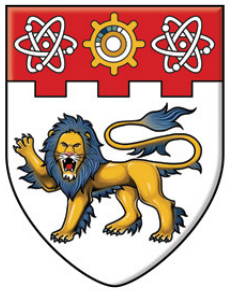
IN(III)-TMSBR-CATALYZED [2+2] CYCLOADDITION AND DEAROMATIZATION CASCADE REACTION

SHEN LIANG 2017



NANYANG TECHNOLOGICAL UNIVERSITY

IN(III)-TMSBR-CATALYZED [2+2] CYCLOADDITION AND DEAROMATIZATION CASCADE REACTION OF ARYL ALKYNE AND ACRYLATE

SHEN LIANG

SCHOOL OF PHYSICAL ANDMATHEMATICAL SCIENCES

2017

IN(III)-TMSBR-CATALYZED [2+2] CYCLOADDITION AND DEAROMATIZATION CASCADE REACTION OF ARYL ALKYNE AND ACRYLATE

SHEN LIANG

School of Physical and Mathematical Sciences

A thesis submitted to the Nanyang Technological University
in partial fulfillment of the requirement for the degree of
Doctor of Philosophy

2017

ACKNOWLEDGEMENTS

First and foremost, I would like to express my deepest gratitude towards Prof Loh Teck Peng for the opportunity to pursue my PhD studies in his research group. His untiring dedication and passion in research as well as his efforts in guiding me towards completing this thesis is very much appreciated and will continue to inspire me in future.

I am also indebted to all technical and administrative staff in CBC. Thanks to Ms. Chen Xiaoping, Ms. Florence Ng Pei Fan and Ms. Celine Hum Wei Mei for all administrative assistance. Special mention goes to Ms. Goh Ee Ling, Ms. Zhu Wen Wei, Dr. Li Yongxin and Dr. Rakesh Ganguly for their assistance in NMR, HRMS as well as X-ray crystallography.

I would also like to thank amazing past and present members in Prof Loh's group for their supports and insightful discussion in research: Dr. Shen Zhiliang, Dr. Sreekumar Pnkajakshan, Dr. Jakson Koh Peng Fei, Zhang Yong hui, Manikantha Raj, Zhang Qiuchi, Wu Liuhai, etc. Besides, I appreciate all the helpful research discussion held with CBC faculty members.

Lastly, I dedicate this thesis to my beloved parents and sister for all the sacrifice made to nurture and educate me. Words cannot describe my gratitude towards them for their endless encouragement and support.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

δ	chemical shift
°C	degree centigrade
Ac	acetyl
acac	acetylacetonate
Ac_2O	acetic anhydride
AcOH	acetic acid
aq	aqueous
Ar	aryl
atm	atmosphere
ATPH	aluminium tris(2,6-diphenylphenoxide)
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Box	bisoxazoline
BTF	2,2-bis(trifluoromethyl)ethylene-1,1-dicarbonitrile
brs	broad singlet
Cp	cyclopentadienyl
Cod	1,5-cyclooctadiene
Cy	cyclohexane
d	doublet
DBE	1,2-dibromoethane
DCE	1,2-dichloroethane
DMAD	diethyl acetylenedicarboxylate
DMF	*N,N*-dimethylformamide
2D NMR	two-dimensional nuclear magnetic resonance spectroscopy
dppe	1,2-bis(diphenylphosphino)ethane
dppp	1,3-bis(diphenylphosphanyl)propane
dr	diastereomeric ratio
EDA	electron-donor-accptor
ee	enantiomeric excess

ESI	electrospray ionization
Et	ethyl
Et_3SiH	triethylsilane
EWG	electron-withdrawing group
h	hour
HFTA	hexafluorothioacetone
HRMS	high resolution mass spectrometry
hv	photoirradiation
Hz	Hertz
^{i}Bu	*iso*butyl
In_3X	indium(III) halide
^{i}Pr	*iso*propyl
J	coupling constant
m-CPBA	3-chloroperbenzoic acid
MeIm	Methylimidazole
MS	molecular sieve
^{n}Pr	*n*-propyl
^{n}Bu	*n*-butyl
^{n}Hex	*n*-hexane
NMM	*N*-methylmaleimide
NOESY	Nuclear Overhauser Enhancement spectroscopy
p	*para*
TADDOL	*a, a, a, a*-tetraaryl-1,3-dioxolane-4.5-dimethanol
m	multiplet
MAT	methylaluminumbis(2,4,6-tri-butylphenoxide)
Me_2SiClH	chlorodimethylsilane
NBD	1,5-norbornadiene
NMR	nuclear magnetic resonance
NHC	*N*-heterocyclic carbene
OTf	triflate
PCy_3	tricyclohexylphosphine

Ph	phenyl
Ph_2SiHCl	chlorodiphenylsilane
PIDA	(diacetoxyiodo)benzene
PivOH	pivalic acid
p-TsOH	*p*-toluenesulfonic acid
q	quartet
rt	room temperature
rr	regioisomeric ratio
s	singlet
t	triplet
TCNE	tetracyanoethylene
TBAB	tetrabutylammonium bromide
TBDPSCl	*t*-butyldiphenylsilane
TBSCl	*t*-butyldimethylsilyl chloride
^{t}Bu	*tert*-butyl
TESH	triethylsilane
tfacac	trifluoroacetylacetonate
Tf_2NH	trifluoromethanesulfonimide
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSX	trimethylsilyl halide

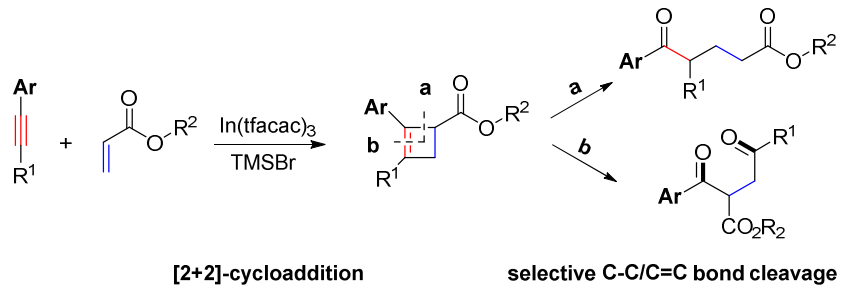
SUMMARY

Since the last decade, indium metal and its salts have found wide-ranging applications in organic synthesis. In view of the relatively weak Lewis acidity of indium salts, trimethylsilyl halides or other silane derivatives are often incorporated with In(III) salts as robust combined Lewis acid catalysts. The combined use of In(III) catalyst and halotrimethylsilane was seminally disclosed by Kobayashi and Mukaiyama in early 1990s. Subsequently, Mukaiyama, Baba, Lee, Loh, and others reported on an array of reactions utilizing this combined Lewis acid system. In continuation of our group's research interest in novel indium-mediated organic reactions, this thesis focuses on development of some novel organic transformations using In(III)-TMSBr as catalyst system.

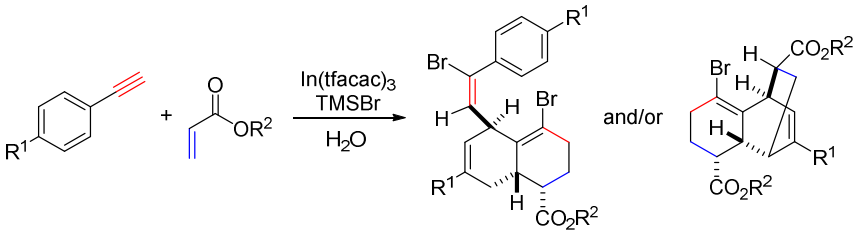
In the first chapter, the development of reactions promoted by this combined Lewis acid catalyst system together with the development of transition metals- and Lewis acids-mediated alkynes-alkenes [2+2] cycloaddition to prepare cyclobutenes is highlighted. In general, the combined catalyst promotes the reactions through selective activation of functional groups including *O*-trimethylsilyl monothiacetal, dimethyl acetals, carbonyl group of aldehyde and ketone, carboxylic acid, hydroxyl group and silyl ether group. The established transition-metal catalysts for [2+2] cycloaddition of alkynes and alkenes include complexes of nickel, ruthenium, rhodium, cobalt, palladium, copper, iron, silver, rhenium, iridium and gold. On the other hand, the acid catalysts employed for titled reaction could be Bronsted acid (Tf_2NH) or Lewis acids such as Zn(II), Ti(IV), Al(III), Zr(IV) and In(III).

In the second chapter, the first example of $In(tfacac)_3$-TMSBr-catalyzed [2+2] cycloaddition reaction of aryl alkynes with acrylates that could assemble cyclobutenes with aryl and ester

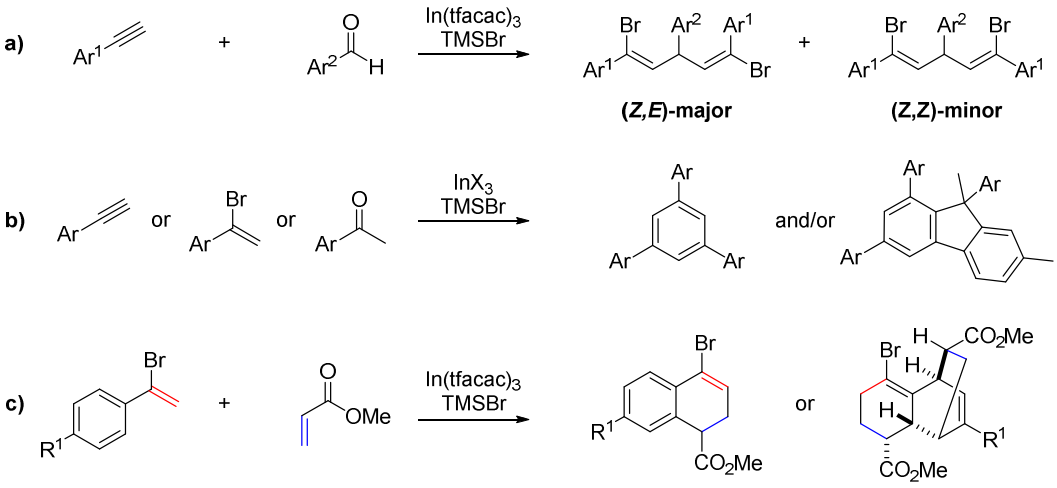
substituents in moderate to good yields is discussed. A plausible mechanism proposed for this transformation is included and the structures of these new cyclobutene products are confirmed by X-ray crystallography of their derivatives. The obtained cyclobutenes are demonstrated to be versatile reaction intermediates which could undergo diversified functional group transformations (such as diastereoselective hydrogenation and epoxidation) while the four-membered rings remain intact. Also, selective cleavage of C-C/C=C bond is attained to afford synthetically useful 1,4- and 1,5-dicarbonyl compounds which are otherwise difficult to prepare by conventional methods, render this protocol of demonstrable synthetic value.



In the third chapter, a novel In(tfacac)$_3$-TMSBr-catalyzed dearomatization cascade reaction of aryl alkynes with acrylates is disclosed for efficient assembly of densely functionalized polycyclic skeletons, the commonly encountered molecular entities in natural products, with high stereocontrol. Based on isotopic labelling experiment, crossover expremient, controlled experiment, and other mechanistic studies, a plausible mechanistic pathway is devsied for this serendipitously discovered reaction which involves a tandem Diels-Alder reaction of *in situ* generated vinyl bromide with acrylate followed by an interception of the thus-formed Diels-Alder adduct by another molecule of ary alkyne or acrylate.



In chapter four, the first example of catalytic coupling of aryl alkynes and aryl aldehydes for the synthesis of 1,5-dibromo-1,4-pentadienes with high stereoselectivity is discussed. Moreover, the facile synthesis of a series of 1,3,5-triaryl benzenes through trimerization of aryl alkynes, α-aryl vinyl bromides or acetophenone is described by using In(III)-TMSBr catalyst. Finally, the preliminary study for In(tfacac)$_3$-TMSBr-catalyzed [4+2] cycloaddition of α-aryl vinyl bromides and methyl acrylate is also disclosed.



CHAPTER 1

INTRODUCTION

1.1 Development of combination of indium(III) salts and silane derivatives as catalysts

In the past decade, indium metal and its salts have found widespread applications in organic synthesis owning to their characteristic properties.[1] First, indium metal or indium salts are readily transformed into organoindium reagents. In comparison with conventional organometallic reagents, for instance, organozinc, organolithium, or organomagnesium reagents, condition is wild leading to the simplified operation in their preparation and handling. Generally, they are insensitive to moisture so the solvents do not need to be dry. Moisture exclusion and glasswares pre-drying is also not required. Second, organoindium reagents and several indium salts possess high tolerance towards functionalities including halides, ester, ketone, nitrile, nitro, and hydroxyl groups. This has allowed water-soluble carbohydrate substrates to undergo indium salts-catalyzed reactions or direct functionalization with organoindium reagents. Another prominent advantage is brought about by low toxicity of both indium metal and its derivatives.[1]

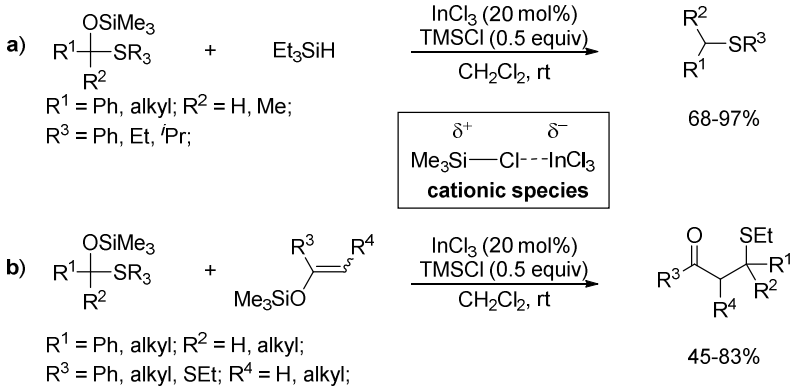
Despite the remarkable advantages aforementioned, the catalytic usage of In(III) salts is confined to a relatively narrow area, which is in contrary to that attained with aluminium or boron compounds. This could be attributed to their inherent weaker Lewis acidity than related Al(III) or B(III) reagents. Given the relatively weak strength of indium salts as Lewis acids, trimethylsilyl halides or other silane derivatives are often employed together with In(III) salts as robust combined Lewis acid catalyst systems. A series of reactions utilizing this combined Lewis acid

[1]For selected reviews on indium chemistry, see: (a) Li, C. J. *Chem. Rev.* **1993**, *93*, 2023-2035; (b) Li, C. J. *Tetrahedron* **1996**, *52*, 5643-5668; (c) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149-11176; (d) Li, C. J. *Chem. Rev.* **2005**, *105*, 3095-3165; (e) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739-2749; (f) Li, C. J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68-82; (g) Babu, G.; Perumai, P. T. *AldrichimicaActa* **2000**, *33*, 16-22; (h) Yadav, J. S.; Antony, A.; George, J.; Subba Reddy, B. V. *Curr. Org. Chem.* **2010**, *14*, 414-424; (i) Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 17-28; (j) Shen, Z.-L.; Wang, S.-Y.; Chok, Y.-K.; Xu, Y.-H.; Loh, T.-P. *Chem. Rev.* **2013**, *113*, 271-401.

system have been reported by Mukaiyama, Baba, Lee, Loh, and others. In this section, the development of reactions promoted by this combined Lewis acid catalyst system will be summarized.

1.1.1 Activation of *O*-trimethylsilyl monothiacetal using $InCl_3$-TMSCl system

The use of In(III) catalyst and halotrimethylsilane as combined Lewis acid catalyst was seminally disclosed by Mukaiyama and Kobayashi in early 1990s.[2] They found that concomitant use of trimethylsilyl chloride (TMSCl) and indium(III) chloride ($InCl_3$) could catalyze reactions of triethylsilane (Et_3SiH) or silyl enol ethers with *O*-trimethylsilyl monothioacetals effectively to yield sulfides or ketone derivatives, respectively (**Scheme 1-1**).



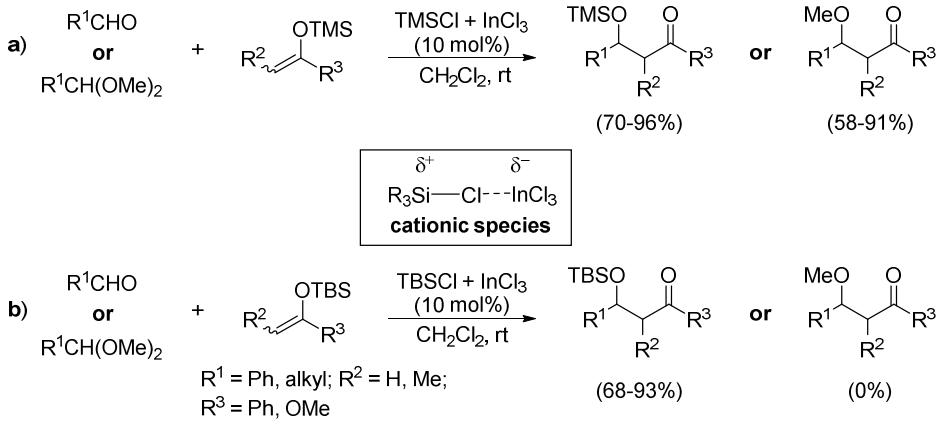
Scheme 1-1. Activation of *O*-trimethylsilyl monothiacetals using $InCl_3$-TMSCl catalytic system

Common Lewis acids such as $SnCl_4$, $ZnCl_2$, BF_3-Et_2O, $TiCl_4$, TMSOTf or TMSI were not effective in this reaction. Also, neither TMSCl nor $InCl_3$ could effect this reaction. They hypothesized the generation of a cationic species from TMSCl and $InCl_3$ in this reaction and the higher affinity of silicon atom toward oxygen atom than sulfur atom results in preferential activation of trimethylsiloxy group to ethylthio group (**Scheme 1-1**).

[2](a) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1990**, 2239–2242; (b) Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 2524-2527.

1.1.2 $InCl_3$-TMSCl-catalyzed Mukaiyama aldol reaction

Aside from the above protocol, the same group also demonstrated the application of $InCl_3$-TMSCl system to Mukaiyama aldol reaction.[3] Using silyl enol ethers, aldehydes or the respective dimethyl acetals underwent facile reactions to afford high yields of aldol adducts using catalytic amount of TMSCl and $InCl_3$ (**Scheme 1-2**). Substituting TMSCl with *t*-butyldimethylsilyl chloride (TBSCl), aldol reaction occurred readily in good yields with aldehydes and *t*-butyldimethylsilyl enol ethers but acetals remained unreacted under the same reaction conditions (**Scheme 1-2b**). This chemoselectivity observed contradicts the common observation that acetals are more reactive than aldehydes under acidic conditions.



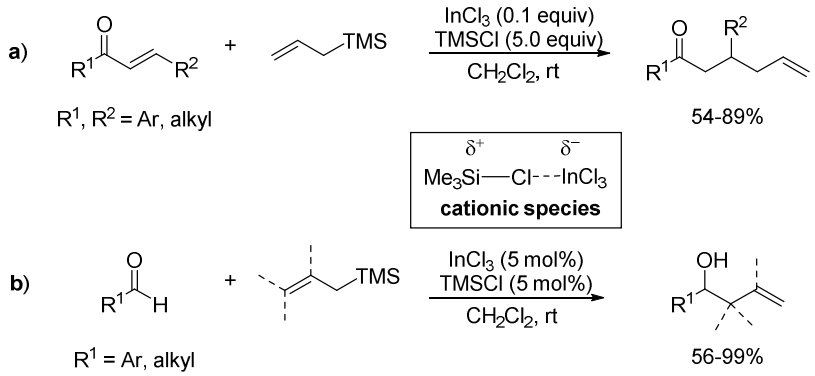
Scheme 1-2. $InCl_3$-TMSCl-catalyzed Mukaiyama aldol reactions

1.1.3 $InCl_3$-TMSCl-catalyzed Sakurai-Hosomi reaction

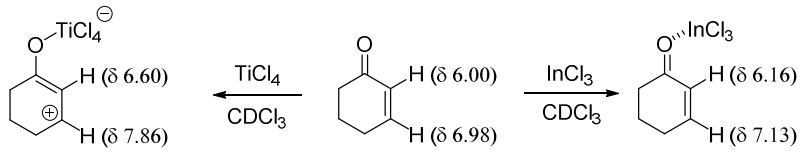
Sakurai-Hosomi allylation refers to regiospecific introduction of allyl moiety onto varied carbon electrophiles with possible formation of new chiral center(s). This reaction is promoted by Lewis acids and owns extensive applications in organic synthesis. Nonetheless, performing this reaction in a catalytic manner is often challenging due to the difficulty in regenerating the catalyst from

[3]Mukaiyama, T.; Ohno, T.; Nishimura, T.; Han, J. S.; Kobayashi, S. *Chem. Lett.* **1991**, 949–952.

the thus-formed homoallylic metal oxides.[4]



Scheme 1-3. $InCl_3$-TMSCl-catalyzed Sakurai-Hosomi reaction



Scheme 1-4. ^1H NMR Values of 2-cyclohexen-1-one in the presence of stoichiometric amount of $TiCl_4$ and $InCl_3$

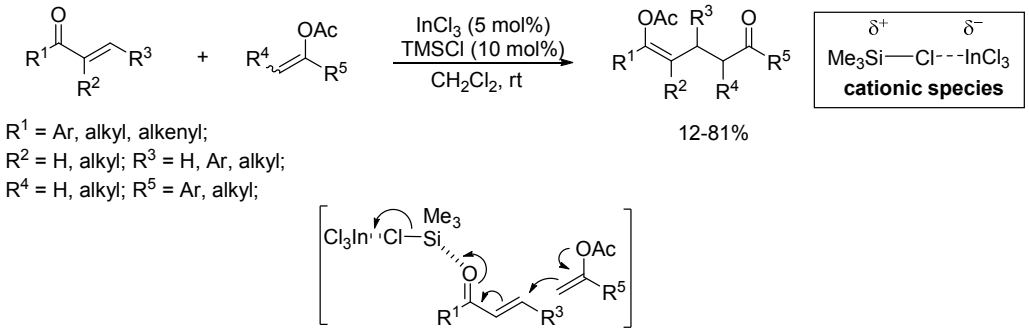
In 2001, Lee and co-worker reported on addition of allyltrimethylsilane to conjugated enones using catalytic amount of $InCl_3$ and 5 equivalents of TMSCl to yield δ,ε-enones (**Scheme 1-3a**).[5]Almost concurrently, Baba's group also exhibited the application of $InCl_3$-TMSCl catalyst system for the Sakurai-Hosomi reaction (**Scheme 1-3b**).[6] β- and γ-substituted allylsilanes also forged the respective C-C bond with aldehydes in a highly selective and efficient manner despite the steric hindrance. Lewis acids such as $AlCl_3$ and BF_3-Et_2O from group 13 alone could not catalyze this reaction. Attempts to incorporate TMSCl with these acids were unfruitful as well.

[4](a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, 1295-1296; (b) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200-206; (c) Hosomi, A.; Shirahata, A.; Sakurai, H. *Tetrahedron Lett.* **1978**, 3043-3046; (d) Gauthier, D. R. Jr.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2363-2365; (e) Aggarwal, V. K.; Vennall, G. P. *Synthesis* **1998**, 1823-1826; (f) Marx, A.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2000**, *39*, 178-181; (g) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490-11495.
[5](a) Lee, P. H.; Lee, K.; Sung, S.; Chang, S. *J. Org. Chem.* **2001**, *66*, 8646–8649; (b) Lee, P. H.; Seomoon, D.; Kim, S.; Nagaiah, K.; Damle, S. V.; Lee, K. *Synthesis* **2003**, 2189-2193.
[6](a) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Eur. J. Org. Chem.* **2002**, 1578–1581; (b) Onishi, Y.; Ito, T.; Yasuda, M.; Baba, A. *Tetrahedron* **2002**, *58*, 8227–8235.

This intriguing achievement is thought to be realized by the weak activation of carbonyl group by $InCl_3$ in an extent that allows a reversible coordination to allow the regeneration of $InCl_3$catalyst for Sakurai-Hosomi reactions (Scheme 1-4).[5a]

1.1.4 $InCl_3$-TMSCl-catalyzed Mukaiyama-Michael reaction

Mukaiyama-Michael reaction of enolates with α,ß-unsaturated carbonyl compounds is a venerable methodology to prepare 1,5-dicarbonyl compounds.[7] In this context, this reaction couples α,ß-unsaturated carbonyl compounds with enol acetates instead of allylsilanes in Sakurai-Hosomi reaction.



Scheme 1-5. Michael addition of α,ß-unsaturated ketones with enol acetates

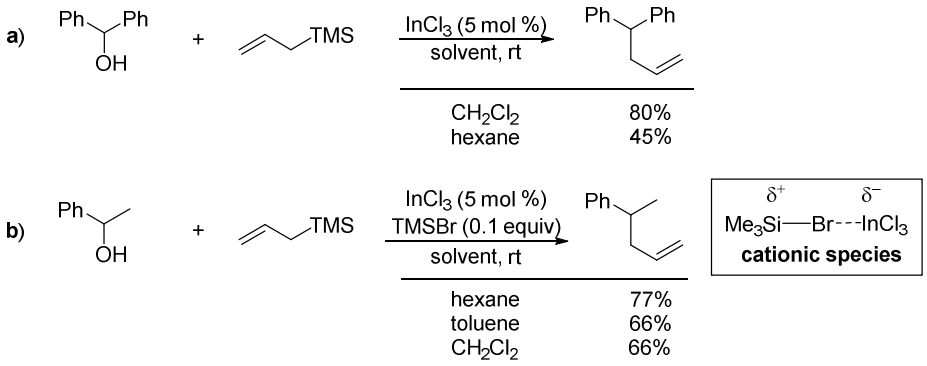
In 2012, Baba *et al.* reported on using catalytic combination of $InCl_3$ and Me_3SiCl to activate α,ß-unsaturated ketone substrates specifically (**Scheme 1-5**).[8] This report has exemplified the seminal direct incorporation of enol acetates for Michael addition and remarkably the isolation of Michael adduct products in the pure enol-form is viable here due to their considerably higher stability than the corresponding metal enolates. It was thought that through combination with $InCl_3$, Lewis acidity of TMSCl is enhanced with the silicon center being the activation site for

[7]Selected works of the Mukaiyama-Michael reaction: (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223-1224; (b) Narasaka, K.; Soai, K.; Aikawa, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779-783; (c) Kobayashi, S.; Hachiya, I.; Ishitani, H.; Araki, M. *Synlett* **1993**, 472-474; (d) Loh, T.-P.; Wei, L.-L. *Tetrahedron* **1998**, *54*, 7615-7624.
[8]Onishi, Y.; Yoneda, Y.; Nishimoto, Y.; Yasuda, M.; Baba. *Org. Lett.* **2012**, *14*, 5788-5791.

carbonyl oxygen of enone. Thereof, successive nucleophilic attack of enol acetate gives rise to silyl enolate. Intramolecular migration of acyl group then produces the acylated adduct product.

1.1.5 $InCl_3$-TMSX-mediated hydroxyl group activation

Hydroxyl functionality-containing compounds are prevalent intermediate compounds in natural product syntheses and they often serve as key precursors for olefinic, etheric or carbonyl compounds. On the other hand, direct hydroxyl groups substitution is an efficient entry to prepare synthetically useful building blocks. Nonetheless, the direct substitution pathway is often impeded by the low leaving ability of hydroxyl group.[9]



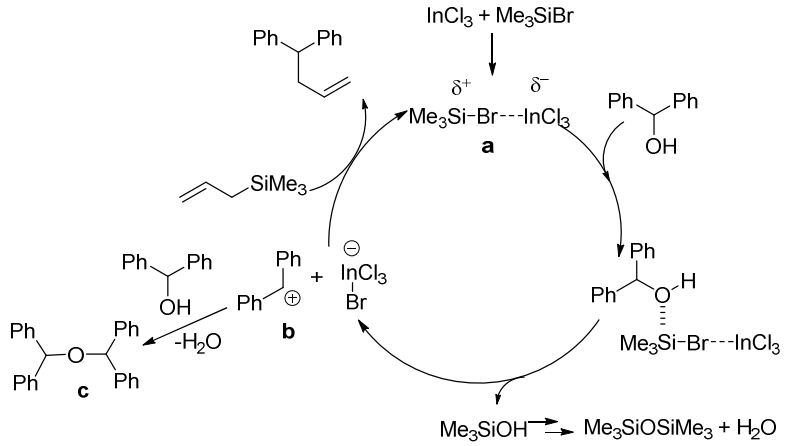
Scheme 1-6. Direct substitution of hydroxyl group with silyl nucleophiles

In 2004, Baba and co-workers demonstrated an $InCl_3$-catalyzed direct hydroxyl group substitution in alcohols with silanes.[10] Allylsilanes, propargylsilane, alkynylsilane as well as benzyl alcohols could undertake this novel alkylative substitution. Presence of CH_2Cl_2 as reaction solvent is paramount and when replaced by hexane, the reaction yields were hampered significantly (**Scheme 1-6a**). In a later report, they identified a catalytic combination of $InCl_3$ and TMSBr could also effectively catalyze the alcohol dehydroxylation-allylation using

[9](a) Ozawa, F.; Okamoto, H.; Kawagishi, S.; Yamamoto, S.; Minami, T.; Yoshifuji, M. *J. Am. Chem. Soc.* **2002**, *124*, 10968-10969; (b) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846-11847; (c) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760-15761.
[10]Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem. Int. Ed*. **2004**, *43*, 1414-1416.

nonhalogenated solvents like hexane and toluene (**Scheme 1-6b**).[11]

The tentative underlying mechanistic pathway for this transformation is delineated in **Scheme 1-7**. The initial step involves strong coordination of hydroxyl group to the silicon center of **a**, a Lewis acidic complex formed from $InCl_3$ and TMSBr. This activation of alcohol promotes the formation of carbocation **b**. Allylated product is formed following addition of allylsilane to the cation **b** which simultaneously regenerates the combined catalyst **a** to complete the catalytic cycle. A dimeric ether **c** is formed if an alcohol molecule reacts with cation **b**. The weak oxophilicity and strong halophilicity of indium(III) halides is the determining criterion to complete this catalytic cycle. If the former outweighs the latter, siloxane would entrap the indium species, thus interferes with the regeneration of the combined catalyst.



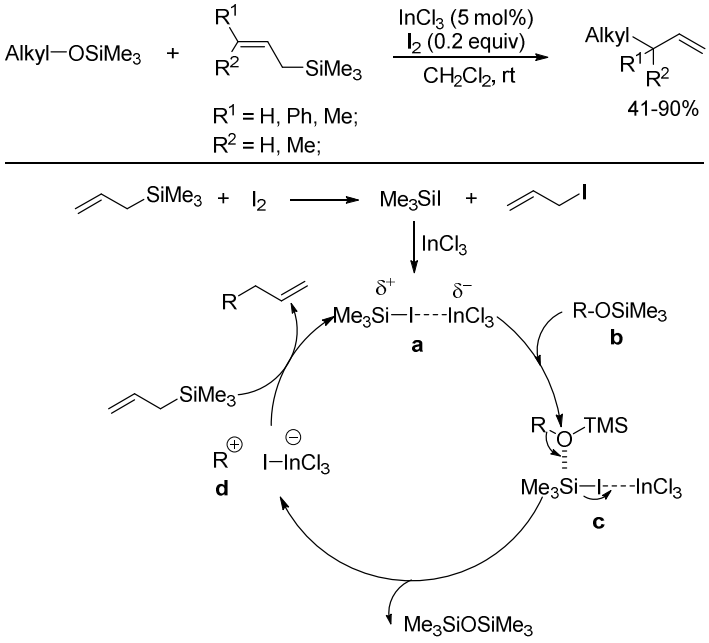
Scheme 1-7. Plausible mechanism for direct hydroxy group substitution by silane

1.1.6 $InCl_3$-TMSCl-mediated activation of silyl ether group

In 2007, Baba and co-workers demonstrated cross coupling of alkyl trimethylsilyl ethers and allylsilanes catalyzed by combined Lewis acid species of $InCl_3$ and Me_3SiI which is generated *in*

[11](a) Saito, T.; Yasuda, M.; Baba, A. *Synlett* **2005**, 1737–1739; (b) Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 8516–8522.

situ from $InCl_3$ and I_2 (**Scheme 1-8**).[12] Prior to this, the use of silyl ethers for alkylation was not fully established as silyl–derivatized alcohols is an important protection form of hydroxyl functionality and they exhibit high tolerance to nucleophilic substitution.[13] Additional synthetic steps to transform them into good leaving group are often necessary.

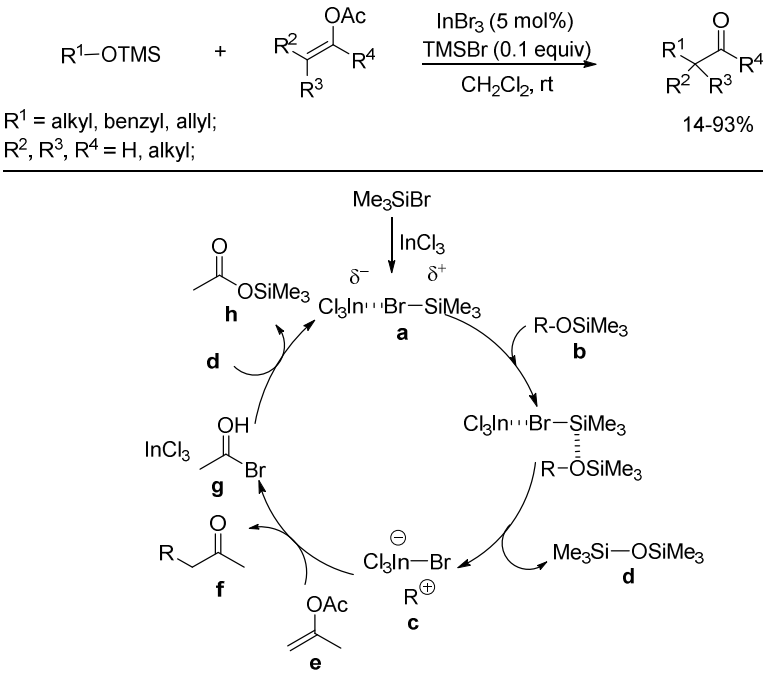


Scheme 1-8. Cross reaction of allylsilane and alkyl trimethylsily ether

A plausible reaction route was put forward for this reaction: I_2 first reacts with allylsilane to give Me_3SiI which in turn with $InCl_3$, gives a combined Lewis acid **a**. The silicon center in **a** has aggrandized Lewis acidity following iodine coordination to $InCl_3$. Subsequently, interaction of siloxyl oxygen with silicon in **a** weakens the C-O bond of trimethylsilyl ether thus allowing formation of carbocation **d** and hexamethyl disiloxane. The coupling product is afforded upon nucleophilic attack of allylsilane on **d** which also regenerates the combined catalyst

[12]Saito, T.; Nishimoto, Y.; Yasuda, M.; Baba, A. *J. Org. Chem*. **2007**, *72*, 8588-8590.
[13]For reports using silyl ethers as alkylating reagents, see: (a) Kira, M.; Hino, T.; Sakurai, H. *Chem. Lett.* **1992**, *21*, 555-558; (b) Yokozawa, T.; Furuhashi, K.; Natsume, H.; *Tetrahedron Lett.* **1995**, *36*, 5243-5246; (c) Braun, M.; Kotter, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 514-517.

($InCl_3$/Me_3SiI).



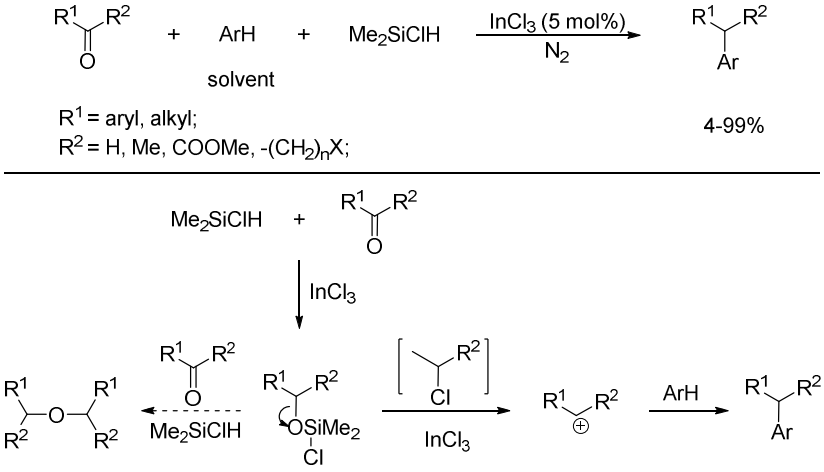
Scheme 1-9. $InCl_3$/TMSBr-catalyzed cross coupling between silyl ethers and enol acetates

Aside from allylsilane, enol acetates could also be used as the nucleophile to couple with silyl ethers. In 2011, Baba *et al.* reported on a $InCl_3$-TMSBr-catalyzed direct coupling of enol acetates with silyl ethers (**Scheme 1-9**).[14] A plausible mechanism was demonstrated: first, a combined Lewis acid **a** is formed from $InCl_3$ and TMSBr. The silicon center of **a** interacts with oxygen in silyl ether **b** to facilitate the generation of a carbocation species **c** along with $Me_3SiOSiMe_3$ **d**. The carbocation reacts with enol acetate **e** to produce α-alkylated carbonyl compound **f**. The combined Lewis acid **a** is regenerated along with the formation of byproduct **h** following reaction of acid bromide **g** with **d**. The observed chemoselectivity could source from weak interaction of oxygen and silicon while the reaction was thought to be driven by the formation of stable hexamethyldisiloxane.

[14]Onishi, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett*. **2011**, *13*, 2762-2765.

1.1.7 $InCl_3$-hydrosilane-mediated reductive Friedel-Crafts alkylation

"Reductive Friedel-Crafts reaction" featuring the use of carbonyls as direct alkylating reagents for aromatics, is yet another attractive synthetic approach in organic synthesis. In contrast to alkyl halides, alkenes, alcohols, or ethers as alkylation reagents, direct use of carbonyl compounds is challenging because the choice for effective hydride source is lacking which in turn may require excessive use of strong acids.[15]



Scheme 1-10. $InCl_3$-hydrosilane-mediated reductive Friedel-Crafts alkylation

In 1998, Baba and co-workers presented the first $InCl_3$-catalyzed reductive Friedel-Crafts alkylation wherein the chlorodimethylsilane (Me_2SiClH) acts as reductant to carbonyl substrates and the hydrosilylation precedes the alkylation of aromatics (**Scheme 1-10**).[16] The proposed mechanism depicted in **Scheme 1-10** consists of initial carbonyl hydrosilylation, carbocation

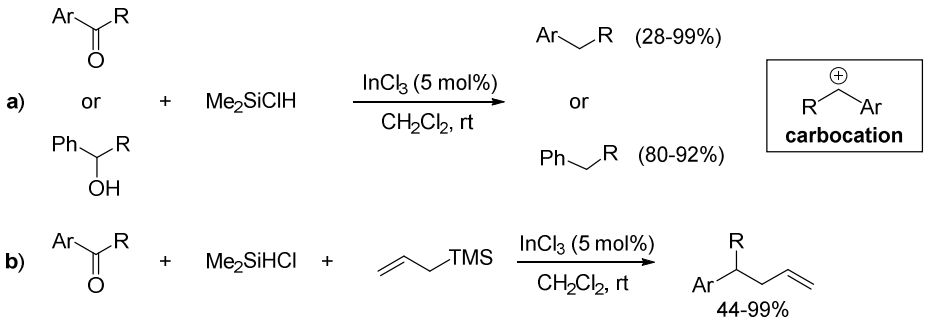
[15](a) Hashimoto, Y.; Hirata, K.; Kihara, N.; Hasegawa, M.; Saigo, K. *Tetrahedron Lett.* **1992**, *33*, 6351-6354; (b) Hashimoto, Y.; Hirata, K.; Kagoshima, H.; Kihara, N.; Hasegawa, M.; Saigo, K. *Tetrahedron* **1993**, *49*, 5969-5978; (c) Tsuchimoto, T.; Hiyama, T.; Fukuzawa, S.-I. *Chem. Commun.* **1996**, 2345-2346; (d) Tsuchimoto, T.; Tobita, K.; Hiyama, T. *J. Org. Chem*. **1997**, *62*, 6997-7005.

[16](a) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron Lett*. **1998**, *39*, 6291-6294; (b) Miyai, T.; Onishi, Y.; Baba, A. *Tetrahedron* **1999**, *55*, 1017–1026.

formation through desiloxylation or from alkyl chloride, and lastly the arene alkylation.

1.1.8 $InCl_3$-Me_2SiClH-mediated reductive deoxygenation of ketones and alcohols

In continuance of the reductive Friedel-Crafts alkylation reaction, the Baba group also employed the same $InCl_3$-Me_2SiClH system to study the reductive deoxygenation reaction using aromatic ketones and secondary benzylic alcohols to give respective hydrocarbons as well as deoxygenation-allylation reaction of aryl ketones (**Scheme 1-11**).[17] These reactions place basis on the interception of the carbocation intermediates with nucleophiles: hydride in the deoxygenation protocol and allylsilane in allylation protocol.



Scheme 1-11. $InCl_3$-hydrosilane-mediated deoxygenation and deoxygenative allylation

1.1.9 $InCl_3$-Me_2SiClH-mediated direct deoxy-halogenation of carbonyl compounds

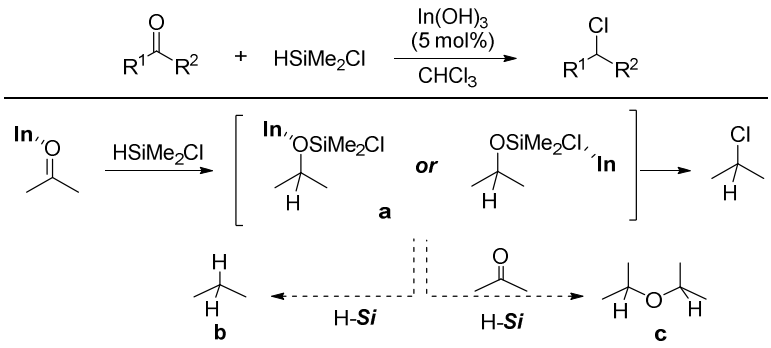
In comparison to the widely studied carbonyl transformations to other functionalities, deoxygenative halogenation of carbonyl compounds to the respective alkyl halides remains underdeveloped. Conventionally, reduction-chlorination reaction of carbonyls depends upon a multistep protocol under harsh conditions.[18] In 2002, Baba and co-workers disclosed a novel

[17](a) Miyai, T.; Ueba, M.; Baba, A. *Synlett* **1999**, 182-184; (b) Yasuda, M.; Onishi, Y.; Ito, T.; Baba, A. *Tetrahedron Lett*. **2000**, *41*, 2425-2428.

[18]Selected examples of the multistep chlorination of carbonyl compounds, see: (a) Tani, F.; Matsu-ura, M.; Nakayama, S.; Ichimura, M.; Nakamura, N.; Naruta, Y. *J. Am. Chem. Soc.* **2001**, *123*, 1133-1142; (b) Hamashima, Y.; Sawada, D.; Nogami, H.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2001**, *57*, 805-814; (c) Tanaka, K.; Katsurada, M.; Ohno, F.; Shiga, Y.; Oda, M. *J. Org. Chem*. **2000**, *65*, 432-437.

access to alkyl halides directly from carbonyls catalyzed by $In(OH)_3$ using chlorodimethylsilane (**Scheme 1-12**).[19]

The tentative mechanistic pathway is illustrated where hydrosilylation first occurs to give silyl ether **a** that will be activated by indium catalyst through coordination with oxygen or chloride to give chloride product upon leaving of the siloxy group. The observed formation of side products **b** and **c** could support the speculated intermediacy of **a**. While indium catalyst is thought to expedite the reaction from silyl ether to chloride product given the excellent high desiloxylation property, its weak Lewis acidity and oxophilicity of indium are thought to be equally crucial. The oxygen functionality could have trapped a stronger Lewis acid, inhibiting the completion of catalytic cycle.



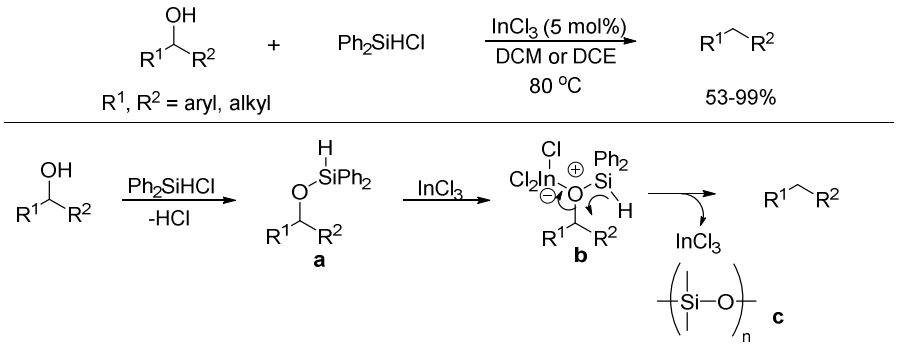
Scheme 1-12. In(III)-catalyzed direct deoxy-halogenation of carbonyls

1.1.10 $InCl_3$-hydrosilane-mediated alcohols transformation

An exemplary transformation of alcohols is the deoxygenative reaction to form respective alkanes. In view of the poor leaving property, the hydroxyl group is often activated prior to treatment with a reducing reagent.[20] In 2001, Baba reported the highly chemoselective

[19]Onishi, Y.; Ogawa, D.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13690–13691.
[20](a) *Comprehensive Organic Syntheses*; Trost, B. M., Ed.; PergamonPress: Oxford, U.K., **1991**; Vol. 8, pp 811-826; (b) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609-2645.

$InCl_3$-catalyzed direct reduction of benzylic alcohols, secondary alcohols as well as tertiary alcohols to respective alkanes in high yields (**Scheme 1-13**).[21] With chlorodiphenylsilane to provide hydride, a high chemoselectivity is evident from the intactness of otherwise reduction-labile functional group such as nitro, ester or halides under this condition.



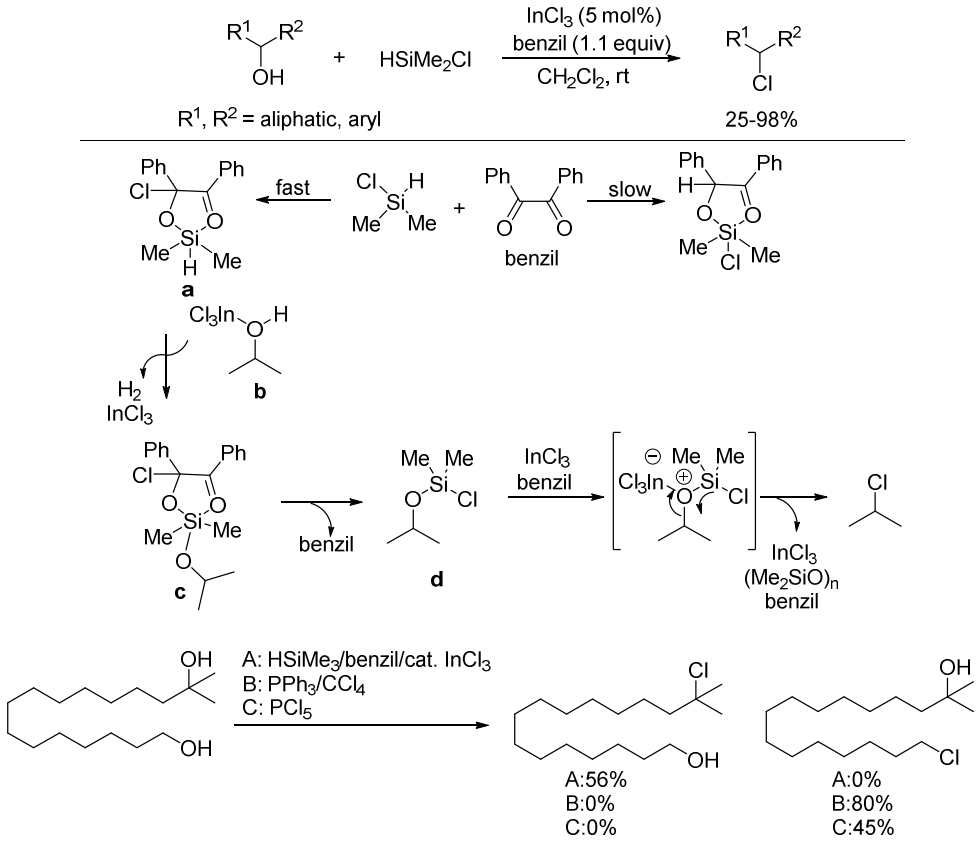
Scheme 1-13. $InCl_3$-hydrosilane-mediated direct reduction of alcohols

In proposed mechanism (**Scheme 1-13**), a key intermediate hydrosilyl ether **a** is converted from the alcohol by Ph_2SiHCl. The Lewis acidic $InCl_3$ will accelerate the desiloxylation of oxonium complex **b** with an accompanying hydride transfer from silyl moiety. Lastly, $InCl_3$ is regenerated upon the formation of the siloxane **c**. In this case, the catalytic loading of $InCl_3$ is also devoted by the moderate oxophilicity relative to the related Al(III) or B(III) compounds.

In this study, Baba and co-workers also observed that the presence of benzil (PhCOCOPh) substantially diverted the reaction pathway to yield a chlorination product instead (**Scheme 1-14**).[22] They have devised a plausible mechanistic pathway for this observation as shown. Hydrosilylation or chlorosilylation of benzil by $HSiMe_2Cl$ could take place at initial stage. Since the former is slower, the benzil chlorosilylation occurs to give intermediate **a**, after which an intramolecular carbonyl coordination of Si center with adjacent ketone group will weaken the

[21]Yasuda, M.; Onishi, Y.; Ueba, M.; Miyai, T.; Baba, A. *J. Org. Chem.* **2001**, *66*, 7741–7744.
[22]Yasuda, M.; Yamasaki, S.; Onishi, Y.; Baba, A. *J. Am. Chem. Soc.* **2004**, *126*, 7186–7187.

Si-H bond. The kinetically unstable thus-formed **a** reacts facilely with indium-activated alcohol **b** to give **c** and concomitant hydrogen ga**s** expulsion. The alkoxysilyl ether **c** will transform to **d** and release the benzil molecule. $InCl_3$ then mediates the formation of chloride product from silyl ether **d**. A distinctive reaction pattern was also exhibited by this system that the tertiary alcohol site was preferentially chlorinated when both primary and tertiary alcohol moieties were present in a single molecule. This is in contrast with the reactivity pattern normally observed with conventional chlorination protocol such as PPh_3/CCl_4 or PCl_5.



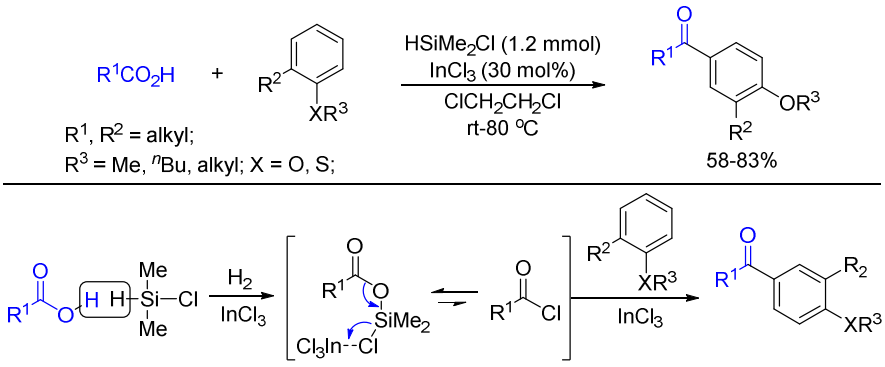
Scheme 1-14. $InCl_3$-catalyzed direct chlorination of alcohols

1.1.11 $InCl_3$-$HSiMe_2Cl$-mediated Friedel-Crafts reaction

Aromatic ketones are conventionally prepared through electrophilic aromatic substitution of arenes with reactive acylation agents such as acid-derived halides or anhydrides (Friedel-Crafts

acylation) in which an excess amount of strong Lewis acids are typically necessary. This downside has drawn research attentions to develop acylation protocol using stable and easily accessible reagents under mild conditions.[23]

In 2007, Baba's group reported on an $InCl_3$-mediated aromatic ethers acylation with carboxylic acids directly (**Scheme 1-15**).[24] In the presence of $InCl_3$, a transient silyl species **A** that participates readily in the ensuing synthetic steps is envisaged following the expulsion of H_2 by chemoselective interaction of $ClMe_2SiH$ with acids. It is hypothesized the electro positivity of the silicon center is aggrandized to have allowed the dehydrogenation and subsequent Friedel-Crafts acylation steps.

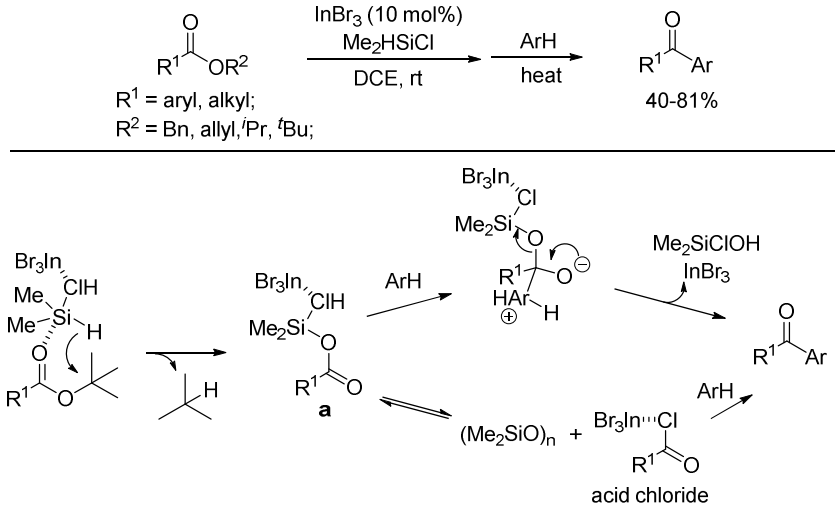


Scheme 1-15. Friedel-Crafts acylation of aromatic ethers using carboxylic acids

Employing similar catalyst system, Baba's group later performed Friedel-Crafts acylation with esters on arenes.[25] A similar mechanism is put forward as depicted in **Scheme 1-16**. With the silicon acting as acidic site, the combined Lewis acid comprises of $InBr_3$ and Me_2HSiCl interacts selectively with carbonyl oxygen. An intramolecular transfer of hydride to the *tert*-butyl group

[23](a) Ranu, B. C.; Ghosh, K.; Jana, U. *J. Org. Chem.* **1996**, *61*, 9546-9547; (b) Smith, K.; El-Hiti, G. A.; Jayne, A. J.; Butters, M. *Org. Biomol. Chem.* **2003**, *1*, 2321-2325; (c) Wang, Q. L.; Ma, Y.; Ji, X.; Yana, H.; Qiub, Q. *J. Chem. Soc., Chem. Commun.* **1995**, 2307-2308; (d) Firousabadi, H.; Iranpoor, N.; Nowrouzi, F.; *Tetrahedron Lett.* **2003**, *44*, 5343-5345; (e) Sarvari, M. H.; Sharghi, H. *Synthesis* **2004**, 2165-2168; (f) Cui, D.-M.; Zhang, C.; Kawamura, M.; Shimada, S. *Tetrahedron Lett.* **2004**, *45*, 1741-1745.
[24]Babu, S. A.; Yasuda, M.; Baba, A. *Org. Lett*. **2007**, *9*, 405-408.
[25]Nishimoto, Y.; Babu, S. A.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2008**, *73*, 9465-9468.

generates intermediate **a** with *iso*butane expulsion. Activation of the thus-formed **a** by $InBr_3$ through Me_2SiCl will promote the direct arene acylation to deliver the ketone product. Nonetheless, the alternative reaction pathway proceeding through acid chloride formed *in-situ* cannot be ruled out.

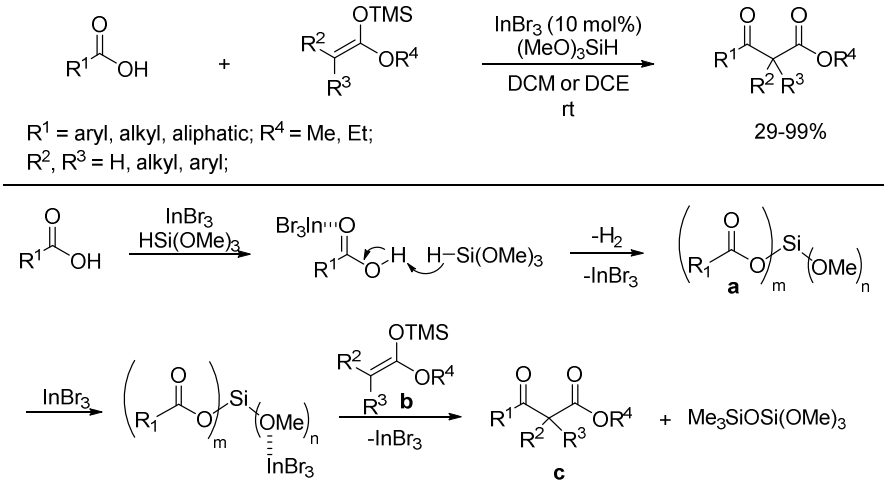


Scheme 1-16. Esters as acylating agent in Friedel-Crafts acylation

1.1.12 In(III)-catalyzed cross-coupling of silyl enolates and carboxylic acid

Carboxylic acids are expedient acylating agents, but the direct use of non-derived acids is still challenging due to the acidity of carboxyl proton. Catalyst degradation as well as undesired side reaction is often observed. Moreover, $SOCl_2$ or *N,N′*-carbonyldiimidazoleas strong activators is often mandatory to generate reactive intermediates from carboxylic acids in most reported reactions, which have resulted in formation of problematic by-products.[26]

[26]Aberhart, D. J.; Lin, H.-J.; Weiller, B. H. *J. Am. Chem. Soc.* **1981**, *103*, 6750-6752; (b) Kende, A. S.; Koch, K.; Smith, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 2210-2218; (c) Williams, M. A.; Miller, M. J. *Tetrahedron Lett*. **1990**, *31*, 1807-1810; (d) Nagao, Y.; Kumagai, T.; Nagase, Y.; Tamai, S.; Inoue, Y.; Shiro, M. *J. Org. Chem*. **1992**, *57*, 4232-4237.



Scheme 1-17. In(III)-catalyzed cross-Claisen condensation

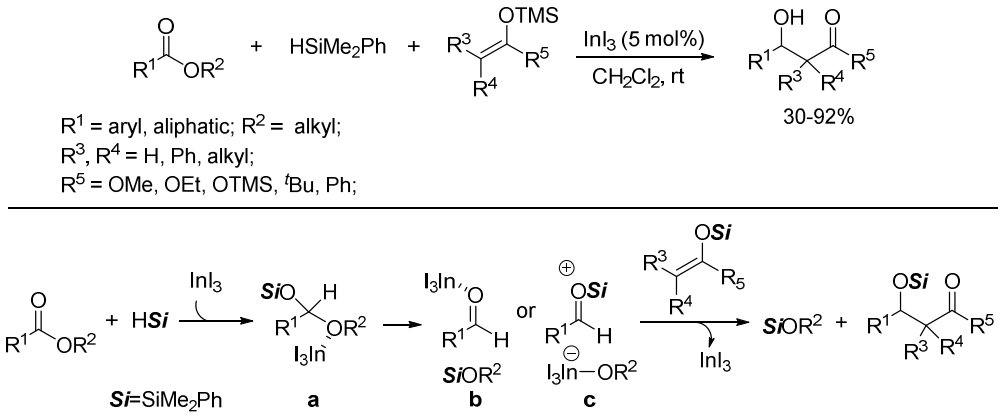
In 2011, Baba's group reported a convenient cross-Claisen protocol to prepare β-keto esters with an indium-catalyzed condensation reaction of carboxylic acids and ketene silylacetals (**Scheme 1-17**).[27] Varied functionalities were well tolerated under this reaction condition such as alkynes, halides, ester, nitro and hydroxyl group. The generation of silyl carboxylate **a** is tentatively proposed following the acidic proton abstraction by $(MeO)_3SiH$ from an $InBr_3$-activated carboxylic acid and expulses a hydrogen molecule. Subsequently, the $InBr_3$-activated silyl carboxylate **a** will react with ketene silylacetal **b** to form the Claisen-condensation product **c**. The interaction between oxygen on methoxy group and $InBr_3$ at this stage could have necessitated the reaction, evident from the indispensable alkoxy group in hydrosilane for efficient transformation. The use of Me_2ClSiH resulted in only 62% conversion of acid and 39% yield of keto ester whereas the use of $(MeO)_2SiH$ gave 100% conversion and 90% yield of product, with all other parameters kept constant.

1.1.13 In(III)-catalyzed cross-coupling of silyl enolates and esters

Mukaiyama aldol reaction remains one of the most powerful tool to forge new C-C bond

[27]Nishimoto, Y.; Okita, A.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed*. **2011**, *50*, 8623-8625.

between aldehydes and silyl enolates in synthetic toolbox. Despite the versatility as electrophiles, stability and storage issues persist for some aldehydes.[28] In 2011, Baba and co-workers demonstrated a practical alternative synthetic protocol of ß-hydroxycarbonyl compounds using esters, silylenolates and hydrosilanes in single operation. This could complement the conventional Mukaiyama aldol reaction using aldehydes (**Scheme 1-18**).[29]



Scheme 1-18. Cross-aldol reaction of ester and silyl enol ether

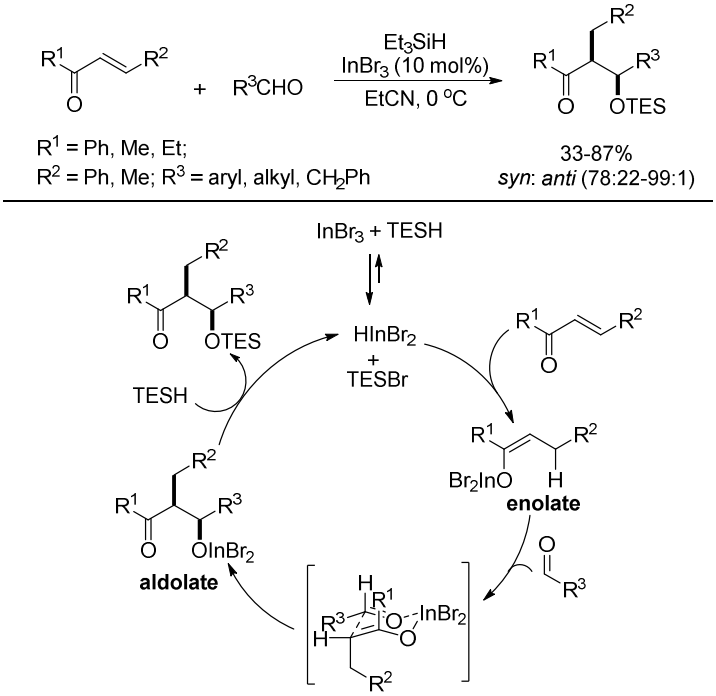
From the proposed mechanism, InI_3 first promotes the hydrosilylation of ester to form acetal intermediate **a**. Oxonium ion **b** or aldehyde **c** could then be generated when InI_3-coordinated alkoxy group eliminates to alleviate steric strain. The prompt reaction of **b** or **c** with silyl enolate then gives the ß-siloxycarbonyl product along with InI_3 to complete the catalytic cycle.

1.1.14 In(III)-catalyzed reductive aldol reaction of aldehydes and enones

The reductive aldol reaction of metal hydrides, enones and aldehydes is also highly preferable in furnishing ß-hydroxyketones. The prominent advantage with this strategy lies with the convenience in generating the metal enolate *in-situ* from the conjugate addition of metal hydrides

[28]Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011-1014; (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-7509.
[29]Inamoto, Y.; Nishimoto, Y.; Yasuda, M.; Baba, A. *Org. Lett.* **2012**, *14*, 1168-1171.

onto enones, thus circumvents additional synthetic step to prepare metal enolates. However, chemoselectivity issue often arises from higher reactivity of aldehydes than enones to conventional metal hydrides.[30] In 2004, a diastereoselective reductive aldol reaction of aldehydes and enones promoted by Et_3SiH which afforded only silyl aldolate products in the presence of $InBr_3$ catalyst was disclosed by Baba's group (**Scheme 1-19**).[31]



Scheme 1-19. Reductive aldol reaction of conjugated ketones and aldehydes

In the proposed catalytic cycle (**Scheme 1-19**), Br_2InH is initially generated from slow transmetalation between $InBr_3$ and Et_3SiH. Br_2InH then adds onto enoneto give enolate. This indium enolate together with aldehyde forms a Zimmerman-Traxler six-membered cyclic transition state, which will yield *syn*-indium aldolate. Titled product is yielded upon TESH

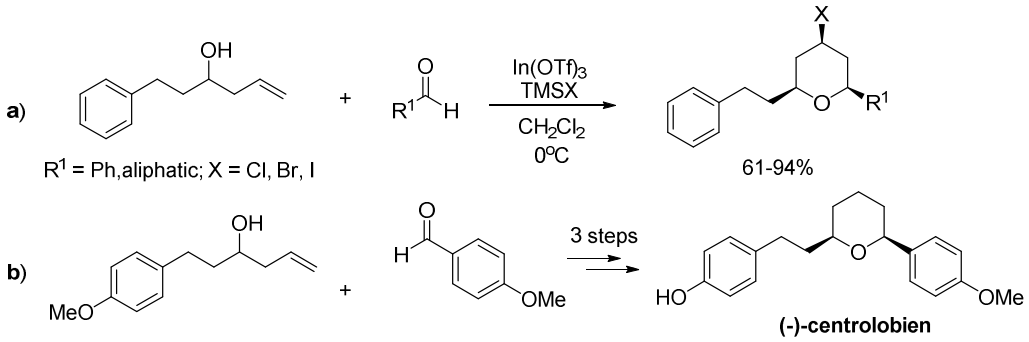
[30](a) Matsuda, I.; Takahashi, K.; Sato, S. *Tetrahedron Lett.* **1990**, *31*, 5331-5334; (b) Enholm, E. J.; Xie, Y.; Abboud, A. A. *J. Org. Chem.* **1995**, *60*, 1112-1113; (c) Ooi, T.; Doda, K.; Sakai, D.; Maruoka, K. *TetrahedornLett.* **1990**, *40*, 2133-2136; (d) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122,* 4528-4529.

[31]Shibata, I.; Kato, H.; Ishida, T.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 711-714.

trapping.

1.1.15 In(III)-TMSX-mediated synthesis of tetrahydropyran ring

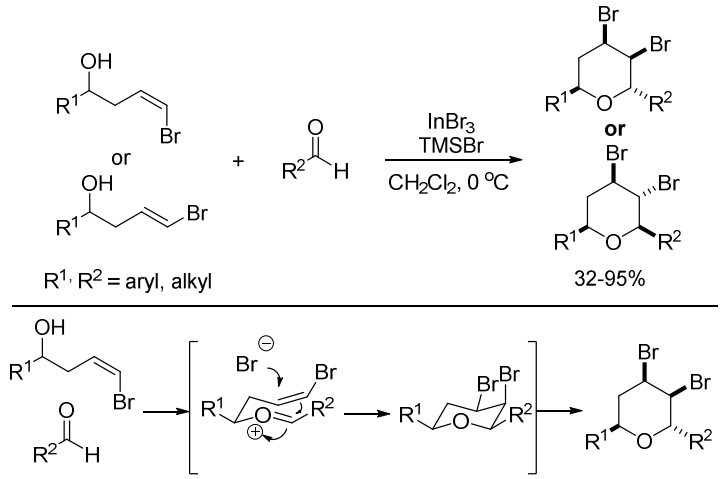
The tetrahydropyran (THP) ring presents in ubiquity in many naturally-occurring compounds. Within the numerous established methods, Prins cyclization represents a versatile entry to construct THP ring. [32] In this regard, Loh *et al*. has demonstrated a series of In(III)-TMSX-mediated formation of functionalized THP rings from aldehydes and alkenes/allenes.



Scheme 1-19. Catalytic Prins cyclizations with trimethylsilyl halides

In 2005, Loh and Chan described a novel strategy to build 4-halo tetrahydropyran rings with catalytic combination of indium salt and trimethylsilyl halide additive that successfully suppressed undesirable epimerization (**Scheme 1-19a**).[33] The efficiency and synthetic values of this strategy are attested when employed as key steps in the highly convergent asymmetric synthesis of (-)-centrolobineas well as formal synthesis of (+)-SCH 351448 (**Scheme 1-19b**)[34].

[32](a) Ramesh, J.; Vitale, J.; Rychnovsky, S. D. *J. Am. Chem.Soc.* **2004**, *126*, 9904-9905; (b) Dalgard, J. E.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2004**, *126*, 15662-15663; (c) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Angew.Chem. Int. Ed.* **2001**, *40*, 2921-2922; (d) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T.*J. Am. Chem. Soc.* **2001**, *123*, 2450-2451.
[33]Chan, K.-P.; Loh, T.-P. *Org. Lett*. **2005**, *7*, 4491-4494.
[34]Chan, K.-P.; Lin, H. Y.; Loh, T.-P. *Chem. Commun.* **2007**, 939-941.



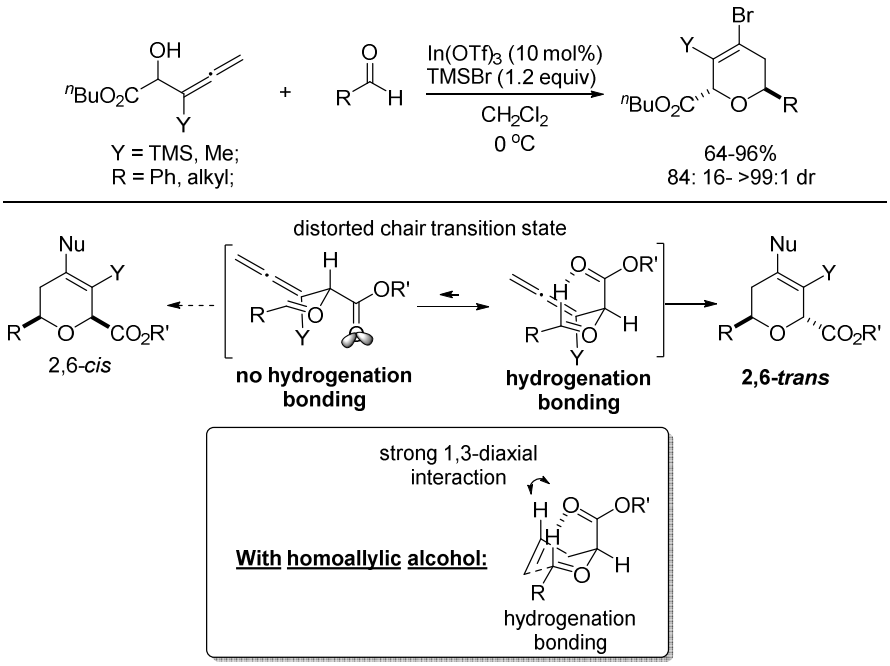
Scheme 1-20. Brominated homoallylic alcohols for stereoselective Prins cyclization

In 2007, Loh and Liu reported yet another efficient method to construct moderate to high yields of 2,6-*cis*-4,5-dibromo tetrahydropyrans in the stereospecific manner (**Scheme 1-20**).[35] Note-worthily, this is the first example to form *cis*-dibromo-tetrahydropyran ring through Prins cyclization by using (*Z*)-boromohomoallylic alcohols. Usually, bromination of dihydropyrans gives only *trans*-dibromo-tetrahydropyran products.

Subsequently in 2009, they achieved a highly efficient complementary indium-catalyzed Prins cyclization for the synthesis 2,6-*trans*dihydropyrans from allenic alcohols and aldehydes (**Scheme 1-21**).[36] This protocol demonstrates the plausibility to steer the reaction to desired pathway by modulating the stereoelectronic against steric effect. Importantly, the success of this strategy is made viable by the employment of carboalkoxyl allenic alcohol substrates in which the C-H bond of the aldehydes could form hydrogenation bonding with the axial ester group in the chair TS. Furthermore, using allenic alcohols could obviate the 1,3-steric repulsion between ester moiety and hydrogen as presents in the case of homoallylic alcohols. Transition state adopting a distorted six-membered ring conformation promotes the preferential axial orientation

[35]Liu, F.; Loh, T.-P. *Org. Lett*. **2007**, *9*, 2063-2066.
[36]Hu, X.-H.; Liu, F.; Loh, T.-P. *Org. Lett*. **2009**, *11*, 1741-1743.

of the ester group.



Scheme 1-21. Highly stereoselective Prins cyclization of allenic alcohols

This section has highlighted the employment of combined Lewis acid system comprises of indium(III) salts and silane derivatives including halosilanes and hydrosilanes for varied chemical transformations of alcoholic or carbonyl substrates. In most cases, these reactions were plausible with indium(III) salts owing to their tempered oxophilicilities as compared to Al(III) or boron compounds. In instances wherein aggrandized Lewis acidity is required, the halosilanes could form complex with indium(III) salts because of their higher halophilicity, resulting in combined catalyst system with silicon as the acidic center.

1.2 [2+2] Cycloaddition of alkynes and alkenes

Strained carbocyclic molecules have served as highly effective synthetic building blocks in the past decades. Among them, the most widely-investigated ones are the derivatives of cyclopropane and cyclobutane where their versatility is evident. Four-member rings are

ubiquitous motifs present in many naturally occurring and/or bioactive compounds (**Figure 1-1**).[37,38] The significant synthetic and bioactive values brought about by their inherent ring strain results in commendable research attentions paid in devising synthetic strategies for their construction.[39,40,41,42,43]

Although the concerted [2+2] cycloaddition of alkenes and alkynes under thermal conditions is forbidden as inferred from Woodward-Hoffman rules[44], this methodology is nonetheless an efficient one to assemble cyclobutene ring systems.[45,46,47,48,49] It could be attained by thermal

[37]Dembitsky, V. M. *J. Nat. Med*. **2008**, *62*, 1-33.
[38](a) Wani, M. C.; Taylor, H. L.; Wall, M. E.; Coggon, P.; McPhail, A. T. *J. Am. Chem. Soc*. **1971**, *93*, 2325-2327; (b) Boumchita, H.; Legraverend, M.; Zerial, A.; Lemaitre, M.; Huel, C.; Bisagni, E. *Eur. J. Med. Chem*. **1991**, *26*, 613-617; (c) Bassett, C.; Sherwood, R. T.; Kepler, J. A.; Hamilton, P. B. *Phytopathology* **1967**, *57*, 1046-1057; (d) Marrero, J.; Rodriguez, A. D.; Baran, P.; Raptis, R. G.; Sánchez, J. A.; Ortega-Barria, E.; Capson, T. L. *Org. Lett*. **2004**, *6,* 1661-1664; (e) Corey, E. J.; Mitra, R. B.; Uda, H. *J. Am. Chem. Soc.* **1964**, *86*, 485-492; (f) König, G. M.; Wright, A. D. *J. Org. Chem.* **1997**, *62*, 3837; (g) Arnone, A.; Nasini, G.; Vajna de Pava, O. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2723; (h) Leimmer, J.; Marshall, H.; Meier, N.; Weyerstahl, P. *Chem. Lett.* **1984**, 1769; (i) Parés, S.; Alibés, R.; Figueredo, M.; Font, J.; Parella, T. *Eur. J. Org. Chem.* **2012**, *7*, 1404-1417.
[39]Bioactive compounds with four membered rings: (a) Valasinas, A.; Sarkar, A.; Reddy, V. K.; Marton, L. J.; Basu, H. S.; Frydman, B. *J. Med. Chem.* **2001**, *44*, 390-403; (b) Marson, C. M. *Chem. Soc. Rev.* **2011**, *40*, 5514-5533; (c) Kallemeyn, J. M.; Ku, Y.-Y.; Mulhern, M. W.; Bishop, R.; Pal, A.; Jacob, L. *Org. Process. Res. Dev.* **2014**, *18*, 191-197.
[40](a) Toda, F.; Garratt, P. *Chem. Rev.* **1992**, *92*, 1685-1707; (b) Dolbier, W. R. Jr.; Koroniak, H.; Houk, K, N.; Sheu, C. *Acc. Chem. Res.* **1996**, *29*, 471-477; (c) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.***2003**, *103*, 1449-1483; (d) Namyslo, J. C.; Kaufmann, D. E. *Chem. Rev.* **2003**, *103*, 1485-1537; (e) Hall, H. K. Jr.; Padias, A. B. *J. Polym. Sci. Part A: Polym. Chem.* **2003**, *41*, 625-635; (f) Parker, K. A.; Sampson, N. S. *Acc. Chem. Res.* **2016**, *49*, 408-417.
[41](a) Gauvry, N.; Lescop, C.; Huet, F. *Eur. J. Org. Chem*. **2006**, 5207-5218; (b) Murakami, M.; Miyamoto, Y.; Hasegawa, M.; Usui, I.; Matsuda, T. *Pure. Appl. Chem.* **2006**, *78*, 415-423; (c) Nemoto, H. *Chem. Pharm. Bull*. **2007**, *55*, 961-974; (c) Leemans, E.; D'hooghe, M.; De Kimpe, N. *Chem. Rev*. **2011**, *111*, 3268-3333; (d) Mack, D. J.; Njardarson, J. T. *ACS catal*. **2013**, *3*, 272-286; (e) Walczak, M. A. A.; Krainz, T.; Wipf, P. *Acc. Chem. Res*. **2015**, *48*, 1149-1158; (f) Deprés, J.; Delair, P.; Poisson, J.; Kanazawa, A.; Greene, A. E. *Acc. Chem. Res*. **2016**, *49*, 252-261.
[42](a) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev*. **2014**, *114*, 7317-7420; (b) Carreira, E. M.; Fessard, T. C. *Chem. Rev*. **2014**, *114*, 8257-8322.
[43](a) de Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. *Chem. Commun*. **2014**, *50*, 10912-10928; (b) Matsuo, J. *Tetrahedron Lett*. **2014**, *55*, 2589-2595; (c) Reissig, H.; Zimmer, R. *Angew. Chem. Int. Ed*. **2015**, *54*, 5009-5011.
[44](a) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 2046-2048; (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem. Ind. Ed.* **1969**, *8*, 781-932.
[45]Formation of four-membered heterocycle: (a) Robin, S.; Rousseau, G. *Eur. J. Org. Chem*. **2002**, 3099-3114; (b) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res*. **2004**, *37*, 592-600; (c) Secci, F.; Frongia, A.; Piras, P. P. *Molecules* **2013**, *18*, 15541-15572; (d) R. Tuba. *Org. Biomol. Chem*. **2013**, *11*,

reaction of biradical intermediates,[50] photoreactions,[46] or by mediation or catalysis of transition metals[47] or Lewis acids[48]. In view of the possibly laborious procedures and limited reaction scope with the former two pathways, the development of efficient metal- or acid-mediated or catalyzed procedures would be highly desirable. In this section, the development of transition metals- and Lewis acids-mediated alkynes-alkenes [2+2] cycloaddition to prepare cyclobutenes will be summarized.

5976-5988.

[46]Photochemical reaction: (a) Winkler, J. D.; Bowen, C. M.; Liotta, F. *Chem. Rev.* **1995**, *95*, 2003-2020; (b) Iriondo-Alberdi, J.; Greaney, M. F. *Eur. J. Org. Chem*. **2007**, 4801-4815; (c) Hoffmann, N. *Chem. Rev*. **2008**, *108*, 1052-1103; (d) Bach, T.; Hehn, J. P. *Angew. Chem. Int. Ed*. **2011**, *50*, 1000-1045; (e) Frébault, F.; Maulide, N. *Angew. Chem. Int. Ed.* **2012**, *51*, 2815-2817; (f) Yoon, T. P. *ACS catal*. **2013**, *3*, 895-902; (g) Margaretha, P. *Hel.Chim.Acta* **2014**, *97*, 1027-1035; (h) Brimioulle, R.; Lenhart, D.; Maturi, M. M.; Bach, T. *Angew. Chem. Int. Ed*. **2015**, *54*, 3872-3890; (i) Poplata, S.; Troster, A.; Zou, Y.-Q.; Bach, T. *Chem. Rev*. **2016**, *116*, 9748-9815.

[47]Transition-metal: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49-92; (b) Tam, W.; Goodreid, J.; Cockburn, N. *Curr. Org. Synth*. **2009**, *6*, 219-238.

[48]Acid catalyst: (a) Takasu, K. *Synlett* **2009**, *12*, 1905-1914; (b) Schmidt, A. W.; Knölker, H.-J. *Synlett* **2010**, 2207-2239; (c) Rasik, C. M.; Brown, M. K. *Synlett* **2014**, *25*, 760-765; (d) Xu, Y.; Conner, M. L.; Brown, M. K. *Angew. Chem. Int. Ed*. **2015**, *54*, 11918-11928; (e) Akiyama, T.; Mori, K. *Chem. Rev.* **2015**, *115*, 9277-9306; (f) Fructos, M. R.; Prieto, A. *Tetrahedron* **2016**, *72*, 355-369.

[49]Ficini reaction: (a) Ficini, J. *Tetrahedron* **1976**, *32*, 1449-1486; (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575-7606; (c) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840-2859; (d) DeKorver, K. A.; Li, H. Y.; Lohse, A. G.; Hayashi, R.; Lu, Z. J.; Yang, Y.; Hsung, R. P. *Chem. Rev*. **2010**, *110*, 5064-5106; (e) Lu, T.; Lu, Z. J.; Ma, Z.-X.; Zhang, Y.; Hsung, R. P. *Chem. Rev*. **2013**, *113*, 4862-4904; (f) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S. Z.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res*. **2014**, *47*, 560-578.

[50]Ma, S. M. *Chem. Rev.* **2005**, *105*, 2829-2871; (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev*. **2010**, *39*, 783-816; (c) Muratore, M. E.; Homs, A.; Obradors, C.; Echavarren, A. M. *Chem. Asian. J*. **2014**, *9*, 3066-3082.

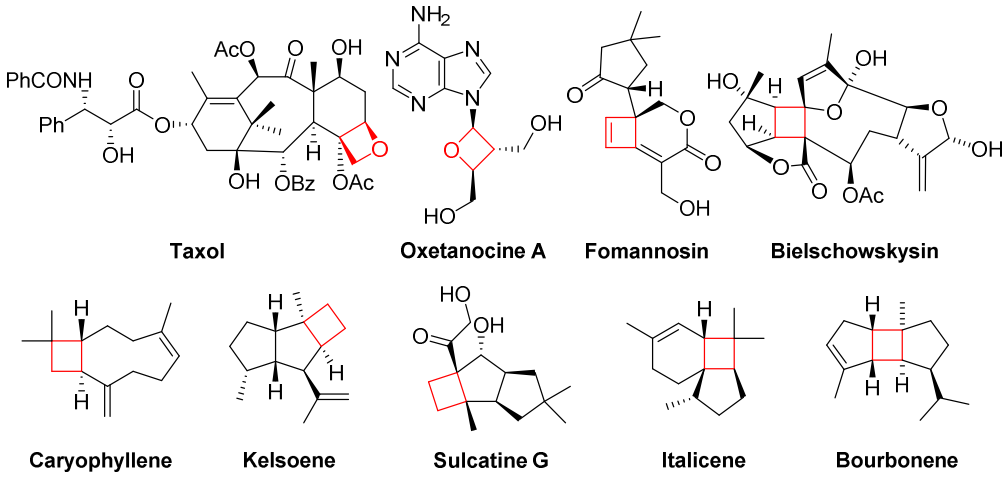
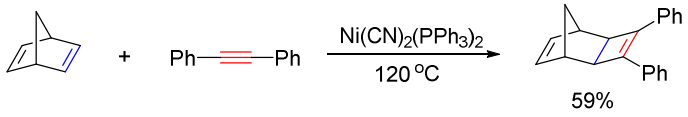


Figure 1-1. Bioactive compounds containing four-membered ring moiety

1.2.1 Metals-Catalyzed Alkynes-Alkenes [2+2] Cycloaddition

1.2.1.1 Nickel

Early ventures of catalytic [2+2] alkene-alkyne cycloaddition began with nickel in the 1960s where Schrauzer and Glockner presented the pioneering example of transition metal-catalyzed alkene-alkyne [2+2] cycloaddition to form cyclobutene through the cross-coupling of highly-strained 1,5-norbornadiene (NBD) and 1,2-diphenylethyne using nickel catalyst (**Scheme 1-22**).[51]

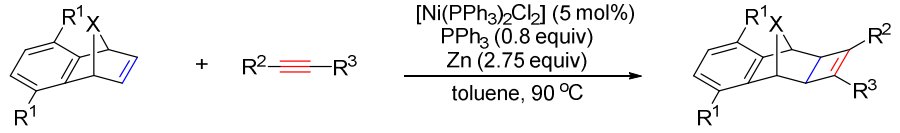


Scheme 1-22. Ni-catalyzed alkyne-norbornadiene [2+2] cycloaddition

More recently, a [2+2] cycloaddition using activated norbornadienes and also nickel catalyst was reported by Cheng *et al.* in 2000. In their findings, the nickel phosphine complex $[Ni(PPh_3)_2Cl_2]$ reduced *in-situ* by zinc powder could catalyze a stereoselective [2+2] cycloaddition between oxa-/aza-benzonorbornadienes with a plethora of alkynes to prepare moderate to excellent yields

[51]Schrauzer, G. N.; Glockner, P. *Chem. Ber*. **1964**, *97*, 2451-2462.

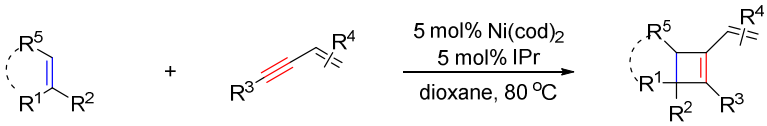
of exo-cyclobutene derivatives (**Scheme 1-23**).[52]



X = O, -NCO$_2$Me; R^1 = H, OMe;
R^2, R^3 = H, Ph, alkyl, CO$_2$Et, CH(OEt)$_2$;

Scheme 1-23. Ni-catalyzed alkynes-oxa(aza)benzonorbornadienes [2+2] cycloaddition

Aside from exploiting the structural advantage of highly strained alkene, another report by Ogoshi *et al.* in 2012 features highly chemo- and regioselective [2+2] cycloaddition of 1,3-enynes with electron-poor alkenes or electronically neutral norbornene or 1-decane to form cyclobutenes by an *in situ* formed NHC-nickel(0) complex (**Scheme 1-24**).[53] It was observed that undesired oligomerization and cyclotrimerization of alkynes could be successfully hindered with the use of conjugated enynes.

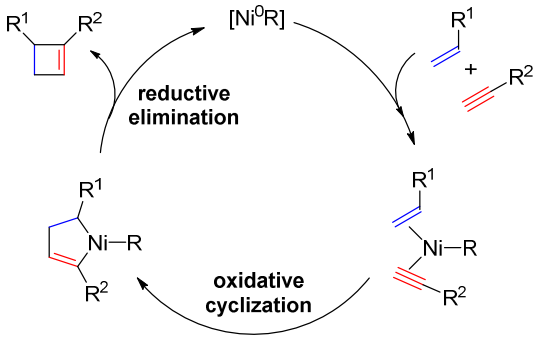


R^1, R^2, R^3, R^4 = H, alkyl, Ph;
R^5 = COR, CO$_2$R, CONR, PO(OEt)$_2$, alkyl

Scheme 1-24. Ni-catalyzed enynes-electron-deficient alkenes [2+2] cycloaddition

A general mechanism proposed underlying the zerovalent nickel-catalyzed [2+2] cycloaddition is depicted (**Scheme 1-25**).[53] Simultaneous coordination of both alkene and alkyne substrates to zerovalent nickel center and the ensuing oxidative cyclometallation gives nickellacycle-complex intermediate. Reductive elimination of metallacycle intermediate then affords cyclobutene while regenerates the nickel(0) species for the catalytic cycle.

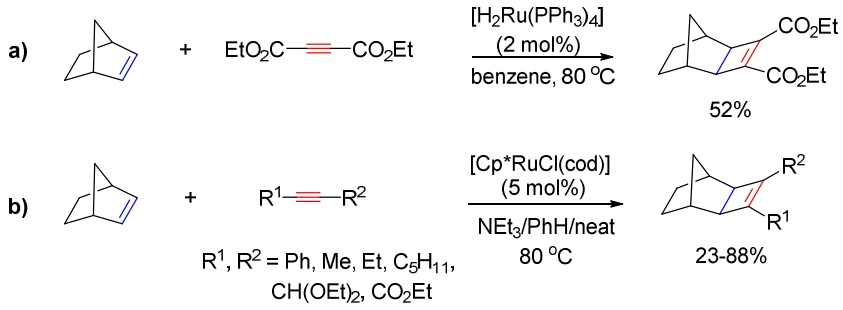
[52]Huang, D.-J.; Rayabarapu, D. K.; Li, L.-P.; Sambaiah, T.; Cheng, C.-H. *Chem. Eur. J.* **2000**, *6*, 3706-3713.
[53]Nishimura, A.; Ohashi, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2012**, *134*, 15692-15695.



Scheme 1-25. Mechanism for Ni(0)-catalyzed [2+2] cycloadditon of alkene and alkyne

1.2.1.2 Ruthenium

Aside from nickel catalyst, Mitsudo's group on the other hand, pioneered the alkyne-alkene cross cycloaddition with ruthenium catalytic systems. Early in 1976, they seminally reported the [2+2] cycloaddition of norbornene with diethyl acetylenedicarboxylate (DMAD) in benzene using the ruthenium complex: $[H_2Ru(PPh_3)_4]$ (**Scheme 1-26a**).[54] Subsequently, they identified another three catalysts: $RuH_2(CO)[P(p\text{-}FC_6H_4)_3]_3$, $[RuH_2(CO)(PPh_3)_3]$ and $[Ru(cod)(cot)]/PR_3$ that were equally compatible for this reaction.[55] While several bicyclic[2.2.1] alkenes reacted effectively, the alkyne coupling partner was limited to ethynedicarboxylates.



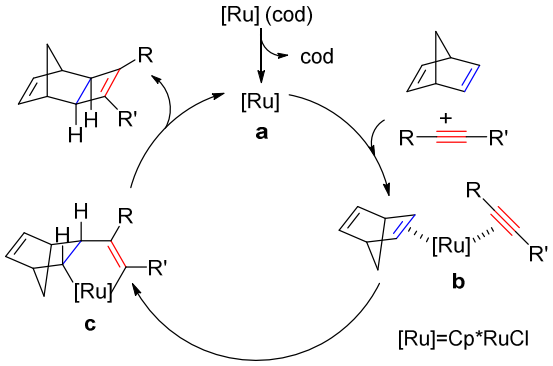
Scheme 1-26. Ruthenium-catalyzed norbornenes-alkynes cycloaddition

This issue was later addressed with the use of [CpRuCl(cod)] that could accommodate

[54]Mitsudo, T.; Kokuryo, K.; Takegami, Y. *J. Chem. Soc., Chem. Commun*. **1976**, 722-723.
[55](a) Mitsudo, T.; Kokuryo, k.; Shinsugi, T.; Nakagawa, Y.; Watanabe, Y.; Takegami, Y. *J. Org. Chem*. **1979**, *44*, 4492-4496; (b) Mitsudo, T.; Hori, Y.; Watanabe, Y. *J. Organomet. Chem*. **1987**, *334*, 157-167.

non-activated alkynes while also further enhanced the efficiency of the [2+2] cycloaddition of various norbornenes (**Scheme 1-26b**).[56] The use of $CpRuCl(PPh_3)_2$ alone did not effect the reaction; it was speculated that the labile cod ligand could enable the generation of reactive unsaturated ruthenium species which is essential to mediate the cycloaddition.

The exact mechanism of this [2+2] cycloaddition remains elusive and a plausible one was devised by Mitsudo as illustrated in **Scheme 1-27**. First, the dissociation of cod from [Cp*RuCl(cod)] generates unsaturated complex **a** [Cp*RuCl] with a vacant site that allows both norbornene and alkyne to coordinate (Ru complex **b**). An ensuing oxidative cyclization forms the ruthenacyclopentene **c** that forms cycloadduct and releases unsaturated Ru complex **a** after reductive elimination.

