Catalytic Tandem Nucleophilic Addition for the Synthesis of Heterocycles

René-Viet Nguyen

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Department of Chemistry
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To Vinh and My-Anh

Catalytic Tandem Nucleophilic Addition for the Synthesis of Heterocycles

René-Viet Nguyen – Department of Chemistry – McGill University

Abstract: Classical methodologies for carbon-carbon bond formation often require stoichiometric amount of reagent to prefunctionalize a C-H bond. Such methods generate a lot of waste and are therefore not atom-efficient. On the other hand, the use of catalysts for the direct use of C-H bond without prior functionalization is a more desirable approach for carbon-carbon formation. For example, an overall addition reaction is 100% atom economical. This thesis focuses on the catalytic addition of the three types of C-H bonds (C_{sp}-H, C_{sp}^2-H and C_{sp}^3-H) to unsaturated molecules such as conjugated dienes, imines and carbon dioxide to form heterocycles.

The first chapter describes the direct single addition of 1,3-diketones (C_{sp}^3-H bond) to conjugated dienes and enol ethers catalyzed by gold(III) chloride and silver(I) trifluoromethanesulfonate. The reaction is highly regioselective, although the overall yields are modest (up to 70%) due to the oxidative nature of the catalysts. Under certain conditions, the addition product undergoes a subsequent cyclization to form dihydrofurans. This tandem addition/cyclization reaction is catalyzed by trifluoromethanesulfonic acid and is discussed in the second part of the chapter.

The second chapter deals with the addition of phenol derivatives (C_{sp}^2-H bond) to conjugated dienes catalyzed by gold(III) chloride and silver(I) trifluoromethanesulfonate. The reaction affords dihydrobenzofurans via an

intramolecular O-H cyclization. Investigation into the sequence of the reaction shows that the C-C bond is formed before the C-O bond.

The third chapter presents the addition of terminal alkynes (C_{sp}-H bond) to imines catalyzed by cheap copper(I) iodide salt via a three-component coupling of salicylaldehyde derivatives, secondary amines and alkynes. Microwave irradiation is used which considerably shortens the reaction time and eliminate the use of solvents. Dihydrobenzofurans with an exocylic double bond are formed via an intramolecular O-H cyclization. The use of aliphatic alkynes molecules containing a heteroatom is critical to the success of the reaction.

Finally, in the last chapter, the addition of terminal alkynes (C_{sp}-H bond) to carbon dioxide (catalyzed by gold(I) chlorotriphenylphosphine and silver trifluoromethanesulfonate) is applied to the synthesis of arynaphthalene lactones via a multicomponent coupling of phenylacetylene, CO_2 and 3-bromo-1-phenyl-1-propyne.

Addition Nucléophile Catalytique en Tandem pour la Synthèse d'Hétérocycles

René-Viet Nguyen – Département de Chimie – Université McGill

Résumé : Les méthodes de la chimie organique traditionnelle pour la formation de liens carbone-carbone nécessitent, pour la plupart, une quantité stoechiométrique de réactifs pour la fonctionnalisation des liens C-H et génèrent une quantité considérable de produits secondaires. Par contre, l'addition directe de liens C-H sans préfonctionnalisation est une approche plus économique en terme d'atomes. De plus, ces additions requièrent uniquement un catalyseur et sont généralement parfaitement économique en termes d'atomes. La thématique de recherche de cette thèse se concentre sur l'addition catalytique des trois types de liens C-H (C_{sp}-H, C_{sp}^2-H et C_{sp}^3-H) sur des molécules insaturées comme des dienes conjugués, imines et dioxide de carbone.

Le premier chapitre décrit l'addition directe des 1,3-dicétones (lien C_{sp}^3-H) sur des dienes conjugués et des éthers énoliques catalysée par le trichlorure d'or et le trifluorométhanesulfonate d'argent. Bien que la réaction soit parfaitement régiosélective, les rendements sont plutôt modestes dus à la nature oxidative des catalyseurs. Sous certaines conditions, le produit d'addition cyclise et forme un dihydrofurane. Cette réaction tandem est catalysée par l'acide trifluorométhanesulfonique et est discutée dans la deuxième partie du chapitre.

Le deuxième chapitre traite de l'addition des dérivés du phénol (lien C_{sp}^2-H) sur des dienes conjugués. La réaction est catalysée par le trichlorure d'or et le trifluorométhanesulfonate d'argent et produit des dihydrobenzofuranes par le biais

d'une cyclization intramoléculaire du lien O-H. Étant une réaction tandem, la séquence de la réaction est aussi étudiée si bien que le lien C-C est formé avant le lien C-O.

Le troisième chapitre se base sur l'addition d'alcynes terminaux (lien C_{sp}-H) sur des imines pour la synthèse de dihydrobenzofuranes portant une double liaison exocyclique en couplant des dérivés de salicylaldéhydes, des amines secondaires et des alcynes. La réaction est catalysée par le iodure de cuivre. L'irradiation par ondes micro-ondes permet de diminuer considérablement le temps de réaction et élimine l'utilisation de solvant. L'utilisation d'alcynes aliphatiques contenant un hétéroatome est primordiale pour la réaction.

Finalement, dans le dernier chapitre, l'addition des alcynes terminaux (lien C_{sp}-H) sur le dioxide de carbone (catalysée par le complex du chlorotriphénylphosphine d'or et le trifluorométhanesulfonate d'argent) est appliquée à la synthèse de lactones arylnaphthaliques à partir du phénylacétylène, du CO_2 et du 3-bromo-1-phényl-1-propyne.

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Contributions of Authors

This thesis contains excerpts from 3 previously published publications. In accordance with Section C of McGill University's "Thesis Guidelines Preparation", the contribution of authors is herein described. The copyright waivers from the publishers and from the co-authors can be found in Appendix III of this thesis.

Professor Chao-Jun Li was my supervisor throughout my degree and is a co-author for each publication.

Chapter 1: I wrote the introduction. This chapter is not published.

Chapter 2, part 1: This part of the chapter contains excerpts from the journal "Organic Letters" and is reproduced with permission from: Nguyen, R.-V.; Yao, X.; Bohle, D.S.; Li, C.-J. "Gold- and Silver-Catalyzed Highly Regioselective Addition of Active Methylenes to Dienes, Triene, and Cyclic Enol Ethers" *Organic Letters* **2005**, *7*, 673-675. Copyright 2005 American Chemical Society. I performed all experiments and synthesized all compounds. Dr. Xiaoquan Yao, a research assistant in our group, provided additional help with spectroscopy analysis. Prof. D. Scott Bohle provided the crystal structure analysis of compound **50**. I wrote the publication with Prof. Chao-Jun Li.

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J. "Highly Efficient Gold-Catalyzed Atom-Economical Annulation of Phenols with Dienes" *Organic Letters* **2006**, *8*, 2397-2399. Copyright 2006 American Chemical Society. I performed all experiments and synthesized all compounds. Dr. Xiaoquan Yao, a research assistant in our group, provided additional help with spectroscopy analysis. I wrote the publication with Prof. Chao-Jun Li.

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Chapter 5: This chapter is not published. I performed all experiments and synthesized all compounds.

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Abbreviations:

+ve	positive
Ac	Acetyl
Bn	Benzyl
Bu	Butyl
C	Celsius
ca	circa
d	doublet
DCE	Dichloroethane
dd	doublet of doublet
dt	doublet of triplet
DHP	Dihydropyran
EI	Electron Ionization
ee	enantiomeric excess
e.g.	exempli gratia
ESI	Electron Spray Ionization
equiv.	equivalent
Et	Ethyl
h	hours
HRMS	High Resolution Mass Spectra
Hz	Hertz
IR	Infra – Red
^{i}Pr	isopropyl

J	Coupling constant
M	Molar
m	multiplet
Me	Methyl
MHz	Mega Hertz
mol	mole
mg	milligram
min	minutes
mL	milliliter
mmol	millimole
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Quinap	(R)-(2-Diphenylphosphino-1-naphthyl)isoquinoline
quint	quintet
Ph	Phenyl
Pinap	4-[2-(Diphenylphosphino)-1-naphthalenyl]-N-[(R)-1-phenylethyl]-1-phthalazinamine
PyBox	2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine
Rf	Retention Factor
rt	room temperature
s	singlet
sept	septuplet
t	triplet

T	Temperature
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Tetramethylsilyl
Ts	p-toluenesulfonyl
μL	microliter

Chapter 1:

An Introduction to Catalytic C-H Bond Addition

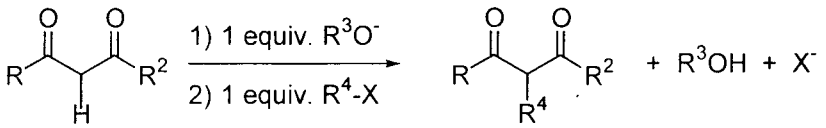
Chapter 1: An Introduction to Catalytic C-H Bond Addition

1.1 Preface

The formation of a C-C bond is the essence of organic chemistry. It allows chemists to construct simple and complex organic molecules, transforming chemical compounds into new ones. The arsenal of transformations available to chemists has dramatically expanded over the last hundred years.[1] However, many of these methodologies, although efficient, are no longer desirable due to health and environmental issue.[2] For example, hexavalent chromium-promoted oxidation reactions are now known to be very toxic.[3] To this end, over the last 15 years, chemists have developed many innovative reactions based on "atom economy", such as the overall catalytic C-H bond addition reaction. A few examples of these reactions are presented in this chapter.

1.2 Classical Methods for Carbon-Carbon Formation[4]

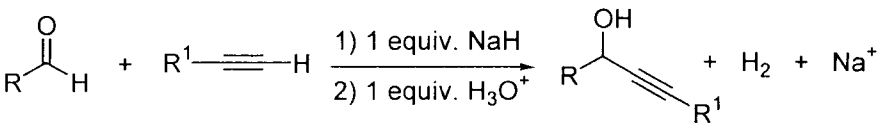
Many fundamental methodologies for carbon-carbon formation rely on activation of a carbon as its carbanion. For example, prefunctionalization of a C_{sp}^3-H bond typically requires a stoichiometric amount of base (e.g. alkoxide anion). In the alkylation of 1,3-dicarbonyl compounds **1**, such transformation is followed by the attack of the resulting carbanion to an organic halide as an electrophilic substrate to afford the alkylated product **2**.



1 **2**

Scheme 1. Alkylation of 1,3-dicarbonyls

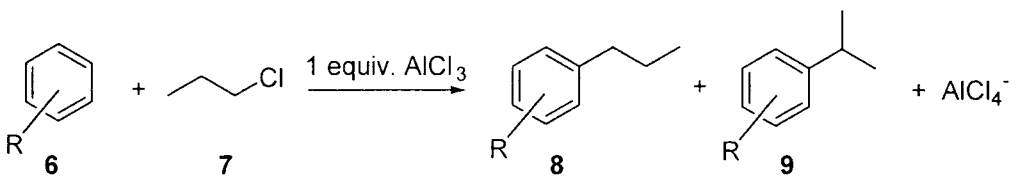
Similarly, the first step for the alkynylation of aldehydes **3** typically requires a strong base (e.g. hydride anion) to deprotonate the acetylenic proton of **4** (C_{sp}-H bond). The attack of the alkynilide to an electrophile such as an aldehyde is usually followed by an acidic workup to give propargyl alcohols **5**.



3 **4** **5**

Scheme 2. Alkynylation of aldehydes

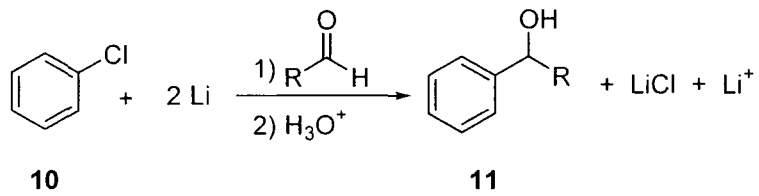
In the case of C_{sp}^2-H bonds, prefunctionalization of arenes **6** is usually not necessary. In the Friedel-Crafts reaction, the electrophile (usually an alkyl halide **7**) is activated by a stoichiometric amount of strong Lewis acid, such as $AlCl_3$ to afford a mixture of alkylated products **8** and **9**.



6 **7** **8** **9**

Scheme 3. Friedel-Crafts alkylation of arenes.

On the other hand, when the electrophile is an aldehyde or a ketone, the arene must first be functionalized as an aryl halide **10**. It can then be converted to an organolithium reagent. Subsequent attack of this reagent to the aldehyde or ketone followed by acidic workup affords the desired product **11**.



10 **11**

Scheme 4. Reaction of aryl halide **10** with aldehydes

In all these examples, the reactions generate a fair amount of by-products. They require stoichiometric amount of reagent (base or acid) which is not found in the product, resulting in waste.

1.3 The Principle of Atom Economy[5]

In 1991, Trost postulated a concept known as atom economy. It is a percentage obtained by dividing the molecular weight of the final product by the molecular weight of all stoichiometric reactants and reagents. It is independent of yield and does not account for the solvent, energy or catalyst. It does, however, help in comparing different pathways to a desired product. If all the reactants and reagents used are found in the final product, the reaction is said to be 100% atom-economical.

1.4 Catalytic C-H Bond Addition

To overcome the issues associated with the reactions listed in the first section, chemists have developed similar reactions using the C-H bond directly without prefunctionalization. These addition reactions are often catalyzed by transition metals, are highly atom-economical and generate little or no by-products.

1.4.1 Catalytic C_{sp}-H Bond Addition

Typically, terminal alkynes are used as the source of C_{sp}-H bonds. These alkynes are generally added to aldehydes or imines, generating propargyl alcohols and propargylamines respectively. These reactions, also known as alkynylation reactions, still generally require a base, albeit milder than hydrides.

1.4.1.1 Catalytic C_{sp}-H Bond Addition to Carbonyls

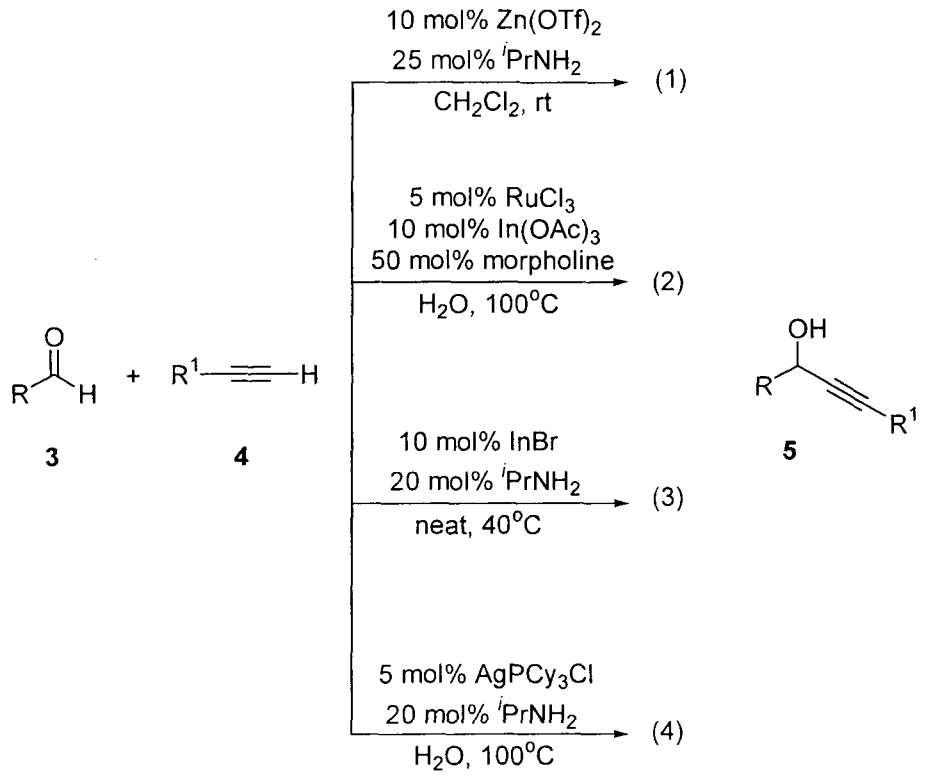
The first addition of terminal alkynes to aldehydes and ketones (without pre-formation of the alkynilide carbanion) was reported by Yamaguchi in 1991 using $Sn(OTf)_2$.[6] However, the reaction originally required stoichiometric amount of metal and mild base. In 1999, Carreira reported the first catalytic addition of alkyne **4** to aldehyde **3** for the formation of propargyl alcohol **5** using $Zn(OTf)_2$ and Hunig's base (scheme 5, eq. 1).[7] He later developed an enantioselective version of this reaction using an amino alcohol as a chiral ligand.[8] Presumably, the alkyne is activated by the zinc catalyst, while the base deprotonates the

activated alkyne. The zinc acetylide is then added to the aldehyde followed by protonation to afford the propargylic alcohol.

In 2002, Li described this reaction using a combination of $RuCl_3$ and $In(OAc)_3$.[9] In this case, morpholine was used as the catalytic base. The reaction does not occur with $RuCl_3$ or $In(OAc)_3$ alone. It is believed that ruthenium activates the alkyne while indium activates the aldehyde. While the scope is limited to phenylacetylene and the yields are modest, water is used as a solvent, a key feature of this reaction. Indeed, it was generally believed that acetylides were unstable in water (Scheme 5, eq. 2).

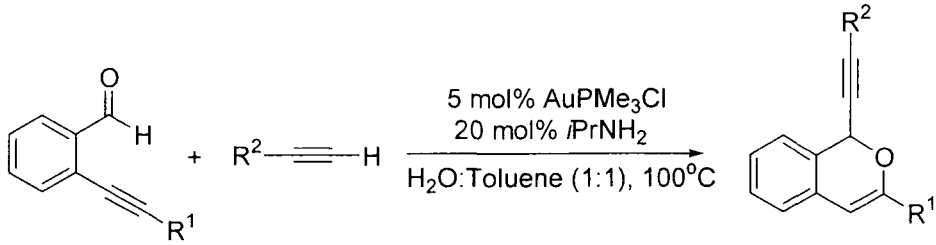
In 2005, Shibasaki proposed an interesting mechanism of the same reaction using InBr as the catalyst under neat conditions.[10] This latter can activate simultaneously both the alkyne and the aldehyde. The scope of the reaction is also broader as ketones can be used as electrophiles (Scheme 5, eq. 3).

Li was later able to increase the yield of this reaction in water by using $AgPCy_3Cl$ as the catalyst (Scheme 5, eq. 4).[11] If the reaction is performed without the phosphine ligand, the addition of alkyne to imine is observed (this reaction will be discussed in the next section).



Scheme 5. Metal-catalyzed alkynylation of aldehydes

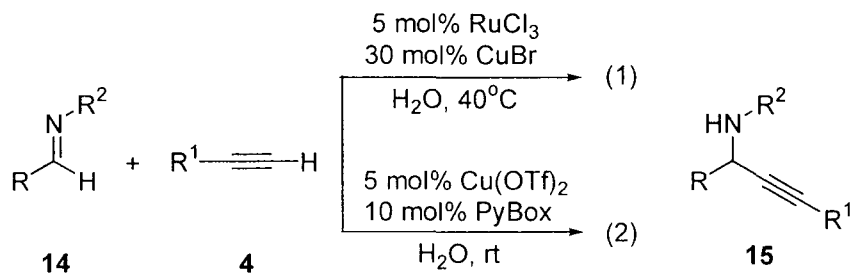
Li has also described the gold-catalyzed addition of terminal alkynes **4** to 2-ethynyl-benzaldehyde **12** (Scheme 6).[12] In this case, no reaction was observed in the absence of the ethynyl moiety. In the first step of the reaction, Au(I) acetylide complex coordinates to the triple bond and the oxygen. The terminal alkyne is then added to the aldehyde followed by cyclization. Coumarins **13** are obtained in high yields.



Scheme 6. Gold-catalyzed alkynylation of 2-ethynyl-benzaldehyde derivatives

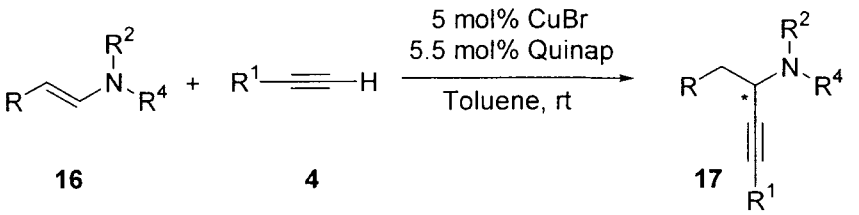
1.4.1.2 Catalytic C_{sp}-H Bond Addition to Imines

In 2001, Li reported the direct addition of terminal alkynes **4** to various imines **14** for the synthesis of propargylamines **15** catalyzed by a combination of $RuCl_3$ and CuBr (scheme 7).[13] At the same time, Carreira reported a similar iridium-catalyzed reaction. However, in his case, the terminal alkyne was limited to TMS-acetylene.[14] In 2002, Li was the first to report the enantioselective addition of terminal alkyne to imines. The combination of 5% $Cu(OTf)_2$/10% PyBox afforded various propargylamines up to 99.6% ee. This high ee reaction is limited to phenylacetylene derivatives and arylaldehydes. The imine was generated *in situ* by mixing the aldehyde and the amine for 2 h.[15]



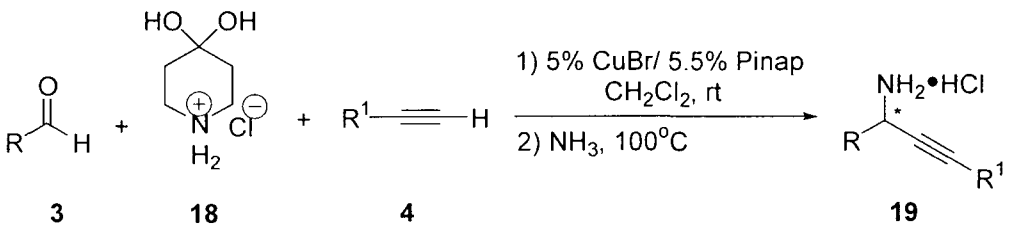
Scheme 7. Ru- and Cu-catalyzed alkynylation of imines and its enantioselective version

Following this seminal publication, many chemists started to report similar enantioselective reactions. For example, Knochel reported a highly efficient alkyne-enamine **16** addition using QUINAP as a chiral ligand to yield **17** (Scheme 8).[16]



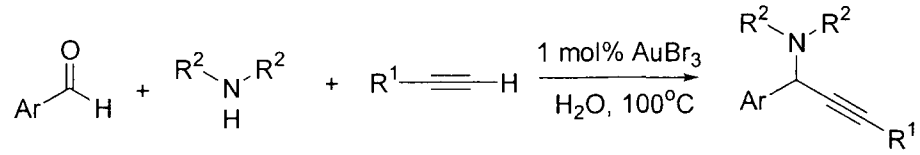
Scheme 8. Copper-catalyzed enantioselective alkynylation of enamines

Carreira also reported the use of PINAP for the synthesis of chiral primary propargylamines **19** using 4-piperidinone **18** as a protecting group (Scheme 9).[17]



Scheme 9. Copper-catalyzed enantioselective alkynylation of imines

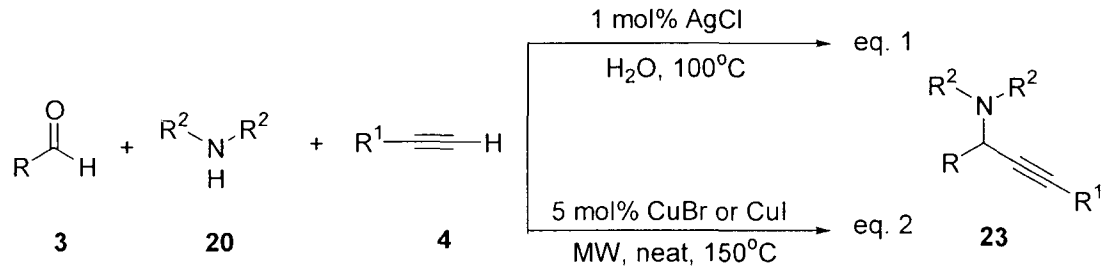
Propargylamines **22** can also be synthesized by combining the aldehyde **20**, amine **21** and alkyne **4** in a one-pot reaction. In 2003, Li was the first to publish this reaction by using $AuBr_3$ as a catalyst in water (Scheme 10).[18]



20 21 4 22

Scheme 10. Gold-catalyzed multicomponent coupling of aldehydes, amines and alkynes

The iminium and the gold acetylide species are formed *in situ*. The acetylide then adds to the iminium. Water is the only by-product for this reaction. Excellent yields can be obtained but the reaction is limited to aryl aldehydes. In an effort to expand the scope of this reaction, Li later reported the Ag-catalyzed version of this reaction. In this case, alkyl aldehydes can be used as substrates (Scheme 11).[19]



3 20 4 23

Scheme 11. Silver- and copper-catalyzed multicomponent coupling of aldehydes, amines and alkynes

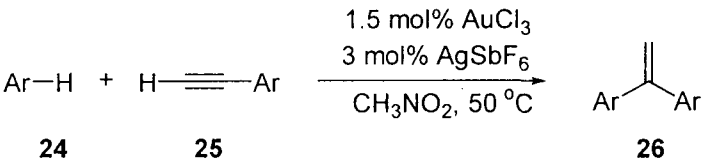
The three-component coupling generally requires high temperature and long reaction times (usually overnight). In 2004, Li and Fan were independently able to shorten the reaction and eliminate the use of solvent by carrying out the

multicomponent coupling under microwave irradiation. They found that microwave reaction at 150°C for 15 min. with 5 mol% of CuBr (or CuI) led to excellent yields of propargylamines derivatives.[20]

1.4.2 Catalytic C_{sp}^2-H Bond Addition to Double and Triple Bonds

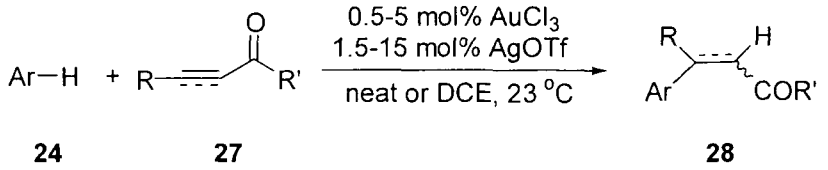
Typically, arenes (including furans and indoles) are used as the source of C_{sp}^2-H and add directly to double or triple bonds (known as the hydroarylation reaction) using catalytic amount of transition metal.

The addition of arenes **24** to terminal alkynes **25** can be catalyzed by a combination of gold and silver salts.[21] The Markovnikov product **26** was obtained exclusively while internal alkynes did not give any product (Scheme 12)



Scheme 12. Gold-catalyzed hydroarylation of alkynes

A similar reaction occurred when activated alkynes and alkenes **27** were used. In this case, a Michael-type product is formed.[22] Depending on the substrates, the reaction can be carried out under neat conditions with the product **28** forming after only 1h (Scheme 13).

