DESIGN OF CHIRAL INDIUM COMPLEXES FOR ENANTIOSELECTIVE CARBON-CARBON BOND FORMATION REACTIONS

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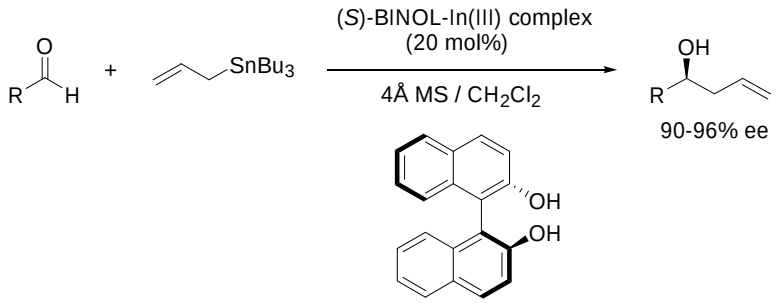
SUMMARY

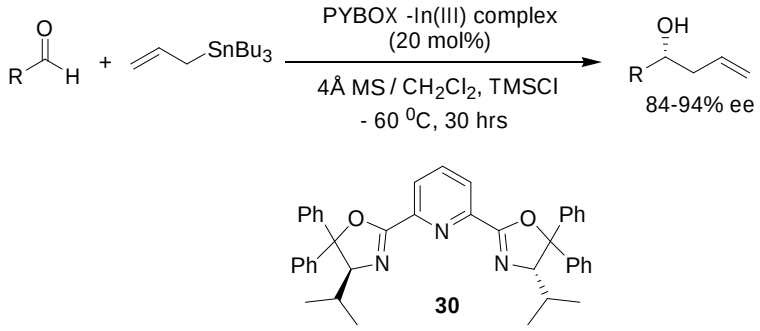
This thesis involves the design of two novel chiral indium complexes, namely (*S*)-BINOL-$InCl_3$ and (*S*,*S*)-*i*-Pr-PYBOX-$In(OTf)_3$ and their application for various catalytic enantioselective organic transformations.

I. CATALYTIC ENANTIOSELECTIVE ALLYLATION OF ALDEHYDES

A novel chiral indium complex generated from indium(III) chloride and (*S*)-1,1-Bi-2-naphthol (BINOL) has been discovered to effect high enantioselectivities in the catalytic enantioselective addition of allyltributylstannanes to aldehydes. It is important to note that allyltributylstannanes facilitates the formation of the chiral indium complex. The allylation of a variety of aromatic, α-β-unsaturated and aliphatic aldehydes resulted in good yields and high enantioselectivities (90-96% ee). Moreover, the successful application of this chiral BINOL-In(III) catalyst for the enantioselective allylation of aldehydes in ionic liquid [hmim][PF_6^-] as an environmentally benign reaction media was also achieved with moderate to good enantiomeric excess (70 - 90% ee) for aromatic and α-β-unsaturated aldehydes.

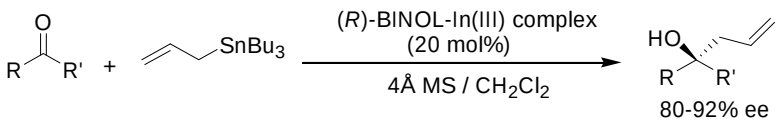


Another effective approach towards the synthesis of optically pure secondary homoallylic alcohols was accomplished by the reaction of aldehydes with allyltributylstannanes catalyzed by another novel chiral indium(III) complex prepared from modified (*S*,*S*)-PYBOX **30** ligand and $In(OTf)_3$. The allylation of a variety of aromatic, α-β-unsaturated and aliphatic aldehydes afforded the products in good yields and high enantioselectivities (up to 94% ee).

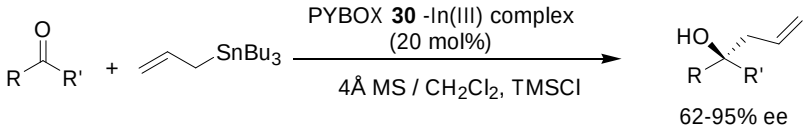


II. CATALYTIC ENANTIOSELECTIVE ALLYLATION OF KETONES

The successful extension of the two novel chiral Indium(III) complexes, (*S*)-BINOL-$InCl_3$ and (*S*,*S*)-PYBOX-$In(OTf)_3$ to catalytic enantioselective allylation of ketones was achieved. The BINOL-In(III) chiral indium complex has been discovered to effect high enantioselectivities in the addition of allyltributylstannanes to ketones. The allylation of a variety of aromatic, α-β-unsaturated, cyclic aromatic and aliphatic ketones resulted in good yields and high enantioselectivities (up to 92% ee).

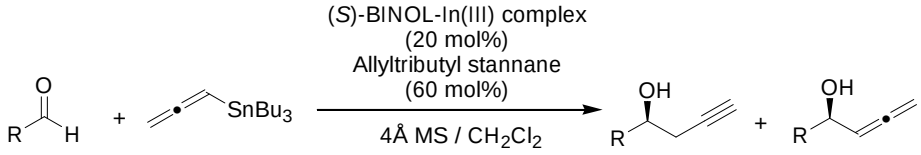


Moreover, the (*S*,*S*)-PYBOX-In(III) complex was also effective in catalyzing the enantioselective addition of allyltributylstannanes to a variety of aromatic, α-β-unsaturated, cyclic aromatic and aliphatic ketones. The corresponding tertiary homoallylic alcohols were isolated in good yields and moderate to high enantioselectivities (up to 95% ee).

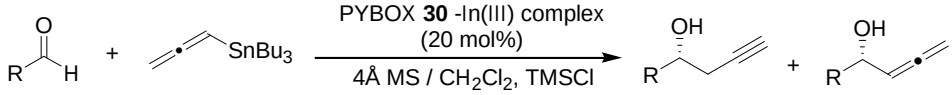


III. CATALYTIC ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF ALDEHYDES

The application of the two newly developed chiral indium metal complexes for the catalytic enantioselective propargylation and allenylation of aldehydes was realized in this part of the thesis. The chiral BINOL-In(III) indium complex has been shown to effect high enantioselectivities in catalyzing enantioselective allenylation and homopropargylation reaction. The addition of allenyltributylstannanes to a variety of aldehydes including aromatic, α,β-unsaturated and aliphatic aldehydes afforded the respective propargyl and allenyl alcohols in good yields and high enantioselectivities (up to 92% ee for propargylic and 90% ee for allenylic).

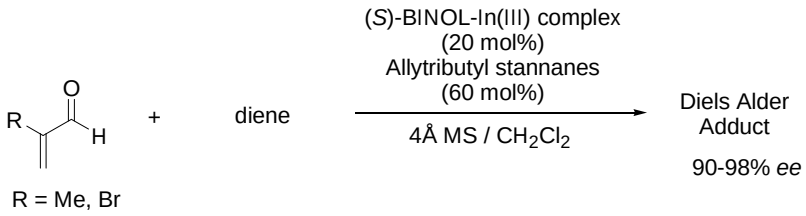


Similarly, the (*S,S*)-PYBOX-In(III) complex was also effective in catalyzing the enantioselective addition of allenyltributylstannanes to a variety of aromatic, α-β-unsaturated and aliphatic aldehydes. The corresponding propargylic and allenylic alcohols were isolated in good yields and moderate to high enantioselectivities (up to 88% ee for propargylic and 90% ee for allenylic).

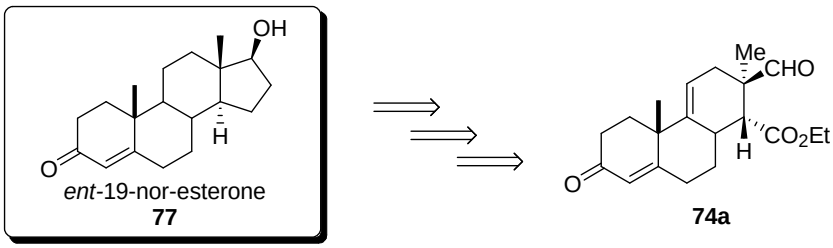


IV. CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTION

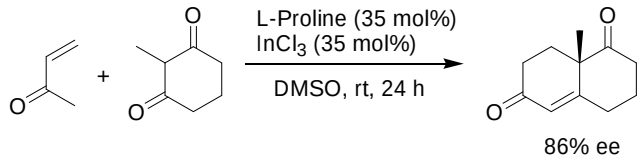
In this part, the successful application of the chiral (*S*)-BINOL-In(III) complex as precatalyst and allytributylstannane as activator to catalyze enantioselective Diels-Alder reaction was realized. The cycloaddition of a variety of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein resulted in good yields and excellent enantioselectivities (up to 98% ee).



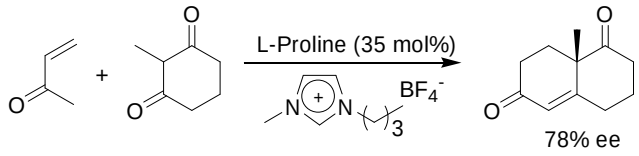
The application of the (*S*)-BINOL-In(III) complex for the construction of ring C in the steroidal scaffold **74a** was undertaken in this part of the thesis. **74a** was envisioned to be a key intermediate in the total synthesis of *ent*-19-nor-testosterone **77**.



In addition, the Wieland Miescher ketone was obtained with higher yield and enantiopurity via the introduction of the equimolar of Lewis acid $InCl_3$ to the L-proline catalyzed Robinson annulation reaction along the synthesis route towards **74a.**



The first L-proline catalyzed Robinson annulation in imidazolium-based ionic liquid [bmim][BF_4^-] was also successfully realized with good enantioselectivity and the catalyst could be reused for up to 5 times with comparable yields and enantioselectivity.



LIST OF ABBREVIATIONS

*Aux	chiral auxiliary
Ac	Acetyl
anhyd.	Anhydrous
Ar	Aryl
aq	Aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-napthol
Bn	Benzyl
b.p.	boiling point
brs	broad singlet
c	Concentration
CAB	(acyloxy)borane
cald	Calculated
cat.	Catalyst
°C	degree centigrade
d	Density
d	Doublet
dd	doublet of doublet
ddd	doublet of a doublet of a doublet
de	Diastereomeric excess
DMAP	4-*N*,*N*-dimethylamino pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ee	enantiomeric excess
EI	electron-impact ionization
equiv.	equivalent(s)
ESI	electrospray ionization
Et	Ethyl
FGI	Functional group interconversion

FTIR	fourier transform infrared spectrometry
g	Gram
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
M	molar concentration
m	Multiplet
m/z	mass per charge ratio
M^+	parent ion peak (mass spectrum)
Me	Methyl
MHz	mega hertz
min	minute(s)
mL	Milliliters
μL	Microlitres
mmol	Millimole
mol%	mole percent
m.p.	melting point
MS	mass spectrometry
ms	molecular sieves
nm	nanometres
NMR	Nuclear magnetic resonance
Nu	nucleophile
OTf	trifluoromethane sulfonate (triflate)
p	Para
Ph	Phenyl
ppm	parts per million
Pr	Propyl
Py	Pyridine

PYBOX	bis(oxazolinyl)pyridine
q	Quartet
qn	Quintet
R_f	retention factor
R_t	retention time
rbf	round-bottom flask
rt	room temperature
s	Singlet
t	Triplet
^{t}Bu	*tert*-but(yl)
td	triplet of doublets
tert	Tertiary
temp.	temperature
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tf	Trifluoromethanesulfonyl
Ts	*p*-toluenesulfonyl (tosyl)
tt	triplet of triplets
UV	Ultraviolet
vol.	volume

CHAPTER 1

Catalytic Enantioselective Allylation of Aldehydes

1.1 OVERVIEW OF ENANTIOSELECTIVE ALLYLATIONS OF ALDEHYDES

Over the last few decades, homoallylic alcohols have become an indispensable moiety for the construction of complex organic molecules, securing its widespread involvement in both natural products and medicinal agent synthesis.[1] Being important building blocks and versatile synthons, homoallylic alcohols are featured in many medicinal agents such as Prostaglandin E_3,[2] Prostaglandin F_{3a},[2] (+)-Amphidinolide K,[3] and Leukotriene B_4[4], etc (Figure 1).