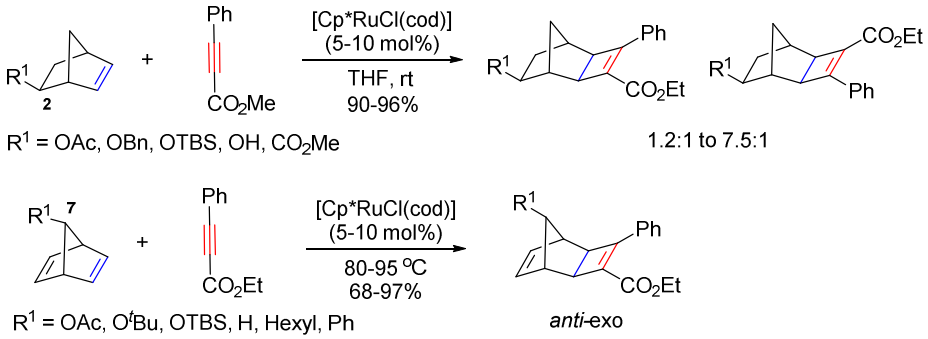


Scheme 1-27. Proposed catalytic cycle for Ru-catalyzed cycloaddition

Tam and co-workers reinvestigated the [2+2] cycloaddition with substituted 2-norbornenes[57], 2,3-disubstituted norbornadienes[58] or 7-norbornadienes[59] with electron-deficient alkynes using Mitsudo's protocol (**Scheme 1-28**). These studies demonstrated the induction of regio- and stereoselectivies using remote substituent effects on bicyclic alkenes. The same group later

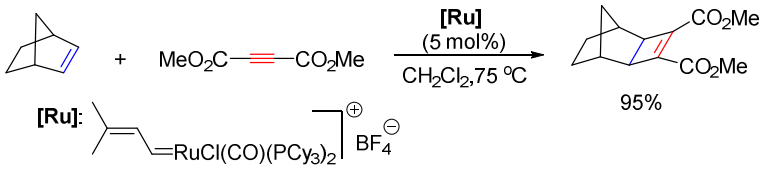
[56]Mitsudo, T.; Naruse, H.; Kondo, T.; Ozaki.; Watanabe, Y. *Angew. Chem. Int. Ed*. **1994**, *33*, 580-581.
[57]Jordan, R. W.; Tam, W. *Org. Lett*. **2000**, *2*, 3031-3034.
[58]Jordan, R. W.; Tam, W. *Tetrahedron Lett*. **2002**, *43*, 6051-6054.
[59]Jordan, R. W.; Tam, W. *Org. Lett*. **2001**, *3*, 2367-2370.

achieved asymmetric induction with the use of and a chiral acetylenic acyl sultam for [2+2] cycloaddition with bicyclic alkenes. Upon removal of recyclable chiral auxiliary, enantioselective cyclobutene rings could be furnished in up to 98.8% ee.[60]



Scheme 1-28. Remote substituent effect on [2+2] cycloaddition

A separate group demonstrated that with catalytic amount of methyl iodide, $CpRuCl(PPh_3)_2$ could also be used to generate $[Cp^*RuI(PPh_3)_2]$ to effect the cycloaddition of norbornenes with alkynes wherein a heightened reaction temperature (90 ^oC) should account for the sluggishness of PPh_3dissociation in this case.[61]



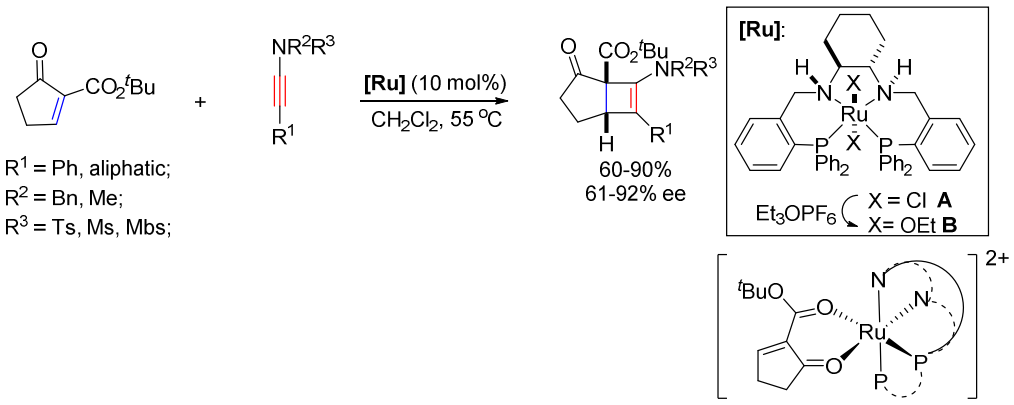
Scheme 1-29. Cationic Ru complex-catalyzed norbornene-alkyne [2+2] cycloaddition

A well-designed cationic ruthenium-alkylidene complex was successfully employed by Yi and co-workers for catalysis of [2+2] cycloaddition between dimethyl acetylenedicarboxylate and norbornene or ethylene in high yield (**Scheme 1-29**).[62] The otherwise commonly encountered ring-opening metathesis products with cationic Ru complex were at all absent, thereby attesting

[60]Villeneuve, K.; Tam, W. *Angew. Chem. Int. Ed.* **2004**, *43*, 610-613.
[61]Tenaglia, A.; Giordano. L. *Synlett* **2003**, 2333-2336.
[62]Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043-2045.

the high chemoselectivity of this reaction.

In 2011, Mezzetti *et al.* described the first enantioselective ruthenium-catalyzed Ficini cycloaddition of cyclic unsaturated ß-ketoesters and ynamides to produce cyclobutene amides (**Scheme 1-30**).[63] The active catalytic species is generated *in situ* by treatment with triethyloxoniumhexafluorophosphate to form the chiral and oxophilicdicationic complex $[Ru(OEt)_2(PNNP)](PF_6)_2$, which could coordinate the unsaturated ß-ketoesters for enantioselection of the ensuing cycloaddition step.

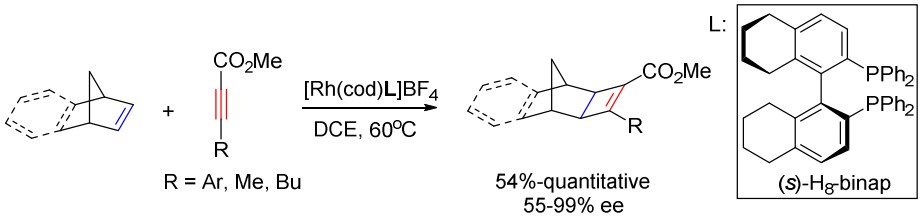


Scheme 1-30. Ru-catalyzed enantioselective Ficini cycloaddition

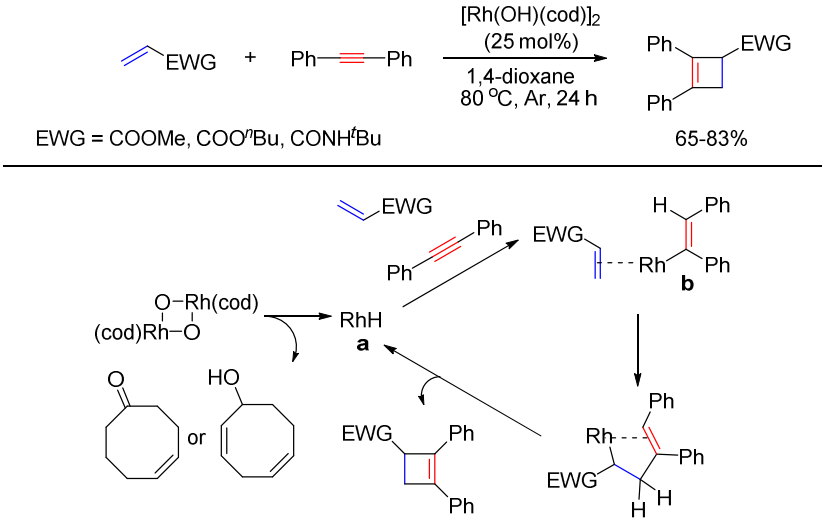
1.2.1.3 Rhodium

In 2006, Shibata *et al.* demonstrated the employment of chiral rhodium catalyst ($[Rh(cod)(H_8\text{-binap})]BF_4$) which enantioselectively catalyzed the [2+2] cycloaddition between norbornenes and electron-poor alkynyl esters for the synthesis of polycyclic cyclobutenes in synthetically useful ee values (**Scheme 1-31**).[64]

[63](a) Schotes, C.; Mezzetti, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 3072-3074; (b) Schotes, C.; Bigler, R.; Mezzetti, A. *Synthesis* **2012**, *44*, 513-526.
[64]Shibata, T.; Takami, K.; Kawachi, A. *Org. Lett*. **2006**, *8*, 1343-1345.



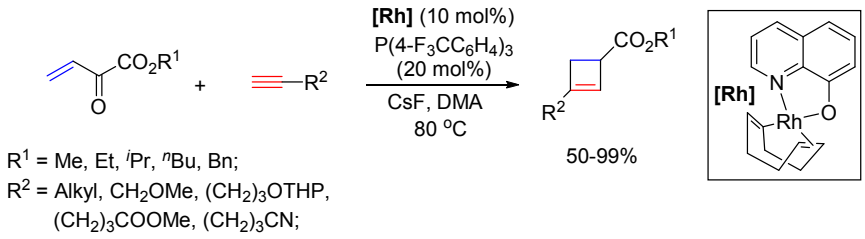
Scheme 1-31. Rh-catalyzed enantioselective norbornenes-alkynes [2+2] cycloaddition



Scheme 1-32. Ligand-consuming methodology in Rh-catalyzed [2+2] cycloaddition

Baba's group reported on a [2+2] cross cycloaddition between electron-poor alkenes and diphenylethyne (**Scheme 1-32**).[65] The authors described a novel catalytic behaviour of $[Rh(OH)(cod)]_2$ that forms "Rh-H" species *in situ* without an external hydride source (ligand-consuming methodology). Oxidation of the cyclooctadiene (cod) ligand of complex $[Rh(OH)(cod)]_2$ releases the coordinatively unsaturated Rh-H species **a** and "oxidized" cod(s) *in situ*. The *syn*-hydrometalation of the alkyne forms vinyl rhodium species **b** which can add across the electron-poor alkene. Intramolecular C-H bond insertion and ß-H elimination releases the cyclobutene adduct and the Rh-H species **a** back into catalytic cycle.

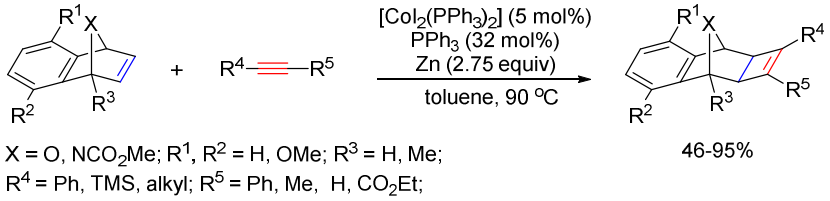
[65]Motokura, K.; Nakayama, K.; Miyaji, A.; Baba, T. *ChemCatChem.* **2011**, *3*, 1419-1421.



Scheme 1-33. [2+2] Terminal alkynes-alkenes cycloaddition with Rh catalytic system

In 2013, F. Kakiuchi group utilized terminal alkynes and electron-deficient alkenes to perform a seminal [2+2] cycloaddition with catalytic amount of 8-quinnolinolato rhodium-phosphine complex (**Scheme 1-33**).[66] Absolute regioselective construction of cyclobutenes carrying diversified polar functionalities in moderate to excellent yields was realized in this protocol.

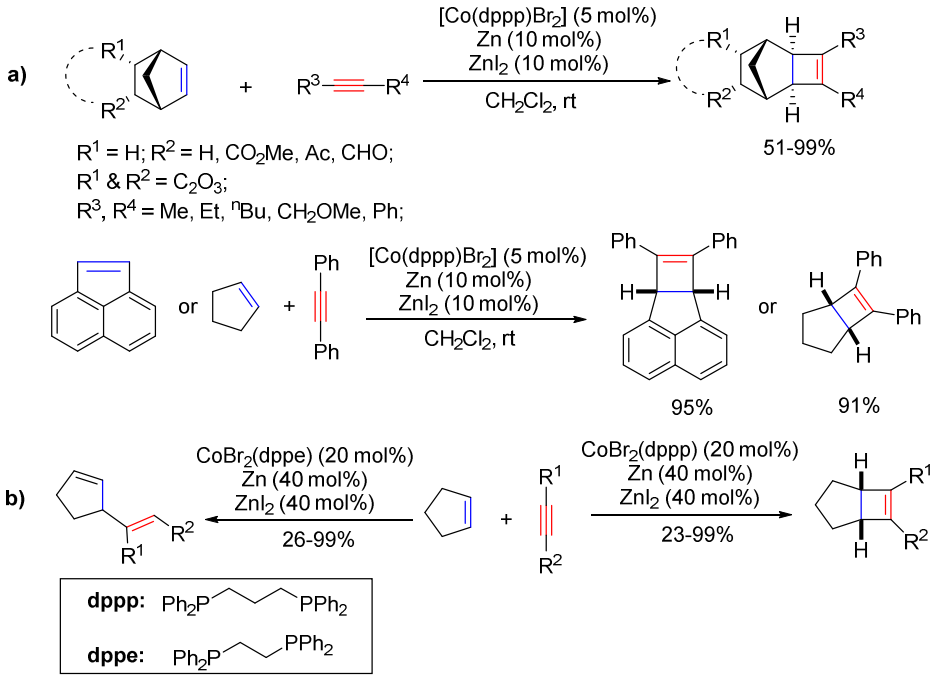
1.2.1.4 Cobalt



Scheme 1-34. Co-catalyzed cycloaddition between oxa(aza)benzonorbornenes and alkynes

Cobalt complex is another important class of catalyst to mediate [2+2] cycloaddition. Cheng *et al.* employed a catalytic system comprises of cobalt and phosphine for cross cycloaddition between bicyclic alkenes and structurally diverse alkynes (**Scheme 1-34**).[67] Bicyclic alkenes and alkynes in toluene reacted smoothly using $[CoI_2(PPh_3)_2]$ salt, additional triphenylphosphine ligand together with zinc as reducing agent to generate respective *exo*-cyclobutenes in moderate to excellent yields. Complementing their previous similar works with Ni catalyst (**Scheme 1-23**), this work allows the use of mono- and dialkyl alkynes while suppressing the undesired cyclotrimerization of alkyne substrates.

[66]Sakai, K.; Kochi, T.; Kakiuchi, F. *Org. Lett*. **2013**, *15*, 1024-1027.
[67]Chao, K. C.; Rayabarapu, D. K.; Wang, C.-C.; Cheng, C.-H. *J. Org. Chem*. **2001**, *66*, 8804-8810.



Scheme 1-35. Co-catalyzed [2+2] cycloaddition protocols by Hilt's group

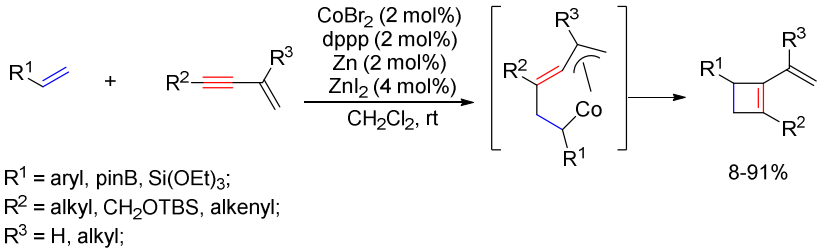
In 2008, Hilt and co-workers reported an improvised cobalt catalytic system by replacing the triphenylphosphine ligand with the bidentate 1,3-bis(diphenylphosphanyl)propane (dppp) and using zinc iodide as additive (**Scheme 1-35a**).[68] Under modified catalytic conditions, the cobalt-catalyzed [2+2] cycloaddition gave better yields and accommodated wider substrate scope as compared with the one in prior report which seem confined to 7-oxa-bicyclo[2.2.0]heptenes (**Scheme 1-34**). Electronically neutral cyclopentene and acenapthylene were well suited to undertake this [2+2] cycloaddition chemistry as well. Moreover, this reaction could obviate the use of excess of either coupling partner and additional equivalent of phosphine ligand.

Later, the same group communicated Alder-ene reaction *vs* [2+2] cross addition protocol involving cyclic alkenes and internal alkynes, wherein the reaction pathway depends upon the

[68]Treutwein, J.; Hilt, G. *Angew. Chem. Int. Ed*. **2008**, *47*, 6811-6813.

electronic property of the alkynes and the phosphine ligand bite angle (**Scheme 1-35b**).[69] Alder-ene product was obtained with dppe ligand, while dppp ligand gave rise to [2+2] cycloaddition product. Similarly, cyclopentenes participated efficiently in the [2+2] cycloaddition pathway whereas cyclohexene was found incompatible for this reaction.

On the other hand, Ogashi and co-workers disclosed the cross cycloaddition between alkenes and 1,3-enynes to prepare conjugated vinyl cyclobutenes (**Scheme 1-36**), in continuation of their works with nickel catalyst.[70] Similar to the mechanism with Ni catalyst (**Scheme 1-25**), the cyclobutene is generated following the reductive elimination of the η^3-butadienyl cobaltacycle.

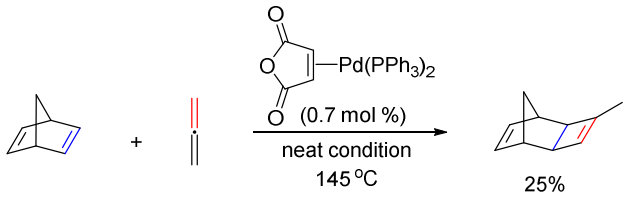


Scheme 1-36. Co-catalyzed alkenes-1,3-enynes [2+2] cycloaddition

1.2.1.5 Palladium

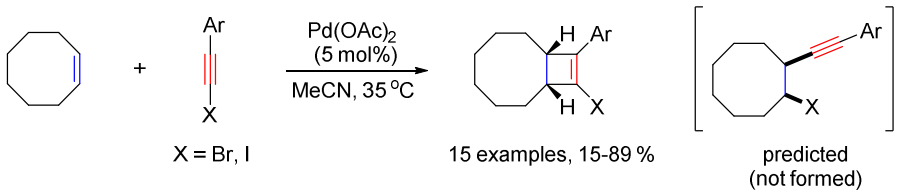
Palladium complex was also studied for the [2+2] cycloaddition since the early 1970s where Coulson described the palladium-catalyzed [2+2] cycloaddition between norbornadiene and allene to give *exo*-3-methyltricyclo[4.2.1.0]nona-3,7-diene product.[71] Only one substrate was examined for this reaction and when propa-1,2-diene was replaced with methylacetylene, no cycloaddition reaction occurred thus ruling out the hypothesis of the *in-situ* isomerization of allene to alkyne in this reaction (**Scheme 1-37**).

[69]Hilt, G.; Paul, A.; Treutwein, J. *Org. Lett*. **2010**, *12*, 1536-1539.
[70]Nishimura, A.; Tamai, E.; Ohashi, M.; Ogoshi, S. *Chem. Eur. J*. **2014**, *20*, 6613-6617
[71]Coulson, D. R. *J. Org. Chem*. **1972**, *37*, 1253-1254.



Scheme 1-37. Pd-catalyzed [2+2] cycloaddition of propadiene and norbornadiene

On the other hand, Jiang and co-workers discovered an intriguing [2+2] cycloaddition between cyclooctene and bromo-/iodoalkyne to form cyclobutene ring (**Scheme 1-38**).[72] Aromatic alkynyl halides with substituents of varying electronic properties formed the cyclobutene products in reasonable yields with cyclooctene but not linear 4-octene which yielded mixture of products instead. The ring size is also critical for this reaction where cycloheptene gave low yield of product while cyclododecene was completely incompatible for this reaction.



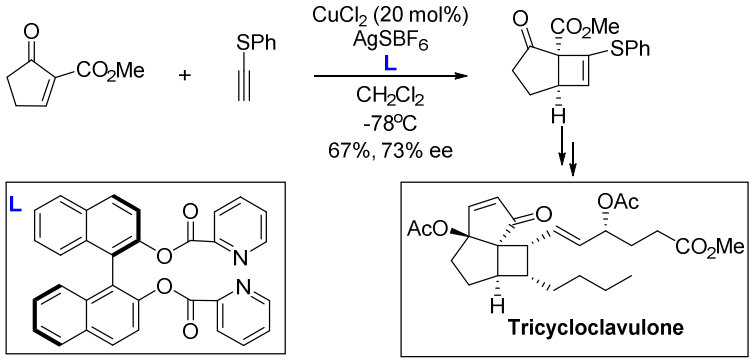
Scheme 1-38. Pd-catalyzed [2+2] cycloaddition of cyclooctene with haloalkynes

1.2.1.6 Copper

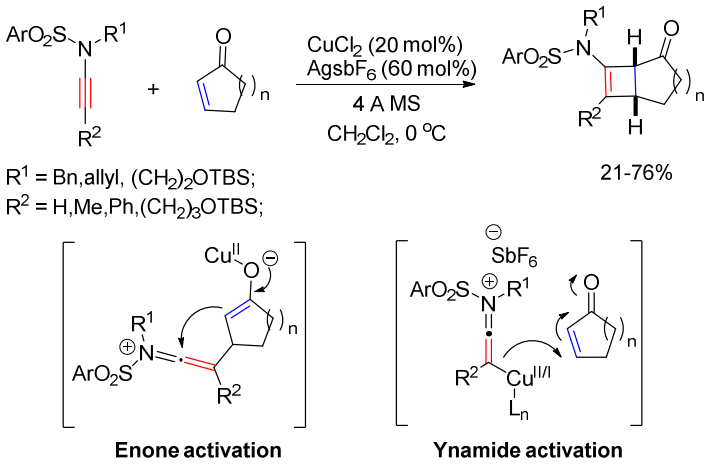
In their studies to achieve enantioselective synthesis of (+)-tricycloclavulone, Iguchi and Ito have developed the stereoselective [2+2] cycloaddition of 2-methoxycarbonyl-2-cyclopentene-1-one and thioalkynes in 73 % ee with copper(II) salt in catalytic amount and simple chiral binol-derived bis-pyridine ligand (**Scheme 1-39**).[73] This reaction gave poor enantiomeric excess value or poor chemical yield when tested with established asymmetric Lewis acids including Titanium-TADDOL, Titanium-BINOL or Copper-BOX complex. Following the successful

[72]Li, Y.; Liu, X.; Jiang, H.; Liu, B.; Chen, Z.; Zhou, P. *Angew. Chem. Int. Ed*. **2011**, *50*, 6341-6345.
[73](a) Ito, H.; Hasegawa, M.; Takenaka, T.; Kobayashi, T.; Iguchi, K. *J. Am. Chem. Soc*. **2004**, *126*, 4520-4521; (b) Takenaka, Y.; Ito, H.; Hasegawa, M.; Iguchi, K. *Tetrahedron* **2006**, *62*, 3380-3388.

establishment of this methodology as the key reaction, they achieved the first chiral (+)-tricycloclavulone synthesis that contains unique tricyclo[5.3.0.0]decane moiety with six chiral centers.



Scheme 1-39. Cu-catalyzed [2+2] cycloadditonen en route to (+)-tricycloclavulone



Scheme 1-40. Cu-catalyzed Ficini [2+2] cycloaddition between ynamides and cyclic enones

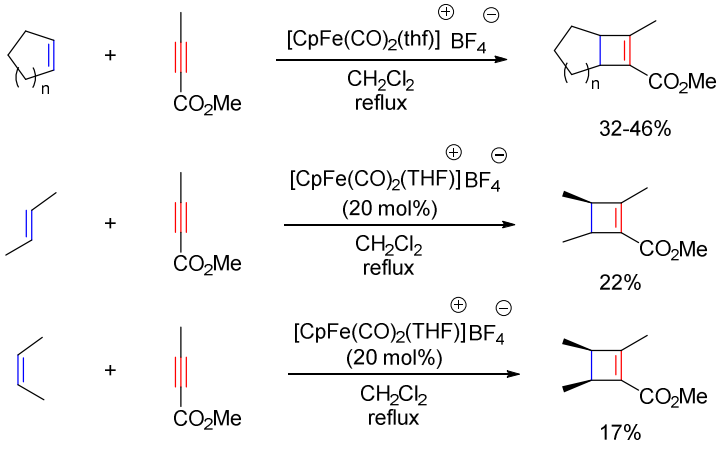
Another example of constructing 4-membered carbocyclic scaffold using copper catalyst was reported by Hsung's group. The Ficini reaction of *N*-sulfonylynamides and cyclic enones was achieved with cationic Cu(II) species catalyst (**Scheme 1-40**).[74] The reaction is thought to occur through conjugate addition of ynamide nucleophile onto Cu(II)-activated enone. An alternative

[74]Li, H.; Hsung, R. P.; Dekorver, K. A.; Wei, Y. *Org. Lett*. **2010**, *12*, 3780-3783.

pathway was also considered which involves a cationic keteniminium-copper species formed from Cu(II)-activated ynamide; the former could also perform a conjugate addition to the enone (cuprate- like 1,4-addition).

1.2.1.7 Iron

The iron-catalyzed [2+2] cross cycloaddition of methyl tetrolate with alkenes preparing cyclobutenyl ester was reported by Rosenblum and Scheck in 1982 (**Scheme 1-41**).[75] The reaction was carried out using a cationic cyclopentadienyl iron complex as the catalyst and 1,2-disubstituted alkenes. Reactions of (*E*)- and (*Z*)- but-2-enes exhibited the stereospecificity of the cycloaddition in consistency with a concerted mechanism.



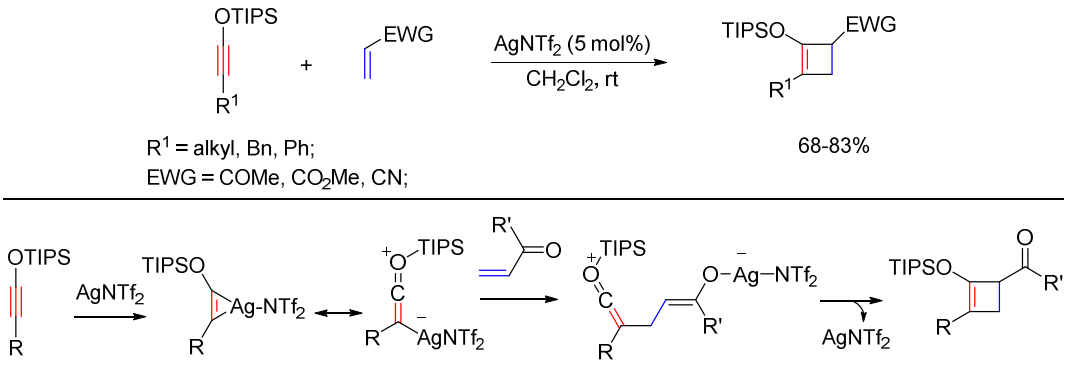
Scheme 1-41. Iron-catalyzed cross cycloaddition between electron-poor alkynes and 1,2-disubstituted alkenes

1.2.1.8 Silver

Silver catalysts are known to mediate efficient carbon-carbon bond forging protocols under mild conditions.[76] In 2004, Kozmin group disclosed the first Ag-catalyzed [2+2] cross addition of

[75]Rosenblum, M.; Scheck, D. *Organometallics* **1982**, *1*, 397-399.
[76](a) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132-3148; (b) Abbiati, G.; Rossi, E. *Beilstein J.*

labile siloxylated alkynes with varied electron-poor alkenes (α,ß-unsaturated ketones, nitriles, and esters) as an efficient protocol to prepare densely functionalized siloxycyclobutenes (**Scheme 1-42**).[77] This speculation was further backed by the formation of identical trans-substituted siloxycyclobutene when (*E*)- and (*Z*)-corotonates were applied individually for this reaction. Overall, the delineated mechanism consists of prior activation of siloxy alkyne by $AgNTf_2$ catalyst, followed by 1,4-addition of resulting complex onto enone and ketenium ion trapping to deliver cyclobutene product. This nucleophile-based activation was thought to be the unique activity of $AgNTf_2$, which distinguishes this protocol from [2+2] cycloaddition pathway underwent by other heteroatom-functionalized alkynes.



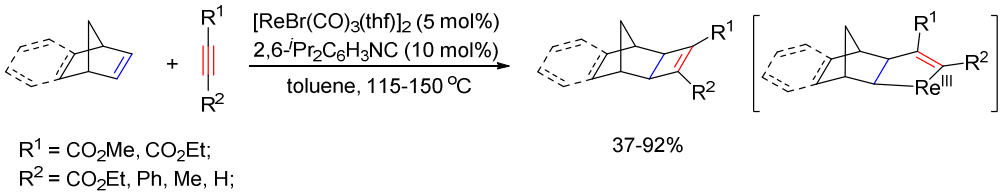
Scheme 1-42. Nucleophile-based activation in silver-catalyzed [2+2] cycloaddition

1.2.1.9 Rhenium

Kuninobu *et al.* reported on the first Re-catalyzed cycloaddition for norbornenes and electron-deficient alkynes using catalytic amount of $[ReBr(CO)_3(thf)]_2$ and 1,6-diisopropylphenyl isocyanide as additive (**Scheme 1-43**). The cyclobutene products were furnished in synthetically useful yields at a heightened reaction temperature with both internal

Org. Chem. **2014**, *10*, 481-513.
[77]Swiss, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc*. **2004**, *126*, 7442-7443.

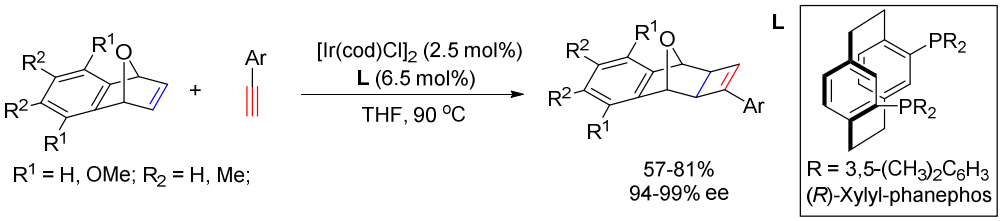
and terminal alkynes.[78] While the exact role of isocyanide additive was yet to be fully understood, it was observed to inhibit the unwanted alkyne polymerization. This reaction was thought to proceed through a rhenacyclopentene intermediate following coordination of both coupling partners to the rhenium center.



Scheme 1-43. Re-catalyzed [2+2] cycloaddition

1.2.1.10 Iridium

With $[Ir(COD)Cl]_2$/(*R*)-Xylyl-phanephos catalytic system, Shao's group reported seminally the employment of oxabicyclic alkeneyl and terminal alkynyl substrates in the enantioselective [2+2] cycloaddition in 2010 (**Scheme 1-44**).[79] Ligand-assisted enantioselection is efficient to generate four stereocenters in the cycloadducts in a single step. While this reaction efficiently accommodated aryl alkynes carrying different functionalities including a CF_3 group, it was found that methyl propiolate could not undertake this chemistry.

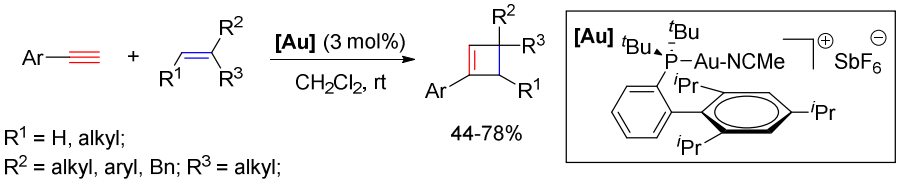


Scheme 1-44: Ir-catalyzed enantioselective [2+2] cycloaddition

[78]Kuninobu, Y.; Yu, P.; Takai, K. *Chem. Lett*. **2007**, *36*, 1162-1163.
[79]F, B.-M.; Li, X.-J.; Peng, F.-Z.; Zhang, H.-B.; Chan, A. S. C.; Shao, Z.-H. *Org. Lett*. **2010**, *12*, 304-306.

1.2.1.11 Gold

Although gold-catalyzed cyclization reactions of 1,n-enynes and reactivity of alkynes with various electrophilic catalysts have been well studied, the intermolecular cross coupling of alkynes and alkenes with electrophilic gold catalyst was thought to be challenging as competitive coordination of both substrates possessing π-electrons would suppress the desired reaction.



Scheme 1-45. [2+2] Cross cycloaddition with cationic gold(I)catalyst

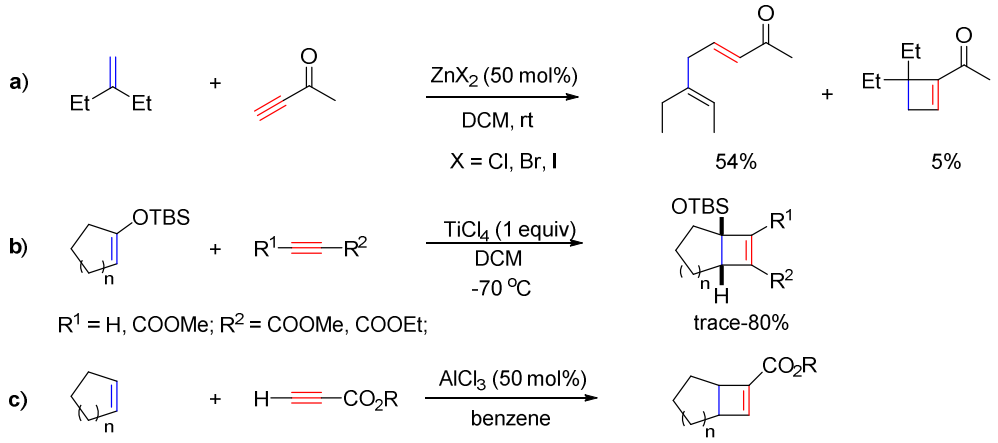
It is not until 2010 when Echavarren and co-workers showed that sterically hindered cationic Au(I) complexes are also capable of catalyzing a regioselective, intermolecular terminal alkynes-alkenes coupling to give cyclobutene products in reasonable yields (**Scheme 1-45**).[80] Remarkably, the competitive alkene coordination to the Au(I) complex as well as the polymerization side reaction due to the overreaction of gold complex were successfully hindered with the use of bulky ligands that could activate alkynes selectively.

1.2.2 Acids-Catalyzed/-Mediated [2+2] Cycloaddition

When Snider's group was studying a Lewis acid-catalyzed ene reaction of alkenes and 3-butyn-2-one, they observed an unexpected formation of [2+2] cycloaddition product in trace amount (5%) along with the ene adduct (**Scheme 1-46a**).[81] A close examination of alkenyl substrates revealed that selective formation of either the [2+2] cycloadducts or the ene adducts

[80]López-Carrillo, V.; Echavarren, A. M. *J. Am. Chem. Soc*. **2010**, *132*, 9292-9294.
[81]Snider, B. B.; Brown, L. A.; Conn, R. S. E.; Killinger, T. A. *Tetrahedron Lett*. **1977**, *18*, 2831-2834.

could be achieved with $AlCl_3$ or $EtAlCl_2$, determined by the substitution pattern on alkenes.[82] The ene adducts dominates in reactions of geminal di-, tri- or tetra-substituted alkenes whilst the vicinal disubstituted alkenes form the stereospecific [2+2] adducts. Around the same time, the Untch group and the Hoffmann group reported similar findings. Untch and Clark reported on a [2+2] cross cyclodimerization using cyclic silyl enol ethers and ethyl propiolates, dimethyl acetylenedicarboxylates, dimethyl fumaratesas well as methyl crotonates using $TiCl_4$ (**Scheme 1-46b**)[83]. On the other hand, Hoffmann and Fienemann demonstrated cyclobutene carboxylic esters formation *via* [2+2] cycloaddition of 2-propiolate with cyclic alkenes, catalyzed by $AlCl_3$ (**Scheme 1-46c**)[84].

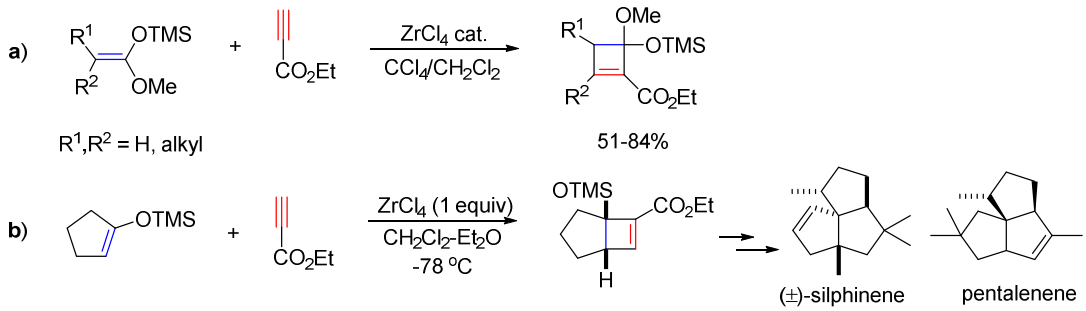


Scheme 1-46. Seminal studies of Lewis acids-mediated/-catalyzed [2+2] cycloaddition

Rousseau's group reported on the [2+2] cycloaddition of ketenealkylsilylacetals with ethyl propiolate, leading to highly-functionalized derivatives of cyclobutene in 1988 (**Scheme 1-47a**).[85] Franck-Neumann and co-workers, on the other hand, have synthesized cyclobutenic

[82](a) Snider, B. B.; Rodini, D. J.; Conn, R. S. E.; Sealfon, S. *J. Am. Chem. Soc*. **1979**, *101*, 5283-5293; (b) Snider, B. B.; Roush, D. M.; Rodini, D. J. ; Gonzalez. D.; Spindell, D. *J. Org. Chem*. **1980**, *45*, 2773-2785.
[83](a) Clark, R. D.; Untch, K. G. *J. Org. Chem*. **1979**, *44*, 248-253; (b) Clark, R. D.; Untch, K. G. *J. Org. Chem*. **1979**, *44*, 253-255.
[84]Fienemann, H.; Hoffmann, H. M. R. *J. Org. Chem*. **1979**, *44*, 2802-2804.
[85]Quendo, A.; Rousseau, G. *Tetrahedron Lett*. **1988**, *29,* 6443-6446.

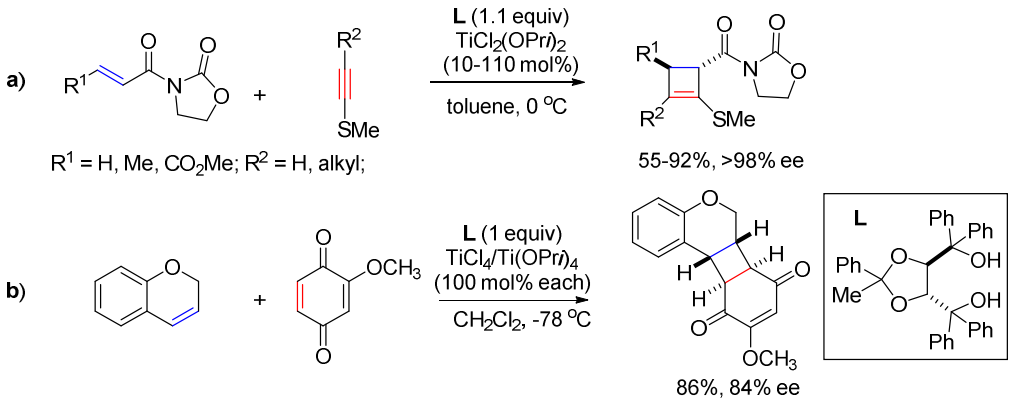
adducts *via* $ZrCl_4$-mediated [2+2] cycloaddition using silyl enol ether of cycloalkanones as well as ethyl propyonates (**Scheme 1-47b**).[86] These adducts formed serve as versatile building blocks for downstream chemical synthesis to prepare diquinane alcohols, (±) Silphinene and angular triquinane (±)-pentalenene.



Scheme 1-47. [2+2] Cyclodimerization between silyl enol ethers and ethyl propynoate with $ZrCl_4$

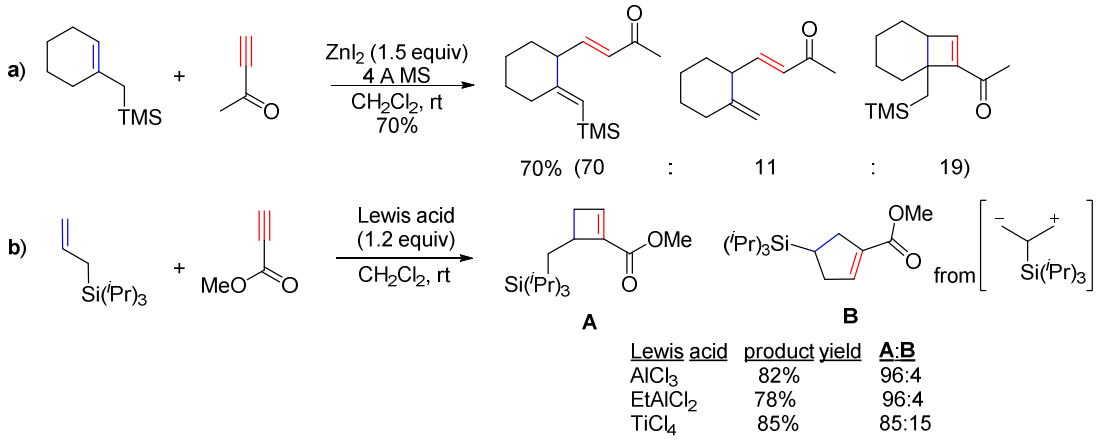
In 1992, Narasaka reported on enantiospecific [2+2] cross dimerization between electron-rich alkynes with electron poor conjugated carbonyls affording good yields of cyclobutenes in excellent ee values by utilizing a asymmetric titanium complex formed by dichlorodiisopropoxytitanium ($TiCl_2(O^iPr)_2$) and tartarate-derived chiral 1,4-diol (**Scheme 1-48a**) *in situ*.[87] Prior to this, the same complex was employed to mediate similar [2+2] cycloaddition with 1,2-bis(methylthio)ethylene to prepare respective stereospecific cyclobutanes.[88] Engler *et al.* also applied the similar Lewis acid system for the [2+2] cycloaddtion of styrene derivatives with 1,4-benzoquinones with excellent yield and enantioselectivity (**Scheme 1-48b**).[89]

[86] (a) Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett*. **1990**, *31*, 5027-5030; (b) Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett*. **1991**, *32*, 2135-2136; (c) Franck-Neumann, M.; Miesch, M.; Gross, L. *Tetrahedron Lett*. **1992**, *33*, 3879-3882.
[87]Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Nihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869-8885.
[88]Hayashi, Y.; Narasaka, K. *Chem. Lett.* **1990**, 1295-1298.
[89]Engler, T. A.; Letavic, M. A.; Reddy, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 5068-5070.



Scheme 1-48. Asymmetric [2+2] cycloaddition mediated by chiral Titanium reagents

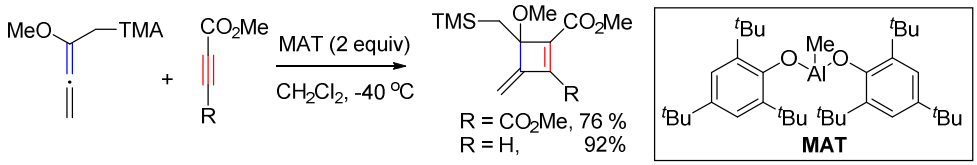
In 1993, Monti and co-worker reported the unanticipated trace formation of cyclobutene product when they studied the ene reaction of allylsilane with 3-butyn-one (**Scheme 1-49a**).[90] It has been established that allylsilanes could serve as three-carbon components in [3+2] annulations with electron poor alkenes or alkynes *via* cationic 1,2-silyl shift.[91] A more detailed study by the same group with different Lewis acids successfully steered the [2+2] cycloaddition pathway to dominate thus complements the chemistry of [3+2] annulation (**Scheme 1-49b**).[92]



Scheme 1-49. [2+2] Cycloaddition of allylsilanes and 3-bytyn-one/methyl propiolate

[90]Audran, G.; Monti, H.; Léandri, G.; Monti, J.-P. *Tetrahedron Lett*. **1993**, *34*, 3417-3418.
[91](a)Danheiser, R. L.; Takahashi, T.; Bertok, B.; Dixon, B. R. *Tetrahedron Lett.* **1993**, *34*, 3845-3848; (b) Knölker, H.-J.; Graf, R. *Synlett* **1994**, 131-133; (c) Panek, J. S.; Jain, N. F. *J. Org. Chem.* **1993**, *58*, 2345-2348.
[92](a) Monti, H.; Audran, G.; Monti, J.-P.; Léandri, G. *Synlett* **1994**, 403-404; (b) Monti, H.; Audran, G.; Léandri, G.; Monti, J.-P. *Tetrahedron Lett*. **1994**, *35*, 33073-3076.

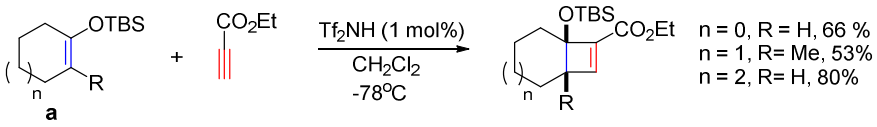
In 1998, Hosomi demonstrated di-*exo*-methylenecyclobutenes synthesis *via* [2+2] corss addition of allenylmethylsilane and electron-deficient alkynes in the presence of MAT (methylaluminumbis(2,4,6-tri-butylphenoxide) (**Scheme 1-50**).[93] In the presence of $TiCl_4$, methoxy and silyl group in the cycloadduct eliminates to give di-*exo*-methylenecyclobutenes. Ensuing Diels-Alder reaction allowed formation of fused bi- and tricyclic molecules.



Scheme 1-50: MAT-mediated [2+2] cycloaddition of allenylmethylsilane and electron-deficient alkynes

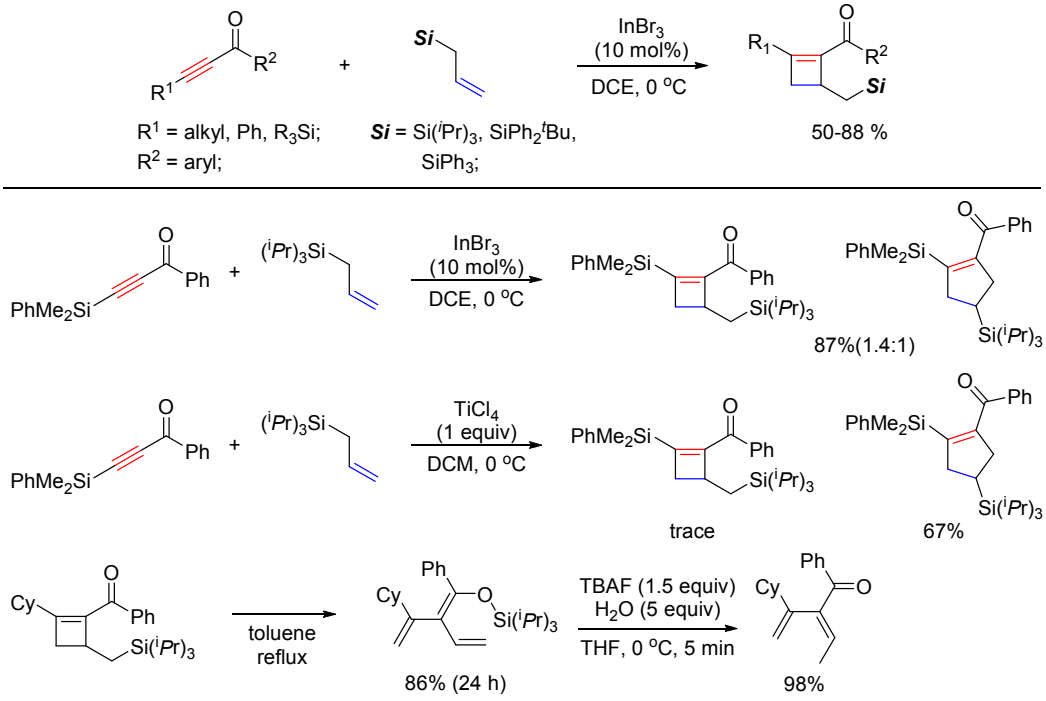
In 2005, the Ihara group reported a reaction protocol featuring the catalytic use of trifluoromethanesulfonimide (Tf_2NH) in [2+2] corss cyclodimerization reaction between silyl enol ethers and terminal alkynyl ester (**Scheme 1-51**).[94] This methodology addresses the existing limitation in this transformation which often requires Lewis acid in stoichiometric amount. Tf_2NH was speculated to be a precatalyst that will give rise to the actual catalyst $TBSNTf_2$ *in situ*. A similar *in-situ* generated highly reactive $TMSNTf_2$ was disclosed by Yamamoto *et al.* for a Tf_2NH-promoted aldol reaction for trimethylsilyl enol ethers and aldehydes.[95] Tf_2NH could react consistently with TBS enol ether substrates in reaction to generate $TBSNTf_2$, which in turn accounts for the high catalyst turnover.

[93]Hojo, M.; Murakami, C.; Nakamura, S.; Hosomi, A. *Chem. Lett*. **1998**, 331-332.
[94](a) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc*. **2005**, *127*, 3668-3669; (b) Takasu, K.; Hosokawa, N.; Inanaga, K.; Ihara, M. *Tetrahedron Lett*. **2006**, *47*, 6053-6056.
[95]Ishihara, K.; Hiraiwa, Y.; Yamamoto, H. *Synlett* **2001**, 1851-1854.



Scheme 1-51. [2+2] Cycloaddition catalyzed by Tf_2NH

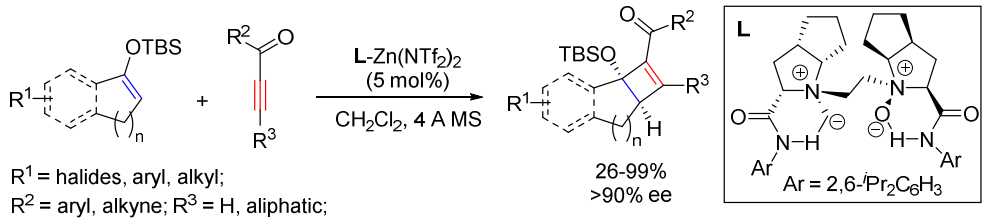
More recently, in 2015, Ohe presented a [2+2] cycloaddition reaction with allylsilanes and electron-deficient internal conjugated alkynones in the presence of indiumcatalyst (**Scheme 1-52**).[96] The selectivity for[3+2] and [2+2]cycloaddition mode is interchangeable by changing the silyl substituents at the *ß*-position of alkynones to dimethylphenylsilyl group and the use of 1 equiv of $TiCl_4$. The synthetic practicality of this methodology is further enhanced as cyclobutenone product could undergo thermal electrocyclic ring opening reaction facilely.



Scheme1-52. [2+2] Cycloaddition of alkynones and allylsilanes by indium catalysis

[96]Okamoto, K.; Shimbayashi, T.; Tamura, E.; Ohe, K. *Org. Lett.***2015**, *17*, 5843-5845.

In 2016, Feng *et al.* reported the chiral zinc complex *N,N′*-dioxide-Zn(NTf$_2$)$_2$-catalyzed cross cyclodimerization of cyclic enolsilyl ethersand alkynyl ketones to generate variousfully substituted fused cyclobutenes in high yields and ee values (Scheme 1-53).[97] Furthermore, this method is applicable to terminal and internal alkynes. The cyclobutenes could undergo reduction or addition readily with C-, O-, S-, and N-nucleophiles under mild conditions to form cyclobutanes with 4 contiguous stereocenters in excellent ee values.



Scheme 1-53. Alkynones and cyclic silyl enol ethers for enantioselective [2+2] cycloaddition

In a nutshell, preparation of synthetically useful cyclobutenes *via* [2+2] cycloaddition of alkenyl with alkynyl substrates represents a highly desirable approach in view of the efficiency to build molecular complexity, atom-economy and the easy availability of starting materials. The preceding sections have described discrete variants of [2+2] cycloadditions employing transition metals or acids. Transition metals including Ni, Co, Ru, Rh, etc have been explored and these reactions generally occur through initial coordination of both coupling partners at the low valent metal center. Key step involves oxidative cyclometallation that generates metallacycle. Upon reductive elimination, cyclobutene product is formed and the catalyst is regenerated in the catalytic cycle.

On the contrary, earlier studies on acids-mediated [2+2] cycloaddition focus on coupling partners with electronic imbalance as well as the use of terminal alkynes. However, advancement is

[97]Kang, T.; Ge, S.; Lin, L.; Lu, Y.; Liu, X.; Feng, X. *Angew. Chem. Int. Ed*. **2016**, *55*, 5541-5544.

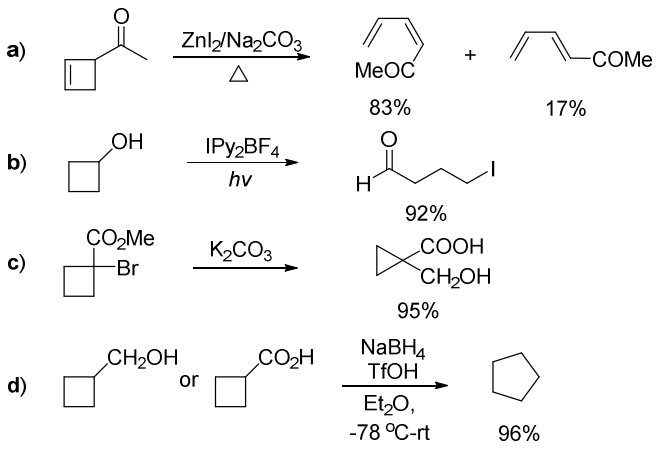
evidenced to establish the catalytic versions and extend the scope of these reactions to substrate class that remains underdeveloped such as weakly polarized alkenes. Expanded scope, novel strategies and increased usefulness of these reactions could be anticipated with on-going active research efforts in these areas.

CHAPTER 2

IN(III)-TMSBr-CATALYZED [2+2] CYCLOADDITION OF ALKYNE WITH ACRYLATE AND SELECTIVE RING OPENING OF CYCLOBUTENE

2.1 Introduction

Among the strained carbocyclic molecules that have emerged in the past decades as highly versatile synthetic building blocks, derivatives of cyclopropane and cyclobutane inarguably are the most well studied and useful organic compounds. Four member rings are molecular entities found prevalently in numerous natural products where most of which carry commendable bioactivities (**Figure 2-1**).[98] The bioactivities as well as profound synthetic values risen from their inherent ring strain have led to intensive research activities on the synthetic strategies to assemble these structures.[3]



Scheme 2-1. Selected transformations of 4-membered rings

[98](a) Zhou, M.; Li, X.-R.; Tang, J.-W.; Liu, Y.; Li, X.-N.; Wu, B.; Qin, H.-B.; Du, X.; Li, L.-M.; Wang, W.-G.; Pu, J.-X.; Sun, H.-D. *Org. Lett.* **2015**, *17*, 6062-6065; (b) Zhou, M.; Zhang, H.-B.; Wang, W.-G.; Gong, N.-B.; Zhang, R.; Li, X.-N.; Du, Xue.; Li, L.-M.; Li, Y.; Lu, Y.; Pu, J.-X.; Sun, H.-D. *Org. Lett.* **2013**, *15*, 4446-4449; (c) Berger, W. T.; Ralph, B. P.; Kaczocha, M.; Sun, J.; Balius, T. E.; Rizzo, R. C.; Haj-Dahmane, S.; Ojima, I.; Deutsch, D. G. *PLOS ONE* **2012**, *7*, e50968; (d) Wei, K.; Li, Wei.; Koike, K.; Chen, Y. J.; Nikaido, T. *J. Org. Chem*. **2005**, *70*, 1164-1176; (e) Li, Y.-Z.; Tong, A.-P.; Huang, J. *Chem. Biodivers.* **2012**, *9*, 769-776; (f) Lee, F. P.; Chen, Y.-C.; Chen, J.-J.; Tsai, I.-L.; Chen, I.-S. *Helv. Chim. Acta* **2004**, *87*, 463-468; (g) Tsai, I.-L.; Lee, F.-P.; Wu, C.-C.; Duh, C.-Y.; Ishikawa, T.; Chen, J.-J.; Chen, Y.-C.; Seki, H.; Chen, I.-S. *Planta Med*. **2005**, *71*, 535-542; (h) Takeda, R.; Hasegawa, J.; Shinozaki, M.; *Tetrahedron Lett*. **1990**, *31*, 4159-4162; (i) Fujiwara, Y.; Naithou, K.; Miyazaki, T.; Hashimoto, K.; Mori, K.; Yamamoto, Y. *Tetrahedron Lett*. **2001**, *42*, 2497-2499; (j) Tsukamoto, S.; Tomise, K.; Miyakawa, K.; Cha, B.-C.; Abe, T.; Hamada, T.; Hirota, H.; Ohta, T. *Bioorg. Med. Chem*. **2002**, *10*, 2981-2985; (k) Neve, J. E.; Wijesekera, H. P.; Duffy, S.; Jenkins, I. D.; Ripper, J. A.; Teague, S. J.; Campitelli, M.; Garavelas, A.; Nikolakopoulos, George.; Le, P. V.; Leone, P. de A.; Pham, N. B.; Shelton, P.; Praser, N.; Carroll, A. R.; Avery, V. M.; McCrae, C.; Williams, N.; Quinn, R. J. *J. Med. Chem*. **2014**, *57*, 1252-1275.

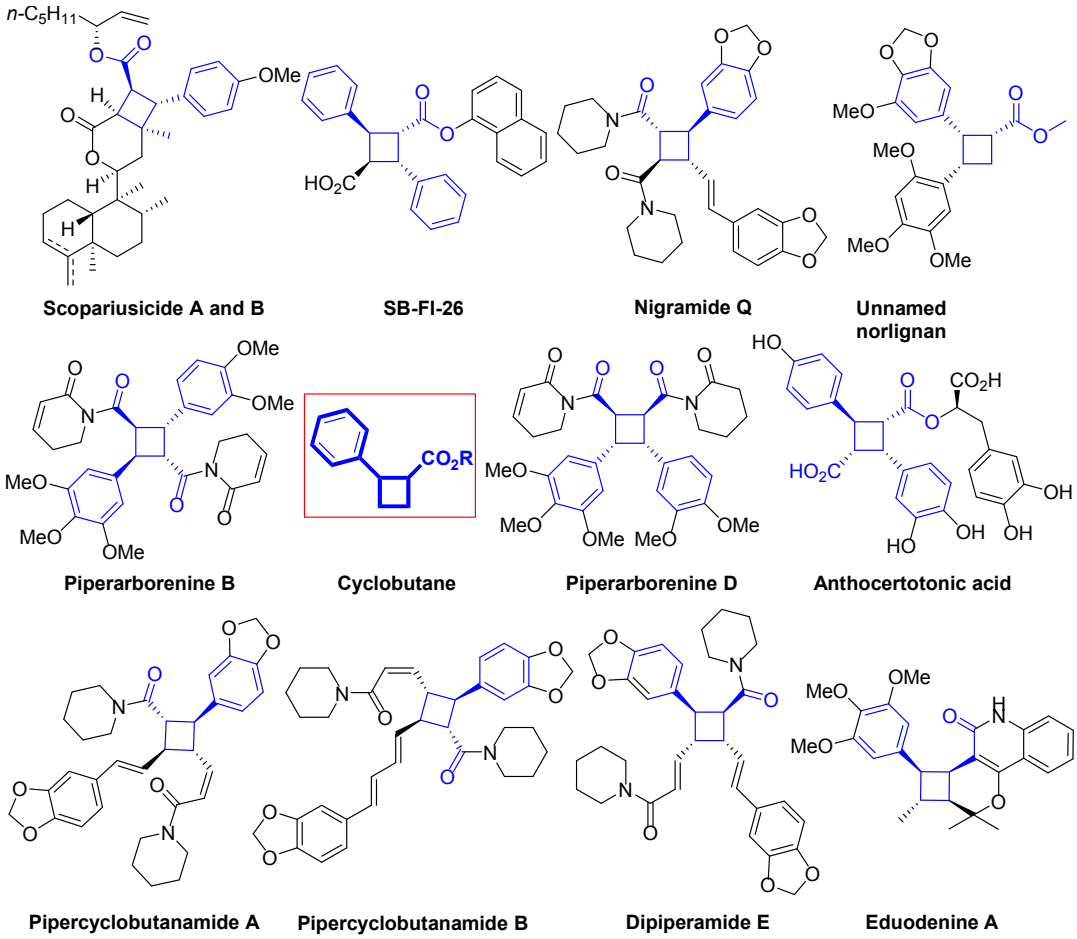


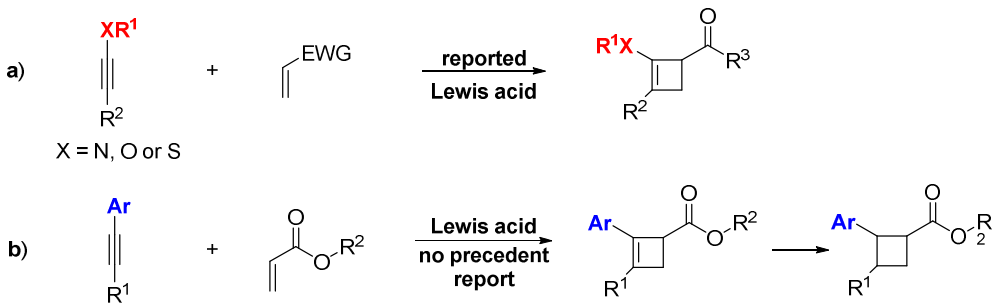
Figure 2-1. Natural products with arylated cyclobutane moiety

The constitutional ring strain renders the construction of 4-membered ring structure difficult, yet it is the same factor that makes it a useful intermediate in organic synthesis as well as a versatile platform for varied derivatizations. Cyclobutanes and cyclobutenes undergo reactions such as ring opening to acyclic products accompanied by energy release of 23-26 kcal mol^{-1} (**Scheme 2-1-a,b**).[99,100] Additionally, ring contraction of cyclobutanes to form cyclopropanes is also established due to their comparable ring strain energies (the ring strain energy of cyclopropane is

[99]Minami, T.; Chikugo, T.; Hanamoto, T. *J. Org. Chem.* **1986**, *51*, 2210-2214.
[100]Barluenga, J.; Gonzalez-Bobes, F.; Ananthoju, S. R.; Garcia-Martin, M. A.; Gonzalez, J. M. *Angew. Chem. Int. Ed.* **2001**, *40*, 3389-3392.

27.5 kcal mol^{-1} while that of cyclobutane is 26.7 kcal mol^{-1}) (**Scheme 2-1-c**).[101] The cyclobutane can also transform readily to five or six-membered ring compounds with energy release of 20-25 kcal mol^{-1} (**Scheme 2-1-d**).[102]

Among the various methods developed, transition metals- or Lewis acids-catalyzed-[2+2] cycloaddition between an alkyne and an alkene grants one of the most straightforward accesses to prepare cyclobutenes. The development of the transition metals- and Lewis acids-catalyzed [2+2] cycloaddition of alkynes with alkenes to give cyclobutenes have been summarized in **Chapter 1.2**.



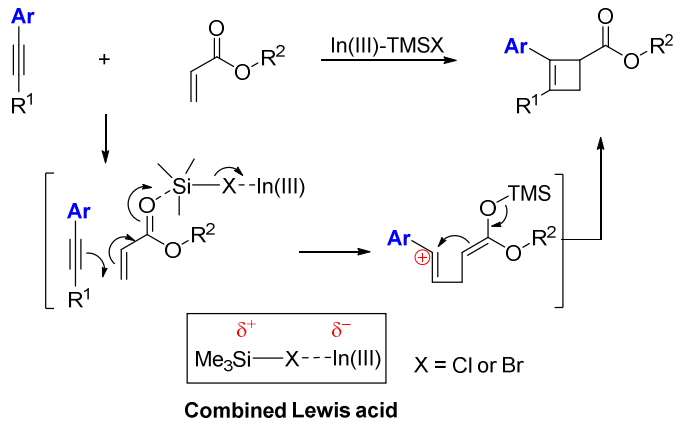
Scheme 2-2. Lewis acid-catalyzed [2+2] cycloaddition of alkynes with alkenes

An electronic imbalance between the two coupling partners often necessitates the Lewis acids-catalyzed [2+2] cycloaddition of alkynes with alkenes where a combination of electron-rich alkynes and electron-deficient alkenes or vice versa is required (see **Chapter 1.2.2** for details). For the former set of substrates, a number of elegant seminal works have been reported but the substrate scopes are mainly limited to more activated alkynes bearing a heteroatom substituent (**Scheme 2-2a**). In view of this, the use of non-activated alkynes such as aryl alkynes as coupling partners could be challenging. Moreover, cyclobutanes bearing both aryl and ester functionalities are molecular frameworks found in ubiquity in a myriad of natural

[101]Estieu, K.; Ollivier, J.; Salaün, J. *Tetrahedorn* **1998**, *54*, 8075-8090.
[102]Olah, G. A.; Wu, A. H.; Farooq, O. *J. Org. Chem*. **1989**, *54*, 1452-1453.

products and bioactive intermediates (**Figure 2-1**). In this regard, we envisioned that direct [2+2] cycloaddition of unactivated aryl alkynes with easily accessible acrylates followed by hydrogenation will give an easy entry to above-mentioned cyclobutanes. To the best of our knowledge, there is no precedent report on employment of Lewis acid catalyst system for this reaction (**Scheme 2-2b**).

On the other hand, indium(III) salts are widely used as effective Lewis acids in organic synthesis in recent decades. Pertaining to the weaker Lewis acidity of indium salts compared with other group 13 elements such as aluminum and boron, trimethylsilyl halide is often added to serve as robust combined Lewis acid catalyst with indium salt. Baba's, Lee's, our group, and others have studied a series of reactions utilizing this combined Lewis acid system as afore-discussed in **Chapter 1**.



Scheme 2-3. Proposed In(III)-TMSX-catalyzed [2+2] cycloaddition of aryl alkynes and acrylates

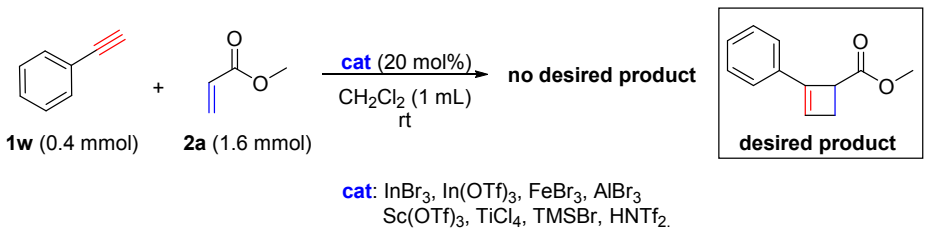
In continuation of our research interest in the application of indium in organic synthesis, we envisioned to use this robust catalyst system to realize the [2+2] cycloaddition of aryl alkynes and acrylates. The hypothesized reaction pathway is illustrated in **Scheme 2-3**: first, the high halophilicity of In(III) complex would facilitate its formation of combined Lewis acidic complex

with TMSX carrying enhanced Lewis acidity than either of them alone; second, the high oxophilicity of silicon would allow the thus-formed combined Lewis acid complex to activate the acrylate through coordination of carbonyl oxygen to silicon center; third, the aryl alkyne could perform a nucleophlic attack onto the activated acrylate to generate an enolate intermediate. Ensuing intramolecular nucleophilic attack will then furnish the cyclobutene product. Importantly, the low oxophilicity of In(III) should result in reversible coordination with enolate oxygen, thereby allowing it to re-enter the catalytic cycle facilely.

2.2 In(III)-TMSBr-catalyzed [2+2] cycloaddition of aryl alkyne and acrylate

2.2.1 Preliminary results of [2+2] cycloaddition of aryl alkynes and methyl acrylates

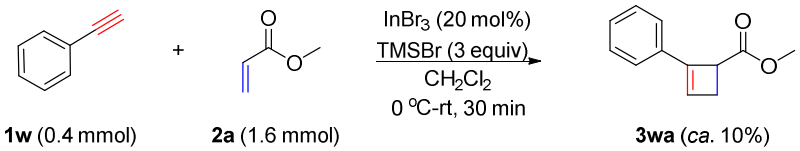
At the outset, 1-phenylacetylene (**1w**) and methyl acrylate (**2a**) were chosen as the model substrates in a test reaction with catalytic amount of $InBr_3$ (20 mol%) in CH_2Cl_2 (1 mL) at room temperature (**Scheme 2-4**). However, no reaction occurred under this condition. Increasing the loading of $InBr_3$ to 1 equiv or heating the reaction mixture did not effect the reaction, either. Other common Lewis acid catalysts $In(OTf)_3$, $FeBr_3$, $AlBr_3$, $Sc(OTf)_3$, $TiCl_4$, TMSBr and Brønsted acid $HNTf_2$ were also examined, which all resulted in no desired cyclobutene formation.



Scheme 2-4. Initial attempts of [2+2] cycloaddition with **1w** and **2a**

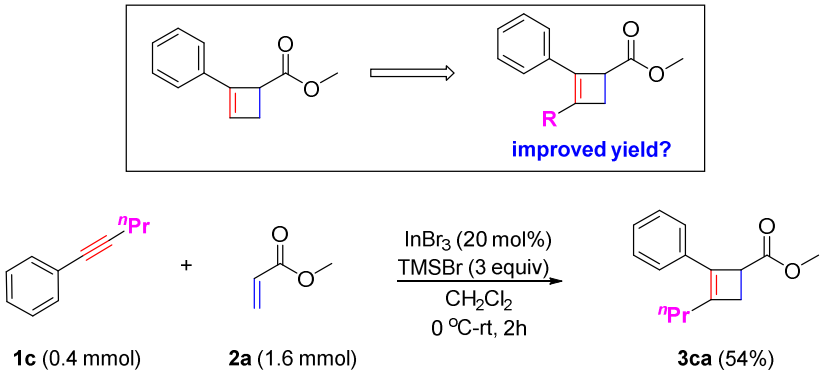
Gratifyingly, the desired cyclobutene product **3wa** could be obtained in *ca*. 10% yield together with intractable mixture when 20 mol% of $InBr_3$ was used with 3 equiv of TMSBr (**Scheme 2-5**).

However, the formed cyclobutene product **3wa** was unstable and slowly decomposed during flash column chromatography in silica gel. As a result, cyclobutene **3wa** was always isolated with unknown impurities, as observed on TLC and NMR spectrum. The instability of 3wa posed hurdles for isolation of pure product purification and yield quantification.



Scheme 2-5. In(III)-TMSBr-catalyzed [2+2] cycloaddition of 1-phenylacetylene and acrylate

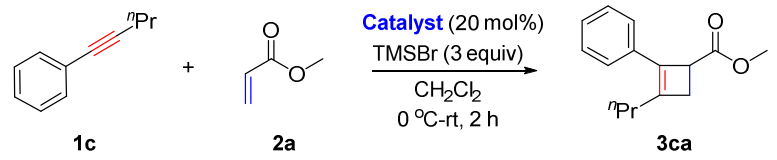
We thought that the introduction of another substituent on the double bond of cycobutene product could improve yield (**Scheme 2-6**). To test this hypothesis, 1-phenyl-1-pentyne (**1c**) and methyl acrylate (**2a**) were chosen as the model substrates to attempt the reaction with $InBr_3$ and TMSBr. After being stirred at room temperature for 2 h, the corresponding cyclobutene product **3ca** could be obtained in 54% yield (**Scheme 2-6**). Pleasingly, not only the yield of cyclobutene **3ca** is much higher than that of **3wa**, **3ca** is also much more stable than **3wa**, making it more convenient for purification and further study.



Scheme 2-6. Preliminary result of [2+2] cycloaddition with **1c** and **2a**

2.2.2 Effects of indium catalysts on the [2+2] cycloaddition of 1c and 2a

Table 2-1. Effects of indium catalysts on the [2+2] cycloaddition of **1c** and **2a**[a]



1c **2a** **3ca**

Entry	**Catalyst**	Solvent	TMSX	Yield (%)[b]
1	$InBr_3$	CH_2Cl_2	-	0
2[c]	$InBr_3$	CH_2Cl_2	-	0
3[d]	$InBr_3$	CH_2Cl_2	-	0
4[e]	-	CH_2Cl_2	TMSBr	0
5	InF_3	CH_2Cl_2	TMSBr	54
6	$InCl_3$	CH_2Cl_2	TMSBr	24
7	InI_3	CH_2Cl_2	TMSBr	49
8	$In(OTf)_3$	CH_2Cl_2	TMSBr	0
9	$In(CH_3CO_2)_3$	CH_2Cl_2	TMSBr	< 5
10	$In(CF_3CO_2)_3$	CH_2Cl_2	TMSBr	<5
11	$In_2(SO_4)_3$	CH_2Cl_2	TMSBr	0
12	$In(acac)_3$	CH_2Cl_2	TMSBr	0
13	**$In(tfacac)_3$**	**CH_2Cl_2**	**TMSBr**	**68**
14	InI	CH_2Cl_2	TMSBr	0
15	$InBr_2$	CH_2Cl_2	TMSBr	0
16[f]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	57
17[g]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	67

[a] Reaction condition: **1c** (0.4 mmol), **2a** (1.6 mmol), catalyst (20 mol%), TMSBr (3 equiv), CH_2Cl_2 (1 mL), 0 °C-rt, 2 h, N_2. [b] Isolated yields. [c] 1 equiv of $InBr_3$ was added. [d] The reaction temperature was 40 °C. [e] $InBr_3$ was not added. [f] 10 mol% of $In(tfacac)_3$ was added. [g] 30 mol% of $In(tfacac)_3$ was added.

With these promising preliminary results in hand, we commenced the optimization of reaction conditions using different indium catalysts with 1-phenyl-1-pentyne **1c** and methyl acrylate **2a** as model substrates (**Table 2-1**). Both indium catalyst and TMSBr were found indispensable for the formation of cyclobutene **3ca**. In the absence of TMSBr, no reaction occurred for **1c** and **2a** with 20 mol% of $InBr_3$ in CH_2Cl_2 from 0 °C to room temperature (entry 1). The attempts continued with 1 equiv of $InBr_3$ or reaction temperature of 40 °C but were futile (entries 2-3). With only

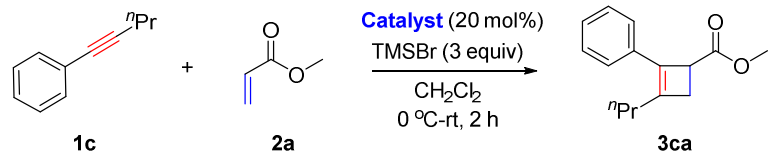
TMSBr, no cyclobutene could be obtained either (entry 4).

Having recongnized the mandatory presences of the indium catalyst and TMSBr to current reaction, different indium catalysts were screened (**Table 2-1**, entries 5-15). Among the different indium(III) catalysts studied, only indium(III) halides (InF_3, $InCl_3$, $InBr_3$, InI_3, entries 5-7) and indium(III) trifluoroacetylacetonate [$In(tfacac)_3$] (entry 13) could afford measurable cyclobutene product **3ca** and $In(tfacac)_3$ was found to exhibit the best catalytic activity to afford **3ca** in 68% yield. A similar catalyst, indium(III) acetylacetonate [$In(acac)_3$] (entry 12) was found to be completely incompatible for this reaction. In(I) and In(II) catalysts (InI, $InBr_2$, entries 14-15) were also screened but were found to be ineffective as well. A lower catalyst loading (10 mol%) resulted in lower product yield but a higher loading of 30 mol% could not further improve the product yield either (entries 16-17).

2.2.3 Effects of common Lewis acid catalysts on the [2+2] cycloaddition of 1c and 2a

Aside from the indium salts, other common Lewis acid catalysts (eg., $AlBr_3$, $ZnCl_2$, $TiCl_4$, $FeBr_3$, $Fe(tfacac)_3$, $Sc(OTf)_3$, $GaCl_3$, $MgCl_2$, AgCl, $SnCl_2$, and $AuCl_3$) tested mostly could not promote the reaction except of iron(III) catalysts which provided **3ca** in moderate yields (**Table 2-2**, entries 4-5). To the best of our knowledge, this is the first example of iron(III) and TMSX as combined Lewis acid catalyst although other combinations have been reported in precedence.

Table 2-2. Effects of Lewis acid catalysts on the [2+2] cycloaddition of **1c** and **2a**[a]



1c **2a** **3ca**

Entry	**Catalyst**	Solvent	TMSX	Yield (%)[b]
1	$AlBr_3$	CH_2Cl_2	TMSBr	0
2	$ZnCl_2$	CH_2Cl_2	TMSBr	0
3	$TiCl_4$	CH_2Cl_2	TMSBr	0
4	**$FeBr_3$**	**CH_2Cl_2**	**TMSBr**	**23**
5	**$Fe(tfacac)_3$**	**CH_2Cl_2**	**TMSBr**	**31**
6	$Sc(OTf)_3$	CH_2Cl_2	TMSBr	0
7	$GaCl_3$	CH_2Cl_2	TMSBr	0
8	$MgCl_2$	CH_2Cl_2	TMSBr	0
9	AgCl	CH_2Cl_2	TMSBr	0
10	$SnCl_2$	CH_2Cl_2	TMSBr	0
11	$AuCl_3$	CH_2Cl_2	TMSBr	0

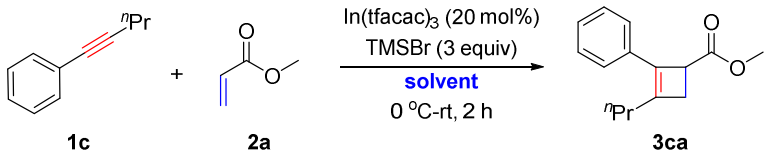
[a] Reaction condition: **1c** (0.4 mmol), **2a** (1.6 mmol), catalyst (20 mol%), TMSBr (3 equiv), CH_2Cl_2 (1 mL), 0 °C-rt, 2 h, N_2. [b] Isolated yields.

2.2.4 Effects of solvents on the [2+2] cycloaddition of 1c and 2a

With identification of $In(tfacac)_3$ as the optimal catalyst for this [2+2] cycloaddition (**Table 2-1**, entry 13), different solvents were tested and the results were summarized in **Table 2-3**. This reaction was found to be highly solvent-dependent and only chlorinated solvents such as CH_2Cl_2, 1,2-dichloroethane (DCE), 1,2-dibromoethane (DBE) as well as CH_3NO_2 could give measurable yield of **3ca** (entries 11-12, 14-15). Among them, reaction performed in DCE gave the highest yield of **3ca**. Although Baba and co-workers reported examples of reaction promoted by In(III)-TMSBr in non-polar or weakly polar solvents (eg., hexane, benzene and toluene, entries 1-3), current reaction performed in these solvents gave only trace amount of cyclobutene product. The common polar aprotic solvents (eg., Et_2O, THF, 1,4-dioxane, EtOAc, CH_3CN, DMF and DMSO, entries 4-10) and polar protic solvent (MeOH, entry 16) were found to be ineffective for

this reaction. The molarity of this reaction was also checked (entries 14, 17 and 18) and 0.4 M was found to be optimal (entry 14).

Table 2-3. Effects of solvents on the [2+2] cycloaddition of **1c** and **2a**[a]



1c **2a** **3ca**

Entry	Catalyst	Solvent	TMSX	Yield (%)[b]
1	$In(tfacac)_3$	hexane	TMSBr	< 5
2	$In(tfacac)_3$	benzene	TMSBr	< 5
3	$In(tfacac)_3$	toluene	TMSBr	< 5
4	$In(tfacac)_3$	Et_2O	TMSBr	< 5
5	$In(tfacac)_3$	THF	TMSBr	0
6	$In(tfacac)_3$	1,4-dioxane	TMSBr	0
7	$In(tfacac)_3$	EtOAc	TMSBr	0
8	$In(tfacac)_3$	CH_3CN	TMSBr	0
9	$In(tfacac)_3$	DMF	TMSBr	0
10	$In(tfacac)_3$	DMSO	TMSBr	0
11	$In(tfacac)_3$	CH_3NO_2	TMSBr	47
12	$In(tfacac)_3$	CH_2Cl_2	TMSBr	68
13	$In(tfacac)_3$	$CHCl_3$	TMSBr	0
14	**$In(tfacac)_3$**	**DCE**	**TMSBr**	**81**
15	$In(tfacac)_3$	DBE	TMSBr	45
16	$In(tfacac)_3$	MeOH	TMSBr	0
17[c]	$In(tfacac)_3$	DCE	TMSBr	72
18[d]	$In(tfacac)_3$	DCE	TMSBr	70

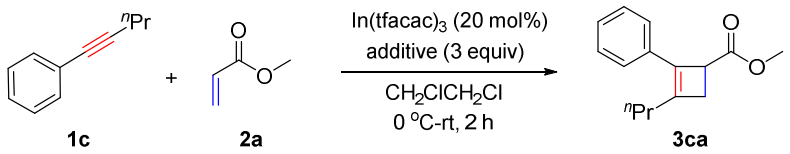
[a] Reaction condition: **1c** (0.4 mmol), **2a** (1.6 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (3 equiv), solvent (1 mL), 0 °C-rt, 2 h, N_2. [b] Isolated yields. [c] 0.5 mL of DCE was used as solvent. [d] 2 mL of DCE was used as solvent.

2.2.5 Effects of additives and other parameters on the [2+2] cycloaddition of 1c and 2a

We proceeded to examine the compatibility of different additives with $In(tfacac)_3$ and DCE (**Table 2-4**). When chlorotrimethylsilane (TMSCl), iodotrimetylsilane (TMSI), or chlorotriethylsilane (TESCl) were used instead of TMSBr as the additive in cooperation with

$In(tfacac)_3$, the desired cyclobutene **3ca** could be obtained in notable lower yields (entries 1-3).

Table 2-4. Effects of additives and other parameters on the [2+2] cycloaddition of **1c** and **2a**[a]



1c **2a** **3ca**

Entry	Catalyst	Solvent	**Additive**	Yield (%)[b]
1	$In(tfacac)_3$	DCE	TMSCl	33
2	$In(tfacac)_3$	DCE	TMSI	38
3	$In(tfacac)_3$	DCE	TESCl	<5%
4	$In(tfacac)_3$	DCE	TBSCl	0
5	$In(tfacac)_3$	DCE	TIPSCl	0
6	$In(tfacac)_3$	DCE	TBDPS	0
7	$In(tfacac)_3$	DCE	TBSOTf	0
8	$In(tfacac)_3$	DCE	Et_3SiH	0
9	$In(tfacac)_3$	DCE	$PhSiMe_3$	0
10	$In(tfacac)_3$	DCE	NaBr	0
11	$In(tfacac)_3$	DCE	$HBr\text{-}H_2O$	0
12	$In(tfacac)_3$	DCE	TBAB	0
13	$In(tfacac)_3$	DCE	$PhCO_2H$	21
14[c]	$In(tfacac)_3$	DCE	TMSBr	34
15[d]	$In(tfacac)_3$	DCE	TMSBr	56
16[e]	$In(tfacac)_3$	DCE	TMSBr	78
17[f]	$In(tfacac)_3$	DCE	TMSBr	66
18[g]	$In(tfacac)_3$	DCE	TMSBr	70
19[h]	$In(tfacac)_3$	DCE	TMSBr	61

[a] Reaction condition: **1c** (0.4 mmol), **2a** (1.6 mmol), catalyst (20 mol%), TMSBr (3 equiv), 0 °C-rt, 2 h, N_2. [b] Isolated yields. [c] 0.25 equiv of TMSBr was added. [d] 2.0 equiv of TMSBr was added. [e] 4.0 equiv of TMSBr was added. [f] 3 equiv of **2a** was added. [g] Reaction temperature was 0 °C. [h] Reaction time was 3 hour.

Other additives containing silicon or halogen atoms were also tested with $In(tfacac)_3$, for instance, *t*-butyldimethylsilyl chloride (TBSCl), triisopropylsilyl chloride (TIPSCl), *t*-butyldiphenylsilane (TBDPSCl), *t*-butyldimethylsily trifluoromethanesulfonate (TBSOTf), triethylsilane (TESH), $PhSiMe_3$, NaBr, $HBr\text{-}H_2O$, tetrabutylammonium bromide (TBAB) (entries 4-12), but none promoted this [2+2] cycloaddition. These results complied with the conclusion reported by Baba:

the direct coordination between silicon and halogen atom of the additive is virtually essential. It was intriguing to observe PhCOOH could mediate this reaction albeit the low yield (entry 13).

Other parameters of present [2+2] cycloaddition of **1c** and **2a** were varied in pursuit of the best optimized reaction condition (**Table 2-4**, entries 14-19). Attempts to decrease the amount of TMSBr or methyl acrylate (**2a**) led to decreasing product yields (entries 14-15, 17). The reaction yield was also compromised when additional equivalent (4 equiv) of TMSBr was added (entry 16). It should be noted that when 0.25 equiv of TMSBr was used, the desired product could also be obtained in 34% yield (entry 8). The reaction of **1c** and **2a** went smoothly at 0 °C (entry 18), but the reaction left warming up to and stirring at ambient temperature after addition of reagents at 0 °C gave better result. Furthermore, performing this reaction for a prolonged reaction time resulted in decreased yield of the cyclobutene product (entry 19). Even though we have previously established that **3ca** is more stable than **3wa**, we reasoned this experimental observation to be caused by the inherent instability of cyclobutene especially in the relatively acidic reaction conditions.

2.2.6 Substrate scope of aryl alkynes for [2+2] cycloaddition

With the optimized reaction conditions in hand, we went on to probe the generality of alkyne substrate scope of this [2+2] cycloaddition with respect to methyl acrylate (**2a**) and the results are summarized in **Table 2-5**. Both internal and terminal aryl alkynes were effective substrates for this reaction protocol to give **3aa-3va** and **3wa-3za** in moderate to good yields.

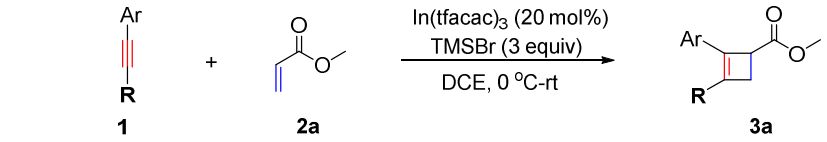
Alkynes bearing linear alkyl substituents with increasing carbon chain underwent smooth transformation to afford **3aa-da** in 73-85% isolated yields. Presence of sterically more demanding substituents such as *i*-butyl (**1e**, **1p**, **1s** and **1t**), *t*-butyl (**1f**) and *c*-hexyl (**1h**) groups

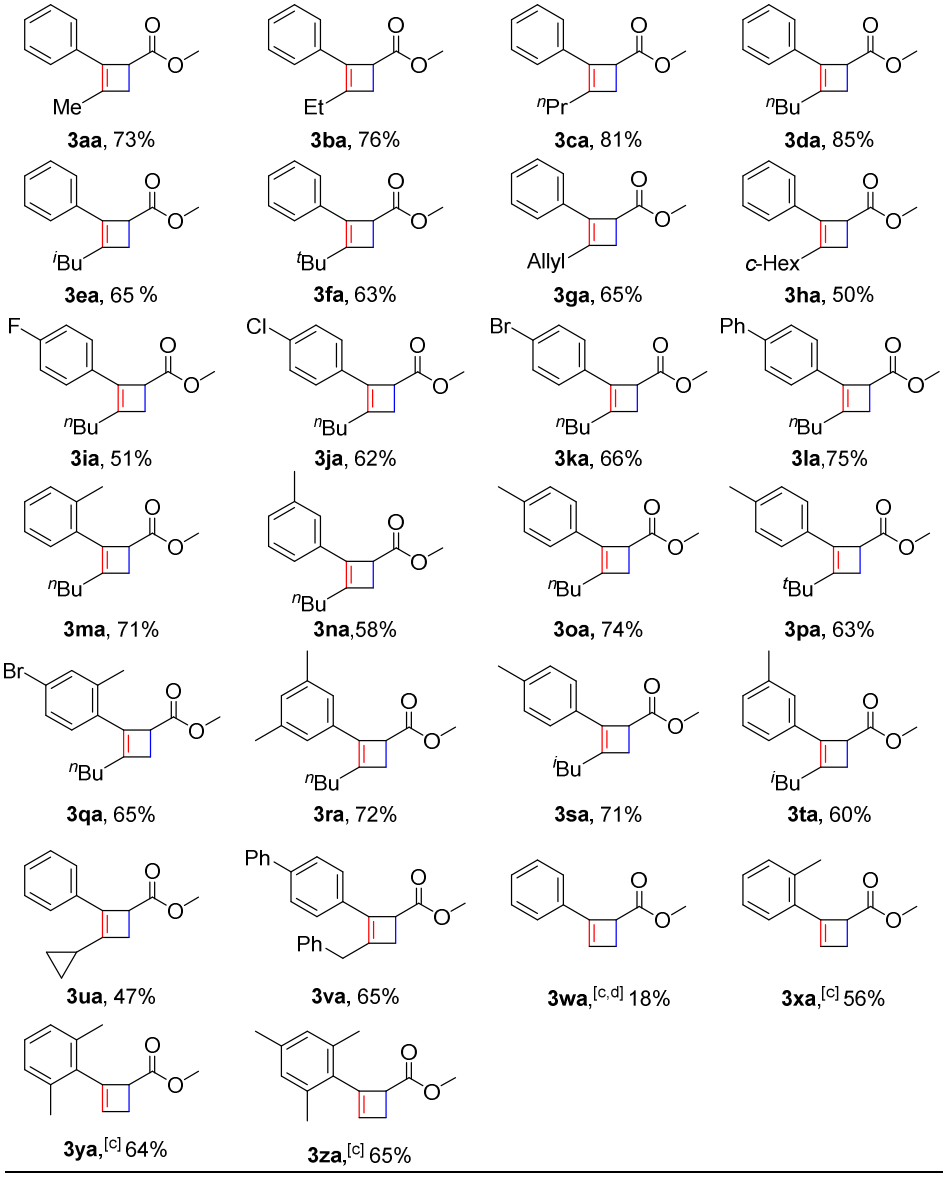
on alkynes gave respective cyclobutene **3ea**, **3fa**, **3ha**, **3pa**, **3sa**, **3ta** and **3ua** in reasonable yields. The gradual increase of the yield from **3aa** to **3da** led to a deduction that the presence of alkyl substituent could prevent the formed cyclobutene to undergo further side reaction and improved the stablity of cyclobutene products. On the other hand, the bulkier R substituent could prevent the cycloaddtion of alkyne with acrylate, evident from the decreasing yield of **3da** to **3fa** as the substituent got bulkier from *n*-Bu, *i*-Bu to *t*-Bu. Aside from acyclic alkyl moieties, cyclohexyl or cyclopropyl substituents also reacted with **2a** to give the tri-cyclic cyclobuene **3ha** and **3ua** in moderate yields.

Alkynes carrying allyl group was congruent with current reaction conditions, leading to **3ga** in 65% yield. The reactions worked in equal efficiency for aryl rings with halogen substituents to deliver the corresponding **3ia**-**3ka** and **3qa** in moderate to good yields. These provide chemical handles for downstream chemical modification.

Different terminal alkynes were also tested for their effectiveness in reaction with **2a**. Due to the absence of R substituents, the reaction time was observed to be shorter than that of internal alkynes. Structurally simple phenylacetylene (**1w**) gave **3wa** in only 18% yield. The instability of **3wa** in the relative acidic reaction condition and on silica during column purification could have led to its decomposition and thus low yield. When one or more methyl substituents were introduced at ortho/para position on phenyl ring, the corresponding yields were much better (**3xa-za**). We speculated that the *ortho*-methyl group could have inhibited further side reactions at the double bond of cyclobutene product.

