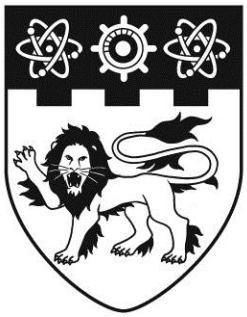

NANYANG TECHNOLOGICAL UNIVERSITY

PART I: BIOINSPIRED REACTIONS IN THE SYNTHESIS OF COMPLEX MOLECULES
PART II: NEW GENERATION OF IN(III)-PYBOX COMPLEX IN ASYMMETRIC SYNTHESIS

ZHAO JUNFENG

SCHOOL OF PHYSICAL AND MATHEMATICAL SCIENCES

2010

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PART I

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PART II

NEW GENERATION OF IN(III)-PYBOX COMPLEX IN ASYMMETRIC SYNTHESIS

ZHAO JUNFENG

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

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TABLE OF CONTENTS

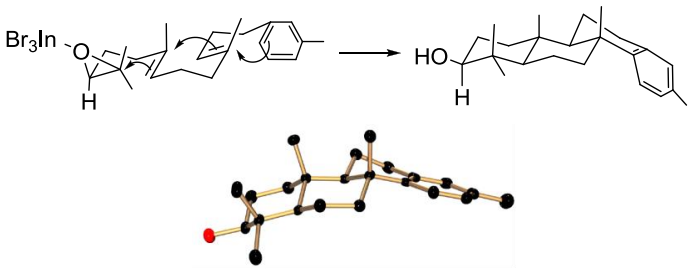
Summary

This thesis includes two parts: Part **I**, bioinspired reactions in the synthesis of complex molecules; Part **II**, new generation of In(III)-pybox complex in asymmetric synthesis.

I. BIOINSPIRED REACTIONS IN THE SYNTHESIS OF COMPLEX MOLECULES

There are two chapters (Chapter **1** and Chapter **2**) in Part **I** which involves the application of bioinspired reactions in the synthesis of complex molecules. Nature knows best! The biosynthesis of many complex natural products involved highly efficient cascade reactions catalyzed by enzymes under mild conditions. Mimicking these breathtakingly high efficient cascade reactions is an effective strategy toward the total synthesis of complex natural and unnatural products. Among them, the biomimetic polyene cyclization is one of the most extensively studied one both in biology and chemistry.

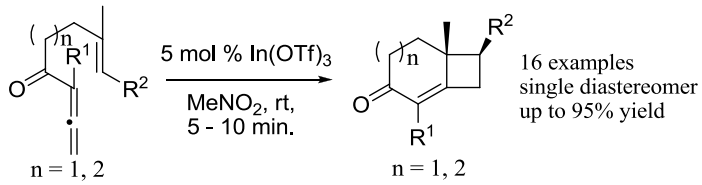
Chapter 1. Indium tribromide-promoted arene-terminated epoxy olefin cyclization



Scheme 1

In the first chapter of this thesis, we reported a highly efficient epoxide opening-initiated cascade polyene cyclization (Scheme 1) in the presence of water-tolerant Lewis acid ($InBr_3$). According to Stork-Eschenmoser's hypothesis, Lewis acid promoted epoxide opening-initiated cascade *anti* parallel addition of olefins furnished the *trans*, *trans*-tetracyclized products with excellent regio- and diastereoselectivity. Up to five chiral centers could be created in a single operational step and only one pair enantiomer out of 32 isomers is formed. The water-tolerant Lewis acid ($InBr_3$) mediated epoxide opening-initiated cascade polyene cyclization afforded *tri*- and *tetra*-cyclic 3-*β*-hydroxy terpenoids and steroids derivatives in 57 and 37% yields, respectively, yield per ring of up to 75%. The reaction conditions are mild and its efficiency is higher than those of the reported strategies. What is more, this reaction can be carried out in aqueous media which makes it more close to nature. This study provides an efficient methodology to the total synthesis of terpenoids and steroids derivatives containing a 3-hydroxy group and one terminal aromatic ring.

Chapter 2. Acid-catalyzed intramolecular [2 + 2] cycloaddition of ene-allenones: facile access to bicyclo[n.2.0] frameworks



Scheme 2

The second chapter of this thesis described an intramolecular [2 + 2]-cycloaddition reaction of ene-allenone (Scheme 2), which was discovered

unexpectedly in the course of our effort toward biomimetic polyene cyclization. With an additional alkene carbon-carbon double bond in the right place, the ene-allenone gave the intramolecular [2 + 2]-cycloaddition product through the less activated distal allenic double bond and the unactivated alkene in the presence of acid. This new reactivity is significantly different from the well-known Lewis acid catalyzed cycloisomerization of allenone. This intramolecular [2 + 2]-cycloaddition reaction afforded the strained bicyclo[n.2.0] frameworks , which are the key components and building blocks of many natural products, with excellent yields, chemo-, regio-, and diastereoselectivities. This method is practical and it works with a wide variety of substrates. The mild reaction conditions, good to excellent yields, excellent diastereoselectivities, and the simplicity of the reaction procedure make this method attractive for the synthesis of complex polycyclic natural products.

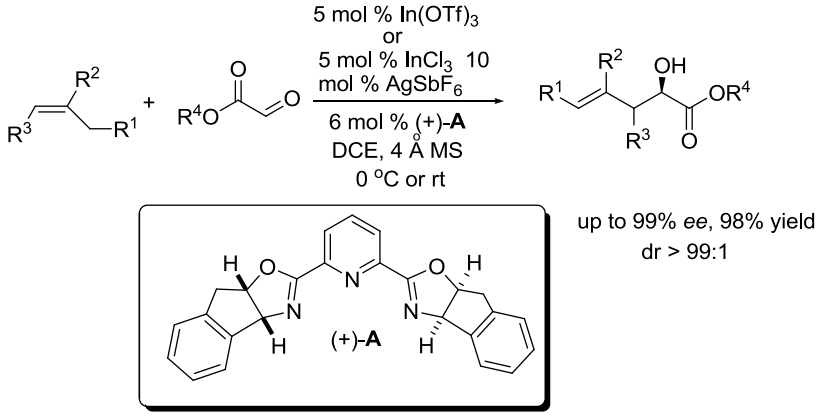
II. NEW GENERATION OF IN(III)-PYBOX COMPLEX IN ASYMMETRIC SYNTHESIS

Asymmetric synthesis and development of new chiral catalyst system continue to be one of the most active research areas of organic synthesis. In the second part of this thesis, we demonstrated that the In(III)-pybox complex is an efficient catalyst for bidentate substrates by using the asymmetric carbonyl-ene reaction of glyoxylate esters as the model reaction. In addition, a new generation of In(III)-pybox complexes based on the counterion effect has been developed and applied to asymmetric ketone-ene reaction of trifluoropyruvate and a challenging Mukaiyama aldol reacton successfully. The increased catalytic efficiency will expand further application of

chiral indium complex in the asymmetric synthesis.

In Chapter 3, a highly efficient asymmetric carbonyl-ene reaction of glyoxylate esters catalyzed by In(III)-pybox complex was described. Firstly, we found that the In(III)-pybox complex, formed *in situ* from commercially available $In(OTf)_3$ and pybox (+)-**A**, is an efficient catalyst for the asymmetric carbonyl-ene reaction of ethyl glyoxylate. In the presence of this catalyst, both the aromatic and aliphatic alkenes

Chapter 3. Highly enantioselective carbonyl-ene reactions catalyzed by In(III)-pybox complex

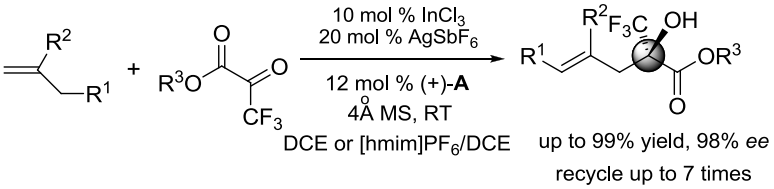


Scheme 3

afforded the expected homoallylic alcohol products in good to excellent yields and excellent enantioselectivities up to 97% *ee*. Besides 1,1-disubstitued alkenes, 1,1,2-trisubstituted alkenes also could be used as the effective substrate. However, the long reaction times retarded its further application of this catalyst system. Furthermore, this catalyst is ineffective for asymmetric ketone-ene reactions. Fortunately, by taking advantage of the counterion effect, we developed a more active new generation of In(III)-pybox complex. The catalytic efficiency of the new catalyst has been improved

significantly as compared with that of the parent In(III)-pybox complex.

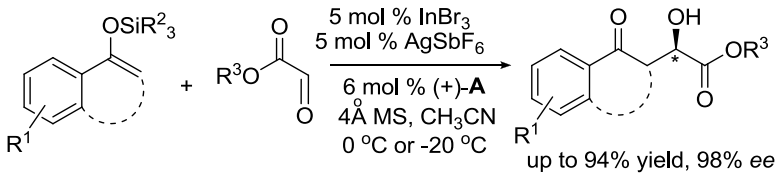
Chapter 4. Highly enantioselective ketone-ene reactions of trifluoropyruvate: significant counterion effect of the In(III)-pybox complex



Scheme 4

The asymmetric ketone-ene reaction is an atom-economic method for the construction of enantioenriched tertiary homoallylic alcohols, which are important building blocks for the synthesis of many natural products and pharmaceutical compounds. However, the asymmetric ketone-ene reaction is less developed as compared to the extensive studies of the asymmetric aldehyde-ene reaction. With the more active In(III)-pybox complex in hand, we attempted to use it in the more challenging asymmetric ketone-ene reaction of trifluoropyruvate and we found that this catalyst works well for ketone-ene reaction of trifluoropyruvate (Scheme 4). Both the aromatic and aliphatic alkenes afforded the expected CF_3- group containing tertiary homoallylic alcohols in good to excellent yields and with excellent enantioselectivities up to 98% *ee*. In addition, this catalyst system can be used in ionic liquid and can be recycled up to 7 times with excellent catalytic efficiency.

Chapter 5. In(III)-pybox complex catalyzed enantioselective Mukaiyama aldol reactions of glyoxylates and enolsilanes derived from aryl ketones



Scheme 5

The enantioselective Mukaiyama aldol reaction of 1,2-dicarbonyl compounds has emerged as an efficient strategy to construct enantioenriched *β*-hydroxy ketones and esters, which are key intermediates or synthetic building blocks for the synthesis of many natural products and pharmaceutical compounds. A number of chiral catalysts have been developed to mediate the asymmetric aldol reaction of *α*-keto esters and glyoxylates both in direct aldol and Mukaiyama aldol. To our surprise, although there are a lot of chiral catalysts to mediate the asymmetric aldol reaction of glyoxylates as well as aryl ketones, individually, none of them are effective for the asymmetric aldol reaction between aryl ketones and glyoxylates. The In(III)-pybox complex, designed based on counterion effect, catalyzed highly enantioselective Mukaiyama aldol reactions between glyoxylate esters and enolsilanes derived from a broad scope of aryl ketones. They afforded the enantioenriched *β*-hydroxy ketones bearing an additional ester group in excellent yields and with excellent enantioselectivities under mild conditions. This work complements the well-developed Mukaiyama aldol reactions of α-ketone esters. In addition, solvents were used without distillation and the reaction could be carried out in open air. The great synthetic advantage is that glyoxylate can be used in polymeric or hydrate form. All of these advantages should render this methodology very practical.

List of Abbreviations

δ	chemical shift
aq.	aqueous
Ar	aryl
bmim	1-methyl-3-butylimidazolium
Box	Bisoxazoline
br	broad singlet
Bu	butyl
calcd	calculated
°C	degree centigrade
$CDCl_3$	deuterated chloroform
cm^{-1}	inverse centimeter
d	doublet
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
dd	doublet of doublets
de	diastereomeric excess
DIBAL-H	diisobutylaluminium hydride
DMAP	4-*N*,*N*-dimethylamino pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sufoxide
dt	doublet of triplets
ee	enantiomeric excess
EI	electron-impact ionization
equiv.	equivalent(s)
ESI	electrospray ionization
Et	ethyl
FTIR	fourier transform infrared spectrometry

g	gram
h or hrs	hour(s)
hmim	1-methyl-3-hexylimidazolium
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	hertz
IL	ionic liquid
i-Pr	isopropyl
J	coupling constant
M	molar concentration
m	multiplet
m/z	mass per charge ratio
m	meta
M^+	parent ion peak (mass spectrum)
Me	methyl
MeCN	acetonitrile
MHz	mega hertz
min	minute(s)
mL	millilitres
mmol	millimole
mol%	mole percent
MS	molecular sieves
NMR	Nuclear magnetic resonance
Nu	nucleophile
o	*ortho*
OTf	trifluoromethane sulfonate (triflate)
omim	1-methyl-3-octylimidazolium
p	para
Ph	phenyl

ppm	parts per million
Pr	propyl
py	pyridine
Pybox	Bis(oxazolinyl)pyridine
q	quartet
R_f	retention factor
R_t	retention time
rt	room temperature
s	singlet
sat.	saturated
t	triplet
TBS	*t*-butyldimethylsilyl
td	triplet of doublets
TES	tiethylsilyl
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
UV	ultraviolet
V	volume

PART I: BIOINSPIRED REACTIONS IN THE SYNTHESIS OF COMPLEX MOLECULES

Discovery of efficient methodologies to construct complex molecules with excellent regio-, diastereo- and enantioselectivity has been an important target for organic chemists. Nature knows best! The biosynthesis of many complex natural products involved highly efficient cascade reactions catalyzed by enzymes under mild conditions. "Cascade reaction" refers to the formation of multiple C-C bonds and chiral centers in one pot without isolation of any intermediates. Only a single reaction solvent, workup procedure, and purification step may be required to provide a product that would otherwise have to be made over the course of several steps. Cascade reactions should be regarded as "green chemistry" when considering atom economy, as well as economies of time, labor, resource management and waste generation. Designing a fantastic cascade process to mimic nature is an effective strategy for the total synthesis of complex natural and unnatural products.

Inspired by nature, two methodologies focusing on the synthesis of complex molecules have been developed in this part.

CHAPTER 1

Indium Tribromide-Promoted Arene-Terminated Epoxy Olefin Cyclization

1.1 OVERVIEW OF LEWIS ACID CATALYZED-EPOXIDE OPENGING-INITIATED POLYENE CYCLIZATION

The discovery of efficient methodologies to construct complex molecules with excellent chemo-, regio-, diastereo- and enantioselectivity has been an important goal for organic chemists.[1] Nature knows best! The biosynthesis of many complex natural products involved highly efficient cascade reactions catalyzed by enzymes under mild conditions. Mimicking these breathtakingly highly efficient biosynthetic pathways is an effective strategy for total synthesis of complex natural products.[2] Among them, the biomimetic polyene cyclization is the most extensively studied both in biology[3] and chemistry.[4]

In 1945, on the basis of experimental evidence,[5] K. Bloch and D. Rittenberg proposed that tetracyclic cholesterol, a key intermediate for the biosynthesis of other steroids *in vivo*, had its origin in the linear polyolefin, squalene. Later on, K. Bloch, R. B. Woodward and the Zürich School coalesced to a unified theme of

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[1] Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim, **2006**.

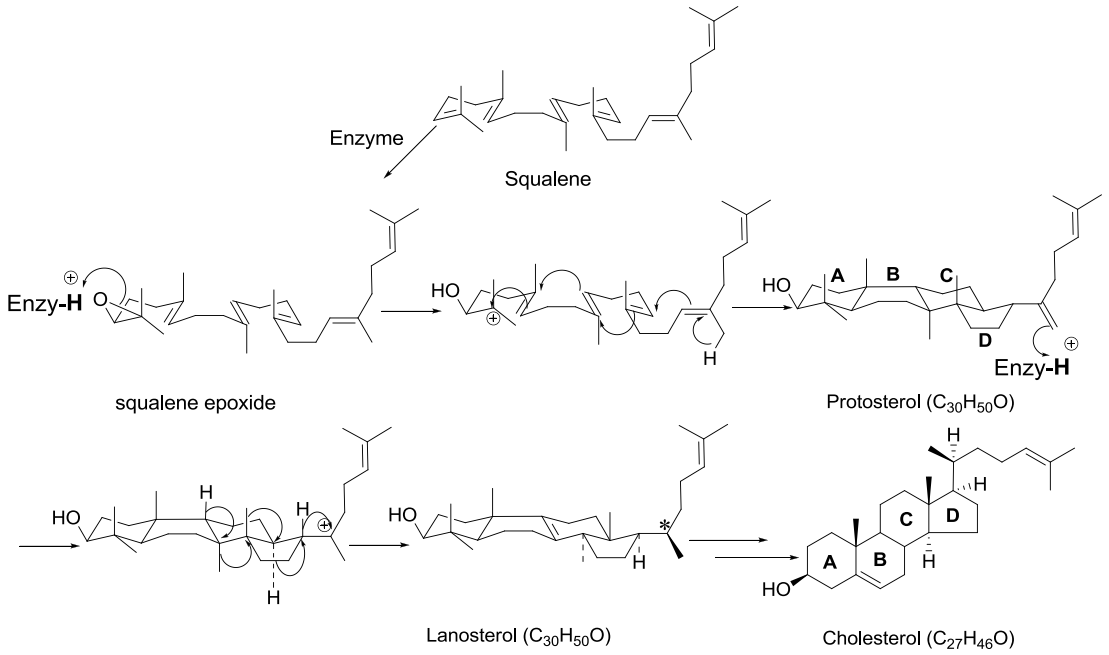
[2] For reviews on recent achievements in biomimetic organic synthesis, see: (a) Torre, M. C.; Sierra, M. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 160. (b) Yoder, R. A.; Johnston, J. N. *Chem. Rev.* **2005**, *105*, 4730.

[3] (a) For reviews on enzymatic polyene cyclization, see: Abe, I.; Rohmer, M.; Prestwich, G. D. *Chem. Rev.* **1993**, *93*, 2189. (b) Wendt, K. U. *Angew. Chem., Int. Ed.* **2005**, *44*, 3966. (c) Wendt, K. U.; Schulz, G. E.; Corey, E. J.; Liu, D. R. *Angew. Chem., Int. Ed.* **2000**, *39*, 2812. For recent examples of enzymatic polyene cyclization, see: (d) Abe, I.; Sakano, Y.; Tanaka, H.; Lou, W. W.; Noguchi, H.; Shibuya, M.; Ebizuka, Y. *J. Am. Chem. Soc.* **2004**, *126*, 3426. (e) Shan, H.; Segura, M. J. R.; Wilson, W. K.; Lodeiro, S.; Matsuda, S. P. T. *J. Am. Chem. Soc.* **2005**, *127*, 18008. (f) Thoma, R.; Schulz-Gasch, T.; Benz, B. D. J.; Aebi, J.; Dehmlow, H.; Hennig, M.; Stihle, M.; Ruf, A. *Nature* **2004**, *432*, 118.

[4] Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, **1984**; Vol. 3, pp 341-409.

[5] Bloch, K.; Rittenberg, D. *J. Bio.Chem*. **1945**, *159*, 45.

squalene-terpene-steroid biosynthesis (Scheme 1.1).[6] Their early studies on these enzyme-catalyzed processes have identified the intermediacy of 2,3-oxidosqualene in steroid biosynthesis. [7]



Scheme 1.1 Biosynthesis of cholesterol

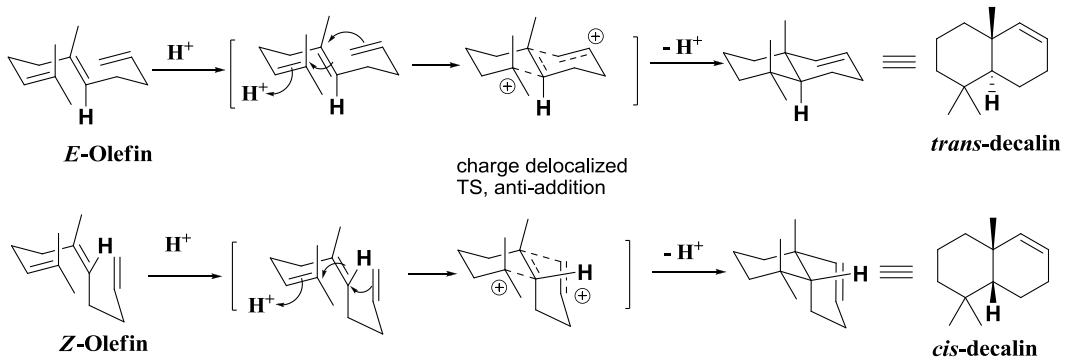
In 1955, Stork[8] and Eschenmoser[9] independently proposed a model for explaining the highly stereoselective chemistry of polyene cyclization, namely the Stork-Eschenmoser postulate (SEP) (Scheme 1.2). The Stork-Eschenmoser postulate was one of the key early findings of cationic polyene cyclization which translated C-C

[6] (a) Langdon, R. G.; Bloch, K. *J. Am. Chem. Soc*. **1952**, *74*, 1869. (b) Woodward, R. B.; Bloch, K. *J. Am. Chem. Soc.* **1953**, *75*, 2023. (c) Langdon, R. G.; Bloch, K. *J. Biol. Chem*. **1953**, *200*, 135. (d) Stork, G.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (e) Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* **1955**, *38*, 1890.

[7] (a) R. G. Langdon, K. Bloch, *J. Am. Chem. Soc*., **1952,** *74*, 1869. (b) R. B. Woodward, K. Bloch, *J. Am. Chem. Soc*., **1953**, ***75***, 2023. (c) R. G. Langdon, K. Bloch, *J. Bio. Chem.*, **1953**, *200*, 135. (d) M. B. Jarstfer, B. S. J. Blagg, D. H. Rogers, C. D. Poulter, *J. Am. Chem. Soc*., **1996**, *118*, 13089. (e) E. J. Corey, H. Cheng, C. H. Baker, S. P. T. Matsuda, D. Li, X. Song, *J. Am. Chem. Soc*., **1997**, *119*, 1289. (f) E. J. Corey, H. Cheng, C. H. Baker, S. P. T. Matsuda, D. Li, X. Song, *J. Am. Chem. Soc*., **1997**, *119*, 1277. (g) R. Thoma, T. S. Gasch, B. D'Arcy, J. Benz, J. Aebi, H. Dehmlow, M. Hennig, M. Stihle, A. Ruf, *Nature*, **2004**, *432*, 118.

[8] (a) Stork, T.; Burgstahler, A. W. *J. Am. Chem. Soc.* **1955**, *77*, 5068. (b) Stork, G.; Conroy, H. *J. Am. Chem. Soc*. **1951**, *73*, 4748.

[9] (a) A. Eschenmoser, D. Arigoni, *Helv. Chim. Acta*, **2005**, *88*, 3011. (b) A. Eschenmoser, L. Ruzicka, O. Jeger, D. Arigoni, *Helv. Chim. Acta* **1955**, *38*, 1890.



Scheme 1.2 Stork-Eschenmoser postulate

double bond geometry into relative stereochemistry of ring fusion. Firstly, linear polyalkenes folded into well-defined chair-like conformations in solution. Once the polyalkenes are subjected to electrophiles, the cascade cyclization will be initiated with predictable stereochemistry: *E*-alkenes will give *trans*-ring junctions while *Z*-alkenes will give *cis*-ring junctions. The postulate is a manifestation of the favorable *anti* addition of electrophile and nucleophile across the original alkene. According to the Stork-Eschenmoser postulate, the preorganized conformation of polyene is crucial for the stereochemistry of this process.

In terms of initiating modes, a large number of functional groups such as sulfonate esters,[10] trisubstituted[11] or monosubstituted[12] olefins, allylic alcohols,[13]

[10] (a) Johnson, W.S.; Crandall, J.K. *J. Org. Chem*. **1965**, *30*, 1785. (b) Johnson, W.S. *Bioorg. Chem.* **1976**, *5*, 51.

[11] (a) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2004**, *126*, 11122. (b) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc.* **2002**, *124*, 3647.

[12] (a) Kerber, W. D.; Gagné, M. R. *Org. Lett.* **2005**, *7*, 3379. (b) Kerber, W. D.; Koh, J. H.; Gagné, M. R. *Org. Lett.* **2004**, *6*, 3013. (c) Koh, J. H.; Mascarenhas, C.; Gagné, M. R. *Tetrahedron* **2004**, *60*, 7405. (d) Mullen, C. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880. (e) Feducia, J. A.; Gagné, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 592.

[13] (a) Johnson, W.S.; Semmelhack, M.F.; Sultanbawa, M.U.S.; Dolak, L.A. *J. Am. Chem. Soc*. **1968**, *90*, 2994. (b) Bartlett, W.R.; Johnson, W.S. *J. Am. Chem. Soc*. **1974**, *96*, 2549. (c) Garst, M.E.; Cheung, Y-F; Johnson, W.S. *J. Am. Chem. Soc.* **1979**, *101*, 4404. (d) Johnson, W.S.; Daub, G.W.; Lyle, T.A.; Niwa, M. *J. Am. Chem. Soc*. **1980**, *102*, 7800. (e) Johnson, W.S.; Bunes, L.A. *J. Am. Chem. Soc*. **1976**, *98*, 5597. (f) Johnson, W.S.; Gravestock, M.B.; McCarry, B.E. *J. Am. Chem. Soc.* **1971**, 93, 2994. (g) Johnson, W.S.; Hughes, L.R.; Kloek, J.A.; Niem, T.; Shenvi, A. *J. Am. Chem. Soc*. **1979**, 101,1279. (h) Johnson, W.S.; Hughes, L.R.; Carlson, J.L. *J. Am. Chem. Soc*. **1979**, 101, 1281.

acetals,[14] epoxides[15] and others[16] have been used as initiating groups for the cascade cyclizations.[17] Among them, the use of epoxide has been the most popular strategy for construction of natural products. Acid-catalyzed or radical-mediated epoxide opening not only initiate the cascade polyene cyclization but also affords a hydroxy group at 3' position, which is frequently observed in many natural products.

In 1962, Goldsmith *et al.* reported the first Lewis acid-catalyzed cyclization of epoxyolefins and studied the mechanism (Scheme 1.3).[18] They proposed that there are two pathways, namely concerted pathway **A** and stepwise pathway **B**, from epoxyolefin **1** to alcohol **2.** Their study demonstrated that opening of the epoxide and ring formation prefers a stepwise mechanism in benzene, while being more concerted in ether solvent. Seven years later, Goldsmith's group reported the Lewis acid-catalyzed epoxide opening-initiated polyene cyclization with an aryl group as the terminator (Scheme 1.4).[19] When epoxyolefin *cis*-**3** was treated with boron trifluoride

[14] (a) Johnson, W.S.; Kinnel, R. B. *J. Am. Chem. Soc.* **1966**, *88*, 3861. (b) Johnson, W.S.; Wiedhaup, K.; Brady, S. F.; Olson, G. *J. Am. Chem. Soc.* **1968**, *90*, 5277. (c) Johnson, W. S.; Harbert, C. A.; Stipanovic, R. D. *J. Am. Chem. Soc.* **1968**, *90*, 5279. (d) Bartlett, P. A.; Johnson, W. S.; Elliott, J. D. *J. Am. Chem. Soc*. **1983**, *105*, 2088. (e) Dijkink, J.; Speckamp, W.N. *Tetrahedron Lett.* **1977**, *18*, 935. (f) Romero, A.G.; Leiby, J.A.; Mizak, S.A. *J. Org. Chem*. **1996**, *61*, 6974.

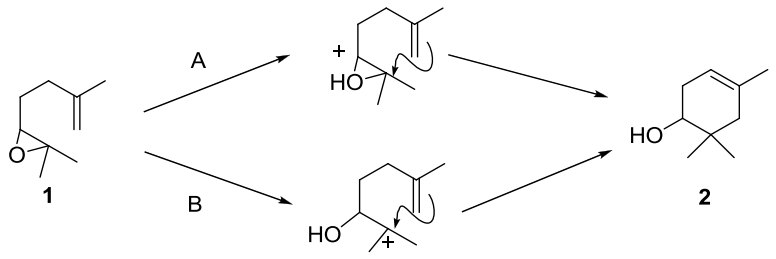
[15] (a) van Tamelen, E.E.; Seiler, M.P.; Wierenga, W. *J. Am. Chem. Soc*. **1972**, *94*, 8229-8231. (b) van Tamelen, E.E.; Hwu, J.R. *J. Am. Chem. Soc*. **1983**,*105*, 2490-2491. (c) van Tamelen, E.E.; Willet, J.; Schwartz, M.; Nadeau, R. *J. Am. Chem. Soc*. **1966**, *88*, 5937. (d) Goldsmith, D. J. *J. Am. Chem. Soc*. **1962**, *84*, 3913. (e) Goldsmith, D. J. Philips, C. F. *J. Am. Chem. Soc*. **1969**, *91*, 5862. (f) Corey, E. J.; Staas, D. D. *J. Am. Chem. Soc*. **1998**, *120*, 3562. (g) J. Justicia, J. E. Oltra, J. M. Cuerva, *J. Org. Chem.* **2004**, *69*, 5803.

[16] (a) For Nazarov cyclization initiated polyene cyclization, see: Bender, J. A.; Arif, A. M. and West, F. G. *J. Am. Chem. Soc*. **1999**, *121*, 7443. (b) Bender, J.A.; Blize, A.E.; Browder, C.C.; Giese, S.; West, F.G. *J. Org. Chem*. **1998**, 63, 2430-2431. (c) Koster, F. H.; Wolf, H. *Tetrahedron Lett*. **1981**, *22*, 3927. (d) Ireland, R. E.; Dawson, M. J.; Bordner, J.; Dickerson, R. E. *J Am. Chem. Soc.* **1975,** *92*, 2568.

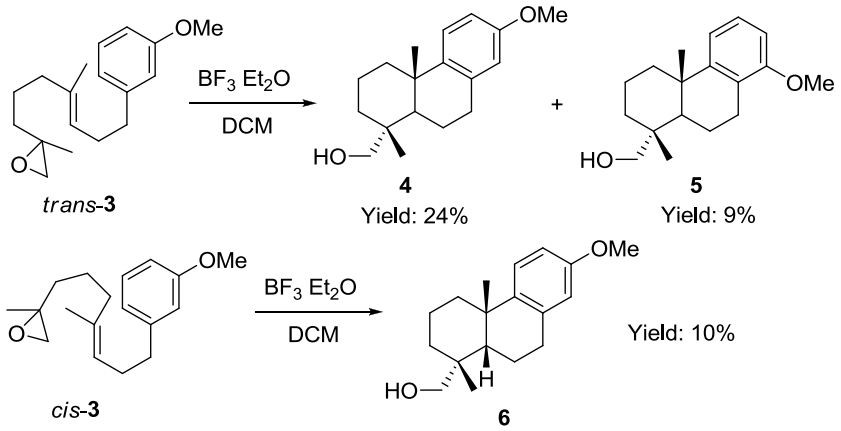
[17] For reviews, see: (a) R. A.Yoder and J. N. Johnston, *Chem. Rev.*, 2005, **105**, 4730. (b) K. U. Wendt, G. E. Schulz, E. J. Corey, D. R. Liu, *Angew. Chem. Int. Ed.*, 2000, **39**, 2812. (c) E. E. van Tamelen, *Acc. Chem. Res.*, 1968, **1**, 111. (d) W. S. Johnson, *Acc. Chem. Res.*, 1968, **1**, 1. (e) A. Eschenmoser, D. Arigoni, *Helv. Chim. Acta*, 2005, **88**, 3011.

[18] Goldsmith, D. J. *J. Am. Chem. Soc*. **1962**, *84*, 3913.

[19] Goldsmith, D. J. Philips, C. F. *J. Am. Chem. Soc*. **1969**, *91*, 5862.



Scheme 1.3



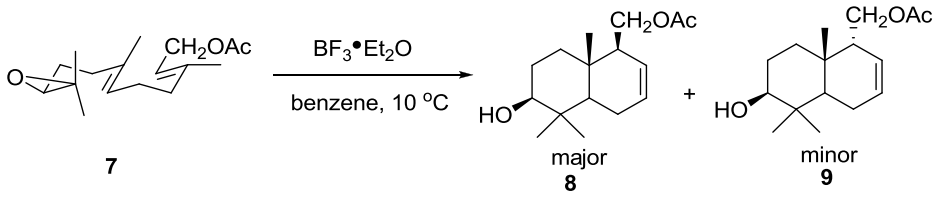
Scheme 1.4

etherate, the tricyclic products **4** and **5**, both of which possess *trans*-fused A/B rings, could be obtained in a single operation with a combined yield of 33%. The stereochemistry of the product is dependent on the configuration of the original alkene. In other words, *trans*-alkene leads to *trans*-fused A/B rings while *cis*-alkene gives *cis*-fused A/B rings. These results are consistent with the well-known Stork-Eschenmoser postulate. The side products in this study indicated that the cyclization occurs *via* cationic intermediates with fixed geometry rather than a concerted process.

In 1963, van Tamelen *et al.* expanded this strategy to construct two rings by using epoxide opening-initiated polyene cyclization (Scheme 1.5).[20] On treatment

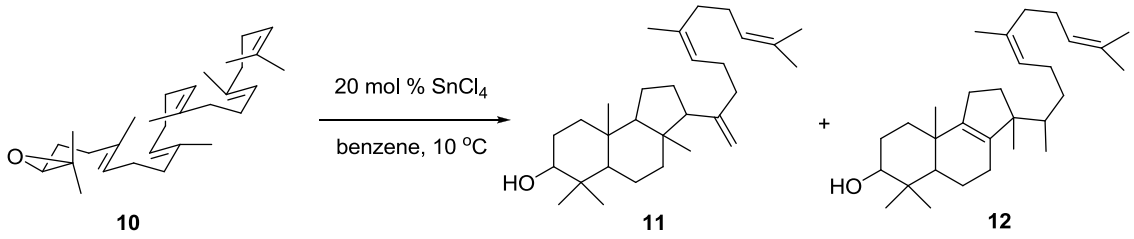
[20] van Tamelen, E. E.; Storni, A.; Hessler, E. J.; Schwartz, M. *J. Am. Chem. Soc.*, **1963**, *85*, 3295.

with boron trifluoride etherate in benzene, epoxide **7** was transformed into a variety of products, among which the bicyclic diol monoacetate **8** and **9** could be isolated as major components in modest yields. This study is the first demonstration of the application of Lewis acid-catalyzed epoxide opening-initiated polyene cyclization in chemistry laboratory.



Scheme 1.5

In 1966, almost at the same time, Corey and van Tamelen independently showed that the acid-catalyzed epoxide opening-initiated polyene cyclization is the actual pathway used by cholesterol synthesizing enzymatic systems, independently.[21] In



Scheme 1.6

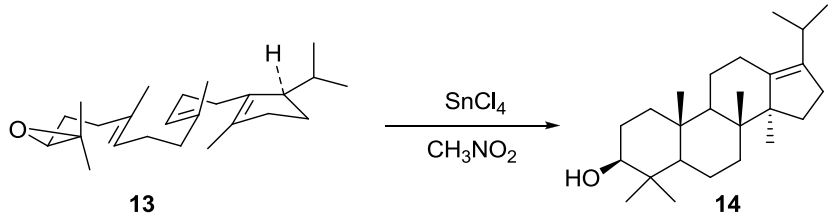
view of the utilization of 2,3-oxidosqualene (**10)** in the biosynthesis of lanosterol and cholesterol, van Tamelen et al. studied the first nonenzymatic laboratory cyclization of 2,3-oxido-squalene (Scheme 1.6).[22] In the presence of 20 mol% of stannic chloride, the epoxide opening-initiated polyene cyclization indeed proceeded to provide the tricyclic compounds **11** and **12** as the major products, which are significantly different

[21] (a) Corey, E. J.; Russey, W. E.; Ortiz de Montellano, R. O. *J. Am. Chem. Soc*.,**1966**, *88*, 4750. (b) van Tamelen, E. E.; Willett, J. D.; Clayton, R. B.; Lord, K. E., *J. Am. Chem. Soc*., **1966**, *88*, 4752.

[22] van Tamelen, E. E.; Willett, J. D.; Nadeau, R. *J. Am. Chem. Soc*., **1966**, *88*, 5937.

with the enzyme-catalyzed product. This can be rationalized by the relative stabilities of secondary and tertiary cationic intermediates.

The Lewis acid-catalyzed epoxide opening-initiated polyene cyclization of 2,3-oxidosqualene provided a tricyclic six-six-five framework (Scheme 1.6), which



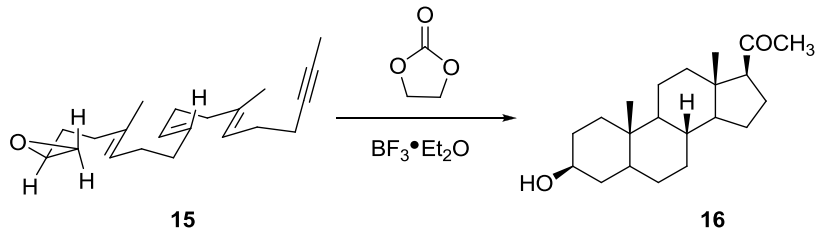
Scheme 1.7

is significantly different with the enzymic tetracyclic six-six-six-five system (Scheme 1.7). To achieve a six-membered C-ring closure over an otherwise favored 5-exo Markovnikov addition, in the 1970s, van Tamelen's group carried out extensive studies to mimic the biosynthesis of cholesterol and lanosterol.[23] With the elaborate designs, their results represent the closest approach to the basic (all-chair) biosynthesis of steroid derivatives.

Significant improvement was achieved in 1982 (Scheme 1.8)[24] when van Tamelen *et al*. constructed the tetracyclic six-six-six-five system by non-enzymatic strategy from an acyclic chain (**15**). With an alkyne as the terminating group, they

[23] (a) van Tamelen, E. E.; Milne, G. M.; Suffness, M. i.; Rudler Chauvin, M.C.; Anderson, R. J.; Achini, R. S. *J. Am. Chem. Soc*., **1970**, *92*, 7202. (b) van Tamelen, Murphy, J. W. *J. Am. Chem. Soc*., **1970**, *92*, 7204. (c) van Tamelen, Freed, J. H. *J. Am. Chem. Soc*., **1970**, *92*, 7206. (d) van Tamelen, E. E.; Anderson, R. J. *J. Am. Chem. Soc*., **1972**, *94*, 8225. (e) van Tamelen, E. E.; Holton, R. A.; Hopla, R. E.; Konz, W. E. *J. Am. Chem. Soc*., **1972**, *94*, 8228. (f) van Tamelen, E. E.; Seiler, M. P.; Wierenga, W. *J. Am. Chem. Soc*., **1972**, *94*, 8229. (g) van Tamelen, E. E.; Lees, R. G.; Grieder, A. *J. Am. Chem. Soc*., **1974**, *96*, 2255. (h) van Tamelen, E. E.; James, D. R. *J. Am. Chem. Soc*., **1977**, *99*, 950. (i) van Tamelen, E. E.; Pedlar, A. D.; Li, E.; James, D. R. *J. Am. Chem. Soc*., **1977**, *99*, 6778.

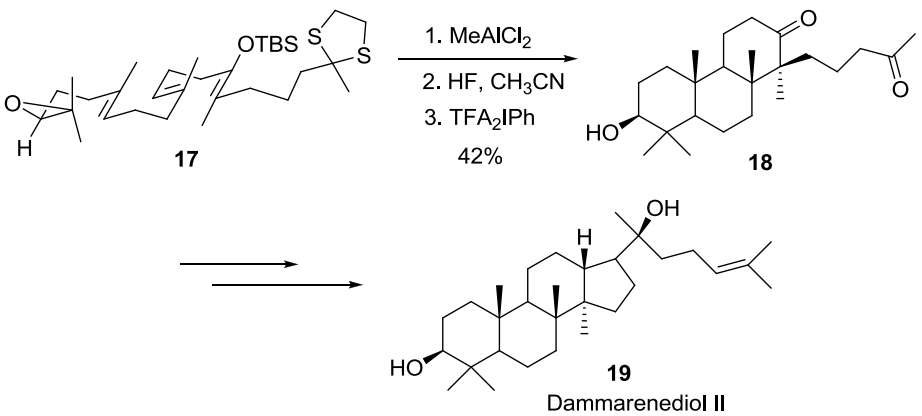
[24] (a) van Tamelen, E. E.; Leiden, T. M. *J. Am. Chem. Soc*., **1982**, *104*, 2061. (b) van Tamelen, E. E.; Hwu, J. R. *J. Am. Chem. Soc*., **1983**, *105*, 2490.



Scheme 1.8

constructed both the six-membered C-ring and the five-membered D-ring with excellent diastereoselectivity. Notably, the cascade process achieves generation of not only four new rings but also seven new chiral centers, one more than the biosynthesis of lanosterol, all possessing the proper relative configuration characteristic of normal steroids.

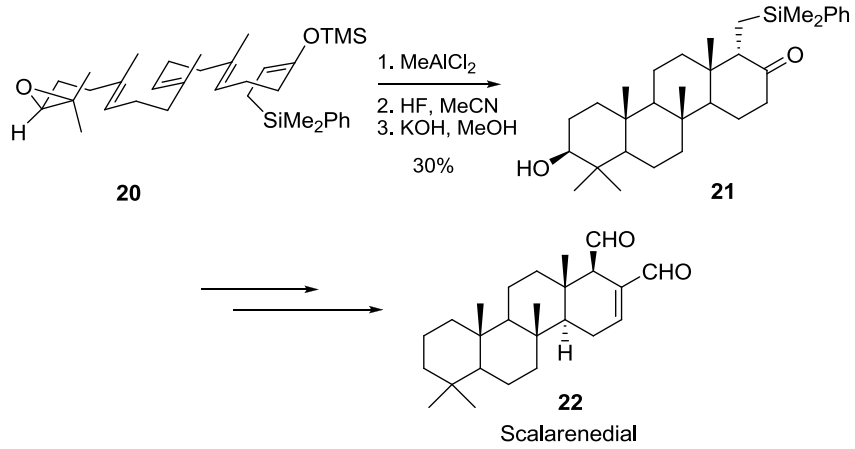
The first application of Lewis acid-catalyzed epoxide opening-initiated polyene cyclization in total synthesis was reported by Corey in 1996 (Scheme 1.9).[25] In the total synthesis of Dammarenediol II, Lewis acid-catalyzed epoxide opening-initiated polyene cyclization proceeded through a chair-chair-chair transition state to construct the A, B and C rings with the desired stereochemistry in one operation. The six-membered C ring that was formed over 5-exo closure was guaranteed by the



Scheme 1.9

[25] Corey, E. J.; Lin, S. *J. Am. Chem. Soc*., **1996**, *118*, 8765.

deliberate introduction of a silyl ether group at C14. Dammarenediol II could be obtained in good yield after several more steps. This study demonstrated the potential application of Lewis acid catalyzed-epoxide opening-initiated polyene cyclization in the total synthesis of complex natural products.[26] Later, Corey's group extended this strategy to construct tetracycles and applied it to the total synthesis of Scalarenedial



Scheme 1.10

(Scheme 1.10).[27] The methyl group at C14 instead of C15 as in oxidosqualene is crucial for construction of the six-membered C ring. Again, the enolsilane group as the terminator not only favored the formation of the six-membered D ring but also offered a carbonyl group after the cascade cyclization for further elaboration.

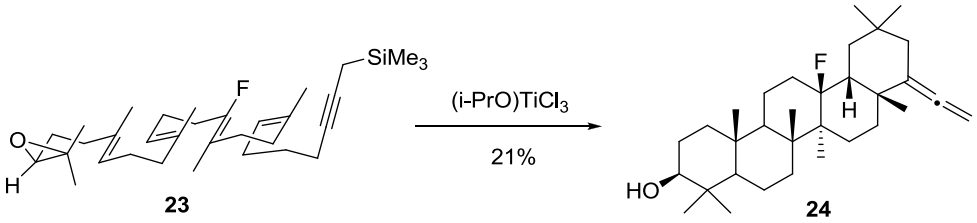
In 1994, Johnson's group reported the first example of non-enzymatic, biomimetic polyene pentacyclization by employing a fluorine atom at C14 as a cation-stabilizing auxiliary (Scheme 1.11).[28] This fluorine atom played an important

[26] (a) Corey, E. J.; Luo, G.; Lin, S. *Angew. Chem., Int. Ed.* **1998**, *37*, 1126. (b) Corey, E. J.; Lee, J. *J. Am. Chem. Soc*., **1993**, *115*, 8873. (c) Behenna, D. C.; Corey, E. J. *J. Am. Chem. Soc*., **2008**, *130*, 6720. (d) Kurti, L.; Chein, R. J.; Corey, E. J. *J. Am. Chem. Soc*., **2008**, *130*, 9031. (e) Surendra, K.; Corey, E. J. *J. Am. Chem. Soc*., **2009**, *131*, 13928.

[27] Corey, E. J.; Luo, G.; Lin, S. *J. Am. Chem. Soc*., **1997**, *119*, 9927.

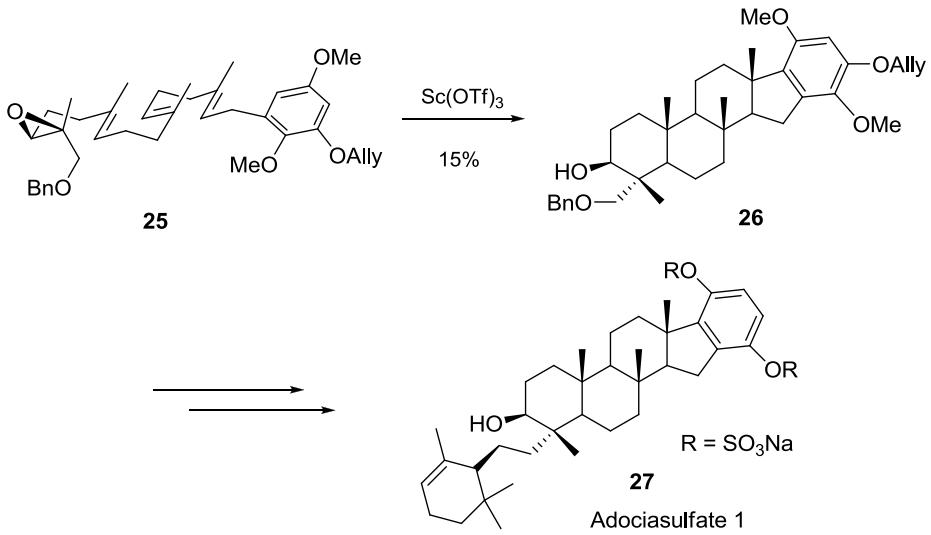
[28] Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem.* **1999**, *64*, 9587.

role in the cascade process because it not only enhanced the cyclization but also controlled the regioselectivity to give exclusively the six-membered C ring.



Scheme 1.11

In 1999, Overman *et al*. designed a non-enzymatic epoxide-initiated polyene tetracyclization to construct a complex pentacycle in the total synthesis of Adociasulfate 1 (Scheme 1.12).[29] This is the first example of using an aryl group to terminate an epoxide-initiated polyene tetracyclization with the formation of five-membered D ring.



Scheme 1.12

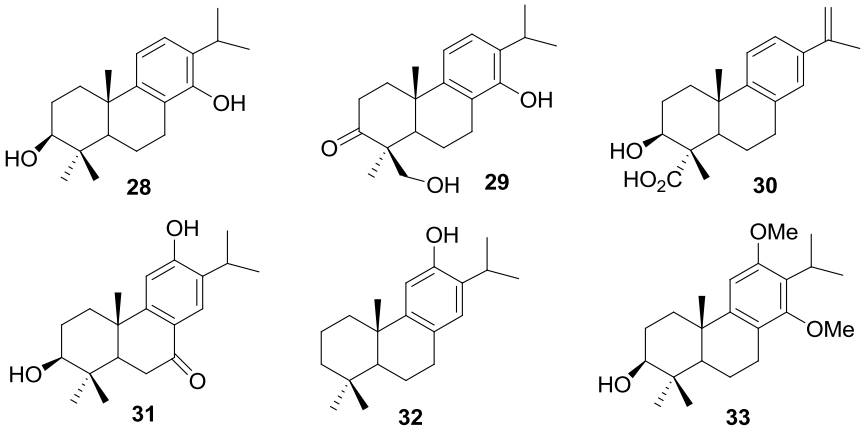
The extraordinary reaction efficiency of enzyme-catalyzed epoxide opening initiated polyene cyclization was demonstrated in Scheme 1.1. Only one out of 128 stereoisomers of lanosterol with seven chiral centers was formed in a single step

[29] Bogenstatter, M.; Limberg, A.; Overman, L. E.; Tomasi, A. L. *J. Am. Chem. Soc*., **1999**, *121*, 12206.

starting from the linear substrate 2,3-oxidosqualene. This highly efficient bio-synthetic achievement can hardly be surpassed by stepwise techniques. Mimicking this natural transformation, Goldsmith, van Tamelen, and Corey, among others, have exploited the acid-promoted cascade cyclization of epoxyolefin as a very useful protocol in the building of polycyclic terpenoids. However, the catalysts typically employed are sensitive to moisture, difficult to handle and the yields are not satisfactorily. In this chapter, we have described a mild, convenient, and simple procedure for investigating the Lewis acid-catalyzed epoxide opening-initiated polyene cyclization with the object of preparing arene terminated 3-hydroxy terpenoids and steroids derivatives.

1.2 RESULTS AND DISCUSSION

According to the literature, there are numerous reports regarding the isolation of and biological data[30] for polycyclic compounds containing a 3-hydroxy group and one terminal aromatic ring but there are only few reported synthetic studies toward these structures (Scheme 1.13).[31] Recently, our group has embarked on Lewis acid-promoted polyene cyclization[32] and the development of indium salts



Scheme 1.13

mediated carbon-carbon bond forming reactions.[33] Previous work demonstrated that indium salts could act as water stable Lewis acid, which made us question whether

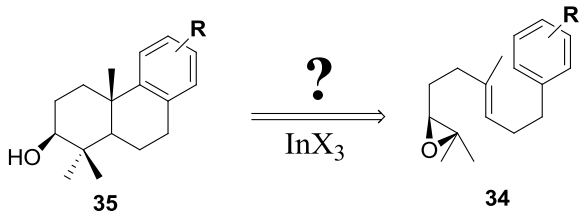
[30] (a) Orihara, Y.; Yang, J.W.; Komiya, N.; Koge, K.; Yoshikawa, T. *Phytochemistry* **2002**, *59*, 385. (b) Ara, I.; Siddiqui, B. S.; Faizi, S.; Siddiqui, S. *J. Nat. Prod.* **1990**, *53*, 816. (c) Takaishi, Y.; Wariishi, N.; Tateishi, H.; Kawazoe, K.; Miyagi, K.; Li, K.; Duan, H. *Phytochemistry* **1997**, *45***,** 979. (d) Fujita, R.; Duan, H.; Takaishi, Y. *Phytochemistry* **2000**, *53*, 715. (e) Antioxidant: Haragushi, H.; Ishikawa, H.; Kubo, I. *Planta Med.* **1997**, *63*, 213. (f) Cathartic and emetic: Appendino, G.; Belloro, E.; Tron, G. C.; Jakupovic, J.; Ballero, M. *Fitoterapia* **2000**, *71*, 134.

[31] (a) Rosales, V.; Zambrano, J.; Demuth, M. *Eur. J. Org. Chem.* **2004**, 1798. (b) Ralph, M.; peter, R. *Helv. Chim. Acta*, **2003**, *86*, 439. (c) Lavallee, J. F.; Doyle, T. W.; Rioux, E.; Belec, L.; Rabouin, D.; Billot, X. U. S. Pat., 2005032802, **2005**.

[32] (a) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc*., **2007**, *129*, 492. (b) Zhao, Y. J.; Loh, T. P. *J. Am. Chem. Soc*., **2008**, *130*, 10024. (c) Zhao, Y. J.; Loh, T. P. *Chem. Commun*. **2008**, 1434.

[33] (a) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739. (b) Lu, J.; Hong, M. L.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 1010; (c) Lu, J.; Hong, M. L.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Chem. Commun.* **2005**, 4217; (d) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 2345; (e) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Organic Lett.* **2005**, *7*, 159; (f) Fu, F.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 4267. (g) Loh, T. P.; Chen, S. L. *Organic Lett.* **2002**, *4*, 3647. (h) Teo, Y. C.; Loh, T. P. *Organic Lett.* **2005**, *7*, 2539. (i) Loh, T. P.; Wei, L. L.; Feng, L. C. *Synlett*, **1999**, 1059. (j) Loh, T. P.; Wei, L. L. *Synlett*, **1998**, 975.

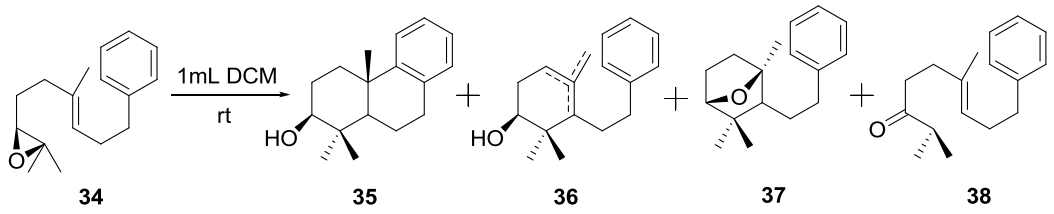
indium salts, the water-stable Lewis acid can be used in the Lewis acid-catalyzed epoxide opening- initiated polyene cyclization (Scheme 1.14).



Scheme 1.14

We were gratified to find that, with the exception of InF_3, indium salts do indeed promote the fast epoxyolefin cyclization in high yields and with good

Table 1. Indium salt induced epoxy olefin cyclization[a]



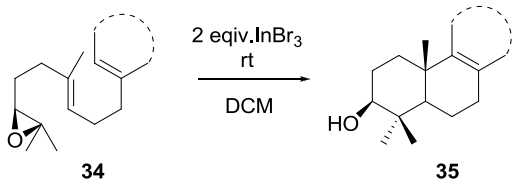
			% Yield[b]			
Entry	Solvent	Catalyst	45	46	47	48
1	CH_2Cl_2	InF_3/0.2 equiv	trace	trace	trace	trace
2	CH_2Cl_2	$InCl_3$/0.2 equiv	45	8	12	4
3	CH_2Cl_2	$InBr_3$/0.2 equiv	50	11	17	8
4	CH_2Cl_2	InI_3/0.2 equiv	35	8	9	14
5	CH_2Cl_2	$In(OTf)_3$/0.2 equiv	28	27	8	12
6	CH_2Cl_2	$InBr_3$/0.5 equiv	54	11	18	9
7	**CH_2Cl_2**	**$InBr_3$/2 equiv**	**57**	**10**	**18**	**trace**
8	CH_3NO_2	$InBr_3$/2 equiv	54	9	17	8
9	Toluene	$InBr_3$/2 equiv	40	7	20	trace
10	CH_3CN	$InBr_3$/2 equiv	trace	12	trace	trace
11	$CHCl_3$	$InBr_3$/2 equiv	52	11	21	5
12	Et_2O	$InBr_3$/2 equiv	trace	12	trace	14

[a] All reactions were performed with **34** (0.1 mmol), and Lewis acid in 1 mL solvent at room temperature for 1h. [b] Isolated yield.

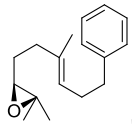
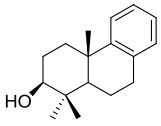
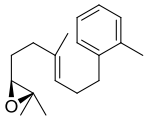
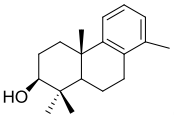
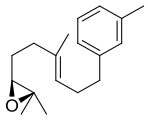
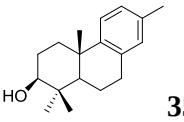
selectivities. As shown in Table 1, with the concentration of 0.1 M in DCM, the epoxyolefin cyclization proceeded smoothly at ambient temperature and in open air, going to completion within 1Hour. In terms of yield and selectivity of the tricyclic product, $InBr_3$ is the most promising Lewis acid. Even 0.2 equiv of $InBr_3$ is enough to give combined yield up to 86% with moderate selectivity for the tricyclic product (Table 1, entry 3). The yield and selectivity can be further increased when more $InBr_3$ was used. To get more tricyclic products we used 2 equiv of $InBr_3$ instead of 0.2 equiv (Table 1, entry 7).

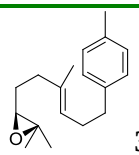
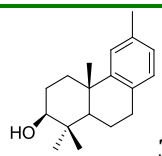
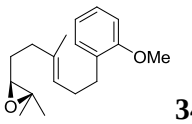
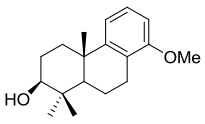
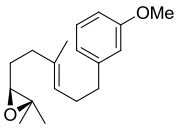
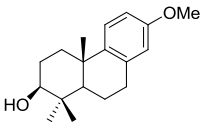
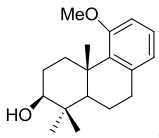
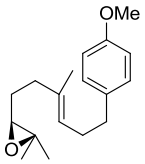
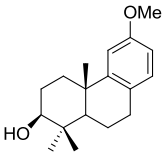
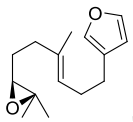
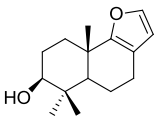
Encouraged by the remarkable results obtained using the above reaction conditions, and in order to show the generality and scope of this new protocol, we explored the reaction with various substituted aromatic terminators. The results are

Table 2. Indium tribromide induced epoxy olefin cyclization for tricyclic compounds[a]



34 **35**

Entry	Epoxy olefin	Product	Yield (%)[b]
1	 **34a**	 **35a**	57% (40)[c]
2	 **34b**	 **35b**	54%
3	 **34c**	 **35c**	51% (30)[c]

4	 **34d**	 **35d**	51%
5	 **34e**	 **35e**	33%
6[d]	 **34f**	 **35fa**  **35fb**	37% 40%
7	 **34g**	 **35g**	58% (31)[c]
8[e]	 **34h**	 **35h**	57%

[a] All reactions were performed with **34** (0.1 mmol), and 2 equiv of $InBr_3$ in 1 mL solvent at room temperature for 1H unless otherwise stated. [b] Isolated yield. [c] Reactions were carried out with **34** (0.1 mmol) in 1mL DCM/H_2O (10:1) in the presence of 4 equiv of $InBr_3$. [d] The combined yield of **35 ea** and **35 eb** and the ratio of **35 ea : 35 eb** is 37 : 40. [e] 0.2 equiv of $InBr_3$ was used.

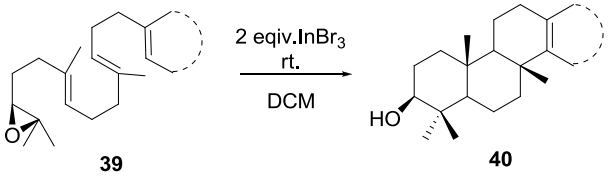
summarized in Table 2. In all cases, the tricyclic products were obtained in good yields up to 58%, with yield per ring of up to 76%. According to Yamamoto's strategy, the monocyclic alkene can be further converted to the tricyclic products.[34] When the 3-methoxybenzene was used as the terminator, two kinds of tricyclic products were obtained in a combined yield of 77% (Table 2, entry 6). However, only one tricyclic product was formed when the 3-methyoxy moiety was replaced by a 3-methyl group (Table 2, entry 3). This may be due to strong steric hindrance between the 3-methyl

[34] (a) Ishihara, K.; Ishibashi, H.; Yamamoto, H. *J. Am. Chem. Soc*. **2002**, *124*, 3647. (b) Ishibashi, H.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc*. **2004**, *126*, 11122.

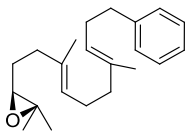
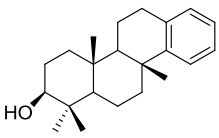
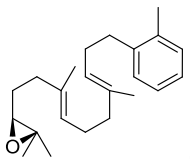
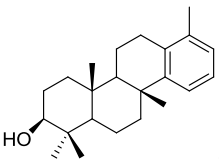
and the angular methyl, prohibiting one of the two cyclization pathways. 3-Methoxy group is more flexible than the 3-methyl group so both cyclization pathways become possible.

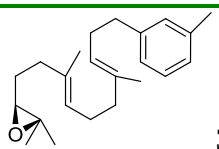
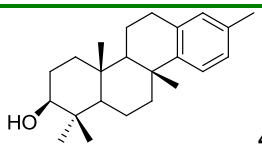
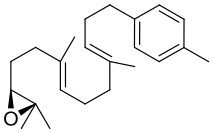
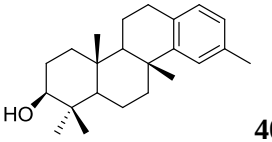
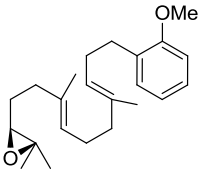
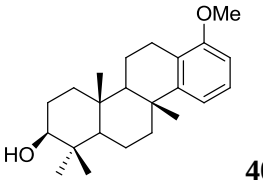
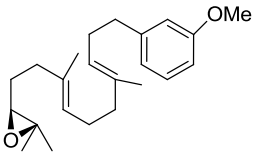
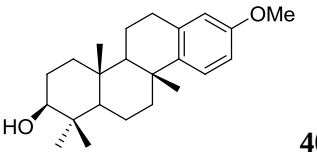
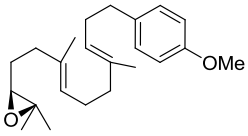
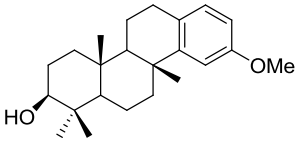
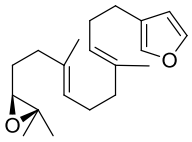
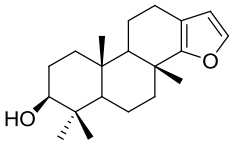
To demonstrate the applicability and versatility of this synthetic strategy, we further extended this method to the preparation of tetracyclic compounds. The results are summarized in Table 3. As expected, the yields were lowered as compared to those of tricyclic compounds due to the formation of many more side-products. Even though the indium tribromide catalyzed-epoxyolefin cyclization still gave the tetracyclic products in just one step with yields up to 35%, per ring up to 70%, unlike for tricyclic products, only one tetracyclized product was isolated when 3-methoxy benzene was employed as the terminator (Table 2, entry 6).

Table 3. Indium tribromide induced epoxy olefin cyclization for preparation of tetracyclic compounds[a]



39 **40**

Entry	Epoxy olefin	Product	Yield (%)[b]
1	 **39a**	 **40a**	35 (15)[c]
2	 **39b**	 **40b**	31

3	 **39c**	 **40c**	31
4	 **39d**	 **40d**	28
5	 **39e**	 **40e**	27
6	 **39f**	 **40f**	30
7	 **39g**	 **40g**	27
8[d]	 **39h**	 **40h**	37

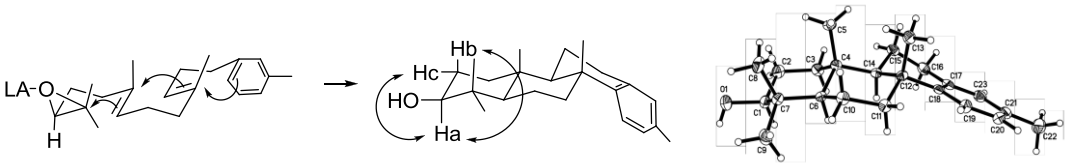
[a] All reactions were performed with **39** (0.1 mmol), and 2 equiv of $InBr_3$ in 1 mL solvent at room temperature for 1H unless otherwise stated. [b] Isolated yield. [c] Reactions were carried out with **39** (0.1 mmol) in 1ml DCM/H_2O (10:1) in the presence of 4 equiv of $InBr_3$. [d] 0.2 equiv of $InBr_3$ was used.

Furan-terminated polycyclic compounds have been used as important intermediate in the synthesis of terpenes because furan acts as a shielded 1,4-dicarbonyl functional group.[35] Both in tri- and tetra- cyclizations, furyl terminators are more reactive than their phenyl counterparts as the furyl group is more electron rich. In the presence of 0.2 equiv of indium tribromide, furan terminated epoxy olefin cyclization proceeded

[35] (a) Tanis, S. P.; Herrinton, P. M. *J. Org. Chem.*, **1983**, *48*, 4572. (b) Tanis, S. P. *J. Org. Chem.*, **1988**, *53*, 4929.

smoothly to give tri- and tetracyclic products in 52% and 37% yield, respectively (Table 2, entry 8 and Table 3, entry 8).

To mimic the mild reaction conditions in the biosynthesis of steroids and terpenoids, we tested this cyclization in aqueous media with water-tolerant Lewis acid indium tribromide as the catalyst. To our delight, the cyclization went well in aqueous media albeit in decreased yields (Table 2, entries 1, 3, 7 and Table 3, entry 1).



Scheme 1.15

According to Stork-Eschenmoser's hypothesis,[9,10] the pre-organized *chair-chair-chair* conformation is important for the diastereoselectivity. Lewis acid-promoted epoxide opening-initiated cascade anti-parallel addition of olefins furnished the *trans*, *trans*-tetracyclized products with excellent regio- and diastereoselectivity. Five chiral centers are created in a single operational step and only two out of 32 isomers are formed (Scheme 1.17). The relative stereochemical configurations of the products were determined by X-ray analysis as well as detailed 1D and 2D NMR. The stereochemistry of the 3-OH group (*β*-face) was further assigned from the coupling constant between 3-CH_a and 2-$CH_{2\ (b,\ c)}$ (^3J-H_{axial}-H_{axial} ≈ 11Hz, ^3J-H_{axial}-$H_{equatorial}$ ≈ 5 Hz). The physical and spectroscopic properties of **35a**, **35g**, **35h** and **35a** obtained in our conversion, were identical with those reported previously.[40a, 44]

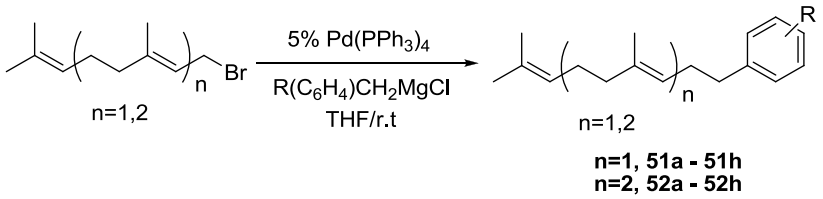
1.3 CONCLUSION

In conclusion, we reported the first $InBr_3$-catalyzed, epoxide opening-initiated and arene-terminated polyene cyclization. This procedure offers several advantages including mild conditions and good yields, which make it a useful and attractive strategy for the synthesis of steroids derivatives. In addition, this reaction can be carried out in aqueous environment which makes strict anhydrous conditions not necessary. Our group is now attempting to perform this reaction in water and apply it in the total synthesis of natural products.[36]

[36] Very recently, this methodology had been employed in the total synthesis of (+)-Totarol and related Totarane diterpenes by Shaw and coworker. Kim, M. B.; Shaw, J. T. *Organic Lett.* **2010**, *12*, 3324.

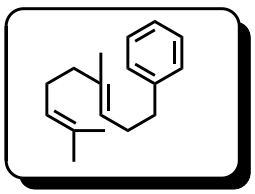
1.4 EXPERIMENTAL SECTION

General procedure for preparation of polyene 41a~41h and 42a~42h



The procedure was following the method developed by Demuth.[37] To an oven-dried 100 mL round-bottom flask with a magnetic stirring bar was added [$(Ph_3P)_4Pd$] (0.25 mmol, 5 mol%) and dry THF (20 mL). The solution was cooled to 0 ^oC prior to addition of allylic bromide (5.0 mmol, 1.0 equiv). The solution was stirred for 5 minutes followed by the addition of Grignard reagent (7.5 mmol in 1.0M THF solution, 1.5 equiv). The reaction mixture was stirred at room temperature for another 24 hours before quenching with ice water (30 mL). The aqueous layer was extracted with diethyl ether (2 × 30 mL), and the combined organic extracts were washed with water (30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by column chromatography to afford the desired product.

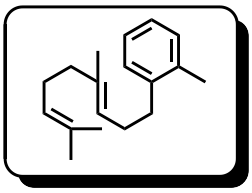
(*E*)-(4,8-Dimethylnona-3,7-dienyl)benzene (**41a**)



Colorless oil, 86% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR(400 MHz, $CDCl_3$): 7.30–7.20 (m, 5H), 5.21 (tq, *J* = 7.1, 1.2 Hz, 1H), 5.11 (tt *J* = 6.8, 1.4 Hz, 1H), 2.66 (t, *J* = 6.7 Hz, 2H), 2.34 (dt, *J* = 7.7, 7.6 Hz, 2H), 2.08 (t, *J* = 7.1, 6.6 Hz, 2H), 2.01 (t, *J* = 7.1Hz, 2H), 1.71(s, 3H), 1.58 (s, 3H), 1.63 (s, 3H); ^{13}C NMR(100 MHz, $CDCl_3$): 142.5, 135.8, 131.4, 128.5, 128.2, 125.7. 124.4, 123.6, 39.8, 36.2, 30.0, 26.7, 25.7, 17.7, 16.0; FTIR (KBr): 3085, 2923, 1653, 1604, 1496, 1453, 1376, 1108, 1030, 836, 746, 698 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{17}H_{24}$ $[M]^+$: 228.1878 Found: 228.1877.

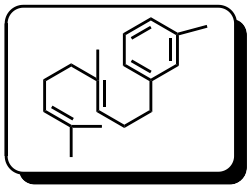
[37] Rosales, V.; Zambrano, J. L.; Demuth, M. *J. Org. Chem.* **2002**, *67*, 1167.

(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-2-methylbenzene (**41b**)



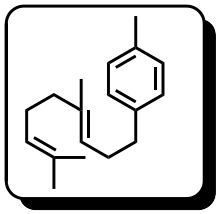
Colorless oil, 68% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.20–7.10 (m, 4H), 5.27 (t, *J* = 6.1Hz, 1H), 5.15 (m, 1H), 2.66 (m, 2H), 2.37 (s, 3H), 2.27–2.31 (m, 2H), 2.15–2.09 (m, 2H), 2.06–2.01 (m, 2H), 1.74 (s, 3H), 1.66 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 140.6, 135.9, 135.8, 131.4, 130.1, 128.9, 125.9, 125.8, 124.4, 123.8, 39.7, 33.4, 28.7, 26.7, 25.7, 19.3, 17.7, 15.9; FTIR (KBr): 2924, 1491, 1449, 1437, 1383, 1320, 741, 698 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}$ $[M]^+$: 242.2035, Found: 242.2022.

(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-3-methylbenzene (**41c**)



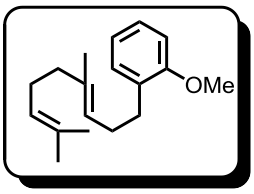
Colorless oil, 63% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.23–7.19 (m, 1H), 7.05–7.03 (m, 3H), 5.24 (tq, *J* = 6.8, 1.2 Hz, 1H), 5.14 (tt, *J* = 7.9, 1.5 Hz, 1H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.37 (s, 3H), 2.37–2.31 (m, 2H), 2.14–2.09 (m, 2H), 2.05–2.01 (m, 2H), 1.74 (s, 3H), 1.65 (s, 3H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 137.7, 135.7, 131.4, 129.3, 128.2, 126.4, 125.5, 124.4, 123.8, 39.8, 36.1, 30.1, 26.8, 25.8, 21.5, 17.7, 16.0; FTIR (KBr): 2922, 1608, 1489, 1448, 1375, 1107, 1093, 781, 698 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}$ $[M]^+$: 242.2035, Found: 242.2028.

(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-4-methylbenzene (**41d**)



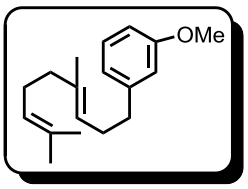
Colorless oil, 61% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.13–7.11 (m, 4H), 5.24 (tq, *J* = 6.1, 1.0 Hz, 1H), 5.16 (tt, *J* = 6.3,1.3 Hz, 1H), 2.65 (t, *J* = 7.4 Hz, 2H), 2.37 (s, 3H), 2.34–2.31 (m, 2H), 2.14–2.07 (m, 2H), 2.05–2.02 (m, 2H), 1.66 (s, 3H), 1.64 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 135.7, 135.1, 131.3, 128.9, 128.4, 124.4, 123.8, 39.8, 35.8, 30.2, 26.8, 25.8, 21.1, 17.7, 16.0; FTIR (KBr): 2965, 2920, 2854, 1514, 1448, 1375, 808 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}$ $[M]^+$: 242.2035, Found: 242.2031.

(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-2-methoxybenzene (**41e**)



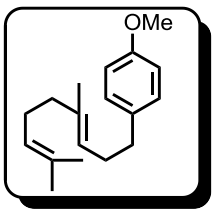
Colorless oil , 65% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (300 MHz, $CDCl_3$): 7.10–7.18 (m, 2H), 6.80–6.88 (m, 2H), 5.22 (m, 1H), 5.10 (m, 1H), 3.80 (s, 3H), 2.66 (m, 2H), 2.20–2.31 (m, 3H), 2.10–1.95 (m, 3H), 1.68 (s, 3H), 1.60 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.5, 135.4, 131.2, 130.8, 129.9, 126.9, 124.5, 124.1, 120.3, 110.1, 55.2, 39.7, 30.6, 28.2, 26.8, 25.7, 17.7, 15.9; FTIR (KBr): 2920, 2833, 1600, 1587, 1493, 1464, 1439, 1242, 1151, 1033, 750 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1983.

(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-3-methoxybenzene (**41f**)



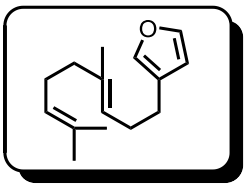
Colorless oil , 63% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.25–7.15 (m, 1H), 6.84–6.77 (m, 3H), 5.23 (tq, *J* = 7.1, 1.2 Hz, 1H), 5.13 (tt, *J* = 6.7, 1.2 Hz, 1H), 3.83 (s, 3H), 2.66 (t, *J* = 7.4 Hz, 2H), 2.37–2.35 (m, 2H), 2.13–2.08 (m, 2H), 2.04–2.00 (m, 2H), 1.72 (s, 3H), 1.64 (s, 3H), 1.60 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 144.1, 135.8, 131.4, 129.2, 124.4, 123.6, 120.9, 114.3, 110.9, 55.1, 39.8, 36.2, 29.9, 26.8, 25.7, 17.7, 16.0; FTIR (KBr): 2916, 2835, 1602, 1583, 1489, 1452, 1437, 1261, 1151, 1045, 777, 694 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1980.

