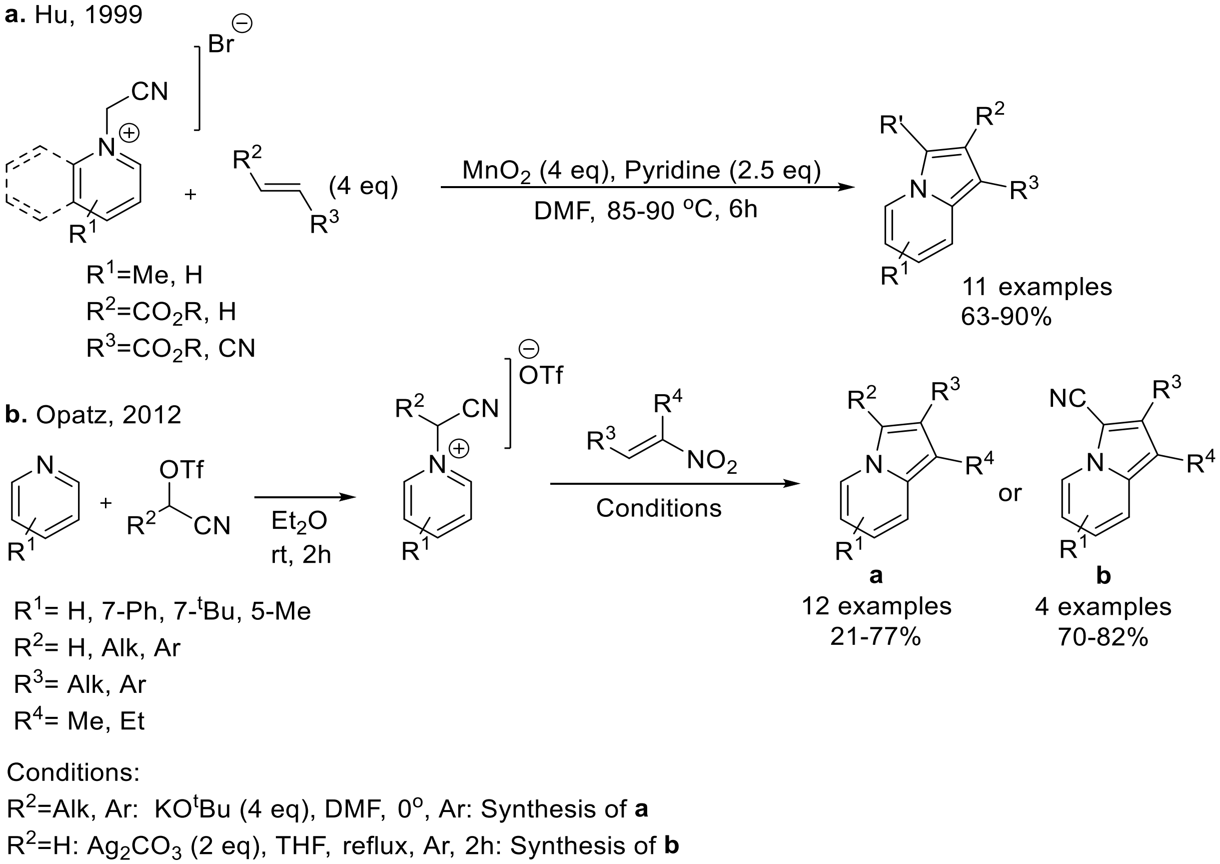
1.4. Synthesis of indolizines by [3 + 2] cycloaddition

A convergent approach to indolizines is via 1,3-dipolar cycloaddition reactions of N-pyridinium ylides. This reaction was first reported by Boekelheide in 1961 in the coupling of an *N*-alkylated pyrinium salt with dimethylacetylene dicarboxylate in the presence of base (Scheme 1.4.1a).[73] Deprotonation of the pyridinium salt in this system generates the pyridine 1,3-dipole that undergoes spontaneous cycloaddition with the electron poor alkyne. Subsequent studies have shown that an array of substituted 1,3-dipole precursors and cycloaddition reagents can be used in this reaction (e.g. Scheme 1.4.1b-d).[74] In general, electron withdrawing groups on the α-carbon are required for deprotonation and dipole formation. Other less used approaches to access these 1,3-dipoles involve nucleophilic attack of pyridine on carbenes,[75,76] or the electron poor epoxides.[77]



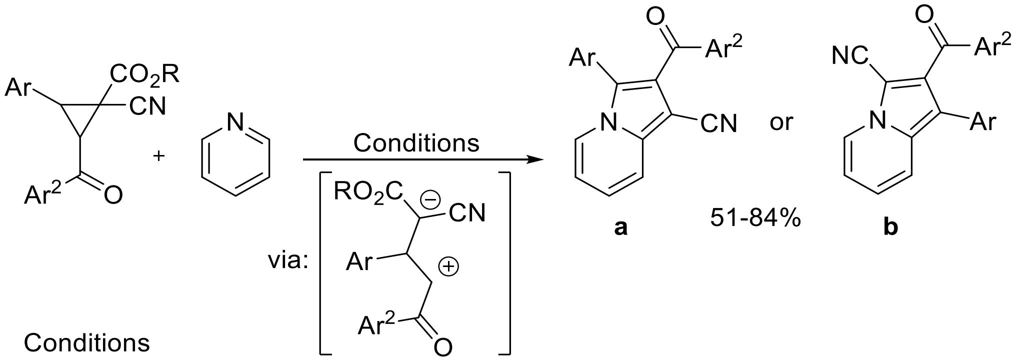
Scheme 1.4.1. Synthetic routes to pyridinium ylids

As shown in Scheme 1.4.1c, alkenes can also undergo cycloaddition to afford indolizines. Olefins can be more challenging substrates in these reactions since the intermediate formed is a saturated tetrahydroindolizine that needs to be aromatized. The latter often involves the use of a synthetic oxidant or transition metal catalyst (e.g. Scheme 1.4.2a).[78] However, if the substituents on the 5-membered ring are good leaving groups, they may undergo elimination under basic conditions.[79] For example, this approach has been exploited by the Opatz lab,[80] where cyano-substituted pyridinium 1,3-dioles undergo cycloaddition with nitroolefins followed by spontaneous HNO_2 and HCN elimination to afford indolzines (Scheme 1.4.2b). Other π-systems have also been used in cycloaddition, such as ynamides,[81] phosphorylated hydroxyketenimines[82] and specific alkenes such as dephenylthiirene-S,S-dioxide.[83]



Scheme 1.4.2. 1,3-cycloaddition for the synthesis of indolizines from alkenes

In a different approach, Wang reported the synthesis of indolizines from pyridine and strained cyclopropanes. In this, cyclopropane ring opening forms the 1,3-dipole for reaction while the pyridine serves as the dipolarophile (Scheme 1.4.3).[84] This offers an approach to various keto-substituted indolizines, although requires the initial formation of the cyclopropane reagent.



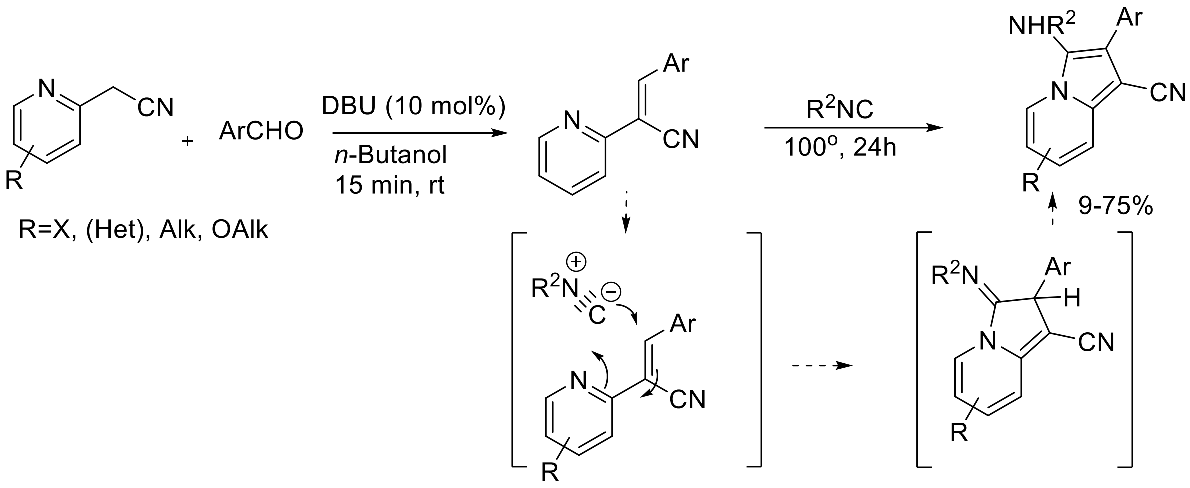
Conditions

I_2 (0.2 eq), pyridine (1 eq), toluene, 120°, 20h: synthesis of **a**

I_2 (0.4 eq), pyridine (0.2M), 120°, 15h: synthesis of **b**

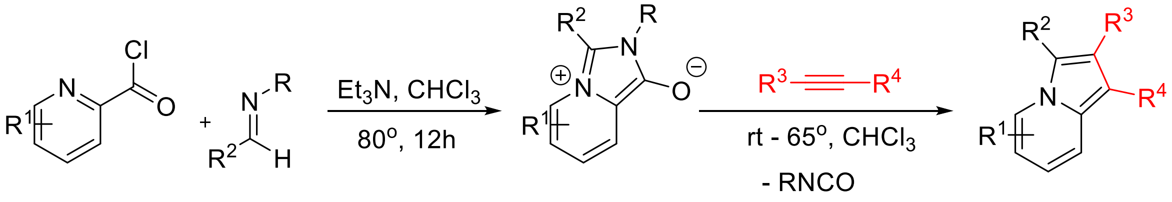
Scheme 1.4.3. Aroylcyclopropanes as dipole precursors in indolizine synthesis

A formal [4+1] cycloaddition using an *in situ* generated 2-vinylpyridine and cyanide anion[85] or isocyanides[86] has been reported for the synthesis of indolizines (Scheme 1.4.4). In this, nucleophilic attack of the isocyanide on the alkene is presumably followed by the addition of pyridine onto the same carbon to afford indolizine.



Scheme 1.4.4. [4+1] cycloaddition approach to indolizines

Our lab has recently reported a new class of mesoionic 1,3-dipole for use in indolizine synthesis. Mesoionic heterocycles are typically 5-membered heteroatom-containing aromatic rings that can only be represented with charge separation (at least in their non-radical form). Our group has found that mesoionic 1,3-dipoles can be easily generated from 2-pyridine acid chlorides and imines, and unlike most acyclic 1,3-dipoles, can be isolated and characterized (Scheme 1.4.5).[87] Coupling their formation with alkyne cycloaddition (and isocyanate elimination) can be used to develop a one-pot, multicomponent synthesis of indolizines. Unlike the use of pyridinium ylide 1,3-dipoles, this system does not require electron deficient substituents to facilitate deprotonation, and can offer access to an array of substituted indolizine products by variation of these three substrates.



Scheme 1.4.5. Synthesis of indolizines by 1,3-cycloaddition of a mesoionic dipole

1.5. Overview of the thesis

Over the last several decades, the field of indolizine synthesis has seen significant growth, offering a plethora of new platforms to access these structures. However, many of these methods either show limitations in their versatility or require the synthesis of one or more precursor. For example, cycloisomerization reactions with 2-alkynylpyridines can generally only access mono- or di-substituted indolizines on the five-membered ring. Similarly, 1,3-dipolar cycloadditions require electron withdrawing groups on the pyridinium salt to promote the formation of the dipole, limiting indolizines to those incorporating this substituent. While more complex and variable indolizines can be synthesized, these often involve multistep protocols to build-up precursors or add substituents to the pre-formed and activated heterocycle. Considering the breadth of applications indolizines have found, the development of new indolizine syntheses, especially those with the ability to systematically modulate their structure with multiple different substituents, could prove of utility.

As noted in section 1.4 above, our lab has recently reported a step toward addressing these limits in the multicomponent synthesis of indolizines from 2-pyridyl acid chlorides, imines and alkynes. This transformation proceeds through a new class of mesoionic 1,3-dipole intermediate. While the imines and alkynes employed in the reaction are stable, easily handled, and broadly available, one limitation to this approach is the need for the pyridinyl acid chloride substrate. The latter are high energy electrophiles that must first be prepared, and, as they contain both nucleophilic and electrophilic components in the same molecule, can be sensitive and only a few of these structures are known. In order to address these limitations, we describe in Chapter 2 our development of an alternative palladium catalyzed synthesis of indolizines from 2-bromopyridines, imines, CO and alkynes. Reaction offers a route to access these same 1,3-dipole intermediates, but does so now from combination of reagents that are all stable and accessible in many forms. This can therefore offer a diversifiable platform to access an array of indolizine structures through systematic modification of any the three building blocks.

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2. Palladium Catalyzed, Multicomponent Synthesis of Indolizines via the Carbonylative Coupling of Bromopyridines, Imines and Alkynes

2.1. Preface

As outlined in chapter 1, the ability to efficiently synthesize indolizines, especially in a manner amenable to structural diversification, remains a challenge. Our laboratory has recently reported a modular synthesis of indolizines from 2-pyridyl acid chlorides, imines, and alkynes (section 1.4). While alkynes and imines are broadly available reagents, a limitation of this approach is its reliance on pyridinyl acid chlorides, which are high energy compounds available only in certain stabilized forms. In order to address this challenge, I have conducted research on the application of palladium-catalyzed carbonylation to generate those high-energy acid chlorides *in situ* from more stable and easily diversified 2-bromopyridines. The following chapter is a manuscript that reports this research and been published in Chemical Science (*Chem. Sci.*, **2021**, *12*, 2251-2256).

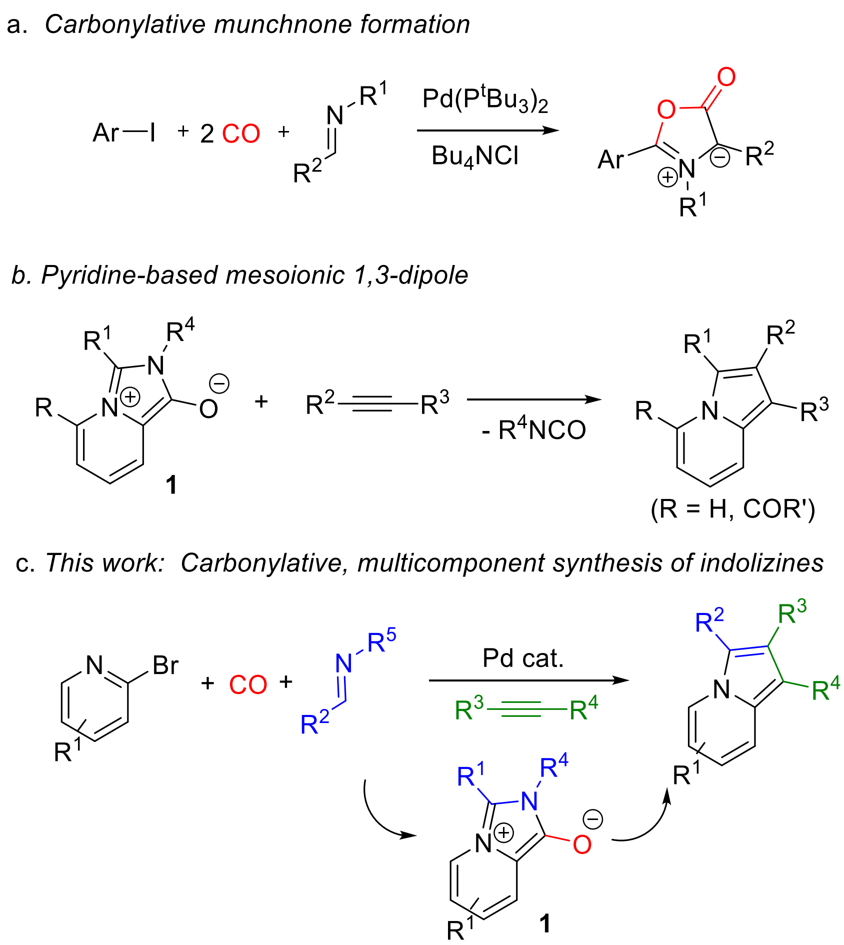
All experiments detailed in this chapter were performed by me, except for the catalytic reaction with tetrabutylammonium bromide instead of chloride (Fig 2.3.2.a), the one-pot synthesis of **2m** (Fig 2.5.2.1) and the synthesis of **2o** (Table 2.3.3), which were performed by labmates and co-authors on the paper, Jose Zgheib and Cuihan Zhou.

2.2.Introduction

Metal catalyzed carbonylations offer an efficient platform to assemble carbonyl-based products from feedstock chemicals.[1] In addition to their classical use in carboxylic acid, ester, amide or ketone synthesis, there has been recent research effort directed toward employing carbonylations to generate products that are themselves reactive.[2,3] These highlight an additional useful feature of carbon monoxide, its energetics, where its conversion to carboxylic acid derivatives is often exergonic. Carbonylations have been exploited to access various reactive acylating electrophiles and even non-CO containing products.[4] Our lab has reported several examples of the latter, wherein the carbonylative formation of 1,3-dipoles (e.g. Münchnones) can be coupled with cycloaddition reactions to afford heterocycles (Fig. 2.2.1a).[4e-g] In these, carbon monoxide is initially incorporated into the reactive 1,3-dipole, yet is ultimately converted to CO_2 to drive the assembly of heterocycles from combinations of reagents.

Considering the high value of carbonyl-based building blocks, the use of carbonylation reactions to effectively assemble other classes of reactive substrates could be of synthetic utility. One possibility is the pyridine-based 1,3-dipole **1** (Fig. 2.2.1b).[5] **1** has been recently described as a reactive version of the mesoionic dye Besthorn's Red,[6] and can undergo 1,3-dipolar cycloaddition with alkynes to generate indolizines. These heterocycles, and their reduced derivatives, represent the core of a wide variety of pharmaceutically relevant molecules and natural products,[7,8] and their extended conjugation has made them attractive as components in electronic materials.[9] Indolizines are classically prepared by cyclizations of substituted pyridines[10-12] or pyrroles.[13] While some variants of these substrates can be easily generated, they more often require the build-up of the appropriate substituted core for cyclization, which adds synthetic steps, creates waste, and can limit their ease of diversification. Similarly, a limitation of the use of **1** in indolizine synthesis is the initial formation of the 1,3-dipole itself from high energy 2-pyridyl acid chlorides that must first be synthesized, and, due to their incorporation of both nucleophilic and electrophilic components, have limited scope and stability. Only certain variants of the 1,3-dipole **1** can therefore be accessed.

We hypothesized that carbonylations might provide a solution to these challenges. The mesoionic core of **1** contains a carbonyl-unit, which could in principle be derived by palladium catalyzed carbonylation (Fig. 2.2.1c). In addition to representing a new route to exploit carbonylation in synthesis, this would allow the formation of 1,3-dipole **1** from combinations of reagents that are all by themselves stable, functional group compatible, and readily available: halopyridines, imines and carbon monoxide. We describe in this report our development of a palladium catalyzed route to such a synthesis. Coupling the formation of **1** with cycloaddition has opened a new multicomponent synthesis of indolizines, where these heterocycles can now be formed from three simple, easily diversified reagents.


a. *Carbonylative munchnone formation*

b. *Pyridine-based mesoionic 1,3-dipole*

c. *This work: Carbonylative, multicomponent synthesis of indolizines*

Figure 2.2.1. Carbonylative approaches to 1,3-dipoles and their use in multicomponent heterocycle synthesis.

2.3. Results and Discussion

The carbonylative generation of 1,3-dipole **1** presents several design challenges. Imines are rarely employed in carbonylation chemistry due to their weak nucleophilicity and poor reactivity with the palladium-acyl intermediates generated in this chemistry. We envisionned that this might be addressed by instead using carbonylations to build-up *in situ* acid chloride electrophiles. Recent studies have shown that such a transformation is viable using sterically encumbered phosphines such as P^tBu_3 on palladium catalysts to favor the challenging reductive elimination and build-up of these products.[2e] However, the carbonylative formation of acid chlorides with coordinating substrates such as 2-bromopyridines has not been previously reported, and even simple aryl bromides require pressing conditions (110°, 20 atm CO) to be converted to acid chloride products.[2d] The latter could prove problematic for the formation of a reactive 1,3-dipole **1**.

To probe this potential, we first examined the carbonylative reaction of 2-bromopyridine and the imine *p*-tolyl(H)C=N(benzyl) in the presence of a chloride source (Bu_4NCl, Table 2.3.1). Using $Pd(P^tBu_3)_2$ as catalyst, which was previously noted to allow acid chloride generation,[2b,d] does indeed lead to the *in situ* build-up of dipole **1a** in low yield (38%) at 100° (entry 1), but we noted the growth of other decomposition products upon extended reaction. In order to improve the yield of **1a**, the influence of ligands on the reaction was examined. The use of Pd_2dba_3 without added ligand (entry 2) or with various common phosphines (entries 3-6) leads to decreased product yield. Simple bidentate ligands also inhibit catalysis (entries 7,8). However, we were pleased to find that large bite angle ligands such as DPE-Phos and Xantphos significantly increase catalytic activity, with the latter forming **1a** in near quantitative yield (94%, entry 10). Similar yields were noted at 80 °C (entry 11). Xantphos is a rigid, large bite angle bidentate ligand that can create steric strain in Pd(II) and potentially favor reductive elimination (*vide infra*). In addition to the formation of 1,3-dipole **1a**, this reaction can be coupled with a cycloaddition. Thus, the palladium catalysed build-up of **1a**, followed by the addition of the electron deficient alkyne dimethylacetylene dicarboxylate (DMAD) leads to the overall one-pot formation of indolizine **2a** in 76% yield (Figure 2.3.1). The multicomponent reaction of 2-bromopyridine, imine, carbon monoxide and the less electron deficient alkyne ethyl 3-phenyl-2-propynoate can even be performed in a single operation to access indolizine in good yield (Fig. 2.5.2.1). While these experiments use imine as the limiting reagent, only slightly diminished yield are observed when a stoichiometric amount of imine is used (entry 12), and **1a** can be formed in high yield with 2-bromopyridine as the limiting reagent.