Table 2-5. Substrate scope of aryl alkynes for [2+2] cycloaddition[a,b]



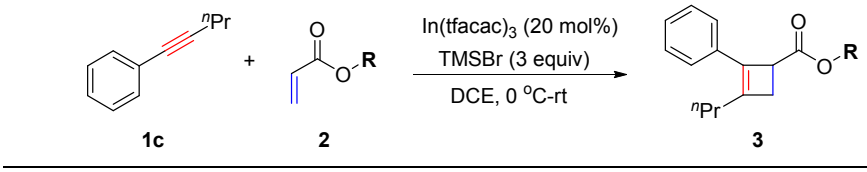


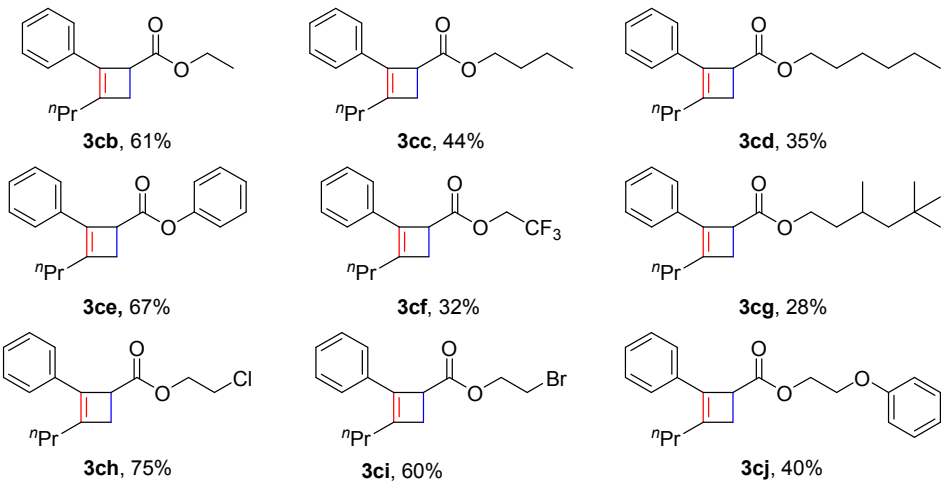
[a] Reaction condtition: **1** (0.4 mmol), **2a** (1.6 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (3 equiv), 0 °C-rt, 2 h, N_2. [b] Isolated yields. [c] The reaction time was 30 min. [d] **3wa** was combined with unknown inpurity

2.2.7 Substrate scope of acrylate for [2+2] cycloaddition

Next, compatibility of different acrylates **2** to current reaction was examined with 1-phenyl-1-pentyne (**1c**) as standard coupling partner (**Table 2-6**). Acrylates bearing long *O*-alkyl substituents (eg., ethyl, butyl, hexyl and 3,5, 5-trimethyl-hexyl) gave cyclobuteene **3cb**, **3cc**, **3cd** and **3cg** smoothly albeit in relatively low yields compared to methyl acrylate (**3ca**). Acrylates tethered with varied substituents other than simple aliphatic chain such as phenyl, trifluoroethyl, chloroethyl, bromoethyl and phenoxyethyl group undertook this chemistry readily to the cyclobutenes **3ce**, **3cf**, **3ch**, **3ci** and **3cj** in moderate to good yields (40-75%).

Table 2-6. Substrate scope of acrylates for [2+2] cycloaddition[a,b]





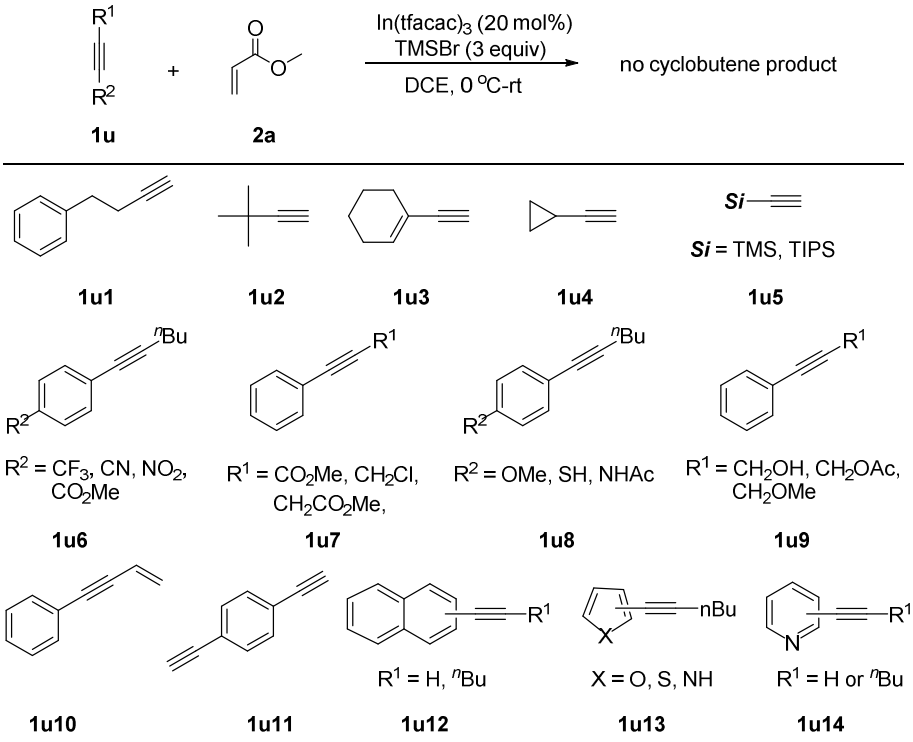
[a] Reaction condition: **1c** (0.4 mmol), **2** (1.6 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (3 equiv), 0 °C-rt, 2 h, N_2. [b] Isolated yields.

2.2.8 Unsuitable alkyne substrates for present [2+2] cycloaddition

In addition to alkyne substrates **1a-z** shown in **Table 2-5**, other common alkynes were also tested but none gave the cyclobutene products (**Table 2-7**). The aryl substitutent is vital for the

formation of cyclobutene products. Alkyne substrates with alkyl, alkenyl, cyclopropyl and silyl substituents (**1u1-1u5**) were tested, and no corresponding cyclobutene products could be obtained. The presence of aryl group on alkyne could be mandatory to promote the conjugate addition of alkyne to acrylate as well as stablize the vinyl carbocation intermediate. For the same reason, substrates with strong electron-withdrawing groups (eg., CF_3, CN, NO_2, CO_2Me, CH_2CO_2Me, **1u6-1u7**) on phenyl ring or triple bond were also found unsuitable for this reaction.

Table 2-7. Unsuitable alkyne substrates for present [2+2] cycloaddition[a]



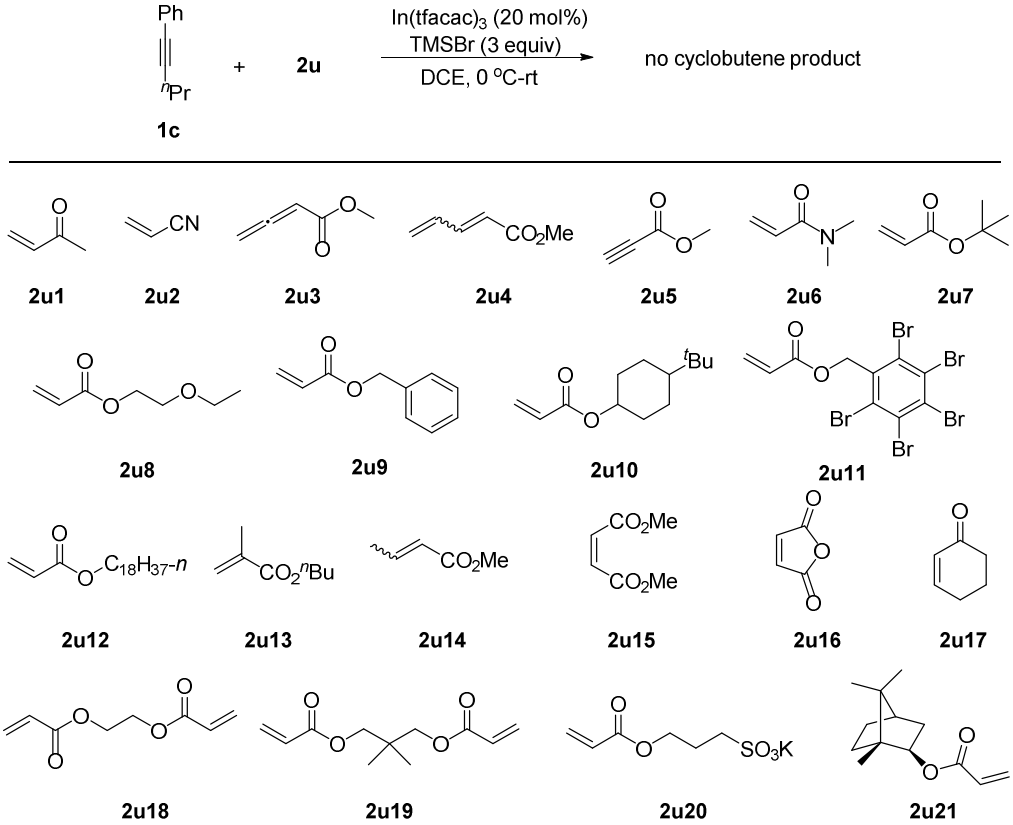
[a] Reaction condition: **1u** (0.4 mmol), **2a** (1.6 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (3 equiv), 0 °C-rt, 2 h, N_2.

Aryl alkynes with acid sensitive substituents, for examples, OMe, SH, NHAc, CH_2OH, CH_2OAc, CH_2OMe, were found unsuitable for this cycloaddition reaction due to substrate decomposition or salts formation under the relative acidic reaction conditions (**1u8-1u9**). In addition, 1,3-enyne (**1u10**) and 1,4-diethynylbenzene (**1u11**) also could not afford the cyclobutene products. When the aryl substituent on alkynes was replaced by naphthyl or heteroaromatic rings (**1u12-1u14**),

no desired products could be obtained either.

2.2.9 Unsuitable alkene, alkyne and allene substrates for present [2+2] cycloaddition

Table 2-8. Unsuitable alkene, alkyne and allene substrates for present [2+2] cycloaddition[a]



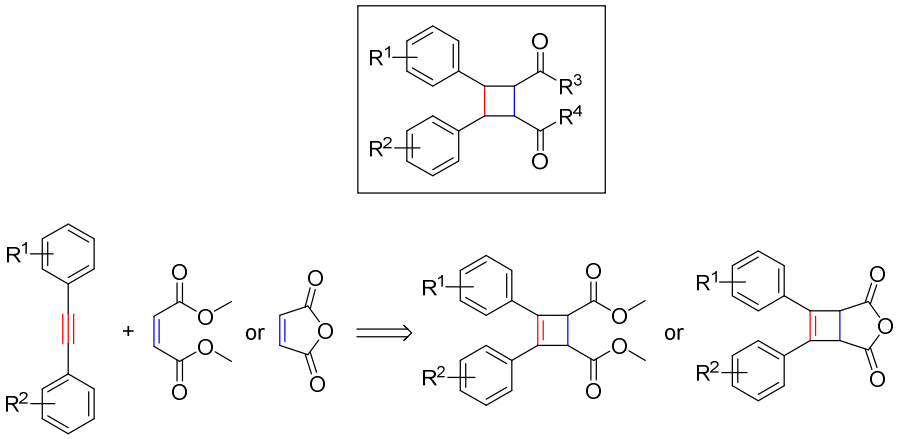
[a] Reaction condition: **1c** (0.4 mmol), **2u** (1.6 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (3 equiv), 0 °C-rt, 2 h, N_2.

Aside from acrylates, the compatibility of other alkene, alkyne and allene substrates with strong electron-withdrawing group were also tested with **1c** but none afforded the corresponding cyclobutene product (**Table 2-8**). These include methyl vinyl ketone (**2u1**), acrylonitrile (**2u2**), methyl 2,3-butadienoate (**2u3**) and methyl penta-2,4-dienoate (**2u4**). Reactions with *N,N*-dimethylacrylamide (**2u5**), 4-acryloylmorpholine (**2u6**), *t*-butyl acrylate (**2u7**), 2-ethoxyethyl acrylate (**2u8**) were also unfruitful for their functional groups could react with TMSBr or decomposed under our reaction conditions. Although reaction of phenyl acrylate (**2e**)

generated 67% of cyclobutene **3ce**, benzyl acrylate (**2u9**), bulkier 4-*t*-butylcyclohexyl acrylate (**2u10**) and pentabromobenzyl acrylate (**2u11**) could not give desired product. Moreover, di-substituted alkenes including butyl methacrylate (**2u13**), methyl but-2-enoate (**2u14**), dimethyl maleate (**2u15**), maleic anhydride (**2u16**) and cyclohex-2-en-1-one (**2u17**) failed to provide respective cyclobutene products. Diacrylate substrates such as ethane-1,2-diyl diacrylate (**2u18**) and neopentyl glycol diacrylate (**2u19**) gave only trace (<10%) mixture of mono-cyclobutene and dicyclobutene. Other unsuitable acrylates include 3-sulfopropyl acrylate potassium salt (**2u20**) and isobornyl acrylate (**2u21**).

2.2.10 Attempts of [2+2] cycloaddition with 1,2-diphenyl acetylene and alkenes

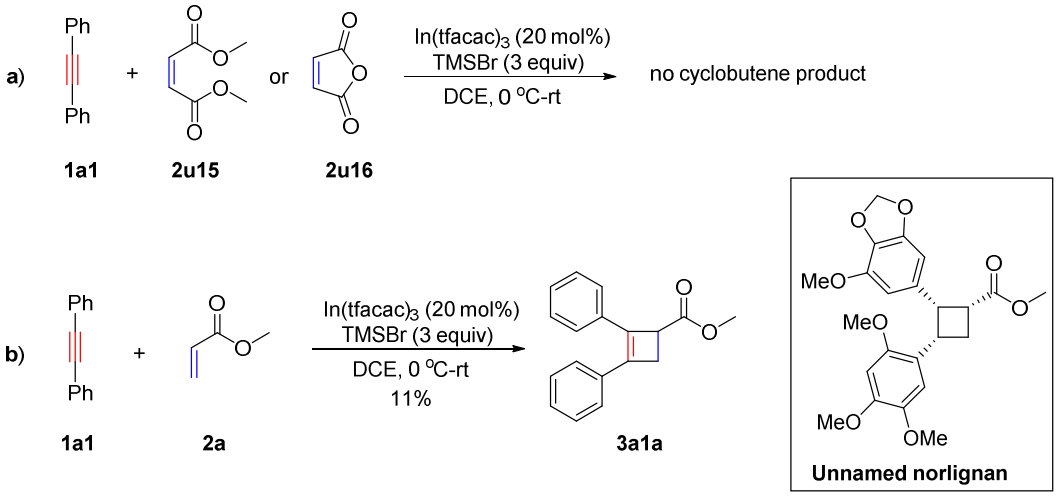
Cyclobutane with 1,2-diaryl and 3,4-dicarbonyl substituents is a common molecular framework in cyclobutane ring containing natural products (**Figure 2-1**). Thus, we envisioned that current [2+2] cycloaddition reaction between aryl alkyne and acrylate could provide a convenient strategy for quick assembly of this structure (**Scheme 2-7**).



Scheme 2-7. Proposed retrosynthetic route of natural product skeletons

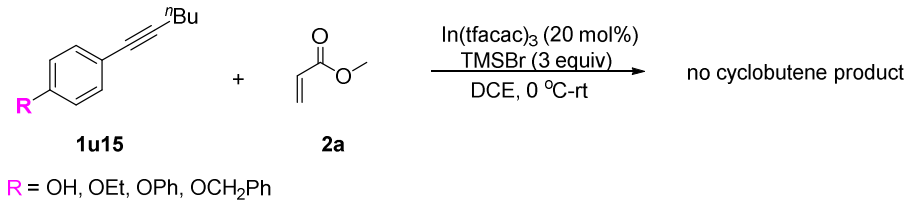
In order to test this hypothesis, 1,2-diphenyl acetylene (**1a1**) was used to react with dimethyl maleate (**2u15**) or maleic anhydride (**2u16**) under standard conditions. However, similar results

as **1c** (**Table 2-8**) were obtained where no cyclobutene formation could be observed (**Scheme 2-8a**). When diphenylacetylene **1a1** was reacted with **2a**, corresponding cyclobutene **3a1a** was formed in 11% yield (**Scheme 2-8b**). Note-worthily, **3a1a** resembles the structure of the natural product of an unnamed norlignan.



Scheme 2-8. [2+2] Cycloaddition of 1,2-diphenyl acetylene and methyl acrylate

2.2.11 Attempts of [2+2] cycloaddition with alkynes bearing oxygen containing substituents

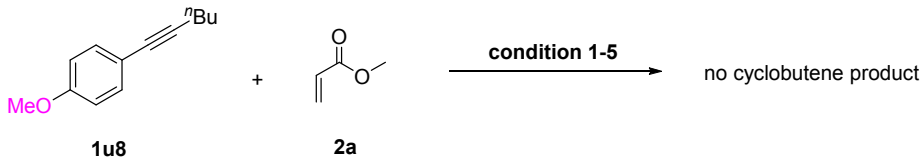


Scheme 2-9. Attemped [2+2] cycloaddition of aryl alkynes with oxygen containing functionalities

It was previously mentioned in **Table 2-7** that aryl alkyne **1u8** carrying a *para*-methoxy group was not an effective substrate for this reaction due to substrate decomposition. Given the ubiquitous occurence of alkoxy groups in cyclobutane ring containing natural product (**Figure 2-1**), we continued the studies with aryl alkynes bearing other oxygen containing functionalities

such as hydroxyl, ethoxyl, phenoxyl and benzyloxyl (**1u15**) with respect to methyl acrylate **2a** as standard coupling partner (**Scheme 2-9**). However, these experiments were unsuccessful to prepare desired cyclobutene products due to the unstablity of these alkynes under current reaction conditions.

Having recognized the incompatibility of current protocol for substrates with oxygen-containing groups, modification of standard reaction conditions was done in hope to accommodate them. With 1-(hex-1-yn-1-yl)-4-methoxybenzene (**1u8**) and methyl acrylate **2a**, different modified reaction conditions were tested: reaction at low temperature (condition 1), decreased amount of TMSBr (condition 2), reaction at 80 ^{o}C without TMSBr (condition 3), replacing TMSBr with TMSCl (condition 4) and replacing PhCOOH with TMSBr (condition 5). Nonetheless, neither of these conditions furnished cyclobutene product (**Scheme 2-10**).



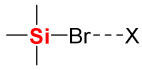
Conditions: **1**. In(tfacac)$_3$ (20 mol%), TMSBr (3 equiv), DCE, -15 ^{o}C;
2. In(tfacac)$_3$ (20 mol%), TMSBr (0.5 equiv), DCE, 0 ^{o}C-rt;
3. In(tfacac)$_3$ (20 mol%), DCE, 80 ^{o}C;
4. In(tfacac)$_3$ (20 mol%), TMSCl (3 equiv), DCE, 0 ^{o}C-rt;
5. In(tfacac)$_3$ (20 mol%), PhCOOH (1 equiv), DCE, 0 ^{o}C-rt;

Scheme 2-10. Attemped [2+2] cycloaddition of alkyne **1u8** and acrylate **2a** under modified conditions

2.2.12 Experimental and computational Studies of [2+2] cycloaddition

First, ^{29}Si NMR studies of TMSBr in the presence of additives were performed (**Scheme 2-11**). Upon mixing with equimolar amounts of In(tfacac)$_3$ (0.2 M), the ^{29}Si signal of TMSBr shifted from 27.6 ppm to 7.4 ppm. On the other hand, when TMSBr was mixed with $AlBr_3$, the

corresponding signal hardly changed (27.8 ppm). These results indicate that TMSBr was activated by $In(tfacac)_3$ by the formation of a Lewis acid complex while this kind of activation did not occur when $In(tfacac)_3$ was replaced by $AlBr_3$.



TMSBr + additive (X)

additive (X)	^{29}Si NMR value (ppm)
-	27.6
$In(tfacac)_3$	7.4
$AlCl_3$	27.8

Scheme 2-11. ^{29}Si NMR studies of TMSBr in the presence of additive

The chemical shifts δ (^{13}C) of carbonyl carbon of methyl acrylate in the presence of $In(tfacac)_3$ and/or TMSBr also were measured (**Scheme 2-12**). When no $In(tfacac)_3$ was used, almost no shift was observed. When only $In(tfacac)_3$ was added, this value changed from 166.4 ppm to 168.4 ppm. Finally, when both $In(tfacac)_3$ and TMSBr were added, the degree of low-field shift was enhanced (170.2 ppm). These results show that the methyl acrylate was effectively activated by the combined Lewis acid complex of $In(tfacac)_3$ and TMSBr.

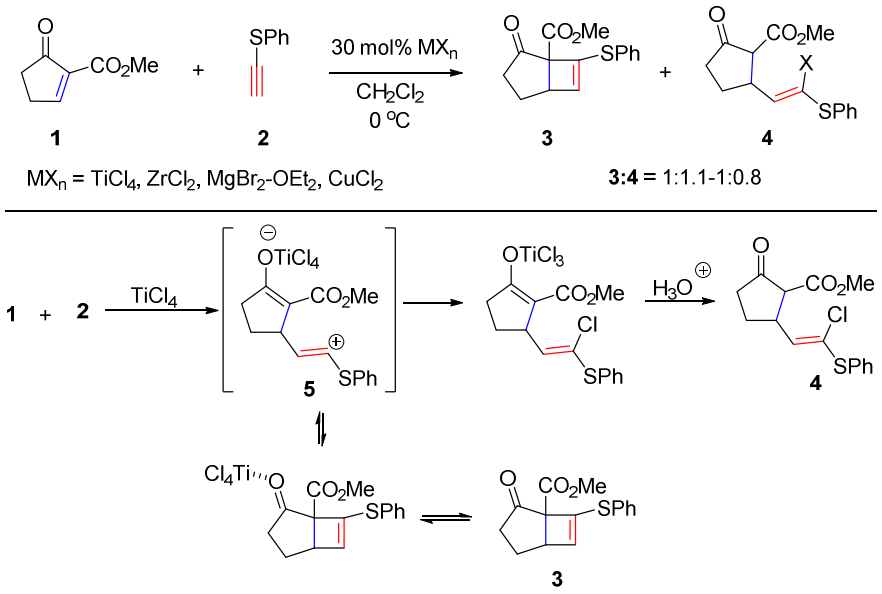
+ additive

additive	^{13}C NMR value (ppm)
-	166.4
TMSBr	166.4
$InBr_3$	168.4
TMSBr + $InBr_3$	170.2

Scheme 2-12. ^{13}C NMR studies of methyl acrylate in the presence of $In(tfacac)_3$ and/or TMSBr

2.2.13 Plausible reaction mechanism of [2+2] cycloaddition

In the study of catalytic enantioselective [2+2] cycloaddition reaction of 2-methoxycarbonyl-2-cyclopenten-1-one (**1**) and phenylthioacetylene (**2**) (**Scheme 1-39**)，Iguchi and co-workers found that in the presence of different halogenated Lewis acids, the reaction proceeded to give cycloaddition product **3** along with a significant amount of by-product **4**.[70]

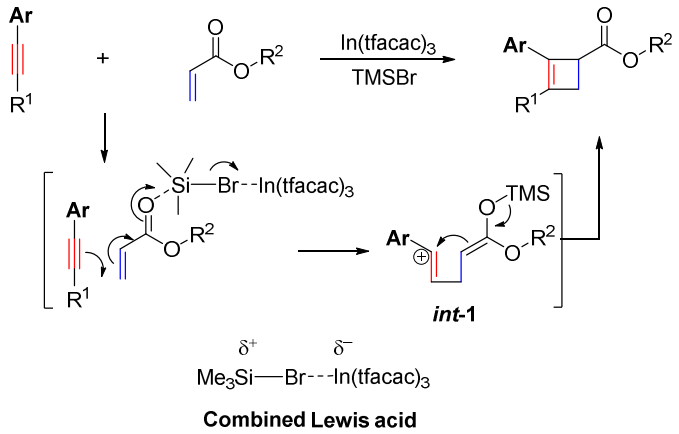


Scheme 2-13. Iguchi-proposed plausible pathway for [2+2] cycloaddition of **1** and **2**

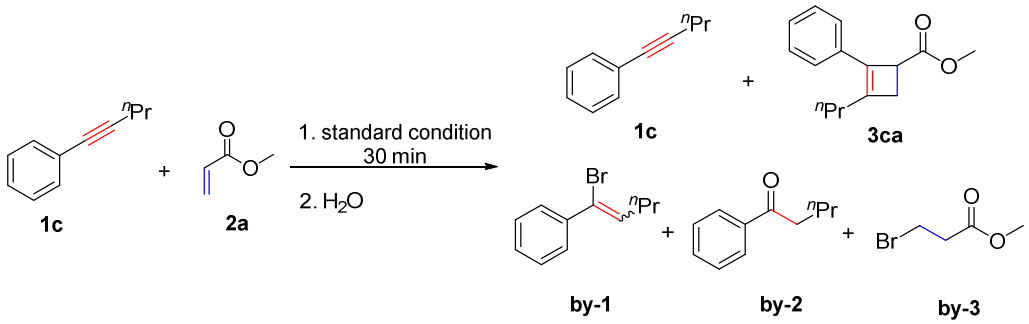
The authors postulated a plausible mechanism for the formation of cyclobutene **3** and vinyl chloride **4** (**Scheme 2-13**). The 1,4-addition of alkyne **2** to the conjugated ketone **1** yields titanium enolate **5**. Ensuing intramolecular reaction of **5** with carbocation bearing the thiophenyl group gives the [2+2] cycloadduct **3**. Along this reaction pathway, the reaction of the chloride anion to the carbocation in intermediate **5** could compete to generate by-product **4**. However, they also considered alternative pathway for the formation of vinyl chloride **4**. After the formation of the cycloadduct **3**, the decomposition of **3** could occur following a Lewis acid coordination to the carbonyl group on the cyclopentane ring. In fact, compound **4** could be obtained when **3** was treated separately with titanium chloride.

Based on the Iguchi's work, a possible reaction pathway for current reaction was illustrated in **Scheme 2-14**: first, $In(tfacac)_3$ and TMSBr form the combined Lewis acid complex with aggrandized acidity than either of them alone; second, the thus formed combined Lewis acid activates the acrylate through preferential coordination of silicon center to carbonyl group due to

the high oxophilicity of silicon; third, aryl alkyne could act as nucleophile and attacks the activated acrylate to give the enolate intermediate. An intramolecular nucleophilic attack then furnishes the cyclobutene product. Note-worthily, low oxophilicity of In(III) allows it to dissociate from enolate and the catalytic cycle could then be facilely completed.



Scheme 2-14. Plausible mechanism of In(tfacac)$_3$-TMSBr-catalyzed [2+2] cycloaddition



Scheme 2-15. Attempt to intercept intermediate of [2+2] cycloaddition of **1c** and **2a**

In order to obtain more insights into the above mechanism, we intended to trap the proposed ***int*-1**. After alkyne **1c** and methyl acrylate **2a** were stirred for 30 min under standard conditions, water was added to the reaction mixture (**Scheme 2-13**). In addition to alkyne **1c** and cyclobutene product **3ca**, vinyl bromide (**by-1**), ketone (**by-2**) and ester (**by-3**) were isolated but not ***int*-1**. There are two possible reasons for the futile attempt to intercept ***int*-1**, (i) the ***int*-1** is highly reactive that it converts into cyclobutene product quickly upon its formation; (ii) this [2+2]

cycloaddition reaction proceeds in a concert manner rather than a stepwise one.

2.2.14 Computational Studies of the Mechanisms of [2+2]-Cycloaddition Catalyzed by In(III)-TMSBr.[103]

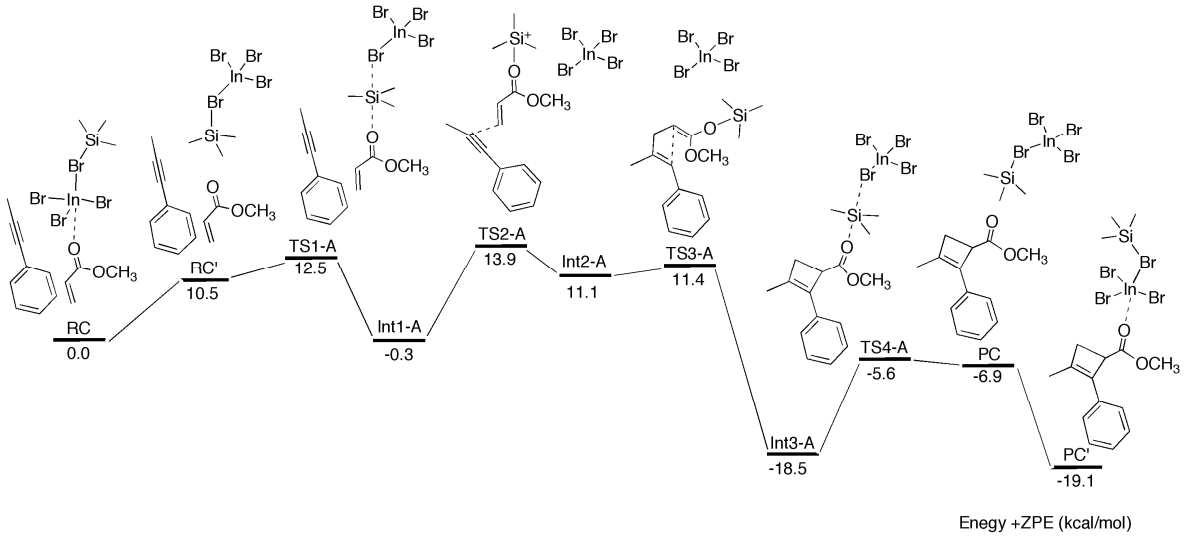


Figure 2-2. Energy profile (in kcal/mol) of the most plausible reaction pathway.

We performed a density functional theory (DFT) study to find the most plausible reaction pathway of this [2+2]-cycloaddition. To make our computational investigation easier, $InBr_3$, which also showed the catalytic activity in this reaction, was used instead of $In(tfacac)_3$. In the most plausible pathway (**Figure 2-2**), $InBr_3$ initially abstracts a Br^- ion from TMSBr to form TMS^+, which in turn coordinates to methyl acrylate to lower the barrier for cycloaddition. Significantly, our calculations show that the activated methyl acrylate reacts with phenyl acetylene in a *stepwise* manner to form a [2+2]-cycloaddition adduct. The TMS^+ moiety in the adduct then accepts a Br^- ion from $InBr_4^-$ to regenerate TMSBr, thereby resulting in dissociation of the TMS moiety from the carbonyl group and completion of the reaction.

We also examined a mechanism in which $InBr_3$, in place of TMS^+, coordinates to methyl acrylate

[103]Computational studies were co-operated with Dr. Kazuki Doitomi and Prof. Hajime Hirao of City University of Hong Kong.

(**Figure 2-3**). However, DFT results suggest that this reaction is less likely than the above-examined one, probably because of lower Lewis acidity of $InBr_3$. One may also wonder if both $InBr_3$ and TMSBr coordinate to methyl acrylate as separate Lewis acids to facilitate the reaction. However, this pathway could not be found by DFT calculations, leading us to rule out this reaction mode.

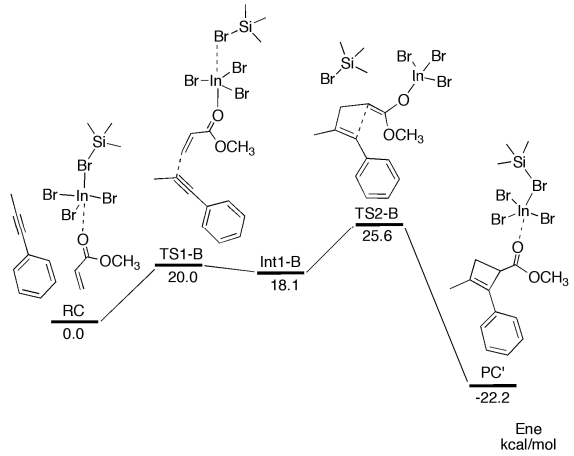


Figure 2-3. Energy profile for a reaction in which methyl acrylateis activated by $InBr_3$. Relative energies are presented in kcal/mol.

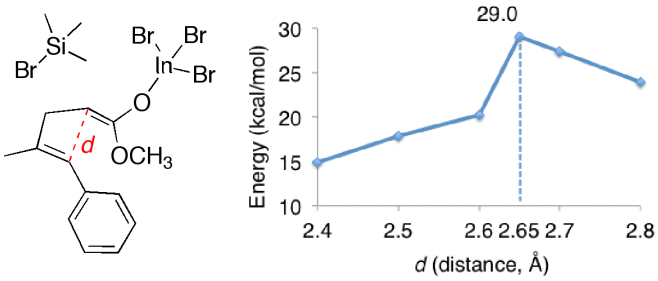


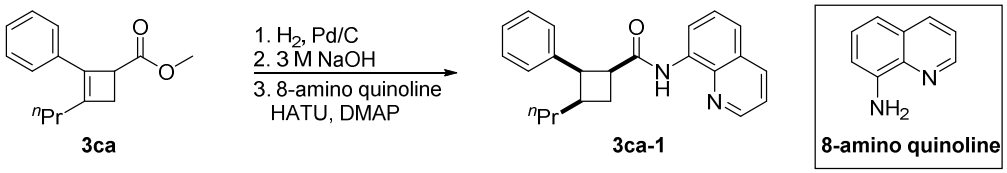
Figure 2-4. A relaxed scan calculationwith the C–C distance marked in the figure used as the reaction coordinate (*d*). Relative energies (kcal/mol) are with respect to RC.

We failed to optimize the transition state for ring closure (**TS2-B** in **Figure 2-3**) precisely. Therefore, the energy of this state was obtained from relaxed scan calculations shown in **Figure 2-4**. In the figure, the maximum energy point is found at d = 2.65 Å, and thus this geometry was

used as approximate TS2-B. Despite the approximate nature of this transition-state optimization, it is clear that TS2-B is much higher in energy than TS2-A in **Figure 2-2**. These data suggest that the combined Lewis acid uses the silicon center of TMS, rather than the In center, in coordinating to the carbonyl oxygen of methyl acrylate.

2.2.15 Structural determination through X-ray single crystal analysis

Since all of the cyclobutene products synthesized under current protocol shown in **Table 2-5** and **2-6** are new compounds, the structural determination was done by comparing ^{1}H and ^{13}C spectra of similar structures found in literature. Though 2D NMR was also performed, we aimed to to obtain absolute determination through X-ray crystallography of cyclobutene product or its derivatives. However, all of the obtained cyclobutene products exist in oil form. We decided to take advantage of the ester group on the cyclobutene as chemical handle for derivatization to obtain solid compound.



Scheme 2-16. Synthesis of cyclobutane amide **3ca-1** from cyclobutene **3ca**

The cyclobutene **3ca** was subjected for one-pot hydrogenation, hydrolysis and amide coupling with 8-amino quinoline to give cyclobutane amide **3ca-1** as a brown solid (**Scheme 2-16**). After several trials with different combinations of solvents, the crystal of **3ca-1** was obtained with ethyl acetate. The result of the X-ray crystallograhy analysis of **3ca-1** was shown in **Figure 2-5**.

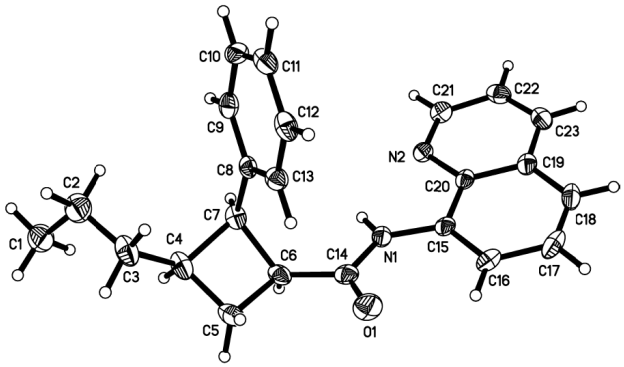
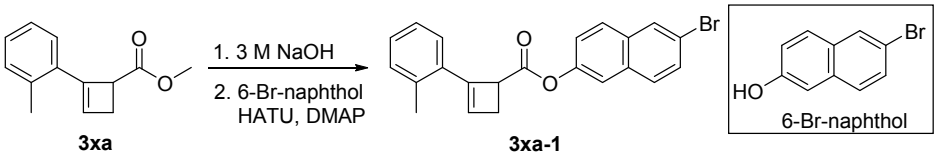


Figure 2-5. X-ray crystallograhy structure of **3ca-1**, (1*S**,2*R**,3*R**)-2-phenyl-3-propyl-*N*-(quinolin -8-yl) cyclobutane-1-carboxamide



Scheme 2-17. Synthesis of **3xa-1** from **3xa**

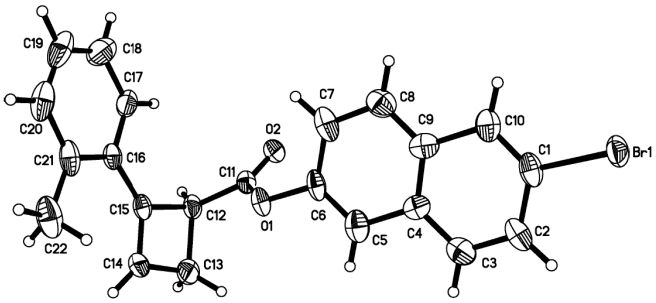
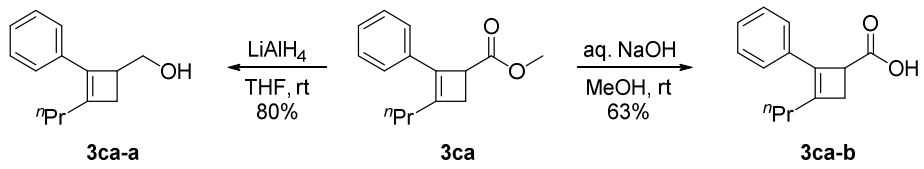


Figure 2-6. X-ray crystallograhy structure of **3xa-1**, 6-bromonaphthalen-2-yl 2-(*o*-tolyl)cyclobut -2-ene-1-carboxylate

The X-ray crystallograhy structure of cyclobutene **3xa-1**, a derivative of **3xa**, was also obtained after crystallization in hexane/$CHCl_3$ (10:1). **3Xa-1** was prepared as a white solid by ester saponification of **3xa** followed by esterification with 6-Br-naphthol in the presence of HATU and DMAP (**Scheme 2-17**). The absolute structure of **3xa-1** was unambiguously confirmed by single-crystal X-ray diffraction as shown in **Figure 2-6**.

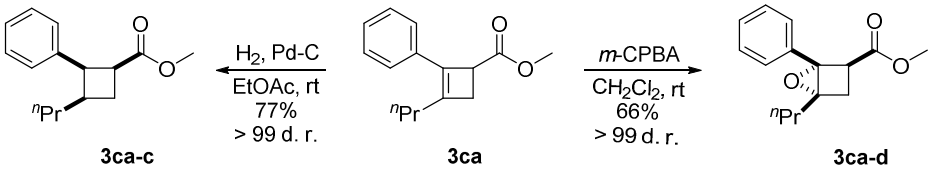
2.2.16 Functional group transformation of cyclobutene 3ca

The existence of ester and alkene functionalities in the cyclobutene products granted access for various downstream chemical transformations on these products. The ester group could either be reduced by $LiAlH_4$ to afford the corresponding alcohol **3ca-a** or hydrolysis could took place in the presence of aqueous NaOH to deliver the corresponding carboxylic acid **3ca-b** (**Scheme 2-18**). The choice of solvent is vital for the reduction of **3ca** to **3ca-a**; when Et_2O was used as solvent in place of THF, only complicated mixture with trace amount of **3ca-a** was obtained.



Scheme 2-18. Reduction and hydrolysis of ester group in **3ca**

Moreover, the C-C double bond of **3ca** could be selectively reduced by H_2 in the presence of Pd/C (**Scheme 2-19**) to give cyclobutane **3ca-c** as a single diastereomer, which is found closely related to the cyclobutane key skeleton shown in **Figure 2-1**. Furthermore, C-C double bond of **3ca** could be selectively oxidized by *m*-CPBA to generate epoxide **3ca-d** as a single diastereoisomer. Under these transformation conditions, the four-membered ring moiety remained intact. Solvent was also a critical factor to determining the fate of hydrogenation reaction to **3ca-c**: when the EtOAc was replaced by MeOH, no hydrogenation occurred.



Scheme 2-19. Diastereoselective hydrogenation and epoxidation of **3ca**

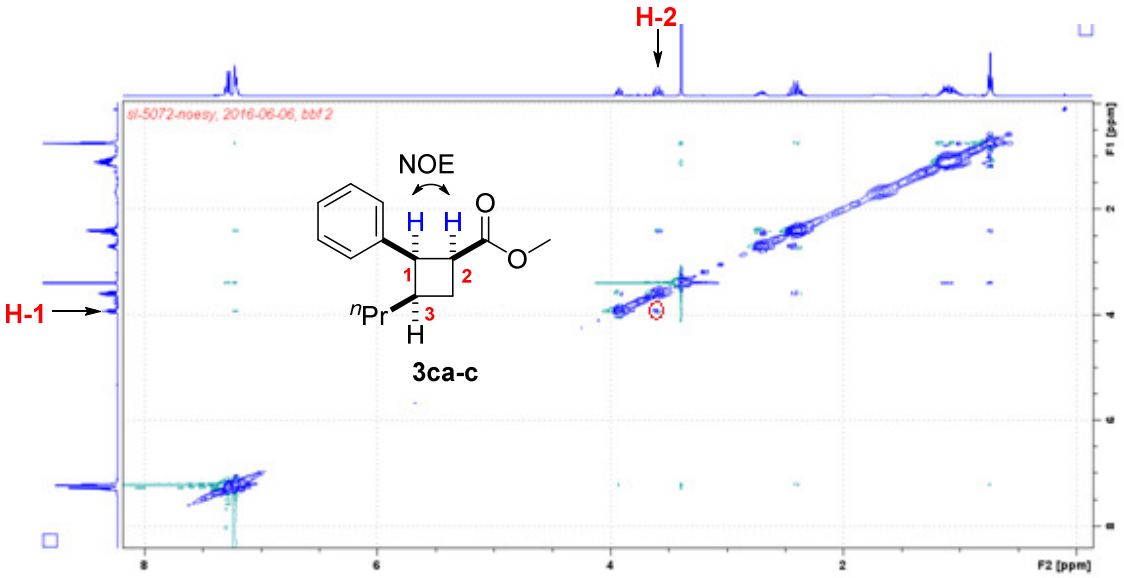
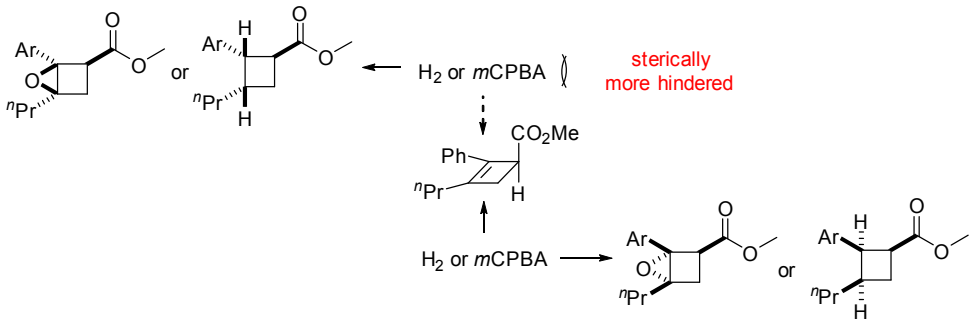


Figure 2-7. 2D NOESY spectrum of cyclobutane **3ca-c**

The relative stereochemistry of **3ca-c** was confirmed on the basis of 2D NMR spectra. As shown in **Figure 2-7**, nuclear overhausal effect (NOE) occurs between the spatially related H-1 and H-2 due to their proximity in space. This dictates that they are on the same side of the cyclobutane rings. While H-1 and H-3 are introduced in a *syn*-fashion from hydrogenation, the phenyl, propyl and methyl ester group thus reside at the same side of cyclobutane ring. This is justifiable as the hydrogenation should proceed favourably on the less hindered face of cyclobutene ring (**Scheme 2-20**).



Scheme 2-20. Schematic illustration for diastereoselectivity of hydrogenation and epoxidation

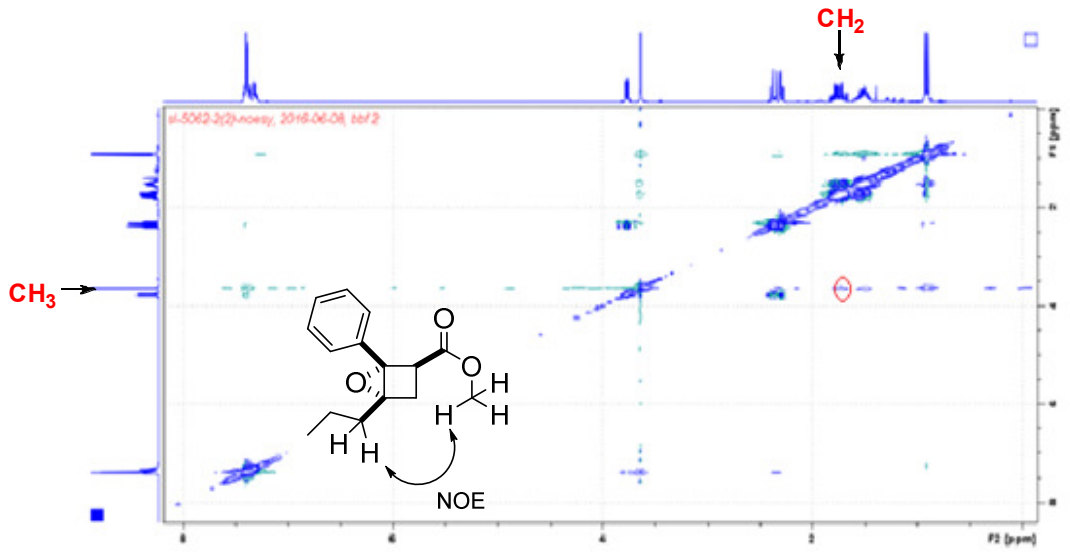


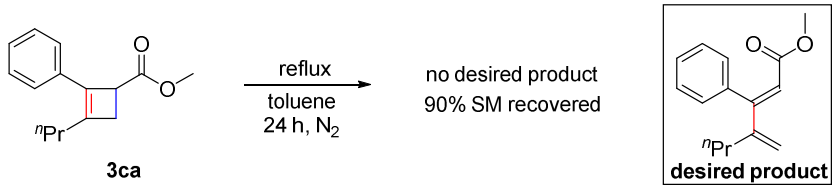
Figure 2-8. 2D NOESY spectrum of epoxide **3ca-d**

In a similar way, the relative stereochemistry of the product **3ca-d** was also determined. In the NOESY spectrum of **3ca-d** (**Figure 2-8**), NOE signal appears from the correlation between the protons of carbon carrying propyl and methyl ester group. This indicates that propyl and methyl ester groups are on the same side of the cyclobutane ring, which is reasonable as epoxidation should also take place on the less hindered face of cyclobutene ring (**Scheme 2-20**).

2.3 Acid- and molecular oxygen-mediated ring opening of cyclobutene

2.3.1 Attempted conversion of 3ca into diene through ring opening reaction

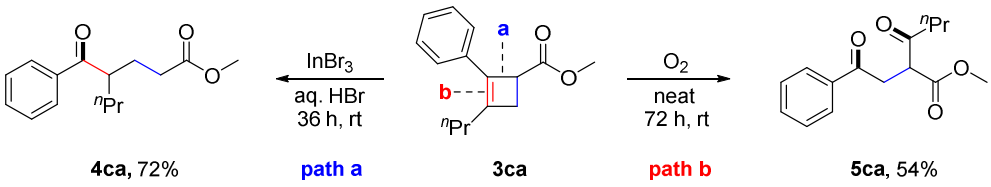
In addition to the above-mentioned functional group transformations, it was speculated that the existence of phenyl and ester substituents could install some new reaction modes. It is commonly known that cyclobutene could transform easily to related diene under thermal conditions. However, when **3ca** was refluxed in toluene for 12 h, most of the starting material was recovered and no diene product could be observed (**Scheme 2-21**).



Scheme 2-21. Attempted conversion of **3ca** into diene through ring opening

2.3.2 Acid- and molecular oxygen-mediated ring opening of cyclobutene 3ca

After several attempts, we were pleased to find that the cyclobutene **3ca** could undergo selective cleavage of C-C to give methyl 4-benzoylheptanoate **4ca** in the presence of $InBr_3$-aq.HBr (**Scheme 2-22**, path **a**). Alternatively, **3ca** could be selectively transformed to methyl 3-oxo-2-(2-oxo-2-phenylethyl)hexanoate **5ca** in the presence of atmospheric O_2 at room temperature through selective cleavage of C=C bond of **3ca** (path **b**).



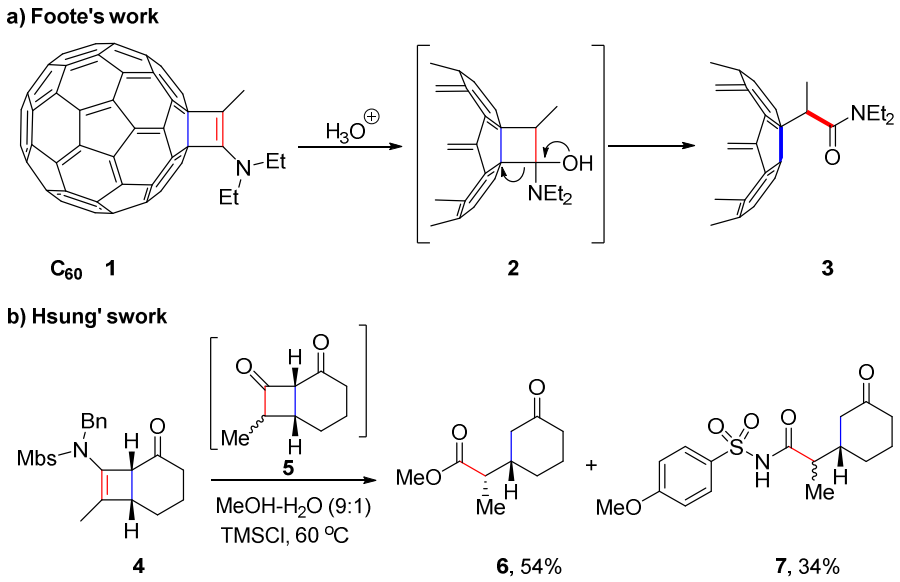
Scheme 2-22. Acid- and O_2-mediated selective cleavage of C-C/C=C Bond of **3ca**

2.3.3 Molecular oxygen-mediated ring opening of cyclobutene

It should be noted that the present method to access 1,5-dicarbonyl compound is the first example of acid-mediated conversion of arylated cyclobutene into linear ketone, although there were two similar works on acid-mediated conversion of *N*-substituted cyclobutene reported in precedence by Foote[104] and Hsung[105]. In Foote's work, the C_{60}-fused cyclobutenamine **1** was hydrolyzed to amide **3** with SiO_2 catalysis. The author thought that the amide is produced instead

[104](a) Zhang, X. J.; Romero, A.; Foote, C. S. *J. Am. Chem. Soc*. **1993**, *115*, 11024-11025; (b) Bernstein, R.; Foote, C. S. *Tetrahedron Lett*. **1998**, *39*, 7051-7054.
[105]Li, H. Y.; Hsung, R. P.; DeKorver, K. A.; Wei, Y. G. *Org. Lett*. **2010**, *12*, 3780-3783.

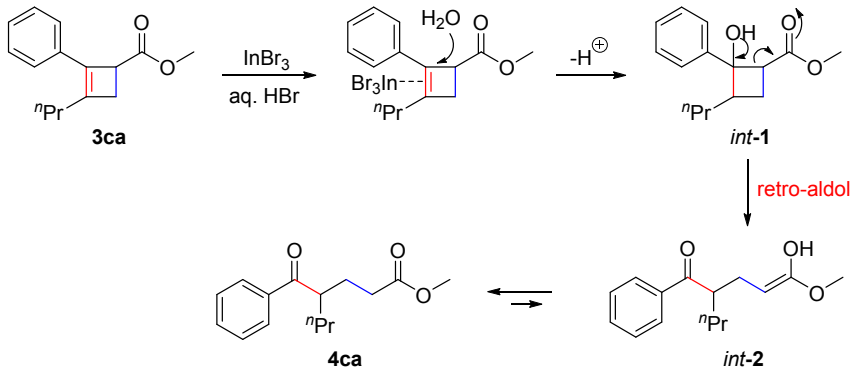
of cyclobutanone and diethylamine because the dihydrofullerene ring is an apparent strong electron acceptor that serves as better leaving group than diethylamine (**Scheme 2-23a**). In Hsung's work, cyclobutene **4** underwent hydrolysis and subsequent retro-Claisen *via* intermediate diketone **5**, leading to keto-ester **6** and amide **7** (**Scheme 2-23b**).



Scheme 2-23. Seminal reports on acid-mediated ring opening of *N*-substituted cyclobutene

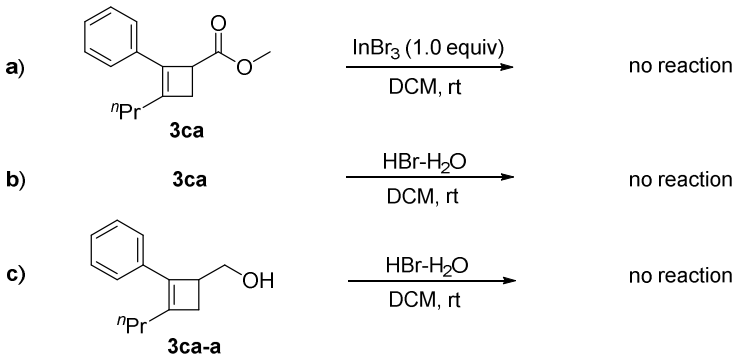
2. 3.4 Plausible mechanism of acid-mediated ring opening of cyclobutene

Inspired by the mechanistic pathways proposed in Foote and Hsung's works, we also devised a plausible pathway for our ring-opening reaction (**Scheme 2-24**). The $InBr_3$-activated double bond of the cyclobutene could react with water to give cyclobutanol *int*-**1** through proton elimination. Then, *int*-**1** undergoes retro-aldol reaction to give enol *int*-**2**. The existence of aryl substituent and $InBr_3$ are imperative to accelerate the nucleophilic attack of H_2O towards the double bond whereas the ester group could facilitate the ring opening of *int*-**1**.



Scheme 2-24. Plausible pathway for acid-mediated ring opening of cyclobutene **3ca**

In order to gain more insights into the above-proposed mechanism, three control experiments were conducted. In the absence of either HBr-H_2O or $InBr_3$, neither of the desired product was formed (**Scheme 2-25a,b**). Moreover, no similar ring opening product could be obtained when cyclobutene alcohol **3ca-a** was used in place of **3ca** (**Scheme 2-25c**).



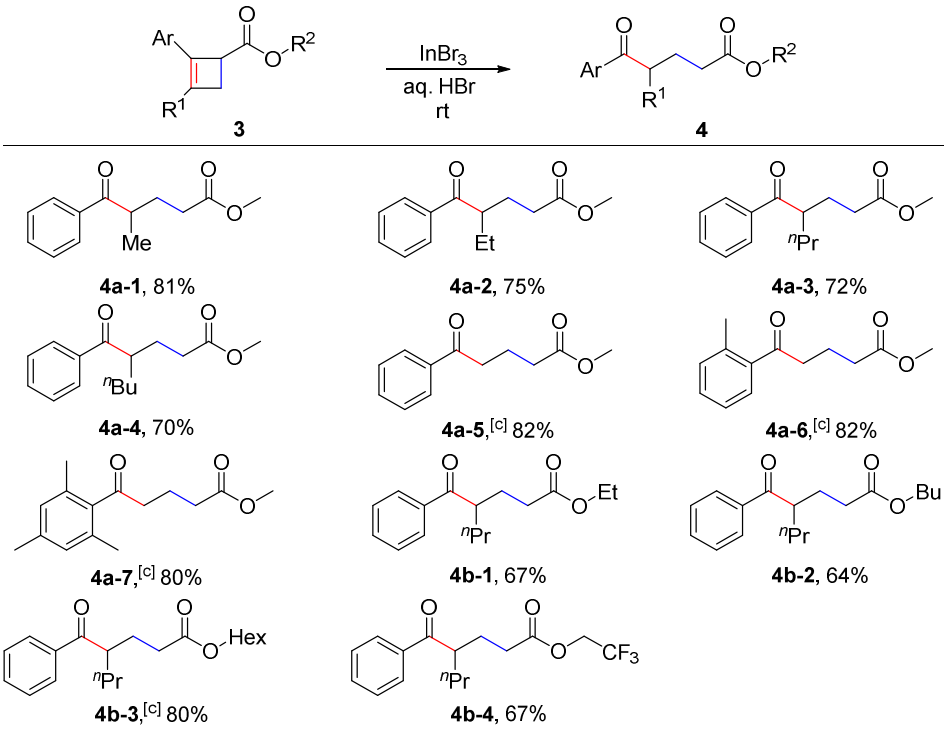
Scheme 2-25. Control experiments for acid-mediated ring opening of **3ca** and **3ca-a**

2.3.5 Substrate generality of acid-mediated ring opening of cyclobutene

The cyclobutene products synthesized using present methodology were examined to probe the generality of this acid-mediated ring opening reaction (**Table 2-9**). It was found that when Ar was phenyl and R^1 was a linear alkyl group (**3aa-3da**), the cyclobutenes could convert into the corresponding ketones (**4a-1-4a-4**) in moderate to good yields. As the linear alkyl chain elongated from methyl to butyl, the product yields decreased accordingly. When Ar was phenyl

and R^1 was other alkyl substituents, for example, *iso*-butyl (**3ea**), *tert*-butyl (**3fa**), allyl (**3ega**), cyclohexyl (**3ha**) and cyclopropyl (**3ua**), trace or no corresponding ketone compounds could be obtained. With R^1 being *n*-Bu, cyclobutenes bearing halogens (**3ia-3ka**), phenyl (**3la**) and methyl groups (**3ma-3oa**) could hardly or could not yield the corresponding ketones. Most cyclobutenes formed from terminal alkynes (**3wa**, **3xa** and **3za**) would convert into ketones (**4a-5-4a-7**) in good yields and shorter reaction time. However, it is interesting to observe that cyclobutene **3ya** could not give any desired product. When the R^2 was not methyl, **3cb**, **3cc**, **3dc** and **3cf** could convert into ketones (**4b-1-4b-4**) in moderate yields while other cyclobutenes (**3ce**, **3cg-3cj**) only gave trace or no ketone products.

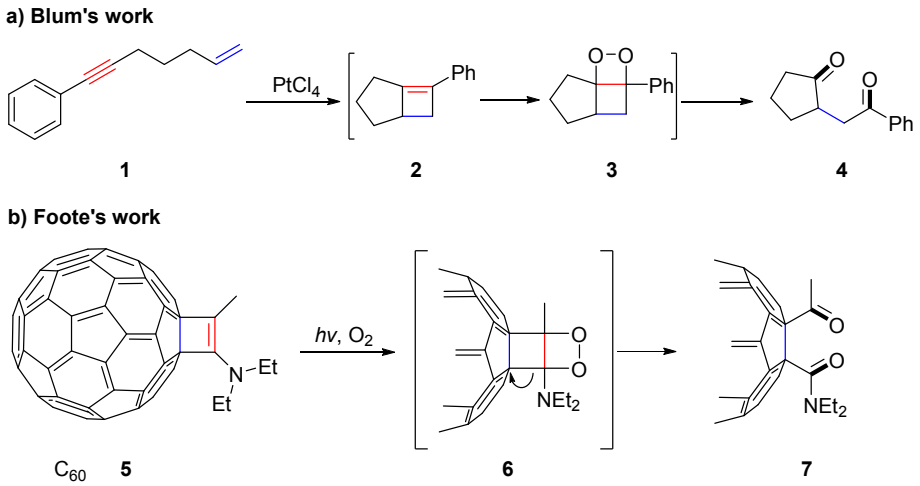
Table 2-9. Acid-mediated selective cleavage of C-C bond in cyclobutene[a,b]



[a] Reaction condition: **3** (0.1 mmol), $InBr_3$ (1 equiv), 48% HBr (1.5 equiv), DCM (1 mL), 36 h, rt, N_2. [b] Isolated yield. [c] Reaction time was 12 h.

2.3.6 Reported examples on O_2-mediated ring opening of cyclobutenes

From the literature findings, two examples on molecular O_2-mediated oxidative ring opening of cyclobutene have been disclosed (**Scheme 2-26**). When Blum and co-workers were studying the $PtCl_4$-catalyzed cyclorearrangement of enynes, they found that (6-hepten-1-ynyl)benzene (**1**) underwent rearrangement at room temperature under inert atmosphere to a labile hydrocarbon **2** that polymerized readily during workup. However, this unstable cyclorearrangement product **2** could trap molecular oxygen to form the 2-(2-oxo-2-phenylethyl)-cyclopentanone (**4**) through intermediacy of **3**.



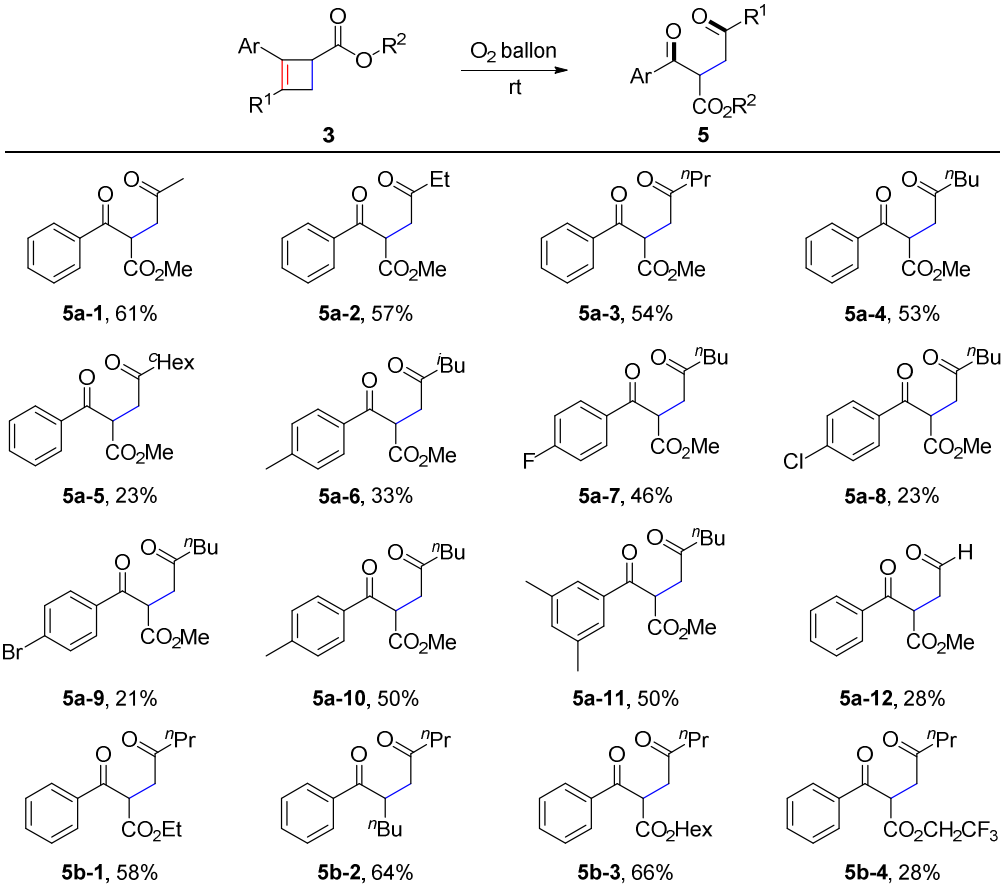
Scheme 2-26. Two reported examples on O_2-mediated ring-opening of cyclobutene

Aside from the afore-discussed SiO_2-catalyzed hydrolysis of C_{60}-fused cyclobutenamine **5** into amide (**Scheme 2-23a**), it was also reported that the enamine double bond of **5** could cleave to give ketamide **7** through the intermediacy of **6** under exposure of air and light. The authors justified this observation by the unique structure of cyclobutenamide **5** bearing both a photosensitizer (the dihydrofullenrene mioety) and a photooxidizable group (the enamine moiety) on the same molecular scaffold.

2.3.7 Substrate generality of O_2-mediated ring opening of cyclobutene

Notably, 1,4-dicarbonyl compounds are useful building blocks towards varied carbocyclic and heterocyclic structural motifs. Moreover, the examples on ring opening of cyclobutene using molecular O_2 were rare (only single substrate was examined for both previous examples) and required substrates with specific structure. Thus, we went on to examine the generality of currently-observed O_2-mediated ring opening reaction.

Table 2-10. O_2-mediated selective cleavage of C=C Bond of cyclobutene[a,b]

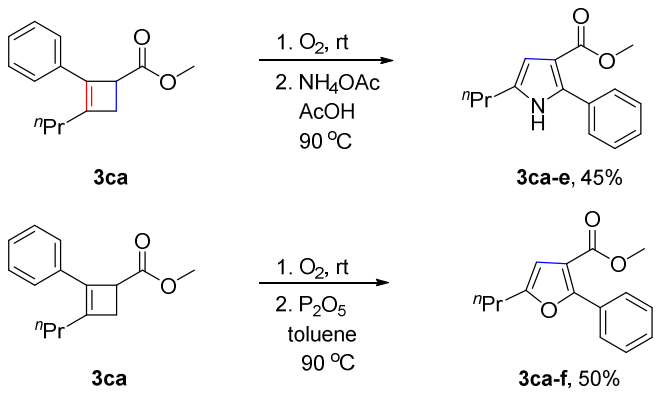


[a] Reaction condition: **3** (0.1 mmol), O_2 ballon, rt, neat, 72 h. [b] Isolated yield.

The cyclobutenes prepared using present protocol were used as the substrates for this purpose (**Table 2-10**). It was found that when Ar was phenyl and R^1 was linear alkyl substituent

(**3aa-3da)**, the respective 1,4-diketones (**5a-1-5a-4**) were delivered in moderate yields. As the linear alkyl chain got longer from one carbon to four carbons, a slight decrease in product yield was observed. When Ar was phenyl and R_1 was *iso*-butyl (**3ea**), *tert*-butyl (**3fa**), allyl (**3ega**), cyclopropyl (**3ua**) or benzyl (**3va**), trace or no corresponding ketone could be obtained. However, cyclobutene **3ha** and **3fa** could convert into **5a-5** and **5a-6** in 23% and 33% yield, respectively. For R_1 being *n*-Bu while substituents on phenyl ring being halogens (**3ia-3ka**) or methyl (**3oa and 3ra**), the corresponding 1,4-diketones were formed in moderated yields. Cyclobutene **3wa** could give rise to aldehyde **5a-12** in 28 % yield but other cyclobutenes prepared from terminal alkynes (**3xa-3za**) failed to give any similar aldehyde product. When R^2 was ethyl (**3cb)**, butyl (**3cc)**, hexyl (**3dc)** or trifluoroethyl (**3cf)** group, these cyclobutenes yielded the ketones (**5b-1-5b-4**) while other cyclobutenes (**3ce**, **3cg-3cj**) only gave trace or no ketone products.

2.3.8 One-pot conversion of cyclobutene 3ca into heterocycles



Scheme 2-27. One-pot synthesis of pyrrole and furan derivatives from **3ca**

Furthermore, by employing this protocol of O_2-mediated ring opening of cyclobutenes, tri-substituted pyrrole **3ca-e** and furan **3ca-f** could be facilely synthesized in a one-pot manner by subjecting cyclobutene **3ca** to oxygen-mediated cleavage followed by ring-closure in the

presence of NH_4OAc/AcOH or P_2O_5 (**Scheme 2-27**).[106]

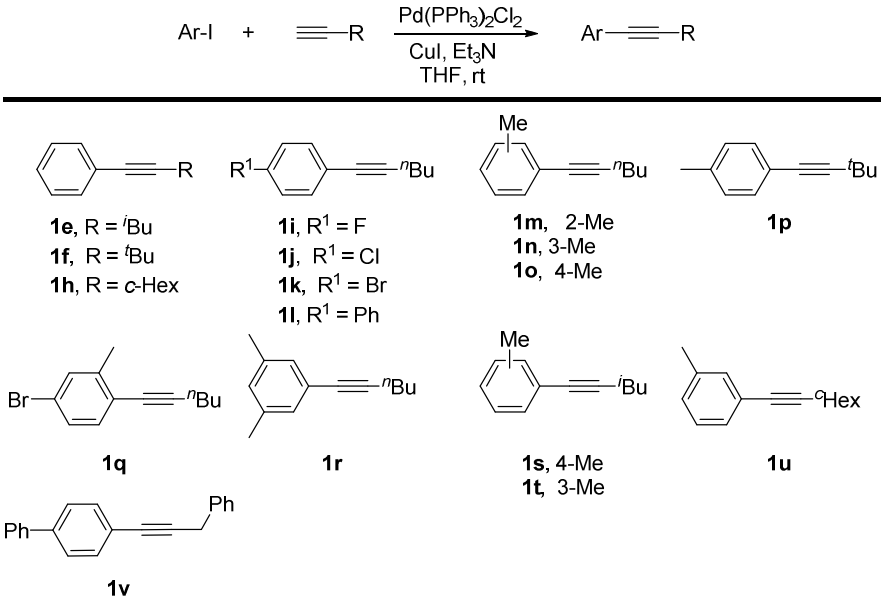
2.4 Conclusion

In conclusion, we have described a novel indium(III)-catalyzed [2+2] cycloaddition reaction of aryl alkynes with acrylates in the presence of TMSBr that could afford cyclobutenes with aryl and ester substituents in moderate to good yields. The versatility of cyclobutene products for diversified functional group transformations were proven thorugh diastereoselective hydrogenation and epoxidation with the intactness of four-membered ring moiety. Notably, selective cleavage of C-C/C=C bond on cyclobutenes was achieved to generate an array of synthetically useful 1,4- and 1,5-dicarbonyl compounds. These transformations give this protocol demonstrable synthetic values.

2.5 Experimental section and spectral data

2.5.1 General procedure for the pynthesis of aryl alkynes substrates

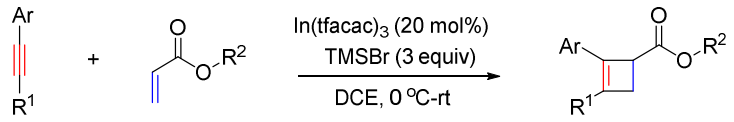
Table 2-11: Synthesis of alkyne substrate *via* Sonogashira coupling



[106]Xuan, J.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. *Chem. Eur. J.* **2014**, *20*, 3045.

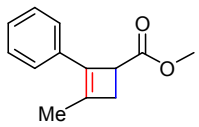
Alkynes **1e-f** and **1h-v** were synthesized based on the following reported method[1] *via* Sonogashira coupling of corresponding aryl iodides and alkynes without the optimization of reaction conditions: a dry reaction tube was charged with aryl iodide (2.45 mmol), alkyne (3 equiv, 7.35 mmol), Et_3N (0.8 mL, 6.12 mmol) and THF (7 mL). $PdCl_2(PPh_3)_2$ (86 mg, 0.12 mmol) was added at room temperature and the reaction mixture was stirred at the same temperature for 5 min before CuI (47 mg, 0.25 mmol) was introduced. The reaction mixture was stirred at room temperature for 24 h and the ammonium salt was removed through filtration. The filtrate was concentrated *in vacuo* and purified by silica gel column chromatography (hexane/ethyl acetate = 100:1) to give the desired product as colorless oil. Other alkynes and acrylates substrates were purchased from commerical resources.

2.5.2. General Procedure for In(III)-TMSBr catalyzed [2+2] cycloaddition of aryl alkyne and acrylate and Spectral Data



1 **2** **3**

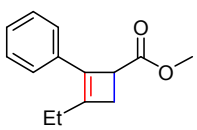
General Procedure for the Synthesis of Cyclobutene. A dry reaction tube was charged with aryl alkyne **1** (0.4 mmol), acrylate **2** (1.6 mmol), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg) and DCE (1 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 3 equiv, 1.2 mmol, 183.6 mg) was added and the reaction mixture was stirred at room temperature for 2 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to afford the desired product **3**.



Methyl 3-methyl-2-phenylcyclobut-2-ene-1-carboxylate (3aa)

Colorless oil, 59.1 mg, 0.293 mmol, 73% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 - 7.29 (m, 4H), 7.24 - 7.19 (m, 1H), 3.85 - 3.80 (m, 1H), 3.69 (s, 3H), 2.71 - 2.59 (m, 2H), 2.07 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.5, 141.2, 136.7, 134.5, 128.4, 126.9, 125.5, 51.7, 42.1, 34.0, 16.1. **HRMS** (ESI) calcd for $C_{13}H_{15}O_2$ $(M+H)^+$ 203.1072, found 203.1078.

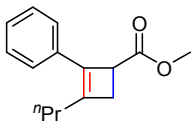


Methyl 3-ethyl-2-phenylcyclobut-2-ene-1-carboxylate (3ba)

Colorless oil, 65.7 mg, 0.304 mmol, 76% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 - 7.31 (m, 4H), 7.24 - 7.17 (m, 1H), 3.81 - 3.79 (m, 1H), 3.69 (s, 3H), 2.70 (dd, J = 4.8, 13.6 Hz, 1H), 2.62 (dd, J = 1.2, 13.6 Hz, 1H), 2.53 - 2.46 (m, 2H), 1.13 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.5, 146.8, 135.5, 134.5, 128.4, 126.9, 125.8,

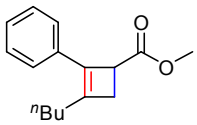
51.8, 41.6, 31.3, 22.9, 11.1. **HRMS** (ESI) calcd for $C_{14}H_{17}O_2$ $(M+H)^+$ 217.1229, found 217.1238.



Methyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3ca)

Colorless oil, 74.5 mg, 0.324 mmol, 81% yield.

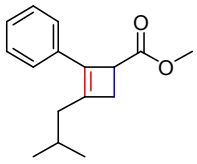
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 - 7.29 (m, 4H), 7.24 - 7.18 (m, 1H), 3.84 - 3.79 (m, 1H), 3.69 (s, 3H), 2.68 (dd, *J* = 4.4, 13.6 Hz, 1H), 2.63 - 2.59 (m, 1H), 2.52 - 2.41 (m, 2H), 1.64 - 1.54 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.6, 145.8, 136.3, 134.6, 128.4, 126.9, 125.8, 51.8, 41.8, 31.9, 31.8, 20.2, 14.2. **HRMS** (ESI) calcd for $C_{15}H_{19}O_2$ $(M+H)^+$ 231.1385, found 231.1390.



Methyl 3-butyl-2-phenylcyclobut-2-ene-1-carboxylate (3da)

Colorless oil, 82.9 mg, 0.340 mmol, 85% yield.

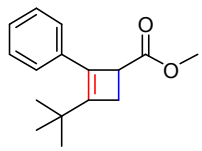
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 - 7.29 (m, 4H), 7.23 - 7.18 (m, 1H), 3.83 - 3.78 (m, 1H), 3.69 (s, 3H), 2.68 (dd, *J* = 4.4, 13.6 Hz, 1H), 2.61 (dd, *J* = 1.6, 13.6 Hz, 1H), 2.51 - 2.45 (m, 2H), 1.59 - 1.48 (m, 2H), 1.45 - 1.36 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$,): δ (ppm) 174.6, 145.9, 136.1, 134.6, 128.4, 126.9, 125.8, 51.8, 41.8, 31.9, 29.6, 29.1, 22.8, 14.0. **HRMS** (ESI) calcd for $C_{16}H_{21}O_2$ $(M+H)^+$ 245.1542, found 245.1554.



Methyl 3-*iso*butyl-2-phenylcyclobut-2-ene-1-carboxylate (3ea)

Colorless oil, 63.4 mg, 0.260mmol, 65% yield.

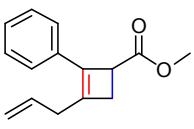
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 - 7.29 (m, 4H), 7.23 - 7.18 (m, 1H), 3.85 - 3.81 (m, 1H), 3.68 (s, 3H), 2.68 (dd, *J* = 4.6, 13.8 Hz, 1H), 2.64 - 2.58 (m, 1H), 2.41 - 2.28 (m, 2H), 1.97 - 1.87 (m, 1H), 1.00 (dd, *J* = 6.8 Hz, 6 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.6, 145.4, 137.1, 134.6, 128.4, 127.0, 125.8, 51.8, 42.0, 39.2, 32.5, 27.2, 22.9, 22.9. **HRMS** (ESI) calcd for $C_{16}H_{21}O_2$ $(M+H)^+$ 245.1542, found 245.1532.



Methyl 3-(*tert*-butyl)-2-phenylcyclobut-2-ene-1-carboxylate (3fa)

Colorless oil, 61.5 mg, 0.252 mmol, 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 - 7.17 (m, 5H), 3.71 - 3.67 (m, 1H), 3.62 (s, 3H), 2.63 (dd, *J* = 4.8, 13.2 Hz, 1H), 2.56 (dd, *J* = 2.0, 13.6 Hz, 1H), 1.13 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.5, 153.5, 135.8, 135.0, 127.9, 127.9, 127.0, 51.6, 42.7, 33.6, 29.7, 28.6. **HRMS** (ESI) calcd for $C_{16}H_{21}O_2$ $(M+H)^+$ 245.1542, found 245.1553.

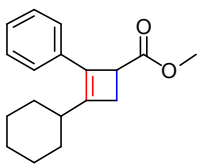


Methyl 3-allyl-2-phenylcyclobut-2-ene-1-carboxylate (3ga)

Colorless oil, 59.3 mg, 0.26 mmol, 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 - 7.30 (m, 4H), 7.26 - 7.20 (m, 1H), 5.94 - 5.83 (m, 1H), 5.20 (dd, *J* = 1.6, 17.2 Hz, 1H), 5.12 (dd, *J* = 1.6, 10.0 Hz, 1H), 3.86 - 3.82 (m, 1H), 3.69 (s, 3H), 3.25 - 3.19 (m, 2H), 2.70 (dd, *J* = 4.6, 13.8 Hz, 1H), 2.64 - 2.61 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm)

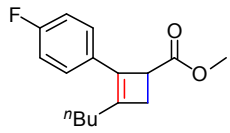
174.3, 142.3, 137.4, 134.2, 133.2, 128.5, 127.2, 125.8, 116.8, 51.8, 42.1, 34.3, 32.2. **HRMS** (ESI) calcd for $C_{15}H_{17}O_2$ $(M+H)^+$ 229.1229, found 229.1234.



Methyl 3-cyclohexyl-2-phenylcyclobut-2-ene-1-carboxylate (3ha)

Colorless oil, 54.1 mg, 0.20 mmol, 50% yield.

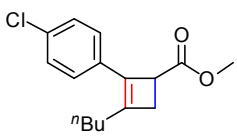
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 - 7.30 (m, 4H), 7.22 - 7.18 (m, 1H), 3.77 - 3.76 (m, 1H), 3.68 (s, 3H), 2.71 - 2.63 (m, 1H), 2.59 - 2.56 (m, 1H), 1.91 - 1.88 (m, 1H), 1.82 - 1.70 (m, 5H), 1.39 - 1.20 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.6, 150.2, 134.6, 134.2, 128.4, 126.8, 125.9, 51.7, 41.5, 38.2, 30.3, 30.2, 29.6, 26.0×2, 25.9. **HRMS** (ESI) calcd for $C_{18}H_{23}O_2$ $(M+H)^+$ 271.1698, found 271.1704.



Methyl 3-butyl-2-(4-fluorophenyl)cyclobut-2-ene-1-carboxylate (3ia)

Colorless oil, 53.6 mg, 0.204 mmol, 51% yield.

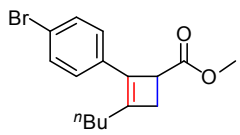
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 - 7.26 (m, 2H), 7.04 - 6.97 (m, 2H), 3.80 - 3.75 (m, 1H), 3.68 (s, 3H), 2.67 (dd, J = 4.6, 13.8 Hz, 1H), 2.62 - 2.58 (m, 1H), 2.45 - 2.38 (m, 2H), 1.56 - 1.48 (m, 2H), 1.44 - 1.36 (m, 2H), 0.93 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.4, 161.7 (d, $J_{C\text{-}F}$ = 245.0 Hz), 145.2 (d, $J_{C\text{-}F}$ = 2.0 Hz), 135.0, 130.9 (d, $J_{C\text{-}F}$ = 3.0 Hz), 127.4 (d, $J_{C\text{-}F}$ = 7.0 Hz), 115.4 (d, $J_{C\text{-}F}$ = 22.0 Hz), 51.8, 41.9, 31.9, 29.4, 29.0, 22.7, 14.0. **HRMS** (ESI) calcd for $C_{16}H_{20}FO_2$ $(M+H)^+$ 263.1447, found 263.1447.



Methyl 3-butyl-2-(4-chlorophenyl)cyclobut-2-ene-1-carboxylate (3ja)

Colorless oil, 68.7 mg, 0.247 mmol, 62% yield.

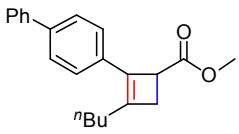
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 - 7.23 (m, 4H), 3.80 - 3.76 (m, 1H), 3.68 (s, 3H), 2.68 (dd, J = 4.6, 13.8 Hz, 1H), 2.63 - 2.57 (m, 1H), 2.47 - 2.40 (m, 2H), 1.57 - 1.47 (m, 2H), 1.45 - 1.35 (m, 2H), 0.93 (t, J = 7.2 Hz, 3 H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.3, 146.7, 135.0, 133.0, 132.5, 128.6, 127.0, 51.8, 41.8, 32.0, 29.6, 29.0, 22.7, 14.0. **HRMS** (ESI) calcd for $C_{16}H_{20}ClO_2$ $(M+H)^+$ 279.1152, found 279.1158.



Methyl 2-(4-bromophenyl)-3-butylcyclobut-2-ene-1-carboxylate (3ka)

Colorless oil, 85.2 mg, 0.265 mmol, 66% yield.

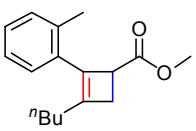
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.43 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H), 3.79 - 3.76 (m, 1H), 3.68 (s, 3H), 2.70 - 2.56 (m, 2H), 2.46 - 2.40 (m, 2H), 1.55 - 1.48 (m, 2H), 1.44 - 1.34 (m, 2H), 0.93 (t, J = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.3, 146.9, 135.1, 133.4, 131.6, 127.3, 120.7, 51.8, 41.7, 32.1, 29.6, 28.9, 22.7, 14.0. **HRMS** (ESI) calcd for $C_{16}H_{20}BrO_2$ $(M+H)^+$ 323.0647, found 323.0653.



Methyl 2-([1,1'-biphenyl]-4-yl)-3-butylcyclobut-2-ene-1 -carboxylate (3la)

Colorless oil, 95.8 mg, 0.299 mmol, 75% yield.

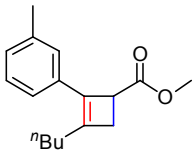
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.60 - 7.55 (m, 4H), 7.45 - 7.38 (m, 4H), 7.36 - 7.32 (m, 1H), 3.86 - 3.81 (m, 1H), 3.71 (s, 3H), 2.71 (dd, *J* = 4.6, 13.8 Hz, 1H), 2.66 - 2.62 (m, 1H), 2.53 - 2.45 (m, 2H), 1.62 - 1.52 (m, 2H), 1.45 - 1.35 (m, 2H), 0.96 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.6, 146.2, 140.8, 139.6, 135.7, 133.6, 128.8, 127.3, 127.1, 127.0, 126.2, 51.8, 41.8, 32.1, 29.7, 29.1, 22.8, 14.0. **HRMS** (ESI) calcd for $C_{22}H_{25}O_2$ $(M+H)^+$ 321.1855, found 321.1853.



Methyl 3-butyl-2-(*o*-tolyl)cyclobut-2-ene-1-carboxylate (3ma)

Colorless oil, 73.3 mg, 0.284 mmol, 71% yield.

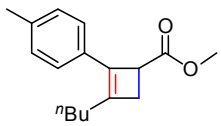
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.20 - 7.11 (m, 4H), 3.95 - 3.88 (m, 1H), 3.60 (s, 3H), 2.70 (dd, *J* = 4.8, 13.2 Hz, 1H), 2.63 - 2.58 (m, 1H), 2.35 (s, 3H), 2.25 - 2.12 (m, 2H), 1.50 - 1.39 (m, 2H), 1.38 - 1.27 (m, 2H), 0.88 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR**(100 MHz, $CDCl_3$): δ (ppm) 174.3, 146.9, 137.7, 135.8, 134.2, 130.2, 128.6, 127.3, 125.4, 51.6, 44.9, 32.1, 29.2, 29.0, 22.7, 20.4, 13.9. **HRMS** (ESI) calcd for $C_{17}H_{23}O_2$ $(M+H)^+$ 259.1698, found 259.1697.



Methyl 3-butyl-2-(*m*-tolyl)cyclobut-2-ene-1-carboxylate (3na)

Colorless oil, 59.6 mg, 0.231 mmol, 58% yield.

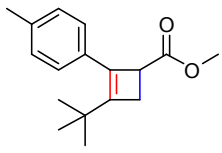
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 - 7.18 (m, 1H), 7.14 - 7.10 (m, 2H), 7.05 - 7.00 (m, 1H), 3.81 - 3.78 (m, 1H), 3.68 (s, 3H), 2.67 (dd, *J* = 4.8, 13.6 Hz, 1H), 2.61 - 2.56 (m, 1H), 2.53 - 2.41 (m, 2H), 2.33 (s, 3H), 1.56 - 1.48 (m, 2H), 1.45 - 1.36 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.7, 145.7, 137.9, 136.2, 134.6, 128.3, 127.8, 126.4, 122.9, 51.8, 41.8, 31.9, 29.5, 29.1, 22.7, 21.6, 14.0. **HRMS** (ESI) calcd for $C_{17}H_{23}O_2$ $(M+H)^+$ 259.1698, found 259.1701.



Methyl 3-butyl-2-(*p*-tolyl)cyclobut-2-ene-1-carboxylate (3oa)

Colorless oil, 76.3 mg, 0.296 mmol, 74% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.22 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.80 - 3.75 (m, 1H), 3.67 (s, 3H), 2.66 (dd, *J* = 4.6, 13.4 Hz, 1H), 2.60 - 2.56 (m, 1H), 2.45 - 2.35 (m, 2H), 2.32 (s, 3H), 1.55 - 1.48 (m, 2H), 1.45 - 1.38 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.7, 144.7, 136.7, 136.0, 131.9, 129.1, 125.7, 51.8, 41.8, 31.9, 29.5, 29.1, 22.7, 21.3, 14.0. **HRMS** (ESI) calcd for $C_{17}H_{23}O_2$ $(M+H)^+$ 259.1698, found 259.1706.

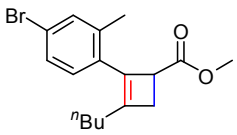


Methyl 3-(*tert*-butyl)-2-(*p*-tolyl)cyclobut-2-ene-1-carboxylate (3pa)

Colorless oil, 64.8 mg, 0.251 mmol, 63% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.17 (d, *J* = 8.2 Hz, 2H), 7.10 (d, *J* = 8.2 Hz, 2H), 3.69 - 3.67 (m, 1H), 3.62 (s, 3H), 2.62 (dd, *J* = 4.8, 13.2 Hz, 1H), 2.54 (dd, *J* = 2.0, 13.2 Hz, 1H), 2.33 (s, 3H), 1.13 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.6, 152.8, 136.7, 134.9, 132.9,

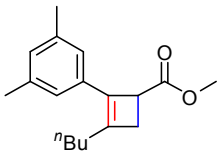
128.6, 127.8, 51.6, 42.6, 33.6, 29.6, 28.6, 21.2. **HRMS** (ESI) calcd for $C_{17}H_{23}O_2$ $(M+H)^+$ 259.1698, found 259.1708.



Methyl 2-(4-bromo-2-methylphenyl)-3-butylcyclobut-2-ene-1- carboxylate (3qa)

Colorless oil, 87.2 mg, 0.259 mmol, 65% yield.

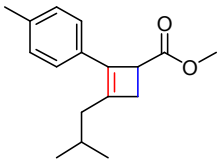
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.32 - 7.26 (m, 2H), 7.06 - 7.03 (m, 1H), 3.92 - 3.86 (m, 1H), 3.61 (s, 3H), 2.70 (dd, *J* = 4.4, 13.2 Hz, 1H), 2.63 - 2.58 (m, 1H), 2.32 (s, 3H), 2.21 - 2.10 (m, 2H), 1.50 - 1.40 (m, 2H), 1.37 - 1.28 (m, 2H), 0.89 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.0, 147.9, 138.1, 136.6, 133.1, 130.2, 128.6, 121.0, 51.7, 44.7, 32.2×2, 29.2, 28.9, 22.7, 20.2, 13.9. **HRMS** (ESI) calcd for $C_{17}H_{12}BrO_2$ $(M+H)^+$ 327.0021, found 327.0014.



Methyl 3-butyl-2-(3,5-dimethylphenyl)cyclobut-2-ene-1-carboxylate (3ra)

Colorless oil, 78.1 mg, 0.287 mmol, 72% yield.

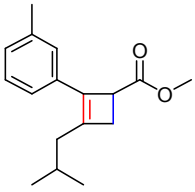
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.93 (s, 2H), 6.85 (s, 1H), 3.79 - 3.76 (m, 1H), 3.68 (s, 3H), 2.66 (dd, *J* = 4.8, 13.6 Hz, 1H), 2.60 - 2.54 (m, 1H), 2.50 - 2.43 (m, 2H), 2.29 (s, 6H), 1.56 - 1.48 (m, 2H), 1.46 - 1.36 (m, 2H), 0.94 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (400 MHz, $CDCl_3$): δ (ppm) 174.7, 145.5, 137.9, 136.2, 134.5, 128.8, 123.6, 51.8, 41.8, 31.9, 29.5, 29.1, 22.7, 21.4, 14.0. **HRMS** (ESI) calcd for $C_{18}H_{25}O_2$ $(M+H)^+$ 273.1855, found 273.1853.



Methyl 3-*iso*butyl-2-(*p*-tolyl)cyclobut-2-ene-1-carboxylate (3sa)

Colorless oil, 73.5 mg, 0.285 mmol, 71% yield.

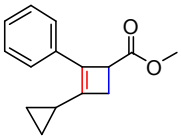
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.82 - 3.77 (m, 1H), 3.67 (s, 3H), 2.66 (dd, *J* = 4.8, 13.6 Hz, 1H), 2.62 - 2.57 (m, 1H), 2.38 - 2.24 (m, 5H), 1.91 (sept, *J* = 6.6 Hz, 1H), 1.00 (d, *J* = 6.6, 3H), 0.96 (d, *J* = 6.6, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.7, 144.1, 137.0, 136.7, 131.9, 129.1, 125.7, 51.7, 42.0, 39.2, 32.4, 27.2, 22.9, 22.9, 21.3. **HRMS** (ESI) calcd for $C_{17}H_{23}O_2$ $(M+H)^+$ 259.1698, found 259.1704.



Methyl 3-*iso*butyl-2-(*m*-tolyl)cyclobut-2-ene-1-carboxylate (3ta)

Colorless oil, 61.7 mg, 0.239 mmol, 60% yield.

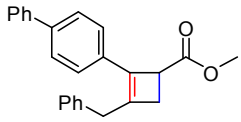
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 - 7.18 (m, 1H), 7.16 - 7.12 (m, 2H), 7.05 - 7.01 (m, 1H), 3.82 - 3.79 (m, 1H), 3.68 (s, 3H), 2.67 (dd, *J* = 4.8, 13.6 Hz, 1H), 2.62 - 2.57 (m, 1H), 2.44 - 2.27 (m, 5H), 1.92 (sept, *J* = 6.8 Hz, 1H), 1.02 - 0.96 (dd, *J* = 6.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.7, 145.1, 137.9, 137.1, 134.5, 128.3, 127.8, 126.4, 122.9, 51.8, 42.0, 39.2, 32.4, 27.2, 22.9, 22.9, 21.6. **HRMS** (ESI) calcd for $C_{17}H_{23}O_2$ $(M+H)^+$ 259.1698, found 259.1707.



Methyl 3-cyclopropyl-2-phenylcyclobut-2-ene-1-carboxylate (3ua)

Colorless oil, 42.8 mg, 0.188 mmol, 47% yield.

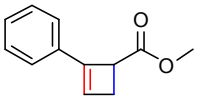
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 - 7.45 (m, 2H), 7.39 - 7.35 (m, 2H), 7.28 - 7.25 (m, 1H), 3.73 (s, 3H), 3.44 - 3.42 (m, 1H), 2.85 -2.72 (m, 2H), 1.92 - 1.87 (m, 1H), 0.84 - 0.80 (m, 2H), 0.70 - 0.65 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.4, 140.6, 139.9, 135.0,128.3, 127.2, 125.9, 51.8, 41.4, 29.3, 11.0, 5.5, 5.3. **HRMS** (ESI) calcd for $C_{15}H_{17}O_2$ $(M+H)^+$ 229.1223, found 229.1227.



Methyl 2-([1,1'-biphenyl]-4-yl)-3-benzylcyclobut-2-ene-1-carboxylate (3va)

Colorless oil, 92.2 mg, 0.260 mmol, 65% yield.