(*E*)-1-(4,8-Dimethylnona-3,7-dienyl)-4-methoxybenzene (**41g**)



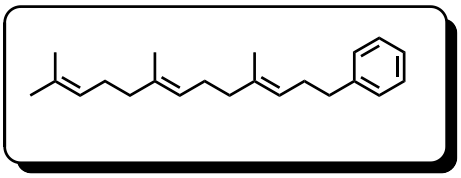
Colorless oil, 65％ yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.14–7.11 (m, 2H), 6.85–6.33 (m, 2H), 5.19 (tq, *J* = 6.9, 0.8 Hz, 1H), 5.11 (tt, *J* = 6.8, 1.3 Hz, 1H), 3.80 (s, 3H), 2.60 (t, *J* = 7.3 Hz, 2H), 2.32-2.26 (m, 2H), 2.11–2.26 (m, 2H), 2.02–2.06 (m, 2H), 1.71 (s, 3H), 1.63 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 135.7, 134.6, 131.3, 129.4, 124.4, 123.7, 113.6, 55.3, 39.8, 35.2, 30.2, 26.7, 25.7, 17.7, 16.0; FTIR (KBr): 2962, 2922, 2833, 1612, 1512, 1454, 1440, 1300, 1246, 1176, 1039, 821 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1975.

(E)-3-(4,8-dimethylnona-3,7-dienyl)furan (**41h**)



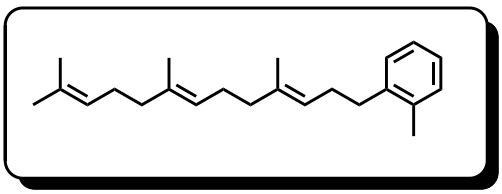
Colorless oil, 65% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (300 MHz, $CDCl_3$): 7.34 (t, *J* = 1.60 Hz, 1H), 7.22 (m, 1H), 6.29 (d, *J* = 0.9 Hz, 1H), 5.17 (td, *J* =7.0, 1.1Hz, 1H), 5.09 (m, 1H), 2.46(t, *J* = 7.6 Hz, 2H), 2.25 (q, *J* = 7.3 Hz, 2H), 1.97 -2.11 (m, 4H), 1.69 (s, 3H), 1.61 (s, 3H), 1.59 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 142.5, 138.8, 135.8, 131.4, 125.0, 124.3, 123.8, 111.1, 39.7, 28.5, 26.7, 25.7, 25.0, 17.7, 16.0; FTIR (KBr): 2964, 2916, 2852, 1500, 1438, 1382, 1163, 1026, 873, 777 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{15}H_{22}O$ $[M]^+$: 218.1671, Found: 218.0437.

(3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (42a)



Colorless oil, 87% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.32–7.25 (m, 2H), 7.22–7.16 (m, 3H), 5.25–5.18 (m, 1H), 5.17–5.08 (m, 2H), 2.66 (t, *J* =7.9 Hz, 2H), 2.32 (q, *J* = 8.4 Hz, 2H), 2.09 (q, *J* = 6.6 Hz, 4H), 2.01 (q, *J* = 3.7 Hz, 4H), 1.71 (s, 3H), 1.62 (s, 6H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 135.8, 135.0, 131.3, 128.5, 128.2, 125.7, 124.4, 124.2, 123.6, 39.8, 39.7, 36.2, 30.0, 26.8, 26.6, 25.7, 17.7, 16.0, 16.0; FTIR (KBr): 2965, 2920, 1495, 1452, 1381, 1029, 746, 698 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{22}H_{32}$ $[M]^+$: 296.2504, Found: 296.2494.

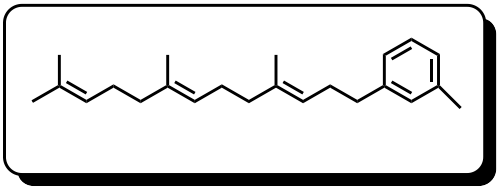
1-methyl-2-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (42b)



Colorless oil, 68% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.22–7.03 (m, 4H), 5.22 (t, *J* = 6.6 Hz, 1H), 5.16–5.04 (m, 2H), 2.60 (dd, *J* = 9.8, 7.4 Hz, 2H), 2.32 (s, 3H), 2.31–2.20 (m, 2H), 2.14–2.02 (m, 4H), 2.02–1.94 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 140.6, 135.9, 135.8, 135.0, 131.3, 130.1, 128.9, 125.9, 125.8, 124.4, 124.2, 123.8, 39.8, 39.8, 33.4, 28.7, 26.8, 26.6, 25.7, 19.3, 17.7, 16.0, 15.9; FTIR (KBr): 2965, 2922, 2857, 1491, 1449, 1383, 1107, 908, 736 cm^{-1}; HRMS

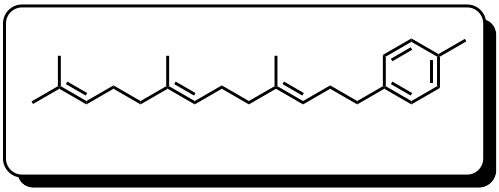
(EI): *m*/*z* calculated for $C_{23}H_{34}$ $[M]^+$: 310.2661, Found: 310.2647.

1-methyl-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (42c)



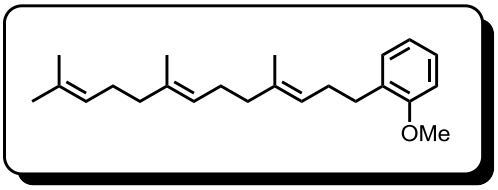
Colorless oil, 66% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.20–7.10 (m, 1H), 7.04–6.90 (m, 3H), 5.19 (td, *J* = 7.1, 1.3 Hz, 1H), 5.15–5.05 (m, 2H), 2.59 (dd, *J* = 9.7, 7.5 Hz, 2H), 2.32 (s, 3H), 2.33–2.23 (m, 2H), 2.13–2.02 (m, 4H), 2.02–1.93 (m, 4H), 1.68 (s, 3H), 1.56 (s, 6H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.4, 137.7, 135.7, 135.0, 131.3, 129.3, 128.1, 126.4, 125.5, 124.4, 124.2, 123.7, 39.8, 39.7, 36.1, 30.1, 26.8, 26.7, 25.7, 21.4, 17.7, 16.0, 16.0; FTIR (KBr): 2965, 2918, 2853, 1608, 1443, 1383, 1094, 1041, 781, 698 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}$ $[M]^+$: 310.2661, Found: 310.2645.

1-methyl-4-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (42d)



Colorless oil, 78% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.12–7.04 (m, 4H), 5.19 (td, *J* = 7.0, 0.9 Hz, 1H), 5.14–5.05 (m, 2H), 2.59 (dd, *J* = 9.6, 7.3 Hz, 2H), 2.31 (s, 3H), 2.32–2.23 (m, 2H), 2.13–2.02 (m, 4H), 2.02–1.92 (m, 4H), 1.68 (s, 3H), 1.60 (s, 6H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 139.4, 135.7, 135.1, 135.0, 129.0, 128.9, 128.3, 124.4, 124.2, 123.8, 39.8, 39.7, 35.7, 30.1, 26.8, 26.6, 25.7, 21.0, 17.7, 16.0, 16.0; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}$ $[M]^+$: 310.2661, Found: 310.2650; FTIR (KBr): 2965, 2920, 2855, 1514, 1448, 1381, 1107, 806 cm^{-1}.

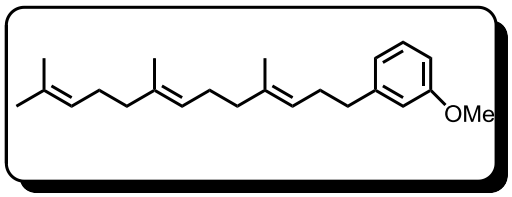
1-methoxy-2-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (42e)



Colorless oil, 66% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (300 MHz, $CDCl_3$): 7.22 – 6.84 (m, 4H), 5.26 (t, *J* = 6.2, Hz, 1H), 5.15–5.08 (m, 2H), 3.85 (s, 3H), 2.66 (dd, *J* = 9.4, 7.4 Hz, 2H), 2.25–2.34 (m, 2H), 2.14–2.02 (m, 8H), 1.71 (s, 3H), 1.63 (s, 6H), 1.60 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.5, 135.5, 134.9, 131.2, 130.8, 129.9, 126.9, 124.5, 124.3, 124.1, 120.3,

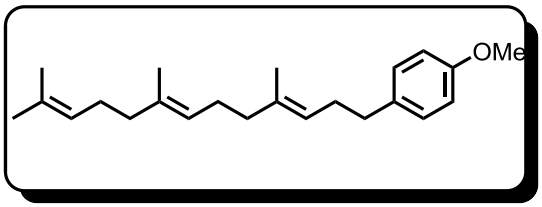
110.1, 55.2, 39.7, 30.6, 28.2, 26.8, 26.7, 25.7, 17.7, 16.2, 16.0, 15.9; FTIR (KBr): 2962, 2919, 2853, 1600, 1587, 1492, 1383, 1242, 1177, 1036, 750 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2596.

1-methoxy-3-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (42f)



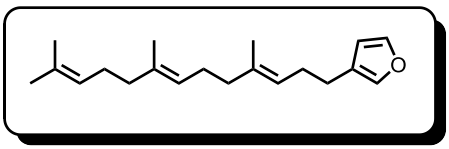
Colorless oil, 67% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (300 MHz, $CDCl_3$): 7.17 (d, *J* = 7.12, 1H), 6.70–6.79 (m, 3H), 5.06 -5.24 (m, 3H), 3.78 (s, 3H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.32–2.23 (m, 2H), 1.96–2.08 (m, 8H), 1.70 (s, 3H), 1.59 (s, 6H), 1.57 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.6, 144.1, 135.8, 134.9, 131.2, 129.1, 124.4, 124.2, 123.6, 120.9, 114.2, 110.9, 55.1, 39.8, 39.7, 36.2, 29.8, 26.9, 26.8, 26.6, 25.7, 17.7, 16.0; FTIR (KBr): 2963, 2919, 2855, 1602, 1585, 1489, 1382, 1261, 1153, 1045, 876, 777 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2594.

1-methoxy-4-((3*E*,7*E*)-4,8,12-trimethyltrideca-3,7,11-trienyl)benzene (42g)



Colorless oil, 60% yield; R_f = 0.91 (Hexane : Et_2O = 9:1); ^1H NMR (400 MHz, $CDCl_3$): 7.14–7.04 (m, 2H), 6.86–6.76 (m, 2H), 5.18 (td, *J* = 6.98, 1.1Hz, 1H), 5.15–5.06 (m, 2H), 3.79 (s, 3H), 2.58 (dd, *J* = 9.3, 7.4 Hz, 2H), 2.32–2.23 (m, 2H), 2.05 (q, *J* = 7.2 Hz, 4H), 2.02–1.94 (m, 4H), 1.69 (s, 3H), 1.60 (s, 6H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 135.7, 135.0, 134.6, 131.3, 129.3, 124.4, 124.2, 123.7, 113.6, 55.2, 39.8, 39.7, 35.2, 30.2, 26.8, 26.6, 25.7, 17.7, 16.0, 16.0; FTIR (KBr): 2963, 2919, 2853, 1612, 1512, 1440, 1382, 1246, 1177, 1040, 823 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2596.

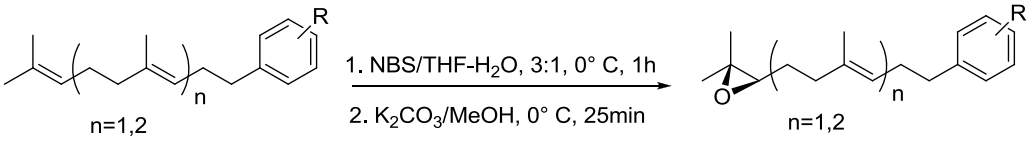
3-((3E,7E)-4,8,12-trimethyltrideca-3,7,11-trienyl)furan (42h)



Colorless oil, 70% yield; ^1H NMR (300 MHz, $CDCl_3$): 7.24 (t, *J* = 1.6 Hz, 1H), 7.21 (br. s, 1H), 6.28 (d, *J* = 0.8 Hz, 1H), 5.18 (td, *J* = 7.0, 1.2 Hz,

1H), 5.11 (m, 2H), 2.46 (t, *J* = 6.9 Hz, 2H), 2.25 (q, *J* = 7.3 Hz, 2H), 1.96 – 2.07 (m, 8 H), 1.69 (s, 3H), 1.61 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$): 142.5, 138.8, 135.8, 135.0, 131.3, 125.0, 124.4, 124.2, 123.7, 111.1, 39.7, 39.6, 28.5, 26.8, 26.6, 25.7, 25.1, 17.7, 16.1, 16.0; FTIR (KBr): 2965, 2918, 2853, 1500, 1440, 1383, 1165, 1064, 1026, 873, 777 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O$ $[M]^+$: 286.2297, Found: 286.2291.

General procedure for preparation of polyene 34a~34h and 39a~39h

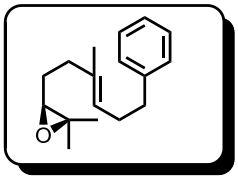


n=1, 41a - 41h
n=2, 42a - 42h

n=1, 34a - 34h
n=2, 39a - 39h

According to the procedure developed by van Tamelen[38], epoxy olefins were easily prepared from polyenes. A total amount of NBS (3.35 mmol) in a THF-H_2O solution (68:32, 20 mL) in freshly prepared 4 mL portions was added dropwise to polyene (2.58 mmol) in a THF-H_2O solution (68:32, 25 mL) over 0.5 h at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and then diluted with $CHCl_3$ (30 mL). The organic solution was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford an oil. Chromatography on silica gel eluting with ethyl acetate-hexanes gave bromohydrin of about 30% yield**.** K_2CO_3 (2.65 mmol) was added to bromohydrin (2.65 mmol) in absolute MeOH (10 mL). The reaction mixture was stirred at room temperature for 30 min, diluted with H_2O, and extracted with CH_2Cl_2. The organic solution was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo* to give an oil. Chromatography on silica gel eluting with ethyl acetate-hexanes gave the epoxy olefin of about 95% yield.

2,2-dimethyl-3-(3-methyl-6-phenylhex-3-enyl)oxirane (34a)

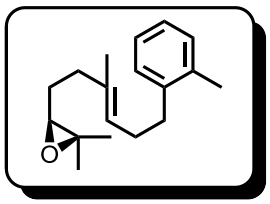


Colorless oil, 28% yield; ^{1}H NMR (300 MHz, $CDCl_3$): 7.17 -7.26 (m, 5H), 5.29 (t, *J* = 7.2 Hz, 1H), 2.67 (m, 3H), 2.31 (m, 2H), 2.02 – 2.20 (m, 2H), 1.62-1.73 (m, 2H), 1.57 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 142.3, 134.9, 128.5, 128.3, 125.7, 124.2,

[38] (a) Tamelen, E. E. van; Curphey, T. J. *Tetrahedron Lett.* **1962**, *3*, 121. (b) Zoretic, P. A.; Fang, H. Q. *J. Org. Chem.*, **1998**, *63*, 7213

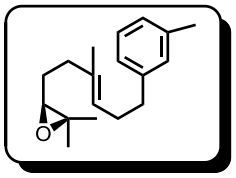
64.1, 58.3, 36.3, 36.1, 29.9, 27.5, 24.9, 18.8, 15.9; FTIR (KBr): 3370, 2959, 2924, 1495, 1452, 1377, 1122, 876, 748, 698 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{17}H_{24}O$ $[M]^+$: 244.1827, Found: 244.1830.

2,2-dimethyl-3-(3-methyl-6-o-tolylhex-3-enyl)oxirane (34b)



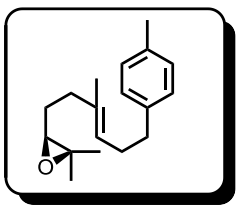
Colorless oil, 27% yield; ^1H NMR (400 MHz, $CDCl_3$): 7.14 (m, 4H), 5.30 (t, *J* = 6.4 Hz, 1H), 2.73 (t, *J* = 6.3 Hz, 1H), 2.65 (dd, *J* = 7.7, 8.2 Hz, 2H), 2.35 (s, 3H), 2.28 (m, 2H), 2.08 – 2.22 (m, 2H), 1.62-1.77 (m, 2H), 1.61 (s, 3H), 1.33 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 140.3, 135.7, 134.7, 130.0, 128.8, 125.8, 125.7, 124.3, 64.1, 58.2, 36.3, 33.3, 28.6, 27.4, 24.8, 19.3, 18.7, 15.9; FTIR (KBr): 3370, 2960, 2926, 1491, 1456, 1377, 1122, 876, 740 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1981.

(E)-2,2-dimethyl-3-(3-methyl-6-m-tolylhex-3-enyl)oxirane (34c)



Colorless oil, 29% yield; ^1H NMR (400 MHz, $CDCl_3$): 7.17 (t, *J* = 7.4 Hz, 1H), 7.00 (m, 3H), 5.24 (t, *J* = 6.9 Hz, 1H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.61 (dd, *J* = 7.7, 8.2 Hz, 2H), 2.34 (s, 3H), 2.29 (m, 2H), 2.05 – 2.22 (m, 2H), 1.62-1.72 (m, 2H), 1.59 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.2, 137.7, 134.7, 129.2, 128.1, 126.4, 125.4, 124.3, 64.2, 58.3, 36.0, 30.0, 27.5, 24.9, 21.4, 18.7, 16.0; FTIR (KBr): 3406, 2960, 2922, 1608, 1485, 1450, 1377,1248, 1122, 876, 783, 700 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1981.

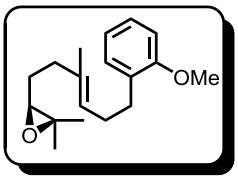
2,2-dimethyl-3-(3-methyl-6-p-tolylhex-3-enyl)oxirane (34d)



Colorless oil, 28% yield; ^1H NMR (400 MHz, $CDCl_3$): 7.09 (m, 4H), 5.24 (t, *J* = 7.1Hz, 1H), 2.69 (t, *J* = 6.1Hz, 1H), 2.61 (dd, *J* = 7.3, 8.3 Hz, 2H), 2.32 (s, 3H), 2.28 (m, 2H), 2.04 – 2.20 (m, 2H), 1.62-1.73 (m, 2H), 1.59 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 139.1, 135.1, 134.7, 128.8, 128.3, 124.3, 64.1, 58.3, 36.3, 35.6, 30.0, 27.4, 24.8, 20.9, 18.7, 15.9; FTIR (KBr): 3368, 2958, 2956, 1514, 1449, 1437, 1377, 1120, 876, 806 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$:

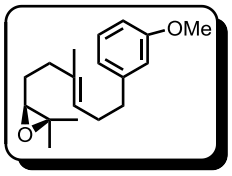
258.1984, Found: 258.1977.

3-(6-(2-methoxyphenyl)-3-methylhex-3-enyl)-2,2-dimethyloxirane (34e)



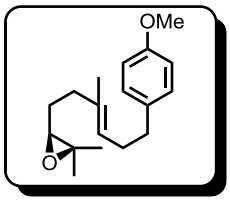
Colorless oil, 28% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.15 (m, 2H), 6.87 (m, 2H), 5.27 (dd, *J* = 6.1, 7.2 Hz, 1H), 3.83 (s, 3H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.65 (dd, *J* = 7.5, 8.2 Hz, 2H), 2.29 (m, 2H), 2.08 – 2.22 (m, 2H), 1.60-1.73 (m, 2H), 1.59 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.4, 134.5, 130.5, 129.8, 126.9, 124.7, 120.2, 110.1, 64.2, 58.3, 55.2, 36.3, 30.5, 28.2, 27.4, 24.9, 18.7, 15.9; FTIR (KBr): 3405, 2958, 2922, 1600, 1587, 1492, 1462, 1439, 1377, 1242, 1031, 874, 752 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^+$: 274.1933, Found: 274.1930.

3-(6-(3-methoxyphenyl)-3-methylhex-3-enyl)-2,2-dimethyloxirane (34f)



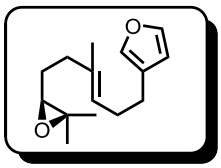
Colorless oil, 28% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.19 (td, *J* = 7.4, 0.9 Hz, 1H), 6.76 (m, 3H), 5.23 (td, *J* = 7.0, 1.0 Hz, 1H), 3.79 (s, 3H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.62 (dd, *J* = 7.3, 8.1Hz, 2H), 2.30 (m, 2H), 2.04 – 2.20 (m, 2H), 1.60-1.73 (m, 2H), 1.59 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 143.9, 134.9, 129.2, 124.2, 120.9, 114.2, 110.9, 64.1, 58.3, 55.1, 36.3, 36.1, 29.8, 27.4, 24.9, 18.7, 15.9; FTIR (KBr): 3387, 2958, 2922, 1600, 1584, 1487, 1454, 1437, 1377, 1261, 1151, 874, 779, 696 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^+$: 274.1933, Found: 274.1919.

(E)-3-(6-(4-methoxyphenyl)-3-methylhex-3-enyl)-2,2-dimethyloxirane (34g)



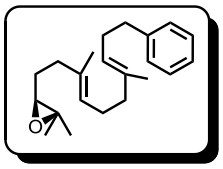
Colorless oil, 28% yield; ^{1}H NMR (300 MHz, $CDCl_3$): 7.10 (d, *J* = 8.6Hz, 2H), 6.82 (d, *J* = 8.6Hz, 2H), 5.22 (t, *J* = 6.9 Hz, 1H), 3.78 (s, 3H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.62 (dd, *J* = 7.3, 7.9 Hz, 2H), 2.28 (q, *J* = 7.6 Hz, 2H), 2.04 – 2.20 (m, 2H), 1.60-1.73 (m, 2H), 1.57 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 157.7, 134.8, 134.4, 131.6, 129.3, 124.3, 113.7, 113.0, 64.2, 58.3, 55.2, 36.3, 35.1, 30.2, 27.4, 24.9, 18.7, 15.9; FTIR (KBr): 3340, 2959, 2924, 1612, 1512, 1454, 1443, 1377, 1246, 1176, 1037, 823 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^+$: 274.1933, Found: 274.1870.

3-(6-(3,3-dimethyloxiran-2-yl)-4-methylhex-3-enyl)furan (34h)



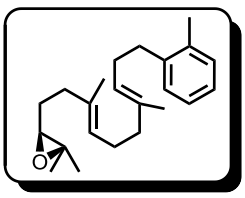
Colorless oil, 29% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.32 (s, 1H), 7.19 (s, 1H), 6.26 (s, 1H), 5.20 (dd, *J* = 6.9, 5.9 Hz, 1H), 2.68 (t, *J* = 6.1Hz, 1H), 2.45 (dd, *J* = 7.1, 8.1Hz, 2H), 2.26 (m, 2H), 2.04 – 2.20 (m, 2H), 1.58-1.73 (m, 2H), 1.59 (s, 3H), 1.28 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.5, 138.8, 134.8, 124.8, 124.3, 110.9, 64.0, 58.3, 36.3, 28.4, 27.3, 24.9, 24.8, 18.7, 16.0; FTIR (KBr): 3404, 2960, 2920, 1500, 1444, 1379, 1163, 1122, 1024, 874, 779 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{15}H_{22}O_2$ $[M]^+$: 234.1620, Found: 234.1613.

3-((3E,7E)-3,7-dimethyl-10-phenyldeca-3,7-dienyl)-2,2-dimethyloxirane (39a)



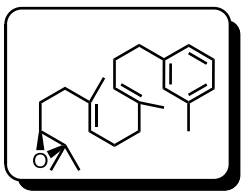
Colorless oil, 37% yield; ^{1}H NMR (300 MHz, $CDCl_3$): 7.14 -7.29 (m, 5H), 7.00 (m, 3H), 5.18 (m, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.64 (dd, *J* = 7.4, 8.2 Hz, 2H), 2.29 (q, *J* = 7.6 Hz, 2H), 1.96 – 2.20 (m, 6H), 1.59-1.70 (m, 5H), 1.55 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 142.3, 135.6, 134.0, 128.5, 128.2, 125.6, 124.8, 123.7, 64.2, 58.3, 39.6, 36.3, 36.1, 30.0, 27.5, 26.6, 24.9, 18.8, 16.0, 15.9; FTIR (KBr): 3404, 2959, 2922, 2855, 1495, 1452, 1377, 1122, 1030, 876, 748, 698 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{22}H_{32}O$ $[M]^+$: 312.2453, Found: 312.1124.

(3,7-dimethyl-10-tolydeca-3,7-dienyl)-2,2-dimethyloxirane (39b)



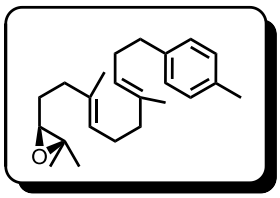
Colorless oil, 38% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.10 (m, 4H), 5.21 (t, *J* = 6.1Hz, 1H), 5.16 (t, *J* = 6.1Hz, 1H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.60 (dd, *J* = 7.7, 8.2 Hz, 2H), 2.3 (s, 3H), 2.24 (q, *J* = 8.0 Hz, 2H), 1.96 – 2.16 (m, 6H), 1.59-1.70 (m, 5H), 1.56 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 140.5, 135.9, 135.6, 134.1, 130.1, 128.9, 125.9, 125.8, 124.9, 123.9, 64.2, 58.3, 39.7, 36.4, 33.5, 28.8, 27.5, 26.7, 24.9, 19.4, 18.8, 16.1, 16.0; FTIR (KBr): 2960, 2924, 2862, 1491, 1454, 1377, 1122, 910, 874, 738 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2616.

(3,7-dimethyl-10-*m*-tolydeca-3,7-dienyl)-2,2-dimethyloxirane (39c)



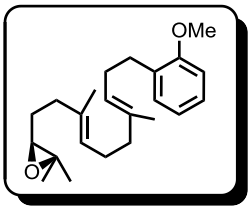
Colorless oil, 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (t, *J* = 7.23 Hz, 1H), 7.00 (m, 3H), 5.18 (m, 2H), 2.69 (t, *J* = 6.4 Hz, 1H), 2.60 (dd, *J* = 7.7, 8.2 Hz, 2H), 2.34 (s, 3H), 2.29 (q, *J* = 7.6 Hz, 2H), 1.96 – 2.20 (m, 6H), 1.59-1.70 (m, 5H), 1.58 (s, 3H), 1.31 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.3, 137.7, 135.5, 134.0, 129.3, 128.1, 126.4, 125.4, 124.8, 123.8, 64.2, 58.3, 39.6, 36.3, 36.1, 30.0, 27.5, 26.6, 24.9, 21.4, 18.8, 16.0, 15.9; FTIR (KBr): 2958, 2922, 2855, 1608, 1487, 1449, 1377, 1248, 1122, 876, 781, 700 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2611.

(3,7-dimethyl-10-*p*-tolydeca-3,7-dienyl)-2,2-dimethyloxirane (39d)



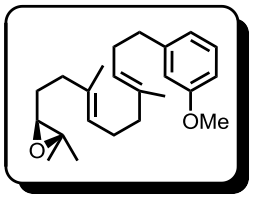
Colorless oil, 37% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.09 (s, 4H), 5.17 (m, 2H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.60 (dd, *J* = 7.3, 8.3 Hz, 2H), 2.32 (s, 3H), 2.28 (q, *J* = 8.0Hz, 2H), 1.97 – 2.16 (m, 6H), 1.59-1.70 (m, 5H), 1.57 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 139.3, 135.5, 135.0, 134.0, 128.9, 128.3, 124.9, 123.8, 64.2, 58.3, 39.6, 36.3, 35.7, 30.1, 27.5, 26.6, 24.9, 21.0, 18.7, 16.0; FTIR (KBr): 2959, 2922, 2857, 1514, 1449, 1248, 1121, 873, 808, 681 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2607.

(10-(2-methoxyphenyl)-3,7-dimethyldeca-3,7-dienyl)-2,2-dimethyloxirane (39e)



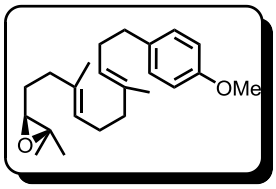
Colorless oil, 34% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.15 (m, 2H), 6.86 (m, 2H), 5.21 (t, *J* = 6.7 Hz, 1H), 5.16 (t, *J* = 6.1Hz, 1H), 3.81 (s, 3H), 2.70 (t, *J* = 6.12 Hz, 1H), 2.63 (dd, *J* = 7.5, 8.2 Hz, 2H), 2.26 (q, *J* = 8.0 Hz, 2H), 1.96 – 2.16 (m, 6H), 1.59-1.70 (m, 5H), 1.56 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.5, 135.3, 134.0, 130.7, 129.9, 126.9, 124.9, 120.3, 110.1, 64.2, 58.3, 55.2, 39.7, 36.3, 30.6, 28.2, 27.5, 26.7, 24.9, 18.8, 16.0, 15.9; FTIR (KBr): 2959, 2922, 2855, 1600, 1492, 1456, 1439, 1377, 1242, 1113, 1034, 752 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, Found: 342.2562.

(10-(3-methoxyphenyl)-3,7-dimethyldeca-3,7-dienyl)-2,2-dimethyloxirane (39f)



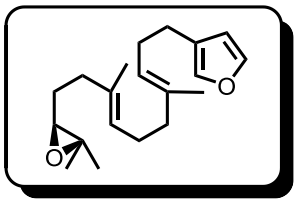
Colorless oil, 37% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.18 (t, *J* = 7.7 Hz, 1H), 6.75 (m, 3H), 5.16 (m, 2H), 3.78 (s, 3H), 2.69 (t, *J* = 6.3 Hz, 1H), 2.61 (dd, *J* = 7.5, 8.2 Hz, 2H), 2.29 (q, *J* = 7.5 Hz, 2H), 1.97 – 2.15 (m, 6H), 1.59-1.70 (m, 5H), 1.56 (s, 3H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.5, 143.9, 135.5, 133.9, 129.0, 124.8, 123.6, 120.8, 110.8, 64.1, 58.2, 55.2, 39.5, 36.2, 36.1, 29.8, 27.4, 26.5, 24.8, 18.7, 15.9; FTIR (KBr): 2959, 2922, 2855, 1600, 1584, 1454, 1437, 1377, 1261, 1053, 910, 732, 696 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, Found: 342.2566.

(10-(4-methoxyphenyl)-3,7-dimethyldeca-3,7-dienyl)-2,2-dimethyloxirane (39g)



Colorless oil, 35% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.10 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 5.17 (m, 2H), 3.79 (s, 3H), 2.71 (t, *J* = 6.3 Hz, 1H), 2.58 (dd, *J* = 7.3, 8.2 Hz, 1H), 2.26 (q, *J* = 8.0Hz, 2H), 1.97 – 2.16 (m, 6H), 1.64 (m, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 135.5, 134.5, 134.0, 129.3, 124.9, 123.8, 113.6, 64.2, 58.3, 55.2, 39.6, 36.3, 35.2, 30.2, 27.5, 26.6, 24.9, 18.8, 16.1, 16.0; FTIR (KBr): 2959, 2924, 2853, 1612, 1584, 1512, 1454, 1443, 1377, 1246, 1037, 910, 825, 732 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, Found: 342.2552.

3-((3E,7E)-10-(3,3-dimethyloxiran-2-yl)-4,8-dimethyldeca-3,7-dienyl)furan (39h)

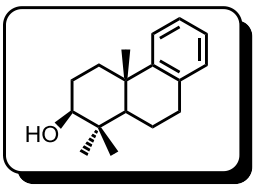


Colorless oil, 37% yield; ^{1}H NMR (400 MHz, $CDCl_3$): 7.33 (br. s, 1H), 7.20 (s, 1H), 6.27 (s, 1H), 5.15 (m, 2H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.44 (dd, *J* = 7.1, 8.2 Hz, 2H), 2.23 (q, *J* = 7.4Hz, 2H), 1.97 – 2.16 (m, 6H), 1.54 – 1.69 (m, 8H), 1.29 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.6, 138.8, 135.6, 134.1, 124.9, 124.8, 123.8, 111.1, 64.2, 58.3, 39.6, 36.3, 28.4, 27.5, 26.5, 25.0, 24.9, 18.7, 16.0, 16.0; Found: 302.2235; FTIR (KBr): 3421, 2961, 2920, 2855, 1500, 1447, 1377, 1248, 1122, 874, 777 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O_2$ $[M]^+$: 302.2246.

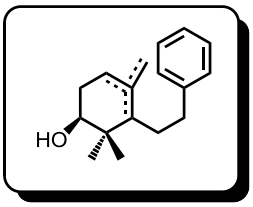
General procedure for the polyenecyclization

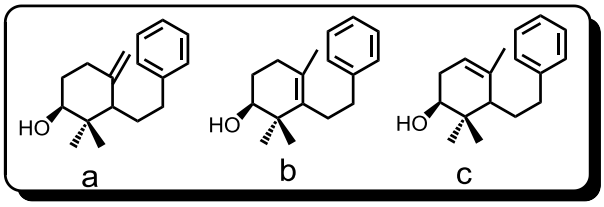
Epoxy olefin (0.1 mmol) was added to dichloromethane (1 mL) and followed by addition of 2 equiv of $InBr_3$. The mixture was stirred at room temperature until the epoxy olefin was completedly disappeared and quenched with saturated $NaHCO_3$ solution (3 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL), and the combined organic extracts were washed with water (5 mL) and brine (10 mL) and dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo*. The residual crude product was purified by column chromatography to afford the desired product.

1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol (35a)



White solid; m.p. 84 – 87 °C; yield: 57%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (d, *J* =7.3 Hz, 1H), 7.04–7.12 (m, 3H), 3.30 (dd, *J* = 11.0, 5.0 Hz, 1H), 2.97 (dd, *J* = 16.9, 6.4 Hz, 1H), 2.86 (ddd, *J* = 16.9, 11.5, 7.3 Hz, 1H), 2.32 (dt, *J* = 13.0, 3.5 Hz, 1H), 1.71-1.89 (m, 4H), 1.57 (br. s, OH), 1.55 (td, *J* = 12.8, 4.6 Hz, 1H), 1.33 (dd, *J* = 12.3, 2.2 Hz, 1H), 1.20 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 149.3, 135.0, 129.0, 125.7, 125.4, 124.5, 126.4, 125.5, 124.4, 78.7, 49.7, 39.0, 37.6, 36.9, 30.7, 28.1, 28.0, 24.9, 18.8, 15.4; FTIR (KBr): 3306, 2970, 2933, 2876, 1487, 1435, 1217, 1092, 1026, 762 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{17}H_{24}O$ $[M]^+$: 244.1827, Found: 244.1819.



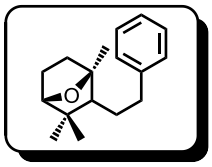


Monocyclic products (36)

Yield: mixture of isomers, isomer ratio: 1 : 1 : 2 based on ^{13}C NMR; ^{1}H NMR (400 MHz, $CDCl_3$): 7.32–7.17 (m, 20H), 5.27 (bs, 2H), 4.95 (s, 1H), 4.72 (s, 1H), 3.54 (dd, *J* = 8.61, 2.48 Hz, 1H), 3.47 (dd, *J* = 8.08, 5.56 Hz, 2H), 3.41 (dd, *J* = 9.61, 4.04 Hz, 1H), 2.88–2.73 (m, 3H), 2.68–2.56 (m, 5H) 2.39 (m, 2H), 2.27 (m, 5H), 2.08 (t, *J* = 6.41Hz, 3H), 1.96 (m, 5H), 1.79 (m, 13H), 1.70 (m, 5H), 1.60 (m, 7H), 1.37 (m, 4H), 1.70 (m, 5H), 1.26 (s, 1H), 1.14 (s, 3H), 1.06 (s, 3H), 1.00 (s, 3H), 0.95 (s, 6H), 0.84 (s, 6H), 0.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 147.2, 143.0, 142.9, 142.7, 136.7,

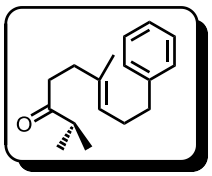
135.2, 128.5, 128.4, 128.4, 128.3, 128.1,126.9, 125.8, 125.7, 118.7, 108.6, 77.2, 76.0, 74.9, 51.2, 48.9, 40.6, 40.2, 38.1, 38.0, 36.5, 34.9, 32.9, 32.2, 31.8, 31.4, 30.8, 29.7, 27.6, 26.7, 26.4, 25.9, 25.3, 22.6, 21.8, 19.7, 16.1, 15.7; FTIR (KBr): 3442 (br. s, OH), 2964, 2935, 1709, 1645, 1602, 1454, 1379, 1363, 1028, 750, 698 cm^{-1}; MS (EI): *m*/*z* calculated for $C_{17}H_{24}O$ $[M]^+$: 244.18, Found: 244.03, 244.05, 244.11.

1,3,3-trimethyl-2-phenethyl-7-oxabicyclo[2.2.1]heptane (37)



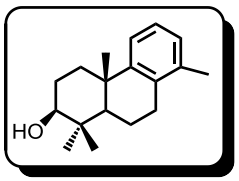
Colorless oil; ^1H NMR (400 MHz, $CDCl_3$): 7.17 – 7.30 (m, 5H), 3.74 (d, *J* = 5.4 Hz, 1H), 2.66 (ddd, *J* = 5.9, 10.6, 13.2 Hz, 1H), 2.55 (ddd, *J* = 6.4, 10.0, 13.6 Hz, 1H), 1.95 (ddd, *J* = 4.8, 8.8, 12.6 Hz, 1H), 1.44-1.75 (m, 5H), 1.38 (s, 3H), 1.30 (dd, *J* = 6.0, 8.5 Hz, 1H), 1.13 (s, 3H), 1.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.8, 128.4, 128.3, 125.8, 86.7, 86.1, 55.5, 45.3, 39.0, 36.2, 30.0, 26.2, 25.8, 23.4, 18.9; FTIR (KBr): 2960, 1728, 1602, 1497, 1454, 1381, 1192, 999, 872, 698 cm^{-1}; MS (EI): *m*/*z* calculated for $C_{17}H_{24}O$ $[M]^+$: 244.18, Found: $[M]^+ + 1$ 245.10.

(E)-2,6-dimethyl-9-phenylnon-6-en-3-one (38)



Colorless oil; ^1H NMR (300 MHz, $CDCl_3$): 7.17 – 7.30 (m, 5H), 5.18 (td, *J* = 6.9, 1.2 Hz, 1H), 2.65 -2.49 (m, 5H), 2.35 -2.19 (m, 4H), 1.55 (s, 3H), 1.10 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 214.5, 142.2, 134.7, 128.5, 128.2, 125.7, 124.1, 40.9, 39.1, 36.0, 33.5, 30.0, 18.3, 16.1; FTIR (KBr): 2968, 2931, 1709, 1613, 1504, 1452, 1383, 1217, 756 cm^{-1}; MS (EI): *m*/*z* calculated for $C_{17}H_{24}O$ $[M]^+$: 244.18, Found: 244.13.

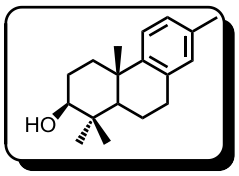
1,1,4a,8-Tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol (35b)



Yield: 54%; ^1H NMR (400 MHz, $CDCl_3$): 7.14 (d, *J* =7.4 Hz, 1H), 7.06 (dd, *J* =7.4, 6.9 Hz, 1H), 6.97 (d, *J* = 6.9 Hz, 1H), 3.30 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.83 (dd, *J* = 16.9, 6.6 Hz, 1H), 2.63 (ddd, *J* = 16.9, 11.5, 7.7 Hz, 1H), 2.33 (dt, *J* = 13.2, 3.4 Hz, 1H), 2.20 (s, 3H), 1.97 (dd, *J* = 13.3, 7.7 Hz, 1H), 1.73-1.83 (m, 3H), 1.53 (m, 1H), 1.40 (br. s, OH), 1.32 (dd, *J* = 12.5, 1.9 Hz, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 149.4, 136.3, 133.6, 127.0, 125.6, 122.2, 78.7, 49.2, 38.9, 37.7, 37.3, 28.5, 28.1, 28.0, 25.0,

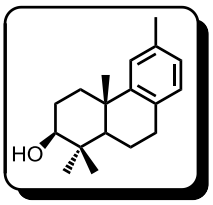
19.9, 18.7, 15.4; FTIR (KBr): 3426, 3007, 2966, 2943, 2868, 1471, 1454, 1375, 1215, 1088, 1034, 756 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1979.

1,1,4a,7-Tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol (35c)



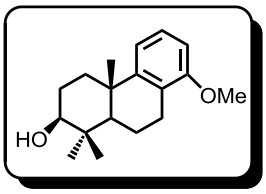
Yield: 51%; ^1H NMR (300 MHz, $CDCl_3$): 7.13 (d, *J* = 8.1Hz, 1H), 6.95 (dd, *J* =8.1Hz, 1H), 6.87 (s, 1H), 3.30 (dd, *J* = 11.0, 4.9 Hz, 1H), 2.76 - 2.97 (m, 2H), 2.31 (dt, *J* = 13.2, 3.2 Hz, 1H), 2.27 (s, 3H), 1.72-1.69 (m, 4H), 1.53 (m, 1H), 1.40 (br. s, OH), 1.32 (dd, *J* = 12.1, 2.3 Hz, 1H), 1.21 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 146.5, 134.9, 134.8, 129.5, 126.6, 124.4, 78.8, 49.9, 39.0, 37.3, 37.0, 30.6, 28.2, 28.0, 24.9, 20.8, 18.8, 15.4; FTIR (KBr): 3342, 2944, 2924, 2862, 1496, 1454, 1375, 1217, 1085, 1030, 813, 756 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1974.

1,1,4a,6-Tetramethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol (35d)



Yield: 51%; white solid; m.p. 86 – 89 °C; ^1H NMR (400 MHz, $CDCl_3$): 7.04 (s, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.90 (dd, *J* = 8.0 Hz, 1H), 3.30 (dd, *J* = 11.0, 4.9 Hz, 1H), 2.77 - 2.96 (m, 2H), 2.32 (dt, *J* = 13.0, 3.6 Hz, 1H), 2.29 (s, 3H), 1.71-1.91 (m, 4H), 1.54 (m, 1H), 1.40 (br. s, OH), 1.32 (dd, *J* = 12.4, 2.4 Hz, 1H), 1.20 (s, 3H), 1.07 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 149.2, 135.0, 131.9, 128.9, 126.3, 125.0, 78.8, 49.9, 39.0, 37.6, 36.9, 30.3, 28.2, 28.0, 24.9, 21.3, 18.9, 15.4; FTIR (KBr): 3400, 2944, 2964, 2943, 2868, 1502, 1454, 1375, 1217, 1089, 1030, 806 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O$ $[M]^+$: 258.1984, Found: 258.1978.

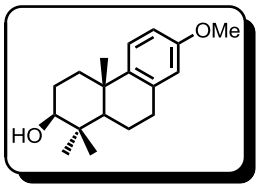
8-methoxy-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol (35e)



Yield: 33%; ^1H NMR (400 MHz, $CDCl_3$): 7.13 (dd, *J* = 7.5, 8.4 Hz, 1H), 6.88 (d, *J* = 7.5, 1H), 6.65 (d, *J* = 8.4 Hz, 1H), 3.80 (s, 3H), 3.30 (dd, *J* = 11.0, 4.7 Hz, 1H), 2.92 (dd, *J* = 17.9, 6.6 Hz, 1H), 2.59 (ddd, *J* = 17.9, 11.5, 7.7 Hz, 1H), 2.31 (dt, *J* = 13.2, 3.4 Hz, 1H), 1.94 (dd, *J*

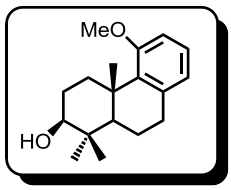
= 13.5, 7.9 Hz, 1H), 1.63-1.85 (m, 3H), 1.53 (m, 1H), 1.40 (br. s, OH), 1.32 (dd, *J* = 12.5, 1.9 Hz, 1H), 1.21 (s, 3H), 1.08 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.0, 150.8, 126.2, 124.1, 116.6, 106.5, 78.8, 55.2, 49.3, 38.9, 37.6, 37.2, 28.2, 28.0, 24.8, 24.7, 18.2, 15.4; FTIR (KBr): 3356, 2960, 2934, 2833, 1581, 1456, 1255, 1215, 1059, 1036, 754 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^+$: 274.1933, Found: 274.1928.

7-methoxy-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol (35fa)



Yield: 37%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.14 (d, *J* = 8.7, 1H), 6.69 (dd, *J* = 8.7, 2.9 Hz, 1H), 6.57 (d, *J* = 2.9 Hz, 1H), 3.75 (s, 3H), 3.30 (dd, *J* = 10.6, 4.0 Hz, 1H), 2.79 - 2.92 (m, 2H), 2.28 (dt, *J* = 13.1, 3.3 Hz, 1H), 1.68 - 1.90 (m, 4H), 1.51 (td, *J* = 13.2, 4.6 Hz, 1H), 1.40 (br. s, OH), 1.30 (dd, *J* = 12.2, 2.3 Hz, 1H), 1.17 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.2, 141.9, 136.4, 125.6, 113.2, 112.0, 78.8, 55.1, 50.0, 38.9, 37.1, 30.9, 28.2, 28.0, 24.8, 24.9, 18.8, 15.4; FTIR (KBr): 3396, 2964, 2941, 2835, 1606, 1573, 1499, 1473, 1242, 1033, 756 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^+$: 274.1933, Found: 274.1913.

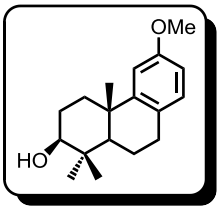
5-methoxy-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol (35fb)



Yield: 40%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.04 (dd, *J* = 7.8, 6.6 Hz, 1H), 6.67 (d, *J* = 6.6, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 3.77 (s, 3H), 3.30 (m, 1H), 3.16 (dt, *J* = 13.7, 3.5 Hz, 1H), 2.86 (m, 2H), 1.79 – 1.83 (m, 1H), 1.79 – 1.83 (m, 1H), 1.55 – 1.62 (m, 1H), 1.40 (br. s, OH), 1.30 (dd, *J* = 12.2, 2.3 Hz, 1H), 1.20 – 1.30 (m, 2H), 1.26 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 158.6, 138.0, 136.7, 126.2, 122.2, 109.1, 78.8, 55.0, 52.7, 39.4, 39.3, 34.6, 33.1, 28.6, 28.3, 19.7, 18.7, 15.9, 15.4; FTIR (KBr): 3426, 2966, 2934, 2868, 1608, 1573, 1454, 1242, 1215, 1032, 756 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^+$: 274.1933, Found: 274.1924.

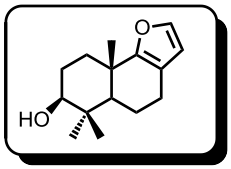
6-methoxy-1,1,4a-Trimethyl-1,2,3,4,4a,9,10,10a-octahydrophenanthren-2β-ol

(35g)



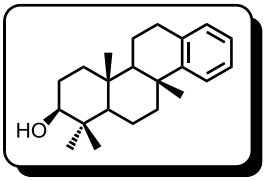
Yield: 58%; ^{1}H NMR (400 MHz, $CDCl_3$): 6.96 (d, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 2.6 Hz, 1H), 6.66 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.76 (s, 3H), 3.30 (dd, *J* = 10.8, 4.6 Hz, 1H), 2.73 - 2.93 (m, 2H), 2.26 (dt, *J* = 13.2, 3.4 Hz, 1H), 1.67 - 1.90 (m, 4H), 1.55 (td, *J* = 13.1, 4.7 Hz, 1H), 1.41 (br. s, OH), 1.30 (dd, *J* = 12.1, 2.1Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 150.6, 129.8, 127.3, 110.9, 110.2, 78.7, 55.3, 49.7, 39.0, 37.8, 36.9, 29.8, 28.2, 28.0, 24.8, 18.9, 15.4; FTIR (KBr): 3439, 2964, 2941, 2835, 1610, 1573, 1505, 1454, 1258, 1039, 806 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{18}H_{26}O_2$ $[M]^+$: 274.1933, Found: 274.1893.

6,6,9a-trimethyl-4,5,5a,6,7,8,9,9a-octahydronaphtho[1,2-b]furan-2β-ol (35h)



Yield: 58%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.18 (d, *J* = 1.8 Hz, 1H), 6.12 (d, *J* = 1.8 Hz, 1H), 3.30 (dd, *J* = 10.8, 4.6 Hz, 1H), 2.51 (m, 1H), 2.36 (m, 1H), 2.14 (dt, *J* = 13.2, 3.5 Hz, 1H), 1.59 - 1.86 (m, 4H), 1.51 (td, *J* = 12.9, 3.5 Hz, 1H), 1.36 (br. s, OH), 1.33 (dd, *J* = 12.1, 1.3 Hz, 1H), 1.19 (s, 3H), 1.06 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.1, 140.3, 113.9, 110.0, 78.9, 51.5, 38.7, 36.2, 33.7, 28.2, 27.5, 22.8, 21.3, 19.4, 15.4; FTIR (KBr): 3326, 2968, 2940, 1505, 1215, 1080, 1016, 756 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{15}H_{22}O_2$ $[M]^+$: 234.1620, Found: 234.1605.

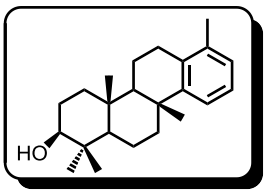
1,1,4a,10b-Tetramethyl-1,2,3,4,4a,5,6,6b,11,12,12a,12b-dodecahydrochrysen-2β-ol (40a)



Yield: 35%; white solid; m.p. 165 – 167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.24 (d, *J* = 8.2 Hz, 1H), 7.12 (td, *J* = 8.2, 1.35 Hz, 1H), 7.06 (td, *J* = 7.6, 1.35 Hz, 1H), 7.01 (d, *J* = 7.6 Hz, 1H), 3.20 (dd, *J* = 11.0, 5.0 Hz, 1H), 2.92 (dd, *J* = 17.1, 5.2 Hz, 1H), 2.82 (ddd, *J* = 17.1, 11.3, 7.1, Hz, 1H), 2.41 (dt, *J* = 12.4, 2.8 Hz, 1H), 1.84 (m, 2H), 1.65 - 1.74 (m, 4H), 1.45 - 1.62 (m, 2H), 1.35 (br. s, OH), 1.25 (dd, *J* = 12.0, 2.0 Hz, 1H), 1.19 (s, 3H), 1.01 (td, *J* = 12.6, 4.8 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H), 0.84 (dd, *J* = 12.1, 2.1Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 150.0, 135.0, 128.8, 125.7, 125.2, 124.6, 78.9,

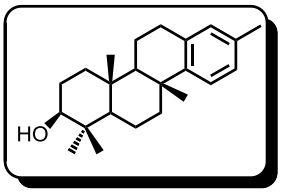
55.12, 55.08, 40.6, 38.8, 38.3, 38.0, 37.4, 30.8, 28.0, 27.3, 26.1, 18.8, 18.1, 16.3, 15.3; FTIR (KBr): 3446, 2992, 2964, 2934, 2868, 1479, 1449, 1028, 669 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{22}H_{32}O$ $[M]^+$: 312.2453, Found: 312.1132.

1,1,4a,7,10b-Pentamethyl-1,2,3,4,4a,5,6,6b,11,12,12a,12b-dodecahydrochrysen-2β-ol (40b):



Yield: 31%; ^1H NMR (400 MHz, $CDCl_3$): 7.15 (d, *J* = 7.3 Hz, 1H), 7.06 (t, *J* = 7.3 Hz, 1H), 6.95 (d, *J* = 7.3 Hz, 1H), 3.20 (dd, *J* = 10.8, 5.2 Hz, 1H), 2.80 (dd, *J* = 17.7, 6.5 Hz, 1H), 2.58 (ddd, *J* = 17.4, 11.5, 7.5 Hz, 1H), 2.42 (dt, *J* = 12.3, 3.2 Hz, 1H), 2.20 (d, *J* = 7.7 Hz, 3H), 1.88 (m, 2H), 1.62 - 1.76 (m, 4H), 1.45 - 1.60 (m, 2H), 1.31 (d, *J* = 5.5 Hz, OH), 1.25 (m, 1H), 1.21 (s, 3H), 1.04 (td, *J* = 11.6, 5.0 Hz, 1H), 0.99 (s, 3H), 0.94 (s, 3H), 0.84 (dd, *J* = 9.6, 2.5 Hz, 1H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 150.1, 136.1, 133.6, 126.8, 125.5, 122.5, 78.9, 55.1, 54.6, 41.0, 38.8, 38.3, 38.1, 37.3, 28.6, 28.0, 27.3, 26.2, 19.9, 18.9, 18.0, 16.3, 15.3; FTIR (KBr): 3300, 2995, 2933, 1471, 1454, 1045, 1006, 756, 667 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2615.

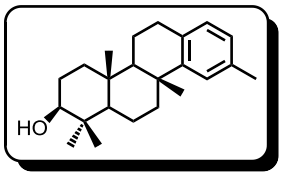
1,1,4a,8,10b-Pentamethyl-1,2,3,4,4a,5,6,6b,11,12,12a,12b-dodecahydrochrysen-2β-ol (40c)



Yield: 31%; ^1H NMR (400 MHz, $CDCl_3$): 7.13 (d, *J* = 8.1Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.84 (s, 1H), 3.20 (dd, *J* = 10.8, 5.2 Hz, 1H), 2.89 (dd, *J* = 16.3, 5.8 Hz, 1H), 2.78 (ddd, *J* = 17.0, 11.4, 7.3 Hz, 1H), 2.39 (dt, *J* = 9.3, 2.9 Hz, 1H), 2.26 (s, 3H), 1.82 (m, 2H), 1.57 - 1.76 (m, 4H), 1.42 - 1.60 (m, 2H), 1.33 (br. s, OH), 1.24 (m, 1H), 1.18 (s, 3H), 1.04 (td, *J* = 11.6, 5.0 Hz, 1H), 0.99 (s, 3H), 0.93 (s, 3H), 0.84 (dd, *J* = 9.6, 2.5 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 147.2, 134.9, 134.6, 129.4, 126.6, 124.6, 78.9, 55.3, 55.2, 40.7, 38.9, 38.3, 37.7, 37.3, 30.7, 28.0, 27.3, 26.1, 20.8, 18.8, 18.1, 16.3, 15.3; FTIR (KBr): 3452, 2988, 2962, 2930, 2868, 1496 1435, 1359, 1215, 756, 669 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.2620.

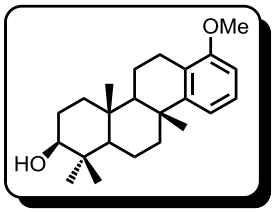
1,1,4a,9,10b-Pentamethyl-1,2,3,4,4a,5,6,6b,11,12,12a,12b-dodecahydrochrysen-2β-

ol (40d)



Yield: 28%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.05 (s, 1H), 6.92 (d, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 7.2 Hz, 1H), 3.20 (dd, *J* = 10.4, 5.4 Hz, 1H), 2.89 (dd, *J* = 16.5, 6.0 Hz, 1H), 2.77 (ddd, *J* = 17.0, 11.4, 7.3 Hz, 1H), 2.41 (dt, *J* = 12.1, 3.0 Hz, 1H), 2.28 (s, 3H), 1.82 (m, 2H), 1.62 - 1.76 (m, 4H), 1.42 - 1.60 (m, 2H), 1.33 (br. s, OH), 1.22 (m, 1H), 1.19 (s, 3H), 1.04 (td, *J* = 11.6, 5.0 Hz, 1H), 0.99 (s, 3H), 0.93 (s, 3H), 0.84 (dd, *J* = 9.6, 2.5 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 149.9, 134.9, 131.9, 128.7, 126.1, 125.1, 78.9, 55.2, 55.15, 40.6, 38.9, 38.3, 37.9, 37.4, 30.4, 28.0, 27.3, 26.0, 21.3, 18.8, 18.2, 16.3, 15.3; FTIR (KBr): 3370, 2961, 2934, 2870, 1500, 1465, 1379, 1215, 1096, 1047, 986, 806, 669 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O$ $[M]^+$: 326.2610, Found: 326.1228.

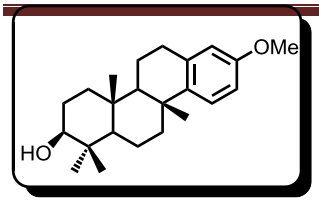
7-methoxy-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydroch rysen-2β-ol (40e)



Yield: 27%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.06 (dd, *J* = 8.3, 7.8 Hz, 1H), 6.90 (d, *J* = 8.3 Hz, 1H), 6.63 (d, *J* = 7.8 Hz, 1H), 3.79 (s, 3H), 3.20 (dd, *J* = 11.1, 5.6 Hz, 1H), 2.90 (dd, *J* = 17.8, 6.1 Hz, 1H), 2.54 (ddd, *J* = 17.8, 11.7, 7.8, Hz, 1H), 2.39 (dt, *J* = 12.5, 3.0 Hz, 1H), 1.85 (m, 2H), 1.62 - 1.74 (m, 4H), 1.45 - 1.60 (m, 2H), 1.35 (br, s, OH), 1.25 (m, 1H), 1.20 (s, 3H), 1.06 (td, *J* = 11.6, 5.0 Hz, 1H), 0.99 (s, 3H), 0.93 (s, 3H), 0.84 (dd, *J* = 9.6, 2.5 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 156.9, 151.5, 126.1, 124.1, 116.8, 106.3, 78.9, 55.2, 55.1, 54.7, 40.8, 38.9, 38.3, 37.9, 37.3, 28.0, 27.3, 25.9, 24.9, 18.9, 17.5, 16.3, 15.3; FTIR (KBr): 3364, 2930, 2868, 1576, 1454, 1367, 1253, 1217, 1089, 1012, 756, 667 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, Found: 342.2560.

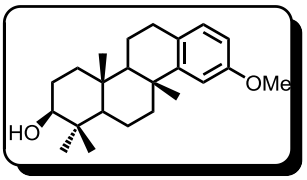
8-methoxy-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydroch rysen-2β-ol (40f)

Yield: 30%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.15 (d, *J* = 8.9 Hz, 1H), 6.70 (dd, *J* =8.9, 2.6 Hz, 1H), 6.55 (d, *J* =2.6 Hz, 1H), 3.76 (s, 3H), 3.20 (dd, *J* = 10.25, 5.4 Hz, 1H),



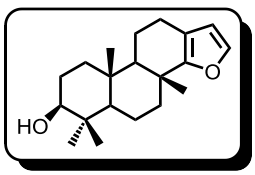
2.89 (dd, *J* = 17.0, 5.8 Hz, 1H), 2.79 (ddd, *J* = 17.8, 11.7, 7.8 Hz, 1H), 2.37 (dt, *J* = 12.5, 3.2 Hz, 1H), 1.85 (m, 2H), 1.62 - 1.74 (m, 4H), 1.45 - 1.60 (m, 2H), 1.32 (br, s, OH), 1.25 (m, 1H), 1.18 (s, 3H), 1.06 (td, *J* = 11.6, 5.0 Hz, 1H), 0.99 (s, 3H), 0.93 (s, 3H), 0.84 (dd, *J* = 9.6, 2.5 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.0, 142.6, 136.3, 125.7, 112.9, 112.0, 78.9, 55.4, 55.2, 55.1, 40.8, 38.9, 38.3, 37.4, 37.3, 31.1, 28.0, 27.3, 26.1, 18.8, 18.1, 16.3, 15.3; FTIR (KBr): 3458, 2930, 2868, 1610, 1499, 1255, 1031, 756 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, Found: 342.2563.

9-methoxy-1,1,4a,10b-tetramethyl-1,2,3,4,4a,4b,5,6,10b,11,12,12a-dodecahydrochrysen-2β-ol (40g)



Yield: 27%; ^{1}H NMR (400 MHz, $CDCl_3$): 6.94 (d, *J* = 8.3 Hz, 1H), 6.79 (d, *J* = 2.3 Hz, 1H), 6.65 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.77 (s, 3H), 3.20 (dd, *J* = 10.5, 4.9 Hz, 1H), 2.87 (dd, *J* = 15.9, 5.5 Hz, 1H), 2.74 (ddd, *J* = 17.8, 11.7, 7.8 Hz, 1H), 2.37 (dt, *J* = 12.1, 3.1Hz, 1H), 1.85 (m, 2H), 1.62 - 1.74 (m, 4H), 1.45 - 1.60 (m, 2H), 1.33 (br, s, OH), 1.25 (m, 1H), 1.20 (s, 3H), 1.07 (td, *J* = 11.6, 5.0 Hz, 1H), 0.99 (s, 3H), 0.93 (s, 3H), 0.84 (dd, *J* = 9.6, 1.9 Hz, 1H), 0.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 157.7, 151.3, 129.6, 127.3, 110.8, 110.3, 78.9, 55.3, 55.1, 40.6, 38.9, 38.3, 38.2, 37.4, 29.9, 28.0, 27.3, 26.0, 18.8, 18.2, 16.3, 15.3; FTIR (KBr): 3287, 2933, 2868, 1610, 1573, 1495, 1250, 1215, 1041, 756 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{23}H_{34}O_2$ $[M]^+$: 342.2559, Found: 342.2556.

3b,6,6,9a-tetramethyl-3b,4,5,5a,6,7,8,9,9a,9b,10,11-dodecahydrophenanthro[1,2-b]furan-2β-ol (40h)



Yield: 37%; ^{1}H NMR (400 MHz, $CDCl_3$): 7.20 (d, *J* = 1.8 Hz, 1H), 6.12 (d, *J* = 1.8 Hz, 1H), 3.30 (dd, *J* = 11.1, 4.9 Hz, 1H), 2.21 - 2.53 (m, 3H), 1.81 (dd, *J* = 13.1, 4.0 Hz, 2H), 1.21 - 1.73 (m, 8 H), 1.13 (m, 1H), 1.35 (br. s, OH), 1.21 (s, 3H), 0.99 (s, 3H), 0.90 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 159.6, 140.1, 113.6, 110.0, 78.8, 56.7, 55.6, 39.0, 38.3, 37.0, 37.0, 36.7, 28.0, 27.2, 25.5, 22.9, 22.4, 18.6, 18.0, 16.5, 15.2; FTIR

(KBr): 3479, 2957, 2928, 2866, 2849, 1504, 1454, 1382, 1215, 1024, 756, 667 cm^{-1}; HRMS (EI): *m*/*z* calculated for $C_{20}H_{30}O_2$ $[M]^+$: 302.2246, Found: 302.2221.

CHAPTER 2

Acid-Catalyzed Intramolecular [2 + 2]-Cycloaddition of Ene-allenones: Facile Access to Bicyclo[n.2.0] Frameworks

2.1 OVERVIEW OF INTRAMOLECULAR [2 + 2]-CYCLO-ADDITION OF ALLENE

The allene group is a popular partner for the [2 + 2] cycloaddition[1] with alkenes and alkynes to afford cyclobutane and cyclobutene fragments, key motifs found in many biologically important natural products such as sterpurene and illudene derivatives.[2] In addition, due to the inherent ring strain, cyclobutanes and cyclobutenes can easily undergo fragmentation and ring-expansion reactions.[3] Many strategies have been developed for transfer of the strained four-membered motif into other complex molecules.[4] Among them, the intramolecular [2 + 2]-cycloaddition reaction between allene moiety and alkene or alkyne stands out as one of the most

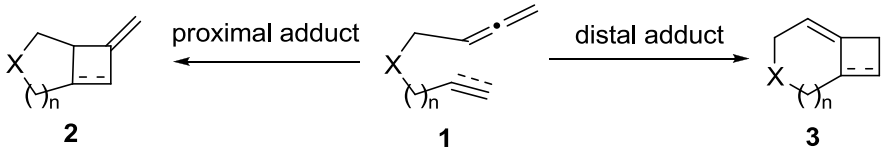
[1] For recent examples of [2+2] cycloaddition: (a) Hayashi, Y.; Nihata, S.; Narasaka, K. *Chem. Lett*. **1990**, 2091. (b) Narasaka, K.; Hayashi, Y.; Shimadzu, H.; Niihata, S. *J. Am. Chem. Soc.* **1992**, *114*, 8869. (c) Trost, B. M.; Yanai, M.; Hoogsteen, K. *J. Am. Chem. Soc*. **1993**, *115*, 5294.(d) Marion, F.; Coulomn, J.; Courillon, C.; Fensterbank, L.; Malacria, M. *Org. Lett.* **2004**, *6*, 1509. (e) Villeneuve, K.; Tam, W. *Angew. Chem. Int. Ed*. **2004**, *43*, 610. (f) Sweis, R. F.; Schramm, M. P.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 7442. (g) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc*. **2005**, *127*, 3668. (h) Canales, E.; Corey, E. J. *J. Am. Chem. Soc.* **2007**, *129*, 12686. (i) Luzung, M. R.; Mauleon, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402. (j) Hiroi, K.; Wantanabe, T.; Tsukui, A. *Chem. Pharm. Bull*. **2000**, *48*, 405. (k) Kurdyumov, A. V.; Hsung, R. P. *J. Am. Chem. Soc.* **2006**, *128*, 6272. (l) Ko, C.; Feltenberger, J. B.; Ghosh, S. K.; Hsung, R. P. *Org. Lett.* **2008**, *10*, 1971.

[2] (a) Semmelhack, M. F.; Tomoda, S.; Hurst, K. M. *J. Am. Chem. Soc.* **1980**, *102*, 7568. (b) Semmelhack, M. F.; Tomoda, S. *J. Am. Chem. Soc.* **1981**, *103*, 2427. (c) Semmelhack, M. F.; Tomoda, S.; Nagaoka, H.; Boettger, S. D.; Hurst, K. M. *J. Am. Chem. Soc.* **1982**, *104*, 745. (d) Gibbs, R. A.; Okamura, W. H. *J. Am. Chem. Soc.* **1988**, *110*, 4062. (e) Gibbs, R. A.; Bartels, K.; Lee, R. W. K.; Okamura, W. H. *J. Am. Chem. Soc.* **1989**, *111*, 3717. (f) Piers, E.; Lu, Y. F. *J. Org. Chem.* **1989**, *54*, 2267. (g) Suginome, H.; Takeda, T.; Itoh, M.; Nakayama, Y.; Kobayashi, K. *J. Chem. Soc. Perkin Trans. 1* **1995**, 49. (h) Crimmins, M. T.; Huang, S.; Guise-Zawacki, L. E. *Tetrahedron Lett.* **1996**, *37*, 6519. (i) Honda, T.; Ueda, K.; Tsubuki, M.; Toya, T.; Kuzorumi, A. *J. Chem. Soc. Perkin Trans. 1* **1991**, 1749.

[3] For a recent review, see: Namyslo, J. C.; Kaufmann, D. *Chem. Rev.* **2003**, *103*, 1485.

[4] (a) Baldwin, J. E. in *Comprehensive Organic Synthesis*, ed. Trost, B. M.; Fleming, I. Pergamon Press, Oxford, **1991**, vol. 5, pp. 63–84. (b) Crimmins, M. T. in *Comprehensive Organic Synthesis*, ed. Trost, B. M.; Fleming, I. Pergamon Press, Oxford, **1991**, vol 5, pp. 123–150. (c) *The Chemistry of Cyclobutanes*, ed. Rappoport, Z.; Liebman, J. F. Wiley, **2005**. (d) *Stereoselective Synthesis, Methods of Organic Chemistry* (Houben-Weyl), ed. Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E. Thieme: Stuttgart, Germany, **1996**, vol. 5, pp. 3061–3125. (e) Lee-Ruff, E.; Mladenova, G. *Chem. Rev.* **2003**, *103*, 1449.

versatile methods that allow the construction of fused systems containing cyclobutane and cyclobutene skeletons in a regio- and stereoselective fashion in one operation.[5] Due to nature of the allene moiety, which contains two cumulated orthogonal π-bonds, [2 + 2]-cycloaddition of allene will offer two regioisomers, the proximal cycloaddtion product **2** and the distal cycloaddition product **3,** by reaction with the internal and external 2π component of the allene moiety **1**, respectively (Scheme 2.1).



Scheme 2.1

According to the Woodward-Hoffmann rules[6] and the Fukui's frontier orbital theory,[7] the [2 + 2]-cycloaddition is photochemically allowed, but thermally forbidden. Thus, the [2 + 2]-cycloaddition of allenes has been investigated photochemically and successfully used in the synthesis of complex natural and unnatural products. However, the thermal [2 + 2]-cycloaddition of allenes, which involves diradical intermediates, generally require high temperature (> 200 °C) and long reaction times. Therefore, a variety of strategies relying on activation of allenes by the use of transition metal as well as Lewis acid catalysts has been developed.

---

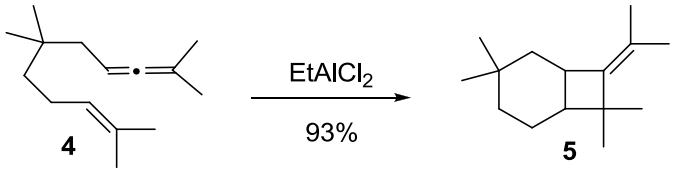
[5] For reviews of [2 + 2]-cycloadditions of allenes, see: (a) Schuster, H. F.; Coppola, G. M. *Allenes in Organic synthesis*, Wiley, New York, **1984**, pp. 286–317. (b) Hopf, H.; Landor, S. R. I. *The Chemistry of Allenes*, Vol. 2, Academic Press, New York, **1982**, pp. 525–562. (c) Ghosez, L.; O'Donnell, M. J.; Marchand, A. P.; Lehr, R. E. *Pericyclic Reactions*, Vol. 2, Academic Press, New York, **1977**, pp. 79–140. (d) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805. (e) Murakami, M.; T. Matsuda, *Modern Allene Chemistry*; Krause, N.; Hashmi, A. S. K. Eds.; Wiley-VCH: Weinheim, **2004**; Vol. 2, pp 727–815. (f) Ma, S. *Chem. Rev.* **2005**, *105*, 2829. (g) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Soc. Rev.* **2010**, *39*, 783.

[6] (a) Hoffmann, R.; Woodward, R. B. *J. Am. Chem. Soc.* **1965**, *87*, 2046. (b) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781. (c) The Conservation of Orbital Symmetry, ed. Woodward, R. B.; Hoffmann, R. Academic Press, New York, **1970.**

[7] Inagaki, S.; Fujimoto, H.; Fukui, K. *J. Am. Chem. Soc.* **1976**, *98*, 4693.

2.1.1 Lewis acid-mediated intramolecular [2 + 2]-cycloaddition reaction

In 1975, Baardman and co-workers reported the first Lewis acid-mediated intermolecular [2 + 2]-cycloaddition between allenes and alkenes.[8] Although their substrate scope is very limited, the Lewis acid-catalyzed thermal [2 + 2]-cycloaddition indeed proceeded to give methylenecyclobutanes in reasonable yields under mild conditions. Later, Hiroi *et al*. demonstrated the intramolecular version of this reaction (Scheme 2.2).[9] By catalysis of the carefully selected Lewis acid, the intramolecular [2 + 2]-cycloaddition product could be isolated as the major product. Their result illustrated that reaction efficiency is strongly related to the acidity of the Lewis acid. Too strong Lewis acidity led to polymerization while weak acidity resulted in the recovery of the starting material. The authors did not mention the mechanism but they did point out that this process involved activation of one of the π-bonds in the allenes by the Lewis acid.

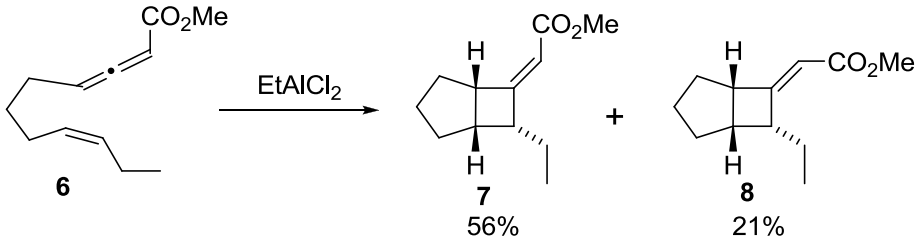


Scheme 2.2

Another Lewis acid-catalyzed intramolecular [2 + 2]-cycloaddition between allene and alkene was developed by Snider[10] and Hoffmann,[11] independently, almost at the same time (Scheme 2.3). Unlike the previous case in which unactivated allene

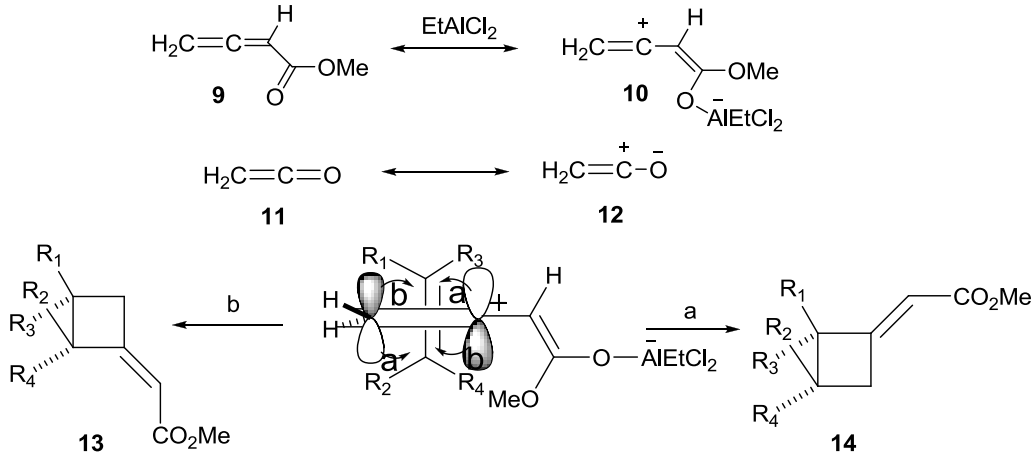
[8] Lukas, J. H.; Kouwenhoven, A. P.; Baardman, F. *Angew. Chem., Int. Ed.* **1975**, *14*, 709.
[9] Hiroi, K.; Watanabe, T.; Tsukui, A. *Chem. Pharm. Bull*. **2000**, *48*, 405.
[10] (a) Snider, B. B.; Spindell, D. K. *J. Org. Chem.* **1980**, *45*, *5017*. (b) Snider, B. B.; Ron, E. *J. Org. Chem.* **1986**, *51*, *3643*.
[11] Hoffmann, H. M. R.; Ismail, Z. M.; Weber, A. *Tetrahedron Lett.* **1981**, *22*, 1953.

was used, both of them used allenic ester as the allene part. Not only the intermolecular but also the intramolecular [2 + 2]-cycloaddition took place smoothly



Scheme 2.3

to afford the fused cyclobutene skeleton with excellent regio- and diastereoselectivities in good yields. The ester group played a key role in the regioselectivity as well as the [2 + 2]-cycloaddition reaction itself. Snider proposed that the Lewis acid complex of methyl 2,3-butadienoate is very similar to a ketene, which undergoes thermal [2 + 2]-



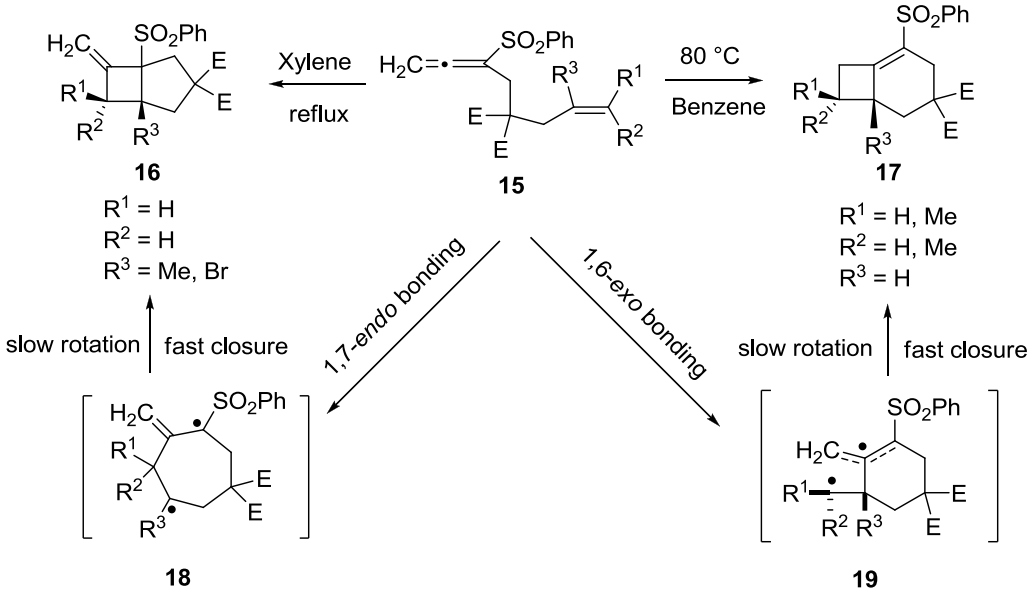
Scheme. 2.4

cycloaddition easily (Scheme 2.4). After systematic studies of the regio- and stereoselectivities of inter- and intramolecular [2 + 2]-cycloaddition of conjugated allenic esters to alkenes, Snider *et al*. suggested that the [$_\pi 2_s$ + $_\pi 2_a$] model for the cycloaddition of ketenes could also be used to rationalize the regio- and stereospecificity of allenic esters.[10b] In the [$_\pi 2_s$ + $_\pi 2_a$] concerted process, the allene part

acts in an antarafacial manner while the alkene part reacts in a suprafacial manner which explain the high stereoselectivities observed in this reaction.