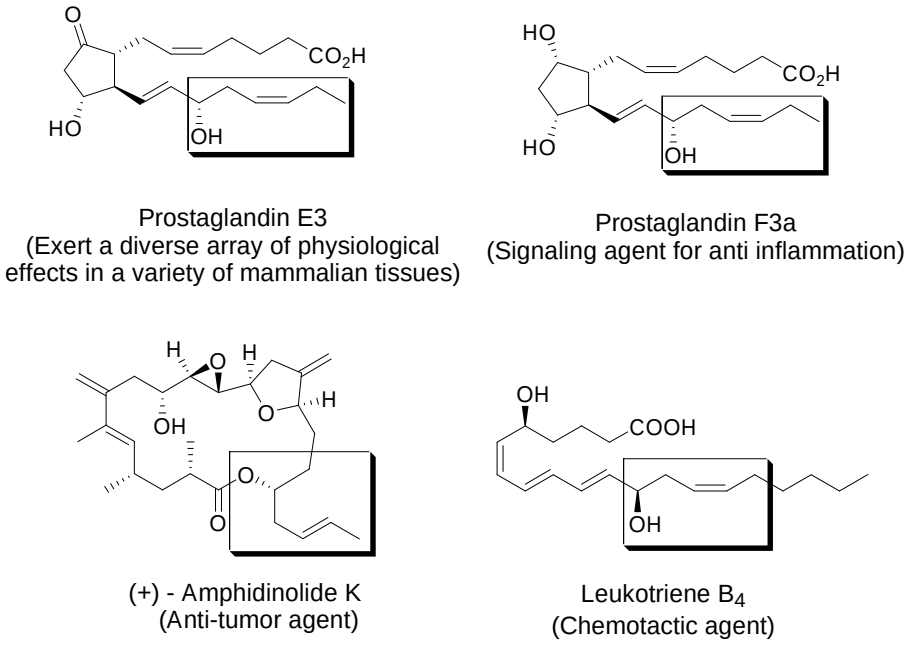


Figure 1. Importance of homoallylic alcohols

[1] (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.

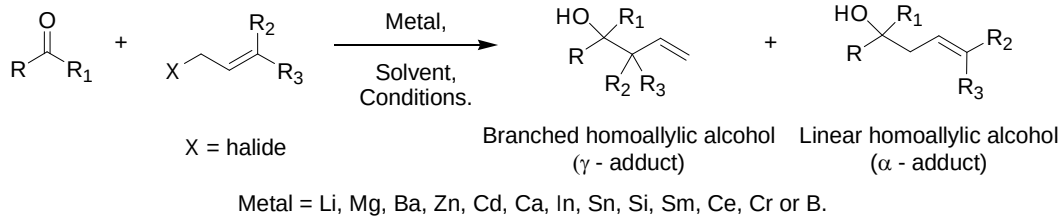
[2] (a) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. K. *J. Am. Chem. Soc*. **1971**, *93*, 1490. (b) Corey, E. J.; Albonico, S. M.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc*. **1971**, *93*, 1491. (c) Corey, E. J.; Ohuchida, S.; Hahl, R. *J. Am. Chem. Soc*. **1984**, *106*, 3875.

[3] William, D. R.; Meyer, K. G. *J. Am. Chem. Soc*. **2001**, *123*, 765.

[4] For the first total synthesis, see: (a) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984. For the recent stereocontrolled total synthesis, see: (b) Kerdesky, F.; Schmidt, S. P.; Brooks, D. W. *J. Org. Chem.* **1993**, *58*, 3516.

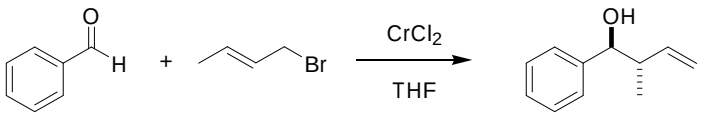
Accordingly, there has been much attention focus in the development of new methodologies for the synthesis of homoallylic alcohols. Among the many such transformations, the most frequently employed methodology for the synthesis of homoallylic alcohols is the allylation of aldehydes and ketones by allylic metals (Scheme 1.1).[5] The use of organometallic reagents is so common that hardly any synthesis is now complete without the inclusion of at least one step involving an organometallic reagent.

Beginning in the late 1970s, considerable synthetic interest began to surface in the stereochemical control of carbon-carbon bond formation in the reactions of allylmetals with aldehydes and ketones. This widespread use of allylic organometallics in stereocontrolled organic synthesis appears to be triggered by the following discoveries: Heathcock's breakthrough that the Hiyama (*E*)-crotylchromium reagent undergoes highly *anti*-selective addition to aldehydes (Scheme 1.2);[5] Hoffmann's discovery that (*Z*)-crotylboronates produce *syn*-homoallylic alcohols stereoselectively;[5] and Yamamoto's innovation that the Lewis acid mediated reaction of crotyltins with aldehydes produces *syn*-homoallylic alcohols regardless of the geometry of the double bond of the allylic tins (Scheme 1.3).[5]

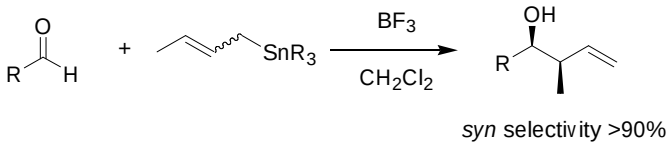


Scheme 1.1 Metal mediated allylation of aldehydes and ketones

[5] (a) Buse, C. T.; Heathcock, C. H. *Tetrahedron Lett.* **1978**, 1685. (b) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 306. (c) Yamamoto, Y.; Yatagi, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107.

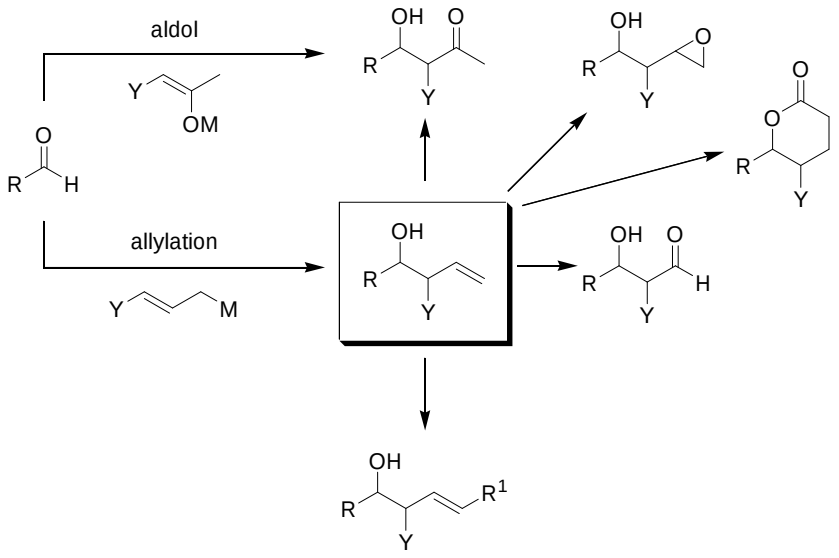


Scheme 1.2 Heathcock's discovery of *anti*-selective addition to aldehydes



Scheme 1.3 Yamamoto's report on addition of crotyltrialkyltins to aldehydes

From a synthetic point of view, the ready formation of homoallylic alcohols into the corresponding aldols rendered the addition of organometallic allylic reagents to carbonyls, a complementary parallel to the aldol additions of metal enolates. Furthermore, the great versatility of the alkene functionality in their capability for various transformations, notably, conversion to the aldehydes *via* ozonolysis, facile one-carbon homologation to δ-lactones *via* hydroformylation, selective epoxidation for introduction of a third stereogenic center, and cross olefin metathesis to various linear homoallylic alcohol fragments, offered the addition of allylic metals considerable advantages over the aldol counterpart (Scheme 1.4).



Scheme 1.4 Versatile building block – homoallylic alcohol

The development of new highly enantioselective carbon-carbon bond forming methods is a continuing interest to organic chemists.[6] In this respect, extensive efforts have been devoted to the exploration of chiral reagents and catalysts for the carbonyl-allylation and carbonyl-ene reactions not least due to the fact that the resulting homoallylic alcohols are versatile building blocks in the synthesis of many natural products and pharmaceuticals.[7] In the past two decades, many enantioselective allylation[8] methods have been developed based on either chiral allylation reagents or chiral catalysts.

Enantioselective Allylation with Allylic Boron

The most well studied and widely used chiral allylation reagents are allylboranes.[9] A series of chiral *B*-allylborolanes **1-6** have been successfully developed (Figure 2). These chiral reagents have been frequently utilized in many natural products synthesis (Scheme 1.5).

---

[6] Ojima, I. In *Catalytic Asymmetric Synthesis*, Wiley-VCH, 2000.
[7] Mikami, K.; Shimuzu, M. *Chem. Rev.* **1992**, *92*, 1021.
[8] For Reviews, see (a) Denmark, S. C.; Fu, J.-P. *Chem. Rev.* **2003**, *103*, 2752 and references therein. For representative examples see (b) Aoki, S.; Mikami, K.; Terada, M.; Nakai, T. *Tetrahedron* **1993**, *49*, 1783. (c) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (d) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (e) Keck, G. E.; Geraci, L. S. *Tetrahedron Lett.* **1993**, *34*, 7827. (f) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (g) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996**, *118*, 4723. (h) Yanagisawa, A.; Ishiba, A.; Nakashima, H.; Yamamoto, H. *Synlett* **1997,** 88. (i) Yanagisawa, A.; Nakatsuka, Y.; Nakashima, H.; Yamamoto, H. *Synlett* **1997**, 933. (j) Yanagisawa, A; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matsumoto, Y.; Yamamoto, H. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3701. (k) Yanagisawa, A.; Nakashima, H.; Nakatsuka, Y; Ishiba, A.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1129. (l) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708.
[9] (a) Racherla, U. S.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 401. (b) Roush, W. R.; Walts, A. E.; Hoong, L.-K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (c) Ito, H.; Tanikawa, S.; Kobayashi, S. *Tetrahedron Lett.* **1996**, *37*, 1795. (d) Schreiber, S.; Groulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. (e) Corey, E. J.; Yu, C.-M.; Kim, S.-S. *J. Am. Chem. Soc.* **1989**, *111*, 5495. (f) Roush, W. R.; Hoong, L.-K.; Palmer, M. A. G.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109.