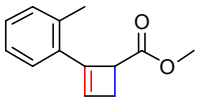
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.61 - 7.55 (m, 4H), 7.48 - 7.41 (m, 4H), 7.36 - 7.22 (m, 6H), 3.86 (m, 3H), 3.71 (s, 3H), 2.69 - 2.56 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.3, 143.0, 140.7, 140.1, 137.6, 137.4, 133.1, 128.8, 128.8, 128.7, 127.4, 127.3, 127.0, 126.4, 126.2, 51.9, 42.0, 36.4, 32.2. **HRMS** (ESI) calcd for $C_{25}H_{23}O_2$ $(M+H)^+$ 355.1693, found 355.1699.



Methyl 2-phenylcyclobut-2-ene-1-carboxylate (3wa)

Colorless oil, 15.8 mg, 0.084 mmol, 21% yield.

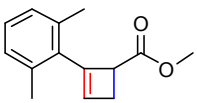
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 - 7.29 (m, 5H), 6.49 (s, 1H), 4.00 (m, 1H), 3.74 (s, 3H), 2.85 - 2.72 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.7, 144.1, 129.2, 128.6, 128.4, 128.3, 124.5, 51.9, 44.6, 30.7. **HRMS** (ESI) calcd for $C_{13}H_{15}O_2$ $(M+H)^+$ 189.0910, found 189.0917.



Methyl 2-(*o*-tolyl)cyclobut-2-ene-1-carboxylate (3xa)

Colorless oil, 45.1 mg, 0.223 mmol, 56% yield (reaction time: 20 min).

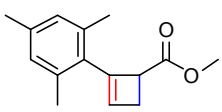
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.23 - 7.16 (m, 4H), 6.36 (s, 1H), 4.07 - 4.03 (m, 1H), 3.70 (s, 3H), 2.81 (dd, J = 4.8, 14.0 Hz, 1H), 2.72 - 2.67 (m, 1H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.0, 144.9, 137.0, 133.4, 132.0, 130.8, 127.7, 126.2, 125.9, 51.9, 46.0, 31.1, 21.9. **HRMS** (ESI) calcd for $C_{13}H_{15}O_2$ $(M+H)^+$ 203.1072, found 203.1062.



Methyl 2-(2,6-dimethylphenyl)cyclobut-2-ene-1-carboxylate (3ya)

Colorless oil, 55.3 mg, 0.256 mmol, 64% yield (reaction time: 20 min).

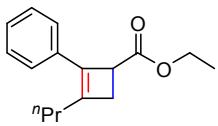
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.09 - 6.96 (m, 3H), 6.20 (s, 1H), 4.14 - 4.09 (m, 1H), 3.59 (s, 3H), 2.88 - 2.76 (m, 2H), 2.35 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.4, 145.6, 136.6, 135.9, 134.0, 127.8, 127.4, 51.7, 49.0, 31.3, 20.9. **HRMS** (ESI) calcd for $C_{14}H_{17}O_2$ $(M+H)^+$ 217.1229, found 217.1238.



Methyl 2-mesitylcyclobut-2-ene-1-carboxylate (3za)

Colorless oil, 59.8 mg, 0.260 mmol, 65% yield (reaction time: 20 min).

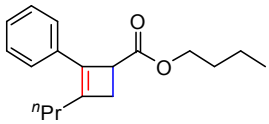
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.83 (s, 2H), 6.18 (s, 1H), 4.11 - 4.01 (m, 1H), 3.60 (s, 3H), 2.84 - 2.76 (m, 2H), 2.32 (s, 6H), 2.26 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.6, 145.7, 137.0, 136.5, 135.7, 131.1, 128.4, 51.7, 49.1, 31.3, 21.0, 20.8. **HRMS** (ESI) calcd for $C_{15}H_{19}O_2$ $(M+H)^+$ 231.1385, found 231.1392.



Ethyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3cb)

Colorless oil, 59.3 mg, 0.246 mmol, 61% yield.

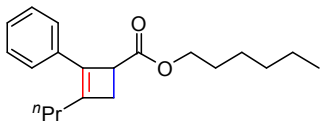
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 - 7.29 (m, 4H), 7.26 - 7.17 (m, 1H), 4.22 - 4.11 (m, 2H), 3.83 - 3.77 (m, 1H), 2.66 (dd, J = 4.4, 14.0 Hz, 1H), 2.62 - 2.58 (m, 1H), 2.50 - 2.39 (m, 2H), 1.62 - 1.55 (m, 2H), 1.22 (t, J = 7.2 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H); **^{13}C NMR**(100 MHz, $CDCl_3$): δ (ppm) 174.1, 145.7, 136.4, 134.7, 128.4, 126.9, 125.8, 60.4, 42.1, 31.8×2, 20.3, 14.3, 14.2. **HRMS** (ESI) calcd for $C_{16}H_{21}O_2$ $(M+H)^+$ 245.1542, found 245.1537.



Butyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3cc)

Colorless oil, 47.7 mg, 0.175 mmol, 44% yield.

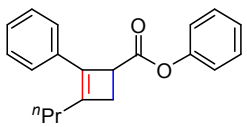
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 - 7.28 (m, 4H), 7.22 - 7.17 (m, 1H), 4.15 - 4.03 (m, 2H), 3.84 - 3.75 (m, 1H), 2.71 - 2.57 (m, 2H), 2.51 - 2.39 (m, 2H), 1.64 - 1.56 (m, 4H), 1.37 - 1.28 (m, 2 H), 0.99 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.2, 145.7, 136.5, 134.6, 128.3, 126.9, 125.8, 61.3, 42.1, 31.8×2, 30.7, 20.3, 19.1, 14.2, 13.7. **HRMS** (ESI) calcd for $C_{18}H_{25}O_2$ $(M+H)^+$ 273.1855, found 273.1860.



Hexyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3cd)

Colorless oil, 42.6 mg, 0.142 mmol, 35% yield.

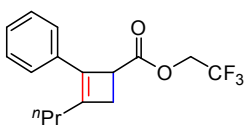
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.33 - 7.16 (m, 5H), 4.09 - 4.01 (m, 2H), 3.82 - 3.81 (m, 1H), 2.68 - 2.54 (m, 2H), 2.49 - 2.37 (m, 2H), 1.62 - 1.56 (m, 2H), 1.29 - 1.27 (m, 6H), 1.02 (t, J = 7.6 Hz, 3H), 0.90 - 0.87 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 145.6, 136.5, 134.6, 128.3, 126.8, 125.8, 64.6, 42.1, 31.8×2, 31.4, 28.6, 25.6, 22.5, 20.2, 14.1, 14.0. **HRMS** (ESI) calcd for $C_{20}H_{29}O_2$ $(M+H)^+$ 301.2168, found 301.2175.



Phenyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3ce)

Colorless oil, 78.3 mg, 0.268 mmol, 67% yield.

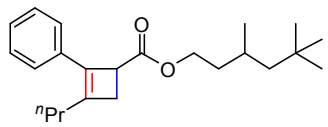
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.44 - 7.41 (m, 2H), 7.38 - 7.30 (m, 4H), 7.26 - 7.16 (m, 2H), 7.04 - 6.98 (m, 2H), 4.05 - 4.01 (m, 1H), 2.79 (m, 2H), 2.54 - 2.41 (m, 2H), 1.68 - 1.57 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 172.7, 150.9, 146.1, 136.4, 134.5, 129.3, 128.5, 127.1, 125.8, 125.7, 121.6, 42.1, 31.8, 31.8, 20.2, 14.2. **HRMS** (ESI) calcd for $C_{20}H_{21}O_2$ $(M+H)^+$ 293.1542, found 293.1542.



2,2,2-Trifluoroethyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3cf)

Colorless oil, 38.1 mg, 0.127 mmol, 32% yield.

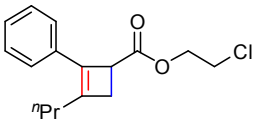
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 - 7.36 (m, 4H), 7.27 - 7.24 (m, 1H), 4.58 - 4.42 (m, 2H), 3.95 - 3.93 (m, 1H), 2.78 - 2.73 (m, 2H), 2.52 - 2.41 (m, 2H), 1.65 - 1.58 (m, 2H), 1.00 (t, J = 3.2, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 172.5, 146.1, 135.9, 134.1, 128.5, 127.1, 125.7, 122.9 (q, $J_{C\text{-}F}$ = 272 Hz), 60.3 (q, $J_{C\text{-}F}$ = 36 Hz), 41.3, 31.7×2, 20.1, 14.1. ^{19}F ($CDCl_3$, 376 M HZ): δ (ppm) -73.6. **HRMS** (ESI) calcd for $C_{16}H_{18}F_3O_2$ $(M+H)^+$ 299.1253, found 299.1262.



3,5,5-Trimethylhexyl 2-phenyl-3-propylcyclobut- 2-ene-1- carboxylate (3cg)

Colorless oil, 38.4 mg, 0.112 mmol, 28% yield.

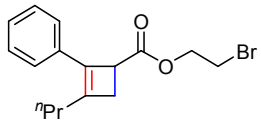
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 - 7.29 (m, 4H), 7.25 - 7.20 (m, 1H), 4.13 - 4.04 (m, 2H), 3.78 (brs, 1H), 2.67 - 2.61 (m, 2H), 2.50 - 2.38 (m, 2H), 1.66 - 0.93 (m, 13H), 0.88 - 0.83 (m, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.2, 145.6, 136.4, 134.6, 128.3, 126.9, 125.8, 63.0, 51.0, 42.1, 37.8, 31.9, 31.0, 29.9, 26.1, 26.0, 22.5, 20.2, 14.2. **HRMS** (ESI) calcd for $C_{23}H_{35}O_2$ $(M+H)^+$ 343.2637, found 343.2625.



2-Chloroethyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3ch)

Colorless oil, 83.5 mg, 0.300 mmol, 75% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 - 7.28 (m, 4H), 7.25 - 7.18 (m, 1H), 4.44 - 4.26 (m, 2H), 3.87 - 3.84 (m, 1H), 3.64 (t, J = 5.6 Hz, 2H), 2.73 - 2.62 (m, 2H), 2.53 - 2.36 (m, 2H), 1.65 - 1.56 (m, 2H), 1.00 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.8, 145.9, 136.2, 134.4, 128.4, 127.0, 125.8, 64.0, 41.8, 41.6, 31.8×2, 20.2, 14.2. **HRMS** (ESI) calcd for $C_{16}H_{20}ClO_2$ $(M+H)^+$ 279.1152, found 279.1151.

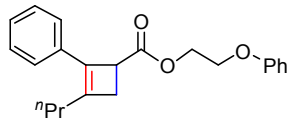


2-Bromoethyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3ci)

Colorless oil, 77.3 mg, 0.239 mmol, 60% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 - 7.35 (m, 4H), 7.25 - 7.22 (m, 1H), 4.49 - 4.36 (m, 2H), 3.89 - 3.87 (m, 1H), 3.49 (t, J = 6.1 Hz, 2H), 2.75 - 2.69 (m, 2H), 2.55 - 2.40 (m, 2H), 1.65 - 1.59 (m, 2H), 1.03 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.6, 145.9, 136.2, 134.4, 128.4, 127.0, 125.8, 63.8, 41.8, 31.9, 31.8, 28.8, 20.2, 14.2.

HRMS (ESI) calcd for $C_{16}H_{20}BrO_2$ $(M+H)^+$ 323.0647, found 323.0655.



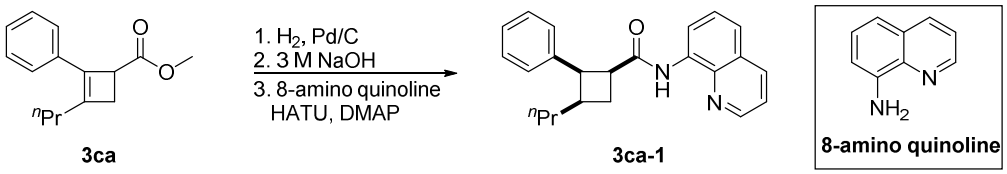
2-Phenoxyethyl 2-phenyl-3-propylcyclobut-2-ene-1-carboxylate (3cj)

Colorless oil, 53.6 mg, 0.160 mmol, 40% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 - 7.21 (m, 6H),7.16 (t, J = 7.3, 1H), 6.96 (t, J =7.3, 1H), 6.77 (d, J = 8.5, 2H), 4.52 - 4.38 (m, 2H), 4.15 - 4.12 (m, 2H), 3.85 - 3.84 (m, 1H), 2.66 - 2.60 (m, 2H), 2.45 - 2.43 (m, 2H), 1.60 - 1.58 (m, 2H), 0.98 - 0.96 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz,

$CDCl_3$): δ (ppm) 174.1, 158.6, 145.8, 136.3, 134.5, 129.5, 128.4, 126.9, 125.8, 121.1, 114.7, 65.9, 62.8, 41.9, 31.8×2, 20.2, 14.1. **HRMS** (ESI) calcd for $C_{22}H_{25}O_3$ $(M+H)^+$ 337.1804, found 337.1805.

(1*S,2*R**,3*R**)-2-phenyl-3-propyl-*N*-(quinolin-8-yl)cyclobutane-1-carboxamide (3ca-1)**

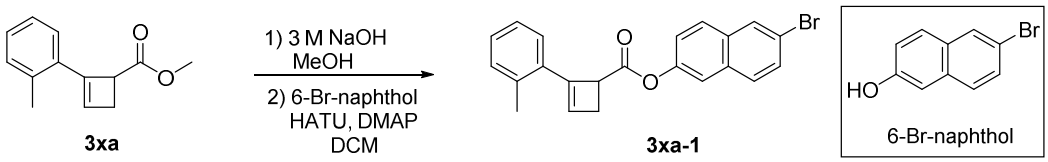


A dry reaction tube was charged with **3ca** (23 mg, 0.1 mmol) and ethyl acetate (1 mL). The solution was degassed thoroughly before careful addition of 10% Pd-C (5 mol%, 5 mg). H_2 gas was bubbled through the solvent for 3 min before the solution was left to stir for 3 h under H_2 atmosphere. The H_2 gas was evacuated and the reaction was filtered to remove the Pd-C catalyst. After concentration under vacumn, the crude product was used directly in subsequent reaction .

A dry reaction tube was charged with above-mentioned crude product and MeOH (2 mL) under N_2. 3 M NaOH (3 equiv, 0.3 mmol, 0.1 mL) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at rt until complete conversion of the starting material as observed from TLC analysis. 3 M HCl was added to acidify the reaction mixture and the resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure after filtration gave the crude product which was used directly in subsequent reaction.

A dry reaction tube was charged with above-mentioned crude product and DCM (2 mL) under N_2. 8-amino quinoline (1.5 equiv, 0.15 mmol, 21.6 mg), HATU (1 equiv, 0.1 mmol, 38 mg) and 4-(dimethylamino)pyridine (DMAP, 0.2 equiv, 0.02 mmol, 2.5 mg) was added at 0 ^oC and the reaction mixture was stirred at rt for 12 h. The crude mixture was subjected to silica gel column chromatograhy (hexane/ethyl acetate = 2:1) to give **3ca-1** (10.7 mg, 0.031 mmol, 31%, 2 steps) as brown solid. The crystal suitable for X-ray single crystal diffraction analysis was obtained from ethyl acetate.

6-Bromonaphthalen-2-yl 2-(*o*-tolyl)cyclobut-2-ene-1-carboxylate (3ua-1)



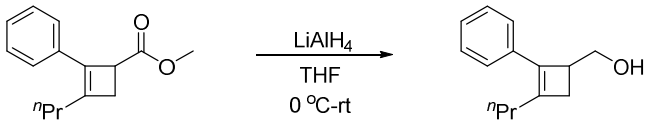
A dry reaction tube was charged with cyclobutene **3xa** (0.2 mmol, 40.4 mg) and MeOH (4 mL) under N_2 atmosphere. Sodium hydroxide solution (3M, 3 equiv, 0.6 mmol, 0.2 mL) was added at 0 ^oC and the reaction mixture was stirred at room temperature until complete conversion of the starting material as observed from

TLC analysis. The hydrogen chloride solution (1 M) was added to acidify the reaction mixture and the resulting mixture was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over sodium sulphate (Na_2SO_4). Concentration under reduced pressure after filtration gave a crude product of carboxylic acid which was used directly in subsequent reaction.

A dry reaction tube was charged with above-mentioned crude product and DCM (2 mL) under N_2. 6-Br-naphthol (1.5 equiv, 0.3 mmol, 66.6 mg), HATU (1 equiv, 0.2 mmol, 76 mg) and 4-(dimethylamino)pyridine (DMAP, 0.2 equiv, 0.04 mmol, 4.9 mg) was added at 0 ^oC and the reaction mixture was stirred at rt for 12 h. The crude mixture was subjected to silica gel column chromatograhy (hexane/ethyl acetate = 5:1) to give **3xa-1** (32.9 mg, 0.084 mmol, 42%, 2 steps) as white solid. The crystal suitable for x-ray single crystal diffraction analysis was obtained from solvent mixture of hexane/$CHCl_3$(10:1).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 - 7.95 (m, 1H), 7.70 (d, *J* = 9.2 Hz, 1H), 7.62 (d, *J* = 8.8 Hz, 1H), 7.52 (dd, *J* = 2.0, 8.8 Hz, 1H), 7.48 - 7.44 (m, 1H), 7.43 - 7.38 (m, 1H), 7.28 - 7.14 (m, 4H), 6.44 (s, 1H), 4.34 - 4.30 (m, 1H), 2.98 - 2.87 (m, 2H), 2.46 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 172.1, 148.7, 144.8, 137.2, 133.7, 132.5, 132.2, 131.9, 130.9, 129.9, 129.8, 129.2, 128.5, 128.0, 126.3, 126.0, 122.3, 119.6, 118.6, 46.2, 31.1, 21.9. **HRMS** (ESI) calcd for $C_{22}H_{25}Br_2O_2$ $(M+H)^+$ 479.0221, found 479.0237. M.p. 134 - 136 ^oC.

(2-Phenyl-3-propylcyclobut-2-en-1-yl)methanol (3ca-a)

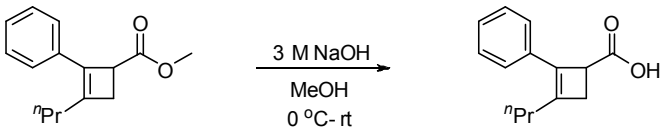


3ca **3ca-a**

A dry reaction tube was charged with **3ca** (23 mg, 0.1 mmol) and THF (1 mL) under N_2 atmosphere. $LiAlH_4$ (1.0 equiv, 0.1 mmol, 3.8 mg) was added to the reaction mixture at 0 ^oC. The reaction mixture was stirred at the same temperature until complete conversion of the starting material as observed from TLC analysis which was then quenched by the slow addition of ethyl acetate. After filtration and concentration of filtrates *in vacuo*, the residue was subjected to silica gel column chromatography (hexane/ethyl acetate = 2:1), affording alcohol **3ca-a** as colorless oil (16.2 mg, 0.080 mmol, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 - 7.27 (m, 4H), 7.24 - 7.19 (m, 1H), 3.93 (dd, *J* = 4.4, 10.8 Hz, 1H), 3.78 (dd, *J* = 6.4, 11.2 Hz, 1H), 3.31 - 3.25 (m, 1H), 2.56 (dd, *J* = 4.6, 13.8 Hz, 1H), 2.47 - 2.33 (m, 2H), 2.24 (dd, *J* = 1.2, 14.0 Hz, 1H), 1.56 (sext, *J* = 7.4 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR:** (100 MHz, $CDCl_3$): δ (ppm) 144.9, 137.6, 135.3, 128.5, 126.6, 126.0, 65.0, 41.0, 31.8, 31.6, 20.5, 14.2. **HRMS** (ESI) calcd for $C_{14}H_{19}O$ $(M+H)^+$ 203.1436, found 203.1440.

2-Phenyl-3-propylcyclobut-2-ene-1-carboxylic acid (3ca-b)

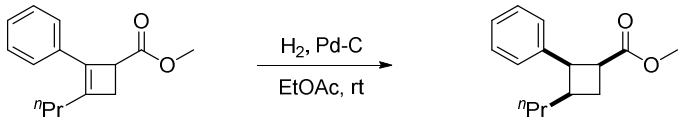


3ca **3ca-b**

A reaction tube was charged with **3ca** (23 mg, 0.1 mmol) and MeOH (1 mL) under N_2 atmosphere. 3 M NaOH (3 equiv, 0.3 mmol, 0.1 mL) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at rt until complete conversion of the starting material as observed from TLC analysis. 3 M HCl was added to acidify the reaction mixture and the resulting solution was extracted with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure after filtration gave the crude product which was subsequently subjected to silica gel column chromatography (hexane/ethyl acetate = 1:2) to yield carboxylic acid **3ca-b** as colorless oil (13.6 mg, 0.063 mmol, 63%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 - 7.29 (m, 4H), 7.24 - 7.18 (m, 1H), 3.83 (brs, 1H), 2.70 (dd, *J* = 3.6, 13.6 Hz, 1H), 2.64 - 2.60 (m, 1H), 2.51 - 2.39 (m, 2H), 1.64 - 1.53 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 179.9, 146.0, 136.0, 134.3, 128.5, 127.1, 125.8, 41.6, 31.9, 31.8, 20.2, 14.2. **HRMS** (ESI) calcd for $C_{14}H_{16}O_2$ $(M+H)^+$ 217.1229, found 217.1221.

Methyl (1*S,2*R**,3*R**)-2-phenyl-3-propylcyclobutane-1-carboxylate (3ca-c)**

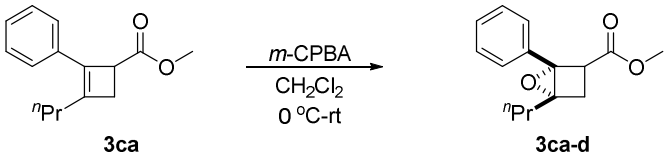


3ca **3ca-c**

A dry reaction tube was charged with **3ca** (23 mg, 0.1 mmol) and ethyl acetate (1 mL). The solution was degassed thoroughly before careful addition of 10% Pd-C (5 mol%, 5 mg). H_2 gas was bubbled through the solvent for 3 min before the solution was left to stir for 3 h under H_2 atmosphere. The H_2 gas was evacuated and the reaction was filtered to remove the Pd-C catalyst. After concentration under vacumn, the crude product was subjected to silica gel column chromatography (hexane/ethyl acetate = 10:1) affording cyclobutane **3ca-c** as colorless oil (17.9 mg, 0.077 mmol, 77%).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.28 - 7.16 (m, 5H), 3.95 - 3.84 (m, 1H), 3.56 (q, *J* = 9.6 Hz, 1H), 3.36 (s, 3H), 2.75 - 2.59 (m, 1H), 2.48 - 2.32 (m, 2H), 1.17 - 0.95 (m, 4H), 0.71 (t, *J* = 7.0 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.8, 139.1, 128.9, 127.9, 126.3, 51.2, 48.5, 39.9, 36.1, 33.2, 29.6, 20.1, 14.0. **HRMS** (ESI) calcd for $C_{15}H_{21}O_2$ $(M+H)^+$ 233.1542, found 233.1545.

Methyl (1*S,4*S**)-1-phenyl-4-propyl-5-oxabicyclo[2.1.0]pentane-2-carboxylate (3ca-d)**

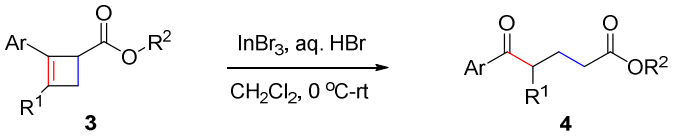


3ca **3ca-d**

A dry reaction tube was charged with cyclobutene **3ca** (23 mg, 0.1 mmol) and CH_2Cl_2 (1 mL) under N_2 atmosphere. 3-Chloroperbenzoic acid (*m*-CPBA, 1.2 equiv, 26.8 mg) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at rt until complete conversion of the starting material as observed from TLC analysis. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ solution followed by extraction with ethyl acetate. The combined organic layers were washed with brine and dried over Na_2SO_4. Concentration under reduced pressure after filtration gave the crude product which was subjected to silica gel column chromatography (hexane/ethyl acetate = 5:1) to give epoxide **3ca-d** as colorless oil (16.2 mg, 0.066 mmol, 66%).

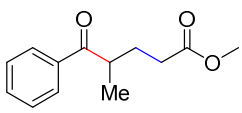
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 - 7.30 (m, 5H), 3.79 - 3.71 (m, 1H), 3.65 (s, 3H), 2.35 (dd, *J* = 9.2, 11.8 Hz, 1H), 2.28 (dd, *J* = 4.0, 11.8 Hz, 1H), 1.84 - 1.65 (m, 2H), 1.56 - 1.42 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 171.4, 133.1, 128.3, 127.8, 126.5, 71.5, 69.4, 51.9, 42.6, 32.3, 29.1, 18.6, 14.1. **HRMS** (ESI) calcd for $C_{15}H_{19}O_3$ $(M+H)^+$ 247.1334, found 247.1329.

2.5.4 General Procedure for Acid-mediated Selective Cleavage of C-C Bond of Cyclobutene and Spectral Data



3 **4**

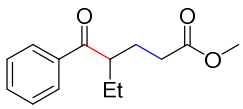
A reaction tube was charged with cyclobutene **3** (0.1 mmol), $InBr_3$ (1 equiv, 0.1 mmol, 35.2 mg) and CH_2Cl_2 (1 mL) under N_2 atmosphere. 48% Hydrobromic acid (1.5 equiv, 0.15 mmol, 25 mg) was added at 0 °C and the reaction mixture was stirred at rt for 36 h. Finally, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 5:1) to afford the desired product **4**.



Methyl 2-acetyl-4-oxo-4-phenylbutanoate (4a-1)

Colorless oil, 17.8 mg, 0.081mmol, 81% yield.

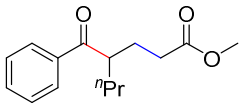
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.00 - 7.95 (m, 2H), 7.60 - 7.54 (m, 1H), 7.51 - 7.44 (m, 2H), 3.65 (s, 3H), 3.61 - 3.53 (m, 1H), 2.45 - 2.27 (m, 2H), 2.22 - 2.12 (m, 1H), 1.83 - 1.73 (m, 1H), 1.21 (d, *J* = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.5, 173.8, 136.4, 133.1, 128.7, 128.4, 51.6, 39.6, 31.5, 28.3, 17.4. **HRMS** (ESI) calcd for $C_{13}H_{17}O_3$ $(M+H)^+$ 221.1177, found 221.1186.



Methyl 4-benzoylhexanoate (4a-2)

Colorless oil, 17.6 mg, 0.075mmol, 75% yield.

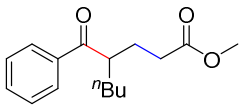
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 - 7.93 (m, 2H), 7.61 - 7.55 (m, 1H), 7.50 - 7.45 (m, 2H), 3.63 (s, 3H), 3.50 - 3.43 (m, 1H), 2.41 - 2.32 (m, 1H), 2.29 - 2.20 (m, 1H), 2.16 - 2.06 (m, 1H), 1.91 - 1.74 (m, 2H), 1.62 - 1.51 (m, 1H), 0.89 (t, J = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.6, 173.8, 137.4, 133.1, 128.7, 128.2, 51.5, 46.4, 31.6, 26.3, 25.4, 11.6. **HRMS** (ESI) calcd for $C_{14}H_{19}O_3$ $(M+H)^+$ 235.1334, found 235.1332.



Methyl 4-benzoylheptanoate (4a-3)

Colorless oil, 17.9 mg, 0.072 mmol, 72% yield.

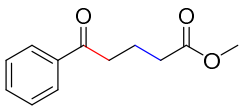
^{1}H NMR (100 MHz, $CDCl_3$): δ (ppm) 8.01 - 7.97 (m, 2H), 7.62 - 7.56 (m, 1H), 7.53 - 7.47 (m, 2H), 3.66 (s, 3H), 3.61 - 3.53 (m, 1H), 2.43 - 2.34 (m, 1H), 2.32 - 2.22 (m, 1H), 2.18 - 2.07 (m, 1H), 1.95 - 1.85 (m, 1H), 1.81 - 1.72 (m, 1H), 1.55 - 1.45 (m, 1H), 1.39 - 1.28 (m, 2H), 0.90 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.7, 173.8, 137.3, 133.1, 128.7, 128.2, 51.5, 44.7, 34.6, 31.6, 26.8, 20.5, 14.2. **HRMS** (ESI) calcd for $C_{15}H_{21}O_3$ $(M+H)^+$ 249.1491, found 249.1495.



Methyl 4-benzoyloctanoate (4a-4)

Colorless oil, 18.3 mg, 0.070mmol, 70% yield.

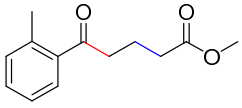
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 - 7.94 (m, 2H), 7.60 - 7.53 (m, 1H), 7.51 - 7.44 (m, 2H), 3.63 (s, 3H), 3.56 - 3.48 (m, 1H), 2.40 - 2.32 (m, 1H), 2.29 - 2.20 (m, 1H), 2.15 - 2.06 (m, 1H), 1.91 - 1.82 (m, 1H), 1.81 - 1.71 (m, 1H), 1.55 - 1.45 (m, 1H), 1.32 - 1.23 (m, 4H), 0.87 - 0.82 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.7, 173.8, 137.3, 133.1, 128.7, 128.3, 51.6, 44.9, 32.2, 31.6, 29.5, 26.8, 22.8, 13.9. **HRMS** (ESI) calcd for $C_{16}H_{23}O_3$ $(M+H)^+$ 263.1647, found 263.1644.



Methyl 5-oxo-5-phenylpentanoate (4a-5)

Colorless oil, 16.9 mg, 0.082mmol, 82% yield.

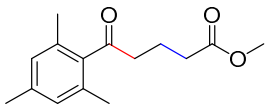
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 (d, J = 7.3 Hz, 2H), 7.58 (t, J = 7.3 Hz, 1H), 7.48 (t, J = 7.3 Hz, 2H), 3.71 (s, 3H), 3.08 (t, J = 7.2 Hz, 2H), 2.47 (t, J = 7.2 Hz, 2H), 2.14 - 2.08 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): 203.5, 173.8, 136.4, 133.1, 128.7, 128.4, 51.6, 37.6, 31.5, 28.3. **HRMS** (ESI) calcd for $C_{12}H_{15}O_3$ $(M+H)^+$ 207.1021, found 207.1027.



Methyl 5-oxo-5-(*o*-tolyl)pentanoate (4a-6)

Colorless oil, 18.1 mg, 0.082 mmol, 82% yield (reaction time: 12 h).

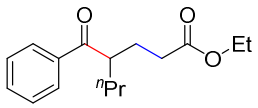
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.65 - 7.61 (m, 1H), 7.40 - 7.33 (m, 1H), 7.28 - 7.21 (m, 2H), 3.68 (s, 3H), 2.97 (t, J = 7.2 Hz, 2H), 2.49 (s, 3H), 2.43 (t, J = 7.2 Hz, 2H), 2.05 (pent, J = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.5, 173.7, 138.1, 137.8, 132.0, 131.3, 128.4, 125.7, 51.6, 40.3, 33.2, 21.3, 19.5. **HRMS** (ESI) calcd for $C_{13}H_{17}O_3$ $(M+H)^+$ 221.1178, found 221.1180.



Methyl 5-mesityl-5-oxopentanoate (4a-7)

Colorless oil, 19.7 mg, 0.080 mmol, 80% yield (reaction time: 12 h).

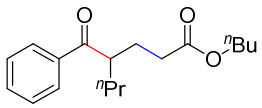
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.83 (s, 2H), 3.68 (s, 3H), 2.76 (t, *J* = 7.2 Hz, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 2.27 (s, 3H), 2.18 (s, 6H), 2.04 (pent, *J* = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 210.0, 173.6, 139.5, 138.4, 132.5, 128.5, 51.6, 43.6, 33.1, 21.1, 19.1, 18.7. **HRMS** (ESI) calcd for $C_{15}H_{21}O_3$ $(M+H)^+$ 249.1491, found 249.1499.



Ethyl 4-benzoylheptanoate (4b-1)

Colorless oil, 17.6 mg, 0.067 mmol, 67% yield.

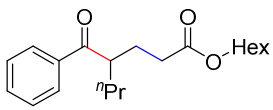
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 - 7.94 (m, 2H), 7.59 - 7.53 (m, 1H), 7.50 - 7.43 (m, 2H), 4.09 (q, *J* = 7.2 Hz, 2H), 3.59 - 3.50 (m, 1H), 2.39 - 2.30 (m, 1H), 2.28 - 2.19 (m, 1H), 2.15 - 2.05 (m, 1H), 1.91 - 1.82 (m, 1H), 1.80 - 1.69 (m, 1H), 1.53 - 1.42 (m, 1H), 1.30 (m, 2H), 1.21 (t, *J* = 7.2, 3H), 0.88 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.8, 173.3, 137.4, 133.1, 128.7, 128.3, 60.4, 44.8, 34.7, 31.9, 26.9, 20.6, 14.2×2. **HRMS** (ESI) calcd for $C_{16}H_{23}O_3$ $(M+H)^+$ 263.1647, found 263.1642.



Butyl 4-benzoylheptanoate (4b-2)

Colorless oil, 18.6 mg, 0.064 mmol, 64% yield.

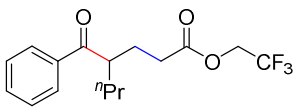
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.98 - 7.93 (m, 2H), 7.59 - 7.54 (m, 1H), 7.50 - 7.43 (m, 2H), 4.04 (t, *J* = 6.8 Hz, 2H), 3.60 - 3.50 (m, 1H), 2.40 - 2.31 (m, 1H), 2.27 - 2.18 (m, 1H), 2.14 - 2.04 (m, 1H), 1.91 - 1.81 (m, 1H), 1.78 - 1.70 (m, 1H), 1.58 - 1.44 (m, 3H), 1.37 - 1.24 (m, 4H), 0.93 - 0.85 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.9, 173.4, 137.4, 133.1, 128.7, 128.3, 64.3, 44.8, 34.7, 31.9, 30.7, 26.9, 20.6, 19.1, 14.2, 13.7. **HRMS** (ESI) calcd for $C_{18}H_{27}O_3$ $(M+H)^+$ 291.1960, found 291.1962.



Hexyl 4-benzoylheptanoate (4b-3)

Colorless oil, 20.7 mg, 0.065 mmol, 65% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 - 7.97 (m, 2H), 7.61 - 7.57 (m, 1H), 7.51 - 7.48 (m, 2H), 4.08 - 4.04 (m, 2H), 3.59 - 3.55 (m, 1H), 2.40 - 2.33 (m, 1H), 2.29 - 2.22 (m, 1H), 2.17 - 2.09 (m, 1H), 1.93 - 1.86 (m, 1H), 1.79 - 1.72 (m, 1H), 1.62 - 1.46 (m, 4H), 1.39 - 1.28 (m, 7H), 0.94 - 0.88 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 203.8, 173.4, 137.4, 133.0, 128.7, 128.2, 64.6 (64.3), 44.7, 34.7, 31.9, 31.4, 30.7, 28.6, 26.9, 25.6, 22.5, 20.6, 19.1, 14.2, 14.0, 13.9, 13.7. HRMS (ESI) calcd for $C_{20}H_{31}O_3$ $(M+H)^+$ 319.2273, found 319.2278.



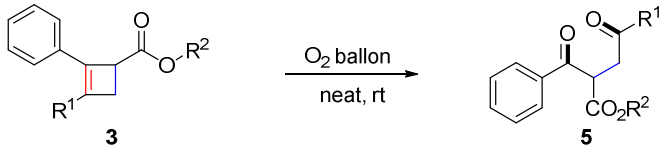
2,2,2-trifluoroethyl 4-benzoylheptanoate (4b-4)

Colorless oil, 18.6 mg, 0.067 mmol, 67% yield

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 (d, *J* = 8.0 Hz, 2H), 7.60 (t, *J* = 7.3 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 4.46 (q, *J* = 8.5 Hz, 2H), 3.60 - 3.53 (m, 1H), 2.54 - 2.46 (m, 1H), 2.41 - 2.33 (m, 1H), 2.22 - 2.13 (m, 1H), 1.97 - 1.88 (m, 1H), 1.55 - 1.46 (m, 2H), 1.39 - 1.28 (m, 2H), 0.90 (t, *J* = 7.2 Hz,

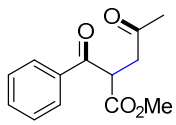
3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 203.8, 171.6, 136.2, 134.3, 128.0, 127.9, 123.7 (q, $J_{C\text{-}F}$ = 279 Hz), 60.1 (q, $J_{C\text{-}F}$ = 62 Hz), 44.7, 34.5, 31.3, 26.2, 20.6, 13.8. **HRMS** (ESI) calcd for $C_{16}H_{20}O_3F_3$ $(M+H)^+$ 317.1365, found 317.1363.

2.5.5 General Procedure for O_2-mediated Selective Cleavage of C=C Bond of Cyclobutene and Spectral Data



3 **5**

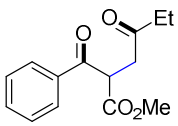
A dry reaction tube was charged with cyclobutene **3** (0.1 mmol) and the air was replaced by O_2. The mixture was stirred at rt for 72 h under O_2 atmosphere and the resulting residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate = 5:1) to afford the desired product **5**.



Methyl 2-benzoyl-4-oxopentanoate (5a-1)

Colorless oil, 14.3 mg, 0.061 mmol, 61% yield.

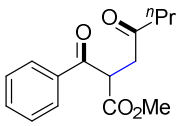
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 - 8.01 (m, 2H), 7.62 - 7.57 (m, 1H), 7.51 - 7.46 (m, 2H), 4.95 - 4.91 (m, 1H), 3.67 (s, 3H), 3.23 (dd, J = 7.6, 18.4 Hz, 1H), 3.16 (dd, J = 6.4, 18.4 Hz, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 205.3, 194.5, 169.7, 135.9, 133.7, 128.9, 128.8, 52.8, 48.5, 42.4, 29.8. **HRMS** (ESI) calcd for $C_{13}H_{15}O_4$ $(M+H)^+$ 235.0970, found 235.0973.



Methyl 2-benzoyl-4-oxohexanoate (5a-2)

Colorless oil, 14.1 mg, 0.057 mmol, 57% yield.

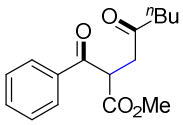
^{1}H NMR(400 MHz, $CDCl_3$): δ (ppm) 8.05 - 8.01 (m, 2H), 7.62 - 7.57 (m, 1H), 7.52 - 7.45 (m, 2H), 4.98 - 4.93 (m, 1H), 3.67 (s, 3H), 3.21 (dd, J = 7.6, 18.0 Hz, 1H), 3.13 (dd, J = 6.4, 18.0 Hz, 1H), 2.53 (q, J = 7.3 Hz, 2H), 1.07 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 208.2, 194.7, 169.8, 135.9, 133.7, 128.9, 128.8, 52.8, 48.4, 41.2, 35.8, 7.7. **HRMS** (ESI) calcd for $C_{14}H_{17}O_4$ $(M+H)^+$ 249.1127, found 249.1122.



Methyl 2-benzoyl-4-oxoheptanoate (5a-3)

Colorless oil, 14.1 mg, 0.054 mmol, 54% yield.

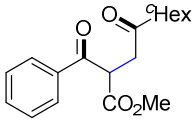
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 - 8.00 (m , 2H), 7.62 - 7.57 (m, 1H), 7.52 - 7.49 (m, 2H), 4.97 - 4.93 (m, 1H), 3.67 (s, 3H), 3.20 (dd, J = 7.4, 18.2 Hz, 1H), 3.12 (dd, J = 6.4, 18.0 Hz, 1H), 2.47 (t, J = 7.4 Hz, 2H), 1.67 - 1.57 (m, 2H), 0.91 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.8, 194.7, 169.8, 135.9, 133.7, 128.9, 128.8, 52.7, 48.4, 44.5, 41.6, 17.2, 13.7. **HRMS (ESI)** calcd for $C_{15}H_{19}O_4$ $(M+H)^+$ 263.1283, found 263.1278.



Methyl 2-benzoyl-4-oxooctanoate (5a-4)

Colorless oil, 14.6 mg, 0.053 mmol, 53% yield.

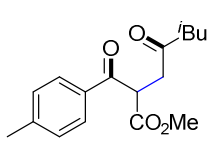
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.03 - 8.00 (m, 2H), 7.61 - 7.56 (m, 1H), 7.49 - 7.45 (m, 2H), 4.96 - 4.92 (m, 1H), 3.66 (s, 3H), 3.20 (dd, *J* = 7.4, 18.2 Hz, 1H), 3.12 (dd, *J* = 6.4, 18.0 Hz, 1H), 2.48 (t, *J* = 7.3 Hz, 2H), 1.61 - 1.52 (m, 2H), 1.36 - 1.24 (m, 2H), 0.89 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.9, 194.7, 169.8, 135.9, 133.6, 128.9, 128.7, 52.7, 48.4, 42.4, 41.5, 25.8, 22.2, 13.8. **HRMS** (ESI) calcd for $C_{16}H_{21}O_4$ $(M+H)^+$ 277.1440, found 277.1439.



Methyl 2-benzoyl-4-oxodecanoate (5a-5)

Colorless oil, 6.9 mg, 0.023 mmol, 23% yield.

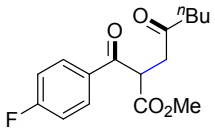
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.08 - 8.03 (m, 2H), 7.66-7.60 (m, 1H), 7.54 - 7.48 (m, 2H), 4.99 - 4.94 (m, 1H), 3.65 (s, 3H), 3.39 - 3.15 (m, 2H), 2.47 - 2.44 (m, 1H), 1.97 - 1.63 (m, 6H), 1.49 - 1.13 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 210.8, 194.8, 169.9, 136.0, 133.6, 128.9, 128.7, 52.7, 50.6, 48.3, 39.8, 28.4, 28.3, 25.8, 25.6×2. **HRMS** (ESI) calcd for $C_{18}H_{23}O_4$ $(M+H)^+$ 303.1596, found 303.1591.



Methyl 6-methyl-2-(4-methylbenzoyl)-4-oxoheptanoate (5a-6)

Colorless oil, 9.6 mg, 0.033 mmol, 33% yield.

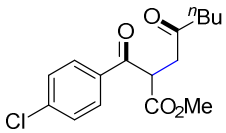
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, *J* = 8.0 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 4.94 (t, *J* = 7.0 Hz, 1H), 3.69 (s, 3H), 3.17 - 3.14 (m, 2H), 2.44 (s, 3H), 2.38 (d, *J* = 7.0 Hz, 2H), 2.21 - 2.14 (m, 1H), 0.93 (d, *J* = 6.6, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.5, 194.2, 169.9, 144.6, 133.4, 129.5, 129.0, 52.7, 48.3, 42.4, 41.5, 25.8, 22.3, 21.7, 13.8. **HRMS** (ESI) calcd for $C_{17}H_{23}O_4$ $(M+H)^+$ 291.1591, found 291.1595.



Methyl 2-(4-fluorobenzoyl)-4-oxooctanoate (5a-7)

Colorless oil, 13.5 mg, 0.046 mmol, 46% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.11 - 8.07 (m, 2H), 7.20 - 7.16 (m, 2H), 4.91 (t, *J* = 6.9 Hz, 1H), 3.69 (s, 3H), 3.30 - 3.11 (m, 2H), 2.51 (t, *J* = 7.4 Hz, 2H), 1.63 - 1.55 (m, 2H), 1.36 - 1.30 (m, 2H), 0.92 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 208.0, 193.1, 169.6, 167.0 (d, $J_{C\text{-}F}$ = 247.1 Hz), 132.5 (d, $J_{C\text{-}F}$ = 10 Hz), 131.7 (d, $J_{C\text{-}F}$ = 10 Hz), 115.9 (d, $J_{C\text{-}F}$ = 80 Hz), 52.8, 48.3, 42.4, 41.6, 25.8, 22.3, 13.8. **HRMS** (ESI) calcd for $C_{16}H_{20}O_4F$ $(M+H)^+$ 295.1346, found 295.1345.

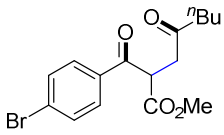


Methyl 2-(4-chlorobenzoyl)-4-oxooctanoate (5a-8)

Colorless oil, 7.1 mg, 0.023 mmol, 23% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.99 (d, *J* = 8.6 Hz, 2H), 7.65 (d, *J*= 8.6 Hz, 2H), 4.91 - 4.88 (m, 1H), 3.69 (s, 3H), 3.30 - 3.11 (m, 2H), 2.53 - 2.49 (m, 2H), 1.62 - 1.55 (m, 2H), 1.38 - 1.28 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.9, 193.5, 169.4, 140.2, 134.4, 130.3,

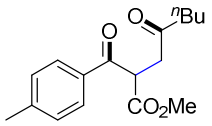
129.1, 52.8, 48.3, 42.3, 41.6, 25.8, 22.3, 13.8. **HRMS** (ESI) calcd for $C_{16}H_{20}O_4Cl$ $(M+H)^+$ 311.1050, found 311.1057.



Methyl 2-(4-bromobenzoyl)-4-oxooctanoate (5a-9)

Colorless oil, 7.4 mg, 0.021 mmol, 21% yield.

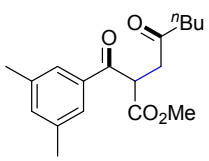
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.91 (d, J = 8.4 Hz, 2H), 7.65 (d, J = 8.4 Hz, 2H), 4.90 - 4.87 (m, 1H), 3.69 (s, 3H), 3.30 - 3.11 (m, 2H), 2.51 (t, J = 7.4Hz, 2H), 1.70 - 1.28 (m, 4H), 0.92 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.9, 193.7, 169.4, 134.8, 132.1, 130.4, 129.0, 52.8, 48.3, 42.3, 41.6, 29.7, 25.8, 22.3, 13.8. **HRMS** (ESI) calcd for $C_{16}H_{20}O_4Br$ $(M+H)^+$ 355.0545, found 355.0541.



Methyl 2-(4-methylbenzoyl)-4-oxooctanoate (5a-11)

Colorless oil, 15.3 mg, 0.050 mmol, 50% yield.

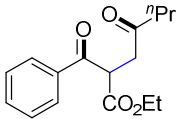
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.94 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 8.2 Hz, 2H), 4.94 (t, J = 6.9 Hz, 1H), 3.69 (s, 3H), 3.18 - 3.15 (m, 2H), 2.53 - 2.49 (m, 2H), 2.44 (s, 3H), 1.63 - 1.56 (m, 2H), 1.36 - 1.30 (m, 2H), 0.92 (t, J = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 208.0, 194.2, 169.9, 144.7, 133.4, 129.5, 129.0, 52.7, 48.3, 42.4, 41.5, 25.8, 22.3, 21.7, 13.8. **HRMS** (ESI) calcd for $C_{17}H_{23}O_2$ $(M+H)^+$ 291.1591, found 291.1598.



Methyl 2-(3,5-dimethylbenzoyl)-4-oxooctanoate (5a-12)

Colorless oil, 15.2 mg, 0.050 mmol, 50% yield.

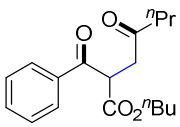
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (s, 2H), 7.25 (s, 1H), 4.95 (t, J = 6.9 Hz, 1H), 3.69 (s, 3H), 3.17 - 3.14 (m, 2H), 2.51 (t, J = 7.4 Hz, 2H), 2.40 (s, 6H), 1.63 - 1.55 (m, 2H), 1.37 -1.26 (m, 2H), 0.92 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 208.0, 195.1, 170.0, 138.4, 135.4, 126.6, 52.7, 48.4, 42.4, 41.6, 25.8, 22.3, 21.3, 13.8. **HRMS** (ESI) calcd for $C_{18}H_{25}O_4$ $(M+H)^+$ 305.1753, found 305.1748.



Ethyl 2-benzoyl-4-oxoheptanoate (5b-1)

Colorless oil, 16.0 mg, 0.058 mmol, 58% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 - 8.01 (m, 2H), 7.61 - 7.56 (m, 1H), 7.50 - 7.45 (m, 2H), 4.94 - 4.90 (m, 1H), 4.12 (q, J = 7.2 Hz, 2H), 3.19 (dd, J = 7.6, 18.0 Hz, 1H), 3.10 (dd, J = 6.4, 18.0 Hz, 1H), 2.48 (t, J = 7.4 Hz, 2H), 1.68 - 1.56 (m, 2 H), 1.15 (t, J = 7.2 Hz, 3H), 0.92 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.8, 194.8, 169.3, 136.1, 133.6, 128.9, 128.7, 61.7, 48.8, 44.6, 41.5, 17.3, 13.9, 13.7. **HRMS** (ESI) calcd for $C_{16}H_{21}O_4$ $(M+H)^+$ 277.1440, found 277.1436.

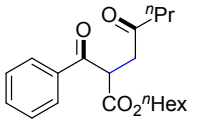


Butyl 2-benzoyl-4-oxoheptanoate (5b-2)

Colorless oil, 19.4 mg, 0.064 mmol, 64% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.04 - 8.01 (m, 2H), 7.61 - 7.55 (m, 1H), 7.51 - 7.44

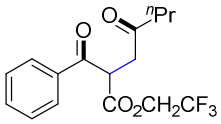
(m, 2H), 4.93 (dd, *J* = 6.0, 7.6 Hz, 1H), 4.06 (t, *J* = 6.4 Hz, 2H), 3.21 (dd, *J* = 7.6, 18.2 Hz, 1H), 3.10 (dd, *J* = 6.4, 18.2 Hz, 1H), 2.48 (t, *J* = 7.4 Hz, 2H), 1.68 - 1.56 (m, 2H), 1.53 - 1.44 (m, 2H), 1.19 (sext, *J* = 7.4 Hz, 2H), 0.92 (t, *J* = 7.4 Hz, 3H), 0.81 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.9, 194.8, 169.4, 136.2, 133.6, 128.9, 128.7, 65.6, 48.8, 44.6, 41.4, 30.4, 18.9, 17.3, 13.7, 13.6. **HRMS** (ESI) calcd for $C_{18}H_{25}O_4$ $(M+H)^+$ 305.1753, found 305.1755.



Butyl 2-benzoyl-4-oxoheptanoate (5b-3)

Colorless oil, 21.7 mg, 0.066 mmol, 66% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.06 - 8.04 (m, 2H), 7.63 - 7.60 (m, 1H), 7.52 - 7.49 (m, 2H), 4.98 - 4.94 (m, 1H), 4.08 (t, *J* = 7.6 Hz, 2H), 3.28 - 3.10 (m, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 1.68 - 1.62 (m, 2H), 1.55 - 1.50 (m, 2H), 1.31 - 1.18 (m, 6H), 0.94 (t, *J* = 7.4 Hz, 3H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 207.9, 194.8, 169.4, 136.2, 133.6, 128.9, 128.7, 65.6, 48.8, 44.6, 41.4, 31.2, 28.3, 25.3, 22.4, 17.2, 13.9, 13.7. HRMS (ESI) calcd for $C_{20}H_{29}O_4$ $(M+H)^+$ 333.2066, found 333.2073.



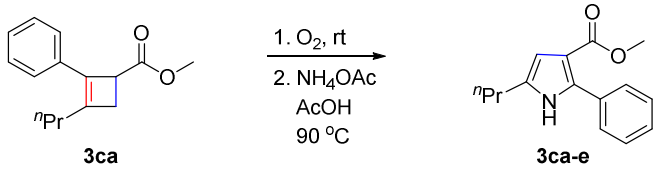
2,2,2-trifluoroethyl 2-benzoyl-4-oxoheptanoate (5b-4)

Colorless oil, 9.1 mg, 0.028 mmol, 28% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.17 (d, *J* = 7.5 Hz, 2H), 7.64 (t, *J* = 7.5 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 2H), 5.05 (t, *J* = 6.9 Hz, 1H), 5.51 - 5.45 (m, 2H), 3.19 (d, *J* = 6.9, 2H), 2.50 (t, *J* = 7.3 Hz, 2H), 1.68 - 1.62 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 207.2, 193.7, 167.9, 135.4, 134.0, 128.8, 124.0 (q, $J_{C\text{-}F}$ = 285 Hz), 61.0 (q, $J_{C\text{-}F}$ = 51 Hz), 48.2, 44.5, 41.2, 17.2, 13.6, 10.5. **HRMS** (ESI) calcd for $C_{16}H_{18}F_3O_4$ $(M+H)^+$ 331.1157, found 331.1167.

2.5.6 One-pot Synthesis of Pyrrole and Furan Derivatives from 3ca and Spectral Data

Methyl 2-phenyl-5-propyl-1H-pyrrole-3-carboxylate (3ca-e)



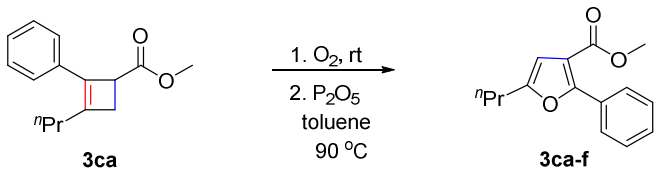
3ca **3ca-e**

A dry reaction tube was charged with **3ca** (0.1 mmol, 23.2 mg) and the air was replaced by O_2. The mixture was stirred at room for 72 h under O_2 atmosphere and then concentrated under reduced pressure to give the crude product. A dry reaction tube was charged with above reaction crude product, ammonium acetate (NH_4OAc, 0.5 mmol, 38.5 mg) and acetic acid (0.3 mL). The mixture was stirred at 90 °C for 24 h under N_2 atmosphere and the resulting residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 5:1) to afford the desired product **3ca-e** (10.9 mg, 0.045 mmol, 45%, 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.13 (brs, 1H), 7.62 - 7.60 (m, 2H), 7.44 - 7.34 (m, 3H), 6.44 (s, 1H),

3.76 (s, 3H), 2.62 - 2.58 (m, 2H), 1.73 - 1.68 (m, 2H), 1.04 - 1.00 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 165.5, 135.9, 132.7, 132.3, 128.8, 128.2, 128.0, 111.7, 108.8, 50.9, 29.4, 22.5, 13.8. **HRMS** (ESI) calcd for $C_{15}H_{18}NO_2$ $(M+H)^+$ 244.1338, found 244.1340.

Methyl 2-phenyl-5-propylfuran-3-carboxylate (3ca-f)



3ca **3ca-f**

A dry reaction tube was charged with cyclobutene **3ca** (23 mg, 0.1 mmol) and the air was replaced by O_2. The mixture was stirred at room for 72 h under O_2 atmosphere and then concentrated under reduced pressure to give the crude product. A dry reaction tube was charged with above reaction crude product, phosphorus pentoxide (P_2O_5, 0.3 mmol, 42.6 mg) and toluene (0.5 mL). The mixture was stirred at 100 ^oC for 24 h under N_2 atmosphere and the resulting residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 5:1) to afford the desired product **3ca-f** (12.2 mg, 0.050 mmol, 50%, 2 steps).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.97 - 7.95 (m, 2H), 7.44 - 7.37 (m, 3H), 6.44 (s, 1H), 3.81 (s, 3H), 2.66 - 2.63 (m, 2H), 1.77 - 1.68 (m, 2H), 1.02 - 0.99 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 164.3, 156.0, 155.4, 130.1, 129.0, 128.1×2, 113.9, 108.1, 51.5, 29.8, 21.1, 13.7. **HRMS (ESI)** calcd for $C_{15}H_{17}O_3(M+H)^+$ 246.1256, found 246.1258.

2.6. Crystal Structure Data

Table 2-12. Sample and crystal data for **3ca-1**

Identification code	**3ca-1**	
Chemical formula	$C_{23}H_{24}N_2O$	
Formula weight	344.44	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.120 x 0.240 x 0.280 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 14.2605(15) Å	α = 90°

	b = 9.0405(10) Å	β = 101.109(4)°
	c = 14.5936(16) Å	γ = 90°
Volume	1846.2(3) $Å^3$	
Z	4	
Density (calculated)	1.239 g/cm^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	736	

Table 2-13. Data collection and structure refinement for **3ca-1**

Theta range for data collection	1.46 to 26.48°	
Index ranges	-17<=h<=17, -9<=k<=11, -18<=l<=17	
Reflections collected	14983	
Independent reflections	3804 [R(int) = 0.0710]	
Coverage of independent reflections	99.6%	
Absorption correction	multi-scan	
Max. and min. transmission	0.9910 and 0.9790	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2013 (Sheldrick, 2013)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	3804 / 0 / 236	
Goodness-of-fit on F^2	1.059	
Final R indices	2423 data; $I>2\sigma(I)$	R1 = 0.0555, wR2 = 0.1370
	all data	R1 = 0.1012, wR2 = 0.1713
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0824P)^2]$ where $P=(F_o^2+2F_c^2)/3$	
Largest diff. peak and hole	0.700 and -0.280 $eÅ^{-3}$	
R.M.S. deviation from mean	0.084 $eÅ^{-3}$	

Table 2-14. Bond lengths (Å) for **3ca-1**

C1-C2	1.543(4)	C1-H1A	0.98
C1-H1B	0.98	C1-H1C	0.98
C2-C3	1.492(4)	C2-H2A	0.99
C2-H2B	0.99	C3-C4	1.521(3)
C3-H3A	0.99	C3-H3B	0.99
C4-C5	1.536(4)	C4-C7	1.584(3)
C4-H4	1.0	C5-C6	1.537(3)
C5-H5A	0.99	C5-H5B	0.99
C6-C14	1.506(3)	C6-C7	1.569(3)
C6-H6	1.0	C7-C8	1.509(3)
C7-H7	1.0	C8-C13	1.393(3)
C8-C9	1.397(3)	C9-C10	1.385(3)
C9-H9	0.95	C10-C11	1.384(4)
C10-H10	0.95	C11-C12	1.382(4)
C11-H11	0.95	C12-C13	1.388(3)
C12-H12	0.95	C13-H13	0.95
C14-O1	1.222(3)	C14-N1	1.372(3)
C15-C16	1.373(3)	C15-N1	1.403(3)
C15-C20	1.424(3)	C16-C17	1.414(4)
C16-H16	0.95	C17-C18	1.362(4)
C17-H17	0.95	C18-C19	1.409(3)
C18-H18	0.95	C19-C23	1.413(3)
C19-C20	1.417(3)	C20-N2	1.367(3)
C21-N2	1.320(3)	C21-C22	1.405(3)
C21-H21	0.95	C22-C23	1.364(4)
C22-H22	0.95	C23-H23	0.95
N1-H1	0.88		

Table 2-15. Bond angles (°) for **3ca-1**

C2-C1-H1A	109.5	C2-C1-H1B	109.5
H1A-C1-H1B	109.5	C2-C1-H1C	109.5
H1A-C1-H1C	109.5	H1B-C1-H1C	109.5
C3-C2-C1	115.0(2)	C3-C2-H2A	108.5
C1-C2-H2A	108.5	C3-C2-H2B	108.5
C1-C2-H2B	108.5	H2A-C2-H2B	107.5
C2-C3-C4	114.6(2)	C2-C3-H3A	108.6
C4-C3-H3A	108.6	C2-C3-H3B	108.6
C4-C3-H3B	108.6	H3A-C3-H3B	107.6
C3-C4-C5	118.4(2)	C3-C4-C7	120.4(2)
C5-C4-C7	89.25(18)	C3-C4-H4	109.1
C5-C4-H4	109.1	C7-C4-H4	109.1
C4-C5-C6	88.51(19)	C4-C5-H5A	113.9
C6-C5-H5A	113.9	C4-C5-H5B	113.9
C6-C5-H5B	113.9	H5A-C5-H5B	111.1
C14-C6-C5	118.2(2)	C14-C6-C7	123.02(19)
C5-C6-C7	89.76(18)	C14-C6-H6	108.1
C5-C6-H6	108.1	C7-C6-H6	108.1
C8-C7-C6	118.5(2)	C8-C7-C4	116.23(19)
C6-C7-C4	85.71(17)	C8-C7-H7	111.4
C6-C7-H7	111.4	C4-C7-H7	111.4
C13-C8-C9	117.6(2)	C13-C8-C7	123.9(2)
C9-C8-C7	118.4(2)	C10-C9-C8	121.6(2)
C10-C9-H9	119.2	C8-C9-H9	119.2
C11-C10-C9	119.9(2)	C11-C10-H10	120.0
C9-C10-H10	120.0	C12-C11-C10	119.2(2)
C12-C11-H11	120.4	C10-C11-H11	120.4
C11-C12-C13	120.9(2)	C11-C12-H12	119.5
C13-C12-H12	119.5	C12-C13-C8	120.7(2)

C12-C13-H13	119.7	C8-C13-H13	119.7
O1-C14-N1	123.1(2)	O1-C14-C6	123.3(2)
N1-C14-C6	113.6(2)	C16-C15-N1	124.8(2)
C16-C15-C20	119.6(2)	N1-C15-C20	115.6(2)
C15-C16-C17	120.0(2)	C15-C16-H16	120.0
C17-C16-H16	120.0	C18-C17-C16	121.5(2)
C18-C17-H17	119.3	C16-C17-H17	119.3
C17-C18-C19	119.9(2)	C17-C18-H18	120.0
C19-C18-H18	120.0	C18-C19-C23	123.4(2)
C18-C19-C20	119.4(2)	C23-C19-C20	117.2(2)
N2-C20-C19	122.8(2)	N2-C20-C15	117.6(2)
C19-C20-C15	119.6(2)	N2-C21-C22	124.0(2)
N2-C21-H21	118.0	C22-C21-H21	118.0
C23-C22-C21	119.0(2)	C23-C22-H22	120.5
C21-C22-H22	120.5	C22-C23-C19	119.6(2)
C22-C23-H23	120.2	C19-C23-H23	120.2
C14-N1-C15	128.6(2)	C14-N1-H1	115.7
C15-N1-H1	115.7	C21-N2-C20	117.4(2)

Table 2-16. Sample and crystal data for **3xa-1**

Identification code	**3xa-1**	
Chemical formula	$C_{44}H_{34}Br_2O_4$	
Formula weight	786.53	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal size	0.060 x 0.180 x 0.400 mm	
Crystal habit	light yellow plate	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 6.6440(10) Å	α = 88.957(4)°
	b = 11.864(2) Å	β = 76.194(4)°

	c = 11.9743(17) Å γ = 76.156(4)°
Volume	889.2(2) $Å^3$
Z	1
Density (calculated)	1.469 g/cm^3
Absorption coefficient	2.323 mm^{-1}
F(000)	400

Table 2-17. Data collection and structure refinement for **3xa-1**

Theta range for data collection	1.75 to 28.31°
Index ranges	-8<=h<=8, -15<=k<=15, -15<=l<=15
Reflections collected	13690
Independent reflections	4391 [R(int) = 0.0684]
Coverage of independent reflections	99.3%
Absorption correction	multi-scan
Max. and min. transmission	0.8732 and 0.4568
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-97 (Sheldrick, 2008)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	4391 / 0 / 227
Goodness-of-fit on F^2	1.041
Final R indices	2228 data; I>2σ(I) R1 = 0.0692, wR2 = 0.1773
	all data R1 = 0.1512, wR2 = 0.2218
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.1092P)^2+0.1293P]$ where $P=(F_o^2+2F_c^2)/3$
Largest diff. peak and hole	1.119 and -0.677 $eÅ^{-3}$
R.M.S. deviation from mean	0.100 $eÅ^{-3}$

Table 2-18. Bond lengths (Å) for **3xa-1**

Br1-C1	1.898(6)	C1-C10	1.312(9)
C1-C2	1.444(9)	C2-C3	1.362(9)
C2-H2	0.95	C3-C4	1.367(9)
C3-H3	0.95	C4-C9	1.380(9)
C4-C5	1.492(9)	C5-C6	1.316(9)
C5-H5	0.95	C6-O1	1.410(6)
C6-C7	1.424(9)	C7-C8	1.385(9)
C7-H7	0.95	C8-C9	1.339(9)
C8-H8	0.95	C9-C10	1.520(9)
C10-H10	0.95	C11-O2	1.193(6)
C11-O1	1.348(6)	C11-C12	1.492(7)
C12-C15	1.527(8)	C12-C13	1.559(9)
C12-H12	1.0	C13-C14	1.507(10)
C13-H13A	0.99	C13-H13B	0.99
C14-C15	1.351(8)	C14-H14	0.95
C15-C16	1.466(8)	C16-C21	1.380(8)
C16-C17	1.407(8)	C17-C18	1.376(9)
C17-H17	0.95	C18-C19	1.351(11)
C18-H18	0.95	C19-C20	1.358(12)
C19-H19	0.95	C20-C21	1.425(10)
C20-H20	0.95	C21-C22	1.479(10)
C22-H22A	0.98	C22-H22B	0.98
C22-H22C	0.98		

Table 2-19. Bond angles (°) for **3xa-1**

C10-C1-C2	123.4(6)	C10-C1-Br1	121.3(6)
C2-C1-Br1	115.3(5)	C3-C2-C1	120.2(7)
C3-C2-H2	119.9	C1-C2-H2	119.9
C2-C3-C4	117.9(7)	C2-C3-H3	121.1
C4-C3-H3	121.1	C3-C4-C9	125.1(6)

C3-C4-C5	117.6(6)	C9-C4-C5	117.2(6)
C6-C5-C4	117.7(7)	C6-C5-H5	121.1
C4-C5-H5	121.1	C5-C6-O1	119.6(6)
C5-C6-C7	121.3(6)	O1-C6-C7	118.9(6)
C8-C7-C6	122.3(7)	C8-C7-H7	118.9
C6-C7-H7	118.9	C9-C8-C7	116.1(7)
C9-C8-H8	121.9	C7-C8-H8	121.9
C8-C9-C4	125.4(7)	C8-C9-C10	118.2(6)
C4-C9-C10	116.3(6)	C1-C10-C9	117.0(6)
C1-C10-H10	121.5	C9-C10-H10	121.5
O2-C11-O1	123.2(5)	O2-C11-C12	126.1(5)
O1-C11-C12	110.7(5)	C11-C12-C15	115.7(4)
C11-C12-C13	116.2(5)	C15-C12-C13	86.4(5)
C11-C12-H12	112.1	C15-C12-H12	112.1
C13-C12-H12	112.1	C14-C13-C12	85.8(5)
C14-C13-H13A	114.4	C12-C13-H13A	114.4
C14-C13-H13B	114.4	C12-C13-H13B	114.4
H13A-C13-H13B	111.5	C15-C14-C13	95.1(5)
C15-C14-H14	132.4	C13-C14-H14	132.4
C14-C15-C16	139.2(5)	C14-C15-C12	92.7(5)
C16-C15-C12	128.1(5)	C21-C16-C17	119.2(6)
C21-C16-C15	124.6(6)	C17-C16-C15	116.2(5)
C18-C17-C16	121.2(7)	C18-C17-H17	119.4
C16-C17-H17	119.4	C19-C18-C17	119.1(8)
C19-C18-H18	120.5	C17-C18-H18	120.5
C18-C19-C20	121.9(8)	C18-C19-H19	119.0
C20-C19-H19	119.0	C19-C20-C21	120.4(7)
C19-C20-H20	119.8	C21-C20-H20	119.8
C16-C21-C20	118.2(7)	C16-C21-C22	121.8(7)
C20-C21-C22	120.1(6)	C21-C22-H22A	109.5

C21-C22-H22B	109.5	H22A-C22-H22B	109.5
C21-C22-H22C	109.5	H22A-C22-H22C	109.5
H22B-C22-H22C	109.5	C11-O1-C6	118.2(4)

2.7 Computational Method and Data

Computational Method

We performed DFT calculations using Gaussian 09 software[107]at the B3LYP/[SDD for In, 6-311+G** for others]//B3LYP/[SDD for In, 6-31G* for others] level.[108] Solvent effects (CH_2Cl_2) were taken into account by using the PCM method[109] in single point calculations.We used $InBr_3$ instead of the best catalyst, $In(tfacac)_3$, to simplify the calculations.We could not precisely locate one of the transition states (TS2-B); therefore, the zero-point energy (ZPE) value could not be obtained for this transition state. To make fair comparisons of the stability of various species under the circumstances, in the energy diagrams below, ZPE corrections are not included.

XYZ coordinates of [2+2]-cycloaddition

RC

C	-3.055591	1.277353	0.751250
C	-2.153863	0.522140	1.050439
C	-4.118212	2.171637	0.410352
C	-3.898859	3.245817	-0.475230
C	-5.404805	1.999307	0.959659
C	-4.935831	4.118462	-0.797665
H	-2.911310	3.381937	-0.905728
C	-6.436554	2.876466	0.632253

[107]Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, Jr. J. A.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Keith, T.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09,Revision D.01,* Gaussian, Inc., (2009).

[108](a)Becke, A. D. *J. Chem. Phys.***1993**, *98*, 5648; (b) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B*1988, *37*, 785; (c) Vosko, S. H.; Wilk, L.; Nusair, M. *Can. J. Phys.***1980**, *58*, 1200; (d) Krishnan, R.; Binkley, J. S.; Seeger, R.; Pople, J. A. *J. Chem. Phys.***1980**, *72*, 650; (e) MacLean, A. D.; Chandler, G. S. *J. Chem. Phys.* **1980***, 72,* 5639. 7.Kuechle, W.; Dolg, M.; Stoll, H.; Preuss, H. *Mol. Phys.***1991**,*74*1245.

[109]Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.***2005**, *105*, 2999.

H	-5.581912	1.169432	1.637306
C	-6.206925	3.938790	-0.245835
H	-4.751632	4.941349	-1.483192
H	-7.423808	2.729136	1.062061
H	-7.013497	4.620947	-0.500068
C	-1.074080	-0.394327	1.404135
H	-0.153539	-0.150700	0.860300
H	-0.846317	-0.356590	2.476781
H	-1.340271	-1.430297	1.160461
C	-2.087569	2.991391	3.533045
C	-1.322971	2.566817	4.547136
H	-3.166356	2.878493	3.535090
H	-1.643988	3.457137	2.659597
H	-0.242342	2.667845	4.541827
C	-1.868370	1.905407	5.737440
O	-1.171917	1.350766	6.606157
O	-3.185548	1.935552	5.857132
C	-3.758099	1.247714	6.993424
H	-3.389705	1.687176	7.922457
H	-4.833564	1.387924	6.893964
H	-3.496116	0.188182	6.960382
H	0.822642	0.443071	6.853519
Br	0.482988	0.109496	9.288710
Br	0.307710	-1.359238	5.218169
Br	2.181280	2.386418	6.096459
Br	3.623493	-1.208426	7.109951
Si	4.734060	-0.661869	9.056096
C	6.540429	-1.079282	8.725964
C	4.477735	1.172393	9.364843
C	3.997418	-1.731353	10.413857
H	4.486804	-1.515642	11.372821
H	2.926924	-1.529662	10.522540
H	4.126760	-2.797557	10.199307
H	7.145262	-0.854779	9.614405
H	6.669668	-2.141090	8.490628
H	6.939045	-0.494555	7.890127
H	5.069751	1.487894	10.234289
H	4.787081	1.773358	8.503750
H	3.425541	1.392777	9.570947

RC'

C	-3.736764	1.838357	-0.779865
C	-2.707431	1.861798	-1.421706
C	-4.951344	1.810333	-0.023367
C	-5.870034	2.876724	-0.101593
C	-5.250312	0.715634	0.811737
C	-7.052166	2.844880	0.636004
H	-5.647983	3.719568	-0.749292
C	-6.434582	0.691021	1.545210
H	-4.547039	-0.109347	0.873367
C	-7.338458	1.753350	1.460950
H	-7.758646	3.667246	0.566560

H	-6.653966	-0.161454	2.182503
H	-8.265124	1.733941	2.027482
C	-1.481084	1.876226	-2.214123
H	-0.652002	1.400038	-1.676461
H	-1.614537	1.336582	-3.160134
H	-1.175811	2.900918	-2.458560
C	-2.331375	3.979884	2.071060
C	-3.414518	4.321767	2.776442
H	-2.419968	3.391850	1.161865
H	-1.335692	4.278146	2.384596
H	-4.411609	4.025833	2.463990
C	-3.379680	5.119745	4.021102
O	-4.380635	5.437807	4.648888
O	-2.137443	5.469074	4.405100
C	-2.045526	6.247532	5.607538
H	-2.454865	5.693571	6.456735
H	-0.981414	6.435063	5.751982
H	-2.588940	7.190031	5.498529
Si	-7.636889	5.788960	5.248238
C	-7.461692	3.927399	5.237975
H	-8.113749	3.475796	4.484087
H	-6.421246	3.684750	4.992304
H	-7.700196	3.492698	6.214195
C	-7.434586	6.619032	3.585500
H	-7.789678	7.654133	3.593050
H	-6.365334	6.613117	3.343753
H	-7.969345	6.076676	2.799498
C	-6.756602	6.647338	6.661911
H	-6.994217	7.715437	6.699229
H	-7.007834	6.201937	7.630229
H	-5.679378	6.533150	6.494286
Br	-9.932727	6.136218	5.855457
Br	-11.486237	6.001261	3.567082
Br	-11.121942	8.220346	2.551777
Br	-13.664422	5.558185	4.618470
Br	-10.453713	4.108167	2.329992

TS1-A

C	-4.319174	2.097491	-0.795738
C	-3.633515	2.682927	-1.607993
C	-5.132976	1.413205	0.162784
C	-6.346608	1.977414	0.603205
C	-4.733935	0.165810	0.682159
C	-7.137382	1.309319	1.536291
H	-6.666350	2.935991	0.206573
C	-5.529818	-0.495528	1.614959
H	-3.801269	-0.275132	0.343115
C	-6.732121	0.072424	2.045002
H	-8.072142	1.759420	1.858263
H	-5.212300	-1.458994	2.004941
H	-7.352275	-0.448132	2.769659
C	-2.830559	3.374393	-2.612917

H	-1.760532	3.172704	-2.480304
H	-3.104216	3.053149	-3.625708
H	-2.975776	4.460264	-2.561156
C	-2.785132	3.948859	2.086517
C	-3.714405	4.396639	2.939831
H	-3.065645	3.538524	1.120455
H	-1.728099	3.983283	2.331687
H	-4.769717	4.360414	2.692409
C	-3.395630	4.967779	4.258664
O	-4.230985	5.442579	5.038302
O	-2.102051	4.940075	4.574711
C	-1.727490	5.495852	5.850681
H	-2.221311	4.953219	6.660091
H	-0.646527	5.373799	5.908103
H	-2.000378	6.552626	5.899353
Si	-6.481612	5.908507	5.050042
C	-6.812211	4.066250	4.845706
H	-7.255495	3.868142	3.863957
H	-5.902924	3.468890	4.951992
H	-7.531425	3.736237	5.601907
C	-6.151369	7.050140	3.591629
H	-6.791065	7.936154	3.637022
H	-5.108291	7.378798	3.582191
H	-6.368126	6.543601	2.644963
C	-6.211857	6.585379	6.784549
H	-6.493649	7.642483	6.827477
H	-6.828694	6.045893	7.510891
H	-5.163234	6.489931	7.077932
Br	-9.020608	6.433655	5.171852
Br	-10.002468	6.643499	2.693781
Br	-9.457160	8.970826	2.035185
Br	-12.390098	6.098160	2.987256
Br	-8.714277	4.940635	1.380633

Int1-A

C	-6.573811	3.894411	0.393354
C	-5.778728	3.573517	-0.711359
C	-4.726915	2.667622	-0.581559
C	-4.453888	2.060334	0.661184
C	-5.260424	2.389564	1.771158
C	-6.308760	3.299062	1.631584
C	-3.392945	1.111861	0.798534
C	-2.515723	0.285124	0.940819
C	-1.489700	-0.736113	1.130638
C	-1.271120	2.725774	3.246611
C	-1.961768	3.686302	3.889244
C	-2.659523	4.727072	3.169938
O	-2.502075	4.779676	1.877851
C	-3.255556	5.745510	1.098466
O	-3.411405	5.608528	3.715185
H	-4.116327	2.407763	-1.441272
H	-5.065925	1.911032	2.727092

H	-5.985761	4.021709	-1.679786
H	-6.935357	3.527092	2.490332
H	-7.403044	4.588775	0.286404
H	-0.563231	-0.479361	0.602151
H	-1.255310	-0.860199	2.194953
H	-1.831135	-1.705993	0.748245
H	-0.789966	1.929779	3.809805
H	-1.207950	2.690034	2.164272
H	-2.043454	3.677968	4.972232
H	-3.025355	6.756438	1.438988
H	-2.921603	5.587764	0.075462
H	-4.320973	5.531327	1.191520
Si	-3.974553	6.027380	5.374133
C	-4.906369	7.606321	4.989307
C	-5.074049	4.633153	5.935849
C	-2.442659	6.333012	6.401705
H	-5.365010	8.002978	5.903445
H	-4.243931	8.382104	4.589267
H	-5.710336	7.434246	4.265223
H	-5.457666	4.861620	6.938741
H	-5.937386	4.512132	5.271769
H	-4.556941	3.670119	6.001276
H	-2.737184	6.847847	7.325408
H	-1.942434	5.405115	6.696796
H	-1.725069	6.979254	5.883065
Br	-4.585314	0.758330	5.387278
Br	-2.476611	0.351707	6.721067
Br	-2.855354	-1.163200	8.642251
Br	-0.684718	-0.496927	5.151070
Br	-1.706743	2.652713	7.507272

TS2-A

C	-4.516389	2.011462	-0.268238
C	-3.838884	2.986461	0.097770
C	-5.384119	0.925496	-0.479323
C	-6.774026	1.164063	-0.611123
C	-4.889020	-0.400271	-0.544333
C	-7.646026	0.095945	-0.783904
H	-7.140628	2.184238	-0.564668
C	-5.770793	-1.455707	-0.730564
H	-3.822261	-0.575937	-0.445166
C	-7.146135	-1.208891	-0.844876
H	-8.712203	0.288455	-0.850857
H	-5.395291	-2.473543	-0.780094
H	-7.830998	-2.041776	-0.978610
C	-2.995300	4.142350	-0.270256
H	-2.009719	4.083180	0.202903
H	-2.867505	4.190936	-1.355616
H	-3.477538	5.066687	0.066014
C	-4.090821	2.939328	2.133665
C	-4.407418	4.226920	2.596282
H	-4.894299	2.214108	2.179719

H	-3.092849	2.547287	2.308123
H	-5.449820	4.512440	2.641104
C	-3.455170	5.135188	3.052279
O	-3.709910	6.278327	3.629579
O	-2.162057	4.824403	2.938428
C	-1.181735	5.707958	3.512561
H	-1.336818	5.809374	4.589401
H	-0.222790	5.231217	3.310471
H	-1.225523	6.692466	3.040874
Si	-5.189616	7.098710	4.148602
C	-6.162244	5.927094	5.236046
H	-6.542748	5.043797	4.712832
H	-5.563466	5.589606	6.090498
H	-7.036028	6.459095	5.633556
C	-6.074329	7.685916	2.610939
H	-7.011560	8.180468	2.895543
H	-5.466493	8.412423	2.058638
H	-6.344837	6.873800	1.927434
C	-4.459396	8.520744	5.132182
H	-5.260427	9.169260	5.507778
H	-3.888643	8.165591	5.997675
H	-3.796300	9.138477	4.516038
Br	-10.142762	5.871071	3.003032
Br	-9.081301	3.996213	1.743105
Br	-7.411528	4.960913	0.080323
Br	-10.667443	2.529691	0.488142
Br	-7.708592	2.589365	3.349991

Int2

C	-4.509254	1.731372	0.125092
C	-3.804751	2.651021	0.670416
C	-5.355193	0.745989	-0.335583
C	-6.728196	1.052854	-0.577348
C	-4.878210	-0.584933	-0.544536
C	-7.593072	0.053296	-0.994555
H	-7.070274	2.072367	-0.430400
C	-5.755480	-1.565351	-0.966484
H	-3.832367	-0.806511	-0.357666
C	-7.108364	-1.246339	-1.185878
H	-8.642263	0.286944	-1.143162
H	-5.406440	-2.581377	-1.122053
H	-7.791296	-2.027868	-1.507914
C	-2.979500	3.694196	-0.041307
H	-1.940726	3.644814	0.301187
H	-3.015089	3.576379	-1.125996
H	-3.379412	4.677296	0.227976
C	-3.798829	2.696016	2.272981
C	-4.210327	4.009572	2.806598
H	-4.468647	1.912827	2.629608
H	-2.767893	2.443175	2.542652
H	-5.271081	4.188836	2.917430
C	-3.328987	4.970363	3.206918

O	-3.628852	6.114455	3.807992
O	-2.003579	4.770959	3.019116
C	-1.082002	5.705582	3.591780
H	-1.189833	5.751985	4.679457
H	-0.093418	5.324407	3.331467
H	-1.220995	6.705872	3.172810
Si	-5.122445	6.800021	4.379952
C	-6.006906	5.552163	5.467813
H	-6.438530	4.711667	4.915002
H	-5.335518	5.147087	6.234482
H	-6.834135	6.054257	5.985607
C	-6.119195	7.359842	2.896867
H	-7.110403	7.704448	3.216855
H	-5.624885	8.189990	2.378267
H	-6.284926	6.557561	2.169919
C	-4.496254	8.255256	5.390947
H	-5.339111	8.837677	5.782910
H	-3.895008	7.924973	6.245772
H	-3.881443	8.930033	4.784414
Br	-10.129915	5.396583	3.153880
Br	-8.978892	3.652763	1.803719
Br	-7.359378	4.731717	0.161456
Br	-10.514806	2.193722	0.459476
Br	-7.545974	2.177589	3.288303

TS3-A

C	-7.413886	0.257869	-0.014951
C	-6.525442	1.009265	-0.806520
C	-5.288871	1.355449	-0.298851
C	-4.927497	0.945660	1.023296
C	-5.844050	0.186055	1.813977
C	-7.080248	-0.148904	1.282825
C	-3.698052	1.285322	1.532856
C	-2.552391	1.610577	2.024768
C	-1.333841	0.712882	1.895630
C	-2.397674	2.929787	2.808112
C	-3.654525	3.717565	3.026038
C	-3.965306	4.816474	2.312053
O	-3.190500	5.177294	1.252111
C	-3.144903	6.563197	0.901793
O	-5.028691	5.619904	2.496906
H	-4.580585	1.938194	-0.878563
H	-5.554990	-0.110413	2.815618
H	-6.814493	1.312789	-1.807524
H	-7.784890	-0.725098	1.873332
H	-8.384656	-0.011743	-0.422872
H	-0.526468	1.282341	1.421296
H	-1.021854	0.424671	2.905534
H	-1.537030	-0.190393	1.319146
H	-1.958004	2.624112	3.767732
H	-1.648819	3.517692	2.264762
H	-4.329126	3.369579	3.799600

H	-2.787336	7.173224	1.739871
H	-2.434685	6.629308	0.075383
H	-4.124368	6.927599	0.581685
Si	-6.050019	5.848570	3.856387
C	-6.999969	7.401988	3.387834
C	-7.219243	4.385269	4.031084
C	-5.004885	6.115036	5.396072
H	-7.720345	7.668748	4.170769
H	-6.327743	8.256491	3.249302
H	-7.559500	7.260418	2.455939
H	-7.991202	4.615147	4.776726
H	-7.730228	4.174948	3.083788
H	-6.715137	3.469532	4.358402
H	-5.652011	6.326238	6.256574
H	-4.401818	5.236108	5.644323
H	-4.326574	6.967693	5.274474
Br	-5.380729	0.994396	5.452790
Br	-3.490503	-0.690675	5.728091
Br	-3.860333	-2.123774	7.713780
Br	-3.472139	-2.040478	3.578072
Br	-1.328116	0.604012	5.833831

Int3-A

C	-7.150965	1.117040	-0.308742
C	-5.888376	1.093985	-0.905835
C	-4.761491	1.472373	-0.177411
C	-4.878413	1.872686	1.165525
C	-6.154196	1.892403	1.756654
C	-7.278822	1.515404	1.024231
C	-3.696165	2.272885	1.934545
C	-2.414337	1.861924	2.046179
C	-1.608729	0.737537	1.500189
C	-2.030929	2.918232	3.061471
C	-3.557253	3.382514	2.980353
C	-3.714028	4.774487	2.501726
O	-3.399086	4.991035	1.257152
C	-3.478186	6.334968	0.716160
O	-4.099022	5.774648	3.191820
H	-3.783937	1.475223	-0.651358
H	-6.253992	2.153340	2.807062
H	-5.781250	0.786267	-1.942659
H	-8.255592	1.519485	1.500305
H	-8.028838	0.822190	-0.877082
H	-0.710356	1.102434	0.984115
H	-1.278486	0.090993	2.323182
H	-2.189412	0.127874	0.802050
H	-1.757541	2.577185	4.065733
H	-1.303929	3.668190	2.723128
H	-4.097651	3.230256	3.919643
H	-2.811382	6.998678	1.269492
H	-3.158850	6.233321	-0.319097
H	-4.506429	6.695793	0.774035

Si	-4.693397	6.147512	4.863197
C	-4.750643	8.016166	4.736635
C	-6.388104	5.374906	4.973382
C	-3.411550	5.537661	6.066739
H	-5.108315	8.442161	5.682156
H	-3.759592	8.440421	4.540335
H	-5.431652	8.351077	3.946281
H	-6.908614	5.784458	5.848802
H	-6.998837	5.602370	4.092224
H	-6.335006	4.290022	5.108734
H	-3.694866	5.867481	7.075201
H	-3.318206	4.447599	6.106913
H	-2.423061	5.961212	5.854394
Br	-5.466843	1.762447	5.846020
Br	-3.402776	0.472046	6.649922
Br	-3.916838	-0.627383	8.812439
Br	-2.724676	-1.115359	4.834114
Br	-1.581453	2.219156	6.889203

TS4-A

C	-4.123928	2.498432	0.964706
C	-3.064031	1.970600	1.620768
C	-4.616675	2.517917	-0.411991
C	-3.748398	2.341003	-1.506068
C	-5.984047	2.722977	-0.670720
C	-4.237210	2.350717	-2.810517
H	-2.683703	2.220014	-1.331450
C	-6.470997	2.733266	-1.976846
H	-6.674901	2.852630	0.158089
C	-5.599989	2.544867	-3.051861
H	-3.551344	2.214574	-3.642433
H	-7.532414	2.883493	-2.153826
H	-5.978718	2.553091	-4.070071
C	-1.903059	1.107505	1.262680
H	-1.791404	0.291452	1.988311
H	-2.013782	0.666118	0.267784
H	-0.962350	1.676080	1.279707
C	-3.472377	2.524410	2.970665
C	-4.743006	3.102299	2.225807
H	-3.715511	1.791722	3.749505
H	-2.807230	3.286070	3.396579
H	-5.677047	2.646018	2.563274
C	-4.885740	4.599433	2.300148
O	-5.770689	5.209527	2.908576
O	-3.924204	5.250609	1.656395
C	-3.960561	6.692116	1.699041
H	-3.876283	7.043460	2.730172
H	-3.104376	7.016046	1.108796
H	-4.892358	7.058473	1.262627
Si	-7.629477	4.676121	4.151945
C	-6.516220	3.657377	5.279189
H	-6.725372	2.589249	5.159605

H	-5.455782	3.840230	5.086213
H	-6.725811	3.916669	6.321646
C	-8.370362	4.038348	2.543626
H	-9.445919	4.233390	2.507746
H	-7.901394	4.527469	1.685015
H	-8.235839	2.954890	2.455459
C	-7.790710	6.514115	4.518120
H	-7.774062	6.696270	5.597711
H	-6.970501	7.071648	4.057854
H	-8.738236	6.899950	4.128173
Br	-9.719111	4.100438	5.566997
Br	-10.584375	1.668946	4.832699
Br	-11.661561	0.824492	6.885002
Br	-12.068651	2.142567	2.903262
Br	-8.509518	0.435116	4.165630

PC

C	-3.438398	2.643361	1.035050
C	-2.088603	2.674538	0.929449
C	-4.567679	2.239502	0.199381
C	-4.454797	2.125591	-1.199988
C	-5.812376	1.955787	0.792026
C	-5.542857	1.722006	-1.970506
H	-3.517217	2.377403	-1.685777
C	-6.900695	1.551392	0.019938
H	-5.923172	2.046107	1.868936
C	-6.768427	1.430175	-1.365032
H	-5.436872	1.642993	-3.049337
H	-7.849987	1.329830	0.500522
H	-7.616061	1.117995	-1.968636
C	-1.083475	2.269939	-0.095004
H	-0.257506	1.718214	0.372621
H	-1.519519	1.634790	-0.872003
H	-0.638100	3.147272	-0.585690
C	-1.878072	3.250240	2.316175
C	-3.439435	3.182290	2.473863
H	-1.333665	2.611895	3.024356
H	-1.460077	4.261708	2.357122
H	-3.778817	2.469610	3.232176
C	-4.192784	4.472626	2.703836
O	-5.183415	4.577676	3.409499
O	-3.673287	5.504018	2.016303
C	-4.359670	6.760045	2.135885
H	-4.408356	7.074726	3.181692
H	-3.774628	7.468466	1.549370
H	-5.374158	6.681609	1.735650
Si	-8.389552	4.209184	4.445790
C	-7.552410	2.611727	4.936920
H	-7.999510	1.754156	4.424697
H	-6.496767	2.690310	4.651010
H	-7.609089	2.442369	6.017275
C	-8.529809	4.525194	2.608303

H	-9.208212	5.355280	2.386855
H	-7.529725	4.776053	2.236033
H	-8.879646	3.640089	2.068704
C	-7.822592	5.699210	5.431279
H	-7.862353	5.518605	6.510475
H	-6.780187	5.898074	5.153266
H	-8.418340	6.589523	5.205422
Br	-10.644796	3.940985	5.203084
Br	-12.013860	2.468749	3.282847
Br	-13.804748	1.573669	4.709805
Br	-12.608642	4.200931	1.630555
Br	-10.291398	0.850273	2.515330

PC'

C	-2.871110	2.285705	1.736494
C	-2.106573	3.100610	2.501673
C	-2.654603	1.280243	0.697795
C	-1.470174	1.248015	-0.063190
C	-3.648954	0.320518	0.431526
C	-1.280989	0.276725	-1.043490
H	-0.706843	2.002737	0.099400
C	-3.456506	-0.648798	-0.552014
H	-4.570425	0.320288	1.008898
C	-2.272158	-0.677058	-1.291154
H	-0.361334	0.269394	-1.622737
H	-4.234349	-1.384247	-0.738484
H	-2.124044	-1.431992	-2.058508
C	-0.646580	3.334035	2.692705
H	-0.335763	4.296758	2.262301
H	-0.399788	3.372654	3.761655
H	-0.042038	2.547070	2.231848
C	-3.284946	3.731724	3.216177
C	-4.182933	2.739686	2.375075
H	-3.360049	3.571001	4.297461
H	-3.460074	4.794070	3.007231
H	-4.689442	1.993795	2.992016
C	-5.203460	3.403196	1.497230
O	-6.434252	3.342856	1.650512
O	-4.691680	4.111953	0.509268
C	-5.617463	4.809985	-0.356767
H	-6.206965	5.524134	0.221817
H	-4.989793	5.319346	-1.086504
H	-6.283842	4.095521	-0.843749
H	-7.844063	2.506223	3.129859
Br	-9.814764	3.452858	1.956259
Br	-7.150569	0.144802	2.765877
Br	-6.865273	3.757667	5.046425
Br	-9.872195	1.113542	5.247777
Si	-11.587160	2.550044	5.812801
C	-12.154661	1.990281	7.518722
C	-10.891887	4.293917	5.833920
C	-12.924222	2.321867	4.512520

H	-13.770662	2.990359	4.718164
H	-12.536030	2.557853	3.516512
H	-13.299987	1.293159	4.500638
H	-12.991646	2.614007	7.859207
H	-12.494389	0.949110	7.506267
H	-11.348446	2.076485	8.254917
H	-11.655845	4.992568	6.200325
H	-10.015071	4.371626	6.484680
H	-10.595590	4.609235	4.828440

TS1-B

C	-2.313132	2.283693	1.301569
C	-1.279289	2.960142	1.540564
C	-3.530086	1.596613	1.252201
C	-4.504797	1.905812	0.268287
C	-3.787861	0.558070	2.187029
C	-5.702042	1.204782	0.232835
H	-4.300046	2.694680	-0.448634
C	-4.986806	-0.139923	2.129270
H	-3.037434	0.321864	2.936109
C	-5.943896	0.181924	1.159070
H	-6.449249	1.446376	-0.517294
H	-5.180698	-0.935963	2.841990
H	-6.880554	-0.367321	1.122109
C	0.168660	2.937459	1.163253
H	0.480921	3.908599	0.761414
H	0.775827	2.726387	2.051433
H	0.363229	2.165436	0.415385
C	-1.621635	4.292677	2.701282
C	-0.986402	3.984863	3.934180
H	-2.704123	4.370373	2.732492
H	-1.173458	5.096014	2.113265
H	0.087405	4.076484	4.044464
C	-1.659689	3.352323	4.995204
O	-1.093789	2.897367	6.047411
O	-2.994154	3.255041	4.890257
C	-3.686130	2.541858	5.931873
H	-3.537194	3.031970	6.896917
H	-4.737624	2.573613	5.644906
H	-3.330986	1.509638	5.985770
H	0.307547	1.334558	6.181383
Br	0.650481	1.194002	8.624920
Br	-1.082152	-0.453955	5.105299
Br	2.248028	2.080842	4.811656
Br	2.641197	-2.086493	6.289135
Si	3.797819	-2.037092	8.253897
C	5.097565	-3.400193	8.155672
C	4.592447	-0.338558	8.402433
C	2.567024	-2.357760	9.640450
H	3.075008	-2.338706	10.613797
H	1.787325	-1.589049	9.647356
H	2.084657	-3.334867	9.528669

H	5.691312	-3.426926	9.078963
H	4.634217	-4.383994	8.024097
H	5.783712	-3.234693	7.318049
H	5.180629	-0.273149	9.327481
H	5.261666	-0.135863	7.559407
H	3.829290	0.446175	8.428241

Int1-B

C	-2.305956	2.277574	1.282206
C	-1.298224	2.935224	1.687415
C	-3.485796	1.586924	1.030768
C	-4.322677	1.942535	-0.063455
C	-3.852045	0.491451	1.864040
C	-5.489127	1.233026	-0.302247
H	-4.034431	2.773257	-0.699698
C	-5.016656	-0.214646	1.599487
H	-3.207962	0.220977	2.696020
C	-5.835591	0.154542	0.524438
H	-6.131515	1.508085	-1.133345
H	-5.293521	-1.052696	2.231874
H	-6.747855	-0.401522	0.327224
C	0.172148	2.803219	1.395053
H	0.576485	3.758930	1.040777
H	0.700439	2.529327	2.315798
H	0.360450	2.035413	0.642061
C	-1.655095	4.155073	2.790450
C	-1.169535	3.762916	4.091661
H	-2.727830	4.329291	2.752014
H	-1.120345	4.996816	2.338915
H	-0.107849	3.766915	4.306605
C	-1.987701	3.160194	5.049619
O	-1.571224	2.637834	6.148938
O	-3.311532	3.154933	4.804421
C	-4.152417	2.467732	5.747146
H	-4.060542	2.911253	6.741410
H	-5.166578	2.593377	5.366048
H	-3.887374	1.408018	5.793416
H	-0.301550	0.992197	6.316571
Br	-0.117439	0.584210	8.741672
Br	-1.643078	-0.689426	5.020618
Br	1.834420	1.588784	5.169202
Br	2.759751	-3.946876	6.447334
Si	4.068933	-2.675410	7.813158
C	5.530814	-3.751139	8.326944
C	4.639473	-1.181538	6.821832
C	3.030824	-2.179895	9.301062
H	3.634089	-1.585919	10.000581
H	2.167977	-1.573146	9.005984
H	2.661091	-3.060260	9.838080
H	6.203105	-3.189103	8.988616
H	5.197511	-4.644901	8.865530
H	6.109524	-4.077512	7.456044

H	5.283803	-0.541839	7.439547
H	5.213641	-1.487036	5.940154
H	3.793084	-0.575531	6.481109

TS2-B

C	-3.169311	1.330516	1.988914
C	-2.204220	1.942290	1.424863
C	-4.241625	0.799543	2.652394
C	-5.568873	1.115894	2.224015
C	-4.046870	-0.060135	3.781832
C	-6.652088	0.579273	2.899291
H	-5.709861	1.796136	1.391900
C	-5.140772	-0.597054	4.426874
H	-3.034862	-0.277895	4.107480
C	-6.439247	-0.277107	3.986331
H	-7.663300	0.839193	2.607682
H	-5.005570	-1.251481	5.282151
H	-7.303143	-0.684706	4.503485
C	-1.292636	1.533945	0.300540
H	-1.433510	2.211738	-0.549076
H	-0.250103	1.625268	0.626660
H	-1.474016	0.508371	-0.027004
C	-1.999897	3.374931	2.078597
C	-3.204411	3.870407	2.744044
H	-1.143303	3.219520	2.752328
H	-1.695342	4.037242	1.263704
H	-3.588979	3.380862	3.631138
C	-3.804034	5.050096	2.376938
O	-4.823309	5.620478	2.948920
O	-3.279173	5.720618	1.310857
C	-3.981860	6.879398	0.853673
H	-4.023188	7.649455	1.628689
H	-3.410271	7.240307	-0.003846
H	-5.002115	6.630482	0.545912
H	-6.498286	5.004871	3.931481
Br	-7.913602	4.021356	2.094122
Br	-5.876306	3.264062	5.629830
Br	-7.472287	7.043883	4.934484
Br	-10.261371	-0.317504	4.245910
Si	-11.088930	1.537925	5.327477
C	-12.705780	0.988588	6.123572
C	-9.820571	2.041656	6.619129
C	-11.367432	2.859936	4.024519
H	-11.776422	3.764336	4.494258
H	-10.434658	3.138430	3.522543
H	-12.079942	2.525037	3.262633
H	-13.166497	1.830800	6.656383
H	-13.420477	0.633416	5.373465
H	-12.542802	0.181799	6.846193
H	-10.181622	2.921316	7.168418
H	-9.653407	1.239090	7.346078
H	-8.855596	2.305035	6.172649

CHAPTER 3

IN(III)-TMSBr-CATALYZED CASCADE DEAROMATIZATION REACTION OF ALKYNES AND ACRYLATES

3.1 Introduction

3.1.1 Development of dearomatization reaction

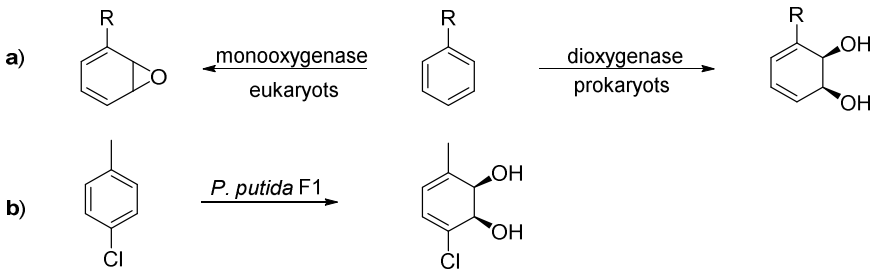
Functionalized alicyclic compounds are ubiquitously present in natural products and bioactive compounds. This leads to active research on developing efficient methods to access them from simple building blocks. Among these, the simple yet efficient strategy granted by arene dearomatization reaction is particularly attractive in view of their prevalence, low cost, and amenability for synthetic derivatizations.[110] The cyclic conjugated π bonds in the arene could be viewed as incognito internal functionalization that is susceptible to exploitation upon overcoming the aromaticity-induced chemical intactness. This brings about extensive research efforts to develop dearomatization protocols as well as the ensuing derivatizations. The most well known dearomatization reaction could be the birch reduction, which involves single electron transfers. Other methods include enzymatic oxidation, reduction, radical cyclization, photo- and therma- induced cycloaddition reaction, nucleophilic addition, transition metals-mediated or -catalyzed reactions. Herein, the representative dearomatization methods available to-date will be highlighted.