2.1.2 Thermal intramolecular [2 + 2]-cycloaddition reaction

Substitution on the allene not only enhances its reactivity but also governs the regioselectivities. In 1993, Padwa's group described another interesting example showing the dependence of the nature of the substituents attached to the allene as well as alkene moiety in the regioselectivity of the [2 + 2] cycloadduct (Scheme 2.5).[12] The thermal intramolecular [2 + 2] cycloaddition of a series of *α*-tethered allenyl sulfones **15** could take place across the non-activated π-system to afford the distal cycloadducts **17** or give the proximal cycloadducts across the more activated π-system just by choosing different substituents at the 2' position of the alkene moiety (R^3). The

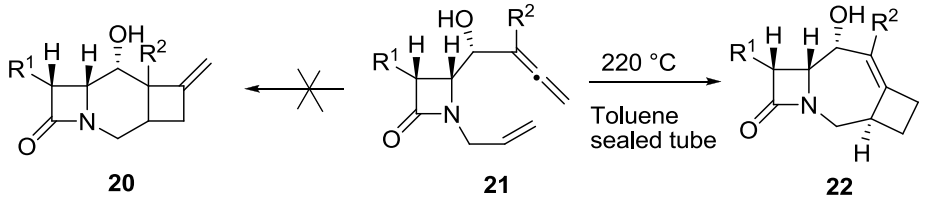


Scheme 2.5

[12] (a) Padwa, A.; Filipkowski, M. A.; Meske, M.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1993**, 115, 3776. (b) Padwa, A.; Meske, M.; Murphree, S. S.; Watterson, S. H.; Ni, Z. *J. Am. Chem. Soc.* **1995**, 117, 7071. (c) Padwa, A.; Lipka, H.; Watterson, S. H.; Murphree, S. S. *J. Org. Chem.* **2003**, 68, 6238.

mechanism of [2 + 2]-cycloaddition reactions involving allenes constitute a topic of much study and debate.[13] It has not been unequivocally established whether the cyclizations are stepwise or concerted in most [2 + 2]-cycloaddition reactions. Here, a stepwise mechanism involving a diradical was proposed to rationalize the regioselectivities in this reaction.

In 2003, Alcaide and Almendros'group employed the thermal intramolecular [2 + 2] cycloaddition of 2-azetidinone-tethered enallenols for the synthesis of racemic and enantiopure strained tricyclic *β*-lactams containing a cyclobutane ring (Scheme 2.6).[14a] When allenenes **21** was treated in toluene at 220 °C in a sealed tube, the



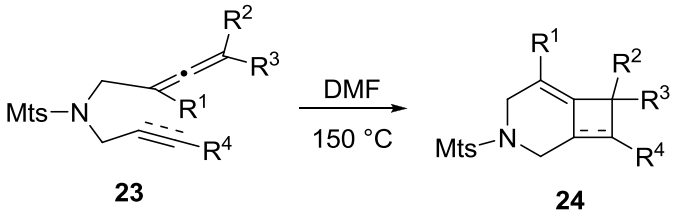
Scheme 2.6

tricyclic compounds **22** were obtained exclusively in a stereospecific manner. The *α*-substituent of allene moiety has no impact on the regioselectivity of this reaction. Interestingly, later the same group found that the regioselectivity could be switched by simple introduction of an internal substituent at the alkene moiety.[16b]

Ohno and Tanaka have presented a stereoselective route to bicyclo-[4,2,0]octane derivatives by using thermal intramolecular [2 + 2] cycloaddition of unactivated allenes with alkenes and alkynes (Scheme 2.9).[15] Allenenes and allenynes

[13] Pasto, D. J.; Sugi, K. D.; Alonso, D. E. *J. Org. Chem.* **1992,** *57,* 1146 and references cited therein.
[14] (a) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Org. Lett.* **2003**, 5, 3795. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C.; Torres, M. R. *Chem.-Eur. J.* **2006**, *12*, 1539.
[15] Ohno, H.; Mizutani, T.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *Angew Chem. Int. Ed.* **2005**, *44*, 5113.

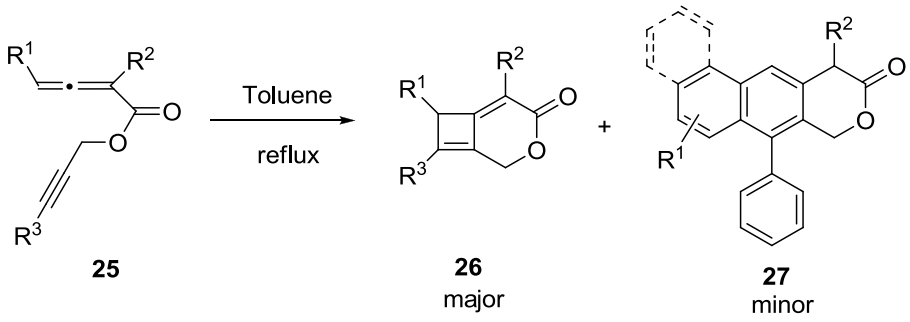
23 that were treated at 150 °C in dimethylformamide (DMF) leding to 3-azabicyclo[4.2.0]oct-5-ene derivatives **24** in high yields with complete regioselectivity and diastereoselectivity. Interestingly, the substitution on the terminal alkyne part is necessary for allenynes to afford the [2 + 2]-cycloaddition products. The author also proposed a stepwise diradical mechanism which is rapid enough to make this reaction proceeds stereospecifically.



23 **24**

Scheme 2.7

More recently, Ma and coworkers have presented a facile access to 3-oxabicylo[4.2.0]-1(8),5-dien-4-ones **26** (Scheme 2.8). [16] The thermal intra-molecular [2 + 2] cycloaddition proceeded smoothly when allenic esters **25** containing a tethered alkyne were refluxed in toluene. They discovered that the substituent R^1 has a big influence on the reaction efficiency.



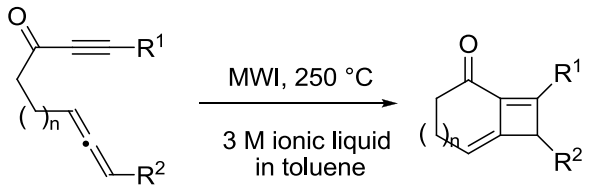
25 **26** major **27** minor

Scheme 2.8

Microwave irradiation (MWI) has been a novel thermal source for many organic

[16] Jiang, X. F.; Ma, S. M. *Tetrahedron* **2007**, *63*, 7589.

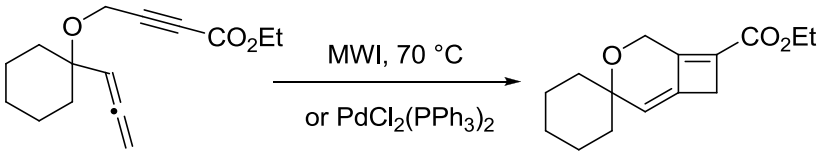
reactions due to its advantages such as eliminating potential temperature gradients and localized overheating, as well as minimization of decomposition of reagents. Brummond reported a microwave irradiation of allenynes **28** to provide intramolecular [2 + 2] cycloaddition products **29** in good yields (Scheme 2.9).[17] Further investigation demonstrated that the carbonyl beside alkyne is not necessary and a wide range of allenynes were suitable substrates for this [2 + 2] cycloaddition.



28 **29**

Scheme 2.9

In 2005, Oh and co-workers have developed a microwave induced intramolecular [2 + 2] cycloaddition of 1,5-, 1,6- and 1,7-allenyne carboxylates for the synthesis of fused bicyclic [m,2,0]alkadienes (Scheme 2.10).[18] In fact they discovered this reaction using $PdCl_2(PPh_3)_2$ as the catalyst.[20a]



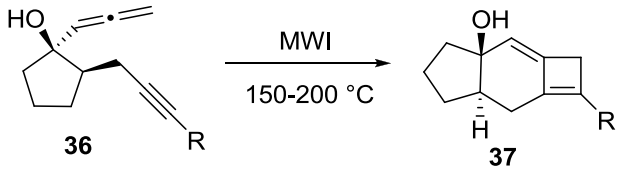
30 **31**

Scheme 2.10

In 2008, a similar microwave irradiation induced intramolecular [2 + 2] cycloaddition of a variety of 1-allenyl-2-propargyl-substituted derivatives has been reported by Ovaska and coworkers to prepare the [5.6.4] skeletons of sterpurene

[17] Brummond, K. M.; Chen, D. T. *Org. Lett.* **2005**, 7, 3473.
[18] (a) Oh, C. H.; Park, D. I.; Jung, S. H.; Reddy, V. R.; Gupta, A. K.; Kim, Y. M. *Synlett*, **2005**, 2092. (b) Oh, C. H.; Gupta, A. K.; Park, D. I.; Kim, Y. M. *Chem. Commun*. **2005**, 5670.

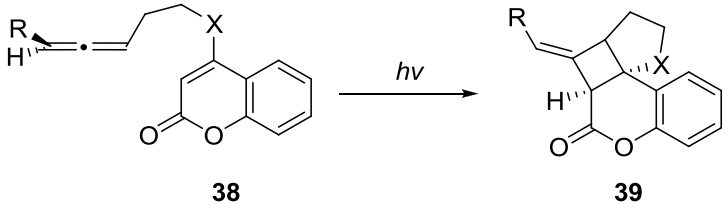
(Scheme 2.11).[19] Although the regio- and stereoselectivities were excellent, the reaction substrate scope is limited to allenynes containing allenic hydroxyl group and require the propargylic moieties in *cis* configuration to the hydroxyl group.



Scheme 2.11

2.1.3 Photochemical intramolecular [2 + 2]-cycloaddition reaction

Photochemical [2 + 2]-cycloadditions are theoretically allowed electrocyclic reactions according to the Woodward-Hoffmann rules and the Fukui's frontier orbital theory. This strategy is frequently employed in the total synthesis of natural products containing cyclobutanes and cyclobutenes frameworks. In terms of photochemical intramolecular [2 + 2]-cycloadditions of allenenes, Carreira's group reported a remarkable example (Scheme 2.15).[20] By using optically active allenic coumarins **38**



Scheme 2.12

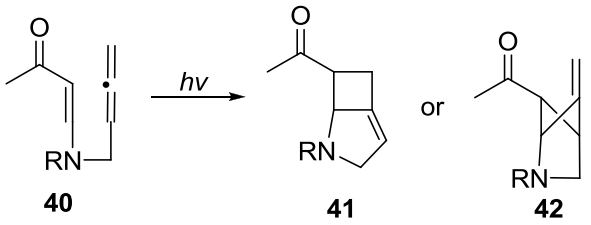
as the precursor, the fused complex product **39** could be obtained in excellent yields

[19] Ovaska, T. V.; Kyne, R. E. *Tetrahedron Lett*. **2008**, *49*, 376.

[20] (a) Carreria, E. M.; Hastings, C. A.; Shepard, M. S.; Yerkey, L. A.; Millward, D. B. *J. Am. Chem. Soc*. **1994,** *116*, 6622. (b) Shepard, M. S.; Carreria, E. M. *J. Am. Chem. Soc.* **1997,** *119*, 2597. (c) Becker, D.; Nagler, M.; Sahali, Y.; Haddad, N. *J. Org. Chem.* **1991**, *56*, 4537.

and with excellent enantioselectivities. The excellent asymmetric induction could be rationalized by the accepted intramolecular allene photocycloaddition model, which was proposed by Becker.[22c]

Winkler's group has presented an intramolecular photocycloaddition of vinylogous allenamide-type compounds **40** (Scheme 2.13).[21] Photochemical



40 **41** **42**

Scheme 2.13

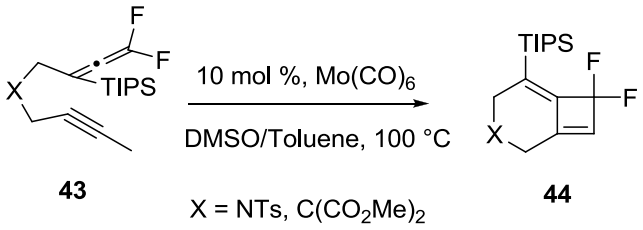
intramolecular [2 + 2]-cycloadditions between alkene and enone had been reported decades ago.[22] Notably, the regioselectivity of this study depends on the presence of an electron-withdrawing group at the nitrogen. In addition, the nitrogen could be replaced by oxygen or methylene which expanded the application of this methodology in the synthesis of complex molecules.

2.1.4 Transition metal-catalyzed intramolecular [2 + 2]-cycloaddition reaction

Transition metal catalysts had been used to mediate the intramolecular [2 + 2]-cycloadditions of allenenes and allenynes. Hammond's group discovered a formal [2 + 2] cycloaddition unexpectedly in their studies of the Pauson-Khand reaction of

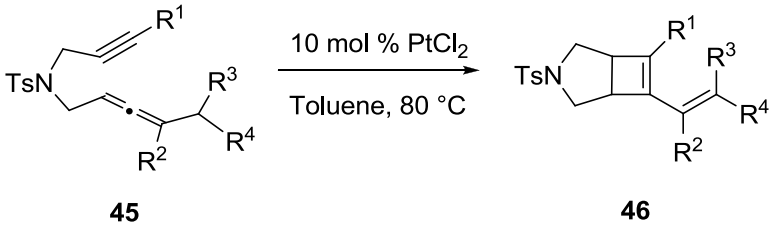
[21] Winkler, J. D.; Ragains, J. R. *Org. Lett.* **2006**, *8*, 4031.
[22] (a) Corey, E. J.; Bass, J. D.; LeMahieu, R.; Mitra, R. B. Cargill, R. L.; Dalton, J. R. *J. Am. Chem. Soc.* **1964,** *86*, 5770. (b) Eaton, P. E. *Tetrahedron Lett*. **1964**, *5*, 3695. (c) O'Connor, W.; Michels, D. G. *Tetrahedron Lett*. **1978**, *19*, 4465.

functionalized *gem*-difluoroallenynes (Scheme 2.14).[23] They rationalized that the formation of four membered-ring might involve the reductive elimination of molybdacyclopentenes.



Scheme 2.14

Transition metal-catalyzed cycloisomerization reactions of enynes also can afford the formal [2 + 2] cycloaddition products. For example, platinum complexes catalyzed cycloisomerization of allenynes **53** has been reported by Murakami's group (Scheme 2.15).[24] The mechanism is significantly different from the previous two

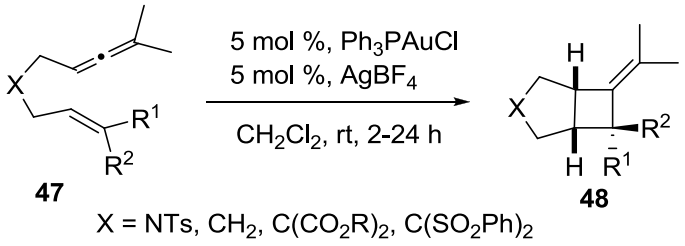


Scheme 2.15

transition metal catalyzed [2 + 2] cycloaddition reactions, which involve the reductive elimination of metallacyclopentenes and metallacyclopentanes. As the authors suggested, this reaction involved a series of cationic intermediates which were derived from the activation of alkyne and isomerisation of proximal allene π-bond. It is noted that the products distribution is dependent on structural variations of substrates such as the substituents on the allene and alkyne moieties and the tethers connecting them.

[23] Shen, Q.; Hammond, G. B. *J. Am. Chem. Soc.* **2002,** *124,* 6534.
[24] Matsuda, T.; Kadowaki, S.; Goya, T.; Murakami, M. *Synlett*, **2006**, 575.

Gold(I) has been used as an effective π-acid for activation of allenes and alkynes. Toste's group has developed the first gold(I)-catalyzed cycloisomerization of 1,6-allenenes **47** to give the formal [2 + 2] cycloaddition products **48** in high yields



Scheme 2.16

with excellent stereoselectivities (Scheme 2.16).[25] Based on the mechanism of gold(I) catalyzed cycloisomerization reactions, they suggested a stepwise mechanism to explain this gold(I)-catalyzed formal [2 + 2] cycloaddition process. Although a series of cationic intermediates are involved, the stereochemistry is very good. When (*R*)-DTBM-SEGPHOS was used as a chiral ligand, the corresponding cyclobutanes **48** could be obtained in excellent yields and enantioselectivities.

As mentioned above, photochemical, thermal and transition metal catalyzed [2 + 2]-cycloadditions between allene and alkene have been extensively investigated. However, most of these reported procedures involves the use of activated alkenes and suffers from many limitations including harsh reaction conditions and narrow substrate scope. Furthermore, selective [2 + 2]-cycloaddition reactions involving one of the allenic double bond remains a contemporary challenge to synthetic chemists. Recently, difluoroallenes, β-lactam-tethered allenes, diyne-diallenes, and allenynes have also been employed as substrates to overcome such drawbacks. Unfortunately, many of

[25] (a) Luzung, M. R.; Mauleon, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007,** *129,* 12402.

them required high temperature conditions which would limit their use in the synthesis of complex molecules. Regarding the potential application of [2 + 2] cycloaddition in the synthesis of complex natural and unnatural products, highly efficient intramolecular [2 + 2] cycloadditions under mild reaction conditions are urgently required.

2.2 RESULTS AND DISCUSSION

2.2.1 The origin of this project

In the course of our efforts towards the development of cationic polyene cyclization,[26] we became interested in an alternative initiating model by activation of C-C double bond with carbophilic transition metals.[27] In the past few years, gold catalyzed organic transformation have attracted much attention due to their versatilities.[28] Most of the gold(I)-catalyzed organic reactions involved the activation of carbon-carbon π-bonds of alkynes and allenes toward a variety of nucleophiles under homogenous conditions in which gold act as electrophile.

In 2008, Fürstner group reported a gold(I) complex-catalyzed cascade cyclization reactions to give the bicyclic products with excellent diastereoselectivities (Scheme 2.17).[29] This reaction is similar to the cationic polyenecyclization which involves a series carbocations and the stereochemistry is governed by chair-chair conformation (Stork-Eschenmoser postulate) of the precursor. Later on, Michelet expanded this strategy to the polyene cyclization (Scheme 2.18).[30] It is noteworthy that the tetracyclic product **55** could be formed in 50% yield with a high degree of

[26] (a) Zhao, Y. J.; Chng, S. S.; Loh, T. P. *J. Am. Chem. Soc.* **2007**, *129*, 492. (b) Zhao, Y. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 10024. (c) Zhao, J. F.; Zhao, Y. J.; Loh, T. P., *Chem. Commun.* **2008**, 1353.

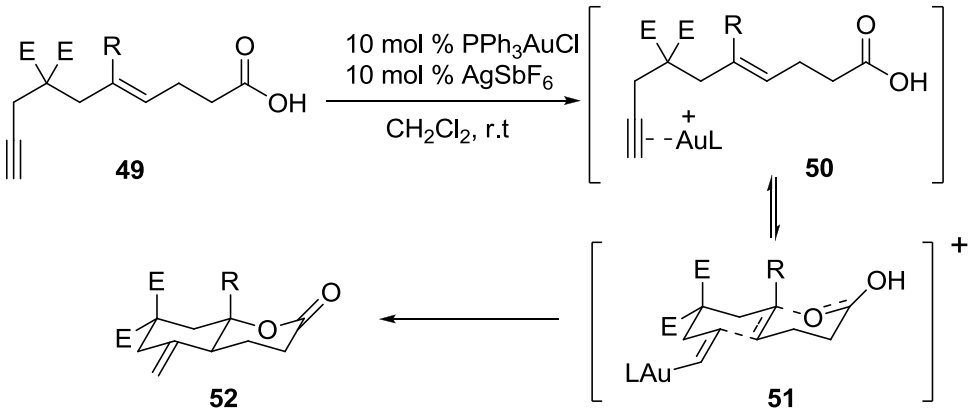
[27] (a) Mullen, C. A.; Gagne, M. R. *J. Am. Chem. Soc.* **2007**, *129*, 11880. (b) Feducia, J. A.; Gagne, M. R. *J. Am. Chem. Soc.* **2008**, *130*, 592. (c) Koh, J. H.; Gagne, M. R., *Angew Chem. Int. Ed.* **2004**, *43*, 3459.

[28] For reviews, see: (a) Hashimi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Li, Z. G.; Brouwer, C.; He, C. *Chem. Rev.* **2008**, *108*, 3239. (c) Jimenez-Nunez, E.; Echavarren, A. M. *Chem. Rev.* **2008**, *108*, 3326. (d) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351.(e) Gorin, D. J.; Toste, F. D. *Nature* **2007**, *446*, 395. (f) Arcadi, A. *Chem. Rev.* **2008**, *108*, 3266.

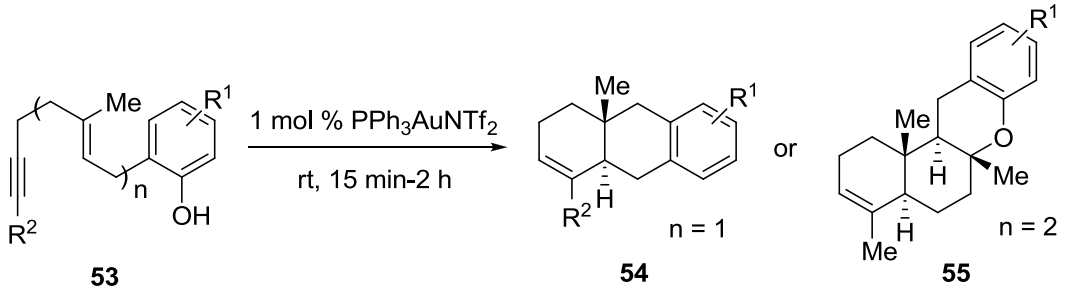
[29] Furstner, A.; Morency, L. *Angew Chem. Int. Ed.* **2008**, *47*, 5030.

[30] Toullec, P. Y.; Blarre, T.; Michelet, V. *Org. Lett.* **2009**, *11*, 2888.

diastereoselectivity (>20/1) just in one operation. Both of them employed alkyne as the initiating group of the cascade polyenecyclizaiton process. The only difference is the length of the tether between alkyne and alkene groups which lead to 6-*exo*-dig and 6-*endo* cyclization products, respectively.



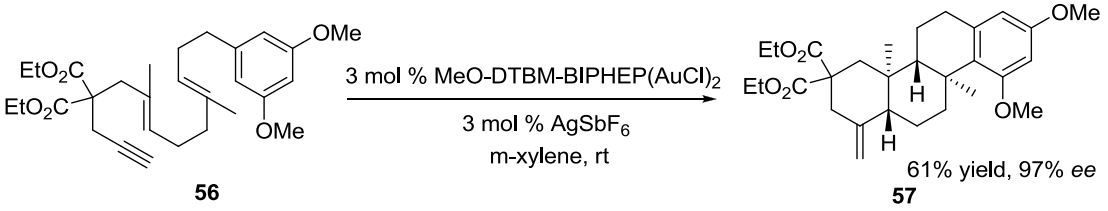
Scheme 2.17



Scheme 2.18

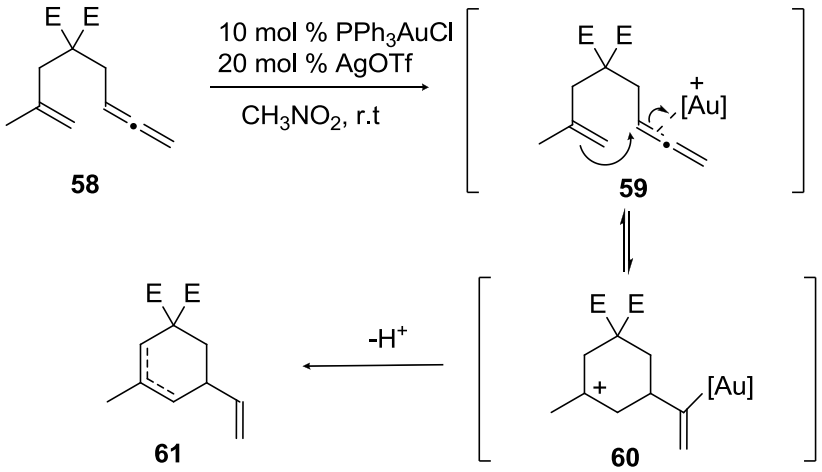
Very recently, Toste and co-workers reported the asymmetric version of this reaction by employing chiral phosphine ligand (Scheme 2.19).[31] By using the alkyne moiety as the initiating group, in the presence of 3 mol% of chiral gold(I) complex, the polyenecyclizaiton proceeded smoothly to give the enantioenriched polycyclic products in high yields with excellent enantioselectivities of up to 97% *ee*. The stereochemistry could be rationalized by the Stork-Eschenmoser postulate.

[31] Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276.



Scheme 2.19

Interestingly, Gagné's group developed a gold(I)-complex catalyzed cycoisomerization of eneallenes (Scheme 2.20).[32] It was presumed that this process involves a carbocationic mechanism as shown in Scheme 2.24. The cycloisomerization was initiated by coordination of Au(I) to the allene moiety. Then activated allene moiety was nucleophilic attacked by the alkene part and lead to carbocation **60**. After deprotonation and protonation, the cyclized products **61** will be formed.



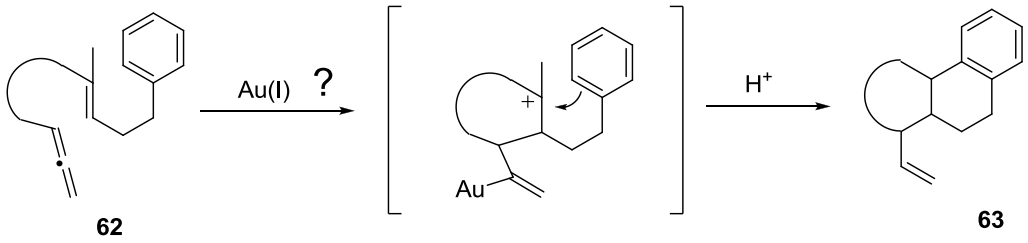
Scheme 2.20

Inspired by these works and considering the parallels in the reactivity of allenes and alkynes toward metal-mediated nucleophilic additions,[33] we hypothesized that

[32] (a) Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagne, M. R. *Angew Chem. Int. Ed.* **2007**, *46*, 6670. (b) Tarselli, M. A.; Gagne, M. R. *J. Org. Chem.* **2008**, *73*, 2439. (c) Weber, D.; Tarselli, M. A.; Gagne, M. R. *Angew Chem. Int. Ed.* **2009**, *48*, 5733.

[33] (a) Trost, B. M. *Acc. Chem. Res.* **2002**, *35*, 695. (b) Rubin, M.; Sromek, A. W.; Gevorgyan, V. Synlett 2003, 2265. (c) Krause, N.; Hashmi, A. S. K. Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, Germany, **2004**. (d) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev*. **2004**, *104*, 3079.

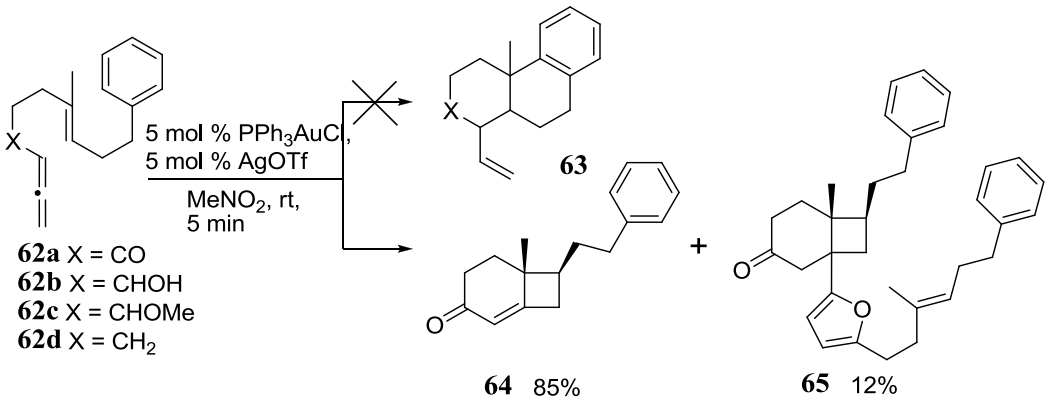
allenes may also be used as the "head" to initiate cationic polyene cyclization by using gold(Ⅰ) complex as the carbophilic π-acid catalyst (Scheme 2.21).



Scheme 2.21

2.2.2 Preliminary study and the discovery of intramolecular [2 + 2]-cycloaddition reaction of ene-allenone

A series of allenenes **62** were prepared and evaluated under gold catalysis conditions. No reaction was detected and the starting material was recovered when **62d** was used as the cyclization precursor. The complicated mixture for **62c** and the

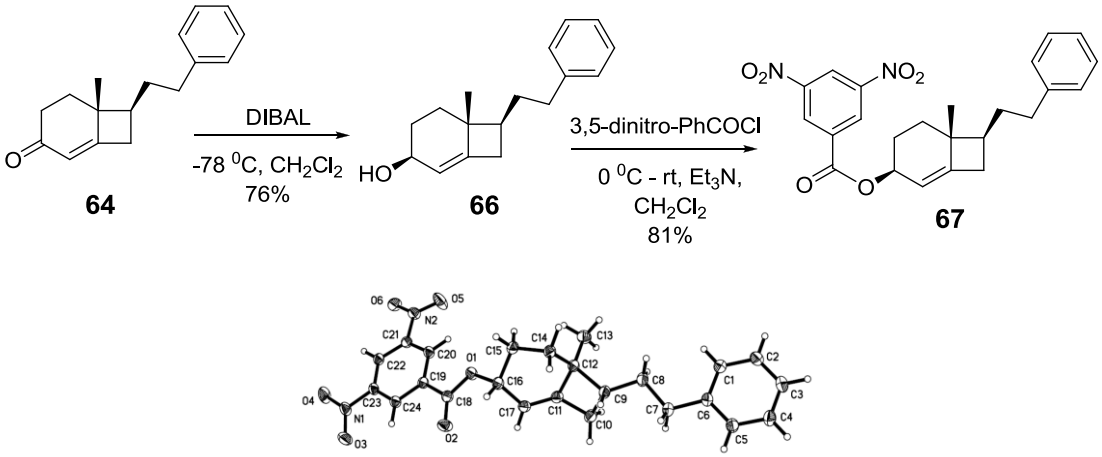


Scheme 2.22

cycloisomerization product 2,5-dihydrofuran was obtained for **62b** as described in literature.[34] Interestingly, when **62a** was treated with 5 mol% of Ph_3PAuCl and AgOTf in 0.1 M $MeNO_2$, only the formal [2 + 2]-cycloaddition product **64** was

[34] Tang, X. P.; Woodward, S.; Krause, N. *Eur. J. Org. Chem.* **2009**, 2836.

obtained as a single diastereomer accompanied by a small amount of dimer **65** (Scheme 2.22). The target cationic polyene cyclization product **63** was not observed at all. The structure of **64** was further confirmed by an X-ray diffraction study of its ester derivative **67** (Scheme 2.23).



Scheme 2.23

With this confirmed structure in hand, we checked the literature and found that the intramolecular [2 + 2]-cycloadditions of ene-allenones such as **62a,** which offer a convenient access to the bicyclo[n.2.0] carbon framework with *α*,*β*-unsaturated ketone fragment, has remained unexplored possibly due to the facile cycloisomerization and dimerization of allenones taking place in the presence of Lewis acid or transition metals.[35]

The excellent regio- and diastereoselectivities as well as the mild reaction conditions of this reaction make us believe that this unexpected discovery could be

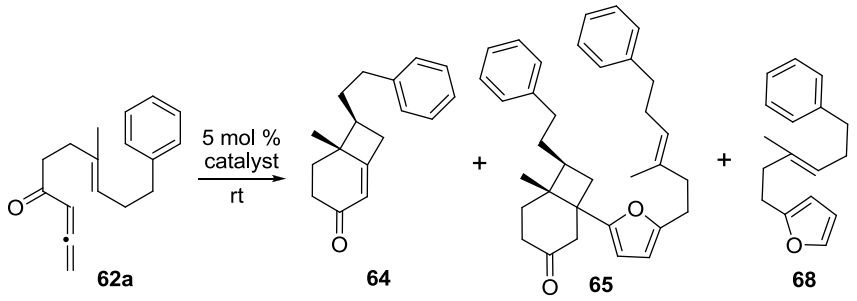
[35] (a) Sromek, A. W.; Rubina, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 10500. (b) Dudnik, A. S.; Sromek, A. W.; Rubina, M.; Kim, J. T.; Kel'in, A. V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2008**, *130*, 1440. (c) Xia, Y. Z.; Dudnik, A. S.; Gevorgyan, V.; Li, Y. H. *J. Am. Chem. Soc.* **2008**, *130*, 6940. (d) Marshall, J. A.; Wallace, *J. Org. Chem.* **1995**, *60*, 796. (e) Hashmi, A. S. K.; Schwarz, L.; Choi, J. H.; Frost, T. M. *Angew Chem. Int. Ed.* **2000**, *39*, 2285. (f) Zhou, C. Y.; Chan, P. W. H.; Che, C. M. *Org. Lett.* **2006**, *8*, 325. (g) Wei, H.; Zhai, H. B.; Xu, P. F. *J. Org. Chem.* **2009**, *74*, 2224.

developed into a useful strategy for constructing fused skeletons containing four-membered rings. In addition, functional groups such as the *α,β*-unsaturated ketone fragment render the products easy to modify and will expand its application in the synthesis of complex molecules.

2.2.3 Detailed study

Further optimization of the reaction conditions demonstrated that this reaction is sensitive to the solvent as well as catalyst used (Table 1). Generally, polar solvents gave **64** as the major product while non-polar solvents provided mainly cycloisomerization product **68** (Table 1, entries 1-7). Interestingly, we did not observe the coexistence of **64** and **68** in all cases but a single diastereomer of the dimer **65** accompanied by **64** or **68**. However, a control experiment demonstrated that gold(I) is not necessary for this reaction (Table 1, entry 11) and it was an acid-catalyzed process. To our delight, the formation of cycloisomerization product **64** and dimer **68** could be suppressed by the use of common Lewis acid as the catalysts (Table 1, entries 9-18). For example, 5 mol% of AgOTf alone is efficient enough to offer **64** in 88% yield by suppressing the cycloisomerization (Table 1, entry 11). A series of Lewis and Brønsted acids were examined and all of them catalyzed the reaction smoothly to give the [2 + 2]-cycloaddition product exclusively in good to excellent yields (Table 1, entries entries 9-22). Finally, 5 mol% of $In(OTf)_3$ in nitromethane were identified as

Table 1. Optimization studies.[a]



Entry	Solvent	Catalyst	Yield (%)[b]	Ratio (**64**/**65**/**68**)[c]
1	THF	$AuClPPh_3/AgOTf$	84	0:5:95
2	$CHCl_3$	$AuClPPh_3/AgOTf$	65/32	0:50:50
3	toluene	$AuClPPh_3/AgOTf$	44/45	0:33:67
4	CH_2Cl_2	$AuClPPh_3/AgOTf$	45/44	67:33:0
5	$(CH_2Cl)_2$	$AuClPPh_3/AgOTf$	70	86:14:0
6	CH_3CN	$AuClPPh_3/AgOTf$	40/40	68:32:0
7	CH_3NO_2	$AuClPPh_3/AgOTf$	85	94:6:0
8	CH_3NO_2	$AuClPPh_3$	trace	-
9	CH_3NO_2	AuCl	83	9:91:0
10	CH_3NO_2	$AuCl_3$	42	91:9:0
11	CH_3NO_2	AgOTf	88	>99:1:0
12	**CH_3NO_2**	**$In(OTf)_3$**	**94**	**>99:1:0**
13	CH_3NO_2	$InBr_3$	84	>99:1:0
14	CH_3NO_2	$InCl_3$	90	>99:1:0
15	CH_3NO_2	$Cu(OTf)_2$	81	>99:1:0
16	CH_3NO_2	$BF_3•Et_2O$	79	>99:1:0
17	CH_3NO_2	$TiCl_4$	92	>99:1:0
18	CH_3NO_2	$SnCl_4$	88	>99:1:0
19	CH_3NO_2	TfOH	82	>99:1:0
20	CH_3NO_2	HCl (4 N)	71	>99:1:0
21	CH_3NO_2	CF_3CO_2H	79	>99:1:0
22	CH_3NO_2	*p*-TSA•H_2O	80	>99:1:0

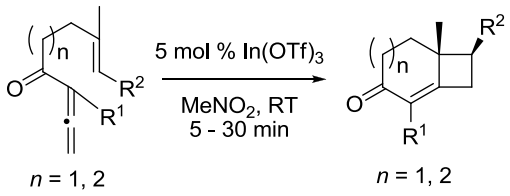
[a] Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. [b] Isolated yield of major product. [c] The ratio was determined by ^1H NMR analysis of the crude product mixture.

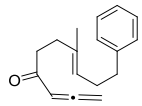
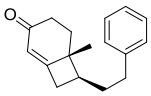
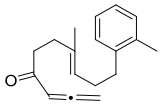
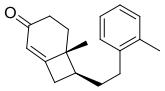
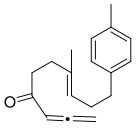
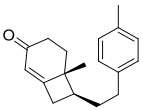
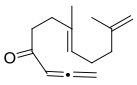
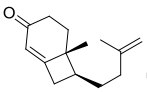
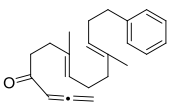
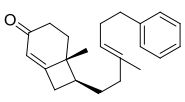
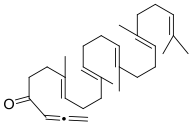
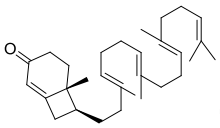
the best conditions in terms of economy, practicality, selectivity and the yield of **64** (Table 1, entry 12).

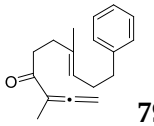
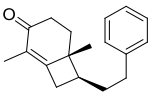
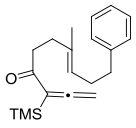
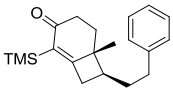
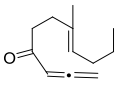
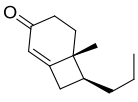
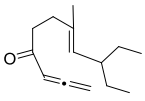
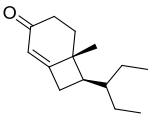
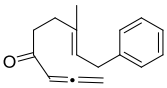
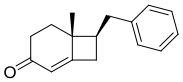
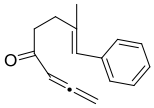
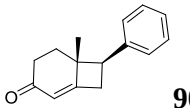
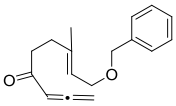
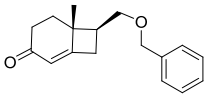
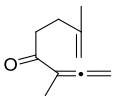
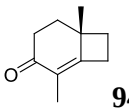
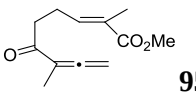
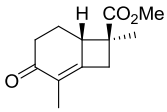
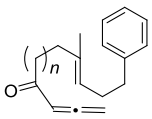
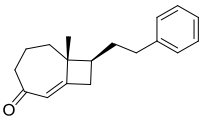
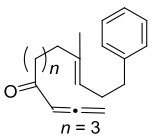
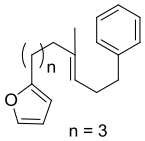
Various substrates were prepared to test the generality of the acid-catalyzed intramolecular [2 + 2]-cycloaddition of ene-allenones under the optimal conditions.

The results are summarized in Table 2. The intramolecular [2 + 2]-cycloaddition reactions proceeded readily for all of the tested ene-allenones to give the strained bicyclo[n.2.0] frameworks in good to excellent yields and with excellent diastereoselectivities. Variation of the tail length had little effect on the reaction efficiency (Table 2, entries 5, 6, 11 and 12). Interestingly, ene-allenones possessing an *α*-substituent at the allenone motif gave [2 + 2]-products in good yields (Table 2, entries 7 and 8). Possessing both *α,β*-unsaturated ketone and vinylsilane fragments

Table 2: $In(OTf)_3$ catalyzed [2 + 2]-cycloadditions.[a]



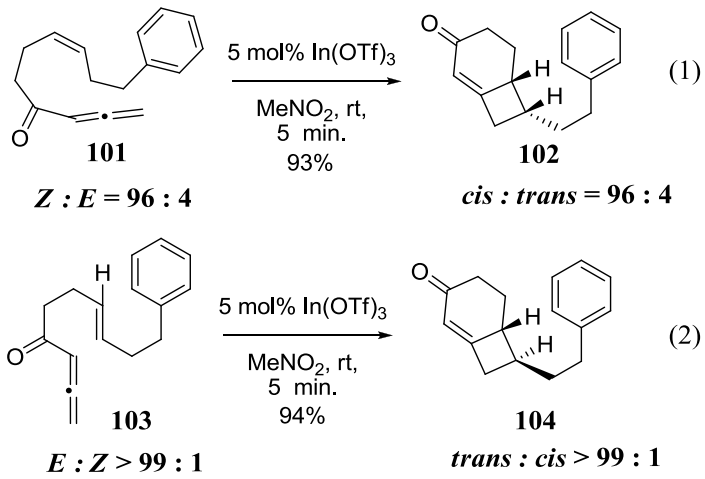
Entry	Substrate	Product[b]	Yield (%)[c]
1	 **62a**	 **64**	94
2	 **69**	 **70**	88
3	 **71**	 **72**	82
4	 **73**	 **74**	83
5	 **75**	 **76**	81
6	 **77**	 **78**	76

7	 **79**	 **80**	80
8	 **81**	 **82**	85
9	 **83**	 **84**	89
10	 **85**	 **86**	95
11	 **87**	 **88**	70
12	 **89**	 **90**	85
13	 **91**	 **92**	91
14	 **93**	 **94**	70
15[d]	 **95**	 **96**	76
16	 **97**	 **98**	82
17	 **99**	 **100**	80

[a] Reactions were carried out on a 0.2 mmol scale with 0.1 M of substrate. [b] Single diastereomer (determined by ^{1}H and ^{13}C NMR analysis). [c] Isolated yield. [d] The reaction time is 16 hours.

concurrently, adduct **82** is rendered more versatile for further modification.[36] The most promising case is the intramolecular [2 + 2]-cycloaddition of ene-allenone **83**, which constructed the core structure of sterpurene and illudene derivatives in one operation. Notably, the [2 + 2]-cycloaddition went smoothly to furnish the [4.2.0] framework in good yield albeit a longer reaction time was required when an electron-withdrawing group was introduced to the alkene motif (Table 2, entry 15). In addition, the bicyclo[5.2.0] compound **98** could also be obtained with good yield and excellent diastereoselectivity (Table 2, entry 16). However, attempts to get bicyclo[6.2.0] skeleton containing eight-membered fused four-membered ring were failed and only the cycloisomerization product **100** was isolated.

To probe the mechanism of this [2 + 2]-cycloaddition reaction, the stereospecificity as well as steric effect on the alkene moiety were examined. Substrates **101** and **103** containing (*Z*) and (*E*) alkene, respectively, were designed and

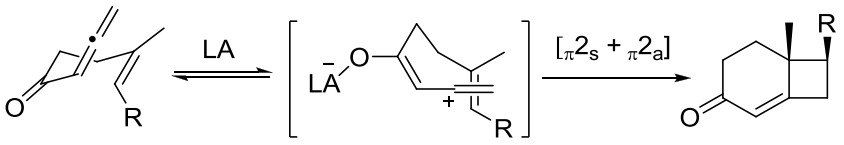


Scheme 2.24

[36] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.

treated with standard conditions (Scheme 2.24). Both **101** and **103**, in the absence of the methyl group on the alkene motif, transformed smoothly to give [2 + 2]-cycloaddition products **102** and **104** with excellent yields and diastereoselectivities, which suggested that the methyl group has no significant effect on the efficiency of the [2 + 2]-cycloadditions. Another interesting observation is that the *cis* and *trans* products were obtained exclusively from (*Z*)- and (*E*)-alkenes, respectively, demonstrating that this is a stereospecific process.

Although stepwise mechanisms have been proposed in some Lewis acid-catalyzed [2 + 2]-cycloadditions,[10,11,28] the debate between a concerted or stepwise mechanism of [2 + 2]-cycloaddition is still ongoing.[12,13] When the reaction was carried out in the presence of 5 equivalents of MeOH, only the [2 + 2] cycloaddition product was isolated. We have not detected any cationic intermediate in this reaction.



Scheme 2.25 Proposed mechanism.

Considering the similarity of allenic ester and allenone in the presence of Lewis acid,[37] we believe that the mechanism proposed for the [2 + 2] cycloaddition of allenic ester[10,11] could also be used to rationalize the intramolecular [2 + 2] cycloaddition of ene-allenone. So far, the stereospecificity of this reaction and the result of control experiment carried out in the presence MeOH supported that this

[37] Nagao, Y.; Lee, W. S.; Jeong, I. Y.; Shiro, M. *Tetrahedron Lett.* **1995**, *36*, 2799.

reaction may prefer a $[_{\pi}2_s+_{\pi}2_a]$ concerted mechanism, which involves the vinyl cation having resonance structures[40] as shown in Scheme 2.25. However, the stepwise mechanism cannot be excluded at this stage. If the stepwise process is rapid enough, the entire cyclization will proceed stereospecifically. Another observation that should be mentioned is that the pre-organized conformation is crucial for the reaction because there is no reaction at all if the alkene moiety is replaced by an alkyne group.

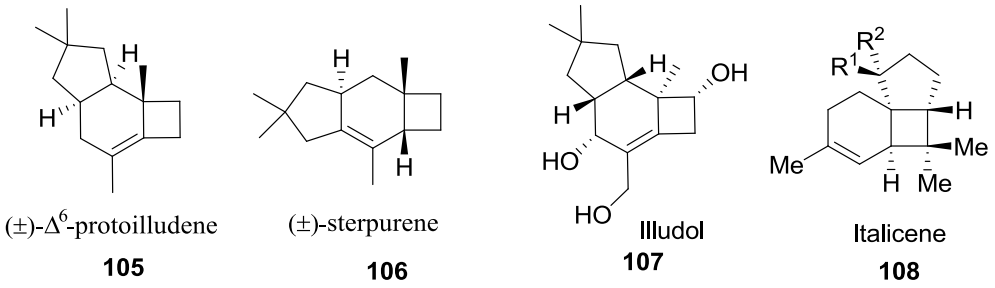
2.2.4 Synthetic study toward Δ^6-Protoilludene

A series of sesquiterpenes such as sterpurenes and illudene derivatives with the 4/6/5 ring system have been isolated since early 1980s (Scheme 2.26).[38] Δ^6-Protoilludene (**105**), the parent compound of the illudene family, has been postulated as an intermediate in the biosynthesis of other sesquiterpenes.[39] The crowded and rigid carbon skeleton of **105** represents a synthetic challenge.[40] Our intramolecular [2 + 2] cycloaddition of ene-allenone can construct the 6/4 ring system in one simple operation under mild conditions. Obviously, with the introduction of an

[38] (a) Ayer, W. A.; Saeedi-Ghomi, M. H. *Can. J. Chem*. **1981**, *59*, 2536. (b) Donnelly, D. M. X.; Abe, F.; Coveney, D. J.; Fukuda, N.; Polonsky, J. *J. Nat. Prod.* **1986**, *49*, 111. (c) Hanssen, H. P.; Sprecher, E.; Abraham, W. R. *Phytochemistry* **1986**, *25*, 1979. (d) Arnone, A.; Cardillo, R.; Nasini, G.; Meille, S. V. *J. Chem. Soc., Perkin Trans. 1* **1988**, 503. (e) Sterner, O.; Anke, T.; Sheldrick, W. S.; Steglich, W. *Tetrahedron* **1990**, *46*, 2389. (f) Donnelly, D. M. X.; Konishi, T.; Dunne, O.; Cremin, P. *Phytochemistry* **1997**, *44*, 1473. (g) Clericuzio, M.; Fu, J.; Pan, F.; Pang, Z.; Sterner, O. *Tetrahedron* **1997**, *53*, 9735. (h) Rasser, F.; Anke, T.; Sterner, O. *Phytochemistry* **2000**, *54*, 511.

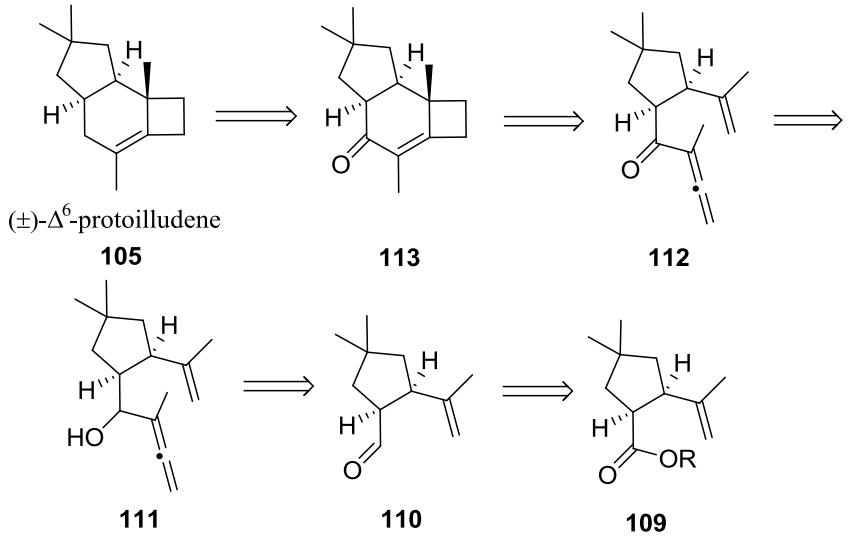
[39] (a) Nozoe, S.; Kobayashi, H.; Urano, S.; Furukawa, J. *Tetrahedron Lett*. **1977**, *18*, 1381. (b) Ayer, W. A.; Browne, L. M. *Tetrahedron* **1981**, *37*, 2199. (c) Arnone, A.; Cardillo, R.; Di Modugno, V.; Nasini, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1989.

[40] (a) Furukawa, J.; Morisaki, N.; Kobayashi, H.; Iwasaki, S.; Nozoe, S.; Okuda, S. *Chem. Pharm. Bull*. **1985**, *33*, 440. (b) Oppolzer, W.; Nakao, A. *Tetrahedron Lett.* **1986**, *27*, 5471. (c) Takeshita, H.; Iwabuchi, H.; Kouno, I.; Iino, M.; Nomura, D. *Chem. Lett.* **1979**, 649. (d) Hansen, T. V.; M.d'achi, S.; Skattebøl, L.; Stenstrøm, Y. *Acta Chem. Scand.* **1998**, *52*, 1373.



Scheme 2.26

additional five-membered ring before or after the intramolecular [2 + 2] cycloaddition, it is possible to construct the framework of protoilludene and sterpurene derivatives. We attempted to apply our methodology to the total synthesis of the parent compound Δ^6-Protoilludene (**105**). We analyzed that construction of a five-membered ring before

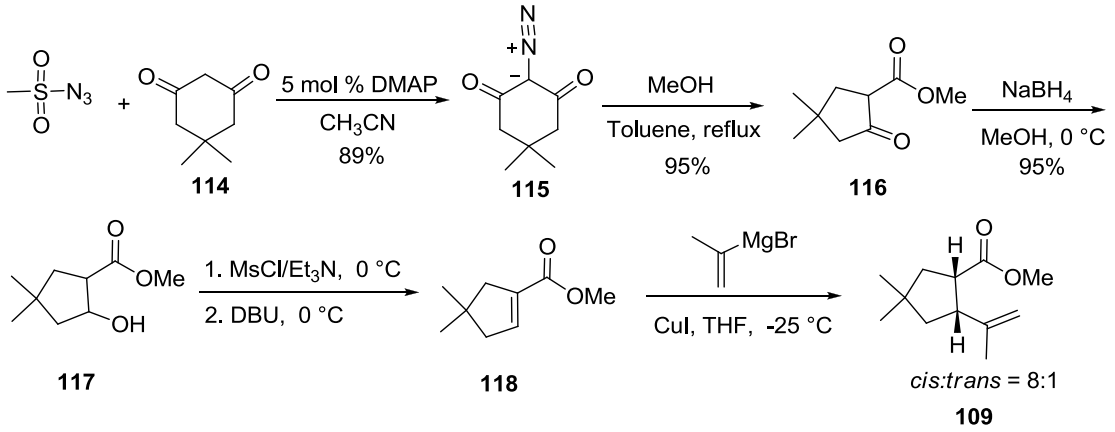


Scheme 2.27

the intramolecular [2 + 2] cycloaddition should be more efficient because the target molecule could be obtained followed by one- or two-step manipulations of [2 + 2] cycloaddition product **113** as shown in the retrosynthetic analysis (Scheme 2.27).

The key intermediate **109** could be synthesized from commercially available dimedone **114** (Scheme 2.28). According to Ramachary's organocatalyzed

diazo-transfer reactions,[41] the diazo-compound **115** can be obtained in excellent yield under mild conditions. The ring contraction of diazo-compound **115** followed by



114 **115** **116** **117** **118** **109**

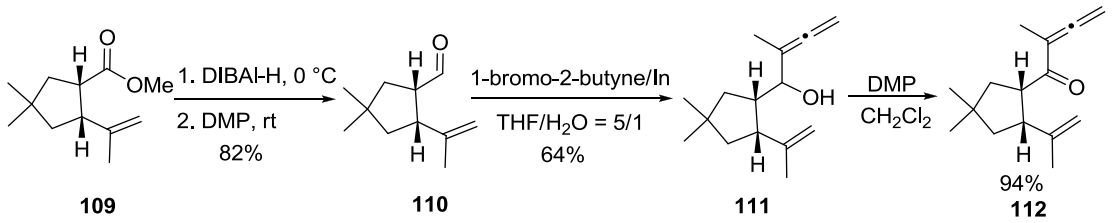
Scheme 2.28

trapping of the transient *α*-oxoketene (Wolff rearrangement product) with methanol afforded the *β*-ketone ester **116.**[42] Selective reduction of the carbonyl group of **116** provided alcohol **117** which could be transferred into *α,β*-unsaturated ester **118** by mesylation and elimination. In the presence of CuI, the 1,4-Michael addition of 1-methyl vinyl Grignard to *α,β*-unsaturated ester **118** gave the key intermediate **109** with good diastereoselectivity (*dr* up to 8:1) in high yield.[43]

The synthesis of ene-allenone **112** commenced with the conversion of ester **109** into the aldehyde **110**. Firstly, the ester **109** was reduced by DIBAL-H to give a primary alcohol which was directly oxidized to the aldehyde **110** by using DMP as the oxidant. The allenic alcohol **111**, obtained by employing indium mediated transformation developed by our group,[44] was subjected to Dess-Martin oxidation to

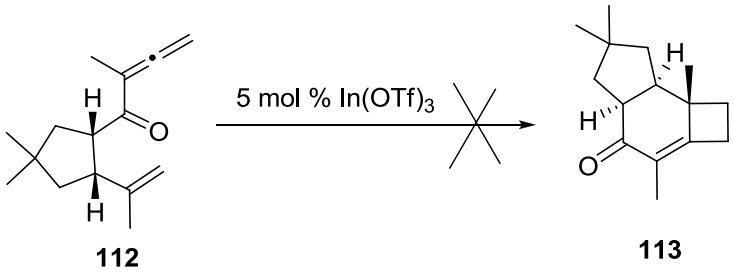
[41] Ramachary, D. B.; Narayana, V. V.; Ramakumar, K. *Tetrahedron Lett.* **2008**, *49*, 2704.
[42] Presset, M.; Coquerel, Y.; Rodriguez, J. *J. Org. Chem.* **2009**, *74*, 415.
[43] Sun, J. W.; Conley, M. P.; Zhang, L. M.; Kozmin, S. A. *J. Am. Chem. Soc.* **2008**, *130*, 6940.
[44] Lin, M. J.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *125*, 13042.

give the desired ene-allenone **112** in 94% yield (Scheme 2.29).



Scheme 2.29

With the ene-allenone **112** in hand, we come to the final stage of our synthetic plan. Unfortunately, the target cycloadduct was not detected when ene-allenone **112** was treated with the optimized intramolecular [2 + 2] cycloaddition conditions (Scheme 2.30). Only polymerization of **112** was observed. This result is similar with that of Stenstrom.[45] We attributed this to the unfavorable conformation of ene-allenone **112**. According to the possible mechanism shown in Scheme 2.25, the



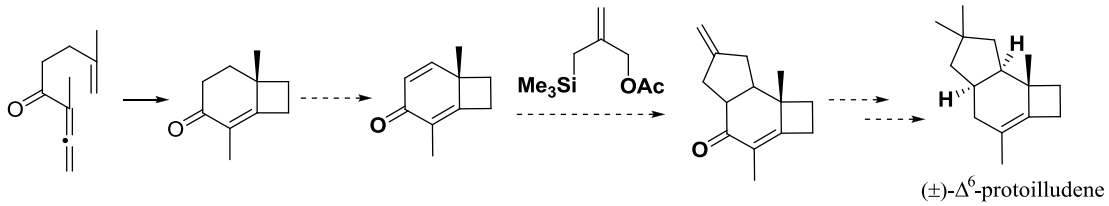
Scheme 2.30

intramolecular [2 + 2] cycloaddition requires that the distal allenic double bond and the alkene double bond be perpendicular to each other. The rigid five membered-ring may have disturbed the conformation and resulted in polymerization instead.

Although the use of this intramolecular [2 + 2] cycloaddition in the late stage of total synthesis of Δ^6-Protoilludene (**105**) failed, we could use another strategy which involves the use of intramolecular [2 + 2] cycloaddition in the early stage followed by

[45] Hansen, T. V.; Skattebøl, L.; Stenstrøm, Y. *Tetrahedron* **2003**, *59*, 3461.

the construction of five-membered ring in the late stage as shown in Scheme 2.31.



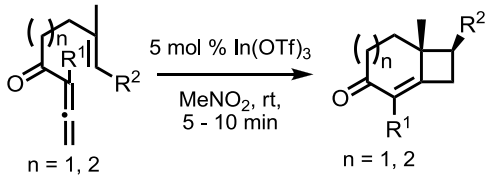
Scheme 2.31

2.3 CONCLUSION

In summary, we have developed the first acid-catalyzed selective intramolecular [2 + 2]-cycloaddition between the less activated distal allenic double bond and the unactivated alkene of ene-allenones. The cycloaddition reactions provide a facile access to the strained carbon bicyclo[n.2.0] frameworks under very mild reaction conditions with high yields and excellent diastereoselectivities. The excellent regioselectivities demonstrate that it is feasible to perform reactions selectively at the distal allenic double bond of ene-allenones. The mild reaction conditions, excellent yields and diastereoselectivities, easy functionalization of the product and the simplicity of the reaction procedure make this method attractive for the synthesis of complex molecules.

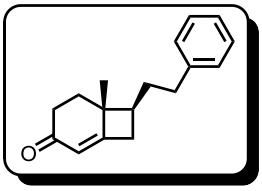
2.4 EXPERIMENTAL SECTION

General procedure for Lewis acid catalyzed intramolecular [2 + 2] cycloaddition of ene-allenones:



General procedure for the Lewis acid catalyzed intramolecular [2 + 2] cycloadditon of eneallenones: A mixture of Lewis acid (5 mol%) and nitromethane (2 mL) was stirred at room temperature for 5 minutes. Then 0.2 mmol of eneallenones was added, and the resulting mixture was stirred at room temperature. The reaction was monitored by TLC analysis, which indicated completed consumption of the eneallenones within 5-10 minutes. The reaction was quenched by the addition of saturated $NaHCO_3$ solution. The layer was separated and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layer was washed with brine (once), dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to give the desired product.

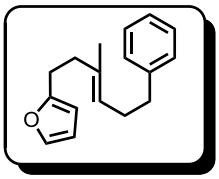
6-methyl-7-phenethylbicyclo[4.2.0]oct-1-en-3-one (64)



This compound was prepared by the General Procedure described above and was obtained as a colourless oil, yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 5.70 (s, 1H), 2.81 (dd, *J* = 7.1 Hz, *J* = 14.9 Hz, 1H), 2.66 (ddd, *J* = 2.1 Hz, *J* = 9.4 Hz, *J* = 14.9 Hz, 1H), 2.57 (td, *J* = 1.9 Hz, *J* = 7.3 Hz, 2H), 2.46 (m, 1H), 2.31 (dt, *J* = 3.4 Hz, *J* = 17.7 Hz, 1H), 2.04 (dt, *J* = 7.4 Hz, *J* = 16.7 Hz, 1H), 1.95-1.90 (m, 3H), 1.81 (dt, *J* = 7.4 Hz, *J* = 15.8 Hz, 1H), 1.30

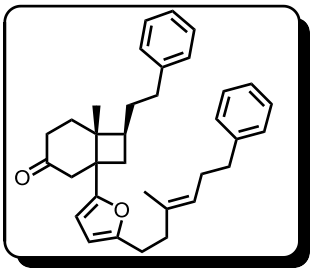
(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 173.3, 141.7, 128.5, 128.4, 126.0, 118.1, 47.6, 44.6, 37.9, 37.0, 34.7, 34.3, 32.6, 15.6; FTIR (neat): 2927, 2854, 1667, 1454, 1192, 849, 748 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}OH^+$ 241.1592, found 241.1595.

(E)-2-(3-methyl-6-phenylhex-3-enyl)furan (68)



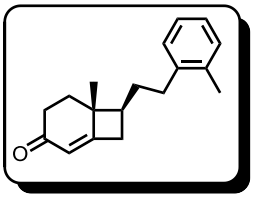
Yield: 93%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 3H), 7.20-7.15 (m, 3H), 6.25 (dd, *J* = 2.0 Hz, *J* = 2.85 Hz, 1H), 5.95 (d, *J* = 3.0 Hz, 1H), 5.21 (t, *J* = 7.0 Hz, 1H), 2.70 (t, *J* = 7.6 Hz, 2H), 2.61 (t, *J* = 7.6 Hz, 2H), 2.30 (m, 4H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 142.3, 140.7, 134.8, 128.5, 128.3, 125.7, 124.4, 110.1, 104.7, 38.0, 36.1, 29.9, 26.9,15.9; FTIR (neat): 2920, 2854, 1597, 1506, 1495, 1452, 1151, 1009, 729, 698 (neat) cm^{-1}; HRMS HRMS (ESI) calcd for $C_{17}H_{20}OH^+$ 241.1592, found 241.1601.

6-methyl-1-(5-((E)-3-methyl-6-phenylhex-3-enyl) furan-2-yl)-7-phenethylbicycle [4.2.0]octan-3-one (65)



Yield: 12%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.26 (m, 4H), 7.22-7.16 (m, 6H), 5.90 (d, *J* = 3.0 Hz, 1H), 5.85 (d, *J* = 3.0 Hz, 1H), 5.20 (t, *J* = 7.0 Hz, 1H), 2.76 (d, *J* = 15.6 Hz, 1H), 2.66-2.52 (m, 7H), 2.50-2.39 (m, 2H), 2.33-2.13 (m, 6H), 2.02 (dd, *J* = 8.6 Hz, *J* = 11.5 Hz, 1H), 1.91 (m, 1H), 1.87-1.78 (m, 2H), 1.72 (m, 1H), 1.57 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.3, 156.7, 155.0, 142.29, 142.27, 134.7, 128.46, 128.41, 128.33, 128.25, 125.9, 125.7, 124.4, 106.2, 105.2, 47.7, 42.9, 41.9, 38.6, 37.9, 36.0, 35.8, 34.4, 34.1, 33.1, 33.0, 29.9, 26.9, 18.6, 15.9; FTIR (neat): 2928, 2855, 2247, 1714, 1603, 1494, 1452, 1028, 910, 732, 698 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{40}OH^+$ 481.3106, found 481.3107.

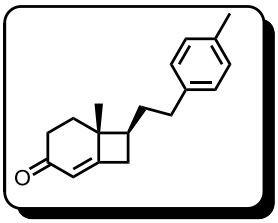
6-methyl-7-(2-methylphenethyl)bicyclo[4.2.0]oct-1-en-3-one (70)



Yield: 88%, oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.17-7.08 (m, 4H), 5.71(d, *J* = 1.56 Hz, 1H), 2.86 (dd, *J* = 7.1 Hz, *J* = 14.7 Hz, 1H), 2.68 (ddd, *J* = 2.1 Hz, *J* = 9.4 Hz, *J* = 14.9 Hz, 1H), 2.55 (t, *J* = 7.9 Hz, 2H), 2.51-2.40 (m, 1H), 2.37-2.28 m, 4H), 2.14-2.02 (m, 1H), 2.00-1.68

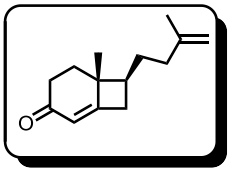
(m, 4H), 1.31 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 199.2, 173.2, 139.9, 135.7, 130.3, 128.8, 126.2, 126.0, 118.2, 47.7, 45.1, 37.9, 37.1, 34.7, 31.7, 31.3, 19.3, 15.6; FTIR (neat): 2961, 2932, 2858, 2249, 1668, 1456, 1192, 908, 733 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}OH^+$ 255.1749, found 255.1747.

6-methyl-7-(4-methylphenethyl)bicyclo[4.2.0]oct-1-en-3-one (72)



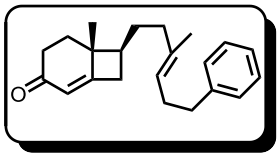
Yield: 82%, oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 8.1 Hz, 2H), 7.06 (d, *J* = 8.1 Hz, 2H), 5.69(d, *J* = 1.5 Hz, 1H), 2.81 (dd, *J* = 7.0 Hz, *J* = 14.6 Hz, 1H), 2.66 (ddd, *J* = 2.1 Hz, *J* = 9.3 Hz, *J* = 14.7 Hz, 1H), 2.53 (t, *J* = 7.7 Hz, 2H), 2.47-2.27 (m, 6H), 2.08-1.73 (m, 5H), 1.30 (s, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 199.2, 173.3, 138.6, 135.5, 129.1, 128.2, 118.1, 47.6, 44.6, 37.9, 37.0, 34.7, 33.9, 32.7, 21.0, 15.6; FTIR (neat): 2960, 2924, 2857,1667, 1514, 1449, 1192, 806 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{23}OH^+$ 255.1749, found 255.1753.

6-methyl-7-(3-methylbut-3-enyl)bicyclo[4.2.0]oct-1-en-3-one (74)



Yield: 83%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 4.71 (s, 1H), 4.66 (s, 1H), 2.83 (dd, *J* = 7.2 Hz, *J* = 14.7 Hz, 1H), 2.81 (ddd, *J* = 2.1 Hz, *J* = 9.5 Hz, *J* = 14.7 Hz, 1H), 2.50-2.40 (m, 1H), 2.31 (dt, *J* = 3.4 Hz, *J* = 17.5 Hz, 1H), 2.04-1.91 (m, 5H), 1.71 (s, 3H), 1.75- 1.55 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 173.4, 145.2, 118.1, 110.4, 47.6, 44.7, 37.9, 37.0, 36.1, 34.6, 28.7, 22.3, 15.5; FTIR (neat): 2965, 2932, 2857, 1651, 1447, 1261, 1192, 885 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}OH^+$ 205.1592, found 205.1586.

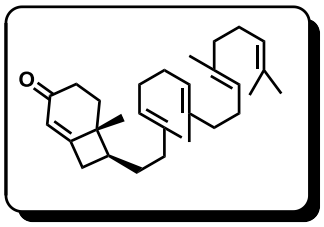
6-methyl-7-((E)-3-methyl-6-phenylhex-3-enyl)bicyclo[4.2.0]oct-1-en-3-one (76)



Yield: 81%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.19-7.16 (m, 3H), 5.70 (s, 1H), 5.13 (t, *J* = 7.0 Hz, 1H), 2.78 (dd, *J* = 7.2 Hz, *J* = 14.8 Hz, 1H), 2.67-2.59 (m, 3H), 2.45 (ddd, *J* = 6.7 Hz, *J* = 12.4 Hz, *J* = 18.3 Hz, 1H), 2.35-2.28 (m, 3H), 1.96-1.86 (m, 5H), 1.71-1.50 (m, 5H), 1.27(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 173.6, 142.2, 135.1, 128.5, 128.2, 125.8, 124.3, 118.0, 47.5, 44.5, 37.93, 37.90, 37.0, 36.0,

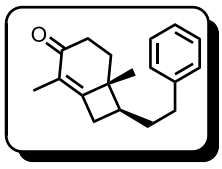
34.7, 29.7, 28.9, 15.8, 15.5; FTIR (neat): 3026, 2960, 2926, 2855, 1651, 1494, 1454, 1261, 1192, 748, 700 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{28}OH^+$ 309.2218, found 309.2211.

6-methyl-7-((3E,7E,11E)-3,8,12,16-tetramethylheptadeca-3,7,11,15-tetraenyl)bicyclo[4.2.0] oct-1-en-3-one (78)



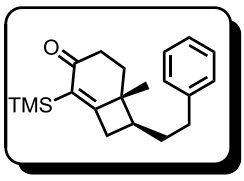
Yield: 76%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.14-5.07 (m, 4H), 2.82 (dd, *J* = 7.2 Hz, *J* = 14.8 Hz, 1H), 2.64 (ddd, *J* = 1.9 Hz, *J* = 9.5 Hz, *J* = 14.7 Hz, 1H), 2.46 (dt, *J* = 9.9 Hz, *J* = 17.3 Hz, 1H), 2.31 (dt, *J* = 3.3 Hz, *J* = 17.6 Hz, 1H), 2.08-1.90 (m, 16H), 1.70 (m, 1H), 1.67 (s, 3H), 1.60 (s, 12H), 1.28 (s, 3H), 1.03-0.81 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.3, 173.6, 135.3, 134.9, 134.4, 131.3, 125.0, 124.4, 124.2, 124.1, 118.0, 47.6, 44.7, 39.7(2C), 38.0, 37.9, 37.0, 34.7, 29.1, 28.25, 28.18, 26.77, 26.64, 25.7, 17.7, 16.1, 16.0, 15.9, 15.5; FTIR (neat): 2962, 2926, 2855, 1667, 1447, 1375, 1192, 732 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{46}OH^+$ 423.3627, found 423.3615.

2,6-dimethyl-7-phenethylbicyclo[4.2.0]oct-1-en-3-one (80)



Yield: 80%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 2.82 (dd, *J* = 7.2 Hz, *J* = 14.8 Hz, 1H), 2.61-2.48 (m, 4H), 2.35 (ddd, *J* = 2.0 Hz, *J* = 4.5 Hz, *J* = 17.7 Hz, 1H), 2.05-1.74 (m, 5H), 1.61 (s, 3H), 1.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.0, 166.2, 141.9, 128.43, 128.36, 126.0, 124.4, 47.2, 44.1, 37.8, 35.5, 35.2, 34.3, 32.6, 15.6, 9.8; FTIR (neat): 3024, 2932, 2857, 1705, 1651, 1203, 910, 752 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}OH^+$ 255.1749, found 255.1750.

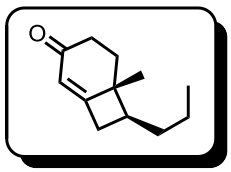
6-methyl-7-phenethyl-2-(trimethylsilyl)bicyclo[4.2.0]oct-1-en-3-one (82)



Yield: 85%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.26 (m, 2H), 7.23-7.18 (m, 3H), 2.98 (dd, *J* = 7.2 Hz, *J* = 15.2 Hz, 1H), 2.75 (dd, *J* = 9.6 Hz, *J* = 15.2 Hz, 1H), 2.58 (td, *J* = 3.1 Hz, *J* = 7.7 Hz, 2H), 2.50-2.41 (m, 1H), 2.34-2.28 (m, 1H), 2.09-1.76 (m, 5H), 1.28 (s, 3H), 0.15 (s, 9H),; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.4, 181.5, 141.9, 128.9, 128.44, 128.36, 126.0,

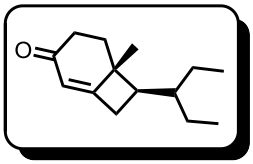
48.4, 43.6, 38.4, 37.2, 35.0, 34.4, 32.7,16.1, 0; FTIR (neat): 3026, 2930, 2855, 2358, 1650, 1624, 1497, 1454, 1244, 858, 837 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}OSiH^+$ 313.1988, found 313.1992.