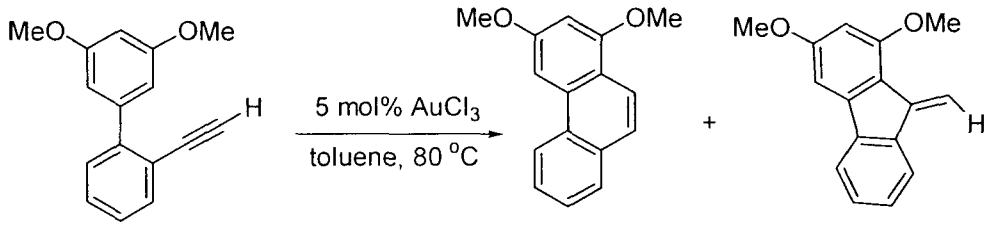


24 **27** **28**

Scheme 13. Gold-catalyzed addition of arenes to activated alkenes and alkynes

The reaction was further extended to heterocyclic arenes such as indoles and furans. The scope of the olefin substrate is fairly wide as the reaction tolerates aldehydes, ketones, esters and carboxylic acids.[23] The intramolecular variant of this reaction yields highly useful coumarin derivatives.

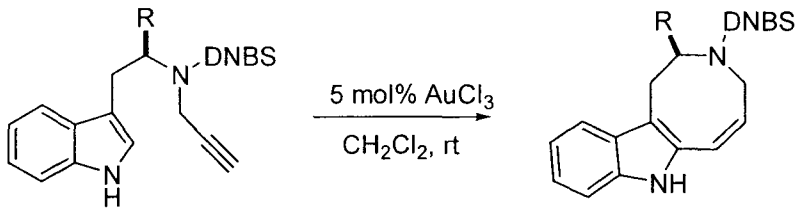
Phenanthrenes **29** can be synthesized via the intramolecular addition of arene to an alkyne moiety. The reaction highly favors the 6-endo-dig cyclization product **30**. Other metal salts, such as $InCl_3$, $GaCl_3$ and particularly $PtCl_2$ were found to be as effective as $AuCl_3$ (Scheme 14).[24]



29 **30** **31**

Scheme 14. Gold-catalyzed intramolecular hydroarylation of alkynes

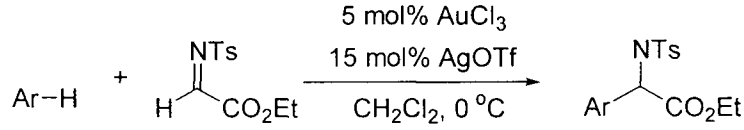
Similar intramolecular addition occurs between indoles and a tethered alkyne **32** to afford a rare 8-endo-dig cyclization **33** (Scheme 15).[25]



32 **33**

Scheme 15. Gold-catalyzed intramolecular hydroarylation of alkynes via 8-endo-dig cyclization

The intermolecular addition of arenes to imines was first described by Li in 2004 using the gold/silver system. The reaction leads to various useful amino acids derivatives **37**.[26]



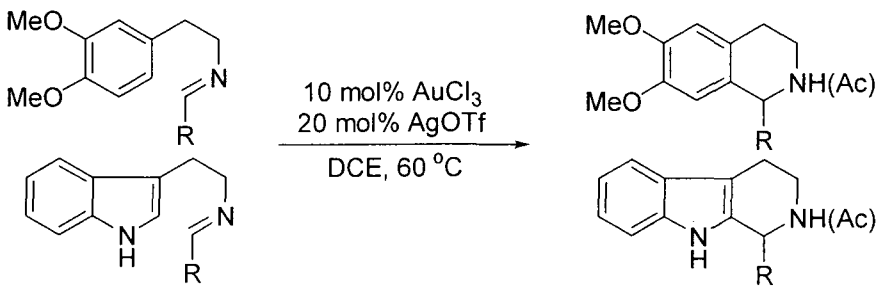
24 **34** **35**

Scheme 16. Gold-catalyzed intermolecular addition of arenes to imines

In this case, the imine **34** is pre-generated from glyoxylate and p-toluenesulfonamide. Heterocyclic arenes such as furan and thiophene can also be used (Scheme 16).

The intramolecular variant of this reaction, known as the Pictet-Spengler reaction, efficiently affords various tetrahydroisoquinoline and tetrahydro-β-carboline rings **37**.[27] When an acylating agent is used, the catalyst loading can be

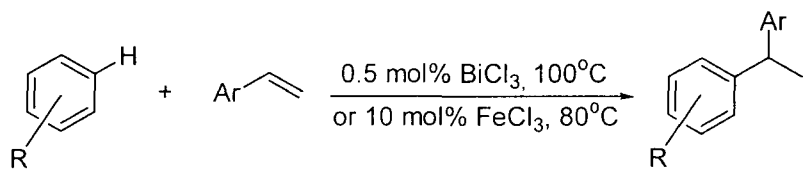
decreased to 1 mol% $AuCl_3$ and 2 mol% AgOTf without affecting the yield of the reaction (Scheme 17).



36 **37**

Scheme 17. Gold-catalyzed intramolecular addition of arenes to imines

The hydroarylation of styrenes **38** has been reported using the cheap and non-toxic $FeCl_3$ [28] or $BiCl_3$ [29] as catalyst. In both cases, good yields of the Markovnikov product **39** were obtained (Scheme 18).



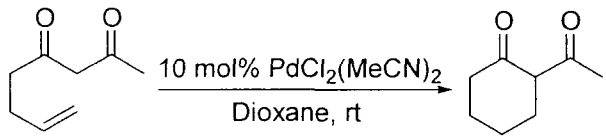
6 **38** **39**

Scheme 18. Bismuth- and iron-catalyzed hydroarylation of styrenes

1.4.3 Catalytic C_{sp}^3-H Bond Addition

The direct addition of C_{sp}^3-H bond to double or triple bonds (known as the hydroalkylation reaction) is more limited since these bonds are generally less reactive. Over the years, there has been great progress involving C_{sp}^3-H activation for the overall addition reaction.[30] Reviewing this chemistry in depth is beyond the scope of this chapter. This section will focus on the use of Lewis acid only.

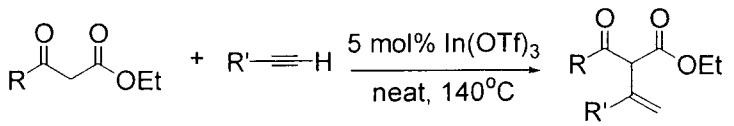
In 2001, Widenhoefer reported the intramolecular hydroalkylation of unactivated alkenes **40** using $PdCl_2(MeCN)_2$ as catalyst to afford **41** (Scheme 19).[31] The mechanism is believed to involve the attack of the activated carbon on the palladium-complexed double bond followed by a series of palladium migration and protonolysis.[32]



40 **41**

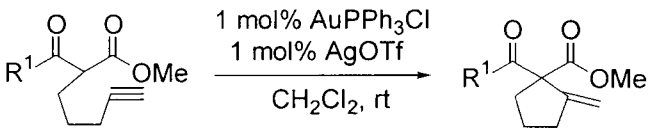
Scheme 19. Palladium-catalyzed intramolecular hydroalkylation of alkenes **40**

The intermolecular hydroalkylation of alkynes **4** by ketoesters **42** was first reported by Nakamura in 2003 (Scheme 20).[33] The catalyst, $In(OTf)_3$, has unique reactivity in this case as it presumably activates subsequently the carbonyl and the alkyne. The Markovnikov product **43** is obtained in excellent yields.



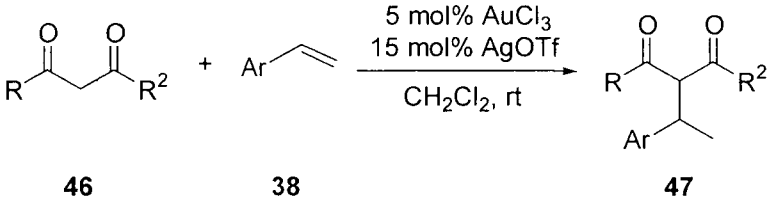
Scheme 20. In-catalyzed intermolecular hydroalkylation of alkynes **4**

Soon after, Toste reported the intramolecular hydroalkylation of unactivated alkynes **44**.[34] The reaction is believed to go through a stable chair-like transition state involving Au(I) to form **45** (Scheme 20).



Scheme 20. Gold-catalyzed intramolecular hydroalkylation of alkynes **42**

Li later reported the first intermolecular hydroalkylation of styrenes **38** by 1,3-diketones **46** catalyzed by the combination of gold and silver to afford **47**.[35] Other metal salts ($FeCl_3$[36], $BiCl_3$[37], $InCl_3$[38], $Cu(OTf)_2$[39] and Ag(OTf)[40]) were later found to catalyze this reaction.



Scheme 22. Gold- and silver-catalyzed hydroalkylation of styrenes **38**

Chapter 2:

Catalytic Addition of Activated Methylenes (C_{sp}^3-H Bond) to Midly Activated Alkenes and Application to the Synthesis of Dihydrofurans

Part 1: Gold- and Silver-Catalyzed Highly Regioselective Addition of Active Methylenes to Dienes, Triene and Cyclic Enol Ethers

Part 2: Brønsted Acid-Catalyzed Addition of Active Methylenes to Dienes for the Synthesis of Dihydrofurans

Chapter 2: Catalytic Addition of Activated Methylenes (C_{sp}^3-H Bond) to Mildly Activated Alkenes and Application to the Synthesis of Dihydrofurans

2.1 Preface

As mentioned in the last part of the introduction, Li was the first to report the intermolecular addition of activated methylenes to styrenes catalyzed by the combination of gold and silver. This reaction is 100% atom economical and provides an efficient and catalytic alternative to the commonly used stoichiometric alkylation of 1,3-dicarbonyls. Hence, the scope of such additions of alkenes other than styrenes was investigated, such as dienes, which could have potential synthetic applications. Indeed, a large class of synthetically important compounds is carbocycles and heterocycles.[41] In part 1 of this chapter, the catalytic addition of activated methylenes (C_{sp}^3-H bond) to midly activated alkenes is reported. Application of this reaction to the synthesis of dihydrofurans is discussed in part 2.

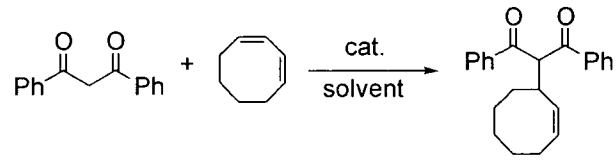
Part 1: Gold- and Silver-Catalyzed Highly Regioselective Addition of Active Methylenes to Dienes, Triene and Cyclic Enol Ethers

2.2 Optimization of the Synthesis

The addition of dibenzoylmethane **48** to 1,3-cyclooctadiene **49** was chosen as the prototype reaction (Table 1). When the reaction was performed in dichloromethane at room temperature using a combination of 5 mol% $AuCl_3$ and 15 mol% AgOTf, product **50** was obtained as a single isomer in 61% isolated yield. The position of the double bond was confirmed by X-ray crystallography analysis (Figure 1). Gold(I) triphenylphosphine complex proved to be ineffective for this transformation and gold(I) cyanide was unsoluble in the solvent (Table 1, entries 2 and 4) while the use of $AuBr_3$ and AgOTf led to a lower yield (Table 1, entry 3). There is no increase in yield when the reaction was conducted at higher temperature with various solvents (Table 1, entries 7-10). The use of a more coordinating solvent decreased the yield dramatically (Table 1, entry 8). It should also be noted that the use of $AuCl_3$ and AgOTf alone did not give any conversion of the starting material at all. Thus, the use of $AuCl_3$ and AgOTf in CH_2Cl_2 at

room temperature was found to be most efficient and was used as the standard conditions. The reaction was run for 16 h.

Table 1. Addition of Dibenzoylmethane to 1,3-Cyclooctadiene



48 **49** **50**

entry[a]	cat[b]	solvent, T°C	yield(%)[c]
1	$AuCl_3$/AgOTf	CH_2Cl_2, 25	61
2	$(PPh_3)AuCl$/AgOTf	CH_2Cl_2, 25	trace
3	$AuBr_3$/AgOTf	CH_2Cl_2, 25	55
4	AuCN	CH_2Cl_2, 25	trace
5	$AuCl_3$	CH_2Cl_2, 25	0
6	AgOTf	CH_2Cl_2, 25	0
7	$AuCl_3$/AgOTf	DCE, 80	38
8	$AuCl_3$/AgOTf	MeCN, 80	25
9	$AuCl_3$/AgOTf	$MeNO_2$, 90	55
10	$AuCl_3$/AgOTf	Dioxane, 100	26

[a] Reactions were run with 2 equiv. of diene. [b] 5 mol% Au salt, 15 mol% Ag salt. [c] Isolated yield.

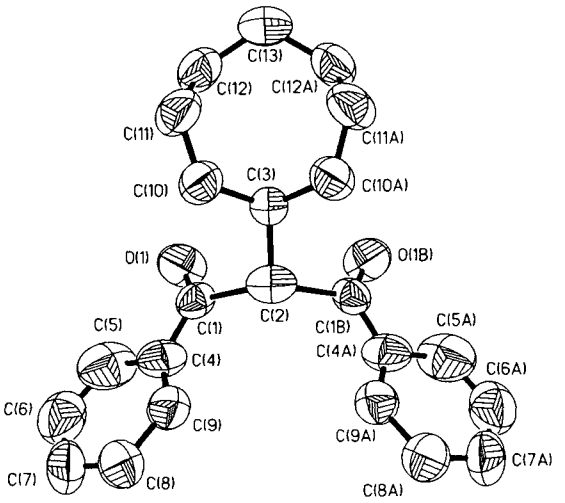


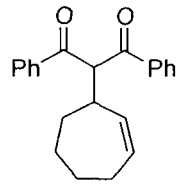
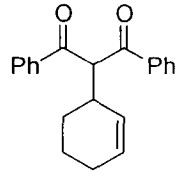
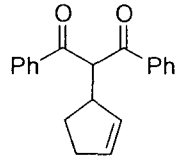
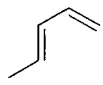
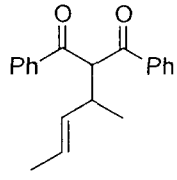
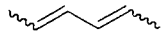
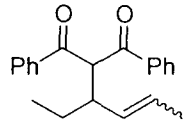
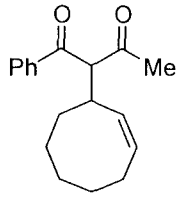
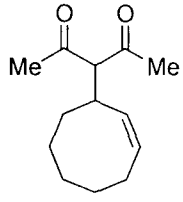
Figure 1. X-ray Structure for Compound **50**

2.3 Scope and Limitations of the Addition Reaction

Subsequently, various dienes were reacted with dibenzoylmethane, 1-benzoylacetone **51** and 2,4-pentanedione **52** under the standard conditions (Table 2). We were able to use only 1.2 equivalent of the diene by using a syringe pump. This prevents dimerization of the diene without hampering the yield of the reaction (Table 2, entry 1). The reaction must be carried out under low temperature in some cases in order to prevent polymerization or dimerization of the diene (Table 2, entries 3 and 4). The use of acyclic 1,3-dienes is also effective (Table 2, entries 5 and 6) while the use of simple cyclic and acylic alkenes did not afford any conversion of the starting material. The use of 1-benzoylacetone and 2,4-pentanedione (Table 2, entres 7 and 8) led to lower conversion under the present conditions while β-keto-esters did not show any reactivity. The use of cyclic alkenes bearing a heteroatom (Table 3) is also selective. However, addition

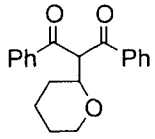
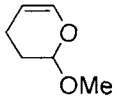
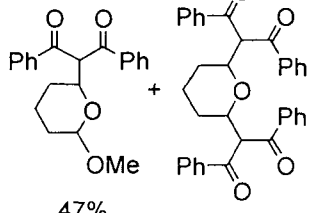
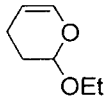
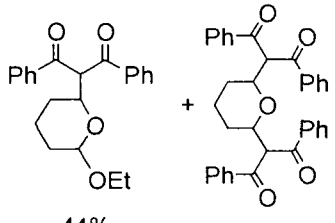
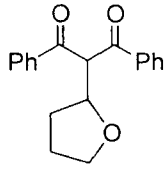
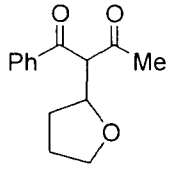
of dibenzoylmethane to an ether-substituted DHP (Table 3, entries 2 and 3) led to a significant amount of bis-alkylation products. All reactions were run for 16 h.

Table 2. Gold-Catalyzed Addition of 1,3-Diketones to Dienes

entry[a]	1,3-diketone	diene[b]	product	isolated yield (%)
1	**48**	**49**	**50**	65
2	**48**			61
3[c]	**48**			51
4[d]	**48**			50
5	**48**			66
6	**48**			67
7	**51**	**49**		38 (1.4:1)[e]
8	**52**	**49**		11

[a] Reactions were run in dry dichloromethane. [b] Dienes were added by syringe pump. [c] Reaction was run at 0°C. [d] Reaction was run at -78°C. [e] The ratio of two diastereoisomers was determined by ^1H NMR.

Table 3. Gold-Catalyzed Addition of 1,3-Diketones to Cyclic Enol Ethers

entry[a]	1,3-diketone	cyclic enol ether	product	isolated yield (%)
1	**48**			68
2	**48**		 47% (1.7:1)[b] + 15%	62
3	**48**		 44% (1.8:1)[b] + 15%	59
4	**48**			58
5	**51**			35[b] (1.2:1)

[a] Reactions were performed in dry dichloromethane. [b] The ratio of two diastereoisomers was determined by ^{1}H NMR.

2.4 Studies into the Deactivation of the Catalyst

Poor conversion of the starting material is the main reason for the low yields. Initially, the deactivation of the catalyst was hypothesized as the source of low conversions. The progress of the reaction was therefore monitored every hour by ^{1}H-NMR (Figure 2).

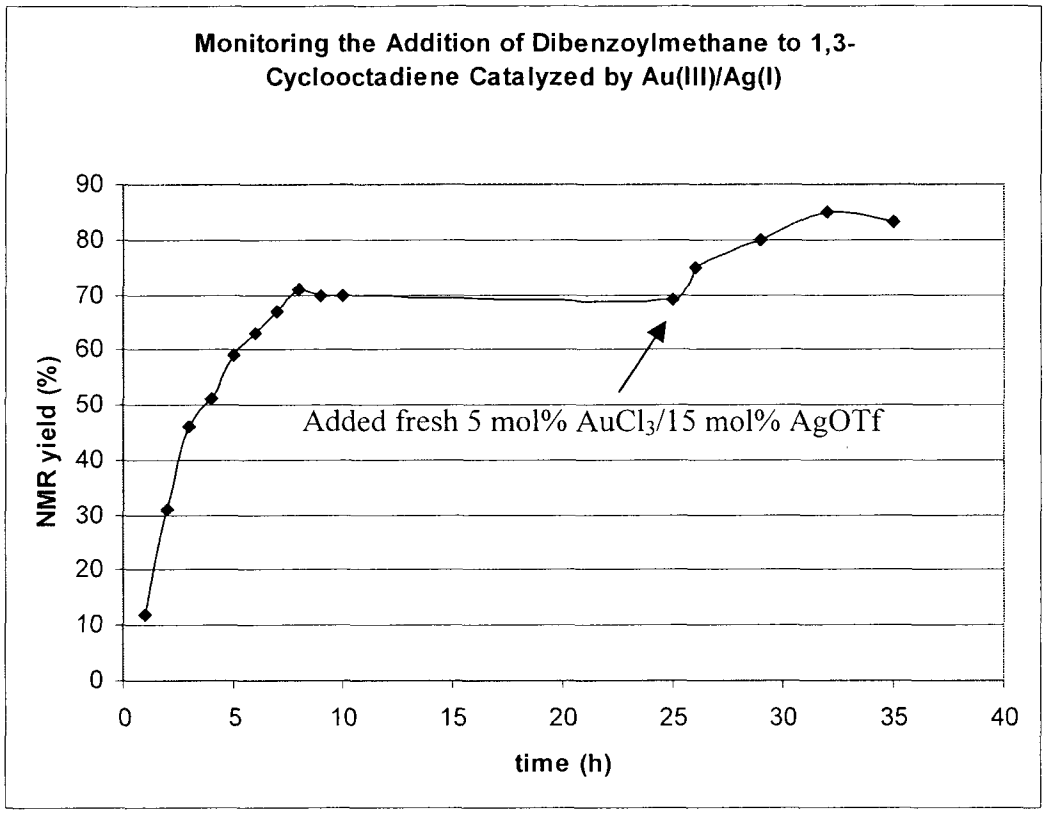
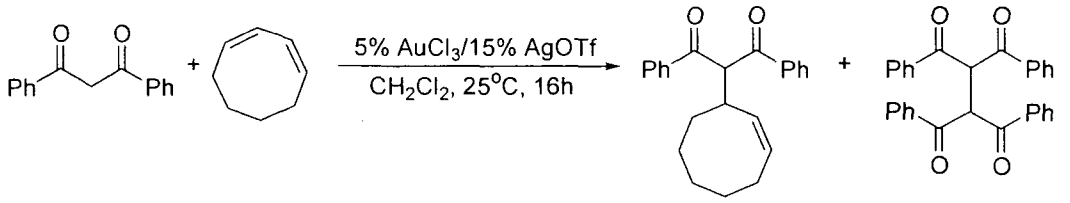


Figure 2. Monitoring the Addition of Dibenzoylmethane to 1,3-Cyclooctadiene Catalyzed by Au(III)/Ag(I)

Over the first 5 hours, the reaction seems to generate the desired product steadily. It then slows down and stops completely at 8 hours affording 70% NMR yield. Letting the reaction run overnight did not afford more desired product. As the two starting materials were still in the crude mixture (as seen by TLC), a fresh mixture

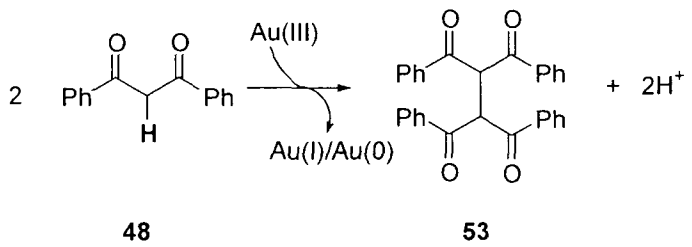
of 5 mol% $AuCl_3$/15 mol% AgOTf was added to the reaction at 25 h. The addition then resumes affording 85% NMR yield after an extra 10 h. This result seems to indicate that the catalyst is deactivated during the course of the reaction.

The source and nature of this deactivation can be explained through the observation of by-product **53** of the addition reaction.



Scheme 23. Observation of by-product **53**

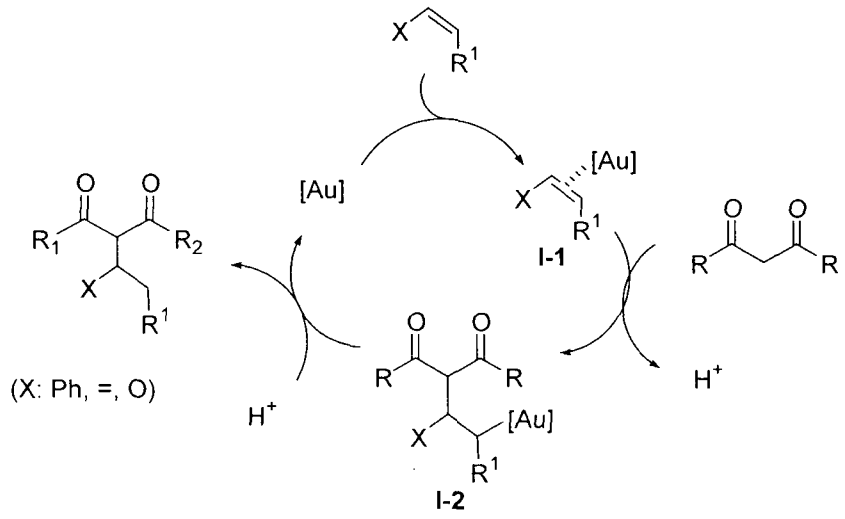
Gold(III), known to be a strong oxidant[42], oxidizes dibenzoylmethane **48** and is therefore reduced to gold(I), which eventually decomposes to gold(0). This form of gold is inactive towards catalytic reactions (Scheme 24).



Scheme 24. Oxidation of dibenzoylmethane **48**

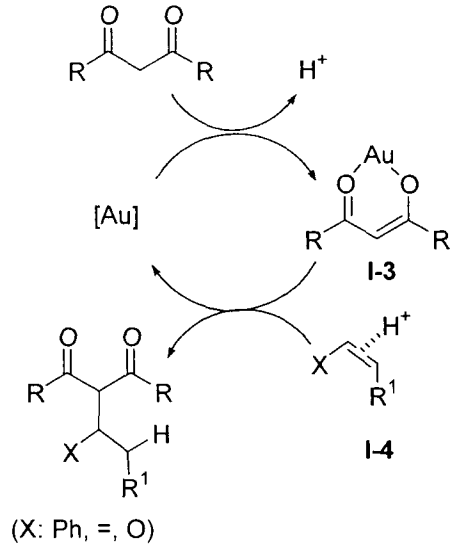
2.5 Proposed Mechanisms

There are two possible mechanisms for this reaction, both involving Au(III) acting as a Lewis acid. In the first (scheme 25), the coordination of electron-rich alkenes with Au(III) activates the double bond **I-1** which is followed by the addition of the 1,3-diketone generating gold intermediate **I-2**. Protonolysis of the C-Au bond affords the final product.



Scheme 25. Proposed mechanism for the addition of 1,3 diketones to alkenes I

Alternatively, Au(III) can coordinate to the 1,3-diketone[43] (scheme 26) generating **I-3**. This liberates a proton which can activate the electron-rich alkene **I-4**. The collapse of these two species then affords the addition product.