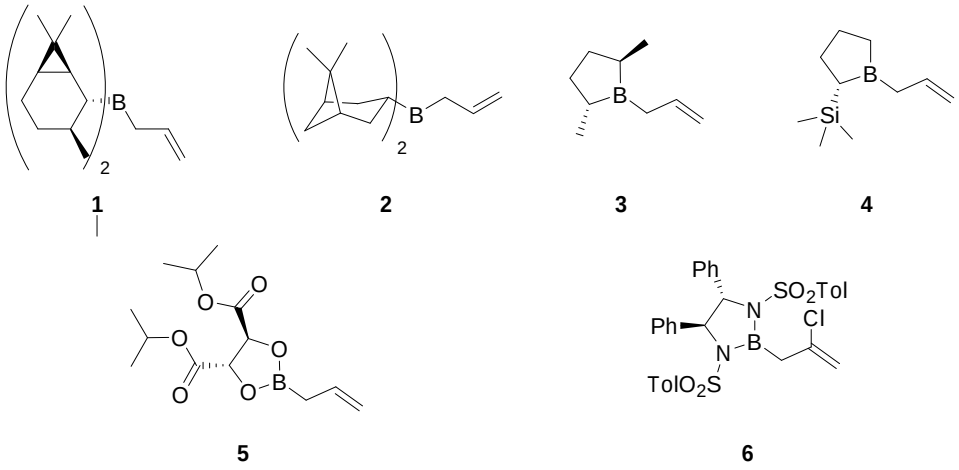
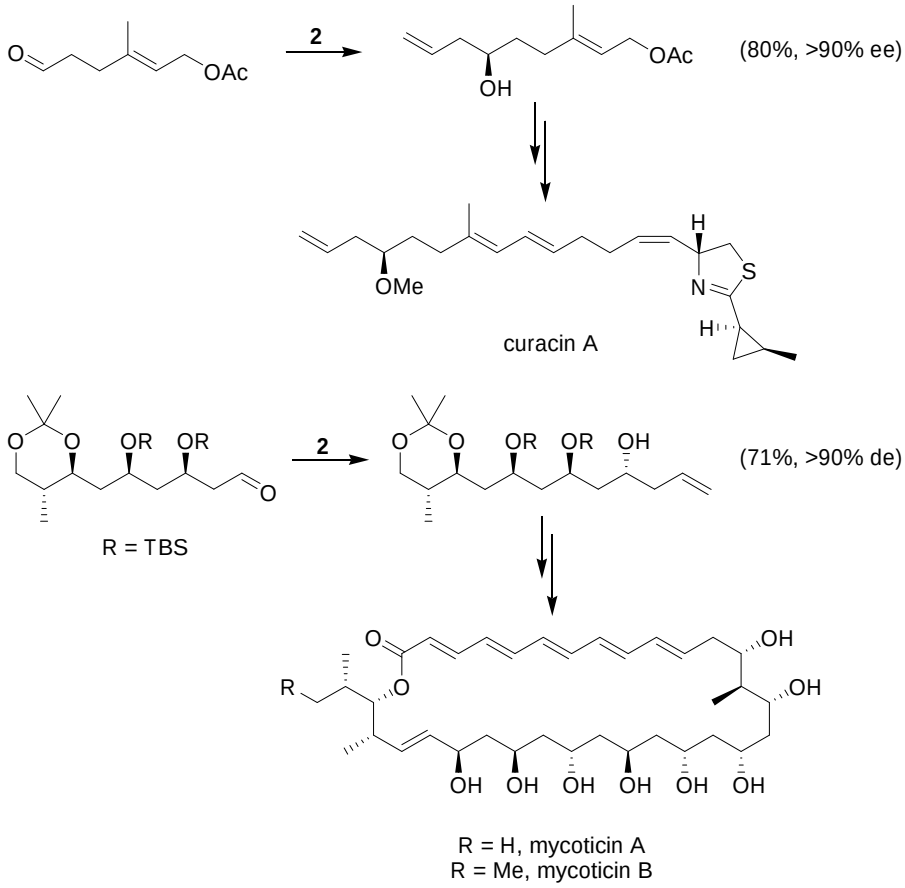


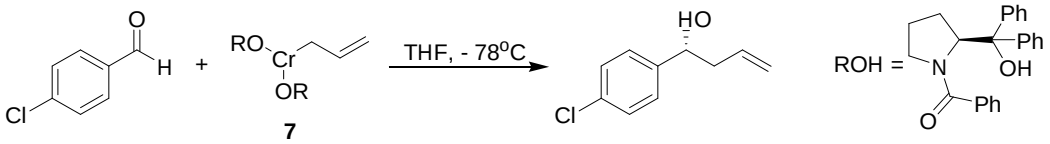
Figure 2. Representative chiral *B*-allylborolanes



Scheme 1.5 Application of chiral *B*-allylborolanes in natural product synthesis

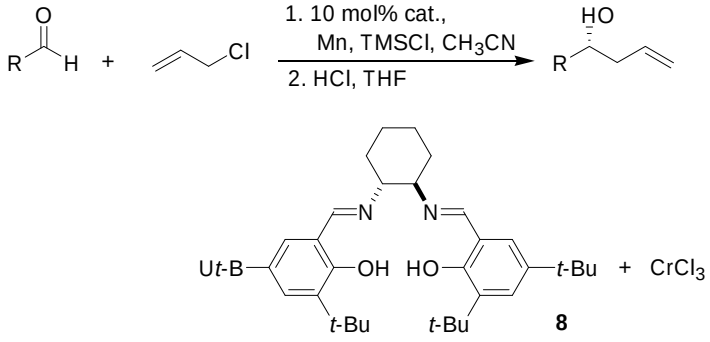
Enantioselective Allylation with Allylic Chromium

A dialkoxyallylchromium complex with *N*-benzoyl-L-proline **7** as chiral ligand gave excellent stereoselectivities in allylation reactions with aldehydes (Scheme 1.6).[10]



Scheme 1.6 Chiral allylchromium reagent for allylation

In the presence of 10 mol% of a chiral chromium salen complex **8**, allylic chloride reacted with both aromatic and aliphatic aldehydes affording the homoallylic alcohols with high enantioselectivities (Scheme 1.7).[11]

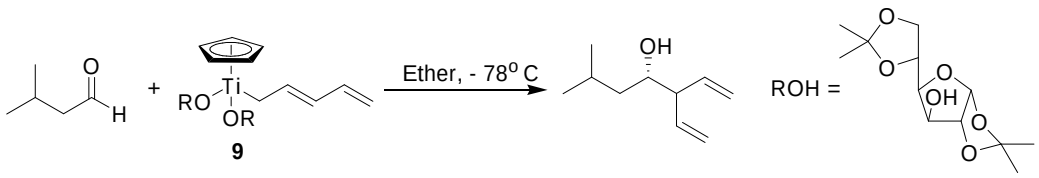


Scheme 1.7 Chiral chromium complex for allylation

[10] Sugimoto, K.; Aoyagi, S.; Kobayashi, C. *J. Org. Chem.* **1997**, *62*, 2322.
[11] Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Umani-Ronchi, A. *Angew. Chem., Int. Ed. Engl.* **1999**, *38,* 3357.

Enantioselective Allylation with Allylic Titanium

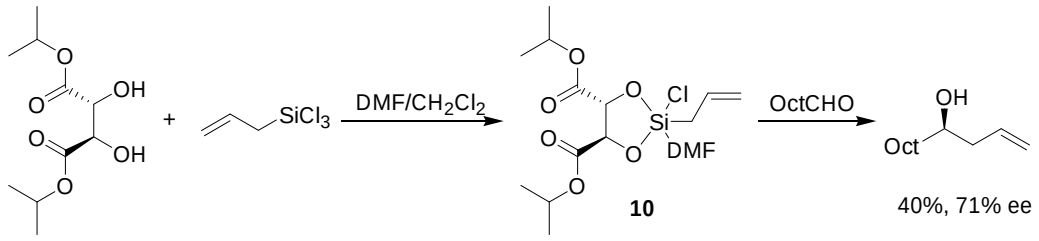
Organotitanates modified with a carbohydrate auxiliary **9** were also successfully applied to the enantioselective allylations of aldehydes (Scheme 1.8).[12]



Scheme 1.8 Chiral allyltitanium reagent for allylation

Enantioselective Allylation with Allylic Silanes

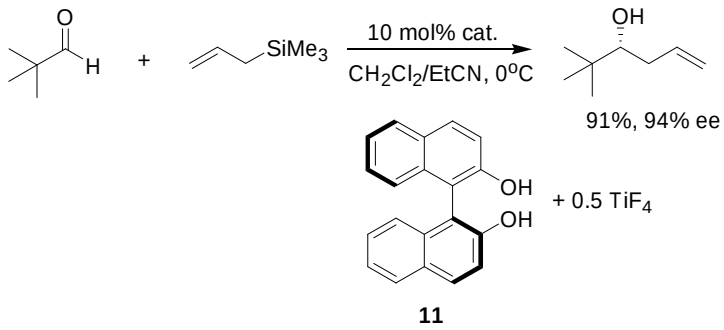
Allyltrichlorosilane, pretreated with (+)-diisopropyl tartrate **10**, has been used to react with aldehydes to afford optically active alcohols up to 71% ee (Scheme 1.9).[13]



Scheme 1.9 Chiral allylsilane reagent for allylation

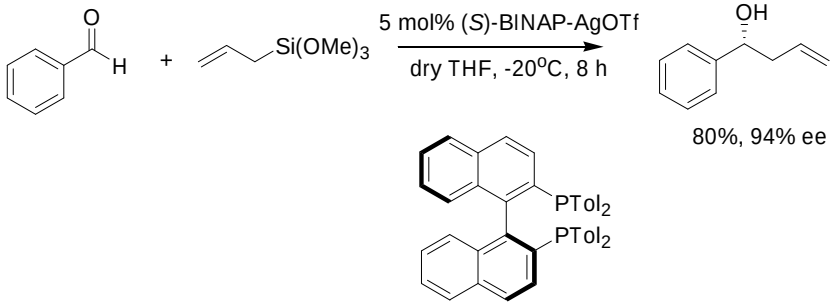
[12] Riediker, M.; Duthaler, R. O. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 494.
[13] Wang, Z.; Wang, D.; Sui, X.-J. *J. Chem, Soc., Chem. Commun.* **1996**, 2261.

The allylation of carbonyl functionality using allylic silanes was found to be promoted effectively in the presence of metal fluorides. A TiF_4-based chiral catalyst **11** was demonstrated to expedite the allylation reaction to afford the homoallylic alcohols in excellent yields and enantioselectivities (Scheme 1.10).[14]



Scheme 1.10 Chiral (*S*)-BINOL-Ti complexes for allylation

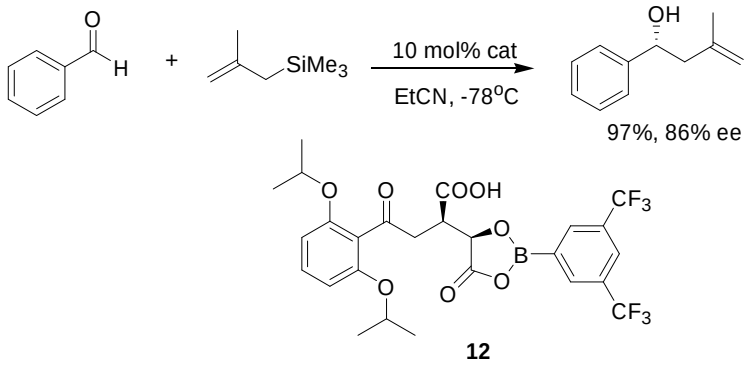
The catalytic system of (*S*)-BINAP-AgOTf was demonstrated to effect the allylation transformation using allylic silanes. A complex generated from *p*-Tol-BINAP and silver fluoride was able to accelerate the allylation with allyltrimethoxysilane as the allylating source (Scheme 1.11).[15]



Scheme 1.11 Chiral (*S*)-BINAP-AgOTf complexes for allylation

[14]Gauthier, D. R. Jr.; Carreirra, E. M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2363.
[15] Yanagisawa, A.; Kageyama, H.; Nakatsuka, Y.; Asakawa, K.; Matrumoto, Y.; Yamamoto, H *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3701.