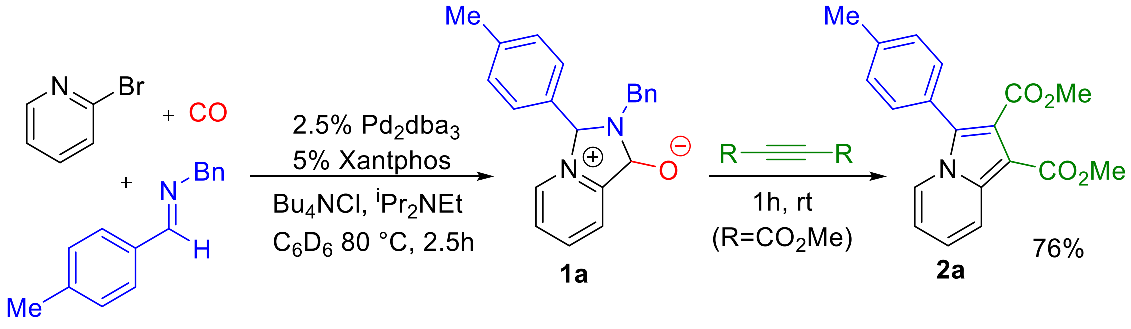
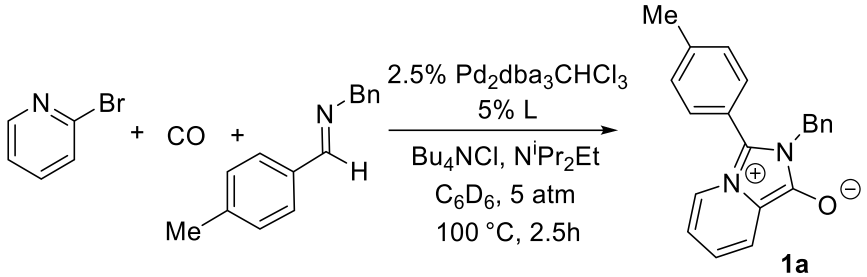
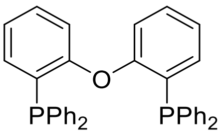
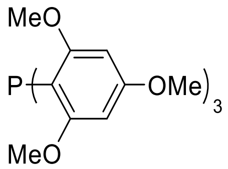
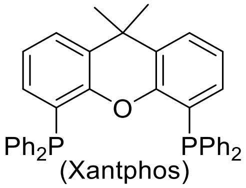
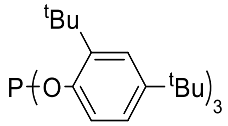


Figure 2.3.1. The one-pot, palladium catalyzed synthesis of indolizines

Table 2.3.1. Catalyst development for the carbonylative formation of 1,3 dipole **1**



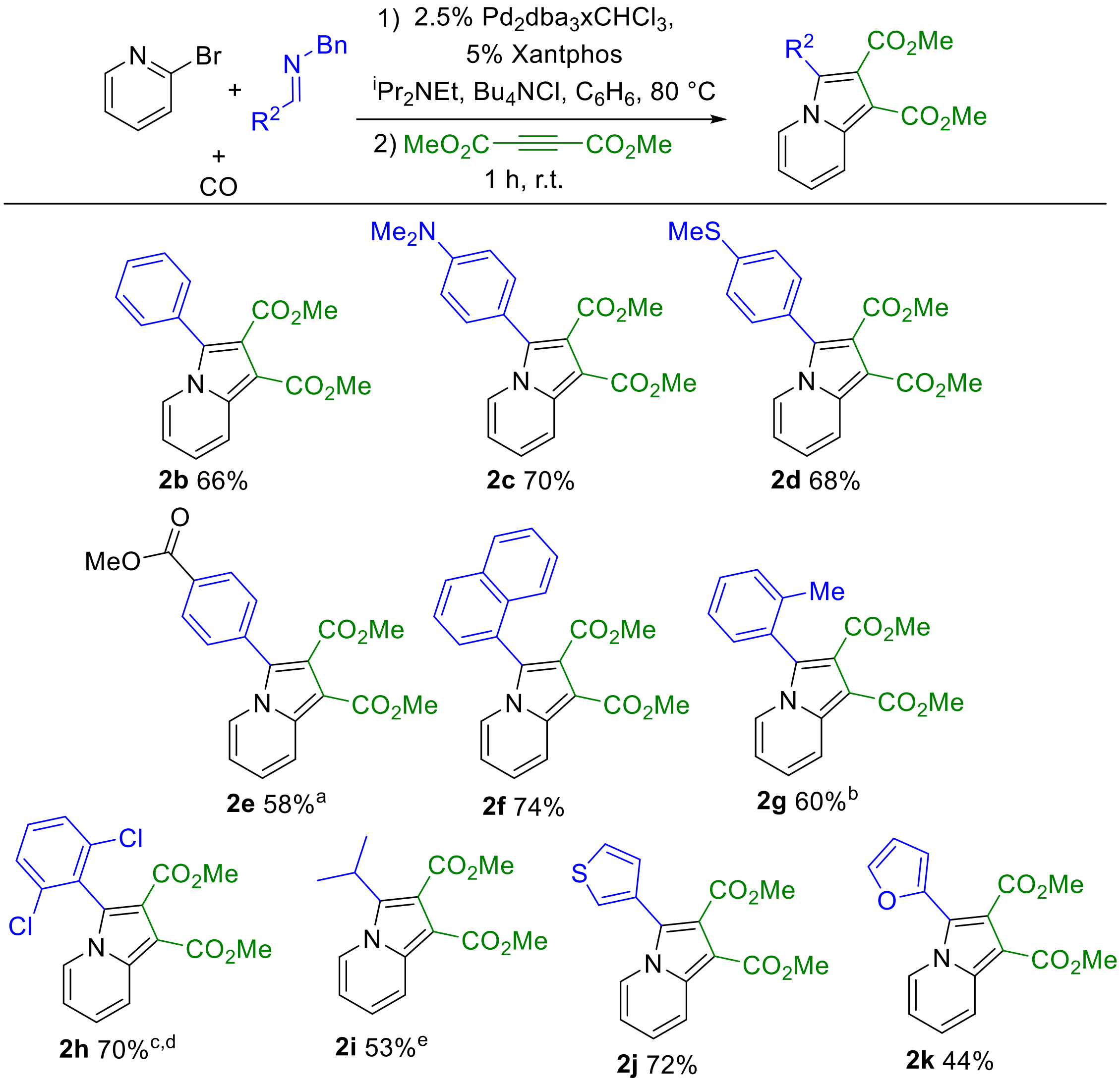
1a

Entry	Ligand	% **1a**	Entry	Ligand	% **1a**
1	P^tBu_3	38	7	dppp	16
			8	dppe	0
2	-	15			
3	PPh_3	26	9		45
4	PCy_3	16			
5		15	10		94
6		15	11	Xantphos	97^b
			12	Xantphos	$89^{b,c}$ $(92)^{b,d}$

2-bromopyridine (9.5 mg, 0.06 mmol), imine (8.4 mg, 0.04 mmol), NEt^iPr_2 (6.2 mg, 0.048 mmol,), C_6D_6 (0.75 mL), Bu_4NCl (17 mg, 0.06 mmol), Pd_2dba_3 (1.0 mg, 0.001 mmol), L (0.004 mmol; 0.002 mmol bidentate) [a] 7.5h [b] 80 °C [c] 0.04 mmol 2-bromopyridine. [d] 0.04 mmol 2-bromopyridine, 0.06 mmol imine.

With a modular method to generate indolizines in hand, we next explored if this system could offer access to various indolizine structures. As shown in Table 2.3.2, a range of *C*-aryl substituted imines can be used in this reaction. This includes simple phenyl substituted (**2b**) and electron-rich (**2c,d**) imines, which lead to the corresponding indolizine in good yield. Imines with electron withdrawing substituents can also be employed, although these require extended reaction times to build-up the 1,3-dipole (**2e**). Sterically hindered 2-naphthyl, 2-tolyl and even 2,6-disubstituted imines are similarly viable substrates (**2f-h**). In the latter two cases, cycloaddition requires elevated temperatures and longer reaction times. Heteroaryl-substituted products are also accessible, such as those with thiophene and furan substituents (**2j,k**). The reaction can even allow the use of *C*-alkyl imines, which have proven problematic in related carbonylations due to their ability to readily convert to enamides upon N-acylation.[5c] However, rapid intramolecular cyclization with the pyridine in the more polar acetonitrile solvent followed by alkyne cycloaddition can afford the isopropyl-substituted indolizine (**2i**).

Table 2.3.2. Scope of imines in multicomponent indolizine synthesis



2b 66% **2c** 70% **2d** 68%

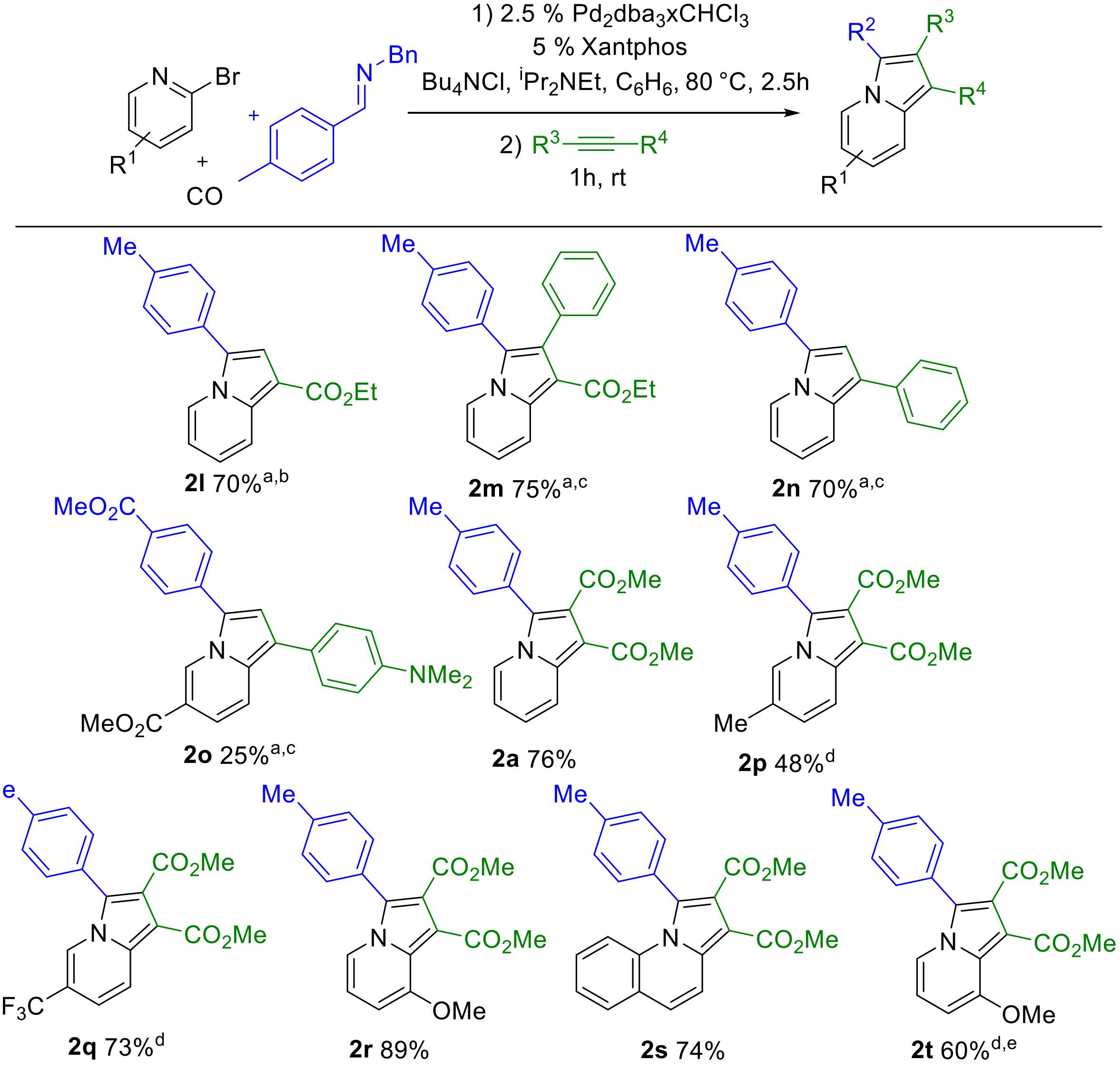
2e 58%[a] **2f** 74% **2g** 60%[b]

2h 70%[c,d] **2i** 53%[e] **2j** 72% **2k** 44%

1) 2-bromopyridine (79 mg, 0.50 mmol), imine (0.75 mmol), $Pd_2dba_3 \cdot CHCl_3$ (13 mg, 0.025 mmol); Xantphos (14 mg, 0.05 mmol); N^iPr_2Et (77 mg, 0.6 mmol); Bu_4NCl (208 mg, 0.75 mmol); 5 atm CO; 10 mL C_6H_6, 2) dimethylacetylene dicarboxylate (85 mg, 0.6 mmol), 1 h, rt [a] 24h [b] Step 2: 12 h [c] 100 °C, 3.5h [d] Step 2: 48 h at 80 °C [e] 21 h, CH_3CN instead of C_6H_6, 0.25 mmol Bu_4NCl.

In addition to the imine, cycloaddition with variously substituted alkynes can be used to modulate the 1- and 2- indolizine substituents. Examples include the terminal alkyne ethyl propiolate (**2l**) or internal alkynes such as ethyl 3-phenyl-2-propynoate (**2m**). The more electron rich phenacyl acetylene also undergoes cycloaddition with catalytically formed **1** to afford indolizine (**2n**), as does dimethylamino-substituted phenyl acetylene in lower yield (**2o**). More pressing conditions are required for the more electron rich alkynes (16 h for **2l**, 80° for **2m** and **2n**) but lead to the formation of the corresponding indolizines in good yields. Notably, only one regioisomeric product is formed with these unsymmetrical alkynes, where the larger substituent is incorporated into the 1-position. This is consistent with steric bias in 1,3-dipole **1** directing the larger alkyne substituent away from R^2.[5] The 2-bromopyridine structure can also be tuned. Thus, pyridines with donor or electron withdrawing substituents in the 5-position can be incorporated in the reaction (**2p-r**). The extended conjugation in 2-bromoquinoline is also tolerated, leading to tricyclic product **2s**. It is even possible to use a more sterically hindered 3-substituted bromopyridine to generate 8-substituted indolizine **2t**. These bromopyridine derivatives are all significantly less expensive and more easily handled than the corresponding acid chlorides or even parent carboxylic acids. Together, this palladium catalyzed carbonylation offers a route to generate indolizines where every substituent can be systematically modulated in a one pot reaction from stable and available reagents.

Table 2.3.3 Scope of bromopyridines and alkynes in indolizine synthesis



2l 70%[a,b]; **2m** 75%[a,c]; **2n** 70%[a,c]; **2o** 25%[a,c]; **2a** 76%; **2p** 48%[d]; **2q** 73%[d]; **2r** 89%; **2s** 74%; **2t** 60%[d,e]

Conditions of Table 2 with alkyne (0.6 mmol) [a] 1.5 eq. imine (157 mg, 0.75 mmol), 1 eq. pyridine (79 mg, 0.5 mmol) [b] Cycloaddition for 16h at rt [c] Cycloaddition for 2 d at 80° [d] 24h [e] 5 eq $NEt^{i}Pr_2$

We have performed several experiments to explore the mechanism of this reaction. Catalysis in the absence of a chloride source significantly diminishes the yield of **1a**, and instead leads to the recovery of starting materials (Fig. 2.3.2a). Low product yields were also observed upon replacing chloride with other salt additives (e.g. Bu_4NOTf: 18%). These observations suggest that chloride is required for an efficient reaction, and are consistent with *in situ* carbonylative acid chloride formation. Competition reaction with two imines varying only in the para-substituent on the *C*-aromatic ring leads to selective incorporation of the more electron rich imine into the product (Fig. 2.3.2b), which supports its role as a nucleophile in the reaction. It is notable, however, that no acid chloride is observed on monitoring the reaction by ^{1}H NMR analysis, nor when performing the reaction in the absence of an imine trap (Fig. 2.5.2.2). This implies that if acid chloride is generated, it either rapidly adds back to palladium, or, in the presence of an imine trap, is converted to the 1,3-dipole. CO pressure can influence the reaction, where performing the reaction at 1 atm CO leads to lower product yields (Fig. 3c), and is consistent with the ability of carbon monoxide ligand to favor reductive elimination and stabilize Pd(0).

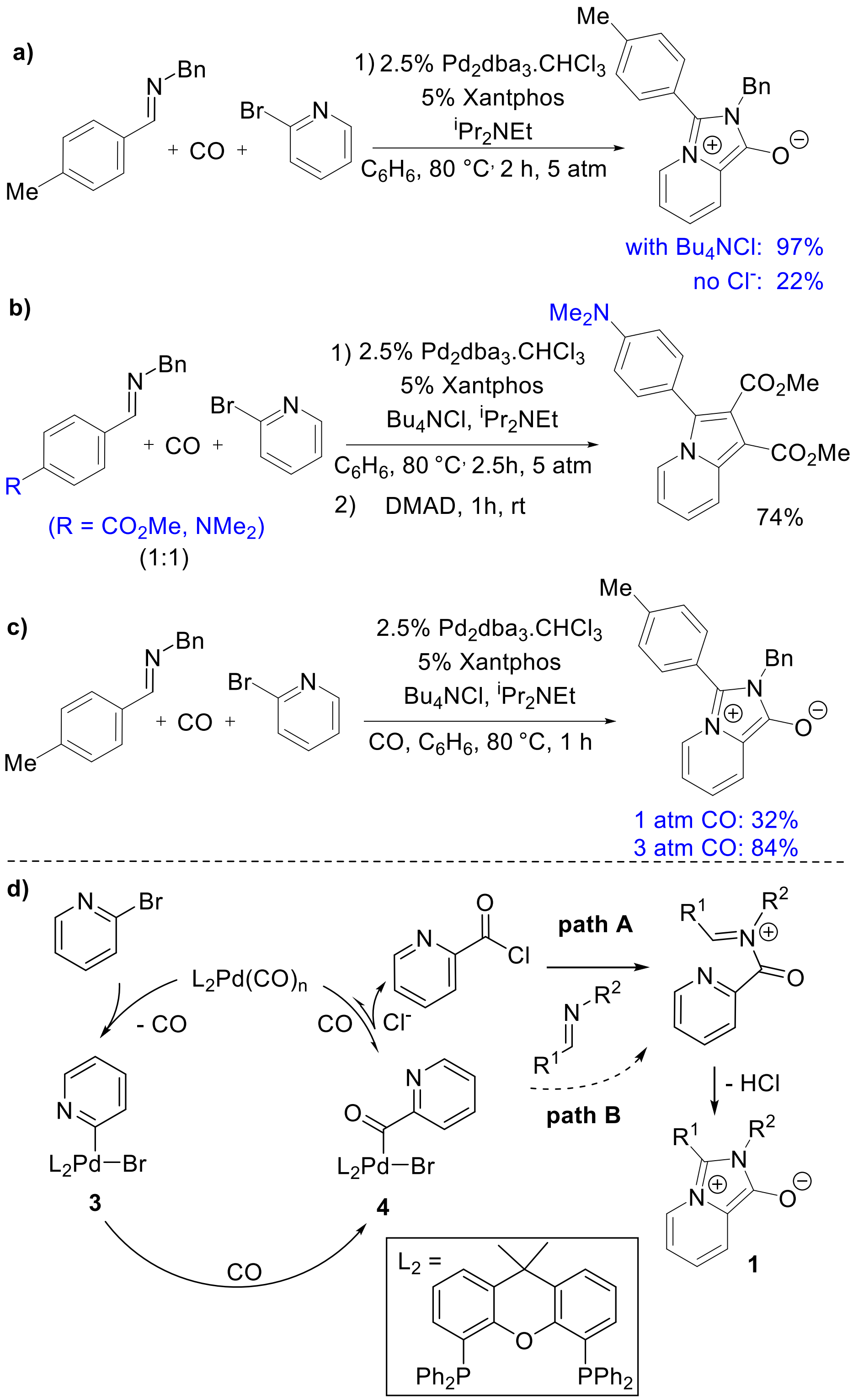


Figure 2.3.2. Mechanistic experiments on the palladium catalyzed synthesis of 1,3-dipole **1** and indolizines.

On the basis of these experiments, we postulate that the catalytic formation of 1,3-dipole **1** proceeds as shown in Fig. 3d. In this, 2-bromopyridine oxidative addition to Pd(0) followed by CO insertion leads to the formation of the palladium-acyl complex **4**. In presence of a chloride source, anion exchange can allow the reversible reductive elimination of acid chloride (path A). The re-addition of acid chloride to Pd(0) is presumably rapid, but can be inhibited by nucleophilic trapping with the imine to generate a *N*-acyl iminium salt for cyclization to 1,3-dipole **2**. The efficiency of the Xantphos ligand in catalysis may be tied to its large bite angle (111°),[14] which creates significant steric and electronic strain in **4** and can favor reductive elimination of a reactive acid chloride intermediate.[3h] Nevertheless, the ability of this system to proceed to product in the absence of chloride implies that the imine can react with other electrophilic intermediates in the reaction, such as the palladium-acyl complex **4** (path B) or potentially an acid bromide, albeit at a slower rate than with acid chloride.

2.4.Conclusions

In conclusion, a palladium catalyzed, multicomponent synthesis of indolizines from 2-bromopyridines, CO, imines and alkynes has been developed. In this, carbon monoxide is not incorporated into the final product, but instead serves to first build-up the high energy 1,3-dipole **1**, and is then liberated with the nitrogen unit from the imine as an isocyanate. From a synthetic perspective, the reaction has opened a route to prepare indolizines from combinations of stable, tunable reagents, and with the ability to modulate all substituents by variation of the pyridine, imine and alkyne units. Considering the utility of 1,3-dipoles in synthesis, we anticipate this chemistry could offer a modular route to access a range of fused-ring heterocyclic products.

2.5. Supporting Information

2.5.1. General Procedures

All manipulations were conducted in a glovebox under a nitrogen atmosphere. Unless otherwise noted, all reagents, including carbon monoxide (99.5%) were purchased from commercial sources and used without purification. Solvents were dried by using a solvent purifier system, then transferred and stored in a glovebox over 4 Å molecular sieves. Liquid reagents were stored over activated 4 Å molecular sieves inside a nitrogen glovebox. Deuterated benzene was stirred over calcium hydride, vacuum transferred, and degassed before being brought in the glovebox. Bu_4NCl and imines that are solids at room temperature were dissolved in dichloromethane in a glovebox, dried with activated 4 Å molecular sieves overnight, then decanted and dried in vacuo. Imines were prepared using standard literature procedures and vacuum distilled.[15] $Pd(P^tBu_3)_2$ and Pd_2dba_3•$CHCl_3$ were prepared according to literature procedures and stored at -35 °C in the glovebox to avoid decomposition.[16]

Nuclear magnetic resonance (NMR) characterization was performed on 500 MHz spectrometers for proton and either 126 and 201 MHz for carbon. ^1H and ^{13}C NMR chemical shifts were referenced to residual solvent. Mass spectra was recorded on a high-resolution electrospray ionization quadrupole mass spectrometer. The NMR spectra of all compounds formed can be found in the supporting information of the published work (*Chem. Sci.*, **2021**, *12*, 2251-2256).

2.5.2. Supplementary Figure

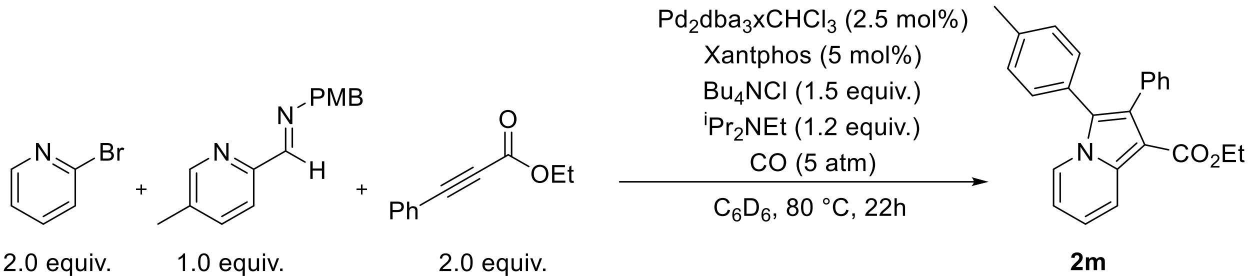


Figure 2.5.2.1. One step synthesis of indolizine 2m with alkyne in situ

In a glovebox, a J-Young NMR tube was charged with 2-bromopyridine (16.0 mg, 0.100 mmol), *p*-tolyl(H)C=N(4-methoxybenzyl) (12.0 mg, 0.050 mmol), ${}^{i}Pr_2NEt$ (12.0 mg, 0.06 mmol), Bu_4NCl (20.8 mg, 0.075 mmol), Pd_2dba_3•$CHCl_3$ (1.3 mg, 0.00125 mmol, Xantphos (1.5 mg, 0.0025 mmol), ethyl 3- phenylpropiolate (17.0 mg, 0.10 mmol), benzyl benzoate as internal standard, and C_6D_6 (for a total of 0.70 mL). Bu_4NCl was dry transferred in the J-Young, and the liquid reagents and leftover solids were washed into the reaction vessel. The NMR tube was then sealed with a screw cap and taken out of the glovebox. The NMR tube was frozen in liquid nitrogen, evacuated, and a known quantity of CO was condensed into the tube, such that the pressure is 5 atm at room temperature. (This was accomplished by condensing 125 torr from a 67 mL CO filled vacuum line into the NMR tube with 2.25 mL headspace.) The reaction mixture was warmed to 80 °C for 22 h. 1H NMR spectra was collected before and after the reaction, and integration relative to the internal standard shows the yield of **2m** is 82%.

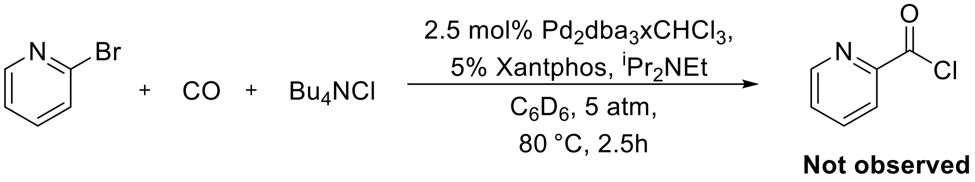
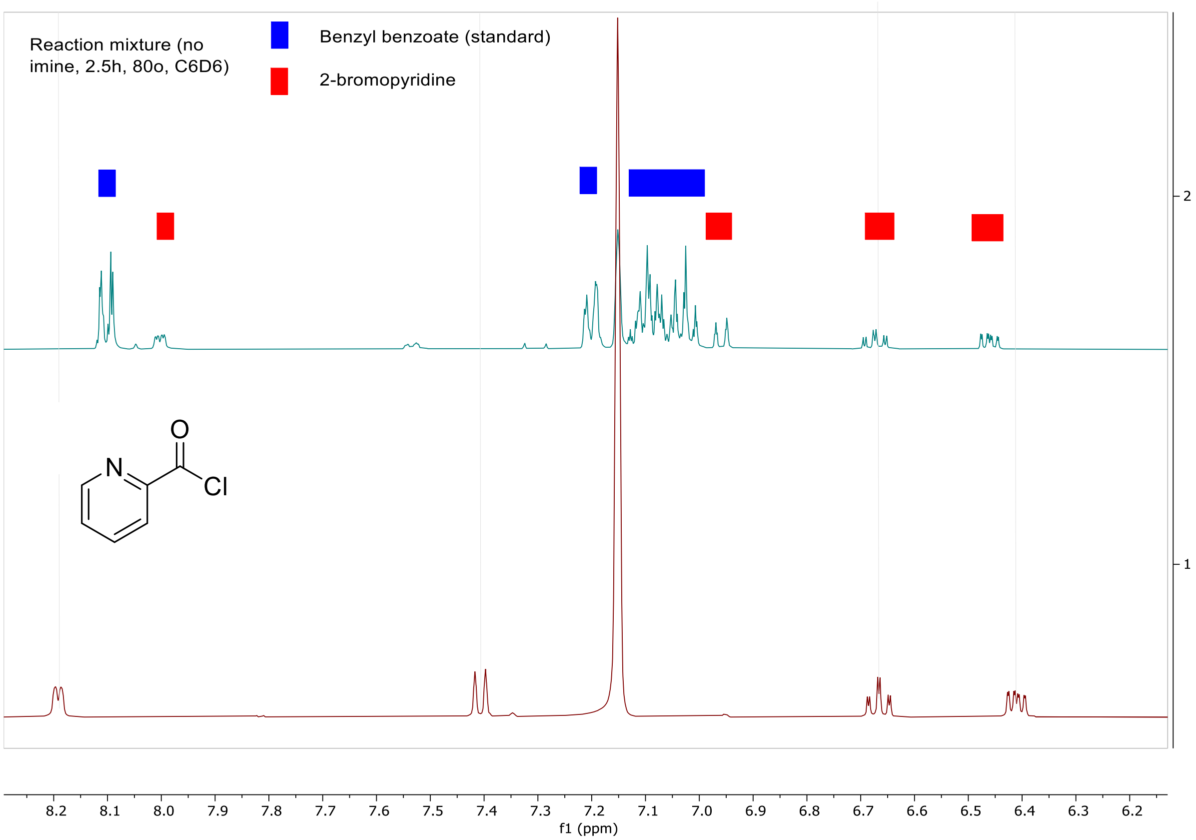


Figure S1. Catalysis in the absence of imine.