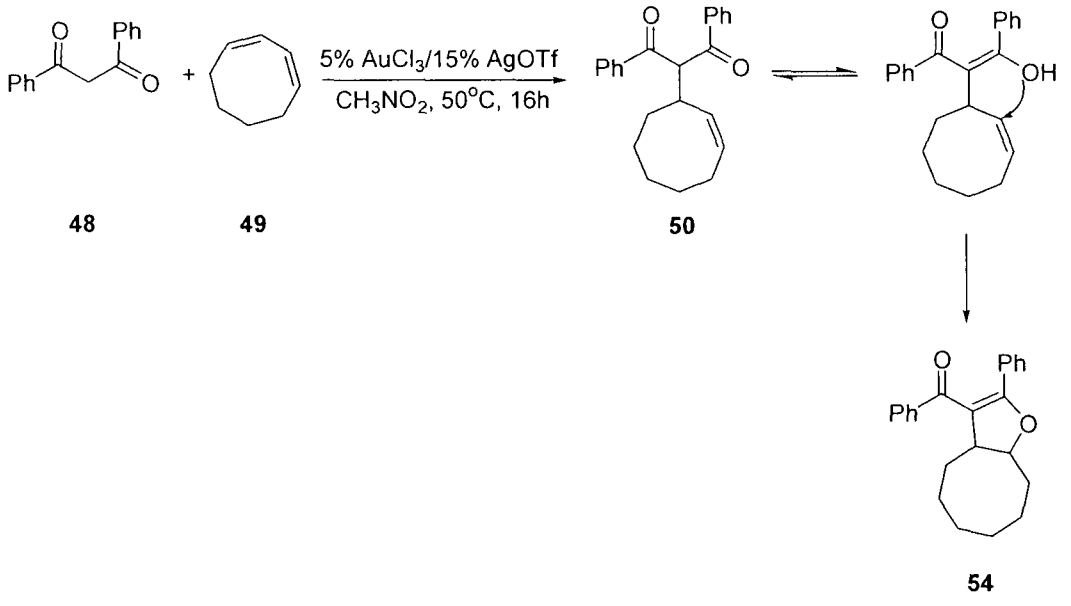


Scheme 26. Proposed mechanism for the addition of 1,3-diketones to alkenes II

Part 2: Brønsted Acid-Catalyzed Addition of Active Methylenes to Dienes for the Synthesis of Dihydrofurans

2.6 Optimization of the Synthesis I

During the optimization of the addition of dibenzoylmethane to 1,3-cyclooctadiene in Part 1, an interesting cyclized product **54** was observed under certain conditions (ratio **50**:**54** = 10:1). The formation of this cyclized product is easy to rationalize. The single addition product is in equilibrium to its enol form, due to the highly acidic α-proton. The resulting O-H bond can add intramolecularly to the remaining double bond, affording dihydrofuran **54** (Scheme 27).



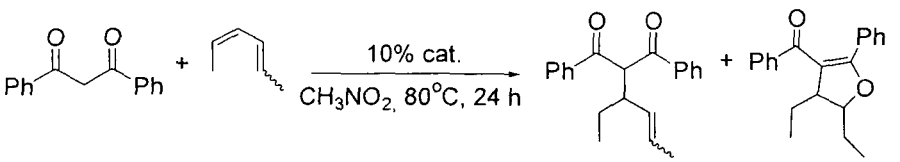
48 **49** **50** **54**

Scheme 27. Observation and rationale for the formation of by-product **54**

Initially, it was hypothesized that under high temperature and acidic solvent, the equilibrium of the single addition product could be pushed to its enol

form, favoring the cyclization step. To this end, many different Lewis acids were tested using the addition of dibenzoylmethane to 2,4-hexadiene (using a syringe pump) as the prototype reaction in nitromethane at 80°C. While many Lewis acids were effective for the single addition product (Table 4, entries 3-8), only trace amount of the cyclized product was observed.

Table 4. Addition of Dibenzoylmethane to 2,4-hexadiene with Various Catalysts I



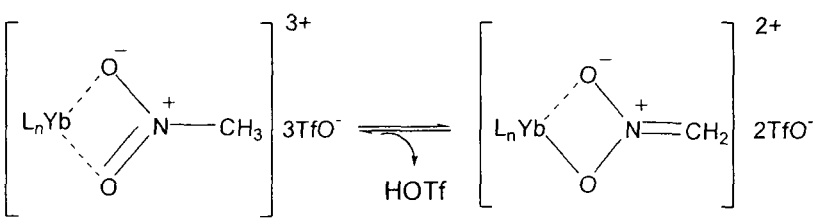
48 **55** **56** **57**

entry[a]	catalyst	conversion of **48** (%)[b]	**56**:**57** (%)[c]
1	5% $AuCl_3$/15% AgOTf	66	56:5
2	5% $AuCl_3$	0	0
3	15% AgOTf	45	42:0
4	$Cu(OTf)_2$	69	68:1
5	$In(OTf)_3$	52	48:1
6	$Bi(OTf)_3$	67	65:2
7	$Yb(OTf)_3$	57	52:2
8	none	0	0

[a] Reactions were run with 2 equiv. of **diene**. [b] Conversion based on recovered material. [c] NMR yield using CH_3NO_2 as internal standard.

2.7 Lewis-Assisted Brønsted Acid Catalysis

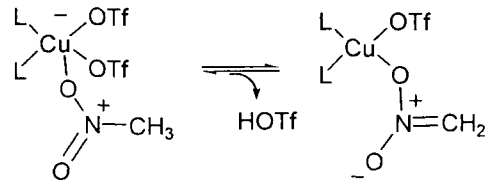
In 2001, Barrett[44] proposed that an ytterbium complex can coordinate to nitromethane (forming **58**) enhancing its acidity leading to the formation of a Lewis-assisted Brønsted acid species **59**. Alternatively, the highly acidic proton can be liberated in the system, forming HOTf *in situ* (Scheme 28).



58 **59**

Scheme 28. Barrett's ytterbium complex

Evans[45] proposed a similar concept involving copper in 2003 (Scheme 29). These observations shed light to the formation of the cyclized product. A small amount of HOTf is released *in situ* favoring the cyclization step.



60 **61**

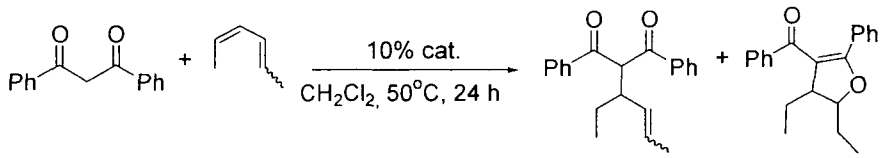
Scheme 29. Evans' copper complex

2.8 Optimization of the Synthesis II

The use of HOTf as the catalyst was highly efficient and the cyclized product was obtained exclusively (Table 5, entry 1). As HOTf is corrosive, its release *in situ* by combining a Lewis and Brønsted acid seems to be more convenient. As the acidic property of nitromethane was no longer needed, the solvent was changed to dichloromethane. The combination of $Yb(OTf)_3$ and acetic acid only led to the single addition product while $Yb(OTf)_3/HNO_3$ gave the cyclized product in poor yield (Table 5, entries 2 and 3). The use of $Yb(OTf)_3/H_2SO_4$ was more efficient than sulfuric acid alone (Table 5, entries 4 and 5). Different combination of Lewis acids and sulfuric acid failed to give exclusively the dihydrofuran (Table 5, entries 6-8). Thus, the use of HOTf in CH_2Cl_2 at 50°C was found to be most efficient and was used as the standard conditions.

Table 5. Addition of Dibenzoylmethane to 2,4-hexadiene with Various Catalysts

II



48 **55** **56** **57**

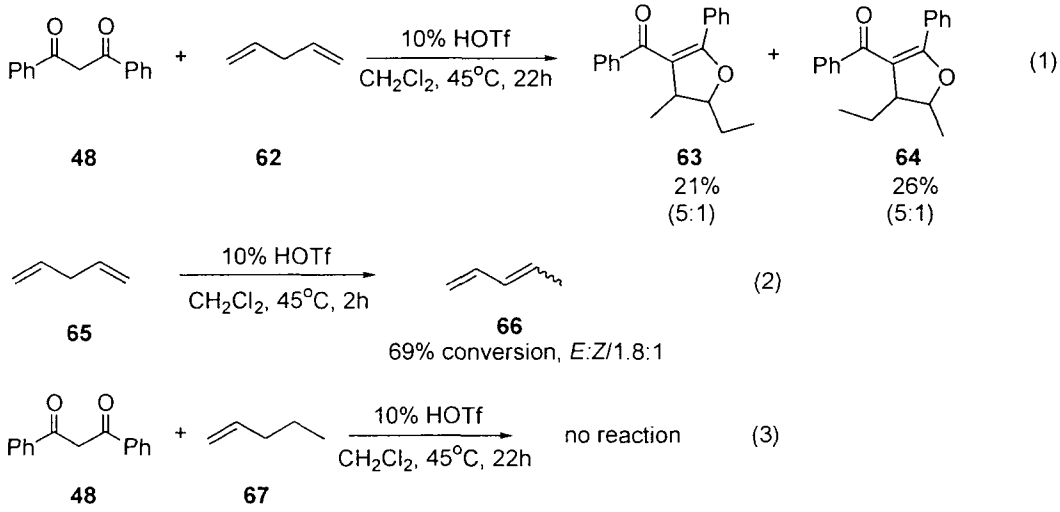
entry[a]	catalyst	conversion of **48** (%)[b]	**56**:**57** (%)[c]
1	HOTf	67	0:63
2	$Yb(OTf)_3$/AcOH	62	59:0
3	$Yb(OTf)_3/HNO_3$	66	54:9
4	$Yb(OTf)_3/H_2SO_4$	71	29:40
5	H_2SO_4	32	19:9
6	$Cu(OTf)_2/H_2SO_4$	63	39:20
7	$In(OTf)_3/H_2SO_4$	48	33:23
8	$Bi(OTf)_3/H_2SO_4$	66	39:21

[a] Reactions were run with 2 equiv. of diene. [b] Conversion based on recovered material.
[c] NMR yield using CH_3NO_2 as internal standard.

2.9 Scope and Limitations of the Cyclization Reaction

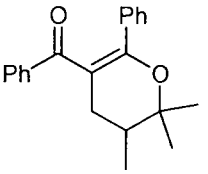
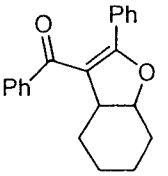
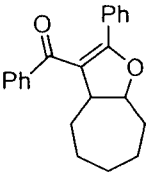
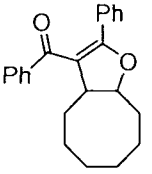
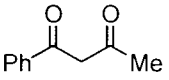
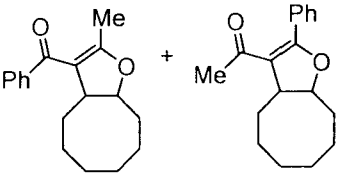
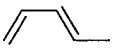
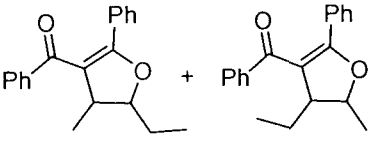
Subsequently, various 1,3-diketones were added to a range of conjugated dienes (using a syringe pump) under our optimized conditions (Table 6, entries 1-7). Note that the addition to 2,3-dimethylbutadiene (Table 6, entry 2) led to a highly substituted dihydropyran whereas the use of cyclic dienes (Table 6, entries 3-6) afforded bicyclic dihydrofuran derivatives. Unsymmetrical 1,3-diketone or diene led to a mixture of two products (Table 6, entries 6 and 7). Unfortunately, less activated 1,3-diketones, such as 2,4-pentanedione were not effective at all. Interestingly, the addition to acyclic diene **62** was also effective (Scheme 30, eq. 1) to afford **63** and **64**. Presumably, the non-conjugated diene isomerizes to a 1,3-diene before the addition of the 1,3-diketone. To confirm this observation, 1,5-

pentadiene **65** was treated under the optimized conditions (Scheme 30, eq. 2). Indeed, the terminal double bond migrates to form 1,3-pentadiene **66** in 69% conversion after 2 h under the standard conditions. Moreover, dibenzoylmethane **48** and 1-hexene **67** did not react under our conditions which strongly suggest that the double bond isomerizes before alkylation (Scheme 30, eq. 3).



Scheme 30. Isomerization of an acyclic diene into a conjugated diene

Table 6. Brønsted Acid-Catalyzed Addition of 1,3-Diketones to Dienes

entry	1,3-diketone	diene[a]	product	Isolated yield (%) (d.r)[b]
1	**48**	**55**	**57**	65 (5.1:1)
2	**48**			59
3	**48**			71 (5.3:1)
4	**48**			48% (5.4:1)
5	**48**			72 (5:1)
6			 28% (5:1) 24% (5:1)	52
7	**48**		 28% (5.2:1) 27% (5.1:1)	55

[a] Diene (1.2 equiv.) was added using a syringe pump over 5h. [b] The ratio of two diastereoisomers was determined by ^{1}H-NMR.

2.10 Conclusion

In summary, the original scope of the addition of activated methylenes to styrenes was extended to dienes and cyclic enol ethers. Both cyclic and acyclic dienes can be used while simple alkenes remain inert to this reaction. The hydroalkylation is highly atom-economical, catalyzed by the combination of $AuCl_3$ and AgOTf and run under mild conditions. The modest conversions and yields were explained by the reduction of the strong oxidant Au(III) into Au(0), deactivating its catalytic activity. The method was also applied to the synthesis of 2,3-dihydrofurans, albeit in a strong acidic environment (10% HOTf). The first step is the C-C bond formation. The tautomerization process occurs readily and is promoted by acid catalysis.

2.11 Appendix for Chapter 2: Part 1 (Experimental Section)

(This section is published as "Supporting Information")

All experiments were carried out under nitrogen atmosphere. Dichloromethane was dried using CaH_2. Analytical and preparative thin-layer chromatography plates (TLC) were ordered from Silicycle Inc. (TLC glass plate). Visualization of the spots on the TLC plates was achieved by exposure to UV light or $KMnO_4$ stain. Column chromatography was performed over Sorbent silica gel 30-60μm. ^1H NMR and ^{13}C NMR spectra were acquired by Varian 400 and 100MHz or 300 and 75MHz, respectively, and referenced to the internal solvent signals. IR spectra were recorded by ABB Bomem MB100 spectrometer. Mass spectra data and HRMS were obtained by Kratos MS25RFA Mass Spectometer. X-ray determination was resolved by Rigaku AFC63 four-circle diffractometer.

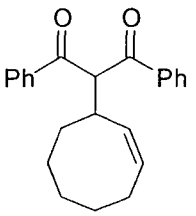
New compounds were fully characterized (^1H NMR, ^{13}C NMR, IR, HRMS) whereas known compounds were partially characterized (^1H NMR and ^{13}C NMR) and compared to the literature reference.

Typical experimental procedure for the addition of 1,3-diketones to 1,3-dienes and cyclic enol ethers catalyzed by gold and silver (Table 2, entry 1) :

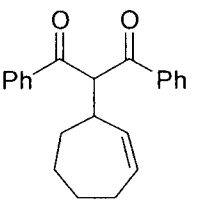
A solution of $AuCl_3$ (7.6 mg, 0.025 mmol) and AgOTf (19.3 mg, 0.075 mmol) was stirred in dichloromethane (2 mL) at room temperature for 2 hrs. Dibenzoylmethane (112 mg, 0.5 mmol) was then added which was followed by the addition of 1,3-cyclooctadiene (128μL, 1 mmol, dissolved in 0.5 mL of

dichloromethane) via an automated syringe pump over 5 h (0.1 mL/h) and the resulting solution was stirred overnight. The solvent was removed under reduced pressure and the product was isolated via column chromatography on silica gel (gradiant eluent: hexane: ethyl acetate = 60:1 to 2:1).

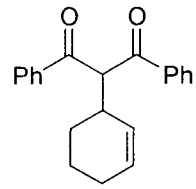
Monitoring of the addition of dibenzoylmethane to 1,3-cyclooctadiene. A solution of $AuCl_3$ (3.8 mg, 0.0125 mmol) and AgOTf (9.2 mg, 0.0375 mmol) in CD_2Cl_2 (0.25 mL) was shaken manually in a NMR tube for 15 min. A mixture of dibenzoylmethane (61 mg, 0.25 mmol) and cyclooctadiene (32 μL, 0.25 mmol) in 0.25 mL of CD_2Cl_2 was then added to the NMR tube, followed by the internal standard CH_3NO_2 (5 μL, 0.083 mmol). The tube was put in an ultrasound bath at 25°C for the duration of the reaction. The NMR yields were determined by looking at the relative amount of the expected hydroalkylation product by integrating the protons signals at 3.83 ppm (product) and 4.50 ppm (internal standard).



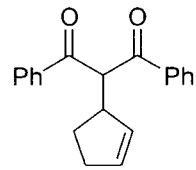
2-Cyclooct-2-enyl-1,3-diphenyl-propane-1,3-dione (Table 2, entry 1). Isolated as a white solid. IR(KBr plate): 2929, 2851, 1688, 1594, 1447, 1239, 976, 776, 715 cm^{-1}; ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 8.04-7.96(m, 5H), 7.46-7.39(m, 5H), 5.63(m, 1H) 5.31-5.22(m, 2H), 3.83(m, 1H), 2.30(m, 1H), 2.04(m, 1H), 1.87-1.22(m, 10H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 195.5, 195.0, 137.3, 137.0, 133.5, 133.7, 133.4, 131.8, 130.5, 129.0, 128.9, 128.0, 63.7, 38.2, 34.5, 31.3, 29.9, 27.1, 25.8; MS(EI): m/z 332, 227, 105, 77; HRMS calc'd for $C_{23}H_{24}O_2$: 332.1776; found, 332.1771.



2-Cyclohepta-2,4-dienyl-1,3-diphenyl-propane-1,3-dione (Table 2, entry 2). Isolated as a white solid. IR(KBr plate): 3008, 2915, 2352, 1696, 1647, 1595, 1442, 1269, 991, 758 cm^{-1}; ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.98-7.39(m, 4H), 7.55-7.40(m, 6H), 5.90(m, 1H), 5.67(m, 1H), 5.54(d, 1H, *J*=9.9 Hz), 3.74(m, 1H), 2.42(m, 4H), 1.95(m, 4H); ^{13}C NMR($CDCl_3$, 100MHz, ppm): δ= 195.3, 194.2, 137.8, 137.3, 134.6, 133.7, 133.3, 132.9, 131.5, 131.0, 129.1, 128.6, 60.6, 38.2, 35.0, 30.1, 30.0, 29.6; MS(EI): m/z 316, 225, 211, 105, 77; HRMS: calc'd for $C_{22}H_{20}O_2$: 316.1463; found, 316.1459.

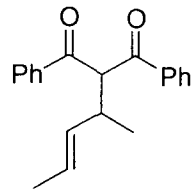


2-Cyclohex-2-enyl-1,3-diphenyl-propane-1,3-dione (Table 2, entry 3). Isolated as a white solid. IR(KBr plate): 2931, 2360, 1679, 1643, 1595, 1446, 1269, 971, 709 cm^{-1}; ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.99-7.97(m, 4H), 7.55(m, 2H), 7.45-7.42(m, 4H), 5.73(m, 1H), 5.52(m, 1H), 5.29(d, 1H, *J*=9.9Hz), 3.49(m, 1H), 2.01(m, 2H), 1.75(m, 2H), 1.37(m, 2H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 201.9, 194.8, 137.3, 137.1, 133.6, 133.2, 132.0, 131.2, 130.4, 129.6, 128.7, 128.2, 62.8, 37.6, 27.8, 25.5, 21.5; MS(EI): m/z 304, 223, 199, 105, 77; HRMS: calc'd for $C_{21}H_{20}O_2$: 304.1463; found, 304.1459.

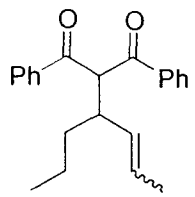


2-Cyclopent-2-enyl-1,3-diphenyl-propane-1,3-dione (Table 2, entry 4). Isolated as a white solid. IR(KBr plate): 2919, 1728, 1695, 1655, 1495, 1265, 987, 693 cm^{-1}; ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 8.00-7.93(m, 4H), 7.59-7.40(m, 6H), 5.58(m, 2H), 5.18(d, 1H, *J*=9.9Hz), 3.84(m, 1H), 2.40-2.19(m, 4H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 203.5, 195.1, 137.8, 137.4, 133.7, 133.3, 132.5, 132.1, 129.7, 129.1, 128.9, 128.3, 62.2, 38.4, 32.1, 29.3; MS(EI): m/z 223, 185,

105, 77; MS(ESI): m/z 290, 223; HRMS calc'd for $C_{13}H_{13}O(M^+$-COPh) : 185.0966; found, 185.0967.

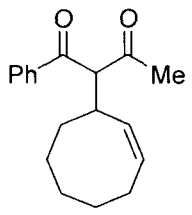


2-(1-Methyl-but-2-enyl)-1,3-diphenyl-propane-1,3-dione (Table 2, entry 5). Isolated as a colorless gummy oil. IR(neat): 3015, 1645, 1567, 1532, 1481, 1190, 846, 735 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 7.99-7.93(m, 4H), 7.56-7.26(m, 10H), 5.42(m, 2H), 5.20(d, 1H, *J*=9.2Hz), 3.40(m, 1H), 1.49(d, 3H, *J*=5.2 Hz), 1.11(d, 3H, *J*=6.4 Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 195.3, 195.1, 137.3, 137.2, 133.6, 133.4, 122.3, 128.9, 128.9, 128.8, 127.9, 126.3, 62.2, 38.4, 32.1, 29.3; MS(EI): m/z 292, 105, 77; MS(ESI): m/z 292, 223; HRMS calc'd for $C_{20}H_{20}O_2$: 292.1463; found, 292.1460.

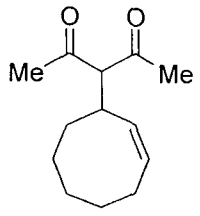


2-(1-Ethyl-but-2-enyl)-1,3-diphenyl-propane-1,3-dione (Table 2, entry 6). Isolated as a colorless gummy oil and a mixture of E/Z isomers; major isomer: IR(neat): 2871, 1926, 1694, 1592, 1471, 1420, 1351, 1281, 1140 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 7.98-7.93(m, 4H), 7.53(m, 2H), 7.43-7.40(m, 4H), 5.43-5.28(m, 2H), 5.22(d, 1H, *J*=6.9Hz), 3.42-3.36(m, 1H), 1.81(m, 2H),

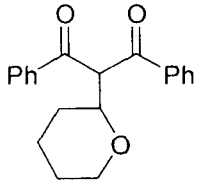
1.12(d, 3H, J=5.1Hz), 0.74(t, 3H, J=5.7Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 195.1, 194.8, 137.6, 137.3, 133.5, 133.3, 132.8, 132.6, 131.1, 129.3, 128.9, 127.3, 63.6, 46.3, 30.0, 25.7, 18.1, 12.3; MS(EI): m/z 306, 224, 105, 77; HRMS calc'd for $C_{21}H_{22}O_2$: 306.1620; found, 306.1614.



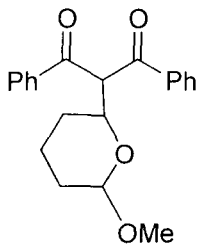
2-Cyclooct-2-enyl-1-phenyl-butane-1,3-dione (Table 2, entry 7). Isolated as a pale yellow gummy oil. One of the diastereoisomer can be partially isolated on a preparative TLC plate (hexanes: ethyl acetate: 10:1). IR(neat): 2923, 2855, 2360, 1708, 1660, 1447, 1354, 970 cm^{-1}; ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 8.00-7.97(m, 2H), 7.57-7.43(m, 3H), 5.63(m, 1H), 5.17(m, 1H), 4.58(d, 1H, J=9.1Hz), 3.61(m, 1H), 2.40(m, 2H), 2.21(s, 3H), 2.11(m, 2H), 1.74(m, 2H), 1.49(m, 4H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 204.4, 195.6, 133.8, 132.0, 130.8, 130.3, 129.0, 128.8, 70.2, 37.5, 33.8, 29.7, 28.1, 27.3, 25.9, 25.6; MS(EI): m/z 270, 227, 165, 105, 77; HRMS calc'd for $C_{18}H_{22}O_2$: 270.1620; found, 270.1616. Another diastereoisomer (from the mixture and some peaks are difficult to distinguished): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 4.41(d, 1H, J=8.6Hz), 3.46(m, 1H), 2.10(s, 3H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 203.6, 194.0, 135.4, 69.6, 36.8, 34.3, 26.8, 24.5.



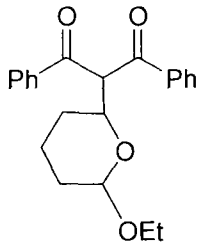
3-Cyclooct-2-enyl-pentane-2,4-dione (Table 2, entry 8).[46] ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 5.75(m, 1H), 5.09(m, 1H), 3.66(d, 1H, *J*=10.8 Hz), 3.39(m, 1H), 3.90(m, 1H), 2.21(s, 3H), 2.10(s, 3H), 1.77-1.09(m, 10H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 203.7, 203.6, 132.0, 129.3, 75.7, 36.5, 33.6, 31.0, 29.3, 27.9, 26.7, 26.5, 25.2.



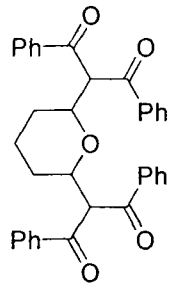
1,3-Diphenyl-2-(tetrahydro-pyran-2-yl)-propane-1,3-dione (Table 3, entry 1). Isolated as a white solid. IR(KBr plate): 2959, 1687, 1653, 1594, 1446, 1196, 1087, 711 686 cm^{-1}; ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.97(m, 5H), 7.59-7.41(m, 5H), 5.48(d, 1H, *J*=9Hz), 4.93(m, 1H), 3.90(m, 1H), 3.45(m, 1H), 1.82(m, 2H), 1.59(m, 2H), 1.40(m, 2H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 194.6, 193.4, 137.5, 136.8, 133.8, 133.3, 129.0, 129.0, 128.9, 128.8, 78.8, 69.2, 63.2, 36.8, 26.2, 23.7; MS(EI): m/z 308, 203, 105, 77; HRMS calc'd for$C_{20}H_{18}O_3$: 308.1399; found, 308.1398.



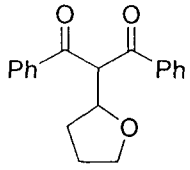
2-(6-Methoxy-tetrahydro-pyran-2-yl)-1,3-diphenyl-propane-1,3-dione (Table 3, entry 2). Isolated as a white solid. One of the diastereoisomer: IR(KBr plate): 2936, 1696, 1596, 1448, 1224, 1119, 1000, 951 $cm^{-1;}$ ^{1}H-NMR($CDCl_3$, 300MHz, ppm): δ= 8.04-7.91(m, 4H), 7.55-7.40(m, 6H), 5.58(d, 1H, *J*=9.3Hz), 4.50(dt, 1H, *J*=9.3, 1.7Hz), 4.29(dd, 1H, *J*=8.5, 1.3Hz), 3.06(s, 3H), 1.83-1.76(m, 4H), 1.66(m, 2H); MS(EI): m/z 233, 224, 184, 105, 77; ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 194.4, 193.3, 137.6, 136.0, 133.8, 133.2, 129.3, 129.0, 128.8, 128.5, 99.2, 70.3, 64.1, 57.7, 30.2, 29.9, 18.3; MS(ESI): m/z 338; HRMS calc'd for $C_{14}H_{17}O_3$(M^+-COPh): 233.11777; found, 233.11752. Another diastereoisomer: ^{1}H-NMR($CDCl_3$, 300MHz, ppm): δ= 8.02-7.94(m, 4H), 7,56-7,40(m, 6H), 5.43(d, 1H, J=9.3Hz), 4.91(dt, 1H, J=9.3, 1.4Hz), 4.58(m, 1H), 3.14(s, 3H), 1.96-1.79(m, 3H), 1.68-1.56(m, 3H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 194.0, 193.1, 136.9, 136.2, 134.2, 133.8, 130.2, 129.8, 129.0, 128.3, 99.4, 70.8, 64.0, 54.1, 29.6, 29.3, 18.8.