3.1.1.1 Enzymatic dearomatization reaction

Nature utilizes enzymes and microorganisms to produce enantiopure building blocks in biosynthesis. This process could be employed to make enantiopure small molecules on preparative scale in organic chemistry laboratories. This method could be exemplified by preparation of *cis*-dihydrodiol or arene oxide through bacterial dioxygenases or cytochrome-type monooxygenases-mediated arene oxidation correspondingly (**Scheme 3-1a**). In 1968, Gibson

[110](a) Roche, S. P.; Porco, J. A. Jr., *Angew. Chem. Int. Ed.* **2011**, *50*, 4068-4093.

reported on utilizing *Pseudomonas putida* F1 to form stable and isolable arene *cis*-dihydrodiol from *p*-chlorotoluene. This represents a pioneering successful effort in enzymatic arene dihydroxylation (**Scheme 3-1b**).[111] It was later recognized that the cyclohexadiene diol products are venerable building blocks owing to the dense and highly differentiated functionalities present on this small scaffold.[112] Now, this enzymatic methodology has been incorporated in industrial-scale production of arene-derived diols.



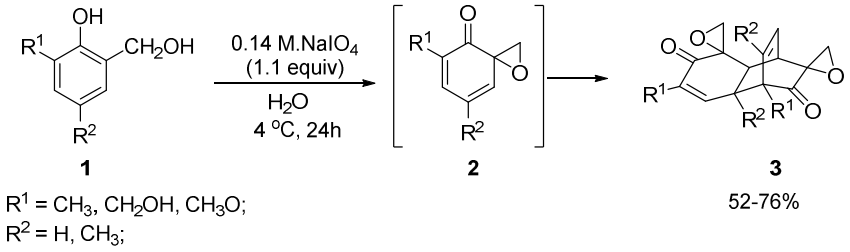
Scheme 3-1. Examples on enzymatic dearomatization reaction of arenes

3.1.1.2 Oxidative dearoamatization reaction

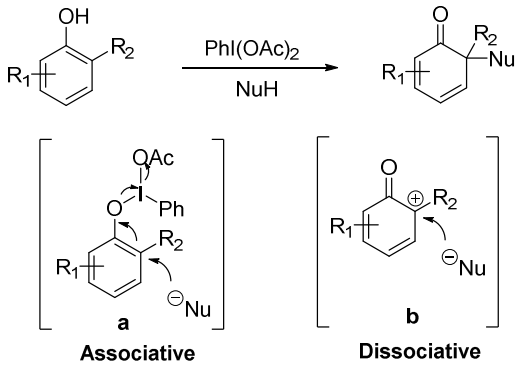
A comprehensive study by Adler and co-workers termed the Adler oxidation refers to oxidation of benzediols (**1**), wherein the respective monoethers or methyphenols forms the Diels-Alder dimer (**3**) through spiro(oxirane-2,4-cyclohexadienones) (**2**) using sodium periodate in aqueous or 80% acetic acid solution (**Scheme 3-2**).[113] This work is a useful supplement to Wessely oxidation, an earlier oxidation protocol developed for phenols, benzenediols, benzenetriols, and

[111](a) Gibson, D. T.; Koch, J. R.; Kallio, R. E. *Biochemistry* **1968**, *7*, 2653-2662; (b) Gibson, D. T.; Koch, J. R.; Schuld, C. L.; Kallio, R. E. *Biochemistry* **1968**, *7*, 3795-3802.
[112](a) Carless, H. A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 795-826; (b) Hudlicky, T.; Thorpe, A. J. *Chem. Commun*. **1996**, 1993-2000; (c) Hudlicky, T.; Olive, H. F. *J. Am. Chem. Soc*. **1992**, *114*, 9694-9696; (d) Mandel, M.; Hudlicky, T.; Kwart, L. D.; Whited, G. M. *J. Org. Chem*. **1993**, *58*, 2331-2333; (e) Hudlicky, T.; Gonzalez, D.; Gibson, D. T. *Aldrichimica Acta*. **1999**, *32*, 35-62; (d) Hudlicky, T.; Reed, J. W. *Synlett* **2009**, 685-703. (e) Lewis, S. E. *Chem. Commun*. **2014**, *50*, 2821-2830.
[113](a) Adler, E.; Hernestam, S. *Acta. Chem. Scand*. **1955**, *9*, 319-334; (b) Adler, E.; Falkenberg, I.; Smith, B. *Acta. Chem. Scand*. **1962**, *16*, 529-540; (c) Adler, E.; Brasen, S.; Miyake, H. *Acta. Chem. Scand.* **1971**, *25*, 2055-2069; (d) Becker, H.-D.; Bremholt, T.; Adler, E. *Tetrahedron Lett*. **1972**, *41*, 4205-4208.

the corresponding ethers described by Wessely *et al.* using lead tetraacetate.[114]



Scheme 3-2. Adler oxidation

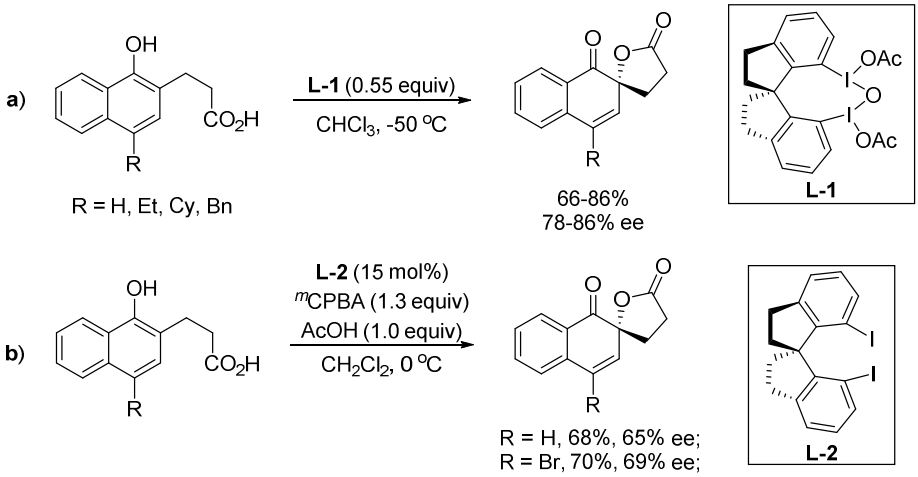


Scheme 3-3. Associative and discrete intermediates in hypervalent iodine-mediated phenol oxidation

In 1886, Willgerodt reported the first preparation of hypervalent iodine reagents. Since then, chemists explore the chemistry of this class of reagent and use them as common oxidizing agents in routine synthesis in view of the lower toxicity compared to metal oxidants.[115] This includes oxidative dearomatization reaction of phenols, wherein two different key intermediates are considered in the postulated mechanism. First being an associative phenoxyl-λ^3-iodane species (**a**) where introduction of chirality is attainable using chiral hypervalent iodine (III) reagents.

[114](a) Wessely, F.; Lauterbach-Keil, G.; Sinwel, F. *Monatsh. Chem*. **1950**, *81*, 811-818; (b) Wessely, F.; Koltan, J.; Sinwel, F. *Monatsh. Chem*. **1950**, *81*, 1055-1070.
[115](a) Moriarty, R. M.; Vaid, R. K. *Synthesis* **1990**, 431-447; (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2002**, *102*, 2523-2584; (b) Zhdankin, V. V.; Stang, P. J. *Chem. Rev*. **2008**, *108*, 5299-5358.

Alternatively, a dissociative phenoxenium ion (**b**) intermediate is involved (**Scheme 3-3**).[116] More recently, Kita reported on a novel asymmetric hypervalent iodine(III) reagent **L-1** possessing rigid scaffold of spirobiindane. With this, chiral oxidative dearomatization reaction of 1-naphthols constructed stereospecific *ortho*-spirolactone structure (**Scheme 3-4a**).[117] Moreover, *in situ* generation of **L-1** from catalytic amount of chiral iodoarene **L-2** and *m*-chloroperoxybenzoic acid is possible, thus circumvents an additional pre-synthetic step without compromising the yield and enantioselectivity (**Scheme 3-4b**).



Scheme 3-4. 1-Naphthols in chiral HIR-catalyzed oxidative dearomatization

Subsequently over the last decade, the strategy to form HIR *in situ* from chiral iodine pre-catalysts as well as *m*-CPBA co-oxidant has been independently studied by the groups of

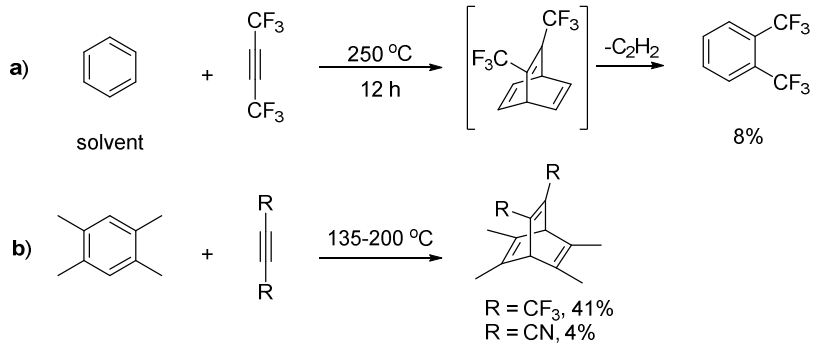
[116](a) Magdziak, D.; Meek, S. J.; Pettus, T. R. R. *Chem. Rev*. **2004**, *104*, 1383-1429; (b) Ciufolini, M. A.; Braun, N. A.; Canesi, S.; Ousmer, M.; Chang, J.; Chai, D. *Synthesis* **2007**, 3759-3772; (c) Ochiai, M.; Miyamoto, K. *Eur. J. Org. Chem.* **2008**, 4229-4239; (d) Quideau, S.; Pouységu, L.; Deffieux, D. *Synlett* **2008**, 467-495; (e) Dohi, T.; Kita, Y. *Chem. Commun*. **2009**, 2073-2085; (f) Pouységu, L.; Deffieux, D.; Quideau, S. *Tetrahedron* **2010**, *66*, 2235-2261; (g) Liang, H.; Ciufolini, M. A. *Tetrahedron* **2010**, *66*, 5884-5892; (h) Uyanik, M.; Ishihara, K. *Chem. Commun.* **2009**, 2086-2099; (i) Zhdankin, V. V. *J. Org. Chem*. **2011**, *76*, 1185-1197; (j) Ding, Q. P.; Ye, Y.; Fan, R. H. *Synthesis* **2013**, *45*, 1-16; (k) Harned, A. M. *Tetrahedron. Lett*. **2014**, *55*, 4681-4689.

[117](a) Dohi, T.; Maruyama, A.; Takenage, N.; Senami, K.; Minamitsuji, Y.; Fujioka, H.; Caemmerer, S.; Kita, Y. *Angew. Chem. Int. Ed*. **2008**, *47*, 3787-3790; (b) Dohi, T.; Takenage, N.; Nakae, T.; Toyoda, Y.; Yamasaki, M.; Shiro, M.; Fujioka, H.; Maruyama, A.; Kita, Y. *J. Am. Chem. Soc*. **2013**, *135*, 4558-4566.

Porco,[118] Pettus,[119] Ishihara,[120] Quideau,[121] Ibrahim[122] and Gong,[123], which contributed to the commendable leap in asymmetric oxidative reactions of phenols and derivatives.

3.1.1.3 Thermal- and photo-promoted dearomatization *via* cycloaddition reaction

Examples on aromatic compounds participating in thermal Diels-Alder reactions have been scarce. There are mainly two approaches to surpass the high resonance energy of arenes. First strategy involves taking advantage on heightened reactivity of highly strained arenes. The diene-like characteristic in aromatic compounds increases from benzene to naphthalene to anthracene, a trend corresponds to the number of fused rings. In other words, a simple benzene is normally a dormant substrate for Diels-Alder reaction. This transformation could nonetheless be driven by stringent conditions (high reaction temperatures and pressures) or strong Lewis acids.

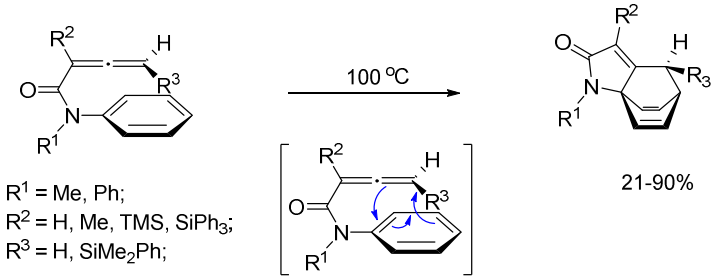


Scheme 3-5. Thermal cycloaddition of electron-deficient alkynes and arenes

It was demonstrated that benzene could undertake the Diels-Alder chemistry with

[118]Dong, S. W.; Zhu, J. L.; Porco, A. Jr. *J. Am. Chem. Soc*. **2008**, *130*, 2738-2739.
[119]Green, J. C.; Pettus, R. R. *J. Am. Chem. Soc*. **2011**, *133*, 1603-1608.
[120](a) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed*. **2010**, *49*, 2175-2177; (b) Uyanik, M.; Yasui, T.; Ishihara, K. *Angew. Chem. Int. Ed*. **2013**, *52*, 9215-9218.
[121](a) Quideau, S.; Lyvinec, G.; Marguerit, M.; Bathany, K.; Ozanne-Beaudenon, A.; Buffeteau, T.; Cavagnat, D.; Chénedé, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 4605-4609; (b) Bosset, C.; Coffinier, R.; Peixoto, P. A.; Assal, M. E.; Miqueu, K.; Sotiropoulos, J. M.; L. Pouységu, L.; Quideau, S. *Angew. Chem. Int. Ed*. **2014**, *53*, 9860-9864.
[122]Murray, S. J.; Ibrahim, H. *Chem. Commun*. **2015**, *51*, 2376-2379.
[123]Zhang, D.-Y.; Xu, L.; Wu, H.; Gong, L.-Z. *Chem.-Eur. J*. **2015**, *21*, 10314-10317.

hexafluorobut-2-yne to form 1,2-bis(trifluoromethyl)benzene through a tandem diene addition-acetylene elimination process (**Scheme 3-5a**). When durene was reacted with bis-(trifluoromethyl)-acetylene, the usual Diels-Alder adduct, benzenoid ring was successfully obtained (**Scheme 3-5b**).[124] Dicyanoacetylene was found to react in a similar manner albeit in only 4% yield.[125]



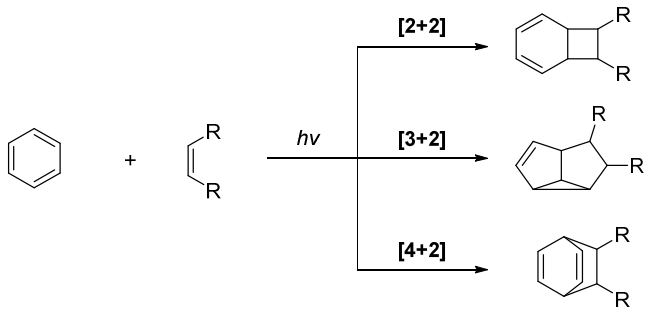
Scheme 3-6. Thermal dearoamatization/cyclization of allenecarboxanilides

In 1982, G. Himbert and L. Henn reported the isomerization of allenecarboxanilides to tricyclic dearomatization products through intramolecular [4+2] cycloaddition at a temperature slightly higher than 100 °C in neat condition or solution (**Scheme 3-6**).[126] The authors attributed the dearomatization as coinciding factors co-exist in this protocol including favourable formation of five-membered lactams, amino-activated benzene in allenecarboxanilides, higher energy of allenic systems than olefinic π bond as well as appropriate reaction geometry installed by allene and carboxamide.

In contrast to aromaticity retention when subjected to thermal reactions where they remain in ground state, benzene or benzene derivatives in excited state possess heightened reactivity to undergo rearrangement to high energy isomers, or to react with external reagents to give

[124]Krespan, C. G.; McKusick, B. C.; Cairns, T. L. *J. Am. Chem. Soc*. **1961**, *83*, 3428-3432.
[125]Weis, C. D. *J. Org. Chem*. **1963**, *28*, 74-78.
[126]Himbert, G.; Henn, L. *Angew. Chem. Int. Ed*. **1982**, *21*, 620.

non-aromatic products.[127] This is clearly evidenced when they are subjected to photochemical reactions with alkenes (**Scheme 3-7**). This reaction could give rise to three distinctive cycloadducts, namely the commonly observed competitive *ortho* ([2+2]) and *meta* ([3+2]) cycloadducts.



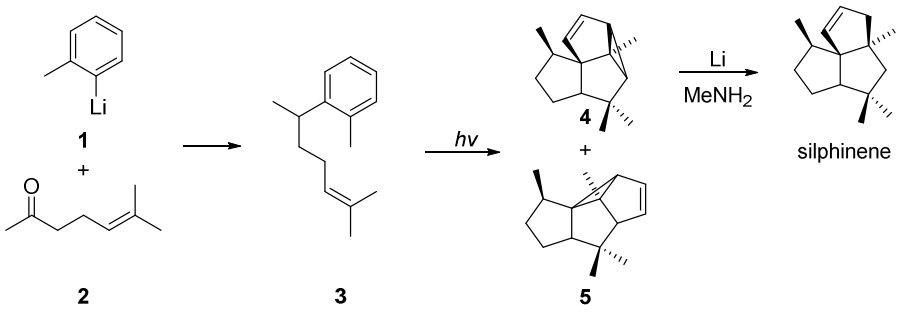
Scheme 3-7. Photo-induced cycloaddition of arene and alkene

The *para* adduct from a photo-Diels-Alder reaction route, on the other hand, is less commonly formed with electron deficient alkenes, for instance, maleic anhydride or acrylonitrile.[128] However, as seminally reported by Angus and Bryce-Smith, *ortho* adduct is normally obtained when benzenes are irradiated in the presence of electron-deficient alkenes.[129] With alkylethylenes, the *meta* cycloaddition pathway dominates.[130] Particularly, this pathway is preferred for substrates with small difference in ionization potentials, as reported by Bryce-Smith and co-workers. Another prominent feature of this reaction is the high regioselectivity when substituted benzenes are used. The synthetic value of this transformation is boosted when this

[127] selected reviews on the photocycloaddition of arenes and alkenes: (a) Bryce-Smith, D.; Gilbert, A. *Tetrahedron* **1976**, *32*, 1309-1326; (b) Bryce-Smith, D.; Gilbert, A. *Tetrahedron* **1977**, *33*, 2459-2489; (c) Wagner-Jauregg, T. *Synthesis* **1980**, 165-214; (d) Morrison, H. *Acc. Chem. Res*. **1979**, *12*, 383-389; (e) Houk, K. N. *Pure. Appl. Chem*. **1982**, *54*, 1633-1650; (e) Keukeleire, D. D.; He, S.-L. *Chem. Rev*. **1993**, *93*, 359-380. (f) Cornelisse, J. *Chem. Rev*. **1993**, *93*, 615-669; (g) Hoffmann, N. *Synthesis* **2004**, 481-495; (h) Wagner, P. J. *Acc. Chem. Res*. **2001**, *34*, 1-8; (i) Mattay, J. *Angew. Chem. Int. Ed*. **2007**, *46*, 663-665; (j) Hoffmann. *Chem. Rev*. **2008**, *108*, 1052-1103; (k) Streit, U.; Bochet, C. G. *Beilstein J. Org. Chem*. **2011**, *7*, 525-542.
[128] Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc.* **1971**, *93*, 2073-2074.
[129] Angus, H. J. F.; Bryce-Smith, D. *Proc. Chem. Soc*. **1959**, 326-327.
[130] (a) Wilzbach, K. E.; Kaplan, L. *J. Am. Chem. Soc*. **1966**, *88*, 2066; (b) Bryce-Smith, D.; Gilbert, A.; Orger, B. H. *Chem. Commun*. **1966**, 512-514.

advantage is exploited in natural products total synthesis.[131,132]

Wender's group first reported natural products synthesis employing an intramolecular *meta*-photo-cycloaddition as a key step.[116] Silphinene has a tricyclopentanoid skeleton with four stereogenic centers, of which two are adjacent to each other. While typical total synthetic route requires 10 to 20 individual steps. arene-alkene *meta* cycloaddition offers an efficient alternative route that takes only 3 steps in total. As shown in **Scheme 3-8**, organolithium intermediate **1** is first derived from 2-bromotoluene. Subsequent condensation with 6-methyl-hept-5-en-2-one **2** and *in-situ* reduction gives arene-alkene **3**. Photolysis of **3** yields a 1:1 mixture of *meta* cycloadducts **4** and **5**. Reductive carbon-carbon bond scission in cyclopropane ring then completes the silphinene synthesis.



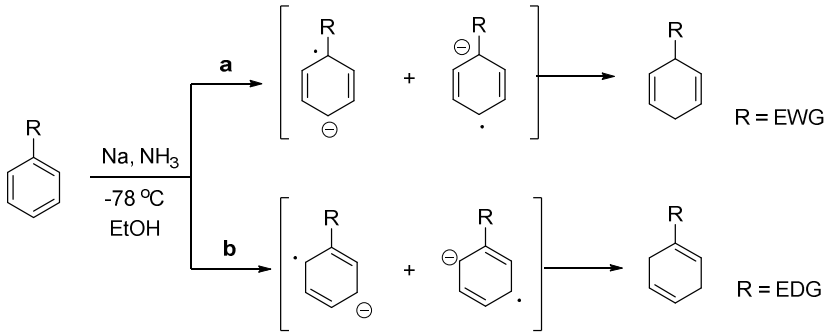
Scheme 3-8. Total synthesis of silphinene using photocycloaddition as the key step

3.1.1.4 Hydrogenation and Birch reaction of arenes

The two major methodologies for reduction/dearomatization of arene is hydrogenation and Birch reduction.[133] Some transition metals are able to catalyze benzene reduction to cyclohexane with

[131](a) Morrison, H.; Ferree, W. Jr. *J. Chem. Soc., Chem. Commun*. **1969**, 268-269; (b) Ferree, W. Jr.; Grutzner, J. B.; Morrison, H. *J. Am. Chem. Soc*. **1971**, *93*, 5502-5512.
[132](a) Wender, P. A.; Howbert, J. J. *J. Am. Chem. Soc.* **1981**, *103*, 688-690; (b) Wender, P. A.; Ternansky, R.; deLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure. Appl. Chem*. **1990**, *62*, 1597-1602; (c) Chappell, D.; Russell, A. T. *Org. Biomol. Chem*. **2006**, *4*, 4409-4430.
[133]Donohoe, T. J.; Garg, R.; Stevenson, C. A. *Tetrahedron: Asymmetry* **1996**, *7*, 317-344.

hydrogen in heterogeneous or homogeneous phase.[134] However, harsh conditions (eg., high pressure, high temperature) are usually required and mixture of reduction products are obtained due to the lack of selectivity.



Scheme 3-9. Birch reduction of arenes

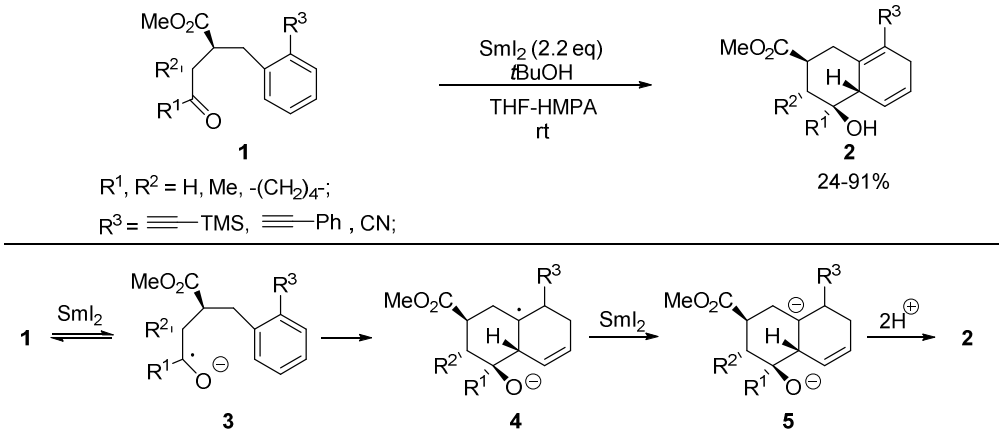
On the contrary, Arthur Birch first introduced Birch reduction in 1944, which is possibly the most robust method hitherto for partial reduction of aromatic rings.[135] Birch reaction could convert aromatic compounds into 1,4-cyclohexadienes with an alkali metal, alcohol in liquid NH_3 as well as alcohol or acid to quench radical anion intermediates or related species whereas the regiochemistry outcome is dictated by electronic nature of substituents. 2,5-Cyclohexadienes or 1,4-cyclohexadienes are respectively obtained with electron-poor (**Scheme 3-9a**) and electron-rich substituents (**Scheme 3-9b**). Later, Schultz *et al.* refined this reaction to asymmetric version and included a reduction-alkylation protocol.[136]

3.1.1.5 Dearomatization *via* radical cyclization

Reissig *et al.* reported that an intramolecular attack by ketyl radical anion onto an aryl group and

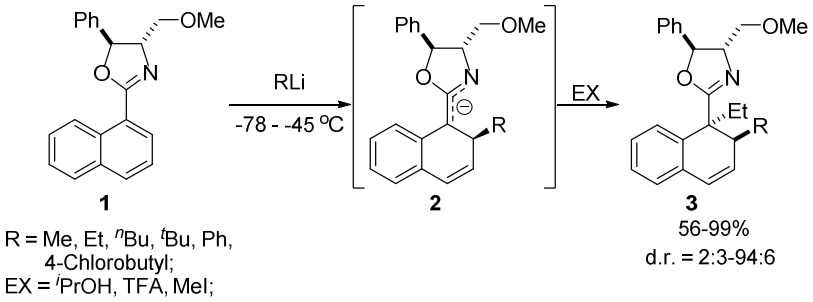
[134](a) Dyson, P. J. *Dalton Trans*. **2003**, 2964-2974; (b) Glorius, F. *Org. Biomol. Chem*. **2005**, *3*, 4171-4175; (c) Wang, D.-S.; Chen, Q.-A.; Lu, S.-M.; Zhou, Y.-G. *Chem. Rev*. **2012**, *112*, 2557-2590.
[135](a) Birch, A. J. *Pure. Appl. Chem*. **1996**, *68*, 553-556; (b) Rao, C. S. R. S. *Pure. Appl. Chem*. **2003**, *75*, 1443-1451; (c) Hook, J. M.; Mander, L. N. *Nat. Prod. Rep*. **1986**, 35-85.
[136]Schultz, A. G. *Chem. Commun*. **1999**, 1263-1271.

the ensuing electron transfer could also form 1,4-cyclohexadiene (**Scheme 3-10**).[137] When disubstituted alkynes **1** were subjected to samarium diiodide-mediated cyclization condition, the anticipated 7-*exo*-dig or 8-e*ndo*-dig cyclization product were not formed, instead single isomeric cyclohexadienes **2** were obtained. A mechanism was devised for the formation of **2**: electron transfer promoted by samarium diiodide generates ketyl anion radical **3** that will attack the aryl group at *ortho* site to give cyclohexadienyl radical **4**. **4** is further reduced to cyclohexadienyl anion **5** with an electron transfer, and the latter is protonated in analogy to Birch reduction to give dearomatization product **2**.



Scheme 3-10. SmI_2-mediated intramolecular radical dearomatization-cyclization

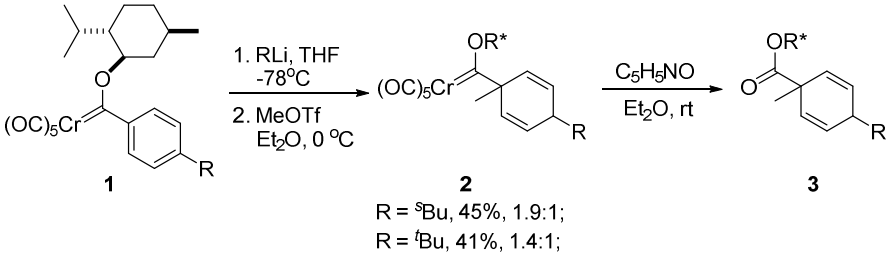
3.1.1.6 Nucleophilic dearomatization reactions



Scheme 3-11. Nucleophilic addition on naphthalenes activated by oxazolidine moiety

[137]Dinesh, C. U.; Reissig, H.-U. *Angew. Chem. Int. Ed*. **1999**, *38*, 789-791.

Arenes with strong electron withdrawing groups require less energy to overcome the aromaticity. Consequently, sequential nucleophilic dearomatization-electrophile trapping reactions on these arenes could form isolable dearomatized products. In this case, the electron withdrawing group has to be sterically hindered in order to prevent nucleophilic attack to itself.[138]



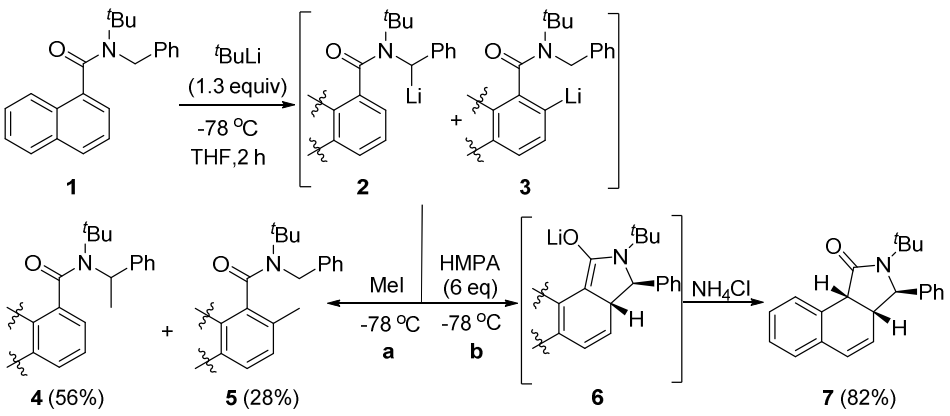
Scheme 3-12. Nucleophilic addition of arenes activated by Fischer carbene

As aforementioned, aromaticity loss of naphthalene ring requires lower energy compensation. Thus, a tethering oxazolidine moiety is sufficiently electron-withdrawing to stimulate nucleophilic addition onto naphthalene.[139] With this approach, Meyers and Barner reported an unprecedented enantiospecific route to generate 1,1,2-trisubstituted-1,2-dihydronaphthalenes in 1984 (**Scheme 3-11**).[140] This tandem reaction brings about excellent diastereofacial selectivity and installs two stereogenic centers in a one-pot manner. The underlying mechanistic pathway involves initial addition of organolithium compounds to 1-naphthyloxazoline **1** then electrophiles trapping of azaenolate **2** to yield dihydronaphtahlene **3**. The authors also developed removal protocol for oxazoline moiety under mild conditions to reveal enantiomerically pure 1,2-dihydronaphthalene aldehydes in high yields.

---

[138]Ortiz, F. L.; Iglesias, J. M.; Fernández, I.; Andújar Sánchez, C. M.; Gómez, G. R. *Chem. Rev.* **2007**, *107*, 1580-1691.
[139](a) Reuman, M.; Meyers, A. I. *Tetrahedron* **1985**, *41*, 837-860; (b) Gant, T. G.; Meyers, A. I. *Tetrahedron* **1994**, *50*, 2297-2360.
[140](a)Barner, B. A.; Meyers, A. I. *J. Am. Chem. Soc.* **1984**, *106*, 1865-1866; (b) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611-4624; (c) Gant, T. G.; Meyers, A. I. *J. Am. Chem. Soc.* **1992**, *114*, 1010-1015; (d) Shimano, M.; Meyers, A. I. *J. Am. Chem. Soc.* **1994**, *116*, 6437-6438.

Under the same concept, several new methods towards nucleophilic dearomatization reactions have been developed. Aside from oxazoline group, pentacarbonyl metallic group in alkoxy(aryl) Fischer carbene complex also possesses strong electron-withdrawing property to activate the tethering aryl moiety towards nucleophilic attack. This work of Barluenga and co-workers affirmed this hypothesis (**Scheme 3-12**).[141] Within minutes at -78 ^{o}C, the nucleophilic organolithiums perform conjugate addition onto aryl group in **1**. Trapping the thus-generated 1,6-adducts by methyl triflates give *Z/E* isomers of 1,4-dialkylation product **2**. Subsequently, $Cr(CO)_5$ group is removed oxidatively using pyridine 1-oxide to give the respective esters **3**.

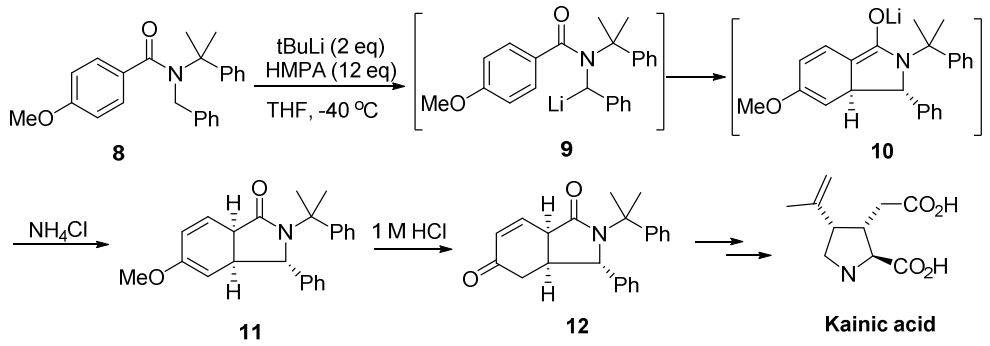


Scheme 3-13. Intramolecular dearomatization-nucleophilic addition of naphthamide

The nucleophilic dearomatization reaction can take place both in the intermolecular as well as intramolecular manner.[142] With organolithium reagents, tertiary aromatic amides typically undergo *ortho*-lithiation.[143] Clayden and co-workers found that with 2 equiv. of ^{t}BuLi, tertiary naphthamide **1** generates the lithiation product which subsequently yields two methylation products **4** and **5** in a ratio of approximately 2:1 upon quenching with MeI (**Scheme 3-13**, path a). α-Nitrogen methylation gives **4** whereas compound **5** results from *ortho*-methylation to amide

[141]Barluenga, J.; Trabanco, A. A.; Flórez, J.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc*. **1996**, *118*, 13099-13100.
[142]Clayden, J.; Kenworthy, M. N. *Synthesis* **2004**, *1721*-1736.
[143](a) Snieckus, V. *Chem. Rev*. **1990**, *90*, 879-933; (b) Familoni. *Synlett* **2002**, 1181.

group on aryl ring. Based on the structures of compound **4** and **5**, it is apparent that lithiation of **1** gives the α- and *ortho*-lithiation intermediate **2** and **3**. Treatment of this mixture with 6 equiv of HMPA mediates a prominent cyclization reaction (**Scheme 3-13**, path b). 82% of tricyclic isoindol-1-one **7** is generated as a single diastereomer after quenching. The intermediacy of enolate **6** in this HMPA-triggered dearomatization cyclization was supported as it could be trapped by electrophiles such as MeI, ^{n}BuBr or BnBr.[144]



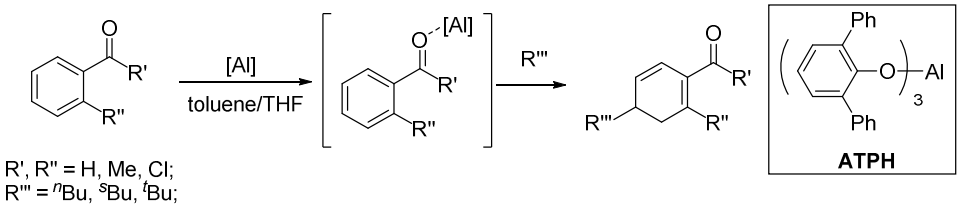
Scheme 3-14. Synthesis of Kainic acid with intramolecular dearomatization-nucleophilic addition of *N*-benzylbenzamide as key step

The same group reported that under a modified one-step condition, *N*-benzylbenzamides **8** could also be dearomatized through anionic cyclization to give an extended amide enolate **10** that could be quenched by water to yield bicyclic cyclohexadiene derivative **11** containing three new chiral centers. Notably, the pyrrolidine moiety in **12** resembles the relative stereochemistry of kainic acid (**Scheme 3-14**). After several steps of downstream transformation, kainic acid was furnished from intermediate **12** as racemic mixture.[145]

In addition to the above-mentioned electron-withdrawing groups applicable for activation of aromatic compounds towards nucleophilic addition, more structurally simple carbonyl groups

[144]Ahmed, A.; Clayden, J.; Rowley, M. *Chem. Commun*. **1998**, 297-298.
[145](a) Ahmed, A.; Clayden, J.; Yasin, S. A. *Chem. Commun*. **1999**, 231-232; (b) Clayden, J.; Tchabanenko, K. *Chem. Commun*. **2000**, 317-320.

containing aromatic moiety such as benzylaldehyde or ketone could also be suitable substrates for this kind of reaction. However, these carbonyl groups are often more reactive toward the nucleophilic reagents itself than the aromatic ring. Yamamoto and co-works solved this problem by the application of bulky Lewis acidic aluminium tris(2,6-diphenylphenoxide) (ATPH).[146] Its bulkiness could not only activate but also hinder the nucleophilic attack onto the carbonyl group. Through this methodology, they reported a series of dearomatization reactions of benzaldehydes, acetophenone and benzoyl chlorides with varied nucleophilic reagents using ATPH (**Scheme 3-15**).[147]



Scheme 3-15. ATPH-catalyzed dearomatization of aryl carbonyl compounds

3.1.1.7 Transition metal-mediated dearomatization reaction

Since the first preparation of ferrocene and determination of its 'sandwich' structure, hundreds of metal complexes of benzene with sandwich or half-sandwich skeletons were synthesized in the following decades. The metal-arene π-complexes became the focus of intensive study because the metal coordination not only activates the arene and functional groups at benzylic position; it also introduces the third dimension to the otherwise planar aryl ring systems. Consequently, if there are different *ortho*- or *meta*-substituents on arene, the two faces of it become enantiotropic to mediate stereoselective reactions.

---

[146]Yamamoto, H. *Tetrahedron* **2007**, *63*, 8377-8412.

[147](a) Maruoka, K.; Ito, M.; Yamamoto, H. *J. Am. Chem. Soc*. **1995**, *117*, 9091-9092; (b) Saito, S.; Shimada, K.; Yamamoto, H.; Marigorta, E. M.; Fleming, I. *Chem. Commun*. **1997**, 1299-1300; (c) Saito, S.; Sone, T.; Yamamoto, H. *Synlett* **1999**, 81-83; (d) Saito, S.; Sone, T.; Murase, M.; Yamamoto, H. *J. Am. Chem. Soc*. **2000**, *122*, 10216-10217.

Through transition metal coordination, aromatic hydrocarbons are activated and prone to undertake dearomatization chemistry. Since 1970s, two complementary methodologies have been developed (i) arenes and electron-deficient transition metals forming η^6-arene complexes wherein the arene ligands are activated toward nucleophilic attack; (ii) arenes and electron-rich transition metals forming η^2-arene complexes that activate arene ligands towards electrophilic reaction. Both metal units could function as stereo-directing groups for the nucleophilic/electrophilic attack as well as side chain reaction of the arene ring.

η^6-Coordination of the arene

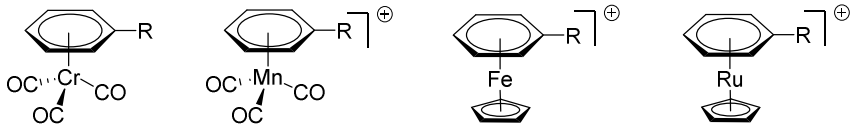


Figure 3-1. Representative η^6-arene complexes

η^6-Arene complex comprise of aromatic hydrocarbons and electron-deficient metal that renders the aromatic ring susceptible toward nucleophilic attack. Representative examples of η^6-arene complex are cationic complexes of iron, manganese and ruthenium ($CpFe^+$, $[Mn(CO)_3]^+$, $CpRu^+$) or $Cr(CO)_3$ (**Figure 3-1**).[148] In 1970s, η^6-arene metal complexes were already known as useful synthetic intermediates for the efficiency with which the arene rings can be modified. Parallel to the advancement of asymmetric reactions, the development of efficient and stereo-defined methodologies which could convert η^6-arene metal complexes into chiral nonaromatic products becomes the subject of research interests.

[148](a) Astruc, D. *Tetrahedron* **1983**, *39*, 4027-4095; (b) Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev*. **1984**, *84*, 525-543; (c) Pike, R. D.; Sweigart, D. A. *Synlett* **1990**, 565-571; (d) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev*. **2000**, *100*, 2917-2940; (e) Rose-Munch, F.; Rose, E. *Eur. J. Inorg. Chem*. **2002**, 1269-1283; (f) Rosillo, M.; Domínguez, G.; Pérez-Castells, J. *Chem. Soc. Rev*. **2007**, *36*, 1589-1604.

The η^6-complex of arene and $Cr(CO_3)_3$ is among the most widely studied one. The electron-deficient property of $Cr(CO)_3$ allows the arene ligand to undergo varied reactions (**Figure 3-2**). $Cr(CO)_3$ unit enhances the acidity of aromatic hydrogens to have allowed deprotonation with strong base such as lithium amides or other organolithium reagents. The benzylic site is also activated as the metal unit could exert stabilization effect on the then-formed benzylic carbocation and anion. Moreover, this metal unit has also been used as stereo-controlling group that could direct the side chain reaction or nucleophilic addition onto the arene ring.

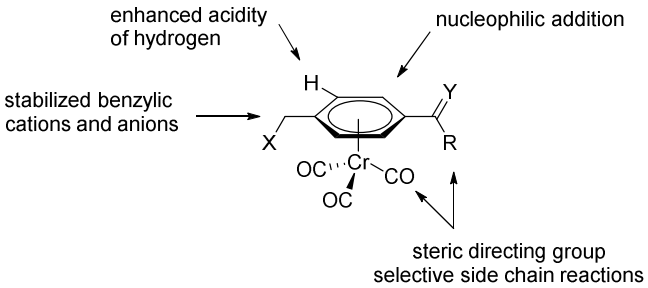


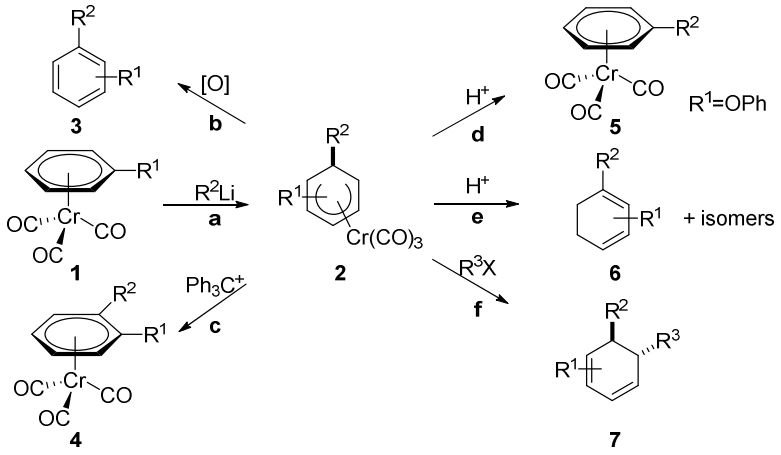
Figure 3-2. Reaction sites of $Cr(CO)_3$-coordinated arene

Among the above-mentioned active reaction sites of arene, the most important application of $Cr(CO)_3$ coordination is promoting nucleophilic addition onto the otherwise inert arene ring due to the strong electron-withdrawing effect of $Cr(CO)_3$ moiety. This reaction occurs at *exo* position with respect to $Cr(CO)_3$ unit under ambient reaction conditions (**Scheme 3-16**, path **a**).

In cases where other substituents are present, the nucleophilic additions occur with excellent regioselectivity. Substituents that could coordinate the nucleophilic metal compound will direct *ortho* attack.[149] Second, electron donating substituents such as alkyl, halide and amine groups

[149]Kündig, E. P.; Ripa, A.; Liu, R.; Amurrio, D.; Bernardinelli, G. *Organometallic* **1993**, *12*, 3724-3737.

often direct *meta* nucleophilic attack.[150] Bulky groups on arene such as *tert*-butyl or dimethylsilyl group often lead to *para* attack.[151]



Scheme 3-16. Selected examples on transformation of cyclohexadienyl complex

Organolithium reagent performs a nucleophilic addition onto $Cr(CO)_3$-arene complex **1** to give intermediate **2** (**Scheme 3-16**, path **a**) which could be converted into various functional synthetic blocks as representatively shown in **Scheme 3-16**. Oxidation (typically with iodine, CeO_2, Fe(III) or molecular oxygen) of the resulting cyclohexadienyl complex **2** affords arene product **3** with a new substituent on the aromatic ring (path **b**).[152] Otherwise, the cyclohexadienyl complex **2** could transform into substituted product **4** bearing arene-metal bond through hydride abstraction of cyclohexadienyl complex **1** with trityl cation (path **c**).[153] Moreover, if R^1 is a leaving group, the formed cyclohexadienyl intermediate **1** could rearomatize to give product **5** through tandem protonation-isomerization-elimination process (path **d**).[154] Also, this cyclohexadienyl

[150]Semmelhack, M. F.; Clark, G. R.; Farina, R.; Saeman, M. J. *J. Am. Chem. Soc*. **1979**, *101*, 217-218.
[151]Semmelhack, M. F.; Garcia, J. L.; Gortes, D.; Farina, R.; Hong, R.; Carpenter, B. K. *Organometallics* **1983**, *2*, 467-477.
[152]Semmelhack, M. F.; Clark, G. R.; Garcia, J. L.; Harrison, J. J.; Thebtaranonth, Y.; Wulff, W.; Yamashita, A. *Tetrahedron* **1981**, *37*, 3957-3965.
[153](a) Kündig, E. P.; Liu, R.; Ripa, A. *Helv. Chim. Acta*. **1992**, *75*, 2657-2660; (b) Fretzen, A.; Ripa, A.; Liu, R.; Bernardinelli, G.; Kündig, E. P. *Chem. Eur. J*. **1998**, *4*, 251-259.
[154]Schmalz, H.-G.; Schellhaas, K. *Angew. Chem. Int. Ed*. **1996**, *35*, 2146-2148.

intermediate **2** could be converted into cyclohexadiene and isomers under strong acidic conditions (path **e**).[155]

In some cases, the formation of cyclohexadienyl intermediate **2** could be followed by a tandem electrophilic attack to give the *trans*-5,6-disubstituted 1,3-cyclohexadienes **7** (path **f**). The electrophile will first add to the metal center of the chromium tricarbonyl complex and then migrates to form the cyclohexadienyl ring.[156] The stereochemical relationship of substituents R^2 and R^3 from this cascade of nucleophilic and electrophilic attack are strictly *trans* because the initial nucleophilic addition of organolithium reagent is *trans* to the $Cr(CO)_3$ unit, followed by sequential *exo* elecleophilic attack and an *endo* migration of electrophile with respect to $Cr(CO)_3$.

η^2-Coordination of arene

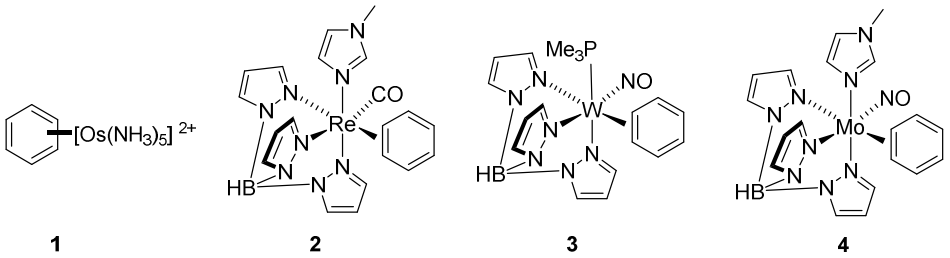


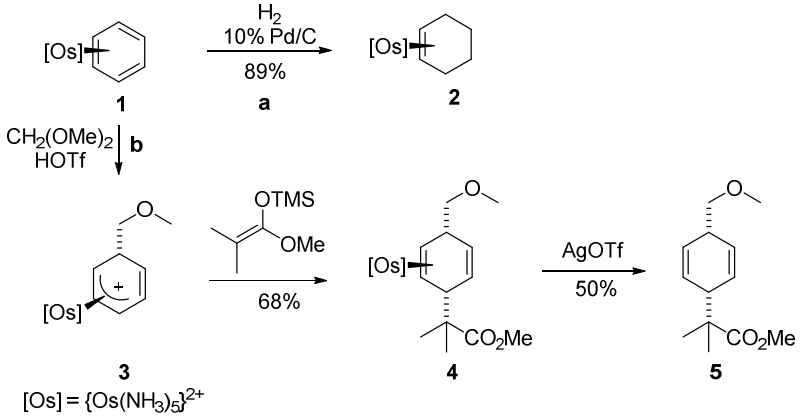
Figure 3-3. Representative η^2-arene complexes

In complement to the η^6-complex, the chemically inert aromatic hydrocarbons could also be activated *via* η^2-coordination with electron-rich metal. Most contributions of this work were made by W. D. Harman and co-workers. Although stable η^2-arene complexes are formed with a number of transition metals, it is found that only the d^6 octahedral metal complexes may activate the arene ligand towards electrophilic attack.[143] At the early stage, only pentaamineosmium (II) system was found applicable for this activation mode (**Figure 3-3**, **1**). Recently, rhenium,

[155]Rose-Munch, F.; Gagliardini, V.; Renard, G.; Rose, E. *Coord. Chem. Rev*. **1998**, *178-180*, 249-268.
[156]Kündig, E. P.; Cunningham, J. A.; Paglia, P.; Simmons, D. P.; Bernardinelli, G. *Helv. Chim. Acta*. **1990**, *73*, 386-404.

tungsten and molybdenum complexes are also found suitable for this mode of activation, for examples, rhenium (I) ([TpRe(CO)(MeIm)]) (**2**), tungsten (0) ([TpW(NO)(PMe_3)]) (**3**) and molybdenum (0) ([TpW(NO) (MeIm)]) (**4**).[157]

The arene ligand of η^2-arene complex can play dual role as π acid or Lewis base. Interaction between antibonding π orbitals of arene ligand and π_d orbital of metal will stabilize the metal-arene bond of the complex when it acts as a π acid. The π back-bonding enhances electron density of arene similar to the effect of electron donating substituents. Additionally, the structural data of the η^2-arene complexes reveal distortions in bonds lengths and π-electron localization of aromatic ring system. Both effects activate the η^2-coordinated aromatic ligand toward electrophilic addition.[153]



Scheme 3-17. Hydrogenation and tandem electrophilic/nucleophilic addition of η^2 benzene complex

Pentaammineosmium(II) system was the first to be identified and has been investigated most extensively. This electron-rich system binds simple benzenes in a η^2 fashion. One of the simplest transforrmations promoted by this coordination of arene to pentaammineosmium (II) is

[157](a) Harman, W. D. *Chem. Rev*. **1997**, *97*, 1953-1978; (b) Brooks, B. C.; Gunnoe, T. B.; Harman, W. D. Cood. *Chem. Rev.* **2000**, *206-207*, 3-61; (c) Smith, P. L.; Chordia, M. D.; Harman, W. D. *Tetrahedron* **2001**, *57*, 8203-8225; (d) Harman, W. D. Cood. *Chem. Rev.* **2004**, *248,* 853-866; (e) Keane, J. M.; Harman, W. D. *Organometallics* **2005**, *24*, 1786-1798; (f) Surendranath, Y.; Harman, W. D. *Dalton Trans*. **2006**, 3957-3965.

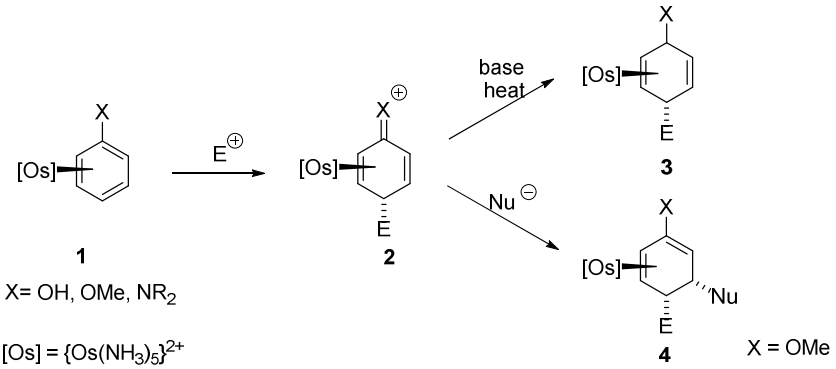
hydrogenation with hydrogen gas and palladium on charcoal (**Scheme 3-17**, path **a**). The reaction proceeds under ambient conditions (1 atm of hydrogen at 30 ^{o}C) to give cyclohexene complex **2** which could be further converted into cyclohexene after oxidative removal of the metal moiety. In this reaction, the pentaammineosmium(II) is the dearomatization agent and also the protective group of cyclohexene formed.[158]

Similar to the cascade nucleophilic/electrophilic addition of η^6-arene complex, the η^2 benzene complex could be derived into highly functionalized *para*-disubstituted 1,4-cyclohexadiene derivatives through a tandem electrophilic/nucleophilic addition reaction (**Scheme 3-17**, path **b**). As shown in **scheme 3-17**, through activation by trifluoromethanesulfonic acid (HOTf), dimethylacetal could add to complex **1** to form the benzenium intermediate **3**. The intermediate **3** could undergo nucleophilic addition reaction to give 1,4-cyclohexadiene complex **4**. An ensuing oxidative removal of metal moiety gives the 1,4-cyclohexadiene **5**. In contrast to the *trans* configuration of two substituents from nucleophilic/electrophilic addition of η^6-arene complex, the substituents introduced from this electrophilic/nucleophilic addition are *cis* to each other since both additions are now opposite to the pentaammineosmium (II) unit.[159]

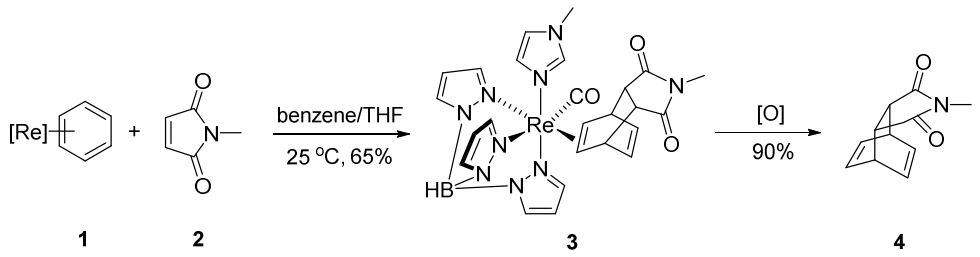
In addition to simple arenes, the pentaammineosmium (II) also binds phenol, aniline and anisole to form η^2-arene complex **1** that will react with electrophile to give stable 4*H*-arenium species **2**. The intermediate **2** is transformed to diene **3** by a basic treatment (**Scheme 3-18**). Alternatively, **2** could react with a nucleophile to give *cis*-1,2-disubstituted cyclohexadiene **4**. However, in the latter reaction, the X group plays a crucial role: the more active 4*H*-anisolium species from η^2-anisole osmium complexes could give product **4** while η^2-4*H*-phenol and 4*H*-anilinium

[158]Harman, W. D.; Taube, H. *J. Am. Chem. Soc*. **1988**, *110*, 7906-7907.
[159]Ding, F.; Kopach, M. E.; Sabat, M.; Harman, W. D. *J. Am. Chem. Soc*. **2002**, *124*, 13080-13087.

species could not undergo similar addition of nucleophiles.[160]



Scheme 3-18. Electrophilic addition and electrophilic/nucleophilic addition cascade of η^2-arene complex



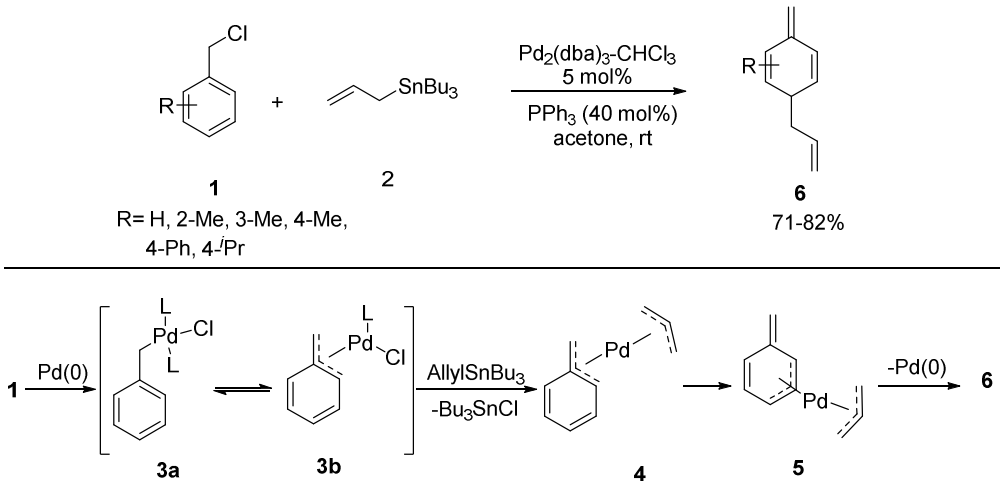
Scheme 3-19. Diels-Alder reaction of Rhenium complex-activated benzene and NMM

Benzenes activated by η^2-coordination of electron-rich metal could undergo reactions which are otherwise very difficult or even impossible without activation. For example, Diels-Alder cycloaddition of benzenes and alkenes is conventionally extremely difficult. Harman *et al.* reported that coordination of electron-rich metal unit {TpRe(CO)(MeIm)} enabled benzene and *N*-methylmaleimide (NMM, **2**) to undergo Diels-Alder reaction under ambient conditions. When arene-Re complex **1** and NMM **2** were stirred in the solvent mixture of benzene and THF at room temperature for 2 days, 65% yield of corresponding Diels-Alder product Re-complex **3** was formed in high diastereoselectivity (single isomer) (**Scheme 3-19**). Varied oxidative conditions

[160]Kopach, M. E.; Kolis, S. P.; Liu, R. G.; Robertson, J. W.; Chordia, M. D.; Harman, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 6199-6204.

enable the liberation of **4** from the Re-complex **3** in up to 90% yield.[161]

Transition metal-catalyzed dearomatization reaction

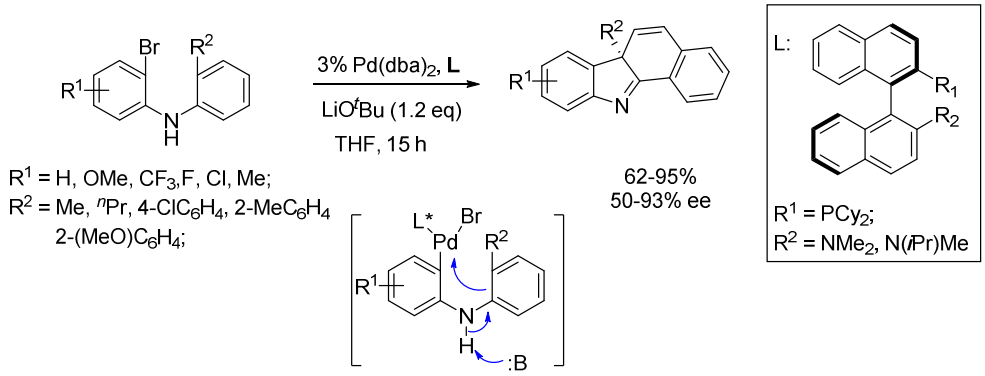


Scheme 3-20. Palladium-catalyzed dearomatization of benzyl chlorides with allyltributylstannane

The dearomatization of aromatic hydrocarbons is known as a fundamental chemical reaction because it could efficiently convert the prevalent planar arene compounds into alicyclic frameworks found in bioactive nature products and drugs. Several strategies have been developed such as oxidation and reduction using metal reagents or complexation of arene ring with transition metals as revealed in the precedent section. Although these methods are widely used and robust, the need of stoichiometric amount of metal reagents or the extra complexation/decomplexation steps limited their synthetic efficiencies. Hence, the discovery of novel catalytic dearomatization methods are being actively pursued by organic chemistry community and several innovative methods have been reported in recent decades.[162]

[161]Chordia, M. D.; Smith, P. L.; Meiere, S. H.; Sabat, M.; Harman, W. D. *J. Am. Chem.Soc*. **2001**, *123*, 10756-10757.
[162](a) Zhuo, C.-X.; Zhang, W.; You, S.-L. *Angew. Chem. Int. Ed*. **2012**, *51*, 12662-12686; (b) Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res*. **2014**, *47*, 2558-2573.

In 2001, Yamamoto *et al.* disclosed an unexpected coupling between benzyl chloride **1** and allyllstannane **2** to give a deraromatized product **6** at ambient temperature with catalytic amount of Pd(0) (**Scheme 3-20**).[163] The authors have proposed the following mechanistic steps underlying this coupling: Pd(II) species **3a** is first formed from oxidative addition of benzyl chloride **1** to Pd(0). At this stage, the related π-allyl species **3b** could present in equilibrium with **3a**. Next, allyltributylstannane **2** would react with **3b** and give bis-π-allyl complex of **4** and **5**. Reductive elimination will furnish the titled product as well as regenerate the palladium catalyst. Later, analogous naphthalene or phenantherene allyl chlorides were also proven to be effective substrates for this chemistry.[159b]

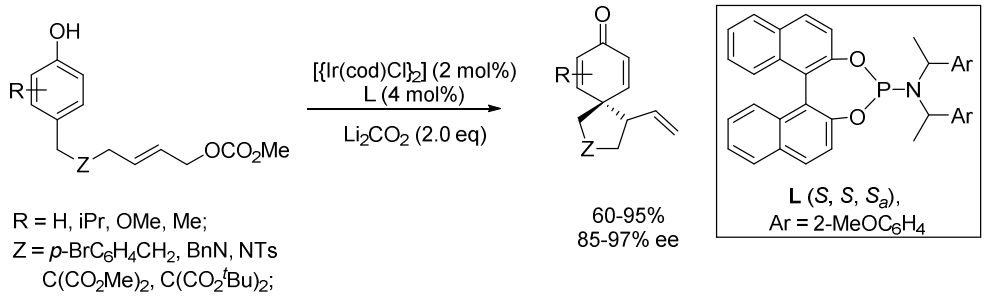


Scheme 3-21. Pd-catalyzed enantioselective naphthalenes dearomatization

Buchwald's group reported a pioneering asymmetric transition metal-catalyzed dearomatization of naphthalene derivatives for the synthesis of benzocarbazole derivatives in good chemical yields and *ee* values (**Scheme 3-21**) in 2009.[164] As the authors proposed, deprotonation of aniline group could increase the electron density of arene ring to allow intramolecular substitution and form the 3*H*-indole compounds. The same group later applied the similar strategy to synthesize a plethora of spirocyclohexadienones through arylative dearomatization of

[163](a) Bao, M.; Nakamura, H.; Yamamoto, Y. *J. Am. Chem. Soc*. **2001**, *123*, 759-760; (b) Lu, S. R.; Xu, Z. W.; Bao, M.; Yamamoto, Y. *Angew. Chem. Int. Ed*. **2008**, *47*, 4366-4369.
[164]García-Fortanet, J.; Kessler, F.; Buchwald, S. L. *J. Am. Chem. Soc*. **2009**, *131*, 6676-6677.

phenols.[165]



R = H, iPr, OMe, Me;
Z = *p*-$BrC_6H_4CH_2$, BnN, NTs
$C(CO_2Me)_2$, $C(CO_2{}^tBu)_2$;

60-95%
85-97% ee

Scheme 3-22. Iridium-catalyzed allylic substitution reaction

In their continuous efforts in developing iridium-catalyzed allylic reactions,[166] You's group developed the first iridium-catalyzed chiral allylic dearomatization reaction for phenols with excellent yields and enantioselectivities (**Scheme 3-22**). Synthesis of enantiomerical spirocyclohexadienone derivatives is conveniently achieved using this protocol.[167] At almost the same time, several analogous transition metals-catalyzed dearomatization were also reported independently by Feringa,[168] Tanaka,[169], Hamada,[170], Luan,[171], Murakama,[172], Mascareñas and Gulías[173] and Trost.[174]

3.1.2 Dearomatization/Diels-Alder Cycloaddition of Styrenes with Alkenes

Decalin is a common structural motif in numerous natural products, for examples, Artemisinic

[165]Rousseaux, S.; García-Fortanet, J.; Sanchez, M. A. D. A.; Buchwald, S. L. *J. Am. Chem. Soc*. **2011**, *133*, 9282-9285.
[166]Zhuo, C.-X.; Zheng, C.; You, S.-L. *Acc. Chem. Res*. **2014**, *47*, 2558-2573.
[167](a)Wu, Q.-F.; Liu, W.-B.; Zhuo, C.-X.; Rong, Z.-Q.; Ye, K.-Y.; You, S.-L. *Angew. Chem. Int. Ed*. **2011**, *50*, 4455-4458; (b) Zhuo, C.-X.; You, S.-L. *Angew. Chem. Int. Ed*. **2013**, *52*, 10056-10059.
[168]Rudolph, A.; Bos, P. H.; Meetsma, A.; Minnaard, A. J.; Feringa, B. L. *Angew. Chem. Int. Ed*. **2011**, *50*, 5834-5838.
[169]Shibuya, T.; Noguchi, K.; Tanaka, K. *Angew. Chem. Int. Ed*. **2012**, *51*, 6219-6222.
[170]Nemoto, T.; Zhao, Z. D.; Yokosaka, T.; Suzuki, Y.; Wu, R.; Homada, Y. *Angew. Chem. Int. Ed*. **2013**, *52*, 2217-2220.
[171]Nan, J.; Zuo, Z.; Luo, L.; Bai, L.; Zheng, H.; Yuan, Y.; Liu, J.; Luan, X.; Wang, Y. *J. Am. Chem. Soc*. **2013**, *135*, 17306-17309.
[172]Miura, T.; Funakoshi, Y.; Murakami, M. *J. Am. Chem. Soc*. **2014**, *136*, 2272-2275.
[173]Seoane, A.; Casanova, N.; Quiñone, N.; Mascareñas, J. L.; Gulías, M. *J. Am. Chem. Soc*. **2014**, *136*, 7607-7610.
[174]Trost, B. M.; Ehmke, V.; O'Keefe, M.; Bringley, D. A. *J. Am. Chem. Soc*. **2014**, *136*, 8213-8216.

acid, Crotomembranafuran, (+)-Bis(carvacrol) and (-)-Grandifloracin, where many of which possess promising bioactivities (**Figure 3-4**).[175] For the significance and wide occurrence of this structure, several excellent methodologies have been developed to assemble decalin.[176] However, efficient synthetic methods for this structure are still underdeveloped in view of atom-economy.

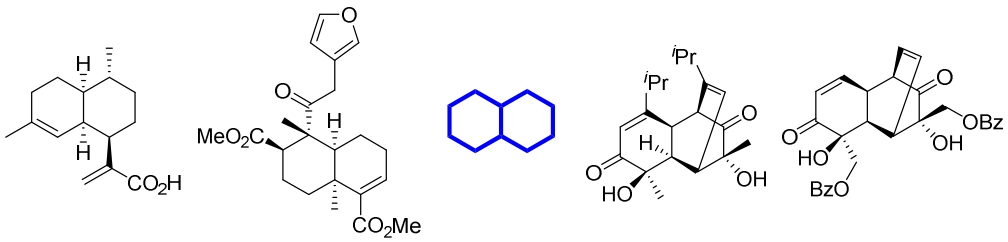
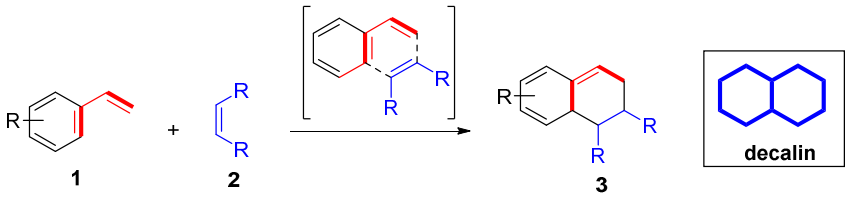


Figure 3-4. Representative natural products containing decalin structure

A conjugate 1,3-diene comprises a vinyl group and an adjacent aromatic double bond of styrene is a potential cycloaddition substrate with an alkene (**Scheme 3-23**). Considering the easy access of the styrene derivatives and the atom-economy of this reaction, this dearomatization/Diels-Alder reaction of styrene and alkene is an ideal method to prepare decalin.



Scheme 3-23. Dearomatization/Diels-Alder reaction of styrene and alkene

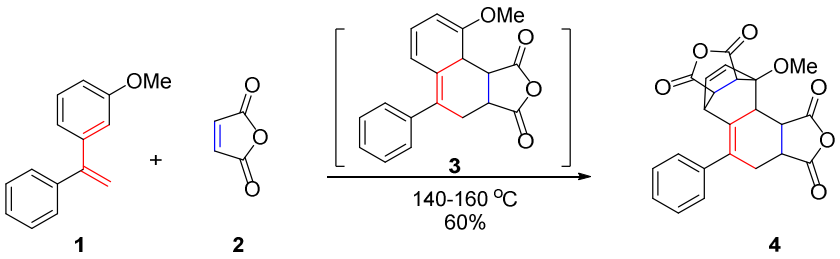
In 1930s, the first Diels-Alder cycloaddition between styrene and alkene was envisaged. Nonetheless, there is no widely applicable method developed in this area for three major reasons: first, styrenes tend to polymerize or copolymerize under thermal conditions and only very

[175](a) Hanson, J. R. *Nat. Prod. Rep.* **2009**, *26*, 1156-1171; (b) Hanson, J. R. *Nat. Prod. Rep.* **2011**, *28*, 1755-1772.
[176](a) Pindur, U.; Schneider, G. H. *Chem. Soc. Rev.* **1994**, 409-415; (b) Singh, V.; Iyer, S. R.; Pal, S. *Tetrahedron* **2005**, *61*, 9197-9231.

reactive dienophiles will react with styrenes to give the Diel-Alder adducts in acceptable yields; second, dienophiles of high reactivity or harsh reaction conditions is mandatory to disrupt the associated aromaticity. Often, common functionalities are not tolerated and results in low yields; third, the newly formed 1:1 Diels-Alder product (**3**, **Scheme 3-23**) is more reactive than styrene to undergo further reaction and give mixture of double Diels-Alder adduct, Diels-Alder-ene adduct and rearomatized product.[177] Herein, the development of dearomatization/Diels-Alder reaction of styrenes and alkenes will be highlighted.

3.1.2.1 Dearomatization/[4+2] cycloaddition of styrene and maleic anhydride

In 1930, Wagner-Jauregg reported the first dearomatization/[4+2] cycloaddition of styrene and alkene.[178] When the mixture of diarylethylene **1** and maleic anhydride **2** was heated, the bis adduct **4** (1:2 Diels-Alder cycloadduct) was formed in 60% yield *via* 1:1 Diels-Alder adduct **3** intermediate (**Scheme 3-24**). The reaction was thought to be unusual as the vinyl group and the adjacent arene double bond functionalize as enophile and the aromaticity of this arene ring was also destroyed.



Scheme 3-24. Dearomatization/[4+2] cycloaddition of diarylethylene **1** and maleic anhydride **2**

It was also found that the presence of the additional *a*-phenyl group on the double bond is vital for this reaction. When unactivated styrene was used instead of diarylethylene **1**, only the

[177]Sauer, J. *Angew. Chem. Int. Ed*. **1966**, *5*, 211-230.
[178](a)Wagner-Jauregg, T. *Ber*. **1930**, *63*, 3213-3224; (b) Wagner-Jauregg, T. *Ber*. **1931**, *491*, 1.

polymerization or copolymerization products of styrene and maleic anhydride were obtained. For this, several plausible reasons for the mandatory presence of *a*-phenyl group were proposed by Bergmann, Szmuszkowicz, and Fawaz: first, it could enhance resonance effect in the styrene system; second, the steric interaction between spatially adjacent hydrogen of the two aryl rings could force one of the two planar aromatic rings out of the plane, thus increases the coplanarity of the other aryl ring with the vinyl group.[179]

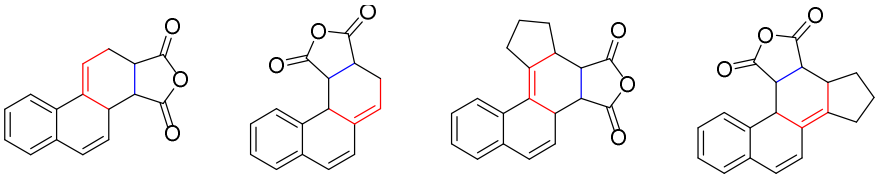
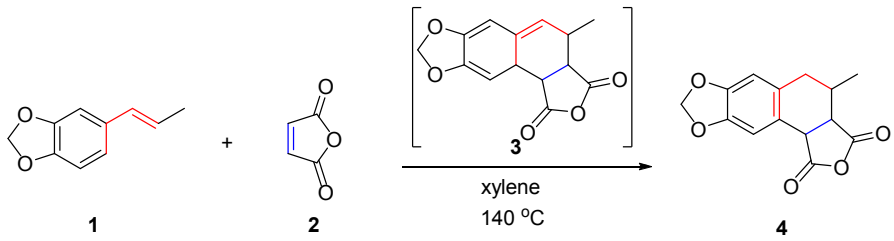


Figure 3-5. 1:1 Diels-Alder adducts of vinylnapthalene derivatives and maleic anhydride

Cohen, Warren, Bachmann and Kloetze found that several vinylnapthalene derivatives could also react with maleic anhydride to give corresponding 1:1 Diels-Alder adducts (**Figure 3-5**).[180] However, when other electron-deficient alkenes such as citraconic-anhydride, cinnamic aldehyde or fumaromyl dichloride was used in place of maleic anhydride, no analogous dearomatized product could be obtained.



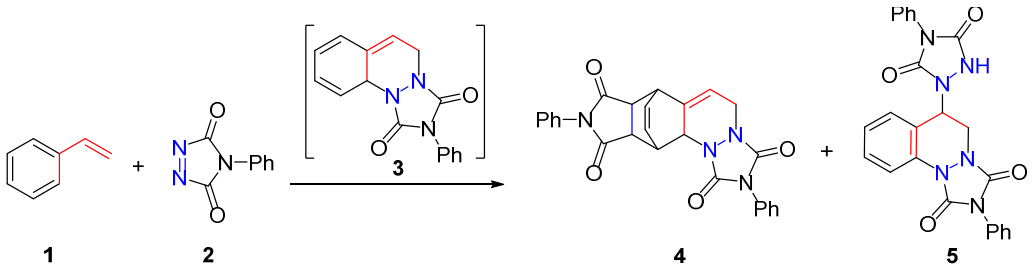
Scheme 3-25. Cycloaddition of *iso*-safrole **1** with maleic ahydride **2**

Hudsond and Robinson found that styrene with a *para*-electron-donating group would also

[179](a)Bergmann, F.; Szmuszkowicz, J.; Fawaz, G. *J. Am. Chem. Soc*. **1947**, *69*, 1773-1777; (b) Bergmann, F.; Szmuszkowicz, J. *J. Am. Chem. Soc*. **1948**, *70*, 2748-2752.
[180](a) Cohen. J.; Warren, F. L. *J. Chem. Soc*. **1937**, 1315; (b) Bergmann, E.; Bergmann, F. *J. Am. Chem. Soc.* **1937**, *59*, 1443-1450; (c) Bachmann, W. E.; Kloetzel, M. C. *J. Am. Chem. Soc*. **1938**, *60*, 2204-2210.

promote this reaction. For example, *iso*-safrole **1** coud react with maleic anhydride to give **4** following the rearrangement of 1:1 Diels-Alder adduct **3** intermediate (**Scheme 3-25**).[181]

Azodicarboxylate esters or amides too could undertake this cycloaddition chemistry with styrene. In the reaction of sytrene **1** and 4-phenyl-3H-1,2,4-triazole-3,5(4H)-dione **2**, an intriguing compound **5** was obtained together with 1:2 Diels-Alder adducts **4** which is the product of ene reaction between **2** with the pre-formed 1:1 Diels-Alder adduct **3** (**Scheme 3-26**).[182] This kind of reaction was first reported by Diels, Alder, Ingold and Meaver. Later, analogous Diels-Alder-ene adduct could also be obtained from the reaction between styrenes, indenes and electron-deficient alkynes.[183]



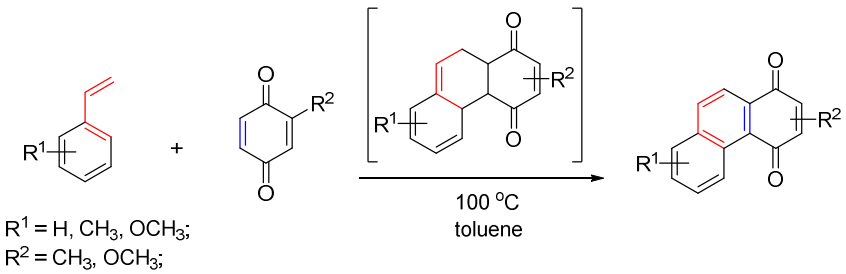
Scheme 3-26. Dearomatization reaction of styrene and 1,2,4-triazoline-3,5-dione

3.1.2.2 [4+2] Cycloaddition of styrene and benzoquinone

Lora-Tamayo and co-workers first reported the reactions of benzoquinone or derivatives with styrenes carrying electron-donating substituent that generate 1:1-tetradehydrogenated adducts

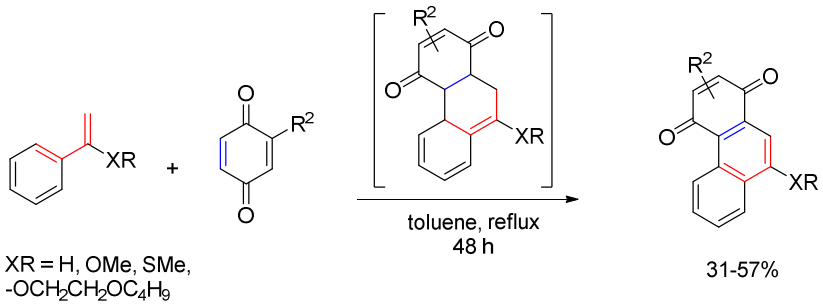
[181](a) Hudson, B. J. F.; Robinson, R. *J. Chem. Soc*. **1941**, 715-722; (b) Arnold, R. T.; Coyner, E. C. *J. Am. Chem. Soc*. **1944**, *66*, 1542-1545; (c) Bruckner, V.; Kovács, J. *J. Org. Chem*. **1948**, *13*, 641; (d) Bruckner, V.; Kovács, J. *J. Org. Chem*. **1949**, *14*, 65; (e) Hukki, J. *Acta. Chem. Scand*. **1951**, *5*, 31-53.
[182](a) Diels, O.; Alder, K. *Ann*. **1926**, *450*, 237; (b) Ingold, C. K.; Weaver, S. D. *J. Chem. Soc*. **1925**, *127*, 378; (c) Alder, K.; Niklas, H. *Ann. Chem*. **1954**, *585*, 97; (d) Cookson, R. C.; Gilani, S. S.; Stevens, D. R. *J. Chem. Soc. (C)* **1967**, 1905-1909.
[183](a) Alder, K.; Pascher, F.; Vagt, H. *Ber*. **1942**, *75*, 1501; (b) Huebner, F.; Strachan, P. L.; Donogue, E. M.; Cahoon, N.; Dorfman, L.; Margerison, R.; Wenkert, E. *J. Org. Chem*. **1967**, *32*, 1126; (c) Ciganek, E. *J. Org. Chem*. **1969**, *34*, 1923-1930; (d) Kotsuki, H.; Yamaguchi, T.; Ohno, K.; Ichikawa, Y.; Ochi, M. *Bull. Chem. Soc. Jpn*. **1994**, *67*, 599-602.

(**Scheme 3-27**).[184]



Scheme 3-27. Cycloaddition of styrenes and benzoquinone derivatives

The general characteristic features of the cycloaddition of styrenes and benzoquinones are as follows: First, this reaction exhibits high regioselectivity. The non-substituted double bond on benzoquinone is the addition site while addition could not take place when both double bonds are substituted (eg., *p*-xyloquinone and 4-methoxytoluquinone). Second, the reaction often give phenanthrenequinone derivative as the final product forming from oxidation of the 1:1 Diels-Alder adduct by bezoquinone derivatives. Aside from styrenes and benzoquinones, naphthoquinones and *a*-substituted styrenes could yield the cycloaddition product, too (**Scheme 3-28**).[185]



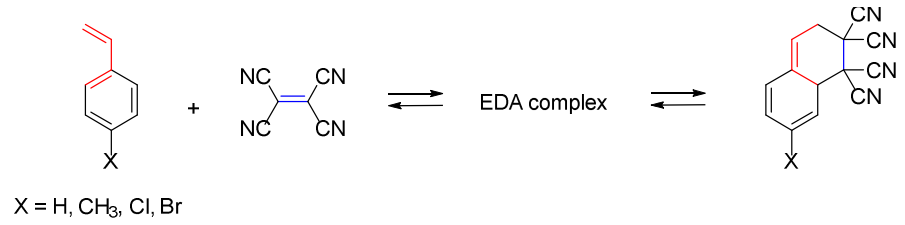
Scheme 3-28. Cycloaddition of *a*-substituted styrenes and *p*-benzoquinone derivatives

[184](a) Lora-Tamayo, M. *Tetrahedron* **1958**, 17-25; (b) Rosen, B. I.; Weber, W. P. *J. Org. Chem*. **1977**, *42*, 3463; (c) Manning, W. B.; Tomaszewski, J. E.; Muschik, G. M.; Sato, R. L. *J. Org. Chem*. **1977**, *42*, 3465; (d) Muschik, G. M.; Tomaszewski, J. E.; Sato, R. I.; Manning, W. B. *J. Org. Chem*. **1979**, *44*, 2150; (e) Manning, W. B.; Wilbur, D. J. *J. Org. Chem*. **1980**, *45*, 733; (f) Manning, W. B.; Kelly, T. P.; Muschik, G. M. *J. Org. Chem*. **1980**, *45*, 2535; (g) Manning, W. B.; *Tetrahedron Lett*. **1981**, *22,* 1571;
[185](a) Inouye, Y.; Kakisawa, H. *Bull. Chem. Soc. Jpn*. **1971**, *44*, 563-564; (b) Willmore, N. D.; Hoic, D. A.; Katz, T. J. *J. Org. Chem*. **1994**, *59*, 1889-1891.

3.1.2.3 Dearomatization/[4+2] cycloaddition of tetracyanoethylene and styrene

Tetracyanoethylene (TCNE) is the simplest analogue of percyanoalkene. The strongly electron-withdrawing cyano group is a poor dipolarophile. This contributes to the high electron-deficiency, electrophilicity and robustness of TCNE as powerful dienophile. Moreover, the four cyano groups of TCNE are too small to pose significant steric issues in adducts formation.[186]

Benzene and naphthalene form colored electron-donor-accptor (EDA) complexes with TCNE in solution. These aromatic hydrocarbons are known as poor diene components and could not form cycloaddition products with TCNE. Styrene composed of conjugated vinyl and phenyl groups are found ineffective to undergo [2+2]-or [4+2] cycloaddition with TCNE under mild conditions as well. Wiley and McKusick observed that its derivatives carrying *para*-electron-donating substituent (eg., CH_3, Cl or Br) could afford [2+2] cycloadducts.[187]



Scheme 3-29. Reversible [4+2] cycloaddition of styrenes and TCNE

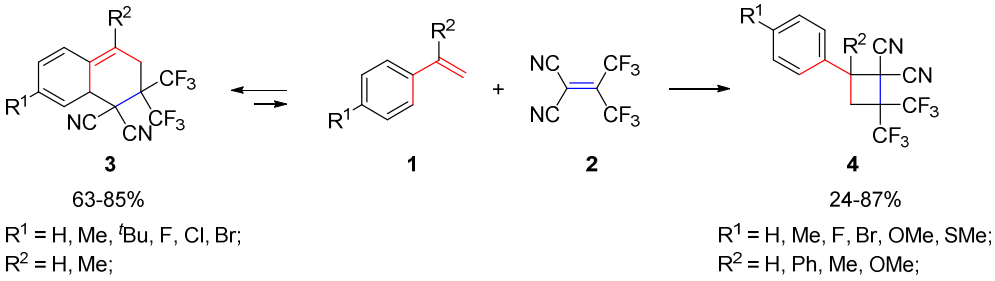
In a more detailed kinetic and mechanistic study, Nakahara and co-workers found that styrenes undergo reversible cycloaddition with TCNE at low temperature and high pressure to afford 1:1 Diels-Alder cycloadducts and EDA complexes (**Scheme 3-29**). Herein, the styrene serves as a diene and loses its aromaticity.[188] However, at ambient pressure or temperature, this cycloadduct

[186]Fatiadi, A. J. *Synthesis* **1987**, 749-789.
[187]Williams, J. K.; Wiley, D. W.; McKusick, B. C. *J. Am. Chem. Soc*. **1962**, *84*, 2210-2215.
[188](a) Nakahara, M.; Tsuda, Y.; Sasaki, M.; Osugi, J. *Chem. Lett*. **1976**, 731-736; (b) Nakahara, M.; Uosaki, Y.;

decomposes facilely and is indetectable. Moreover, other strong electron-deficient alkenes such as 3,3-dicyanoacrylate and hexafluorothioacetone (HFTA) also could undergo similar reactions with styrenes to give bis Diels-Alder adducts.[189]

3.1.2.4 Dearomatization/Diels-Alder reaction of BTF and styrenes

In 1990, Huisgen and co-worker reinvestigated the [2+2] and [4+2] cycloadditions of styrenes **1** with 2,2-bis(trifluoromethyl)ethylene-1,1-dicarbonitrile (BTF, **2**) which were originally reported by Middleton (**Scheme 3-30**).[190,191] They found that when R^1 was H, Me, ^{t}Bu, F, Cl or Br and R^2 was H or Me on styrene **1**, the dearoamtization products, tetrahydronaphthalenes **3** were generated after time span of half hour to one day in pentane at room temperature.