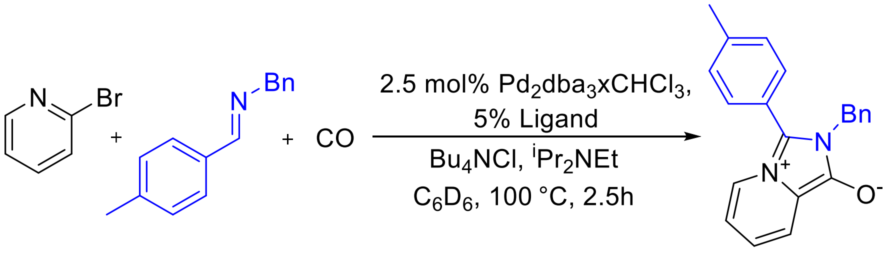
In a glovebox, a J-Young NMR tube was charged with 2-bromopyridine (6.3 mg, 0.040 mmol), ${}^{i}Pr_2NEt$ (6.2 mg, 0.048 mmol), Bu_4NCl (17 mg, 0.060 mmol), Pd_2dba_3•$CHCl_3$ (1.0 mg, 0.0010 mmol) (obtained by taking 0.400 mL of C_6D_6 solution of 2.5 mM Pd_2dba_3•$CHCl_3$), Xantphos (1.1 mg, 0.0020 mmol) (obtained by taking 0.100 mL of a C_6D_6 solution of 20 mM Xantphos), benzyl benzoate as internal standard, and C_6D_6 (0.25 mL, for a total of 0.75 mL). Bu_4NCl was dry transferred in the J-Young, and the liquid reagents and leftover solids were washed into the reaction vessel by portions of 250 μL, first using the stock solutions, then the dry solvent. The NMR tube was then sealed with a screw cap and taken out of the glovebox. The NMR tube was frozen in liquid nitrogen, evacuated, and a known quantity of CO was condensed into the tube, such that the pressure is 5 atm at room temperature. (This was accomplished by condensing 125 torr from a 67 mL CO filled vacuum line into the NMR tube with 2.25 mL headspace.) The reaction mixture was warmed to 80 °C for 2.5 h. ^{1}H NMR spectra shows no detectable amount of acid chloride is generated.



^{1}H NMR spectra (C_6D_6) of the reaction mixture in the absence of imine (top) and the pure 2-pyridyl acid chloride (bottom).

2.5.3. Experimental Procedures

A. Typical Procedure for Catalyst Development (Table 1)



1a

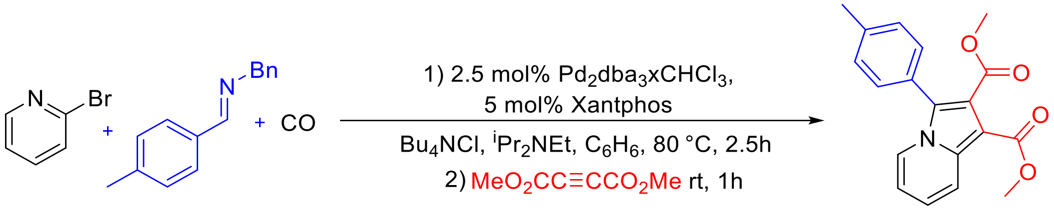
In a glovebox, a J-Young NMR tube was charged with 2-bromopyridine (9.5 mg, 0.060 mmol), *p*-tolyl(H)C=N(benzyl) (8.4 mg, 0.040 mmol), $^{i}Pr_2NEt$ (6.2 mg, 0.048 mmol), Bu_4NCl (17 mg, 0.060 mmol), Pd_2dba_3•$CHCl_3$ (1.0 mg, 0.0010 mmol) (obtained by taking 0.400 mL of C_6D_6 solution of 2.5 mM Pd_2dba_3•$CHCl_3$), Xantphos (1.1 mg, 0.0020 mmol) (obtained by taking 0.100 mL of a C_6D_6 solution of 20 mM Xantphos), benzyl benzoate as internal standard, and C_6D_6 (0.25 mL, for a total of 0.75 mL). Bu_4NCl was dry transferred in the J-Young, and the liquid reagents and leftover solids were washed into the reaction vessel by portions of 250 µL, first using the stock solutions, then the dry solvent. The NMR tube was then sealed with a screw cap and taken out of the glovebox. The NMR tube was frozen in liquid nitrogen, evacuated, and a known quantity of CO was condensed into the tube, such that the pressure is 5 atm at room temperature. (This was accomplished by condensing 125 torr from a 67 mL CO filled vacuum line into the NMR tube with 2.25 mL headspace.) The reaction mixture was warmed to 100 °C for 2.5 h. ^{1}H NMR spectra was collected before and after the reaction, and integration relative to the internal standard shows the yield of **1a** is 94%. A similar procedure was followed with other ligands, except 0.0040 mmol of monodentate ligands was used. In order to prove the presence of the proposed mesoionic dipolar product **1a**, whose NMR is not known in C_6D_6, the reaction mixture was dried under vacuum after completion of the reaction, and NMR spectra were also taken with $CDCl_3$.

*In situ NMR data on **1a***: **^{1}H NMR** ($CDCl_3$, 500 MHz): δ 7.46 (dd, J = 9.0, 1.3 Hz, 1H), 7.31 (d, J = 7.3 Hz, 1H), 7.11-7.21 (m, 5H), 7.01-7.06 (m, 4H), 6.36 (t, J = 6.7 Hz, 1H), 6.00 (dd, J = 8.9, 6.4 Hz, 1H), 5.10 (s, 2H), 2.34 (s, 3H). **^{13}C NMR** ($CDCl_3$, 126 MHz): δ 151.1, 140.5, 137.1, 130.3, 129.3, 129.2, 128.5, 127.41, 127.38, 122.6, 121.2, 119.6, 116.7, 110.1, 109.0, 44.8, 21.4.

*Previously reported **1a:***[5]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.9 Hz, 1H), 7.30 (d, J = 7.3 Hz, 1H), 7.21-7.11 (m, 5H), 7.01-7.07 (m, 4H), 6.35 (ddd, J=7.4, 6.5, 1.3 Hz, 1H), 6.08 (ddd, J = 9.0, 6.4, 0.7 Hz, 1H), 5.11 (s, 2H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 151.1, 140.4, 137.1, 130.3, 129.5, 129.3, 128.5, 127.54, 127.47, 122.9, 121.4, 119.6, 116.7, 110.3, 109.2, 44.9, 21.5.

B. Typical Synthesis of Indolizines (Tables 2 and 3)

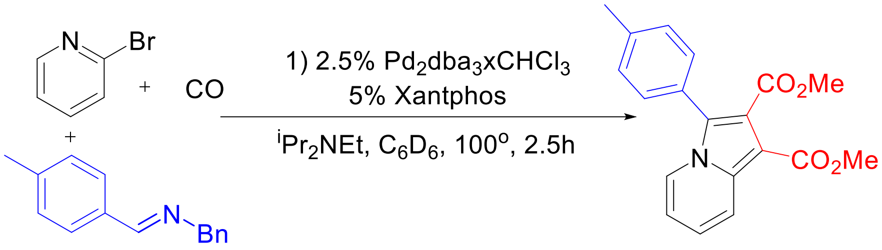


2-bromopyridine (79 mg, 0.50 mmol), p-tolyl(H)C=N(benzyl) (157 mg, 0.75 mmol), NEt^iPr_2 (77 mg, 0.60 mmol), Bu_4NCl (208 mg, 0.75 mmol), Pd_2dba_3•$CHCl_3$ (13 mg, 0.0125 mmol) and Xantphos (14.5 mg, 0.025 mmol) were weighed in a glovebox. The solids were dry transferred into a 50 mL Teflon sealable, thick walled reaction tube, along with a stir bar. 10 mL benzene was used to wash the liquid reagents and leftover solids into the reaction vessel. The vessel was closed and brought out of the glovebox, frozen and its headspace evacuated. The tube was thawed and 5 atm of CO was then added (as measured on a pressure gauge connected to the CO source). The tube was then placed in a 80 °C oil bath for 2.5h. After completion of the reaction, the CO atmosphere was removed on a schlenk line, and the vessel taken into the glovebox. Dimethylacetylenedicarboxylate (DMAD; 85 mg, 0.60 mmol) was then added. The reaction mixture was left to stir at room temperature for 1 h. The solvent was then removed *in vacuo*, and the product purified by column chromatography (Silica gel, 25% ethyl acetate, 75% hexanes) afforded indolizine **2a** as a pale yellow solid (123 mg, 0.38 mmol, 75%).

A similar procedure was followed for the other products. In the case of **2i**, the reaction was performed in acetonitrile. For electron-poor imines or certain pyridine substitution patterns, the reaction temperature and time for generation of the dipole was varied (see product characterization for specific time/temperatures used). In the case of more electron-rich alkynes or sterically hindered imines, the cycloaddition is performed for a longer time and/or at elevated temperatures (see product characterization for details). For **2h**, **2m** and **2n**, the reaction mixture was dried prior to the addition of 2.5 mL of benzene for cycloaddition at 80°C for 48 h. For **2o**, the dipole mixture was concentrated to 2.5 ml for cycloaddition at 80 °C for 48 h, then heated to 100-150 °C for 72 h to complete reaction.

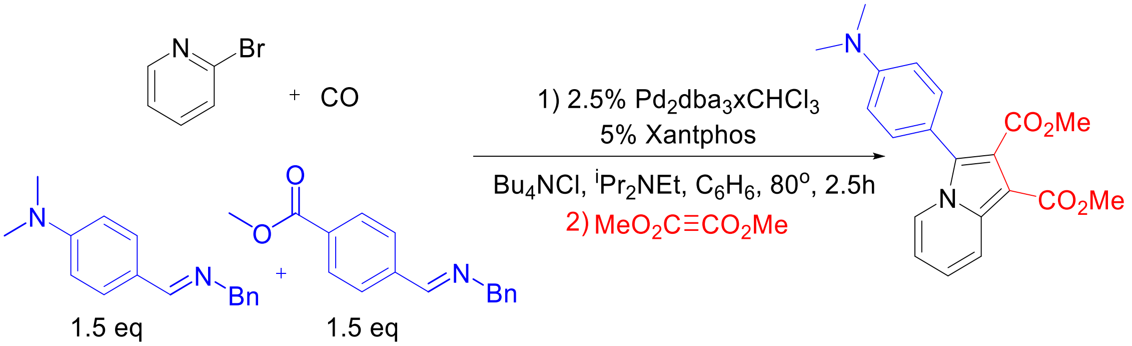
2.5.4. Mechanistic Experiments

A. Reaction in the absence of chloride (Figure 3a)



In a glovebox, a J-Young NMR tube was charged with 2-bromopyridine (9.5 mg, 0.060 mmol), *p*-tolyl(H)C=N(benzyl) (8.4 mg, 0.040 mmol), $^iPr_2NEt$ (6.2 mg, 0.048 mmol), Pd_2dba_3•$CHCl_3$ (1.0 mg, 0.0010 mmol) (obtained by taking 0.400 mL of C_6D_6 solution of 2.5 mM Pd_2dba_3•$CHCl_3$), Xantphos (1.1 mg, 0.0020 mmol) (obtained by taking 0.100 mL of a C_6D_6 solution of 20 mM Xantphos), benzyl benzoate as internal standard, and C_6D_6 (0.25 mL, for a total of 0.75 mL). The reagents were washed into the reaction vessel by portions of 250 µL, first using the stock solutions, then the dry solvent. The NMR tube was then sealed with a screw cap and taken out of the glovebox. The NMR tube was frozen in liquid nitrogen, evacuated, and a known quantity of CO was condensed into the tube, such that the pressure is 5 atm at room temperature. (This was accomplished by condensing 125 torr from a 67 mL CO filled vacuum line into the NMR tube with 2.25 mL headspace.) The reaction mixture was warmed to 80 °C for 2 h. ^1H NMR spectra was collected before and after the reaction, and integration relative to the internal standard shows the yield of **1a** is 22%. Upon extended reaction time (20h), the NMR yield reached 56%.

B. Competition Experiment (Figure 3b)



2-bromopyridine (79 mg, 0.50 mmol), p-$Me_2NC_6H_4$(H)C=N(benzyl) (179 mg, 0.75 mmol), p- $MeO_2CC_6H_4$(H)C=N(benzyl) (190 mg, 0.75 mmol), NEt^iPr_2 (77 mg, 0.60 mmol), Bu_4NCl (208 mg, 0.75 mmol), Pd_2dba_3•$CHCl_3$ (13 mg, 0.0125 mmol) and Xantphos (14.5 mg, 0.025 mmol) were weighed in a glovebox. The solids were dry transferred into a 50 mL Teflon sealable, thick walled reaction tube, along with a stir bar. 10 mL benzene was used to wash the liquid reagents and leftover solids into the reaction vessel. The vessel was closed and brought out of the glovebox, frozen and its headspace evacuated. The tube was thawed and 5 atm of CO was then added (as measured on a pressure gauge connected to the CO source). The tube was then placed in a 80 °C oil bath for 2.5h. After completion of the reaction, the CO atmosphere was removed on a schlenk line, and the vessel taken into the glovebox. Dimethylacetylenedicarboxylate (DMAD; 85 mg, 0.60 mmol) was then added. The reaction mixture was left to stir at room temperature for 1 h. ^1H NMR analysis of the crude reaction mixture shows the formation of indolizine **2c**, and no evidence for the other indolizine product. Purification by column chromatography afforded unreacted (hydrolized) methyl 4-formylbenzoate and indolizine **2c** (139 mg, 0.40 mmol, 79%) as the only major products.

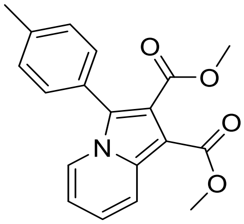
C. Reaction at different pressures of CO (Figure 3c)

In a glovebox, two J-Young NMR tubes were charged with 2-bromopyridine (9.5 mg, 0.060 mmol), *p*-tolyl(H)C=N(benzyl) (8.4 mg, 0.040 mmol), $^iPr_2NEt$ (6.2 mg, 0.048 mmol), Bu_4NCl (17 mg, 0.060 mmol), Pd_2dba_3•$CHCl_3$ (1.0 mg, 0.0010 mmol) (obtained by taking 0.400 mL of C_6D_6 solution of 2.5 mM Pd_2dba_3•$CHCl_3$), Xantphos (1.1 mg, 0.0020 mmol) (obtained by taking 0.100 mL of a C_6D_6 solution of 20 mM Xantphos), benzyl benzoate as internal standard, and C_6D_6 (0.25 mL, for a total of 0.75 mL). Bu_4NCl was dry transferred in the J-Youngs, and the liquid reagents and leftover solids were washed into the reaction vessels by portions of 250 µL, first using the stock solutions, then the dry solvent. The NMR tubes were then sealed with a screw cap and taken out of the glovebox. The NMR tubes were frozen in liquid nitrogen, evacuated, and a known quantity of CO was condensed into the tubes, such that the pressure is 1 atm at room temperature in one, and 3 atm at room temperature in the other. (This was accomplished by respectively condensing 25 and 75 torr, respectively, from a 67 mL CO filled vacuum line into the NMR tubes with 2.25 mL headspace.) The reaction mixture was warmed to 80 °C for 1h h. ^1H NMR spectra was collected before and after the reaction, and integration relative to the internal standard shows the yield of **2a** is 32% under one atm of CO and 84% under 3 atm of CO.

2.5.5. Characterization Data on Indolizines

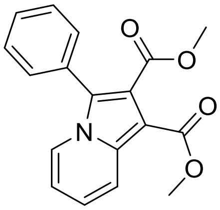
The NMR spectra for all compounds can be found in the supporting information of the published work (Chem. Sci., 2021, 12, 2251-2256).

Dimethyl 3-(p-tolyl)indolizine-1,2-dicarboxylate (2a)[5]



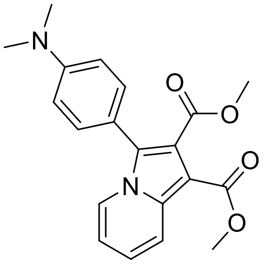
Pale yellow solid, 123 mg, 76%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (dt, J = 9.1, 1.2 Hz, 1H), 8.04 (dt, J = 7.1, 1.1 Hz, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 7.11 (ddd, J = 9.1, 6.6, 1.1 Hz, 1H), 6.71 (td, J = 6.9, 1.3 Hz, 1H), 3.90 (s, 3H), 3.81 (s, 3H), 2.43 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.1, 164.4, 139.2, 135.3, 130.0, 126.0, 125.3, 123.8, 123.6, 122.0, 120.5, 113.5, 102.0, 52.6, 51.4, 21.6. Spectral data is in accordance with the data reported in the literature.[5]

Dimethyl 3-phenylindolizine-1,2-dicarboxylate (2b)[17]



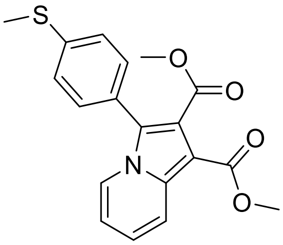
Pale yellow solid, 104 mg, 66%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.23 (dt, J = 9.1, 1.3 Hz, 1H), 8.05 (dt, J = 7.1, 1.1 Hz, 1H), 7.52 – 7.43 (m, 5H), 7.12 (ddd, J = 9.1, 6.6, 1.1 Hz, 1H), 6.72 (td, J = 6.9, 1.3 Hz, 1H), 3.91 (s, 3H), 3.80 (s, 3H).8.26 (dt, J=9.1, 1.3 Hz, 1H), 8.07 (dt, J=7.1, 1.1 Hz, 1H), 7.55-7.45 (m, 5H), 7.15 (ddd, 9.1, 6.6, 1.1 Hz, 1H), 6.74 (td, J=6.9, 1.3 Hz, 1H), 3.93 (s, 3H), 3.83 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 164.4, 135.4, 130.1, 129.24, 129.19, 129.0, 125.2, 123.71, 123.69, 122.2, 120.5, 113.6, 102.1, 52.6, 51.5. Spectral data is in accordance with the data reported in the literature.[17] Melting Point: 95.9-97.2 °C.

Dimethyl 3-(4-(dimethylamino)phenyl)indolizine-1,2-dicarboxylate (2c)



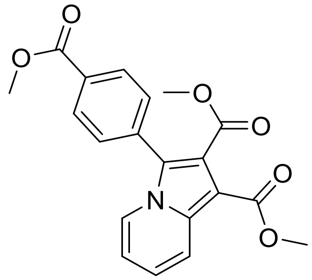
Orange solid, 123 mg, 70%. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.20 (dt, J = 9.1, 1.3 Hz, 1H), 8.05 (dt, J = 7.1, 1.2 Hz, 1H), 7.36 (d, J = 8.8 Hz, 2H), 7.08 (ddd, J = 9.1, 6.6, 1.1 Hz, 1H), 6.80 (d, J = 8.8 Hz, 2H), 6.68 (td, J = 6.9, 1.4 Hz, 1H), 3.89 (s, 3H), 3.82 (s, 3H), 3.03 (s, 6H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 167.4, 164.5, 150.7, 135.1, 131.0, 126.1, 124.0, 123.3, 121.5, 120.4, 115.9, 113.2, 112.4, 101.6, 52.6, 51.4, 40.4. **HRMS** (ESI+) for $C_{20}H_{20}N_2O_4Na^+$: calculated 375.1315, found 375.1315 (error m/z=0.2 ppm). Melting Point: 154.8-156.2 ℃.

Dimethyl 3-(4-(methylthio)phenyl)indolizine-1,2-dicarboxylate (2d)



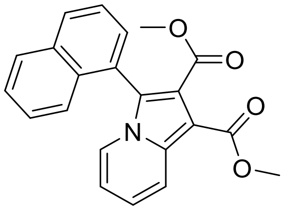
Yellow solid, 122 mg, 68%. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.22 (dt, J = 9.2, 1.3 Hz, 1H), 8.02 (dt, J = 7.1, 1.2 Hz, 1H), 7.45 – 7.40 (d, J=8.4 Hz, 2H), 7.38 – 7.33 (d, J=8.4 Hz, 2H), 7.12 (ddd, J = 9.1, 6.6, 1.1 Hz, 1H), 6.75 – 6.69 (ddd, J=7.0, 6.7, 1.0 Hz, 1H), 3.90 (s, 3H), 3.82 (s, 3H), 2.54 (s, 3H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 167.0, 164.3, 140.3, 135.4, 130.4, 126.6, 125.2, 124.7, 123.7, 123.6, 122.1, 120.5, 113.6, 102.1, 52.7, 51.5, 15.4. **HRMS** (ESI+) for $C_{19}H_{17}NO_4SNa^+$: calculated 378.0770, found 378.0775 (error m/z=-1.1 ppm). Melting Point: 132.7-133.8 ℃.

Dimethyl 3-(4-(methoxycarbonyl)phenyl)indolizine-1,2-dicarboxylate (2e)



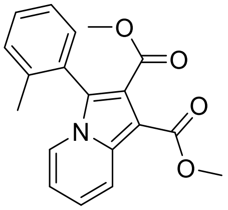
White solid, 106 mg, 58%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.26 (dt, J = 9.1, 1.3 Hz, 1H), 8.17 (d, J=8.5 Hz, 2H), 8.08 (dt, J = 7.2, 1.2 Hz, 1H), 7.61 (d, J=8.5 Hz, 2H), 7.16 (ddd, J = 9.2, 6.6, 1.0 Hz, 1H), 6.77 (td, J = 6.9, 1.3 Hz, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.81 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.7, 166.6, 164.2, 135.8, 133.7, 130.6, 130.5, 129.8, 124.1, 123.9, 123.5, 122.9, 120.7, 114.1, 102.6, 52.7, 52.5, 51.6. **HRMS** (ESI+) for $C_{20}H_{17}NO_6Na^+$: calculated 390.0954, found 390.0954 (error m/z=-1.6 ppm). Melting Point: 142.0-143.8 °C.

Dimethyl 3-(naphthalen-1-yl)indolizine-1,2-dicarboxylate (2f)



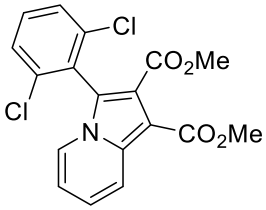
Yellow solid, 132 mg, 74%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (dt, J = 9.2, 1.6 Hz, 1H), 8.12 (dt, J = 6.9, 0.7 Hz, 1H), 8.04 (s, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.95 – 7.88 (m, 2H), 7.62 – 7.55 (m, 3H), 7.16 (ddd, J = 9.2, 6.6, 1.1 Hz, 1H), 6.75 (td, J = 6.8, 1.3 Hz, 1H), 3.95 (s, 3H), 3.81 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.0, 164.4, 135.5, 133.5, 133.4, 129.8, 129.0, 128.4, 128.0, 127.13, 127.08, 126.9, 126.4, 125.1, 123.8, 123.7, 122.5, 120.6, 113.7, 102.2, 52.7, 51.5. **HRMS** (ESI+) for $C_{22}H_{17}NO_4Na^+$: calculated 382.1050, found 382.1038 (error m/z=3.2 ppm). Melting Point: 158.4-159.3 °C.

Dimethyl 3-(o-tolyl)indolizine-1,2-dicarboxylate (2g)



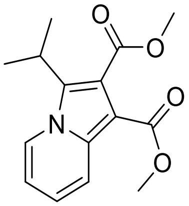
Light brown solid, 98 mg, 60%. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.24 (dt, J = 9.0, 1.2 Hz, 1H), 7.44 (dt, J = 7.1, 1.2 Hz, 1H), 7.38-7.43 (m, 1H), 7.35 (d, J = 7.7 Hz, 1H), 7.28-7.33 (m, 2H), 7.12 (ddd, J = 9.2, 6.6, 1.1 Hz, 1H), 6.70 (td, J = 6.8, 1.3 Hz, 1H), 3.91 (s, 3H), 3.74 (s, 3H), 2.06 (s, 3H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 166.5, 164.5, 139.4, 135.1, 132.0, 130.5, 130.0, 128.3, 126.4, 125.5, 123.9, 123.4, 121.9, 120.5, 113.6, 101.7, 52.4, 51.4, 19.5. **HRMS** (ESI+) for $C_{19}H_{17}NO_4Na^+$: calculated 346.1050, found 346.1041 (error m/z=2.5 ppm). Melting Point: 68.0-69.0 °C.

Dimethyl 3-(2,6-dichlorophenyl)indolizine-1,2-dicarboxylate (2h)



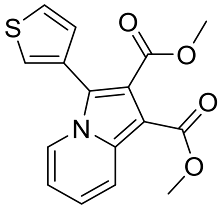
Light brown solid, 137 mg, 70%. **^{1}H NMR** (500 MHz, CDCl$_3$) δ 8.25 (dt, J = 9.2, 1.2 Hz, 1H), 7.50-7.47 (m, 2H), 7.43 – 7.37 (m, 2H), 7.16 (ddd, J = 9.2, 6.7, 1.1 Hz, 1H), 6.76 (td, J = 6.8, 1.3 Hz, 1H), 3.92 (s, 3H), 3.76 (s, 3H). **^{13}C NMR** (126 MHz, CDCl$_3$) δ 165.3, 164.4, 138.1, 135.8, 131.7, 128.4, 127.9, 123.8, 123.5, 122.1, 121.7, 120.7, 114.0, 102.8, 52.3, 51.5 **HRMS** (ESI+) for $C_{18}H_{13}Cl_2NO_4Na^+$: calculated 400.0114, found 400.0110 (error m/z=0.9 ppm).