2-(6-Ethyl-tetrahydro-pyran-2-yl)-1,3-diphenyl-propane-1,3-dione (Table 3, entry 3). Isolated as a white solid. One of the diastereoisomer: IR(KBr plate): 2956, 1704, 1659, 1596, 1498, 1280, 1196, 1029, 760 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 8.02-7.94(m, 4H), 7.54-7.40(m, 6H), 5.40(d, 1H, *J*=9.8Hz), 4.92(dt, 1H, *J*=9.8, 2.4 Hz), 4.69(m, 1H), 3.41(m, 1H), 3.16(m, 1H), 1.95-1.82(m, 2H), 1.63(m, 2H), 1.41(m, 2H), 1.11(t, 3H, *J*=8.1, 4.2 Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 194.5, 193.4, 133.9, 133.3, 130.1, 129.0, 128.8, 128.2, 127.4, 127.2, 102.1, 64.1, 62.3, 37.4, 30.1, 29.0, 15.3, 14.5; MS(EI): m/z 247, 224, 184, 105, 77; MS(ESI): m/z 352; HRMS calc'd for $C_{15}H_{19}O_3(M^+$-COPh): 247.13342; found, 247.13299. Another diastereoisomer ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 8.00-7.92(m, 4H), 7.59-7.40(m, 6H), 5.58(d, 1H, *J*=9.9Hz), 4.50(m, 1H), 4.39(dd, 1H, *J*=8.4, 1.2Hz) 3.35(m, 1H), 3.22(m, 1H), 1.86-1.72(m, 2H), 1.61(m, 2H) 1.39(m, 2H), 0,992(t, 3H, *J*= 8.3, 3,9 Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 195.8, 194.3, 133.1, 133.0, 132.8, 132.4, 130.2, 129.8, 129.1, 128.0, 103.1, 63.5, 61.6, 38.3, 30.9, 28.3, 14.9, 14.0.

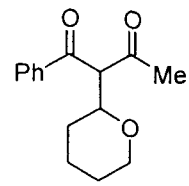


2-[6-(1-Benzoyl-2-oxo-2-phenyl-ethyl)-tetrahydro-pyran-2-yl]-1,3-diphenyl-propane-1,3-dione (Table 3, entries 2 and 3). Isolated as a white solid. IR(KBr plate): 2931, 2344, 1696, 1559, 1450, 1273, 1192, 762 cm^{-1}; ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.89(m, 4H), 7.66(m, 4H), 7.49-7.28(m, 12 H), 5.27(d, 2H, *J*=9Hz), 4.52(m, 2H), 1.82(m, 3H), 1.36(m, 3H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 195.2, 189.2, 133.7, 133.2, 133.1, 129.8, 129.0, 128.8, 128.7, 128.5, 79.2, 63.9, 30.1, 29.0; MS(EI): m/z 306, 223, 146, 105, 77; MS(ESI): m/z (%) 530, 307; HRMS calc'd for $C_{20}H_{18}O_3$(M^+-dibenzoylmethane): 306.12559; found, 306.12531.



1,3-Diphenyl-2-(tetrahydro-furan-2-yl)-propane-1,3-dione (Table 3, entry 4). Isolated as a white solid. IR(KBr plate): 2943, 2319, 1691, 1603, 1442, 1289, 1072, 818, 685 cm^{-1}; ^{1}H-NMR($CDCl_3$, 300MHz, ppm): δ= 8.02(m, 4H), 7.53-7.41(m, 6H), 5.42(d, 1H, *J*=8.1Hz), 4.83(m, 1H), 3.83-3.69(m, 2H), 2.29(m, 2H), 1.95(m, 2H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 194.7, 194.3, 136.9, 136.6, 133.8, 133.5, 130.0, 129.1, 129.0, 128.9, 79.7, 68.4, 63.0, 30.8, 25.9; MS(EI) m/z

224, 189, 105, 77; MS(ESI): m/z 294; HRMS calc'd for $C_{12}H_{13}O_2(M^+$-COPh) : 189.09155; found: 189.09171.



1-Phenyl-2-(tetrahydro-pyran-2-yl)-butane-1,3-dione (Table 3, entry 5). Isolated as a colorless oil. one of the diastereoisomer can be partially isolated on a preparative TLC plate (hexanes: ethyl acetate: ether: 5:1:1). IR(neat): 2936, 2348, 1708, 1656, 1555, 1450, 1233, 976 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 8.03(m, 2H), 7.59-7.45(m, 3H), 4.64(d, 1H, *J*= 9.6Hz), 4.28(m, 1H), 4.01(m, 1H), 3.49(m, 1H), 2.24(s, 3H), 1.82(m, 1H), 1.59(m, 5H). ^{13}C NMR($CDCl_3$, 75MHz, ppm): 202.8, 193.7, 136.9, 134.1, 133.9, 129.1, 70.2, 59.8, 30.5, 27.9, 26.1, 23.5; MS(EI): m/z 203, 147, 105, 77; MS(ESI): m/z 246; HRMS calc'd for $C_{13}H_{15}O_2(M^+$-Ac): 203.10720; found: 203.10752. Another diastereoisomer (from the mixture and some peaks are difficult to distinguished): ^1H NMR($CDCl_3$, 300MHz, ppm): 4.69(d, 1H, *J*=9.6Hz), 3.82(m, 1H), 2.18(s, 3H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): 203.0, 192.2, 148.8, 69.0, 60.4, 31.4, 28.5, 24.0.

2.12 Appendix for Chapter 2: Part 2 (Experimental Section)

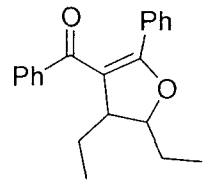
All experiments were carried out under air atmosphere. Dichloromethane was dried using CaH_2. Nitromethane was dried over molecular sieves. Analytical and preparative thin-layer chromatography plates (TLC) were ordered from Silicycle Inc. (TLC glass plate). Visualization of the spots on the TLC plates was achieved by exposure to UV light or $KMnO_4$ stain. Column chromatography was performed over Sorbent silica gel 30-60μm. ^1H NMR and ^{13}C NMR spectra were acquired by Varian 400 and 100MHz or 300 and 75MHz, respectively, and referenced to the internal solvent signals. IR spectra were recorded by ABB Bomem MB100 spectrometer. Mass spectra data and HRMS were obtained by Kratos MS25RFA Mass Spectometer.

New compounds were fully characterized (^1H NMR, ^{13}C NMR, IR, HRMS) whereas known compounds were partially characterized (^1H NMR and ^{13}C NMR) and compared to the literature reference.

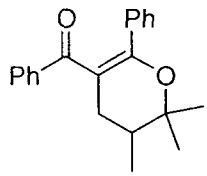
Typical experimental procedure for the addition of 1,3-diketones to 1,3-dienes catalyzed by HOTf (Table 6, entry 1):

In a solution of 1.5 mL of dichloromethane containing dibenzoylmethane (112 mg, 0.5 mmol), was added 2,4-hexadiene (85 μL, 0.75 mmol diluted in 0.5 mL of dichloromethane) via an automated syringe pump over 5h (0.1 mL/h). The resulting solution was allowed to stir overnight at 50°C. The solvent was removed

under reduced pressure and the product was isolated via column chromatography on silica gel (gradiant eluent: hexane: ethyl acetate = 60:1 to 2:1).

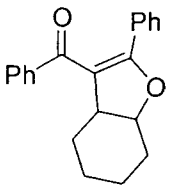


(4,5-Diethyl-2-phenyl-4,5-dihydro-furan-3-yl)-phenyl-methanone (Table 6, entry 1). Isolated as a gummy oil. IR(neat): 3070, 2718, 1718, 1642, 1590, 1572, 1462, 1394, 1203 cm^{-1}; One of the diastereoisomer can be partially separated on a preparative TLC (gradiant eluent: hexane: ethyl acetate:ether = 10:1:1): ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 7.44(m, 2H), 7.24-7.05(m, 4H), 7.03-7.01(m, 4H), 4.74(m, 1H), 3.47(m, 1H), 1.90(m, 2H), 1.73(m, 2H), 1.28(t, 3H, *J*=6.4 Hz), 1.05 (t, 3H, *J*= 6.4 Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 193.9, 166.1, 139.8, 133.7, 131.1, 130.1, 129.7, 129.1, 128.9, 127.74 118.2, 86.6, 43.1, 31.7, 20.1, 14.5, 13.9 MS(EI): m/z 306, 201, 105, 77; HRMS calc'd for $C_{21}H_{22}O_2$: 306.1620; found, 306.1616. another diastereoisomer (from the mixture and some peaks are difficult to distinguished): ^1H NMR($CDCl_3$, 300MHz, ppm): δ=4.38 (m, 1H), 3.45(m, 1H).

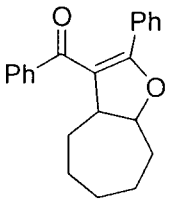


Phenyl-(5,6,6-trimethyl-2-phenyl-5,6-dihydro-4H-pyran-3-yl)-methanone (Table 6, entry 2). Isolated a colorless oil. IR(neat): 2971, 1914, 1699, 1671, 1545, 1482, 1412, 1246, 1223 cm^{-1}; ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 7.45(m, 2H), 7.17(m, 4H), 7.01(m, 4H), 2.93(dd, 1H, *J*=4.5, 13.2Hz), 2.18-1.98(m, 2H),

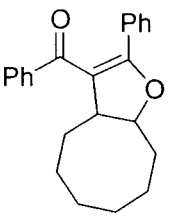
1.49(s, 3H), 1.39(s, 3H), 1.07(d, 3H, J=4.2Hz); ^{13}C NMR(CDl_3, 75MHz, ppm): δ= 198.8, 160.0, 139.6, 130.1, 131.2, 129.7, 129.3, 128.9, 127.7, 127.7, 111.4, 79.8, 35.7, 30.4, 27.4, 19.7, 16.6; MS(EI): m/z 306, 237, 105, 77; HRMS calc'd for $C_{21}H_{22}O_2$: 306.1620; found, 306.1615.



Phenyl-(2-phenyl-3a,4,5,6,7,7a-hexahydro-benzofuran-3-yl)-methanone (Table 6, entry 3). Isolated as a white solid. IR(KBR plate): 2933, 2861, 1619, 1590, 1572, 1489, 1445, 1380, 1216 cm^{-1}; One of the diastereoisomer can be separated partially on a preparative TLC (gradiant eluent: hexane: ethyl acetate:ether = 10:1:1): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.48(m, 2H), 7.20-7.18(m, 4H), 7.05-7.01(m, 4H), 4.78(m, 1H), 3.30(m, 1H), 2.26(m, 2H), 1.92(m, 2H), 1.57(m, 2H), 1.36 (m, 2H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 193.9, 166.5, 139.5, 131.2, 130.7, 130.1, 129.7, 128.7, 128.2, 127.7, 119.5, 87.5, 44.8, 28.5, 27.6, 22.5, 21.0; MS(EI): m/z 304, 199, 105, 77; HRMS calc'd for $C_{23}H_{24}O_2$: 304.1463; found, 304.1460. another diastereoisomer (from the mixture and some peaks are difficult to distinguished): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 4.60(m, 1H), 3.41(m, 1H).

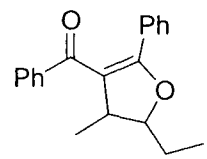


Phenyl-(2-phenyl-4,5,6,7,8,8a-hexahydro-3aH-cyclohepta[b]furan-3-yl)-methanone (Table 6, entry 4). Isolated as a white solid. IR(KBr plate): 3142, 1941, 1681, 1517, 1459, 1402, 1374, 1151, 941 cm^{-1}; One of the diastereoisomer can be partially separated on a preparative TLC (gradiant eluent: hexane: ethyl acetate:ether = 10:1:1): ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 7.44(m, 2H), 7.18-7.15(m, 4H), 7.06-7.02(m, 4H), 5.06(m, 1H), 3.80(m, 1H), 2.19-2.13(m, 2H), 2.11-1.46(m, 8H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 194.2, 165.6, 139.1, 134.0, 133.1, 132.7, 129.8, 129.0, 128.9, 127.7, 118.1, 86.5, 32.5, 31.6, 30.6, 29.5, 28.8, 26.8; MS(EI): m/z 318, 2131, 105, 77; HRMS calc'd for $C_{22}H_{22}O_2$: 318.1620; found, 306.1611. another diastereoisomer (from the mixture and some peaks are difficult to distinguished): ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 4.66(dt, 1H, *J*= 9.6, 1.4 Hz), 3.74(dt, 1H, *J*= 9.6, 1.4 Hz).

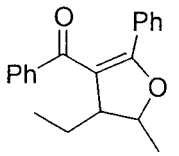


Phenyl-(2-phenyl-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[b]furan-3-yl)-methanone (Table 6, entry 5). Isolated as a white solid. IR(KBr plate): 2920, 2854, 1634, 1584, 1446, 1315, 1132, 1075, 890 cm^{-1}; One of the diastereoisomer can be partially separated on a preparative TLC (gradiant eluent: hexane: ethyl

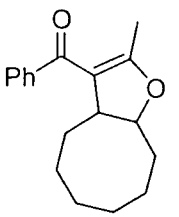
acetate:ether = 10:1:1): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.52(m, 2H), 7.13-7.00(m, 8H), 4.82(dt, 1H, *J*=9.1, 4.4 Hz) 3.78(dt, 1H, *J*=9.2, 4.0 Hz), 2.39-2.22(m, 2H), 1.96-1.25(m, 10H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 194.1, 163.8, 139.5, 131.5, 130.5, 129.8, 129.3, 128.8, 127.8, 127.3, 117.4, 88.7, 50.6, 35.4, 33.3, 31.2, 27.3, 24.2, 22.5; MS(EI): m/z 332, 227, 105, 77; HRMS calc'd for $C_{23}H_{24}O_2$: 332.1763; found, 332.1769; another diastereoisomer (from the mixture and some peaks are difficult to distinguished): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 4.64(m, 1H), 3.35m, 1H).



(4-Methyl-2-phenyl-5-propyl-4,5-dihydro-furan-3-yl)-phenyl-methanone (Table 6, entry 7). Isolated a colorless oil. IR(neat): 2967, 1954, 1671, 1584, 1521, 1485, 1439, 1374, 1231 cm^{-1}; One of the diastereoisomer can be partially separated on a preparative TLC (gradiant eluent: hexane: ethyl acetate:ether = 10:1:1): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.44(m, 2H), 7.25(m, 4H), 7.06-7.00(m, 4H), 4.66(m, 1H), 3.50(quint, 1H, *J*= 7.2 Hz), 1.84-1.79(m, 2H), 1.29(d, 3H, *J*=5.1Hz), 1.15(t, 3H, *J*=5.4Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 193.9, 166.1, 139.7, 131.3, 130.6, 130.1, 129.4, 129.3, 128.8, 127.7, 118.5, 88.2, 42.9, 22.7, 13.7, 11.2; MS(EI): m/z 292, 187, 105, 77; HRMS calc'd for $C_{20}H_{20}O_2$: 292.1463; found, 292.1459. another diastereoisomer (from the mixture and some peaks are difficult to distinguished): 4.29(m, 1H), 3.41(quint, 1H, *J*= 7.6 Hz).

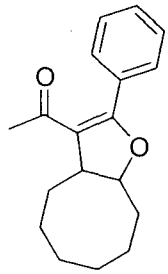


(4-Ethyl-5-methyl-2-phenyl-4,5-dihydro-furan-3-yl)-phenyl-methanone (Table 6, entry 7). Isolated as a colorless oil. IR(neat): 3055, 1801, 1765, 1632, 1507, 1452, 1387, 1321, 1198 cm^{-1}; One of the diastereoisomer can be partially separated on a preparative TLC (gradiant eluent: hexane: ethyl acetate:ether = 10:1:1): ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 7.51(m, 2H), 7.28(m, 4H), 7.10-7.06(m, 4H), 4.65(q, 1H, *J*= 7.6 Hz), 3.53(m, 1H), 1.87-1.82(m, 2H), 1.39(d, 3H, *J*=5.1 Hz), 1.10(t, 3H, *J*=5.4 Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 195.6, 168.3, 137.5, 133.3, 129.2, 129.0, 128.8, 128.5, 128.1, 127.5, 116.2, 90.8, 40.6, 24.65, 16.38, 10.94; MS(EI): m/z 292, 187, 105, 77; HRMS calc'd for $C_{20}H_{20}O_2$: 292.1463; found, 292.1460. another diastereoisomer (from the mixture and some peaks are difficult to distinguished): 4.27(q, 1H, *J*= 7.6 Hz), 3.40(m, 1H).



(2-Methyl-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[b]furan-3-yl)-phenyl-methanone (Table 6, entry 6). Isolated as a colorless oil. IR(neat): 3218, 1680, 1546, 1493, 1421, 1383, 1285, 1143, 1078, 972 cm^{-1}; One of the diastereoisomer can be partially separated on a preparative TLC (gradiant eluent: hexane: ethyl acetate:ether = 10:1:1): ^1H NMR($CDCl_3$, 300MHz, ppm): δ= 7.60(d, 2H, *J*= 8.4

Hz), 7.56(m, 1H), 7.40(t, 2H, *J*= 8.0 Hz), 4.63(dt, 1H, *J*= 8.4, 4.0 Hz), 3.52(dt, 1H, *J*= 2.4 Hz), 2.36-2.17(m, 2H), 1.97-1.43(m, 8H), 1.63(s, 3H), 1.38(m, 2H): δ= 195.2, 166.8, 133.1, 131.7, 130.9, 129.8, 118.4, 88.7, 49.5, 35.9, 31.8, 27.7, 26.2, 25.1, 24.6, 22.8; MS(EI): m/z 270, 165, 105, 77; HRMS calc'd for $C_{18}H_{22}O_2$: 270.1620; found, 270.1625. another diastereoisomer (from the mixture and some peaks are difficult to distinguished): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 4.51(m, 1H), 3.36(m, 1H).



1-(2-Phenyl-3a,4,5,6,7,8,9,9a-octahydro-cycloocta[b]furan-3-yl)-ethanone (Table 6, entry 6). Isolated as a colorless oil. IR(neat): 3158, 1665, 1543, 1520, 1481, 1346, 1297, 1120, 1096, 1025 cm^{-1}; One of the diastereoisomer can be partially separated on a preparative TLC (gradiant eluent: hexane: ethyl acetate:ether = 10:1:1): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.43(m, 5H), 4.74(dt, 1H, *J*= 8.0, 4.4 Hz), 3.48(dt, 1H, *J*= 8.0, 0.9 Hz), 2.42(m, 1H), 2.18(m, 1H), 1.81(s, 3H), 1.76-1.24(m, 10H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 195.1, 165.9, 130.1, 129.7, 129.4, 128.6, 118.1, 89.8, 49.7, 36.0, 34.2, 30.7, 28.1, 27.9, 25.2, 23.7; MS(EI): m/z 270, 227, 105, 77, 43; HRMS calc'd for $C_{18}H_{22}O_2$: 270.1620; found, 270.1616. another diastereoisomer (from the mixture and some

peaks are difficult to distinguished): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 4.64(m, 1H), 3.28(m, 1H).

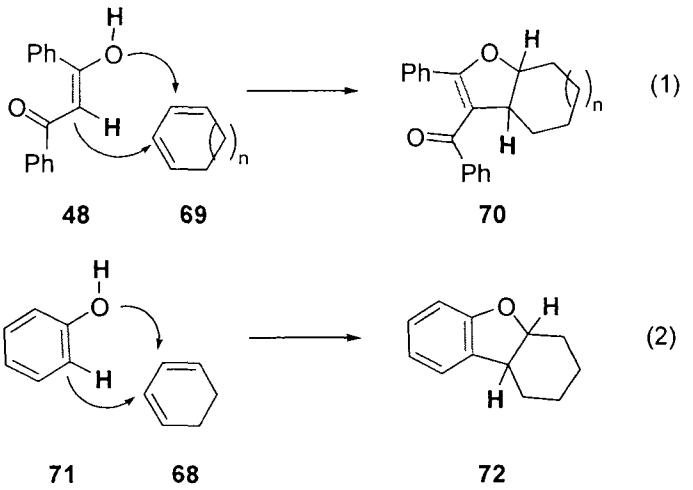
Chapter 3:

Catalytic Addition of Arenes (C_{sp^2}-H Bond) to Dienes: Application to the Synthesis of Dihydrobenzofurans I - Highly Efficient Gold-Catalyzed Atom-Economical Annulation of Phenols with Dienes

Chapter 3: Catalytic Addition of Arenes (C_{sp}^2-H Bond) to Dienes: Application to the Synthesis of Dihydrobenzofurans I - Highly Efficient Gold-Catalyzed Atom-Economical Annulation of Phenols with Dienes

3.1 Preface

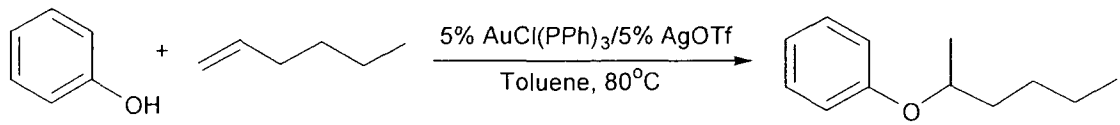
At the end of the previous chapter, dihydrofurans were synthesized by the consecutive addition of C-H and O-H bonds to form **70**. It is possible to assume that the enol form of the activated methylene **48** is responsible for the C-C/C-O bond formation (Scheme 31, eq. 1). Phenol has a similar fragment to the enol form. Therefore, it was hypothesized that the use of phenol **71** and diene **69** would lead to a dihydrobenzofuran **72** by similar consecutive addition (Scheme 31, eq. 2).



Scheme 31. Hypothesis for the formation of dihydrobenzofuran **72**

3.2 Optimization of the Synthesis

As HOTf was efficient for the cyclization reaction in Part 2 of Chapter 2, the reaction of phenol **71** and 1,3-cyclohexadiene **68** was first tested using catalytic amount of HOTf. The desired product **72** was obtained in 23% NMR yield (Table 7, entry 1). In this case, prevention of dimerization and polymerization of the diene by slow addition via syringe pump did not help at all. It would seem that HOTf decomposes phenol (Table 7, entry 2). The use of gold(I) as a catalyst led to very low conversion of the starting materials while cationic gold(I) triphenylphosphine did not lead to any desired product at all (Table 7, entries 3 and 4). Instead, only the single O-H addition to the diene was observed. In 2005, He reported a similar addition using unactivated alkene **73** (Scheme 32).[47]

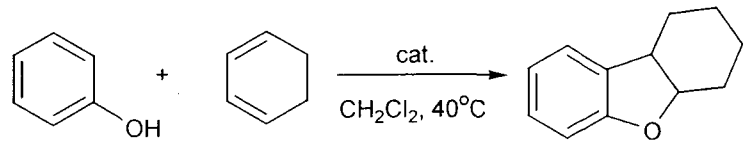


71 73 74

Scheme 32. He's intermolecular addition of phenol to alkenes

A combination of $AuCl_3$ and AgOTf was once again efficient and afforded the dihydrobenzofuran in 85% yield as shown by NMR in the crude reaction mixture (with nitromethane as internal standard) at 40°C in dichloromethane for 8 h using an excess of the diene (Table 7, entry 5). On the other hand, the use of $AuCl_3$ or AgOTf alone did not catalyze the reaction at all (Table 1, entries 6 and 7).

Table 7. Addition of Phenol to 1,3-Cyclohexadiene Catalyzed by Gold and Silver



71 **68** **72**

entry[a]	cat.	NMR yield(%)[c]
1	5% HOTf	23
2[b]	5% HOTf	--
3	5% AuCl/5% AgOTf	trace
4	5% $AuCl(PPh)_3$/5% AgOTf	--
5	5% $AuCl_3$/15% AgOTf	85
6	5% $AuCl_3$	0
7	15% AgOTf	0

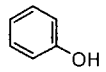
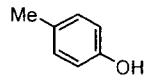
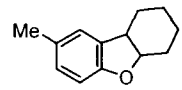
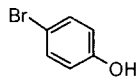
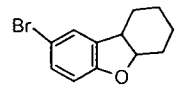
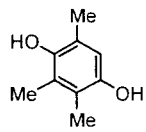
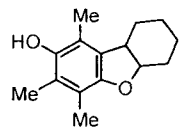
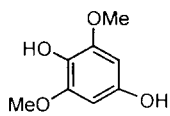
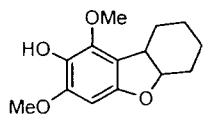
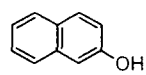
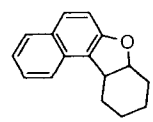
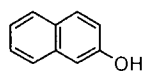
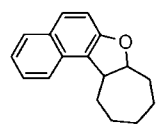
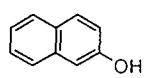
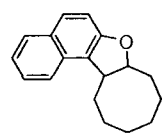
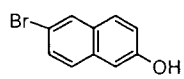
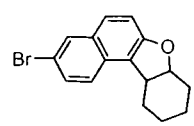
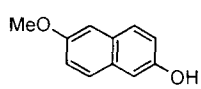
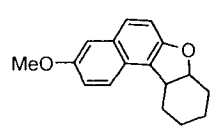
[a] Reactions were run with 1.5 equiv. diene. [b] Diene was added via syringe pump. [c]NMR yield using CH_3NO_2 as internal standard.

3.3 Scope and Limitations of the Cyclization Reaction

Subsequently, various phenols and naphthols were coupled with different dienes (Table 8). The presence of mild electron-donating groups on the aromatic ring seems to promote the reaction as opposed to too many strong donating groups. On the other hand, lower product yields were observed when an electron-withdrawing group is present. (Table 8, entries 2-5) Strong electron-donating group (such as nitro) did not lead to any conversion of the starting material. Similar electronic effects were observed with naphthol derivatives: the presence of the electron-donating methoxy group is more beneficial than electron-withdrawing groups (Table 8, entries 9 and 10). Finally, the use of other cyclic

dienes is also efficient (Table 8, entries 7 and 8). The corresponding reaction of aniline (or *N*-protected aniline) with diene did not give any product at all.