Scheme 3-30. Competing [4+2] and [2+2] cycloadditions of BTF and styrenes

The dearomatization/[4+2] cycloaddition is reversible and competes with the [2+2] cycloaddition of **1** and **2** to give cyclobutane **4**. As energy compensation for aromaticity loss exceeds the ring strain of cyclobutane, **3** would gradually transform to the cyclobutane **4** after prolonged stirring. It should be noted that although the dearomatization products are prone to decomposition, this

---

Sasaki, M.; Osugi, J. *Bull. Chem. Soc. Jpn*. **1980**, *53*, 3395-3399; (c) Uosaki, Y.; Nakahara, M.; Osugi, J. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 2569-2572; (d) Uosaki, Y.; Nakahara, M.; Osugi, J. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 3681-3683.

[189](a) Padias, A. B.; Hall, H. K. Jr. *J. Org. Chem*. **1987**, *52*, 4536-4539; (b) Padias, A. B.; Hall, H. K. Jr. *J. Org. Chem*. **1991**, *56*, 5540-5544; (c) Middleton, W. J. *J. Org, Chem*. **1965**, *30*, 1390-1394.

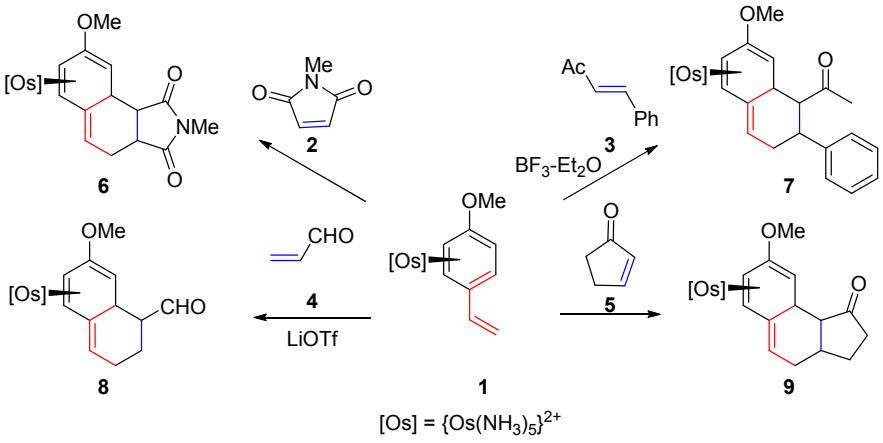
[190]Middleton, W. J. *J. Org. Chem*. **1965**, *30*, 1402.

[191](a) Brückner, R.; Huisgen, R.; Schmid, J. *Tetrahedron Lett*. **1990**, *31*, 7129-7132; (b) Brückner, R.; Huisgen, R. *Tetrahedron Lett*. **1990**, *31*, 7133-7136.

work represents the first isolable dearomatization/1:1 Diels-Alder adducts of styrenes and alkenes.

3.1.2.5 Dearomatization/[4+2] cycloaddition of transition metal-activated styrene and alkenes

Pentaammineosmium(II) has been demonstrated to be effective dearomatization agent to activate arenes for electrophilic additions by partial localization of aromatic π system.. In 1998, Harman and co-workers used this agent to coordinate and activate the aromatic moiety of styrenes selectively (**Scheme 3-31**). Consequently, functionalized decalin ring systems were constructed through [4+2] cycloaddition of metal-coordinated *p*-methoxylstyrene **1** with different electron deficient alkenes including *N*-methylmaleimide (NMM, **2**), *trans*-4-phenyl-3-buten-2-one (**3**), acrolein (**4**), and 2-cyclopenten-1-one (**5**).[192]

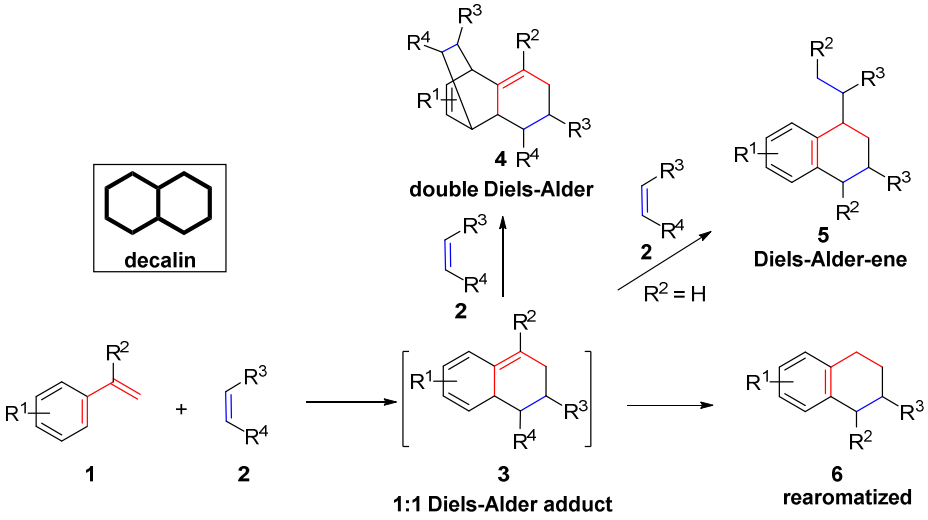


Scheme 3-31. Diels-alder reactions of pentaammineosmium(II)-coordinated styrene and alkenes

[192]Kolis, S. P.; Chordia, M. D.; Liu, R. G.; Kopach, M. E.; Harman, W. D. *J. Am. Chem. Soc.* **1998**, *120*, 2218-2226.

3.2 In(III)-TMSBr-catalyzed cascade dearomatization reaction of aryl alkynes and acrylates

Among the methods developed for the preparation of functionalized alicyclic compounds, the simple yet efficient strategy granted by dearomatization reaction of arenes are particularly attractive in view of their prevalence, low cost, and susceptibility for synthetic derivatizations. The decalin is a common structure in many natural products in which many of them carry promising bioactivities.[193] For the importance and prevalence of this structure, several excellent synthetic methodologies have been developed.[194] However, methods that comply with atom-economy and high efficiency are still in demand.



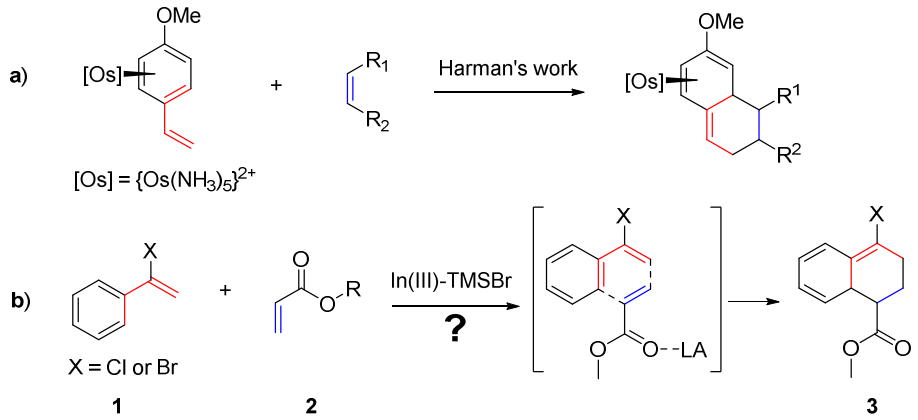
Scheme 3-32. Overview of dearomatization/[4+2] cycloaddition as well as further reactions of styrenes and alkenes

The vinyl group and adjacent arene double bonds of styrene constitute a conjugated diene moiety which is a potent cycloaddition reaction site with alkenes to form decalin (**Scheme 3-32**).

[193](a) Hanson, J. R. *Nat. Prod. Rep.* **2009**, *26*, 1156-1171; (b) Hanson, J. R. *Nat. Prod. Rep.* **2011**, *28*, 1755-1772.
[194](a) Pindur, U.; Schneider, G. H. *Chem. Soc. Rev.* **1994**, 409-415; (b) Singh, V.; Iyer, S. R.; Pal, S. *Tetrahedron* **2005**, *61*, 9197-9231.

Although this pathway was envisioned at early days with a few pioneering reports, wide application of these protocols are hindered by several major factors: (i) the need for dienophiles of exceptional reactivity or harsh reaction conditions to disrupt aromaticy resulting in incompatibility of most functional groups or low yields; (ii) high tendency of styrene polymerization and copolymerization under thermal condition; (iii) the newly formed 1:1 Diels-Alder **3** is of higher reactivity than styrene itself and could undergo further reaction to give a mixture of double Diels-Alder adduct 4, Diels-Alder-ene adduct **5** and rearomatized product **6** (**Scheme 3-32**). Harman and co-workers has reported an elegant Diels-Alder reaction of activated styrene with common dienophilies in good selectivity under ambient conditions, but stoichiometric amount of metal complex is necessary for styrene activation (see section **3.1.2.5**, **Scheme 3-31** for more details).

3.2.1 Proposed dearomatization/Diels-Alder reaction of *α*-halogenated styrenes and acrylates



Scheme 3-33. Diels-Alder reaction of styrenes and alkenes under ambient conditions: (**a**) Selective activation of styrene using transition metal; (**b**) Proposed activation of acrylate using In(III)-TMSBr system

Most of the early reports on dearomatization/[4+2] reactions of styrenes and alkenes focus on probing substrate scopes to include more styrenes derivatives and electron-deficient alkenes.

Usually, high reaction temperature or extremely electron-deficient alkenes is required which causes the moderate isolated yields and by-products formation. W. D. Harman and co-workers used a different strategy: selective styrene activation by coordination of electron-rich transition metal to afford desired product under mild conditions while extremely electron-deficient alkene is also not required (**Scheme 3-33a**).

Inspired by Harman's seminal work, another plausible method envisaged involves application of catalyst to enhance the reactivity of alkene partner to obviate harsh conditions as well as side reactions (**Scheme 3-33b**). There are experimental and theoretical studies on acceleration of Diels-Alder reaction under ambient conditions with the use of Lewis acid catalysts.[195] Moreover, from the above-discussed [2+2] cycloaddition of aryl alkynes and acrylates, acrylates were thought to be activated efficiently by the combined Lewis acid system of In(III)-TMSBr. This enhanced the reactivity of acrylates with moderate electron-deficient property to be used as suitable alkene substrates in the presence of this combined catalyst system.

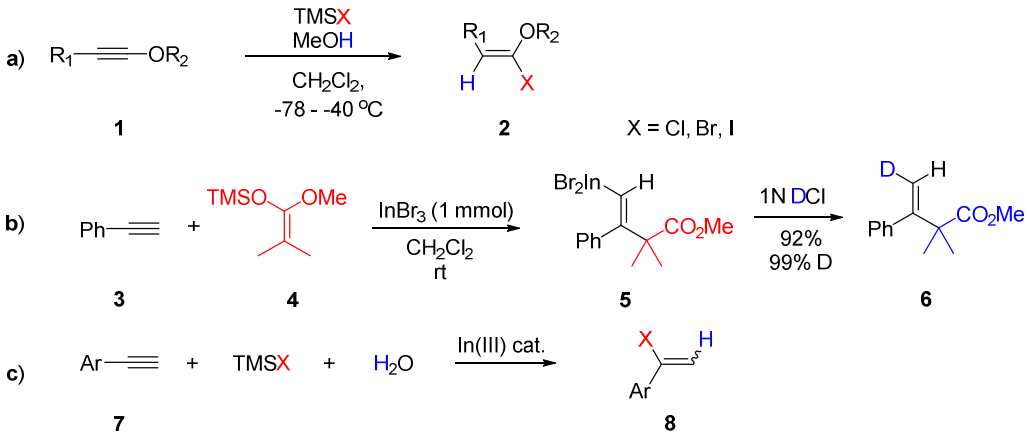
Although employment of varied styrenes derivatives in dearomatization/Diels-Alder reaction is common, there is no report on application of *a*-halogenated styrenes and acrylates in this type of reaction. This could be due to high temperature required to overcome energy barrier for aromaticity loss especially under thermal conditions, which in turn could have decomposed the

[195](a) Sauer, J. *Angew. Chem. Int. Ed.* **1967**, *6*, 16-33; (b) Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed*. **1980**, *19*, 779-807; (c) Brieger, G.; Beennett, J. N. *Chem. Rev*. **1980**, *80*, 63-97; (d) Wagner-Jauregg. *Synthesis* **1980**, 165-214; (e) Oppolzer, W. *Angew. Chem. Int. Ed*. **1984**, *23*, 876-889; (f) Fallis, A. *Can. J. Chem*. **1984**, *62*, 183-234; (h) Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev*. **1993**, *93*, 741-761; (i) Dias, L. *J. Braz. Chem. Soc*. **1997**, *8*, 289-332; (j) Cossu, S.; Fabris, F.; De Lucchi, O. *Synlett* **1997**, 1327-1334; (k) Wender, P. A.; Smith, T. *Tetrahedron* **1998**, *54*, 1255-1275; (l) Barluenga, J.; Suárez-Sobrino, A.; López, L. *Aldrichimica Acta* **1999**, *32*, 4-15; (m) Otto, S.; Gngberts, J. B. F. N. *Pure. Appl. Chem*. **2000**, *72*, 1365-1372; (n) Bear, B. R.; Sparks, S. M.; Shea, B. J. *Angew. Chem. Int. Ed*. **2001**, *40*, 820-849; (o) Kumar, A. *Chem. Rev*. **2001**, *101*, 1-20; (p) Brocksom, T. J.; Nakamura, J.; Ferreira, M. L.; Brocksom, U. *J. Braz. Chem. Soc.* **12**, *2001*, 597-622; (q) Nicolaou, K. C.; Snyder, S. A.; Montagnon, T.; Vassilikogiannakis, G. *Angew. Chem. Int. Ed*. **2002**, *41*, 1668-1698

unstable of *α*-halogenated styrenyl substrates. Ambient reaction conditions and shorter reaction time could thus allow the use of *α*-halogenated styrenes in this reaction. Additionally, the vinyl-bromide group provides handle for further chemical modifications.

Therefore, we proposed that the *α*-halogenated arylalkenes and acrylates could be a suitable substrate combination for dearomatizaiton/Diels-Alder reaction provided mild conditions and short reaction time is possible with the use of the combined Lewis acid system (In(III)-TMSBr). This strategy, if successful, is thought to address existing limitations of poor functional group incompatibility, low yields and lack of reaction selectivity. In addition, this new combination of α-halogenated styrenes, acrylates and Lewis acidic In(III)-TMSBr may bring about novel reaction modes.

3.2.2 Proposed *in situ* generation *α*-halogenated styrenes from aryl alkynes

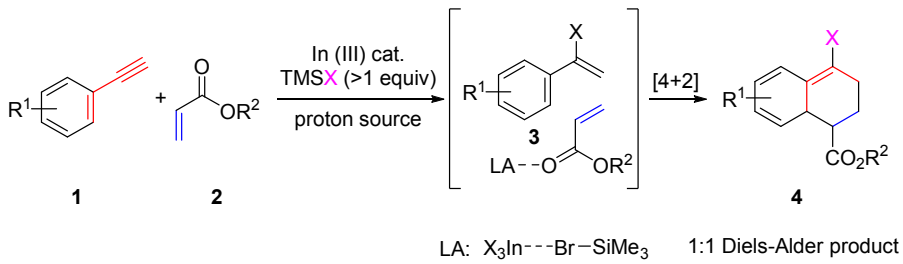


Scheme 3-34. Selected methods on alkenes preparation from alkynes and hypothesized *in situ* generation of *α*-halogenated styrene from aryl alkyne

In 2000, Jin and Yu reported that acetylenic ether **1** could be converted to *α*-halo vinyl ether **2** using hydrogen halide formed *in situ* from trimethylsily halide (TMSX, X = Cl, Br, I) and MeOH

(**Scheme 3-34a**).[196] In 2009, Baba and co-workers reported an $InBr_3$-mediated addition of ketene silyl acetals **4** to alkynes **3** to give alkenylindium species **5** which could react with aqueous deuterium chloride to give styrene **6** (**Scheme 3-34b**).[197] Inspired by these two works, we proposed that the unstable α-halogenated arylalkene could also be prepared *in situ* from aryl alkyne using TMSBr, In(III) catalyst and H_2O as proton source (**Scheme 3-34c**).

Having recognized this possibility, we further considered the realization of one-pot procedure for this cascade of reactions: *in situ* generation of α-aryl vinyl bromide **3** from aryl alkyne **1** in the presence of a proton source and the ensuing [4+2] cycloaddition with Lewis acid-activated acrylate **2** to give 1:1 Diels-Alder product **4** which could presumably undergo further reactions (**Scheme 3-35**).



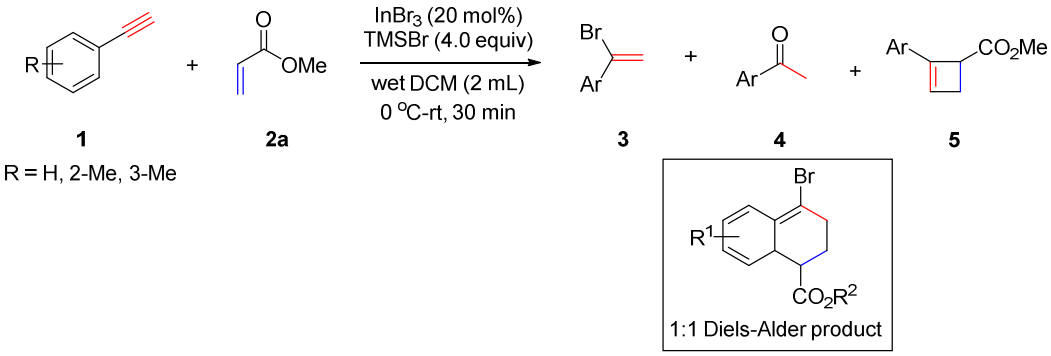
Scheme 3-35. Hypothesized one-pot vinyl halides formation and dearomatization/Diels-Alder reaction

3.2.3 Preliminary results of cascade dearomatization reaction of aryl alkynes and acrylates

To test this hypothesis, reactions of methyl acrylate **2a** with different aryl acetylenes **1** (eg., phenyl acetylene, 2-ethynyltoluene and 3-ethynyltoluene) were attempted employing $InBr_3$ (20 mol%) and TMSBr (4 equiv; serves as both additive and bromine source) in wet CH_2Cl_2 (water

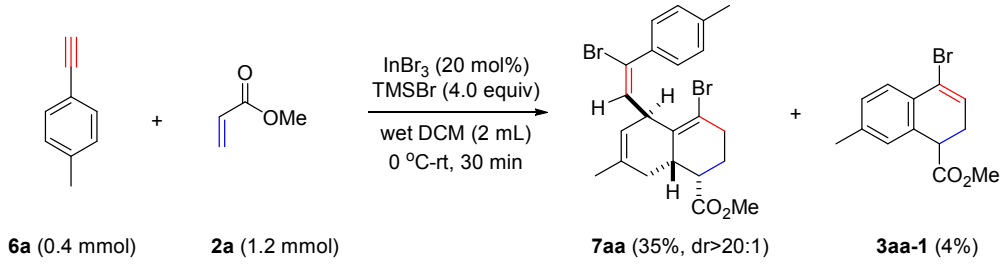
[196]W. S. Yu, Z. D. Jin, *J. Am. Chem. Soc.* **2000**, *122*, 9840.
[197]Nishimoto, Y.; Moritoh, R.; Yasuda, M.; Baba, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 4577-4580.

saturated CH_2Cl_2 which could serve as proton source and solvent).[198] When the reaction mixture was stirred for 30 min while warming up from 0 °C to room temperature, α-aryl vinyl bromides **3**, acetophenones **4** and cyclobutenes **5** were obtained but not the hypothesized 1:1 Diels-Alder product (**Scheme 3-36**).



Scheme 3-36. Attempted one-pot cascade reaction of aryl acetylene **1** and methyl acrylate **2a**

In the reaction using 4-ethynyltoluene **6a** and methyl acrylate **2a** under identical reaction conditions, no hypothesized 1:1 Diels-Alder product was obtained, either. To our surprise, this reaction instead produced a polycyclic ene **7aa** in 37% yield as single isomer, along with **7aa-1** in 4% yield (**Scheme 3-37**).



Scheme 3-37. Preliminary result for cascade dearomatization reaction of 4-ethynyltoluene **6a** and methyl acrylate **2a**

[198]For a typical example using wet CH_2Cl_2 as proton source, see: L. M. Zhang, S. Z. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 1442. The wet CH_2Cl_2 was generated by shaking distilled CH_2Cl_2 with deionized water in a separatory funnel.

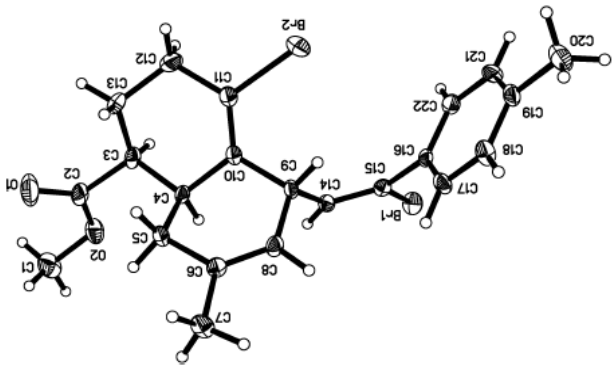
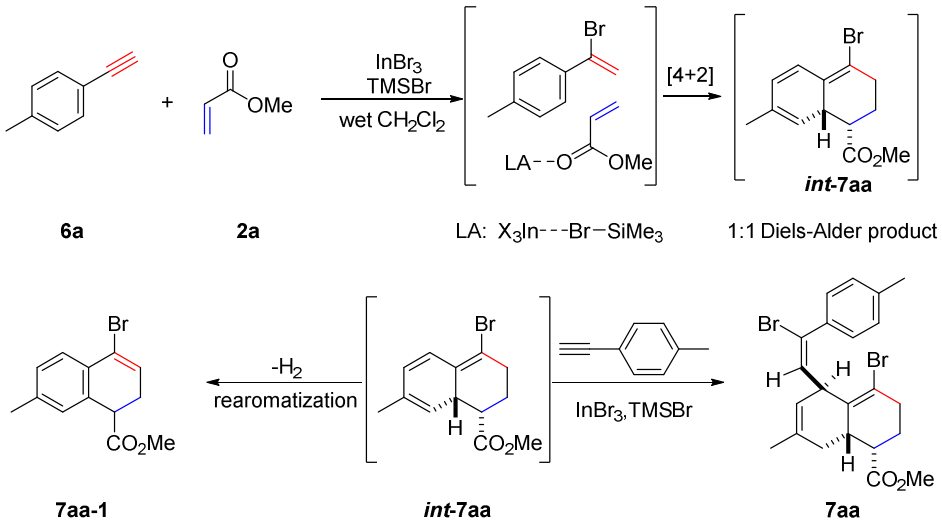


Figure 3-6. X-ray crystallograhy structure of of **7aa**, Methyl (1*S**,5*S**,8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(*p*-tolyl)vinyl)-7-methyl-1,2,3,5,8,8a-hexahydronaphthalene-1-carboxylate

The structure of dearomatized product **7aa** was first determined by ^{1}H, ^{13}C and 2D NMR spectra and was then unequivocally supported by single crystal X-ray diffraction analysis (**Figure 3-6**). Single crystal of **7aa** was obtained from co-solvent system of hexane and MeOH. Prominently, this reaction efficiently built up highly diastereoselective complex molecular architecture containing a decaline ring, three stereogenic centers, three carbon-carbon double bonds and two vinyl bromide motifs, which are ubiquitously found in terpenes, steroids and other natural products from simple substrates under operationally simple procedure.

3.2.4 Tentative proposal of reaction pathway for the formation of 7aa and 7aa-1

After meticulous structural examination of **7aa** and **7aa-1**, we tentatively put forward a pathway for the formation of **7aa** and **7aa-1** (**Scheme 3-38**). The initially postulated [4+2]-cycloaddition could have indeed taken place to give 1:1 Diels-Alder adduct *int*-**3aa** as an intermediate. The expected high reactivity of *int*-**7aa** could have rendered it to participate in tandem reactions through interception by another molecule of aryl alkyne **6a** to generate **7aa** or undergo rearomatization to give **7aa-1**.



Scheme 3-38. Tentatively proposed pathway for the formation of **7aa** and **7aa-1**

To the best of our knowledge, this is the first example of interception of 1:1 Diels-Alder adduct by a nucleophilic addition of alkyne. While in other report, 1:1 Diels-Alder adduct reacts with another dienophile molecule to form double-Diels-Alder adduct or Diels-Alder-ene product (refer to **Section 3.1.2** for details).

3.2.5 Reaction conditions optimization for cascade dearomatization reaction of 6a and 2a

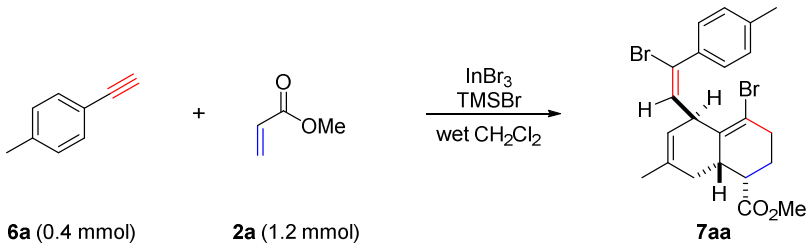
Intrigued by the efficient construction of elaborate molecular framework from simple substrates under operationally simple procedure, we commenced the optimization studies of this reaction with 4-ethynyltoluene (**6a**) and methyl acrylate (**2a**).

3.2.5.1 Effects of indium catalysts, solvents and additives on the formation 7aa

It was found that co-existence of indium catalyst, TMSBr and wet solvent was mandatory for occurrence of reaction. In the absence of In(III) salt as catalyst, no desired product could be obtained, even the reaction was refluxed at 80 ^{o}C (**Table 3-1**, entries 1-2). Without TMSBr, no desired product could be obtained, albeit at 80 ^{o}C or with 1.0 equiv of $InBr_3$ (entries 3-5). When

the wet CH_2Cl_2 was replaced by anhydrous CH_2Cl_2, only trace formation of dearomatization product could be observed in crude NMR (entry 6). We thought that adventitious moisture from reagent and solvent accounted for the trace product formation.

Table 3-1. Effects of indium catalyst, solvents and additives on **7aa** formation[a]



6a (0.4 mmol) **2a** (1.2 mmol) **7aa**

Entry	Catalyst	Solvent	TMSX	Yield [%][b]
1	-	CH_2Cl_2	TMSBr	0
2[c]	-	$ClCH_2CH_2Cl$	TMSBr	0
3	$InBr_3$	CH_2Cl_2	-	0
4[c]	$InBr_3$	$ClCH_2CH_2Cl$	TMSBr	0
5[d]	$InBr_3$	CH_2Cl_2	TMSBr	0
6[e]	$InBr_3$	CH_2Cl_2	TMSBr	<1

[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), $InBr_3$ (20 mol%), TMSBr (4 equiv), wet CH_2Cl_2 (2 mL), 0 °C-rt, 30 min, N_2. [b] Isolated yields. [c] The reaction temperature was 80 °C. [d] 1.0 equiv of $InBr_3$ was used. [e] Andydrous CH_2Cl_2 (2 mL) was used as solvent.

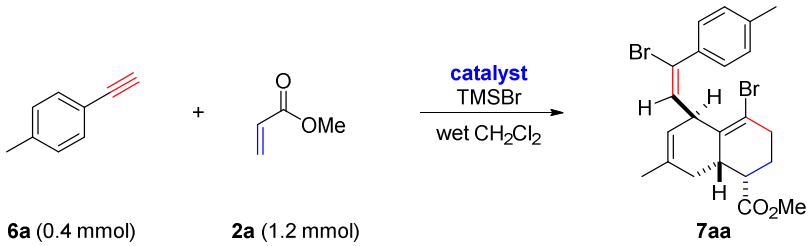
3.2.5.2 Effects of indium catalysts on the yields of 7aa

Having identified the crucial role of catalyst, TMSBr and wet CH_2Cl_2, different indium(III) salts such as $InBr_3$, InF_3, $InCl_3$, InI_3, $In(OTf)_3$, $In(tfacac)_3$, $In(acac)_3$, $In(CF_3CO_2)_3$, $In(CH_3CO_2)_3$ and $In_2(SO_4)_3$ were examined for optimal formation of 6aa and the results were tabulated in **Table 3-2**.

In contrast to the previously discussed [2+2] cycloaddition of aryl alkynes and acrylates which could only be promoted by In(III) halides and $In(tfacac)_3$, most of the tested In(III) catalysts

(**Table 3-2**, entries 1-9) gave the desired dearomatization product except indium (III) sulfate (entry 10). Among the different indium catalysts evaluated, indium(III) trifluoroacetylacetonate [$In(tfacac)_3$] was found to exhibit the best catalytic activity to give 65% yield of **7aa** (entry 6). It should be noted that the $In(acac)_3$ which is inapplicable in the [2+2] cycloaddition could also promote this dearomatization reaction to give **7aa** in 25% yield (entry 7). On the other hand, reactions with In(I) and In(II) catalysts could not furnish any titled product (entries 11-12).

Table 3-2. Effects of indium catalysts on the yields of **7aa**[a]



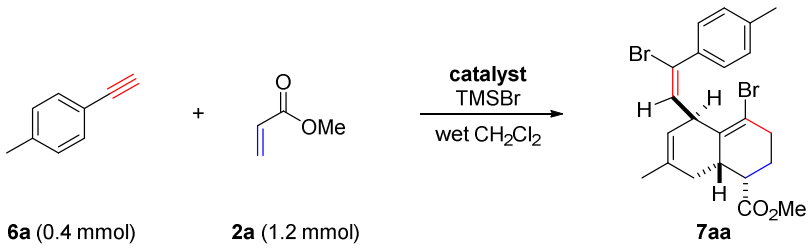
6a (0.4 mmol) **2a** (1.2 mmol) **7aa**

Entry	**Catalyst**	Solvent	TMSX	Yield [%][b]
1	$InBr_3$	CH_2Cl_2	TMSBr	35
2	InF_3	CH_2Cl_2	TMSBr	41
3	$InCl_3$	CH_2Cl_2	TMSBr	14
4	InI_3	CH_2Cl_2	TMSBr	40
5	$In(OTf)_3$	CH_2Cl_2	TMSBr	33
6	$In(tfacac)_3$	CH_2Cl_2	TMSBr	65
7	$In(acac)_3$	CH_2Cl_2	TMSBr	25
8	$In(CF_3CO_2)_3$	CH_2Cl_2	TMSBr	31
9	$In(CH_3CO_2)_3$	CH_2Cl_2	TMSBr	27
10	$In_2(SO_4)_3$	CH_2Cl_2	TMSBr	-
11	InI	CH_2Cl_2	TMSBr	-
12	$InBr_2$	CH_2Cl_2	TMSBr	-

[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), catalyst (20 mol%), TMSBr (4 equiv), wet CH_2Cl_2 (2 mL), 0 ^oC-rt, 30 min, N_2. [b] isolated yields.

3.2.5.3 Effects of Lewis acid catalysts on the reaction of 7aa

Table 3-3. Effects of Lewis acid catalysts on the reaction of **7aa**[a]



6a (0.4 mmol) **2a** (1.2 mmol) **7aa**

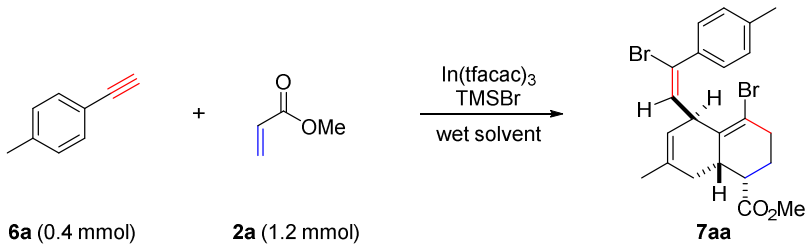
Entry	**Catalyst**	Solvent	TMSX	Yield (%)[b]
1	$AlBr_3$	CH_2Cl_2	TMSBr	0
2	$ZnCl_2$	CH_2Cl_2	TMSBr	0
3	$TiCl_4$	CH_2Cl_2	TMSBr	0
4	$FeBr_3$	CH_2Cl_2	TMSBr	23
5	$Fe(tfacac)_3$	CH_2Cl_2	TMSBr	31
6	$FeCl_3$	CH_2Cl_2	TMSBr	16
7	$Sc(OTf)_3$	CH_2Cl_2	TMSBr	0
8	$GaCl_3$	CH_2Cl_2	TMSBr	0
9	$MgCl_2$	CH_2Cl_2	TMSBr	0
10	AgCl	CH_2Cl_2	TMSBr	0
11	$SnCl_2$	CH_2Cl_2	TMSBr	0
12	$AuCl_3$	CH_2Cl_2	TMSBr	0

[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), catalyst (20 mol%), TMSBr (4 equiv), wet CH_2Cl_2 (2 mL), 0 °C-rt, 30 min, N_2. [b] Isolated yields.

Beside indium catalysts, other common Lewis acid catalysts (eg., $AlBr_3$, $ZnCl_2$, $TiCl_4$, $FeBr_3$, $Fe(tfacac)_3$, $Sc(OTf)_3$, $GaCl_3$, $MgCl_2$, AgCl, $SnCl_2$, and $AuCl_3$) have also been tested and the results were summarized in **Table 3-3**. The reaction outcomes were similar to that of [2+2] cycloaddition. Most of the tested Lewis acid catalysts could not promote the reaction except for iron(III) catalysts which provided **7aa** in moderate yields (entries 4-6).

3.2.5.4 Effect of solvent on 7aa formation

Table 3-4. Effects of wet solvents on the reaction of **7aa**[a]



6a (0.4 mmol) **2a** (1.2 mmol) **7aa**

Entry	Catalyst	**Solvent**	TMSX	Yield (%)[b]
1	$In(tfacac)_3$	hexane	TMSBr	0
2	$In(tfacac)_3$	benzene	TMSBr	0
3	$In(tfacac)_3$	toluene	TMSBr	0
4	$In(tfacac)_3$	Et_2O	TMSBr	0
5	$In(tfacac)_3$	THF	TMSBr	0
6	$In(tfacac)_3$	1,4-dioxane	TMSBr	0
7	$In(tfacac)_3$	EtOAc	TMSBr	0
8	$In(tfacac)_3$	CH_3CN	TMSBr	0
9	$In(tfacac)_3$	DMF	TMSBr	0
10	$In(tfacac)_3$	DMSO	TMSBr	0
11	$In(tfacac)_3$	CH_3NO_2	TMSBr	17
12	$In(tfacac)_3$	CH_2Cl_2	TMSBr	65
13	$In(tfacac)_3$	$CHCl_3$	TMSBr	0
14	$In(tfacac)_3$	DCE	TMSBr	31
15	$In(tfacac)_3$	DBE	TMSBr	25
16	$In(tfacac)_3$	MeOH	TMSBr	0

[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (4 equiv), wet solvent (2 mL), 0 ^oC-rt, 30 min, N_2. [b] Isolated yields.

Having determined the best catalytic activity of $In(tfacac)_3$ in this cascade dearomatization reaction of **6a** and **2a** (**Table 3-2**, entry 6), different water-saturated solvents were screened (**Table 3-4**). Similar to [2+2] cycloaddition of aryl alkynes and acrylates described earlier on, this reaction is also highly solvent-dependent. Only halogenated solvents such as CH_2Cl_2, 1,2-dichloroethane, 1,2-dibromoethane as well as CH_3NO_2 mediated the formation of desired product **7aa** with reaction in wet CH_2Cl_2 gave the highest yield (entries 11-12, 14-15). The

non-polar or weakly polar solvents such as hexane, benzene and toluene (entries 1-3) were tested and no desired product could be obtained. Reactions with common polar aprotic solvents such as Et_2O, THF, 1,4-dioxane, EtOAc, CH_3CN, DMF and DMSO (entries 4-10) and polar protic solvents (MeOH, entry 16) failed to provide **7aa** either.

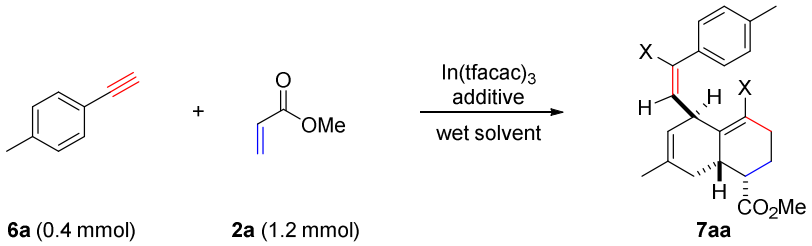
The molarity of this reaction was also checked (entries 12, 17 and 18) and it was shown that 2 mL of wet CH_2Cl_2 (per 0.4 mmol of **1a**) or 0.2 M of **6a** gave the best outcome (entry 12). A plausible reason for the lower yield with 1 mL of wet CH_2Cl_2 could be the inadequate amount of H_2O in wet solvent for the formation **7aa**. However, it is also interesting that when 3 mL of CH_2Cl_2 was used, only trace amount of desired product could be detected from crude NMR.

3.2.5.5 Effects of additives on 7aa formation

With $In(tfacac)_3$ and wet CH_2Cl_2 as the optimal catalyst and solvent for **7aa** formation (**Table 3-4**, entry 12), other additives in addition to TMSBr were tested (**Table 3-5**). When chlorotrimethylsilane (TMSCl), iodotrimetylsilane (TMSI), or chlorotriethylsilane (TESCl) was used individually in conjunction with $In(tfacac)_3$, trace or no corresponding dearomatization product was formed (entries 1-2).

Other additives containing silicon or halogen atoms were also tested, for examples, *t*-butyldimethylsilyl chloride (TBSCl), triisopropylsilyl chloride (TIPSCl), *t*-butyldiphenylsilane (TBDPSCl), *t*-butyldimethylsily trifluoromethanesulfonate (TBSOTf), NaBr, HBr-H_2O and tetrabutylammonium bromide (TBAB) (entries 4-10), but neither promoted this chemistry, similar to the above-mentioned [2+2] cycloaddition of aryl alkynes and acrylates.

Table 3-5. Effect of additives on the yields of **7aa**[a]



6a (0.4 mmol) **2a** (1.2 mmol) **7aa**

Entry	Catalyst	Solvent	TMSX	Yield (%)[b]
1	$In(tfacac)_3$	CH_2Cl_2	TMSCl	<5%
2	$In(tfacac)_3$	CH_2Cl_2	TMSI	0
3	$In(tfacac)_3$	CH_2Cl_2	TESCl	0
4	$In(tfacac)_3$	CH_2Cl_2	TBSCl	0
5	$In(tfacac)_3$	CH_2Cl_2	TIPSCl	0
6	$In(tfacac)_3$	CH_2Cl_2	TBDPS	0
7	$In(tfacac)_3$	CH_2Cl_2	TBSOTf	0
8	$In(tfacac)_3$	CH_2Cl_2	NaBr	0
9	$In(tfacac)_3$	CH_2Cl_2	HBr-H_2O	0
10	$In(tfacac)_3$	CH_2Cl_2	TBAB	0

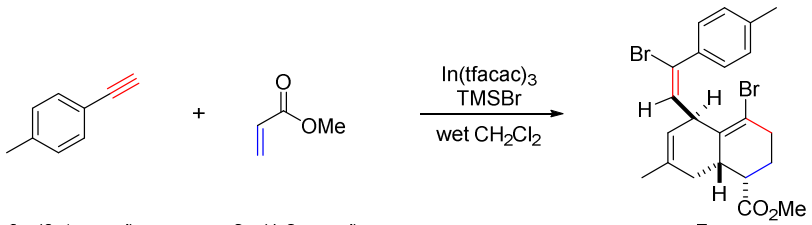
[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), $In(tfacac)_3$ (20 mol%), additive (4 equiv), 0 ^oC-rt, 30 min, N_2. [b] Isolated yields.

3.2.5.6 Effect of other parameters on reaction of 7aa

To further improve the reaction efficiency, other parameters of this reaction were varied to achieve better yield of **7aa** (**Table 3-6**). When the TMSBr loading decreased to 3.0 equiv or increased to 5.0 equiv (entries 1-2), both reaction yields were lower than that with 4.0 equiv of TMSBr (**Table 3-4**, entries 12). The equivalence of methyl acrylate **2a** was also examined: when 2.0 or 4.0 equiv of **2a** was used, the yield was slightly lower than that attainable with 3.0 equiv of **2a** (entries 3-4). In the case where addition of TMSBr was carried out at room temperature instead of 0 °C, an obvious deterioration of the yield could be noted (entry 5). When 1.0 mL of wet CH_2Cl_2 was used as solvent, only 32% of **7aa** could be obtained (entry 6). However, when the amount of wet solvent increased to 3.0 mL, almost no desired product could be obtained

(entry 7). Finally, a shorter reaction time was found to compromise the product yield as well, with only 45% of **7aa** isolated after 15 min and when extended to 1 h, no improvement on the yield was achieved, too (entries 8-9).

Table 3-6. Effects of other parameters on the yield of **7aa**[a]



6a (0.4 mmol) **2a** (1.2 mmol) **7aa**

Entry	Catalyst	Solvent	TMSX	Yield (%)[b]
1[c]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	51
2[d]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	53
3[e]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	59
4[f]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	57
5[g]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	41
6[h]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	32
7[i]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	<5
8[j]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	45
9[k]	**$In(tfacac)_3$**	**CH_2Cl_2**	**TMSBr**	**63**

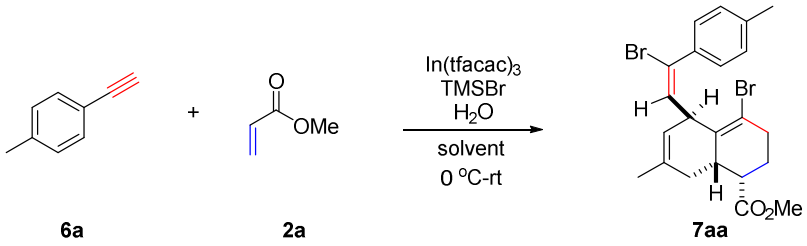
[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (4 equiv), 0 ^oC-rt, 30 min, N_2. [b] Isolated yields. [c] 3.0 equiv of TMSBr was added. [d] 5.0 equiv of TMSBr was added. [e] 2.0 equiv of **2a** was added. [f] 4.0 equiv of **2a** was added. [g] Reaction temperature was 25 ^oC. [h] 1.0 mL of wet CH_2Cl_2 was used as solvent. [i] 3 mL of wet CH_2Cl_2 was used as solvent. [j] Reaction time was 15 min. [k] Reaction time was 1h.

3.2.5.7 Re-optimization of the cascade dearomatization reaction for 6a and 2a

After submission of the manuscript of this work, one reviewer got back and suggested that it is better to use anhydrous solvent with accurate amount of water than using water-saturated wet solvent for this reaction. In response to this suggestion, we started to refine the reaction based on previous results (**Table 3-7** and **Table 3-8**). In order to elucidate effects of moisture to our reaction, we then embarked on using anhydrous solvents and known amount of water for this reaction, rather than using water-saturated wet solvents. This refinement was based on previous

results.

Table 3-7. Re-optimization of the reaction condition of **6a** and **2a**[a]



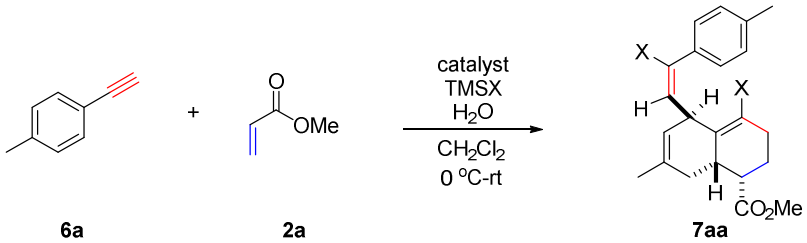
6a **2a** **7aa**

Entry	Catalyst	Solvent	Additive	Yield [%][b]
1	**$In(tfacac)_3$**	**CH_2Cl_2**	**TMSBr**	**66**
2	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSBr	31
3	$In(tfacac)_3$	hexane	TMSBr	0
4	$In(tfacac)_3$	$CHCl_3$	TMSBr	0
5	$In(tfacac)_3$	DMF	TMSBr	0
6	$In(tfacac)_3$	THF	TMSBr	0
7	$In(tfacac)_3$	Toluene	TMSBr	0
8[c]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	36
9[d]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	<5
10[e]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	46
11[f]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	25

[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (4 equiv), H_2O (1 equiv), CH_2Cl_2 (2 mL), 0 °C-rt, 30 min, N_2. [b] Isolated yields. [c] 0.5 equiv of H_2O was added. [d] 2.0 equiv of H_2O was added. [e] 1.0 mL of CH_2Cl_2 was used as solvent. [f] 4.0 mL of CH_2Cl_2 was used as solvent.

Using also 0.4 mmol of **6a**, reaction of **6a** and **2a** with 1.0 equiv of H_2O in 2 mL anhydrous CH_2Cl_2, we were delighted to isolate the desired product **7aa** in 66% yield (**Table 3-7**, entry 1). In other common solvents including DCE, hexane, chloroform, DMF, THF and toluene (entries 2-7), the desired reaction could not occur to provide **7aa** except for DCE (entry 2). Other reaction concentration and amount of H_2O were again examined which were later found to play critical role in determining the fate of reaction. With 0.5 equiv of H_2O, the yield of **7aa** hampered to only 36% while 2.0 equiv of H_2O barely afforded any **7aa** (entries 8-9). Altering the reaction concentration to 0.4 M or 0.1 M, a drop in reaction yields were also observed (entries 10-11).

Table 3-8. Re-optimization of the reaction conditions of **6a** and **2a**[a]



6a **2a** **7aa**

Entry	Catalyst	Solvent	Additive	Yield [%][b]
1	$In(tfacac)_3$	CH_2Cl_2	TMSCl	<5
2	$InBr_3$	CH_2Cl_2	TMSBr	37
3	InF_3	CH_2Cl_2	TMSBr	43
4	$InCl_3$	CH_2Cl_2	TMSBr	12
5	$In(OTf)_3$	CH_2Cl_2	TMSBr	31
6	$In(CF_3CO_2)_3$	CH_2Cl_2	TMSBr	28
7	$In(CH_3CO_2)_3$	CH_2Cl_2	TMSBr	25
8[c]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	57
9[d]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	51
10[e]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	58
11[f]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	52
12[g]	$In(tfacac)_3$	CH_2Cl_2	TMSBr	50

[a] Reaction condition: **6a** (0.4 mmol), **2a** (1.2 mmol), catalyst (20 mol%), TMSX (4 equiv), H_2O (1 equiv), 0 °C-rt, 30 min, N_2. [b] Isolated yields. [c] 3.0 equiv of TMSBr was added. [d] 5.0 equiv of TMSBr was added. [e] 2.0 equiv of **2a** was added. [f] 4.0 equiv of **2a** was added. [g] 10 mol% of $In(tfacac)_3$ was added.

Common indium (III) catalysts (eg., $InBr_3$, InF_3, $InCl_3$, $In(OTf)_3$, $In(CF_3CO_2)_3$, $In(CH_3CO_2)_3$) were also re-investigated under the augmented conditions with the results summarized in **Table 3-8**. While these indium (III) salts could catalyze the titled reaction, they offered lower efficacy compared to $In(tfacac)_3$ (entries 2-8). Attempts to decrease (3.0 equiv) or increase (5.0 equiv) amount of TMSBr failed to deliver **7aa** in comparable yield (entries 8-9) as that with 4 equiv of TMSBr (**Table 3-7**, entry 1). Among reactions with 2.0, 3.0 and 4.0 equiv of **2a**, 3.0 equiv of **2a** gave optimal result (66% *vs* 58% and 52%) (entries 10-11). Decreasing catalyst loading to 10 mol% led to corresponding decrease in product yield, too (entry 12).

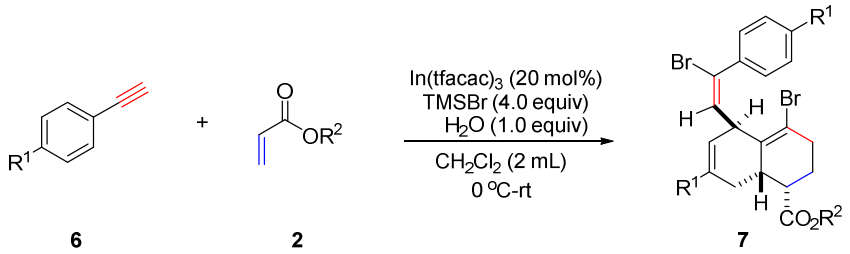
3.2.6 Substrate scope for cascade dearomatization reaction of aryl alkynes and acrylates

With improved optimal reaction conditions, (**Table 3-7**, entry 1), the generality of aryl alkyne substrate scope in this reaction with respect to methyl acrylate **2a** was probed and the results were summarized in **Table 3-9**. After extensive studies, it was observed that *para*-substituted aryl acetylenes were well suited to undergo present reaction in high stereocontrol to yield only single isomer.

Generally, as carbon chain of R^1 extends from Me, Et to *n*-Bu, **7aa**, **7ba** and **7ea** were formed in succesive lower yields (**Table 3-9**, entries 1-2, 4). It is nonethless interesting to pinpoint that the highest yield of product **7ca** was achieved when R^1 is *n*-Pr (entry 3). Substrates tethering longer alkyl chain such as *n*-C_5H_{11} or *n*-C_6H_{13} group were also suitable reaction partners to undergo this transformation smoothly and gave **7ga** and **7ha** in moderate yields (entries 7-8). As R^1 gets bulkier, a proportionate decrease of product yield could be noted (**7ca** *vs* **7da**, **7ea** *vs* **7fa**, entries 3-6). In addition, aryl alkynes with *para*-substituent such as phenyl and fluorine were well accommodated for this reaction (**7ia** and **7ja**, entries 9-10).

Aside from methyl acrylate, ethyl and *n*-butyl acrylates could undertake this chemistry when reacted with 4-ethynyltoluene (**6a**) or 4-ethylphenylacetylene (**6b**) as coupling partner. Their reactions went smoothly to afford respective dearomatization compounds **7ab**, **7bb** and **7ac**, albeit in relatively low yields (55%, 52% and 37%, entries 12-14) as compared to that attainable with methyl acrylate (**7aa**). When *n*-hexyl acrylates (**2d**) was used with respect to **6a**, trace dearomatization product was detected in the crude NMR. (entry 15).

Table 3-9. Substrate scope for cascade dearomatization reaction of aryl alkynes and acrylates[a]



Entry	6	2	time	7	Yield [%][b]
1	**6a**, R = Me	**2a**, R = Me	30 min	**7aa**	66
2	**6b**, R = Et	**2a**, R = Me	30 min	**7ba**	61
3	**6c**, R = *n*-Pr,	**2a**, R = Me	30 min	**7ca**	73
4	**6d**, R = *i*-Pr	**2a**, R = Me	30 min	**7da**	70
5	**6e**, R = *n*-Bu	**2a**, R = Me	30 min	**7ea**	60
6	**6f**, R = *t*-Bu	**2a**, R = Me	30 min	**7fa**	50
7	**6g**, R = *n*-C_5H11	**2a**, R = Me	30 min	**7ga**	56
8	**6h**, R = *n*-C_6H_{13}	**2a**, R = Me	30 min	**7ha**	55
9	**6i**, R = Ph	**2a**, R = Me	30 min	**7ia**	56
10	**6j**, R = F	**2a**, R = Me	30 min	**7ja**	50
11	**6k**, R = 4-propylcyclohexyl	**2a**, R = Me	30 min	**7ka**	55
12	**6a**, R = Me	**2b**, R = Et	30 min	**7ab**	55
13	**6b**, R = Et	**2b**, R = Et	30 min	**7bb**	52
14	**6a**, R = Me	**2c**, R = Bu	30 min	**7ac**	37
15	**6a**, R = Me	**2d**, R = Hex	30 min	**7ad**	< 5

[a] Reaction condition: **6** (0.4 mmol), **2** (1.2 mmol), In(tfacac)$_3$ (20 mol%), TMSBr (4 equiv), H_2O (1 equiv), 0 °C-rt, N_2. [b] Isolated yields.

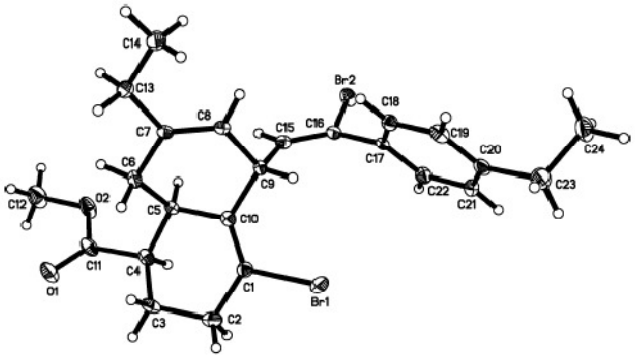
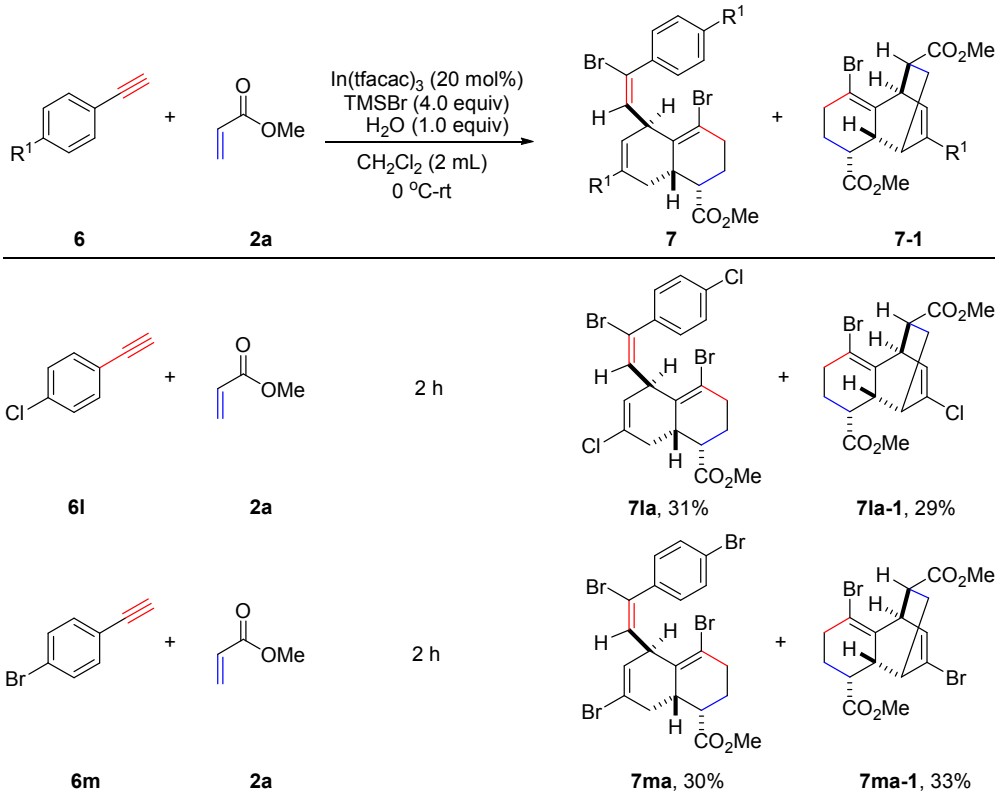


Figure 3-7. X-ray crystallograhy structure of of **7ba**, Methyl (1*S**,5*S**,8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-ethylphenyl)vinyl)-7-ethyl-1,2,3,5,8,8a-hexahydronaphthalene-1-carboxylate

In addition to **7aa** (**figure 3-6**), the single crystal of **7ba** also could be obtained from the solvent combination of hexane and MeOH (**Figure 3-7**).

Table 3-10. Dearomatization and double Diels-Alder products from **6l** and **6m**[a,b]



[a] Reaction condition **6** (0.4 mmol), **2a** (1.2 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (4 equiv), H_2O (1 equiv), 0 °C-rt, 2 h, N_2. [b] Isolated yields.

When 4-chlorophenylacetylene **6l** or 4-bromophenylacetylene **6m** was subjected to react with **2a** under the standard conditions, the double-Diels-Alder adduct **7la-1** or **7ma-1** was formed, along with the respective dearomatization products **7la** and **7ma** (**Table 3-10**). The structures of **7la-1** and **7ma-1** were also confirmed *via* single crystal X-ray diffraction analysis.

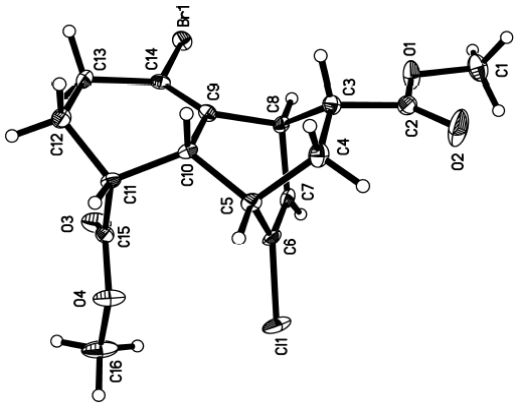


Figure 3-8. X-ray crystallograhy structure of **7la-1**, Dimethyl (1*S**,4*S**,5*R**, 10*S**)-8-bromo-3-chloro-1,4,4a,5,6,7-hexahydro-1,4-ethanonaphthalene-5,10-dicarboxylate

The single crystals of **7la-1** (**Figure 3-8**) and **7ma-1** (**Figure 3-9**) were both obtained from the co-solvent system consisting of hexane and ethyl acetate. From the crystal structures, the respective chiral centers could be determined unambiguously.

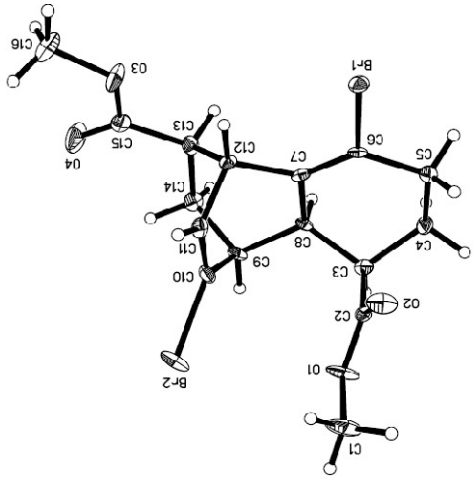


Figure 3-9. X-ray crystallograhy structure of **7ma-1**, dimethyl (1*S**,4*S**,5*R**,10*S**)-3,8-dibromo -1,4,4a,5,6,7-hexahydro-1,4-ethanonaphthalene-5,10-dicarboxylate

The complex tricyclic compounds **7la-1** and **7ma-1** were assembled in a one-step synthesis from simple starting materials albeit the yield and selectivity were only moderate. This tricyclic structure is also a common skeleton in naturally-occurring compounds such as (+)-Bis(carvacrol)

and (-)-Grandifloracin (**Figure 3-10**).

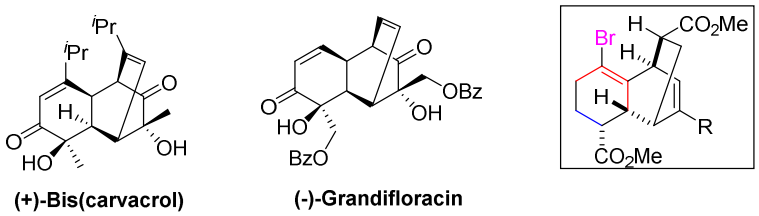
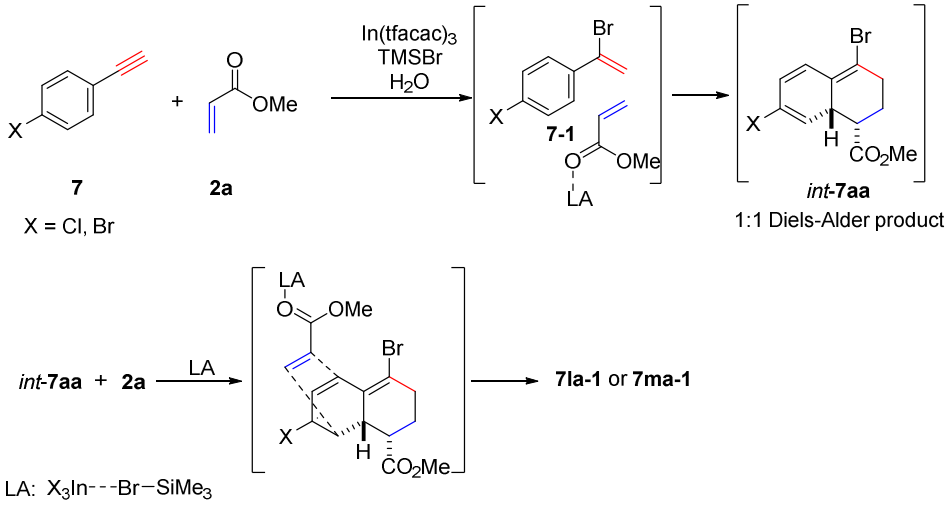


Figure 3-10. Selected nature products with similar tricyclic skeleton as **7la-1** and **7ma-1**



Scheme 3-39. Proposed mechanism for the formation of **7la-1** and **7ma-1**

The formation of **7la-1** and **7ma-1** has also provided mechanistic clues on cascade dearomatization reaction to the formation of **7la** and **7ma**. As depicted in **Scheme 3-39**, the anticipated dearomatization of vinyl bromine and methyl acrylate gave 1:1 Diels-Alder adduct *int*-**7aa** which was trapped by a second intermolecular Diels-Alder reaction with another molecule of methyl acrylate. Hence, **7la-1** and **7ma-1** could be evidence for the dearomatization/Diels-Alder reaction and intermediacy of unstable *int*-**7aa** species.

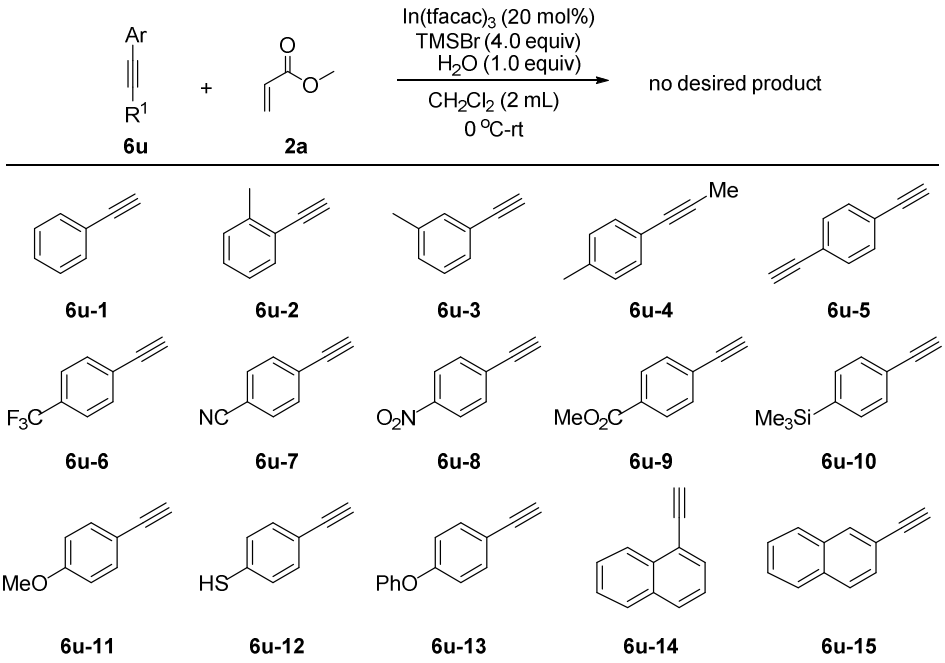
3.2.7 Unsuitable substrates of the dearomatization cascade reaction

In addition to aryl alkynes and acrylates employed in **Table 3-9** and **Table 3-10**, compatibilities

of other aryl alkynes and electron-deficient alkenes were also examined under the optimal conditions.

3.2.7.1 Unsuitable aryl alkyne substrates

Table 3-11. Unsuitable aryl alkyne substrates of the cascade dearoamtization reaction[a]



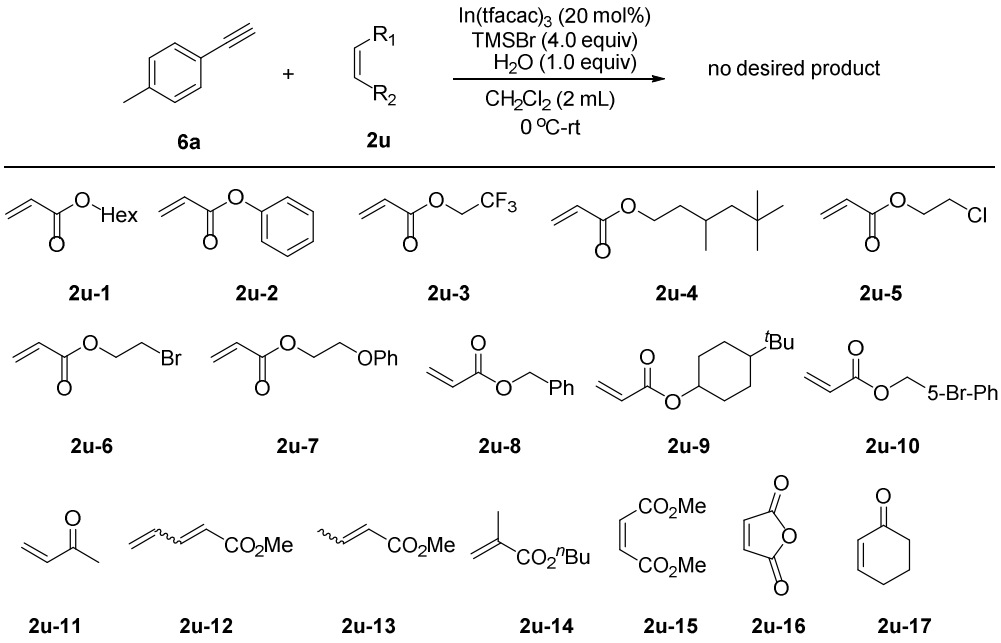
[a] Reaction condition **6u** (0.4 mmol), **2a** (1.2 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (4 equiv), H_2O (1 equiv), 0 °C-rt, 2 h, N_2.

Through extensive substrate scope study, it was found that use of terminal aryl alkynes bearing *para*-substituent on the aryl ring is paramount to neccesitate the cascade reaction. The representative examples of unsuitable aryl alkynes were demonstrated in **Table 3-11**. Terminal aryl alkynes without *para*-substitutent (e.g., phenylacetylene, **6u-1**) or that with *ortho*- or *meta*-substitution (such as 2-ethynyltoluene **6u-2** and 3-ethynyltoluene **6u-3**) could not produce titled products. The incompatibility of 1-methyl-4-(prop-1-yn-1-yl)benzene **6u-4** shows that substituent on triple bond could also hinder the reaction. Aryl alkynes with electron withdrawing substituent were also tested, for example, trifluoromethyl (**6u-6**), nitrile (**6u-7**), nitro (**6u-8**) and

methyl ester functionality (**6u-9**). However, none gave the desired product. Moreover, 1,4-diethynylbenzene (**6u-5**) and (4-ethynylphenyl)trimethylsilane (**6u-10**) are also unsuitable substrates for this reaction. Alkynes with methoxyl (**6u-11**), thiol (**6u-12**) and phenoxyl (**6u-13**) group tend decompose under this relatively acidic conditions. Finally, the alkynes with biaryl rings such as 1-naphthyl- and 2-naphthyl-alkyne (**6u14** and **6u15**) were not suitable for this reaction as well.

3.2.7.2 Unsuitable electron-deficient alkenes

Table 3-12. Unsuitable electron-deficient alkenes of the cascade dearoamtization reaction[a]

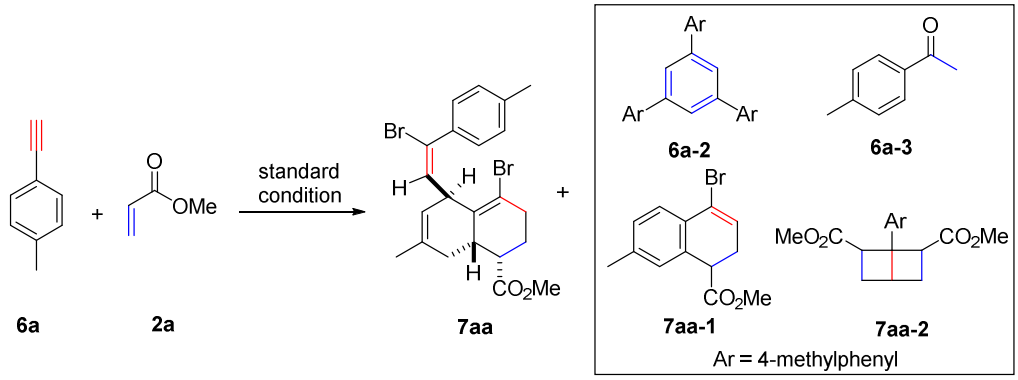


[a] Reaction condition: **6a** (0.4 mmol), **2u** (1.2 mmol), In(tfacac)$_3$ (20 mol%), TMSBr (4 equiv), H_2O (1 equiv), 0 °C-rt, 2 h, N_2.

In addition to methyl, ethyl and *n*-butyl acrylate, reactions of other acrylates and electron-deficient alkenes were also investigated with respect to **6a** (**Table 3-12**). First, acrylates (eg., *n*-hexyl acrylate, phenyl acrylate, trifluoroethyl acrylate, 3,5,5-trimethyl-hexyl acrylate, chloroethyl acrylate, bromoethyl acrylate and phenoxyethyl acrylate, **2u1-7**) which could undergo [2+2] cycloaddition were tested. Nonetheless, none undertook the dearomatization

chemistry. Acrylates with benzyl, 4-*tert*-butylcyclohexyl and pentabromobenzyl group (**2u8-10**), methyl vinyl ketone (**2u-11**) as well as methyl penta-2,4-dienoate (**2u-12**) which could not form cyclobutene product did not give dearomatization product either. In addition, substituted acrylates and ketones, for examples, methyl but-2-enoate (**2u-14**), dimethyl maleate (**2u-15**), maleic anhydride (**2u-16**) and cyclohex-2-en-1-one (**2u-17**) also could not react with the **1a** to give corresponding products.

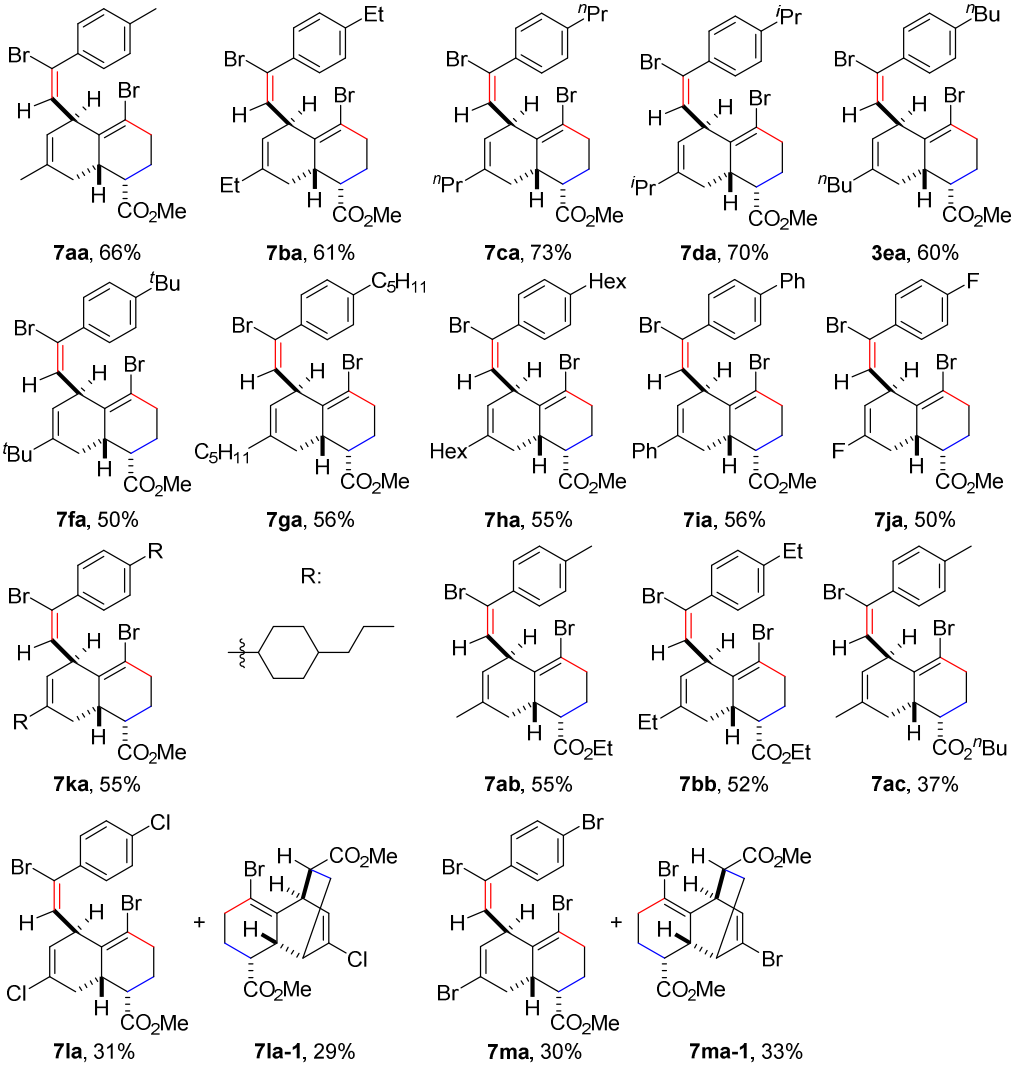
3.2.8 Mechanistic studies of cascade dearomatization reaction



Scheme 3-40: Four by-products from the cascade dearomatization reaction of **6a** and **2a**

This cascade dearomatization reaction of aryl alkyne and acrylate was serendipitously discovered during the study of dearomatization/Diels-Alder cycloaddition between α-aryl vinyl bromide and acrylate under ambient conditions. We have disclosed a tentative reaction pathway speculated for this reaction when it was initially discovered (**Scheme 3-38**). After the optimization study of reaction conditions and substrates scopes, some general properties of this reaction have been recognized. We sought to gain in-depth mechanistic insights into this novel reaction through meticulous examination of by-products, control experiment and cross experiment.

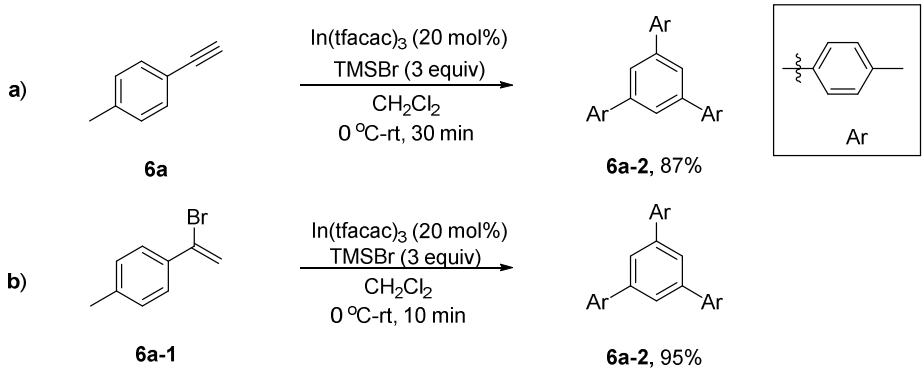
Table 3-13: Summary of the cascade dearomatization reaction of 4-substituted phenyl alkyne and acrylates[a, b]



[a] Reaction condition: aryl alkyne **6** (0.4 mmol), acrylate **2** (1.2 mmol), $In(tfacac)_3$ (20 mol%), TMSBr (4 equiv), H_2O (1 equiv), 0 °C-rt, N_2. [b] Isolated yields.

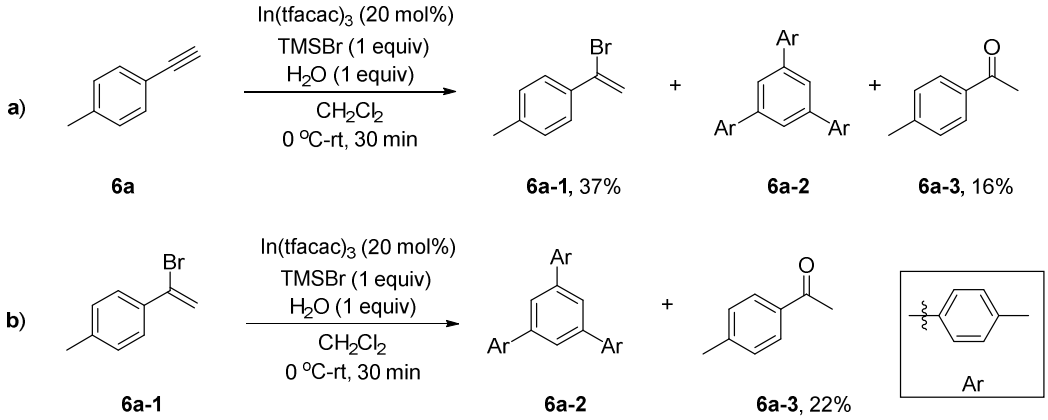
3.2.8.1 Study of by-products formed

A careful scrutiny of crude NMR spectra and dearomatization reaction mixture of 4-ethynyltoluene **6a** and methyl acrylate **2a** led to identification of four by-products along with main dearomatization product **7aa** (**Scheme 3-40**).



Scheme 3-41. Respective conversion of aryl alkyne **6a** and α-aryl vinyl bromide **6a-1** to **6a-2**

The by-product **6a-2** was proposed to form from the trimerization of 4-ethynyltoluene **6a** or the respective *in situ* generated α-vinyl bromine **6a-1**. When **6a** and corresponding α-aryl vinyl bromide **6a-1** were individually stirred in the presence of $In(tfacac)_3$ and TMSBr, **6a-2** was obtained in high yields in both experiments (**Scheme 3-41**). It is worth-noting that α-aryl vinyl bromide **6a-1** is much reactive than aryl alkyne **6a** as the conversion of **6a-1** to **6a-2** completed in 10 min while this reaction of **6a** took 30 min.

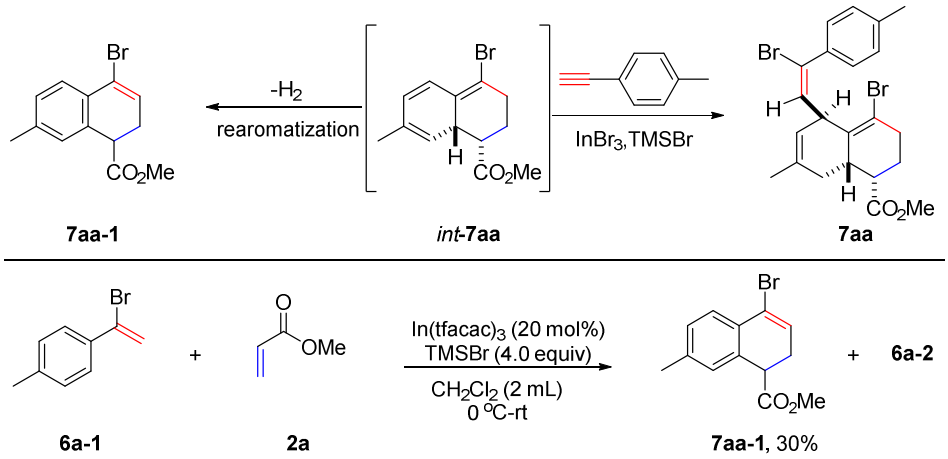


Scheme 3-42. Conversion of aryl alkyne **6a** and α-aryl vinyl bromide **6a-1** to **6a-3** in the presence of $In(tfacac)_3$, TMSBr and H_2O

On the other hand, hydrolysis of alkyne **6a** or corresponding α-aryl vinyl bromine **6a-1** gave by-product **6a-2**. When **6a** and **6a-1** were stirred respectively in the presence of $In(tfacac)_3$,

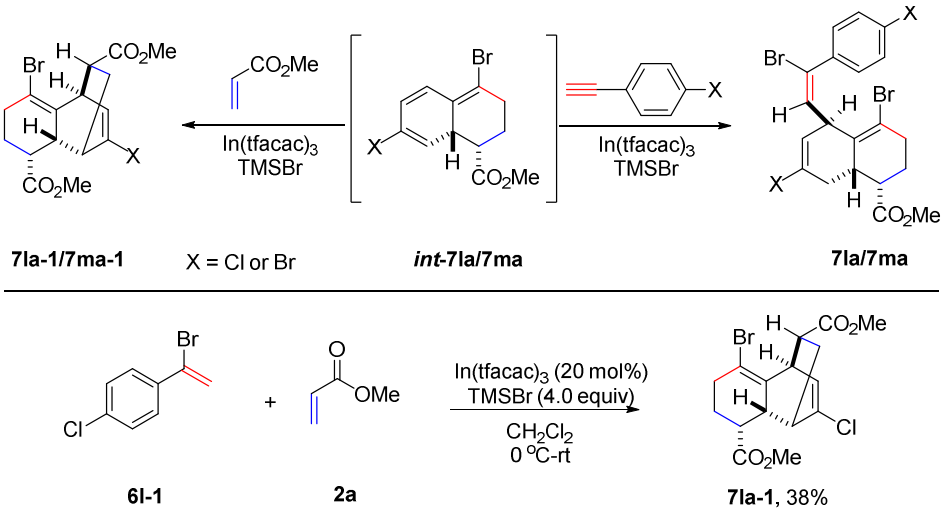
TMSBr and H_2O, the acetophenone **6a-3** was formed alongside with **6a-2** (**Scheme 3-42**) .

The by-product **7aa-1** was proposed to result from the re-aromatization of *int*-**7aa** which is also the competing reaction to the formation of main product **7aa** (**Scheme 3-43**). In the presence of the In(tfacac)$_3$ and TMSBr, *α*-aryl vinyl bromide **6a-1** and methyl acrylate **2a** could react to give **7aa-1** in 30% yield. The formation of the tricyclomerization product **6a-2** resulted in moderate yield of **7aa-1** in this experiment. Based on this result, the **7aa-1** could be indirect evidence for the key dearomatization/Diels-Alder reaction between **6a-1** and **2a** as well as the intermediacy of *int*-**7aa**.

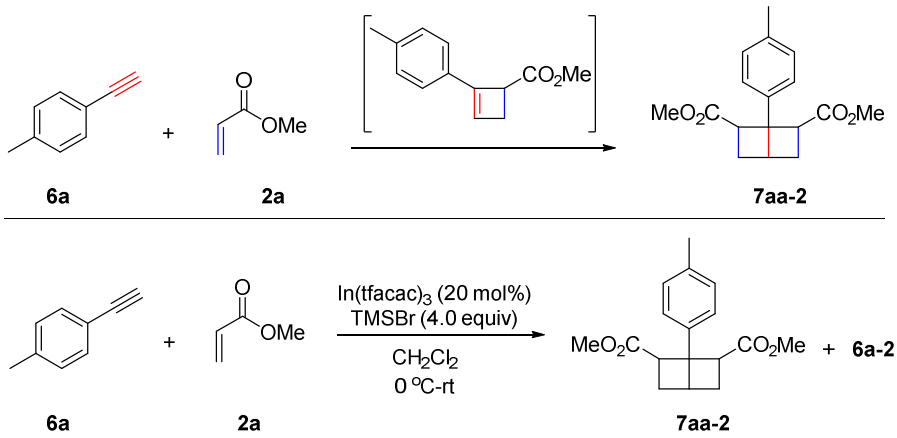


Scheme 3-43. Plausible pathway for the **7aa-1** formation and its synthesis from *α*-aryl vinyl bromide **6a-1** and methyl acrylate **2a**

Another indirect clue to the proceeding of dearomatization/Diels-Alder reaction was the formation tricyclic compounds **7la-1** and **7ma-1** which were proposed to result from a second Diels-Alder reaction between *int*-**7la/7ma** and methyl acrylate **2a**. As expected, the **6l-1** could react with **2a** in the presence of in(tfacac)$_3$ and TMSBr to give the **7la-1** in 38% yield (**Scheme 3-44**). The relatively low yield of this reaction might be attributed to the poor stability of the pre-prepared *α*-aryl vinyl bromide **6l-1**.

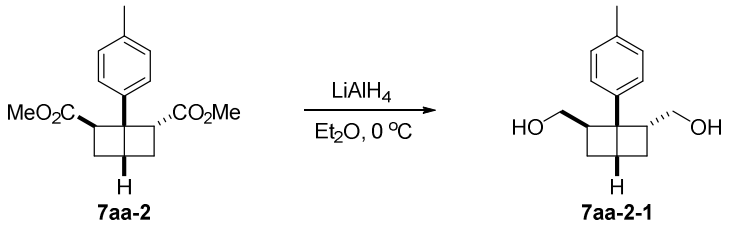


Scheme 3-44. Plausible pathway for the formation of double Diels-Alder adduct **7la-1**/**7ma-1** and synthesis of **7la-1** from **6l-1**



Scheme 3-45. Plausible pathway for the formation of **7aa-2** and double [2+2] cycloaddition of aryl acrylate **6a** and methyl acrylate **2a** to give **7aa-2**

Further, the dicyclobutane **7aa-2** was thought to originate from the double [2+2] cycloaddition of aryl alkyne **6a** and methyl acrylate **2a** *via* the cyclobutene intermediate (**Scheme 3-45**). As expected, **6a** could react with **2a** in the presence of $In(tfacac)_3$ and TMSBr to give **7aa-2** in *ca.* 20% yield in combination with **6a-2**.



Scheme 3-46. Reduction of **7aa-2** to **7aa-2-1** with $LiAlH_4$

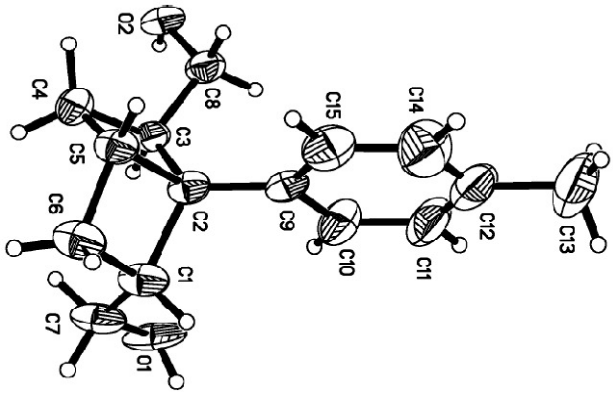


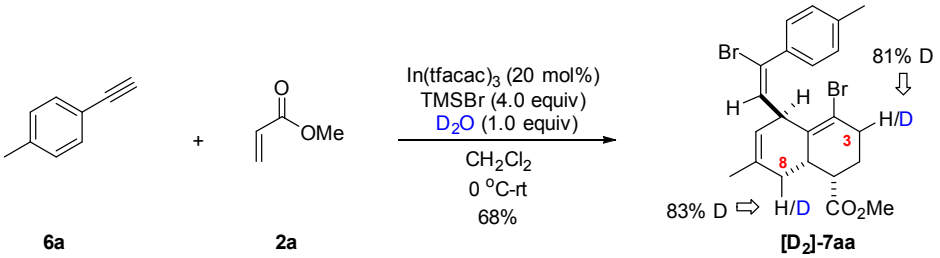
Figure 3-11. X-ray crystallograhy structure of of **7aa-2-1**, ((1*R**,2*R**,4*R**,6*R**)-1-(*p*-tolyl)bicyclo[2.2.0]hexane-2,6-diyl)dimethanol

The structure of **7aa-2** was preliminarily elucidated by 1D and 2D NMR, and further confirmed by the X-ray single crystal analysis of the derivative, **7aa-2-1**. The bicyclobutane **7aa-2** was reduced to the alcohol **7aa-2-1** which appear as colourless solid (**Scheme 3-46**). The single crystal of **7aa-2-1** was obtained from the co-solvent system of hexane and ethyl acetate. The bicyclobutane skeleton was clearly demonstrated in the crystal structure of **7aa-2-1** (**Figure 3-11**).

3.2.8.2 Isotopic labelling experiment of aryl alkyne 6a and methyl acrylate 2a

To acquire in-depth mechanistic details on the role of H_2O in present cascade dearomatization reaction, isotopic labelling experiments were carried out. As demonstrated in **Scheme 3-47**, when the reaction of **6a** and **2a** was conducted with 1 equiv of D_2O, deuterated compound

[D_2]-**7aa** was obtained in 68% yield with ~80% D.



Scheme 3-47. Cascade dearomatization reaction of **6a** and **2a** in the presence of D_2O

Through comparison of ^{1}H NMR spectra of [D_2]-**7aa** and **7aa**, it could be inferred that one of the two protons at C-3 and C-8 had been replaced by deuterium (**Scheme 3-47**, **Figure 3-12**). The adventitious moisture from solvent and reagent could have accounted for the incomplete deuteration.

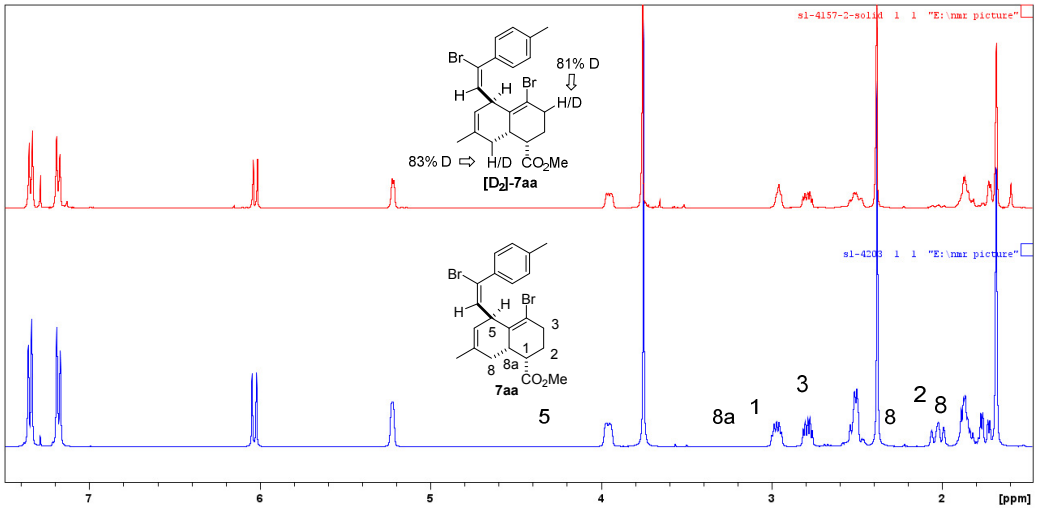
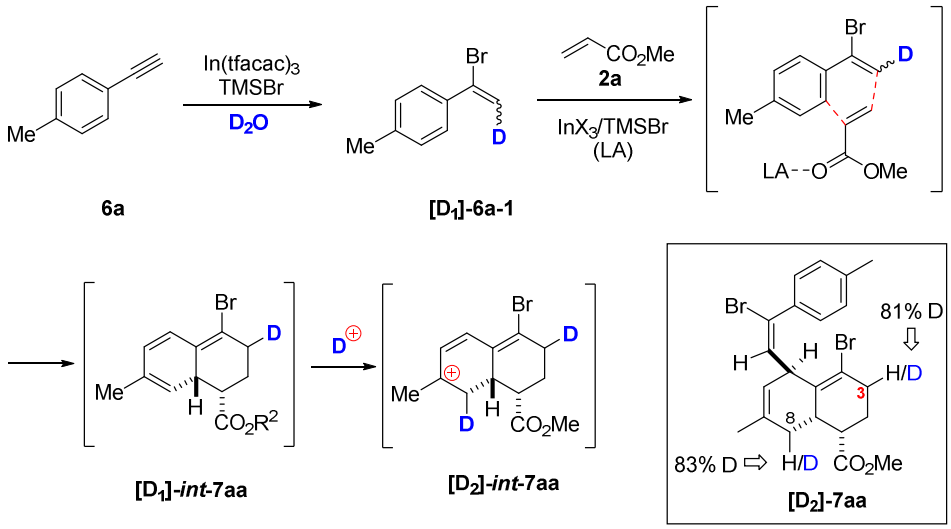


Figure 3-12. Comparison of ^{1}H NMR spectra of [D_2]-**7aa** and **7aa**

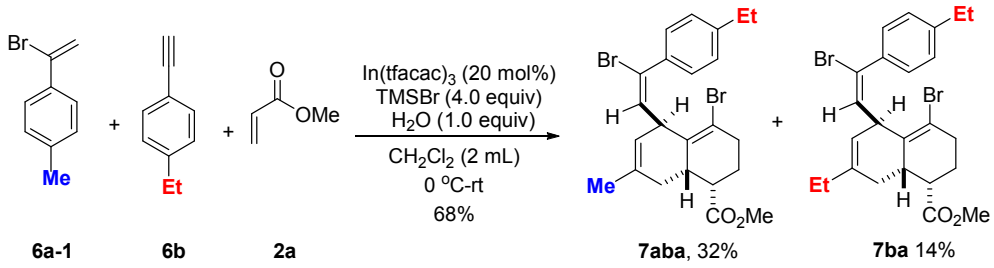
We reasoned the outcome of the isotopic labelling experiment as depicted in **Scheme 3-48**. First, the deuterium at C-3 was introduced during *in situ* generation of *α*-aryl vinyl bromide [D_1]-**6a-1** from aryl alkyne **6a**. The dearomatization/Diels-Alder reaction of [D_1]-**6a-1** and methyl acrylate **2a** took place to give the 1:1 adduct [D_1]-*int*-**7aa**. Through activation by Lewis acid catalyst

formed by $In(tfacac)_3$ and TMSBr, a double bond of $[D_1]$-*int*-**6aa** was deuterated to give$[D_2]$-*int*-**7aa** containing the deuterated C-8.