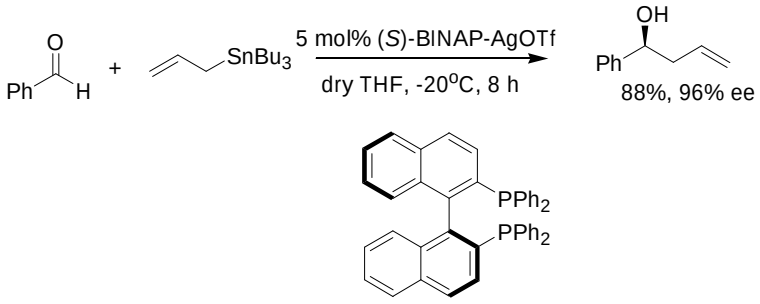
In the presence of a chiral (ACYLOXY)borane (CAB) complex **12**, derived from tartaric acid, allylic silanes reacted with achiral aldehydes to give the corresponding adducts in good yields with high enantioselectivity (Scheme 1.12).[16]



Scheme 1.12 Chiral CAB complexes for allylation

Enantioselective Allylation with Allylic Stannanes

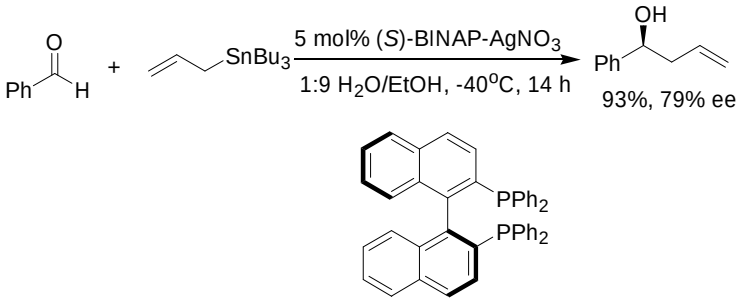
In the presence of 5 mol% of (*S*)-BINAP-AgOTf complex, allylic stannane reacted with both aromatic and olefinic aldehydes to afford the homoallylic alcohols with high enantioselectivities (Scheme 1.13).[17]



Scheme 1.13 Chiral (*S*)-BINAP-AgOTf complexes for allylation

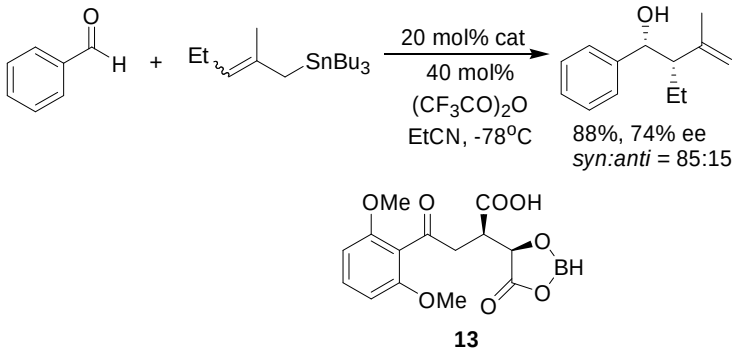
[16] Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490.
[17] Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc*. **1996**, *118*, 4723.

The (*S*)-BINAP-AgOTf complex was modified and extended to catalytic enantioselective allylation of aldehydes in aqueous media (Scheme 1.14).[18] The reaction with aromatic aldehydes afforded the allyl adducts with good selectivity up to 79% ee.



Scheme 1.14 Chiral (*S*)-BINAP-AgOTf complexes for allylation in aqueous media

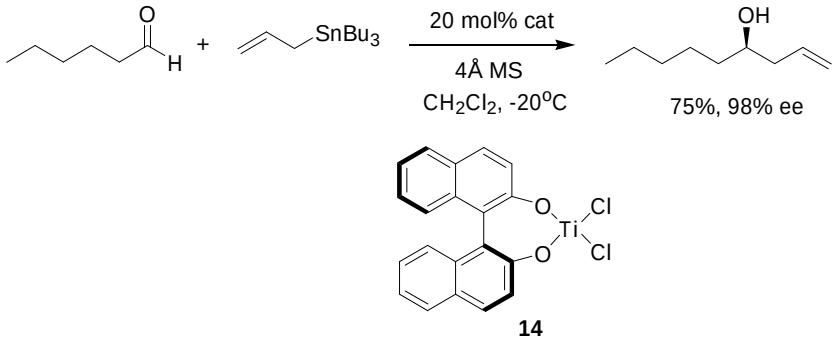
The scope of the CAB catalysts was extended to the allylation with allylic stannanes. With a catalytic amount of the catalyst **13**, the allylation adduct of benzaldehyde was obtained with 74% ee for the major *syn* isomer (Scheme 1.15).[19]



Scheme 1.15 Chiral CAB complexes for allylation

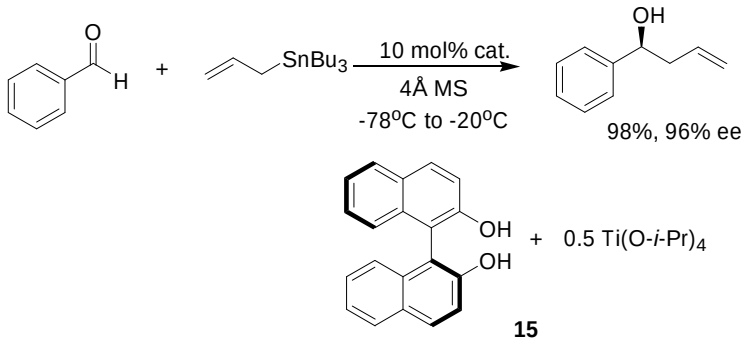
[18] Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **1999**, *41*, 5261.
[19] Marshall, J. A.; Tang, Y. *Synlett* **1992**, 653.

One of the most extensively studied chiral Lewis acid-catalyzed allylation reactions employed titanium complexes of the readily available 1,1'-binaphthalene-2,2'-diol (BINOL) complexes with Ti (IV) Lewis acids as the catalysts. Under the influence of the titanium complex **14** prepared from $TiCl_2(O\text{-}i\text{-}Pr)_2$ and (*S*)-BINOL, aliphatic aldehydes reacted with allyltributylstannane with a high degree of stereoselectivity (Scheme 1.16).[20]



Scheme 1.16 Chiral (*S*)-BINOL-$TiCl_2$ complexes for allylation

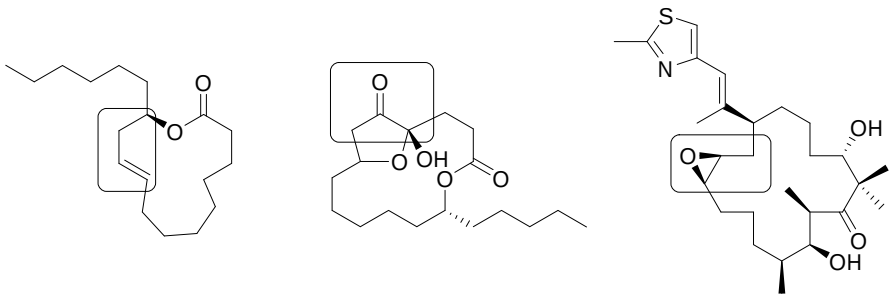
A similar type of titanium catalysts **15** has been developed for the allyltributylstannane allylation of aldehydes. The system display broad substrate generality and high level of stereocontrol (Scheme 1.17).[21]



Scheme 1.17 Chiral (*S*)-BINOL-$Ti(O\text{-}i\text{-}Pr)_2$ complexes for allylation

[20] Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc*. **1993**, *115*, 7001.
[21] Keck, G. E.; Tarbet, K. H.; Geraci, L. S. A. *J. Am. Chem. Soc*. **1993**, *115*, 8467.

The above methodology has been successfully applied in the total syntheses of (*R*)-ricinelaidic lactone, (-)-gloeosporone[22] and epothilone A.[23]



(R)-ricinelaidic acid lactone | (-)-gloeosporone | epothilone A

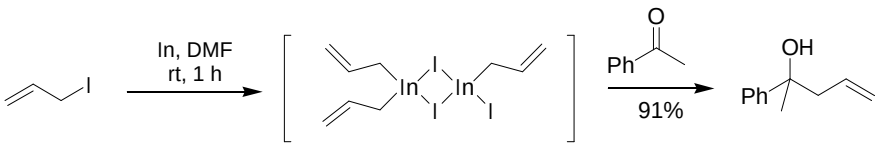
Enantioselective Allylation with Allylic Indium

Among the many organoindium compounds, allylic indium is without doubt one of the most widely used reagents in organic synthesis. It has been used extensively in carbonyl addition reactions and addition to other electron-deficient systems either in organic solvents or aqueous media. A few identities for the active allylic indium species have been put forward, depending on the mode of formation. The allylic indium produced by the addition of allylic metals with indium trihalide is proposed to involve an indium(III) species, whereas the allylic indium produced by allylic bromide and indium powder in water has been confirmed to be in indium(I) species. However, it is not clear whether more than one species is actually involved in the reaction in any particular case. Henceforth, the following sections are not about the isolation of the allylic indium species; rather these are used immediately followed

[22] Fürstner, A.; Langemann, K. *J. Am. Chem. Soc.* **1997**, *119*, 9130.
[23] Meng, D; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; Horwitz, S. B. *J. Am. Chem. Soc.* **1997**, *119*, 2733.

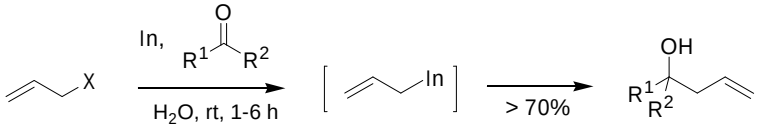
by reaction with carbonyls, reflecting the practical aspects of using such organoindium reagents.

In dimethylformamide, indium reacts with allyl halides to give tentatively assigned allyl indium sesquihalides, which are directly treated with the carbonyl compounds. The desired homoallylic alcohols are obtained in excellent yields under very mild conditions (Scheme 1.18).[24]



Scheme 1.18 In-Situ generation of the allylindium complex in DMF

Allylindium is generated smoothly from indium metal and allyl bromides or iodides in water without the need for acid catalysis, heat or sonication (Scheme 1.19).[25] The reaction is sluggish with the chlorides. Treatment of the allylindium with aldehydes leads to satisfactory yields of the corresponding homoallylic alcohols which are usually unattainable when zinc or tin metals were used under similar conditions.