Dimethyl 3-isopropylindolizine-1,2-dicarboxylate (2i)[5]



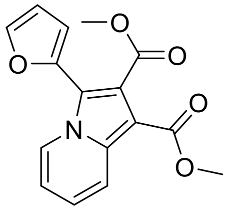
Brown solid, 68 mg, 53%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.19 (dt, J = 9.1, 1.3 Hz, 1H), 7.94 (d, J = 7.3 Hz, 1H), 7.07 (ddd, J = 9.2, 6.6, 1.1 Hz, 1H), 6.79 (td, J = 6.9, 1.4 Hz, 1H), 3.95 (s, 3H), 3.86 (s, 3H), 3.35 (hept, J = 7.0 Hz, 1H), 1.40 (d, J = 7.1 Hz, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 168.4, 164.4, 134.9, 129.0, 123.3, 122.6, 120.7, 119.9, 113.3, 101.2, 52.7, 51.3, 25.9, 20.2. Spectral data is in accordance with the data reported in the literature.[5]

Dimethyl 3-(thiophen-3-yl)indolizine-1,2-dicarboxylate (2j)



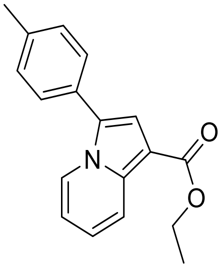
Yellow solid, 114 mg, 72%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.22 (dt, J = 9.2, 1.2 Hz, 1H), 8.10 (dt, J = 7.1, 1.1 Hz, 1H), 7.56 (dd, J = 3.0, 1.3 Hz, 1H), 7.49 (dd, J = 5.0, 3.0 Hz, 1H), 7.28 (dd, J = 5.0, 1.3 Hz, 1H), 7.13 (ddd, J = 9.2, 6.6, 1.1 Hz, 1H), 6.76 (td, J = 6.9, 1.3 Hz, 1H), 3.90 (s, 3H), 3.85 (s, 3H). **^{13}C NMR** (201 MHz, $CDCl_3$) δ 167.0, 164.3, 135.4, 126.8, 126.4, 124.0, 123.7, 122.4, 120.46, 120.45, 113.7, 101.9, 52.7, 51.5. **HRMS** (ESI+) for $C_{16}H_{13}NO_4SNa^+$: calculated 338.0457, found 338.0450 (error m/z=2.2 ppm). Melting Point: 93.0-94.2 °C.

Dimethyl 3-(furan-2-yl)indolizine-1,2-dicarboxylate (2k)



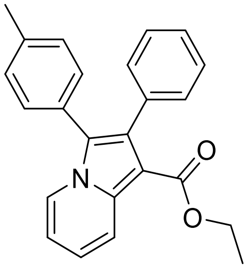
Brown solid, 66 mg, 44%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 (dt, J = 7.1, 1.1 Hz, 1H), 8.23 (dt, J = 9.1, 1.3 Hz, 1H), 7.58 (dd, J = 1.9, 0.8 Hz, 1H), 7.17 (ddd, J = 9.1, 6.6, 1.1 Hz, 1H), 6.84 (td, J = 6.9, 1.4 Hz, 1H), 6.68 (dd, J = 3.5, 0.8 Hz, 1H), 6.55 (dd, J = 3.4, 1.8 Hz, 1H), 3.93 (s, 4H), 3.90 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8, 164.1, 143.6, 143,0, 135.7, 125.3, 124.2, 122.7, 120.4, 115.6, 114.1, 111.7, 110.7, 102.4, 52.9, 51.53. **HRMS** (ESI+) for $C_{16}H_{13}NO_5Na^+$: calculated 322.0686, found 322.0691 (error m/z=-1.6 ppm). Melting Point: 65.9-67.0 °C.

Ethyl 3-(p-tolyl)indolizine-1-carboxylate (2l)[18]



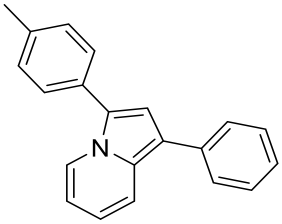
Yellow solid, 98 mg, 70%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.25 (d, J = 8.9 Hz, 2H), 7.42 (d, J = 8.1 Hz, 2H), 7.30 – 7.24 (m, 3H), 7.08 – 7.00 (m, 1H), 6.66 (td, J = 6.7, 1.5 Hz, 1H), 4.38 (q, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.2, 138.1, 136.4, 129.9, 128.7, 128.5, 126.6, 123.5, 122.2, 120.3, 115.9, 112.6, 104.3, 59.7, 21.5, 14.8. Spectral data is in accordance with the data reported in the literature.[18] Melting Point: 79.0-81.2 °C.

Ethyl 2-phenyl-3-(p-tolyl)indolizine-1-carboxylate (2m)



Brown solid, 134 mg, 75%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 8.2 Hz, 2H), 7.46 – 7.38 (m, 5H), 7.31 (d, J = 7.3 Hz, 3H), 6.72 – 6.65 (m, 1H), 6.47 (t, J = 6.9 Hz, 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.45 (s, 3H), 0.93 (dd, J = 7.8, 6.5 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.7, 138.4, 134.7, 130.6, 130.4, 130.0, 129.4, 127.9, 127.8, 127.2, 126.3, 122.8, 119.1, 118.5, 116.9, 115.6, 112.4, 60.1, 21.5, 13.7. **HRMS** (ESI+) for $C_{24}H_{21}NO_2Na^+$: calculated 378.1464, found 378.1465 (error m/z=-0.2 ppm). Melting Point: 86.9-89.0 °C.

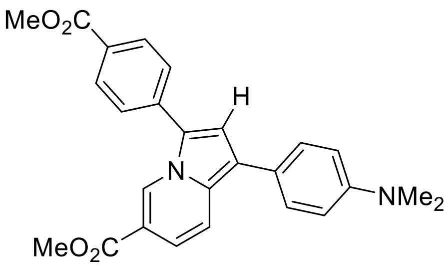
1-phenyl-3-(p-tolyl)indolizine (2n)[5]



Bright yellow oil, 98 mg, 70%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.25 (dt, J = 7.1, 1.2 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.64 (d, J=7.2 Hz, 2H), 7.51 (d, J=8.0 Hz, 2H), 7.44 (t, J = 7.8 Hz, 2H), 7.31 (d, J = 7.8 Hz, 2H), 7.28 – 7.23 (m, 1H), 7.02 (s, 1H), 6.74 (ddd, J = 9.1, 6.4, 1.1 Hz, 1H), 6.50 (td, J = 6.8, 6.3, 1.3 Hz, 1H), 2.44 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.4, 136.5, 130.1, 129.8, 129.4, 128.9, 128.4, 127.7, 125.9, 125.5, 122.9, 118.6, 118.0, 115.2, 113.7, 111.1, 21.5.

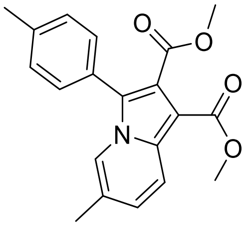
Spectral data is in accordance with the data reported in the literature.[5]

Methyl 1-(4-(dimethylamino)phenyl)-3-(4-(methoxycarbonyl)phenyl)indolizine-6-carboxylate (2o)



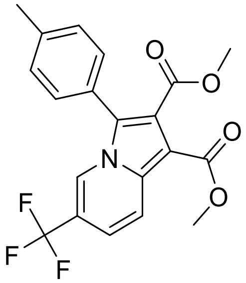
Yellow solid, 54 mg 25%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.06 (t. J = 1.3 Hz, 1H), 8.18 (d, J = 8.5 Hz, 2H), 7.73 – 7.67 (m, 3H), 7.49 (d, J = 8.8 Hz, 2H), 7.23 (dd, J = 9.5, 1.5 Hz, 1H), 7.15 (s, 1H), 6.86 (d, J = 8.8 Hz, 2H), 3.97 (s, 3H), 3.90 (s, 3H), 3.01 (s, 6H) ppm. **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8, 166.3, 149.5, 136.0, 130.6, 130.6, 128.9, 128.6, 127.9, 127.6, 126.0, 123.3, 118.4, 117.7, 117.0, 117.0, 115.3, 113.2, 52.3, 52.2, 40.8 ppm. HRMS (ESI+) for $C_{26}H_{26}N_2O_4^+$: calculated 429.1814, found 429.1809 (error m/z = 1.5 ppm). Melting Point: 124.7-126.1 °C.

Dimethyl 6-methyl-3-(p-tolyl)indolizine-1,2-dicarboxylate (2p)



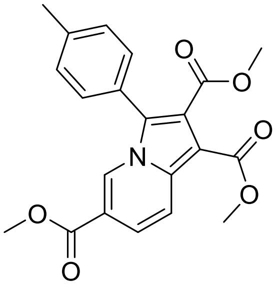
Pale yellow solid, 81 mg, 48%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (d, J = 9.2 Hz, 1H), 7.81-7.79 (m, 1H), 7.39 (d, J = 8.1 Hz, 2H), 7.31 (d, J = 7.9 Hz, 2H), 6.97 (dd, J = 9.2, 1.6 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 2.43 (s, 3H), 2.22 (d, J = 1.1 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.2, 164.5, 139.1, 134.2, 130.0, 129.9, 126.9, 126.2, 125.0, 123.2, 121.7, 121.2, 119.8, 101.6, 52.5, 51.4, 21.6, 18.5. **HRMS** (ESI+) for $C_{20}H_{19}NO_4Na^+$: calculated 360.1206, found 360.1195 (error m/z=3.2 ppm). Melting Point: 118.2-119.5 °C.

Dimethyl 3-(p-tolyl)-6-(trifluoromethyl)indolizine-1,2-dicarboxylate (2q)



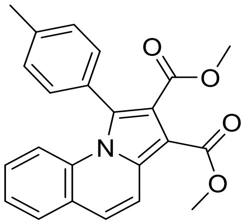
Pale yellow solid, 147 mg, 74%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.37 – 8.29 (m, 2H), 7.39 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.7 Hz, 2H), 7.21 (dd, J = 9.4, 1.7 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 13C NMR (126 MHz, $CDCl_3$) δ 166.3, 163.9, 140.0, 134.6, 130.3, 129.9, 126.9, 124.8, 123.52 (q, J = 271.2 Hz), 123.4, 122.7 (q, J = 5.9 Hz), 121.4, 118.8 (q, J = 2.5 Hz), 117.8 (q, J = 34.2 Hz), 103.9, 52.7, 51.8, 21.6. **HRMS** (ESI+) for $C_{20}H_{16}F_3NO_4Na^+$: calculated 414.0924, found 414.0917 (error m/z=1.6 ppm). Melting Point: 154.9-156.8 °C.

Trimethyl 3-(p-tolyl)indolizine-1,2,6-tricarboxylate (2r)



Yellow solid, 171 mg, 89%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.80 – 8.74 (m, 1H), 8.22 (dd, J = 9.5, 1.0 Hz, 1H), 7.61 (dd, J = 9.5, 1.5 Hz, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.34 (d, J = 7.8 Hz, 1H), 3.92 (s, 3H), 3.89 (s, 3H), 3.82 (s, 3H), 2.45 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.5, 165.4, 164.0, 139.8, 135.4, 130.2, 130.0, 128.3, 126.7, 125.1, 123.5, 122.5, 119.9, 117.5, 103.4, 52.7, 52.6, 51.7, 21.6. **HRMS** (ESI+) for $C_{21}H_{19}NO_6Na^+$: calculated 404.1105, found 404.1109 (error m/z=-1.1 ppm). Melting Point: 129.0-131.1 °C.

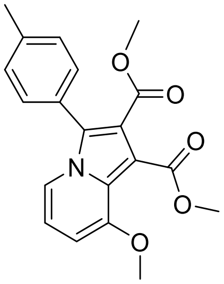
Dimethyl 1-(p-tolyl)pyrrolo[1,2-a]quinoline-2,3-dicarboxylate (2s)[5]



Pale yellow solid, 141 mg, 73%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (d, J = 9.5 Hz, 1H), 7.69 (dd, J = 8.1, 1.5 Hz, 1H), 7.41 – 7.27 (m, 7H), 7.15 (ddd, J = 8.7, 7.0, 1.6 Hz, 1H), 3.91 (s, 3H), 3.73 (s, 3H), 2.47 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.8, 164.5, 139.3, 134.6, 134.1, 130.4, 129.8, 129.5, 129.4, 129.0, 127.8, 125.7, 125.2, 124.9, 122.9, 118.6, 117.9, 104.7, 52.4, 51.6, 21.7.

Spectral data is in accordance with the data reported in the literature.[5] Melting Point: 114.8-116.2 °C.

Dimethyl 8-methoxy-3-(p-tolyl)indolizine-1,2-dicarboxylate (2t)



White solid, 57 mg, 60%. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33 (dd, J = 7.1, 2.0 Hz, 1H), 7.30 – 7.20 (m, 3H), 6.39 (td, J = 7.3, 2.0 Hz, 1H), 6.06 (dd, J = 7.4, 2.0 Hz, 1H), 3.91 (d, J = 2.1 Hz, 2H), 3.87 (d, J = 2.0 Hz, 3H), 3.66 (d, J = 2.1 Hz, 2H), 2.39 (d, J = 2.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 167.5, 164.5, 151.8, 139.1, 130.8, 129.5, 128.6, 126.9, 124.5, 116.5, 115.5, 112.7, 107.4, 96.5, 56.0, 52.6, 51.8, 21.6. **HRMS** (ESI+) for $C_{20}H_{19}NO_5Na^+$: calculated 376.1155, found 376.1143 (error m/z=3.4 ppm). Melting Point: 148.7-150.1 °C.

2.5.6. NMR Spectra

For all ^{1}H and ^{13}C NMR spectra of isolated products, see Appendix A

2.5.7. References

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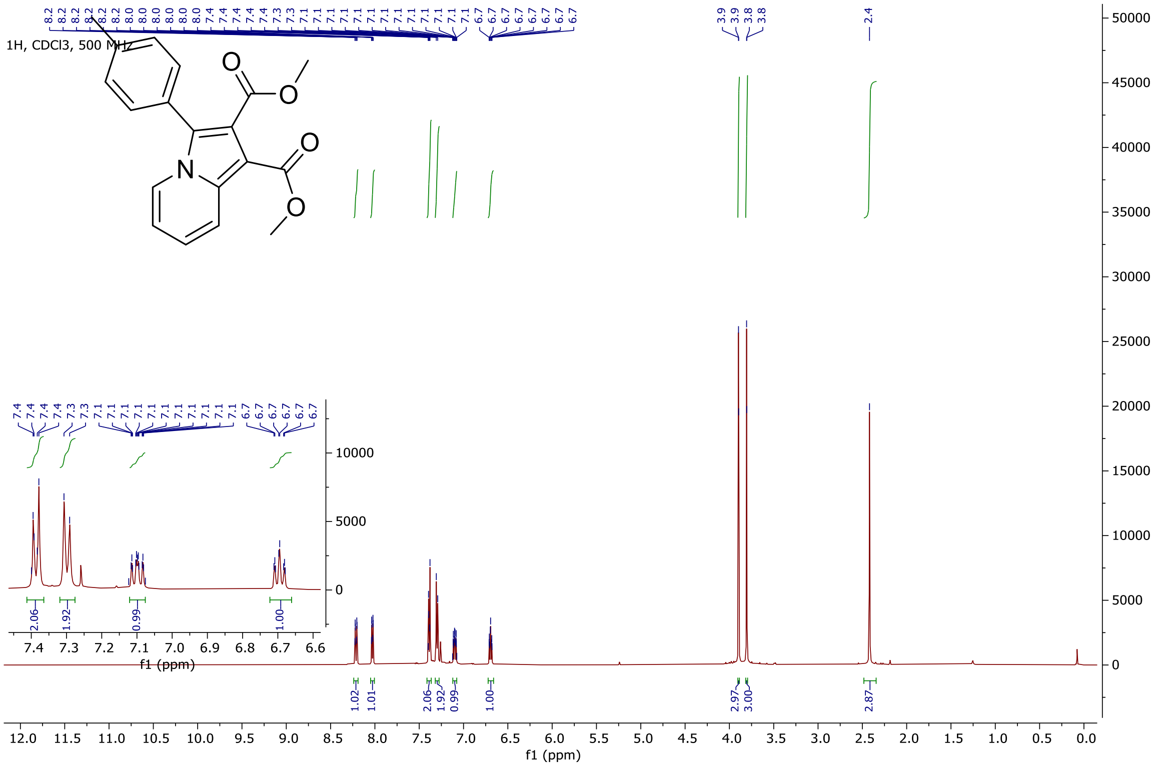
3. Conclusion

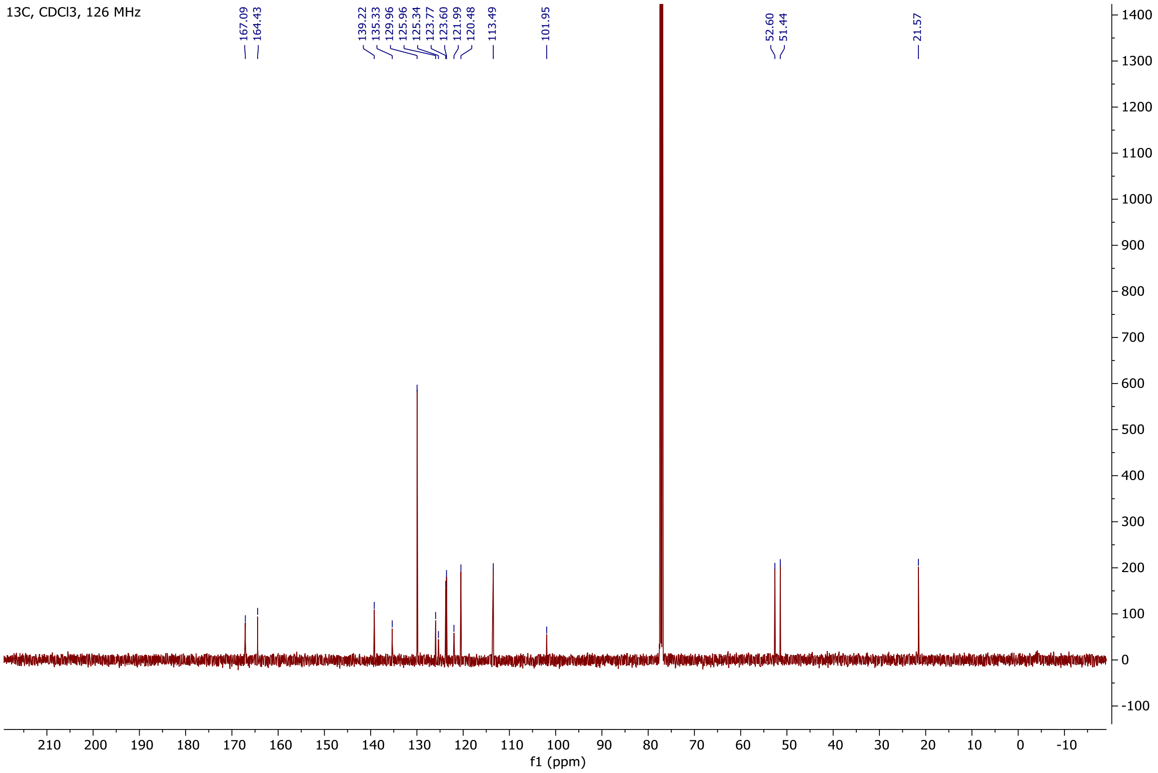
The field of indolizine synthesis has seen immense progress in the past several decades. In this period, metal-catalyzed syntheses of indolizines have appeared as valuable approaches to build this framework. However, there is still much to do in terms of the development of a robust, efficient, simple and tunable synthesis of indolizines, as the existing syntheses generally require prefunctionalized substrates or allow limited substitution due to the nature of reagents or intermediates involved in these reactions.

Chapter 2 of this these describes the development of a synthetic route to indolizines from the palladium catalyzed coupling of imines, 2-bromopyridines, CO and alkynes. This one-pot reaction proceeds via the carbonylative formation of pyridine based mesoionic 1,3-dipoles, and offers a new route to generate these structures wherein any of the product substituents can be modified by systematic variation of the three stable and available building blocks. Mechanistic investigations suggest that catalytic acid chloride formation is followed by cyclization to a mesoionic intermediate that then undergoes cycloaddition with alkynes and extrudes isocyanate to generate indolizines. More generally, these results highlight how metal catalyzed carbonylations can be exploited to drive the build-up of a reactive pyridine-based 1,3-dipole from combinations of reagents that are by themselves broadly accessible and stable. In this, carbon monoxide is ultimately liberated from the cycloaddition product as an isocyanate. Considering the variety of 1,3-dipoles that are known, and the favorable energetics of carbon monoxide oxidation, we believe that this approach could prove useful in the design of efficient routes to alternative classes of reactive cycloaddition substrates.

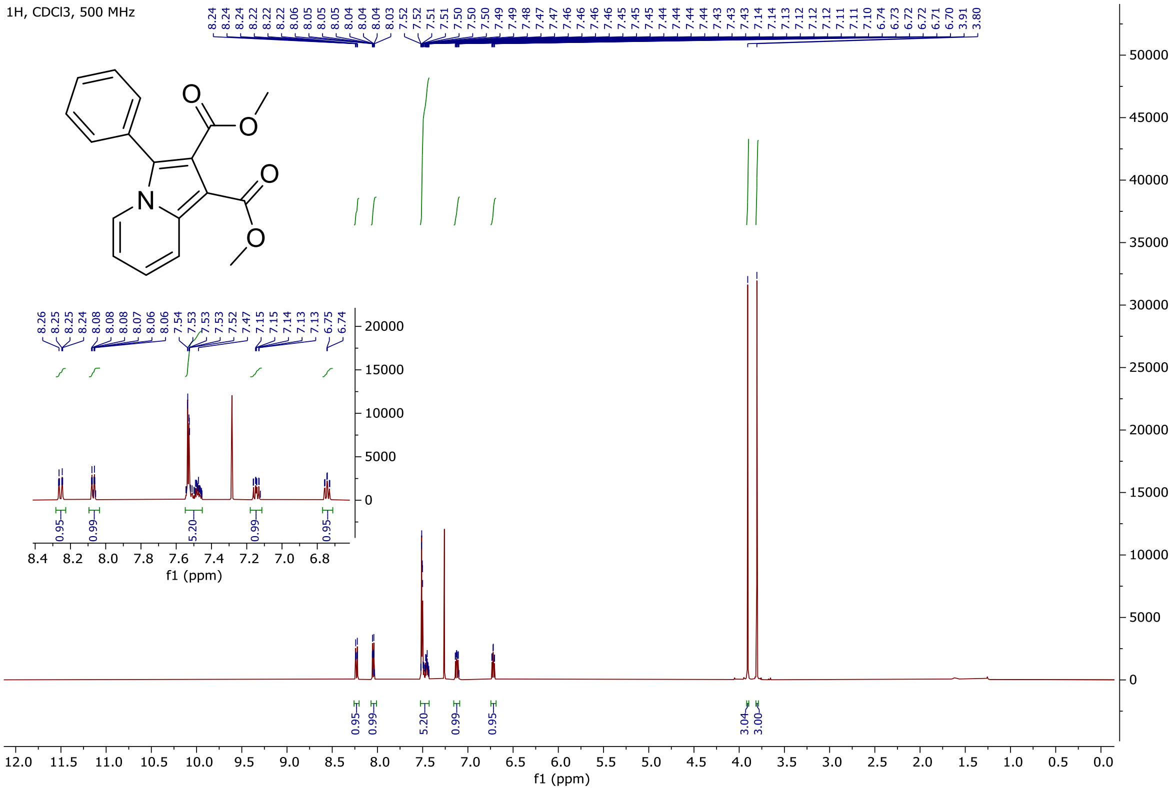
Appendix A. ^{1}H and ^{13}C NMR Spectra for Chapter 2

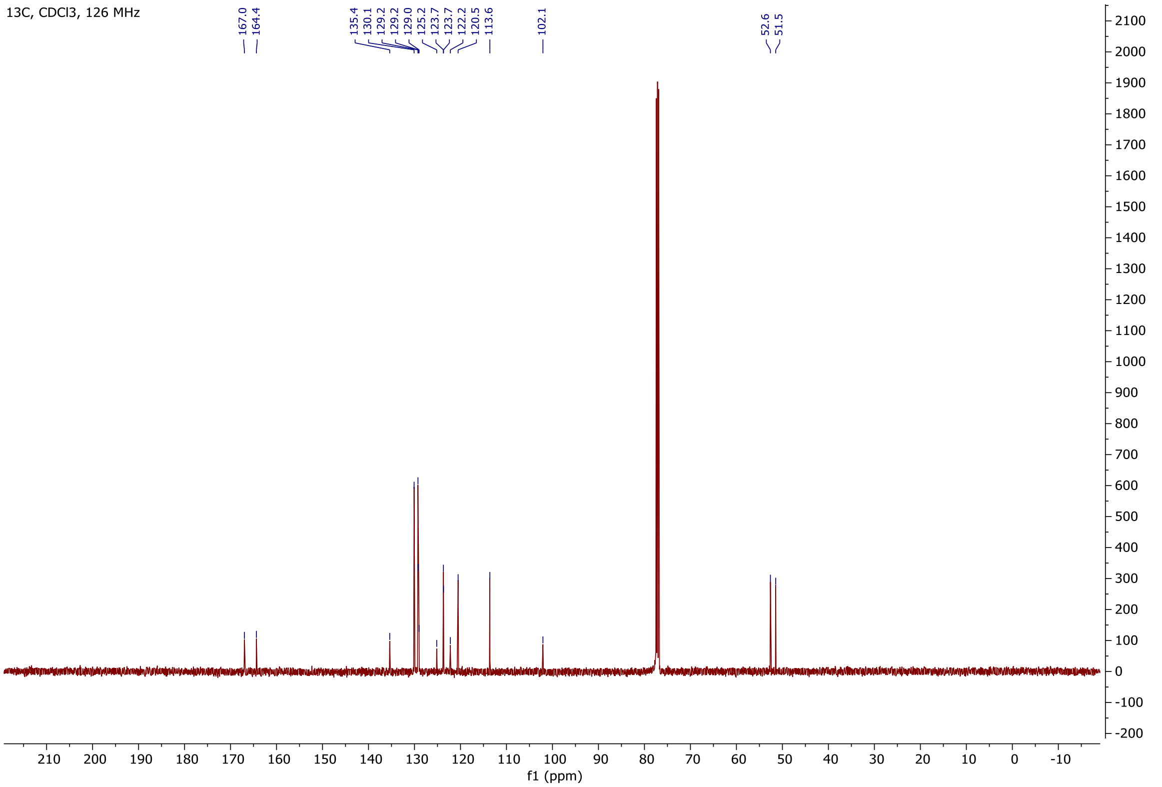
Dimethyl 3-(p-tolyl)indolizine-1,2-dicarboxylate (**2a**)