Table 8. Gold-Catalyzed Addition of Phenols/Naphthols to Dienes

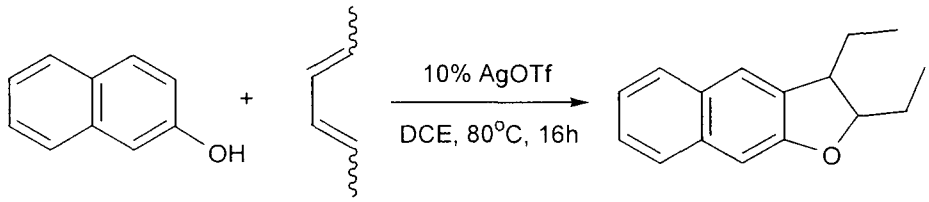
entry[a]	phenol/naphthol	diene[b]	product	Isolated yield (%) (syn:anti)[d]
1			**72**	71(85) (3:1)
2				74 (4:1)
3				53 (3:1)
4				72(88) (12:1)
5				62(68) (10:1)
6				80(96) (11:1)
7				77(88) (8:1)
8				49 (5:1)
9				58 (11:1)
10				71(89) (11:1)

[a] Reactions were run in dry dichloromethane at 40-45 °C for 8 h. [b]Conditions: phenol/naphthol (0.5 mmol), diene (0.75 mmol), $AuCl_3$ (0.025 mmol), AgOTf (0.075 mmol). [c]NMR yields are given in parentheses using CH_3NO_2 as internal standard. [d]The ratio of two diastereoisomers was determined by ^1H NMR.

3.4 Further Studies

3.4.1. Attempts to Expand the Scope

The original scope of the reaction was limited to cyclic dienes. Indeed, the use of acyclic dienes led mainly to dimerization and polymerization of the diene. This is mainly caused by the strong acidity of cationic Au(III). Therefore, a milder catalyst under higher temperature could minimize the dimerization of the diene and favor the addition of phenol to acyclic dienes. The addition of naphthol to 2,4-hexadiene catalyzed by 10% AgOTf in dichloroethane at 80°C led to the formation of the desired product in 82% isolated yield. At the same this reaction was studied, another group reported the same system (Scheme 33). [48] Nevertheless, the scope of this reaction can be extended to acyclic diene, provided that a milder catalyst is used.



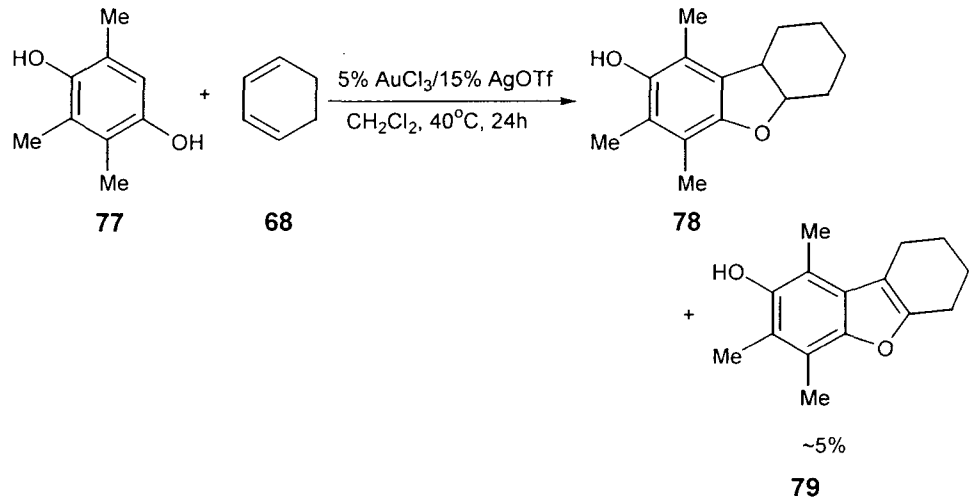
70 75 76

Scheme 33. Silver-catalyzed addition of phenol to acyclic diene

3.4.2 Oxidation of the product

As mentioned in previous chapters, Au(III) is a strong oxidant. It is therefore safe to assume that under these standard conditions, an oxidized by-product from the reaction is expected. Indeed, Au(III) can oxidize

dihydrobenzofuran **78** into benzofuran **79**, resulting in a diminished yield of the desired product if the reaction is allowed to run for more than 16 h (Scheme 34). If the reaction is run for 8 h or less, only trace amount of the oxidized product is found and the yield is not dramatically affected.

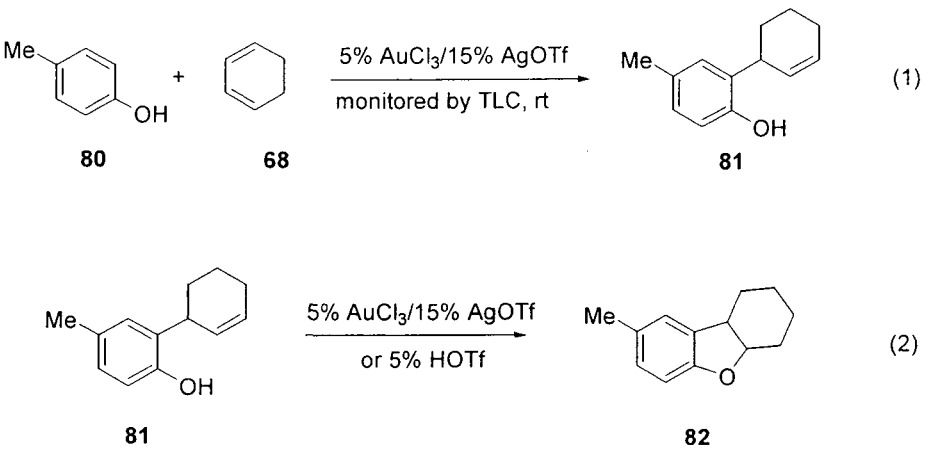


77 **68** **78** **79**

Scheme 34. Oxidation of dihydrobenzofuran **78**

3.4.3 Determination of the Sequence of Reaction

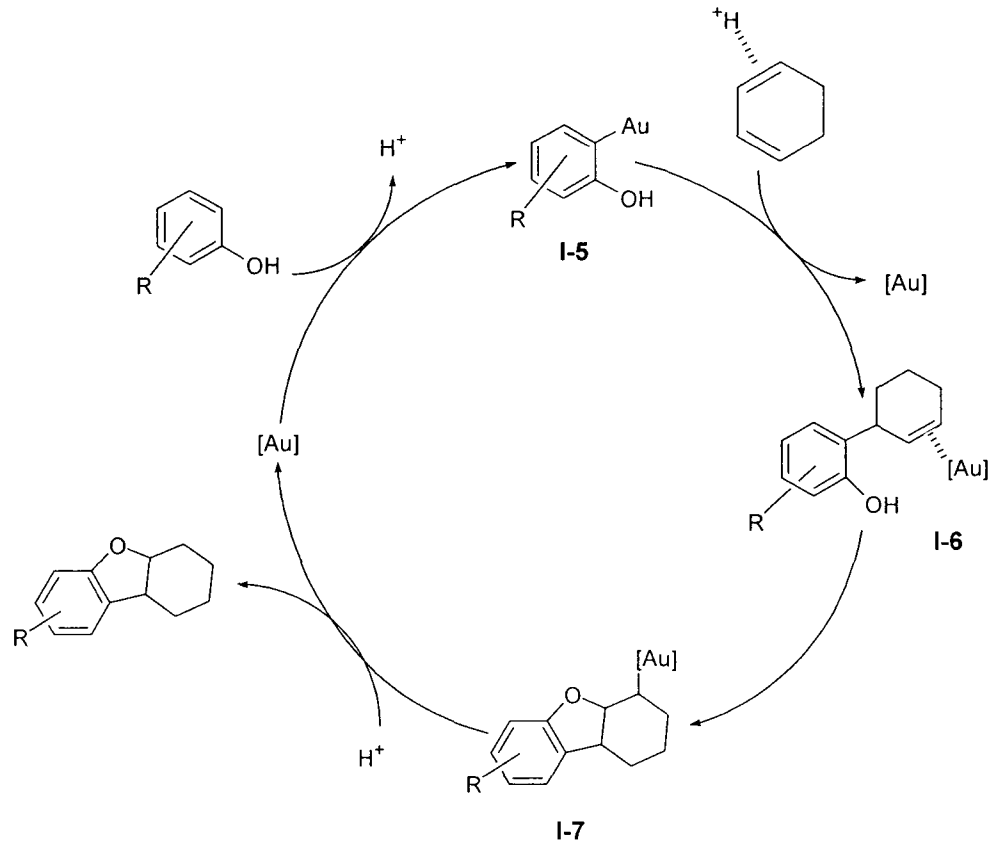
Monitoring the reaction was necessary to determine the exact sequence of the reaction. At room temperature, in dichloromethane, 2-methylphenol **80** was reacted with 1,3-cyclohexadiene **68** and the reaction was monitored by TLC. After 2 h, a new product appeared and was characterized as the addition of the C_{sp}^{2}-H bond to the diene **81** (Scheme 35, eq. 1). When this intermediate was submitted to the standard conditions, the cyclized product **82** is obtained (Scheme 35, eq. 2). The same product is obtained if the intermediate is treated with 5% HOTf. Based on these observations, a mechanism can be proposed.



Scheme 35. Determination of the sequence of the reaction

3.5 Proposed Mechanism

The first step is presumably the auration of the arene (Scheme 36). Gold(III) activates the arene by releasing a proton *in situ*. The formation of an arylgold species **I-5** has been observed as early as 1931 by Kharasch.[49] In 2004, He revisited this reaction with an elegant deuterium-labeling study.[21] The arene then adds to the diene, which is activated by a proton (or by gold), affording intermediate **I-6**. Gold then coordinates to the remaining double bond, which is followed by the intramolecular addition of the O-H bond to generate **I-7**. Protonolysis of the C-Au bond generates the product and regenerates Au(III) for further catalysis. Alternatively, the cyclization step can be acid-catalyzed.



Scheme 36. Proposed mechanism for the addition of phenol to diene

3.6 Conclusion

In summary, an efficient and atom-economical addition of phenol to cyclic dienes was developed to generate various dihydrobenzofurans derivatives using a combination of $AuCl_3$ and AgOTf. On the other hand, the addition of phenol to acyclic dienes can be catalyzed by AgOTf alone, provided that the reaction is run at higher temperature. The reaction first proceeds via a C_{sp}^2-H bond addition to the diene, followed by intramolecular O-H addition. Oxidation of the desired product by Au(III) can be observed if the reaction is run for too long.

3.7 Appendix for Chapter 3 (Experimental Section)

(This section is published as "Supporting Information")

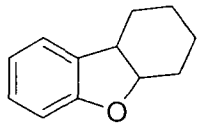
All experiments were carried out under nitrogen atmosphere. Dichloromethane was dried using CaH_2. Analytical and preparative thin-layer chromatography plates (TLC) were ordered from Silicycle Inc. (TLC glass plate). Visualization of the spots on the TLC plates was achieved by exposure to UV light or $KMnO_4$ stain. Column chromatography was performed over Sorbent silica gel 30-60μm. ^1H NMR and ^{13}C NMR spectra were acquired by Varian 400 and 100MHz or 300 and 75MHz, respectively, and referenced to the internal solvent signals. IR spectra were recorded by ABB Bomem MB100 spectrometer. Mass spectra data and HRMS were obtained by Kratos MS25RFA Mass Spectometer.

New compounds were fully characterized (^1H NMR, ^{13}C NMR, IR, HRMS) whereas known compounds were partially characterized (^1H NMR and ^{13}C NMR) and compared to the literature reference. Assignment of the syn/anti isomers NMR peaks were determined by comparing spectroscopic data to the literature reference.

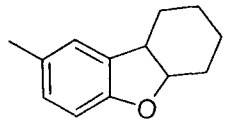
Typical experimental procedure for the addition of arenes to dienes (Table 8, entry 1):

A solution of $AuCl_3$ (7.6 mg, 0.025 mmol) and AgOTf (19.3 mg, 0.075 mmol) was stirred in dry dichloromethane (1.5 mL) at room temperature for 2 hrs. Phenol (94 mg, 0.5 mmol) was then added, which was followed by the dropwise (approx. 1 drop/sec.) addition of cyclohexadiene (124μL, 1.0 mmol diluted in 0.5 mL of

dry dichloromethane) and the resulting solution was stirred overnight at 40-45°C. The resulting solution was filtered through a cotton plug and the solvent was removed under reduced pressure to afford a dark oil. The internal standard (nitromethane) was added and a crude ^{1}H NMR was recorded. The product was isolated via column chromatography on silica gel (gradiant eluent: hexane: dichloromethane = 40:1 to 2:1) to afford 74% of a colorless oil.

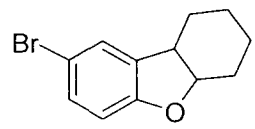


1,2,3,4,4a,9b-Hexahydro-dibenzofuran (Table 8, entry 1).[50] Isolated as a colorless gummy oil. The ratio of two diastereoisomers is 3:1. Syn isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 4.68(q, 1H, *J*=7.2 Hz), 3.20(q, 1H, *J*=7.2 Hz); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 159.4, 133.6, 127.9, 123.7, 120.6, 110.2, 82.8, 41.0, 28.7, 27.9, 22.5, 21.0; Anti isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 4.59(m, 1H), 3.00(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 156.3, 128.6, 127.5, 119.4, 115.3, 109.6, 71.2, 33.7, 33.5, 31.9, 29.9, 17.7; Overlapped peaks: : ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 7.16-7.10(m), 6.88-6.81(m), 2.00-1.75(m), 1.56-1.33(m).



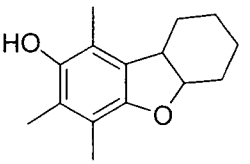
8-Methyl-1,2,3,4,4a,9b-hexahydro-dibenzofuran (Table 8, entry 2). Isolated as a colorless gummy oil. The ratio of two diastereoisomers is 4:1. IR(neat): 2930,

1616, 1514, 1448, 1213, 948, 813 cm^{-1}; Syn isomer: ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 6.95(d, 1H, *J*=8.0 Hz), 6.74(d, 1H, *J*=8.0 Hz), 4.66(m, 1H), 3.17(q, 1H, *J*=7.2 Hz), 2.32(s, 3H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 157.4, 133.7, 129.90, 128.2, 124.4, 109.7, 82.8, 40.9, 28.5, 27.8, 22.4, 21.1, 20.9; MS(EI): m/z 188, 173; HRMS calc'd for $C_{18}H_{16}O$: 188.1201; found, 188.1195; Anti isomer: ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 6.95(d, 1H, *J*=8.0 Hz), 6.75(d, 1H, *J*=8.0 Hz), 4.59(m, 1H), 2.97(m, 1H), 229(s, 3H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 154.2, 129.1, 128.5, 128.2, 126.4, 115.0, 70.9, 33.6, 33.3, 31.7, 29.8, 20.7, 17.5; Overlapped peaks: ^1H NMR($CDCl_3$, 400MHz, ppm): 6.98(s), 1.98(m), 1.90-1.54, 1.57-1.53(m), 1.37(m).

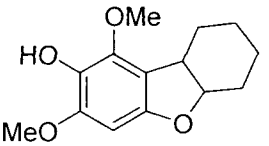


8-Bromo-1,2,3,4,4a,9b-hexahydro-dibenzofuran (Table 8, entry 3). Isolated as a colorless gummy oil. The ratio of two diastereoisomers is 3:1. IR(neat): 2926, 1600, 1446, 1414, 1369, 1217, 1085, 994 cm^{-1}; Syn isomer: ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.22(s, 1H), 7.20(d, 1H, *J*= 8.4 Hz), 6.70(d, 1H, *J*= 8.4Hz), 4.69(m, 1H), 3.20(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 158.7, 134.2, 130.7, 126.8, 117.2, 111.8, 83.4, 40.9, 28.3, 27.6, 22.1, 20.7; MS(EI): m/z 252, 173; HRMS calc'd for $C_{12}H_{13}O^{79}Br$: 252.0150; found, 252.0141; HRMS calc'd for $C_{12}H_{13}O^{81}Br$: 254.0129; found, 254.0123; Anti isomer: ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.23(s, 1H), 7.19(d, 1H, *J*= 8.4 Hz), 6.68(d, 1H, *J*= 8.4Hz), 4.58(m, 1H), 2.96(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 155.6, 131.2,

130.4, 127.7, 113.1, 112.4, 71.3, 33.3, 31.6, 29.3, 28.9, 17.3; Overlapped peaks: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ=1.98-1.78(m), 1.57-1.47(m), 1.39-1.35(m).

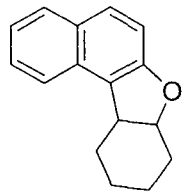


1,3,4-Trimethyl-5a,6,7,8,9,9a-hexahydro-dibenzofuran-2-ol (Table 8, entry 4).[51] Isolated as a pale yellow solid. The eluent gradient was a mixture of hexanes: ethyl acetate (60:1). The ratio of two diastereoisomers is 12:1. Syn isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 4.48(m, 1H), 4.24(s, 1H), 2.16(s, 9H); ^{13}C NMR($CDCl_3$, 100MHz, ppm): δ= 151.5, 145.9, 131.3, 127.1, 121.4, 116.7, 81.8, 40.7, 29.0, 27.9, 23.3, 22.7, 20.8, 12.5, 12.5, 12.2; Anti isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 4.82(m, 1H), 4.22(s, 1H), 3.31(m, 1H), 2.13(s, 9H); ^{13}C NMR($CDCl_3$, 100MHz, ppm): δ= 151.3, 142.5, 133.8, 121.8, 117.3, 115.7, 86.1, 47.7, 31.8, 29.6, 24.8, 23.7, 12.4, 12.2, 11.9; Overlapped peaks: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ=2.97(m), 2.30(m), 1.95(m), 1.76-1.56(m), 1.26-1.13(m).



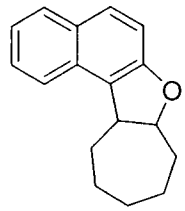
1,3-Dimethoxy-5a,6,7,8,9,9a-hexahydro-dibenzofuran-2-ol (Table 8, entry 4).[52] Isolated as a brown solid. The eluent gradient was a mixture of hexanes: ethyl acetate (20:1). The ratio of two diastereoisomers is 10:1. Syn isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 6.18(s, 1H); ^{13}C NMR($CDCl_3$, 100MHz, ppm):

δ= 152.7, 148.1, 142.8, 130.4, 114.5, 88.9, 87.25 60.7, 56.6, 44.3, 33.3, 30.5, 25.6, 22.01 Anti isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 6.27(s, 1H); ^{13}C NMR($CDCl_3$, 100MHz, ppm): δ= 153.9, 145.4, 141.3, 127.8, 112.6, 86.4, 82.7, 57.8, 56.3, 42.5, 30.6, 27.0, 22.8, 21.4; Overlapped peaks: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ=4.55(m), 3.97(m), 3.88(m), 3.79(m), 2.15-1.22(m).

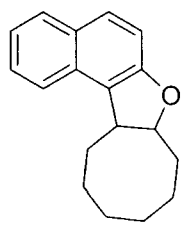


6b,7,8,9,10,10a-Hexahydro-benzo[b]naphtho[2,1-d]furan (Table 8, entry 6).[53]

Isolated as a colorless gummy oil. The ratio of two diastereoisomers is 11:1. Syn isomer: ^{1}H-NMR($CDCl_3$, 400MHz, ppm): δ= 7.88(d, 1H, *J*=8.4 Hz), 7.74(d, 1H, *J*=6.4 Hz), 7.52(t, 1H, *J*=7.2 Hz), 7.35(t, 1H, *J*=7.2 Hz), 7.25(d, 1H, *J*=8.4 Hz), 4.83(m, 1H), 3.48(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 156.8, 130.4, 129.6, 129.0, 128.7, 126.9, 126.6, 122.8, 122.8, 112.8, 83.8, 40.2, 29.4, 27.8, 23.0, 20.8; Anti isomer (some peaks are difficult to distinguished): ^{1}H-NMR($CDCl_3$, 400MHz, ppm): δ= 7.98(d, 1H, *J*=8.4 Hz), 7.59(t, 1H, *J*=7.2 Hz), 7.18(d, 1H, *J*=8.4 Hz), 4.68(m, 1H), 3.69(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 153.7, 128.9, 128.8, 127.8, 126.4, 125.8, 124.0, 123.8, 123.7, 112.5, 70.9, 40.2, 27.4, 26.9, 23.5, 23.1. Overlapped peaks: ^{1}H-NMR($CDCl_3$, 400MHz, ppm): δ=2.46(m), 2.26(m), 1.91(m), 1.73(m), 1.32(m).

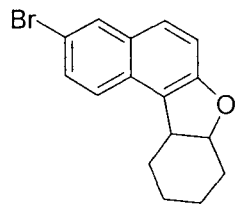


7,8,9,10,11,11a-Hexahydro-6bH-12-oxa-naphtho[2,1-a]azulene (Table 8, entry 7).[51] Isolated as a colorless gummy oil. The ratio of two diastereoisomers is 8:1. Syn isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 7.87(d, 1H, *J*=8.0 Hz), 7.75(d, 1H, *J*=8.0 Hz), 7.71(d, 1H, *J*=8.4 Hz), 7.53(t, 1H, *J*=8.4 Hz), 7.35(t, 1H, *J*=8.4 Hz), 7.08(d, 1H, *J*=8.4 Hz), 5.07(m, 1H), 3.82(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 156.5, 130.8, 129.7, 129.5, 129.3, 126.7, 123.1, 122.7, 122.4, 112.2, 88.0, 47.1, 31.9, 31.8, 29.9, 29.5, 24.2; Anti isomer (some peaks are difficult to distinguished): ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 7.97(d, 1H, *J*=8.0 Hz), 7.69(d, 1H, *J*=8.4 Hz), 7.62(d, 1H, *J*=8.0 Hz), 4.83(m, 1H), 3.75(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 155.9, 128.5, 125.9, 125.6, 124.3, 123.9, 123.38, 122.8, 122.3, 112.4, 73.1, 37.5, 34.8, 29.1, 28.1, 26.3, 26.2. Overlapped peaks: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ=2.37(m), 2.19-1.97(m), 1.97(m), 1.83(m), 1.55(m).



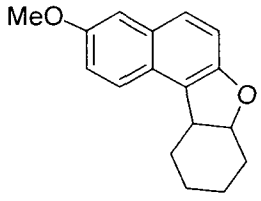
7a,8,9,10,11,12,13,13a-Octahydro-7-oxaoctaleno[2,-a]-naphthalene (Table 8, entry 8).[51] Isolated as a colorless gummy oil. The ratio of two diastereoisomers is

5:1. Syn isomer: ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.85(d, 1H, *J*=9.6 Hz), 7.13(d, 1H, *J*=9.0 Hz), 4.82(m, 1H), 3.61(m, 1H), 2.38(m, 2H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 155.4, 130.4, 129.9, 129.4, 129.2, 126.8, 125.8, 122.8, 122.4, 112.2, 88.8, 45.9, 30.9, 28.5, 26.6, 26.1, 25.8, 25.6; Anti isomer (some peaks are difficult to distinguished): ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.90(d, 1H, *J*=9.6 Hz), 7.11(d, 1H, *J*=9.0 Hz), 4.56(m, 1H), 3.87(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 155.0, 129.1, 128.8, 128.0, 126.2, 124.3, 122.9, 122.8, 120.0, 111.9, 73.5, 34.9, 32.2, 31.5, 29.6, 27.2, 24.5, 23.0; Overlapped peaks: ^{1}H NMR($CDCl_3$, 300MHz, ppm): δ= 7.67(m), 7.51(m), 7.33(m), 2.30-2.22(m), 1.91-1.85(m), 1.69-1.23(m).

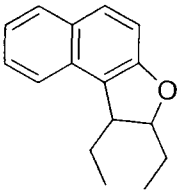


3-Bromo-7a,8,9,10,11,11a-hexahydro-benzo[b]naphtho[1,2-d]furan (Table 8, entry 9). Isolated as a white solid. The ratio of two diastereoisomers is 11:1. IR(KBr plate): 2930, 1626, 1575, 1508, 1474, 1348, 1161, 1061 cm^{-1}; Syn isomer: ^{1}H-NMR($CDCl_3$, 300MHz, ppm): δ= 4.79(m, 1H), 3.44(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 157.2, 131.0, 130.7, 129.8, 127.9, 127.8, 127.33, 124.6, 116.9, 113.8, 83.8, 39.9, 29.30 27.5, 22.7, 20.5; MS(EI) m/z 302, 223; HRMS calc'd for $C_{16}H_{15}O^{79}Br$: 302.0306; found: 302.0297; HRMS calc'd for $C_{16}H_{15}O^{81}Br$: 304.0286; found: 304.0282; Anti isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): 4.67(m, 1H), 3.62(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ=

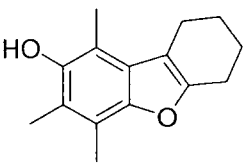
156.6, 131.2, 130.7, 129.7, 129.1, 128.7, 126.9, 126.6, 122.9, 112.8, 71.8, 34.1, 30.5, 27.0, 23.2, 21.8; Overlapped peaks: ^{1}H-NMR($CDCl_3$, 400MHz, ppm): δ=7.96(s), 7.58-4.49(m), 7.17(m), 2.38(m), 2.15(m), 1.86(m), 1.70(m), 1.55(m), 1.34-1.18(m).



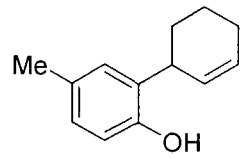
3-Methoxy-7a,8,9,10,11,11a-hexahydro-benzo[b]naphtho[1,2-d]furan (Table 8, entry 10). Isolated as a pale yellow solid. The ratio of two diastereoisomers is 11:1. IR(KBr plate): 2935, 2853, 1626, 1600, 1521, 1347, 1261, 1098, 733 cm^{-1}; Syn isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 4.76(m, 1H), 3.42(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 155.6, 155.3, 130.5, 127.5, 126.0, 124.5, 119.6, 11.11, 107.3, 83.6, 55.6, 40.3, 29.6, 27.8, 23.1, 20.9; MS(EI): m/z 254, 174; HRMS calc'd for $C_{17}H_{18}O_2$: 254.1307; found, 254.1304; Anti isomer: ^{1}H NMR($CDCl_3$, 400MHz, ppm): 4.65(m, 1H), 3.64(m, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 153.8, 152.2, 129.4, 126.1, 125.7, 122.6, 118.0, 114.1, 112.1, 107.8, 70,9, 55.0, 34.2, 31.7, 24.1, 21.9, 18.4; Overlapped peaks: 7.61(m), 7.06(m), 3.91(s, 3H), 2.35(m), 2.04(m), 1.89-1.79(m), 1.71(m), 1.34-1.27(m).