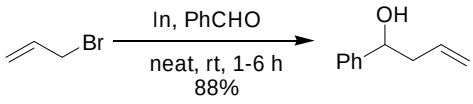


R1 = alkyl, aryl; R2 = H, Me; X = Br, I

Scheme 1.19 In-Situ generation of the allylindium complex in water

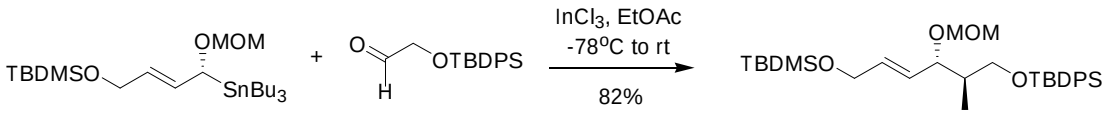
[24] Araki, S.; Ito, H.; Butsugan, Y. *J. Org. Chem.* **1988**, *53*, 1831.
[25] (a) Li, C.-J.; Chan, T. H. *Tetrahedron Lett.* **1991**, *32*, 7017. (b) Chan, T. H.; Li, C.-J.; Lee, M.-C.; Wei, Z. Y. *Can. J. Chem.* **1994**, *72*, 1181.

The indium-mediated allylation of aldehydes and ketones can also be performed under solvent-free conditions to produce allylic alcohols (Scheme 1.20).[26] The use of zinc or tin in most instances is less effective in this case.



Scheme 1.20 Indium-mediated allylation of aldehydes

Indium(III) chloride undergoes transmetalation with allylic stannanes and the resultant allylindium intermediate reacts readily with aldehydes, furnishing predominantly *anti*-adducts (Scheme 1.21).[27] When chiral γ-oxygenated allylic stannanes are used, the reaction produces optically pure 1,2-diols without racemization.

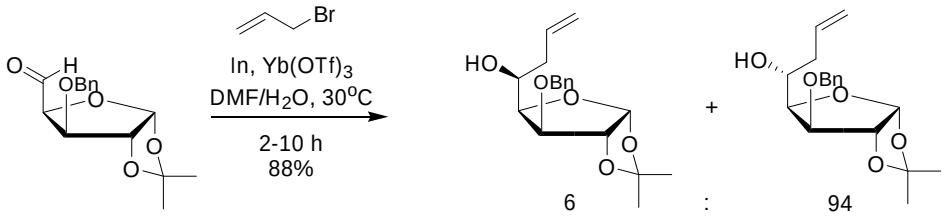


Scheme 1.21 Transmetalation of $InCl_3$ with allylic stannanes

The diastereofacial selectivity of indium-mediated allylation of chiral glucose-derived carbonyl compounds in aqueous media has also been investigated. The allylation of 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylofuraldehyde in aqueous media was found to proceed with high *anti* diastereofacial selectivity under ytterbium

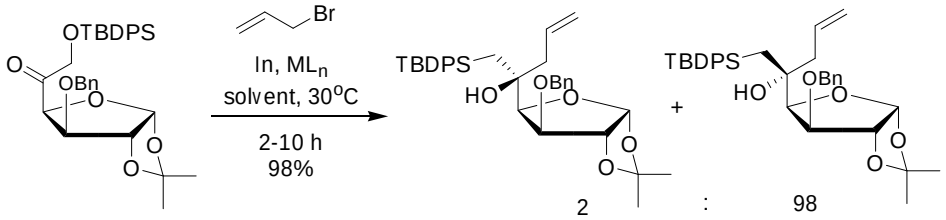
[26] Yi, X.-H.; Haberman, J.-X.; Li, C.-J. *Synth. Commun.* **1998**, *28*, 2999.
[27] (a) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995,** *60*, 1920. (b) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996,** *6*, 105. (c) Marshall, J. A.; Jiang, H. *J. Org. Chem.* **1999,** *64*, 971.

trifluoromethanesulfonate catalysis (Scheme 1.22).[28]



Scheme 1.22 Indium-mediated allylation of glucose-derived carbonyl compounds

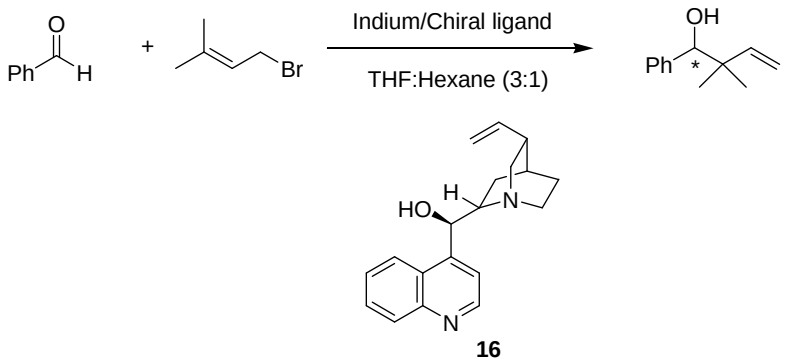
The indium-mediated allylation glucose-derived ketones in water proceeds with chelation control to afford the respective tertiary alcohol in good yields and high diastereofacial selectivity (Scheme 1.23)[29]



Scheme 1.23 Indium-mediated allylation of glucose-derived ketones

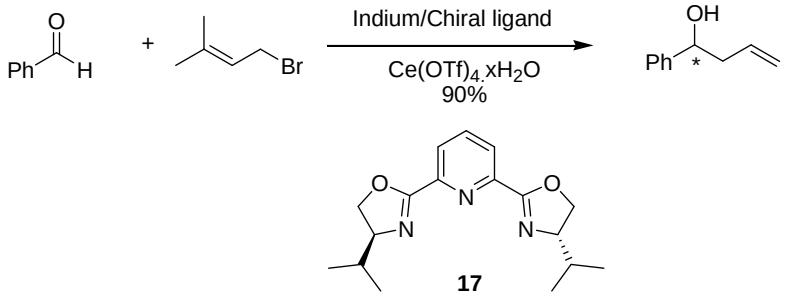
[28] Wang, R.; Lim, C.-M.; Tan, C.-H.; Lim, B.-K.; Sim, K.-Y.; Loh, T.-P. *Tetrahedron: Asymmetry* **1995**, *6*, 1825
[29] Loh, T.-P.; Ho, D. S.-C.; Chua, G.-L.; Sim, K.-Y. *Synlett* **1997**, 563.

In the presence of cinchonidine **16** or cinchonine, indium mediated allylation of aldehydes proceeded in anhydrous organic solvents with high enantioselectivity (Scheme 1.24).[30]



Scheme 1.24 Enantioselective allylation of aldehydes with (-)-cinchonidine

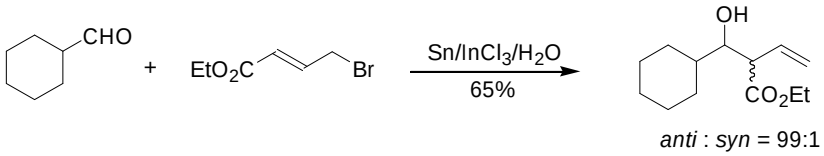
An enantioselective version indium-mediated allylation of aldehydes in aqueous media has also been achieved by employing 2,6-bis[(4*S*)-4-isopropyl-4,5-dihydro-1,3-oxazol-2-yl]pyridine **17** as the chiral source, with observed enantioselectivities up to 92% when used in conjunction with hydrated cerium trifluoromethanesulfonate as Lewis acid (Scheme 1.25).[31]



Scheme 1.25 Enantioselective allylation of aldehydes with (*S*,*S*)-*i*-Pr-PYBOX

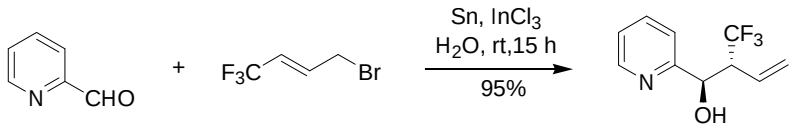
[30] (a) Loh, T.-P.; Zhou, J.-R.; Yin, Z. *Org. Lett.* **1999**, *1*, 1855. (b) Loh, T.-P.; Zhou, J.-R.; Li, X.-R. *Tetrahedron Lett.* **1999**, *40*, 9333.
[31] Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **2000**, *40*, 9115.

Our group observed effective tin-mediated additions of allylic bromides to aldehydes in the presence of indium(III) chloride in water, which was explained by the involvement of a transmetalation process (Scheme 1.26).[32]



Scheme 1.26 Transmetalation in water

In aqueous media, fluorinated containing allylindium generated in situ from a catalytic amount of indium(III) chloride and tin (Scheme 1.27) reacted with aldehydes to gave high regio- and diastereoselectivities.[33] This one pot reaction furnishes the β-trifluoromethylated allylic alcohols in high yields.

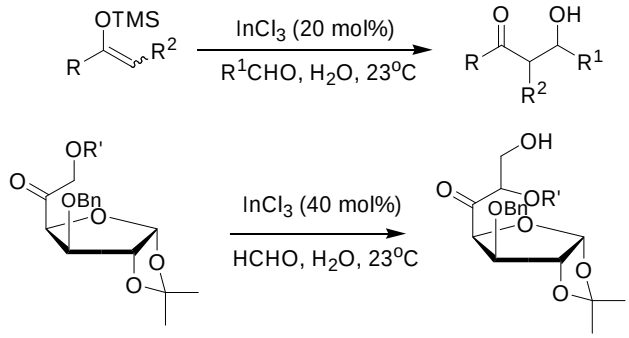


Scheme 1.27 Transmetalation with allylic stannanes in water

These experiments also unveiled a unique property associated with indium chloride, namely, tolerance to water. Therefore, the potential of indium(III) chloride as a water stable Lewis acid for organic synthesis was subsequently investigated in this laboratory.

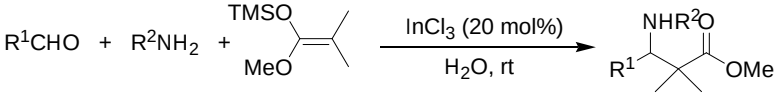
[32] Li, X.-R.; Loh, T.-P. *Tetrahedron Asymmetry* **1996,** *7*, 1535.
[33] (a) Loh, T.-P.; Li, X.-R. *Angew. Chem., Int. Ed. Engl.* **1997**, *109*, 1029. (b) Loh, T.-P.; Li, X.-R. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1736. (c) Loh, T.-P.; Li, X.-R. *Eur. J. Org. Chem.* **1999**, 1893.

Indium(III) chloride was found to be an efficient catalyst in Mukaiyama type reactions of silyl enol ethers with aldehydes in water at room temperature to yield the corresponding aldol products in good yields.[34] The reaction has been successfully applied to the carbon-chain elongation of a glucose derivative.[35] In addition, indium triflate also proved its catalytic efficiency in this reaction (Scheme 1.28).