6-methyl-7-propylbicyclo[4.2.0]oct-1-en-3-one (84)



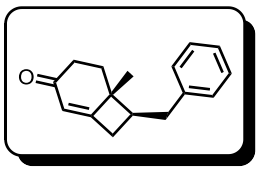
Yield: 89%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 2.82 (dd, *J* = 7.0 Hz, *J* = 14.9 Hz, 1H), 2.64 (ddd, *J* = 1.9 Hz, *J* = 9.5 Hz, *J* = 14.7 Hz, 1H), 2.50-2.41 (m, 1H), 2.30 (dt, *J* = 3.4 Hz, *J* = 17.7 Hz, 1H), 2.03-1.90 (m, 3H), 1.59-1.38 (m, 2H), 1.32-1.20 (m, 5H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 173.8, 117.9, 47.6, 45.1, 37.9, 37.2, 34.7, 32.9, 21.2, 15.4, 14.1; FTIR (neat): 2959, 2928, 2870, 1667, 1458, 1310, 1261, 1194, 855 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{18}OH^+$ 179.1436, found 179.1431.

6-methyl-7-(pentan-3-yl)bicyclo[4.2.0]oct-1-en-3-one (86)



Yield: 95%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.69 (s, 1H), 2.77 (dd, *J* = 7.1 Hz, *J* = 14.6 Hz, 1H), 2.67 (ddd, *J* = 1.8 Hz, *J* = 9.8 Hz, *J* = 14.4 Hz, 1H), 2.47 (ddd, *J* = 6.9, Hz, *J* = 12.4 Hz, *J* = 17.1 Hz, 1H), 2.30 (dt, *J* = 3.4 Hz, *J* = 17.8 Hz, 1H), 2.00-1.91 (m, 2H), 2.30 (td, *J* = 7.3 Hz, *J* = 10.4 Hz, 1H), 1.55 (m, 1H), 1.45-1.30 (m, 2H), 1.28 (s, 3H), 1.25-1.12 (m, 2H), 0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 173.3, 117.7, 48.8, 47.5, 41.0, 38.5, 36.1, 34.6, 23.4, 21.9, 15.4, 10.1, 9.9; FTIR (neat): 2963, 2920, 2874, 1662, 1458, 1381, 1310, 1261, 1196, 853 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}OH^+$ 207.1749, found 207.1748.

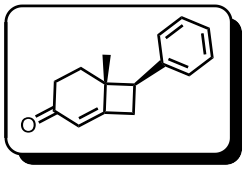
7-benzyl-6-methylbicyclo[4.2.0]oct-1-en-3-one (88)



Yield: 70%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.22-7.16 (m, 3H), 5.71 (s, 1H), 2.91 (dd, *J* = 7.5 Hz, *J* = 14.3 Hz, 1H), 2.84-2.79 (m, 3H), 2.49-2.36 (m, 2H), 2.31 (ddd, *J* = 2.1 Hz, *J* = 4.5 Hz, *J* = 18.1 Hz, 1H), 2.04 (td, *J* = 4.8 Hz, *J* = 12.9 Hz, 1H), 1.85 (ddd, *J* = 2.2 Hz, *J* = 5.3 Hz, *J* = 12.7 Hz, 1H), 1.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 173.0, 140.0, 128.5, 128.3, 126.2, 118.3, 47.9, 45.9, 37.8, 37.3, 36.8, 34.6, 15.8; FTIR (neat): 3026, 2963, 2928, 2857, 1665, 1497, 1452, 1194, 750, 700

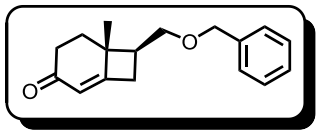
cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}OH^+$ 227.1436, found 227.1434.

6-methyl-7-phenylbicyclo[4.2.0]oct-1-en-3-one (90)



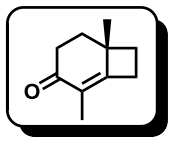
Yield: 85%, oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37-7.13 (m, 5H), 5.87 (s, 1H), 3.44-3.38 (m, 2H), 3.07 (m, 1H), 2.50 (ddd, *J* = 4.9 Hz, *J* = 14.1 Hz, *J* = 17.7 Hz, 1H), 2.41 (dddd, *J* = 0.7 Hz, *J* = 2.1 Hz, *J* = 4.8 Hz, *J* = 17.7 Hz, 1H), 2.23 (td, *J* = 5.1 Hz, *J* = 12.7 Hz, 1H), 2.09 (ddd, *J* = 2.2 Hz, *J* = 4.8 Hz, *J* = 12.4 Hz, 1H), 1.02 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.0, 172.3, 138.7, 128.4, 127.3, 126.7, 118.9, 50.3, 49.2, 38.0, 34.8, 34.0, 16.9; HRMS (ESI) calcd for $C_{15}H_{16}OH^+$ 213.1279, found 213.1276.

7-(benzyloxymethyl)-6-methylbicyclo[4.2.0]oct-1-en-3-one (92)



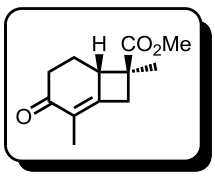
Yield: 91%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.30 (m, 5H), 5.73 (s, 1H), 4.52 (s, 2H), 3.64 (t, *J* = 9.1 Hz, 1H), 3.55 (dd, *J* = 5.8 Hz, *J* = 9.7 Hz, 1H), 2.85-2.73 (m, 2H), 2.52-2.23 (m, 3H), 1.99 (m, 2H), 1.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 172.9, 138.2, 128.4, 127.7, 127.6, 118.5, 73.1, 70.1, 47.5, 43.9, 37.8, 34.7, 34.1, 15.4; FTIR (neat): 3063, 3032, 2930, 2862, 2360, 1715, 1650, 1454, 1271, 1200, 1099, 1070, 750 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}O_2H^+$ 257.1542, found 257.1634.

2,6-dimethylbicyclo[4.2.0]oct-1-en-3-one (94)



Yield: 70%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.01 (m, 1H), 2.70 (ddd, *J* = 15.5 Hz, *J* = 7.9 Hz, *J* = 2.6 Hz, 1H), 2.48 (ddd, *J* = 17.7 Hz, *J* = 14.3 Hz, *J* = 4.9 Hz, 1H), 2.34 (ddd, *J* = 17.7 Hz, *J* = 4.9 Hz, *J* = 2.1 Hz, 1H), 2.00 (td, *J* = 12.8 Hz, *J* = 4.9 Hz, 1H), 1.95 (td, *J* = 9.9 Hz, *J* = 2.7 Hz, 1H), 1.89-1.80 (m, 2H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.9, 169.0, 124.6, 45.5, 37.2, 35.4, 33.5, 29.0, 21.3, 9.6; FTIR (neat): 2957, 2926, 1662, 1654, 1454, 1340, 1205, 997 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{14}OH^+$ 151.1123, found 151.1119.

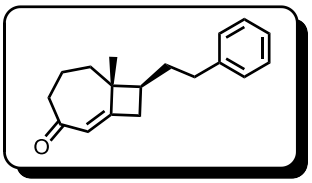
Methyl 2,7-dimethyl-3-oxobicyclo[4.2.0]oct-1-ene-7-carboxylate (96)



yield: 76%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H), 3.50 (m, 1H), 3.33 (m, 1H), 2.46-2.54 (m, 2H), 2.33(ddd, *J* = 16.6 Hz, *J* = 13.9 Hz, *J* = 5.1 Hz, 1H), 1.92-1.81 (m, 2H), 1.63 (s, 3H), 1.27 (s,

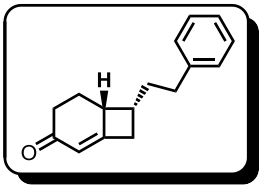
3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 176.3, 159.9, 128.2, 52.3, 48.4, 43.4, 40.9, 37.4, 24.8, 17.4, 9.5; FTIR (neat): 2951, 2874, 1730, 1666, 1452, 1435, 1377, 1354, 1306, 1238, 1134, 1093 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{15}O_3H^+$ 209.1178, found 209.1183.

7-methyl-8-phenethylbicyclo[5.2.0]non-1-en-3-one (98)



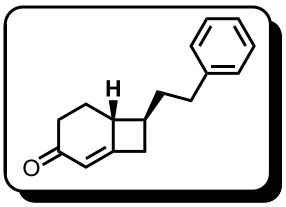
Yield: 82%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 5.77 (s, 1H), 2.73-2.64 (m, 2H), 2.59-2.45 (m, 4H), 2.05-1.66 (m, 7H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.9, 169.5, 141.9, 128.4, 128.3, 125.9, 123.7, 52.9, 43.0, 42.0, 39.0, 35.6, 34.1, 32.1, 20.5, 17.61; FTIR (neat): 3061, 3024, 2959, 2934, 2855, 2247, 1659, 1454, 1244, 910, 733, 700 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}OH^+$ 255.1749, found 255.1742.

7-phenethylbicyclo[4.2.0]oct-1-en-3-one (102)



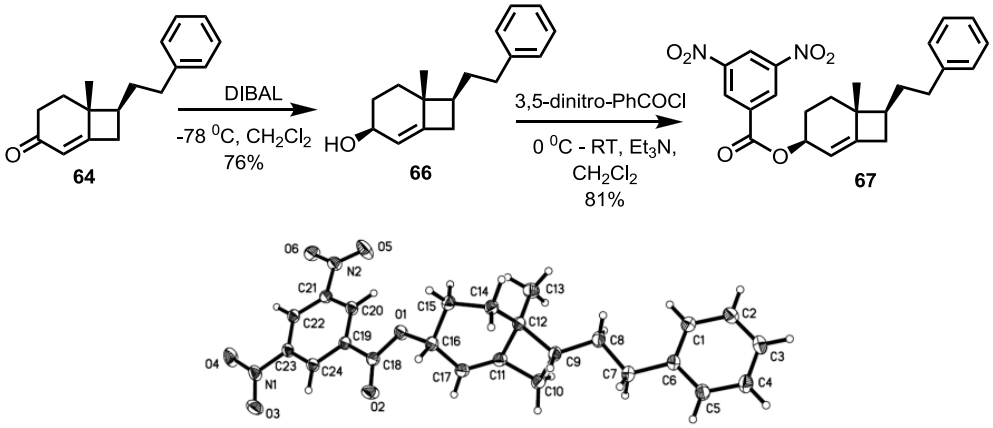
yield: 93%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.21-7.14 (m, 3H), 5.81 (s, 1H), 3.30 (m, 1H), 3.12 (ddd, *J* = 15.9 Hz, *J* = 9.4 Hz, *J* = 1.8 Hz, 1H), 2.68-2.51 (m, 3H), 2.46-2.35(m, 2H), 2.26 (m, 1H), 1.94-1.88 (m, 2H), 1.80 (m, 1H), 1.66 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.2, 173.3, 141.7, 128.5, 128.4, 126.0, 120.8, 44.4, 37.4, 36.5, 34.8, 34.3, 31.4, 25.1; FTIR (neat): 3029, 2930, 2857, 1666, 1497, 1454, 1312 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}OH^+$ 227.1436, found 227.1434.

7-phenethylbicyclo[4.2.0]oct-1-en-3-one (104)



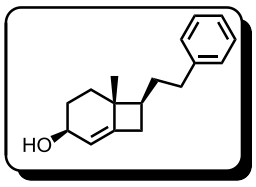
yield: 94%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31-7.26 (m, 2H), 7.21-7.16 (m, 3H), 5.73 (s, 1H), 2.87 (ddd, *J* = 15.0 Hz, *J* = 6.4 Hz, *J* = 2.3 Hz, 1H), 2.79-2.73 (m, 1H), 2.67-2.53 (m, 3H), 2.39(dt, *J* = 17.3 Hz, *J* = 2.6 Hz, 1H), 2.26 (ddd, *J* = 17.0 Hz, *J* = 14.6 Hz, *J* = 4.7 Hz, 1H), 2.18 (m, 1H), 2.03 (m, 1H), 1.97-1.90 (m, 2H), 1.79-1.69 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 170.0, 141.5, 128.5, 128.3, 126.0, 118.7, 49.1, 40.5, 38.0, 37.9, 37.4, 33.9, 30.5; FTIR (neat): 3026, 2922, 2857, 1660, 1497, 1454, 1310, 1186 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}OH^+$ 227.1436, found 227.1438.

Preparation of the ester derivative of 64 for X-ray diffraction study



To a solution of **64** (480 mg, 2 mmol) in 5 mL dry dichloromethane was added DIBAL-H (1 M in heptane, 2.4 mL, 1.2 equiv) dropwise at -78 °C. The mixture was stirred at that temperature for 2 hours, then quenched by the addition of saturated NH_4Cl solution followed by 5 mL 1 N HCl. The layer was separated and the aqueous layer was re-extracted with Et_2O (3 × 5 mL). The combined organic layer was washed with brine (once), dried over MgSO4, filtered, and concentrated in *vacuo* to obtain crude alcohol. Flash chromatography with hexane/EA as the eluent afforded **66** (732 mg) as a colorless oil in 76% yield.

6-methyl-7-phenethylbicyclo[4.2.0]oct-1-en-3-ol (66)

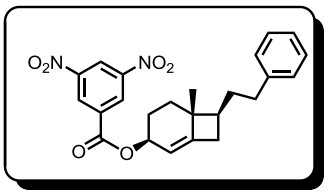


Yield: 76%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.20-7.15 (m, 3H), 5.32 (s, 1H), 4.30 (m, 1H), 2.58 (dd, *J* = 6.5 Hz, *J* = 12.7 Hz, 1H), 2.51 (m, 2H), 2.44(m, 1H), 2.01 (m, 1H), 1.87-1.78 (m, 2H), 1.75-1.67 (m, 1H), 1.62 (m, 1H), 1.56-1.42 (m, 3H), 1.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0, 142.3, 128.4, 128.3, 125.8, 116.7, 69.0, 47.0, 45.7, 37.3, 36.8, 34.6, 32.8, 29.9, 17.3; FTIR (neat): 3450, 2927, 2854, 1451, 1196, 845, 716 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}OH^+$ 243.1749, found 243.1745.

The alcohol **66** (486 mg, 2 mmol) was dissolved in dichloromethane (5 mL) and 3,5 -dinitrobenzoyl chloride (691 mg, 3 mmol) and pyridine (364 mg, 4 mmol) were added. The yellow solution was stirred at room temperature for overnight. Saturated NH_4Cl-solution (10 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was dried with Na $_2SO_4$ and the solvent was

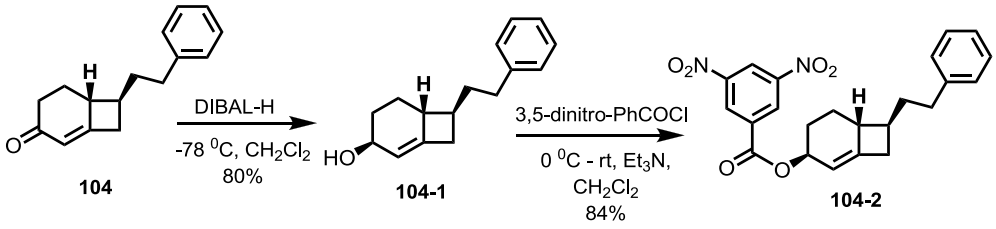
removed in vacuo. The residue was purified by flash chromatography to afford the ester **67** (708 mg) as a pale yellow solid in 81% yield.

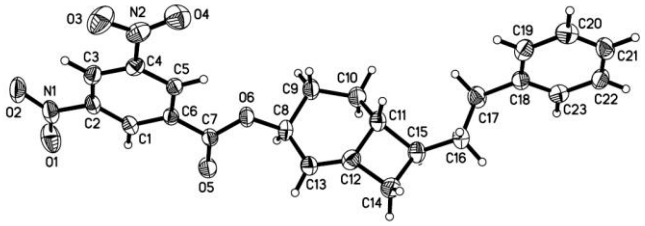
6-methyl-7-phenethylbicyclo[4.2.0]oct-1-en-3-yl 3,5-dinitrobenzoate (67)



Yield: 81%, pale yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (s, 1H), 9.15 (s, 2H), 7.30-7.25 (m, 2H), 7.20-7.15 (m, 3H), 5.74 (m, 1H), 5.42 (m, 1H), 2.67 (dd, *J* = 6.4 Hz, *J* = 12.8 Hz, 1H), 2.56-2.50 (m, 3H), 2.19 (m, 1H), 1.93-1.83 (m, 3H), 1.78-1.72 (m, 2H), 1.66-1.57 (m, 1H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6, 152.2, 148.6, 142.1, 134.6, 129.5, 128.37, 128.36, 125.9, 122.2, 111.7, 75.1, 46.9, 45.5, 37.0, 36.9, 34.5, 32.7, 25.2, 17.0; FTIR (neat): 3019, 2399, 1636, 1215, 771, 756 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{24}N_2O_6H^+$ 437.1713, found 437.1948.

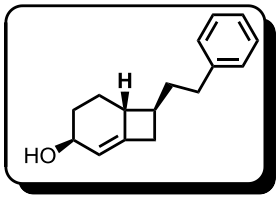
Preparation of the ester derivative of 104 for X-ray diffraction study





The procedure is similar with that of compound **64-2**.

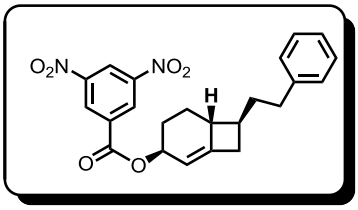
7-phenethylbicyclo[4.2.0]oct-1-en-3-ol (104-1)



Yield: 86%, oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29-7.26 (m, 2H), 7.19-7.15 (m, 3H), 5.32 (s, 1H), 4.33 (bs, 1H), 2.58 (dd, *J* = 4.,8 Hz, *J* = 12.5 Hz, 1H), 2.57 (m, 2H), 2.46 (m, 1H), 2.34 (m, 1H), 2.11 (m, 1H), 1.92 (m, 1H), 1.87-1.78 (m, 3H), 1.37 (m, 1H), 1.34-1.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.9, 142.2, 128.4, 128.3, 125.8, 116.5, 69.0, 49.1, 41.8, 38.1, 37.4, 34.1, 32.7, 29.4; FTIR (neat): 3340, 2922,

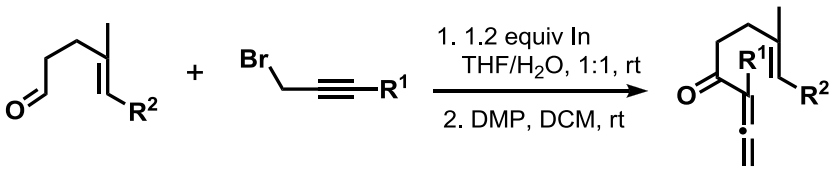
2853, 1697, 1603, 1495, 1452, 1103 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}OH^+$ 251.1412, found 251.1417.

7-phenethylbicyclo[4.2.0]oct-1-en-3-yl 3,5-dinitrobenzoate (104-2)



Yield: 87%, pale yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ 9.20-9.10 (m, 3H), 7.31-7.26 (m, 2H), 7.20-7.16 (m, 3H), 5.78 (m, 1H), 5.41 (m, 1H), 2.73 (dd, *J* = 5.4 Hz, *J* = 13.2 Hz, 1H), 2.64-2.55 (m, 3H), 2.42 (dd, *J* = 7.5 Hz, *J* = 12.9 Hz, 1H), 2.27 (m, 1H), 2.03 (m, 1H), 1.97-1.78 (m, 3H), 1.64 (m, 1H), 1.45 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 149.1, 148.6, 134.6, 129.5, 128.4, 125.9, 122.2, 111.6, 75.1, 48.6, 41.5, 38.0, 37.6, 34.1, 29.0, 27.8; FTIR (neat): 3104, 2928, 1724, 1628, 1543, 1454, 1344, 1273, 1167, 1074 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{22}N_2O_6H^+$ 423.1556, found 423.1557.

Preparation of substrates



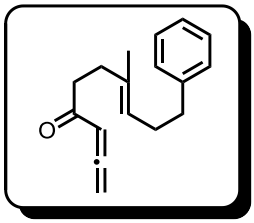
General procedure for preparation of eneallenones:

All of the tested eneallenones were prepared according to a modified procedure of literature.[46] Propargyl bromide (7.5 mmol, 1.5 equiv) was added to a mixture of indium powder (7.5 mmol, 1.5 equiv) and the corresponding aldehyde (5 mmol) in THF/H_2O (1:1) (10 mL) at room temperature. Then, the mixture was stirred at room temperature and monitored by TLC analysis. The mixture was extracted with diethyl ether (3 × 10 mL) after the disappearance of the starting material. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to give a mixture of homopropargylic alcohol and allenic alcohol in 50-90% yields. Then, a solution of the above prepared mixture of alcohols (1 mmol) in dichloromethane (1 mL) was added to a solution of Dess-Martin periodinane (DMP) (509 mg, 1.2 mmol) in

[46] (a) Lin, M. J., Loh, T. P., *J. Am. Chem. Soc.* **2003**, 125, 13042. (b) Hashmi, A. S. K., Ruppert, T. L., Knofel, T., Bats, J. W. *J. Org. Chem*. **1997**, 62, 7295.

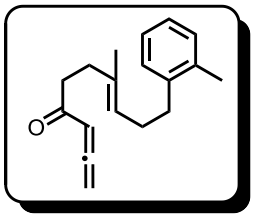
dichloromethane (4 mL) with stirring at room temperature. After disappearance of the starting material (TLC), the solvent was removed under vacuum and the residue was purified by silica gel column chromatography to give analytically pure eneallenones in 70-95% yields.

(E)-7-methyl-10-phenyldeca-1,2,7-trien-4-one



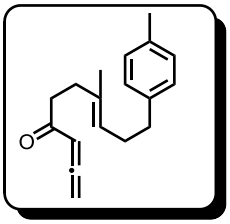
Yield: 96%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.77 (t, *J* = 6.5 Hz, 1H), 5.22 (d, *J* = 6.5 Hz, 2H), 5.18 (t, *J* = 7.2 Hz, 1H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.30 (t, *J* = 7.4 Hz, 2H), 2.26 (t, *J* = 7.4 Hz, 2H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 200.4, 142.2, 134.5, 128.5, 128.2, 125.7, 124.2, 96.7, 79.4, 38.0, 36.0, 34.2, 29.9, 16.0; FTIR (neat): 2922, 2854, 1956, 1932, 1680, 1452, 1155, 849, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{20}OH^{+}$ 241.1592, found 241.1595.

(E)-7-methyl-10-o-tolyldeca-1,2,7-trien-4-one



Yield: 92%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.12 (m, 4H), 5.78 (t, *J* = 6.5 Hz, 1H), 5.24 (d, *J* = 6.5 Hz, 2H), 5.23 (t, *J* = 7.1 Hz, 1H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 2.32 (s, 3H), 2.28 (t, *J* = 7.4 Hz, 2H), 2.26 (t, *J* = 7.4 Hz, 2H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 200.4, 140.3, 135.9, 134.4, 130.1, 128.9, 125.88, 125.86, 124.4, 96.7, 79.5, 38.0, 34.2, 33.3, 28.7, 19.4, 16.0; FTIR (neat): 3017, 2934, 1960, 1931, 1674, 1456, 1215, 849, 754, 667 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}OH^{+}$ 255.1749, found 255.1744.

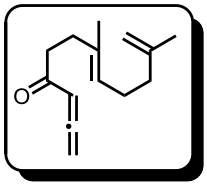
(E)-7-methyl-10-p-tolyldeca-1,2,7-trien-4-one



Yield: 95%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (m, 4H), 5.78 (t, *J* = 6.4 Hz, 1H), 5.23 (d, *J* = 6.4 Hz, 2H), 5.19 (t, *J* = 7.0 Hz, 1H), 2.69 (t, *J* = 8.2 Hz, 2H), 2.59 (t, *J* = 8.2 Hz, 2H), 2.32 (s, 3H), 2.30-2.20 (m, 4H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 200.5, 139.2, 135.1, 134.3, 128.9, 128.3, 124.4, 96.7, 79.4, 38.0, 35.5, 34.2, 30.0, 21.0, 16.0; FTIR (neat): 2980, 2920, 2854, 1958, 1933, 1668, 1514, 1155, 808,

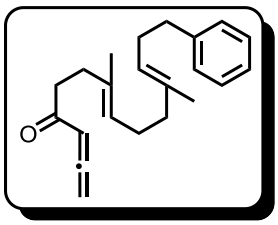
771 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}OH^+$ 255.1749, found 255.1743.

(E)-7,11-dimethyldodeca-1,2,7,11-tetraen-4-one



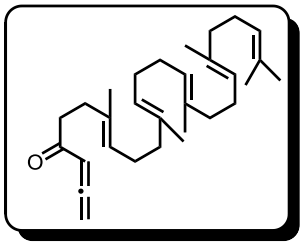
Yield: 81%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (t, *J* = 6.5 Hz, 1H), 5.23 (d, *J* = 6.5 Hz, 2H), 5.13 (t, *J* = 6.6 Hz, 1H), 4.70 (s, 1H), 4.66 (s, 1H), 2.69 (t, *J* = 7.6 Hz, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 2.13 (d, *J* = 7.1 Hz, 1H), 2.09 (d, *J* = 7.1 Hz, 1H), 2.01 (t, *J* = 7.6 Hz, 2H), 1.71 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 200.5, 145.7, 133.8, 124.7, 109.9, 96.7, 79.4, 38.0, 37.7, 34.3, 26.2, 22.5, 16.0; FTIR (neat): 3068, 2966, 2931, 2855, 1957, 1933, 1682, 1649, 1447, 1155, 885, 847 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{20}OH^+$ 205.1592, found 205.1583.

(7E,11E)-7,11-dimethyl-14-phenyltetradeca-1,2,7,11-tetraen-4-one



Yield: 90%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.77 (t, *J* = 6.5 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 2H), 5.17 (td, *J* = 7.0 Hz, *J* = 0.9 Hz, 1H), 5.10 (td, *J* = 6.8 Hz, *J* = 0.9 Hz, 1H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.60 (t, *J* = 7.6 Hz, 2H), 2.30 (t, *J* = 7.6 Hz, 2H), 2.26 (t, *J* = 7.6 Hz, 2H), 2.20 (t, *J* = 7.5 Hz, 2H), 1.96 (t, *J* = 8.2 Hz, 2H), 1.60 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 200.5, 142.4, 135.6, 133.6, 128.5, 128.2, 125.7, 124.9, 123.7, 96.7, 79.4, 39.6, 38.1, 36.1, 34.3, 30.0, 26.7, 16.1, 16.0; FTIR (neat): 3026, 2978, 2926, 2855, 1960, 1933, 1674, 1558, 1452, 1217, 1155 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{28}OH^+$ 309.2218, found 309.2216.

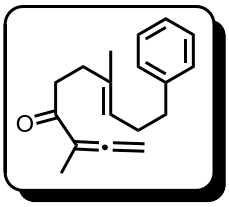
(7E,11E,15E,19E)-7,11,16,20,24-pentamethylpentacosa-1,2,7,11,15,19,23-heptaen-4-one



Yield: 72%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (t, *J* = 6.5 Hz, 1H), 5.23 (d, *J* = 6.5 Hz, 2H), 5.15-5.07 (m, 5H), 2.69 (t, *J* = 7.7 Hz, 2H), 2.26 (t, *J* = 7.7 Hz, 2H), 2.11-1.95 (m, 16H), 1.68 (s, 3H), 1.60 (s, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 200.5, 135.2, 134.9, 133.6, 131.3, 124.9, 124.43, 124.41, 124.3, 96.7, 79.4, 39.8, 39.7, 39.6, 38.1, 34.3, 28.3, 26.8, 26.7, 25.7, 17.7, 16.05, 16.03, 16.01;

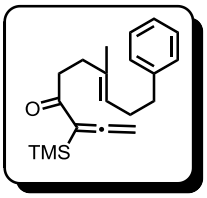
FTIR (neat): 2966, 2916, 2853, 1962, 1933, 1682, 1447, 1153, 846, 758 cm^{-1}; HRMS (ESI) calcd for $C_{30}H_{46}OH^+$ 423.3627, found 423.3623.

(E)-3,7-dimethyl-10-phenyldeca-1,2,7-trien-4-one



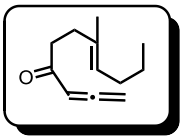
Yield: 82%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.19-7.15 (m, 3H), 5.17 (t, *J* = 7.0 Hz, 1H), 5.12 (q, *J* = 2.9 Hz, 2H), 2.73 (t, *J* = 8.0 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.29 (t, *J* = 8.0 Hz, 2H), 2.22 (t, *J* = 8.0 Hz, 2H), 1.78 (t, *J* = 2.9 Hz, 3H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 201.1, 142.2, 134.7, 128.5, 128.2, 125.7, 124.1, 103.5, 78.5, 37.7, 36.0, 34.8, 30.0, 16.0, 13.2; FTIR (neat): 3026, 2926, 2857, 1958, 1935, 1715, 1494, 1064, 848, 700 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}OH^+$ 255.1749, found 255.1748.

(E)-7-methyl-10-phenyl-3-(trimethylsilyl)deca-1,2,7-trien-4-one



Yield: 80%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.18-7.15 (m, 3H), 5.17 (t, *J* = 7.0 Hz, 1H), 4.8(s, 2H), 2.75 (t, *J* = 7.5 Hz, 2H), 2.62 (t, *J* = 7.5 Hz, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.53 (s, 3H), 0.16 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 218.1, 202.9, 142.3, 134.7, 128.5, 128.2, 125.7, 124.0, 102.6, 72.2, 39.0, 36.0, 34.4, 30.0, 16.0, -1.3; FTIR (neat): 3026, 2955, 2927, 2857, 1911, 1667, 1494, 1454, 1248, 1142, 843, 750, 698 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{28}OSiH^+$ 313.1988, found 313.1980.

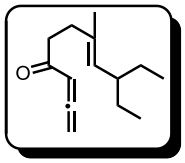
(E)-7-methylundeca-1,2,7-trien-4-one



Yield: 83%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (t, *J* = 6.5 Hz, 1H), 5.22 (d, *J* = 6.5 Hz, 2H), 5.19 (td, *J* = 7.1 Hz, *J* = 1.1 Hz, 1H), 2.68 (t, *J* = 7.6 Hz, 2H), 2.25 (t, *J* = 7.6 Hz, 2H), 1.92 (q, *J* = 7.4 Hz, 2H), 1.58 (s, 3H), 1.38-1.25 (m, 2H), 0.86 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 200.5, 133.6, 125.3, 96.7, 79.4, 38.0, 34.4, 30.0, 22.9, 16.0, 13.8; FTIR (neat): 2959, 2930, 2868, 1960, 1933, 1674, 1155, 849 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{18}OH^+$ 179.1436, found 179.1435.

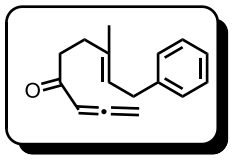
(E)-9-ethyl-7-methylundeca-1,2,7-trien-4-one

Yield: 75%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (t, *J* = 6.5 Hz, 1H), 5.21 (d, *J* =



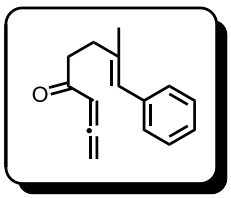
6.5 Hz, 2H), 4.80 (dd, *J* = 9.6 Hz, *J* = 1.0 Hz, 1H), 2.68 (t, *J* = 7.7 Hz, 2H), 2.27 (t, *J* = 7.7 Hz, 2H), 1.98 (m, 1H), 1.58 (d, J = 1.2 Hz, 3H), 1.43-1.29 (m, 2H), 1.17-1.02 (m, 2H), 0.77 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 200.5, 133.5, 130.5, 96.7, 79.3, 41.3, 38.2, 34.7, 28.4, 16.5, 11.8; FTIR (neat): 2959, 2920, 2872, 2855, 1960, 1933, 1682, 1456, 1155, 870, 847, 756 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}OH^+$ 207.1749, found 207.1742.

(E)-7-methyl-9-phenylnona-1,2,7-trien-4-one



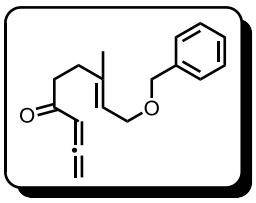
Yield: 86%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.19-7.15 (m, 3H), 5.77 (t, *J* = 6.5 Hz, 1H), 5.35 (t, *J* = 7.4 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 2H), 3.34 (d, *J* = 7.4 Hz, 2H), 2.73 (t, *J* = 7.4 Hz, 2H), 2.33 (t, *J* = 7.4 Hz, 2H), 1.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 200.3, 141.5, 134.9, 128.4, 128.3, 125.8, 123.6, 96.7, 79.5, 37.9, 34.22, 34.20,16.3; FTIR (neat): 3024, 2916, 2847, 2359, 1958, 1950, 1653, 1217, 850, 754 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}OH^+$ 227.1436, found 227.1433.

(E)-7-methyl-8-phenylocta-1,2,7-trien-4-one



Yield: 87%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.28 (m, 2H), 7.22-7.16 (m, 3H), 6.27 (s, 1H), 5.81 (t, *J* = 6.5 Hz, 1H), 5.25 (d, *J* = 6.5 Hz, 2H), 2.83 (t, *J* = 7.5 Hz, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 1.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 200.1, 138.2, 137.5, 128.8, 128.1, 126.1, 125.5, 96.8, 79.6, 37.9, 35.2, 17.9; FTIR (neat): 3061, 3022, 2984, 2934, 2857, 2359, 1958, 1932, 1682, 1489, 1445, 1155, 853, 745 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}OH^+$ 213.1279, found 213.1280.

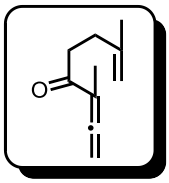
(E)-9-(benzyloxy)-7-methylnona-1,2,7-trien-4-one



Yield: 92%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 5H), 5.78 (t, *J* = 6.5 Hz, 1H), 5.39 (t, *J* = 6.7 Hz, 1H), 5.24 (d, *J* = 6.5 Hz, 2H), 4.50 (s, 2H), 4.01 (d, *J* = 6.7 Hz, 2H), 2.75 (t, *J* = 7.7 Hz, 2H), 2.33 (t, *J* = 7.7 Hz, 2H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 200.0, 139.0, 138.4, 128.4, 127.9, 127.6, 121.3, 96.7, 79.6, 72.2, 66.5, 37.4, 33.8, 16.7; FTIR (neat): 3065, 2976, 2938, 1717, 1454, 1273, 748, 700 cm^{-1};

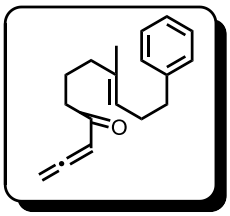
HRMS (ESI) calcd for $C_{17}H_{20}O_2H^+$ 257.1542, found 257.1541.

3,7-dimethylocta-1,2,7-trien-4-one



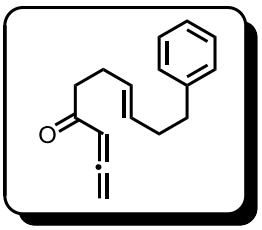
Yield: 96%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (m, 2H), 4.70 (s, 1H), 4.64 (s, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 2.28 (t, *J* = 7.6 Hz, 2H), 1.77 (m, 3H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 200.8, 144.8, 110.0, 103.5, 78.6, 37.1, 32.6, 22.6, 13.1; FTIR (neat): 3076, 2968, 2930, 1960, 1934, 1680, 1444, 1232 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{14}OH^+$ 151.1123, found 151.1121.

(E)-8-methyl-11-phenylundeca-1,2,8-trien-4-one



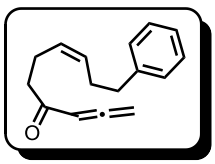
Yield: 94%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.15 (m, 5H), 5.77 (t, *J* = 6.5 Hz, 1H), 5.21 (d, *J* = 6.5 Hz, 2H), 5.18 (t, *J* = 7.0 Hz, 1H), 2.64 (t, *J* = 7.5 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 2.30 (m, 2H), 1.98 (t, *J* = 7.5 Hz, 2H), 1.70 (m, 2H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 200.9, 142.3, 135.0, 128.5, 128.2, 125.7, 124.4, 96.7, 79.3, 39.0, 38.6, 36.1, 29.9, 22.6, 15.7; FTIR (neat): 3063, 3024, 2930, 2855, 1958, 1933, 1678, 1454, 1362, 1152, 847, 748 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{22}OH^+$ 255.1759, found 255.1748.

(E)-10-phenyldeca-1,2,7-trien-4-one (E:Z>99:1)



Yield: 95%, oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.77 (t, *J* = 6.4 Hz, 1H), 5.48 (dt, *J* = 15.4 Hz, *J* = 6.0 Hz, 1H), 5.42 (dt, *J* = 15.4 Hz, *J* = 6.1 Hz, 1H), 5.23 (s, 1H), 5.22 (s, 1H), 2.67-2.62 (m, 4H), 2.31-2.25 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.7, 200.1, 142.0, 130.5, 129.1, 128.5, 128.3, 125.8, 96.7, 79.5, 39.1, 36.0, 34.4, 27.3; FTIR (neat): 3026, 2924, 1958, 1933, 1682, 1495, 1454, 1155, 970 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}OH^+$ 227.1436, found 227.1431.

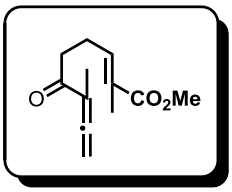
(Z)-10-phenyldeca-1,2,7-trien-4-one (Z:E = 96:4)



Yield: 94%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.25 (m, 2H), 7.19-7.15 (m, 3H), 5.75 (t, *J* = 6.5 Hz, 1H), 5.43 (dt, *J* = 10.7 Hz, *J* = 7.4 Hz, 1H), 5.34 (dt, *J* = 18.2 Hz, *J* = 10.5 Hz, 1H), 5.21 (s, 1H), 5.20 (s, 1H), 2.65 (t, *J* = 7.7 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 2.37 (m, 2H), 2.27 (m,

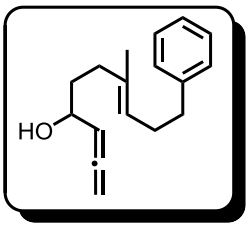
2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.7, 200.0, 141.9, 129.9, 128.6, 128.5, 128.3, 125.8, 96.6, 79.5, 39.0, 35.9, 29.1, 22.2; FTIR (neat): 3063, 3024, 2924, 1958, 1933, 1682, 1495, 1452, 1155, 850 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{18}OH^+$ 227.1436, found 227.1438.

(E)-methyl 2,7-dimethyl-6-oxonona-2,7,8-trienoate



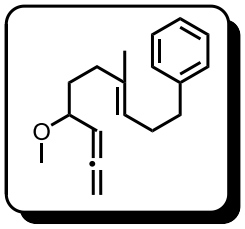
Yield: 92%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (t, *J* = 6.3 Hz, 1H), 5.15-5.13 (m, 2H), 3.71 (s, 3H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.44 (m, 2H), 1.84 (s, 3H), 1.78 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.3, 199.9, 168.6, 140.8, 128.4, 103.5, 78.9, 51.7, 37.4, 23.7, 13.1, 12.4; FTIR (neat): 2951, 2928, 1958, 1934, 1715, 1682, 1435, 1260, 1120, 852 cm^{-1}; ; HRMS (ESI) calcd for $C_{12}H_{15}O_3H^+$ 209.1178, found 209.1174.

(E)-7-methyl-10-phenyldeca-1,2,7-trien-4-ol



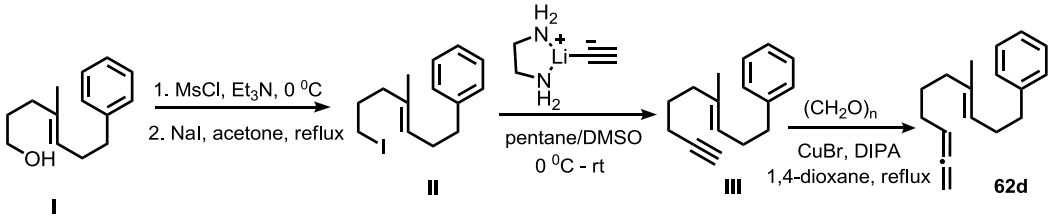
To a solution of ene-allenone **3a** (0.24 g, 1 mmol) in DCM (2 mL) was added DIBAL-H (1M in heptane, 1.2 mL, 1.2 mmol) dropwise at –78 °C. The mixture was stirred at that temperature for 1.5 h, then quenched by the addition of MeOH (1 mL) and saturated aqueous Rochelle's salt (5 mL). The resulting mixture was stirred vigorously until two clear layers were obtained (about 1 h). The two layers were separated and the aqueous layer was extracted with Et_2O (10 mL ×2). The combined organic layer was washed with brine (once), dried over $MgSO_4$, filtered, and concentrated in *vacuo*. Flash chromatography (*n*-hexane/EtOAc= 6:1) of a small amount afforded **3b** 0.22g (91% yield) as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34-7.31 (m, 2H), 7.25-7.22 (m, 3H), 5.31-5.27(m, 2H), 4.91-4.89 (m, 2H), 4.18 (bs, 1H), 2.70 (t, *J* = 7.4 Hz, 2H), 2.38 (m, 2H), 2.14 (m, 2H), 1.99 (s, 1H), 1.69-1.75 (m, 2H), 1.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 142.3, 135.3, 128.5, 128.3, 125.8, 124.2, 94.8, 77.5, 69.4, 36.1, 35.6, 35.5, 30.0, 16.0; FTIR (neat): 3447, 2926, 2855, 1956, 1684, 1454, 1072, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{22}OH^+$ 243.1749, found 243.1748.

(E)-(7-methoxy-4-methyldeca-3,8,9-trienyl)benzene

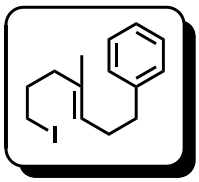


To a suspension of alcohol **70b** (0.194 g, 0.8 mmol) and NaH (~55% dispersion in oil) (0.049 g, 1 mmol) in dry DMF (2 mL) at 0 °C was added iodomethane (0.142 g, 1 mol). The dark red reaction mixture was stirredfrom at 0 °C for 1.5 h. After the completion of the reaction (monitored by TLC), the reaction mixture was poured into ice water and extracted with ethyl acetate (3 × 5 mL). The organic extracts were combined and washed with brine. After drying with anhydrous Na_2SO_4 and evaporation of the solvent, the residue was purified by flash chromatography (*n*-hexane/EtOAc = 10:1) to **70c** as a colorless oil (0.191 g, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.19-7.15 (m, 3H), 5.19 (t, *J* = 7.1 Hz, 1H), 4.97 (m, 1H), 4.77 (m, 2H), 3.60 (m, 1H), 3.30 (s, 3H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.30 (m, 2H), 2.04 (m, 2H), 1.72 (m, 1H), 1.59 (m, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.8, 142.3, 135.2, 128.5, 128.2, 125.7, 124.0, 91.2, 79.6, 75.5, 56.1, 36.1, 35.3, 34.2, 29.9, 16.0; FTIR (neat): 2926, 2855, 1954, 1684, 1497, 1454, 1362, 1105, 1094, 842, 698 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{24}OH^+$ 257.1905, found 257.1909.

Preparation of allene 62d:



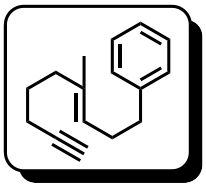
(E)-(7-iodo-4-methylhept-3-enyl)benzene



Triethylamine (0.83 mL, 6 mmol) and methanesulfonyl chloride (0.43 mL, 6 mmol) were added to a solution of the alcohol **I** (1.02 g, 5 mmol) in DCM (20 mL) at 0 °C. The mixture was stirred 1 h at 0 °C and quenched with water (10 mL). The aqueous layer was extracted with ethyl acetate (3 × 15 mL), and the combined organic layer was washed once with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The crude mesylate was used directly without further purification. The above mesylate (5 mmol) and sodium iodide (1.05 g, 7.5 mmol) were refluxed in acetone (30 mL) for 16

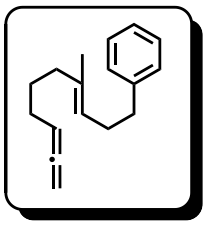
h, and the mixture was quenched with water (25 mL). The aqueous layer was extracted with ethyl acetate (4 × 25 mL), and the combined organic layer was washed once with brine, dried over anhydrous Na_2SO_4, and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-hexane/ether = 20:1) to yield pure iodide **II** (1.4 g, 89% for two steps) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.15 (m, 5H), 5.23 (t, *J* = 7.2 Hz, 1H), 3.08 (t, *J* = 6.9 Hz, 2H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.31 (m, 2H), 2.05 (t, *J* = 7.2 Hz, 1H), 1.88 (m, 2H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.2, 133.7, 128.5, 128.3, 125.8, 125.2, 40.0, 36.0, 31.5, 30.0, 15.8, 6.8; FTIR (neat): 2927, 2853, 1494, 1452, 1217, 1165, 698 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{19}IH^+$ 315.610, found 315.0598.

(E)-(4-methylnon-3-en-8-ynyl)benzene



A solution of the iodide **II** (0.314 g, 1 mmol) in diethyl ether (5 mL) was slowly added to lithium acetylide complexed with ethylene diamine (90%, 0.2 g, 2 mmol) in pentane : DMSO solvent system (5:2, 10 mL) at 0 °C. The mixture was stirred, allowed to slowly warm up to RT for 16 h, and then quenched with a half-saturated NH_4Cl aqueous solution (10 mL). The aqueous layer was extracted with diethyl ether (3 × 5 mL), and the combined organic layer was washed once with water, once with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-hexane/ether = 50:1) to give **III** 0.18 g (85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29-7.15 (m, 5H), 5.20 (t, *J* = 7.1 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.31 (m, 2H), 2.13-2.04 (m, 4H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.60 (m, 2H), 1.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 134.7, 128.5, 128.3, 125.7, 124.5, 84.7, 68.3, 38.6, 36.1, 29.9, 26.7, 17.8, 15.8; FTIR (neat): 2937, 2857, 2116, 1602, 1495, 1452, 746, 698 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}H^+$ 213.1643, found 213.1639.

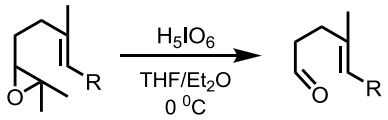
(E)-(4-methyldeca-3,8,9-trienyl)benzene



The preparation of allene **62d** is according to the literature[47]. Diisopropylamine (0.2 g, 2 mmol) was added to a stirred mixture of the alkyne **III** (0.212 g, 1 mmol), paraformaldehyde (60 mg, 2 mmol) and CuBr (43 mg, 0.3 mmol) in 1,4-dioxane (10 mL). The reaction was refluxed for overnight, then cooled to room temperature. The reaction mixture was poured into water and extracted with diethylether (3 × 5 mL), and the combined organic layer was washed once with water, once with brine, dried over anhydrous $MgSO_4$, and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel (*n*-hexane) to give **62d** 0.12 g (60 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.19-7.15 (m, 3H), 5.18 (t, *J* = 7.1 Hz, 1H), 5.09 (m, 1H), 4.67-4.64 (m, 2H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.30 (m, 2H), 2.00 (t, *J* = 7.6 Hz, 2H), 1.94 (m, 2H), 1.53 (s, 3H), 1.50 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 208.6, 142.4, 135.6, 128.5, 128.2, 125.7, 123.9, 90.0, 74.7, 39.0, 36.1, 29.9, 27.7, 27.3, 15.8; FTIR (neat): 2930, 2855, 1956, 1495, 1452, 1439, 842, 698 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}H^+$ 227.1800, found 227.1808.

Preparation of aldehyde:

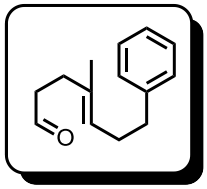
We have two different strategies for the preparation of aldehydes.



Procedure[48] 1: HIO_4•$2H_2O$ (5.5 mmol, 1.1 equiv) in THF (5 mL) was added dropwise to epoxide[49] (5 mmol) in Et_2O (10 mL) at 0 °C under N_2 over 0.5 h. The organic solution was washed with water, saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo to give an oil. The crude oil was purified by silica gel column chromatography to give desired aldehydes in 80-92% yields.

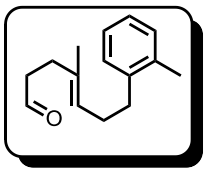
(E)-4-methyl-7-phenylhept-4-enal

[47] Crabbé, P., Fillion, H., André, D., Luche, J. L. J. *Chem. Commun*. **1979**, 859.
[48] Zoretic, P. A., Fang, H. Q., Ribeiro, A. A., *J. Org. Chem.* **1998**, 63, 7213.
[49] Zhao, J. F., Zhao, Y. J., Loh, T. P., *Chem. Commun.* **2008**, 1353.



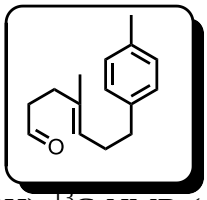
Yield: 92%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H), 7.31-7.25 (m, 2H), 7.21-7.16 (m, 3H), 5.21 (td, *J* = 1.2 Hz, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 2.64 (t, *J* = 7.6 Hz, 2H), 2.50 (m, 2H), 2.35-2.74 (m, 4H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 142.1, 133.8, 128.5, 128.2, 125.8, 124.7, 42.1, 35.9, 31.8, 29.9, 16.0; FTIR (neat): 3026, 2922, 2855, 2717, 1732, 1684, 1497, 1454, 748, 698 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}OH^{+}$ 203.1436, found 203.1434.

(E)-4-methyl-7-o-tolylhept-4-enal



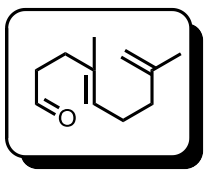
Yield: 86%, oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (t, *J* = 1.9 Hz, 1H), 7.12 (m, 4H), 5.25 (td, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 2.62 (dd, *J* = 7.5 Hz, *J* = 9.7 Hz, 2H), 2.52 (dd, *J* = 1.2 Hz, *J* = 7.8 Hz, 2H), 2.55-2.24 (m, 7H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.6, 140.2, 135.9, 133.8, 130.1, 128.9, 125.93, 125.87, 124.8, 42.1, 33.2, 31.8, 28.6, 19.3, 16.0; FTIR (neat): 2930, 2718, 1722, 1456, 1053, 743, 520 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}OH^{+}$ 217.1592, found 217.1599.

(E)-4-methyl-7-p-tolylhept-4-enal



Yield: 87%, oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H), 7.08 (m, 4H), 5.21 (td, *J* = 1.2 Hz, *J* = 7.2 Hz, 1H), 2.59 (dd, *J* = 7.2 Hz, *J* = 8.2 Hz, 2H), 2.52 (m, 2H), 2.34-2.25 (m, 7H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 139.0, 135.2, 133.6, 128.9, 128.3, 124.8, 42.1, 35.5, 31.8, 30.0, 21.0, 16.1; FTIR (neat): 2920, 2718, 1724, 1514, 1446, 808 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}OH^{+}$ 217.1592, found 217.1598.

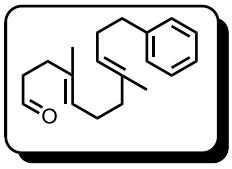
(E)-4,8-dimethylnona-4,8-dienal



Yield: 92%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.9 Hz, 1H), 5.16 (td, *J* = 1.3 Hz, *J* = 6.9 Hz, 1H), 4.70 (s, 1H), 4.67 (s, 1H), 2.52 (m, 2H), 2.32 (t, *J* = 7.5 Hz, 2H), 2.12 (m, 2H), 2.02 (m, 2H), 1.72 (s, 3H), 1.63 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 145.6, 133.1, 125.2, 110.0, 42.1, 37.6, 31.8, 26.1, 22.4, 16.1; FTIR (neat): 3073, 2916, 2955, 2718, 1726, 1649, 1445, 1387, 887, 758 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}OH^{+}$ 167.1436, found

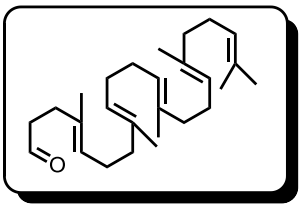
167.1433.

(4E,8E)-4,8-dimethyl-11-phenylundeca-4,8-dienal



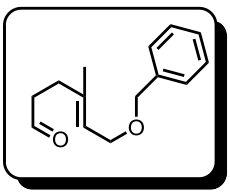
Yield: 85%, oil;^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (t, *J* = 1.9 Hz, 1H), 7.29-7.24 (m, 2H), 7.19-7.15 (m, 3H), 5.19-5.10 (m, 2H), 2.64 (dd, *J* = 7.2 Hz, *J* = 8.3 Hz, 2H), 2.49 (dt, *J* = 1.0 Hz, *J* = 7.6 Hz, 2H), 2.33-2.26 (m, 4H), 2.11-1.95 (m, 4H), 1.61 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 142.4, 135.5, 132.9, 128.5, 128.2, 125.7, 125.4, 123.8, 42.2, 39.5, 36.1, 31.9, 29.9, 26.5, 16.1, 15.9; FTIR (neat): 3061, 3024, 2920, 2855, 2716, 1724, 1495, 1452, 1385, 748, 698 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{26}OH^{+}$ 271.2062, found 271.2064.

(4E,8E,12E,16E)-4,8,13,17,21-pentamethyldocosa-4,8,12,16,20-pentaenal



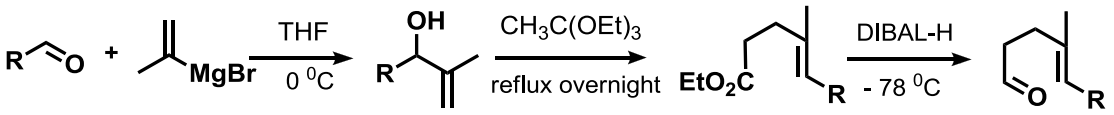
Yield: 82%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.9 Hz, 1H), 5.17-5.07 (m, 5H), 2.50 (td, *J* = 1.2 Hz, *J* = 7.7 Hz, 2H), 2.31 (t, *J* = 7.3 Hz, 2H), 2.11-1.95 (m, 16H), 1.68 (s, 3H), 1.60 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.7, 135.2, 134.9, 134.8, 132.9, 131.3, 125.4, 124.5, 124.4, 124.3(2C), 42.2, 39.7, 39.5, 31.9, 28.3(2C), 26.8, 26.7, 26.6, 25.7, 17.7, 16.08, 16.05,16.0(2C); FTIR (neat): 2965, 2916, 2853, 2716, 1728, 1635, 1446, 1385, 758 cm^{-1}; HRMS (ESI) calcd for $C_{27}H_{44}OH^{+}$ 385.3470, found 385.3456.

(E)-6-(benzyloxy)-4-methylhex-4-enal



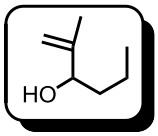
Yield: 80%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.77 (t, *J* = 1.9 Hz, 1H), 7.36-7.27 (m, 5H), 5.42 (t, *J* = 6.6 Hz, 1H), 4.50 (s, 2H), 4.02 (d, *J* = 6.6 Hz, 2H), 2.57 (t, *J* = 7.5 Hz, 2H), 2.37 (t, *J* = 7.5 Hz, 2H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 138.4, 138.52, 128.4, 127.8, 127.6, 121.8, 72.3, 66.4, 41.8, 31.5, 16.7; FTIR (neat): 3065, 3030, 2930, 2857, 1717, 1636, 1454, 1361, 1086, 737 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_2H^{+}$ 219.1385, found 219.1382.

Procedure[50] 2:



To a solution of corresponding aldehyde (30 mmol) in THF (30 mL) was added 2-propenylmagnesium bromide (1.0 M in THF, 45 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 24 h, followed by quenching with saturated NH_4Cl solution (50 mL). The ultimate reaction mixture was extracted with Et_2O (2 × 100 mL), washed with brine (once), dried over anhydrous $MgSO_4$, concentrated in *vacuo*. Purification by flash column chromatography provided the allylic alcohols as colorless oil. A solution of the allylic alcohol (30 mmol) and propanoic acid (1 mL) in triethyl orthoacetate (50 mL) was heated with stirring to 145 °C. Heating was continued until ethanol was no longer distilled from the reaction mixture. The solution was cooled to room temperature and washed successively with 2 M aqueous HCl (100 mL), saturated aqueous $NaHCO_3$ solution (100 mL) and brine (100 mL). The solution was dried ($MgSO_4$) and concentrated *in vacuo* to yield the ester as pungent colourless oil in 85-96% yields. To a solution of the above prepared esters (5 mmol) in 5 mL dry dichloromethane was added DIBAL-H (1 M in heptane, 6 mL, 1.2 equiv) dropwise at -78 °C. The mixture was stirred at that temperature for 2.5 h, then quenched by adding MeOH (5 mL) and saturated aqueous Rochelle's salt (50 mL). The resulting mixture was stirred vigorously until two clear layers were obtained (about 2 h). The two layers were separated and the aqueous layer was re-extracted with Et_2O (3 × 20 mL). The combined organic layer was washed with brine (once), dried over $MgSO_4$, filtered, and concentrated in *vacuo* to obtain crude aldehyde**s**. Flash chromatography with hexane/EA as the eluent afforded the desired products as colorless oil in 75-86% yields.

2-methylhex-1-en-3-ol

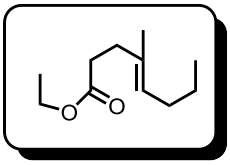


^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.84 (s, 1H), 4.09 (t, *J* = 6.5

[50] Clarke, P. A., Grist, M., Ebden, M., Wilson, C., Blake, A. J. *Tetrahedron* **2005**, *61*, 353.

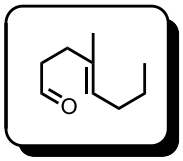
Hz, 1H), 1.74 (s, 3H), 1.65 (bs, 1H), 1.55-1.21 (m, 4H), 0.91 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 110.8, 75.7, 37.1, 18.8, 14.0, 13.7; FTIR (neat): 3073, 2959, 2934, 2872, 1715, 1651, 1456, 1377, 1007, 899 cm^{-1}; HRMS (ESI) calcd for $C_7H_{14}OH^+$ 115.1123, found 115.1113.

(E)-ethyl 4-methyloct-4-enoate



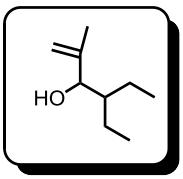
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (t, *J* = 7.2 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 2.39 (td, *J* = 1.4 Hz, *J* = 7.7 Hz, 2H), 2.34-2.27 (m, 2H), 1.94 (q, *J* = 7.4 Hz, 2H), 1.60 (s, 3H), 1.32 (m, 2H), 1.24 (t, *J* = 7.1 Hz, 3H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 133.3, 125.4, 60.2, 34.7, 33.3, 29.9, 22.8, 15.9, 14.2, 13.7; FTIR (neat): 2961, 2932, 2872, 1738, 1447, 1371, 1178, 1157, 1031, 758 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{20}OH^+$ 169.1592, found 169.1609.

(E)-4-methyloct-4-enal



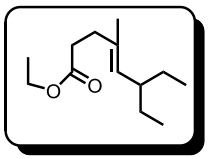
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.9 Hz, 1H), 5.16 (t, *J* = 7.0 Hz, 1H), 2.51 (td, *J* = 0.8 Hz, *J* = 7.0 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 1.99-1.91 (m, 2H), 1.61 (s, 3H), 1.42-1.27 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 132.9, 125.7, 42.2, 31.9, 29.9, 22.8, 16.1, 13.8; FTIR (neat): 2959, 2930, 2862, 2716, 1717, 1636, 1387, 769 cm^{-1}; HRMS (ESI) calcd for $C_9H_{16}OH^+$ 141.1279, found 141.1278.

4-ethyl-2-methylhex-1-en-3-ol



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.95 (s, 1H), 4.89 (s, 1H), 3.99 (m, 1H), 1.70 (s, 3H), 1.61-1.51 (m, 1H), 1.44-1.26 (m, 5H), 0.91-0.87 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 111.7, 77.2, 43.0, 21.9, 20.1, 18.0, 11.1, 11.0; FTIR (neat): 3071, 2955, 2936, 2876, 1705, 1647, 1458, 1379, 1022, 1003, 897 cm^{-1}; HRMS (ESI) calcd for $C_9H_{18}OH^+$ 143.1436, found 143.1499.

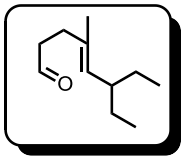
(E)-ethyl 6-ethyl-4-methyloct-4-enoate



^{1}H NMR (400 MHz, $CDCl_3$) δ 4.85 (d, *J* = 9.8 Hz, 1H), 4.11 (q, *J* = 7.1 Hz, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 2.32 (t, *J* = 7.4 Hz, 2H), 2.01 (m, 1H), 1.61 (s, 3H), 1.39 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12

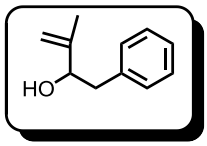
(m, 2H), 0.79 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 133.2, 130.6, 60.2, 41.3, 34.9, 33.5, 28.5(2C), 16.5, 14.2, 11.8(2C); FTIR (neat): 2961, 2920, 2874, 1734, 1636, 1456, 1373, 1159, 758 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{24}O_2H^+$ 213.1855, found 213.1848.

(E)-6-ethyl-4-methyloct-4-enal



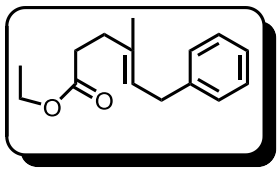
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (t, *J* = 1.9 Hz, 1H), 4.83 (d, *J* = 9.6 Hz, 1H), 2.52 (td, *J* = 1.3 Hz, *J* = 7.3 Hz, 2H), 2.35 (t, *J* = 7.4 Hz, 2H), 2.01 (m, 1H), 1.61 (s, 3H), 1.44-1.07 (m, 4H), 0.79 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.8, 132.9, 131.0, 42.3, 41.3, 32.2, 28.4(2C), 16.7, 11.8(2C); FTIR (neat): 2959, 2920, 2872, 2716, 1726, 1456, 1385,923, 773 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{20}OH^+$ 169.1592, found 169.1592.

3-methyl-1-phenylbut-3-en-2-ol



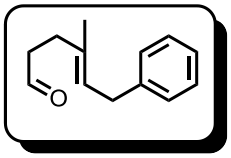
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.28 (m, 2H), 7.24-7.22 (m, 3H), 4.95 (s, 1H), 4.85 (s, 1H), 4.27 (dd, *J* = 4.4 Hz, *J* = 8.6 Hz, 1H), 2.90 (dd, *J* = 4.4 Hz, *J* = 13.7 Hz, 1H), 2.76 (dd, *J* = 8.6 Hz, *J* = 13.7 Hz, 1H), 1.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 138.4, 129.4, 128.5, 126.5, 111.3, 76.5, 42.2, 18.2; FTIR (neat): 3063, 3028, 2972, 2860, 1651, 1492, 1450, 1045, 1026, 903, 763, 700 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{14}OH^+$ 163.1123, found 163.1128.

(E)-ethyl 4-methyl-6-phenylhex-4-enoate



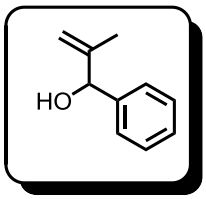
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.26 (m, 2H), 7.20-7.15 (m, 3H), 5.39 (t, *J* = 7.3 Hz, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.36 (d, *J* = 7.4 Hz, 2H), 2.45 (t, *J* = 7.4 Hz, 2H), 2.38 (t, *J* = 7.4 Hz, 2H), 1.74 (s, 3H), 1.23 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 141.4, 134.5, 128.4, 128.3, 125.8, 123.9, 60.3, 34.7, 34.2, 33.2, 16.1, 14.2; FTIR (neat): 2980, 2930, 1734, 1624, 1452, 1373, 1219, 1155, 1030, 772 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}OH^+$ 217.1592, found 217.1605.

(E)-4-methyl-6-phenylhex-4-enal



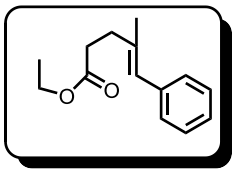
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (t, *J* = 1.9 Hz, 1H), 7.29-7.25 (m, 2H), 7.19-7.13 (m, 3H), 5.37 (t, *J* = 7.2 Hz, 1H), 3.35 (d, *J* = 7.2 Hz, 2H), 2.54 (td, *J* = 1.1 Hz, *J* = 7.7 Hz, 2H), 2.37 (d, *J* = 7.4 Hz, 2H), 1.73 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.4, 141.3, 134.2, 128.5, 128.3, 125.9, 124.2, 42.1, 34.2, 31.8, 16.3; FTIR (neat): 3061, 3026, 2913, 2828, 2720, 1717, 1636, 1493, 1452, 1387, 1072, 746 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}OH^+$ 189.1279, found 189.1275.

2-methyl-1-phenylprop-2-en-1-ol



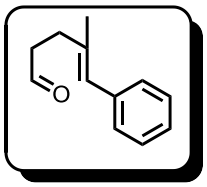
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (m, 5H), 5.20 (s, 1H), 5.12 (s, 1H), 4.96 (s, 1H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.9, 142.0, 128.4, 127.6, 126.5, 111.2, 18.3; FTIR (neat): 3063, 3028, 2943, 2918, 2859, 2359, 1651, 1495, 1030, 901, 698 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{12}OH^+$ 149.0966, found 149.0964.

(E)-ethyl 4-methyl-5-phenylpent-4-enoate



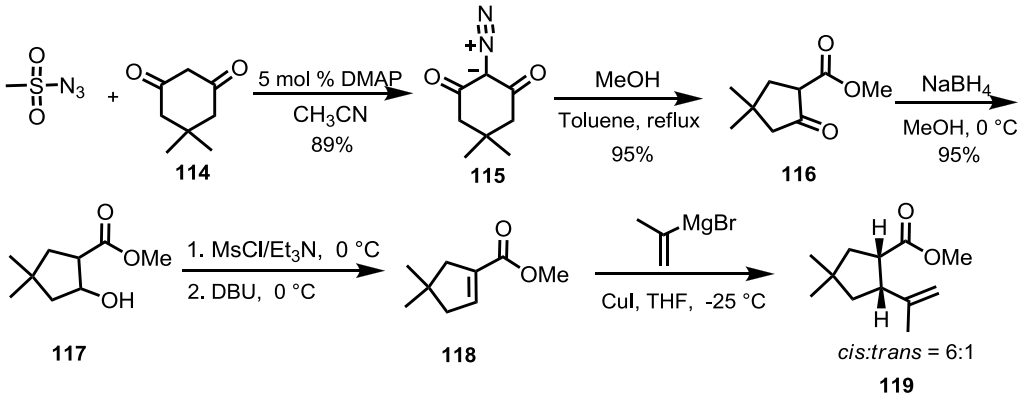
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.18 (m, 5H), 5.29 (s, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 2.52 (m, 4H), 1.89 (s, 3H), 1.27 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 138.2, 137.1, 128.8, 128.1, 126.1, 125.6, 60.4, 35.7, 33.2, 17.7, 14.3; FTIR (neat): 3022, 2980, 2938, 1732, 1445, 1371,1253, 1177, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}OH^+$ 219.1385, found 219.1385.

(E)-4-methyl-5-phenylpent-4-enal

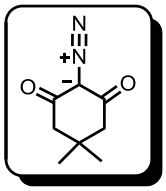


^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (t, *J* = 1.9 Hz, 1H), 7.35-7.31 (m, 2H), 7.24-7.19 (m, 3H), 6.31 (s, 1H), 2.67 (t, *J* = 7.4 Hz, 2H), 2.52 (t, *J* = 7.4 Hz, 2H), 1.88 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.1, 138.0, 136.7, 128.8, 128.1, 126.2, 125.8, 42.2, 32.7, 17.9; FTIR (neat): 3022, 2933, 2722, 1724, 1651, 1491, 1443, 1074, 746 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}OH^+$ 219.1385, found 219.1385.

Synthetic studies toward Δ^6-Protoilludene:



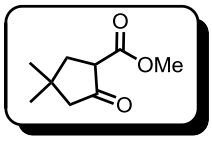
2-Diazo-5,5-dimethylcyclohexane-1,3-dione (115)



Mesyl azide (5 mmol) was added to a solution of dimedone (5 mmol) and DMAP (5 mol%) in acetonitrile. The resulting reaction mixture was stirred at room temperature for 2 hours and then 20 mL water was added. The diazo compound **115** was extracted with ethyl acetate (15 mL × 3). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give **115**, which is pure enough for next step.

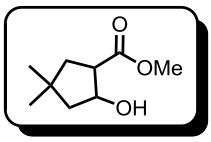
Yield: 89%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 4H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 189.9, 50.5, 31.1, 28.4; FTIR (neat): 3018, 2960, 2815, 2139, 1643, 1303, 1277, 1215, 756 cm^{-1}; HRMS (ESI) calcd for $C_8H_{10}N_2O_2H^+$ 167.0821, found 167.0841.

Methyl 4,4-dimethyl-2-oxocyclopentanecarboxylate (116)



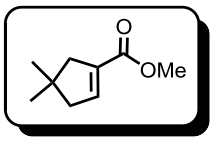
To the solution of 5,5-dimethyl-2-diazo-1,3-cyclohexandione **115** (5 mmol) in toluene (25 mL) was added methanol (10 mmol). The mixture was reflux for overnight and the solvent was removed in *vacuo* to afford compound **116** as a colorless oil. Yield: 95%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.39 (dd, J = 11.0 Hz, J = 9.8 Hz, 1H), 2.26-2.19 (m, 1H), 2.21 (s, 2H), 2.05-2.11 (m, 1H), 1.24 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.6, 169.9, 54.2, 53.0, 52.5, 40.8, 34.5, 28.9, 27.7; HRMS (ESI) calcd for $C_9H_{15}OH^+$ 172.1099, found 172.1105.

Methyl 2-hydroxy-4,4-dimethylcyclopentanecarboxylate (117)



β-Ketone ester **116** (5 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.38 g, 10 mmol) at 0 °C slowly. The mixture was stirred for 1 h at 0 °C and the mixture was concentrated, diluted with water (5 mL), extracted with EtOAc (10 mL × 3), washed with brine, dried over anhydrous $MgSO_4$ and concentrated in *vacuo* to give a crude oil quantitatively (95% crude yield, reasonably pure as observed from ^{1}H-NMR) and can be used without further purification. Yield: 95%, oil; dr = 10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.44 (ddd, *J* = 15.0 Hz, *J* = 8.0 Hz, *J* = 2.0 Hz,1H), 3.69 (s, 3H), 2.85-2.78 (m, 1H), 2.45 (d, *J* = 2.6 Hz, 1H), 1.91-1.80 (m, 2H), 1.67-1.61 (m, 1H), 1.45-1.51 (m, 1H), 1.09 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.5, 76.6, 52.4, 51.8, 48.6, 42.1, 36.4, 30.6, 30.5; FTIR (neat): 3439, 2953, 2868, 1732, 1437, 1367,1201, 1170 cm^{-1}; HRMS (ESI) calcd for $C_9H_{16}O_3H^+$ 173.1178, found 173.1204.

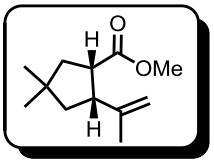
Methyl 4,4-dimethylcyclopent-1-enecarboxylate (118)



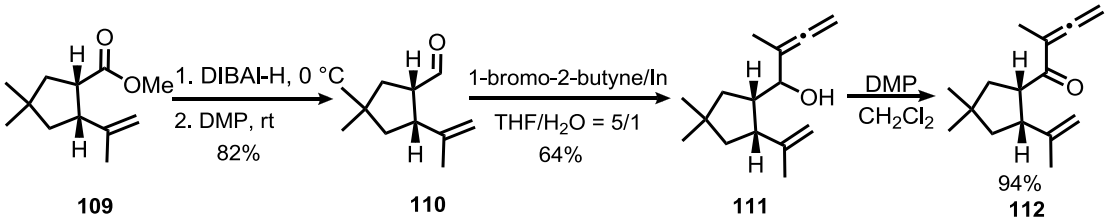
Alcohol **117** (10 mmol) was taken in a 50 mL oven-dried round-bottom flask together with 25 mL CH_2Cl_2 and the resulting solution was cooled to 0 °C under nitrogen. Methanesulfonyl chloride (1.0 mL; 12 mmol) was then added via syringe over 15 min followed by slow addition of Et_3N (1.8 mL; 12 mmol) over 10 min. The resulting yellow slurry was stirred at 0 °C for 1h. Ice-cold water (10 mL) was the added to the reaction mixture was extracted with CH_2Cl_2 (10 mL ×3). Combined organic layer was washed with brine (10 mL) and dried over anhydrous Na_2SO_4 and concentrated in *vacuo* to obtain a yellow oil, which was used directly for next step without further purification. A solution of DBU (15 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of above mesylate in CH_2Cl_2 (30 mL) at 0 °C. After 4 h, the reaction mixture was concentrated *in vacuo* and the residue passed through a plug of silica gel (5% EA : hexane) to give **118** as an oil. Yield: 86%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.67 (s, 1H), 3.73 (s, 3H), 2.41-2.38 (m, 2H), 2.32-2.29 (m, 2H), 1.67-1.61 (m, 1H), 1.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 142.6, 134.9, 51.3, 48.2, 46.3, 38.8, 29.6; FTIR

(neat): 2935, 1716, 1435, 1269, 1240, 1086 cm^{-1}; HRMS (ESI) calcd for $C_9H_{14}O_2H^+$ 155.1072, found 155.1089.