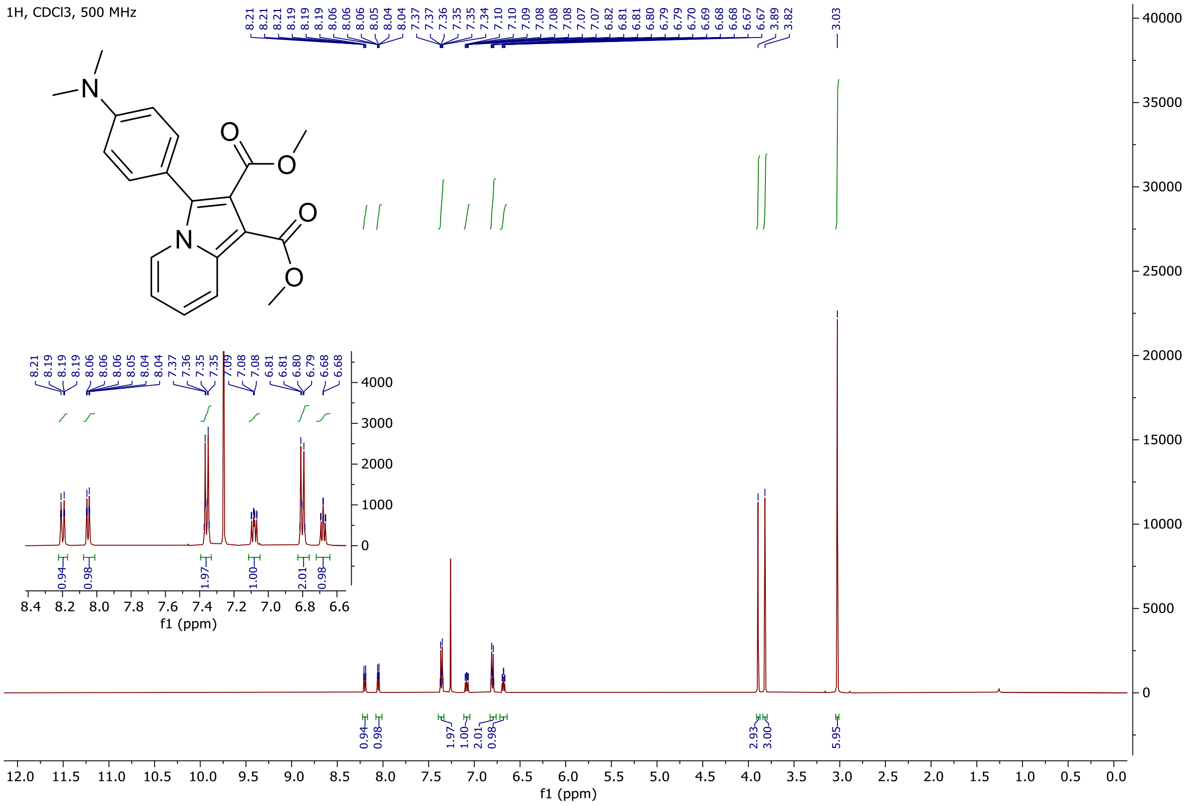


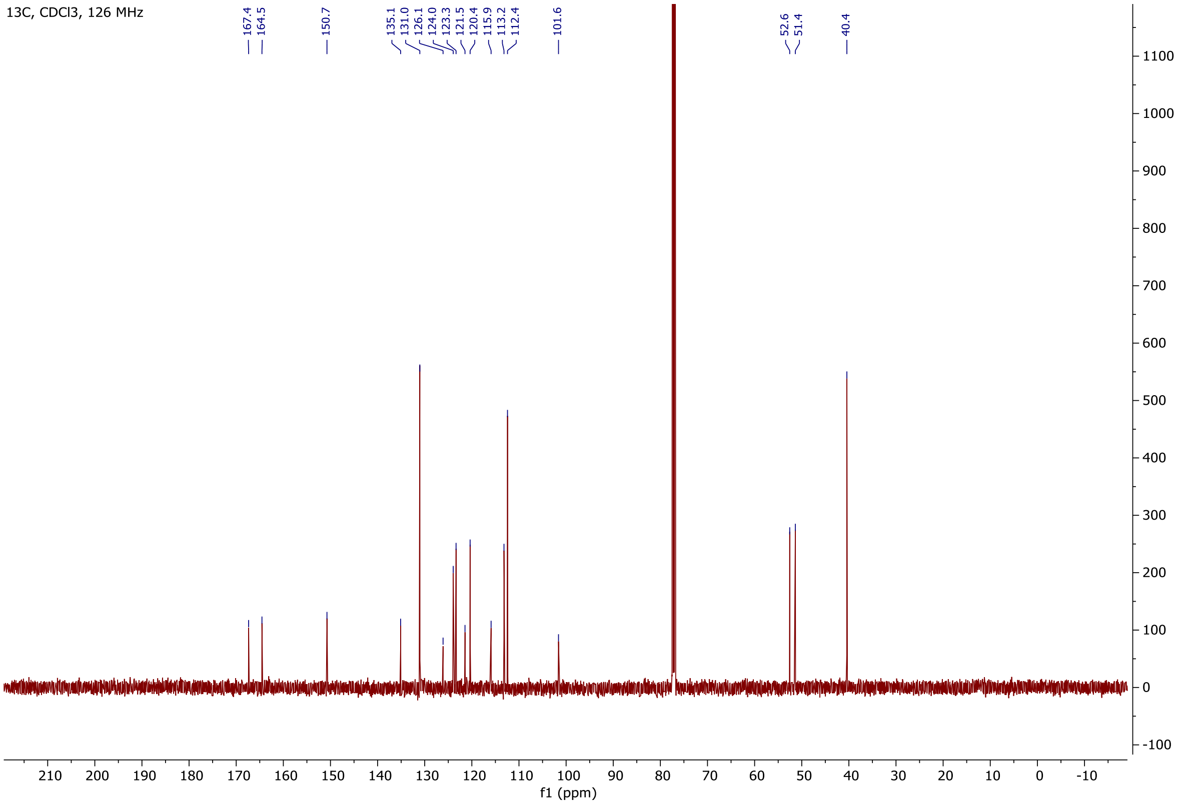
Dimethyl 3-phenylindolizine-1,2-dicarboxylate (**2b**)





Dimethyl 3-(4-(dimethylamino)phenyl)indolizine-1,2-dicarboxylate (**2c**)





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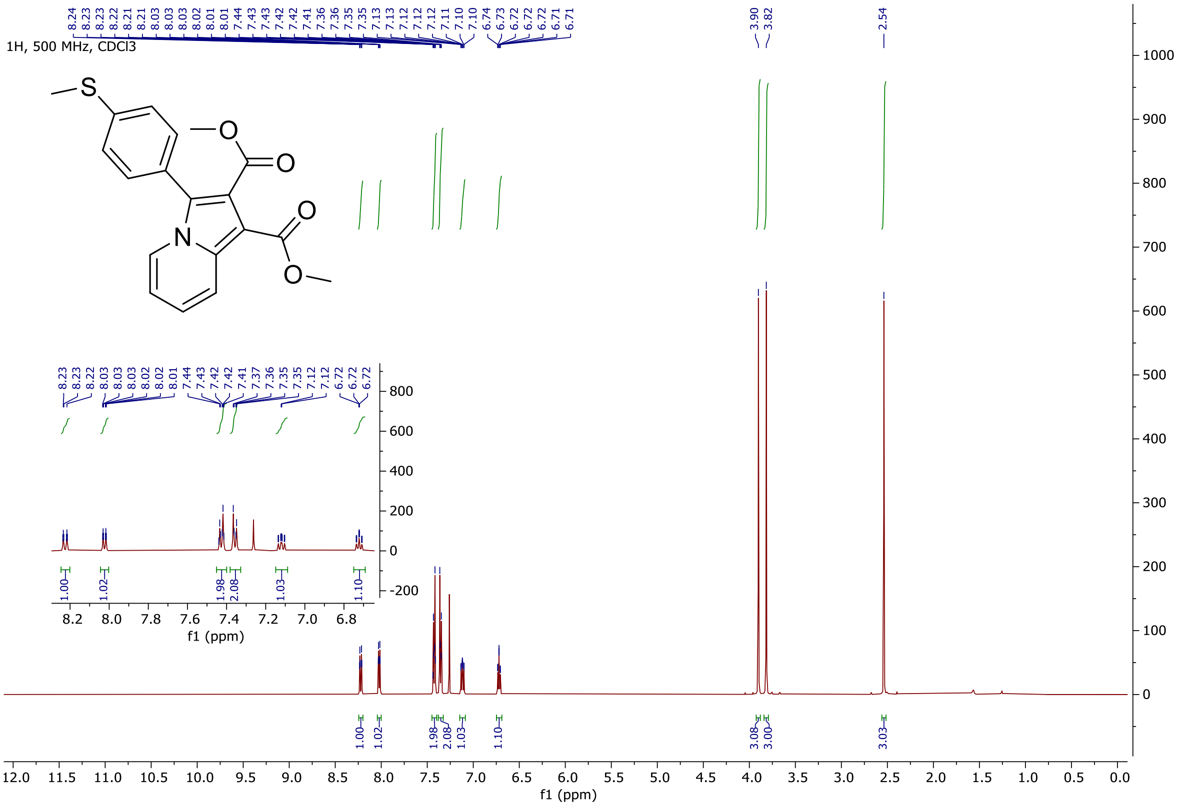

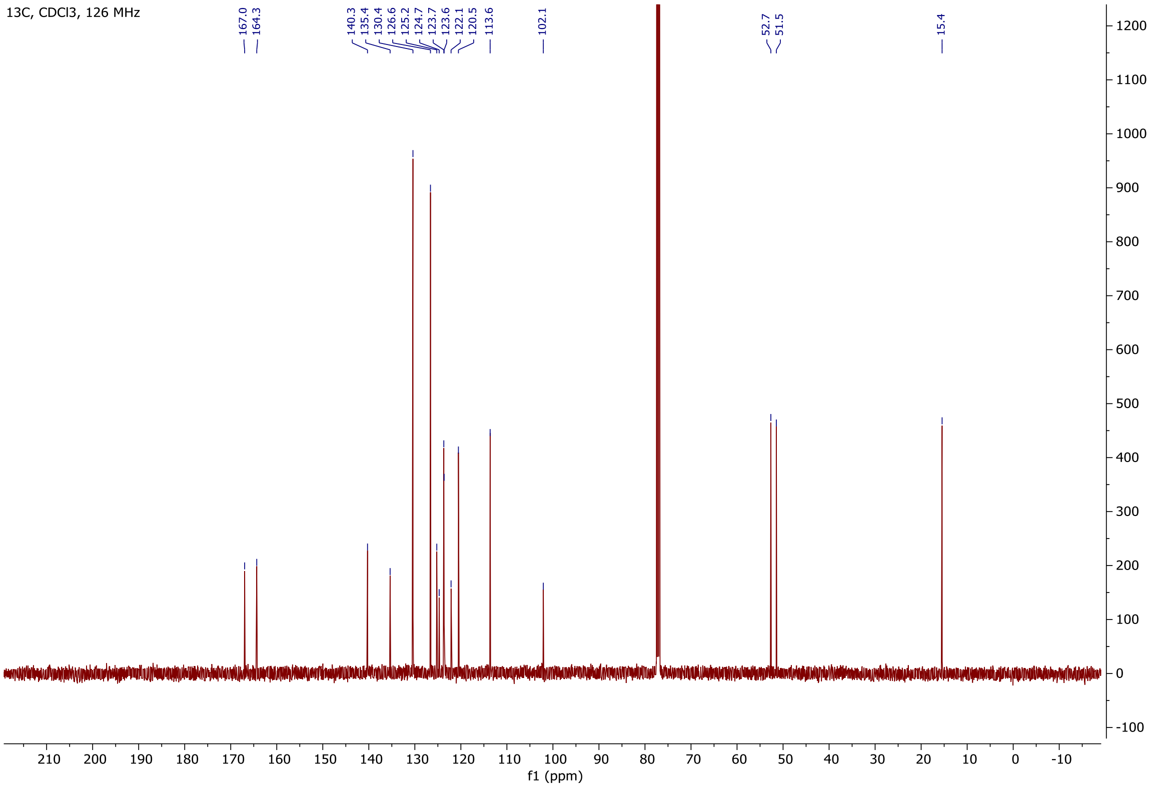

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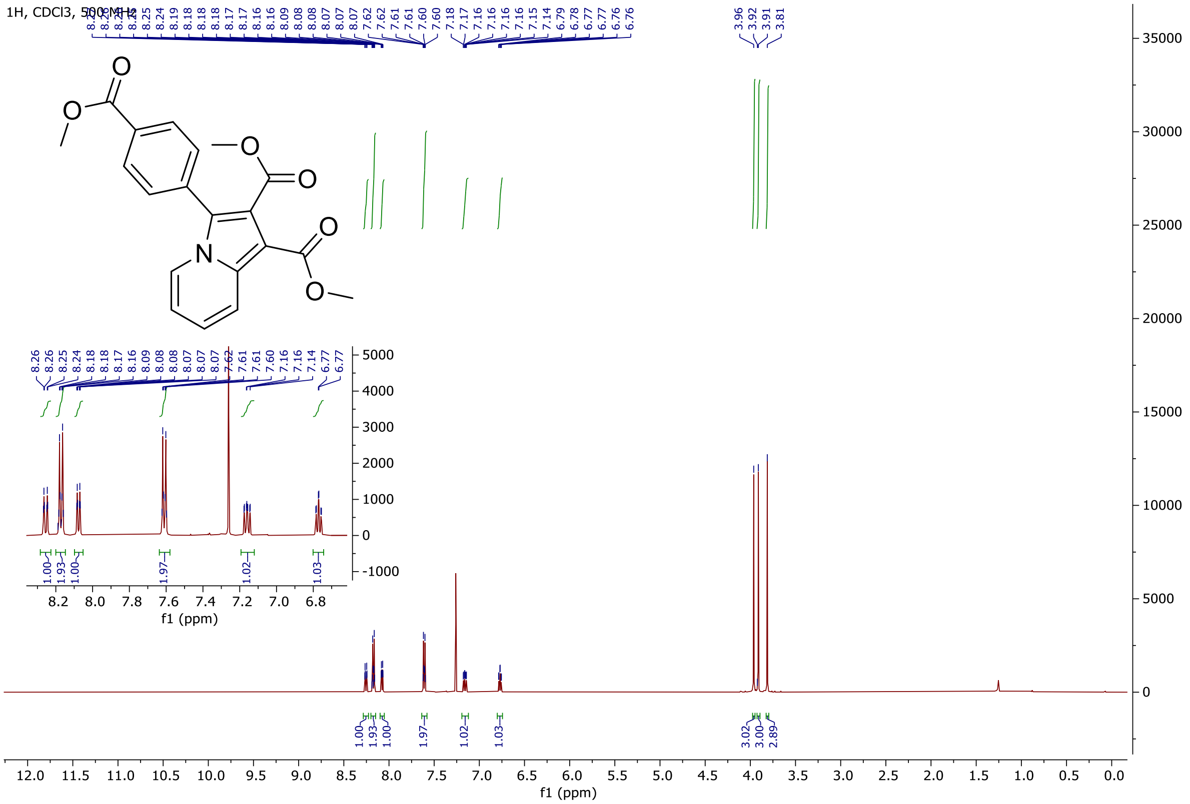

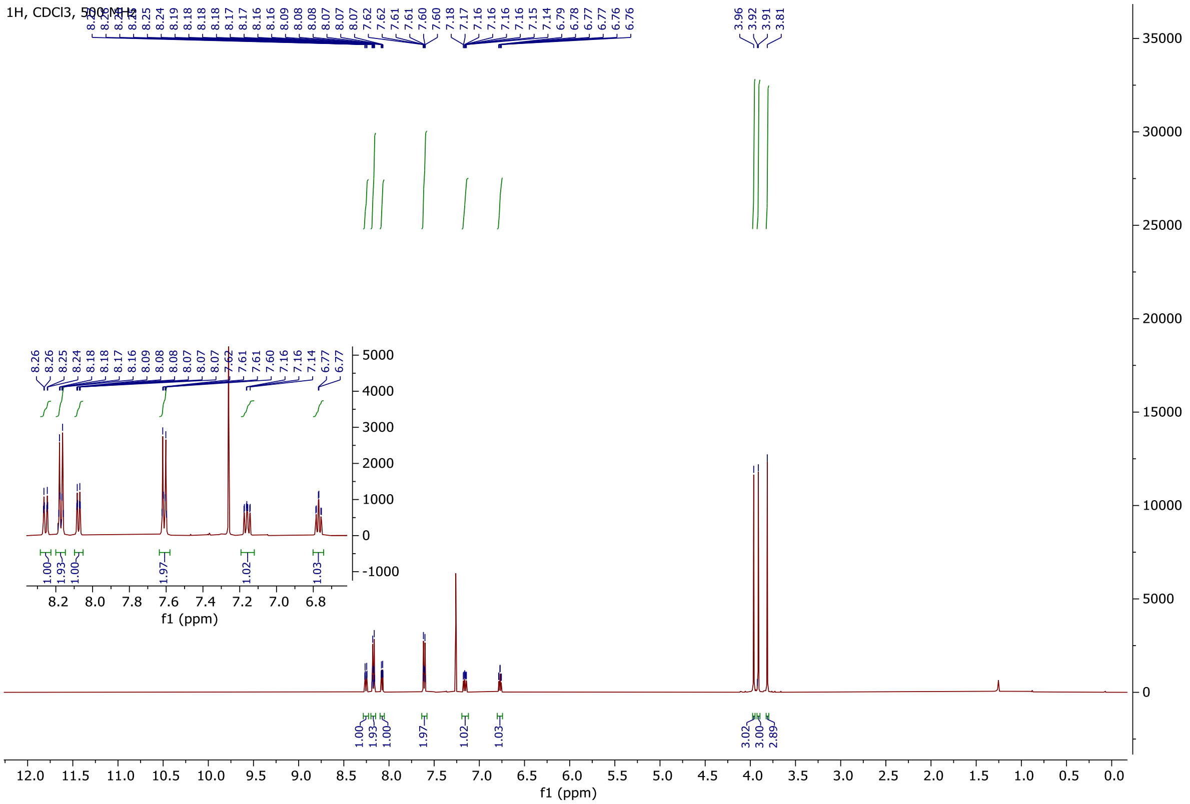

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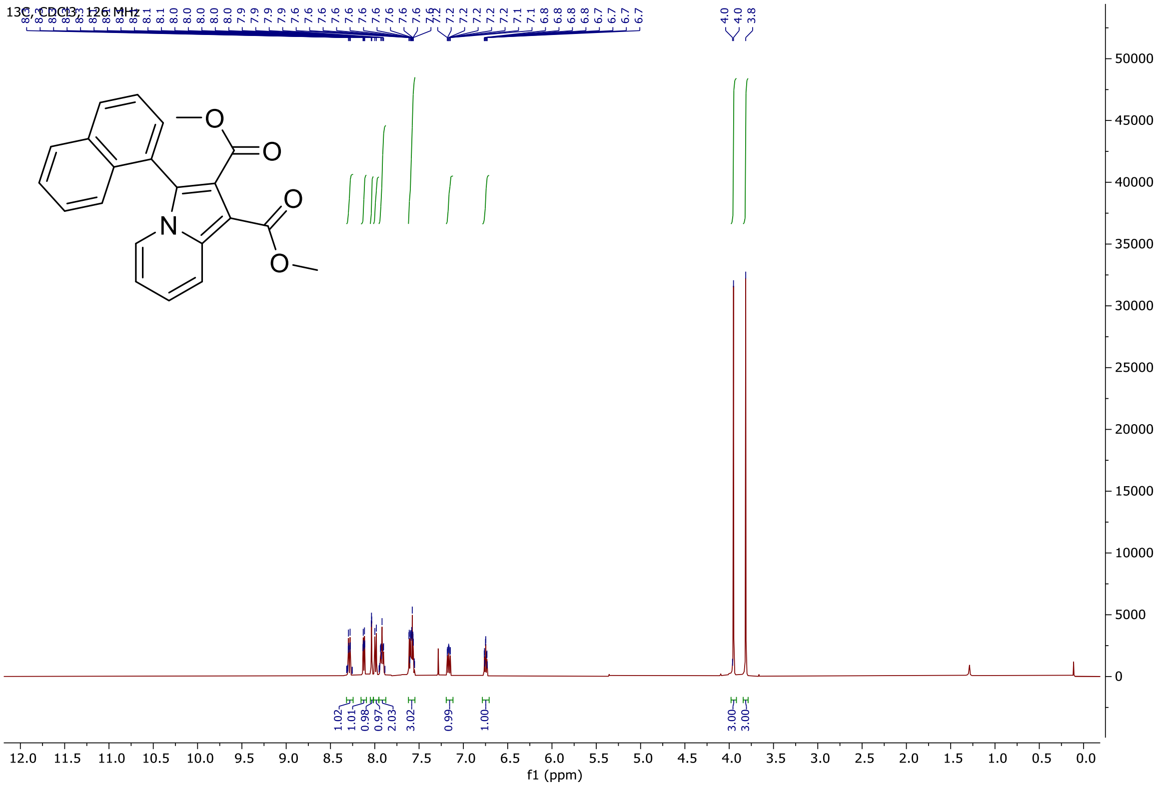