1,2-Diethyl-1,2-dihydro-naphtho[2,1-b]furan (76).[46] Isolated as a pale yellow oil and a 1:1 mixture of two isomers. Representative peaks of the two isomers: ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 4.70(m, 1H), 4.41(m, 1H), 3.67(quint, 1H, *J*= 7.2 Hz), 3.55(m, 1H). Overlapped peaks: ^{1}H-NMR($CDCl_3$, 400MHz, ppm): δ= 7.82-7.10(m), 1.90-1.66(m), 1.22-1.05(m). ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 157.0, 156.6, 131.2, 130.4, 129.8, 129.7, 129.1, 128.7, 128.5, 128.3, 126.7, 126.3, 126.1, 125.8, 122.7, 122.5, 122.3, 122.1, 112.6, 112.4, 92.3, 90.0, 40.7, 37.5, 29.6, 28.0, 25.2, 23.8, 22.4, 20.3, 11.9, 11.2, 10.7, 10.3.



1,3,4-Trimethyl-6,7,8,9-tetrahydro-dibenzofuran-2-ol (79). Isolated as a brown solid. IR(KBr plate): 3520, 1598, 1509, 1455, 1378, 1285, 1158, 1023 cm^{-1}; ^{1}H-NMR($CDCl_3$, 400MHz, ppm): δ= 2.83(m, 1H), 2.71(m, 1H), 2.43(s, 3H), 2.38(s, 3H), 2.26(s, 3H), 2.17 (m, 2H), 1.90-1.83(m, 4H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 153.3, 146.4, 140.8, 138.0, 128.2, 126.4, 122.7, 120.9, 40.7, 29.0, 27.9, 23.3, 22.7, 20.8, 12.5, 12.5, 12.2; MS(EI) m/z 230; HRMS calc'd for $C_{15}H_{18}O_2$: 230.1301; found: 230.1299.



2-Cyclohex-2-enyl-4-methyl-phenol (81). [54] The product was isolated on a preparative TLC plate (gradiant eluent: hexanes: dichloromethane = 3:1). Isolated as a colorless oil. ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 7.12-6.70(m, 3H), 6.22-5.67(m, 2H), 3.54(m, 1H), 2.23(s, 3H), 2.14-1.56(m 6H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 157.8, 132.2, 127.6, 126.2, 123.8, 122.3, 121.8, 120.3, 42.3, 31.4, 25.8, 23.3, 20.6.

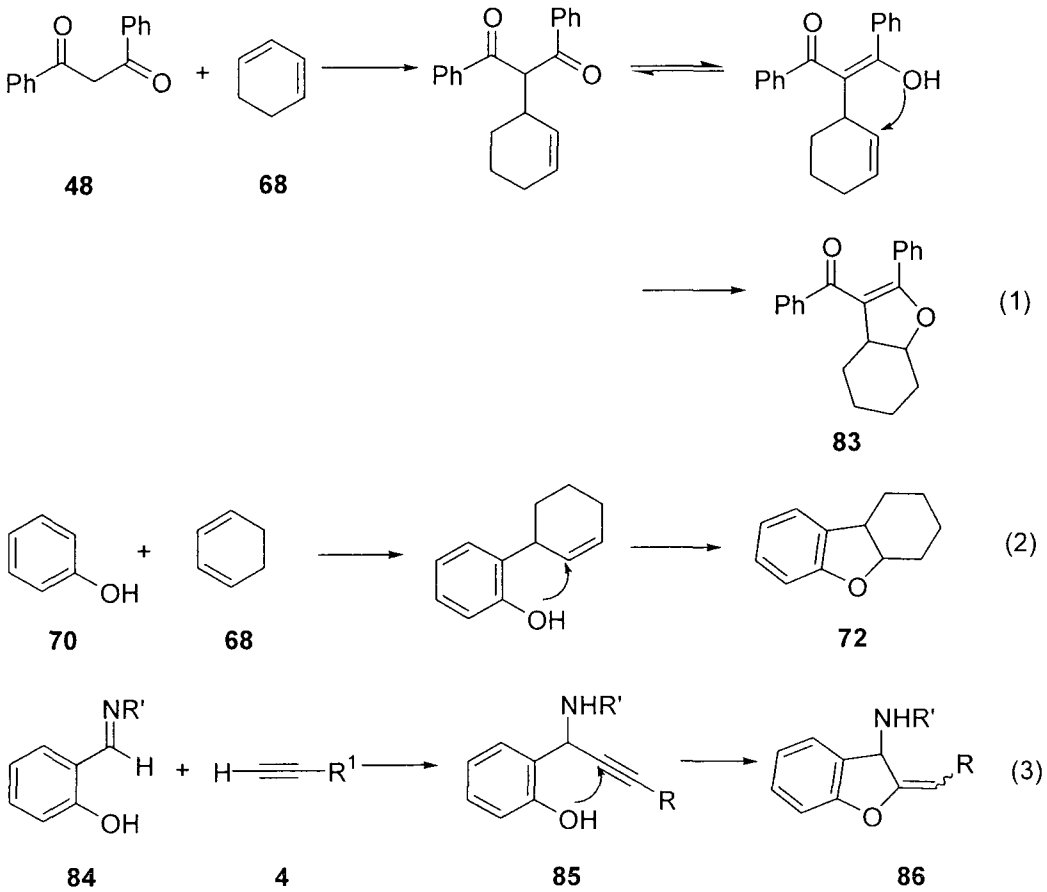
Chapter 4:

Catalytic Addition of Terminal Alkynes (C_{sp}-H Bond) to Imines: Application to the Synthesis of Dihydrobenzofurans II - Efficient Synthesis of Dihydrobenzofurans via a Multicomponent Coupling of Salicylaldehydes, Amines, and Alkynes

Chapter 4: Catalytic Addition of Terminal Alkynes (C_{sp}-H Bond) to Imines: Application to the Synthesis of Dihydrobenzofurans II-Efficient Synthesis of Dihydrobenzofurans via a Multicomponent Coupling of Salicylaldehydes, Amines, and Alkynes

4.1 Preface

In the two previous chapters, the formation of dihydrofurans was accomplished via the sequential addition of C-H and O-H bond to dienes. In both cases, the cyclization occurred via intramolecular addition of the hydroxyl group to the double bond to form **72** and **83** (Scheme 37, eqs. 1 and 2). A similar intramolecular addition of the hydroxyl group to a triple bond would also lead to dihydrofurans with an exocylic double bond **86** (Scheme 37, eq. 3). The formation of intermediate **85** can be obtained by addition of a terminal alkyne (C_{sp}-H bond) **4** to an electrophile, such as a imine **84**. Obviously, the desired imine is formed via condensation of salicylaldehyde and an amine. The alkyne-imine addition is well-known (see Chapter 1) to be catalyzed by group 11 metals. The same metal should be able to catalyze the cyclization step by coordinating to the triple bond, followed by O-H addition.



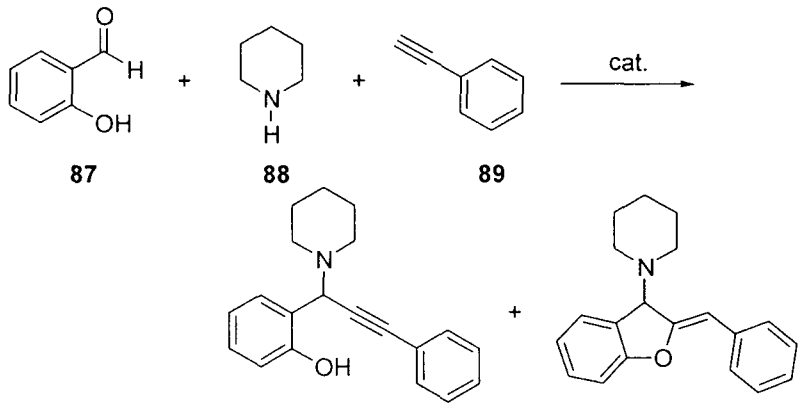
Scheme 37. Hypothesis for the formation of dihydrofurans via the addition of terminal alkyne **84** to imine **4**

4.2 Optimization of the Synthesis I

Salicylaldehyde **87**, piperidine **88** and phenylacetylene **89** were chosen as the three prototype components for this reaction. The imine was formed *in situ* followed by the terminal alkyne addition (the three components were added simultaneously). Various metal salts were tested in toluene at 100°C or dichloroethane at 80°C. A selection of these reactions is shown in Table 9. While the alkyne addition to the imine **90** is efficient, no cyclization product **91** is detected under these conditions. It soon became obvious that the original

hypothesis needed to be modified in order to favor the reaction to the cyclic product.

Table 9. Multicomponent Coupling of Salicylaldehyde, Piperidine and Phenylacetylene Catalyzed by Various Metal Salts



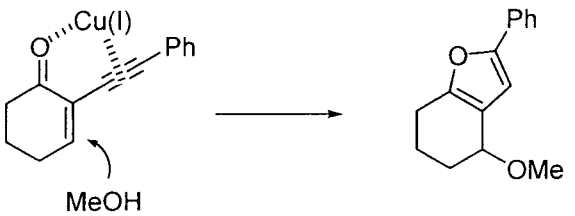
entry[a]	catalyst	Yield (%)[b]	Ratio **90**:**91**
1	10% $AuCl_3$	89	100:0
2	10% $Au(PPh_3)Cl$	91	100:0
3	10% $NaAuCl_4$	88	100:0
4	10% AgOTf	83	100:0
5	10% AgCl	85	100:0
6	10% AgOAc	88	100:0
7	10% CuI	93	100:0
8	10% $Cu(OTf)_2$	91	100:0

[a] Reactions were run with 1 equiv. of aldehyde, 2 equiv. of amine and 2 equiv. of alkyne in toluene at 100°C. [b] NMR yield using CH_3NO_2 as internal standard

4.3 Revision of Hypothesis

In 2003, Yamamoto reported an interesting tentative mechanism for the formation of furans **93**. Presumably, the copper catalyst coordinates to both the

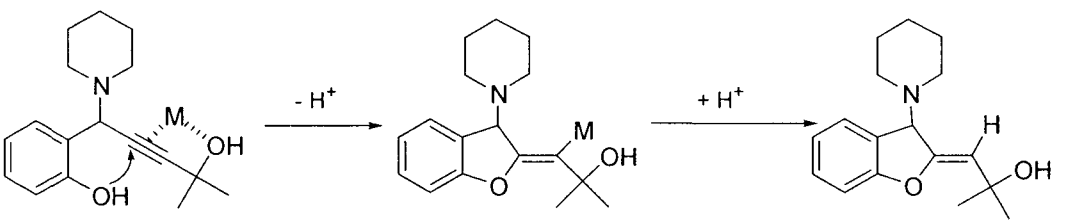
carbonyl and the triple bond **92**, while a nucleophile (such as methanol) attacks the electrophilic site (Michael addition) (Scheme 38).[55]



92 **93**

Scheme 38. Yamamoto's dual activation by Cu(I)

Based on this observation, a modified hypothesis was proposed. The presence of a a heteroatom on alkyne **94** can help the metal to coordinate to the triple bond. The O-H addition then occurs, followed by protonolysis of **95** to afford the desired product **96** (Scheme 39).

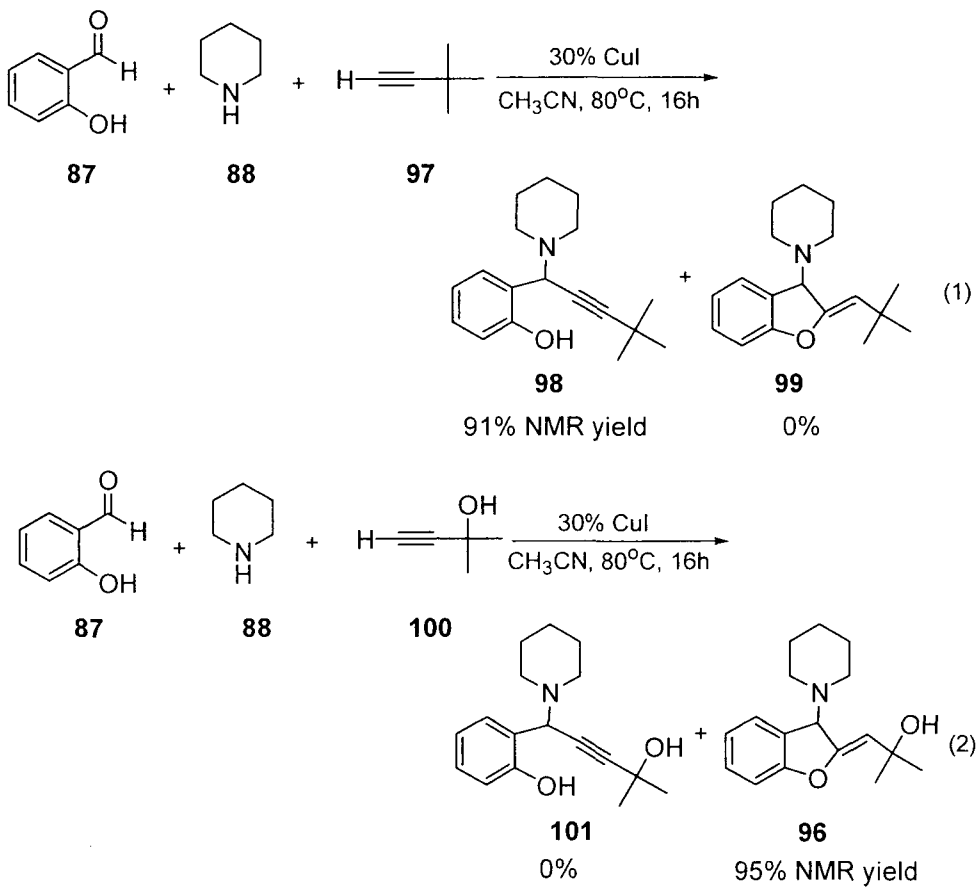


94 **95** **96**

Scheme 39. Revision of hypothesis

To test this hypothesis, two reactions were carried out (Scheme 40). As expected, the coupling of salicylaldehyde **87**, piperidine **88** and 3,3-dimethyl-but-1-yne **97** led to the exclusive formation of the propargylamine **98** (91% NMR yield)

(Scheme 40, eq. 1). However, under the same conditions, if 3,3-dimethyl-but-1-yne is replaced by 2,2-dimethyl-3-butyn-2-ol **100**, the reaction affords the desired cyclized **96** product in excellent yield with no detectable amount of the propargylamine **101** remaining (95% NMR yield) (Scheme 40, eq. 2). Although these results are satisfactory, further studies were conducted in order to decrease the catalyst loading and reaction time.

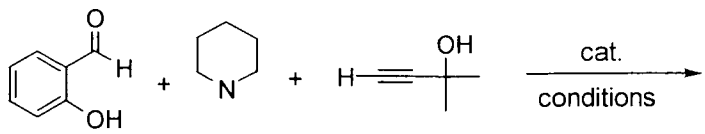


Scheme 40. Copper-catalyzed multicomponent coupling of salicylaldehyde, piperidine and alkyne

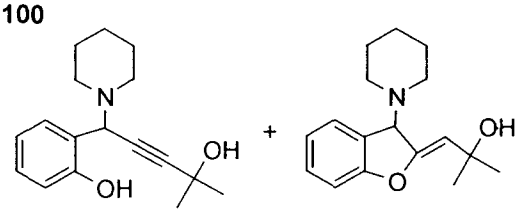
4.4 Optimization of the Synthesis II

When AuI was used as a catalyst, only the alkyne-imine addition product was obtained under the same reaction conditions (Table 10, entry 2). Both AgCl and AgBr were also effective for the cascade reaction (Table 10, entries 3-4). Since CuI is much more economical than silver salts, further investigations were carried out with CuI. Under microwave irradiation, the reaction time is shortened, the amount of required catalyst is reduced and the use of solvent is eliminated (Table 10, entries 6-7). Microwave irradiation at 130°C for 30 min with 5 mol% CuI as catalyst in the absence of solvent provided optimal conditions in terms of yield and reaction time. Further attempts to shorten reaction time resulted in incomplete conversion (Table 10, entry 8-9).

Table 10. Multicomponent Coupling of Salicylaldehyde, Piperidine and 2,2-dimethyl-3-butyn-2-ol



87 **88** **100**



101 **96**

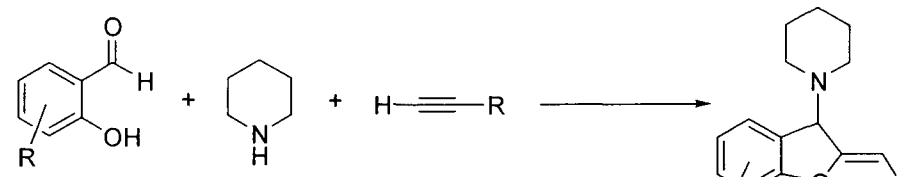
entry[a]	cat.	conditions	yield **101** (%)[b]	yield **96** (%)[b]
1	30% CuI	CH_3CN, 80°C, 16h	0	94
2	30% AuI	CH_3CN, 80°C, 16h	90	0
3	20% AgBr	CH_3CN, 80°C, 16h	0	88
4	20% AgCl	CH_3CN, 80°C, 16h	0	84
5	30% CuI	MW, 130°C, 35 min., CH_3CN	0	74
6	30% CuI	MW, 130°C, 35 min., neat	0	80
7	5% CuI	MW, 130°C, 35 min., neat	0	91
8	5% CuI	MW, 130°C, 15min., neat	18	54
9	5% CuI	MW, 130°C, 5 min., neat	39	28

[a] *Reactions were run with 1 equiv. of aldehyde, 2 equiv. of amine and 2 equiv. of alkyne.* [b] *NMR yield using* CH_3NO_2 as internal standard.

4.5 Scope and Limitations of the Cyclization Reaction

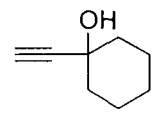
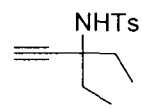
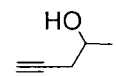
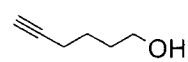
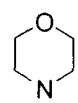
Subsequently, various salicylaldehydes, amines and propargyl alcohols were tested under our optimized reaction conditions (Table 11). Interestingly, the reaction was not limited to propargyl alcohols. Indeed, a protected propargylamine can be used, as well as a homo-propargyl alcohol (Table 11, entries 3-4). The use of 1-hexynol also affords the cyclized product, albeit in a lower yield due to competing dimerization (Table 11, entry 5). Unfortunately, primary amines were not effective for this transformation. The reaction is equally effective with 5% CuI under standard reaction conditions (oil bath at 80°C for 16h) with 1.2 equivalents of amine and alkyne. The *Z* isomer was obtained exclusively for all compounds as determined by NOE experiment (Figure 3). This is consistent with a *5-anti-exo-dig* mechanism[56] proposed in Scheme 39.

Table 11. Copper-Catalyzed Multicomponent Coupling of Salicylaldehyde, Amine and Alkyne

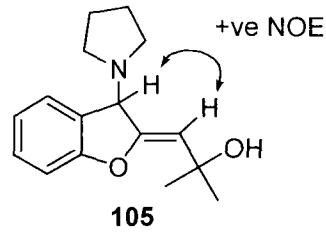


87: R = H
102: R = naphthyl
103: R = 5-Cl
104: R = 3-OMe

88

entry[a]	aldehyde	amine	alkyne	isolated yield (%)
1	**87**	**88**	**100**	85
2	**87**	**88**		81
3	**87**	**88**		53
4	**87**	**88**		88
5	**87**	**88**		58
6	**87**		**100**	44
7	**87**		**100**	88
8[b]	**102**	**88**	**100**	80
9[b]	**103**	**88**	**100**	71
10[b]	**104**	**88**	**100**	82

[a] Reactions were run at 130°C for 30 minutes in a microwave reactor using 1 equiv of aldehyde, 2 equiv of amine and 2 equiv of alkyne under neat conditions with 5% CuI. [b] Acetonitrile was used as a solvent.



105

Figure 3. Determination of Stereochemistry of **105** by NOE Experiment

4.6 Conclusion

In summary, an atom-economical synthesis of dihydrofurans was developed based on the terminal alkyne (C_{sp}-H) addition to imine, followed by intramolecular cyclization. The reaction is run under microwave irradiation or conventional heating and catalyzed by cheap copper iodide. The key to the synthesis is the use of molecules containing both a terminal alkynyl moiety and a heteroatom.

4.7 Appendix for Chapter 4 (Experimental Section)

(This section is published as "Supporting Information")

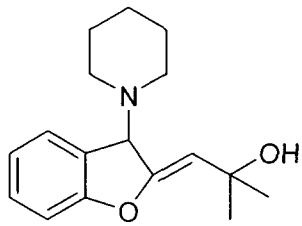
All experiments were carried out under normal air atmosphere. Microwave reactions were performed using a Biotage initiator microwave synthesizer. Analytical and preparative thin-layer chromatography plates (TLC) were ordered from Silicycle Inc. (TLC glass plate). Visualization of the spots on the TLC plates was achieved by exposure to UV light or $KMnO_4$ stain. ^1H NMR and ^{13}C NMR spectra were acquired by Varian 400 and 100MHz or 300 and 75MHz, respectively, and referenced to the internal solvent signals. IR spectra were recorded by ABB Bomem MB100 spectrometer. Mass spectra data and HRMS were obtained by Kratos MS25RFA Mass Spectometer. The N-tosyl propargylamine was prepared according to literature procedure.[57]

New compounds were fully characterized (^1H NMR, ^{13}C NMR, IR, HRMS) whereas known compounds were partially characterized (^1H NMR and ^{13}C NMR) and compared to the literature reference.

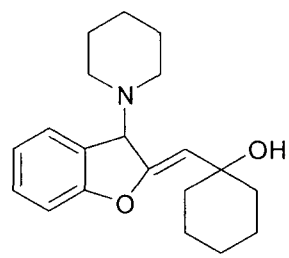
Typical experimental procedure for the addition of alkynes to imines (Table 11, entry 6):

In a 5 mL Biotage microwave vial, salicylaldehyde (209 μL, 2 mmol), morpholine (348 μL, 4 mmol), 2-methyl-3-butyn-2-ol (387 μL, 4 mmol) and CuI (19 mg, 0.10 mmol) were mixed. The vial was then capped and was subjected to microwave irradiation for 30 minutes at 130°C. The crude mixture was directly isolated via

column chromatography on silica gel (gradient eluent: hexane: ethyl acetate = 10:1 to 1:1). Gives 241 mg (44% yield).

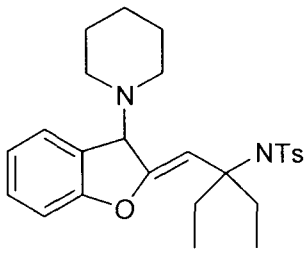


2-Methyl-1-(3-piperidin-1-yl-3H-benzofuran-2-ylidene)-propan-2-ol (Table 11, entry 1). Isolated as a pale yellow solid. IR(KBr plate): 3419 (br), 2933, 1696, 1463, 1158 cm^{-1}; ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.36(d, 1H, *J*= 7.2 Hz), 7.24(t, 1H, *J*= 8.0 Hz), 6.99(t, 1H, *J*= 8.4 Hz), 6.34(d, 1H, *J*=8.4 Hz), 5.13(s, 1H), 4.79(s, 1H), 2.58(m, 2H), 2.40(m, 2H), 1.53-1.39(m, 12H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 157.7, 152.2, 129.5, 126.3, 125.4, 122.2, 113.8, 109.9, 70.6, 67.8, 49.6, 30.9, 30.8, 26.5, 24.6; MS(EI): m/z 223, 214, 189; HRMS calc'd for $C_{17}H_{23}O_2N$: 273.1729; found, 273.1723.

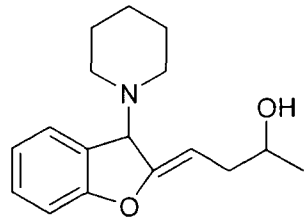


1-(3-Piperidin-1-yl-3H-benzofuran-2-ylidenemethyl)-cyclohexanol (Table 11, entry 2). Isolated as a colorless gummy oil. IR(neat): 3419 (br), 2948, 1698, 1612, 1464, 1289 cm^{-1}; ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.33(m, 1H), 7.17(m, 1H), 6.91(m, 1H), 6.85(m, 1H), 5.08(s, 1H), 4.74(s, 1H), 2.53(m, 2H), 2.32(m, 2H), 1.85-1.36(m, 16H); ^{13}C NMR($CDCl_3$, 100MHz, ppm): δ= 157.6,

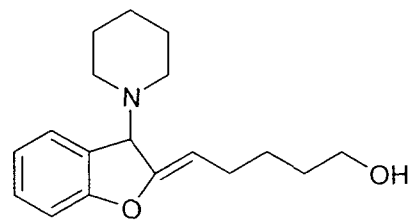
152.9, 129.4, 126.2, 125.2, 122.1, 112.4, 109.9, 71.7, 67.8, 49.6, 30.0, 26.5, 25.8, 24.6, 23.0; MS(EI): m/z 313, 229, 214; HRMS: calc'd for $C_{20}H_{27}O_2N$: 313.2036; found, 313.2042.



N-[1-Ethyl-1-(3-piperidin-1-yl-3H-benzofuran-2-ylidenemethyl)-propyl]-4-methyl-benzenesulfonamide (Table 11, entry 3). Isolated as a pale yellow solid. IR(KBr plate): 2970, 2802, 1696, 1612, 1594, 1461, 1157, 1094 cm^{-1}; ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.64(m, 2H), 7.25(m, 2H), 6.92(m, 2H), 6.92(m, 4H), 5.26(s, 1H), 4.53(s, 1H), 4.19(s, 1H), 2.39(m, 1H), 2.27(m, 1H), 2.19(s, 3H), 2.03(m, 3H), 1.74(m, 3H), 1.34(m, 6H), 0.84(m, 6H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 157.5, 153.6, 142.5, 139.9, 129.6, 129.0, 127.4, 126.0, 125.3, 122.2, 110.0, 108.0, 67.8, 62.7, 49.6, 30.3, 26.3, 24.5, 21.6, 8.4; MS(EI): m/z 454, 283, 214, 155; HRMS: calc'd for $C_{26}H_{34}O_3N_2S$: 454.2290; found, 454.2282.