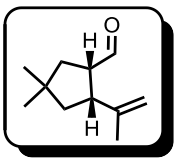
(±)-(1R,2S)-methyl-4,4-dimethyl-2-(prop-1-en-2-yl) cyclopentane carboxylate (109)



Mg turnings (0.43 g, 17.8 mmol) and a crystal of iodine in THF (20 mL) were treated dropwise with 2-bromopropene (1.8 mL, 20.7 mmol) at room temperature. The stirring was continued until most of the Mg was consumed. The reaction mixture was cooled to -25 °C and treated with CuI (0.34 g, 1.8 mmol). After 30 min, methyl cyclopentenecarboxylate **118** (6.2 mmol) was added dropwise. The resulting mixture was stirred at -25 °C for 1 hour, poured into saturated aqueous NH_4Cl and extracted with ether (3 x 40 mL). The combined ether layer was washed with H_2O, brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica gel chromatography to afford ester **109** as a 6:1 mixture of the diastereomers. Yield: 73%, oil; dr = 6:1; ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (s, 1H), 4.70 (s, 1H), 3.65 (s, 3H), 3.01-2.94 (m, 1H), 2.85-2.78 (m, 1H), 1.82-1.68 (m, 3H), 1.70 (s, 3H), 1.37-1.44 (m, 1H), 1.08 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.3, 146.1, 109.9, 51.6, 50.6, 48.0, 46.5, 45.2, 37.9, 30.6, 30.2, 20.4; FTIR (neat): 2953, 2866, 1738, 1645, 1435, 1368, 1165, 891 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{20}O_2H^+$ 197.1542, found 197.1554.



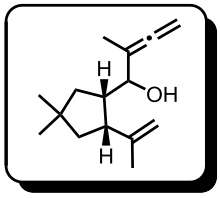
(±)-(1R,2S)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentane carbaldehyde (110)



To a solution of ester **109** (5 mmol) in Et_2O (110 mL) was added DIBAL-H (1M in heptane, 12 mmol, 12 mL) dropwise at 0 °C. After 1.5 h at 0 °C, the reaction was quenched by adding MeOH (10 mL), and saturated potassium sodium tartrate solution (50 mL), followed by stirring until

two clear layer was obtained. The reaction mixture was extracted with EtOAc (10 mL × 3), dried over anhydrous Na_2SO_4, filtered, concentrated in *vacuo* to afford the crude alcohol as a colorless oil. To a mixture of DMP (6 mmol) in CH_2Cl_2 (10 mL) was added solution of the above crude alcohol in CH_2Cl_2 (5 mL) at room temperature during and stirred for 1 h. The solvent was removed in *vacuo* and the residue was purified by flash colum hromatography (*n*-hexane/EtOAc, 10:1) afforded the aldehyde **110**. Yield: 82% for two steps, oil; dr = 10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.58 (d, *J* = 2.8 Hz, 1H), 4.78 (s, 1H), 4.75 (s, 1H), 3.00-2.89 (m, 1H), 2.85-2.74 (m, 1H), 1.76-1.68 (m, 3H), 1.72 (s, 3H), 1.52-1.44 (m, 1H), 1.08 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.6, 145.8, 110.5, 55.5, 47.6, 46.5, 41.3, 38.5, 30.2, 29.5, 20.6; FTIR (neat): 2953, 2866, 2710, 1724, 1645, 1462, 1447, 1368, 891 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}OH^+$ 167.1436, found 167.1445.

(±)-1-((1R,2S)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2-methylbuta-2,3-dien-1-ol (111)

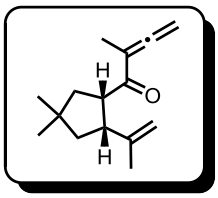


1-Bromo-2-butyne (7.5 mmol, 1.5 equiv) was added to a mixture of the indium powder (7.5 mmol, 1.5 equiv) and the aldehydes (5 mmol) in THF/H_2O (5:1) (10 mL) at room temperature. Then, the mixture was stirred at room temperature and monitored by TLC analysis. The mixture was extracted with diethyl ether (3 × 10 mL) after the disappearance of the starting material. The organic extract was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The crude residue was purified by silica gel column chromatography to give the allenic alcohol as a oil.

Yield: 64%; dr = 10:1; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.86-4.75 (m, 4H), 3.97-3.93 (m, 1H), 2.76-2.68 (m, 1H), 2.25-2.15 (m, 1H), 1.89-1.76 (m, 1H), 1.70 (s, 3H), 1.66 (t, *J* = 3.1 Hz, 3H), 1.64-1.58 (m, 2H), 1.46-1.36 (m, 2H), 1.04 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.2, 146.8, 110.7, 102.9, 78.0, 70.4, 48.6, 47.1, 45.7, 39.6, 36.6, 31.1, 30.6, 19.6, 15.3; FTIR (neat): 3447, 2949, 2864, 1958, 1715, 1641, 1460, 1446, 1366, 889 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{24}OH^+$ 221.1905, found 221.1913.

(±)-1-((1R,2S)-4,4-dimethyl-2-(prop-1-en-2-yl)cyclopentyl)-2-methylbuta-2,3-dien

-1-one (112)



A solution of the allenic alcohol **111** (1 mmol) in dichloromethane (1 mL) was added to a solution of Dess-Martin periodinane (DMP) (509 mg, 1.2 mmol) in dichloromethane (4 mL) with stirring at room temperature. After disappearance of the starting material (TLC), the solvent was removed under vacuum and the residue was purified by silica gel column chromatography to give analytical pure eneallenone. Yield: 94%, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (d, *J* = 2.8 Hz, 1H), 5.13 (d, *J* = 2.8 Hz, 1H), 4.65 (s, 2H), 3.64 (dd, *J* = 19.1 Hz, *J* = 9.4 Hz, 1H), 3.15-3.07 (m, 1H), 1.78 (t, *J* = 2.9 Hz, 3H), 1.76-1.69 (m, 2H), 1.66 (s, 3H), 1.52-1.40 (m, 2H), 1.05 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 216.6, 203.2, 146.8, 109.5, 104.2, 78.4, 50.9, 49.3, 46.48, 46.45, 38.3, 30.6, 29.8, 20.9, 13.3; FTIR (neat): 2951, 2864, 1935, 1676, 1447, 1367, 1204,1041 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{22}OH^{+}$ 219.1749, found 219.1753.

PART II: NEW GENERATION OF IN(III)-PYBOX COMPLEX IN ASYMMETRIC SYNTHESIS

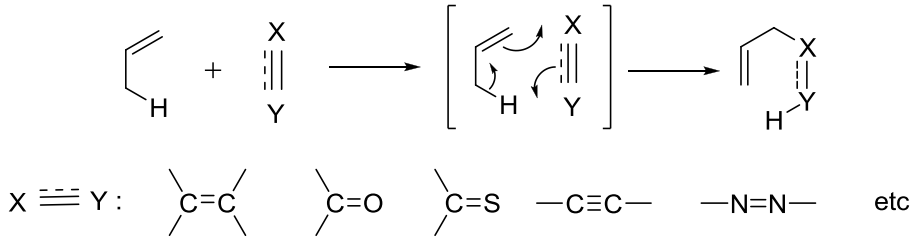
Asymmetric synthesis and the development of new chiral catalyst systems continue to be one of the most active research areas of organic synthesis. In the second part of this thesis, we focused on the design and application of moisture-stable chiral In(III)-pybox complexes, which were developed by our group several years ago. We successfully expanded the In(III)-pybox complex to catalyze asymmetric reaction of bidentate substrates and developed a new generation of In(III)-pybox complexes by taking advantage of the counterion effect. The catalytic efficiency has been improved significantly as compared to the parent In(III)-pybox complex and the catalyst loading could be decreased to 5 mol% from 20 mol%. We further applied this new generation chiral catalyst to the more challenging carbonyl-ene reaction of trifluoropyruvate and asymmetric Mukaiyama aldol between glyoxylate and enol silanes derived from aryl ketones. Both of these two reactions are less explored due to the lack of efficient catalysts. The potent catalytic efficiency of the new generation In(III)-pybox complexes demonstrated in this part has shed light on the further application of chiral indium complex in asymmetric synthesis.

CHAPTER 3

Highly Enantioselective Carbonyl-ene Reactions of Glyoxylate Catalyzed by In(III)-PyBox Complex

3.1 OVERVIEW OF CARBONYL ENE REACTION

The ene reaction, which involved a reaction between an alkene bearing an allylic hydrogen (an ene) and an electron-deficient multiple bond (an enophile) was first recognized by Alder in 1943 and classified as an "indirect substitution addition" or "ene synthesis" in his Nobel lecture in 1950.[1] It is mechanistically related to the well-known Diels-Alder reaction because both of them are considered to be concerted 6-electron pericyclic processes (Scheme 3.1).[2] However, the activation energy for an ene reaction is higher than for an analogous Diels-Alder reaction. Therefore ene reactions typically occur at higher temperatures. Due to its high activation energy, the ene reaction is relatively less explored compared to the extensively studied Diels-Alder reaction.



Scheme 3.1 The ene reaction

The ene reaction encompasses a vast number of variants in terms of the different enophiles used. Among them, the carbonyl-ene reaction, in which the carbonyl group is used as enophile, is one of the most important methodologies from a synthetic point

[1] (a) Alder, K.; Paxcher, F.; Schmitz, A. *Ber. Dtsch, Chem. Ges.* **1943**, *76B*, 27. (b) *Nobel Lectures-Chemistry*, 1942-1962; Elsevier: Amsterdam, pp. 253-305, **1964**.
[2] Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.

of view.[3] The carbonyl-ene reaction constitutes a more efficient alternative to the carbonyl addition reaction of allylmetals, a reaction that has gained significant prominence in the synthetic community.[4] Generally there are two strategies chemists use to overcome the high energy barrier in asymmetric carbonyl-ene reaction. One of them is using activated carbonyl group or alkenes. The other one is putting both the ene and enophile into one molecule (the intramolecular version by taking advantage of entropic effect).

3.1.1 Catalytic asymmetric carbonyl-ene reaction of activated aldehyde

The asymmetric carbonyl-ene reaction has gained tremendous attention[5] because it allows the atom-economic construction of enantioenriched homoallylic alcohols, which are important building blocks for the synthesis of many natural products and pharmaceutical compounds.[6] Use of chiral Lewis acid catalysis is a very efficient strategy to achieve this goal. Coordination between the chiral Lewis acid metal centre and carbonyl group not only forms a facially discriminated complex but also activates the carbonyl group for carbonyl-ene reaction. In 1988, using pentafluorobenzaldehyde as enophile, Yamamoto and co-workers reported the first

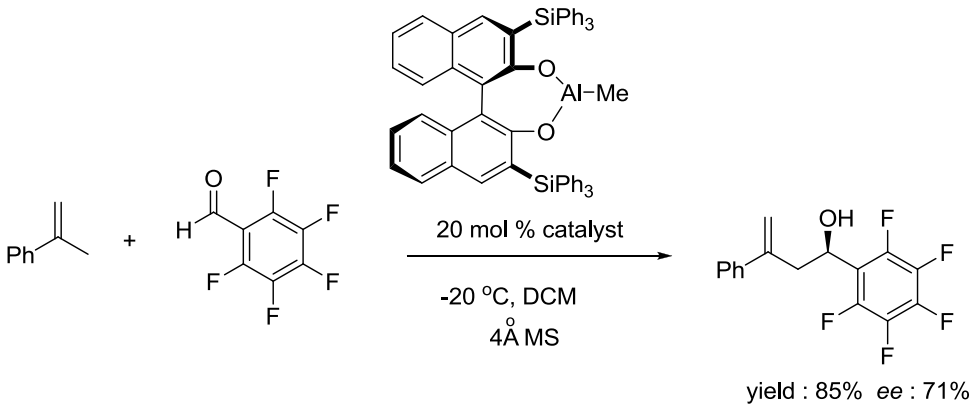
[3] (a) Dias, L. C. *Curr. Org. Chem.* **2000**, *4*, 305. (b) Ho, C. Y.; Schleicher, K. D.; Chan, C. W.; Jamison, T. F. *Synthesis*, **2009**, *16*, 2565. (c) Mikami, K. *Pure Appl. Chem.* **1996**, 68, 639

[4] (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Hoveyda, A. H.; Morken, J. P. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1262. (c) Roush, W. R. *Comprehensive Organic Synthesis*, ed by Trost, B. M.; Fleming, I.; Heathcock, C. H. Pergamon, Oxford, **1991**, *2*, 1.

[5] For a general review of the ene reaction, see: (a) Mikami, K.; Shimizu, M. *Chem. Rev.* **1992**, *92*, 1021. (b) Berrisford, D. J.; Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1717. (c) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255. (d) Mikami, K. *Pure Appl. Chem.* **1996**, 68, 639. (e) Yuan, Y.; Zhang, X.; Ding, K. L. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 5478.

[6] (a) Nicolaou, K. C.; Kim, D.W.; Baati, R. *Angew. Chem. Int. Ed.*, **2002**, *41*, 3701; (b) Hornberger, K. R.; Hamblet, C. L.; Leighton, J. L. *J. Am. Chem. Soc.*, **2000**, *122*, 12894; (c) Felpin, F. X.; Lebreton, J. *J. Org. Chem.*, **2002**, *67*, 9192.

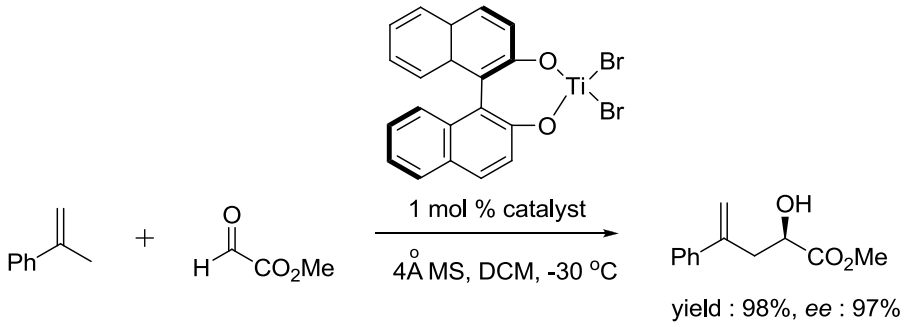
asymmetric carbonyl-ene reaction by employing BINOL-based Al(III) complex as the



Scheme 3.2

catalyst (Scheme 3.2). [7] In the presence of 20 mol% catalyst loading, the homoallylic alcohol could be obtained with good to excellent enantioselectivities (up to 92% *ee*). Different 1,1-disubstituted alkenes had been used as substrates.

Almost at the same time, Mikami and Nakai reported their BINOL-based Ti(IV) complex, formed *in situ* from (*R*)-BINOL and $(^{i}PrO)_2TiBr_2$, catalyzed asymmetric carbonyl-ene reaction (Scheme 3.3).[8] They used a glyoxylate ester as the enophile.



Scheme 3.3

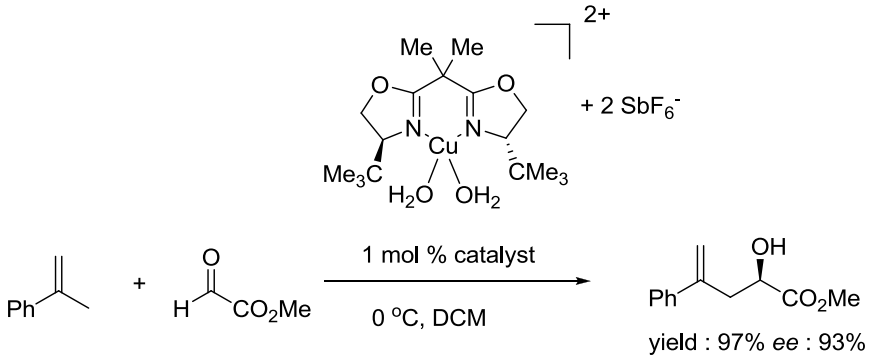
The BINOL-Ti(IV) complex is very effective in mediating this reaction and as low as

[7] Maruoka, K.; Hoshino, Y.; Shirasaka, Y. H.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967.

[8] (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (d) Mikami, K.; Yajima, T.; Terada, M.; Kato, E.; Maruta, M. *Tetrahedron: Asymmetry* **1994**, *6*, 1087. (e) Mikami, K.; Tomoko, Y.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85.

1 mol% of catalyst loading is sufficient to afford the chiral alcohol with up to 97% *ee* and 98% yield. They found that the presence of 4Å molecular sieves was crucial to obtain high enantioselectivities. However, this strategy is only applicable to 1,1-disubstituted alkenes, while other alkenes such as mono- and 1,2-disubstituted olefins were not amenable.

Significant improvement was achieved by Evans *et al.* using Cu(II)-bisoxazoline (Box) complexes[9] as the catalysts (Scheme 3.4). The catalyst efficiency had been improved significantly by taking advantage of counterion effect. In contrast to other moisture- sensitive Cu(II)-based Lewis acid catalyzed reactions which must be carried



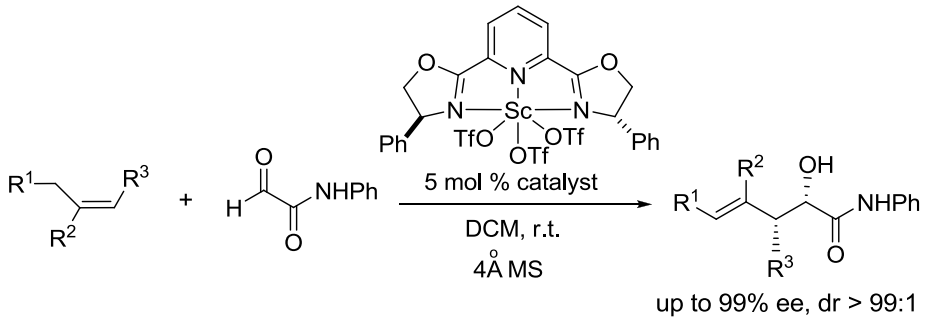
Scheme 3.4

out in a dry box, the newly developed bench-stable catalysts could be used in open air. The catalyst loading could be lowered to 0.1 mol% without sacrificing the reaction efficiency. Notably, this catalytic system is not only applicable to 1,1-disubstituted alkenes but also works well for mono- and 1,2-disubstituted alkenes. Interestingly, Hutchings *et al.* developed a heterogeneous Cu(II) catalyst which derived from box

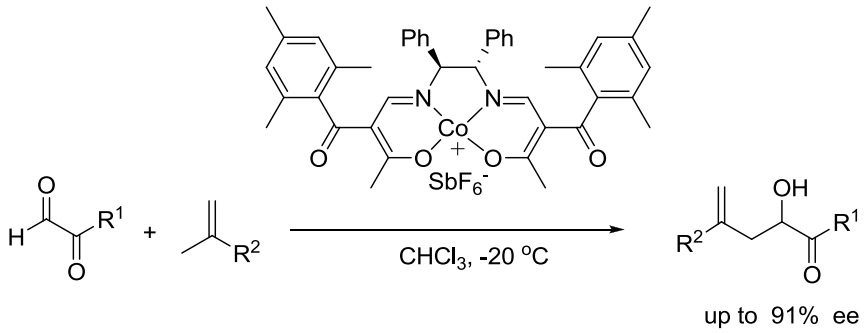
[9] (a) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc*. **2000**, *122*, 7936. (c) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem*. **1998**, *63*, 2133.

and CuH zeolite.[10] Their heterogeneous catalysts are extremely effective for asymmetric carbonyl- and imino-ene reactions of glyoxylate derivatives and, furthermore, these catalysts can be readily recovered and reused without loss of catalyst performance.

Later, Evans group developed another catalyst, which was formed *in situ* from $Sc(OTf)_3$ and pybox ligands (Scheme 3.5).[11] With catalysis by this Sc(III)-pybox complex, excellent diastereoselectivities as well as enantioselectivities were observed in the asymmetric carbonyl-ene reaction of trisubstituted olefins.



Scheme 3.5



Scheme 3.6

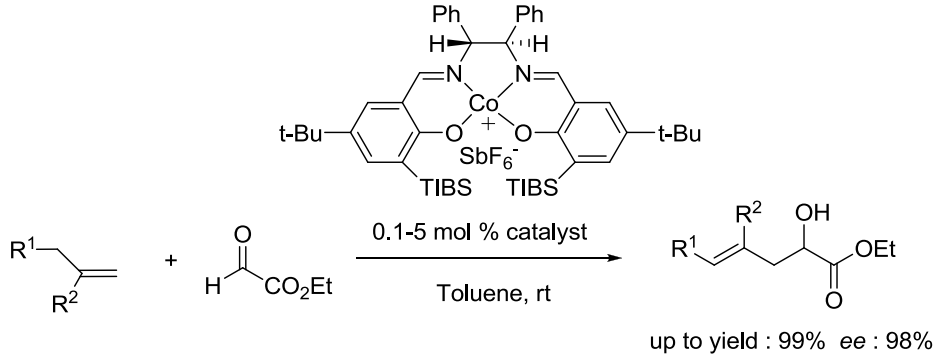
Co(III) complex bearing a C_2-symmetric chiral ligand had also been used as catalyst for asymmetric carbonyl-ene reactions. In 2001, Yamada's group reported the first chiral Co(III) complex, which was derived from optically active 1,2-diphenyl-

[10] Caplan, N. A.; Hancock, F. E.; Bulman Page, P. C.; Hutchings, G. J. *Angew. Chem. Int. Ed.* **2004**, 43, 1685.

[11] Evans, D. A.; Wu, J. *J. Am. Chem. Soc*. **2005**, *127*, 8006.

1,2-ethanediamine, catalyzed carbonyl-ene reactions of a variety of alkenes and glyoxal derivatives (Scheme 3.6).[12] The corresponding enantioenriched homoallylic alcohols were obtained in good to high yields with high enantioselectivities.

Several years later, Rawal *et al.* re-investigated this catalyst system (Scheme 3.7).[13] They replaced the 1,2-diphenyl-1,2-ethanediamine ligand by salen ligands. After systematic screening of salen ligands, they developed a triisobutylsilyl (TIBS)-substituted C_2-symmetrical Co(III)-salen complex, a superb catalyst for promoting the carbonyl-ene reaction of various 1,1-disubstituted and trisubstituted alkenes with ethyl glyoxylate. This catalyst is so powerful that 0.1 mol% of it is enough to give *γ, δ*-unsaturated-*α*-hydroxy carboxylic esters in excellent yields, enantioselectivities, and diastereoselectivities. They attributed the enhanced effectiveness of the silyl salens to



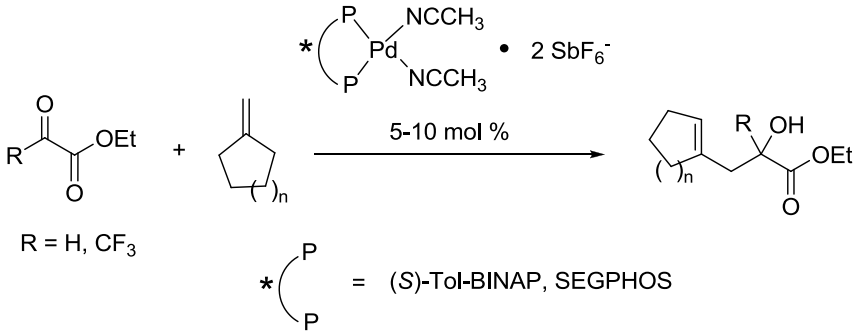
Scheme 3.7

the sterics-based distortion of the otherwise flat salen framework. Similarly, C_2-symmetrical Cr(III)-salen complex also works well for this reaction.[14]

Mikami *et al.* reported a series of chiral dicationic Pd(II) Lewis acids, which are derivatived from chiral phosphine ligand, catalyzed asymmetric carbonyl-ene reactions

[12] Kezuka, S.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 1937.
[13] Hutson, G. E.; Dave, A. H.; Rawal, V. H. *Org. Lett.* **2007**, *9*, 3869.
[14] Chaladaj, W.; Kwiatkowski, P.; Majer, J.; Jurczak, J. *Tetrahedron Lett.* **2007**, *48*, 2405.

(Scheme 3.8).[15] (*S*)-Tol-BINAP and SEGPHOS proved to be the best ligands for asymmetric carbonyl-ene reactions of glyoxylate esters and trifluoropyruvates, respectively. Although good to excellent enantioselectivities could be obtained by using chiral dicationic Pd(II) Lewis acids, the substrate scope of olefins is still limited to 1,1-disubstituted and trisubstituted ones.

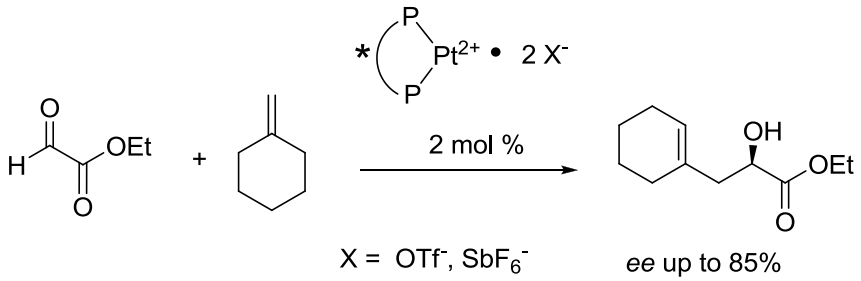


Scheme 3.8

By using the carbonyl-ene reaction of ethyl glyoxylate ester as the model reaction, Gagné and coworkers systematically investigated the ion-paring and stereoelectronic effects in the reactivity of Pt(II) based dicationic complexes (Scheme 3.9).[16] They observed that achiral acidic phenol additives accelerate the rate of the reaction catalyzed by OTf-based catalysts by disrupting contact ion pairs and sequestering traces of water while having no effect on that of the more reactive SbF_6-based catalysts. The basicity of diphosphine ligand also has some effects on the enantioselectivity and reactivity.

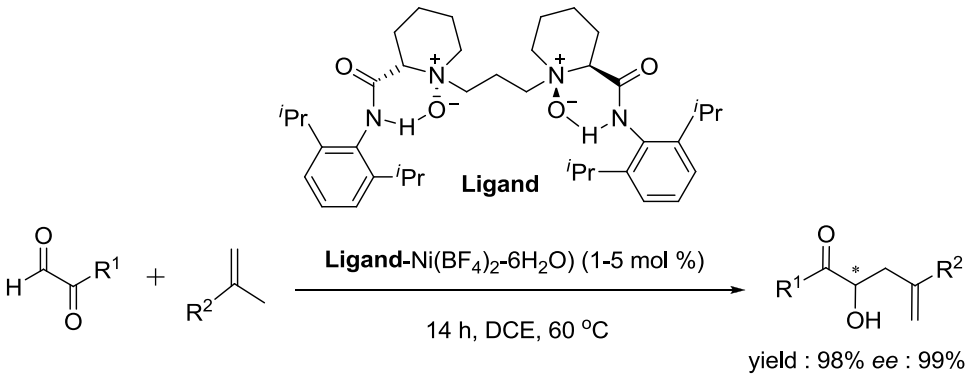
[15] (a) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059. (b) Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 183. (c) Mikami, K.; Aikawa, K.; Kainuma, S.; Kawakami, Y.; Saito, T.; Sayo, N.; Kumobayashi, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3885. (d) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (e) Hatano, M.; Terada, M.; Mikami, K. *Angew. Chem., Int. Ed.* **2001**, 40, 249.

[16] Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233.



Scheme 3.9

Very recently, Feng's group demonstrated that chiral dicationic Ni(II) complexes also are excellent catalysts for asymmetric carbonyl-ene reactions (Scheme 3.10).[17] By taking advantage of steric and electronic effects of ligands, the newly developed Ni(II)- *N,N'*-dioxide complexes were very effective for this reaction. Excellent enatioselectivities were obtained for a broad range of substrates such as aromatic, aliphatic glyoxal derivatives, as well as glyoxylate with various olefins.



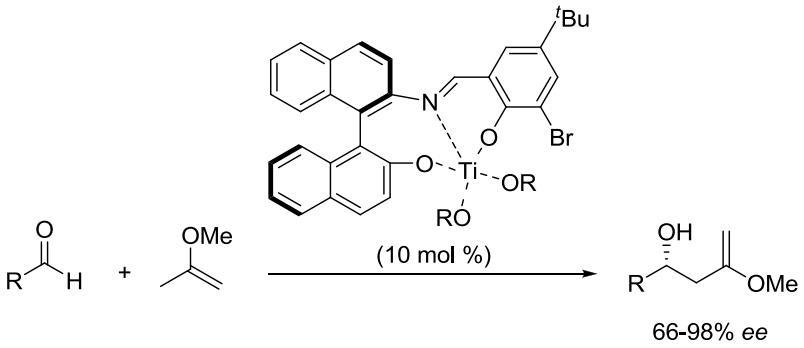
Scheme 3.10

3.1.2 Catalytic asymmetric carbonyl-ene reaction of activated alkenes

As mentioned at the beginning, the activation energy of ene reaction is higher than Diels-Alder reaction. Chemists generally use activated carbonyl such as glyoxylate ester, glyoxal and pyruvate derivatives as the enophile to lower the energy

[17] Zheng, K.; Shi, J.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2008**, *130*, 15770.

barrier. Next we will introduce an alternative strategy in which unactivated aldehydes were used as enophile. Complementary to previous cases, the activated alkenes were used as enes. The first example was presented by Carreira *et al.* using their BINOL-based Ti(IV) complex as the catalyst (Scheme 3.11). [18] Taking 2-methoxypropene as the substrates, the asymmetric carbonyl-ene reactions of various



Scheme 3.11

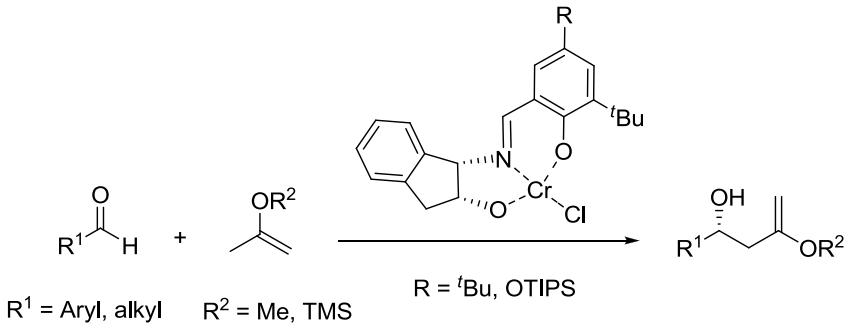
unactivated aliphatic aldehydes proceeded smoothly to give the adducts with excellent enantioselectivities up to 98% *ee*. However, only moderate enantioselectivity was observed when aromatic aldehyde were used as acceptor. The products could be transformed into other useful synthetic intermediates by simple operations.

Due to the versatility of the hetero-ene reaction products, Jacobsen *et al.* further developed this strategy by using chiral tridentate Schiff base Cr(III) complex as catalyst (Scheme 3.12).[19] This catalyst system is very effective for aromatic aldehydes and complemented Carreira's work. They observed that electron-deficient aldehydes reacted faster than electron-rich substrates such as *o*-, *m*-, *p*-tolualdehyde. In addition, *ortho*-substitution on the aromatic ring generated the desired adduct in particularly

[18] (a) Carreira, E. M.; Lee, W.; Singer, R. A. *J. Am. Chem. Soc.* **1995**, *117*, 3649. (b) Berrisford, D. J.; Bolm, C. *Angew. Chem., Int. Ed.* **1995**, 34, 1717.

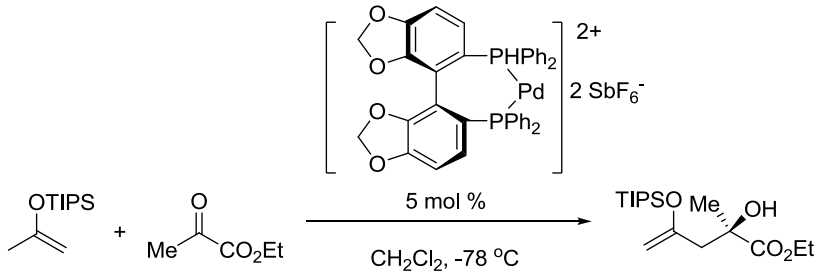
[19] (a) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882. (b) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2003**, *42*, 4771.

good enantioselectivities.[19a] Interestingly, only hetero-ene product was observed when enolsilane used as donor.[19b] None of the product associated with a Mukaiyama aldol reaction pathway was detected.



Scheme 3.12

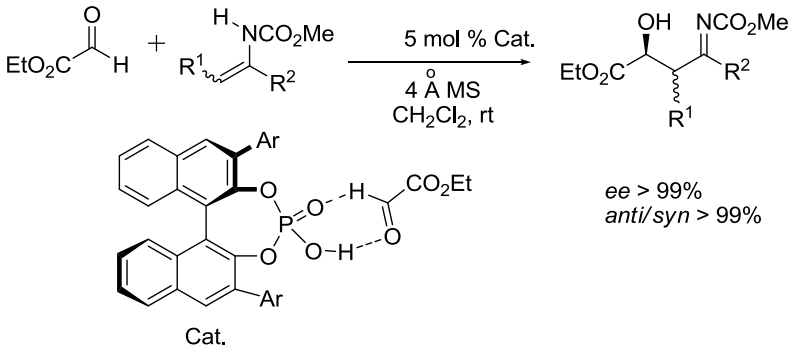
By taking advantage of this strategy, Mikami *et al.* reported the ketone-ene reaction of ethyl pyruvate, which is less explored due to the low reactivity of ketone carbonyl group (Scheme 3.13).[20] In the presence of 5 mol% of chiral cationic Pd(II)-SEGPHOS complex, the optically active *β*-hydroxy silyl enol ether containing a quaternary carbon center could be obtained with excellent enantioselectivities (*ee* up to 98%). The silyl enol ether part in the products is easily transformed into other useful synthetic intermediates.



Scheme 3.13

[20] Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950.

Terada's aza-ene-type reaction of glyoxylate with enecarbamates is a good example of the application of chiral organocatalysts in asymmetric synthesis (Scheme 3.14).[21] At the beginning of this century, chiral organocatalysts[22] attracted much attention due to many advantages such as low cost, environment benignity, use of mild conditions and metal-free. Unlike traditional chiral Lewis acid formed bidentate complex, the chiral Brønsted acid involved a double hydrogen bond activation model, which was proposed based on DFT computational study.



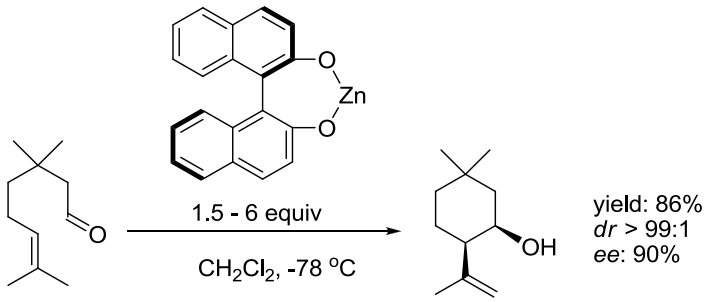
Scheme 3.14

3.1.3 Catalytic asymmetric intramolecular carbonyl-ene reaction of both unactivated alkenes and carbonyl group

Putting both the ene and enophile into one molecule (intramolecular version) is another strategy used to decrease the activation energy of carbonyl-ene reactions. Paralleled with the use of activated aldehyde or alkenes, the intramolecular carbonyl-ene reactions have been explored due to their important synthetic utilities.

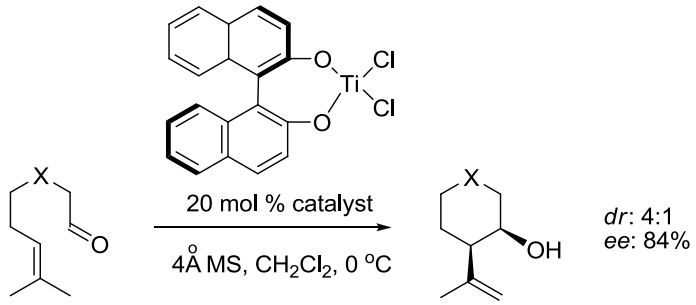
[21] Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4122.
[22] For reviews of organocatalysts, see: (a) Special issue for organocatalysis *Chem. Rev.* **2007**, *107*, 5413-5883. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4638. (c) Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5138.

The first asymmetric intramolecular carbonyl-ene was reported by Yamamotao *et al.* in 1986 albeit more than stoichiometric BINOL-Zn(II) was required (Scheme 3.15).[23]



Scheme 3.15

The first catalytic asymmetric intramolecular carbonyl-ene reaction was reported by Mikami *et al.* using their chiral titanium complex, which was formed *in situ* from $(i\text{-PrO})_2TiX_2$ (X = Cl or Br) and optically pure BINOL in the presence of



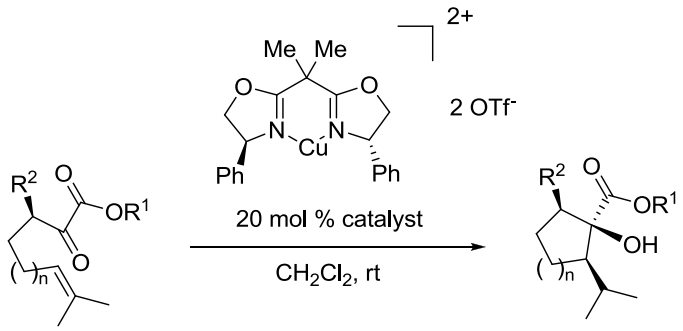
Scheme 3.16

4 Å molecular sieves (Scheme 3.16).[24] In the presence of 20 mol% of Ti(IV)-BINOL complex, the carbonyl-ene cyclization[25] products could be obtained with excellent enantioselectivity in moderate yield.

Not only unactivated aldehyde but also the carbonyl group of α-keto ester could be used as enophile for the intramolecular carbonyl-ene reaction. For example, Yang

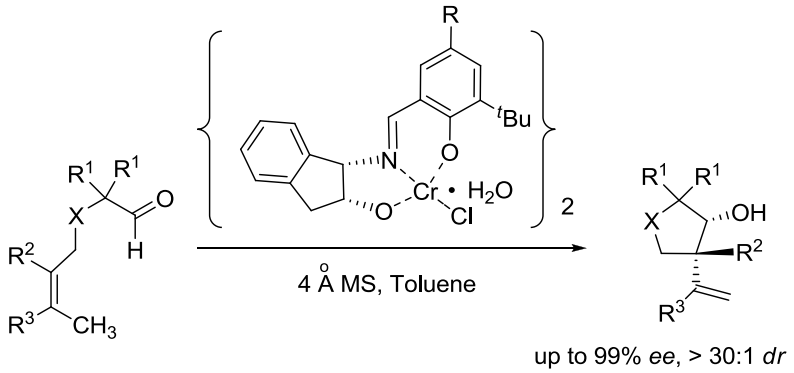
[23] Sakane, S.; Maruoka, K.; Yamamoto, H. *Tetrahedron*, **1986**, *42*, 2203.
[24] Mikami, K.; Sawa, E.; Terada, M. *Tetrahedron: Asymmetry* **1991**, *2*, 1403.
[25] Ziegler, F. E.; Sobolov, S. B. *J. Am. Chem. Soc.* **1990**, *112*, 2749.

et al. reported a Cu(II)-box complex catalyzed enantioselective carbonyl-ene reaction of unsaturated *α*-keto esters (Scheme 3.17).[26] The chelating effect proved to be crucial for high stereoselectivity. Two chiral centers, including one quaternary carbon center, could be constructed in one step with excellent diastereoselectivties (*dr* up to 23:1) and enantioselectivities (*ee* up to 91%).



Scheme 3.17

Very recently, Jacobsen group expanded their Schiff base Cr(III) complex to the intramolecular carbonyl-ene cyclization reaction, which simultaneously uses both unactivated aldehyde and alkenes (Scheme 3.18).[27] This work further demonstrated the potential application of the asymmetric intramolecular carbonyl-ene reaction in the synthesis of complex molecules.



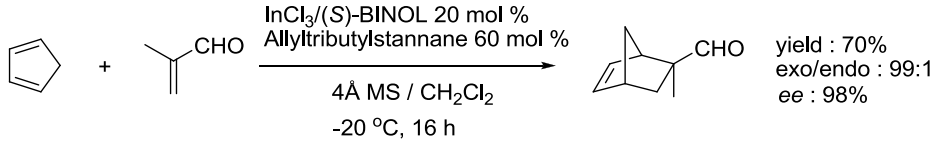
Scheme 3.18

[26] Yang, D.; Yang, M.; Zhu, N. Y. *Org. Lett.* **2003**, *5*, 3749.
[27] Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2008**, *47*, 1469.

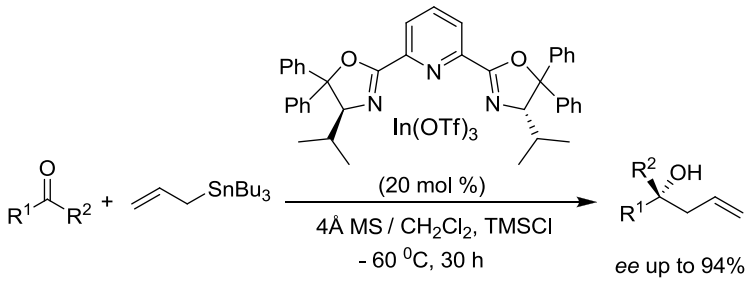
3.2 RESULTS AND DISCUSSION

3.2.1 The design of further application of chiral indium(III) complex

While extraordinary advances have been accomplished with the asymmetric carbonyl-ene reaction, most of them still suffer from limitations such as high catalyst loading, harsh reaction conditions, limited substrate scope, or difficult preparation of catalyst. Therefore, the asymmetric carbonyl-ene reaction still remains a challenging topic. Our group have recently reported that chiral indium complexes[28] are effective catalysts for the Diels-Alder reaction (Scheme 3.19),[29] carbonyl allylation (Scheme 3.20)[30] and aldol[31] reactions. These studies demonstrated that cationic In(III)



Scheme 3.19



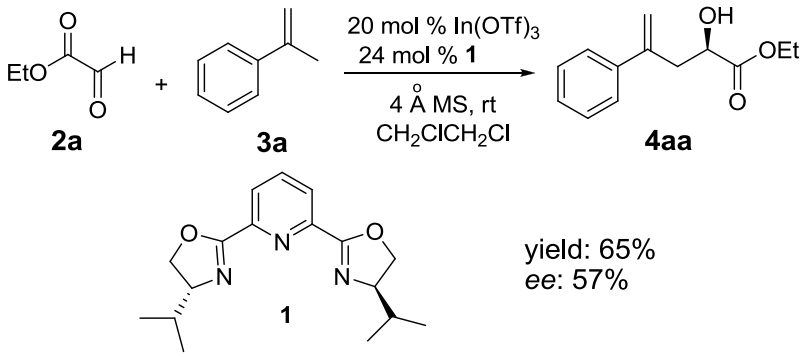
Scheme 3.20

[28] Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739.
[29] (a) Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2539. (b) Fu, F.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2006**, *8*, 5999.
[30] (a) Teo, Y. C.; Goh, J. D.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2743. (b) Lu, J.; Hong, M. L.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 1010. (c) Lu, J.; Hong, M. L.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Chem. Commun.* **2005**, 4217. (d) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 2345. (e) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 159. (f) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, 1318.
[31] Fu, F.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 4267.

complex bearing C_2-symmetric ligand could coordinate with the carbonyl group to form a facially discriminated complex, which is crucial for asymmetric induction. However, the catalytic efficiency is lower and generally 20 mol% of catalyst loading was required to afford good results. We hypothesized that introduction of an extra coordination site to the substrate (bidentate chelating substrates) may favor the formation of facially discriminated complex and subsequently improve the asymmetric induction. In this part, we demonstrated that the In(III)-pybox complex is an efficient catalyst for bidentate substrates by using the asymmetric carbonyl-ene reaction of glyoxylate esters as the model reaction.

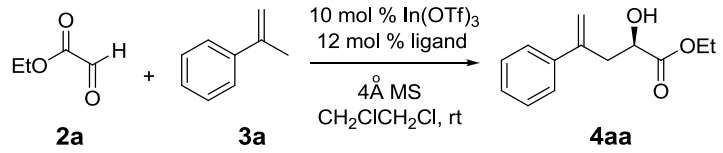
3.2.2 Optimization studies

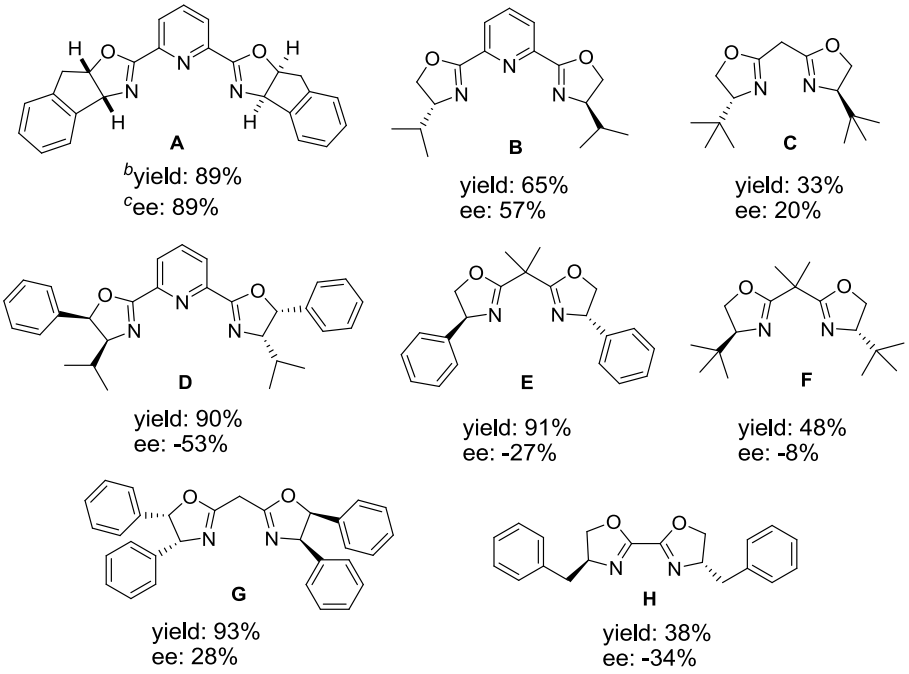
Preliminary studies demonstrated that the chiral indium complex, formed *in situ* from commercially availiable $In(OTf)_3$ and pybox **1** in the presence of 4Å molecular sieves, indeed promotes the asymmetric carbonyl-ene reaction in moderate yield and enantioselectivity (Scheme 3.21). With this encouraging result in hand, we evaluated a series of chiral ligands including box and pybox. Among the ligands screened, we



Scheme 3.21

Table 1. Screening of ligands[a]



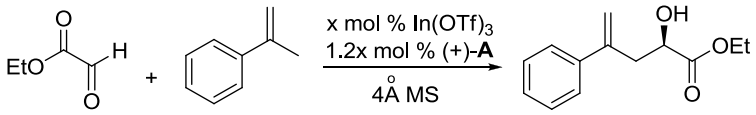


[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of *α*-methylstyrene in 2.0 ml of solvent at room temperature, unless noted otherwise. [b] Isolated yield. [c] Ee values were determined by chiral-phase HPLC analysis and the absolute configuration of the major products was *R*, assigned by comparing HPLC with the literature.

found that pybox ligands are better than box ligands and pybox **A** proved to be the best one, which afforded the carbonyl-ene products in good yields and enantioselectivities (Table 1).

Investigation of the solvent effect, indium salt, temperature, catalyst loading and concentration of the reactant demonstrated that the reaction efficiency could be further improved (Table 2). As shown in Table 2, this reaction is sensitive to the reaction media. Polar non-coordinating solvents are better than other solvents and

Table 2. Optimization studies[a]



2a **3a** **4aa**

Entry	InX_3 (mol %)	Solvent	T (°C)	Time/day	Yield (%)[b]	Ee (%)[c]
1	$In(OTf)_3$, 20	DCM	rt	1	97	83
2	$In(OTf)_3$, 20	CH_3CN	rt	1	trace	nd
3	$In(OTf)_3$, 20	Toluene	rt	1	45	47
4	$In(OTf)_3$, 20	CH_3Cl	rt	1	trace	nd
5	$In(OTf)_3$, 20	THF	rt	1	trace	nd
6	$In(OTf)_3$, 20	DCE	rt	1	98	86
7	$In(OTf)_3$, 10	DCE	rt	2	89	89
8	$InCl_3$, 10	DCE	rt	2	trace	nd
9	$InBr_3$, 10	DCE	rt	2	trace	nd
10	InI_3, 10	DCE	rt	2	trace	nd
11	$In(OTf)_3$, 5	DCE	rt	4	95	91
12	$In(OTf)_3$, 2	DCE	rt	4	63	77
13[d]	$In(OTf)_3$, 5	DCE	rt	4	93	94
14[d]	$In(OTf)_3$, **5**	**DCE**	**0**	**6**	**96**	**95**

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of *α*-methylstyrene in 2.0 ml of solvent at room temperature, unless noted otherwise. [b] Isolated yield. [c] Ee values were determined by chiral-phase HPLC analysis and the absolute configuration of the major products was *R*, assigned by comparing HPLC with the literature. [d] This reaction was carried out in 4.0 ml of solvent at room temperature.

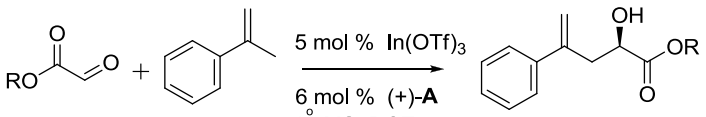
1,2-dichloroethane (DCE) is the optimum choice of solvent (Table 1, entry 6). Beside $In(OTf)_3$, other indium(III) salts such as $InCl_3$, $InBr_3$, and InI_3 are ineffective for this reaction (Table 1, entries 8-10). Decreasing of catalyst loading to 5 mol% leads to a slight increase of enantioselectivity (Table 1, entry 7 *vs* 11). However, further lowering the catalyst loading has detrimental effect on the reaction efficiency. Dilution also has positive effect on enantioselectivity (Table 1, entry 11 *vs* 13). The highest enantioselectivity was obtained in the presence of 5 mol% catalyst loading, with a

0.125 M concentration of alkene in DCE. While room temperature offered good results, the best results were attained at 0 °C (Table 1, entries 13 and 14) at the expense of reaction time.

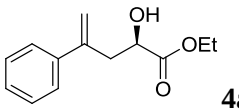
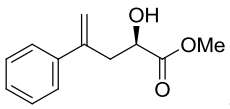
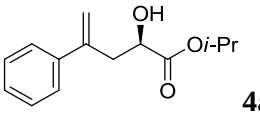
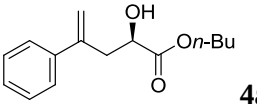
3.2.3 In(III)-Pybox complex catalyzed asymmetric carbonyl-ene reactions of *α*-methylstyrene with various glyoxylates

We then investigated the effect of ester group of glyoxylate and the results are

Table 3. In(III)-Pybox complex catalyzed asymmetric carbonyl-ene reactions of *α*-methyl styrene with various glyoxylate[a]



2a-d **3a** **4aa-da**

entry	R	product	time (day)	yield (%)[b]	ee (%)[c]
1	Et	 **4aa**	4	93	94
2	Me	 **4ab**	4	95	93
3	*i*-Pr	 **4ac**	5	80	92
4	*n*-Bu	 **4ad**	5	96	92

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of alpha-methylstyrene in 4.0 ml of DCE, unless noted otherwise. [b] Isolated yield. [c] Ee values were determined by chiral-phase HPLC analysis and the absolute configuration of the major products was *R*, assigned by comparing HPLC with the literature.

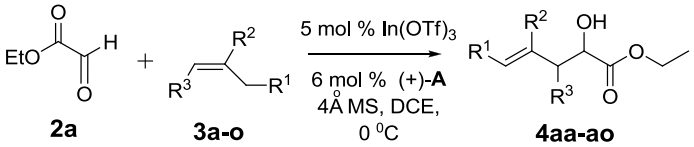
summarized in Table 3. In an oven dried 10 ml round-bottom flask equipped with a stirring bar, indium(III) triflate (14.1 mg, 0.025 mmol), PYBOX-**A** (12 mg, 0.03 mmol) and 4 Å molecular sieves (150 mg) were stirred in a solution of DCE (4 mL) for 2 hours at room temperature. To the pre-prepared catalyst in DCE, *α*-methylstyrene (1 mmol, 2 eq.) and glyoxylate (0.5 mmol, 1 eq.) were added using a syringe and stirred until the glyoxylate disappeared. The solvent was removed *in vacuo*, and the resulting crude product was mixed with dry silica powder and loaded onto a silica gel column and purified by flash column chromatography to obtain the homoallylic alcohol. The carbonyl-ene reactions between α-methyl styrene and representative glyoxylate esters were carried out under the optimized conditions (Table 3). All the glyoxylate esters participated in the reaction proceeded smoothly to give the ene products in good to excellent yields and with high enantioselectivities. Even the bulky isopropyl glyoxylate ester also works well for this reaction (Table 3, entry 3).

3.2.4 In(III)-Pybox complex catalyzed asymmetric carbonyl-ene reactions of ethyl glyoxylate with various olefins

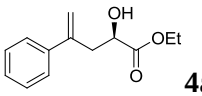
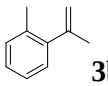
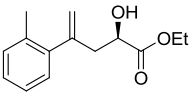
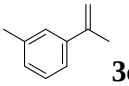
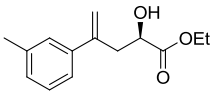
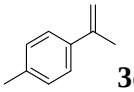
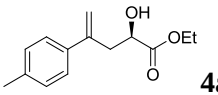
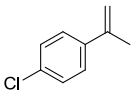
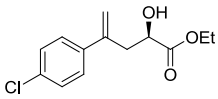
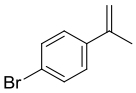
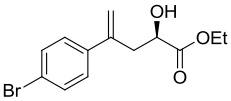
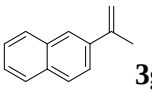
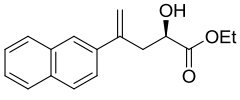
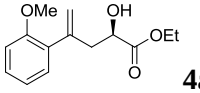
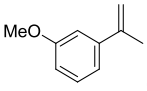
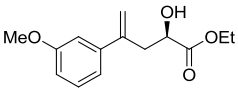
To further examine the scope and limitation of the methodology, carbonyl-ene reactions between the commercially available ethyl glyoxylate and various 1,1-disubstituted and trisubstituted alkenes were explored and the results were summarized in Table 4. To obtain reproducible and excellent enantioselectivities, all of these reactions were carried out at 0 °C. Both aromatic and aliphatic alkenes afforded the expected enantioenriched homoallylic alcohol products in good to

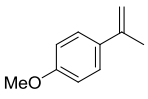
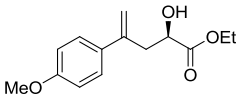
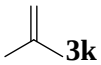
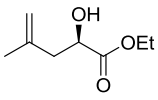
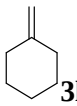
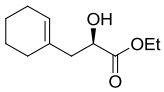
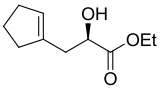
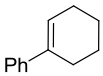
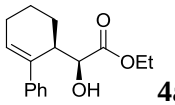
excellent yields and excellent enantioselectivities. Interestingly, the position and the electronic property of the substituents on the phenyl ring of enes has some subtle

Table 4. In(III)-Pybox complex catalyzed aymmetric carbonyl-ene reactions of ethyl glyoxylate with various olefins[a]



2a **3a-o** **4aa-ao**

entry	ene (**3a – 3n**)	product (**4aa – 4an**)	time (day)	yield (%)[b]	ee (%)[c]
1	 **3a**	 **4aa**	6	96	95
2	 **3b**	 **4ab**	6	96	94
3	 **3c**	 **4ac**	6	90	95
4[d]	 **3d**	 **4ad**	6	83	85
5	 **3e**	 **4ae**	6	95	90
6	 **3f**	 **4af**	6	60	97
7	 **3g**	 **4ag**	6	80	90
8	 **3h**	 **4ah**	6	20	91
9	 **3i**	 **4ai**	6	96	96

10	 **3j**	 **4aj**	6	18	77
11	 **3k**	 **4ak**	4	75	95
12	 **3l**	 **4al**	6	96	95
13	 **3m**	 **4am**	6	97	90
14[e]	 **3n**	 **4an**	6	60	99

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of olefins in 4.0 ml of DCE at 0°C, unless indicated otherwise. [b] Isolated yield. [c] Ee values were determined by chiral-phase HPLC analysis or GC, and the absolute (*R*)-configuration of the major products was assigned by comparing HPLC with the literature. [d] Reaction was carried out at room temperature. [e] Regioselectivity and diastereoselectivity were > 99:1.

effects on the reaction efficiency. While weak electron-donating and -withdrawing substituents (Table 4, entries 2-7) were tolerated, strong electron-donating (Table 4, entries 8-10) and withdrawing substituents influenced the reaction significantly. The yield and/or enantioselectivity were sacrificed when the methoxy group is at the *ortho* or *para* position (Table 4, entries 8, 10). There was no reaction at all when 4-nitro-*α*-methyl styrene or 4-methylsulfonly-*α*-methyl styrene was used as substrate. We attributed this electronic effect to the amphibolous mechanism of the carbonyl-ene reaction. There is a debate between a concerted and a stepwise pathway with regard to the mechanism of carbonyl-ene reactions. A general rule is that the more reactive the

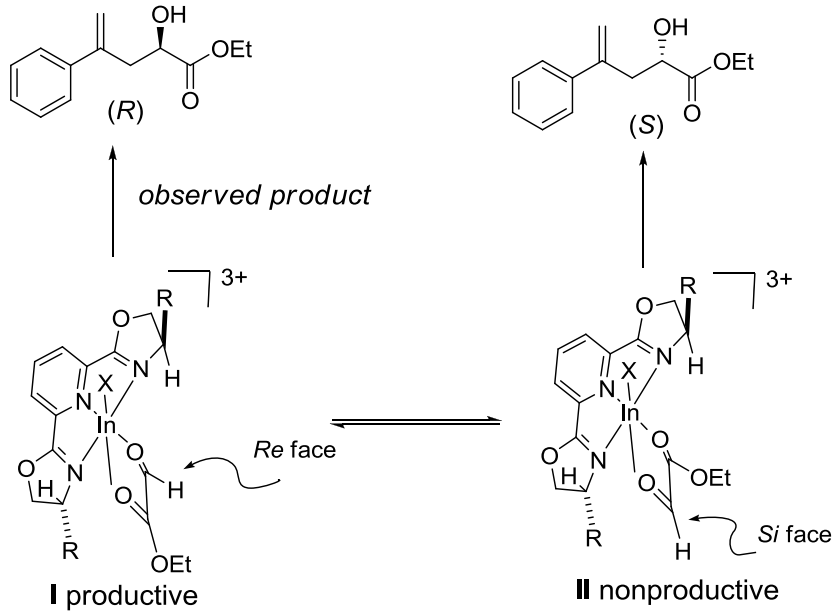
ene or enophile-Lewis acid complex, the more likely the reaction is to be stepwise.[32] So the carbonyl-ene reaction lies in between a fully concerted and a totally stepwise mechanism. Although the carbonyl-ene reaction could be considered as a 6-elecron pericyclic transformation, to some extent, a certain amount of positive charge will buildup as the reaction progresses. The strongly electron-donating substituents activate the alkene too much while the strongly electron-withdrawing lead to low reactivity of alkene. Both of these resulted in the poor results. The reaction of trisubstituted alkene (Table 4, entry 14) is notable: the regio-, diastereo- and enantioselectivity were very high and gave the product in almost optically pure form albeit in moderate yield. In addition, cyclic and acyclic aliphatic alkenes also underwent the carbonyl-ene reaction efficiently to furnish the desired products in high yields and with excellent enantioselectivities (Table 4, entries 11-13).

3.2.5 Proposed transition model to rationalize the observed enantioselectivity

A transition model was proposed to rationalize the observed asymmetric induction. Due to lack of X-ray structural data of In(III)-Pybox complex, a pseudo-octahedral hexa-coordinated model has been proposed as shown in Scheme 3.23. This transition model was proposed based on the crystal structure of In(III) complex formed between $InCl_3$ and 2,6-di-2-pyridylopyridine,[33] a tridentate N-ligand which is structurally similar to pybox ligand. In the $[InCl_3(C_{15}H_{11}N_3)]$ crystal structure, the mutually *trans* bond lengths In-N and In-Cl (in the ligand plane) are

[32] Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426.
[33] Butcher, R. J.; George, C.; Muratore, N.; Purdy, A. P. *Acta Cryst. E* **2003,** m1107.

shorter than the other two In-N and two In-Cl bonds (in the axial position, each *trans* to their own kind). It was reported that this strong *trans* influence was generally



Scheme 3.22

observed in d^{10} metal complexes of tridentate N-ligands.[33,34] Regarding to the strong *trans* influence, we presumed that the strong coordinating site resides in the ligand plane while not in the axial position. Thus the carbonyl coordination occurs prefer in the ligand plane to guarantee the maximal carbonyl activation as shown in model **I** (Scheme 3.22). In model **I**, the *si* face of aldehyde is shielded by the ligand R group exposing the *re* face for nucleophilic attack. As a result, the (*R*)-*β*-hydroxy esters were selectively formed in all of the cases. The stereochemistry of the product supports the proposed pseudo-octahedral hexa-coordinated model.

3.2.6 Design of more active In(III)-pybox complex based on the counterion effect

[34] Beran, G.; Carty, A. J.; Patel, H. A.; Palenik, G. *J. Chem. Soc. D.* **1970**, 222.

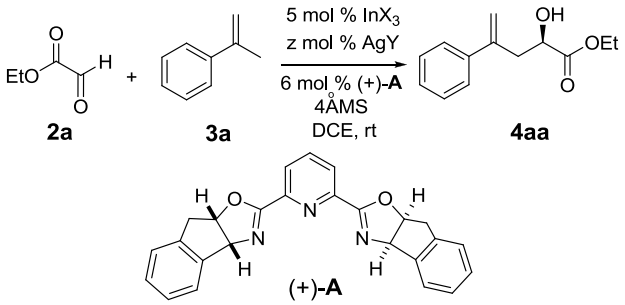
Although various optically active homoallylic alcohols could be obtained with excellent enantioselectivities and yields, there are some limitations in this methodology. For example, long reaction time (4-6 days) was required for the reactions to complete. The alkene scope is limited to 1,1-disubstituted and trisubstituted alkenes. In addition, this catalyst system is ineffective for ketone-ene reactions. All of these disadvantages will immensely impede the synthetic utility of this catalyst system. So, one of the major challenges in this field is to design more active chiral indium(III) complexes which can substantially expand their utility.

Counterion effects had been shown as an efficient strategy in the past decades for improving the catalytic efficiency of chiral Lewis acid complexes.[35] However, most of the successful cases focused on transition metal complexes. We hypothesized that by replacing the counter-anion of the parent indium(III)-pybox complex with a more electronegative and non-coordinating anion may lead to a more powerful indium(III)-pybox complex, which derived from main group metal.

To test this idea, we started with the highly electronegative "non-coordinating" anion SbF_6^-, which is commonly used. The asymmetric carbonyl-ene reaction of ethyl glyoxylate and α-methylstyrene was chose as the model reaction to evaluate the counterion effect of In(III)-pybox complex. Initially, the carbonyl-ene reaction was

[35] (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807. (b) Evans, D. A.; Murry, J. A.; Matt, P.; Norcross, R. D.; Miller, S. J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 798. (c) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059. (d) Johnson, J. S.; Evans, D. A. *Acc. Chem. Res.* **2000**, *33*, 325 and references cited therein. (e) Becker, J. J.; Orden, L. J. V.; White, P. S.; Gagné, M. R. *Org. Lett.* **2002**, *4*, 727. (f) Kezuka, S.; Ikeno, T.; Yamad, T. *Org. Lett.* **2001**, *4*, 1937. (g) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387. (h) Tarselli, M. A.; Chianese, A. R.; Lee, S. J.; Gagné, M. R. *Angew. Chem., Int. Ed. Engl.* **2007**, *46*, 6670. (i) Evans, D. A., Masse, C. E., Wu, J. *Org. Lett.* **2002**, *4*, 3375.

Table 5. Investigation of counterion effect of chiral In(III)-pybox complex[a]



Entry	InX_3	AgY (mol %)	Time/h	Yield (%)[b]	Ee (%)[c]
1[d]	$In(OTf)_3$	-	24	63	94
2	$InCl_3$	-	24	trace	nd
3	$InBr_3$	-	24	trace	nd
4	$InBr_3$	$AgSbF_6$, 15	8	95	81
5	$InCl_3$	$AgSbF_6$, 15	8	96	92
6	**$InCl_3$**	**$AgSbF_6$, 10**	**15**	**98**	**95**
7	$InCl_3$	$AgSbF_6$, 5	24	96	94
8	$InCl_3$	$AgBF_4$, 10	30	94	94
9	$InCl_3$	$AgPF_6$, 10	24	87	90
10	$InCl_3$	$AgClO_4$, 10	24	98	90
11	-	$AgSbF_6$, 10	24	-	-

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of α-methylstyrene in 4.0 mL of solvent at room temperature, unless noted otherwise. [b] Isolated yield. [c] *ee* values were determined by chiral-phase HPLC analysis and the absolute configuration of the major products was *R*, assigned by comparing HPLC with the literature. [d] Reaction is not completed.

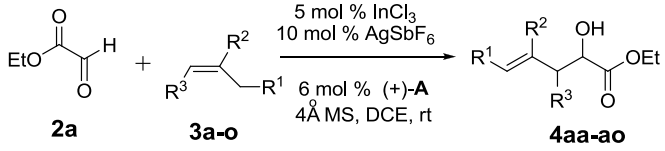
carried out in the presence of chloro chiral indium(III) complex, which was formed *in situ* from 6 mol% pybox (+)-**A** and 5 mol% $InCl_3$. There was only a trace amount of product formed after stirring at room temperature for 1 day (monitored by TLC). Then 15 mol% of silver hexafluoroantimonate ($AgSbF_6$) was added in one portion, and the reaction was found to have completed after 8 hours, furnishing the target product quantitatively with excellent enantioselectivity (up to 92% ee). Encouraged by this

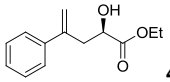
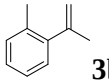
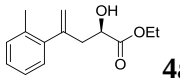
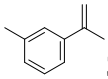
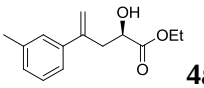
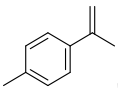
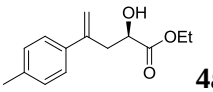
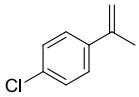
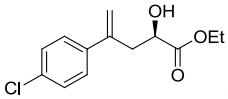
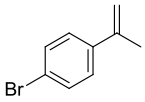
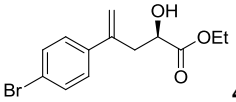
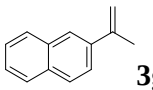
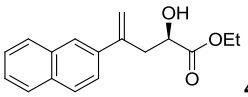
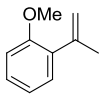
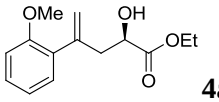
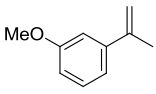
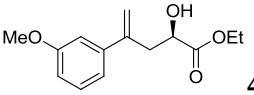
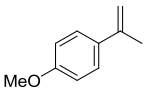
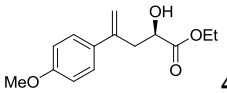
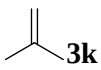
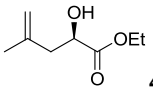
result, we investigated the counterion effect systematically. The results are summarized in Table 5.

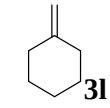
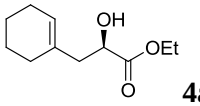
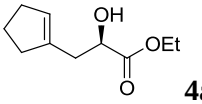
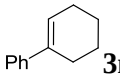
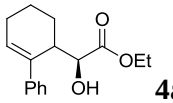
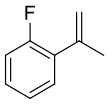
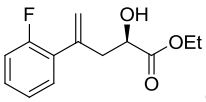
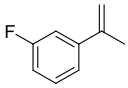
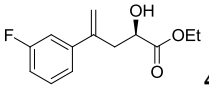
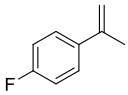
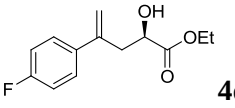
The cationic indium(III)-pybox complexes with various counteranions were prepared by treatment of chloro or bromo indium(III)-pybox complex with the corresponding silver salts. As shown in Table 5, significant counterion effect was observed in the indium(III)-pybox complexes. The catalyst efficiency is positively correlated to the acidities of the conjugated acids of these counter-anions (Table 5, entries 6-10). We were delighted to find that the newly formed In(III)-pybox complexes via anion exchange are more efficient than the parent complexes in catalyzing the asymmetric carbonyl-ene reactions of glyoxylate. The reaction rate was significantly increased (15 hours *vs* 4 days) with retention of excellent yield and enantioselectivity. Interestingly, the catalytic efficiency was also affected by the amount of silver salt (Table 1, entries 5-7). Control experiment indicated that the chiral indium(III) complex is the real catalyst (Table 1, entry 11). Finally, we found that the combination of 5 mol% $InCl_3$, 6 mol% pybox (+)-**A** and 10 mol% $AgSbF_6$ provided the best results in terms of yield, reaction time, and enantioselectivity (Table 5, entry 6).

To test the generality of this strategy, various 1,1-disubstituted and 1,1,2-trisubstituted olefins and ethyl gloxylate were reacted under the optimized conditions and the results are listed in Table 6. In most cases, the new generation of In(III)-pybox complex offered better yields and enantioselectivities than the parent

Table 6. New generation In(III)-pybox complex catalyzed aymmetric carbonyl-ene reactions of ethyl glyoxylate with various olefins[a]



entry	ene (**3a – 3n**)	product (**4aa – 4an**)	time (h)	yield (%)[b]	ee (%)[c]
1	 **3a**	 **4aa**	15	99	94
2	 **3b**	 **4ab**	16	97	85
3	 **3c**	 **4ac**	16	99	93
4	 **3d**	 **4ad**	16	99	90
5	 **3e**	 **4ae**	16	88	94
6	 **3f**	 **4af**	16	99	92
7	 **3g**	 **4ag**	16	99	94
8	 **3h**	 **4ah**	16	99	95
9	 **3i**	 **4ai**	16	99	94
10	 **3j**	 **4aj**	16	92	90
11	 **3k**	 **4ak**	16	99	92

12	 **3l**	 **4al**	16	89	92
13	 **3m**	 **4am**	16	99	90
14	 **3n**	 **4an**	20	72	99
15	 **3o**	 **4o**	20	62	93
16	 **3p**	 **4p**	20	73	94
17	 **3q**	 **4q**	16	99	92

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of olefins in 4.0 ml of DCE at 0°C, unless indicated otherwise. [b] Isolated yield. [c] Ee values were determined by chiral-phase HPLC analysis or GC, and the absolute (*R*)-configuration of the major products was assigned by comparing HPLC with the literature. [d] Reaction was carried out at room temperature. [e] Ratio of hetero Diels-Alder product and carbonyl-ene product is 1:1. [f] Regioselectivity and diastereoselectivity were > 99:1.

In(III)-pybox complex (Table 6). Notably, compared to the long reaction time (4-6 days) reported in the previous case at 0 °C, the reaction time was significantly shortened to 15-20 hours at room temperature with the new generation of In(III)-pybox complexes. Both aromatic and aliphatic olefins afforded the expected enantioenriched homoallylic alcohols with better or comparable yields and enantioselectivities compared to the previous results. Unlike the previous case, in which significant electronic effects had been observed, electronic discrimination in the asymmetric carbonyl-ene reaction was lessened when the new generation of In(III)-pybox complex was used as catalyst. In addition, the counterion effects were

amplified when electron-withdrawing groups were introduced into the olefins (Table 6, entries 5-6 and 15-17). In contrast to the previous case, in which the presence of methoxy group, a strong electron-donating group, both at *ortho* and *para* position led to very poor yields and enantioselectivities, the presence of methoxy group at *ortho* or *para* position has no detrimental effect on the reaction efficiency in the current study (Table 6, entries 8-10).

3.3 CONCLUSION

In conclusion, we have developed a highly enantioselective and efficient indium(III)-pybox complex promoted carbonyl-ene reaction. In the optimization of this reaction, we have developed a new generation of In(III)-pybox complex based on counterion effect and successfully applied it to asymmetric carbonyl-ene reaction of ethyl glyoxylate. The new catalyst system has many advantages compared to the previous case: 1) The reaction rate was increased significantly with retention of excellent yields and enantioselectivities; 2) The reaction can be carried out at room temperature rather than 0 °C, making it more practical, convenient and energy economical; 3) The increased tolerance towards strong electron-withdrawing and -donating group expands the substrate scope of this system; 4) This reaction can be carried out on a 5 mmol scale with excellent results; 5) The bench stable catalyst is easily prepared from commercially available chemicals and the reaction could be carried out in open air; 6) The ethyl glyoxylate and solvent were used directly without further distillation; 7) A pseudo-octahedral hexa-coordinated model has been proposed for the In(III)-pybox and bidentate substrate to rationalize the asymmetric induction. All of these features make this methodology more attractive for the preparation of enantioenriched homoallylic alcohols. In addition, the more active new generation catalyst system might find other applications in asymmetric synthesis in the future.

3.4 EXPERIMENTAL SECTION

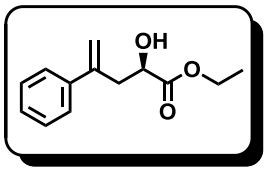
Preparation of catalyst:

In an oven dried 10 mL round-bottom flask equipped with a stirring bar, indium (III) chloride (5.5 mg, 0.025 mmol), PYBOX **(+)-A** (12 mg, 0.03 mmol) and 4Å molecular sieves (150 mg) were stirred in a solution of DCE (4 mL) for 20 minutes at room temperature. To the above mixture, silver hexafluoroantimonate ($AgSbF_6$) (17.2 mg, 0.05 mmol) was added in one portion and stirred for another 20 minutes.

General procedure for carbonyl-ene reaction of alkenes with glyoxylate catalyzed by Indium(III)-1 complex:

To the pre-prepared catalyst in DCE, the alkenes (1 mmol, 2 eq.) and ethyl glyoxylate (0.5 mmol, 1 eq.) were added using a syringe in order under N_2 atmosphere. The reaction process was monitored by TLC. After the reaction finished, the crude product was loaded directly onto a silica gel column and purified by flash column chromatography to afford the enantio-enriched homoallylic alcohol.