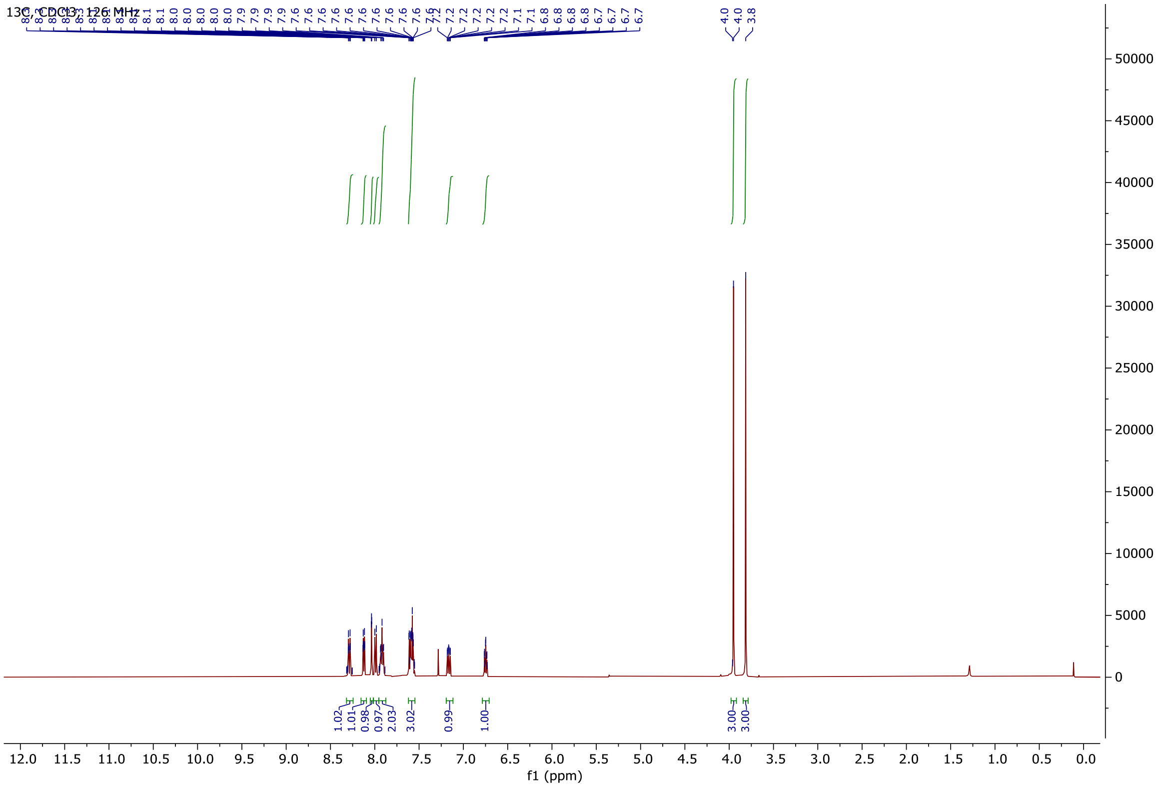

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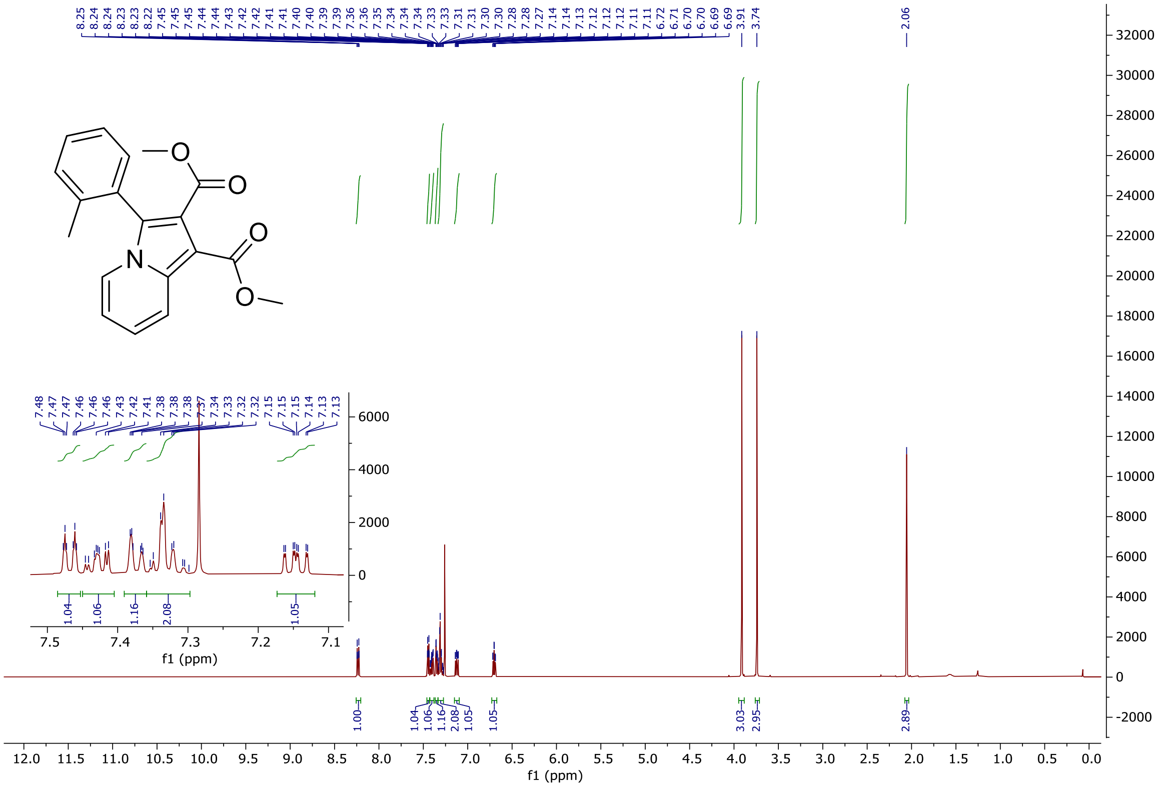
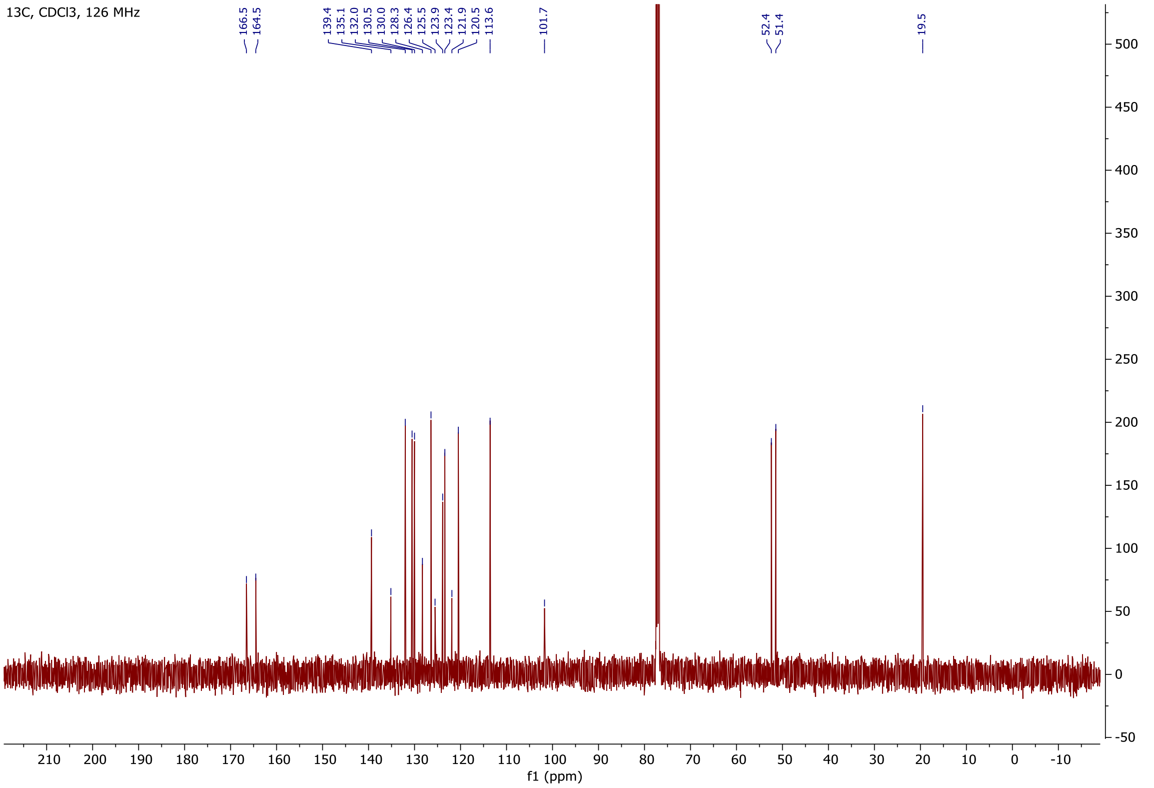
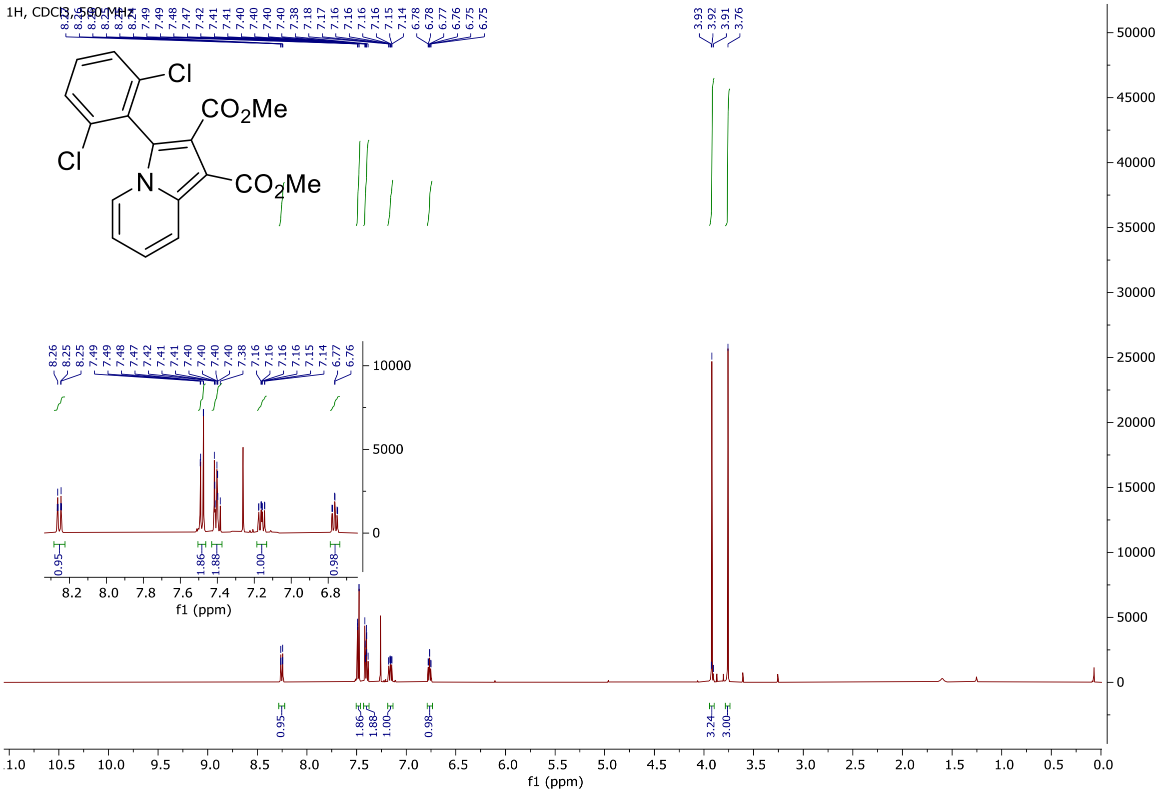
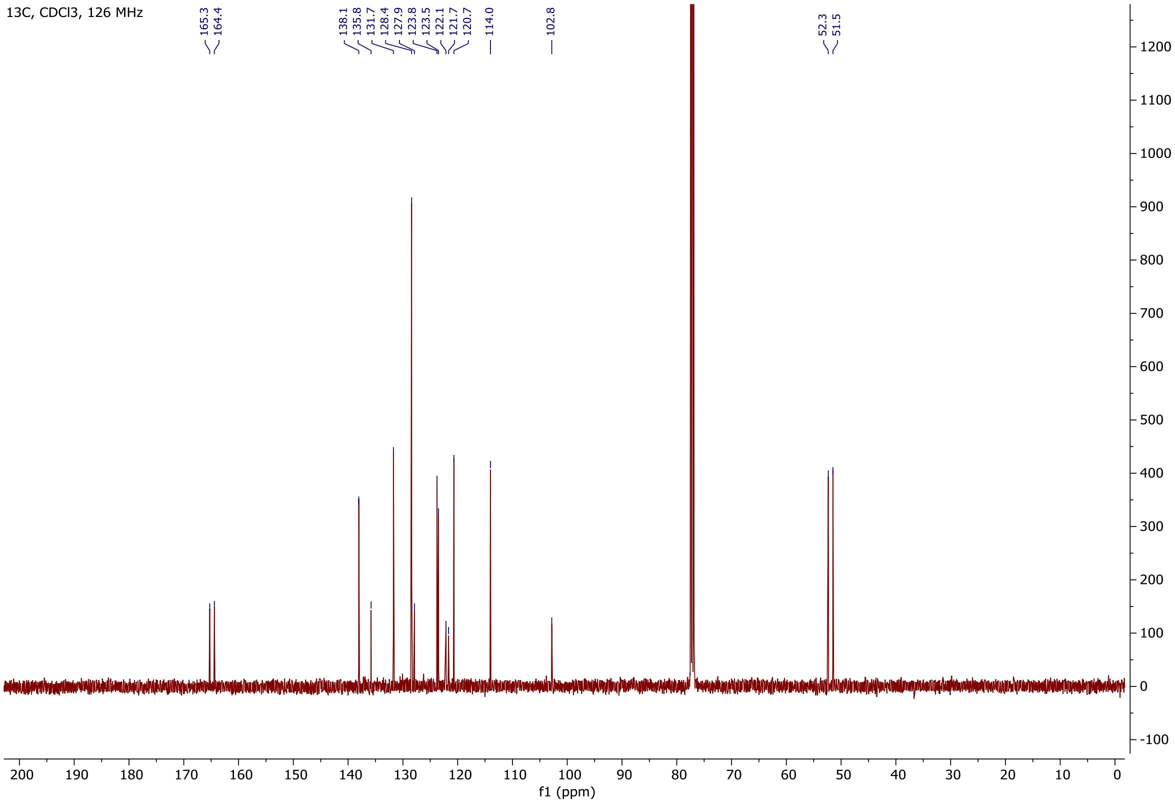


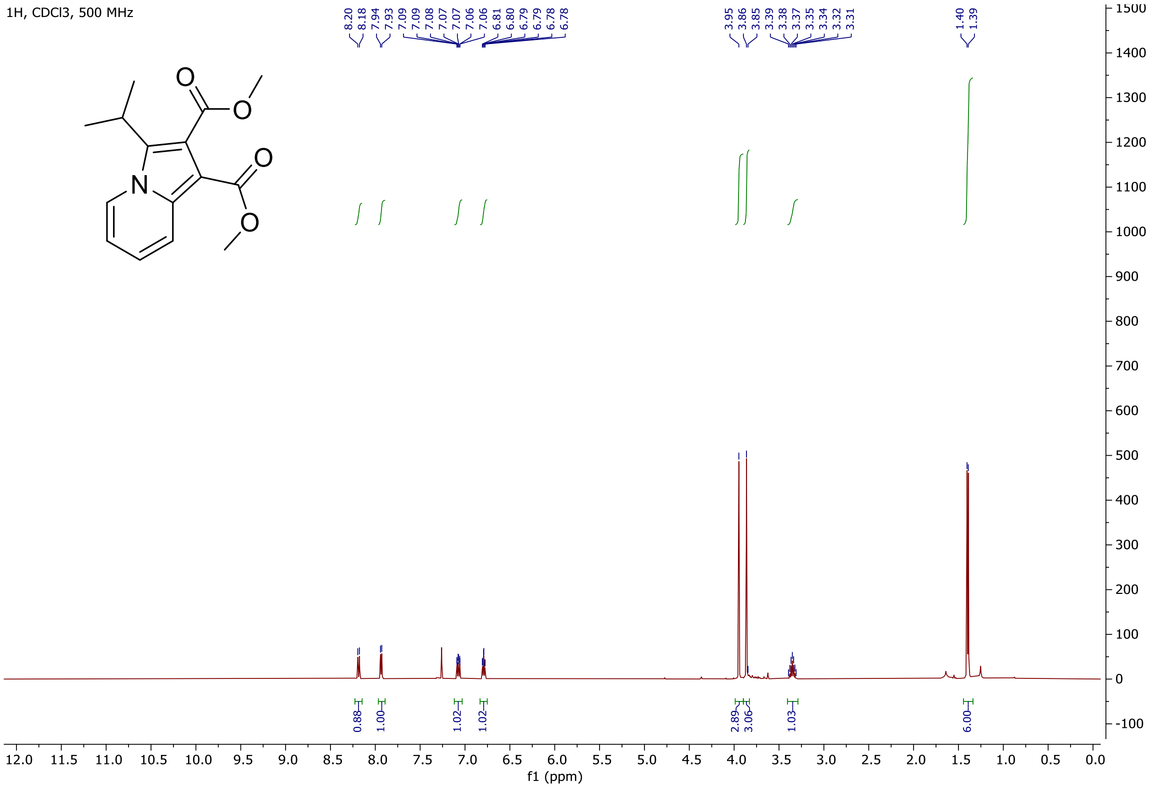


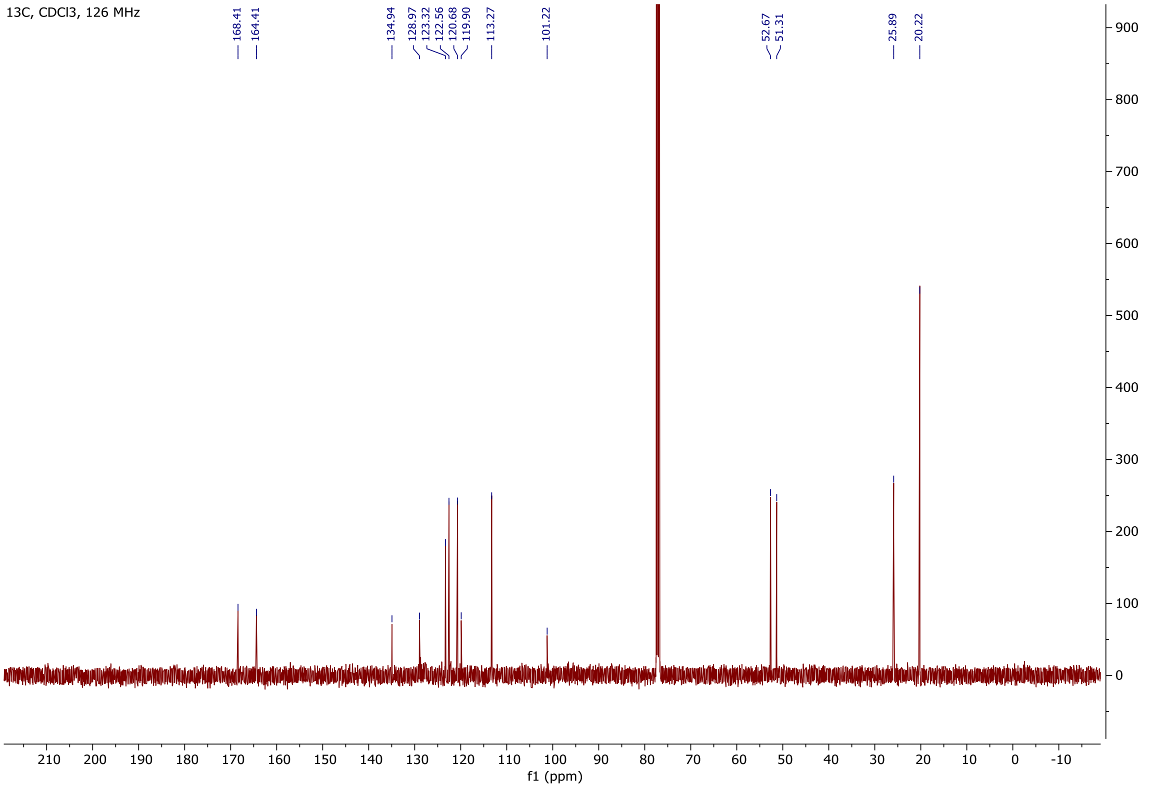
Dimethyl 3-(2,6-dichlorophenyl)indolizine-1,2-dicarboxylate (**2h**)



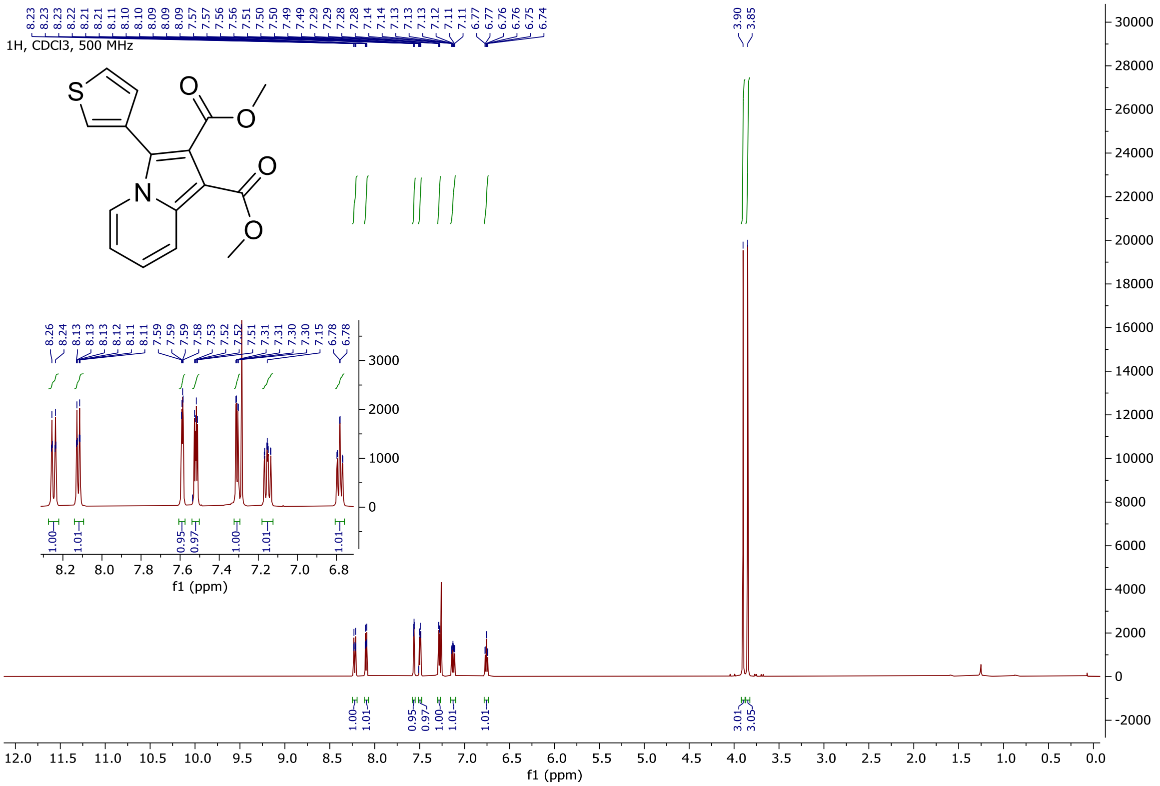


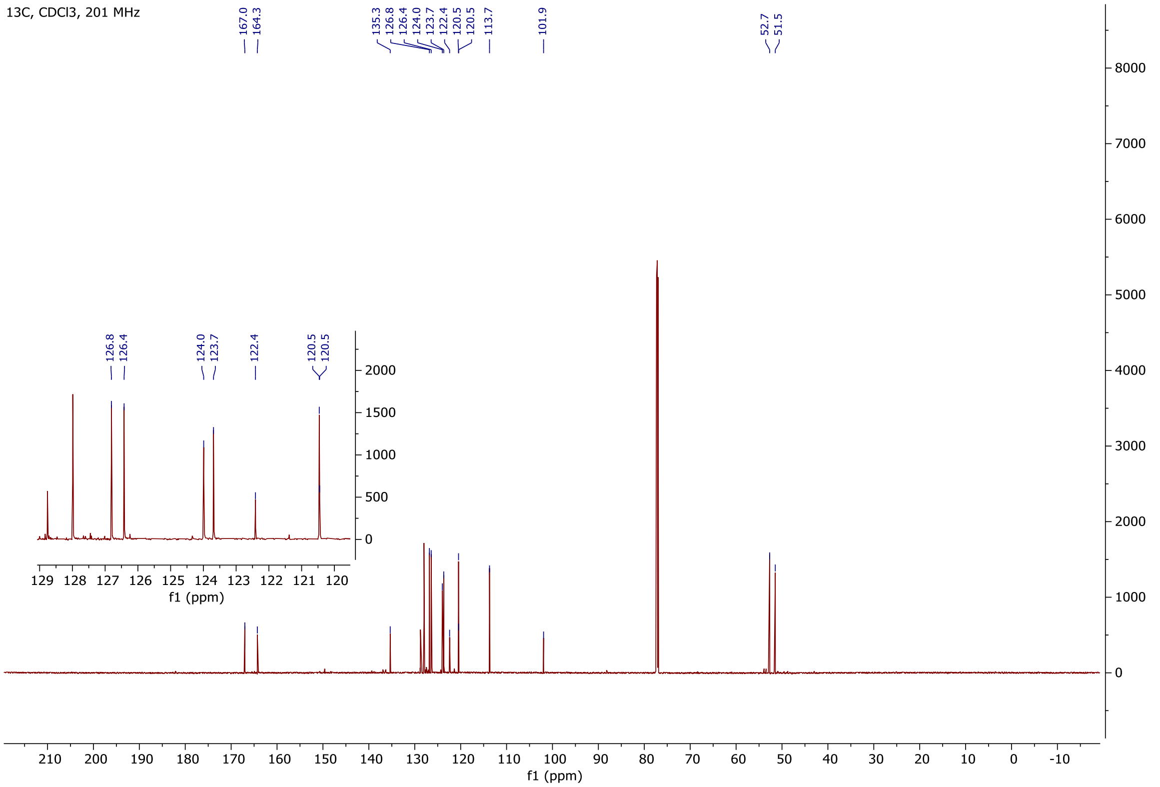
Dimethyl 3-isopropylindolizine-1,2-dicarboxylate (**2i**)