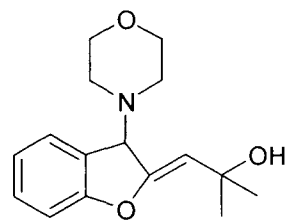


4-(3-Piperidin-1-yl-3H-benzofuran-2-ylidene)-butan-2-ol (Table 11, entry 4). Isolated as a colorless gummy oil. IR(neat): 3382 (br), 2931, 1701, 1612, 1475, 1218, 1151 cm^{-1}; ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.36(d, 1H, *J*= 8.8 Hz), 7.20(t, 1H, *J*= 7.6 Hz), 6.94(t, 1H, *J*= 7.2 Hz), 6.80(d, 1H, *J*= 8.4 Hz), 4.96(t, 1H, *J*= 7.2 Hz), 4.78(s, 1H), 3.93(sept, 1H, J= 6.0 Hz), 2.39(m, 6H), 1.53-1.38(m, 9H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 158.1, 154.9, 129.5, 126.4, 125.9, 121.7, 109.8, 101.7, 68.1, 67.2, 49.6, 35.4, 26.4, 24.6, 23.1; MS(EI): m/z 273, 214, 188; HRMS calc'd for $C_{17}H_{23}O_2N$: 273.1729; found, 273.1723.

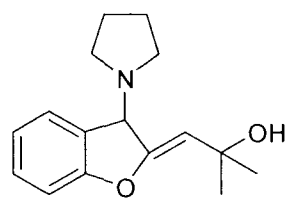


5-(3-Diethylamino-3H-benzofuran-2-ylidene)-pentan-1-ol (Table 11, entry 5). Isolated as a colorless gummy oil. IR(neat): 3412 (br), 2935, 1711, 1611, 1463, 1234 cm^{-1}; ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.27(d, 1H, *J*= 7.2 Hz), 7.11(t, 1H, *J*= 8.0 Hz), 6.84(t, 1H, *J*= 8.4 Hz), 6.74(d, 1H, *J*= 8.0 Hz), 4.78(t, 1H, *J*= 6.4 Hz), 4.62(s, 1H), 3.46(m, 2H), 2.45-2.17(m, 4H), 1.56-1.26(m, 12H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 158.2, 152.6, 129.4, 126.4, 125.7, 121.5, 109.5,

106.3, 66.8, 61.9, 49.2, 35.3, 32.0, 29.8, 25.3, 20.1; MS(EI): m/z 287, 214, 202; HRMS calc'd for $C_{18}H_{25}O_2N$: 287.1872; found, 287.1875.

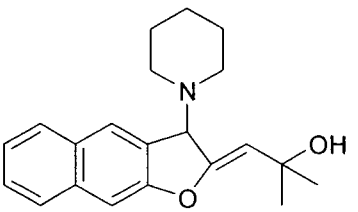


2-Methyl-1-(3-morpholin-4-yl-3H-benzofuran-2-ylidene)-propan-2-ol (Table 11, entry 6). Isolated as a pale yellow gummy oil. IR(neat): 3419 (br), 2967, 1612, 1462, 1374, 1232, 1115 $cm^{-1;}$ ^{1}H-NMR($CDCl_3$, 400MHz, ppm): δ= 7.41(d, 1H, *J*= 8.0 Hz), 7.26(t, 1H, *J*= 8.4), 7.01(t, 1H, *J*= 8.0 Hz), 6.94(d, 1H, *J*= 8.0 Hz), 5.15(s, 1H), 4.79(s, 1H), 3.66(m, 4H), 2.63(m, 2H), 2.41(m, 2H), 1.50(s, 3H), 1.48(s, 3H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 157.7, 151.4, 136.1, 129.9, 126.3, 122.4, 114.5, 110.1, 70.6, 67.4, 48.6, 30.8, 30.8; MS(EI): m/z 275, 216, 189, 131, 86; HRMS calc'd for $C_{16}H_{21}O_3N$: 275.1521; found, 275.1519.

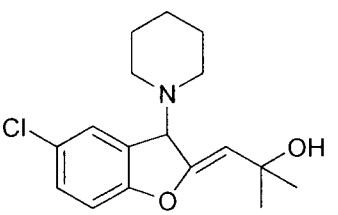


2-Methyl-1-(3-pyrrolidin-1-yl-3H-benzofuran-2-ylidene)-propan-2-ol (Table 11, entry 7). Isolated as a pale yellow solid. IR(KBr): 3430 (br), 2911, 1672, 1561, 1341, 1160 cm^{-1}; ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 7.35(d, 1H, *J*= 7.2 Hz), 7.19(t, 1H, *J*= 8.0 Hz), 6.93(t, 1H, *J*= 8.4 Hz), 6.87(d, 1H, *J*= 8.0 Hz), 5.12(s, 1H), 4.74(s, 1H), 2.57(m, 2H), 2.36(m, 2H), 1.54-1.24(m, 10H); ^{13}C

NMR($CDCl_3$, 75MHz, ppm): δ= 157.6, 152.2, 129.5, 125.4, 122.2, 113.7, 109.9, 70.6, 67.8, 49.6, 30.9, 26.5, 24.6; MS(EI): m/z 258, 189, 131; HRMS calc'd for $C_{16}H_{21}O_2N$: 258.1494; found, 258.1491.

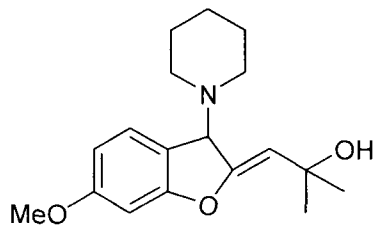


2-Methyl-1-(3-piperidin-1-yl-3H-naphtho[2,3-b]furan-2-ylidene)-propan-2-ol (Table 11, entry 8). Isolated as a white solid. IR(KBr plate): 3581 (br), 2934, 1688, 1522, 1249, 1161 cm^{-1}; ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 8.18(d, 1H, *J*= 8.0 Hz), 7.83(s, 1H), 7.75(s, 1H), 7.52(t, 1H, *J*= 8.0 Hz), 7.38(t, 1H, *J*= 6.8 Hz), 7.18(d, 1H, 8.4 Hz), 5.20 (m, 2H), 2.53(m, 4H), 1.64-1.32(m, 12H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 155.2, 151.2, 131.2, 130.8, 130.5, 128.8, 127.9, 124.0, 124.0, 117.9, 115.1, 111.4, 70.9, 68.2, 49.3, 31.2, 31.1, 26.8, 25.0; MS(EI): m/z 323, 264, 181; HRMS calc'd for $C_{21}H_{25}O_2N$: 323.1885; found, 323.1879.

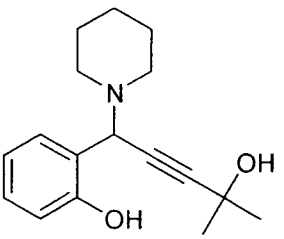


1-(5-Chloro-3-piperidin-1-yl-3H-benzofuran-2-ylidene)-2-methyl-propan-2-ol (Table 11, entry 9). Isolated as a pale yellow solid. IR(KBr plate): 3401 (br), 2936, 1702, 1608, 1469, 1234, 1154 cm^{-1}; ^1H-NMR($CDCl_3$, 400MHz, ppm): δ=

7.34(s, 1H), 7.20(d, 1H, *J*=8.8 Hz), 6.86(d, 1H, *J*= 8.8 Hz), 5.14(m, 1H), 4.76(s, 1H), 2.58(m, 2H), 2.39(m, 2H), 1.54-1.46(m, 12H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 156.2, 152.1, 129.5, 127.4, 126.3, 114.2, 110.9, 70.6, 69.8, 67.8, 49.6, 30.9, 26.5, 24.5; MS(EI) m/z 307, 248, 223; HRMS calc'd for $C_{17}H_{22}O_2N^{35}Cl$: 307.1339; found: 307.1344. HRMS calc'd for $C_{17}H_{22}O_2N^{37}Cl$: 309.1312; found: 309.1312.



1-(6-Methoxy-3-piperidin-1-yl-3H-benzofuran-2-ylidene)-2-methyl-propan-2-ol (Table 11, entry 10). Isolated as a white solid. IR(KBr plate): 3580 (br), 2938, 1736, 1699, 1620, 1444, 1280 cm^{-1}; ^1H NMR($CDCl_3$, 400MHz, ppm): δ= 7.22(d, 1H, *J*= 8.0 Hz), 6.50(m, 2H), 5.09(s, 1H), 4.67(s, 1H), 3.75(s, 3H), 2.53(m, 2H), 2.31(m, 2H), 1.49-1.36(m, 12H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 161.2, 158.9, 153.0, 126.5, 117.2, 113.8, 108.1, 96.1, 70.6, 67.4, 55.7, 49.4, 30.9, 30.8, 26.4, 24.6; MS(EI): m/z 303, 244, 219; HRMS calc'd for $C_{18}H_{25}O_3N$: 303.1834; found, 303.1831.



2-(4,4-Dimethyl-1-piperidin-1-yl-pent-2-ynyl)-phenol (101). Isolated as a pale yellow gummy oil. IR(neat): 2936, 2233, 1644, 1465, 1458, 1362, 1244, 1153 cm^{-1}; ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 7.51(m, 1H), 7.22(m, 1H), 6.87(m, 2H), 4.88(s, 1H), 2.64(m, 4H), 1.68(m, 6H), 1.39(s, 9H). ^{13}C NMR($CDCl_3$, 75MHz, ppm): 158.0, 129.3, 128.7, 122.1, 110.0, 116.4, 99.1, 95.4, 71.3, 60.7, 31.6, 28.0, 26.2, 24.4; MS(EI): m/z 271, 186, 84; HRMS calc'd for $C_{18}H_{25}ON$: 271.1936; found: 271.1933.

Chapter 5:

Catalytic Addition of Terminal Alkynes (C_{sp}-H Bond) to Carbon Dioxide: Application to the Synthesis of Arylnaphthalene Lactones

Chapter 5: Catalytic Addition of Terminal Alkynes (C_{sp}-H Bond) to Carbon Dioxide: Application to the Synthesis of Arylnaphthalene Lactones

5.1 Preface

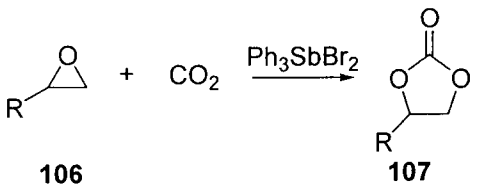
Over the last 15 years, the chemistry of CO_2 has seen an exponential development.[58] Carbon dioxide has been recognized as a cheap, renewable and abundant source of C_1 feedstock for the synthesis of bulk and fine chemicals. For example, the synthesis of carbonates,[59] polycarbonates,[60] carbamates[61] and lactones[62] are well-known to utilize CO_2 fixation. On the other hand, CO_2 incorporation into valuable organic molecules is a growing subject in synthetic organic chemistry. As this thesis focuses mainly on the synthesis of heterocycles, a survey of selected recent cyclization reactions leading to heterocycles using CO_2 fixation is discussed in the next section, followed by preliminary results on the synthesis of lactones based on the addition of terminal alkyne to CO_2.

5.2 Recent Advances in CO_2 Incorporation Reactions for the Synthesis of Heterocycles

5.2.1 Cyclic Carbonates

The coupling of epoxides **106** (oxiranes) with CO_2 is one of the most documented reactions.[57] The cyclic carbonate **107** obtained is a useful intermediate in polymer synthesis. However, such process requires the initial synthesis of the epoxide. Moreover, the reactions generally required

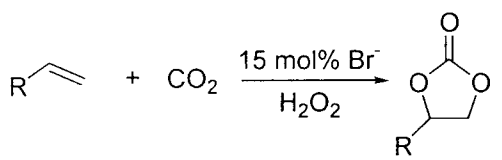
stoichiometric amount of alkali metal salts or main group metal complexes (Scheme 41).



106 **107**

Scheme 41. Cyclic carbonates from epoxides

A more effective approach starting from readily available substrates was developed recently by Eghbali and Li (Scheme 42). Indeed, cyclic carbonates **107** were obtained in high yield by reacting alkenes **108** and CO_2 with a catalytic amount of bromide ion (tetrabutyl ammonium bromide) in hydrogen peroxide. The reaction proceeds via a bromohydrin intermediate. It is noteworthy that the process is metal-free.[63]

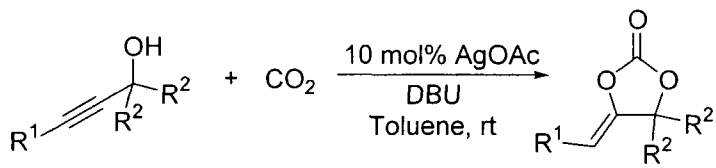


108 **107**

Scheme 42. Conversion of alkenes and CO_2 into cyclic carbonates

Carboxylative cyclization of propargyl alcohol **108** has also been described. In this case, the reaction affords cyclic carbonates with an exocylic double bond **109** and is catalyzed by a silver salt and a base. Alternatively, the

reaction can be promoted by tributylphosphine in super-critical CO_2 (Scheme 43).[64]

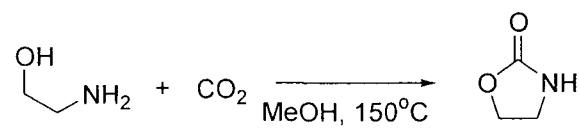


108 **109**

Scheme 43. Cyclic carbonates from propargyl alcohols

5.2.2 Oxazolidinones

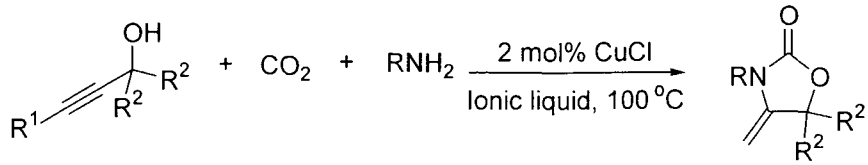
Similar to the cyclic carbonate synthesis, the coupling of aziridines and CO_2 affords oxazolidinones.[59] The reaction is mainly promoted by alkali metal salts. Milder approaches have been developed, such as the coupling of amino alcohol **110** with CO_2 to form oxazolidinones **111** (Scheme 44).[65]



110 **111**

Scheme 44. Oxazolidinone from amino alcohol

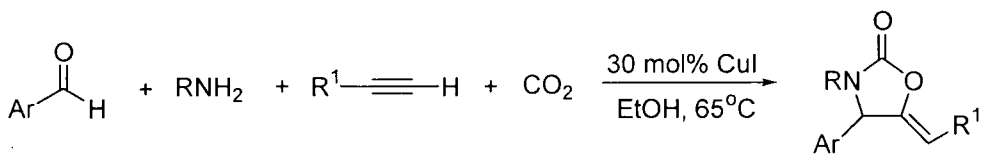
A three-component coupling of propargyl alcohol **108**, amine **112** and CO_2 also affords oxazolidinone with an exocyclic double bond. The reaction is run in ionic liquid with a catalytic amount of copper salt (Scheme 45).[66]



108 **112** **113**

Scheme 45. Copper-catalyzed multicomponent coupling of propargyl alcohol, CO_2 and amine

Recently, Yoo and Li described the synthesis of oxazolidinones **114** via a four-component coupling of aldehyde **19**, amine **112**, alkyne **4** and CO_2. The first step is the addition of the terminal alkyne to the imine, followed by carboxylative cyclization (Scheme 46).[67]

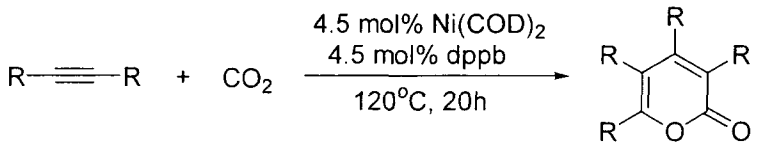


19 **112** **4** **114**

Scheme 46. Copper-catalyzed multicomponent coupling of aldehyde, amine, alkyne and CO_2

5.2.3 Lactones

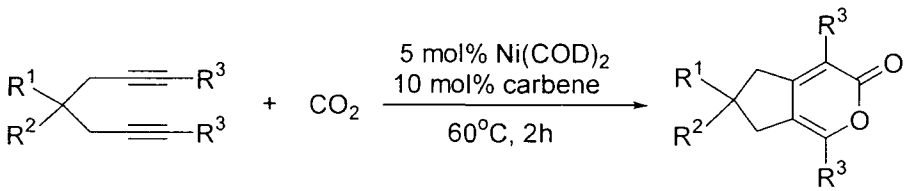
The 1980s saw the emergence of metallacycles for the synthesis of lactones via carbon dioxide incorporation.[61] The key step for these reactions is the oxidative cycloaddition of the metal center into unsaturated molecules such as dienes, allenes and acetylenes. In fact, Inoue was the first to describe the nickel-catalyzed reaction of acetylene and CO_2 to generate lactones (Scheme 47).[68]



115 **116**

Scheme 47. Nickel-catalyzed reaction of acetylene with CO_2

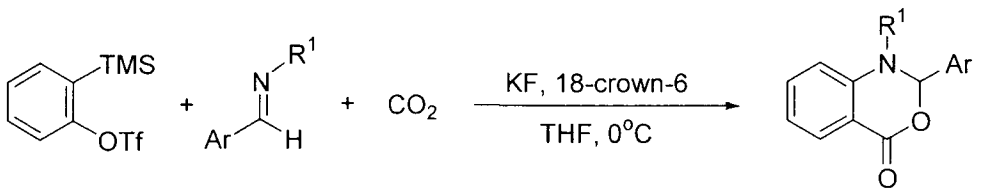
Similarly, in 2002, Louie described the reaction of diacetylene with CO_2 to generate bicyclic lactones (Scheme 48).[69]



117 **118**

Scheme 48. Nickel-catalyzed [2 + 2 + 2] cycloaddition of diacetylene with CO_2

An interesting three-component coupling of arynes, imine and CO_2 was published in 2006. The reaction generates useful benzoxazinones, is metal-free and run in very mild conditions (Scheme 49).[70]

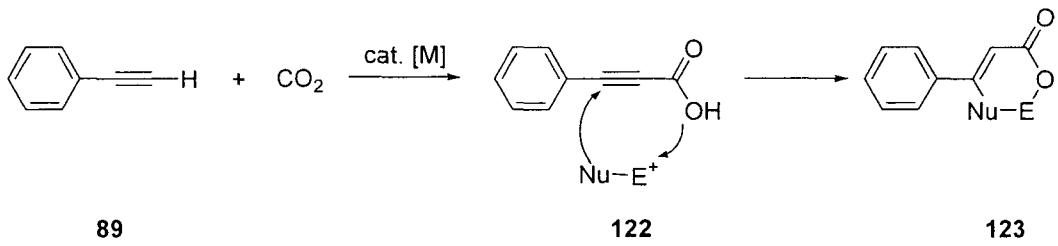


119 **120** **121**

Scheme 49. Multicomponent coupling of benzyne, imine and CO_2

5.3 Preliminary Results

In the previous chapter, the addition of terminal alkyne to imine, followed by intramolecular cyclization led to the synthesis of dihydrobenzofurans. Similarly, the addition of terminal alkynes such as **89** to carbon dioxide could potentially lead to lactones **123** by cyclizing the phenylpropynoic acid intermediate **122** with a molecule bearing both electron-rich (Nu) and electrophilic site (E^+) (Scheme 50).



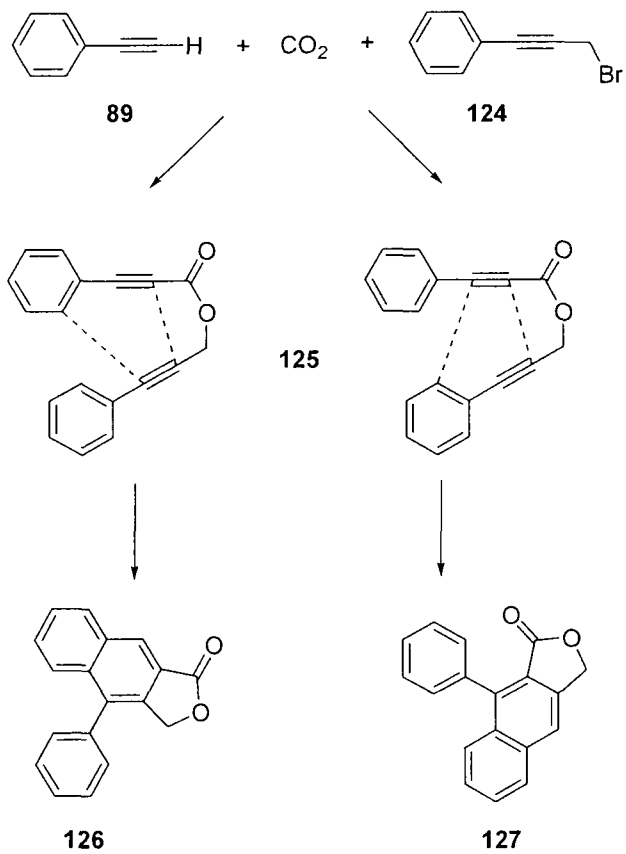
89 **122** **123**

Scheme 50. Application of the addition of terminal alkyne **89** to CO_2 for the formation of lactones

The addition of terminal alkyne to CO_2 was described for the first time in 1994 by Inoue.[71] However, it received very little attention as no applications of this reaction for the synthesis of heterocycles are known. Building on this publication, it was hypothesized that the coupling of phenylacetylene **89**, CO_2 and 3-bromo-1-phenyl-1-propyne **124** could lead to arylnaphthalene lactones **126** and **127**. The key step would be the [2 + 2 + 2] cycloaddition of 1,6-diynes **125** (Scheme 51).

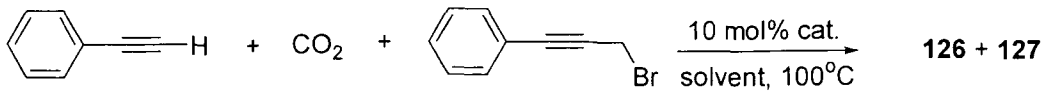
Initially, various copper salts were chosen for the coupling reaction (Table 12, entries 1 and 2). As opposed to its alkyne-imine counterpart, the alkyne-

carbon dioxide coupling did not occur. On the other hand, when a combination of $AuClPPh_3$ and AgOTf was used, modest yield of both regioisomers **126** and **127** are observed (low conversion of phenylacetylene **89** but no detected amount of 1,6-diyne **125**) (Table 12, entry 8). Unfortunately, during the optimization of the reaction conditions, another group published this reaction.[72] Their synthesis is more efficient and uses only AgI as the catalyst. Although a similar yield is obtained with AgOTf alone (higher conversion of phenylacetylene **89** than the gold/silver system), unreacted 1,6-diyne **125** is still observed (Table 12, entry 10).



Scheme 51. Multicomponent coupling of phenylacetylene **89**, CO_2 and 3-bromo-1-phenyl-1-propyne **124**

Table 12. Multicomponent Coupling pf Phenylacetylene, Carbon Dioxide and 3-Bromo-1-Phenyl-1-Propyne



89 **124**

entry[a]	cat.	solvent	Isolated yield(%) **126+127**
1	CuI	DMF	0
2	$Cu(OTf)_2$	DMF	0
3	$AuBr_3$	DMF	0
4	AuI	DMF	0
5	$AuCl_3$	DMF	0
6	AuCN	DMF	0
7	$AuCl_3$/AgOTf	DMF	0
8	$AuClPPh_3$/AgOTf	DMF	6+4
9	$AuClPPh_3$/AgOTf	DMAc	13+8
10	AgOTf	DMAc	12+10
11	$AuClPPh_3$	DMAc	0

[a] Conditions: 0.5 mmol phenylacetylene, 0.5 mmol 3-bromo-1-phenyl-1-propyne, 1 atm CO_2, 1.2 mmol K_2CO_3, 1 mL solvent.

5.4 Perspectives

The use of propargyl bromide is a major shortcoming of this approach as its preparation requires stoichiometric amount of phosphine bromide. In addition, the reaction requires stoichiometric amount of base which generates a fair amount of by-products. A more atom-economical approach would be the use of propargyl alcohol and is currently under investigation.

5.5 Appendix for Chapter 5 (Experimental Section)

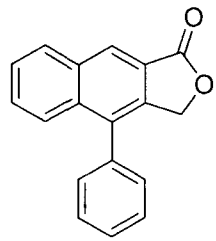
All experiments were carried out under carbon dioxide atmosphere. Analytical and preparative thin-layer chromatography plates (TLC) were ordered from Silicycle Inc. (TLC glass plate). Visualization of the spots on the TLC plates was achieved by exposure to UV light or $KMnO_4$ stain. Column chromatography was performed over Sorbent silica gel 30-60μm. ^1H NMR and ^{13}C NMR spectra were acquired by Varian 400 and 100MHz or 300 and 75MHz, respectively, and referenced to the internal solvent signals. The 3-bromo-1-phenyl-1-propyne was prepared according to literature procedure.[73]

Known compounds were partially characterized (^1H NMR and ^{13}C NMR) and compared to the literature reference.

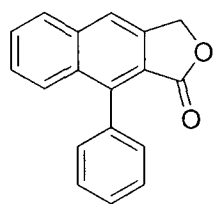
Typical experimental procedure for the coupling of phenylacetylene, carbon dioxide and 3-bromo-1-phenyl-1-propyne (Table 12, entry 9) :

In a schlenk tube, $AuClPPh_3$ (0.025 mmol, 12.3 mg) and AgOTf (0.025 mmol, 6.4 mg) were introduced under CO_2 atmosphere. The solvent DMAc (1 mL) was added and the reaction was allowed to stir for 15 minutes. Then, the base K_2CO_3 (1.2 mmol, 165 mg) diluted in 1 mL of DMAc was added to the solution followed by phenylacetylene (0.5 mmol, 108 μL) and 3-bromo-1-phenyl-1-propyne (0.5 mmol, 97 mg). A balloon of CO_2 was plugged on top of the schlenk tube for the duration of the reaction. The schlenk tube was put in an oil bath at 100°C overnight. The crude mixture was directly isolated via column chromatography on

silica gel (gradient eluent: hexane: ethyl acetate = 50:1). Gives 27 mg (21% combined yield).



4-Phenyl-3H-naphtho[2,3-c]furan-1-one (126).[71] ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 8.53 (s, 1H), 8.11(d, 1H, J= 8.0 Hz), 7.82(d, 1H, J= 8.8 Hz), 7.60-7.38(m, 7H), 5.27 (s, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 171.2, 138.5, 135.7, 134.7, 135.1, 133.7, 130.0, 129.2, 129.1, 129.0, 128.3, 126.8, 126.4, 125.9, 123.0, 69.4.



9-Phenyl-3H-naphtho[2,3-c]furan-1-one (127).[71] ^{1}H NMR($CDCl_3$, 400MHz, ppm): δ= 7.90(d, 1H, J= 7.6 Hz), 7.84(s, 1H), 7.80(d, 1H, J= 8.0Hz), 7.62(t, 1H, J= 8.0 Hz), 7.52-7.34(m, 6H), 5.45(s, 1H); ^{13}C NMR($CDCl_3$, 75MHz, ppm): δ= 170.0, 142.7, 140.5, 136.6, 134.8, 133.4, 130.4, 129.1, 128.6, 128.4, 128.2, 127.1, 127.0, 120.6, 120.3, 68.5.