Scheme 3-48. Plausible reaction pathway for isotopic labelling experiment

3.2.8.3 Crossover reaction of *α*-aryl vinyl bromide, aryl alkyne and methyl acrylate



Scheme 3-49. Crossover experiment of *α*-aryl vinyl bromide **6a-1**, aryl alkyne **6b** and **2a**

Moreover, the crossover reaction of *α*-aryl vinyl bromide **6a-1**, aryl alkye **6b** and methyl acrylate **2a** was conducted in order to get insights on the role of *α*-aryl vinyl bromide in this dearomatization reaction. As demonstrated in **Scheme 3-49**, the cross product **7aba** and homo product **7ba** were obtained from the reaction of **6a-1**, **6b** and **2a** under the standard conditions.

The product mixture of **7aba** and **7ba** was not separable with silica gel column and the yields

were calculated based on the amount of **6b** used. The formation of **7aba** was primarily determined by comparing ^{1}H and ^{13}C NMR spectra of **7aa**, **7ba** and the mixture of **7ba** and **7aba** (**Figure 3-13**). It was later confirmed without ambiguity by the X-ray single crystal analysis of **7aba**. The ratio of **7ba** and **7aba** was determined according to the ^{1}H NMR of this mixture.

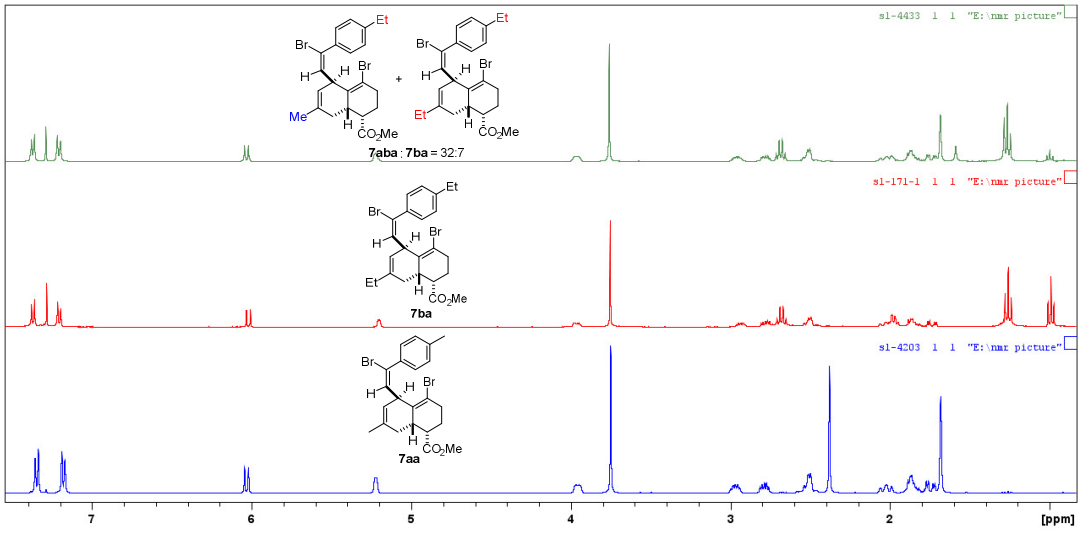


Figure 3-13. ^{1}H NMR spectra of **7aa**, **7ba** and the mixture of **7aba** and **7ba**

The single crystal of cross product **7aba** was obtained from the mixture of **7ba** and **7aba** using the co-solvent system of hexane and MeOH. From the X-ray single crystal structure, both phenyl ring bearing a *para*-ethyl group and dearomatized phenyl ring with methyl group were evident (**Figure 3-14**).

This result suggested the *in situ* generated α-aryl vinyl bromide **6a-1** should be a key intermediate and its participation in dearomatization/Diels-Alder reaction with methyl acrylate **2a** should be a key step of this cascade reaction. The result also further emphasized the role of 1:1 Diels-Alder adduct *int*-**7aa** as key intermediate in following transformation: the carbocation *int*-**7aa-1** generated from *int*-**7aa** was intercepted by another molecule of aryl alkyne (in this case is **6b**) by a S_N2'-type reaction to give the cross product **7aba** (Scheme **3-50**).

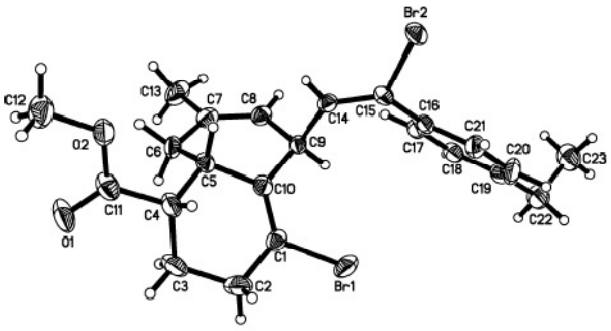
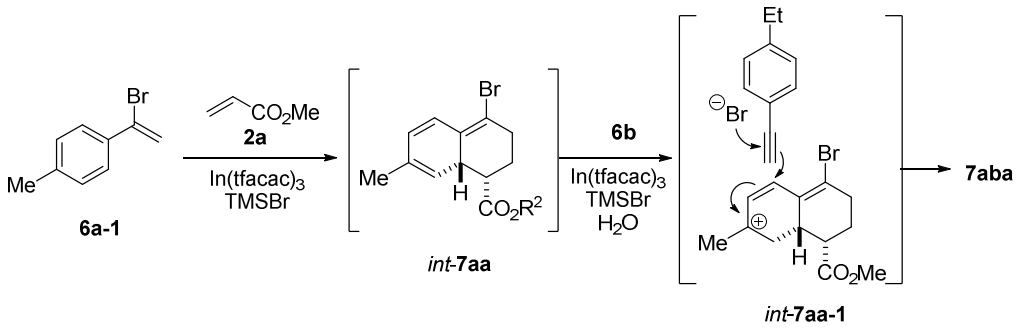
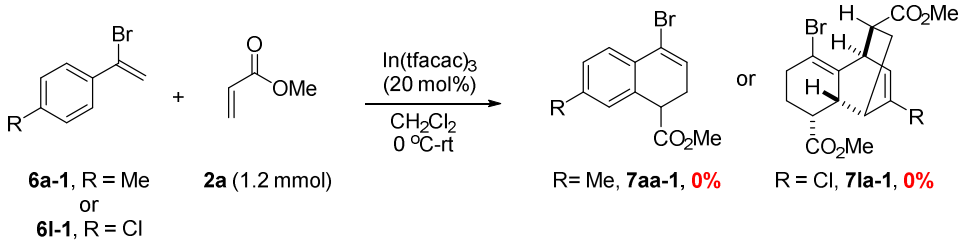


Figure 3-14. X-ray crystallograhy structure of of **7aba**, Methyl (1*S**,5*S**,8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-ethylphenyl)vinyl)-7-methyl-1,2,3,5,8,8a-hexahydronaphthalene-1-carboxylate



Scheme 3-50. Plausible pathway for the formation of cross dearomatization product **7aba**

3.2.8.4 The role of TMSBr



Scheme 3-51. Control experiments of *α*-aryl vinyl bromide **6a-1**/**6l-1** and methyl acrylate **2a** without TMSBr

It is also worthwhile to note that in the absence of TMSBr, neither **7aa-1** nor **7la-1** could be produced from the reaction of *α*-aryl vinyl bromide **6a-1**/**6l-1** and methyl acrylate **2a** in the presence of In(tfacac)$_3$ (**Scheme 3-51**). This result implied that the TMSBr was not only the bromine source, but also acted synergistically with indium(III) salt in the catalysis of this

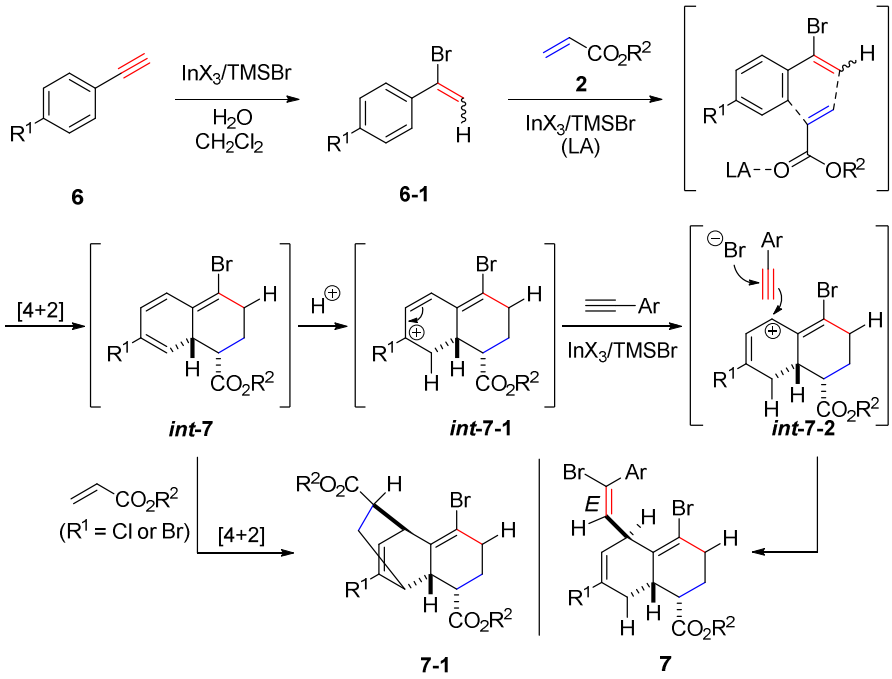
reaction.

3.2.8.5 Proposed Plausible Mechanism

Based on the above results, a plausible mechanistic pathway is devised for this novel cascade dearomatization reaction (**Scheme 3-52**). Initially, *α*-aryl vinyl bromide **6-1** generated from aryl alkyne **6** would undergo a dearomatization/Diels-Alder reaction with acrylate **2** catalyzed by the combined Lewis acid system to give a 1:1 Diels-Alder adduct *int*-**7**. When R^1 is an electron-donating group, adduct *int*-**7** is readily trapped by a proton to generate a stabilized tertiary allylic carbocation *int*-**7-1**. Next, the *int*-**7-1** undergo rearrangement to give *int*-**7-2**. Finally, the attack of the bromide ion to alkyne and a concomitant attack of aryl alkyne to the allylic carbocation *int*-**7-2** from the less hindered face of bicyclic ring occurs *via* a concerted S_N2'-type pathway, leading to dearomatized product **7** bearing a newly formed C-C double bond with *E*-geometry. On the other hand, when R^1 is Cl or Br, attack of alkyne to *int*-**7** might not be as rapid, allowing considerable amount of *int*-**7** to undergo another Diels-Alder reaction with acrylate **2** from sterically less hindered side, furnishing the double-Diels-Alder adduct **7-1**.

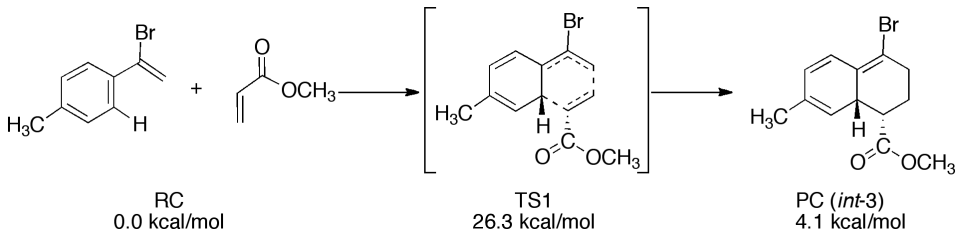
According to the proposed pathway, some characteristic properties of this reaction could then be explained. First, the existence of the electron donating *para*-substituents on the phenyl ring is crucial for this reaction because it could accelerate the dearomatization/Diels-Alder reaction step as well as stabilize *int*-**7-1** to decrease the energy barrier. For this reason, aryl alkynes with electron-deficient group on phenyl ring were found unsuitable for this reaction. Phenylacetylene **6u-1**, 2-ethynyltoluene **6u-2** and 3-ethynyltoluene **6u-3** also could not give the desired product (**Table 3-11**). The existence of substituent on the triple bond (**6u-4**) or bulky substituents on acrylates could result in the difficulty to generate *int*-**7**. When the linear alkyl substituent

elongates from methyl, ethyl, butyl to hexyl, the corresponding decrease in product yields was apparent.



Scheme 3-52. Plausible pathway for cascade dearomatization reaction of aryl alkynes and acrylates

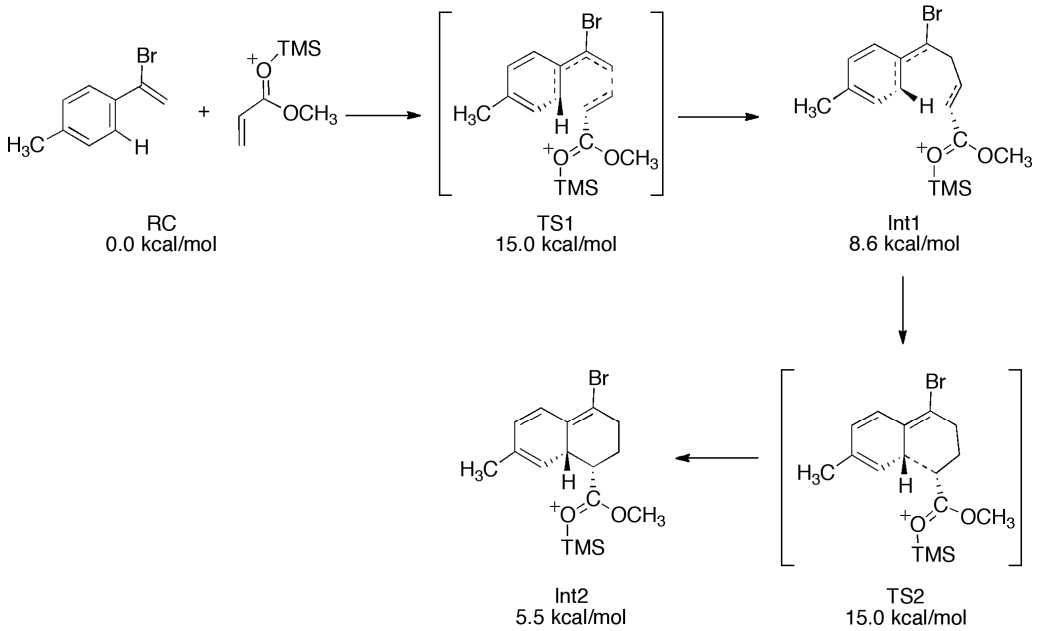
3.2.8.6 Computational Study the Key Dearomatizing [4+2] Cycloaddition



Scheme 3-53. Dearomatizing Diels-Alder reaction between α-aryl vinyl-Brand acrylate in the absence of a Lewis acid.

We also examined the effect of the Lewis acid on the [4+2] cycloaddition. Based on the computational outcomes presented above, here we assumed that TMS^+ is used as the real Lewis acid species. The DFT results shown in **Schemes 3-53** and **3-54** show that this type of

Lewis-acid coordination indeed decreases the energy barriers for [4+2] cycloaddition significantly.



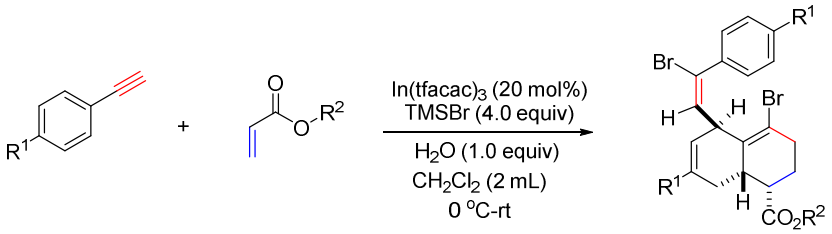
Scheme 3-54. Dearomatization reaction between α-aryl vinyl-Brand acrylate in the presence of a Lewis acid (TMS^+)

3.3 Conclusion

In conclusion, this chapter disclosed a novel tandem dearomatization reaction which allowed efficient construction of elaborate molecule scaffold from structurally simple substrates such as aryl alkynes and acrylates. Based on the isotope labelling experiment, crossover and control experiments, this protocol is proposed to proceed *via* a tandem Diels-Alder reaction of *in situ* generated *α*-aryl vinyl bromide with acrylate followed by interception of the thus-formed Diels-Alder adduct by another molecule of aryl alkyne or acrylate.

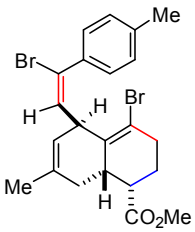
3.4 Experimental section and spectral data

3.4.1 General procedure for the dearomatization reaction and spectral data



6 **2** **7**

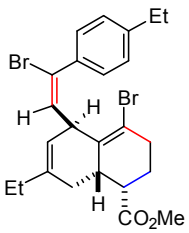
General Procedure for the dearomatization reaction. A dry reaction tube was charged with aryl alkyne **6** (0.4 mmol), acrylate **2** (1.2 mmol), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg), H_2O (0.4 mmol, 7.2 mg), and CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature for 0.5-2 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to afford the desired product **7**.



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(*p*-tolyl)vinyl)-7- methyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7aa)**

White solid, 63.1 mg, 0.132 mmol, 66% yield, 30 min. M.p.: 161 - 163 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (d, *J* = 7.8 Hz, 2H), 7.18 (d, *J* = 7.8 Hz, 2H), 6.03 (d, *J* = 10 Hz, 1H), 5.22 (brs, 1H), 3.97 - 3.95 (m, 1H), 3.75 (s, 3H), 3.00 - 2.94 (m, 1H), 2.82 - 2.76 (m, 1H), 2.54 - 2.50 (m, 2H), 2.38 (s, 3H), 2.06 - 1.99 (m, 1H), 1.89 - 1.82 (m, 2H), 1.75 (dd, *J* = 16.5, 5.1 Hz, 1H), 1.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.0, 138.5, 136.0, 135.2, 134.6, 132.1, 129.0, 128.8, 122.1, 121.9, 118.7, 51.7, 45.6, 42.3, 36.2, 35.3, 33.9, 23.3, 21.8, 21.4. **HRMS** (ESI) calcd for $C_{22}H_{25}O_2{}^{81}Br_2$ $(M+H)^+$ 483.0180, found 483.0197. The crystal suitable for X-ray single crystal diffraction analysis was obtained from solvent mixture of hexane/MeOH (5:1).

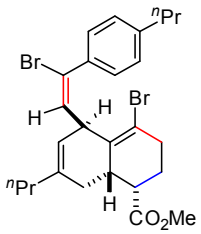


Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-ethylphenyl)vinyl)- 7-ethyl- 1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ba)**

Colorless oil, 61.7 mg, 0.122 mmol, 61% yield, 30 min. M.p.: 166 - 167 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.02 (d, *J* = 10.0 Hz, 1H), 5.21 (brs, 1H), 3.98 - 3.95 (m, 1H), 3.75 (s, 3H), 2.96 - 2.91 (m, 1H), 2.81 - 2.75 (m, 1H), 2.68 (q, *J* = 7.6 Hz, 2H), 2.54 - 2.50 (m, 2H), 2.06 - 1.95 (m, 3H), 1.88 -1.82 (m, 2H), 1.74 (dd, *J* = 15.3, 5.0 Hz, 1H), 1.26 (t, *J* = 7.6 Hz, 3H), 0.99 (t, *J* = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 144.8, 140.0, 136.2, 135.6, 132.3, 128.9, 127.6, 121.9, 120.4, 118.6, 51.7, 45.5, 42.3, 36.2, 35.4, 32.3, 30.1, 28.7, 21.8, 15.4, 12.2. **HRMS** (ESI) calcd for $C_{24}H_{29}O_2Br_2$ $(M+H)^+$ 507.0534, found 507.0540. The crystal suitable for X-ray single crystal diffraction analysis was obtained from solvent mixture of

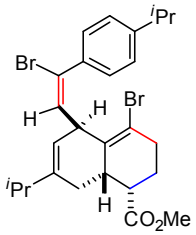
hexane/MeOH (5:1).



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-propylphenyl)vinyl) -7-propyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ca)**

Colorless oil, 77.9 mg, 0.146 mmol, 73% yield, 30 min.

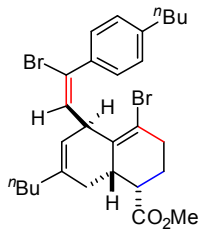
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (d, *J* = 8.0 Hz, 2H), 7.18 (d, *J* = 8.0 Hz, 2H), 6.02 (d, *J* = 10.0 Hz, 1H), 5.22 (brs, 1H), 3.99 - 3.95 (m, 1H), 3.75 (s, 3H), 2.95 - 2.90 (m, 1H), 2.81 - 2.75 (m, 1H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.54 - 2.49 (m, 2H), 2.04 - 1.92 (m, 3H), 1.88 - 1.84 (m, 2H), 1.74 (dd, *J* = 16.1, 5.0 Hz, 1H), 1.67 (q, *J* = 7.3 Hz, 2H), 1.47 - 1.34 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H), 0.90 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 143.3, 138.6, 136.2, 135.6, 132.3, 128.8, 128.2, 121.9, 121.6, 118.6, 51.6, 45.5, 42.4, 39.5, 37.8, 36.2, 35.4, 32.3, 24.3, 21.8, 20.9, 13.8, 13.7. **HRMS** (ESI) calcd for $C_{26}H_{33}O_2Br_2$ $(M+H)^+$ 535.0847, found 535.0853.



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-isopropylphenyl) vinyl)-7-isopropyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7da)**

Colorless oil, 74.1 mg, 0.138 mmol, 70% yield, 30 min.

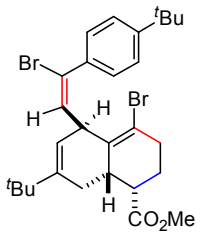
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 (d, *J* = 8.2 Hz, 2H), 7.24 (d, *J* = 8.2 Hz, 2H), 6.01 (d, *J* = 9.9 Hz, 1H), 5.22 (brs, 1H), 3.98 - 3.95 (m, 1H), 3.77 (s, 3H), 2.98 - 2.86 (m, 2H), 2.81 - 2.76 (m, 1H), 2.54 - 2.50 (m, 2H), 2.22 - 2.17 (m, 1H), 2.03 - 1.96 (m, 1H), 1.89 - 1.84 (m, 2H), 1.78 (dd, *J* = 16.1, 4.8 Hz, 1H), 1.28 (d, *J* = 6.8 Hz, 6H), 1.01 - 0.99 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_{3,}$): δ (ppm) 174.1, 149.4, 144.1, 136.3, 135.8, 132.3, 128.9, 126.2, 121.9, 119.4, 118.6, 51.7, 45.5, 42.4, 36.2, 35.6, 34.9, 33.9, 30.1, 23.9, 23.8, 21.8, 21.5, 20.9. **HRMS** (ESI) calcd for $C_{26}H_{33}O_2Br_2$ $(M+H)^+$ 535.0847, found 535.0854.



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-butylphenyl)vinyl)- 7-butyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ea)**

Colorless oil, 67.4 mg, 0.120 mmol, 60% yield, 1 h.

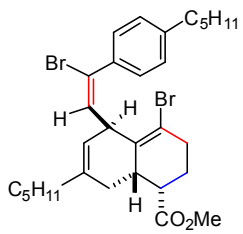
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.01 (d, *J* = 10.0 Hz, 1H), 5.21 (brs, 1H), 3.98 - 3.94 (m, 1H), 3.75 (s, 3H), 2.94 - 2.89 (m, 1H), 2.80 - 2.75 (m, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.53 - 2.49 (m, 2H), 2.04 - 1.94 (m, 3H), 1.88 - 1.81 (m, 2H), 1.73 (dd, *J* = 16.3, 5.0 Hz, 1H), 1.66 - 1.58 (m, 2H), 1.41 - 1.27 (m, 6H), 0.96 - 0.90 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 143.5, 138.8, 136.1, 135.6, 132.3, 128.8, 128.1, 121.9, 121.4, 118.6, 51.7, 45.5, 42.3, 37.2, 36.2, 35.4×2, 33.4, 32.3, 29.9, 22.5, 22.3, 21.8, 14.0, 13.9. **HRMS** (ESI) calcd for $C_{28}H_{37}O_2Br_2$ $(M+H)^+$ 563.1160, found 563.1165.



Methyl (1*S,5*S**,8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-(*tert*-butyl)phenyl) vinyl)-7-(*tert*-butyl)-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7fa)**

Colorless oil, 56.2 mg, 0.200 mmol, 50% yield, 1 h.

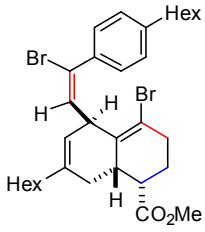
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 (s, 4H), 5.99 (d, *J* = 10.0 Hz, 1H), 5.26 - 5.25 (m, 1H), 3.98 - 3.95 (m, 1H), 3.76 (s, 3H), 2.85 - 2.75 (m, 2H), 2.53 - 2.45 (m, 2H), 1.94 - 1.93 (m, 2H), 1.88 - 1.84 (m, 2H), 1.34 (s, 9H), 1.02 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 151.7, 146.3, 135.9, 135.8, 132.4, 128.7, 125.0, 121.8, 118.6, 118.4, 51.6, 45.6, 42.5, 36.1, 36.0, 35.5, 34.7, 31.3, 28.8, 28.7, 21.8. **HRMS** (ESI) calcd for $C_{28}H_{37}O_2Br_2$ $(M+H)^+$ 563.1160, found 563.1153.



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-pentylphenyl) vinyl)-7-pentyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ga)**

Colorless oil, 58.1 mg, 0.112 mmol, 56% yield, 2 h.

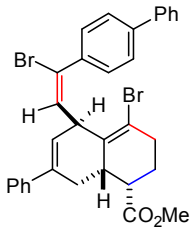
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (d, *J* = 8.1 Hz, 2H), 7.19 (d, *J* = 8.1 Hz, 2H), 6.02 (d, *J* = 10.1 Hz, 1H), 5.22 (brs, 1H), 3.99 - 3.95 (m, 1H), 3.76 (s, 3H), 2.94 - 2.90 (m, 1H), 2.81 - 2.75 (m, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.54 - 2.50 (m, 2H), 2.05 - 1.94 (m, 3H), 1.88 - 1.84 (m, 2H), 1.74 (dd, *J* = 16.2, 5.0 Hz, 1H), 1.68 - 1.62 (m, 2H), 1.41 - 1.23 (m, 10H), 0.94 - 0.90 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 143.5, 138.8, 136.1, 135.6, 132.3, 128.9, 128.1, 121.9, 121.3, 118.6, 51.7, 45.5, 42.3, 37.5, 36.2, 35.7, 35.4, 32.3, 31.6, 31.4, 30.9, 27.4, 22.5×2, 21.8, 14.0×2. **HRMS** (ESI) calcd for $C_{30}H_{40}O_2Br_2Na$ $(M+Na)^+$ 613.1303, found 613.1293.



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-hexylphenyl)vinyl) -7-hexyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ha)**

Colorless oil, 67.9 mg, 0.110 mmol, 55% yield, 2 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.36 (d, *J* = 8.1 Hz, 2H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.02 (d, *J* = 10.0 Hz, 1H), 5.22 - 5.21 (brs, 1H), 3.99 - 3.98 (m, 1H), 3.76 (s, 3H), 2.95 - 2.90 (m, 1H), 2.81 - 2.75 (m, 1H), 2.63 (t, *J* = 7.7 Hz, 2H), 2.54 - 2.50 (m, 2H), 2.05 - 1.94 (m, 3H), 1.88 - 1.81 (m, 2H), 1.74 (dd, *J* = 16.3, 4.9 Hz, 1H), 1.65 - 1.61 (m, 2H), 1.38 - 1.29 (m, 14H), 0.93 - 0.89 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 143.6, 138.8, 136.1, 135.6, 132.3, 128.8, 128.1, 121.9, 121.3, 118.6, 51.7, 45.5, 42.3, 37.5, 36.2, 35.7, 35.4, 32.3, 31.7×2, 31.2, 29.1, 28.9, 27.7, 22.6×2, 21.8, 14.1×2. **HRMS** (ESI) calcd for $C_{32}H_{45}O_2{}^{81}Br_2$ $(M+H)^+$ 623.1745, found 623.1749.

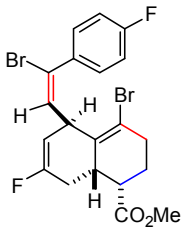


Methyl (1*S, 5*S**, 8a*S**)-5-((*E*)-2-([1,1'-biphenyl]-4-yl)-2-bromovinyl)-4-bromo-7-phenyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ia)**

Colorless oil, 67.4 mg, 0.112 mmol, 56% yield, 1 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 (d, *J* = 8.4 Hz, 4H), 7.57 (d, *J* = 8.4 Hz, 2H), 7.50 - 7.46 (m, 2H), 7.41 - 7.37 (m, 2H), 7.35 (d, *J* = 4.3 Hz, 4H), 6.16 (d, *J* = 9.9 Hz, 1H),

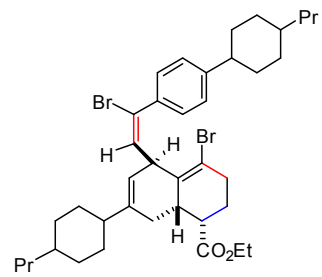
5.88 - 5.86 (m, 1H), 4.25 - 4.21 (m, 1H), 3.76 (s, 3H), 3.14 - 3.08 (m, 1H), 2.91 - 2.86 (m, 1H), 2.61 - 2.47 (m, 3H), 2.29 (dd, J = 16.2, 4.9 Hz, 1 H), 1.98 - 1.94 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.9, 141.5, 141.0, 140.4, 137.7, 137.5, 134.7, 131.9, 129.4, 128.9, 128.4, 127.7, 127.5, 127.1, 126.9, 125.3, 124.5, 122.0, 119.4, 51.8, 45.9, 42.4, 36.2, 35.5, 31.7, 21.9. **HRMS** (ESI) calcd for $C_{32}H_{29}O_2Br_2$ $(M+H)^+$ 603.0534, found 603.0533.



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-fluorophenyl)vinyl) -7-fluoro-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ja)**

Colorless oil, 48.7 mg, 0.100 mmol, 50% yield, 2 h.

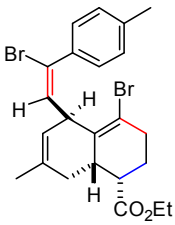
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.41 - 7.37 (m, 2H), 7.10 - 7.05 (m, 2H), 6.05 (d, J = 10.0 Hz, 1H), 5.11 - 5.05 (m, 1H), 4.03 - 4.00 (m, 1H), 3.77 (s, 3H), 3.09 - 3.03 (m, 1H), 2.89 - 2.79 (m, 1H), 2.55 - 2.53 (m, 2H), 2.29 - 2.21 (m, 1H), 2.11 - 2.03 (m, 1H), 1.97 - 1.92 (m, 1H), 1.88 - 1.77 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.3, 162.7 (d, $J_{C\text{-}F}$ = 247.8 Hz), 158.9 (d, $J_{C\text{-}F}$ = 258.0 Hz), 134.6 (d, $J_{C\text{-}F}$ = 3.4 Hz), 133.1 (d, $J_{C\text{-}F}$ = 2.8 Hz) , 132.2 (d, $J_{C\text{-}F}$ = 3.1 Hz), 130.7 (d, $J_{C\text{-}F}$ = 8.4 Hz), 121.1 (d, $J_{C\text{-}F}$ = 42.6 Hz), 115.5, 115.3, 103.6 (d, $J_{C\text{-}F}$ = 16.1 Hz), 51.9, 42.4 (t, $J_{C\text{-}F}$ = 8.5 Hz), 42.0, 36.1 (d, $J_{C\text{-}F}$ = 25.6 Hz), 34.3 (d, $J_{C\text{-}F}$ = 8.1 Hz), 29.2 (d, $J_{C\text{-}F}$ = 23.9 Hz), 21.7. **HRMS** (ESI) calcd for $C_{20}H_{19}O_2F_2{}^{81}Br_2$ $(M+H)^+$ 490.9679, found 490.9684.



Ethyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-(4-propyl cyclohexyl) phenyl)vinyl)-7-(4-propylcyclohexyl)-1,2,3,5,8,8a -hexahydronaphthalene-1-carboxylate (7ka)**

Colorless oil, 78.5 mg, 0.111 mmol, 55% yield, 2 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.39 - 7.35 (m, 2H), 7.26 - 7.20 (m, 2H), 6.01 - 5.99 (m, 1H), 5.20 (brs, 1H), 3.96 (brs, 1H), 3.76 (s, 3H), 2.89 - 2.85 (m, 1H), 2.79 - 2.74 (m, 1H), 2.60 - 2.46 (m, 3H), 2.05 - 1.91 (m, 1H), 2.07 - 1.52 (m, 28H), 0.97 - 0.89 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): 174.1, 148.4 (148.1), 143.9 (142.9), 136.3 (136.2), 135.9, 132.4 (132.3), 128.9 (128.8), 126.7 (126.5), 121.8, 119.9 (119.8), 118.4 (118.3), 51.7 (51.6), 45.5 (45.4), 44.4, 42.4, 39.7 (39.6), 37.1 (37.0), 36.1, 35.7 (35.6), 34.3, 34.2 (34.1), 33.5, 33.3 (33.2), 32.9 (32.7), 31.9, 31.3, 30.9, 30.0, 29.9 (29.8), 28.8 (28.7), 26.6, 26.1, 21.8, 20.9 (20.8), 20.0 (19.9), 14.4 (14.3). **HRMS** (ESI) calcd for $C_{38}H_{53}O_2Br_2$ $(M+H)^+$ 699.2412, found 699.2409.

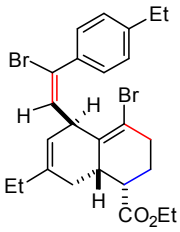


Ethyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(*p*-tolyl)vinyl)-7-methyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ab)**

Colorless oil, 54.1 mg, 0.110 mmol, 55% yield, 1 h.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.04 (d, J = 10.0 Hz, 1H), 5.22 (brs, 1H), 4.22 (q, J = 7.1 Hz, 2H), 3.96 - 3.94 (m, 1H), 2.99 - 2.93 (m, 1H), 2.79 - 2.74 (m, 1H), 2.54 - 2.50 (m, 2H), 2.38 (s, 3H), 2.06 - 1.99 (m, 1H), 1.88 - 1.81 (m, 2H),

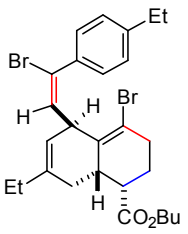
1.77 (dd, J = 8.2, 5.2 Hz, 1H), 1.68 (s, 3H), 1.33 (t, J = 7.1 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.6, 138.5, 135.9, 135.3, 134.7, 132.2, 128.9×2, 122.1, 121.8, 118.8, 60.5, 45.6, 42.4, 36.2, 35.3, 33.8, 23.3, 21.8, 21.3, 14.3. **HRMS** (ESI) calcd for $C_{23}H_{27}O_2Br_2$ $(M+H)^+$ 493.0378, found 493.0387.



Ethyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-ethylphenyl)vinyl)- 7-ethyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7bb)**

Colorless oil, 54.0 mg, 0.104 mmol, 52% yield, 1 h.

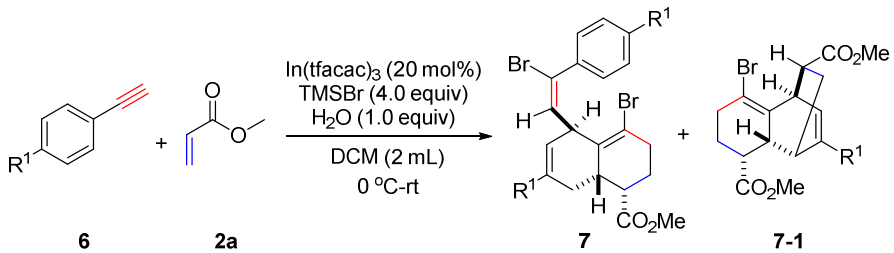
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 6.03 (d, J = 10.0 Hz, 1H), 5.21 - 5.20 (m, 1H), 4.25 - 4.19 (m, 2H), 3.98 - 3.96 (m, 1H), 2.95 - 2.91 (m, 1H), 2.78 - 2.66 (m, 3H), 2.54 - 2.50 (m, 2H), 2.06 - 1.95 (m, 3H), 1.88 - 1.83 (m, 2H), 1.79 (dd, J = 16.2, 4.7 Hz, 1H), 1.33 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.6 Hz, 3H), 0.99 (t, J = 7.5 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.6, 144.8, 140.1, 136.2, 135.6, 132.3, 128.9, 127.6, 121.8, 120.4, 118.7, 60.5, 45.5, 42.4, 36.2, 35.4, 32.1, 30.1, 28.7, 21.8, 15.3, 14.4, 12.2. **HRMS** (ESI) calcd for $C_{25}H_{31}O_2{}^{81}Br_2$ $(M+H)^+$ 525.0650, found 525.0654.



Butyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(*p*-tolyl)vinyl)-7-methyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ac)**

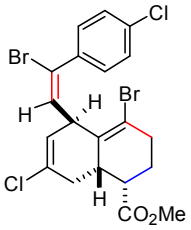
Colorless oil, 38.4 mg, 0.074 mmol, 37% yield, 2h.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.35 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.03 (d, J = 10.0 Hz, 2H), 5.22 (brs, 1H), 4.16 (t, J = 6.6 Hz, 2H), 3.96 - 3.94 (m, 1H), 2.98 - 2.93 (m, 1H), 2.80 - 2.74 (m, 1H), 2.54 - 2.50 (m, 2H), 2.39 (s, 3H), 2.06 - 1.99 (m, 1H), 1.89 - 1.84 (m, 2H), 1.79 (dd, J = 16.4, 5.0 Hz, 1H), 1.72 - 1.65 (m, 4H), 1.65 - 1.39 (m, 2H), 0.99 (t, J = 7.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.7, 138.5, 135.9, 135.3, 134.7, 132.2, 128.8×2, 122.1, 121.8, 118.8, 64.5, 45.6, 42.4, 36.2, 35.3, 33.8, 30.7, 23.3, 21.8, 21.3, 19.2, 13.7. **HRMS** (ESI) calcd for $C_{25}H_{31}O_2Br_2$ $(M+H)^+$ 521.0691, found 521.0691.



A dry reaction tube was charged with aryl alkyne **6** (0.4 mmol), acrylate **2a** (1.2 mmol), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg), H_2O (0.4 mmol, 7.2 mg) and CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature for 2 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent:

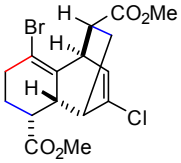
hexane/ethyl acetate 20:1) to afford the desired product **7** and **7a-1**.



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-chlorophenyl)vinyl)- 7-chloro-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7la)**

White solid, 32.1 mg, 0.062 mmol, 31% yield. M.p.: 178 - 180 °C.

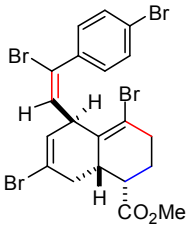
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.40 - 7.35 (m, 4H), 6.05 (d, *J* = 10.0 Hz, 1H), 5.66 - 5.62 (m, 1H), 4.04 - 4.00 (m, 1H), 3.78 (s, 3H), 3.11 - 3.05 (m, 1H), 2.84 - 2.79 (m, 1H), 2.56 - 2.54 (m, 2H), 2.43 - 2.34 (m, 1H), 2.18 (dd, *J* = 16.7, 5.3 Hz, 1H), 1.97 - 1.93 (m, 1H), 1.89 - 1.80 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.2, 136.9, 134.9, 132.6, 132.1, 131.4, 130.2, 128.6, 124.5, 121.5, 120.8, 51.9, 45.9, 42.1, 36.3, 36.2, 35.5, 21.7. **HRMS** (ESI) calcd for $C_{20}H_{19}O_2Cl_2Br_2$ $(M+H)^+$ 518.9129, found 518.9121.



Dimethyl (1*S, 4*S**, 5*R**, 10*S**)-8-bromo-3-chloro-1, 4, 4a, 5, 6, 7- hexahydro-1, 4-ethanonaphthalene-5, 10-dicarboxylate (7la-1)**

White solid, 22.5 mg, 0.058 mmol, 29% yield. M.p.: 108 - 110 °C.

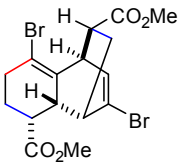
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.10 (dd, *J* = 7.2, 2.2 Hz, 1H), 4.14 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.97 - 2.87 (m, 3H), 2.85 - 2.81 (m, 1H), 2.57 (brs, 1H), 2.52 - 2.45 (m, 1H), 2.12 - 2.06 (m, 1H), 2.02 - 1.84 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 172.4, 133.9, 132.5, 125.1, 114.2, 52.2, 51.7, 45.4, 44.3, 42.7, 40.2, 40.0, 33.5, 32.8, 26.9. **HRMS** (ESI) calcd for $C_{16}H_{19}O_4ClBr$ $(M+H)^+$ 389.0155, found 389.0148. The crystal suitable for X-ray single crystal diffraction analysis was obtained from solvent mixture of hexane/EtOAc (5:1).



Methyl (1*S, 5*S**, 8a*S**)-4, 7-dibromo-5-((*E*)-2-bromo-2-(4-bromophenyl) vinyl)-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7ma)**

White solid, 36.3 mg, 0.060 mmol, 30% yield. M.p.: 184 - 185 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (d, *J* = 8.4 Hz, 2H), 7.29 (d, *J* = 8.4 Hz, 2H), 6.05 (d, *J* = 10.0 Hz, 1H), 5.82 - 5.80 (m, 1H), 4.00 - 3.96 (m, 1H), 3.77 (s, 3H), 3.11 - 3.06 (m, 1H), 2.94 - 2.77 (m, 1H), 2.55 - 2.43 (m, 3H), 2.31 (dd, *J* = 16.8, 5.2 Hz, 1H), 1.96 - 1.92 (m, 1H), 1.86 - 1.77 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.2, 137.2, 132.4, 131.6, 131.0, 130.4, 128.5, 123.2, 121.8, 121.6, 120.9, 52.0, 47.3, 42.0, 38.6, 36.2, 36.1, 21.7. **HRMS** (ESI) calcd for $C_{20}H_{19}O_2Br_3{}^{81}Br$ $(M+H)^+$ 608.8100, found 608. 8109.



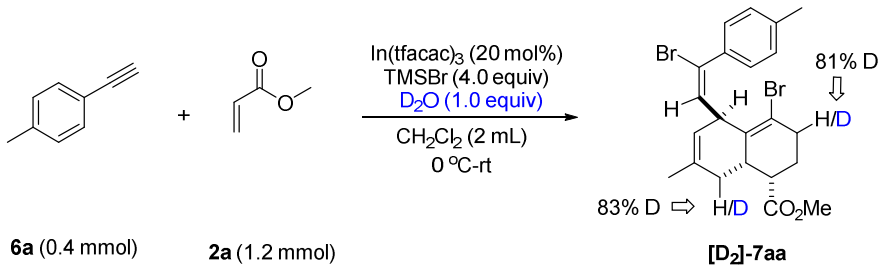
Dimethyl (1*S, 4*S**, 5*R**, 10*S**)-3,8-dibromo-1, 4, 4a, 5, 6, 7-hexahydro-1, 4-ethanonaphthalene-5, 10-dicarboxylate (7ma-1)**

White solid, 28.4 mg, 0.066 mmol, 33% yield. M.p.: 112 - 113 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.33 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.13 (dd, *J* = 7.1, 1.7 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.06 (brs, 1H), 2.95 - 2.80 (m, 3H), 2.59 (brs, 1H), 2.52 - 2.46 (m, 1H),

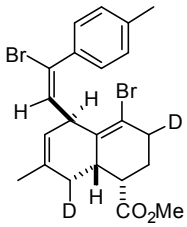
2.11 - 2.04 (m, 1H), 2.02 - 1.87 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.0, 172.4, 132.3, 129.8, 122.0, 114.3, 52.1, 52.0, 46.1, 45.9, 43.8, 40.1, 40.0, 33.6, 32.9, 27.1. **HRMS** (ESI) calcd for $C_{16}H_{19}O_4Br_2$ $(M+H)^+$ 432.9650, found 432.9655. The crystal suitable for X-ray single crystal diffraction analysis was obtained from solvent mixture of hexane/EtOAc (5:1).

3.4.2 Mechanistic Study and Spectral Data



6a (0.4 mmol) **2a** (1.2 mmol) **[D$_2$]-7aa**

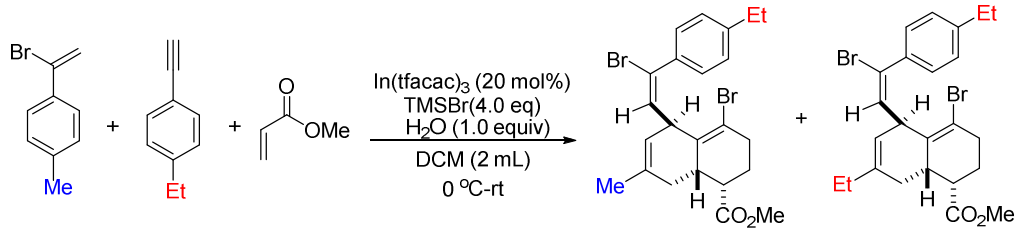
A dry reaction tube was charged with aryl alkyne **6a** (0.4 mmol, 46.4 mg), acrylate **2a** (1.2 mmol, 103.2 mg), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg) D_2O (0.4 mmol, 8 mg), CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature for 0.5 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to afford the desired product **[D$_2$]-7aa**.



Methyl (1*S, 5*S**, 8*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(*p*-tolyl)vinyl)-7- methyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate-3, 8-d ([D$_2$]-7aa)**

White solid, 65.3 mg, 0.136 mmol, 68% yield (~80% D).

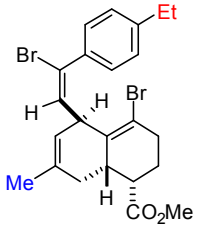
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.34 (d, J = 8.0 Hz, 2H), 7.18 (d, J = 8.0 Hz, 2H), 6.03 (d, J = 10.0 Hz, 1H), 5.22 - 5.21 (m, 1H), 3.97 - 3.94 (m, 1H), 3.75 (s, 3H), 2.97 - 2.95 (m, 1H), 2.82 - 2.76 (m, 1H), 2.54 - 2.47 (m, 1H), 2.38 (s, 3H), 1.89 - 1.82 (m, 2H), 1.73 - 1.72 (m, 1H), 1.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.0, 138.5, 136.0, 135.3, 134.6, 132.2, 128.9, 128.8, 122.2, 122.1, 118.7, 51.7, 45.6, 42.3, 35.9 (t, J_{D-C} = 34 Hz), 35.3, 33.5 (t, J_{D-C} = 42 Hz), 23.2, 23.8, 21.3.



6a-1 **6b** **2a** **7aba**, 32% **7ba**, 14%

A dry reaction tube was charged with *α*-aryl vinyl bromide **6a-1** (0.2 mmol, 39.2 mg), alkyne **6b** (0.2 mmol, 26.0 mg), acrylate **2a** (1.2 mmol, 103.2 mg), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08

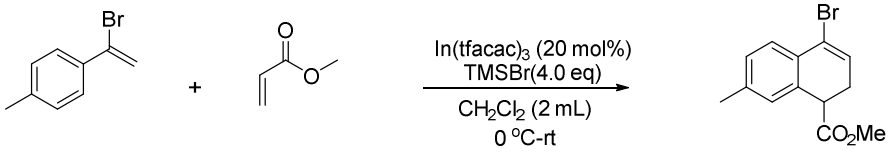
mmol, 45.9 mg), H_2O (0.2 mmol, 3.6 mg), CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature for 0.5 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to afford the desired product **7aba** (31.5 mg, 32%) with **7ba** (7.1 mg, 14%). The mixture of **7aba** and **7ba** cannot be separated on the silica gel column and the yields were based on the amount of **6b** used. The crystal of **7aba** suitable for X-ray single crystal diffraction analysis was obtained from solvent mixture of hexane/MeOH (5:1).



Methyl (1*S, 5*S**, 8a*S**)-4-bromo-5-((*E*)-2-bromo-2-(4-ethylphenyl)vinyl)- 7-methyl-1, 2, 3, 5, 8, 8a-hexahydronaphthalene-1-carboxylate (7aba)**

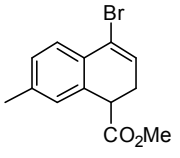
White solid, 31.5 mg, 0.064 mmol, 32% yield (with 14% yield of **7ba**).

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.37 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.1 Hz, 2H), 6.03 (d, *J* = 10.0 Hz, 1H), 5.22 (brs, 1H), 3.98 - 3.96 (m, 1H), 3.76 (s, 3H), 2.98 - 2.95 (m, 1H), 2.81 - 2.75 (m, 1H), 2.69 (q, *J* = 8.1 Hz, 2H), 2.54 - 2.50 (m, 2H), 2.06 - 1.99 (m, 1H), 1.89 - 1.82 (m, 2H), 1.74 (dd, *J* = 16.6, 5.1 Hz, 1H), 1.69 (s, 3H), 1.26 (t, *J* = 7.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.0, 144.8, 136.1, 135.2, 134.6, 132.2, 128.9, 127.6, 122.1, 121.9, 118.7, 51.7, 45.6, 42.3, 36.2, 35.2, 33.9, 28.7, 23.3, 21.8, 15.3. **HRMS** (ESI) calcd for $C_{23}H_{27}Br_2O_2$ $(M+H)^+$ 493.0372, found 493.0367.



6a-1 (0.4 mmol) **2a** (1.2 mmol) **7aa-1** (30%)

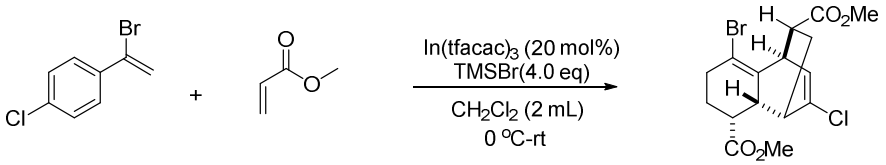
A dry reaction tube was charged with α-aryl vinyl bromide **6a-1** (0.4 mmol, 78.4 mg), acrylate **2a** (1.2 mmol, 103.2 mg), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg) and CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature for 0.5 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to afford the desired product **7aa-1**.



Methyl 4-bromo-7-methyl-1,2-dihydronaphthalene-1-carboxylate (7aa-1)

Colorless oil, 33.6 mg, 0.121 mmol, 30% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 3.78 (t, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 2.90 - 2.83 (m, 1H), 2.63 - 2.56 (m, 1H), 2.38 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.4, 138.6, 132.5, 129.3, 128.9, 128.6, 127.3, 126.9, 120.8, 52.3, 43.5, 28.2, 21.2. **HRMS** (ESI) calcd for $C_{13}H_{14}O_2Br$ $(M+H)^+$ 281.0177, found 281.0175.



6l-1 (0.4 mmol) **2a** (1.2 mmol) **7la-1** (38%)

A dry reaction tube was charged with α-aryl vinyl bromide **6l-1** (0.4 mmol, 86.4 mg), acrylate **2a** (1.2 mmol, 103.2 mg), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg) and CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 ^oC. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature for 1 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to afford the desired product **7la-1** in 38% yield.

3.5 Crystal Structure Data

Table 3-15. Sample and crystal data for **7aa**

Identification code	CCDC 1500385	
Chemical formula	$C_{22}H_{24}Br_2O_2$	
Formula weight	480.23	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal size	0.280 x 0.320 x 0.400 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21/n 1	
Unit cell dimensions	a = 11.9006(12) Å	α = 90°
	b = 12.1348(10) Å	β = 105.775(3)°
	c = 14.5838(11) Å	γ = 90°
Volume	2026.7(3) $Å^3$	
Z	4	
Density (calculated)	1.574 g/cm^3	
Absorption coefficient	4.013 mm^{-1}	
F(000)	968	

Table 3-16. Data collection and structure refinement for **7aa**

Theta range for data collection	3.08 to 32.25°
Index ranges	-17<=h<=17, -17<=k<=18, -21<=l<=21
Reflections collected	38959
Independent reflections	7153 [R(int) = 0.0897]
Coverage of independent	99.5%
Absorption correction	multi-scan

Max. and min. transmission	0.3995 and 0.2967
Structure solution technique	direct methods
Structure solution program	SHELXS-97 (Sheldrick, 2008)
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-97 (Sheldrick, 2008)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	7153 / 0 / 238
Goodness-of-fit on F^2	0.997
Δ/σ_{max}	0.001
Final R indices	4494 data; $I>2\sigma(I)$ R1 = 0.0468, wR2 =
	all data R1 = 0.1027, wR2 =
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0387P)^2+0.9631P]$
Largest diff. peak and hole	0.767 and -1.041 eÅ^{-3}
R.M.S. deviation from mean	0.121 eÅ^{-3}

Table 3-17. Bond lengths (Å) for **7aa**

Br1-C15	1.928(2)	Br2-C11	1.912(3)
C1-O2	1.446(3)	C1-H1A	0.98
C1-H1B	0.98	C1-H1C	0.98
C2-O1	1.203(3)	C2-O2	1.336(3)
C2-C3	1.512(4)	C3-C13	1.523(4)
C3-C4	1.548(3)	C3-H3	1.0
C4-C10	1.515(3)	C4-C5	1.533(3)
C4-H4	1.0	C5-C6	1.510(3)
C5-H5A	0.99	C5-H5B	0.99
C6-C8	1.328(3)	C6-C7	1.502(3)
C7-H7A	0.98	C7-H7B	0.98
C7-H7C	0.98	C8-C9	1.508(3)
C8-H8	0.95	C9-C14	1.506(3)
C9-C10	1.519(3)	C9-H9	1.0
C10-C11	1.325(3)	C11-C12	1.501(4)
C12-C13	1.526(4)	C12-H12A	0.99
C12-H12B	0.99	C13-H13A	0.99
C13-H13B	0.99	C14-C15	1.334(3)
C14-H14	0.95	C15-C16	1.473(4)
C16-C17	1.390(4)	C16-C22	1.392(4)
C17-C18	1.388(4)	C17-H17	0.95
C18-C19	1.392(4)	C18-H18	0.95
C19-C21	1.387(4)	C19-C20	1.507(4)
C20-H20A	0.98	C20-H20B	0.98
C20-H20C	0.98	C21-C22	1.381(4)

C21-H21	0.95	C22-H22	0.95

Table 3-18. Bond angles (°) for **7aa**

O2-C1-H1A	109.5	O2-C1-H1B	109.5
H1A-C1-H1B	109.5	O2-C1-H1C	109.5
H1A-C1-H1C	109.5	H1B-C1-H1C	109.5
O1-C2-O2	123.4(3)	O1-C2-C3	125.4(3)
O2-C2-C3	111.2(2)	C2-C3-C13	113.4(2)
C2-C3-C4	111.4(2)	C13-C3-C4	110.7(2)
C2-C3-H3	107.0	C13-C3-H3	107.0
C4-C3-H3	107.0	C10-C4-C5	109.8(2)
C10-C4-C3	110.7(2)	C5-C4-C3	115.0(2)
C10-C4-H4	107.0	C5-C4-H4	107.0
C3-C4-H4	107.0	C6-C5-C4	111.5(2)
C6-C5-H5A	109.3	C4-C5-H5A	109.3
C6-C5-H5B	109.3	C4-C5-H5B	109.3
H5A-C5-H5B	108.0	C8-C6-C7	121.6(2)
C8-C6-C5	121.9(2)	C7-C6-C5	116.5(2)
C6-C7-H7A	109.5	C6-C7-H7B	109.5
H7A-C7-H7B	109.5	C6-C7-H7C	109.5
H7A-C7-H7C	109.5	H7B-C7-H7C	109.5
C6-C8-C9	125.9(2)	C6-C8-H8	117.0
C9-C8-H8	117.0	C14-C9-C8	111.7(2)
C14-C9-C10	110.9(2)	C8-C9-C10	110.2(2)
C14-C9-H9	108.0	C8-C9-H9	108.0
C10-C9-H9	108.0	C11-C10-C4	121.3(2)
C11-C10-C9	124.8(2)	C4-C10-C9	113.8(2)
C10-C11-C12	126.3(2)	C10-C11-Br2	120.3(2)
C12-C11-Br2	113.32(19)	C11-C12-C13	110.2(2)
C11-C12-H12A	109.6	C13-C12-H12A	109.6
C11-C12-H12B	109.6	C13-C12-H12B	109.6
H12A-C12-H12B	108.1	C3-C13-C12	108.8(2)
C3-C13-H13A	109.9	C12-C13-H13A	109.9
C3-C13-H13B	109.9	C12-C13-H13B	109.9
H13A-C13-H13B	108.3	C15-C14-C9	123.8(2)
C15-C14-H14	118.1	C9-C14-H14	118.1
C14-C15-C16	128.1(2)	C14-C15-Br1	117.9(2)
C16-C15-Br1	113.96(17)	C17-C16-C22	118.1(2)
C17-C16-C15	119.8(2)	C22-C16-C15	122.1(2)
C18-C17-C16	120.9(2)	C18-C17-H17	119.5
C16-C17-H17	119.5	C17-C18-C19	121.1(3)

C17-C18-H18	119.5	C19-C18-H18	119.5
C21-C19-C18	117.5(3)	C21-C19-C20	121.7(3)
C18-C19-C20	120.8(3)	C19-C20-H20A	109.5
C19-C20-H20B	109.5	H20A-C20-H20B	109.5
C19-C20-H20C	109.5	H20A-C20-H20C	109.5
H20B-C20-H20C	109.5	C22-C21-C19	121.9(3)
C22-C21-H21	119.1	C19-C21-H21	119.1
C21-C22-C16	120.5(3)	C21-C22-H22	119.7
C16-C22-H22	119.7	C2-O2-C1	116.3(2)

Table 3-19: Sample and crystal data for **7ba**

Identification code	CCDC 1500386	
Chemical formula	$C_{24}H_{28}Br_2O_2$	
Formula weight	508.28 g/mol	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.200 x 0.260 x 0.420 mm	
Crystal habit	colorless block	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.8298(3) Å	α = 92.876(3)°
	b = 10.7707(4) Å	β = 96.754(2)°
	c = 13.5049(5) Å	γ = 97.138(2)°
Volume	1119.80(7) $Å^3$	
Z	2	
Density (calculated)	1.507 g/cm^3	
Absorption coefficient	3.636 mm^{-1}	
F(000)	516	

Table 3-20. Data collection and structure refinement for **7ba**

Theta range for data collection	2.64 to 31.11°
Index ranges	-11<=h<=11, -15<=k<=15, -19<=l<=19
Reflections collected	31905
Independent reflections	7194 [R(int) = 0.0727]
Coverage of independent	99.6%
Absorption correction	multi-scan
Max. and min. transmission	0.5300 and 0.3100
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/6 (Sheldrick, 2014)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	7194 / 0 / 256

Goodness-of-fit on F^2	1.007
Δ/σ_{max}	0.002
Final R indices	5046 data; I>2σ(I) R1 = 0.0380, wR2 =
	all data R1 = 0.0729, wR2 =
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0237P)^2+0.2362P]$
Largest diff. peak and hole	0.669 and -0.529 eÅ^{-3}
R.M.S. deviation from mean	0.105 eÅ^{-3}

Table 3-21. Bond lengths (Å) for **7ba**

Br1-C1	1.923(2)	Br2-C16	1.927(2)
C1-C10	1.325(3)	C1-C2	1.502(3)
C2-C3	1.527(3)	C3-C4	1.522(3)
C4-C11	1.507(3)	C4-C5	1.541(3)
C5-C10	1.512(3)	C5-C6	1.533(3)
C6-C7	1.513(3)	C7-C8	1.332(3)
C7-C13	1.503(3)	C8-C9	1.508(3)
C9-C10	1.513(3)	C9-C15	1.514(3)
C11-O1	1.203(3)	C11-O2	1.340(3)
C12-O2	1.444(3)	C13-C14	1.519(3)
C15-C16	1.321(3)	C16-C17	1.485(3)
C17-C18	1.390(3)	C17-C22	1.394(3)
C18-C19	1.386(3)	C19-C20	1.387(3)
C20-C21	1.395(3)	C20-C23	1.508(3)
C21-C22	1.391(3)	C23-C24	1.527(3)

Table 3-22. Bond angles (°) for **7ba**

C10-C1-C2	126.4(2)	C10-C1-Br1	120.72(16)
C2-C1-Br1	112.89(16)	C1-C2-C3	110.79(19)
C4-C3-C2	110.33(18)	C11-C4-C3	111.92(18)
C11-C4-C5	111.23(19)	C3-C4-C5	111.28(18)
C10-C5-C6	108.43(18)	C10-C5-C4	112.15(18)
C6-C5-C4	113.89(17)	C7-C6-C5	112.27(17)
C8-C7-C13	123.8(2)	C8-C7-C6	121.7(2)
C13-C7-C6	114.44(18)	C7-C8-C9	125.17(19)
C8-C9-C10	109.89(17)	C8-C9-C15	108.95(17)
C10-C9-C15	112.44(18)	C1-C10-C5	120.98(19)
C1-C10-C9	125.4(2)	C5-C10-C9	113.45(18)
O1-C11-O2	123.3(2)	O1-C11-C4	125.8(2)
O2-C11-C4	110.90(18)	C7-C13-C14	115.28(19)
C16-C15-C9	124.7(2)	C15-C16-C17	128.9(2)
C15-C16-Br2	117.35(17)	C17-C16-Br2	113.71(14)

C18-C17-C22	118.8(2)	C18-C17-C16	120.5(2)
C22-C17-C16	120.6(2)	C19-C18-C17	120.8(2)
C18-C19-C20	121.0(2)	C19-C20-C21	118.1(2)
C19-C20-C23	120.8(2)	C21-C20-C23	121.0(2)
C22-C21-C20	121.3(2)	C21-C22-C17	119.9(2)
C20-C23-C24	113.1(2)	C11-O2-C12	115.42(18)

Table 3-23. Sample and crystal data for **7la-1**

Identification code	CCDC 1500387	
Chemical formula	$C_{16}H_{18}BrClO_4$	
Formula weight	389.66 g/mol	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.220 x 0.400 x 0.420 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 9.0743(6) Å	α = 90°
	b = 17.4986(10) Å	β = 106.558(3)°
	c = 10.3332(7) Å	γ = 90°
Volume	1572.74(18) $Å^3$	
Z	4	
Density (calculated)	1.646 g/cm^3	
Absorption coefficient	2.798 mm^{-1}	
F(000)	792	

Table 3-24. Data collection and structure refinement for **7la-1**

Theta range for data collection	2.62 to 31.17°
Index ranges	-13<=h<=13, -25<=k<=25, -14<=l<=15
Reflections collected	22690
Independent reflections	5047 [R(int) = 0.0929]
Coverage of independent	99.1%
Absorption correction	multi-scan
Max. and min. transmission	0.5780 and 0.3860
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/6 (Sheldrick, 2014)
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5047 / 0 / 201
Goodness-of-fit on F^2	1.018
Δ/σ_{max}	0.001
Final R indices	3494 data; I>2σ(I) R1 = 0.0451, wR2 = 0.0814

	all data	R1 = 0.0844, wR2 = 0.0939
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0280P)^2+0.6202P]$	
Largest diff. peak and hole	0.884 and -0.975 eÅ^{-3}	
R.M.S. deviation from mean	0.123 eÅ^{-3}	

Table 3-25. Bond lengths (Å) for **7la-1**

Br1-C14	1.915(2)	C1-O1	1.447(3)
C2-O2	1.191(3)	C2-O1	1.337(3)
C2-C3	1.511(4)	C3-C4	1.551(4)
C3-C8	1.557(3)	C4-C5	1.553(4)
C5-C6	1.507(4)	C5-C10	1.553(3)
C6-C7	1.324(4)	C6-Cl1	1.731(3)
C7-C8	1.513(4)	C8-C9	1.515(4)
C9-C14	1.323(3)	C9-C10	1.518(3)
C10-C11	1.536(3)	C11-C15	1.512(4)
C11-C12	1.534(4)	C12-C13	1.542(4)
C13-C14	1.497(4)	C15-O3	1.200(3)
C15-O4	1.342(3)	C16-O4	1.449(3)

Table 3-26. Bond angles (°) for **7la-1**

O2-C2-O1	123.0(3)	O2-C2-C3	125.7(3)
O1-C2-C3	111.2(2)	C2-C3-C4	112.6(2)
C2-C3-C8	112.0(2)	C4-C3-C8	109.5(2)
C3-C4-C5	109.2(2)	C6-C5-C4	105.4(2)
C6-C5-C10	109.5(2)	C4-C5-C10	106.7(2)
C7-C6-C5	116.4(2)	C7-C6-Cl1	123.4(2)
C5-C6-Cl1	120.09(19)	C6-C7-C8	113.0(2)
C7-C8-C9	105.8(2)	C7-C8-C3	108.2(2)
C9-C8-C3	107.9(2)	C14-C9-C8	127.3(2)
C14-C9-C10	119.9(2)	C8-C9-C10	112.5(2)
C9-C10-C11	111.4(2)	C9-C10-C5	107.8(2)
C11-C10-C5	119.0(2)	C15-C11-C12	110.7(2)
C15-C11-C10	114.0(2)	C12-C11-C10	107.0(2)
C11-C12-C13	114.3(2)	C14-C13-C12	112.6(2)
C9-C14-C13	125.8(2)	C9-C14-Br1	121.7(2)
C13-C14-Br1	112.46(18)	O3-C15-O4	122.6(2)
O3-C15-C11	126.4(2)	O4-C15-C11	111.0(2)
C2-O1-C1	116.5(2)	C15-O4-C16	115.6(2)

Table 3-27. Sample and crystal data for **7ma-1**

Identification code	CCDC 1500388	
Chemical formula	$C_{16}H_{18}Br_2O_4$	
Formula weight	434.12 g/mol	
Temperature	103(2) K	
Wavelength	0.71073 Å	
Crystal size	0.220 x 0.360 x 0.420 mm	
Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 9.2410(12) Å	α = 90°
	b = 17.454(2) Å	β = 106.183(4)°
	c = 10.4075(13) Å	γ = 90°
Volume	1612.1(4) $Å^3$	
Z	4	
Density (calculated)	1.789 g/cm^3	
Absorption coefficient	5.043 mm^{-1}	
F(000)	864	

Table 3-28. Data collection and structure refinement for **7ma-1**

Theta range for data collection	2.29 to 32.22°	
Index ranges	-13<=h<=13, -25<=k<=25, -15<=l<=15	
Reflections collected	21838	
Independent reflections	5641 [R(int) = 0.1235]	
Coverage of independent reflections	98.9%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.4030 and 0.2260	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2014/4	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	5641 / 0 / 201	
Goodness-of-fit on F^2	0.990	
Δ/σ_{max}	0.001	
Final R indices	3305 data; I>2σ(I)	R1 = 0.0601, wR2 = 0.0906
	all data	R1 = 0.1313, wR2 = 0.1072
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0310P)^2]$	
Largest diff. peak and hole	1.318 and -1.109 $eÅ^{-3}$	
R.M.S. deviation from mean	0.164 $eÅ^{-3}$	

Table 3-29. Bond lengths (Å) for **7ma-1**

Br1-C6	1.919(3)	Br2-C10	1.890(4)
C1-O1	1.447(4)	C2-O2	1.205(4)
C2-O1	1.333(4)	C2-C3	1.516(5)
C3-C4	1.532(5)	C3-C8	1.533(5)
C4-C5	1.538(5)	C5-C6	1.504(5)
C6-C7	1.320(5)	C7-C12	1.514(5)
C7-C8	1.526(4)	C8-C9	1.542(5)
C9-C10	1.515(5)	C9-C14	1.549(5)
C10-C11	1.328(5)	C11-C12	1.507(5)
C12-C13	1.557(5)	C13-C15	1.507(5)
C13-C14	1.550(5)	C15-O4	1.188(5)
C15-O3	1.346(4)	C16-O3	1.447(4)

Table 3-30. Bond angles (°) for **7ma-1**

O2-C2-O1	122.5(3)	O2-C2-C3	125.8(3)
O1-C2-C3	111.6(3)	C2-C3-C4	110.5(3)
C2-C3-C8	114.4(3)	C4-C3-C8	107.7(3)
C3-C4-C5	114.4(3)	C6-C5-C4	112.1(3)
C7-C6-C5	126.4(3)	C7-C6-Br1	121.5(3)
C5-C6-Br1	112.0(3)	C6-C7-C12	128.0(3)
C6-C7-C8	119.8(3)	C12-C7-C8	111.8(3)
C7-C8-C3	110.9(3)	C7-C8-C9	108.3(3)
C3-C8-C9	119.2(3)	C10-C9-C8	109.2(3)
C10-C9-C14	104.8(3)	C8-C9-C14	107.3(3)
C11-C10-C9	116.5(3)	C11-C10-Br2	123.1(3)
C9-C10-Br2	120.3(3)	C10-C11-C12	112.7(3)
C11-C12-C7	106.2(3)	C11-C12-C13	108.1(3)
C7-C12-C13	108.3(3)	C15-C13-C14	112.3(3)
C15-C13-C12	112.2(3)	C14-C13-C12	109.3(3)
C9-C14-C13	109.4(3)	O4-C15-O3	122.5(4)
O4-C15-C13	126.3(4)	O3-C15-C13	111.2(3)
C2-O1-C1	115.8(3)	C15-O3-C16	116.1(3)

Table 3-31. Sample and crystal data for **7aa-2-1**

Identification code	**7aa-2-1**
Chemical formula	$C_{15}H_{20}O_2$
Formula weight	232.31 g/mol
Temperature	103(2) K
Wavelength	0.71073 Å
Crystal size	0.140 x 0.180 x 0.340 mm

Crystal habit	colorless block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 7.8411(5) Å	α = 90°
	b = 30.729(2) Å	β = 93.030(3)°
	c = 10.9853(8) Å	γ = 90°
Volume	2643.2(3) $Å^3$	
Z	8	
Density (calculated)	1.168 g/cm^3	
Absorption coefficient	0.076 mm^{-1}	
F(000)	1008	

Table 3-32. Data collection and structure refinement for **7aa-2-1**

Theta range for data collection	1.97 to 27.82°	
Index ranges	-8<=h<=10, -40<=k<=39, -11<=l<=14	
Reflections collected	25163	
Independent reflections	6135 [R(int) = 0.0764]	
Coverage of independent	97.7%	
Absorption correction	Multi-Scan	
Max. and min. transmission	0.9890 and 0.9750	
Structure solution technique	direct methods	
Structure solution program	XT, VERSION 2014/4	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	6135 / 0 / 313	
Goodness-of-fit on F^2	1.033	
Δ/σ_{max}	0.001	
Final R indices	3194 data; I>2σ(I)	R1 = 0.0721, wR2 = 0.1645
	all data	R1 = 0.1466, wR2 = 0.1999
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0812P)^2+0.5180P]$	
Largest diff. peak and hole	0.355 and -0.257 $eÅ^{-3}$	
R.M.S. deviation from mean	0.050 $eÅ^{-3}$	

Table 3-33. Bond lengths (Å) for **7aa-2-1**

C1-C7	1.495(4)	C1-C6	1.556(4)
C1-C2	1.586(4)	C2-C9	1.497(4)
C2-C3	1.557(4)	C2-C5	1.573(3)
C3-C8	1.501(4)	C3-C4	1.557(4)
C4-C5	1.535(4)	C5-C6	1.533(4)
C7-O1	1.432(3)	C8-O2	1.435(3)

C9-C15	1.373(4)	C9-C10	1.396(4)
C10-C11	1.393(4)	C11-C12	1.365(5)
C12-C14	1.371(5)	C12-C13	1.522(5)
C14-C15	1.402(5)	C16-C22	1.497(4)
C16-C21	1.544(4)	C16-C17	1.563(3)
C17-C24	1.502(3)	C17-C20	1.576(4)
C17-C18	1.576(3)	C18-C23	1.500(4)
C18-C19	1.545(4)	C19-C20	1.536(4)
C20-C21	1.543(4)	C22-O3	1.436(3)
C23-O4	1.434(3)	C24-C30	1.373(4)
C24-C25	1.382(4)	C25-C26	1.393(4)
C26-C27	1.380(4)	C27-C29	1.371(5)
C27-C28	1.524(4)	C29-C30	1.377(4)

Table 3-34. Bond angles (°) for **7aa-2-1**

C7-C1-C6	115.2(3)	C7-C1-C2	119.9(2)
C6-C1-C2	89.26(19)	C9-C2-C3	119.2(2)
C9-C2-C5	124.7(2)	C3-C2-C5	90.20(19)
C9-C2-C1	114.5(2)	C3-C2-C1	114.4(2)
C5-C2-C1	88.34(19)	C8-C3-C2	114.1(2)
C8-C3-C4	112.2(2)	C2-C3-C4	88.55(19)
C5-C4-C3	91.6(2)	C6-C5-C4	114.6(2)
C6-C5-C2	90.6(2)	C4-C5-C2	88.76(19)
C5-C6-C1	90.9(2)	O1-C7-C1	112.8(3)
O2-C8-C3	111.6(2)	C15-C9-C10	117.3(3)
C15-C9-C2	122.1(3)	C10-C9-C2	120.6(3)
C11-C10-C9	121.5(3)	C12-C11-C10	120.8(3)
C11-C12-C14	117.9(3)	C11-C12-C13	120.9(4)
C14-C12-C13	121.2(4)	C12-C14-C15	122.1(3)
C9-C15-C14	120.3(3)	C22-C16-C21	113.0(2)
C22-C16-C17	114.7(2)	C21-C16-C17	89.98(19)
C24-C17-C16	118.6(2)	C24-C17-C20	125.3(2)
C16-C17-C20	89.15(18)	C24-C17-C18	115.7(2)
C16-C17-C18	114.0(2)	C20-C17-C18	88.46(19)
C23-C18-C19	115.5(2)	C23-C18-C17	119.4(2)
C19-C18-C17	89.96(19)	C20-C19-C18	91.1(2)
C19-C20-C21	113.8(2)	C19-C20-C17	90.3(2)
C21-C20-C17	89.54(19)	C20-C21-C16	91.10(19)
O3-C22-C16	111.8(2)	O4-C23-C18	111.3(2)
C30-C24-C25	116.7(3)	C30-C24-C17	121.3(2)
C25-C24-C17	122.0(2)	C24-C25-C26	121.7(3)

C27-C26-C25	120.7(3)	C29-C27-C26	117.3(3)
C29-C27-C28	120.5(3)	C26-C27-C28	122.2(3)
C27-C29-C30	121.8(3)	C24-C30-C29	121.8(3)

Table 3-35. Sample and crystal data for **7aba**

Identification code	CCDC 1500389	
Chemical formula	$C_{23}H_{26}Br_2O_2$	
Formula weight	494.26 g/mol	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal size	0.080 x 0.140 x 0.180 mm	
Crystal habit	light yellow block	
Crystal system	triclinic	
Space group	P -1	
Unit cell dimensions	a = 7.7807(4) Å	α = 89.442(3)°
	b = 10.8974(5) Å	β = 82.532(3)°
	c = 12.8013(6) Å	γ = 83.422(3)°
Volume	1069.11(9) $Å^3$	
Z	2	
Density (calculated)	1.535 g/cm^3	
Absorption coefficient	3.806 mm^{-1}	
F(000)	500	

Table 3-36. Data collection and structure refinement for **7aba**

Theta range for data collection	1.88 to 31.08°	
Index ranges	-11<=h<=11, -15<=k<=15, -18<=l<=18	
Reflections collected	21246	
Independent reflections	6844 [R(int) = 0.0752]	
Coverage of independent	99.6%	
Absorption correction	multi-scan	
Max. and min. transmission	0.7510 and 0.5470	
Refinement method	Full-matrix least-squares on F^2	
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)	
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$	
Data / restraints / parameters	6844 / 0 / 248	
Goodness-of-fit on F^2	0.989	
Δ/σ_{max}	0.001	
Final R indices	4009 data; I>2σ(I)	R1 = 0.0444, wR2 = 0.0941
	all data	R1 = 0.1052, wR2 = 0.1224
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.0527P)^2]$	
Largest diff. peak and hole	1.629 and -0.623 $eÅ^{-3}$	

R.M.S. deviation from mean	0.165 eÅ^{-3}

Table 3-37. Bond lengths (Å) for **7aba**

Br1-C1	1.910(4)	Br2-C15	1.929(3)
C1-C10	1.334(5)	C1-C2	1.502(5)
C2-C3	1.528(6)	C3-C4	1.534(5)
C4-C11	1.488(5)	C4-C5	1.536(5)
C5-C10	1.512(5)	C5-C6	1.535(4)
C6-C7	1.494(5)	C7-C8	1.326(5)
C7-C13	1.520(5)	C8-C9	1.517(4)
C9-C14	1.511(4)	C9-C10	1.512(5)
C11-O1	1.205(4)	C11-O2	1.339(4)
C12-O2	1.442(5)	C14-C15	1.325(5)
C15-C16	1.472(5)	C16-C21	1.391(4)
C16-C17	1.394(4)	C17-C18	1.393(5)
C18-C19	1.375(5)	C19-C20	1.386(5)
C19-C22	1.509(5)	C20-C21	1.374(5)
C22-C23	1.518(6)		

Table 3-38. Bond angles (°) for **7aba**

C10-C1-C2	125.6(3)	C10-C1-Br1	121.0(3)
C2-C1-Br1	113.4(2)	C1-C2-C3	111.1(3)
C2-C3-C4	109.7(3)	C11-C4-C3	111.4(3)
C11-C4-C5	113.0(3)	C3-C4-C5	110.6(3)
C10-C5-C6	108.2(3)	C10-C5-C4	112.5(3)
C6-C5-C4	113.5(3)	C7-C6-C5	112.9(3)
C8-C7-C6	122.4(3)	C8-C7-C13	121.4(4)
C6-C7-C13	116.2(3)	C7-C8-C9	124.9(3)
C14-C9-C10	112.6(3)	C14-C9-C8	110.1(3)
C10-C9-C8	109.3(3)	O1-C11-O2	122.5(4)
O1-C11-C4	125.9(4)	O2-C11-C4	111.6(3)
C1-C10-C5	121.2(3)	C1-C10-C9	124.7(3)
C5-C10-C9	113.9(3)	C15-C14-C9	124.9(3)
C14-C15-C16	129.3(3)	C14-C15-Br2	117.0(3)
C16-C15-Br2	113.6(2)	C21-C16-C17	117.8(3)
C21-C16-C15	121.6(3)	C17-C16-C15	120.6(3)
C18-C17-C16	120.9(3)	C19-C18-C17	120.8(3)
C18-C19-C20	118.1(3)	C18-C19-C22	120.5(4)
C20-C19-C22	121.3(3)	C21-C20-C19	121.7(3)
C20-C21-C16	120.7(3)	C19-C22-C23	113.8(3)
C11-O2-C12	115.2(3)		

3.6 Computational Method and Data

Computational Method

We performed DFT calculations using Gaussian 09 software[105] at the B3LYP/[SDD for In, 6-311+G** for others]//B3LYP/[SDD for In, 6-31G* for others] level.[106] Solvent effects (CH_2Cl_2) were taken into account by using the PCM method[107] in single point calculations.We used $InBr_3$ instead of the best catalyst, $In(tfacac)_3$, to simplify the calculations.We could not precisely locate one of the transition states (TS2-B); therefore, the zero-point energy (ZPE) value could not be obtained for this transition state. To make fair comparisons of the stability of various species under the circumstances, in the energy diagrams below, ZPE corrections are not included.

XYZ coordinates of Dearomatization Diels-Alder reaction

RC (withouta Lewis acid)

C	-0.422402	-0.447704	0.720787
C	-0.077027	0.101590	1.889023
H	0.334529	-0.676434	-0.024084
C	1.296556	0.409228	2.338307
C	1.588192	1.499723	3.174619
C	2.899815	1.790728	3.536304
C	3.971831	1.002901	3.092930
C	3.677779	-0.091944	2.270961
C	2.367155	-0.390387	1.901411
H	0.779201	2.124177	3.538511
H	3.094507	2.646125	4.179570
C	5.390210	1.322013	3.502467
H	4.485257	-0.734289	1.926921
H	2.173749	-1.259190	1.279955
H	-1.453542	-0.668953	0.472161
Br	-1.500716	0.543120	3.123429
C	1.223481	-3.946874	-1.946174
C	0.583062	-4.023144	-0.776352
C	2.088044	-2.823571	-2.381953
O	2.190291	-1.827238	-1.465384
O	2.654767	-2.795755	-3.456016
C	3.028696	-0.725954	-1.858114
H	3.040483	-0.049244	-1.003723
H	4.037860	-1.077396	-2.087693
H	2.617656	-0.229010	-2.740914
H	1.151358	-4.738016	-2.686828
H	-0.032845	-4.884135	-0.532229
H	0.646310	-3.236473	-0.031515
H	6.101617	0.612565	3.068299
H	5.681974	2.329148	3.179233
H	5.508410	1.288940	4.592783

TS1 (without a Lewis acid)

C	0.368853	-0.070115	-0.138697
C	0.155181	0.387191	1.189649
H	1.262157	0.330578	-0.617865
C	1.192757	0.453060	2.152310
C	0.974659	0.678657	3.544151
C	2.013055	0.620528	4.442316
C	3.340931	0.334635	4.028647
C	3.573549	0.132039	2.675333
C	2.530947	0.184081	1.737865
H	-0.032891	0.874817	3.892022
H	1.813939	0.790296	5.498033
C	4.454799	0.279857	5.043304
H	4.583880	-0.064295	2.326198
H	2.785101	0.164208	0.688208
H	-0.494846	0.010438	-0.795279
Br	-1.668418	0.545444	1.739216
C	0.738652	-1.827334	-0.154800
C	1.916353	-2.221772	0.538555
H	0.795225	-1.945281	-1.238670
H	-0.174306	-2.250151	0.263143
C	1.811250	-2.821342	1.854861
H	2.887576	-2.215107	0.056173
O	3.022295	-3.260845	2.313951
O	0.777014	-2.948340	2.498718
C	2.985781	-3.877350	3.602555
H	4.016010	-4.163435	3.823231
H	2.612554	-3.180257	4.358675
H	2.340227	-4.761263	3.596775
H	5.418441	0.065292	4.571603
H	4.547227	1.229428	5.586014
H	4.267307	-0.497971	5.794917

Int1 (without a Lewis acid)

C	2.288540	-0.045786	1.659994
C	0.968285	0.578390	2.114441
C	0.863786	1.098585	3.461435
C	1.900317	1.032686	4.325914
C	3.186604	0.436320	3.959698
C	3.356083	-0.066735	2.722230
C	-0.001947	0.602594	1.174375
Br	-1.724029	1.382015	1.479479
C	0.233593	-0.037409	-0.160446
C	0.828790	-1.450327	0.049489
C	2.063544	-1.461002	0.985315
C	1.924070	-2.536482	2.054788
O	0.895271	-2.844655	2.616409
O	3.117851	-3.114520	2.323437
C	3.101919	-4.091012	3.376786
H	0.936268	0.577050	-0.747966
H	-0.082544	1.535677	3.762622

H	1.788132	1.425689	5.333787
C	4.279535	0.418712	4.998879
H	4.306766	-0.513747	2.439653
H	2.673091	0.569126	0.827376
H	-0.688987	-0.103142	-0.741715
H	1.092732	-1.882714	-0.922062
H	0.050278	-2.077180	0.491921
H	2.975895	-1.680718	0.422681
H	4.123619	-4.466426	3.444400
H	2.798320	-3.629464	4.320304
H	2.408267	-4.901801	3.139151
H	5.190680	-0.053146	4.618503
H	4.533715	1.436876	5.322742
H	3.962165	-0.127761	5.897048

RC (with a Lewis acid (TMS^+))

C	-0.372999	-1.796381	1.055981
C	0.473143	-0.906363	0.531183
H	-0.571223	-1.783648	2.124242
C	1.281788	0.091711	1.255724
C	1.523649	1.378495	0.745523
C	2.251532	2.308827	1.482414
C	2.772095	1.995055	2.747286
C	2.542783	0.704028	3.245835
C	1.812557	-0.232631	2.517485
H	1.127302	1.654592	-0.226440
H	2.413478	3.301720	1.070279
C	3.530099	3.020798	3.554133
H	2.942629	0.427222	4.218217
H	1.659495	-1.227793	2.925360
H	-0.918499	-2.511984	0.452678
Br	0.680396	-0.913909	-1.407334
C	2.820650	-4.154066	-0.656917
C	2.329823	-4.433332	0.560477
C	3.557360	-2.926343	-0.934344
O	3.794056	-2.142868	0.068920
O	3.999345	-2.606579	-2.086734
C	4.472009	-0.866613	-0.141093
H	4.485950	-0.405534	0.843399
H	5.479668	-1.051863	-0.515703
H	3.890552	-0.269643	-0.843734
H	2.678051	-4.828076	-1.493217
H	1.782402	-5.353520	0.738815
H	2.458810	-3.756957	1.398540
Si	3.941568	-3.255017	-3.772561
C	4.527154	-1.765306	-4.728161
C	5.143078	-4.688058	-3.761777
C	2.163261	-3.725625	-4.122570
H	4.589326	-2.005044	-5.796760
H	3.840207	-0.918843	-4.619888
H	5.522905	-1.443427	-4.404467
H	2.012056	-3.748325	-5.209203

H	1.891599	-4.715478	-3.740805
H	1.458314	-2.994448	-3.711446
H	5.212609	-5.114552	-4.770454
H	6.150322	-4.369166	-3.472020
H	4.832696	-5.496235	-3.089919
H	4.221300	2.548908	4.259513
H	4.103109	3.696728	2.911041
H	2.839209	3.640637	4.140368

TS1 (with a Lewis acid (TMS^+))

C	2.508471	-0.238427	1.743801
C	1.095418	0.145948	1.784360
C	0.470314	0.288938	3.075915
C	1.184884	0.112537	4.220277
C	2.600949	-0.177768	4.193443
C	3.227837	-0.330314	2.983879
C	0.441528	0.215792	0.574658
Br	-1.396824	0.627750	0.450515
C	1.124610	-0.219902	-0.668309
C	1.586081	-1.729084	-0.544081
C	2.449098	-2.057040	0.650403
C	1.954928	-2.918936	1.656815
O	2.681899	-3.527494	2.545780
O	0.645851	-3.012315	1.778088
C	0.074213	-3.756776	2.880446
H	2.015260	0.395651	-0.849610
H	-0.587559	0.523779	3.114938
H	0.696137	0.222704	5.184508
C	3.350603	-0.236934	5.496344
H	4.303061	-0.477895	2.945739
H	3.088758	0.126319	0.902181
H	0.479421	-0.122388	-1.542181
H	2.136684	-1.960376	-1.461479
H	0.682626	-2.342347	-0.539779
H	3.518128	-2.136180	0.484081
H	-1.000184	-3.723466	2.708609
H	0.434053	-4.786989	2.871091
H	0.329766	-3.273520	3.825656
Si	4.204656	-4.428412	2.509909
C	5.641166	-3.239679	2.310478
C	4.193921	-5.251781	4.186273
C	4.043865	-5.620118	1.072303
H	6.577846	-3.810159	2.356847
H	5.640043	-2.709087	1.352122
H	5.674283	-2.499495	3.116866
H	5.102373	-5.851332	4.320575
H	4.163172	-4.515113	4.996790
H	3.335873	-5.922519	4.303737
H	4.945113	-6.241546	1.002372
H	3.190650	-6.295850	1.199588
H	3.930223	-5.105029	0.111587
H	4.412243	-0.452653	5.348906

H	3.267307	0.714970	6.035360
H	2.928637	-1.007547	6.154143

Int1 (with a Lewis acid (TMS^+))

C	1.245717	-0.287327	-0.424334
C	0.669390	0.316300	0.774914
H	2.290168	-0.002621	-0.563247
C	1.368738	0.525358	1.984680
C	0.748977	1.037527	3.167120
C	1.467336	1.194999	4.329074
C	2.841515	0.854815	4.397251
C	3.460263	0.346922	3.245548
C	2.756534	0.190789	2.060014
H	-0.301162	1.303778	3.143288
H	0.975598	1.592429	5.212515
C	3.609656	1.068894	5.669426
H	4.516560	0.096250	3.273630
H	3.285196	-0.153325	1.182346
H	0.682571	-0.002294	-1.313870
Br	-1.175038	0.667370	0.671438
C	1.193163	-1.919647	-0.374199
C	2.064327	-2.577640	0.614722
H	1.493822	-2.191997	-1.390679
H	0.142653	-2.185697	-0.240847
C	1.596317	-3.009909	1.832101
H	3.096462	-2.784792	0.359597
O	0.332046	-2.703409	2.159187
O	2.263735	-3.701730	2.737839
C	-0.217435	-3.210147	3.388822
H	-1.247762	-2.855439	3.403079
H	-0.195202	-4.302436	3.402356
H	0.332196	-2.820727	4.249392
Si	3.712636	-4.667922	2.671130
C	5.181161	-3.520529	2.412097
C	3.742257	-5.452793	4.369092
C	3.508314	-5.917196	1.287327
H	6.114392	-4.080277	2.551310
H	5.216520	-3.080715	1.409341
H	5.178982	-2.704735	3.144375
H	4.404971	-6.544633	1.212611
H	2.657492	-6.581883	1.475194
H	3.355597	-5.442886	0.312087
H	4.621039	-6.099651	4.478389
H	3.786840	-4.697774	5.162040
H	2.854291	-6.071187	4.540898
H	4.617203	0.649246	5.615630
H	3.700292	2.141775	5.885065
H	3.088262	0.620270	6.523356

TS2 (with a Lewis acid (TMS^+))

C	2.508471	-0.238427	1.743801

C	1.095418	0.145948	1.784360
C	0.470314	0.288938	3.075915
C	1.184884	0.112537	4.220277
C	2.600949	-0.177768	4.193443
C	3.227837	-0.330314	2.983879
C	0.441528	0.215792	0.574658
Br	-1.396824	0.627750	0.450515
C	1.124610	-0.219902	-0.668309
C	1.586081	-1.729084	-0.544081
C	2.449098	-2.057040	0.650403
C	1.954928	-2.918936	1.656815
O	2.681899	-3.527494	2.545780
O	0.645851	-3.012315	1.778088
C	0.074213	-3.756776	2.880446
H	2.015260	0.395651	-0.849610
H	-0.587559	0.523779	3.114938
H	0.696137	0.222704	5.184508
C	3.350603	-0.236934	5.496344
H	4.303061	-0.477895	2.945739
H	3.088758	0.126319	0.902181
H	0.479421	-0.122388	-1.542181
H	2.136684	-1.960376	-1.461479
H	0.682626	-2.342347	-0.539779
H	3.518128	-2.136180	0.484081
H	-1.000184	-3.723466	2.708609
H	0.434053	-4.786989	2.871091
H	0.329766	-3.273520	3.825656
Si	4.204656	-4.428412	2.509909
C	5.641166	-3.239679	2.310478
C	4.193921	-5.251781	4.186273
C	4.043865	-5.620118	1.072303
H	6.577846	-3.810159	2.356847
H	5.640043	-2.709087	1.352122
H	5.674283	-2.499495	3.116866
H	5.102373	-5.851332	4.320575
H	4.163172	-4.515113	4.996790
H	3.335873	-5.922519	4.303737
H	4.945113	-6.241546	1.002372
H	3.190650	-6.295850	1.199588
H	3.930223	-5.105029	0.111587
H	4.412243	-0.452653	5.348906
H	3.267307	0.714970	6.035360
H	2.928637	-1.007547	6.154143

PC (with a Lewis acid (TMS^+))

C	2.155341	-0.103805	2.008766
C	0.679354	0.133437	1.702202
C	-0.206648	0.512150	2.784065
C	0.237242	0.638857	4.054292
C	1.640798	0.421479	4.413776
C	2.526210	0.067275	3.459692
C	0.324310	-0.040208	0.407352

Br	-1.447247	0.222119	-0.229945
C	1.346016	-0.519985	-0.579990
C	2.073560	-1.762079	-0.009692
C	2.653900	-1.497068	1.417150
C	2.301882	-2.600468	2.368585
O	3.132977	-3.350531	2.975829
O	1.041448	-2.776279	2.583730
C	0.583627	-3.781333	3.538955
H	2.082645	0.274445	-0.777637
H	-1.250152	0.686534	2.543587
H	-0.453763	0.922779	4.843431
C	2.043313	0.642695	5.849034
H	3.580171	-0.040319	3.709858
H	2.748577	0.616968	1.421986
H	0.891830	-0.775273	-1.539466
H	2.884713	-2.062130	-0.680338
H	1.355363	-2.586220	0.019599
H	3.744352	-1.451270	1.374517
H	-0.500583	-3.701400	3.516475
H	0.915878	-4.768754	3.216213
H	0.978353	-3.541685	4.526865
Si	4.910242	-3.703169	2.946727
C	5.298610	-4.151604	1.172415
C	5.781860	-2.173288	3.576905
C	4.983533	-5.142391	4.128839
H	6.340873	-4.489739	1.109850
H	4.670890	-4.975240	0.814221
H	5.192911	-3.309406	0.480049
H	6.841034	-2.413878	3.736087
H	5.745357	-1.331034	2.878116
H	5.377305	-1.844305	4.540286
H	6.017265	-5.497132	4.222947
H	4.640745	-4.861159	5.130634
H	4.377300	-5.986282	3.782054
H	3.107336	0.446532	6.010873
H	1.840406	1.677593	6.151855
H	1.466110	-0.000376	6.525772

CHAPTER 4

APPENDIX

In addition to the above-mentioned In(III)-TMSBr-catalyzed [2+2] cycloaddition (**Chapter 2**) and cascade dearomatization reaction of aryl alkyne and acrylate (**Chapter 3**), we attempted to apply this catalyst system to other substrates, in order to get more insights into the catalyst properties and broaden its synthetic utilities. The obtained results will be discussed in this chapter. This chapter will further disclose an In(III)-TMSBr-catalyzed stereoselective coupling of aryl aldehyde and alkyne, In(III)-TMSBr-catalyzed trimerization of aryl alkyne and acetophenone, facile synthesis of α-aryl vinyl bromides and the ensuing [4+2] cycloaddition with methyl acrylate catalyzed by In(III)-TMSBr catalytic system.