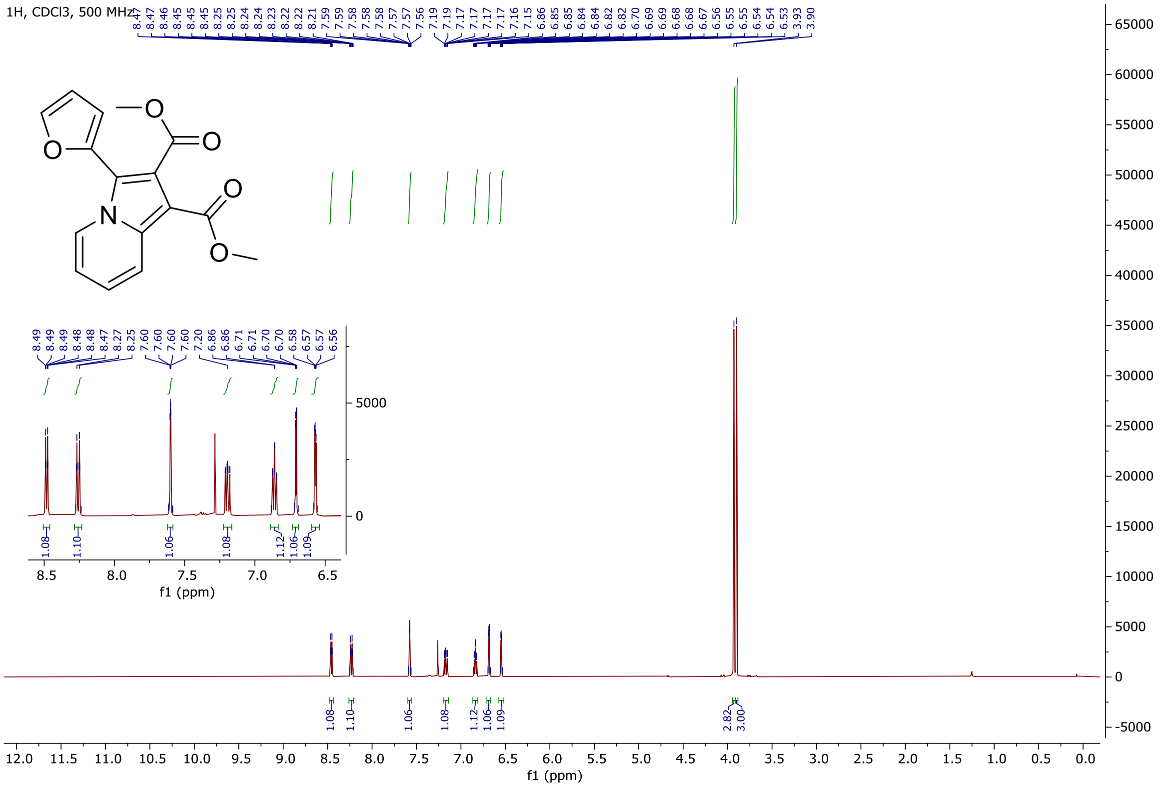


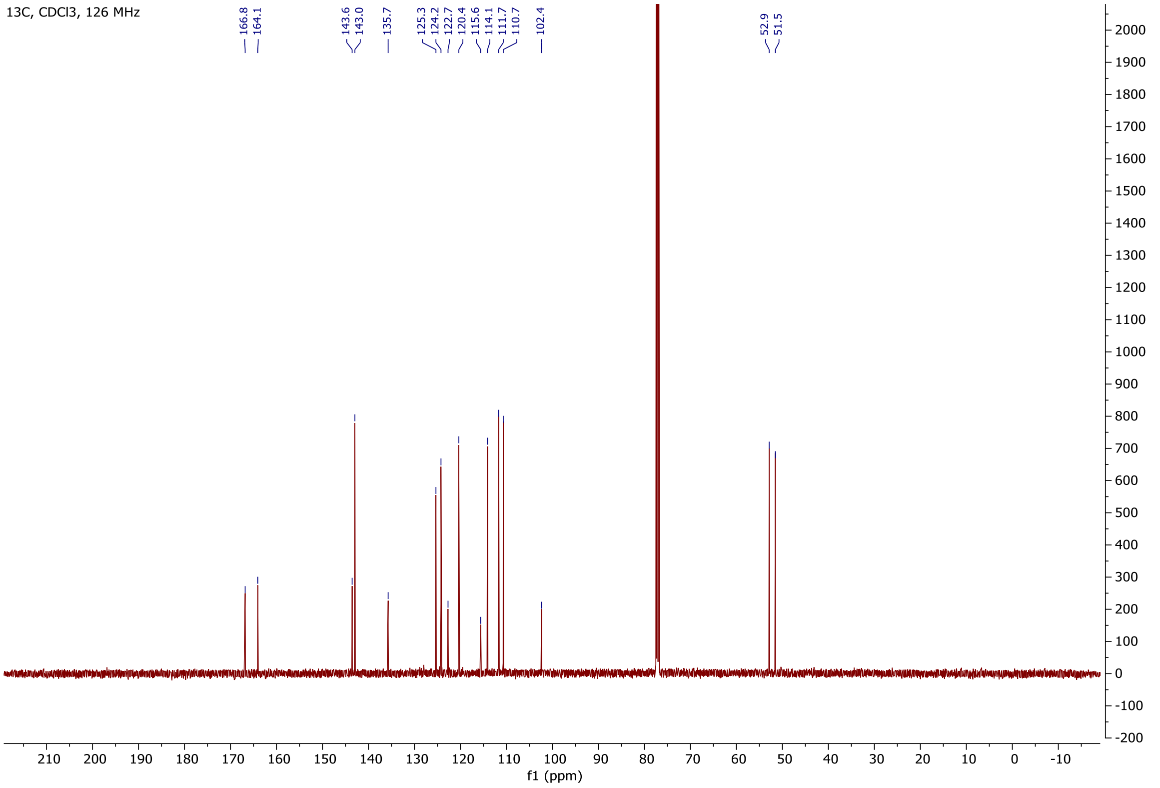
Dimethyl 3-(thiophen-3-yl)indolizine-1,2-dicarboxylate (**2j**)



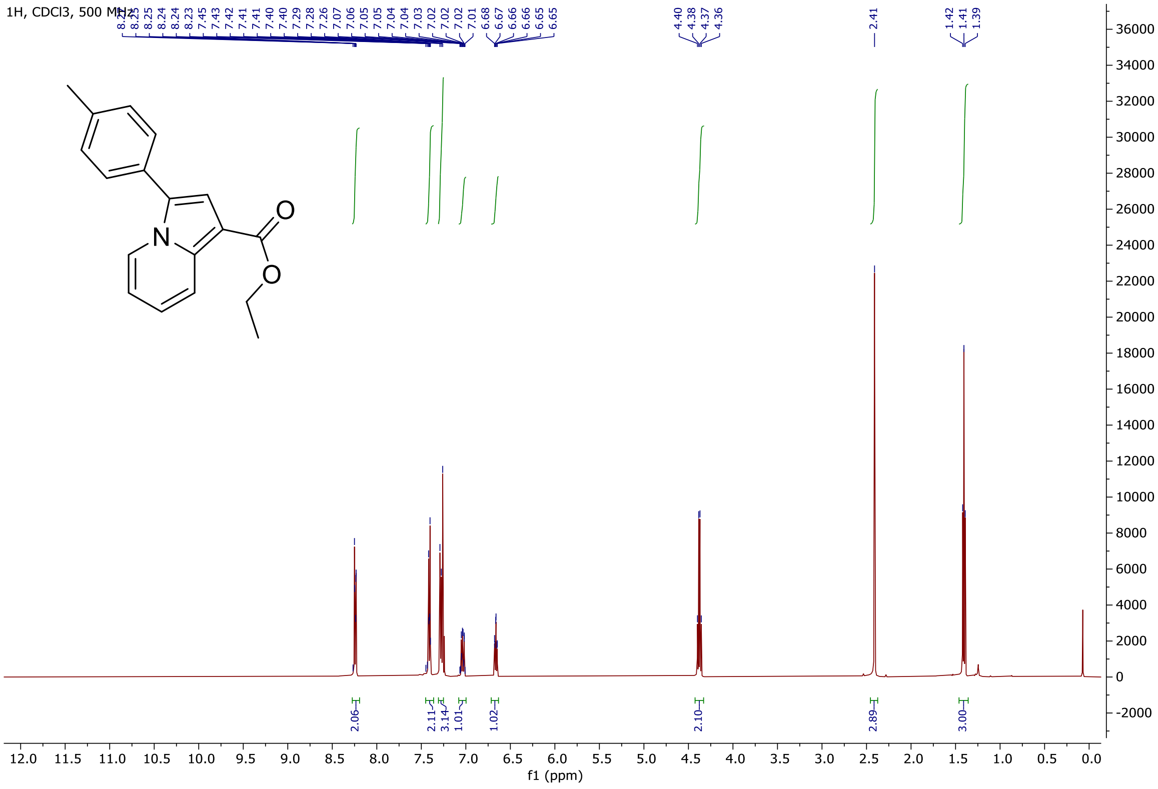


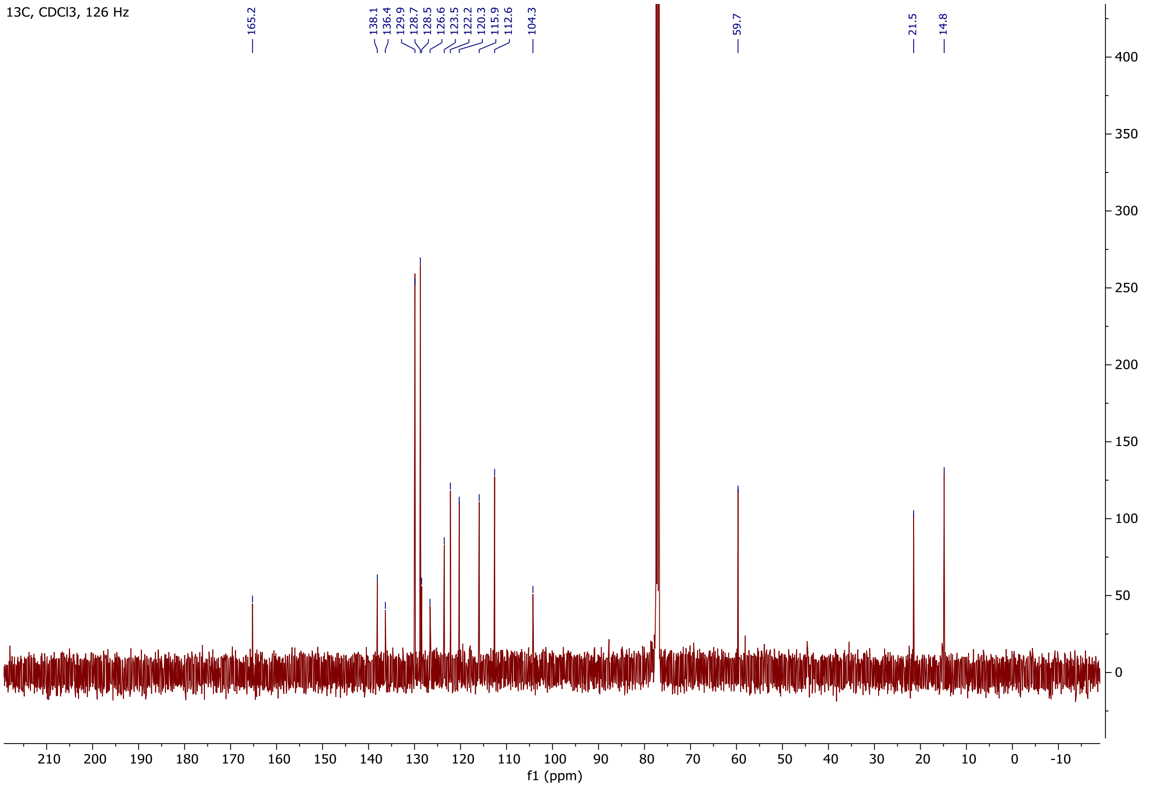
Dimethyl 3-(furan-2-yl)indolizine-1,2-dicarboxylate (**2k**)



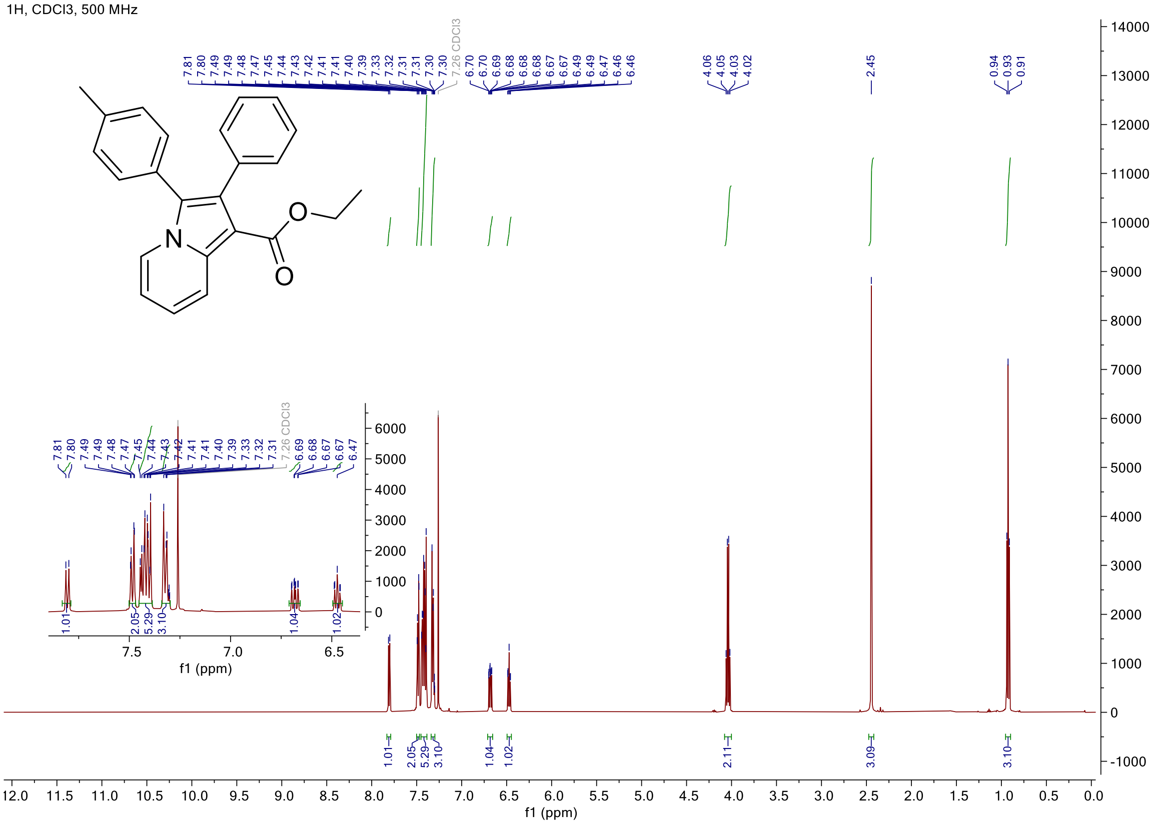


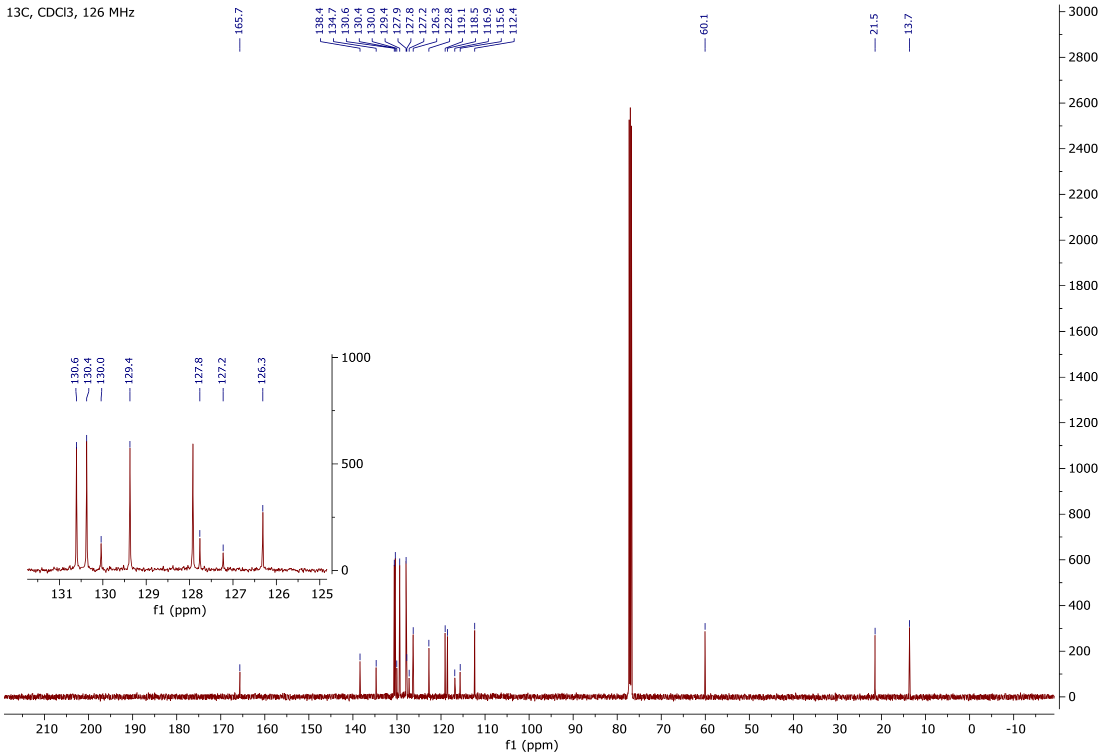
Ethyl 3-(p-tolyl)indolizine-1-carboxylate (**2l**)



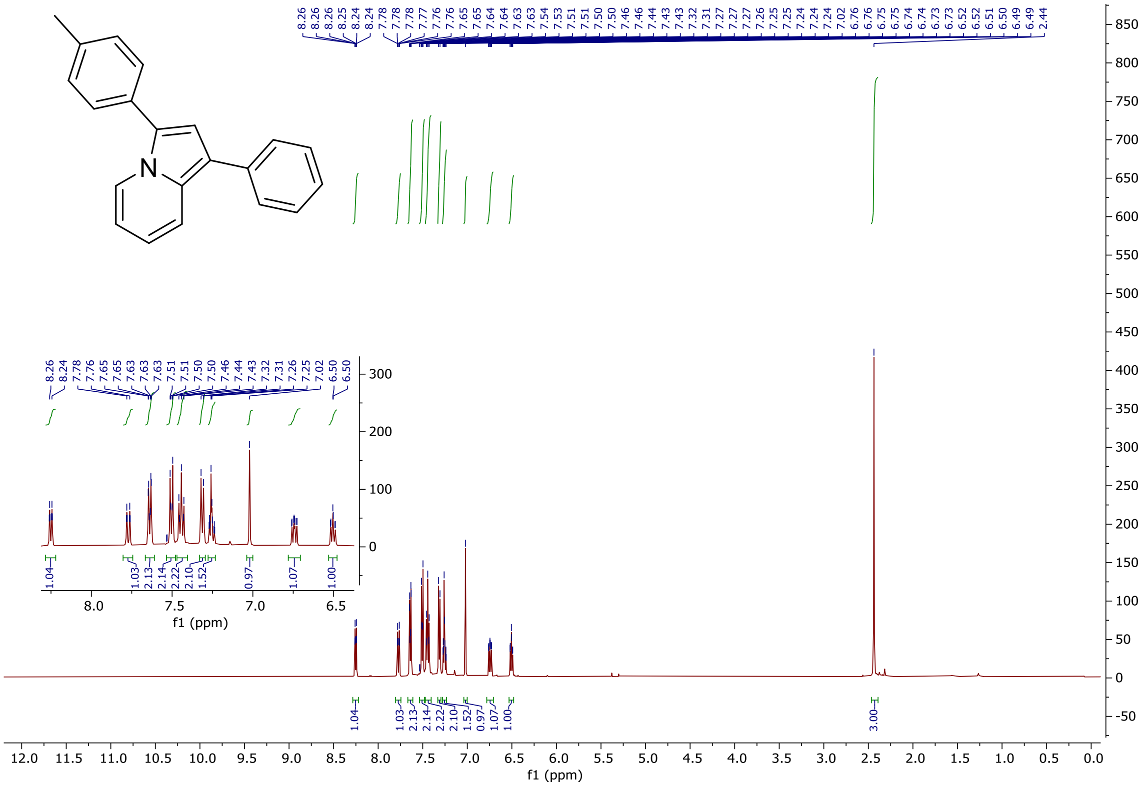


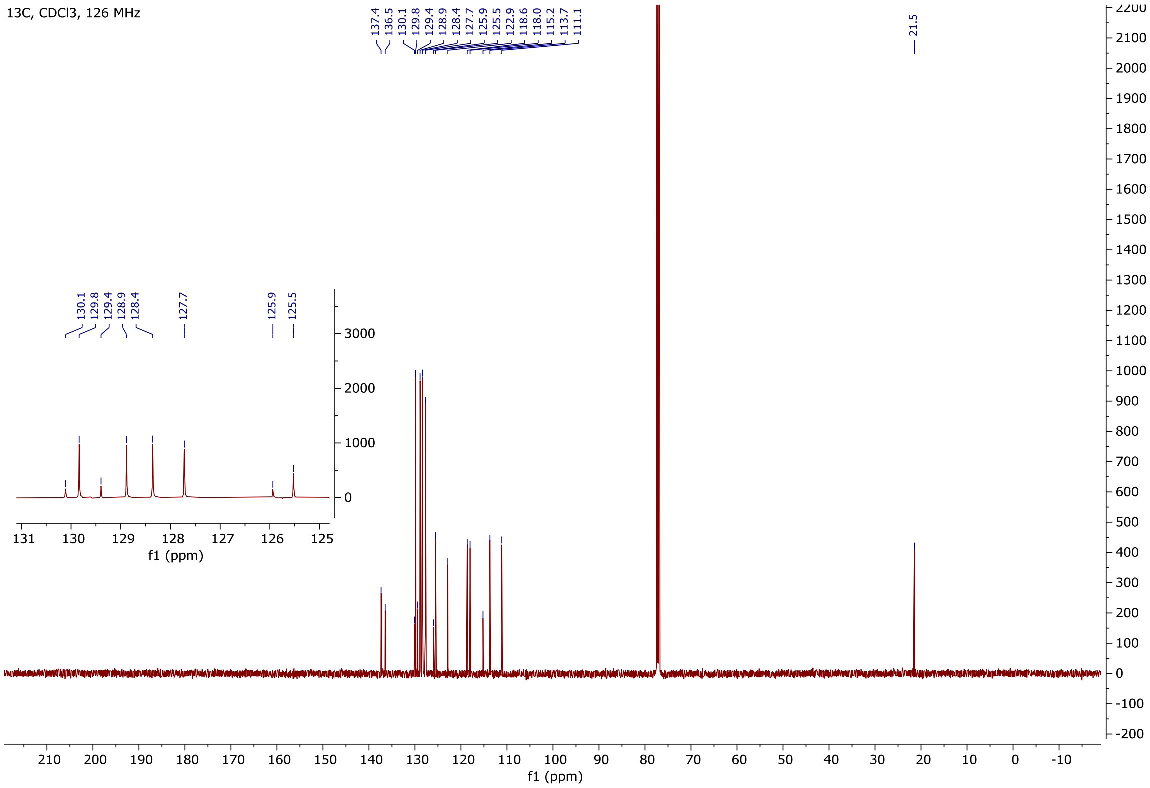
Ethyl 2-phenyl-3-(p-tolyl)indolizine-1-carboxylate (**2m**)



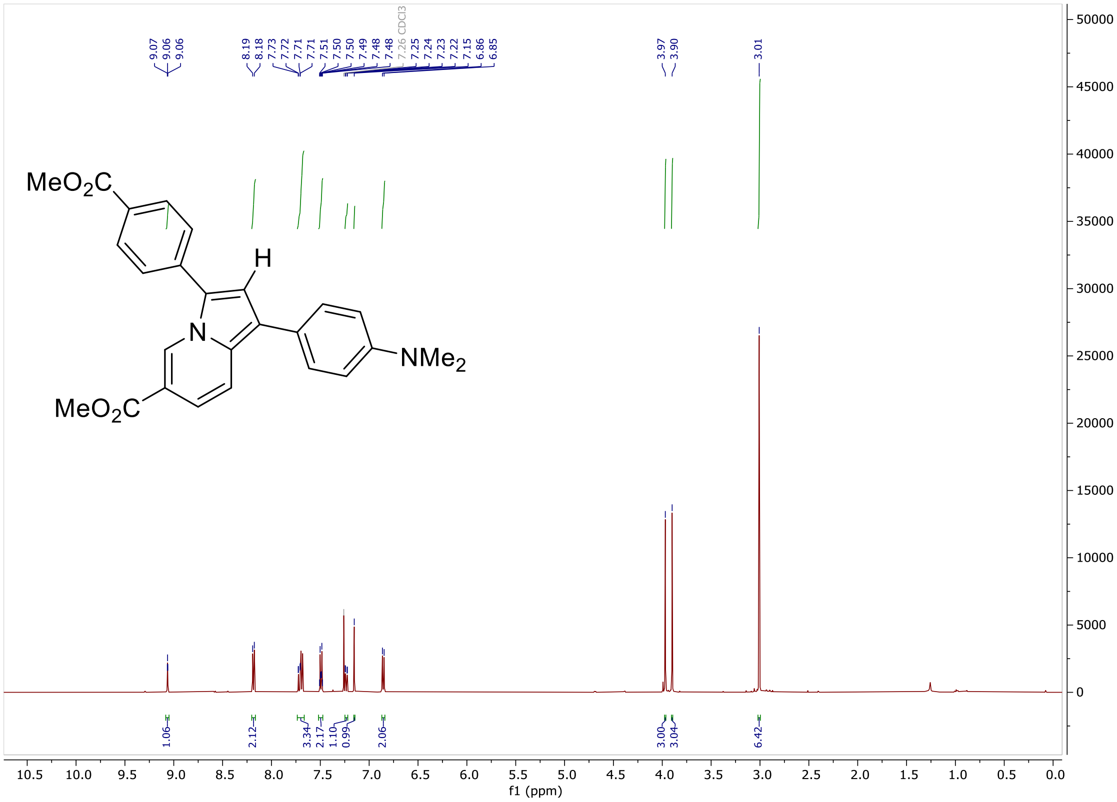


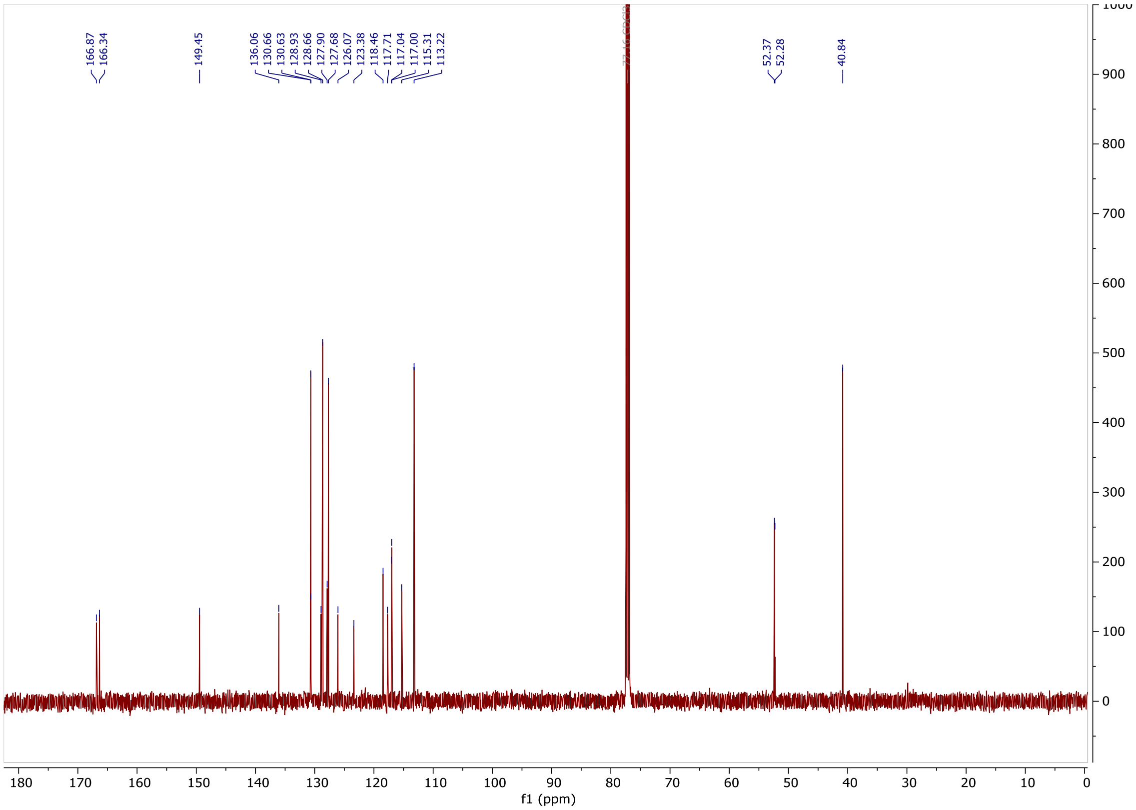
1-phenyl-3-(p-tolyl)indolizine (**2n**)