Scheme 1.28 Mukaiyama-Aldol reaction

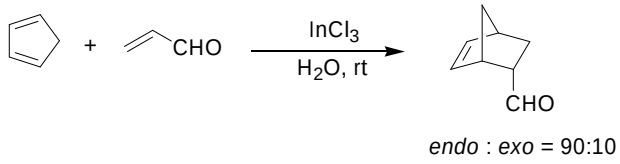
The Mannich-type addition of silyl enol ethers to imines was found to proceed smoothly in water under the catalysis of indium(III) chloride (Scheme 1.29).[36] It is interesting to note that the catalyst can be recycled for use in this reaction up to twenty times without significant influence on the yield.[37]



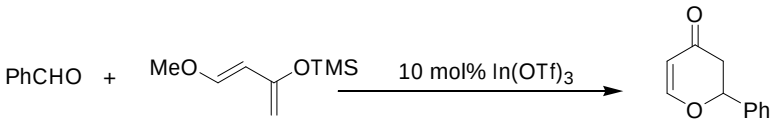
Scheme 1.29 Mannich-type reaction in water

[34] (a) Loh, T.-P.; Pei, J.; Cao, G.-Q.; *J. Chem. Soc., Chem. Commun.* **1996,** 1819. (b) Loh, T.-P.; Pei, J.; Koh, K.-S.; Cao, G.-Q.; Li, X.-R. *Tetrahedron Lett.* **1997,** *38,* 3993. (c) Loh, T.-P.; Huang, J.-M.; Goh, S. H. *Org. Lett.* **2000,** *2*,1291.
[35] Loh, T.-P.; Chua, G.-L.; Vittal, J. J.; Wong, M.-W. *J. Chem. Soc., Chem. Commun.* **1998**, 861.
[36] Loh, T.-P.; Wei, L.-L. *Tetrahedron Lett.* **1998**, *39*, 323.
[37] Loh, T.-P.; Liung, S. B. K. W.; Tan, K. L. *Tetrahedron* **2000,** *56*, 3227.

Indium(III) chloride has also been used as a catalyst for Diels-Alder reactions in water (Scheme 1.30).[38] Recently, the high catalytic activity of indium triflate in hetero-Diels-Alder reactions in organic solvent was noted by Frost's group (Scheme 1.31).[39]



Scheme 1.30 Diels-Alder reaction

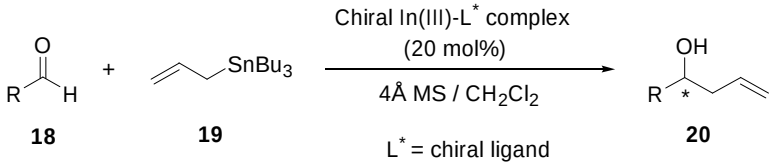


Scheme 1.31 Hetero-Diels-Alder reaction

Indium chemistry has constantly obtained unprecedented triumph in the past decade. However, the design of a chiral indium Lewis acid for various catalytic enantioselective organic transformations has yet to be achieved. This encouraged us to continue our pioneering research in this fertile area, especially the design of novel chiral indium(III) complexes for catalytic enantioselective carbon-carbon bond formation and their application to the synthesis of bioactive molecules.

In this part of the thesis, the successful application of a novel chiral indium complex based on indium(III) chloride and *(S)*-BINOL for catalytic enantioselective allylation will be described (Scheme 1.32).

[38] Loh, T.-P.; Pei, J.; Lin, M. *J. Chem. Soc., Chem. Commun.* **1996,** 2315.
[39] Ali, T.; Chauhan, K. K.; Frost, C. G. *Tetrahedron Lett.* **1999,** *40,* 5621.



18 **19** **20**

Scheme 1.32 Enantioselective allylation of aldehydes with chiral In(III)-L^* complex

1.2 CATALYTIC ENANTIOSELECTIVE ALLYLATION OF ALDEHYDES VIA A CHIRAL BINOL-INDIUM(III) COMPLEX

1.2.1 INTRODUCTION

The enantioselective allylation of carbonyl functionality to furnish homoallylic alcohols has acquired a major role due to the versatility of the products, which are important building blocks for the synthesis of many natural products and pharmaceuticals.[40] Accordingly, much effort has been directed towards the development of an efficient chiral indium complex for enantioselective transformations[41] with limited success. This continues to pose a challenge to synthetic chemists.

Along with the rapid growth of indium metal chemistry, various indium(III) complexes have gained widespread application as efficient Lewis acid catalysts for carbon-carbon bond formation and organic synthetic transformations.[42]

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

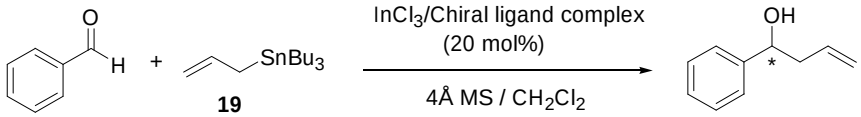
[41] Zhu, C.-J.; Yuan, F.; Gu, W.-J.; Pan, Y. *J. Chem. Soc., Chem. Commun.* **2003**, 692.

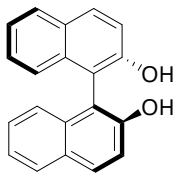
[42] For Reviews, see (a) Loh, T.-P. in *Science of Synthesis*; Yamamoto, H, Ed; Georg Thieme Verlag Stuttgart: New York, **2004**; 413.(b) Loh, T.-P.; Chua, G.-L. in *Advances in Organic Synthesis* – Online, Vol. 1 Activation of Reactions by Lewis Acid Derived from Ga, In, Sb and Bi.Atta-ur-Rahman (Ed) 2005, *In press*. (c) Chauhan, K. K.; Frost, C. G. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3015. (d) Babu, G.; Perumal, P. T. *Aldrichim. Acta* **2000**, *33*, 16. For representative examples see; (e) Chauhan, K. K.; Frost, C. G.; Love, I.; Waite, D. *Synlett* **1999**, 1743. (f) Tsuchimoto, T.; Maeda, T.; Shirakawa, E.; Kawakami, Y. *J. Chem. Soc., Chem. Commun*. **2000**, 1573. (g) Gadhwal, S.; Sandhu, J. S. *J. Chem. Soc., Perkin Trans.* 1 **2000**, 2827. (h) Loh, T.-P.; Hu, Q.-Y.; Ma, L.-T. *J. Am. Chem. Soc*. **2001**, *123,* 2450.

1.2.2 RESULTS AND DISCUSSIONS

In our initial study, we investigated the addition of allyltributylstannanes **19** to benzaldehyde using a catalytic amount of chiral complex prepared from $InCl_3$ and various chiral ligands. The chiral indium complexes were prepared by mixing indium(III) chloride (0.20 equiv) with the respective chiral ligand (0.22 equiv) at room temperature in dichloromethane with addition of activated 4Å MS . After stirring for 2 h, allyltributylstannane (1.0 equiv) was added followed by benzaldehyde (1.0 equiv). The results are shown in Table 1.

Table 1. Screening of chiral ligand for the indium-mediated enantioselective allylation reaction[a]





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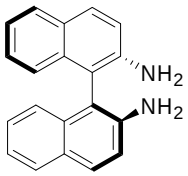

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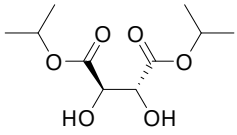

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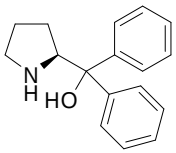

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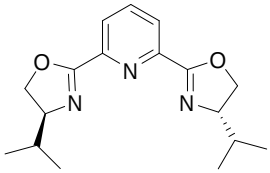


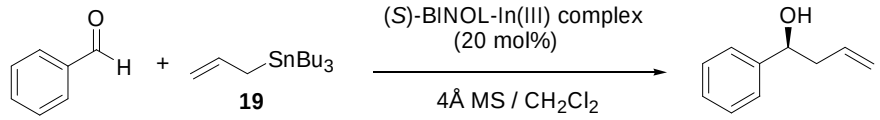
25

Entry	Chiral ligand	Yield (%)[b]	ee (%)[c]
1	**21**	52	78
2	**22**	32	0
3	**23**	35	15
4	**24**	42	12
5	**25**	42	40

[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (0.5 mmol) and aldehyde (0.5 mmol) using the chiral indium(III) catalyst prepared from chiral ligand (22 mol%), $InCl_3$ (20 mol%) and 15 mg powdered activated 4Å MS in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at –78 °C and then 16 h at rt. [b]Isolated yield. [c]Determined by HPLC analysis.

Investigation into the utility of the various chiral ligands for enantioselective allylation reaction revealed that chiral indium complex prepared from (*S*)-BINOL (Table 1, entry 1) was the optimal catalyst in this series, affording the homoallylic alcohol in 52% yield and 78% ee. With this encouraging result, a study was initiated to explore the merits of various indium salts and optimization of the reaction parameters with this catalytic system (Table 2).

Table 2. Evaluation of various indium reagents for the enantioselective allylation reaction[a]



Entry	Indium reagent	Solvent	**19** (equiv)	Yield (%)[b]	ee (%)[c]
1	InF_3	CH_2Cl_2	1.0	0	-
2	In(O-*i*-Pr)$_3$[d]	CH_2Cl_2	1.0	36	0
3	$InBr_3$	CH_2Cl_2	1.0	38	73
4	$InCl_3$	CH_2Cl_2	1.0	52	78
5	$InCl_3$	CH_2Cl_2	2.0	76	92
6	$InCl_3$[e]	CH_2Cl_2	2.0	36	83
7	$InCl_3$[f]	CH_2Cl_2	2.0	12	73
8	$InCl_3$	$CHCl_3$	2.0	52	90

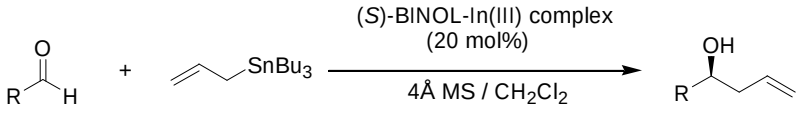
[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (0.5 mmol) and aldehyde (0.5 mmol) using the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and 15 mg activated 4Å MS in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at –78 °C and then 16 h at rt. [b]Isolated yield. [c]Determined by HPLC analysis. [d]The catalyst preparation involved refluxing for 1 h prior to the addition of allyltributylstannane and aldehyde. [e]The reaction was carried out using 50 mg of 4Å molecular sieves. [f]The reaction was carried out with 10 mol% catalyst loading.

The chiral indium complexes formed from the representative indium salts were generated using the abovementioned procedure. Among them, the reaction catalyzed by the (*S*)-BINOL-$InCl_3$ complex exhibited the best conversion and enantiomeric excess (Table 2, entry 4). The corresponding BINOL-In(O-*i*-Pr)$_3$ complex was inferior catalyst for the reaction (entry 2) whereas the fluoride counterpart did not exhibit any catalytic activity (entry 1). The reaction carried out using 2.0 equivalent of allyltributylstannane afforded the homoallylic alcohol in 76% yield with 92% ee (entry 5). It is important to note that the reaction carried out with higher 4Å MS loading resulted in the formation of the product in lower yield and enantiomeric excess (entry 6). Moreover, the reaction carried out in chloroform was found to give the product in good yield with similar enantioselectivities (entry 8). It is

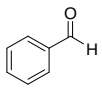
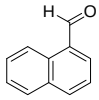
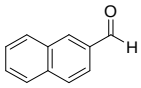
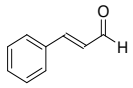
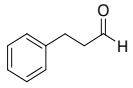
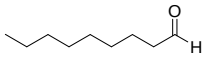
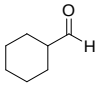
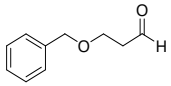
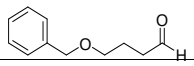
noteworthy that the chiral ligand, (S)-BINOL, can be easily recovered by silica gel chromatography in almost quantitative yield (98%), making the amount of the chiral (*S*)-BINOL used in this reaction irrelevant and the allylation process cost effective.

After determination of the optimized reaction parameters, extension of the catalytic enantioselective addition of allyltributylstannane to a wide variety of aldehydes was investigated and the results are shown in Table 3.