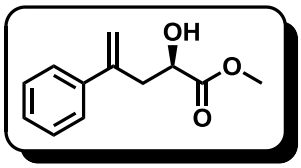
(R)-ethyl 2-hydroxy-4-phenylpent-4-enoate (4aa)



This compound was prepared following the general procedure described above and was obtained as a colourless oil in 98% yield (0.119 g, 95% ee): R_f = 0.28 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -53.0° (c = 1.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.40 (m, 2H), 7.35-7.32 (m, 2H), 7.30-7.28 (m, 1H), 5.40 (d, *J* = 1.1 Hz, 1H), 5.21 (d, *J* = 1.1 Hz, 1H), 4.27 (dd, *J* = 7.3 Hz, *J* = 4.3 Hz, 1H), 4.14-4.08 (m, 1H), 4.07-4.00 (m, 1H), 3.04-3.08 (m, 1H), 2.84 (dd, *J* = 14.4 Hz, *J* = 7.8 Hz, 1H), 2.72 (br s, 1H), 1.23 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 143.6, 140.4, 128.4, 127.7, 126.4, 116.2, 69.2, 61.6, 40.5, 14.1; FTIR (neat): *v* 3462, 2980, 2934, 1734, 1620, 1600, 1570, 1490, 1209, 1096, 1028, 905 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}O_3Na^+$

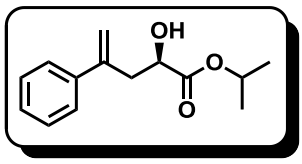
243.0997, found 243.0989; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 7.9 min (minor), t_2 = 10.7 min (major).

(R)-methyl 2-hydroxy-4-phenylpent-4-enoate (4ba)



This compound was prepared following the general procedure described above and was obtained as a colourless oil in 95% yield (0.098 g, 93% ee), R_f = 0.26 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -18.7° (c = 2.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41-7.39 (m, 2H), 7.31-7.35 (m, 2H), 7.29-7.27 (m, 1H), 5.40(s, 1H), 5.20 (s, 1H), 4.29 (dd, *J* = 11.9 Hz, *J* = 4.9 Hz, 1H), 3.62 (s, 3H), 3.06 (dd, *J* = 14.4 Hz, *J* = 4.3 Hz, 1H), 2.84 (dd, *J* = 14.4 Hz, *J* = 7.5 Hz, 1H), 2.72 (d, *J* = 5.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 143.5, 140.2, 128.4, 127.8, 126.4, 116.3, 69.2, 52.3, 40.5; FTIR (neat): *v* 3466, 2951, 1734, 1628, 1574, 1495, 1437, 1269, 1217, 1115, 1028, 980 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}O_3Na^+$ 229.0841, found 229.0837; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 8.9 min (minor), t_2 = 11.0 min (major).

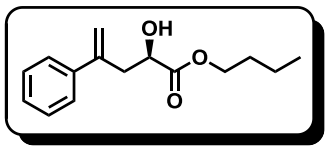
(R)-isopropyl 2-hydroxy-4-phenylpent-4-enoate (4ca)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 80% yield (0.093 g, 92% ee), R_f = 0.28 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -19.3° (c = 2.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.31-7.35 (m, 2H), 7.29-7.27 (m, 1H), 5.39(s, 1H), 5.21 (s, 1H), 4.98 (m, 1H), 4.22 (dd, *J* = 12.3 Hz, *J* = 5.4 Hz, 1H), 3.05 (dd, *J* = 14.5 Hz, *J* = 4.6 Hz, 1H), 2.83-2.78 (m, 2H), 1.24 (d, *J* = 6.3 Hz, 1H), 1.21 (d, *J* = 6.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 143.8, 140.5, 128.4, 127.7, 126.4, 116.1, 69.7, 69.2, 40.6, 21.74, 21.73; FTIR (neat): *v* 3462, 2980, 2936, 1732, 1628, 1599, 1576, 1495, 1449, 1375, 1271, 1217, 1105, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_3Na^+$ 257.1154, found 257.1156; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1

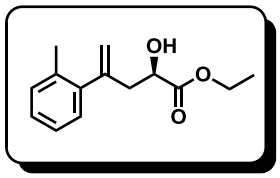
= 6.4 min (minor), t_2 = 7.7 min (major).

(R)-butyl 2-hydroxy-4-phenylpent-4-enoate (4da)



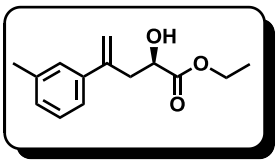
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 96% yield (0.119 g, 92% ee), R_f = 0.29 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -15.2^o (c=1.97, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.36-7.32 (m, 2H), 7.30-7.28 (m, 1H), 5.40(d, *J* = 1.1 Hz, 1H), 5.21 (d, *J* = 1.1 Hz, 1H), 4.27 (m, 1H), 4.07 (m, 1H), 3.97 (m, 1H), 3.07 (dd, *J* = 14.6 Hz, *J* = 3.6 Hz, 1H), 2.83 (dd, *J* = 14.6 Hz, *J* = 7.7 Hz, 1H), 2.76 (d, *J* = 6.1 Hz, 1H), 1.59 (m, 2H), 1.36 (m, 2H), 0.93 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.61, 143.6, 140.3, 128.4, 127.7, 126.4, 116.2, 69.2, 65.5, 40.6, 30.5, 19.1, 13.7; FTIR (neat): *v* 3464, 2959, 1732, 1628, 1599, 1574, 1495, 1207, 1269, 1115, 1028, 903 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}O_3Na^+$ 271.1310, found 271.1304; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 6.7 min (minor), t_2 = 9.9 min (major).

(R)-ethyl 2-hydroxy-4-o-tolylpent-4-enoate (4ab)



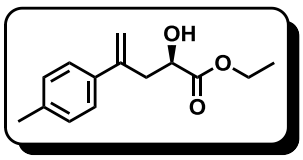
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 97% yield (0.124 g, 91% ee): R_f = 0.29 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ +11.1^o (c = 2.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.18-7.13 (m, 4H), 5.35 (s, 1H), 5.05 (s, 1H), 4.16 (m, 1H), 4.12-4.06 (m, 1H), 4.03-3.95 (m, 1H), 2.91 (dd, *J* = 14.4 Hz, *J* = 4.2 Hz, 1H), 2.80 (d, *J* = 5.7 Hz, 1H), 2.73 (dd, *J* = 14.4 Hz, *J* = 7.7 Hz, 1H), 2.33 (s, 3H), 1.20 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 144.7, 141.4, 135.2, 130.2, 128.8, 127.2, 125.5, 118.1, 68.8, 61.7, 42.4, 19.9, 14.1; FTIR (neat): *v* 3466, 2980, 2930, 1732, 1636, 1447, 1265, 1209, 1099, 1034, 910cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_3Na^+$ 257.1154, found 257.1146; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 5.6 min (minor), t_2 = 7.1min (major).

(R)-ethyl 2-hydroxy-4-m-tolylpent-4-enoate (4ac)



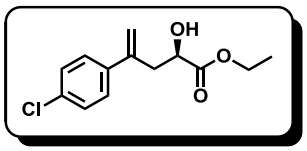
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 98% yield (0.125 g, 93% ee): R_f = 0.30 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -23.1° (c = 1.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.20 (m, 3H), 7.11-7.09 (m, 1H), 5.38 (s, 1H), 5.19 (s, 1H), 4.27 (m, 1H), 4.15-4.10 (m, 1H), 4.08-4.01 (m, 1H), 3.05 (dd, *J* = 14.4 Hz, 4.4 Hz, 1H), 2.80 (d, *J* = 5.7 Hz, 1H), 2.86-2.78 (m, 2H), 2.36 (s, 3H), 1.24 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 143.8, 140.4, 137.9, 128.5, 128.3, 127.2, 123.5 116.0, 69.2, 61.6, 40.6, 21.5, 14.1; FTIR (neat): *v* 3464, 2980, 2926, 1732, 1628, 1600, 1445, 1300, 1267, 1215, 1096, 1034, 903 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_3Na^+$ 257.1154, found 257.1142; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 7.0 min (minor), t_2 = 10.9 min (major).

(R)-ethyl 2-hydroxy-4-p-tolylpent-4-enoate (4ad)



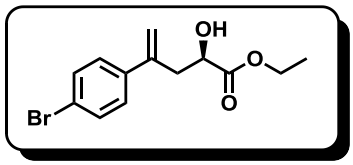
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 98% yield (0.125 g, 89% ee): R_f = 0.29 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -10.5° (c = 2.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 8.0 Hz, 2H), 5.37 (s, 1H), 5.16 (s, 1H), 4.27 (m, 1H), 4.17-4.04 (m, 2H), 3.05 (dd, *J* = 14.2 Hz, 4.3 Hz, 1H), 2.81 (dd, *J* = 14.4 Hz, 7.7 Hz, 1H), 2.75 (d, *J* = 6.2 Hz, 1H), 2.34 (s, 3H), 1.24 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.4, 137.5, 137.4, 129.1, 126.3, 115.4, 69.2, 61.6, 40.6, 21.1, 14.1; FTIR (neat): *v* 3464, 2980, 2924, 1732, 1626, 1514, 1445, 1300, 1266, 1207, 1089, 1034, 900 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_3Na^+$ 257.1154, found 257.1142; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 0.5 mL/min): t_1 = 15.4 min (minor), t_2 = 23.0 min (major).

(R)-ethyl 4-(4-chlorophenyl)-2-hydroxypent-4-enoate (4ae)



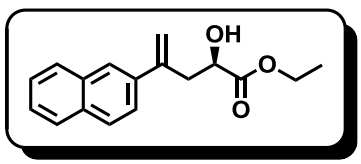
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 88% yield (0.121 g, 93% ee): R_f = 0.24 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -24.2° (c = 1.84, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (m, 4H), 5.38 (s, 1H), 5.22 (s, 1H), 4.24 (m, 1H), 4.17-4.04 (m, 2H), 3.03 (dd, *J* = 14.4 Hz, *J* = 3.8 Hz, 1H), 2.85-2.74 (m, 2H), 1.24 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 142.6, 138.9, 133.5, 128.5, 127.8, 116.7, 69.2, 61.8, 40.4, 14.1; FTIR (neat): *v* 3466, 2982, 2936, 1734, 1628, 1593, 1491, 1447, 1395, 1369, 1267, 1209, 1113, 1032, 1013 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}O_3ClNa^+$ 277.0607, found 277.0604; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 7.5 min (minor), t_2 = 10.6 min (major).

(R)-ethyl 4-(4-bromophenyl)-2-hydroxypent-4-enoate (4af)



This compound was prepared by the general procedure described abo ve and was obtained as a colourless oil in 98% yield (0.157 g, 92% ee): R_f = 0.23 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -20.6° (c = 1.92, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (m, 2H), 7.29 (m, 2H), 5.38 (d, *J* = 0.7 Hz, 1H), 5.22 (d, *J* = 0.7 Hz, 1H), 4.25 (m, 1H), 4.19-4.03 (m, 2H), 3.02 (m, 1H), 2.81 (dd, *J* = 14.4 Hz, *J* = 7.7 Hz, 1H), 2.74 (d, *J* = 6.0 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 142.7, 139.4, 131.5, 128.1, 121.7, 116.8, 69.2, 61.8, 40.3, 14.1; FTIR (neat): *v* 3462, 2980, 2934, 1734, 1628, 1587, 1489, 1445, 1393, 1267, 1209, 1111, 1009 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}O_3BrNa^+$ 321.0102, found 321.0103; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 7.5 min (minor), t_2 = 11.3 min (major).

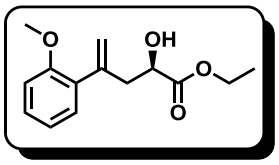
(R)-ethyl 2-hydroxy-4-(naphthalen-2-yl)pent-4-enoate (4ag)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 98% yield (0.143 g, 93% ee): R_f = 0.28 (ethyl acetate :

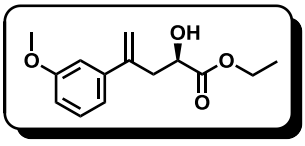
hexane = 1/5), R_f = 0.20 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -20.8° (c=2.26, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (m, 4H), 7.59 (dd, *J* = 8.5 Hz, *J* = 1.4 Hz, 1H), 7.46 (m, 2H), 5.55 (s, 1H), 5.32 (s, 1H), 4.27 (dd, *J* = 11.2 Hz, *J* = 6.5 Hz, 1H), 4.13-4.04 (m, 1H), 4.05-3.98 (m, 1H), 3.19 (dd, *J* = 14.4 Hz, *J* = 4.3 Hz, 1H), 2.96 (dd, *J* =14.4 Hz, *J* = 7.5 Hz, 1H), 2.81 (d, *J* = 6.3 Hz, 1H), 1.22 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 143.5, 137.6, 133.3, 132.9, 128.2, 128.0, 127.6, 126.3, 126.0, 125.1, 124.8, 116.7, 69.3, 61.7, 40.6, 14.1; FTIR (neat): *v* 3466, 3055, 2980, 2934, 1746, 1732, 1632, 1597, 1504, 1445, 1371, 1273, 1215, 1098, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_3Na^+$ 293.1154, found 293.1141; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 9.0 min (minor), t_2 = 12.7 min (major).

(R)-ethyl 2-hydroxy-4-(2-methoxyphenyl)pent-4-enoate (4ah)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 96% yield (0.131 g, 95% ee): R_f = 0.17 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -13.3° (c = 1.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28-7.23 (m, 1H), 7.16 (dd, *J* = 7.5 Hz, *J* = 1.7 Hz, 1H), 6.92 (td, *J* = 7.5 Hz, *J* = 0.9 Hz, 1H), 6.87 (d, *J* = 8.3 Hz, 1H), 5.27 (d, *J* = 0.8 Hz, 1H), 5.15 (d, *J* = 0.8 Hz, 1H), 4.15 (m, 1H), 4.07 (m, 1H), 3.97 (m, 1H), 3.83 (s, 3H), 3.06 (dd, *J* = 14.0 Hz, *J* = 4.2 Hz, 1H), 2.88-2.84 (m, 1H), 2.83 (d, *J* = 6.0 Hz, 1H),1.19 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 156.5, 143.4, 130.7, 130.5, 128.9, 120.7, 118.6, 110.6, 69.2, 61.4, 55.4, 41.5, 14.1; FTIR (neat): *v* 3485, 2980, 2936, 1732, 1632, 1597, 1489, 1435, 1240, 1098, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_4Na^+$ 273.1103, found 273.1093; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 8.7 min (minor), t_2 = 17.2 min (major).

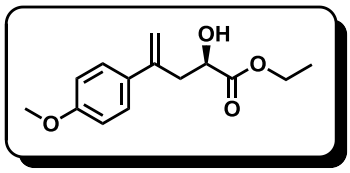
(R)-ethyl 2-hydroxy-4-(3-methoxyphenyl)pent-4-enoate (4ai)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in

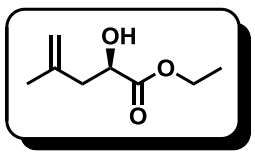
97% yield (0.132 g, 96% ee): R_f = 0.16 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -23.4° (c = 2.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 6.96 (s, 1H), 6.83 (dd, *J* = 8.2 Hz, *J* = 2.2 Hz, 1H), 5.40 (s, 1H), 5.20 (s, 1H), 4.27 (m, 1H), 4.18-4.04 (m, 2H), 3.82 (s, 3H), 3.04 (dd, *J* = 14.4 Hz, *J* = 4.2 Hz, 1H), 2.80 (dd, *J* = 14.4 Hz, *J* = 7.8 Hz, 1H), 2.74 (d, *J* = 6.2 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.6, 143,5, 141.9, 129.3, 118.9, 116.3, 113.0, 112.4, 69.2, 61.7, 55.2, 40.6, 14.1; FTIR (neat): *v* 3447, 2980, 2938, 1734, 1628, 1599, 1576, 1489, 1458, 1429, 1287, 1229, 1096, 1040 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_4Na^+$ 273.1103, found 273.1102; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 9.8 min (minor), t_2 = 15.9 min (major).

(R)-ethyl 2-hydroxy-4-(4-methoxyphenyl)pent-4-enoate (4aj)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 92% yield (0.122 g, 90% ee): R_f = 0.18 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ -25.2° (c = 1.68, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, *J* = 8.9 Hz, 2H), 6.86 (d, *J* = 8.5 Hz, 2H), 5.33 (d, *J* = 0.72 Hz, 1H), 5.12 (d, *J* = 0.72 Hz, 1H), 4.27 (m, 1H), 4.17-4.04 (m, 2H), 3.80 (s, 3H), 3.03 (dd, *J* = 14.4 Hz, *J* = 4.3 Hz, 1H), 2.81 (dd, *J* = 14.4 Hz, *J* = 7.7 Hz, 1H), 2.72 (d, *J* = 6.0 Hz, 1H), 1.24 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 159.3, 142.9, 132.7, 127.5, 114.7, 113.7, 69.2, 61.6, 55.3, 40.6, 14.1; FTIR (neat): *v* 3466, 2980, 2959, 2936, 2837, 1736, 1607, 1574, 1512, 1464, 1369, 1248, 1180, 1090, 1032 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_4Na^+$ 273.1103, found 273.1100; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 11.6 min (minor), t_2 = 18.1 min (major).

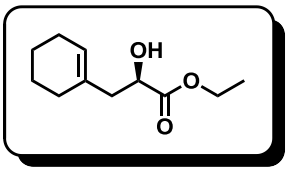
(R)-ethyl 2-hydroxy-4-methylpent-4-enoate (4ak)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 98% yield (0.088 g, 92% ee): R_f = 0.26 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$

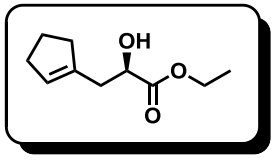
+13.8^{o} (c = 1.59, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) 4.87 (s, 1H), 4.80 (s, 1H), 4.31 (m, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 2.78 (d, *J* = 5.9 Hz, 1H), 2.52 (dd, *J* = 14.1 Hz, *J* = 4.1 Hz, 1H), 2.35 (dd, *J* = 14.1 Hz, *J* = 8.2 Hz, 1H), 1.78 (s, 2H), 1.74 (s, 1H), 1.29 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 141.0, 114.0, 69.1, 61.7, 42.7, 22.5, 14.2; FTIR (neat): *v* 3466, 2980, 2918, 1734, 1647, 1447, 1373, 1265, 1204, 1099, 1026 cm^{-1}; HRMS (ESI) calcd for $C_8H_{14}O_3Na^+$ 181.0841, found 181.0834; The enantiomeric excess was determined by GC analysis employing CYCLODEX-B chiral column (isothermal 90 °C 30 min, 10 °C /min increasing): t_1 = 34.9 min (major), t_2 = 35.3 min (minor).

(R)-ethyl 3-cyclohexenyl-2-hydroxypropanoate (4al)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 89% yield (0.098 g, 90% ee): R_f = 0.28 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ +17.0^{o} (c = 1.98, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.52 (s, 1H), 4.28-4.18 (m, 3H), 2.67 (d, *J* = 6.4 Hz, 1H), 2.44 (dd, *J* = 14.0 Hz, *J* = 3.9 Hz, 1H), 2.27 (dd, *J* = 13.9 Hz, *J* = 8.0 Hz, 1H), 1.99 (m, 4H), 1.64-1.52 (m, 4H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.9, 133.0, 125.3, 69.2, 61.5, 43.3, 28.4, 25.3, 22.8, 22.2, 14.2; FTIR (neat): *v* 3468, 2928, 2835, 1728, 1437, 1369, 1206, 1136, 1098, 1030 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{18}O_3Na^+$ 221.1154, found 221.1145; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 5.7 min (minor), t_2 = 6.5 min (major).

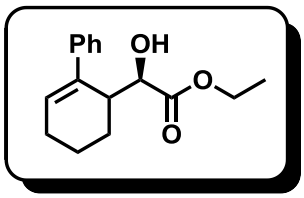
(R)-ethyl 3-cyclopentenyl-2-hydroxypropanoate (4am)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 98% yield (0.101 g, 90% ee): R_f = 0.29 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ +15.3^{o} (c = 2.34, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.49 (s, 1H), 4.28 (dd, *J* = 12.1 Hz, *J* = 5.5 Hz, 1H), 4.21 (q, *J* = 7.11 Hz, 2H), 2.81 (d, *J* = 5.9 Hz, 1H), 2.58 (dd, *J* = 11.8 Hz, *J* = 3.4 Hz, 1H), 2.47 (dd, *J* = 14.7 Hz, *J* = 7.6 Hz, 1H), 2.27 (m,

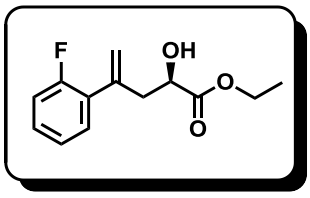
4H), 1.85 (m, 2H), 1.27 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.8, 139.3, 127.7, 69.4, 61.6, 36.2, 35.2, 32.5, 23.5, 14.2; FTIR (neat): *v* 3464, 2949, 2845, 1734, 1445, 1369, 1209, 1094, 1028 cm^{-1}; HRMS (ESI) calcd for $C_{10}H_{16}O_3Na^+$ 207.0997, found 207.0997; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 5.6 min (minor), t_2 = 6.7 min (major).

(R)-ethyl 2-hydroxy-2-((S)-2-phenylcyclohex-2-enyl) acetate (4an)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 72% yield (0.101 g, 99% ee): R_f = 0.31 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{25}$ +98.8^o (c = 1.29, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (m, 5H), 5.95 (td, *J* = 4.0 Hz, *J* = 1.6 Hz, 1H), 4.14 (dd, *J* = 6.2 Hz, *J* = 3.2 Hz, 1H), 3.92 (qd, *J* = 7.1 Hz, *J* = 1.0 Hz, 2H), 3.30 (m, 1H), 2.83 (d, *J* = 6.2 Hz, 1H), 2.16 (m, 2H), 1.94 (m, 1H), 1.80 (m, 1H), 1.74-1.57 (m, 2H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.4, 142.5, 137.3, 130.0, 128.1, 126.83, 126.80, 72.6, 61.4, 40.7, 25.7, 25.6, 19.6, 14.0; FTIR (neat): *v* 3501, 2980, 2934, 2870, 1732, 1599, 1493, 1445, 1219, 1090, 1026 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{20}O_3Na^+$ 283.1310, found 283.1297; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 12.3 min (minor), t_2 = 17.6 min (major).

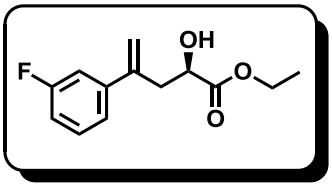
(*R*)-ethyl 4-(2-fluorophenyl)-2-hydroxypent-4-enoate (4ao)



This compound was prepared by the general procedure described above and was obtained as colourless oil in 62% yield (0.074 g, 93% ee): R_f = 0.22 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{24}$ -9.4^o (c = 1.69, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (m, 2H), 7.06 (m, 2H), 5.35 (s, 1H), 5.28 (s, 1H), 4.20 (q, *J* = 4.6 Hz, 1H), 4.14-3.92(m, 2H), 3.04 (dd, *J* = 14.5 Hz, *J* = 4.6 Hz, 1H), 2.86 (dd, *J* = 7.4 H, *J* = 14.5 Hz, 1H), 1.21 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.4, 159.8 (d, *J* = 246 Hz), 134.0, 130.4 (d, *J* = 246 Hz), 129.2 (d, *J* = 8.3 Hz), 128.9 (d, *J* = 14.3 Hz),

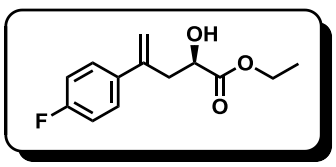
124.1 (d, *J* = 3.8 Hz), 119.8 (d, *J* = 2.3 Hz), 115.6 (d, *J* = 22.5 Hz), 69.1, 61.6, 41.26 (d, *J* = 3.8 Hz), 14.0; FTIR (neat): *v* 3500, 2980, 2935, 2872, 1732, 1634, 1487, 1448, 1369, 1253, 1015 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}FO_3H^+$ 239.1083, found 239.1076; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 7.6 min (minor), t_2 = 10.7 min (major).

(*R*)-ethyl 4-(3-fluorophenyl)-2-hydroxypent-4-enoate (4ap)



This compound was prepared by the general procedure described above and was obtained as colourless oil in 73% yield (0.087 g, 93% ee): R_f = 0.22 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{24}$ -19.0^o (c = 1.74, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (m, 1H), 7.16 (m, 2H), 7.00 (m, 2H), 5.42 (s, 1H), 5.25 (s, 1H), 4.27 (m, 1H), 4.20-4.01 (m, 2H), 3.03 (dd, *J* = 14.8 Hz, *J* = 4.6 Hz, 1H), 2.85-2.78 (m, 1H), 1.25 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.3, 162.5 (d, *J* = 210 Hz), 142.8, 142.6 (d, *J* = 12 Hz), 129.8 (d, *J* = 8.3 Hz), 122.1 (d, *J* = 2.3 Hz), 117.2, 114.5 (d, *J* = 21 Hz), 113.4 (d, *J* = 21.8 Hz), 69.1, 61.8, 40.3, 14.1; FTIR (neat): *v* 3466, 3086, 2981, 2937, 2907, 1732, 1610, 1580, 1487, 1441, 1300, 1267, 1213 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}FO_3H^+$ 239.1083, found 239.1076; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 7.8 min (minor), t_2 = 12.3 min (major).

(*R*)-ethyl 4-(4-fluorophenyl)-2-hydroxypent-4-enoate (4aq)



This compound was prepared by the general procedure described above and was obtained as colourless oil in 98% yield (0.117 g, 93% ee): R_f = 0.24 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{24}$ -18.8^o (c = 1.55, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.34 (m, 2H), 7.05-6.97 (m, 2H), 5.33 (s, 1H), 5.18 (s, 1H), 4.25 (q, *J* = 4.6 Hz, 1H), 4.14-4.00 (m, 2H), 3.02 (dd, *J* = 14.4 Hz, *J* = 4.5 Hz, 1H), 2.90 (s, 1 H), 2.81 (dd, *J* = 7.6 H, *J* = 14.5 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 174.4, 162.4 (d, *J*

= 248 Hz), 142.7, 136.5 (d, *J* = 3.0 Hz), 128.1 (d, *J* = 8.3 Hz), 116.1, 115.2 (d, *J* = 21.8 Hz), 69.1, 61.7, 40.6, 14.0; FTIR (neat): *ν* 3500, 2980, 2935, 2872, 1732, 1634, 1487, 1448, 1369, 1253, 1015 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}FO_3H^+$ 239.1083, found 239.1076; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 90:10, 1.0 mL/min): t_1 = 7.6 min (minor), t_2 = 10.7 min (major).

CHAPTER 4

Highly Enantioselective Ketone-ene Reactions of Trifluoropyruvate Catalyzed by In(III)-PyBox Complex

4.1 OVERVIEW OF KETONE-ENE REACTION

As one of the most important methodologies for carbon-carbon bond construction, asymmetric carbonyl-ene reactions have received great attention in recent years.[1] This field has been spurred by the development of various chiral metal-complexes, pioneered by Mikami's [2] titanium-based and Yamamoto's [3] aluminum-based BINOL complex as the catalysts. Subsequently, Cu,[4] Sc,[5] Pd,[6] Cr,[7] Co,[8] Ni,[9] Pt,[10] and several lanthanides[11] had also been used to mediate the asymmetric carbonyl-ene reactions. Most recently, Terada *et al.*[12] reported an organocatalyzed enantioselective aza-ene-type reaction. However, most of these studies focused on aldehyde-ene reactions. Compared with the extensive study of

[1] For a general review of the ene reaction, see: (a) Mikami, K.; Shimizu, M. *Chem. Re*v. **1992**, *92*, 1021. (b) Berrisford, D. J.; Bolm, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1717. (c) Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* **1992**, 255. (d) Mikami, K. *Pure Appl. Chem.* **1996**, 68, 639.

[2] (a) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1989**, *111*, 1940. (b) Mikami, K.; Terada, M.; Nakai, T. *J. Am. Chem. Soc.* **1990**, *112*, 3949. (c) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (d) Mikami, K.; Yajima, T.; Terada, M.; Kato, E.; Maruta, M. *Tetrahedron: Asymmetry* **1994**, 1087. (e) Mikami, K.; Tomoko, Y.; Takasaki, T.; Matsukawa, S.; Terada, M.; Uchimaru, T.; Maruta, M. *Tetrahedron* **1996**, *52*, 85.

[3] Maruoka, K.; Hoshino, Y.; Shirasaka, Y. H.; Yamamoto, H. *Tetrahedron Lett.* **1988**, *29*, 3967.

[4] (a) Evans, D. A.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T.; Tregay, S. W. *J. Am. Chem. Soc.* **1998**, *120*, 5824. (b) Evans, D. A.; Tregay, S. W.; Burgey, C. S.; Paras, N. A.; Vojkovsky, T. *J. Am. Chem. Soc*. **2000**, *122*, 7936. (c) Gao, Y.; Lane-Bell, P.; Vederas, J. C. *J. Org. Chem*. **1998**, *63*, 2133.

[5] Evans, D. A.; Wu, J. *J. Am. Chem. Soc*. **2005**, *127*, 8006.

[6] (a) Hao, J.; Hatano, M.; Mikami, K. *Org. Lett.* **2000**, *2*, 4059. (b) Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* **2003**, *125*, 4704. (c)Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 183. (d) Mikami, K.; Aikawa, K.; Kainuma, S.; Kawakami, Y.; Saito, T.; Sayo, N.; Kumobayashi, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3885. (e) Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950.

[7] (a) Ruck, R. T.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 2882. (b) Ruck, R. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **2003**, *42*, 4771; (c) Grachan, M. L.; Tudge, M. T.; Jacobsen, E. N. *Angew. Chem., Int. Ed. Engl.* **2008**, *47*, 1469.

[8] (a) Kezuka, S.; Ikeno, T.; Yamada, T. *Org. Lett.* **2001**, *3*, 1937. (b) Hutson, G. E.; Dave, A. H.; Rawal, V. H. *Org. Lett.* **2007**, *9*, 3869.

[9] Zheng, K.; Shi, J.; Liu, X. H.; Feng, X. M. *J. Am. Chem. Soc.* **2008**, *130*, 15770.

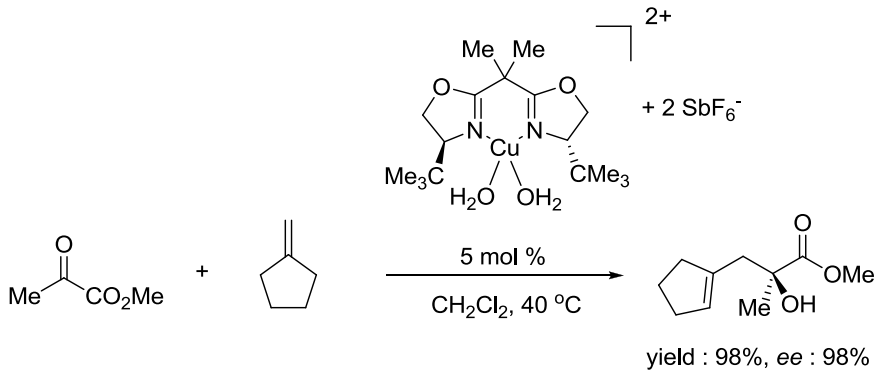
[10] (a) Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233. (b) Mikami, K.; Kakuno, H.; Aikawa, K. *Angew. Chem., Int. Ed. Engl.* **2005**, *44*, 7257.

[11] Qian, C.; Wang, L. *Tetrahedron: Asymmetry* **2000**, *11*, 2347.

[12] Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem., Int. Ed. Engl.* **2008**, *47*, 4122.

aldehyde-ene reaction, the asymmetric ketone-ene reaction is less explored, which is somewhat surprising since it provides a straightforward access to enantioenriched homoallylic alcohols containing a quaternary carbon center.[13] This is presumably due to the low ene reactivities of ketones.

The first successful asymmetric ketone-ene reaction was developed by Evans' group in 2000, using [Cu(Ⅱ){(*S*,*S*)-*t*-Bu-box}][SbF_6]$_2$ complex as the catalyst (Scheme 4.1).[4b] The asymmetric ketone-ene reactions between methyl pyruvate and different 1,1-disubstituted olefins proceeded smoothly to give the optical active tertiary alcohols in good to excellent yields and with excellent enantioselectivities. However, large excess (5 to 10 equiv) of olefins and relatively high reaction temperature (40 °C) are necessary to achieve high reaction efficiency.

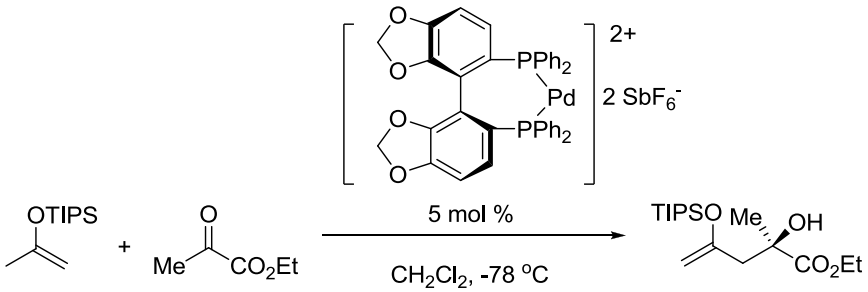


Scheme 4.1

In their study of chiral binaphthol-derived titanium dichloride catalyzed Mukaiyama aldol reaction between glyoxylate esters and silyl enol ethers derived from ketones, Mikami *et al.* made an unanticipated observation that carbonyl-ene-type products were obtained exclusively as the corresponding silyl enol ethers while no

[13] Doherty, S.; Knight, J. G.; Smyth, C. H.; Harrington, R. W.; Clegg, W. *J. Org. Chem*. **2006**, *71*, 9751 and references cited therein.

aldol products were formed.[14] On the basis of this observation, they developed an asymmetric ketone-ene reaction of ethyl pyruvate by using activated olefins (silyl enol ethers derived from ketones) as ene (Scheme 4.2).[15] In the presence of 5 mol% of chiral cationic Pd(II)-SEGPHOS complex, the optically active *β*-hydroxy silyl enol ether containing a quaternary carbon center could be obtained with excellent enantioselectivities (*ee* up to 98%). Notably, the catalyst loading could be further decreased to 0.01 mol% with retention of excellent catalytic efficiency. The silyl enol ether part of the products are easily transformed into other useful synthetic intermediates.

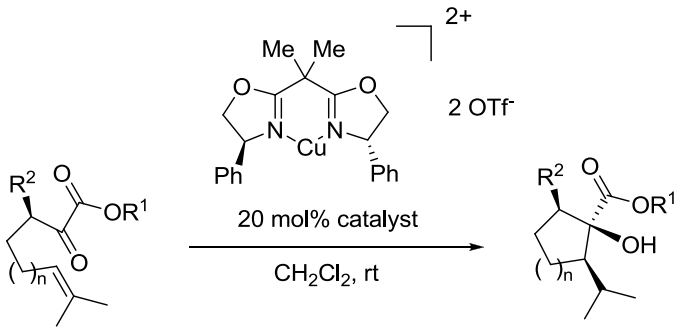


Scheme 4.2

Putting two reacting parts into the same molecule is an effective strategy to decrease the high energy barrier of a reaction. The intramolecular enantioselective carbonyl-ene reaction had been used in the total synthesis of natural products. Not only unactivated aldehyde but also the carbonyl group of *α*-keto ester could be used as enophile for the intramolecular carbonyl-ene reaction. Yang *et al.* reported a Cu(II)-box complex catalyzed enantioselective carbonyl-ene reaction of unsaturated

[14] Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039.
[15] Mikami, K.; Kawakami, Y.; Akiyama, K.; Aikawa, K. *J. Am. Chem. Soc.* **2007**, *129*, 12950.

α-keto esters (Scheme 4.3) which was carried out under high temperature in the absence of Lewis acid.[16] The chelating effect proved to be crucial for high stereoselectivity. Two chiral centers, including one quaternary carbon center, could be constructed in one step with excellent diastereoselectivties (dr up to 23:1) and enantioselectivities (ee up to 91%).



Scheme 4.3

Possessing a unique reactivity which lies between pyruvate and glyoxylate, trifluoropyruvate could potentially be regarded as an ideal substrate for ketone-ene reaction. In addition, organofluorine compounds have attracted much attention in many science disciplines owing to the unique physical and biological properties of fluorine.[17] With its strong electronegativity, stability and lipophilicity, introduction of trifluoromethyl group often induces considerable change in the chemical, physical, and physiological properties of the parent molecules and these make CF_3-containing compounds particularly interesting.[18] Consequently, synthetic methods for

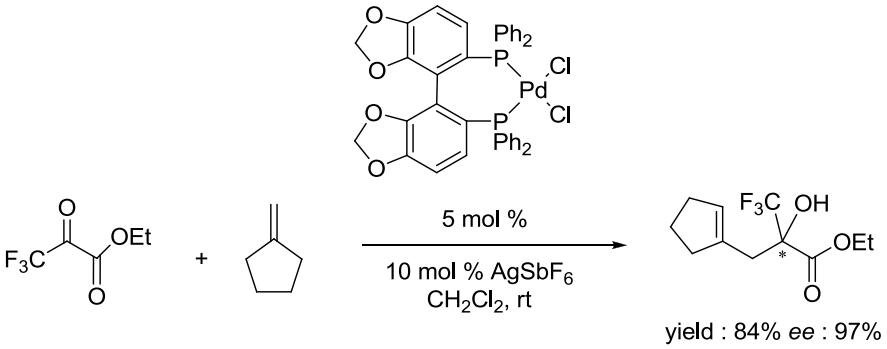
[16] (a) Yang, D.; Yang, M.; Zhu, N. Y. *Org. Lett.* **2003**, *5*, 3749. (b) Hiersemann, M. *Synlett* **2000**, 415. (c) Hiersemann, M. *Eur. J. Org. Chem.* **2001**, 483.

[17] (a) *Organofluorine chemistry –Principle and Commercial Application*; Banks, R. E.; Smart, B. E.; Tatlow, J. C.; Eds.; Plenum Press: New York, **1994**. (b) *Fluorine-containing Molecules, Structure, Reactivity, Synthesis and Applications*; Liebman, J.F.; Greenberg, A., Dolbier, W. R., Jr., Eds.; VCH Publishers: Weiheim, **1988**. (c) *Fluorine-containing Amino Acids, Synthesis and Propeties*, Kukhar', V. P., Soloshonok, V. A., Eds.; John Wiley & Sons Ltd.: New York, **1995**.

[18] For recent reviews on fluorinated pharmaceuticals, see: (a) Müller, K.; Faeh, C.; Diederich, F. *Scienece* **2007**, 317, 1881; (b) Shimizu, M.; Hiyama, T. *Angew. Chem., Int. Ed.* **2005**, 44, 214; (c)

introducing the trifluoromethyl group into an organic compound selectively have generated an important field of chemistry.[19] From the point of view of unique reactivity and broad application of trifluoromethyl containing compounds, the enantioselective carbonyl-ene reaction of trifluoropyruvate is more important and feasible than the corresponding pyruvate, even though there are still only few successful examples of ketone-ene reaction of trifluoropyruvates.

Mikami *et al.* reported a palladium(II) complex catalyzed ketone-ene reaction of ethyl trifluoropyruvate (Scheme 4.4).[20] A variety of 1,1-disubstituted and



Scheme 4.4

trisubstituted olefins gave the ketone-ene reaction products in good yield and with excellent enantioselectivity. Notably, reaction of mono- and 1,2-disubstituted olefins with low ene reactivities also proceeded with high level of enantio- and diastereoselectivity. The increased reactivity of ketone-ene reaction might be

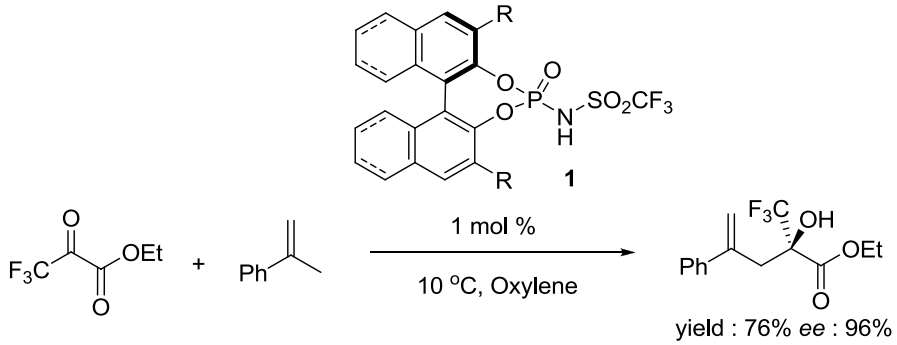
Begue, J.; Bonnet-Delpon, D.; Crousse, B.; Legros, J. *Chem. Soc. Rev.* **2005**, 34, 562; (d) Purser, S.; Moore, R. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, 37, 320.

[19] (a) Lin, P.; Jiang, J. *Tetrahedron* **2000**, 56, 3635. (b) Loh, T. P.; Li, X. R.; *Angew. Chem., Int. Ed.* **1997**, *36*, 980-986. (c) Allen, A. E.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2010**, *132*, 4986. (d) Ball,N. D.; Kampf, J. W.; Sanford, M. S. *J. Am. Chem. Soc.* **2010**, *132*, 2878. (e) Wang, X. S.; Truesdale, L.; Yu, J. Q. *J. Am. Chem. Soc.* **2010**, *132*, 3648.

[20] (a) Aikawa, K.; Kainuma, S.; Hatano, M.; Mikami, K. *Tetrahedron Lett.* **2004**, *45*, 183. (b) Mikami, K.; Aikawa, K.; Kainuma, S.; Kawakami, Y.; Saito, T.; Sayo, N.; Kumobayashi, H. *Tetrahedron: Asymmetry* **2004**, *15*, 3885.

attributed to activation of the carbonyl group by the strong electron-withdrawing trifluoromethyl substituent.

Very recently, Rueping *et al.* developed a highly efficient enantioselective ketone-ene reaction of trifluoropyruvates by using metal-free chiral *N*-triflylphosphoramide as organocatalyst (Scheme 4.5). [21] This concept is based on the activation of the carboyl group by catalytic protonation to form an intermediary ion pair composed of the activated carbonyl and a chiral phosphate counterion, which is crucial for asymmetric induction. After systematic investigation, the best result with regard to both reactivity and selectivity was observed with 1 mol% of the chiral Brønsted acid **1**. A broad range of styrene derivatives, with electron-withdrawing and electron-donating substituents underwent the desired reaction to provide the enantioenriched homo-allylic alcohols with a quaternary chiral carbon center, in excellent yields and with excellent enantioselectivity. However, the substrate scope is limited to 1,1-disubstituted aromatic alkenes.



Scheme 4.5

As mentioned above, there are only few successful reports regarding to asymmetric ketone-ene reaction although it is a very efficient strategy to construct

[21] Rueping, M.; Theissmann, T.; Kuenkel, A.; Koenigs, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 6798.

chiral quaternary carbon center. Therefore, the asymmetric ketone-ene reaction remains a formidable challenge and more effective catalyst systems are highly anticipated.

Among the Lewis acid complexes, indium(III) complexes[22] have recently emerged as a popular choice due to their versatility in effecting various organic transformations in ionic liquids, aqueous media as well as organic solvents. Our group[23] and others[24] have developed several chiral indium(III) complexes which could be used as chiral catalysts for a series of asymmetric reactions. Unlike other chiral metal complexes catalyzed reactions which must be carried out under strictly anhydrous conditions, chiral indium(III) complexes are water-tolerant catalysts. Moreover, chiral indium(III) complexes could be used in ionic liquid, which enables the recycle and reuse of the chiral catalysts.[25] We have recently demonstrated that indium(III)-pybox complex is an effective catalyst for asymmetric carbonyl-ene reactions of glyoxylates.[26] Considering the synthetic versatility and potential utility of asymmetric ketone-ene product of trifluoropyuvate and the challenges of ketone-ene

[22] (a) Loh, T. P.; Chua, G. L. *Chem. Commun.* **2006**, 2739. (b) Podlech, J.; Maier, T. C. *Synthesis* **2003**, 633 and references cited therein.

[23] (a) Y. C. Teo, J. D. Goh, T. P. Loh, *Org. Lett.* **2005**, *7*, 2743. (b) Lu, J.; Hong, M. L.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 1010. (c) Lu, J.; Hong, M. L.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Chem. Commun.* **2005**, 4217. (d) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 159; e) Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem. Commun.* **2005**, 1318. (f) Fu, F.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2006**, *47*, 4267. (g) Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, *7*, 2539. (h) Teo, Y. C.; Loh, T. P. *Organic Lett.* **2005**, *7*, 159.

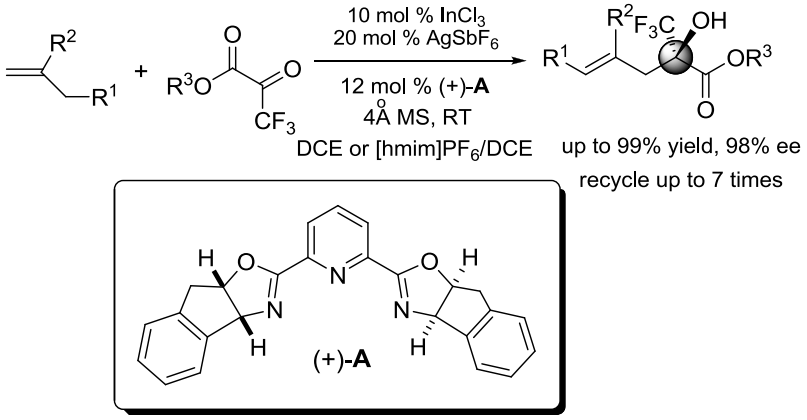
[24] (a) Takita, R.; Yakura, K.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 13760. (b) Yu, Z. P.; Liu, X. H.; Dong, Z. H.; Xie, M. S.; Feng, X. M. *Angew. Chem., Int. Ed. Engl.* **2008**, *47*, 1308. (c) Zhang, X.; Chen, D. H.; Liu, X. H.; Feng, X. M. *J. Org. Chem*. **2007**, *72*, 5227.

[25] (a) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 2345. (b) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2005**, *46*, 7435-7437.

[26] (a) Zhao, J. F.; Tsui, H. Y.; Wu, P. J.; Loh, T. P. *J. Am. Chem. Soc.* **2008**, *130*, 16492. (b) Zhao, J. F.; Tian, T. B.; Loh, T. P. *Tetrahedron Lett.* **2010,** *51*, 5649.

reaction, we attempted to use this catalyst system to mediate the asymmetric ketone-ene reaction of trifluoropyuvate.

In an effort to expand the application of chiral In(III)-pybox complex, we herein present the In(III)-pybox complex, which is recyclable in ionic liquid, catalyzes highly enantioselective ketone-ene reactions of trifluoropyuvate under mild reaction conditions (Scheme 4.6).



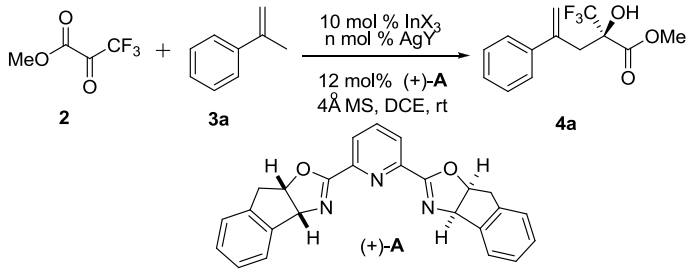
Scheme 4.6

4.2 RESULTS AND DISCUSSION

4.2.1 In(III)-pybox complex catalyzed ketone-ene reaction of trifluoropyruvate in pure organic solvent

Initially, the asymmetric ketone-ene reaction of trifluoropyruvate had been carried out in the presence of 10 mol% of the first generation In(III)-pybox complex, which was formed *in situ* from $In(OTf)_3$ and pybox ligand. The ene product was obtained in poor yield and with low enantioselectivity (Table 1, entry 1) after stirring at room temperature for 6 days. Interestingly, when $AgSbF_6$ was added to this catalyst system, the reaction rate as well as enantioselectivity increased significantly (Table 1, entry 2). Encouraged by this promising result, we investigated the counterion effect systematically with the hope of increasing the catalytic efficiency. The cationic indium(III)-pybox complexes with various counter-anions were prepared by treatment of chloro or bromo indium(III)-pybox complex with the corresponding silver salts. Significant counterion effect was observed in the indium(III)-pybox complex and the catalytic efficiency is positively correlated to the acidity of the conjugated acid of these counter anions (Table 1, entries 4, 7, 8, 9). In addition, the catalytic efficiency was also affected by the amount of silver salt (Table 1, entries 4-6). Control experiment indicated that the chiral indium complex is the real catalyst (Table 1, entry 12). Finally, we found that the combination of 10 mol% $InCl_3$, 12 mol% pybox (+)-**A** and 20 mol% $AgSbF_6$ provided the best results in terms of yield, reaction time,

Table 1. Optimization studies[a]



Entry	InX_3	AgY (mol %)	Time/h	Yield (%)[b)]	Ee (%)[c)]
1	$In(OTf)_3$	-	144	33	8
2	$In(OTf)_3$	$AgSbF_6$ (20%)	18	63	57
3	$InBr_3$	$AgSbF_6$ (20%)	3	94	95
4	**$InCl_3$**	**$AgSbF_6$ (20%)**	**3**	**99**	**95**
5	$InCl_3$	$AgSbF_6$ (10%)	22	99	92
6	$InCl_3$	$AgSbF_6$ (30%)	3	93	92
7	$InCl_3$	$AgPF_6$ (20%)	48	80	62
8	$InCl_3$	$AgBF_4$ (20%)	48	59	90
9	$InCl_3$	$AgClO_4$ (20%)	48	53	85
10[d]	$InCl_3$	$AgSbF_6$ (20%)	3	95	95
11[e]	$InCl_3$	$AgSbF_6$ (10%)	48	92	94
12	-	$AgSbF_6$ (20%)	24	-	-

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of trifluoropyruvate in 4.0 mL of 1,2-dichloroethane (DCE) at room temperature, unless noted otherwise. [b] Isolated yield. [c] The *ee* values were determined by chiral-phase HPLC analysis and the absolute configuration of the major products was *R*, assigned by comparing HPLC with the literature.[6e] [d] Ethyl trifluoropyruvate was used. [e] 5 mol% of $InCl_3$ and 6 mol% of (+)-**A** were used.

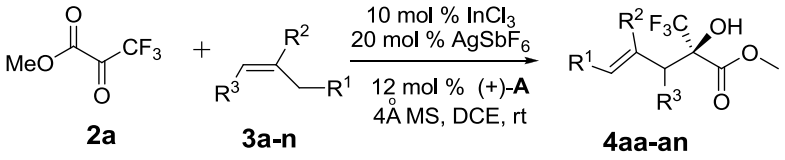
and enantioselectivity (Table 1, entry 4).[27] The catalyst loading could be lowered to 5mol% with no detrimental effect on yield and enantioselectivity albeit a longer reaction time required (Table 1, entry 11). The ester group of trifluoropyruvate has no significant influence on the reaction efficiency (Table 1, entry 10).

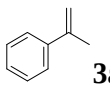
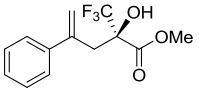
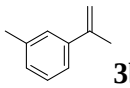
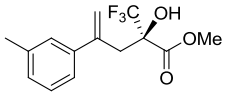
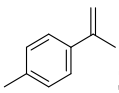
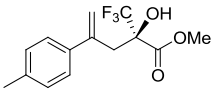
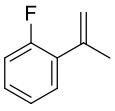
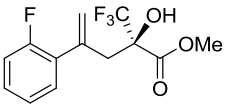
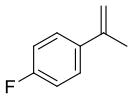
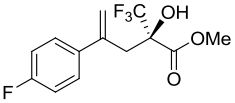
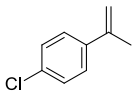
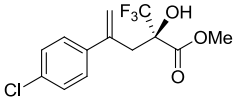
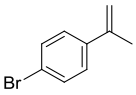
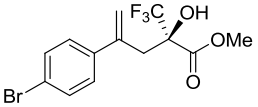
With the optimized conditions in hand, we next evaluated the substrate scope of this ketone-ene reaction. The results are listed in Table 2. As shown in Table 2, both

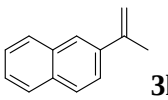
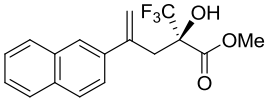
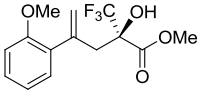
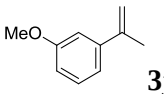
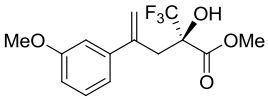
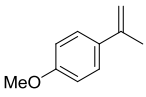
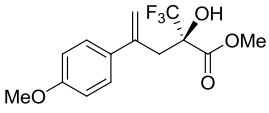
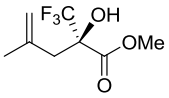
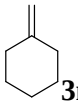
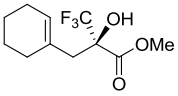
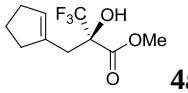
[27] Because similar results were obtained when the AgX salt was filtered from the reaction system, AgX salt was not precipitated in this work.

aromatic and aliphatic alkenes afforded the expected enantioenriched tertiary homoallylic alcohols, containing a trifluoromethyl group, in good to excellent yields and excellent enantioselectivities. Significant electronic and steric effects were observed in the ketone-ene reaction of aromatic alkenes. This might be due to the

Table 2. In(III)-pybox complex-catalyzed asymmetric ketone-ene reactions of methyl trifluoropyruvate with various olefins[a]



entry	ene (**3a – 3n**)	product (**4aa – 4an**)	time (h)	yield (%)[b]	ee (%)[c]
1	 **3a**	 **4aa**	3	99	95
2	 **3b**	 **4ab**	3	99	94
3	 **3c**	 **4ac**	3	99	94
4	 **3d**	 **4ad**	12d	56	87
5	 **3e**	 **4ae**	72	92	92
6	 **3f**	 **4af**	144	90	93
8	 **3g**	 **4ag**	48	97	89

9	 **3h**	 **4ah**	3	91	95
10	 **3i**	 **4ai**	72	86	85
11	 **3j**	 **4aj**	3	99	95
12	 **3k**	 **4ak**	2	99	64
13[d]	 **3l**	 **4al**	6	79	98
14[e]	 **3m**	 **4am**	48	95	98
15	 **3n**	 **4an**	3	94	97

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of methyl trifluoropyruvate in 4.0 mL of DCE at room temperature, unless indicated otherwise. [b] Isolated yield. [c] The *ee* values were determined by chiral-phase HPLC analysis or GC, and the absolute (*R*)-configuration of the major products was assigned by X-ray analysis of **4af** & **4ag** or comparing HPLC with the literature. [d] Excess of isobutene was used. [e] This reaction was carried out at 0 ℃.

positive charge built up in the process of carbonyl-ene reaction.[28] For example, the presence of electron-withdrawing group decreases reactivity of the alkene significantly and longer reaction time was required (Table 2, entries 4-7). On the contrary, electron-donating group increases the reactivity of alkene a little. 4-Methoxy-α-methyl styrene is too reactive to give satisfactory enantioselectivity (Table 2, entry 11) due to the strong electron donating ability of 4-methoxy group. The position of the substituents on the phenyl ring of the aromatic alkene also has some subtle effects on

[28] Snider, B. B. *Acc. Chem. Res.* **1980**, *13*, 426 and references cited therein.

the reaction efficiency. For example, the yield and the enantioselectivity were both significantly sacrificed when the substituent, either electron-withdrawing or donating group, was at *ortho* position (Table 2, entries 4 and 10),[11] which is presumably due to steric hindrance in the transition state.

4.2.2 In(III)-pybox complex catalyzed ketone-ene reaction of trifluoropyruvate in ionic liquid

Recently, our laboratory has been interested in using ionic liquid as an alternative to conventional organic solvent.[29] Employing ionic liquid as reaction media has many advantages among which the most important is the easy isolation of product by simple extraction, which enable recycling of the ionic liquid containing the chiral catalyst.[30] As far as we know, no asymmetric carbonyl-ene in ionic liquid has been reported. Considering the stability and recyclability of indium(III)-pybox complex in ionic liquid,[31] we attempted to know whether the new generation of can be used in ionic liquid. We carried out the new indium(III)-pybox complex catalyzed ketone-ene reaction in ionic liquid. The catalyst was prepared by mixing indium(III) chloride, pybox (+)-**A** and 4Å molecular sieves in a solution of 1,2-dichloroethane (DCE) and

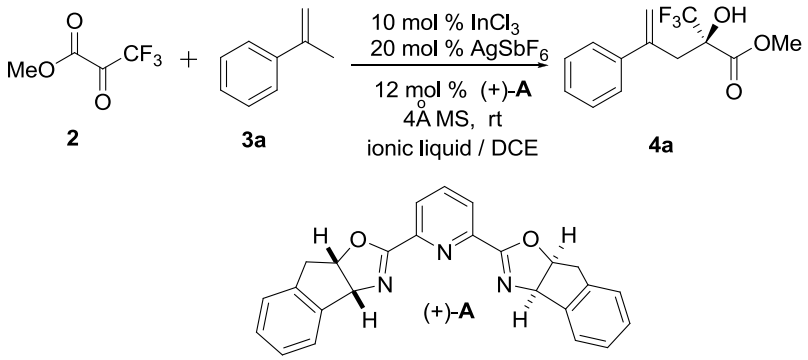
[29] (a) Loh, T. P.; Feng, L. C.; Yang, H. Y.; Yang, J. Y. *Tetrahedron Lett*. **2003**, *44*, 2405. (b) Lu, J.; Ji, S. J.; Qian, R; Chen, J. P.; Liu, Y.; Loh, T. P. *Synlett* **2004**, 534. (c) Shen, Z. L.; Zhou, W. J.; Liu, Y. T.; Ji, S. J.; Loh, T. P. *Green Chem.* **2008**, *10*, 283. (d) Chen, S. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 375. (e) Shen, Z. L.; Ji, S. J.; Loh, T. P. *Tetrahedron Lett.* **2005**, *46*, 3137. (f) Teo, Y. C.; Goh, Y. L.; Loh, T. P. *Tetrahedron Lett.* **2005**, *46*, 4573.

[30] For reviews, see: (a) Trindade, A. F.; Gois, P. M. P.; Afonso, C. A. M. *Chem. Rev.* **2009**, *109*, 418. (b) María, P. D. *Angew. Chem. Int. Ed. Engl.* **2008**, *47*, 6960. For recent examples of recycle of catalyst in ionic liquid, see: (c) Guo, H. M.; Cun, L. F.; Gong, L. Z.; Mi, Q. A.; Jiang, Y. Z. *Chem. Commun.* **2005**, 1450. (d) Audic, N.; Clavier, H.; Mauduit, M.; Guillemin, J. C. *J. Am. Chem. Soc.* **2003**, *125*, 9248. (e) Guo, H. M.; Niu, H. Y.; Xue, M. X.; Guo, Q. X.; Cun, L. F.; Mi, A. Q.; Jian, Y. Z.; Wang, J. J. *Green Chem.* **2006**, *8*, 682. (f) Huang, K.; Huang, Z. Z.; Li, X. L. *J. Org. Chem*. **2006**, *71*, 8320. (g) Fu. F; Teo, Y. C.; Loh, T. P. *Org. Lett.* **2006**, *8*, 5999.

[31] (a) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 2345. (b) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T. P. *Tetrahedron Lett.* **2005**, *46*, 7435.

stirring for 20 minutes at room temperature. Then, $AgSbF_6$ was added to replace the anion of the parent indium(III)-pybox complex. After stirring for another 20 minutes,

Table 3. Screening of ionic liquid[a]



entry	ionic liquid	time (h)	yield[b] (%)	ee[c] (%)
1	$[bmim]PF_6$	1	95	93
2	$[hmim]PF_6$	1	96	96
3	$[omim]PF_6$	1	94	92
4	$[hmim]BF_4$	24	trace	--
5	[bmim]Br	24	trace	--
6[d]	$[hmim]PF_6$	1	95	96

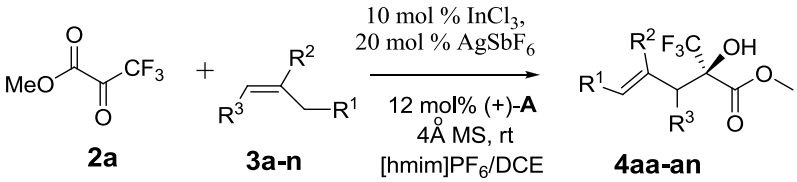
[a] Unless otherwise noted, reactions were carried out on a 0.3 mmol scale with 2 equiv of trifluoropyruvate in a mixture of 0.5 mL of ionic liquid and 0.5 mL 1,2-dichloroethane (DCE) at room temperature. [b] Isolated yield. [c] The ee values were determined by chiral-phase HPLC. [d] DCE was removed before the addition of reactant.

ionic liquid $[bmim]PF_6$ was added, followed by sequential addition of α-methylstyrene and methyl trifluoropyruvate. To our delight, the carbonyl-ene reaction indeed proceeded smoothly to afford the enantioenriched tertiary allylic alcohol in 95% yield and with 93% ee (Table 3, entry 1). Throughout screening of a series of ionic liquids we found that $[hmim]PF_6$ proved is the best choice of solvent (Table 3, entry 2). The reaction efficiency is dependent on the identity of the counteranion of the ionic liquid

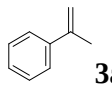
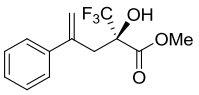
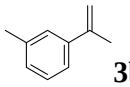
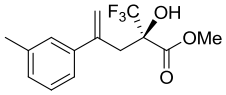
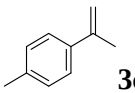
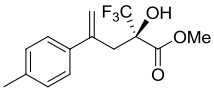
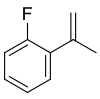
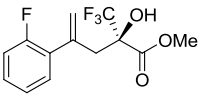
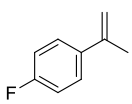
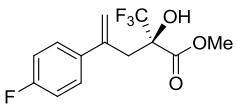
(Table 3, entries 2, 4 and 6) while identity of the counter-cation has slight effect on the enantioselectivity (Table 3, entries 1-3).

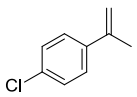
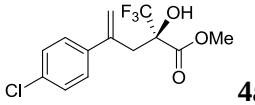
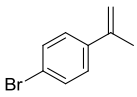
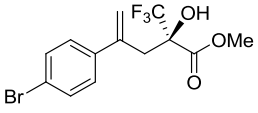
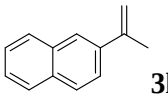
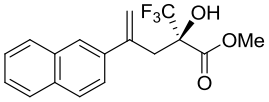
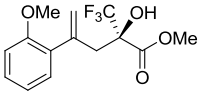
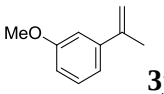
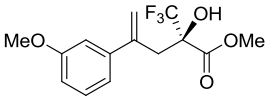
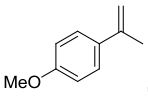
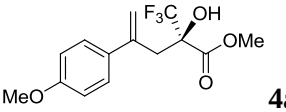
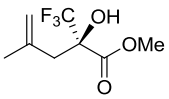
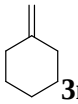
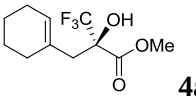
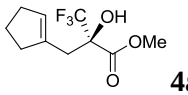
We next examined the generality of this methodology and the results are summarized in Table 4. As shown in Table 4, the asymmetric ketone-ene reactions of trifluoropyruvate proceeded smoothly to give the products with excellent yields and enantioselectivities. In addition, most of the reactions carried out in ionic liquid proceeded faster than that carried out in pure organic solvent with comparable or

Table 4. In(III)-pybox complex-catalyzed asymmetric ketone-ene reactions of methyl trifluoropyruvate with various olefins in ionic liquid[a]



2a **3a-n** **4aa-an**

entry	ene (**3a – 3n**)	product (**4aa – 4an**)	time (h)	yield (%)[b]	ee (%)[c]
1	 **3a**	 **4aa**	1(3)	95(99)	96(95)
2	 **3b**	 **4ab**	1(3)	92(98)	95(94)
3	 **3c**	 **4ac**	1(3)	93(97)	94(94)
4	 **3d**	 **4ad**	162(240)	90(56)	97(87)
5	 **3e**	 **4ae**	5(72)	91(92)	97(92)

6	 **3f**	 **4af**	4(144)	91(90)	97(95)
7	 **3g**	 **4ag**	7(48)	97(97)	98(91)
8	 **3h**	 **4ah**	4(3)	80(91)	96(95)
9	 **3i**	 **4ai**	72(72)	74(86)	80(85)
10	 **3j**	 **4aj**	20(3)	91(99)	97(95)
11	 **3k**	 **4ak**	1(2)	85(99)	55(64)
12[d]	 **3l**	 **4al**	3(6)	78(79)	98(98)
13[e]	 **3m**	 **4am**	43(48)	98(95)	98(98)
14	 **3n**	 **4an**	43(3)	98(94)	92(98)

[a] Reactions were carried out on a 0.5 mmol scale with 2 equiv of methyl trifluoropyruvate in 4.0 mL of DCE at room temperature, unless indicated otherwise; the results in parentheses are for the reactions carried out in DCE.[32] [b] Isolated yield. [c] The *ee* values were determined by chiral-phase HPLC analysis or GC, and the absolute (*R*)-configuration of the major products was assigned by X-ray analysis of **4af** & **4ag** or comparing HPLC with the literature. [d] Excess of isobutene was used. [e] This reaction was carried out at 0 ℃.

better yields and enantioselectivities. Similar with the reactions carried out in pure organic solvent, significant electronic and steric effects were also observed in this system. Electron-withdrawing group on the phenyl ring of substituted α-methylstyrene prolonged the reaction time (Table 4, entries 4-7). The position of the substituted

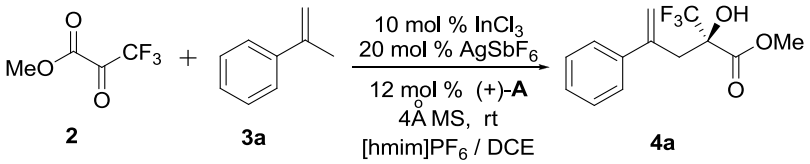
[32] Zhao, J. F.; Tjan, T. B.; Tan, B. H.; Loh, T. P. *Org. Lett.* **2009**, *11*, 5714.

group also has effect on the reaction efficiency. Due to steric effect, both electron-withdrawing and donating groups at the *ortho* position led to lower yields and enantioselectivities (Table 4, entries 4 and 9). The lowest enantioselectivity observed in **4ak** might be due to the more reactive nature of substrate **3k** (Table 4, entry 11).

4.2.3 Recyclability study of the chiral catalyst in ionic liquid

In terms of cost-effectiveness, the recyclability of the chiral catalyst is a very important and challenging task for possible industrial application. Therefore, we

Table 5. Recyclability study[a]



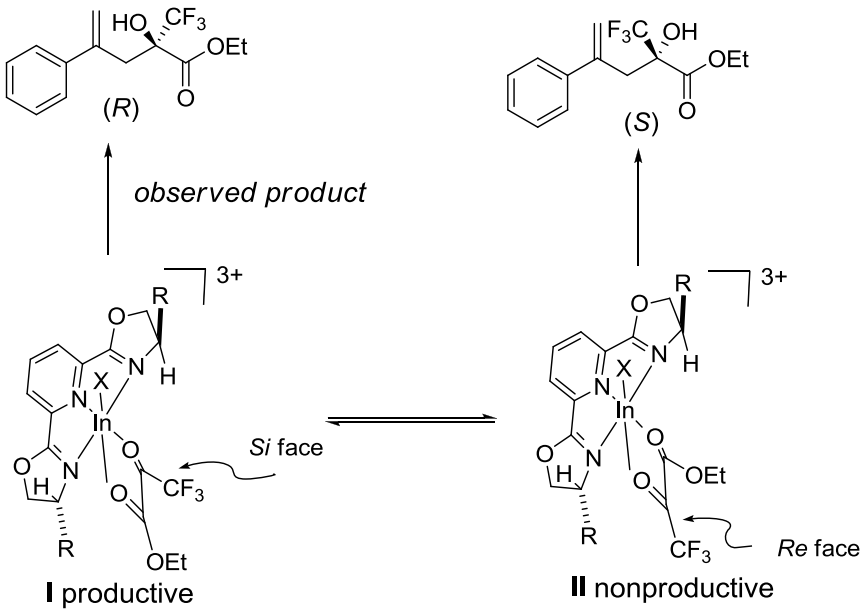
cycle	time (h)	yield[b] (%)	ee[c] (%)
1	1	95	96
2	1	97	95
3	1	93	96
4	1	96	96
5	1	95	95
6	1.5	98	94
7	1.5	96	94

[a] Unless otherwise noted, reactions were carried out on a 0.3 mmol scale with 2 equiv of trifluoropyruvate in a mixture of 0.5 mL [hmim]PF_6 and 0.5 mL 1,2-dichloroethane (DCE) at room temperature. [b] Isolated yield. [c] The *ee* values were determined by chiral-phase HPLC.

further investigated the recyclability of indium(III)-pybox complex by using the ketone-ene reaction of methyl trifluoropyruvate and α-methylstyrene as the model reaction and the results were listed in Table 5. After the reaction was completed, the reaction mixture was extracted with hexane (5 × 5 mL) to give ionic liquid [hmim]PF_6

containing the chiral indium(III)-pybox complex, which can be used directly for the next cycle. It is noteworthy that this catalytic system can be reused for up to seven cycles with retention of excellent catalytic efficiency (Table 5).

4.2.4 Proposed transition model to rationalize the observed enantioselectivity



Scheme 4.7

We believed that the transition model proposed in Chapter **3** could also be used to explain the asymmetric induction in the In(III)-pybox catalyzed enantioselective ketone-ene reaction. Due to the strong *trans* influence observed in d^{10} metal complexes of tridentate N-ligands,[33] we postulate that ketone coordination occurs in the ligand plane as shown in model **I** for maximal carbonyl activation (Scheme 4.7). In model **I**, the *re* face of ketone is shielded by the ligand R group exposing the *si* face for

[33] (a) Beran, G.; Carty, A. J.; Patel, H. A.; Palenik, G. *J. Chem. Soc. D.* **1970**, 222. (b) Butcher, R. J.; George, C.; Muratore, N.; Purdy, A. P. *Acta Cryst. E* **2003,** m1107.

nucleophilic attacking. The stereochemistry of the product is consistent with the proposed pseudo-octahedral hexa-coordinated model.

4.3 CONCLUSION

In summary, we have successfully developed a highly enantioselective ketone-ene reactions of trifluoropyruvate catalyzed by a new generation of indium(III)-pybox, which was designed based on counterion effect. The bench-stable catalyst is easily prepared from commercially available $InCl_3$, pybox (+)-**A** and $AgSbF_6$. Further study demonstrated that this catalyst system could be used in ionic liquid which enable the recycle and reuse of the chiral catalyst.

This methodology has many advantages such as: (1) The moisture-tolerant catalyst, which is easily prepared from commercially available chemicals, renders strict anhydrous conditions unnecessary; (2) CF_3-containing homoallylic alcohols, important building blocks of pharmaceuticals and agrochemicals, can be obtained with excellent enantioselectivities and yields; (3) The chiral indium(III)-pybox complex in ionic liquid could be recycled up to seven times with retention of excellent catalytic efficiency; (4) The operationally simple procedure will make this catalytic system more attractive for possible applications in industry as well as in academia.

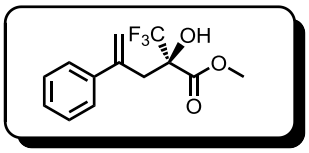
4.4 EXPERIMENTAL SECTION

General procedure for ketone-ene reaction of alkenes with trifluoro-methylpyruvate catalyzed by Indium(III)-pybox complex in 1,2-dichloroethane (DCE):

In an oven dried 10 mL round-bottom flask equipped with a stirring bar, indium (III) chloride (11.1 mg, 0.05 mmol), PYBOX (+)-**A** (24 mg, 0.06 mmol) and 4Å molecular sieves (150 mg) were stirred in a solution of DCE (4 mL) for 20 minutes at room temperature. To the above mixture, silver hexafluoroantimonate ($AgSbF_6$) (34.4 mg, 0.1 mmol) was added in one portion and stirred for another 20 minutes. To the pre-prepared catalyst in DCE, the alkenes (0.5 mmol, 1 eq.) and trifluoro-methylpyruvate (156 mg, 1 mmol, 2 eq.) were added using a syringe sequentially. It was stirred until the alkene was consumed completely as indicated by TLC analysis. The crude product was loaded directly onto a silica gel column and purified by flash column chromatography to give the enantio-enriched tertiary homoallylic alcohol.

Characterization data for chiral homoallylic alcohols

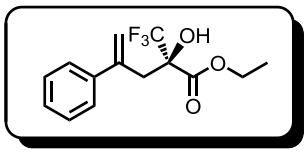
(*R*)-Methyl 2-hydroxy-4-phenyl-2-(trifluoromethyl) pent-4-enoate (4aa)



This compound was prepared by the general procedure described above and was obtained as colourless oil in 99% yield (0.135 g, 95% ee): R_f = 0.56 (ethyl acetate : hexane = 1/5); $[\alpha]_D^{23}$ = 32.0^o (c = 1.71, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.23 (m, 5H), 5.38 (d, *J* = 1.3 Hz, 1H), 5.25 (d, *J* = 0.6 Hz, 1H), 3.79 (s, 1H), 3.36 (s, 3H), 3.29 (d, *J* = 13.9 Hz, 1H), 3.01 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 141.0, 140.8, 128.2, 127.8, 126.9, 123.4 (q, *J* = 287.1 Hz), 119.6, 77.1 (q, *J* = 28.9 Hz), 53.5, 37.3; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.4; FTIR (neat): *v* 3493, 3084, 3057, 3024, 2957, 1746, 1630, 1445, 1315, 1231, 1188, 1136 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{13}F_3O_3H^+$ 275.0895, found 275.0888; The enantiomeric excess was

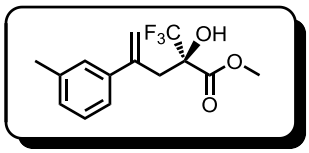
determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 99:1, 1.0 mL/min): t_1 = 6.1 min (major), t_2 = 6.9 min (minor).