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Conclusions and Claims to Original Knowledge

The addition of 1,3-diketones (C_{sp}^3-H bond) to dienes and cyclic enol ethers was catalyzed by gold(III) and silver(I). *This provided an atom-economical alternative to the usual stoichiometric alkylation of alkyl halides.* The reaction was regioselective and run under mild conditions. Dihydrofurans can be synthesized when the catalyst is a strong Brønsted acid.

The addition of arenes (C_{sp}^2-H bond) to dienes was also catalyzed by gold(III) and silver(I). *Prefunctionalization to the halide derivative was not necessary as is usually the case with these types of reactions.* A variety of phenols and naphthols was allowed to react with different dienes to afford various dihydrobenzofurans. The reaction was sequential; C-H addition occurred first, followed by intramolecular O-H addition.

The multicomponent coupling of salicylaldehyde derivatives, amines and alkynes afforded various dihydrobenzofurans with an exocylic double bond via the addition of terminal alkynes (C_{sp}-H bond) to imines catalyzed by copper(I). *The alkyne did not require prefunctionalization (Barbier-Grignard reaction).* Moreover, microwave irradiation allowed the reaction time to be shortened, a lower catalyst loading and the elimination of solvent. The use of molecules bearing both a terminal alkynyl group and a heteroatom was found to be critical to the success of the reaction.

Finally, preliminary studies on the synthesis of arylnaphthalene lactones were conducted. Based on the addition of terminal alkynes (C_{sp}-H bond) to carbon dioxide, the reaction was catalyzed by gold and silver via a multicomponent coupling of phenylacetylene, CO_2 and 3-bromo-1-phenyl-1-propyne. The use of propargyl alcohol as a substrate would be a more atom-economical approach to this reaction and is currently being investigated.

Appendix I X-Ray Structure Parameters for Compound **50**

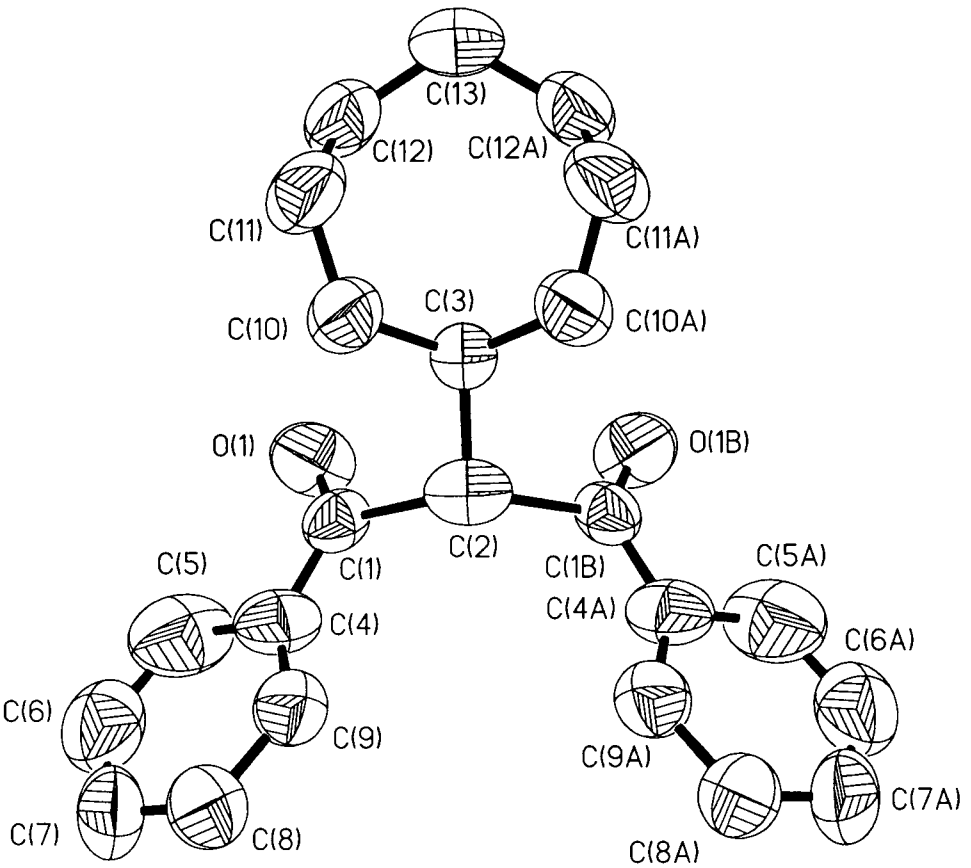

C(13)
C(12)
C(12A)
C(11)
C(11A)
C(10)
C(3)
C(10A)
O(1)
O(1B)
C(5)
C(1)
C(2)
C(1B)
C(5A)
C(4)
C(4A)
C(6A)
C(6)
C(9)
C(9A)
C(7)
C(8)
C(8A)
C(7A)

Table 1. Crystal data and structure refinement for cjli23m.

Identification code	cjli23m
Empirical formula	C11.50 H11 O
Formula weight	165.20
Temperature	571(2) K
Wavelength	0.71073 A
Crystal system, space group	orthorhomic, Pmn21
Unit cell dimensions	a = 17.307(14) A alpha = 90 deg. b = 5.500(5) A beta = 90 deg. c = 9.735(8) A gamma = 90 deg.
Volume	926.6(13) A^3
Z, Calculated density	4, 1.184 Mg/m^3
Absorption coefficient	0.074 mm^-1
F(000)	352
Crystal size	.4 x .2 x .2 mm
Theta range for data collection	3.70 to 26.69 deg.
Limiting indices	-21<=h<=21, -6<=k<=6, -6<=l<=12
Reflections collected / unique	4302 / 1348 [R(int) = 0.1328]
Completeness to theta = 26.69	94.9 %
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1348 / 1 / 138
Goodness-of-fit on F^2	1.013
Final R indices [I>2sigma(I)]	R1 = 0.0722, wR2 = 0.2040
R indices (all data)	R1 = 0.0959, wR2 = 0.2295
Absolute structure parameter	-1(5)
Largest diff. peak and hole	0.255 and -0.290 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for cjli23m. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	1045(6)	-712(15)	925(8)	119(3)
C(1)	865(6)	1189(18)	402(10)	72(2)
C(2)	0	2376(9)	849(6)	76(2)
C(3)	0	2299(7)	2399(5)	61(1)
C(4)	1265(3)	2209(8)	-659(5)	86(1)
C(5)	1949(5)	1008(14)	-965(8)	136(3)
C(6)	2453(4)	1914(18)	-1901(9)	131(2)
C(7)	2309(3)	3937(15)	-2579(8)	126(2)
C(8)	1635(3)	5235(9)	-2300(7)	109(2)
C(9)	1129(3)	4317(9)	-1345(5)	87(1)
C(10)	706(2)	3467(8)	2984(6)	88(1)
C(11)	927(3)	3071(11)	4335(6)	106(2)
C(12)	754(3)	778(10)	5059(6)	99(2)
C(13)	0	697(14)	5884(8)	98(2)
C(1A)	502(7)	940(20)	187(14)	57(3)
O(1A)	528(7)	-1248(12)	383(14)	113(4)

Table 3. Bond lengths [A] and angles [deg] for cjli23m.

O(1)-C(1)	1.204(11)
C(1)-C(4)	1.364(12)
C(1)-C(2)	1.690(10)
C(2)-C(3)	1.509(8)
C(2)-C(1)#1	1.690(10)
C(3)-C(10)	1.493(5)
C(3)-C(10)#1	1.493(5)
C(4)-C(9)	1.358(7)
C(4)-C(5)	1.388(9)
C(5)-C(6)	1.357(11)
C(6)-C(7)	1.317(9)
C(7)-C(8)	1.395(9)
C(8)-C(9)	1.373(8)
C(10)-C(11)	1.387(8)
C(11)-C(12)	1.476(8)
C(12)-C(13)	1.533(7)
C(13)-C(12)#1	1.533(7)
C(1A)-O(1A)	1.222(14)
C(1A)-C(1A)#1	1.74(2)
O(1A)-O(1A)#1	1.83(2)
O(1)-C(1)-C(4)	123.1(8)
O(1)-C(1)-C(2)	117.1(9)
C(4)-C(1)-C(2)	119.1(6)
C(3)-C(2)-C(1)#1	104.3(4)
C(3)-C(2)-C(1)	104.3(4)
C(1)#1-C(2)-C(1)	124.7(8)
C(10)-C(3)-C(10)#1	109.8(5)
C(10)-C(3)-C(2)	111.7(3)
C(10)#1-C(3)-C(2)	111.7(3)
C(9)-C(4)-C(1)	129.4(5)
C(9)-C(4)-C(5)	116.6(6)
C(1)-C(4)-C(5)	113.6(6)
C(6)-C(5)-C(4)	121.2(7)
C(7)-C(6)-C(5)	121.7(6)
C(6)-C(7)-C(8)	119.6(6)
C(9)-C(8)-C(7)	118.5(5)
C(4)-C(9)-C(8)	122.5(5)
C(11)-C(10)-C(3)	121.3(4)
C(10)-C(11)-C(12)	122.1(5)
C(11)-C(12)-C(13)	116.6(5)
C(12)-C(13)-C(12)#1	116.6(6)
O(1A)-C(1A)-C(1A)#1	92.1(7)
C(1A)-O(1A)-O(1A)#1	87.9(7)

Symmetry transformations used to generate equivalent atoms: #1 -x,y,z

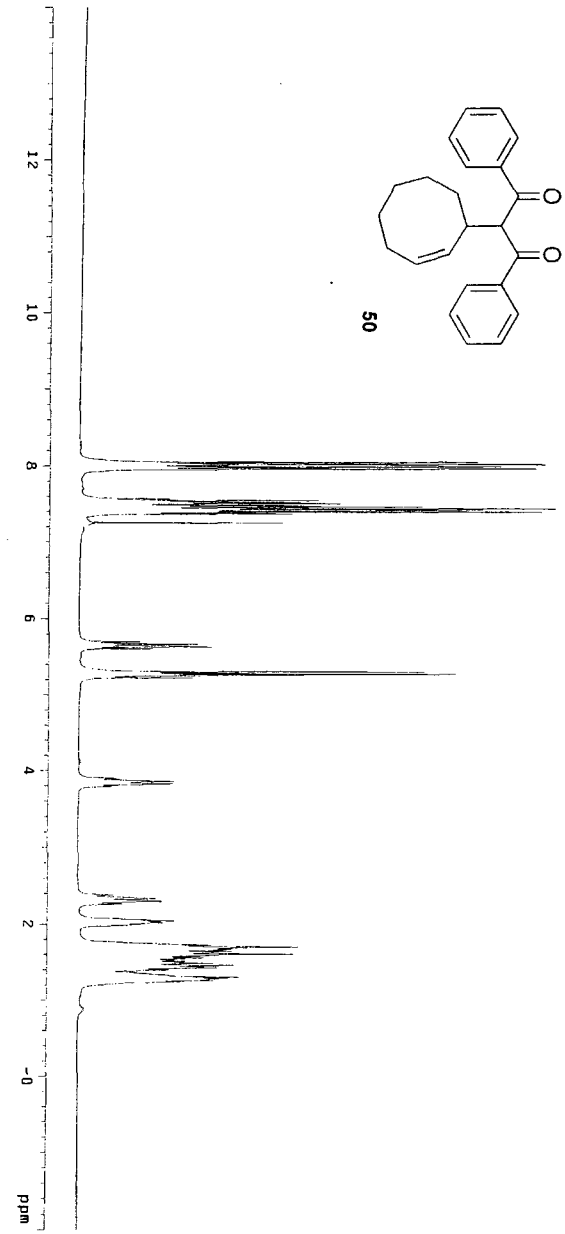
Table 4. Anisotropic displacement parameters (A^2 x 10^3) for cjli23m. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	154(6)	100(5)	103(5)	28(4)	30(5)	66(5)
C(1)	77(6)	77(5)	62(5)	-2(4)	-4(5)	25(5)
C(2)	120(4)	48(2)	62(3)	0(2)	0	0
C(3)	66(3)	53(2)	66(3)	2(2)	0	0
C(4)	112(3)	87(3)	59(2)	-7(2)	0(2)	14(2)
C(5)	165(6)	148(5)	95(4)	-13(4)	4(4)	60(4)
C(6)	95(4)	187(7)	110(5)	-26(5)	-7(4)	18(4)
C(7)	74(3)	188(6)	116(5)	-11(5)	-7(3)	-37(3)
C(8)	100(3)	120(3)	107(4)	23(3)	-8(3)	-31(3)
C(9)	77(2)	97(3)	87(3)	8(2)	-7(2)	-7(2)
C(10)	79(2)	96(3)	87(3)	21(2)	-13(2)	-21(2)
C(11)	98(3)	127(4)	92(3)	24(3)	-33(3)	-41(3)
C(12)	83(3)	124(3)	89(3)	26(3)	-21(2)	1(3)
C(13)	114(5)	105(4)	75(4)	16(3)	0	0
C(1A)	54(7)	60(5)	57(7)	-11(4)	8(6)	0(5)
O(1A)	141(8)	43(3)	156(10)	-8(5)	64(8)	11(4)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for cjli23m.

	x	y	z	U(eq)
H(2A)	0	4089	573	150(40)
H(3A)	0	588	2681	74
H(5A)	2064	-444	-520	163
H(6A)	2912	1087	-2069	157
H(7A)	2655	4497	-3238	151
H(8A)	1529	6688	-2752	131
H(9A)	677	5169	-1160	104
H(10A)	1003	4481	2431	105
H(11A)	1192	4290	4799	127
H(12A)	1178	433	5680	118
H(12B)	739	-521	4385	118
H(13A)	0	2058	6518	118
H(13B)	0	-778	6430	118

Appendix II ^{1}H NMR Spectrum for Compounds **50**, **54**, **71**, **96** and **126**



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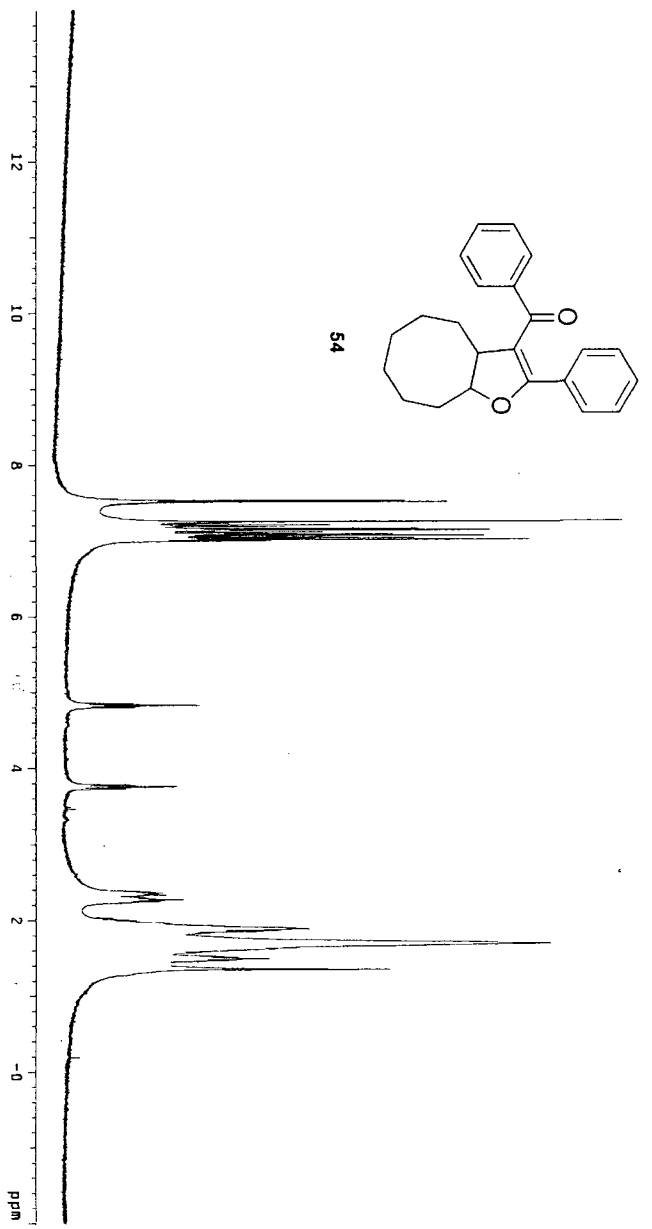

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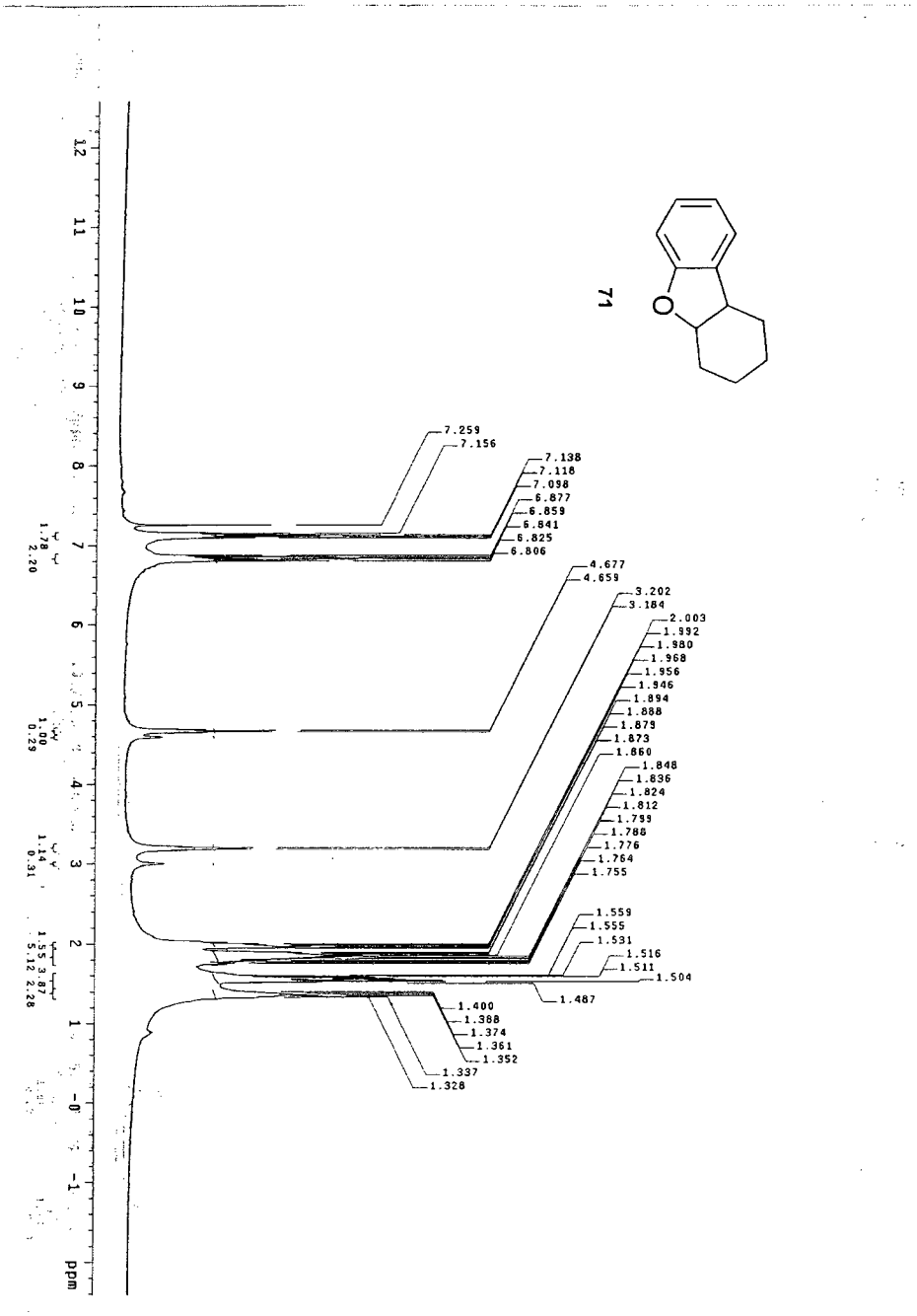
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7.156
7.138
7.118
7.098
6.877
6.859
6.841
6.825
6.806
4.677
4.659
3.202
3.184
2.003
1.992
1.980
1.968
1.956
1.946
1.894
1.888
1.879
1.873
1.860
1.848
1.836
1.824
1.812
1.799
1.788
1.776
1.764
1.755
1.559
1.555
1.531
1.516
1.511
1.504
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1.400
1.388
1.374
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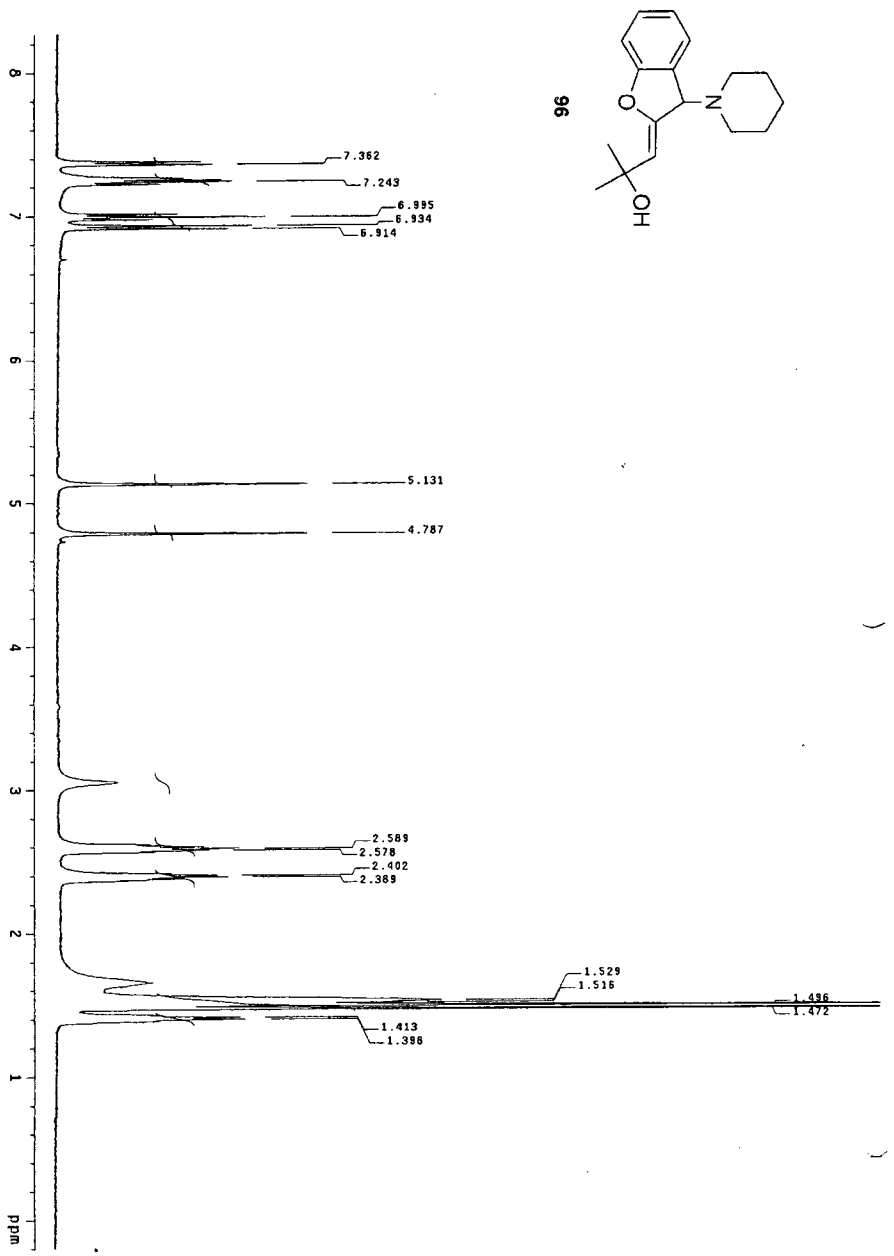
1.337
1.328
ppm


96
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OH
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6.995
6.934
6.914
5.131
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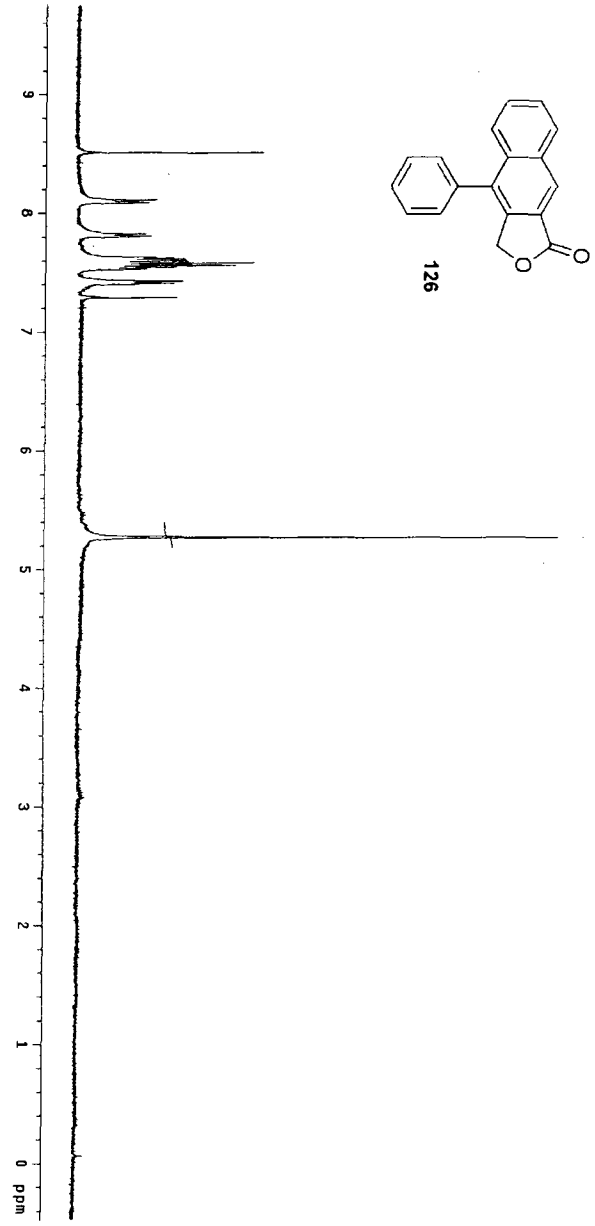
2.578
2.402
2.389
1.529
1.516
1.436
1.472
1.413
1.398
ppm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8
7
6
5
4
3
2
1
0 ppm
O
O
126

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