Table 3. Enantioselective allylation of various aldehydes catalyzed by (*S*)-BINOL-In(III) complex[a]



18 **19** **20**

Entry	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1		**20a**	76	92
2		**20b**	55	90
3		**20c**	58	90
4		**20d**	72	96
5		**20e**	64	90
6		**20f**	72	94[d]
7		**20g**	53	94[e]
8		**20h**	70	94
9		**20i**	70	94

[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) using the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and 15 mg activated 4Å MS in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at –78 °C and then 16 h at rt. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Determined by HPLC analysis after conversion to its benzoate. [e]Determined by ^1H NMR analysis after conversion to its Mosher ester.

In all cases, the homoallylic alcohols were obtained in good yields and high enantioselectivities (up to 96% ee) not only with aromatic aldehydes but also with α,β-unsaturated and aliphatic aldehydes. The allylation of 1-naphthaldehyde and 2-

naphthaldehyde both gave the corresponding homoallylic alcohols in 90% ee, respectively (Table 3, entries 2 and 3).

The allylation of a representative conjugated enone gave exclusively 1,2-allylation products in high yield and excellent enantioselectivity (entry 4). Interestingly, while *trans*-3-phenyl-2-butene underwent allylation with 96% ee, the saturated derivative reacted to give the homoallylic alcohol with 90% ee and a lower yield. (entry 5). Moreover, the allylation of nonanal and cyclohexanecarbaldehyde both afforded the products in excellent ee of 94% (entries 6 and 7).

Interestingly, both the functionalized 3-benzyloxypropionaldehyde and 4-benzyloxybutyroaldehyde underwent the allylation reaction to afford the corresponding homoallylic alcohols in similar enantioselectivities of 94% ee (entries 8 and 9).

The absolute configuration of the homoallylic alcohols was determined by the comparison of the sign of the optical rotation and HPLC results with the literature value.[43] The *si* face of the aldehyde is attacked when the (*S*)-catalyst is used, in agreement with the persistent preference shown by BINOL-based catalysts.[8]

The stereochemical course of the allylation process catalyzed by the chiral (*S*)-BINOL-In (III) complex can be envisaged in terms of the catalyst-aldehyde pre-transition state assembly depicted in Figure 3. In Figure 3, the aromatic rings of the (*S*)-BINOL effectively screens the *re* face of the complexed aldehyde from attack by

[43](a) Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc.* **1998**, *120*, 6419. (b) Lee, C.-H.-A.; Loh, T. P. *Tetrahedron Lett.* **2004**, *45*, 5819.

allyltributylstannanes. As such, this facilitated the addition of the allylic moieties to the *si* face of the aldehydes leading to the enantiomers shown in Table 3.

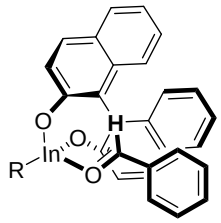


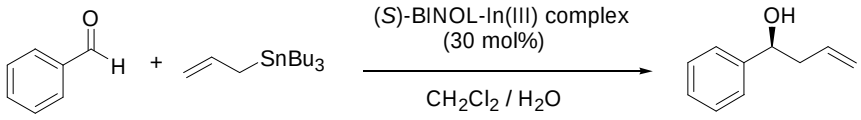
Figure 3. Pre-transition state assembly of catalyst and aldehyde

Despite the fact that various kinds of Lewis acid promoted reactions have been developed, these reactions must be carried out under strictly anhydrous conditions. The presence of even a small amount of water can stop the progress of the reaction because most Lewis acids react immediately with water than with the substrate. This leads to decomposition or deactivation of the catalyst. Henceforth, we proceed to extend the catalytic protocol to aqueous media as a preliminary study.

To evaluate the (*S*)-BINOL-$InCl_3$ catalyst for the enantioselective allylation of aldehydes in aqueous media, the reaction of benzaldehyde and allyltributylstannane in the presence of 3.7 equiv of water (relative to $InCl_3$) was carried out. In this experiment, the reaction was executed by adding water to a stirred solution of the pre-formed catalyst prior to the addition of the aldehyde and allyltributylstannane. The homoallylic alcohol was obtained in 40% yield and 80% ee. In contrast, a racemic product was obtained in <10% yield when water was added prior to the formation of the active catalytic indium species. This result demonstrated that the chiral catalyst was able to maintain its reactivity in the presence of a small amount of water.

Due to the good enantioselectivity exhibited by the water-tolerant chiral indium complex, a study was initiated to explore the optimum water-tolerance limit of the chiral catalyst for the allylation reaction. The results are shown in Table 4.

Table 4. Evaluation of optimal water-tolerant limit for the enantioselective allylation reaction[a]



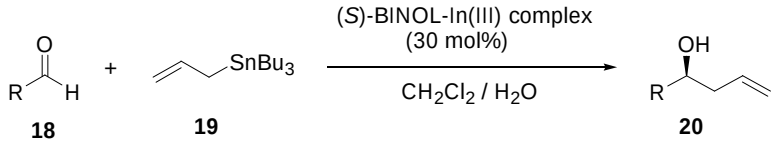
Entry	H_2O equiv (relative to $InCl_3$)	Yield (%)[b]	ee (%)[c]
1	3.7	40	80
2	7.4	53	83
3	11.1	43	78
4	18.5	41	77
5	22.2	40	74
6	37.0	23	50
7	7.4	30	74[d]

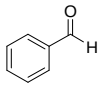
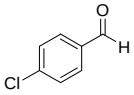
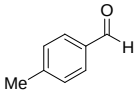
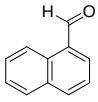
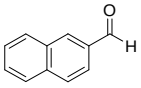
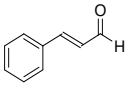
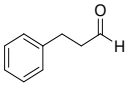
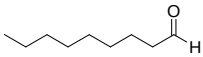
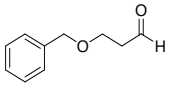
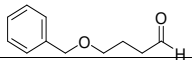
[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) using the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%). The reaction mixture was kept for 20 h at rt. [b]Isolated yield. [c]Determined by HPLC analysis. [d]$InBr_3$ was use as the indium reagent for the catalyst formation.

Investigations into the water-tolerance limit of the chiral indium complex revealed that the addition of 37.0 equiv of water (relative to $InCl_3$) to the pre-formed catalyst in this series gave the lowest yield and enantioselectivity (Table 4, entry 6). The optimum water-tolerance limit was achieved at 7.4 equiv of water relative to the pre-formed catalyst, which afforded the homoallylic alcohol in 53% yield and 83% ee (entry 2). Although an attempt was made to increase the chemical yield by using $InBr_3$ for catalyst formation due to its higher Lewis acidity, the product was isolated in a lower yield and enantioselectivity (entry 7).

After determination of the optimized reaction parameters for the allylation reaction in aqueous media, we extended the catalytic enantioselective addition of allyltributylstannane to a wide variety of aldehydes. The results are shown in Table 5.

Table 5. Enantioselective allylation of various aldehydes catalyzed by (*S*)-BINOL-In(III) complex[a]



Entry	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1		**20a**	53	83
2		**20j**	65	80
3		**20k**	51	81
4		**20b**	51	72
5		**20c**	47	78
6		**20d**	76	85
7		**20e**	57	80
8		**20f**	75	78[d]
9		**20h**	46	86
10		**20i**	42	86

[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) using the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) .The reaction mixture was kept for 20 h at rt. [b]Isolated yield. [d]Determined by HPLC analysis. [d]Determined by ^1H NMR analysis after conversion to its Mosher ester.

Substitution of benzaldehyde with a 4-chloro group resulted in comparable enantioselectivity and a higher yield, with the allylation product formed in 65% yield and 80% ee (Table 5, entry 2). A marginal electronic influence was also observed with 4-methylbenzaldehyde which afforded the product with 51% yield and 81% ee. (entry 3). In addition, the allylation of 2-naphthaldehyde and 1-naphthaldehyde gave the corresponding homoallylic alcohols in 78% and 72% ee, respectively (entries 4 and 5).

The allylation of a representative conjugated enone gave exclusively 1,2-allylation product in high yield and good enantioselectivity (entry 6). Interestingly, while *trans*-3-phenyl-2-butene underwent allylation with 85% ee, the saturated derivative reacted to give the homoallylic alcohol with 80% ee and a lower yield. (entry 7). Moreover, the allylation of nonanal also gave the product in good yield but moderate ee (entry 8).

The functionalized 3-benzyloxypropionaldehyde and 4-benzyloxy butyroaldehyde both underwent the allylation reaction to afford both homoallylic alcohols with 86% ee and yield of 46% and 42%, respectively (entries 9 and 10).

1.2.3 MECHANISTIC STUDIES

It is of mechanistic interest to note that the chiral indium complex can function as a catalyst even though indium trichloride has been known to undergo transmetalation reaction with allylic stannanes. Henceforth, ^{1}H NMR studies were conducted to gain insight to the active species of the catalyst and to understand the origin of the high enantioselectivities.

In the preliminary ^{1}H NMR study, equimolar of allyltributylstannane was added to the mixture of (*S*)-BINOL-$InCl_3$ in $CDCl_3$. ^{1}H NMR spectrum indicated the formation of a set of new allylic signal together with quantitative formation of tributyl stannane chloride (Figure 4); the proton chemical shift of this new set of allyl signals [(δ5.91-5.75 (m, 1H), 5.06-4.92 (m, 2H)] was significantly different from that of allyltributylstannane [(δ6.01-5.86, (m, 1H), 4.81-4.62 (m, 2H)]. Nevertheless, the allylindium derivative thus formed did not afford any detectable amounts of products upon addition of an equimolar amount of benzaldehyde after 24 h. This study shows that indium probably underwent transmetalation reaction with allyltributylstannane to generate an allylic species which forms a chiral complex with (*S*)-BINOL. An intramolecular allyl transfer from indium to aldehyde can be excluded as the actual reaction pathway since (*S*)-1-phenylbut-3-en-1ol was not observed.

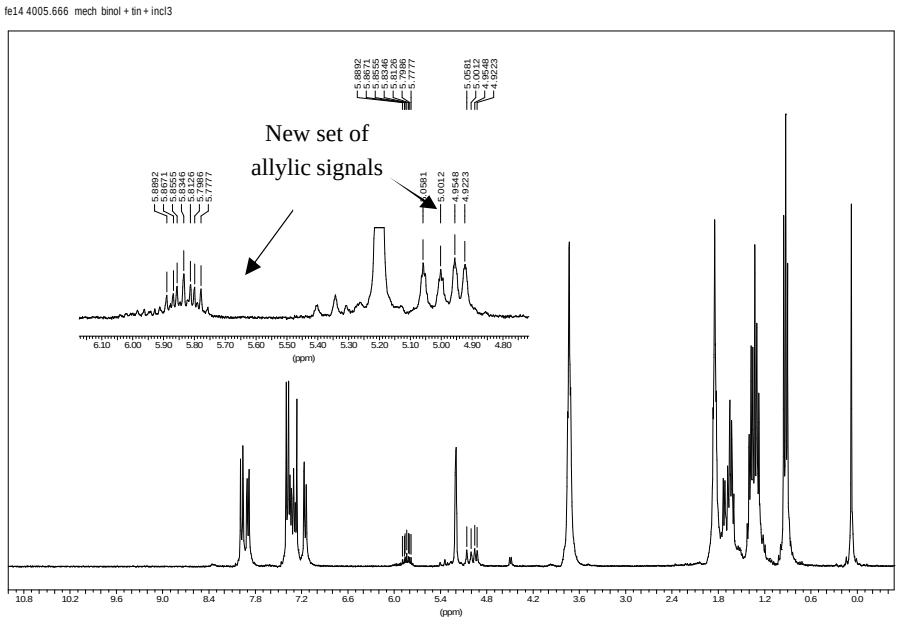


Figure 4. NMR spectrum indicating the formation of a new set of allylic signals.