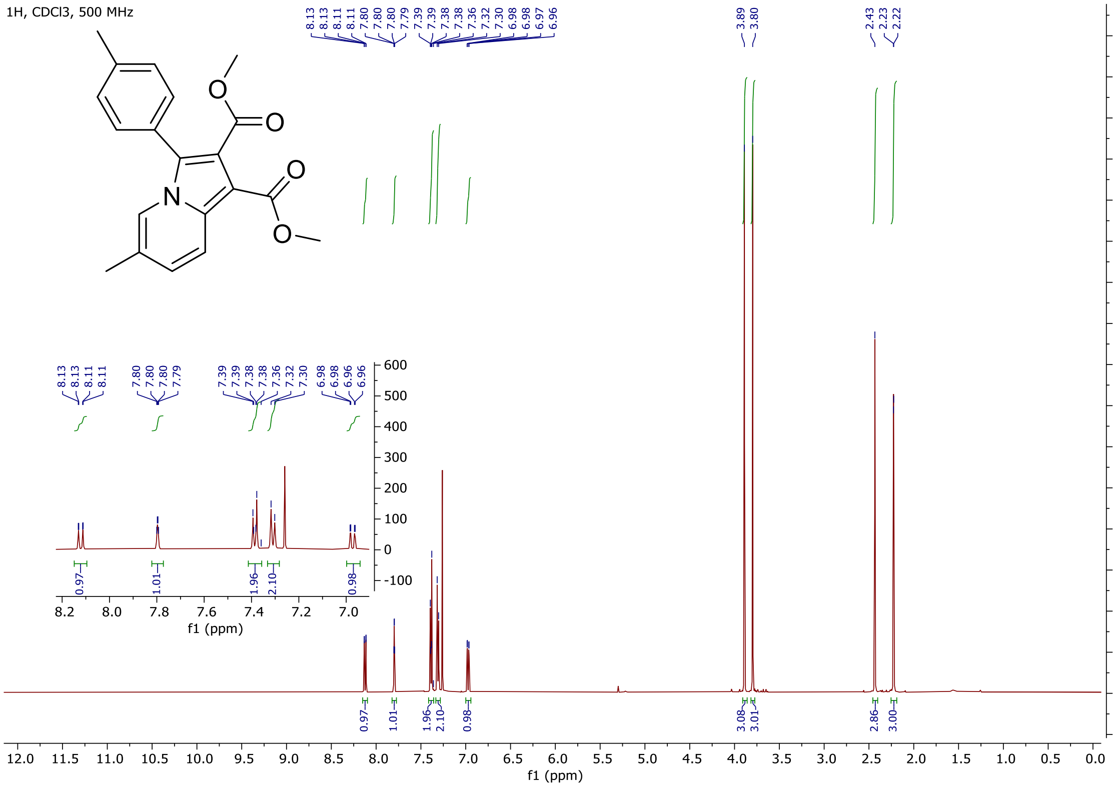


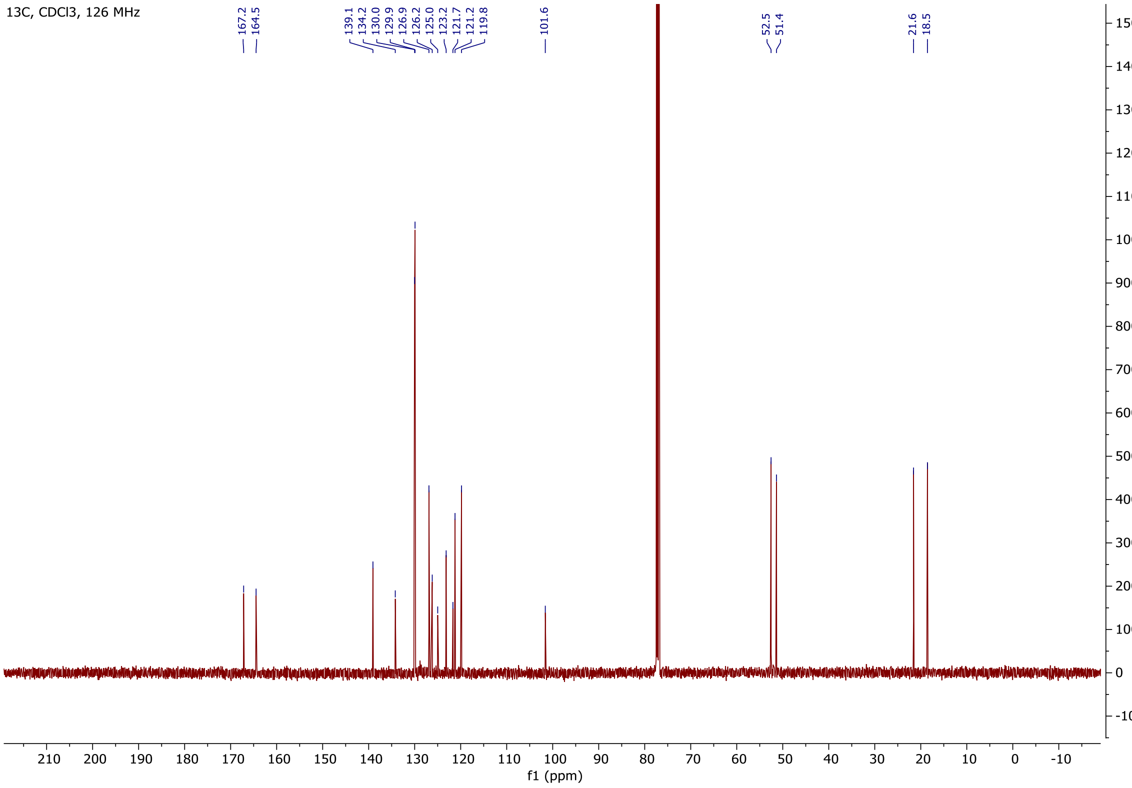
Methyl 1-(4-(dimethylamino)phenyl)-3-(4-(methoxycarbonyl)phenyl)indolizine-6-carboxylate (**2o**)



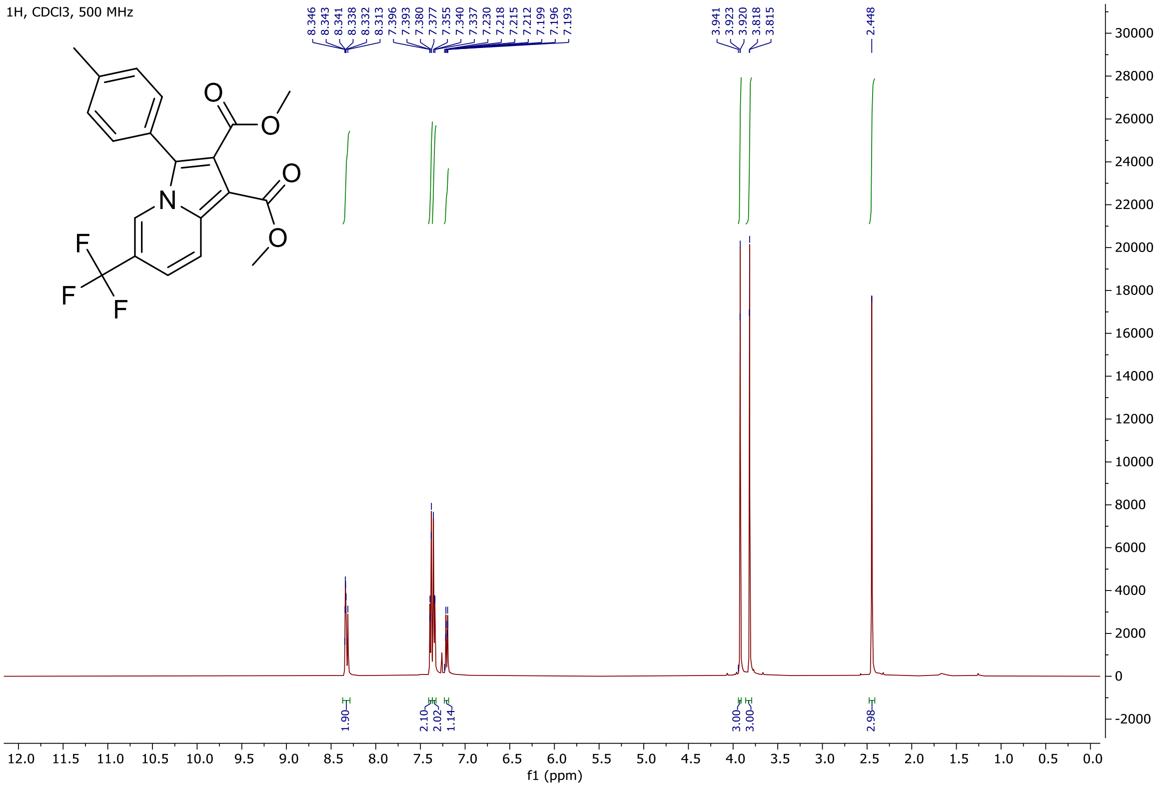


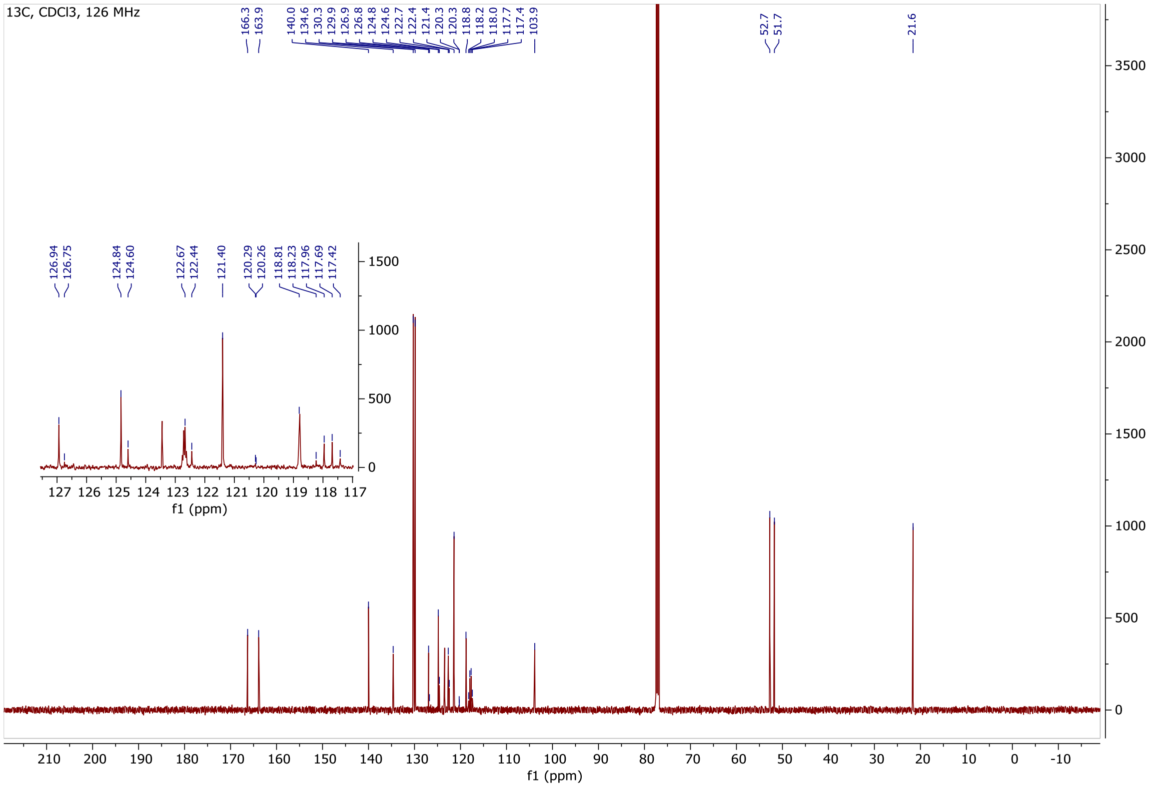
Dimethyl 6-methyl-3-(p-tolyl)indolizine-1,2-dicarboxylate (**2p**)



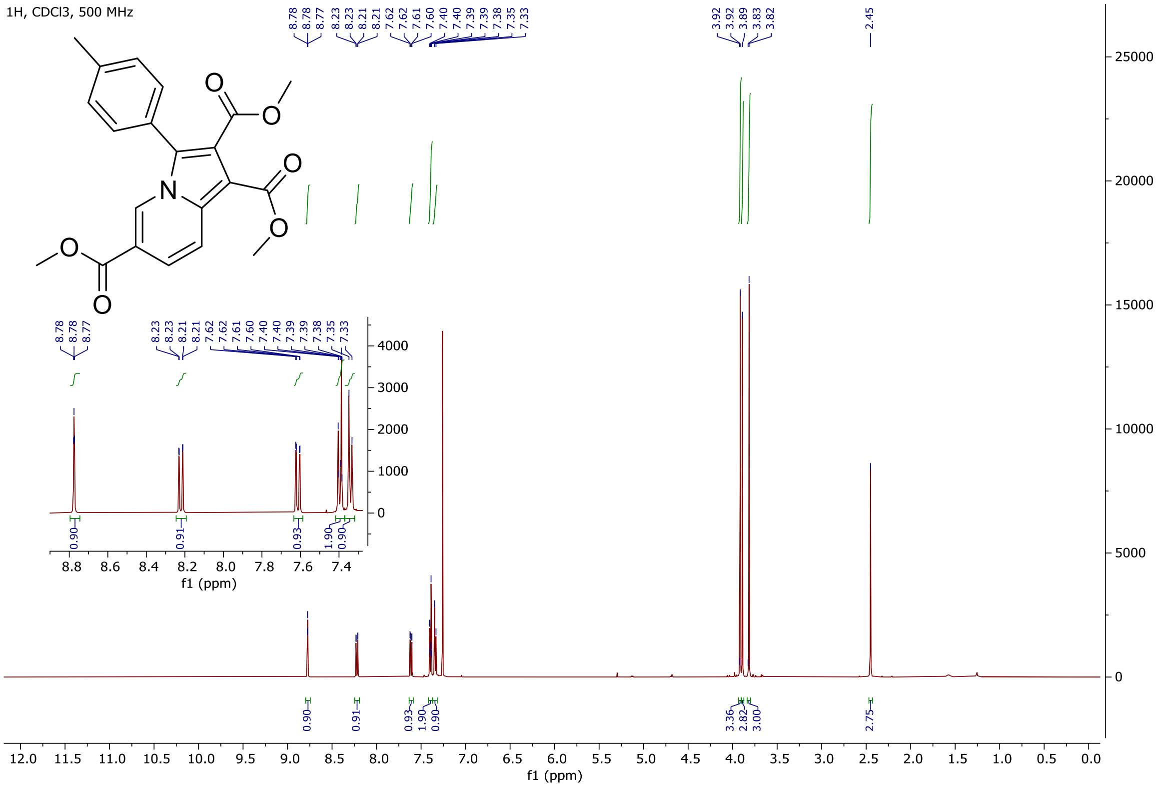


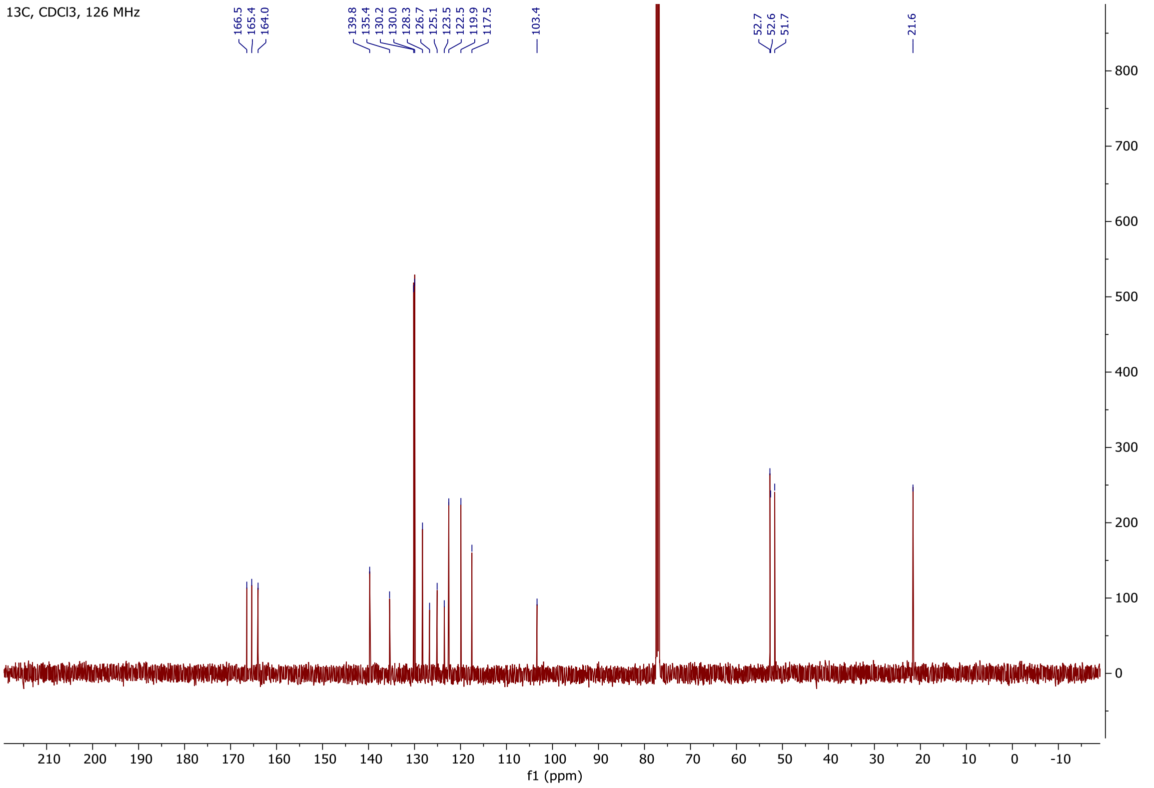
Dimethyl 3-(p-tolyl)-6-(trifluoromethyl)indolizine-1,2-dicarboxylate (**2q**)





Trimethyl 3-(p-tolyl)indolizine-1,2,6-tricarboxylate (**2r**)





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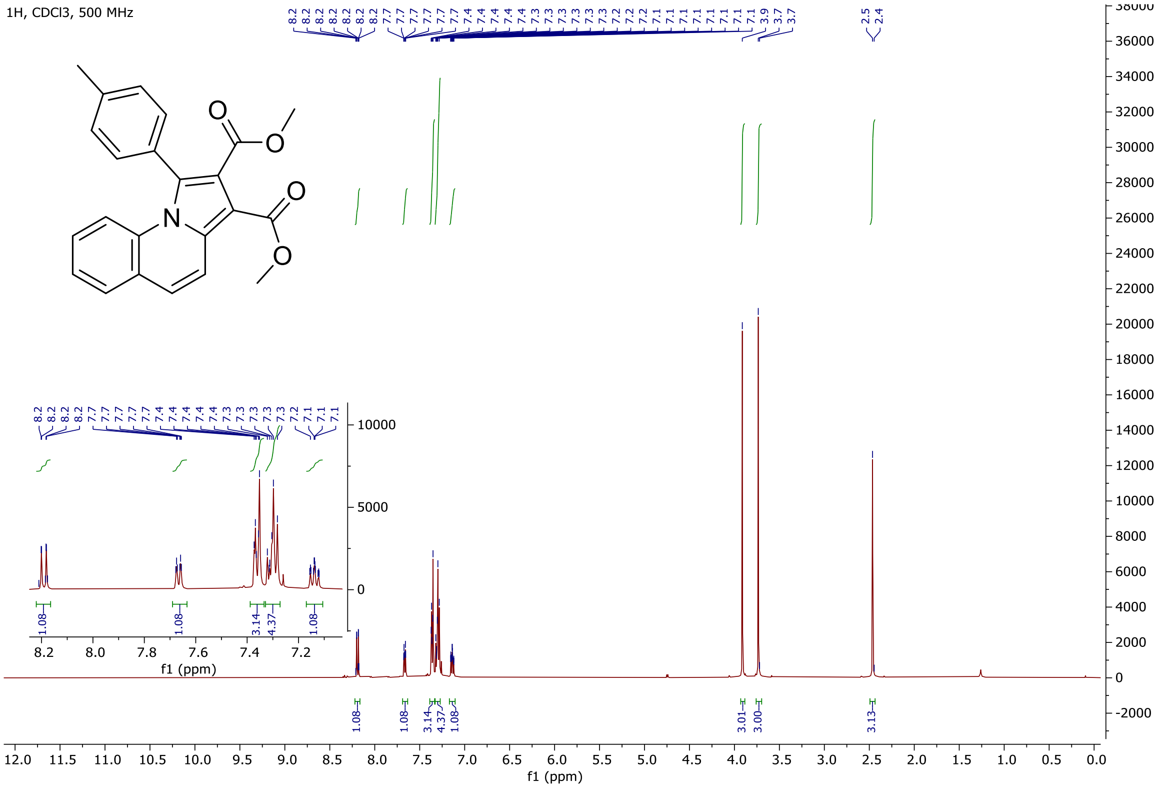

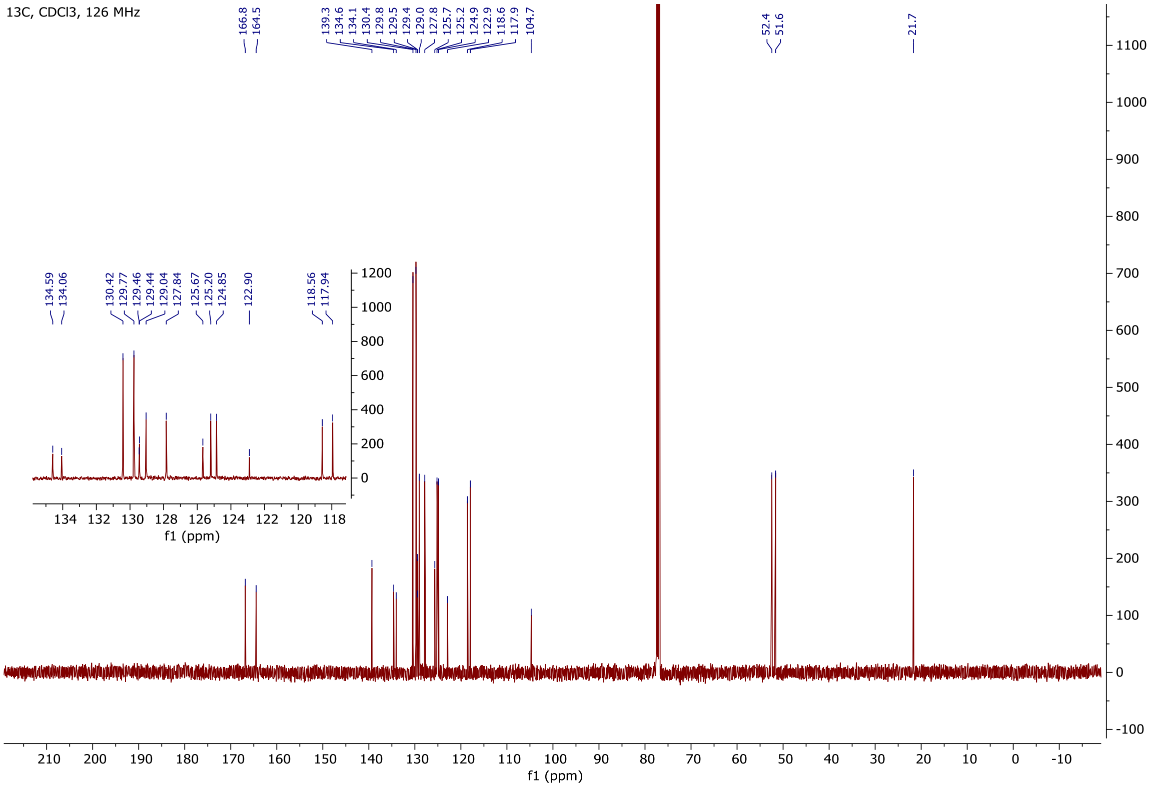

Dimethyl 8-methoxy-3-(p-tolyl)indolizine-1,2-dicarboxylate (**2t**)