(*R*)-Ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl) pent-4-enoate (Table 1, entry 10)



This compound was prepared by the general procedure described above and was obtained as colourless oil in 95% yield (0.136 g, 95% ee): R_f = 0.55 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{22}$ = 34.4° (c = 1.89, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.22 (m, 5H), 5.37 (d, *J* = 1.3 Hz, 1H), 5.27 (d, *J* = 0.8 Hz, 1H), 4.01 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.81 (s, 1H), 3.62 (dq, *J* = 10.7, 7.2 Hz, 1H), 3.28 (d, *J* = 13.7 Hz, 1H), 3.03 (dd, *J* = 13.9, 0.6 Hz, 1H), 1.09 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.9, 141.10, 141.07, 128.2, 127.7, 126.8, 123.5 (q, *J* = 284.0 Hz), 119.4, 77.1 (q, *J* = 28.5 Hz), 63.5, 37.04 (d, *J* = 1.2 Hz), 13.5; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.5; FTIR (neat): *v* 3484, 1742, 1630, 1494, 1447, 1370, 1314, 1231, 1180, 1135 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{15}F_3O_3H^+$ 289.1052, found 289.1052; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 99:1, 1.0 mL/min): t_1 = 4.9 min (major), t_2 = 5.5 min (minor).

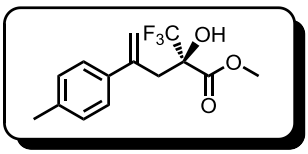
(*R*)-Methyl 2-hydroxy-4-m-tolyl-2-(trifluoro- methyl)pent-4-enoate (4ab)



This compound was prepared by the general procedure described above and was obtained as colourless oil in 98% yield (0.141 g, 94% ee): R_f = 0.58 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ = 26.4° (c = 1.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23-7.06 (m, 4H), 5.36 (d, *J* = 1.4 Hz, 1H), 5.23 (d, *J* = 1.0 Hz, 1H), 3.76 (s, 1H), 3.39 (s, 3H), 3.28 (d, *J* = 13.8 Hz, 1H), 3.00 (d, *J* = 13.8 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 141.1, 140.7, 137.7, 128.5, 128.1, 127.5, 124.0, 123.4 (q, *J* = 285.7 Hz), 119.3, 77.1 (q, *J* = 28.7 Hz), 53.4, 37.4, 21.4; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.4; FTIR (neat): *v* 3495, 3034, 2957, 1746, 1630, 1600, 1445, 1315, 1234, 1188, 1134 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{15}F_3O_3H^+$ 289.1052, found 289.1051; The enantiomeric excess was determined by chiral GC analysis employing CYCLODEX-B

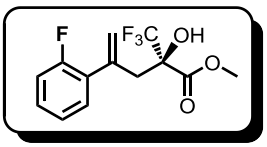
chiral column (isotherm at 120 ^{o}C for 60 mins, 4 ^{o}C /min gradient, 0.5 mL/min): t_1 = 72.4 min (major), t_2 = 72.7 min (minor).

(*R*)-Methyl 2-hydroxy-4-p-tolyl-2-(trifluoro- methyl)pent-4-enoate (4ac)



This compound was prepared by the general procedure described above and was obtained as white solid in 97% yield (0.140 g, 94% ee): R_f = 0.58 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ = 33.4^{o} (c = 2.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* = 8.5 Hz, 2H), 7.11 (d, *J* = 8.7 Hz, 2H), 5.35 (d, *J* = 1.3 Hz, 1H), 5.21 (d, *J* = 0.8 Hz, 1H), 3.74 (s, 1H), 3.41 (s, 3H), 3.27 (d, *J* = 13.9 Hz, 1H), 3.00 (dd, *J* = 13.9, 0.5 Hz, 1H), 2.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 140.8, 137.8, 137.6, 128.9, 126.7, 123.4 (q, *J* = 285.7 Hz), 118.7, 77.1 (q, *J* = 28.7 Hz), 53.5, 37.3 (d, *J* = 1.0 Hz), 21.1; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.4; FTIR (neat): *v* 3503, 3019, 2957, 2924, 1746, 1628, 1514, 1445, 1315, 1215, 1190, 1134 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{15}F_3O_3H^+$ 289.1052, found 289.1055; The enantiomeric excess was determined by chiral GC analysis employing Chiral-GTA column (isotherm at 140 ^{o}C for 55 mins, 0.5 mL/min): t_1 = 51.3 min (major), t_2 = 55.0 min (minor).

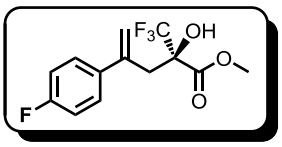
(*R*)-Methyl 4-(2-fluorophenyl)-2-hydroxy-2- (trifluoromethyl)pent-4-enoate (4ad)



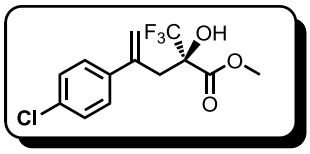
This compound was prepared by the General Procedure described above and was obtained as white solid in 56% yield (0.082 g, 87% ee): R_f = 0.57 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ 34.6^{o} (c=1.80, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29-6.99 (m, 4H), 5.41 (s, 1H), 5.32 (s, 1H), 3.74 (s, 1H), 3.42 (s, 3H), 3.31 (d, *J* = 13.9 Hz, 1H), 3.04 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 159.7 (d, *J* = 248 Hz), 136.9, 130.5 (d, *J* = 4.0 Hz), 129.4 (d, *J* = 8.3 Hz), 128.9 (d, *J* = 13.8 Hz), 124.0 (d, *J* = 3.4 Hz), 123.2 (q, *J* = 287.0 Hz), 123.1, 115.5 (d, *J* = 22.5 Hz), 77.0 (q, *J* = 29.4 Hz), 53.6, 38.0 (d, *J* = 2.7 Hz); ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.6, -114.5; FTIR (neat): *v* 3503, 3019, 1744, 1489, 1447, 1314, 1215, 1138 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{12}F_4O_3H^+$ 293.0801, found 293.0803; The enantiomeric excess was determined by

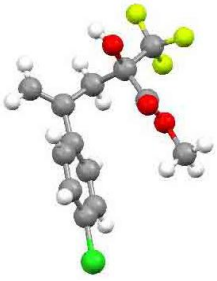
HPLC analysis employing Daicel Chiracel OJ-H column (hexane/i-propanol = 99.5:0.5, 1.0 mL/min): t_1 = 9.6 min (minor), t_2 = 10.2 min (major).

(*R*)-Methyl 4-(4-fluorophenyl)-2-hydroxy-2- (trifluoromethyl)pent-4-enoate (4ae)



This compound was prepared by the General Procedure described above and was obtained as white solid in 92% yield (0.134 g, 92% ee): R_f = 0.54 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ 25.9° (c=1.81, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32-7.26 (m, 2H), 7.04-6.97 (m, 2H), 5.34 (d, *J* = 1.0 Hz, 1H), 5.24 (s, 1H), 3.76 (s, 1H), 3.48 (s, 3H), 3.24 (d, *J* = 13.9 Hz, 1H), 3.02 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 162.4 (d, *J* = 247.3 Hz), 140.0, 136.9 (d, *J* = 3.4 Hz), 128.5 (d, *J* = 8.1 Hz), 123.3 (q, *J* = 286.3 Hz), 119.5, 115.0 (d, *J* = 21.6 Hz), 77.0 (q, *J* = 44.3 Hz), 53.7, 37.3 (d, *J* = 0.9 Hz); ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.4, -114.5; FTIR (neat): *v* 3503, 3019, 2957, 1746, 1603, 1510, 1445, 1313, 1215, 1192, 1134 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{12}F_4O_3H^+$ 293.0801, found 293.0810; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 99.5:0.5, 1.0 mL/min): t_1 = 8.3 min (major), t_2 = 9.0 min (minor).

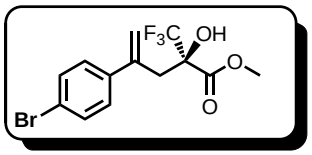


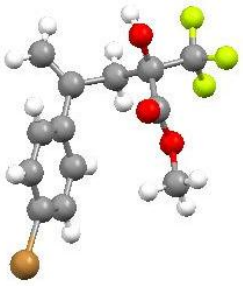


(*R*)-Methyl 4-(4-chlorophenyl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (4af)

This compound was prepared by the General Procedure described above and was obtained as white solid in 90% yield (0.138 g, 95% ee): R_f = 0.53 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ = 28.9° (c = 1.14, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30-7.23 (m, 4H), 5.37 (d, *J* = 1.1 Hz, 1H), 5.26 (d, *J* = 0.8 Hz, 1H), 3.76 (s, 1H), 3.49 (s, 3H), 3.22 (d, *J* = 13.6 Hz, 1H), 3.02 (dd, *J* = 13.6, 0.6 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 140.0, 139.3, 133.6, 128.3, 128.1, 123.3 (q, *J* = 286.5 Hz), 119.9, 77.3 (q, *J* = 29.3 Hz), 53.6, 37.10 (d, *J* = 1.0 Hz); ^{19}F NMR (338 MHz, $CDCl_3$):

δ -78.4; FTIR (neat): *v* 3503, 3019, 2957, 1746, 1493, 1315, 1215, 1192, 1136 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{12}F_3O_3ClH^+$ 309.0505, found 309.0508; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 99.8:0.2, 0.5 mL/min): t_1 = 27.3 min (major), t_2 = 30.4 min (minor).

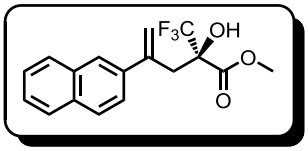




(*R*)-Methyl 4-(4-bromophenyl)-2-hydroxy-2-(trifluoromethyl)pent-4-enoate (4ag)

This compound was prepared by the General Procedure described above and was obtained as white solid in 97% yield (0.171 g, 91% ee): R_f = 0.52 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ 27.1° (c=1.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, *J* = 8.5 Hz, 2H), 7.19 (d, *J* = 8.7 Hz, 2H), 5.38 (d, *J* = 0.9 Hz, 1H), 5.27 (s, 1H), 3.77 (s, 1H), 3.49 (s, 3H), 3.22 (d, *J* = 14.1 Hz, 1H), 3.02 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 140.1, 139.8, 131.3, 128.4, 123.3 (q, *J* = 285.2 Hz), 121.8, 120.0, 77.3 (q, *J* = 29.2 Hz), 53.7, 37.1; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.4; FTIR (neat): *v* 3503, 3019, 2957, 1746, 1489, 1445, 1314, 1215, 1192, 1136 cm^{-1}; HRMS (ESI): calcd. for $C_{13}H_{12}F_3O_3BrH^+$ 353.0000, found 352.9986; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel OJ-H column (hexane/i-propanol = 99.5:0.5, 1.0 mL/min): t_1 = 21.2 min (minor), t_2 = 22.7 min (major).

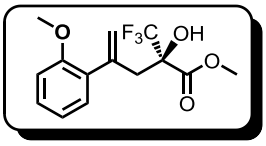
(*R*)-Methyl 2-hydroxy-4-(naphthalen-2-yl)-2-(trifluoromethyl)pent-4-enoate (4ah)



This compound was prepared by the General Procedure described above and was obtained as white solid in 91% yield (0.142 g, 95% ee): R_f = 0.56 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{24}$ = 16.6° (c = 1.68, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84-7.76 (m, 4H),

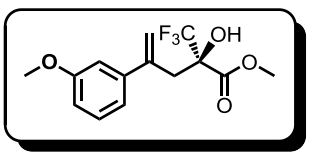
7.50-7.41 (m, 3H), 5.52 (d, *J* = 1.2 Hz, 1H), 5.35 (d, *J* = 0.7 Hz, 1H), 3.78 (s, 1H), 3.41 (d, *J* = 14.2 Hz, 1H), 3.25 (s, 3H), 3.13 (dd, *J* = 13.9, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 140.9, 138.0, 133.1, 132.8, 128.1, 127.8, 127.6, 126.4, 126.2, 125.6, 125.0, 123.4 (q, *J* = 286.3 Hz), 120.1, 76.9 (q, *J* = 44.0 Hz), 53.5, 37.3 (d, *J* = 0.9 Hz); ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.3; FTIR (neat): *v* 3503, 3019, 2957, 1744, 1443, 1314, 1215, 1190, 1138, 1126 cm^{-1}; HRMS (ESI): calcd. for $C_{17}H_{15}F_3O_3H^+$ 325.1052, found 325.1048; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel OJ-H column (hexane/i-propanol = 98:2, 1.0 mL/min): t_1 = 26.4 min (minor), t_2 = 30.9 min (major).

(*R*)-Methyl 2-hydroxy-4-(2-methoxyphenyl)-2-(tri-fluoromethyl)pent-4-enoate (4ai)



This compound was prepared by the General Procedure described above and was obtained as white solid in 86% yield (0.131 g, 85% ee): R_f = 0.52 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{24}$ = 16.6^o (c = 2.51, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27-7.20 (m, 1H), 7.05-7.00 (m, 1H), 6.92-6.82 (m, 2H), 5.32 (d, *J* = 1.6 Hz, 1H), 5.21 (d, *J* = 1.8 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 1H), 3.43 (dd, *J* = 13.7, 4.9 Hz, 1H), 3.32 (s, 3H), 3.00 (dd, *J* = 13.7, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.5, 156.5, 140.3, 130.5, 130.4, 129.1, 123.4 (q, *J* = 287.3 Hz), 121.7, 120.5, 110.5, 77.0 (q, *J* = 28.8 Hz), 55.4, 53.4, 37.9; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.6; FTIR (neat): *v* 3495, 3005, 2957, 1746, 1632, 1599, 1578, 1491, 1437, 1184 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{15}F_3O_4H^+$ 305.1001, found 305.0998; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel OJ-H column (hexane/i-propanol = 99.5:0.5, 1.0 mL/min): t_1 = 10.3 min (minor), t_2 = 10.9 min (major).

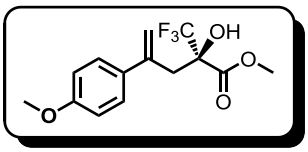
(*R*)-Methyl 2-hydroxy-4-(3-methoxyphenyl)-2-(tri-fluoromethyl)pent-4-enoate (4aj)



This compound was prepared by the General Procedure described above and was obtained as white solid in 99% yield (0.150 g, 95% ee): R_f = 0.53 (ethyl acetate : hexane = 1/5),

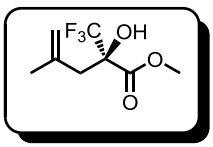
$[\alpha]_D^{24}$ = 28.7° (c = 3.6, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.22 (t, *J* = 7.9 Hz, 1H), 6.92-6.79 (m, 3H), 5.39 (d, *J* = 1.3 Hz, 1H), 5.26 (s, 1H), 3.86 (s, 1H), 3.80 (s, 3H), 3.44 (s, 3H), 3.27 (d, *J* = 14.2 Hz, 1H), 3.00 (d, *J* = 14.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 159.4, 142.3, 140.9, 129.2, 123.3 (q, *J* =285.6 Hz), 119.5, 119.3, 113.0, 112.8, 77.1 (q, *J* = 29.0 Hz), 55.2, 53.5, 37.3; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.4; FTIR (neat): *v* 3489, 3005, 2957, 2837, 1748, 1599, 1578, 1489, 1445, 1315, 1186, 1134 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{15}F_3O_4H^+$ 305.1001, found 305.0995; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/i-propanol = 99:1, 0.5 mL/min): t_1 = 8.2 min (major), t_2 = 11.5 min (minor).

(*R*)-Methyl 2-hydroxy-4-(4-methoxyphenyl)-2-(trifluoromethyl)pent-4-enoate (4ak)



This compound was prepared by the General Procedure described above and was obtained as white solid in 99% yield (0.150 g, 64% ee): R_f = 0.54 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{24}$ = 30.3° (c = 2.80, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.29-7.24 (m, 2H), 6.87-6.82 (m, 2H), 5.32 (d, *J* = 1.3 Hz, 1H), 5.17 (d, *J* = 0.7 Hz, 1H), 3.80 (s, 3H), 3.73 (s, 1H), 3.45 (s, 3H), 3.25 (d, *J* = 13.9 Hz, 1H), 3.00 (dd, *J* = 13.9 Hz, 0.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.4, 159.3, 140.3, 133.1, 128.0, 123.4 (q, *J* = 286.1 Hz), 118.0, 113.5, 77.3 (q, *J* = 28.4 Hz), 55.2, 53.6, 37.3; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.3; FTIR (neat): *v* 3501, 3019, 2957, 2839, 1746, 1607, 1512, 1443, 1315, 1215 cm^{-1}; HRMS (ESI): calcd. for $C_{14}H_{15}F_3O_4H^+$ 305.1001, found 305.0993; The enantiomeric excess was determined by HPLC analysis employing Daicel Chiracel OJ-H column (hexane/i-propanol = 98:2, 1.0 mL/min): t_1 = 28.1 min (minor), t_2 = 31.8 min (major).

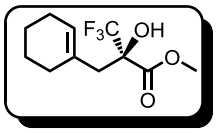
(*R*)-Methyl 2-hydroxy-4-methyl-2-(trifluoromethyl)pent- 4-enoate (4al)



This compound was prepared by the General Procedure described above and was obtained as colourless oil in 79% yield (0.084 g, 96% ee): R_f = 0.59 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{24}$ = -18.1° (c

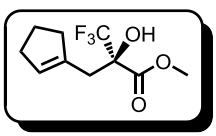
= 1.82, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.91 (t, *J* = 1.6 Hz, 1H), 4.80 (d, *J* = 0.8 Hz, 1H), 3.88 (s, 3H), 3.83 (s, 1H), 2.75 (d, *J* = 13.9 Hz, 1H), 2.58 (d, *J* = 14.0 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$): δ 170.1, 138.7, 123.2 (q, *J* = 286.6 Hz), 116.1, 78.3 (q, *J* = 28.7 Hz), 54.0, 38.9 (d, *J* =1.0 Hz), 23.9; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.8; FTIR (neat): *v* 3487, 1746, 1443, 1312, 1248, 1227, 1186, 1128 cm^{-1}; HRMS (ESI): calcd. for $C_8H_{11}F_3O_3H^+$ 213.0739, found 213.0735; The enantiomeric excess was determined by chiral GC analysis employing CYCLODEX-B chiral column (isotherm at 45 ^oC for 10 mins, 5 ^oC /min gradient, 0.5 mL/min): t_1 = 24.9 min (major), t_2 = 25.3 min (minor).

(*R*)-Methyl 2-(cyclohexenylmethyl)-3,3,3-trifluoro-2- hydroxypropanoate (4am)



This compound was prepared by the General Procedure described above and was obtained as colourless oil in 95% yield (0.120 g, 98% ee): R_f = 0.60 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ = 7.6^o (c = 1.77, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.54 (s, 1H), 3.87 (s, 3H), 3.75 (d, *J* = 0.8 Hz, 1H), 2.65 (d, *J* = 13.7 Hz, 1H), 2.49 (d, *J* = 13.8 Hz, 1H) 2.10-1.80 (m, 4H), 1.61-1.46 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.3, 130.8, 127.8, 123.4 (q, *J* = 285.2 Hz), 78.4 (q, *J* = 28.4 Hz), 53.8, 39.7, 29.8, 25.5, 22.8, 21.9; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.5; FTIR (neat): *v* 3495, 2932, 2859, 2839, 1744, 1443, 1308, 1233, 1179, 1125 cm^{-1}; HRMS (ESI): calcd. for $C_{11}H_{15}F_3O_3H^+$ 253.1052, found 253.1042; The enantiomeric excess was determined by chiral GC analysis employing CYCLODEX-B chiral column (isotherm at 100 ^oC for 30 mins, 4 ^oC /min gradient, 0.5 mL/min): t_1 = 43.6 min (major), t_2 = 44.1 min (minor).

(*R*)-Methyl 2-(cyclopentenylmethyl)-3,3,3-trifluoro-2- hydroxypropanoate (4an)



This compound was prepared by the General Procedure described above and was obtained as colourless oil in 94% yield (0.112 g, 98% ee): R_f = 0.61 (ethyl acetate : hexane = 1/5), $[\alpha]_D^{23}$ = 8.3^o (c = 2.06, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.53 (s, 1H), 3.88 (s, 3H), 3.82 (s, 1H), 2.86 (d, *J* = 14.4 Hz, 1H), 2.68 (d, *J* = 14.4 Hz, 1H) 2.38-2.13 (m, 4H), 1.88-1.78 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.2, 136.4, 130.2, 123.3 (q, *J* = 287.0 Hz), 77.9

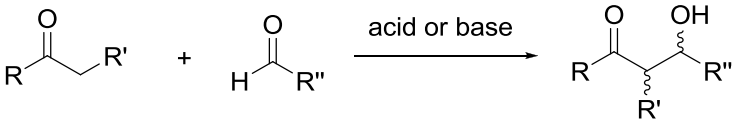
(q, *J* = 28.7 Hz), 53.9, 35.9, 33.2 (d, *J* = 1.4 Hz), 32.5, 23.5; ^{19}F NMR (338 MHz, $CDCl_3$): δ -78.7; FTIR (neat): *v* 3495, 2957, 2851, 1746, 1443, 1310, 1246, 1188, 1121, 1055 cm^{-1}; HRMS (ESI): calcd. for $C_{10}H_{13}F_3O_3H^+$ 239.0895, found 239.0903; The enantiomeric excess was determined by chiral GC analysis employing CYCLODEX-B chiral column (isotherm at 100 ^oC for 40 mins, 5 ^oC /min gradient, 0.5 mL/min): t_1 = 41.6 min (major), t_2 = 43.9 min (minor).

CHAPTER 5

In(III)-Pybox Complex Catalyzed Enantioselective Mukaiyama Aldol Reactions between Glyoxylates and Enolsilanes Derived from Aryl Ketones

5.1 OVERVIEW OF CATALYTIC ENANTIOSELECTIVE MUKAIYAMA ALDOL REACTION

Aldol reaction discovered in 1872 is one of the most important synthetic tools for carbon-carbon bond formation.[1] It involves the reaction between a ketone containing α-proton and an aldehyde in the presence of acid or base to give a β-hydroxy carbonyl compound, which is known as "aldol" (aldehyde + alcohol). Aldol structural units are found in many important molecules, whether naturally occurring or synthetic[2] and this makes aldol reaction very attractive to synthetic chemists. However, the classical aldol reaction is known to be plagued by the following problems: 1) self-condensation of the ketone or/and dimerization of aldehyde; 2) the harsh reaction conditions employed hampers its application in the synthesis of complex molecules which containing acid- or base-sensitive groups; 3) the desired aldol product is usually accompanied by elimination products, dimers and polymers; 4) low regioselectivity was observed in most cases. Therefore, efficient methods which involving mild conditions are much sought after to overcome some if not all the problems mentioned above.

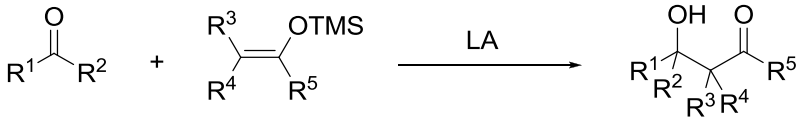


Scheme 5.1 The conventional aldol reaction

[1] (a) Wurtz, C. A. *Bull. Soc. Chim. Fr.* **1872**, *17*, 436. (b) Nielsen, A. T.; Houlihan, W. J. *Organic Reactions*, John Wiley & Sons, New York, **1968**, Vol. *16*, 1.

[2] (a) Heathcock, C. H. In *Comprehensive Organic Synthesis*, Vol. *1* (Eds.: Trost, B. M.; Fleming, I.), Pergamon Press, Oxford, **1991**, pp. 133. (b) Mukaiyama, T. *Org. React.* **1982**, *28*, 203. (c) Paterson, I. *Chem. Ind.* **1988**, *12*, 390.

An important and useful variant of the conventional aldol reaction was developed by Mukaiyama and co-workers in 1970s, which came to be known as the Mukaiyama aldol reaction.[3] By taking advantage of preformed silyl enol ethers or silyl ketene acetals, they tamed the wild and hard-to-control aldol reaction ingeniously to realize the chemoselectivity. The regioselectivity of Mukaiyama aldol could be controlled by selective preparation of silyl enol ether through either kinetic or thermodynamic control.[4] There are numerous advantages over the conventional aldol reactions.



Scheme 5.2 Mukaiyama aldol reaction

In view of this advancement, the Lewis acid-promoted Mukaiyama aldol reaction has received much attention. Since then, a large number of Lewis acids had been used to mediate this reaction.[5] Here we will focus on the asymmetric version of Mukaiyama aldol. The enantioselective Mukaiyama aldol reaction allows the preparation of enantioenriched alcohols, which are key intermediates and building blocks for biologically active molecules.[6] There are two classes of asymmetric

[3] (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett*. **1973**, 1012. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc*. **1974**, *96*, 7503. (c) Mukaiyama, T. *Angew. Chem. Int. Ed. Engl*. **1977**, *16*, 817.

[4] (a) Colvin, E.; *Silicon in Organic Synthesis*, Butterworths, **1981**, 198. (b) Thomas, S. E.; *Organic Synthesis, the roles of boron and silicon*, Oxford, **1991**.

[5] (a) Mahrwald, R. *Chem. Rev.* **1999**, *99*, 1095-1120. (b) Mahrwald, R., *Modern Aldol Reactions*, Ed.; Wiley-VCH: Weinheim **2004**.

[6] (a) Schwartz, A.; Van Wart, H. E. *Prog. Med. Chem.* **1992**, *29*, 271. (b) Babine, R. E.; Bender, S. L. *Chem. Rev*. **1997**, *97*, 1359. (c) Coppola, G. M.; Schuster, H. F. R-Hydroxy Acids in Enantioselective Synthesis; VCH: Weinheim, Germany, **1997**. (d) Davidson, A. H.; Drummond, A. H.; Galloway, W. A.; Whittaker, M. *Chem. Ind.* **1997**, 258. (e) Levy, D. E.; Lapierre, F.; Liang, W.; Ye, W.; Lange, C. W.; Li, X.; Grobelny, D.; Casabonne, M.; Tyrell, D.; Holme, K.; Nadzan, A.; Galardy, R. E. *J. Med. Chem.* **1998**, *41*, 199 and references therein.

inductions in the Mukaiyama aldol reaction: chiral substrates (asymmetric modified enolates or electrophiles) control[7] and chiral Lewis acids induction.[6,8] The chiral enolate or electrophile represents a traditional approach and affords high diastereoselectivities attributed to the highly ordered conformation of transition structures ("closed" transition models). However, the pre-introduced chiral center needs to be removed after the reaction had completed and this chiral wastage hampered its practical applications. The other one relying on the chiral Lewis acid induction is more attractive because only catalytic amount of chiral catalyst is enough to obtain optical pure products. This strategy is developed based on the coordination ability of carbonyl group of aldol acceptor. The coordination between acceptor carbonyl group and chiral Lewis acid metal centre not only activate the acceptor but also forms a facially discriminated complex which is crucial for enantioselective induction. The chiral Lewis acid complex could be released to take part in the next catalytic cycle after the aldol addition is completed.

5.1.1 Catalytic asymmetric Mukaiyama aldol reaction of mono-dentate acceptor

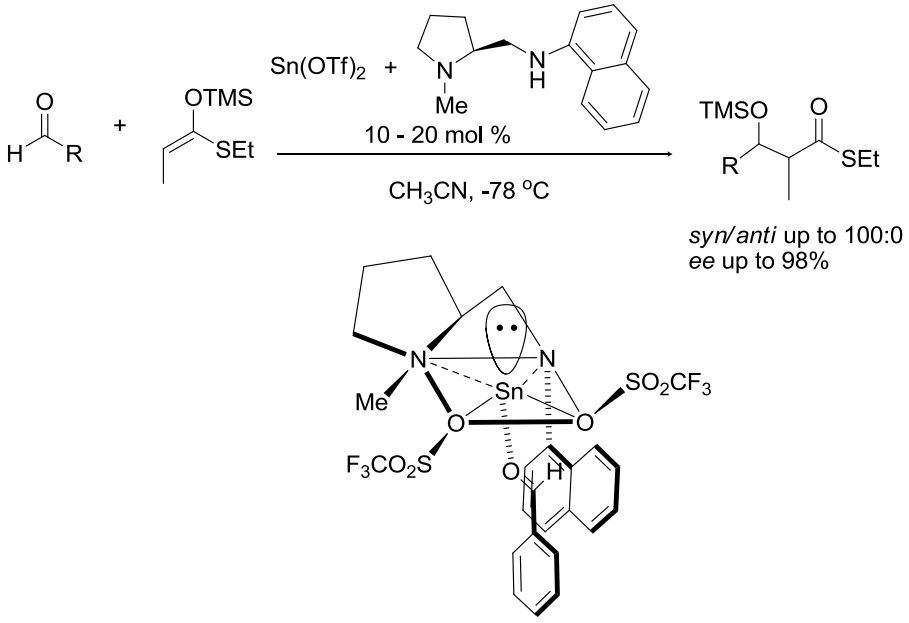
The first chiral Lewis acid catalyzed asymmetric Mukaiyama aldol reaction was introduced by Mukaiyama *et al.* (Scheme 5.3).[9] By employing chiral tin(II) complex (chiral diamine coordinated with $Sn(OTf)_2$ as the catalyst, they realized the first

[7] (a) Braun, M. *Methoden Org. Chem. (Houben Weyl), 4th Ed.* **1952-1986**, E21, 1603. (b) Paterson, I. *Org. React.* **1997**, *51*, 1. (c) Mukaiyama, T. *Org. React.* **1994**, *46*, 1. (d) Siegel, C.; Thorton, E. R. *J. Am. Chem. Soc*. **1989**, *111*, 5722. (e) Evans, D. A.; McGee, L. R. *J. Am. Chem. Soc*. **1981**, *103*, 2876.

[8] Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; Wiley: New York, **1994**; 835.

[9] (a) Mukaiyama, T.; Kobayashi, S.; Uchiro, H.; Shiina, I. *Chem. Lett.* **1990**, 129. (b) Kobayashi, S.; Fujishita, Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455**.**

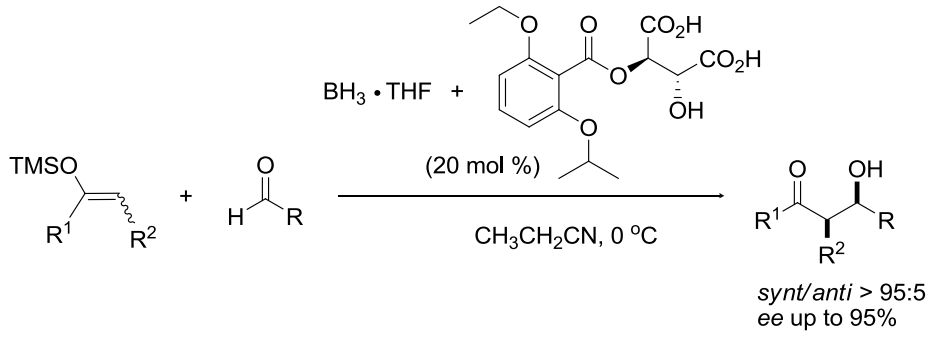
catalytic (only 10 - 20 mol % catalyst) asymmetric Mukaiyama aldol with excellent diastereoselectivities (*syn/anti* up to 100:0) and enantioselectivities (*ee* up to 98%). In the proposed transition state model, which involved a rigid bicyclic



Scheme 5.3 The first catalytic asymmetric Mukaiyama aldol reaction

structure, the *Re* face approach to the aldehyde is almost completely shielded. Only *Si* face attack of nucleophile is available which led to excellent enantioselectivitiy.

Subsequently, Yamamoto *et al.* reported another good example of pioneering



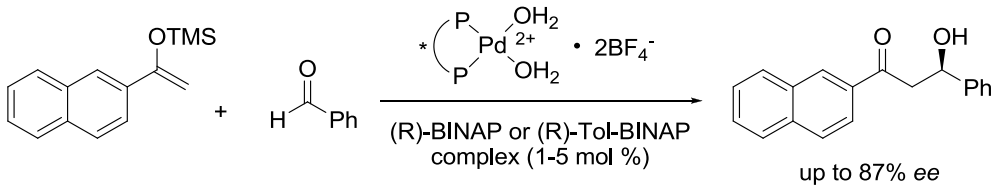
Scheme 5.4 Chiral boron complex catalyzed asymmetric Mukaiyama aldol reaction

works in asymmetric Mukaiyama aldol reactions (Scheme 5.4).[10] In the presence of

[10] Furuta, K.; Maruyama, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 1041.

20 mol% of their chiral (acyloxy)borane (CAB) complex, which was formed *in situ* from tartaric acid derivative and BH_3•THF, the enantioselective Mukaiyama aldol proceeded smoothly to give the enantioenriched aldols with excellent steoselectivities (*syn/anti* up to 95:5, *ee* up to 95%).

A chiral Lewis acid catalyzed asymmetric Mukayama aldol, which is mechanistically different from the conventional approach was reported by Shibasaki *et al.* by using an isolable air- and moisture stable Pd(II)-BINAP derived complex as catalyst (Scheme 5.5).[11] Their experimental results supported that the addition of enolsilane to aldehydes proceeds through a chiral Pd(II) enolate intermediate to give the aldol products in high yields and with good enantioselectivities. This is the first example of a catalytic asymmetric aldol reaction that occurrs via a chiral metal enolate. Later, Carreira *el al.* also observed a chiral copper enolate in their Cu(II)-Tol-BINAP catalyzed vinylogous Mukayama-type aldol reaction.[12]

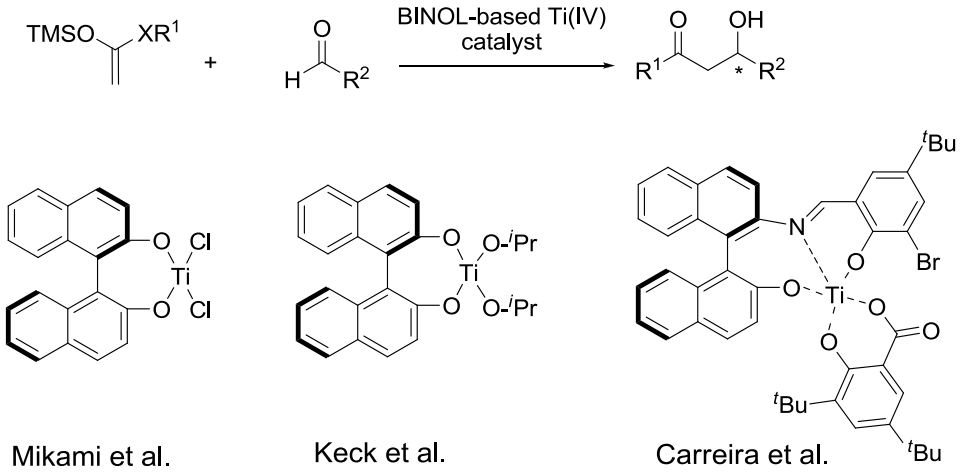


Scheme 5.5 Pd(II)-BINAP complex catalyzed asymmetric Mukaiyama aldol reaction

Chiral Ti(IV)-BINOL complexes had been used in catalytic asymmetric Mukaiyama aldol reaction successfully by Mikami,[13] Keck[14] and Carreira[15]

[11] Sodeoka, M.; Ohrai, K.; Shibasaki, M. *J. Org. Chem*. **1995**, *60*, 2648.
[12] Krüger, J.; Carreira, E. M. *J. Am. Chem. Soc.* **1998**, *120*, 837.
[13] (a) Mikami, K.; Matsukawa, M. *J. Am. Chem. Soc*. **1994**, *116*, 4077. (b) Mikami, K.; Matsukawa, M. *J. Am. Chem. Soc.* **1993**, *115*, 7039. (c) Mikami, K. *Pure Appl. Chem*. **1996**, *68*, 639.
[14] Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.
[15] (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (b) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

independently (Scheme 5.6). Mikami *et al.* presented an application of chiral titanium dichloride in the Mukaiyama aldol reaction. As low as 5 mol % of catalyst loading is efficient enough to get up to 96% ee with a broad range of functionalized aldehydes and thioester-derived ketene silyl acetals.[13a] In addition, this catalyst also works well for the asymmetric Mukaiyama aldol reaction of ketone enolsilanes with glyoxylates (*syn/anti* ratio 99:1; *ee* (*syn*) up to >99%.[13b] Keck group reported another Ti(IV)-BINOL complex which derived from BINOL and Ti(O-^{i}Pr)$_4$ instead of Ti(O-^{i}Pr)$_2$Cl$_2$.[14] With a hypothesis that ligands bearing functional groups which may act as a silyl group shuttle should be beneficial for the catalyst turnover, Carreira *et al.* developed a new BINOL-based ligand and found that this catalyst is more efficient

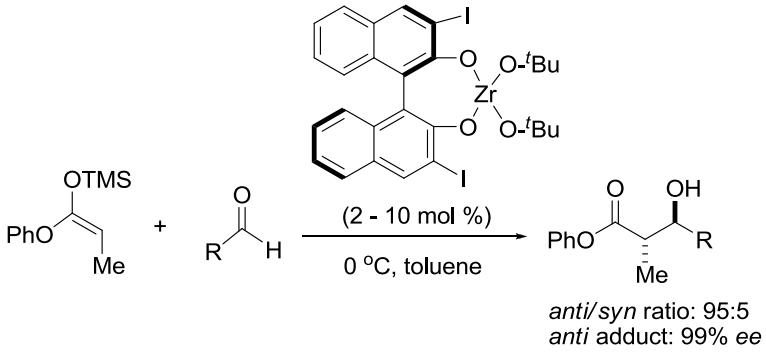


Scheme 5.6 Chiral Ti(IV) complex catalyzed asymmetric Mukaiyama aldol reaction

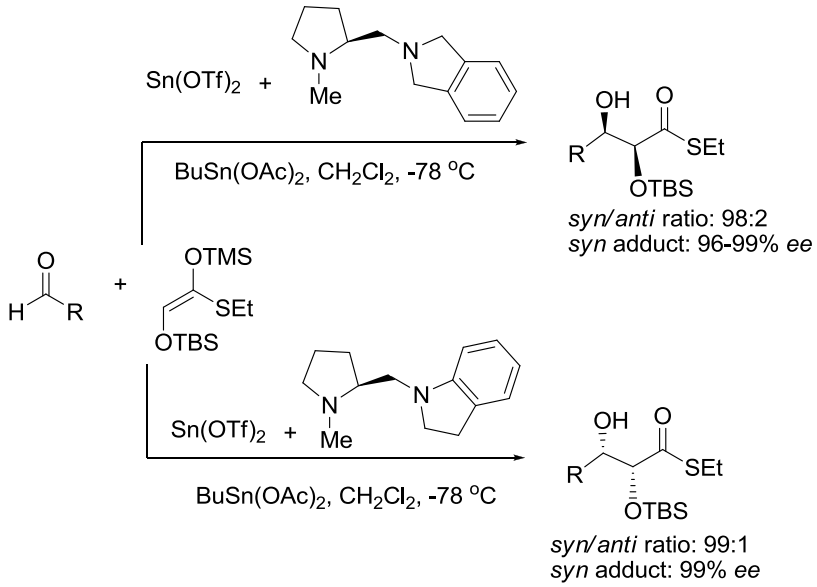
than the previous two. With the use of 2–5 mol % of catalyst, the reaction went smoothly with excellent enantioselectivities between 94% and 97% *ee*.[15]

By replacing of Ti(IV) with Zr(IV), a new BINOL-based chiral Lewis acid was

developed by Kobayashi *et al.* (Scheme 5.7).[16] In the presence of this catalyst, the *anti*-selective Mukaiyama aldol reaction have been controlled perfectly which is not easy to achieve previously. The aldol adducts were obtained with *dr* up to 95:5 (*anti/syn*) and *ee* up to 99%.



Scheme 5.7 Zr(IV)-BINOL complex catalyzed *anti* selective Mukaiyama aldol reaction



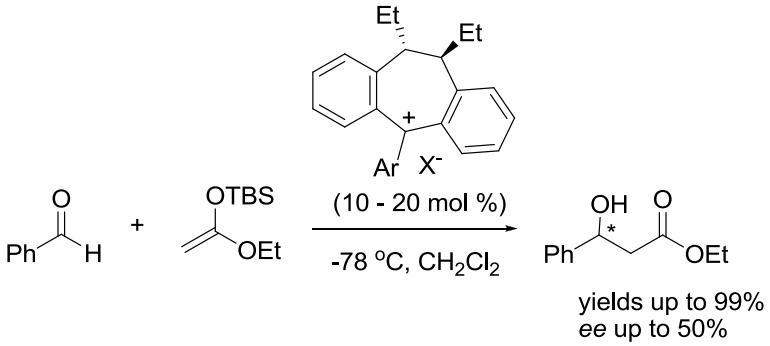
Scheme 5.8 Chiral Sn(II) complex catalyzed asymmetric Mukaiyama aldol reaction

Selectively obtaining one of both enantiomers of the *syn* adduct by using the same initial source of chirality, which sounds impossible, was achieved by Kobayashi

[16] Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403.

group (Scheme 5.8).[17] Employing $Sn(OTf)_2$ and L-proline framework based diamine as ligands, both of the enantiomers could be obtained selectively only by adjusting the position of the nitrogen atom on the bicyclic system.

Metal-free organocatalysts attracted much attention in asymmetric synthesis recently.[18] In terms of Mukaiyama aldol reactions, there are two catalyst systems had



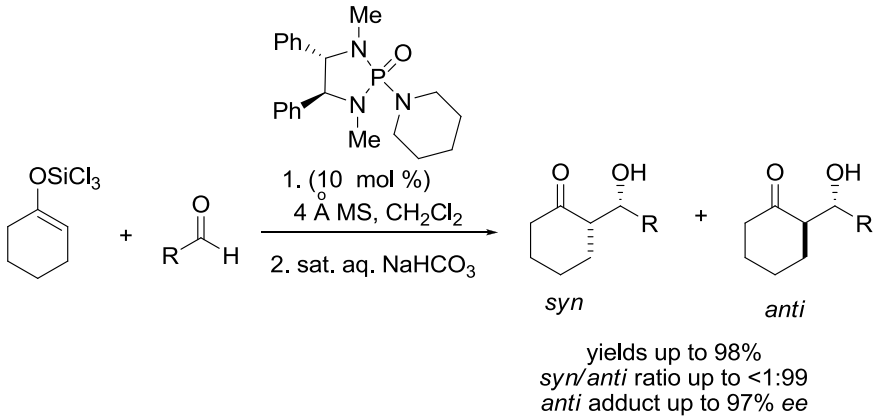
Scheme 5.9 Chiral triaryl carbenium ion catalyzed asymmetric Mukaiyama aldol reaction

been developed in past decades. Mukaiyama *et al.* have demonstrated novel uses of various trityl salts that act as efficient Lewis acids in various aldol type transformations.[19] Based on Mukaiyama's studies, Chen and co-worker designed a chiral trityl cationic catalyst and successfully applied it to asymmetric Mukaiyama aldol reaction albeit moderate enantioselectiviy was obtained (Scheme 5.9).[20] This is the first example of asymmetric Mukaiyama aldol additions mediated by chiral triarylcarbenium ions.

Another metal-free organocatalyst is reported by Denmark *et al.* (Scheme

[17] Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472.
[18] For reviews, see: (a) Dondoni, A.; Massi, A. *Angew Chem. Int. Ed.* **2008**, *47*, 4638. (b) Dalko, P. I.; Moisan, L. *Angew Chem. Int. Ed.* **2004**, *43*, 5138.
[19] (a) Kobayashi, S. *Kagaku Kogyo* **1989**, *42*, 245 and references cited therein. (b) Denmark, S. E.; Chen, C. T. *Tetrahedron Lett.* **1994**, *35*, 4327.
[20] Chen, C. T.; Chao, S. D.; Yen, K. C.; Cheng, C. H.; Chou, I. C.; Hon, S. W. *J. Am. Chem. Soc.* **1997**, *119*, 11341.

5.10).[21] In contrast to previously used chiral Lewis acids, this work utilizes chiral bases which seem to coordinate temporarily to the silicon atom of trichlorosilyl



Scheme 5.10 Chiral triaryl carbenium ion catalyzed asymmetric Mukaiyama aldol reaction

enolates and activate ketones which react spontaneously with a number of aldehyde. It is noteworthy that in the absence of catalyst the (*E*)-enolate affords mainly the *syn* adduct (*syn/anti* ratio 16:1) while in the presence of the chiral Lewis base catalyst there is a dramatic reversal in diastereoselectivity and the *anti* product is formed with excellent selectivity (*anti/syn* ratio up to > 99:1; *anti* up to 97% *ee*).

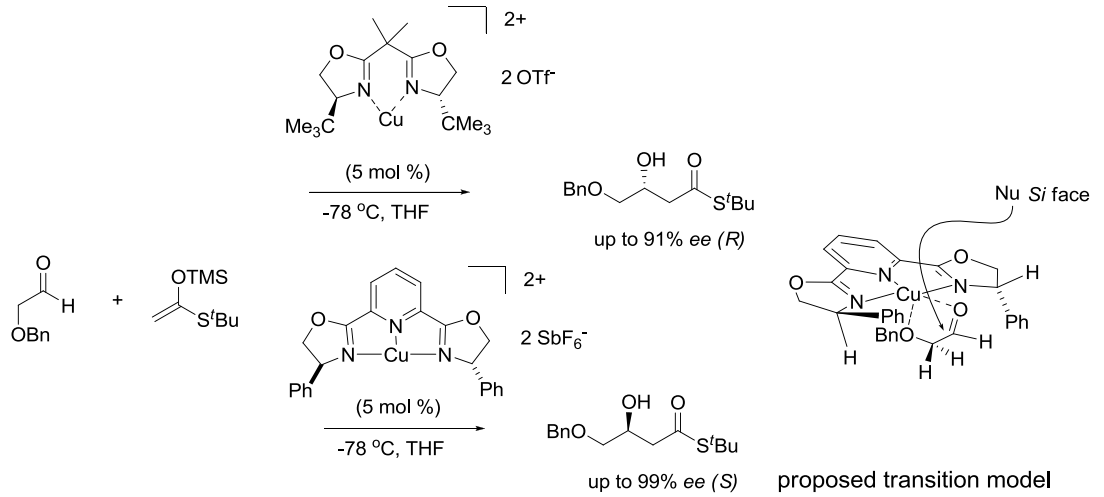
5.1.2 Catalytic asymmetric Mukaiyama aldol reaction of bidentate acceptor

The chiral Lewis acid catalyzed asymmetric Mukaiyama aldol reaction involved the formation of a facially discriminated complex between aldol acceptor and Lewis acid metal center through coordination. The examples mentioned above focused on mono-dentate aldol acceptor. To induce a high level of stereoselection, it will be helpful if an additional coordination was introduced into the catalyst-substrate

[21] Denmark, S. E.; Wong, K. T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, *119*, 2333.

complex. Based on this hypothesis, specific substrates, which contain two binding sites (bidentate aldol acceptor) to the metal centre of the chiral Lewis acid, such as (benzyloxy)acetaldehyde, glyoxylate esters, *α*-diketones and *α*-keto esters had been used in asymmetric Mukaiyama aldol reactions successfully. Besides their ability to form bidentate complexes, introduction of additional functional group in the adol product made them more attractive in the synthesis of complex chiral alcohols.

C_2-symmetric Cu(II) complexes had been extensively studied in asymmetric Mukaiyama aldol reactions of bidentate aldol acceptor since the pioneer work of Evans' group (Scheme 5.10).[22] In this work, (benzyloxy)acetaldehyde was chosen on the assumption that effective catalyst-substrate organization might be achieved through bidentate chelation to the aldehyde. Their result supported this hypothesis very well. Both Mukaiyama aldol and vinylogous Mukayama-type aldol reaction proceeded



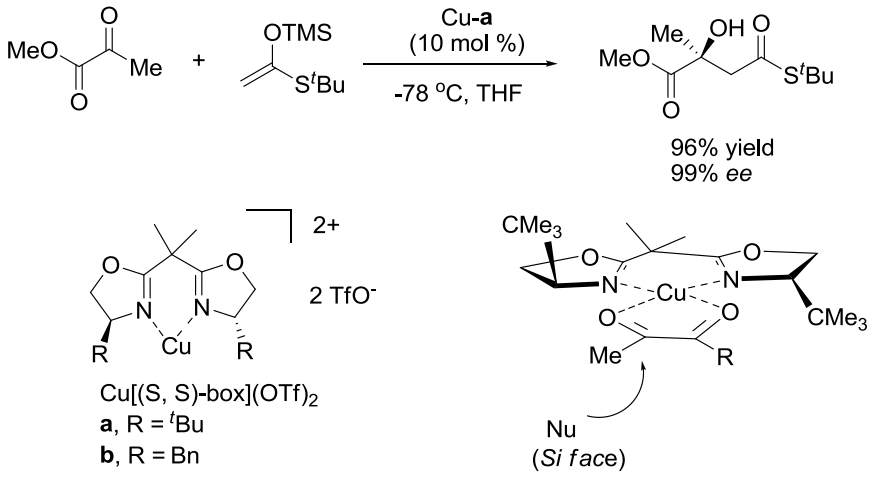
Scheme 5.10

readily to give target products with excellent enantioselectivities and diastereoselectivities. Control experiments demonstrated that the five-membered

[22] Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814.

catalyst-aldehyde chelate, which was formed through bidentate coordination beween Cu(II) centre and aldehyde, is crucial for high stereoselectivity. In addition, they found that bis(oxazolinyl) (box) and bis(oxazolinyl)pyridine (pybox) have different coordination manners because (*S*,*S*)-box and (*S*,*S*)-pybox ligands gave the opposite configuration of chiral centre. A square pyramidal coordination model was proposed for pybox ligand.

The well-designed Cu(II)-box complexes also can act as effective enantio-selective catalysts for α-diketones and α-keto esters (Scheme 5.11).[23] The enantio-



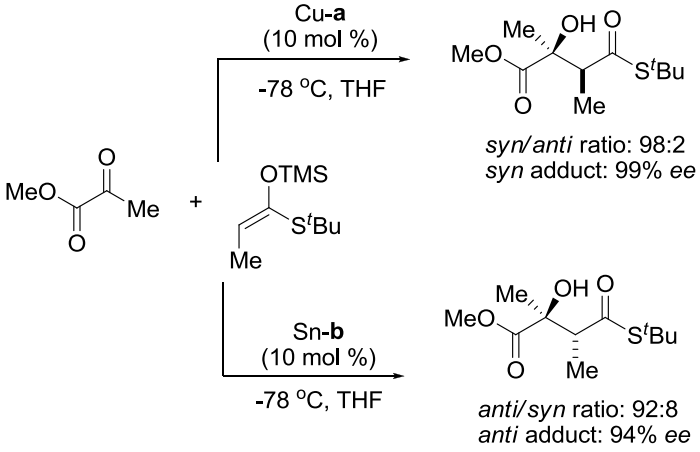
Scheme 5.11

enriched tertiary alcohols were obtained with up to 99% ee and quantitive yields even in the presence of only 1 mol % catalyst. In contrast the (benzyloxy) acetaldehyde case, both (*S*,*S*)-box and (*S*,*S*)-pybox ligands gave the (*S*)-hydroxy succinates.

An extension of this part work had been done by Evans *et al.* by using substituted enolsilanes to probe the diastereoselectivities of this method (Scheme

[23] Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMilllan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893.

5.12).[33, 24] Notably, stereoconvergence was observed for both the (*Z*)- and (*E*)-enolsilanes isomers. Another interesting observation is that the Cu(II)-box and Sn(II)-box gave different diasteroselectivities (Cu(II)-box prefer *syn* while Sn(II) prefer *anti*) although they containing the same box ligand. With these catalysts in hand, both *syn* and *anti* aldol adducts are accessible with excellent stereoselectivities.

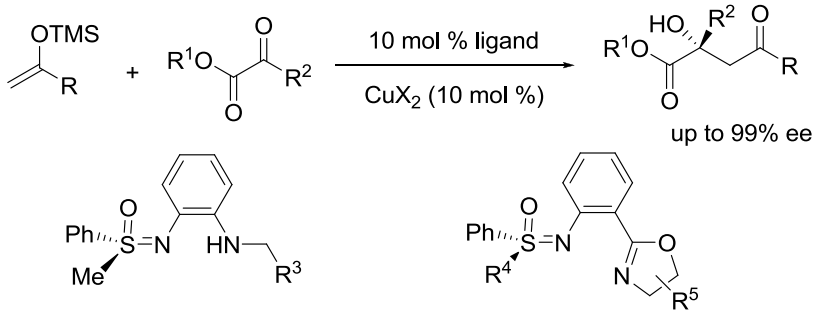


Scheme 5.12

Besides box and pybox derivatives, other nitrogen ligands had been developed recently. For example, Bolm et al. developed a series of newly designed oxazolinyl sulfoximines which demonstrated to be good ligands for Cu(II) (Scheme 5.13).[25] Their studies illustrated the potential application of this catalyst system on the basis of the recognition between these copper(II) complexes bearing C_1-symmetric amino-sulfoximines and α-keto esters. With the catalysis of these copper(II) complexes, both

[24] (a) Evans, D. A.; MacMilllan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (b) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686.

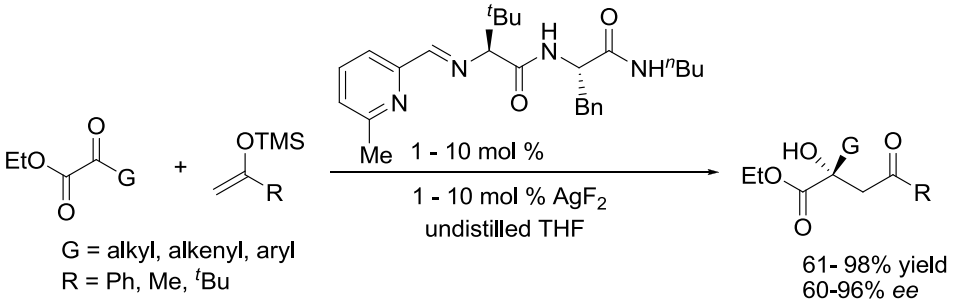
[25] (a) Langner, M.; Bolm, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 5984. (b) Langner, M.; Rémy, P.; Bolm, C. *Chem.-Eur. J.* **2005**, *11*, 6254. (c) Rémy, P.; Langner, M.; Bolm, C. *Org. Lett.* **2006**, *6*, 1209. (d) Sedelmeier, J.; Hammerer, T.; Bolm, C. *Org. Lett.* **2008**, *8*, 917.



Scheme 5.13 Newly designed nitrogen ligands for copper(II)

the asymmetric Mukaiyama aldol[8a,b,d] and vinylogous Mukaiyama-type aldol[8c] reactions proceeded smoothly and various *α*-hydroxy esters with quaternary stereogenic centers have been obtained in good yields with excellent enantioselectivities.

Recently, Hoveyda and Snapper *et al.* reported a novel Ag(II) complex catalyzed enantioselective Mukaiyama aldol of *α*-keto esters (Scheme 5.14).[26] The complex was formed from AgF_2 and an amino acid-based ligand that bears a pyridyl Schiff base. Unlike Evans' Cu(II) complex which acts on pyruvate derivatives, this catalytic



Scheme 5.14

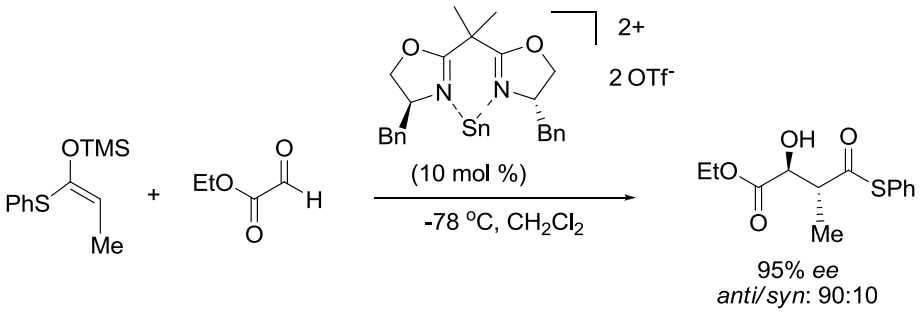
process is particularly effective with substrates that bear sterically hindered alkyl substituents, the method is complementary to previous catalytic enantioselective

[26] Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 6532.

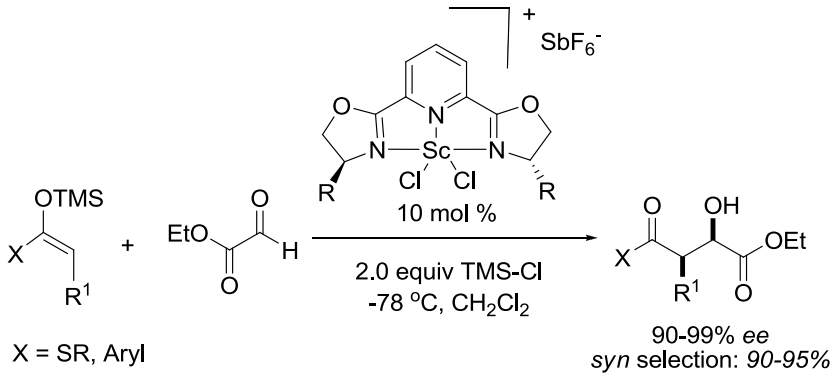
procedures. In addition, this reaction can be easily carried out in air (dry box techniques are required to exclude air and moisture for Cu(II) catalyzed process) with commercially available Ag salts (without purification) and undistilled solvent.

Although the Cu(II) complexes are effective catalysts for bidentate aldol acceptor such as (benzyloxy)acetaldehyde, α-diketones and α-keto esters, there is no successful example with regard to glyoxylate esters. The enantioselective Mukaiyama aldol reactions of glyoxylate esters are less developed compared to the extensive studies on α-keto esters, possibly due to their highly reactive nature. To the best of our knowledge, there are only three catalysts which had been developed for glyoxylate esters.

The first one is Mikami's Ti(IV)-BINOL complex[13] which exhibited high efficiency for enantioselective Mukaiyama aldol reactions of glyoxylate esters albeit with a limited substrate scope. It is notable that the chiral Cu(II)-box or pybox, which are good catalysts for α-keto esters, are not effective for glyoxylate esters. For such



Scheme 5.15



Scheme 5.16

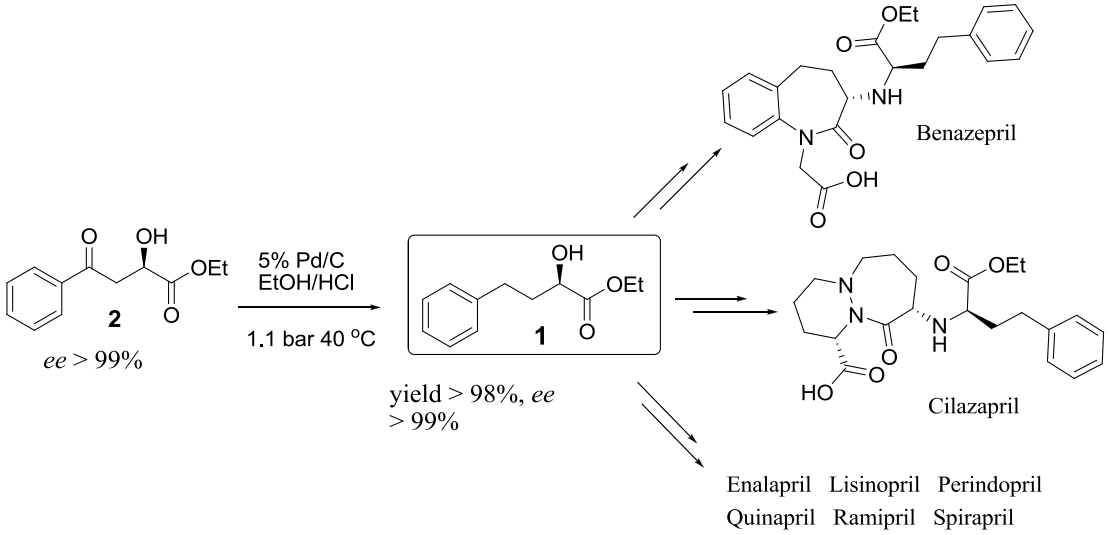
purpose, Evans' group developed other two catalyst systems which can complement one another (Schemes 5.15 & 5.16) with regard to glyoxylate esters.[34a, 27] The Sn(II)-box complex afforded the *syn* adducts with 90-99% *ee* and 90-95% *syn* selection (Scheme 5.15) while Sc(III)-pybox provided *anti* aldols with up to 95% ee and *anti/syn* ration of 90:10 (Scheme 5.16).

[27] Evans, D. A.; Masse, C. E.; Wu, J. M. *Org. Lett.* **2002**, *2*, 3375.

5.2 RESULTS AND DISCUSSION

5.2.1 Our proposal

The asymmetric synthesis of versatile chiral β-hydroxy carbonyl compounds is an area of organic chemistry which attracted a great deal of interest, since chiral β-hydroxy ketones and esters are key intermediates or synthetic building blocks of many biologically active molecules.[2] For example, ethyl (*R*)-2-hydroxy-4-phenylbutyrate (HPB ester) **1** is an important intermediate for several Angiotesin-Converting Enzyme (ACE) inhibitors, which are a group of pharmaceuticals primarily used in the treatment of hypertension and congestive heart failure (Scheme 5.17).[28] In

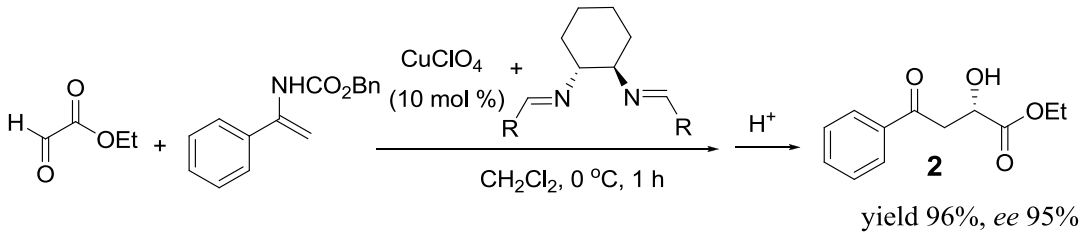


Scheme 5.17

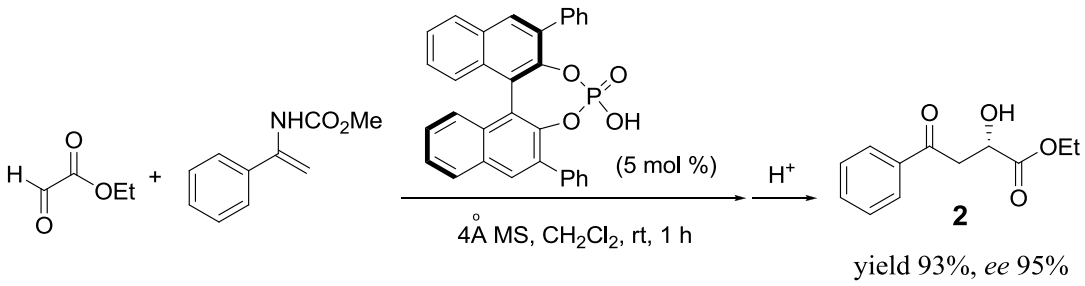
2000, Indolese and coworkers reported a process via the preparation of optical active ethyl (*R*)-2-hydroxy-4-oxo-4-phenylbutanoate **2**, which could be transferred into HPB

[28] Herold, P.; Indolese, A. F.; Studer, M.; Jalett, H. P.; Siegrist, U.; Blaser, H. U. *Tetrahedron* **2000**, *56*, 6497.

ester **1** quantitively with retention of optical activities.[29] This work shifted the attention from HPB ester **1** to **2**. Containing an additional carbonyl group made **2** easier to be prepared by catalytic asymmetric synthesis. Kobayashi *et al.* developed a highly enantioselective Cu(II)-diimine-catalyzed addition reactions of enecarbamates with ethyl glyoxylate having excellent *ee* up to 98% (Scheme 5.18).[30] Very recently, Terada's group reported another catalytic system by using BINOL-based chiral phosphoric acid as the catalyst (Scheme 5.19).[31] They also demonstrated that the double hydrogen bonding interaction between the phosphoric acid and the glyoxylate is crucial in providing good steroselectivities.



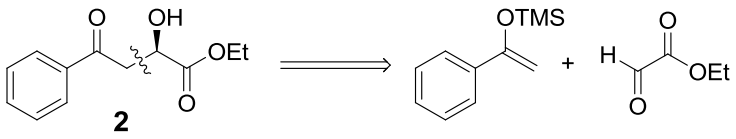
Scheme 5.18



Scheme 5.19

As shown in Scheme 5.20, the catalytic asymmetric Mukaiyama aldol reaction

[29] Fadnavis, N. W., Radhika, K. R. *Tetrahedron: Asymmetry* **2004**, *15*, 3443.
[30] Matsubara, R.; Nakamura, Y.; Kobayashi, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3258.
[31] Terada, M.; Soga, K.; Momiyama, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 4122.



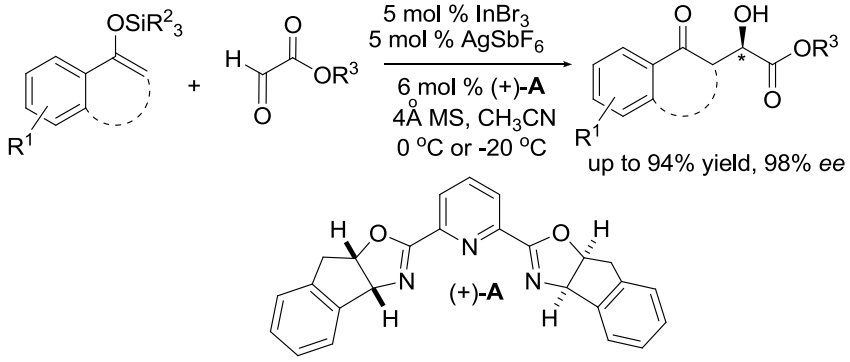
Scheme 5.20

between ethyl glyoxylate and enolsilane derived from acetophenone should offer a straightforward access to **2**. However, to our surprise, except a racemic version there is no successful report on the asymmetric version of this reaction both in organoctalytic direct aldol and in chiral Lewis acid catalyzed Mukaiyama aldol.[37] After searching the literature we found that compared to the extensive studies of asymmetric Mukaiyama aldol reaction of α-diketones and α-keto esters, there are only few asymmetric Mukaiyama aldol of their more reactive analogs, the glyoxylate esters, especially when the less reactive[32] planar aryl enolsilanes are employed as nucleophiles.

In the previous two chapters, we have demonstrated that the In(III)-pybox complexes, formed *in situ* from commercially available In(III) salts and pybox ligands, are efficient catalysts for asymmetric carbony-ene reactions of glyoxylates and trifluoropyruvates.[7] This may be attributed to the ability of glyoxylate and trifluoropyruvate to function as bidentate substrates, coordinating to the cationic In(III) centre to form a facially discriminated complex, which is crucial for inducing high enantioselectivity. We hypothesized that maybe this strategy could also be applied to the more challenging asymmetric Mukaiyama aldol reaction of glyoxylate esters. In this part of the thesis, we developed a highly efficient In(III)-pybox complex catalyzed

[32] (a) Burfeindt, J.; Patz, M.; Muller, M.; Mayr, H. *J. Am. Chem. Soc.* **1998**, *120*, 3629. (b) Mayr, H.; Patz, M. *Angew. Chem. Int. Ed.* **1994**, *33*, 938.

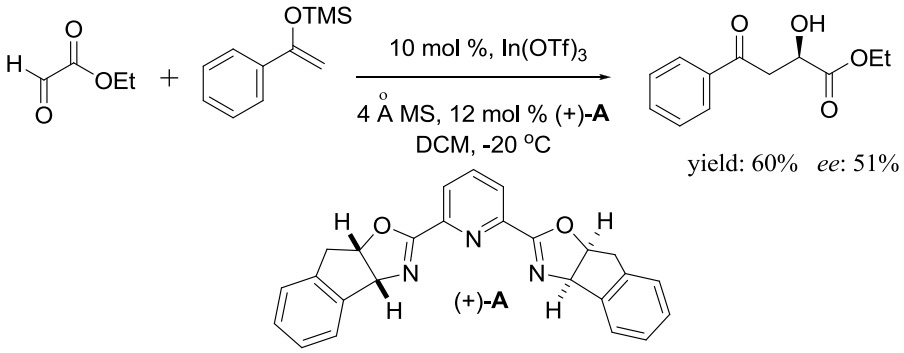
enantioselective Mukaiyama aldol reaction between glyoxylate esters and aryl enolsilanes (Scheme 5.21).



Scheme 5.21

5.2.2 Optimization studies

Initially, asymmetric Mukaiyama aldol of ethyl glyoxylate and trimethylsilyl enol ether derived from acetophenone was chosen as the model reaction to screen the reaction conditions. In the presence 10 mol% of In(III)-pybox complexe, formed *in situ* from commercially available $In(OTf)_3$ and pybox ligand (+)-**A**, this reaction proceeded smoothly to give the aldol product in moderate yield and enantioselectivity (Scheme 5.22). However, this is an encouraging result for this reaction because only 11% *ee* was obtained in Evans' study. We believed that the result could be further improved by optimization of reaction conditions.

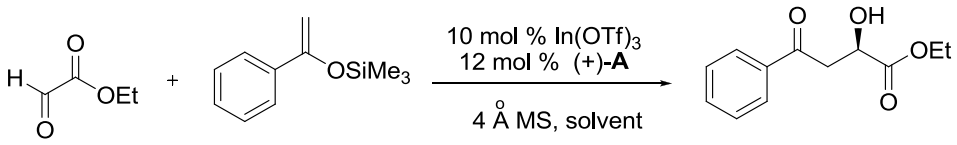


Scheme 5.22

Firstly, we screened the solvent and the results are summarized in Table 1. The effect of solvent was evaluated in the Mukaiyama aldol reaction between 1 equivalent (equiv) of 0.25 M ethyl glyoxylate and 1.5 equiv of trimethyl(1-phenylvinyloxy)silane catalyzed by In(III)-pybox complex, which was formed *in situ* from 10 mol% $In(OTf)_3$ with 12 mol% Pybox-**A** ligand in the presence of powdered activated 4Å molecular sieves. As shown in Table 1, the reaction efficiency is sensitive to reaction media. The polar aprotic solvents such as CH_3CN, EtCN, $^{i}PrNO_2$ and THF proved to be better than

other non-polar solvents. To our delight, 80% ee could be obtained when the reaction was carried out in CH_3CN at -40 °C albeit in moderate yield.

Table 1. Screening of solvent[a]

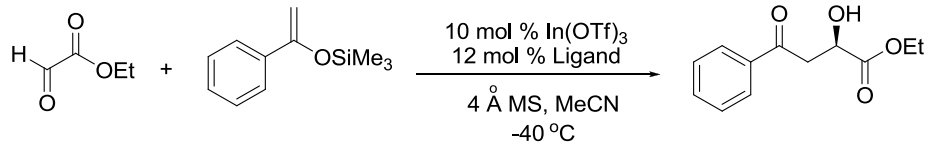


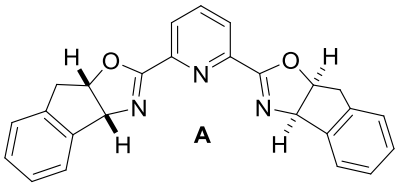
entry	solvent	T (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	$(CH_2Cl)_2$	-20	28	60	51
2	$MeNO_2$	-20	27	68	74
3	Acetone	-40	35	63	11
4	Toluene	-40	35	22	11
5	MeOH	-40	39	46	15
6	CH_2Cl_2	-40	39	71	53
7	$CHCl_3$	-40	35	86	54
8	EtOAc	-40	35	49	69
9	THF	-40	39	34	71
10	$^{i}PrNO_2$	-40	35	42	76
11	EtCN	-40	39	71	78
12	MeCN	-40	39	56	80

[a] Reactions were carried out with 0.75 mmol of ethyl glyoxylate and 0.50 mmol of enolsilane in the presence of 150 mg powdered activated 4Å molecular sieves in 2.0 mL of solvent. [b] Isolated yield. [c] *ee* values were determined by chiral stationary phase HPLC analysis. The absolute configuration of the major products was *R*, assigned by comparing the optical rotation with the literature.

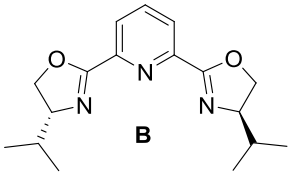
Next, we move our focus to the screening of ligands. A number of chiral oxazoline-containing ligands were screened using CH_3CN as solvent with the hope of finding better ligands for this reaction. Interestingly, only pybox ligands were effective for this reaction while box ligands exhibited almost no asymmetric induction. Pybox

Table 2. Screening of ligand

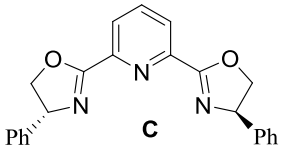




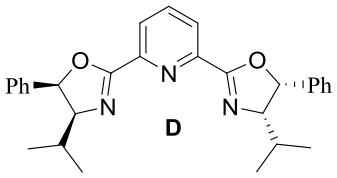
yield: 56% *ee*: 80%



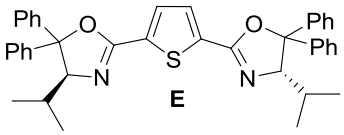
yield: 78% *ee*: 64%



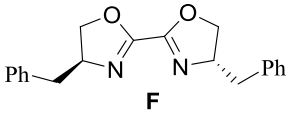
yield: 79% *ee*: 49%



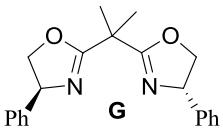
yield: 90% *ee*: -72%



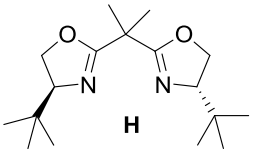
yield: 24% *ee*: 2%



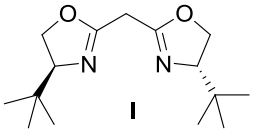
yield: 35% *ee*: 1%



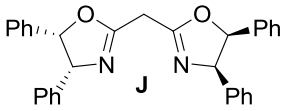
yield: 28% *ee*: 0%



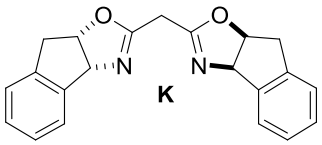
yield: 26% *ee*: 0%



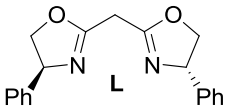
yield: 50% *ee*: 0%



yield: 40% *ee*: 2%



yield: 28% *ee*: 0%



yield: 28% *ee*: 3%

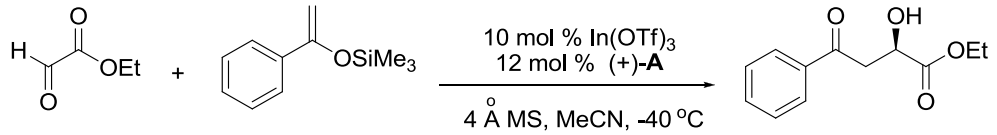
[a] Reactions were carried out with 0.75 mmol of ethyl glyoxylate and 0.50 mmol of enolsilane in the presence of 150 mg powdered activated 4Å molecular sieves in 2.0 mL of solvent. [b] Isolated yield. [c] *ee* values were determined by chiral stationary phase HPLC analysis. The absolute configuration of the major products was *R*, assigned by comparing the optical rotation with the literature.

ligands were able to induce moderate ee of aldol adduct ranging from 49% to 80% (Table 2, entries 1 – 6), among which Pybox-**A** ligand exhibited the highest ee (Table 2, entry 1). Bisoxazoline (box) ligands, box-analogue **K** ligand**,** and pybox-analogue **E** sulfur-containing ligand gave no enantioselectivity at all (Table 3, entries 7 – 14). Thus,

Pybox-**A** ligand remained as the optimum choice for the enantioselective Mukaiyama aldol reaction.