4.1 In(III)-TMSBr-catalyzed Stereoselective Coupling of Aryl Aldehyde and Aryl Alkyne

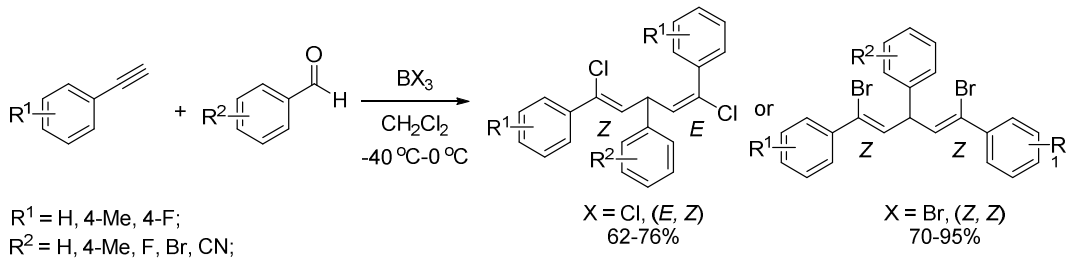
Efficient one-step synthesis of complicated and densely functionalized molecules from readily available starting materials is always the target of organic synthetic community. The cross coupling reaction of alkyne and aldehyde is a representative example of this transformation. Numerous compounds and synthetic building blocks could be prepared from this coupling reaction using different Lewis acid catalysts and transition metal catalysts. The reported products from the reactions of alkynes and aldehydes include allylic and propargylic alcohols, conjugated ketones, enynols and functionalized naphthalene derivatives. In an intramolecular manner, cycloalkanones, cycloalkenones, and alkylidene could be constructed. The application of transition metal catalysts, on the other hand, often gives addition products through scission of triple bond or decarbonylation of carbonyl group.

Recently, 2:1 coupling of aryl alkynes and aryl aldehydes was attained employing BX_3, $TiCl_4$, $FeCl_3$ and GaX_3 to give 1,5-di-halo-1,4-pentadienes. These halo diene compounds are potent organic intermediates in view of the multi-functionality presents which could be handles for

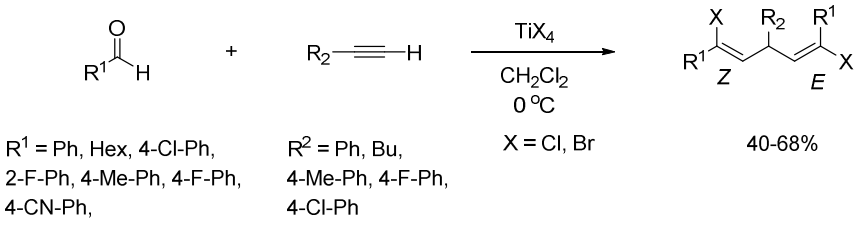
subsequent substitution, coupling and cyclization reactions.

4.1.1 Overview of the reported coupling reactions of aldehyde and alkyne

In exploratory studies of novel synthetic methodologies with boron halide chemistry, Kabalka and co-workers found that using boron trihalides, aryl alkynes and aryl aldehydes could react to generate dialkenylation products, namely 1,3,5-triaryl-1,5-dihalo-1,4-pentadienes (**Scheme 4-1**).[199] Note-worthily, the choice of boron halide will dictate the stereochemistry of diene products. With BCl_3, the formation of (*E,Z*)- 1,4-pentadienes dominates with minor amount of (*Z,Z)*-isomers while BBr_3 leads to formation of (*Z,Z*)-1,4-pentadienes as major isomers.



Scheme 4-1. Boron trihalides-promoted cross coupling of aryl alkynes and aryl aldehydes

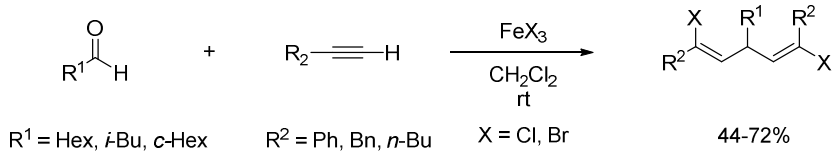


Scheme 4-2. Titanium tetrahalides-mediated synthesis of (*E,Z*)-1,5-dihalo-1,4-dienes

Subsequently, the same group found that titanium(IV) halides could also promote this reaction to give only (*E,Z*) isomer of diene products with $TiCl_4$ or $TiBr_4$ (**Scheme 4-2**). Moreover, some aliphatic aldehydes and alkynes could be employed in this protocol to give the corresponding

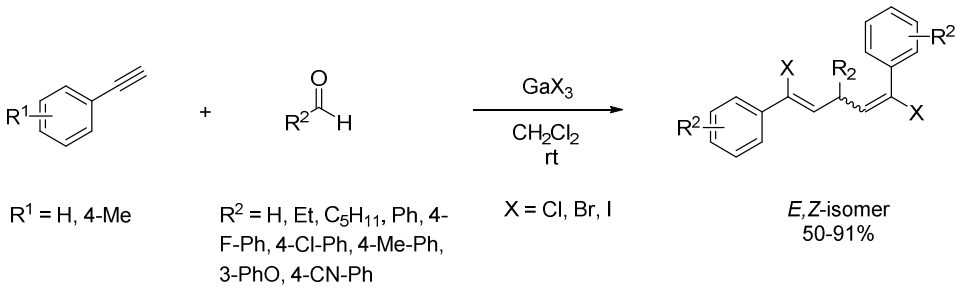
[199](a) Kabalka, G. W.; Wu, Z. Z.; Ju, Y. H. *Org. Lett*. **2002**, *4*, 1491-1493; (b) Kabalka, G. W.; Yao, M.-L.; Borella, S.; W, Z. Z.; Ju, Y.-H.; Quick, T. *J. Org. Chem*. **2008**, *73*, 2668-2673.

diene products.[200]



Scheme 4-3. FeX_3-mediated aliphatic aldehydes-alkynes coupling

In 2005, V. S. Martín and co-workers found that Fe(III) halides were also effective catalysts to form similar 1,5-dihalo-1,4-diene products through the coupling of aliphatic alkynes and aldehydes (**Scheme 4-3**).[201] Aliphatic and aromatic alkynes could undertake this chemistry but not aryl aldehydes.



Scheme 4-4. Synthesis of 1,4-pentadienes with Gallium(III) halides

In the same year, Yadav *et al.* disclosed a similar reaction of alkynes and aldehydes also to assemble 1,3,5-triaryl-1,5-dihalo-1,4-pentadienes with gallium(III) halide (**Scheme 4-4**).[202] The reactions were stereoselective to give high yields of (*E,Z*)-isomers exclusively except with benzaldehydes carrying *para*-chloro or cyano group, that also formed (*Z,Z)*-isomer in minor amount.

[200]Kabalka, G. W.; Wu, Z. Z.; Ju, Y. H. *Org. Lett*. **2002**, *4*, 3415-3417.
[201]Miranda, P. O.; Díaz, D. D.; Padrón, J. I.; Ramírez, M. A.; Martín, V. S. *J. Org. Chem*. **2005**, *70*, 57-62.
[202]Yadav, J. S.; Reddy, B. V. S.; Eeshwaraiah, B.; Gupta, M. K.; Biswas, S. K. *Tetrahedron Lett*. **2005**, 1161-1163

4.1.2 Proposed In(III)-TMSX-catalyzed coupling of aryl alkyne and aryl aldehyde

For the potential synthetic values possessed by dihalodiene compounds, several methodologies have been devised for their synthesis as highlighted in the section above. However, all of the reports hitherto require stoichiometric amount of reagents. To the best of our knowledge, a catalytic version of this transformation is lacking.

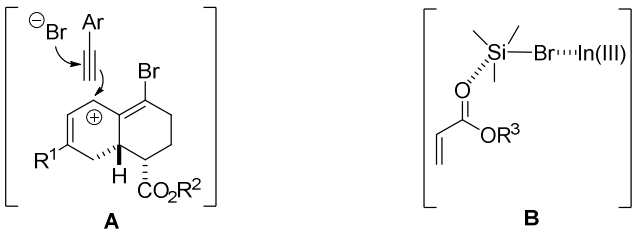
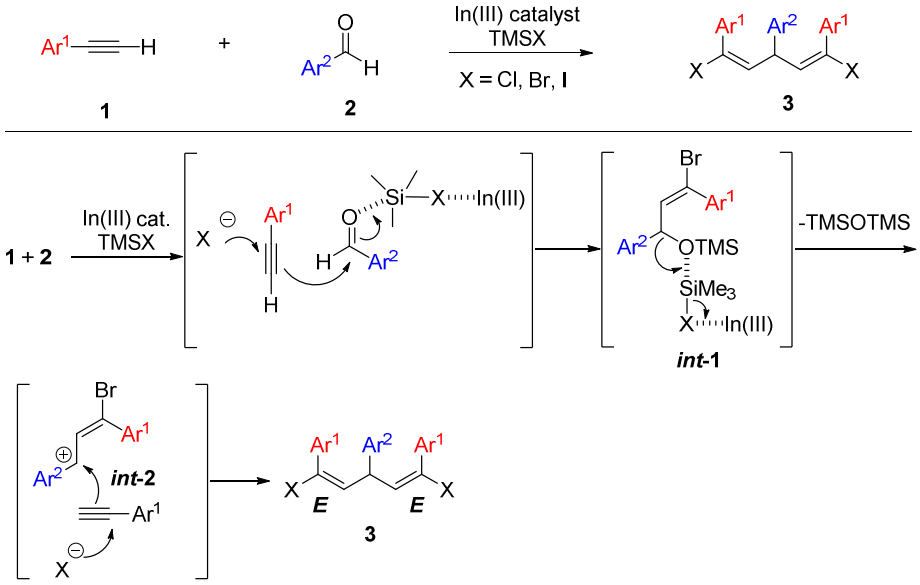


Figure 4-1. (A) S_N2'-type cascade pathway and (**B**) In(III)-TMSBr activation of acrylate

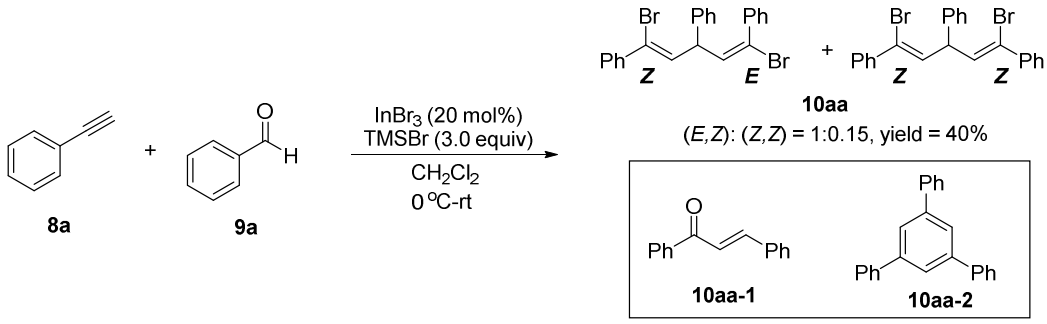


Scheme 4-5. Proposed In(III)-TMSX-catalyzed coupling of aryl alkyne and aryl aldehyde

Inspired by the postulated S_N2'-type cascade pathway for the cascade dearomatization reaction of aryl alkyne and carbocation (**Figure 4-1A**) and the unique activation of acrylate by the In(III)-TMSBr combined Lewis acid (**Figure 4-1B**), we envisioned the plausibility to apply this

catalyst system to realize the catalytic coupling of aryl alkynes and aryl aldehydes. The proposed reaction pathway is illustrated in **Scheme 4-5**: first, the carbonyl group of aryl aldehyde **2** will be activated by the combined Lewis acid catalyst to undergo a concerted S_N2'-type attack to generate a silyl ether *int*-**1**; second, the silyl ether group of *int*-**1** will also be activated by the same catalyst system to give *int*-**2** and followed by a second concerted S_N2'-type attack to yield diene product **3** and regenerate the In(III) catalyst.

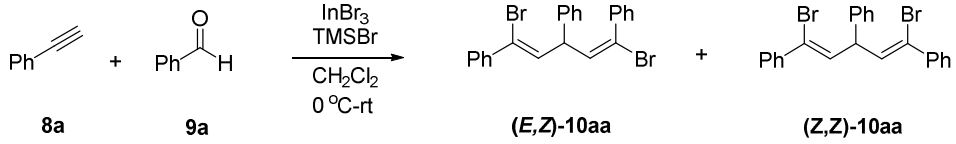
4.1.3 Reaction condition optimization for In(III)-TMSBr-catalyzed coupling of aryl alkyne and aryl aldehyde



Scheme 4-6. The preliminary result of $InBr_3$-TMSBr-catalyzed coupling of **8a** and **9a**

To test our hypothesis, phenylacetylene **8a** and benzaldehyde **9a** were chosen as model substrates in the reaction containing $InBr_3$ (20 mol%) and TMSBr (3 equiv; serves as both additive and bromine source) in CH_2Cl_2. When stirred at 0 ^oC to ambient temperature for 1 h, 40% yield of diene **10aa** was obtained in good stereoselectivity ((*E,Z*):(*Z,Z*) = 1:0.15) in combination with by-products **10aa-1** and **10aa-2** (**Scheme 4-6**). However the double bond's geometry is different from originally propozed one. The ^1H and ^{13}C NMR spectra of (*E,Z*)-**10aa** and (*Z,Z*)-**10aa** were consistent with the reported ones and the ratio was determined through the crude NMR of reaction mixture before column purification. Moreover, the two isomers of **10aa** could be seperated by the silica gel column chromatography.

Table 4-1. Reaction conditions optimization for diene **10aa** formation[a]



8a **9a** (*E,Z*)-**10aa** (Z,Z)-**10aa**

Entry	Catalyst	Solvent	TMSX	Yield [%][b]	(*E,Z*)/(*Z,Z*)[c]
1	-	CH_2Cl_2	TMSBr	-	-
2[d]	-	$ClCH_2CH_2Cl$	TMSBr	-	-
3[e]	$InBr_3$	CH_2Cl_2	-	<5	-
4[f]	$InBr_3$	$ClCH_2CH_2Cl$	-	0	-
5	$InBr_3$	CH_2Cl_2	TMSBr	40	1:0.15

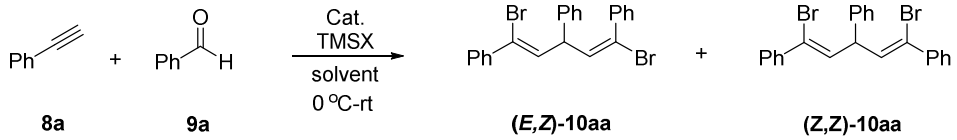
[a] Reaction condition: **8a** (0.4 mmol), **9a** (0.8 mmol), $InBr_3$ (10 mol%), additive (3 equiv), solvent (2 mL), 0 °C-rt, 1 h, N_2. [b] Isolated yields. [c] The ratio of (*Z,E*)/(*Z,Z*) was determined by the crude NMR before purification.[d] Reaction temperature was 80 °C. [e] 1.0 equiv of $InBr_3$ was used. [f] 1.0 equiv of $InBr_3$ was used and reaction temperature was 80 °C.

With this promising result in hand, we commenced the optimization studies of this reaction using **8a** and **9a** and the results were summarized in **Table 4-1**. It was found that the indium catalyst and TMSBr were indispensable for formation of diene product **10aa**. Without In(III) catalyst, no desired product could be obtained, even at 80 °C (**Table 4-1**, entries 1-2). In the absence of TMSBr, the reaction did not take place even at 80 °C and using 1.0 equiv of $InBr_3$ (entries 3-4).

Having recognized the crucial roles of catalyst and TMSBr in this reaction, several indium (III) and iron (III) catalysts were screened (**Table 4-2**, entries 1-5) and all afforded the desired diene products with $In(tfacac)_3$ giving the optimal yield and excellent stereoselectivity (entry 3). Additionally, reaction in DCE gave the best yield of **10aa** (entries 5-8). Replacing TMSBr with other bromine source such as tetrabutylammonium bromide (TBAB) and aqueous HBr, trace or no desired product could be obtained (entries 9-10). With TMSCl, the chloride substituted diene product was obtained in relatively lower yield (entry 11). The reaction molarity, amount of aryl aldehyde and TMSBr together with the catalyst loading of $In(tfacac)_3$ have also been evaluated

for optimal reaction efficiency (entries 12-16). Both an increase and a decrease of reaction concentration have led to lower product yields (entries 12-13). Moreover, lesser amount of aryl aldehyde and TMSBr also resulted in lower yield of **10aa** (entries 14-15). Finally, using 20 mol% of $In(tfacac)_3$ instead of 10 mol% could not further improve the yield of **10aa**, too (entry 16).

Table 4-2. Reaction conditions optimization for diene **10aa** formation[a]



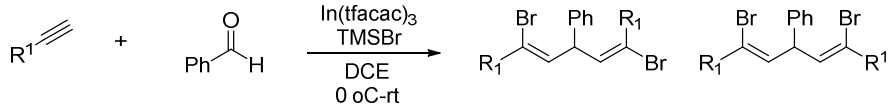
8a **9a** **(*E*,*Z*)-10aa** **(Z,Z)-10aa**

Entry	Catalyst	Solvent	Additive	Yield [%][b]	(*E*,*Z*)/(*Z*,*Z*)[c]
1	$InBr_3$	CH_2Cl_2	TMSBr	40	1:0.15
2	$In(OTf)_3$	CH_2Cl_2	TMSBr	45	1:0.24
3	$In(tfacac)_3$	CH_2Cl_2	TMSBr	58	1:0.05
4	$FeBr_3$	CH_2Cl_2	TMSBr	37	1:0.14
5	$Fe(tfacac)_3$	CH_2Cl_2	TMSBr	49	1:0.06
6	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSBr	63	1:0.05
7	$In(tfacac)_3$	toluene	TMSBr	< 5	-
8	$In(tfacac)_3$	$CHCl_3$	TMSBr	<5	-
9	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TBAB	0	
10	$In(tfacac)_3$	$ClCH_2CH_2Cl$	48% aq. HBr	0	
11	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSCl	31	1:0.08
12[d]	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSBr	50	1:0.06
13[e]	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSBr	53	1:0.05
14[f]	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSBr	50	1:0.05
15[g]	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSBr	54	1:0.05
16[h]	$In(tfacac)_3$	$ClCH_2CH_2Cl$	TMSBr	64	1:0.05

[a] Reaction condition: **8a** (0.4 mmol), **9a** (0.8 mmol), catalyst (10 mol%), additive (3 equiv), solvent (2 mL), 0 ^{o}C-rt, 1 h min, N_2. [b] Isolated yields. [c] The ratio of (*Z,E*)/(*Z,Z*) was determined by the crude NMR before purification. [d] 1 mL of $ClCH_2CH_2Cl$ was used as solvent. [e] 3 mL of $ClCH_2CH_2Cl$ was used as solvent. [f] 0.4 mmol of **9a** was added. [g] 2.0 equiv of TMSBr was used. [h]. 20% of $In(tfacac)_3$ was used.

4.1.4 Substrate scope of In(III)-TMSBr-catalyzed cross coupling of alkyne and aldehyde

Table 4-3. Aryl alkyne substrate scope for $In(tfacac)_3$-TMSBr-catalyzed cross coupling with benzaldehyde[a]



8 **9a** **(*Z,E*)-10** **(*Z,Z*)-10**

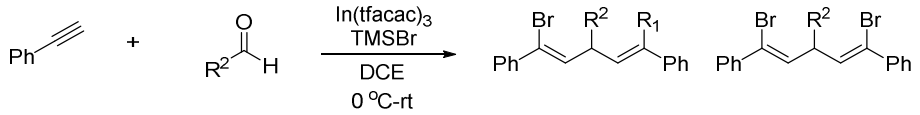
Entry	R^1	**10**	Yield [%][b]	(*Z,E*)/(*Z,Z*)[c]
1	**8a**, R^1 = Ph	**10aa**	63	1:0.05
2	**8b**, R^1 = 4-Me-Ph	**10ba**	61	1:0.07
3	**8c**, R^1 = 4-Et-Ph	**10ca**	73	1:0.11
4	**8d**, R^1= 4-Bu-Ph	**10da**	70	1:0.31
5	**8e**, R^1 = 4-*t*-Bu-Ph	**10ea**	60	1:0.10
6	**8f**, R^1 = 4-Hex-Ph	**10fa**	50	1:0.11
7	**8g**, R^1 = 4-F-Ph	**10ga**	56	1:0.16
8	**8h**, R^1 = 4-Cl-Ph	**10ha**	55	1:0.06
9	**8i**, R^1 = 4-Br-Ph	**10ia**	56	1:0.04
10	**8j**, R^1 = 4-Ph-Ph	**10ja**	30	1:0.12
11	**8k**, R^2 = 3-Me-Ph	**10ka**	53	1:0.08
12	**8l**, R^1 = 2-Me-Ph	-	-	-
13	**8m**, R^1 = 4-MeO-Ph	-	-	-
14	**8n**, R^1 = 1-naph	-	-	-
15	**8o**, R^1 = *n*-Hex	-	-	-

[a] Reaction condition: **8** (0.4 mmol), **9a** (0.8 mmol), $In(tfacac)_3$ (10 mol%), additive (3.0 equiv), $ClCH_2CH_2Cl$ (2 mL), 0 ^{o}C-rt, N_2. [b] Isolated yields. [c] The ratio of (*Z,E*)/(*Z,Z*) was determined by the crude NMR before purification.

With the optimized reaction conditions, we sought to probe the generality of aryl alkyne substrate scope of this reaction with respect to **9a** (**Table 4-3**). Generally, the aryl alkynes with electronically netural or electron rich substituents (eg., Me, Et, *t*-Bu, *n*-Hex, F, Cl, Br, Ph, entries 1-3 and 5-10) on the phenyl ring provided the expected diene products in moderate to excellent

yields and good stereoselectivities. However, it is intriguing to observe that when there was 4-butyl substituent on the phenyl ring, the ratio of (*Z,E*) and (*Z,Z*)-isomer increased to 1:0.31 (entry 4), while other 4-alkyl substituted phenyl alkyne furnished the (*Z,E*) and (*Z,Z*)-isomers in an approximate ratio of 10:1 (entries 2-3 and 5-6). In the presence of *meta*-methyl substituent on phenyl ring (entry 11), the diene product was obtained in 53% yield while the phenyl alkyne with *ortho*-methyl group could not afford any titled product (entry 12). This could be attributed to the steric hindrance posed by an *ortho*-substituion. Alkyne with methoxyl group on the pheny ring was found incompatible for this reaction due to decomposition (entry 13). In addition to aryl alkynyl substrates, alkyne with naphthalene ring or aliphatic alkyne have also been examined, but none gave the desired product (entries 14-15).

Table 4-4. Aryl aldehyde substrate scope for In(tfacac)$_3$-TMSBr-catalyzed cross coupling with phenylacetylene [a]



8a **9** **(*Z,E*)-10** **(*Z,Z*)-10**

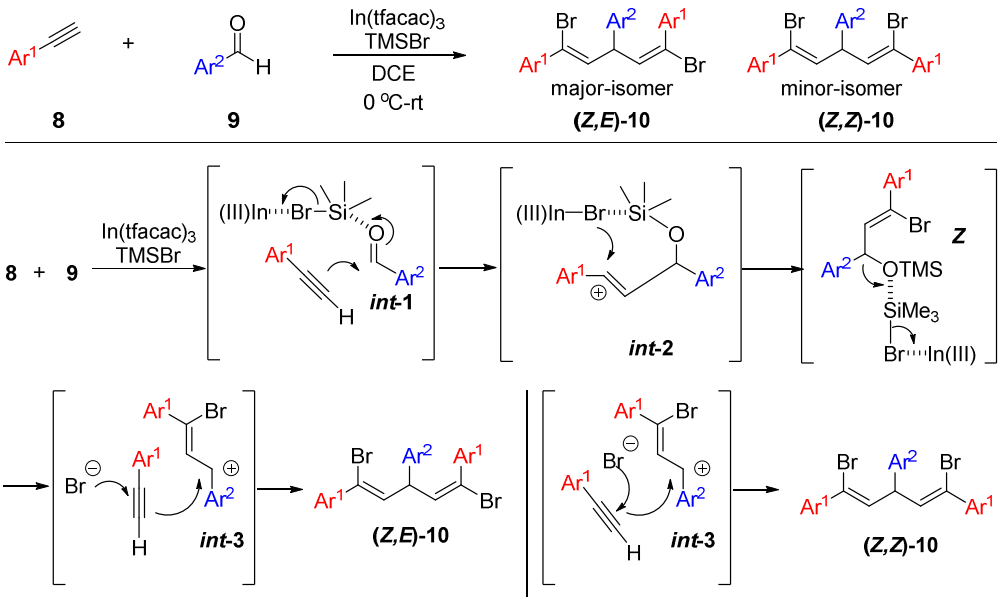
Entry	**9**	**10**	Yield [%][b]	(*E*,*Z*)/(*Z*,*Z*)[c]
1	**9a**, R^2 = Ph	**10aa**	63	1:0.05
2	**9b**, R^2 = 4-Me-Ph	**10ab**	61	1:0.09
3	**9c**, R^2 = 4-F-Ph	**10ac**	70	1:0.08
4	**9d**, R^2 = 4-Br-Ph	**10ad**	60	1:0.08
5	**9e**, R^2 = 4-CF_3-Ph	**10ae**	50	1:0.58
6	**9f**, R^2 = 4-NO_2-Ph	**10af**	56	1:0.09
7	**9g**, R^2 = 2,6-Me-Ph	-	-	-
8	**9h**, R^2 = 4-CN-Ph	-	-	-
9	**9i**, R^2 = 4-OMe-Ph	-	-	-
10	**9j**, R^2 = *n*-Hex	-	-	-
11	**9k**, R^2 = *c*-Hex	-	-	-

[a] Reaction condition: **8a** (0.4 mmol), **9** (0.8 mmol), In(tfacac)$_3$ (10 mol%), additive (3.0 equiv), $ClCH_2CH_2Cl$ (2 mL), 0 °C-rt, N_2. [b] Isolated yields. [c] The ratio of (*Z,E*)/(*Z,Z*) was determined by the crude NMR before purification.

The substrate generality of aryl aldehydes was also probed and the results were demonstrated in **Table 4-4**. Generally, aryl aldehydes with electron-rich or electron-deficient properties could afford the desired diene products with moderate to good yields and excellent steroselectivities (entries 1-4 and 6). However, when 4-(trifluoromethyl)benzaldehyde was used, the ratio of (*Z,E*) and (*Z,Z*) isomer increased to about 2:1 (entry 5) and no product was formed with 4-cyanobenzaldehyde (entry 8). Similar to the steric hindrance conferred by *ortho*-substituent in the case of alkyne susbtrate, reaction of 2,6-dimethylbenzaldehyde also did not proceed (entry 7). Parallel to the trend observed for alkyne substrates, *p*-anisaldehyde and aliphatic aldehydes were found unsuitable for this reaction as well (entries 9-11).

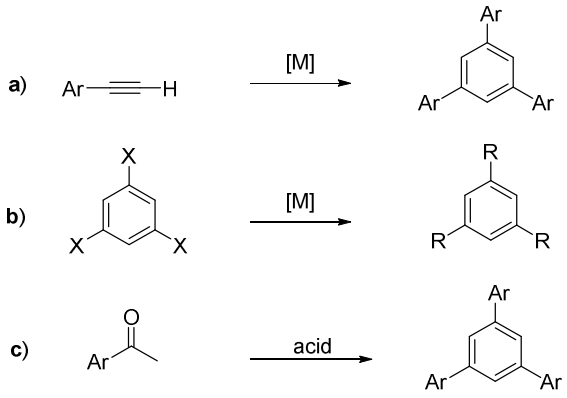
4.1.4 Plausible mechanism of In(tfacac)$_3$-TMSBr-catalyzed stereoselective coupling of aryl alkyne and aryl aldehyde

Based on precedent reports and results obtained, the plausible mechanism for the first example on In(III)-TMSBr-catalyzed coupling of aryl aldehyde and alkyne is depicted in **Scheme 4-7**. Due to the dissimilar stereochemisty as originally proposed (**Scheme 4-5**), a different reaction pathway is devised (**Scheme 4-7**). First, the combined Lewis acid catalyst activates the carbonyl group of aryl aldehyde **9** to form intermediate *int*-**1**. The *int*-**1** is then attacked by aryl alkyne **8** and the generated vinyl cation *int*-**2** is trapped by bromide ion to give the *Z*-vinyl-bromide species. The trimethylsilyl group of *Z*-vinyl-bromide is activated by the combined Lewis acid giving rise to carboncation *int*-**3** which will further undergo S_N2' type reaction and gives the major diene isomer (*Z,E*)-**10**. On the other hand, if the bromide ion and carbocation undergo *cis*-addition to aryl alkyne, the minor diene isomer (*E,E*)-**10** will be generated instead.



Scheme 4-7. Plausible reaction mechanism for In(III)-TMSBr-catalyzed stereoselective coupling of aryl alkyne and aryl aldehyde

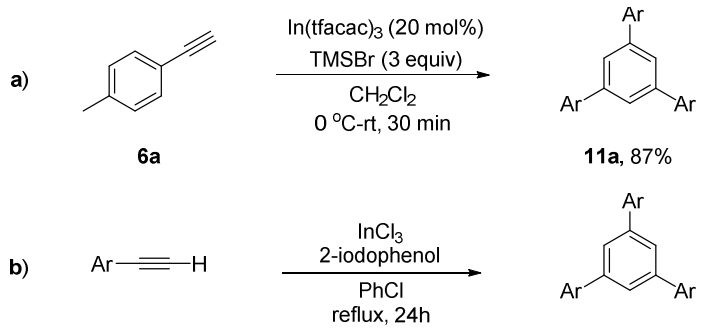
4.2 In(III)-TMSBr-catalyzed trimerization of aryl alkyne



Scheme 4-8. Conventional methods for synthesis of 1,3,5-triarylbenzenes

In our study of the cascade dearoamtization reaction with aryl alkynes and acrylates, we found that the 1,3,5-triarylbenzenes predominate as one of the major by-products. After some control experiments, the reaction could be selectively steered towards prevailing formation of 1,3,5-triarylbenzene (87% yield) (**Scheme 4-8a**). Although there are extensive studies of transition metals-catalyzed trimerization of alkynes, examples using Lewis acid catalysts are rare.

To the best of our knowledge, there is only one former work using $InCl_3$ to catalyze trimerization of aryl alkyne in the presence of 2-iodophenol (**Scheme 4-8b**). Compared with the reported protocol which requires reflux in PhCl for 24 h, our reaction conditions are much milder, requiring only ambient temperature (0 ^{o}C to rt) as well as shorter reaction time (1 h). Current trimerization protocol has also verified the stronger catalytic ability of combined Lewis acid catalyst with reference to In(III) catalyst by itself.



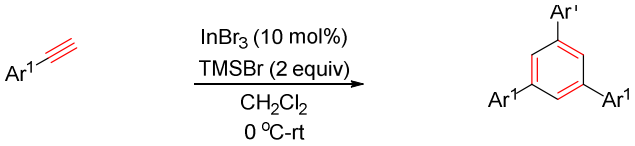
Scheme 4-8. In(III)-TMSBr-catalyzed trimerization of aryl alkyne **6a** and the reported example of In(III)-catalyzed trimerization of aryl alkynes

In addition to aryl alkyne, it was previously established that the corresponding *a*-aryl vinyl bromide could also undergo trimerization to 1,3,5-triarylbenzene in the presence of the In(III)-TMSBr catalyst in even higher efficiency (shorter reaction time and higher yield, **Scheme 3-41**). However, compared with the commercially available aryl alkyne, the preparation of α-aryl vinyl bromide needs extra synthetic step and its instability also brings storage issue. Moreover, cooperation of $InBr_3$ with TMSBr could also afford 1,3,5-triarylbenzenes in similar yields from the common and much cheaper aryl alkynes the. Thus, various aryl alkynes were examined for their compatibilities in this In(III)-TMSBr-catalyzed trimerization (**Table 4-5**).

Generally, the aryl alkynes with the electronically-neutral or electron-rich substituents at *para*-position gave the desired product in 75-85% yield (e.g., H, Me, Et, Bu, *t*-Bu, Hex, Cl, and

Br, entries 1-8). However, presence of electron-deficient group such as CF_3 inhibited the reaction (entry 9). *ortho*-and *meta*-substituted aryl alkynes were found unsuitable for this chemistry as well (entries 10-12). Also, trimethylsilyl acetylene and aliphatic alkynes could not undertake the tricyclomerization chemistry (entries 13-15).

Table 4-5. In(III)-TMSBr-catalyzed trimerization of aryl alkyne[a]



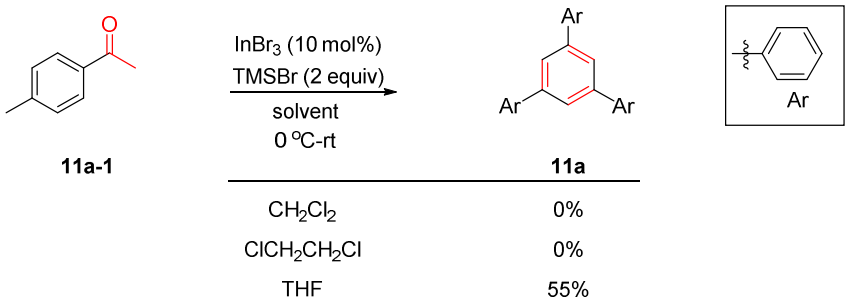
6 **11**

Entry	**6**	**11**	time	Yield [%][b]
1	**6a**, R^1 = Ph	**11a**	30 min	80
2	**6b**, R^1 = 4-Me-Ph	**11b**	30 min	85
3	**6c**, R^1 = 4-Et-Ph	**11c**	30 min	83
4	**6d**, R^1 = 4-Bu-Ph	**11d**	1 h	80
5	**6e**, R^1 = 4-*t*-Bu-Ph	**11e**	1 h	78
6	**6f**, R^1 = 4-Hex-Ph	**11f**	1 h	75
7	**6g**, R^1 = 4-Cl-Ph	**11g**	2 h	75
8	**6h**, R^1 = 4-Br-Ph	**11h**	2 h	77
9	**6i**, R^1 = 4-CF_3-Ph	-	2 h	-
10	**6j**, R^1 = 2-Me-Ph	-	30 min	-
11	**6k**, R^1 = 3-Me-Ph	-	30 min	-
12	**6l**, R^1= 2,4,6-Me-Ph			
13	**6m**, R^1 = TMS	-	-	-
14	**6n**, R^1 = *n*-Hex	-	-	-
15	**60**, R^2 = *c*-Hex	-	-	-

[a] Reaction condition: **6** (0.4 mmol), $InBr_3$ (10 mol%), TMSBr (2.0 equiv), CH_2Cl_2 (1 mL), 0 °C-rt, N_2. [b] Isolated yields.

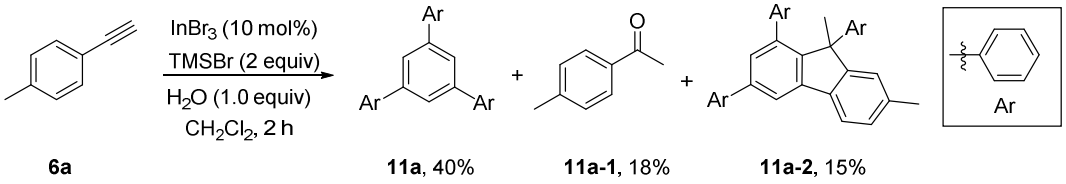
It is interesting that 4-methylacetophenone **11a-1** also converted into the corresponding 1,3,5-triaryl benzene product **11a** in 55% yield in the presence of $InBr_3$, TMSBr and THF as the reaction solvent (**Scheme 4-9**). The solvent choice is critical and when replaced with DCM and DCE which are often the optimal solvents for In(III)-TMSX catalyzed reactions, the

tricyclomerization did not proceed.



Scheme 4-9. In(III)-TMSBr-catalyzed trimerization of **12a** into 1,3,5-triaryl benzene **11b**

When water was added and the reaction time was extended to 2 h, reaction of **6a** yielded an unexpected tricyclic product **11a-2** along with **11a** and **11a-1**. The structure of **11a-2** was primarily determined by ^{1}H and ^{13}C NMR and further confirmed by the X-ray single crystal analysis. The single crystal of **11a-2** was obtained from the co-solvent of hexane and ethyl acetate.



Scheme 4-10. Reaction of aryl alkyne **6a** in the presence of $InBr_3$, TMSBr and H_2O

We thought that the tricyclic product **11a-2** was resulted from the reaction of **11a** and **11a-1** catalyzed by the combined Lewis acid catalyst (**Scheme 4-11**). First, the Lewis acid promotes the Friedel-Crafts reaction of triarylbenzne and acetophenone to give the trimethylsilane ether *int*-**1**. The silyl ether group of *int*-**1** was activated by the combined Lewis acid to give carbocation *int*-**2** and then a sequential intramolecular Friedel-Crafts reaction take places to give the tricyclic product. Its facile formation also attested the versatility and synthetic value of the combined Lewis acid catalyst.

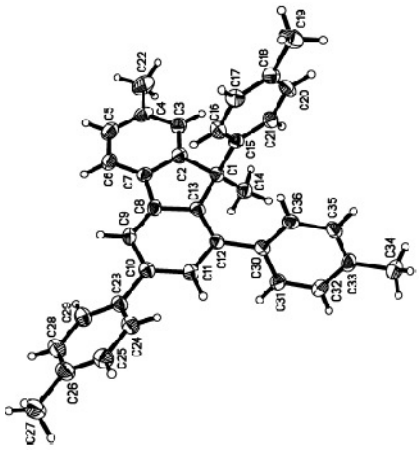
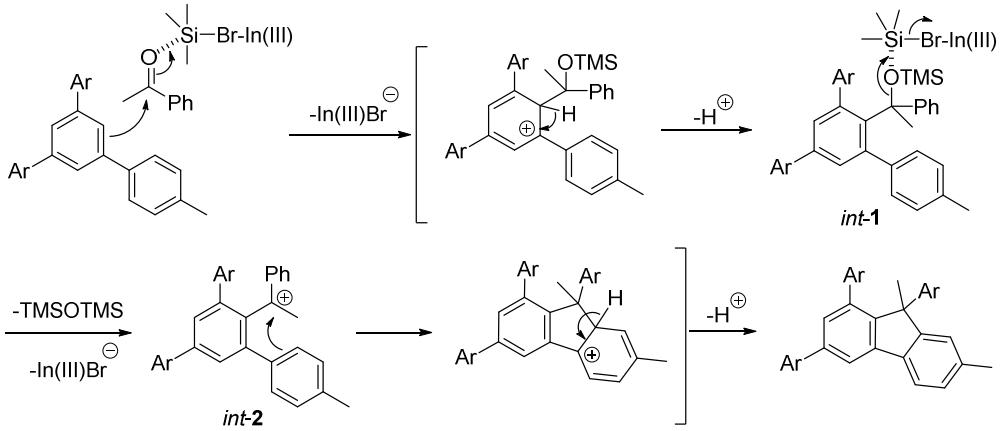


Figure 4-1. X-ray crystallograhy structure of **11a-2**, 7,9-dimethyl-1,3,9-tri-*p*-tolyl-9*H*-fluorene



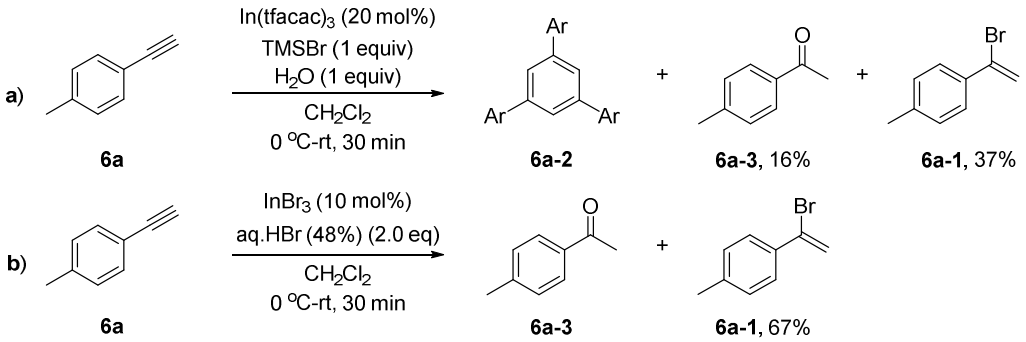
Scheme 4-11. Plausible mechanism for the formation of **11a-2**

4.3 In(III)-TMSBr-catalyzed [4+2] Cycloaddition of *α*-Aryl Vinyl Halides and Acrylates

4.3.1 Facile synthesis of *α*-aryl vinyl halides

Vinylhalides are important intermediates in many organic reactions both in industry and on researchers' benches. In transition metal-catalyzed amination and Suzuki-Miyaura reactions, they are robust reaction partners in these cross-coupling reactions that forge C-N and C-C bonds. Vinylhalides especially vinylchloride moiety are prevalently found in many natural or synthetic compounds which often carry wide-ranging bioactivities. This leads to the active pursuit of regio- and stereoselective synthetic methodologies for vinylchlorides. These reactions often

involve the use of different precursors. For instance, Shapiro reaction uses methyl hydrazones, methyl ketones for bromo-deoxygenation, 1,2-dibromoalkanes *via* HBr elimination pathway and the employment of terminal alkynes in bromoboration/protodeboration and hydrobromination reaction.



Scheme 4-12. Facile synthesis of *a*-vinyl aryl bromides

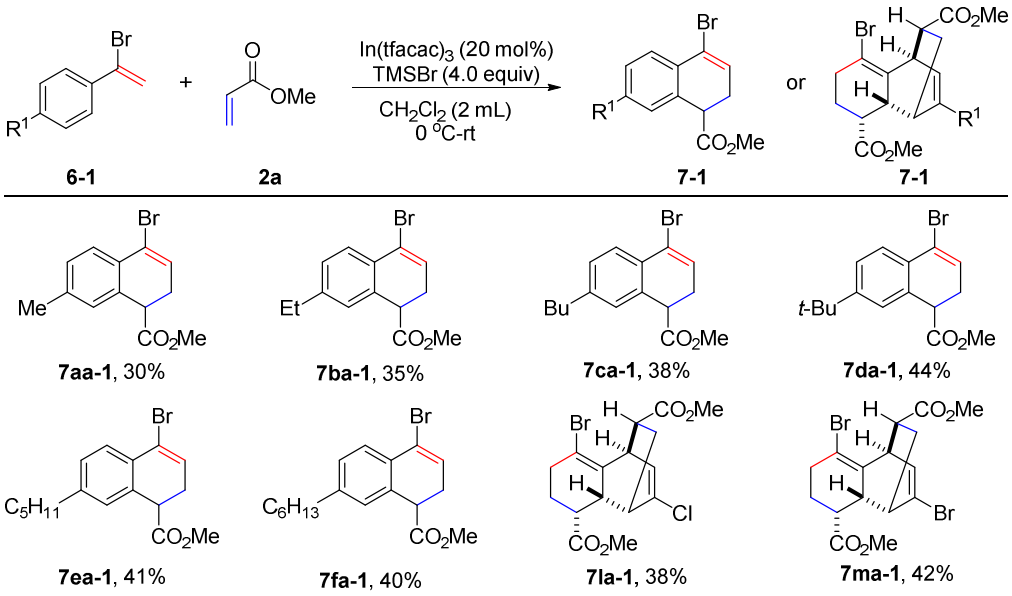
Seemingly straightforward, the direct addition of hydrogen bromide to alkynes is not practically useful. The toxicity and corrosiveness of HBr gas often hurdle its direct application. In addressing these hazardous issues brought by HBr gas, *in situ* HBr generation protocols involving conveniently-handled non- or low toxic reagents were devised to prepare vinyl bromides.

During the study of cascade dearomatization reaction, we found that a-aryl vinyl bromide could be facilely generated from aryl alkyne in the presence of In(III) catalyst, TMSBr and H_2O (**Scheme 4-12a**). A search into the literatures reveals established methodologies to prepare vinyl halides through HCl formed *in situ* from TMSCl and MeOH or HI generated *in situ* from H_2O and TMSI. However, report on the synthesis of vinyl bromide from *in situ* generated HBr using TMSBr and proton source is absent.

Nonetheless, there are several problems accompanying this strategy: first, the reaction yield is

only moderate; second, **6a-1** and **6a-2** own similar polarity, rendering the column purification difficult. After several attempts, we found that when the commercially sourced aq. HBr replaces TMSBr and H_2O, the yields of this reaction could be improved significantly and formation of **6a-1** was completely inhibited (**Scheme 4-12b**).

Table 4-6. In(III)-TMSBr-catalyzed [4+2] cycloaddition of α-aryl vinyl bromide and acrylate[a,b]



[a] Reaction condition **6-1** (0.4 mmol), **2a** (1.2 mmol), $InBr_3$ (10 mol%), TMSBr (2.0 equiv), CH_2Cl_2 (1 mL), 0 °C-rt, N_2. [b] Isolated yields.

By the above-mentioned method (**Scheme 4-12b**), the *a*-aryl vinyl bromide could be prepared in larger scale. However, aryl alkynes with electron-withdrawing group as *para*-substituent including nitrile, nitro, methyl ester are inconvertable under this reaction condition. We related this observation to the incompatibility of these aryl alkynes to undergo dearomatization with methyl acrylate (**Table 3-11**).

With α-aryl vinyl bromides, we started to study their [4+2] reactions with methyl acrylate **2a** (**Table 4-6**). The α-aryl vinyl bromides bearing alkyl substituents (eg., Me, Et, *n*-Bu, *t*-Bu, C_5H_{11} and C_6H_{13}) on the *para*-position could give the bicyclic products (**7aa-1-7af-1**) and those with

the *para*-chloro or bromo group furnished the tricyclic products exclusively (**7al-1** and **7am-1**). It is interesting to note that the tricyclic product was not formed in the reactions of former class of substrates and vice versa. The reaction condition has been primarily optimized, although these products were obtained in moderate yields. This is attributed to the decomposition of vinyl bromides and competing formation of 1,3,5-triaryl benzenes.

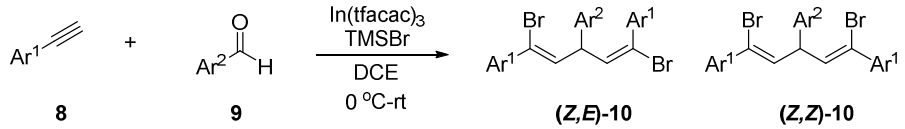
This unusual [4+2] cycloaddition beween α-aryl vinyl bromide and methyl acrylate also highlights the prominent catalytic property of this combined Lewis acid catalyst. Without either In(III) catalyst or TMSBr, reactions did not take place. Other common Lewis acid catalysts tested did not exhibit any catalytic activity except iron(III) catalysts which provided the [4+2] cycloadduct in lower yields.

4.4 Conclusion

In a nutshell, the combined Lewis acid catalyst comprises of In(III) and TMSBr has shown excellent catalytic properties in the stereoselective coupling of aryl alkynes and aryl aldehydes, alkynes or acetopheone trimerization and the [4+2] cycloaddition of α-aryl vinyl bromides and methyl acrylate. All compounds prepared serve as useful synthetic blocks and some of them are difficult to prepare otherwise However, there are some limitations with this catalyst system. The relatively acidic reaction condition is not well tolerated by acid sensitive functional groups. Furthermore, this catalyst system is found robust only for aryl substrates. Aryl substrates with strong electron-withdrawing substituent are also unreactive under this catalyst system.

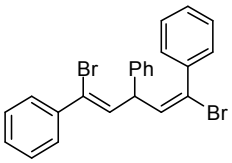
4.5 Experimental section and spectral data

4.5.1 General procedure for the In(III)-TMSBr-catalyzed coupling of aryl alkyne and aryl aldehyde and spectral data



8 **9** **(*Z*,*E*)-10** **(*Z*,*Z*)-10**

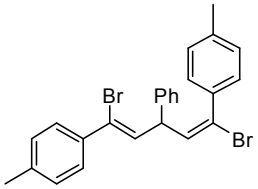
General Procedure. A dry reaction tube was charged with aryl alkyne **8** (0.4 mmol), aryl aldehyde **9** (0.8 mmol), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 10 mol%, 0.04 mmol, 29.0 mg) and DCE (2 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 3 equiv, 1.2 mmol, 183.6 mg) was added and the reaction mixture was stirred at room temperature. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 100:1) to afford the desired product **10**.



((1*Z*,4*E*)-1,5-dibromopenta-1,4-diene-1,3,5-triyl)tribenzene (10aa)

Colorless oil, 56.9 mg, 0.127 mmol, 63% yield.

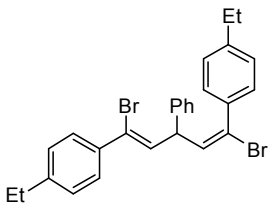
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 - 7.55 (m, 2H), 7.47 - 7.33 (m, 10H), 7.30 - 7.27 (m, 3H), 6.47 (d, *J* = 10.4 Hz, 1H), 6.38 (d, *J* = 9.1Hz, 1H), 4.81 (t, *J* = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 141.0, 139.4, 138.2, 132.9, 131.0, 129.1, 128.9, 128.8, 128.3, 128.2, 127.7, 127.3, 127.0, 126.4, 123.0, 49.4.



1-((1*Z*,4*E*)-1,5-dibromo-3-phenyl-5-(*p*-tolyl)penta-1,4-dien-1-yl)-3-methylbenzene (10ba)

Colorless oil, 59.0 mg, 0.123 mmol, 61% yield.

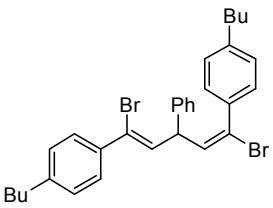
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.45 (d, *J* = 8.1 Hz, 2H), 7.37 - 7.34 (m, 4H), 7.30 - 7.29 (m, 3H), 7.21 - 7.16 (m, 4H), 6.43 (d, *J* = 10.4 Hz, 1H), 6.34 (d, *J* = 9.1 Hz), 4.80 (t, *J* = 9.7 Hz, 1H), 2.40 (s, 3H), 2.39 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 141.2, 138.9, 138.8, 136.7, 135.4, 132.6, 130.3, 129.0, 128.8, 127.6, 127.3, 126.9, 126.4, 123.2, 49.4, 21.4, 21.1.



1-((1*Z*,4*E*)-1,5-dibromo-5-(4-ethylphenyl)-3-phenylpenta-1,4-dien-1-yl)-3-ethylbenzene (10ca)

Colorless oil, 74.2 mg, 0.146 mmol, 73% yield.

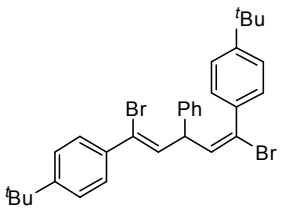
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 8.2 Hz, 2H), 7.38 - 7.34 (m, 4H), 7.30 - 7.27 (m, 3H), 7.23 - 7.17 (m, 4H), 6.42 (d, *J* = 10.3 Hz, 1H), 6.34 (d, *J* = 9.1 Hz, 1H), 4.81 (t, *J* = 9.7 Hz, 1H), 2.72 - 2.65 (m, 4H), 1.29 - 1.24 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 145.2, 145.1, 141.2, 136.9, 135.5, 132.6, 130.3, 129.0, 128.8, 127.8, 127.7, 127.3, 126.9, 126.5, 123.3, 49.4, 28.7, 28.5, 15.5, 15.3.



1-Butyl-3-((1*Z*,4*E*)-1,5-dibromo-5-(4-butylphenyl)-3-phenylpenta-1,4-dien-1-yl) benzene (10da)

Colorless oil, 78.9 mg, 0.140 mmol, 70% yield.

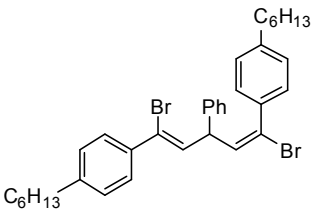
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (d, *J* = 6.2 Hz, 2H), 7.37 - 7.35 (m, 3H), 7.30 - 7.28 (m, 4H), 7.21 - 7.16 (m, 4H), 7.42 (d, *J* = 10.3 Hz, 1H), 6.34 (d, *J* = 9.1 Hz, 1H), 4.81 (t, *J* = 9.7 Hz, 1H), 2.67 - 2.62 (m, 4H), 1.66 - 1.59 (m, 4H), 1.41 - 1.35 (m, 4H), 0.97 - 0.94 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 144.0, 143.9, 141.2, 136.8, 135.6, 132.7, 130.2, 128.9, 128.8, 128.3, 127.6, 127.3, 126.9, 126.5, 123.3, 49.4, 35.4, 35.3, 33.5, 33.4, 22.4, 22.3, 14.0, 13.9.



4,4'-((1*Z*,4*E*)-1,5-dibromo-3-phenylpenta-1,4-diene-1,5-diyl)bis(*tert*-butylbenzene) (10ea)

Colorless oil, 67.7 mg, 0.120 mmol, 60% yield.

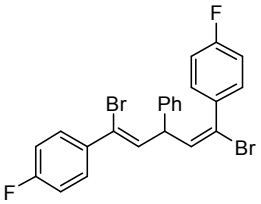
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 4H), 7.38 - 7.35 (m, 5H), 7.31 - 7.28 (m, 2H); 6.43 (d, *J* = 10.2 Hz, 1H), 6.36 (d, *J* = 9.1 Hz, 1H), 4.83 (t, *J* = 9.6 Hz, 1H), 1.36 (s, 9H), 1.35 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 152.1, 151.9, 141.1, 136.6, 135.3, 132.7, 130.3, 128.8, 128.7, 127.5, 127.4, 127.3, 126.9, 126.4, 125.2, 123.3, 49.3, 34.7, 34.6, 31.2.



4,4'-((1*Z*,4*E*)-1,5-dibromo-3-phenylpenta-1,4-diene-1,5-diyl)bis (hexylbenzene) (10fa)

Colorless oil, 62.2 mg, 0.100 mmol, 50% yield.

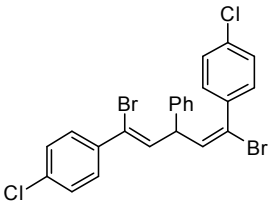
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.47 (d, *J* = 8.0 Hz, 2H), 7.38 - 7.35 (m, 4H), 7.30 - 7.27 (m, 3H), 7.21 - 7.15 (m, 4H), 6.42 (d, *J* = 10.3 Hz, 1H), 6.34 (d, *J* = 9.1 Hz, 1H), 4.81 (t, *J* = 9.7 Hz, 1H), 2.66 - 2.61 (m, 4H), 1.64 - 1.61 (m, 4H), 1.35 - 1.30 (m, 12H), 0.93 - 0.90 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 143.9, 143.8, 141.2, 136.8, 135.5, 132.7, 130.2, 128.9, 128.8, 128.3, 127.6, 127.3, 126.9, 126.5, 123.3, 49.4, 35.8, 35.6, 31.7, 31.2, 31.1, 28.9, 22.6, 22.5, 14.1.



4,4'-((1*Z*,4*E*)-1,5-dibromo-3-phenylpenta-1,4-diene-1,5-diyl)bis(fluorobenzene) (10ga)

Colorless oil, 54.6 mg, 0.112 mmol, 56% yield.

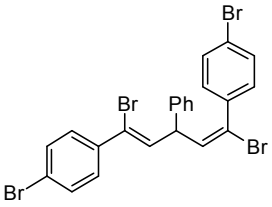
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.55 - 7.51 (m, 2H), 7.44 - 7.37 (m, 4H), 7.32 - 7.27 (m, 3H), 7.12 - 7.03 (m, 4H), 6.47 (d, *J* = 10.4 Hz, 1H), 6.31 (d, *J* = 9.1 Hz, 1H), 4.74 (t, *J* = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 163.0 (d, $J_{C\text{-}F}$ = 247.8 Hz), 162.8 (d, $J_{C\text{-}F}$ = 247.7 Hz), 140.7, 135.9 (d, $J_{C\text{-}F}$ = 3.4 Hz), 134.3 (d, $J_{C\text{-}F}$ = 3.4 Hz), 131.1, 131.0, 130.9, 130.9, 129.5 (d, $J_{C\text{-}F}$ = 8.4 Hz), 129.0, 127.2 (d, $J_{C\text{-}F}$ = 4.7 Hz), 125.2, 121.8, 115.4 (d, $J_{C\text{-}F}$ = 21.7 Hz), 115.2 (d, $J_{C\text{-}F}$ = 21.7 Hz), 49.5.



4,4'-((1*Z*,4*E*)-1,5-dibromo-3-phenylpenta-1,4-diene-1,5-diyl)bis(chlorobenzene) (10ha)

Colorless oil, 57.1 mg, 0.110 mmol, 55% yield.

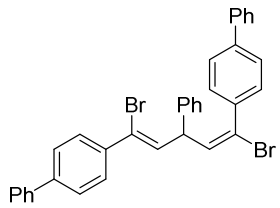
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (d, *J* = 8.0 Hz, 2H), 7.41- 7.37 (m, 5H), 7.35 - 7.30 (m, 4H), 7.29 -7.26 (m, 2H), 6.47 (d, *J* = 10.4 Hz, 1H), 6.35 (d, *J* = 9.1 Hz, 1H), 4.74 (t, *J* = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 140.7, 137.7, 136.4, 134.9, 133.2, 131.4, 130.4, 129.0, 128.9, 128.6, 128.5, 127.2, 124.9, 121.7, 49.5.



4,4'-((1*Z*,4*E*)-1,5-Dibromo-3-phenylpenta-1,4-diene-1,5-diyl)bis(bromobenzene) (10ia)

Colorless oil, 68.0 mg, 0.112 mmol, 56% yield.

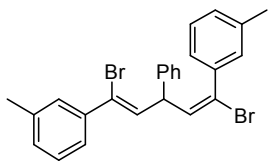
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (d, *J* = 8.4 Hz), 7.50 - 7.48 (m, 2H), 7.42 - 7.36 (m, 4H), 7.30 - 7.25 (m, 5H), 6.47 (d, *J* = 10.4 Hz, 1H), 6.35 (d, *J* = 9.1 Hz, 1H), 4.72 (t, *J* = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 140.5, 138.2, 137.1, 133.2, 131.6, 131.5, 131.4, 130.6, 129.2, 129.0, 127.2, 127.1, 125.2, 123.2, 123.0, 121.7, 49.6.



4,4''-((1*Z*,4*E*)-1,5-dibromo-3-phenylpenta-1,4-diene-1,5-diyl)di-1,1'-biphenyl (10ja)

Colorless oil, 36.2 mg, 0.060 mmol, 30% yield.

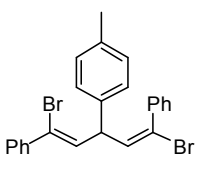
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.66 - 7.64 (m, 6H), 7.62 - 7.59 (m, 3H), 7.56 -7.54 (m, 2H), 7.50 - 7.47 (m, 4H), 7.42 - 7.38 (m, 4H), 7.35 - 7.31 (m, 4H), 6.52 (d, *J* = 10.3 Hz, 1H), 6.47 (d, *J* = 9.1 Hz, 1H), 4.90 (t, *J* = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 141.7, 141.6, 140.9, 140.4, 140.2, 138.2, 137.1, 133.0, 130.9, 129.6, 128.9, 128.8, 128.7, 128.1, 127.7, 127.3, 127.2, 127.1, 127.0, 127.0, 126.9, 126.2, 122.8, 49.6.



3,3'-((1*Z*,4*E*)-1,5-dibromo-3-phenylpenta-1,4-diene-1,5-diyl)bis(methylbenzene) (10ka)

Colorless oil, 50.9 mg, 0.106 mmol, 53% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.42 - 7.34 (m, 5H), 7.28 - 7.23 (m, 6H), 7.18 - 7.14 (m, 2H), 6.45 (d, *J* = 10.3 Hz, 1H), 6.37 (d, *J* = 9.2 Hz, 1H), 4.79 (t, *J* = 9.8 Hz, 1H), 2.39 (s, 3H), 2.38 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 141.0, 139.4, 138.1, 138.0, 137.9, 132.9, 130.8, 129.7, 129.6, 128.8, 128.3, 128.2, 128.2, 127.3, 126.9, 126.1, 124.9, 123.2, 49.4.

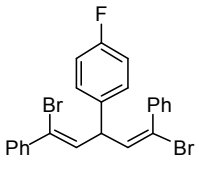


((1*Z*,4*E*)-1,5-dibromo-3-(*p*-tolyl)penta-1,4-diene-1,5-diyl)dibenzene (10ab)

Colorless oil, 58.1 mg, 0.121 mmol, 61% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 - 7.55 (m, 2H), 7.47 - 7.45 (m, 2H), 7.43 - 7.34 (m, 6H), 7.17 (s, 4H), 6.46 (d, *J* = 10.4 Hz, 1H), 6.38 (d, *J* = 9.2 Hz, 1H), 4.77 (t, *J* = 9.8

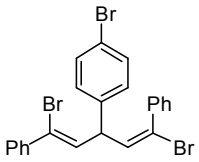
Hz, 1H), 2.42 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 139.5, 138.3, 138.0, 136.7, 133.1, 131.2, 129.6, 129.1, 128.8, 128.3, 128.2, 127.7, 127.2, 126.1, 122.8, 49.1.



((1*Z*,4*E*)-1,5-dibromo-3-(4-fluorophenyl)penta-1,4-diene-1,5-diyl)dibenzene (10ac)

Colorless oil, 68.3 mg, 0.140 mmol, 70% yield.

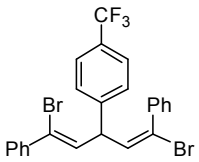
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 - 7.55 (m, 2H), 7.45 - 7.46 (m, 7H), 7.26 - 7.23 (m, 2H), 7.08 - 7.03 (m, 3H), 6.43 (d, J = 10.3 Hz, 1H), 6.35 (d, J = 9.1 Hz, 1H), 4.77 (t, J = 9.7, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 161.8 (d, $J_{C\text{-}F}$ = 245.0 Hz), 139.3, 138.1, 136.6 (d, $J_{C\text{-}F}$ = 3.1 Hz), 132.7, 130.8, 129.0, 128.9, 128.8, 128.7, 128.4, 128.3, 127.7, 126.6, 123.3, 115.7 (d, $J_{C\text{-}F}$ = 21.1 Hz), 48.7.



((1*Z*,4*E*)-1,5-dibromo-3-(4-bromophenyl)penta-1,4-diene-1,5-diyl)dibenzene (10ad)

Colorless oil, 63.5 mg, 0.120 mmol, 60% yield.

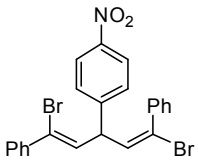
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.57 - 7.55 (m, 2H), 7.51 - 7.48 (m, 2H), 7.45 - 7.35 (m, 8H), 7.18 - 7.16 (m, 2H), 6.43 (d, J = 10.3 Hz, 1H), 6.32 (d, J = 11.0 Hz, 1H), 4.76 (t, J = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 140.0, 139.2, 138.1, 132.3, 132.0, 131.9, 130.4, 129.0, 128.9, 128.8, 128.4, 128.3, 128.2, 127.7, 126.9, 123.5, 121.0, 48.9.



((1*Z*,4*E*)-1,5-dibromo-3-(4-(trifluoromethyl)phenyl)penta-1,4-diene-1,5-diyl) dibenzene (10ae)

Colorless oil, 52.0 mg, 0.100 mmol, 50% yield

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.64 - 7.62 (m, 2H), 7.57 - 7.55 (m, 2H), 7.43 - 7.37 (m, 10H), 6.46 (d, J = 10.3 Hz, 1H), 6.37 (d, J = 9.1 Hz, 1H), 4.85 (t, J = 9.7 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 145.0, 139.1, 138.0, 132.0, 130.0, 129.1, 128.9×2, 128.5, 128.4×2, 127.7×2, 127.6, 127.3, 125.8 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.9, 49.7.

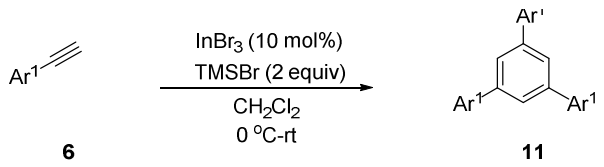


((1*Z*,4*E*)-1,5-dibromo-3-(4-nitrophenyl)penta-1,4-diene-1,5-diyl)dibenzene

Colorless oil, 55.7 mg, 0.112 mmol, 56% yield

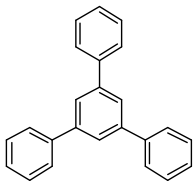
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.22 (d, J = 8.8 Hz, 2H), 7.58 - 7.55 (m, 2H), 7.45 - 7.38 (m, 10H), 6.45 (d, J = 10.2 Hz, 1H), 6.37 (d, J = 9.0 Hz, 1H), 4.89 (t, J = 9.6 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 148.4, 147.0, 138.9, 137.9, 131.4, 129.3, 129.2, 129.1, 128.8, 128.6, 128.5, 128.2, 128.0, 127.7, 124.5, 124.1, 49.3.

4.5.2 General Procedure for the trimerization of aryl alkyne and Spectral Data



6 **11**

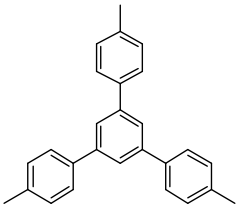
General Procedure for the Synthesis of 1,3,5-triaryl benzene. A dry reaction tube was charged with aryl alkyne **6** (0.4 mmol), indium(III) tribromide ($InBr_3$, 10 mol%, 0.04 mmol, 35.1 mg) and CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 ^oC. Bromotrimethylsilane (TMSBr, 2 equiv, 0.8 mmol, 122.4 mg) was added and the reaction mixture was stirred at room temperature. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 100:1) to afford the desired product **11**.



5'-phenyl-1,1':3',1''-terphenyl (11a)

Colorless solid, 32.6 mg, 0.106 mmol, 56% yield

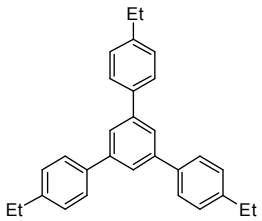
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.81 (s, 3H), 7.73 - 7.72 (m, 6H), 7.51 - 7.49 (m, 6H), 7.42 - 7.39 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 142.4, 141.2, 128.8, 127.5, 127.4, 125.5.



4,4''-Dimethyl-5'-(*p*-tolyl)-1,1':3',1''-terphenyl (11b)

Colorless solid, 39.5 mg, 0.113 mmol, 85% yield

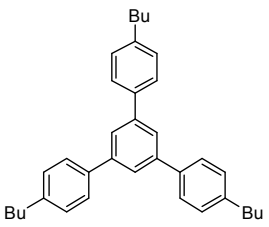
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (s, 3H), 7.62 (d, *J* = 8.1 Hz, 6H), 7.32 (d, *J* = 8.1 Hz, 6H), 2.45 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 142.2, 138.4, 137.3, 129.6, 127.2, 124.6, 21.2.



4,4''-Diethyl-5'-(4-ethylphenyl)-1,1':3',1''-terphenyl (11c)

Colorless solid, 43.3 mg, 0.111 mmol, 83% yield

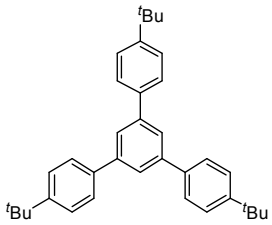
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.76 (s, 3H), 7.65 (d, *J* = 8.2 Hz, 6H), 7.34 (d, *J* = 8.2 Hz, 6H), 2.75 (q, *J* = 7.6 Hz, 6H), 1.33 (t, *J* = 7.6 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 143.6, 142.2, 138.7, 128.4, 127.3, 124.7, 28.6, 15.6.



4,4''-dibutyl-5'-(4-butylphenyl)-1,1':3',1''-terphenyl (11d)

Colorless solid, 50.6 mg, 0.107 mmol, 80% yield

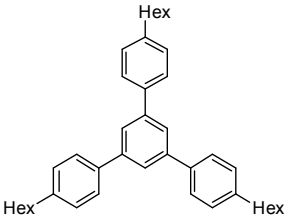
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (s, 3H), 7.63 (d, *J* = 8.0 Hz, 6H), 7.31 (d, *J* = 8.0 Hz, 6H), 2.70 (t, *J* = 7.7 Hz, 6H), 1.72 - 1.65 (m, 6H), 1.46 - 1.39 (m, 6H), 0.99 (t, *J* = 7.3 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 142.3, 142.2, 138.6, 128.9, 127.1, 124.6, 35.3, 33.7, 22.4, 14.0.



4,4''-Di-*tert*-butyl-5'-(4-(*tert*-butyl)phenyl)-1,1':3',1''-terphenyl (10e)

Colorless oil, 49.3 mg, 0.104 mmol, 78% yield

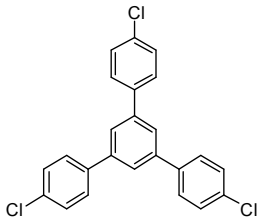
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.78 (s, 3H), 7.65 (d, *J* = 8.3 Hz, 6H), 7.52 (d, *J* = 8.3 Hz, 6H), 1.41 (s, 27H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 150.5, 142.0, 138.4, 127.0, 125.8, 124.7, 34.6, 31.4



4,4''-dihexyl-5'-(4-hexylphenyl)-1,1':3',1''-terphenyl (10f)

Colorless oil, 55.8 mg, 0.100 mmol, 75% yield

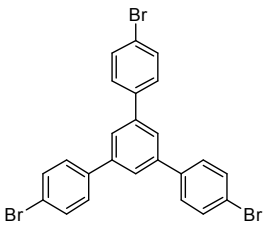
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.77 (s, 3H), 7.63 (d, *J* = 8.0 Hz, 6H), 7.31 (d, *J* = 8.0 Hz, 6H), 2.69 (t, *J* = 7.72, 6H), 1.71 - 1.65 (m, 6H), 1.43 - 1.28 (m, 18H), 0.92 (t, *J* = 7.3 Hz, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 142.3, 142.2, 138.6, 128.9, 127.2, 124.6, 35.7, 31.8, 31.5, 29.1, 22.6, 14.1.



4,4''-dichloro-5'-(4-chlorophenyl)-1,1':3',1''-terphenyl (10g)

Colorless oil, 40.8 mg, 0.100 mmol, 75% yield

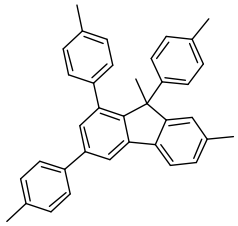
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.73 (s, 3H), 7.64 (d, *J* = 8.6 Hz, 6H), 7.49 (d, *J* = 8.6 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 141.5, 139.2, 134.0, 129.1, 128.6, 125.1.



4,4''-dibromo-5'-(4-bromophenyl)-1,1':3',1''-terphenyl

Colorless oil, 55.4 mg, 0.103 mmol, 77% yield

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.72 (s, 3H), 7.64 (d, *J* = 8.5 Hz, 6H), 7.57 (d, *J* = 8.5 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 141.5, 139.6, 132.1, 128.9, 125.0, 122.1.

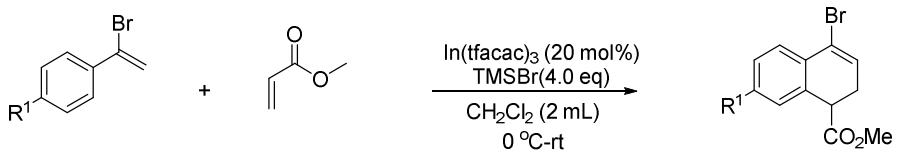


7,9-dimethyl-1,3,9-tri-*p*-tolyl-9*H*-fluorene

Colorless solid, 55.7 mg, 0.112 mmol, 56% yield

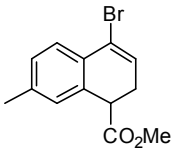
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.95 (d, *J* = 1.7 Hz, 1H), 7.71 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.1 Hz, 2H), 7.27 - 7.23 (m, H), 7.13 - 7.11 (m, 1H), 6.94 - 6.90 (m, 4H), 6.83 (s, 1H), 6.79 (d, *J* = 8.1 Hz), 6.55 (d, *J* = 7.9 Hz, 2H); 2.40 (s, 3H), 2.33 (s, 3H), 2.30 (s, 3H), 2.29 (s, 3H), 1.55 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 149.6, 142.7, 141.4, 140.3, 140.2, 138.2, 137.8, 137.7, 137.0, 136.3, 136.1, 135.3, 129.5, 129.3, 128.7, 128.6, 127.8, 127.8, 127.0, 126.6, 124.3, 119.6, 116.9, 54.5, 22.4, 21.7, 21.2, 21.1, 21.0.

4.5.3 General Procedure for the In(III)-TMSBr-catalyzed [4+2] cycloaddition of*α*-aryl vinyl bromide and methyl acrylate and Spectral Data



6-1 (0.4 mmol) **2a** (1.2 mmol) **7a-1** (30%)

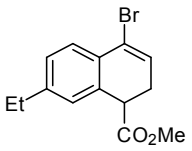
A dry reaction tube was charged with *α*-aryl vinyl bromide **6-1** (0.4 mmol), acrylate **2a** (1.2 mmol, 103.2 mg), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg) and CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 ^oC. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 20:1) to afford the desired product **7a-1**.



Methyl 4-bromo-7-methyl-1,2-dihydronaphthalene-1-carboxylate (7aa-1)

Colorless oil, 33.6 mg, 0.121 mmol, 30% yield.

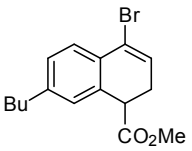
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.50 (d, *J* = 7.9 Hz, 1H), 7.14 (d, *J* = 7.9 Hz, 1H), 6.99 (s, 1H), 3.78 (t, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 2.90 - 2.83 (m, 1H), 2.63 - 2.56 (m, 1H), 2.38 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.4, 38.6, 132.5, 129.3, 128.9, 128.6, 127.3, 126.9, 120.8, 52.3, 43.5, 28.2, 21.2. **HRMS** (ESI) calcd for $C_{13}H_{14}O_2Br$ $(M+H)^+$ 281.0177, found 281.0175.



methyl 4-bromo-7-ethyl-1,2-dihydronaphthalene-1-carboxylate (7ba-1)

Colorless oil, 41.1 mg, 0.141 mmol, 35% yield.

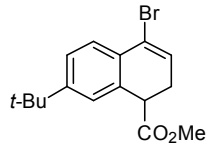
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.01 (s, 1H), 6.37 - 6.35 (m, 1H), 3.84 - 3.77 (m, 1H), 3.72 (s, 3H), 2.91 - 2.74 (m, 1H), 2.71 - 2.57 (m, 3H), 1.27 (t, *J* = 7.6 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.4, 38.6, 132.5, 129.3, 128.9, 128.6, 127.3, 126.9, 120.8, 52.3, 43.5, 28.2, 21.2, 14.5.



Methyl 4-bromo-7-butyl-1,2-dihydronaphthalene-1-carboxylate (7ca-1)

Colorless oil, 48.9 mg, 0.152 mmol, 38% yield.

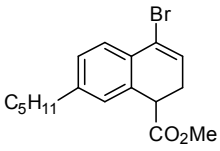
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, *J* = 8.0 Hz, 1H), 7.16 - 7.13 (m, 1H), 6.99 (s, 1H), 6.37 - 6.34 (m, 1H), 3.81 - 3.73 (m, 1H), 3.72 (s, 3H), 2.91 - 2.84 (m, 1H), 2.65 - 2.57 (m, 3H), 1.65 - 1.59 (m, 2H), 1.49 - 1.36 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.3, 143.6, 132.5, 130.1, 128.3, 127.9, 127.4, 126.9, 120.8, 52.3, 43.6, 35.3, 33.4, 28.2, 22.3, 13.9.



Methyl 4-bromo-7-(*tert*-butyl)-1,2-dihydronaphthalene-1-carboxylate (7da-1)

Colorless oil, 56.6 mg, 0.176 mmol, 44% yield.

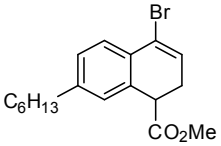
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.54 (d, J = 8.2 Hz, 1H), 7.37 - 7. 34 (m, 1H), 7.20 (s, 1H), 6.38 - 6.35 (m, 1H), 3.84 - 3.77 (m, 1H), 3.72 (s, 3H), 2.91 - 2.84 (m, 1H), 2.66 - 2.59 (m, 1H), 1.35 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.4, 151.8, 132.3, 129.9, 127.5, 126.6, 125.4, 124.8, 120.7, 52.3, 43.7, 34.6, 31.2, 28.2.



Methyl 4-bromo-7-pentyl-1,2-dihydronaphthalene-1-carboxylate (7ea-1)

Colorless oil, 55.0 mg, 0.164 mmol, 41% yield.

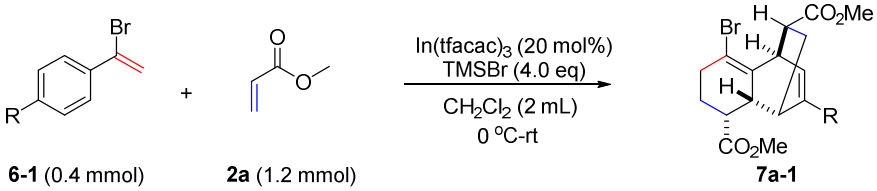
^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.53 (d, J = 7.9 Hz, 1H), 7.15 (d, J = 7.9 Hz, 1H), 6.99 (s, 1H), 6.37 - 6.35 (m, 1H), 3.81 - 3.78 (m, 1H), 3.72 (s, 3H), 2.91 - 2.84 (m, 1H), 2.65 - 2.58 (m, 3H), 1.67 - 1.60(m, 2H), 1.44 - 1.33 (m, 4H), 0.92 (t, J = 6.8 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.3, 143.7, 132.5, 130.1, 128.3, 127.9, 127.4, 126.9, 120.9, 52.3, 43.6, 35.6, 31.4, 31.0, 28.2, 22.5, 14.0.



Methyl 4-bromo-7-hexyl-1,2-dihydronaphthalene-1-carboxylate (7fa-1)

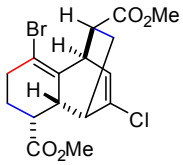
Colorless oil, 56.6 mg, 0.176 mmol, 44% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.52 (d, J = 7.9 Hz, 1H), 7.16 - 7.13 (m, 1H), 6.99 (s, 1H), 6.37 - 6.34 (m, 1H), 3.81 - 3.78 (m, 1H), 3.71 (s, 3H), 2.94 - 2.84 (m, 1H), 2.64 - 2.57 (m, 3H), 1.72 - 1.61 (m, 2H), 1.39 - 1.32 (m, 6H), 0.91 (t, J = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 173.3, 143.7, 132.5, 130.1, 128.3, 127.9, 127.4, 126.9, 120.8, 52.3, 43.6, 35.6, 31.7, 31.2, 28.9, 28.2, 22.6, 14.1.



6-1 (0.4 mmol) **2a** (1.2 mmol) **7a-1**

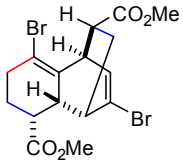
A dry reaction tube was charged with α-aryl vinyl bromide **6-1** (0.4 mmol, 86.4 mg), acrylate **2a** (1.2 mmol, 103.2 mg), indium(III) trifluoroacetylacetonate ($In(tfacac)_3$, 20 mol%, 0.08 mmol, 45.9 mg) and CH_2Cl_2 (2 mL) under N_2 atmosphere at 0 °C. Bromotrimethylsilane (TMSBr, 4 equiv, 1.6 mmol, 243.2 mg) was added and the reaction mixture was stirred at room temperature for 1 h. Upon completion of the reaction as indicated by TLC analysis, the residue was directly purified by flash column chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) to afford the desired product **7a-1** in 38% yield.



Dimethyl (1*S, 4*S**, 5*R**, 10*S**)-8-bromo-3-chloro-1, 4, 4a, 5, 6, 7-hexahydro -1, 4-ethanonaphthalene-5, 10-dicarboxylate (7la-1)**

White solid, 59.0 mg, 0.152 mmol, 38% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.10 (dd, *J* = 7.2, 2.2 Hz, 1H), 4.14 (dd, *J* = 7.2, 1.8 Hz, 1H), 3.70 (s, 3H), 3.66 (s, 3H), 2.97 - 2.87 (m, 3H), 2.85 - 2.81 (m, 1H), 2.57 (brs, 1H), 2.52 - 2.45 (m, 1H), 2.12 - 2.06 (m, 1H), 2.02 - 1.84 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.1, 172.4, 133.9, 132.5, 125.1, 114.2, 52.2, 51.7, 45.4, 44.3, 42.7, 40.2, 40.0, 33.5, 32.8, 26.9. **HRMS** (ESI) calcd for $C_{16}H_{19}O_4ClBr$ $(M+H)^+$ 389.0155, found 389.0148. The crystal suitable for X-ray single crystal diffraction analysis was obtained from solvent mixture of hexane/EtOAc (5:1).



Dimethyl (1*S, 4*S**, 5*R**, 10*S**)-3,8-dibromo-1, 4, 4a, 5, 6, 7-hexahydro-1, 4-ethanonaphthalene-5, 10-dicarboxylate (7ma-1)**

White solid, 72.6 mg, 0.168 mmol, 42% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 6.33 (dd, *J* = 7.1, 2.0 Hz, 1H), 4.13 (dd, *J* = 7.1, 1.7 Hz, 1H), 3.71 (s, 3H), 3.70 (s, 3H), 3.06 (brs, 1H), 2.95 - 2.80 (m, 3H), 2.59 (brs, 1H), 2.52 - 2.46 (m, 1H), 2.11 - 2.04 (m, 1H), 2.02 - 1.87 (m, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ (ppm) 174.0, 172.4, 132.3, 129.8, 122.0, 114.3, 52.1, 52.0, 46.1, 45.9, 43.8, 40.1, 40.0, 33.6, 32.9, 27.1. **HRMS** (ESI) calcd for $C_{16}H_{19}O_4Br_2$ $(M+H)^+$ 432.9650, found 432.9655. The crystal suitable for X-ray single crystal diffraction analysis was obtained from solvent mixture of hexane/EtOAc (5:1).

4.5 Crystal structure data

Table 4-7. Sample and crystal data for **11a-1**

Identification code	**11a-1**	
Chemical formula	$C_{18}H_{16}$	
Formula weight	232.31 g/mol	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal size	0.060 x 0.100 x 0.120 mm	
Crystal habit	light yellow block	
Crystal system	monoclinic	
Space group	P 1 21/c 1	
Unit cell dimensions	a = 11.3506(8) Å	α = 90°
	b = 24.330(2) Å	β = 102.668(2)°
	c = 9.8671(8) Å	γ = 90°
Volume	2658.6(4) Å^3	
Z	8	
Density (calculated)	1.161 g/cm^3	

Absorption coefficient	0.065 mm^{-1}
F(000)	992

Table 4-8. Data collection and structure refinement for **11a-1**

Theta range for data collection	1.67 to 25.78°
Index ranges	-13<=h<=10, -29<=k<=29, -12<=l<=12
Reflections collected	24234
Independent reflections	5068 [R(int) = 0.0983]
Coverage of independent	99.4%
Absorption correction	multi-scan
Max. and min. transmission	0.9960 and 0.9920
Refinement method	Full-matrix least-squares on F^2
Refinement program	SHELXL-2014/7 (Sheldrick, 2014)
Function minimized	$\Sigma\, w(F_o^2 - F_c^2)^2$
Data / restraints / parameters	5068 / 0 / 330
Goodness-of-fit on F^2	1.054
Final R indices	2760 data; R1 = 0.0580, wR2 =
	all data R1 = 0.1387, wR2 =
Weighting scheme	$w=1/[\sigma^2(F_o^2)+(0.1134P)^2]$
Largest diff. peak and hole	0.494 and -0.510 $eÅ^{-3}$
R.M.S. deviation from mean	0.168 $eÅ^{-3}$

Table 4-9. Bond lengths (Å) for **11a-1**

C1-C13	1.530(4)	C1-C15	1.538(4)
C1-C2	1.539(4)	C1-C14	1.544(4)
C2-C3	1.386(4)	C2-C7	1.396(4)
C3-C4	1.390(5)	C4-C5	1.393(5)
C4-C22	1.506(5)	C5-C6	1.384(5)
C6-C7	1.395(4)	C7-C8	1.468(4)
C8-C9	1.388(4)	C8-C13	1.409(4)
C9-C10	1.395(4)	C10-C11	1.396(4)
C10-C23	1.482(4)	C11-C12	1.402(4)
C12-C13	1.400(4)	C12-C30	1.492(4)
C15-C21	1.391(4)	C15-C16	1.397(4)
C16-C17	1.383(4)	C17-C18	1.382(4)
C18-C20	1.391(5)	C18-C19	1.506(4)
C20-C21	1.383(4)	C23-C24	1.392(4)
C23-C29	1.396(4)	C24-C25	1.381(4)
C25-C26	1.387(5)	C26-C28	1.385(5)
C26-C27	1.510(5)	C28-C29	1.381(5)
C30-C31	1.390(4)	C30-C36	1.395(4)

C31-C32	1.386(4)	C32-C33	1.387(5)
C33-C35	1.385(5)	C33-C34	1.511(5)
C35-C36	1.388(4)		

Table 4-10. Bond angles (°) for **11a-1**

C13-C1-C15	112.0(2)	C13-C1-C2	100.8(2)
C15-C1-C2	107.5(2)	C13-C1-C14	111.5(2)
C15-C1-C14	113.8(3)	C2-C1-C14	110.5(2)
C3-C2-C7	121.1(3)	C3-C2-C1	127.8(3)
C7-C2-C1	111.1(3)	C2-C3-C4	119.9(3)
C3-C4-C5	118.9(3)	C3-C4-C22	120.2(3)
C5-C4-C22	120.9(3)	C6-C5-C4	121.5(3)
C5-C6-C7	119.5(3)	C6-C7-C2	119.1(3)
C6-C7-C8	132.3(3)	C2-C7-C8	108.6(3)
C9-C8-C13	121.2(3)	C9-C8-C7	130.0(3)
C13-C8-C7	108.7(3)	C8-C9-C10	119.9(3)
C9-C10-C11	118.2(3)	C9-C10-C23	121.0(3)
C11-C10-C23	120.8(3)	C10-C11-C12	123.3(3)
C13-C12-C11	117.5(3)	C13-C12-C30	123.7(3)
C11-C12-C30	118.7(3)	C12-C13-C8	119.8(3)
C12-C13-C1	129.4(3)	C8-C13-C1	110.7(3)
C21-C15-C16	117.5(3)	C21-C15-C1	122.5(3)
C16-C15-C1	120.0(3)	C17-C16-C15	121.1(3)
C18-C17-C16	121.6(3)	C17-C18-C20	117.2(3)
C17-C18-C19	120.9(3)	C20-C18-C19	121.9(3)
C21-C20-C18	121.8(3)	C20-C21-C15	120.7(3)
C24-C23-C29	117.8(3)	C24-C23-C10	120.7(3)
C29-C23-C10	121.5(3)	C25-C24-C23	121.2(3)
C24-C25-C26	121.4(3)	C28-C26-C25	117.2(3)
C28-C26-C27	121.9(3)	C25-C26-C27	120.9(3)
C29-C28-C26	122.3(3)	C28-C29-C23	120.2(3)
C31-C30-C36	118.2(3)	C31-C30-C12	118.8(3)
C36-C30-C12	123.0(3)	C32-C31-C30	120.7(3)
C31-C32-C33	121.5(3)	C35-C33-C32	117.5(3)
C35-C33-C34	121.4(3)	C32-C33-C34	121.1(3)
C33-C35-C36	121.7(3)	C35-C36-C30	120.4(3)

List of publications:

1. Indium(III)-catalyzed [2+2]-cycloaddition of unactivated aryl alkynes with acrylates and selective cleavage of cyclobutenes for the efficient synthesis of 1,4- and 1,5-dicarbonyl compounds. Shen, L.; Shen, Z.-L.; Loh, T.-P. Submitted

2. Lewis acid-catalyzed dearomatic cascade reaction of aryl alkynes with acrylates towards the synthesis of densely functionalized polycyclic enes. Shen, L.; Zhao, K.; Ganguly, R.; Li, Y.-X.; Shen, Z.-L.; Loh, T.-P. Submitted

3. Transition metal-catalyzed cross-coupling reactions using organoindium reagents. Zhao, K.; Shen, L.; Shen, Z.-L.; Loh, T.-P. *Chem. Soc. Rev*. Accepted