A number of literatures have documented the dramatic impact of alcoholic additives on catalyst turnover in asymmetric Lewis acid catalyzed carbon-carbon bond-forming reactions. Achiral acidic phenol additives accelerated the rate of triflate-anion-based catalysts in asymmetric Pt(II)-catalyzed ene reactions by disrupting contact ion pairs and sequestering traces of water.[33] Protonic additives such as $(CF_3)_2CHOH$ accelerated [Cu((*S*,*S*)-*t*-Bu-box)](X_2) (X = OTf^-, SbF_6^-) Lewis acid-

Table 3. Investigation of additive effect[a]



entry	additive	time (h)	yield (%)[b]	*ee* (%)[c]
1	--	30	76	80
2	PhOH	35	47	67
3	$HOCH(CF_3)_2$	35	59	57
4	CF_3CH_2OH	54	20	79
5	$PhCO_2H$	44	30	13
6	Me_3SiBr	10	11	79

[a] Reactions were carried out with 0.75 mmol of ethyl glyoxylate and 0.50 mmol of enolsilane in the presence of 150 mg powdered activated 4Å molecular sieves in 2.0 mL of solvent. [b] Isolated yield. [c] *ee* values were determined by chiral stationary phase HPLC analysis. The absolute configuration of the major products was *R*, assigned by comparing the optical rotation with the literature.

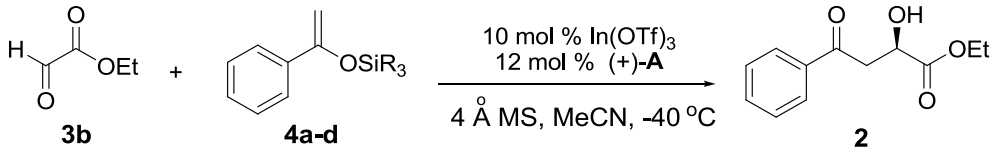
catalyzed Mukaiyama Michael-type reactions by decomposing a turnover- inhibiting catalyst-product complex; and in the Mukaiyama Michael reaction of alkylidene

[33] Koh, J. H.; Larsen, A. O.; Gagné, M. R. *Org. Lett.* **2001**, *3*, 1233.

malonates and enolsilanes, the alcoholic additives significantly enhanced the enantioselectivity.[34] Besides, halo trimethylsilane was previously reported by our group as a reaction "promoter" in the highly enantioselective allylation of aldehydes catalyzed by In(III)-pybox complex.[35] These reports prompted us to evaluate a number of additives in an attempt to improve reaction efficiency (Table 3). Unfortunately, no increase in yield or *ee* was observed for all the additives screened.

Significant steric effects were observed in Evans' work in which only steric bulky enolsilanes derived from aryl ketones provided high levels of induction in the Mukaiyama aldol of ethyl glyoxylate.[37] Inspired by these results, we hypothesized that

Table 4. Evaluation of steric effect of enolsilane[a]



entry	SiR_3	time (h)	yield (%)[b]	*ee* (%)[c]
1	$SiMe_3$ (**4a**)	30	76	80
2	$SiEt_3$ (**4b**)	30	80	82
3	$SiMe_2{}^tBu$ (**4c**)	59	88	83
4	Si^iPr_3 (**4d**)	46	76	85

[a] Reactions were carried out with 0.75 mmol of ethyl glyoxylate and 0.50 mmol of enolsilane in the presence of 150 mg powdered activated 4Å molecular sieves in 2.0 mL of solvent. [b] Isolated yield. [c] *ee* values were determined by chiral stationary phase HPLC analysis. The absolute configuration of the major products was *R*, assigned by comparing the optical rotation with the literature.

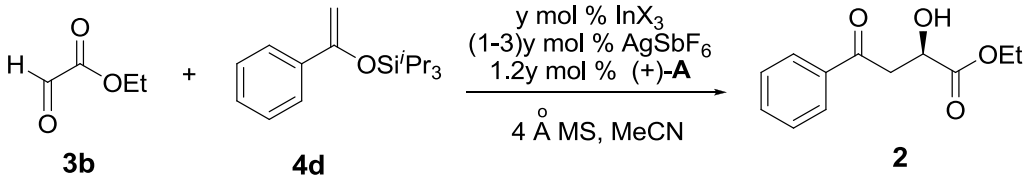
[34] (a) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Downey, C. W.; Tedrow, J. S. *J. Am. Chem. Soc.* **2000**, *122*, 9134. (b) Evans, D. A.; Willis, M. C.; Johnson, J. N. *Org. Lett.* **1999**, *1*, 865. (c) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994

[35] (a) Lu, J.; Ji, S. J.; Teo, Y. C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (b) Lu, J.; Hong, M. L.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 1010. (c) Lu, J.; Ji, S. J.; Loh, T. P. *Chem. Commun.* **2005**, 2345.

we could take advantage of the steric effect to improve the reaction efficiency. A series of enolsilanes were prepared from acetophenone and various silyl trifluoro-methanesulfonates and were evaluated in the asymmetric Mukaiyama aldol of ethyl glyoxylate. As shown in Table 4, steric effect indeed played a role albeit only moderate improvement of enantioselectivity was observed. The enantioselectivities were increased steadily with the increasing of sterically hindered of silyl groups. Up to 85% *ee* could be obtained by using the most steric bulky enolsilane derived from triisopropylsilyl (TIPS) as the aldol donor. Another advantage of using TIPS silyl enol ether as the donor is that the steric bulk makes it stable enough for purification by flash column chromatography.

Due to the significant counterion effect of In(III)-pybox complex observed in asymmetric carbonyl-ene reaction, further optimization focused on systematic evaluation of counterion effect. The enantioselectiviy was further increased when new In(III)-pybox complex, designed based on the counterion effect, was used as the catalyst. With the catalysis of 5 mol% new In(III)-pybox complex, formed *in situ* from commercially available $InBr_3$, $AgSbF_6$ and pybox **A** in the presence of 4 Å molecular sieve, the precursor of HPB ester could be obtained in 91% yield and with 89% ee (Table 5, entries 4 and 7). Interestingly, we found that this reaction is sensitive to temperature. For example, comparable yield and enantioselectivity could be obtained at -40 °C and -20 °C. However, the reaction rate was decreased significantly at -40 °C and 3 days are required for the completetion of the reaction. Meanwhile, other silver

Table 5. Investigation of counterion effect[a]



3b **4d** **2**

entry	InX_3 (mol %)	$AgSbF_6$ (mol %)	T (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	$InCl_3$, 10	20	-40	20	70	85
2	$InCl_3$, 10	20	-60	60	63	87
3	$InCl_3$, 10	20	-78	60	54	88
4	$InBr_3$, 10	20	-78	48	53	89
5	$InBr_3$, 5	15	-40	36	49	84
6	$InBr_3$, 5	10	-40	72	71	88
7	$InBr_3$, 5	5	-40	72	91	89
8	$InBr_3$, 5	5	-20	19	89	87

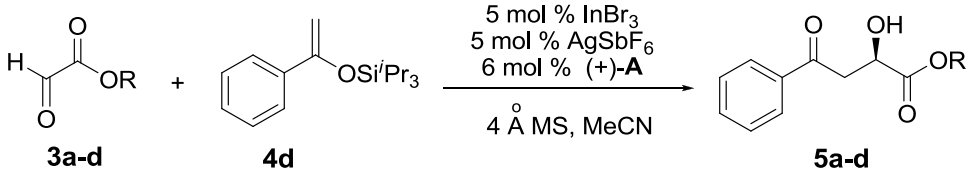
[a] Reactions were carried out with 0.75 mmol of ethyl glyoxylate and 0.50 mmol of enolsilane in the presence of 150 mg powdered activated 4Å molecular sieves in 2.0 mL of solvent. [b] Isolated yield. [c] *ee* values were determined by chiral stationary phase HPLC analysis. The absolute configuration of the major products was *R*, assigned by comparing the optical rotation with the literature.

salts such as $AgBF_4$, $AgClO_4$, $AgPF_6$ and AgOAc have also been tested. However, no improvement was observed.

Although good yield and enantioselectivity could be obtained, there remained some room for the improvement of enantioselectivity. Because the steric bulk of enolsilane has positive effect on the enantioselectivity, we anticipated that the steric bulk of glyoxylate may also have some effect on the reaction efficiency. A series of glyoxylate esters were surveyed. The results are listed in Table 6. Gratifyingly, similar trend with that of enolsilanes was observed. The enantioselectivities were increased steadily with the increase of the steric bulk of the ester group of the glyoxylate esters

(Table 6, entries 1-4). With *iso*-propyl glyoxylate as the aldol acceptor, 89% ee could be obtained in excellent yield even at room temperature (Table 6, entry 4). With slight

Table 6. Investigation of steric effect of glyoxylate[a]



3a-d **4d** **5a-d**

entry	R	T (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	Me(**3a**)	rt	12	86	72
2	Et(**3b**)	rt	12	95	77
3	^{n}Bu(**3c**)	rt	12	90	84
4	^{i}Pr(**3d**)	rt	18	96	89
5	^{i}Pr(**3d**)	0	20	96	92
6	^{i}Pr(**3d**)	-20	20	96	96
7[d]	^{i}Pr(**3d**)	-40	72	28	97

[a] Reactions were carried out with 0.75 mmol of ethyl glyoxylate and 0.50 mmol of enolsilane in the presence of 150 mg powdered activated 4Å molecular sieves in 2.0 mL of solvent. [b] Isolated yield. [c] *ee* values were determined by chiral stationary phase HPLC analysis. [d] This reaction is not completed.

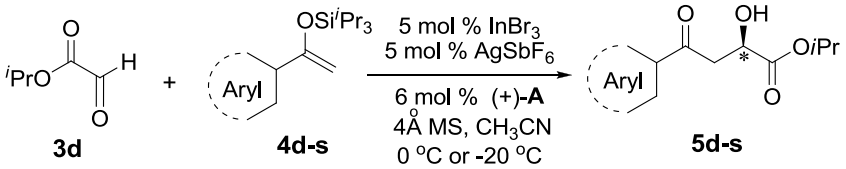
decrease of temperature, the enantioselectivity could be further improved to 96% (Table 6, entries 5 and 6). However, too low temperature led to a very sluggish reaction rate although it afforded the highest *ee* (Table 6, entry 7). Thus, -20 °C was the temperature of choice for this reaction in terms of yield, enantioselectivity and reaction time.

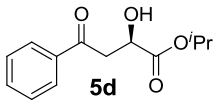
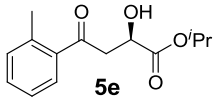
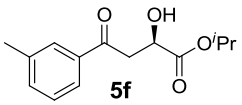
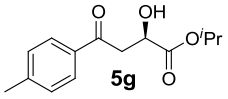
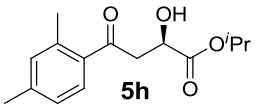
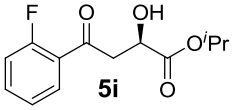
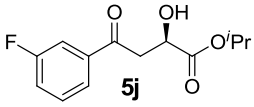
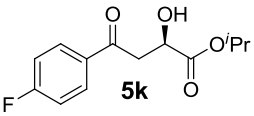
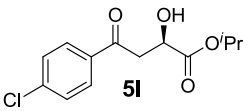
5.2.3 Substrate scope

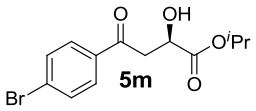
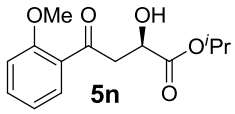
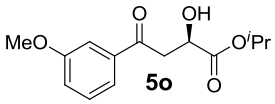
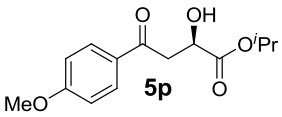
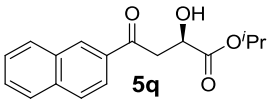
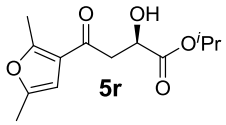
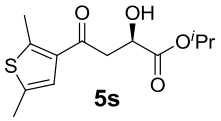
Next a series of TIPS enolsilanes derived from aryl ketones were prepared to

evaluate the substrate scope of this reaction. The results are summarized in Table 2. Aryl enolsilanes containing both electron-withdrawing and -donating groups on the aromatic ring proceeded smoothly to give the aldol adducts in good to excellent yields

Table 7. Substrate scope of aryl enolsilanes[a]



Entry	product	T (°C)	time (h)	yield (%)[b]	*ee* (%)[c]
1	 **5d**	-20	19	91	96
2	 **5e**	0	70	81	94
3	 **5f**	-20	22	88	94
4	 **5g**	-20	22	94	96
5	 **5h**	0	70	80	95
6	 **5i**	0	68	60	93
7	 **5j**	0	68	85	93
8	 **5k**	-20	72	71	94
9	 **5l**	-20	64	82	97

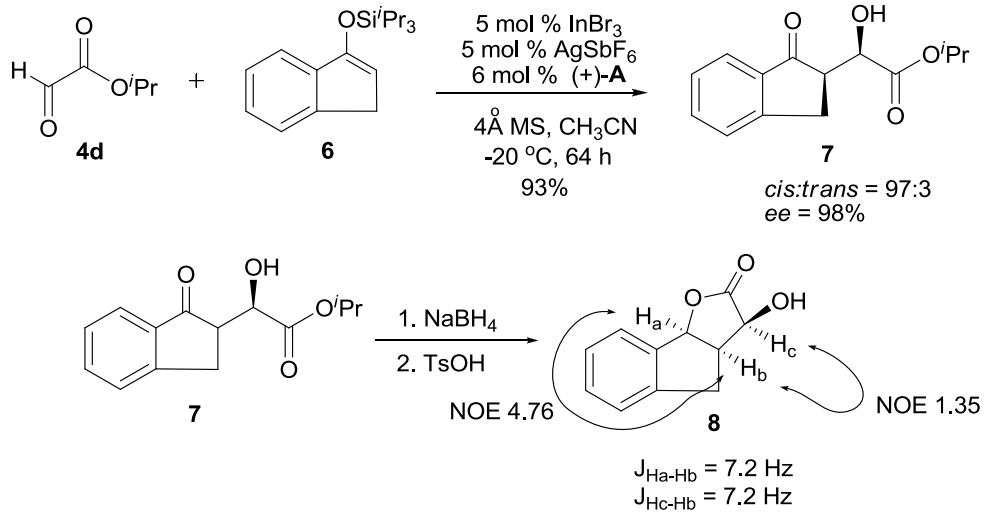
10	 **5m**	-20	64	85	97
11	 **5n**	-20	68	83	92
12	 **5o**	-20	48	85	95
13	 **5p**	-20	48	88	96
14	 **5q**	-20	64	89	98
15	 **5r**	-20	68	76	90
16	 **5s**	-20	68	92	96

[a] Reactions were carried out with 0.75 mmol of ethyl glyoxylate and 0.50 mmol of enolsilane in the presence of 150 mg powdered activated 4Å molecular sieves in 2.0 mL of solvent. [b] Isolated yield. [c] *ee* values were determined by chiral stationary phase HPLC analysis. The absolute configuration of the major products was *R*, assigned by comparing the optical rotation with the literature.

and with excellent enantioselectivities albeit longer reaction time were required for electron-deficient substrates (Table 2, entries 6-10). Interestingly, although the steric hindrance is favorable for the enantioselectivies, excessive steric hindrance in the transition state has a negative effect on the reaction efficiency. For example, the presence of substituent at *ortho* position of enolsilane prolonged the reaction time (up to 3 days) and required higher reaction temperature (0 °C), regardless whether the substituents are electron-neutral (Table 2, entries 2 and 5) or withdrawing group (Table 2, entry 6). The disadvantage caused by steric hindrance of *ortho* methyl or methoxy

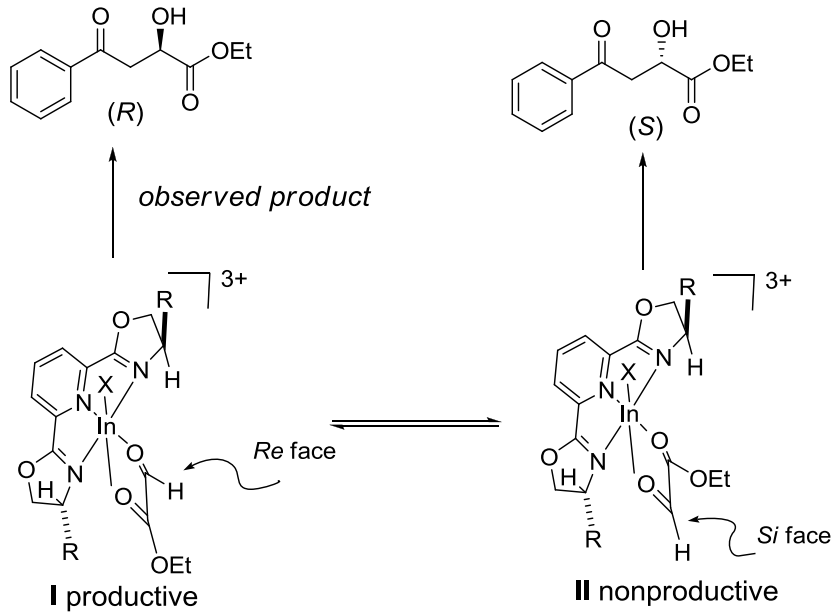
group might be compensated by the electron-rich nature of the substrates **4n**, **4r** and **4s** (Table 2, entries 11, 15 and 16). This observation demonstated that both the electronic effect and steric effect play some roles in reaction. It is noteworthy that enolsilanes derived from heterocyclic aryl ketones also worked well to give enantioenriched alcohols which could be elaborated to other useful chemicals (Table 2, entries 15 and 16).

To further probe the stereoselectivity of this reaction, α-substituted aryl ketone-derived enolsilane **6**, which will lead two chiral centres in the aldol product **7**, was reacted under the standard reaction conditions. As a result, excellent diastereoselectivity (dr = 97:3) as well as enantioselectivity (98% *ee*) could be obtained, with the *syn* diastereomer as the major product (Scheme 5.23).



Scheme 5.23

5.2.4 Proposed transition model to rationalize the observed enantioselectivity



Scheme 5.24

The pseudo-octahedral hexa-coordinated model proposed in Chapter **3** can also be used to rationalize the observed stereoselectivity of the asymmetric Mukaiyama Aldol reaction. The strong *trans* influence observed in d^{10} metal complexes of tridentate N-ligands[36] enable model **I**, in which the carbonyl coordination occurs in the ligand plane**,** more productive (Scheme 5.24). In model **I**, the *si* face of aldehyde is masked by the ligand R group exposing the *re* face for nucleophilic attack. The experimental results are consistent with the proposed model.

[36] (a) Beran, G.; Carty, A. J.; Patel, H. A.; Palenik, G. *J. Chem. Soc. D.* **1970**, 222. (b) Butcher, R. J.; George, C.; Muratore, N.; Purdy, A. P. *Acta Cryst. E* **2003,** m1107.

5. 3 CONCLUSION

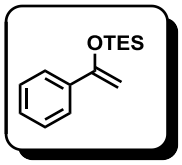
In summary, we have successfully developed a highly enantioselective Mukaiyama aldol reaction between glyoxylate esters and enolsilanes derived from aryl keones. This work complements the well-developed Mukaiyama aldol reactions of pyruvates. The reaction conditions are mild. For example, solvent and chemicals could be used without distillation and the reaction could be carried out in an open air. Both of these features make this methodology very practical. In addition, this work demonstrated the advantage of new generation In(III)-pybox complex in the application of asymmetric synthesis and supported the transition model proposed for In(III)-pybox complex catalyzed asymmetric reactions involved bidentate substrates.

5.4 EXPERIMENTAL SECTION

5.3.1 General procedure for the preparation of silyl enol ethers

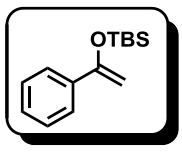
To in a 50 mL round-bottom flask equipped with a stirring bar and filled with CH_2Cl_2 (20 mL), acetophenone (5.0 mmol) and triethylamine (1.3 mL, 9.0 mmol) were added. The solution was stirred at room temperature for 15 mins before cooling down to 0 ^oC. Triisopropylsilyl trifluoromethanesulfonate (1.7 mL, 6.0 mmol) was added by a syringe slowly over 2 min at 0 ^oC. The resulting mixture was stirred under N_2 atmosphere at 0 ^oC for 30 min. The reaction was quenched with saturated $NaHCO_3$ solution (20 mL) and diluted by cold CH_2Cl_2 (10 mL). The organic layer was washed with cold saturated $NaHCO_3$ solution twice, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography on Et_3N-treated silica gel eluting with hexane to afford silyl enol ethers **7b-s** as a colourless oils.

Triethyl(1-phenylvinyloxy)silane (4b)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 62% yield (0.726 g); R_f = 0.94 (ethyl acetate/hexane = 1/4); ^1H NMR (300 MHz, $CDCl_3$): δ 7.63–7.59 (m, 2H), 7.35 – 7.27(m, 3H), 4.87 (d, *J* = 1.7 Hz, 1H), 4.42 (d, *J* = 1.7 Hz, 1H), 1.01 (t, *J* = 7.8 Hz, 9H), 0.76 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.9, 137.7, 128.2, 128.1, 125.2, 90.4, 6.7, 5.0; FTIR (neat): *v* 2955, 2876, 1614, 1458, 1414, 1317, 1117, 1009, 737 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}OSiH^+$: 235.1518, found: 235.1517.

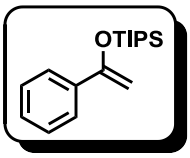
Tert-butyldimethyl(1-phenylvinyloxy)silane (4c)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 64% yield (0.752 g); R_f = 0.92 (ethyl acetate/hexane = 1/4); ^1H NMR (300 MHz, $CDCl_3$): δ 7.60–7.56 (m, 2H), 7.31 – 7.23 (m, 3H), 4.85 (d, *J* = 1.5 Hz, 1H), 4.39 (d, *J* = 1.6 Hz,

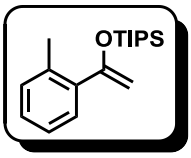
1H), 0.98 (s, 9H), 0.18 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.0, 137.9, 128.2, 128.1, 125.3, 90.9, 25.9, 18.4, -4.6; FTIR (neat): *v* 2957, 2930, 2859, 1614, 1472, 1315, 1256, 1117, 1013, 833, 772, 700 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{22}OSiH^+$: 235.1518, found: 235.1514.

Triisopropyl(1-phenylvinyloxy)silane (4d)



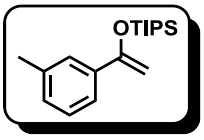
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 83% yield (1.146 g); R_f = 0.90 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.69 – 7.59 (m, 2H), 7.37 – 7.21 (m, 3H), 4.85 (d, *J* = 1.8 Hz, 1H), 4.41 (d, *J* = 1.7 Hz, 1H), 1.38 – 1.21 (m, 3H), 1.13 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 138.0, 128.11, 128.05, 125.3, 90.0, 18.1, 12.8; FTIR (neat): *v* 2945, 2866, 1612, 1464, 1385, 1317, 1117, 1015, 883, 772, 687 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{28}OSiH^+$: 277.1988, found: 277.1990.

Triisopropyl(1-o-tolylvinyloxy)silane (4e)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 77% yield (1.117 g); R_f = 0.89 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, *J* = 7.4 Hz, 1H), 7.22 – 7.07 (m, 3H), 4.54 (d, *J* = 0.9 Hz, 1H), 4.35 (d, *J* = 0.9 Hz, 1H), 2.42 (s, 3H), 1.31 – 1.13 (m, 3H), 1.08 (d, *J* = 6.9 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 139.5, 135.8, 130.3, 128.6, 127.8, 125.3, 94.3, 20.6, 18.1, 12.7; FTIR (neat): *v* 2945, 2866, 1622, 1464, 1383, 1312, 1132, 1094, 1016, 883, 729, 687 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}OSiH^+$: 291.2144, found: 291.2140.

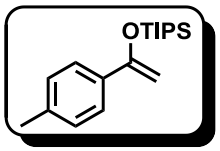
Triisopropyl(1-m-tolylvinyloxy)silane (4f)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 79% yield (1.146 g); R_f = 0.91 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45 (d, *J* = 7.5 Hz, 2H), 7.25 – 7.16 (m, 1H), 7.08 (d, *J* = 7.3 Hz, 1H), 4.83 (d, *J* = 1.4 Hz, 1H), 4.39 (d, *J* = 1.5 Hz, 1H), 2.34 (s, 3H), 1.37 – 1.21 (m, 3H), 1.13 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 138.0, 137.5, 128.9, 128.0, 126.1,

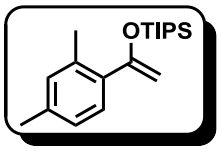
122.6, 89.9, 21.6, 18.2, 12.9; FTIR (neat): *v* 2943, 2866, 1601, 1582, 1464, 1383, 1310, 1207, 1016, 883, 789, 685 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}OSiH^+$: 291.2144, found: 291.2140.

Triisopropyl(1-p-tolylvinyloxy)silane (4g)



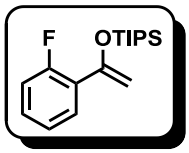
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 80% yield (1.161 g); R_f = 0.90 (ethyl acetate/hexane = 1/4); ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.2 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 4.80 (d, *J* = 1.6 Hz, 1H), 4.36 (d, *J* = 1.6 Hz, 1H), 2.36 (s, 3H), 1.38 – 1.20 (m, 3H), 1.12 (d, *J* = 7.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 137.9, 135.3, 128.8, 125.3, 89.2, 21.2, 18.2, 12.9; FTIR (neat): *v* 2943, 2866, 1611, 1510, 1464, 1383, 1315, 1113, 1016, 883, 762, 681 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}OSiH^+$: 291.2144, found: 291.2146.

(1-(2,4-Dimethylphenyl)vinyloxy)triisopropylsilane (4h)



This compound was prepared by the general procedure described above and was obtained as a yellow oil in 75% yield (1.145 g); R_f = 0.92 (ethyl acetate/hexane = 1/4); ^1H NMR (300 MHz, $CDCl_3$): δ 7.24 (d, *J* = 7.6 Hz, 1H), 6.96 (s, 1H), 6.93 (d, *J* = 7.6 Hz, 1H), 4.51 (d, *J* = 0.7 Hz, 1H), 4.32 (d, *J* = 0.7 Hz, 1H), 2.39 (s, 3H), 2.30 (s, 3H), 1.23 – 1.16 (m, 3H), 1.08 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.2, 137.4, 136.7, 135.6, 131.1, 128.6, 125.9, 94.0, 21.1, 20.5, 18.1, 12.7; FTIR (neat): *v* 2943, 2866, 1614, 1464, 1383, 1308, 1090, 1016, 883, 824, 683 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{32}OSiH^+$: 305.2301, found: 305.2298.

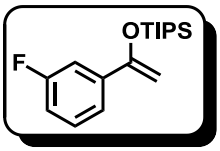
(1-(2-Fluorophenyl)vinyloxy)triisopropylsilane (4i)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 82% yield (1.206 g); R_f = 0.93 (ethyl acetate/hexane = 1/4); ^1H NMR (300 MHz, $CDCl_3$): δ 7.69 – 7.63 (m, 1H), 7.27 – 6.99 (m, 3H), 4.99 – 4.94 (m, 1H), 4.70 – 4.67 (m, 1H), 1.34 – 1.21 (m, 3H), 1.12 (d, *J* = 7.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 160.01 (d, *J* = 250.9 Hz), 150.72 (d, *J* = 4.0 Hz), 129.2 (d, *J* = 8.7 Hz), 128.8 (d, *J* = 2.7 Hz),

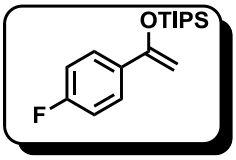
126.0 (d, *J* = 11.1 Hz), 123.7 (d, *J* = 3.7 Hz), 116.0 (d, *J* = 23.6 Hz), 96.0 (d, *J* = 11.4 Hz), 18.1, 12.8; FTIR (neat): *v* 2945, 2868, 1612, 1489, 1385, 1312, 1090, 1018, 883, 760, 685 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}FOSiH^+$: 295.1893, found: 295.1884.

(1-(3-Fluorophenyl)vinyloxy)triisopropylsilane (4j)



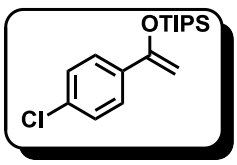
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 72% yield (1.059 g); R_f = 0.90 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.44 – 7.22 (m, 3H), 7.01 – 6.92 (m, 1H), 4.86 (d, *J* = 2.0 Hz, 1H), 4.45 (d, *J* = 2.0 Hz, 1H), 1.36 – 1.22 (m, 3H), 1.13 (d, *J* = 7.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.9 (d, *J* = 244.4 Hz), 155.0 (d, *J* = 2.6 Hz), 140.4 (d, *J* = 7.5 Hz), 129.4 (d, *J* = 8.2 Hz), 120.9 (d, *J* = 2.8 Hz), 114.8 (d, *J* = 21.4 Hz), 112.3 (d, *J* = 23.0 Hz), 90.8, 18.1, 12.8; FTIR (neat): *v* 2945, 2868, 1614, 1582, 1464, 1385, 1315, 1308, 1207, 1016, 883, 787, 685 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}FOSiH^+$: 295.1893, found: 295.1910.

(1-(4-Fluorophenyl)vinyloxy)triisopropylsilane (4k)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 74% yield (1.089 g); R_f = 0.92 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.68 – 7.49 (m, 2H), 7.04 – 6.93 (m, 2H), 4.77 (d, *J* = 1.9 Hz, 1H), 4.39 (d, *J* = 1.9 Hz, 1H), 1.36 – 1.21 (m, 3H), 1.12 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.8 (d, *J* = 247.1 Hz), 155.4, 134.1 (d, *J* = 3.2 Hz), 127.1 (d, *J* = 8.1 Hz), 114.9 (d, *J* = 21.5 Hz), 89.6 (d, *J* = 1.4 Hz), 18.1, 12.8; FTIR (neat): *v* 2945, 2868, 1607, 1508, 1464, 1385, 1314, 1115, 1015, 841, 762, 681 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}FOSiH^+$: 295.1893, found: 295.1937.

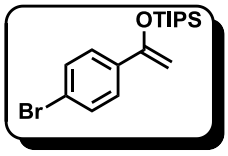
(1-(4-Chlorophenyl)vinyloxy)triisopropylsilane (4l)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 71% yield (1.101 g); R_f = 0.92 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.6 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 4.82 (d, *J* = 2.0 Hz, 1H), 4.42 (d, *J* = 2.0 Hz, 1H), 1.37 – 1.20 (m, 3H), 1.12 (d, *J* = 7.0 Hz, 18H); ^{13}C NMR (75 MHz,

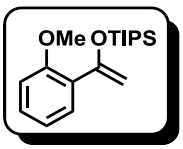
$CDCl_3$): δ 155.2, 136.5, 133.9, 128.2, 126.6, 90.4, 18.1, 12.8; FTIR (neat): *v* 2945, 2866, 1612, 1489, 1396, 1314, 1117, 1013, 835, 741, 683 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}ClOSiH^+$: 311.1598, found: 311.1608.

(1-(4-Bromophenyl)vinyloxy)triisopropylsilane (4m)



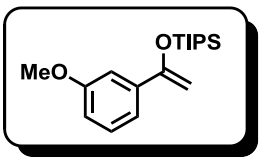
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 78% yield (1.369 g); R_f = 0.88 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 – 7.48 (m, 2H), 7.45 – 7.42 (m, 2H), 4.83 (d, *J* = 2.0 Hz, 1H), 4.42 (d, *J* = 2.0 Hz, 1H), 1.37 – 1.21 (m, 3H), 1.12 (d, *J* = 7.1 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.2, 136.9, 131.2, 126.9, 122.2, 90.4, 18.1, 12.8; FTIR (neat): *v* 2945, 2866, 1611, 1485, 1391, 1314, 1115, 1009, 831, 735, 657 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{27}BrOSiH^+$: 355.1093, found: 355.1111.

Triisopropyl(1-(2-methoxyphenyl)vinyloxy)silane (4n)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 71% yield (1.087 g); R_f = 0.89 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 – 7.59 (m, 1H), 7.26 – 7.20 (m, 1H), 6.95 – 6.86 (m, 2H), 5.01 (s, 1H), 4.65 (s, 1H), 3.84 (s, 3H), 1.31 – 1.17 (m, 3H), 1.10 (d, *J* = 6.9 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.0, 153.2, 129.0, 128.9, 127.3, 120.1, 111.1, 95.5, 55.3, 18.1, 12.8; FTIR (neat): *v* 2943, 2866, 1612, 1489, 1464, 1383, 1277, 1018, 883, 752, 685 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_2SiH^+$: 307.2093, found: 307.2097.

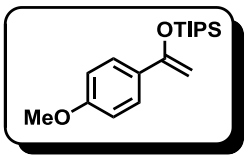
Triisopropyl(1-(3-methoxyphenyl)vinyloxy)silane (4o)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 70% yield (1.072 g); R_f = 0.91 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 – 7.16 (m, 3H), 6.85 – 6.82 (m, 1H), 4.85 (d, *J* = 1.2 Hz, 1H), 4.42 (d, *J* = 1.2 Hz, 1H), 3.80 (s, 3H), 1.37 – 1.23 (m, 3H), 1.13 (d, *J* = 7.0 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 159.5, 155.9, 139.5, 129.0, 117.9, 113.9, 110.8, 90.2, 55.1, 18.1, 12.8; FTIR (neat): *v* 2945, 2866, 1578, 1464, 1383, 1310, 1238, 1016,

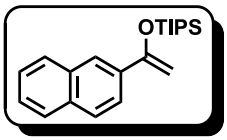
883, 685 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_2SiH^+$: 307.2093, found: 307.2095.

Triisopropyl(1-(4-methoxyphenyl)vinyloxy)silane (4p)



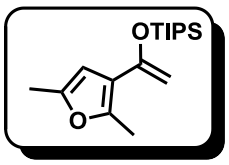
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 74% yield (1.133 g); R_f = 0.89 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 4.80 (d, *J* = 1.6 Hz, 1H), 4.36 (d, *J* = 1.6 Hz, 1H), 2.34 (s, 3H), 1.45 – 1.19 (m, 3H), 1.12 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.3, 137.9, 135.2, 128.8, 125.3, 89.2, 21.2, 18.2, 12.9; FTIR (neat): *v* 2943, 2866, 1611, 1510, 1464, 1383, 1315, 1113, 1016, 883, 824, 762, 681 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{30}O_2SiH^+$: 307.2093, found: 307.2094.

Triisopropyl(1-(naphthalen-2-yl)vinyloxy)silane (4q)



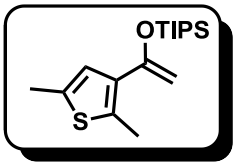
This compound was prepared by the general procedure described above and was obtained as a yellow oil in 81% yield (1.321 g); R_f = 0.93 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.85 – 7.71 (m, 4H), 7.49 – 7.37 (m, 2H), 5.00 (d, *J* = 1.5 Hz, 1H), 4.52 (d, *J* = 1.5 Hz, 1H), 1.42 – 1.26 (m, 3H), 1.16 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.2, 135.3, 133.34, 133.30, 128.6, 127.7, 127.6, 126.14, 126.11, 124.5, 123.6, 90.9, 18.2, 12.9; FTIR (neat): *v* 3059, 2943, 2866, 1611, 1464, 1385, 1364, 1310, 1094, 1015, 881, 748, 677 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{30}OSiH^+$: 327.2144, found:327.2143.

(1-(2,5-Dimethylfuran-3-yl)vinyloxy)triisopropylsilane (4r)



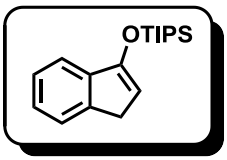
This compound was prepared by the general procedure described above and was obtained as a yellow oil in 63% yield (0.927 g); R_f = 0.9 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.97 (s, 1H), 4.32 (d, *J* = 1.3 Hz, 1H), 4.27 (d, *J* = 1.3 Hz, 1H), 2.38 (s, 3H), 2.21 (s, 3H), 1.33 – 1.19 (m, 3H), 1.12 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 148.9, 147.2, 119.7, 105.9, 90.0, 18.0, 13.6, 13.3, 12.9; FTIR (neat): *v* 2943, 2866, 1651, 1570, 1464, 1412, 1383, 1290, 1215, 1080, 1013, 883, 799, 681 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{30}O_2SiH^+$: 295.2093, found: 295.2104.

(1-(2,5-Dimethylthiophen-3-yl)vinyloxy)triisopropylsilane (4s)



This compound was prepared by the general procedure described above and was obtained as a yellow oil in 73% yield (1.132 g); R_f = 0.89 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.70 (s, 1H), 4.43 (d, *J* = 1.1 Hz, 1H), 4.33 (d, *J* = 1.0 Hz, 1H), 2.45 (s, 3H), 2.37 (s, 3H), 1.30 – 1.16 (m, 3H), 1.10 (d, *J* = 6.8 Hz, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 135.9, 134.3, 133.5, 126.1, 92.6, 18.1, 15.0, 14.9, 12.8; FTIR (neat): *v* 2943, 2866, 1614, 1464, 1385, 1337, 1269, 1015, 883, 752, 682 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{30}OSSiH^+$: 311.1865, found: 311.1873.

(1H-inden-3-yloxy)triisopropylsilane (6)



This compound was prepared by the general procedure described above and was obtained as a yellow oil in 85% yield (1.229 g); R_f = 0.90 (ethyl acetate/hexane = 1/4); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.5 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.31 – 7.26 (m, 1H), 7.21 – 7.16 (m, 1H), 5.40 (t, *J* = 2.4 Hz, 1H), 3.26 (d, *J* = 2.1 Hz, 2H), 1.36 – 1.27 (m, 3H), 1.14 (d, *J* = 7.2 Hz, 18H); ^{13}C NMR (75 MHz, CDCl3): δ 154.00, 142.8, 142.1, 126.1, 125.1, 123.8, 118.3, 105.2, 33.9, 18.1, 12.7; FTIR (neat): *v* 3072, 2943, 2866, 1603, 1576, 1464, 1362, 1308, 1248, 1180, 1126, 881, 850, 752 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{28}OSiH^+$: 289.1988, found: 289.1985.

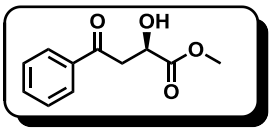
5.3.2 General procedure for In(III)-pybox complex catalyzed asymmetric Mukaiyama Aldol reactions of glyoxylates and enolsilanes derived from aryl ketones:

In a 5 mL round-bottom flask containing CH_3CN (1.5 mL) with a stirring bar, $InBr_3$ (8.9 mg, 0.025 mmol), pybox-**A** (11.8 mg, 0.03 mmol) and 4Å molecular sieves (90.0 mg) were added and stirred at room temperature for 30 minutes. To the above mixture, silver hexafluoroantimonate ($AgSbF_6$) (8.6 mg, 0.025 mmol) was added in one portion. The resulting mixture was stirred for another 30 minutes. To the pre-prepared catalyst in CH_3CN, the glyoxylate ester (1.0 mmol, 2 eq.) was added via

syringe sequentially under N_2 atmosphere. The resulting mixture was cooled to -20°C before enolsilane (0.5 mmol, 1 eq.) was added via syringe under N_2 atmosphere. The reaction mixture was stirred until the enolsilane was fully consumed as monitored by TLC. The reaction was quenched by saturated $NaHCO_3$ solution (5 mL). The solution was extracted with ethyl acetate twice. The combined organic layer was washed with brine and dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was loaded directly onto a silica gel column and purified by flash column chromatography to obtain the enantio-enriched β-hydroxy ketones.

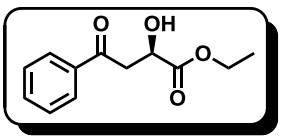
Characterization data for enantioenriched *β*-hydroxy ketones

(*R*)-methyl 2-hydroxy-4-oxo-4-phenylbutanoate (5a)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 62% yield (0.064 g, 43% *ee*): R_f = 0.24 (ethyl acetate : hexane = 1/4), $[\alpha]D^{21}$ = -3.8 (c = 1.72, $CHCl_3$, for 43% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.97 – 7.94 (m, 2H), 7.63 – 7.58 (m, 1H), 7.51 – 7.46 (m, 2H), 4.70 – 4.67 (m, 1H), 3.82 (s, 3H), 3.57 (dd, *J* = 17.6, 3.9 Hz, 1H), 3.47 (dd, *J* = 17.6, 5.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.6, 174.2, 136.3, 133.7, 128.7, 128.2, 67.2, 52.7, 42.2; FTIR (neat): *v* 3503, 2956, 1744, 1685, 1598, 1581, 1450, 1369, 1220, 1108, 1041 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{12}O_4H^+$: 209.0814, found: 209.0811; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 13.2 min (minor), t_2 = 15.6 min (major).

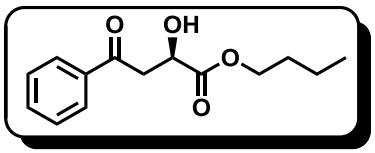
(*R*)-ethyl 2-hydroxy-4-oxo-4-phenylbutanoate (5b)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 88% yield (0.098 g, 89% *ee*): R_f = 0.26 (ethyl acetate : hexane = 1/4), $[\alpha]D^{22}$ = -4.7 (c = 1.86, $CHCl_3$, for 89% *ee*); ^{1}H NMR (300 MHz, CDCl3): δ 7.97 – 7.94 (m, 2H), 7.61 – 7.56 (m, 1H), 7.50 – 7.44 (m, 2H), 4.69 – 4.65 (m, 1H), 4.27 (q, *J* = 7.1 Hz, 2H), 3.55 (dd, *J* = 17.5, 4.0 Hz, 1H), 3.46 (dd, *J* = 17.5, 5.9 Hz, 1H), 3.43 (bs, 1H), 1.28 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 197.5, 173.8, 136.4,

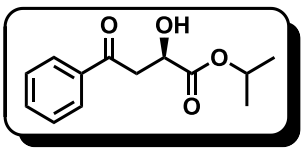
133.6, 128.7, 128.2, 67.2, 61.9, 42.2, 14.1; FTIR (neat): ν 3485, 2982, 2934, 1736, 1686, 1597, 1580, 1449, 1368, 1273, 1215, 1101 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{14}O_4H^+$: 223.0970, found: 223.0969; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 12.2 min (minor), t_2 = 14.7 min (major).

(*R*)-*n*-butyl 2-hydroxy-4-oxo-4-phenylbutanoate (5c)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 92% yield (0.115 g, 73% *ee*): R_f = 0.28 (ethyl acetate : hexane = 1/4), [α]D^{21} = 3.78 (c = 1.72, $CHCl_3$, for 73% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94 – 7.97 (m, 2H), 7.57 – 7.62 (m, 1H), 7.45 – 7.50 (m, 2H), 4.64 – 4.69 (m, 1H), 4.21 (t, *J* = 6.7 Hz, 2H), 3.54 (dd, *J* = 17.5, 4.0 Hz, 1H), 3.45 (dd, *J* = 17.5, 5.9 Hz, 1H), 3.31 (d, *J* = 5.8 Hz, 1H), 1.59 – 1.68 (m, 2H), 1.29 – 1.41 (m, 2H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.5, 173.9, 136.4, 133.6, 128.7, 128.2, 67.2, 65.7, 42.2, 30.5, 19.0, 13.6; FTIR (neat): *v* 3481, 2961, 2874, 1740, 1686, 1597, 1580, 1449, 1368, 1275, 1105 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_4H^+$: 251.1283, found: 251.1284; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 9.8 min (minor), t_2 = 11.4 min (major).

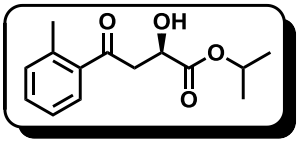
(*R*)-isopropyl 2-hydroxy-4-oxo-4-phenylbutanoate (5d)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 91% yield (0.107 g, 96% *ee*): R_f = 0.27 (ethyl acetate : hexane = 1/4), [α]D^{22} = +2.6 (c = 1.59, $CHCl_3$, for 96% *ee*); ^{1}H NMR (300 MHz, CDCl3): δ 7.97 – 7.94 (m, 2H), 7.62 – 7.57 (m, 1H), 7.50 – 7.45 (m, 2H), 5.20 – 5.08 (m, 1H), 4.62 (dd, *J* = 9.5, 5.2 Hz, 1H), 3.53 (dd, *J* = 17.5, 4.1 Hz, 1H), 3.44 (dd, *J* = 17.4, 5.8 Hz, 1H), 3.36 (d, *J* = 5.5 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ 197.5, 173.4, 136.5, 133.6, 128.7, 128.2, 69.7, 67.3, 42.2, 21.72, 21.66; FTIR (neat): ν 3520, 3019, 2984, 1728, 1682, 1597, 1580, 1449,

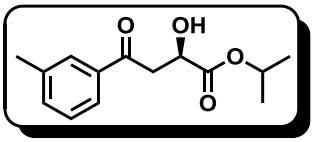
1375, 1215, 1105 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{16}O_4H^+$: 237.1127, found: 237.1136; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 9.4 min (minor), t_2 = 12.0 min (major).

(*R*)-isopropyl 2-hydroxy-4-oxo-4-o-tolylbutanoate (5e)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 81% yield (0.101 g, 94% *ee*): R_f = 0.26 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +2.7 (c = 1.69, $CHCl_3$, for 94% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.9 Hz, 1H), 7.43 – 7.37 (m, 1H), 7.30 – 7.25 (m, 2H), 5.21 – 5.08 (m, 1H), 4.60 – 4.55 (m, 1H), 3.45 (dd, *J* = 17.5, 4.3 Hz, 1H), 3.37 (dd, *J* = 17.6, 5.8 Hz, 1H), 3.31 (d, *J* = 5.6 Hz, 1H), 2.51 (s, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 201.0, 173.5, 138.7, 137.0, 132.1, 131.8, 128.8, 125.8, 69.7, 67.5, 44.8, 21.74, 21.70, 21.4; FTIR (neat): *v* 3489, 2980, 2930, 1732, 1686, 1600, 1570, 1456, 1375, 1265, 1215, 1107 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_4H^+$: 251.1283, found: 251.1290; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 8.7 min (minor), t_2 = 10.7 min (major).

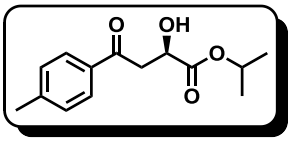
(*R*)-isopropyl 2-hydroxy-4-oxo-4-m-tolylbutanoate (5f)



This compound was prepared by the general procedure described above and was obtained as white solid in 88% yield (0.110 g, 97% *ee*): R_f = 0.26 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +3.3 (c = 1.87, $CHCl_3$, for 97% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, *J* = 7.9 Hz, 2H), 7.42 – 7.31 (m, 2H), 5.21 – 5.01 (m, 1H), 4.62 (d, *J* = 4.2 Hz, 1H), 3.57 – 3.34 (m, 3H), 2.40 (s, 3H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 7.76 – 7.73 (m, 2H), 7.40 – 7.32 (m, 2H), 5.19 - 5.06 (m, 1H), 4.62 (d, *J* = 4.2 Hz, 1H), 3.54 – 3.39 (m, 3H), 2.40 (s, 3H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); FTIR (neat): *v* 3499, 3019, 2982, 1732, 1684, 1605, 1585, 1215, 1105, 756 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_4H^+$: 251.1283, found:

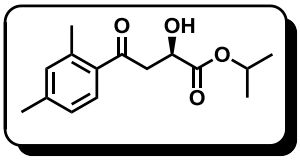
251.1284; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 9.5 min (minor), t_2 = 12.0 min (major).

(*R*)-isopropyl 2-hydroxy-4-oxo-4-p-tolylbutanoate (5g)



This compound was prepared by the general procedure described above and was obtained as white solid in 94% yield (0.118 g, 97% *ee*): R_f = 0.29 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +2.0 (c = 1.92, $CHCl_3$, for 97% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 8.1 Hz, 2H), 7.27 (d, *J* = 8.1 Hz, 2H), 5.21 – 5.07 (m, 1H), 4.61 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.49 (dd, *J* = 17.5, 4.2 Hz, 1H), 3.41 (dd, *J* = 17.9, 6.0 Hz, 1H), 3.37 – 3.34 (m, 1H), 2.42 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 197.2, 173.5, 144.6, 134.2, 129.4, 128.4, 69.7, 67.5, 42.1, 21.80, 21.76, 21.75; FTIR (neat): *v* 3676, 3019, 2934, 1728, 1684, 1607, 1215, 1105 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_4H^+$: 251.1283, found: 251.1287; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 9.3 min (minor), t_2 = 11.9 min (major).

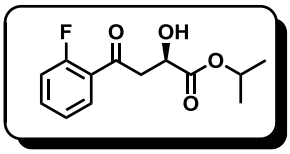
(*R*)-isopropyl 4-(2,4-dimethylphenyl)-2-hydroxy-4-oxobutanoate (5h)



This compound was prepared by the general procedure described above and was obtained as a colourless oil in 80% yield (0.106 g, 95% *ee*): R_f = 0.27 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +1.3 (c = 2.10, $CHCl_3$, for 95% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (d, *J* = 8.6 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 2H), 7.06 (s, 1H), 5.20 – 5.08 (m, 1H), 4.59 – 4.54 (m, 1H), 3.43 (dd, *J* = 17.5, 4.2 Hz, 1H), 3.36 (dd, *J* = 17.1, 5.5 Hz, 1H), 3.34 (d, *J* = 5.8 Hz, 1H), 2.50 (s, 3H), 2.36 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 200.2, 173.6, 142.6, 139.2, 134.0, 133.0, 129.4, 126.4, 69.6, 67.5, 44.5, 21.72, 21.68, 21.63, 21.4; FTIR (neat): *v* 3676, 2980, 2926, 1732, 1682, 1611, 1566, 1267, 1213, 1107 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}O_4H^+$: 265.1440, found: 265.1440; The enantiometric excess was determined by

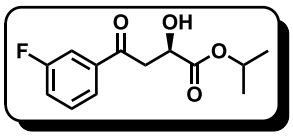
HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 8.0 min (minor), t_2 = 10.1 min (major).

(*R*)-isopropyl 4-(2-fluorophenyl)-2-hydroxy-4-oxobutanoate (5i)



This compound was prepared by the general procedure described above and was obtained as a yellow oil in 60% yield (0.076 g, 93% *ee*): R_f = 0.26 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +5.1 (c = 1.51, $CHCl_3$, for 93% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 – 7.86 (m, 1H), 7.59 – 7.51 (m, 1H), 7.28 –7.12 (m, 2H), 5.20 – 5.08 (m, 1H), 4.58 (dd, *J* = 9.7, 5.4 Hz, 1H), 3.59 – 3.41 (m, 2H), 3.31 (d, *J* = 5.6 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO): δ 195.3 (d, *J* = 3.9 Hz), 173.4, 162.1 (d, *J* = 255.0 Hz), 135.1 (d, *J* = 9.1 Hz), 130.6 (d, *J* = 2.4 Hz), 125.1 (d, *J* = 12.6 Hz), 124.6 (d, *J* = 3.4 Hz), 116.7 (d, *J* = 23.7 Hz), 69.7, 67.1 (d, *J* = 2.7 Hz), 47.1 (d, *J* = 8.1 Hz), 21.7, 21.6; FTIR (neat): *v* 3676, 3082, 3021, 1730, 1686, 1609, 1481, 1452, 1215, 1103cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}FO_4H^+$: 255.1033, found: 255.1033; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/ hexane/*i*-PrOH = 92.5:7.5, 0.75 mL/min): t_1 = 23.2 min (minor), t_2 = 26.9 min (major).

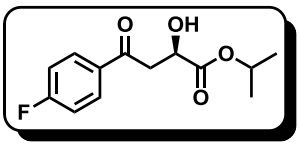
(*R*)-isopropyl 4-(3-fluorophenyl)-2-hydroxy-4-oxobutanoate (5j)



This compound was prepared by the general procedure described above and was obtained as white solid in 85% yield (0.108 g, 93% *ee*): R_f = 0.23 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +6.1 (c = 1.62, $CHCl_3$, for 93% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.75 – 7.72 (m, 1H), 7.66 – 7.61 (m, 1H), 7.50 – 7.42 (m, 1H), 7.32 – 7.26 (m, 1H), 5.20 – 5.07 (m, 1H), 4.63 (dd, *J* = 9.5, 5.1 Hz, 1H), 3.50 (dd, *J* = 17.4, 4.1 Hz, 1H), 3.41 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.38 (bs, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.1, 173.3, 162.8 (d, *J* = 248.3 Hz), 138.6 (d, *J* = 6.5 Hz), 130.4 (d, *J* = 7.6 Hz), 124.0 (d, *J* = 3.0 Hz), 120.6 (d, *J* = 21.5 Hz), 114.9 (d, *J* = 22.4 Hz), 69.8, 67.1, 42.3, 21.68, 21.64; FTIR (neat): *v* 3377, 3019, 2984, 1730, 1692, 1589, 1445, 1215, 1105 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}FO_4H^+$: 255.1033, found:

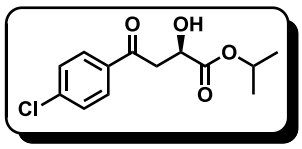
255.1039; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 8.6 min (minor), t_2 = 10.4 min (major).

(*R*)-isopropyl 4-(4-fluorophenyl)-2-hydroxy-4-oxobutanoate (5k)



This compound was prepared by the general procedure described above and was obtained as white solid in 71% yield (0.090 g, 96% *ee*): R_f = 0.31 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +3.9 (c = 1.88, $CHCl_3$, for 96% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.01 – 7.95 (m, 2H), 7.17 – 7.11 (m, 2H), 5.20 – 5.07 (m, 1H), 4.64 – 4.59 (m, 1H), 3.49 (dd, *J* = 17.3, 4.0 Hz, 1H), 3.40 (dd, *J* = 17.3, 5.8 Hz, 1H), 3.32 (d, *J* = 5.6 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 195.8, 173.3, 166.0 (d, *J* = 255.4 Hz), 133.1 (d, *J* = 3.0 Hz), 130.9 (d, *J* = 9.4 Hz), 116.0 (d, *J* = 2.9 Hz), 115.7 (d, *J* = 2.9 Hz), 69.7 (d, *J* = 5.2 Hz), 67.2, 42.1, 21.7 (d, *J* = 2.8 Hz), 21.6 (d, *J* = 2.8 Hz) ; FTIR (neat): *v* 3198, 2984, 2938, 1802, 1732, 1686, 1599, 1468, 1375, 1231, 1103, 1049 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}FO_4H^+$: 255.1033, found: 255.1037; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 10.7 min (minor), t_2 = 12.2 min (major).

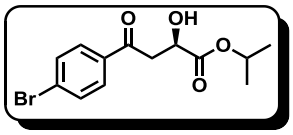
(*R*)-isopropyl 4-(4-chlorophenyl)-2-hydroxy-4-oxobutanoate (5l)



This compound was prepared by the general procedure described above and was obtained as white solid in 82% yield (0.111 g, 97% *ee*): R_f = 0.23 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +5.3 (c = 2.07, $CHCl_3$, for 97% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 7.44 (d, *J* = 8.2 Hz, 2H), 5.19 – 5.07 (m, 1H), 4.64 – 4.59 (m, 1H), 3.48 (dd, *J* = 17.3, 4.1 Hz, 1H), 3.40 (dd, *J* = 17.2, 5.9 Hz, 1H), 3.39 (bs, 1H)., 1.28 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.2, 173.3, 140.1, 134.9, 129.6, 129.0, 69.8, 67.2, 42.1, 21.71, 21.67; FTIR (neat): *v* 3441, 3401, 3019, 2984, 1732, 1682, 1589, 1400, 1215, 816, 756 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}ClO_4H^+$: 271.0737, found: 271.0735; The enantiometric excess was determined

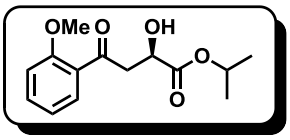
by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 9.9 min (minor), t_2 = 11.0 min (major).

(*R*)-isopropyl 4-(4-bromophenyl)-2-hydroxy-4-oxobutanoate (5m)



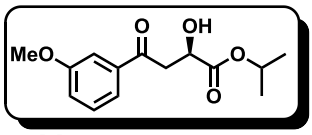
This compound was prepared by the general procedure described above and was obtained as white solid in 85% yield (0.134 g, 98% *ee*): R_f = 0.26 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +3.1 (c = 1.67, $CHCl_3$, for 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84 – 7.79 (m, 2H), 7.64 – 7.59 (m, 2H), 5.17 – 5.09 (m, 1H), 4.63 – 4.60 (m, 1H), 3.48 (dd, *J* = 17.3, 4.1 Hz, 1H), 3.39 (dd, *J* = 17.4, 5.8 Hz, 1H), 3.36 (bs, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.4, 173.3, 135.3, 132.0, 129.7, 128.8, 69.8, 67.2, 42.1, 21.70, 21.66; FTIR (neat): *v* 3516, 3019, 2982, 1730, 1682, 1585, 1466, 1398, 1215, 1105, 752 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}BrO_4H^+$: 315.0232, found: 315.0250; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 10.2 min (minor), t_2 = 11.3 min (major).

(*R*)-isopropyl 2-hydroxy-4-(2-methoxyphenyl)-4-oxobutanoate (5n)



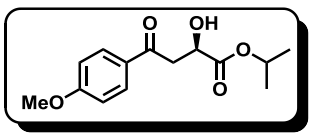
This compound was prepared by the general procedure described above and was obtained as a yellow oil in 83% yield (0.111 g, 92% *ee*): R_f = 0.14 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{22}$ = -1.0 (c = 1.57, $CHCl_3$, for 92% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.79 – 7.75 (m, 1H), 7.52 – 7.46 (m, 1H), 7.03 – 6.96 (m, 2H), 5.19 – 5.06 (m, 1H), 4.58 – 4.52 (m, 1H), 3.92 (s, 3H), 3.57 (dd, *J* = 18.0, 4.0 Hz, 1H), 3.46 (dd, *J* = 18.0, 6.0 Hz, 1H), 3.33 (d, *J* = 5.3 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 198.9, 173.7, 159.0, 134.3, 130.6, 127.1, 120.7, 111.6, 69.4, 67.6, 55.5, 47.7, 21.73, 21.65; FTIR (neat): *v* 3522, 2980, 2940, 1732, 1668, 1597, 1485, 1246, 1105, 1022 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_5H^+$: 267.1232, found: 267.1239; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 15.8 min (minor), t_2 = 22.1 min (major).

(*R*)-isopropyl 2-hydroxy-4-(3-methoxyphenyl)-4-oxobutanoate (5o)



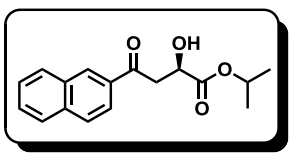
This compound was prepared by the general procedure described above and was obtained as a colourless oil in 85% yield (0.113 g, 95% *ee*): R_f = 0.14 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{22}$ = +2.9 (c = 1.54, $CHCl_3$, for 95% *ee*); ^{1}H NMR (300 MHz, CDCl3): δ 7.54 – 7.47 (m, 2H), 7.41 – 7.35 (m, 1H), 7.15 – 7.11 (m, 1H), 5.20 – 5.07 (m, 1H), 5.20 – 5.07 (m, 1H), 4.62 (dd, *J* = 9.5, 5.1 Hz, 1H), 3.85 (s, 3H), 3.51 (dd, *J* = 17.4, 4.0 Hz, 1H), 3.42 (dd, *J* = 17.4, 5.8 Hz, 1H), 3.37 (d, *J* = 4.4 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.24 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.3, 173.4, 159.9, 137.9, 129.7, 120.8, 120.1, 112.3, 69.7, 67.3, 55.4, 42.3, 21.71, 21.66; FTIR (neat): *v* 3493, 2982, 2939, 1744, 1688, 1597, 1467, 1260, 1105, 1042 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_5H^+$: 267.1232, found: 267.1235; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 12.1 min (minor), t_2 = 15.5 min (major).

(*R*)-isopropyl 2-hydroxy-4-(4-methoxyphenyl)-4-oxobutanoate (5p)



This compound was prepared by the general procedure described above and was obtained as white solid in 88% yield (0.117 g, 98% *ee*): R_f = 0.19 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{21}$ = +0.7 (c = 1.51, for 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.26 (d, *J* = 7.7 Hz, 2H), 5.18 – 5.06 (m, 1H), 4.62 (dd, *J* = 9.5, 5.1 Hz, 1H), 3.52 – 3.37 (m, 3H), 2.40 (s, 3H), 1.27 (d, *J* = 6.3 Hz, 3H), 1.23 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.1, 173.4, 144.4, 134.1, 129.3, 128.5, 128.3, 69.5, 67.3, 42.1, 21.7, 21.6; FTIR (neat): *v* 3566, 3019, 2984, 1730, 1680, 1607, 1215, 1105, 754 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{18}O_5H^+$: 267.1232, found: 267.1227; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 9.7 min (minor), t_2 = 12.4 min (major).

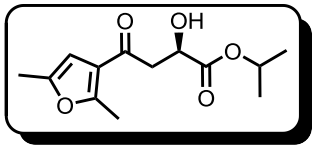
(*R*)-isopropyl 2-hydroxy-4-(naphthalen-2-yl)-4-oxobutanoate (5q)



This compound was prepared by the general procedure

described above and was obtained as a colourless oil in 89% yield (0.127 g, 98% *ee*): R_f = 0.21 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{22}$ = -0.6 (c = 1.60, $CHCl_3$, for 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.46 (s, 1H), 8.02 – 7.94 (m, 2H), 7.89 – 7.85 (m, 2H), 7.63 – 7.52 (m, 2H), 5.21 – 5.10 (m, 1H), 4.72 – 4.67(m, 1H), 3.65 (dd, *J* = 17.4, 4.3 Hz, 1H), 3.58 (dd, *J* = 17.4, 5.9 Hz, 1H), 3.48 (d, *J* = 5.2 Hz, 1H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 197.4, 173.5, 135.8, 133.9, 132.4, 130.1, 129.6, 128.7, 128.6, 127.8, 126.9, 123.6, 69.7, 67.4, 42.3, 21.74, 21.69; FTIR (neat): *v* 3503, 3059, 2982, 2936, 1734, 1680, 1628, 1470, 1375, 1215, 1105 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{18}O_4H^+$: 287.1283, found: 287.1290; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0mL/min): t_1 = 11.2 min (minor), t_2 = 15.6 min (major).

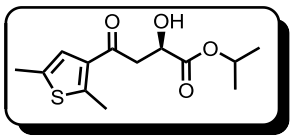
(*R*)-isopropyl 4-(2,5-dimethylfuran-3-yl)-2-hydroxy-4-oxobutanoate (5r)



This compound was prepared by the general procedure described above and was obtained as a yellow solid in 76% yield (0.097 g, 90% *ee*): R_f = 0.22 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{22}$ = +1.2 (c = 1.89, $CHCl_3$, for 90% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.19 (d, *J* = 0.7 Hz, 1H), 5.19 – 5.06 (m, 1H), 4.56 – 4.50 (m, 1H), 3.37 (d, *J* = 5.8 Hz, 1H), 3.20 (dd, *J* = 17.3, 4.2 Hz, 1H), 3.12 (dd, *J* = 17.4, 6.0 Hz, 1H), 2.54 (s, 3H), 2.26 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.5, 173.4, 157.7, 150.2, 121.4, 105.4, 69.5, 67.3, 44.4, 21.71, 21.66, 14.4, 13.2; FTIR (neat): *v* 3508, 2982, 2924, 1732, 1674, 1572, 1402, 1375, 1233, 1107 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}O_5H^+$: 255.1232, found: 255.1240; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 7.9 min (minor), t_2 = 9.4 min (major).

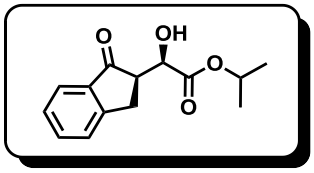
(*R*)-isopropyl 4-(2,5-dimethylthiophen-3-yl)-2-hydroxy-4-oxobutanoate (5s)

This compound was prepared by the general procedure described above and was obtained as a yellow oil in 92% yield (0.124 g, 96% *ee)*: R_f = 0.24 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{22}$ = -0.8 (c = 1.62, $CHCl_3$, for 96% *ee*); ^{1}H NMR (300 MHz,

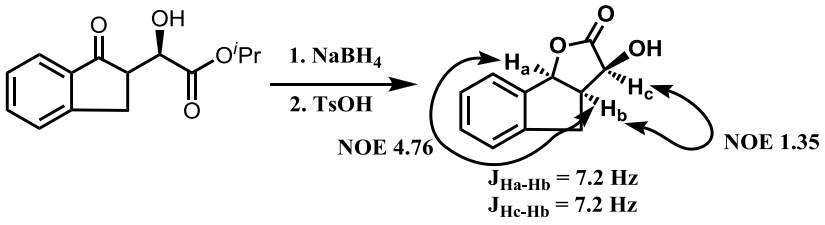


$CDCl_3$): δ 6.98 (d, *J* = 1.0 Hz, 1H), 5.19 – 5.07 (m, 1H), 4.57 – 4.52 (m, 1H), 3.37 (d, *J* = 5.8 Hz, 1H), 3.31 (dd, *J* = 17.5, 4.3 Hz, 1H), 3.24 (dd, *J* = 17.5, 5.7 Hz, 1H), 2.66 (s, 3H), 2.41 (s, 3H), 1.28 (d, *J* = 6.3 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.2, 173.5, 148.5, 135.4, 135.0, 125.8, 69.5, 67.4, 44.9, 21.72, 21.66, 16.09, 15.0; FTIR (neat): *v* 3505, 2980, 2922, 1732, 1670, 1549, 1481, 1373, 1265, 1225, 1107 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{18}O_4SH^+$: 271.1004, found: 271.1005; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 85:15, 1.0 mL/min): t_1 = 9.9 min (minor), t_2 = 12.5 min (major).

(2*R*)-isopropyl 2-hydroxy-2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetate (7)



This compound was prepared by the general procedure described above and was obtained as a yellow oil in 94% yield (0.117 g, 97:3 dr, 98% *ee* (major), 92% *ee* (minor)): R_f = 0.24 (ethyl acetate : hexane = 1/4), $[\alpha]_D^{22}$ = +65.8 (c = 1.51, $CHCl_3$, for 98% *ee*); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.62 – 7.57 (m, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.4 Hz, 1H), 5.22 – 5.10 (m, 1H), 4.91 (dd, *J* = 4.4, 2.1 Hz, 1H), 3.18 – 3.08 (m, 3H), 2.98 (d, *J* = 4.4 Hz, 1H), 1.30 (d, *J* = 3.6 Hz, 3H), 1.28 (d, *J* = 3.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 205.1, 173.6, 154.0, 136.7, 135.0, 127.5, 126.5, 124.1, 70.1, 69.6, 50.0, 26.5, 21.74, 21.68; FTIR (neat): *v* 3503, 2982, 2936, 1712, 1609, 1466, 1281, 1105 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{16}O_4H^+$: 249.1127, found: 249.1123; The enantiometric excess was determined by HPLC analysis employing Daicel Chiracel AS-H column (hexane/*i*-PrOH = 97:3, 1.25 mL/min): (major diastereomer) t_1 = 32.3 min (minor), t_2 = 49.5 min (major); (minor diastereomer) t_3 = 27.9 min (minor), t_4 = 40.4 min (major).



(3*S*)-3-hydroxy-3,3a,4,8b-tetrahydro-2H-indeno[1,2-b]furan-2-one (8)

To a solution of (2*R*)-isopropyl 2-hydroxy-2-(1-oxo-2,3-dihydro-1H-inden-2-yl)acetate (0.124 g, 0.5 mmol) in MeOH (2 mL) was added $NaBH_4$ (0.038 g, 1.0 mmol) at -20 °C. The reaction mixture was stirred for 30 minutes, and the reaction was quenched by addition of acetone. The mixture was kept stirring for 10 minutes, and then saturated NH_4Cl aqueous solution was added. The mixture was extracted with CH_2Cl_2 three times, and the extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a crude alcohol. To a solution of the crude product in CH_2Cl_2 (2 mL) was added $TsOH•H_2O$, and the reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by addition of a saturated $NaHCO_3$ aqueous solution, and was extracted with CH_2Cl_2 three times. The extract was dried over anhydrous $MgSO_4$. The solvents were evaporated to give a residue, followed by purification on silica gel chromatography to afford the title compound as a yellow oil in 67% yield (0.064 g); R_f = 0.26 (ethyl acetate/hexane = 1/4); $[\alpha]_D^{21}$ = 81.32 (c = 1.30, $CHCl_3$, for 98% *ee*) ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (d, *J* = 7.5 Hz, 1H), 7.36 – 7.26 (m, 3H), 5.94 (d, *J* = 7.2 Hz, 1H), 4.12 (dd, *J* = 7.2, 3.4 Hz, 1H), 3.92 (d, *J* = 3.6 Hz, 1H), 3.31 – 3.23 (m, 2H), 3.16 –3.10 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 178.2, 141.7, 138.5, 130.0, 127.7, 125.81, 125.79, 85.2, 73.6, 46.1, 34.9; FTIR (neat): *v* 3429, 2928, 2857, 1769, 1609, 1462, 1317, 1182, 1119, 995, 743 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{10}O_3H^+$: 191.0708, found: 191.0712.

List of Publication and Award

1. **Jun-Feng Zhao,** Yu-Jun Zhao and Teck-Peng Loh, Indium tribromide-promoted arene-terminated epoxy olefin cyclization, *Chem. Commun*. **2008,** 1353-1355.
2. **Jun-Feng Zhao,** Hoi-Yan Tsui, Pei-Jia Wu, Jun Lu and Teck-Peng Loh, Highly enantio- selective carbonyl-ene reactions catalyzed by In(III)-pybox complex, *J. Am. Chem. Soc.* **2008,** *130*, 16492-16493. (Highlighted by *SYNFACT*, **2009**, 2, 0187 and **2009**, 3, 0283.)
3. **Jun-Feng Zhao,** and Teck-Peng Loh, Acid-catalyzed intramolecular [2 + 2] cycloaddition of ene-allenones: facile access to bicyclo[n.2.0] frameworks, *Angew. Chem. Int. Ed.* **2009,** *48*, 7232-7235.
4. **Jun-Feng Zhao,** Teguh-Budiono Tjan, Boo-Hong Tan and Teck-Peng Loh, Highly enantioselective ketone-ene reactions of trifluoropyruvate: significant counterion effect of the In(III)-pybox complex, *Org. Lett.* **2009,** *11*, 5714-5716. (Highlighted by *SYNFACT*, **2010**, 2, 0206.)
5. Ming-Kui Zhu, **Jun-Feng Zhao**, Teck-Peng Loh, Palladium-Catalyzed Oxime Assisted Intramolecular Dioxygenation of Alkenes with 1 atm of Air as the Sole Oxidant *J. Am. Chem. Soc.* **2010,** *132*, 6294-6295.
6. **Jun-Feng Zhao,** Boo-Hong Tan, Ming-Kui Zhu, Teguh-Budiono Tjan, and Teck-Peng Loh, Enantioselective carbonyl-ene reactions of trifluoropyruvate in ionic liquid via a recyclable In(III)-pybox complex, *Adv. Synth. & Catal*. **2010,** *352*, 2085-2088.
7. **Jun-Feng Zhao**, Teguh-Budiono Tjan, and Teck-Peng Loh, Significant counterion effect of In(III)-pybox complex in highly enantioselective carbonyl-ene reactions of glyoxylate, *Tetrahedron Lett.* **2010,** *51*, 5649-5652**.**
8. **Jun-Feng Zhao,** Boon-Hong Tan and Teck-Peng Loh, In(III)-pybox complex catalyzed enantioselective Mukaiyama aldol reactions of glyoxylates and enolsilanes derived from aryl ketones, *Chem. Sci.* **2011,** in press**.**

Conference papers

1. **Jun-Feng Zhao,** Yu-Jun Zhao and Teck-Peng Loh, Lewis acid mediated epoxide opening intiated polyene cyclization in aqueous media, **5th PERCH-CIC Congress, Pattaya, Thailand, May 6-9, 2007**.
2. **Jun-Feng Zhao,** and Teck-Peng Loh, In(III)-Pybox complex catalyzed highly enantioselective carbonyl-ene reactions, ***the ACS National Meeting & Exposition, Fall 2009***.
3. **Jun-Feng Zhao,** and Teck-Peng Loh, Lewis Acid Catalyzed Intramolecular [2 + 2]-Cycloaddition of Ene-allenones, **6th Asia Euro Symposium, 2010.**
4. **Jun-Feng Zhao,** and Teck-Peng Loh, In(III)-Pybox Complex Catalyzed Enantioselective Mukaiyama Aldol Reactions of Glyoxylates and Silyl Enol Ethers Derived from Aryl Ketones, **6th Asia Euro Symposium, 2010.**
5. **Jun-Feng Zhao,** and Teck-Peng Loh, In(III)-PyBox Complex Catalyzed Highly Enantioselective Carbonyl-Ene Reactions, **6th Asia Euro Symposium, 2010.**
6. Ming-Kui Zhu, **Jun-Feng Zhao**, Teck-Peng Loh, Palladium-Catalyzed Oxime Assisted Intramolecular Dioxygenation of Alkenes with 1 atm of Air as the Sole Oxidant, **6th Asia Euro Symposium, 2010.**

Awards

1. Chinese Government Award for Outstanding Self-financed Students Abroad (**2009)**
2. Best Poster Award, **6th Asia Euro Symposium, 2010.**
3. Humboldt Research Fellowship for Postdoctoral Researchers (**2011-2013).**