In another ^{1}H NMR study, 1.0 mmol of allyltributylstannanes (10 equiv) was added to a 0.1 mmol mixture of (*S*)-BINOL-$InCl_3$. The ^{1}H NMR spectrum indicated the formation of the new allylic signal with excess allyltributylstannanes. The ratio of peak intensities of this new allylic signal relative to the allyltributylstannanes was 10:90 (Figure 5). Subsequent addition of 0.5 mmol benzaldehyde and 4 h of reaction time indicated similar allylic signals with initial product formation (Figure 6). The product was isolated in 52% yield with 90% ee after 12 h of reaction time (Figure 7). This study shows that 10% of allyltributylstannanes underwent transmetalation reaction with $InCl_3$ to form the chiral indium complex and the excess allyltributylstannane act as the allylating reagent for the subsequent reaction.

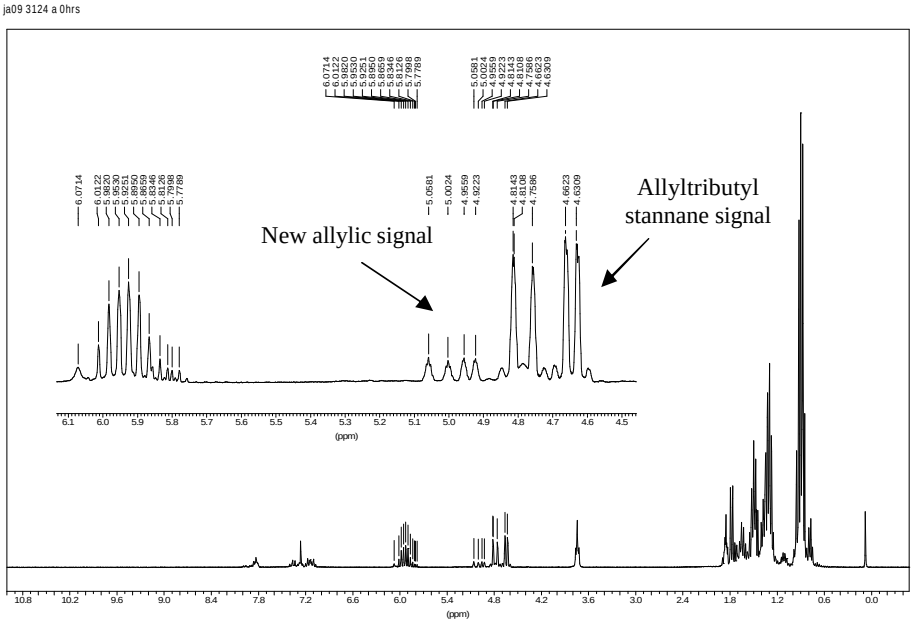


Figure 5. The intensity ratio of this new allylic signal relative to the allyltributylstannanes was 10:90.

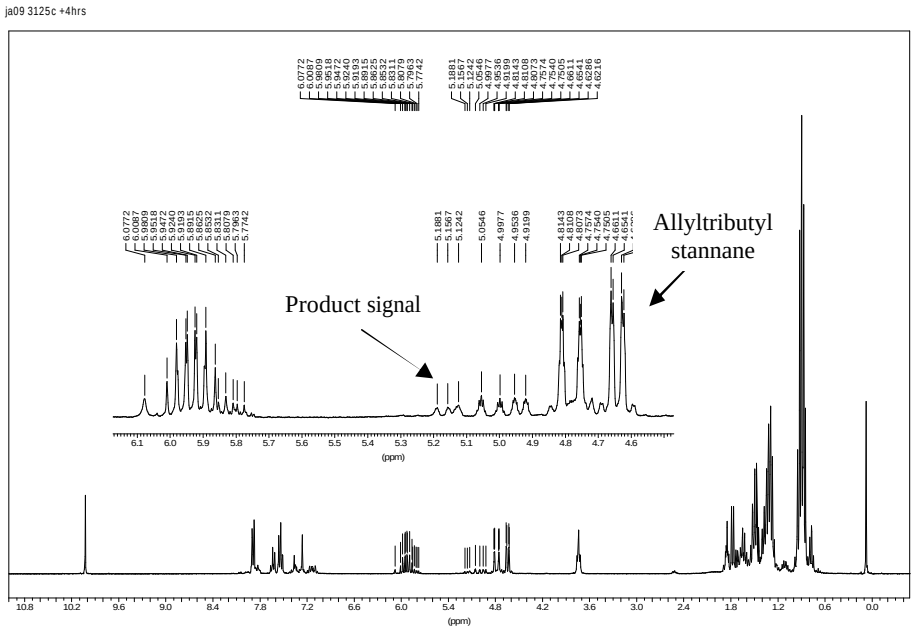


Figure 6. NMR indicates the presence of two allylic signals with initial product formation.

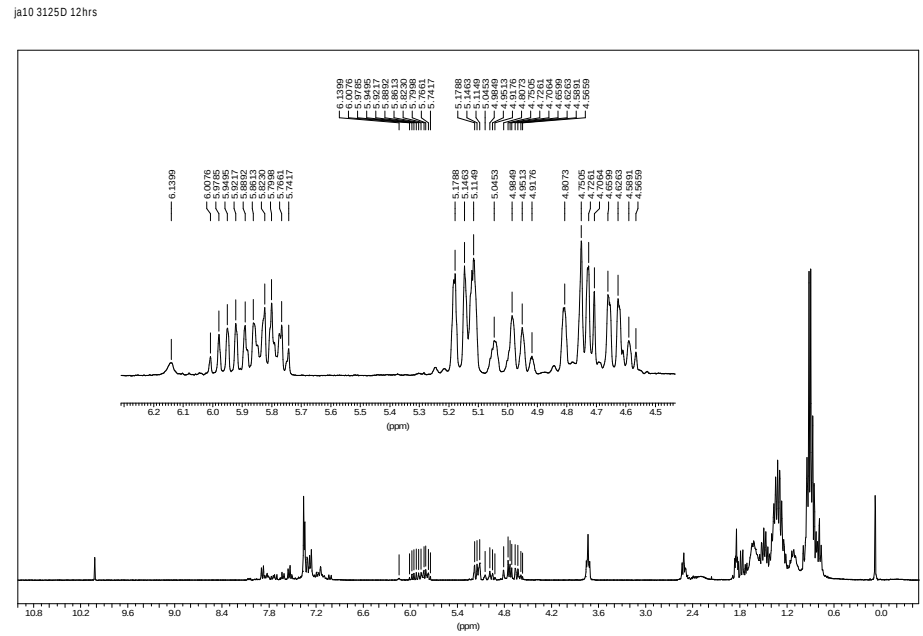


Figure 7. The homoallylic alcohol was isolated in 52% yield with 90% ee after 12 h.

On the basis of the above NMR studies, we postulated that $InCl_3$ underwent transmetalation with allyltributylstannane to form a new allylic species. This subsequently forms a chiral indium complex with BINOL. A (*S*)-BINOL-In-allyl complex probably acts as the chiral Lewis acid for the enantioselective allylation reaction but further mechanistic investigations are in progress. The intramolecular allyl transfer from indium to aldehyde can be excluded as the reaction pathway based on the results obtained from the preliminary NMR studies (pathway a). Instead, the allylation most probably occur via an intermolecular allyl transfer from the allyltributylstannane to the aldehyde catalyzed by the active chiral indium(III) species (pathway b). The proposed mechanism for the enantioselective allylation process catalyzed by the chiral (*S*)-BINOL-In(III) complex is depicted in Figure 8.

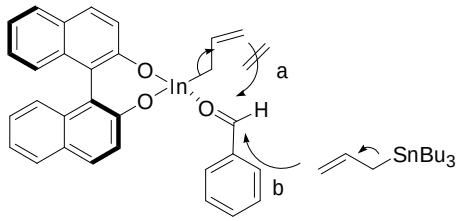


Figure 8. Proposed mechanism for the (*S*)-BINOL-In(III) catalyzed enantioselective allylation reaction (a) Intramolecular transfer of the ally group from the indium to the aldehyde can be excluded from the actual pathway. (b) A chiral BINOL-In-allyl complex probably mediates the enantioselective allylation of the benzaldehyde via an external pathway.

Nonlinear effects (NLE) can provide useful insight into both the behavior of enantioselective catalyst systems and the mechanisms of the processes they mediate. Consequently, experiments were performed to determine if NLE were operative in the BINOL-In(III) catalyzed allylation reaction under investigation. A study with the BINOL ligand of different optical purity exhibited negative non-linearity in correlating the enantiopurity of the allylation product **20a** (R = Ph) with the ee of (*S*)-BINOL (Chart 1). For example, the use of BINOL ligand of 20% ee afforded the allylation product in 24% ee.

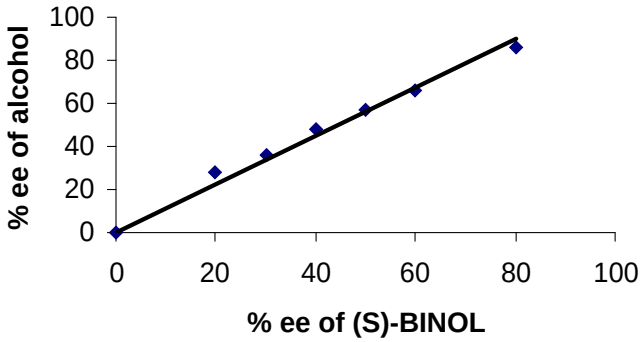


Chart 1. Non-linear effect in enantioselective allylation catalyzed by non racemic (*S*)-BINOL

This study also suggested that the BINOL-In(III) complex most probably exists as a monomeric species in solution. Even if aggregates are present, they have no catalytic effect.

1.2.4 CONCLUSIONS

In conclusion, we have demonstrated the first highly enantioselective addition of allylic moiety to aldehydes using a catalytic amount of the (*S*)-BINOL-In(III) complex. The main features of this reaction are as follows: (1) the procedure is operationally simple and can furnish a wide variety of homoallylic alcohols in good yields with high levels of enantioselectivities; (2) the allylation can be performed exclusively by using commercially available chemicals; (3) the chiral ligand can be recovered in high yield thus, making this method attractive for scale-up preparation of homoallylic alcohols with high enantioselectivities. (4) preliminary extension of the catalytic system to aqueous media provided insights to designing better chiral ligand for stronger complexation with the indium salts. Continuing investigations in this laboratory will attempt to elucidate the identity of the BINOL-In(III) species and further expand the scope of the process. Moreover, the modifications of the BINOL ligand in order for the chiral indium complex to function in fully aqueous media are currently in progress.

1.3 CATALYTIC ENANTIOSELECTIVE ALLYLATION OF ALDEHYDES VIA A CHIRAL BINOL-INDIUM(III) COMPLEX IN IONIC LIQUIDS

1.3.1 INTRODUCTION

The synthesis of enantiomerically enriched homoallylic alcohols has represented a main goal in enantioselective organic methodologies due to the broad availability of allylmetal compounds and the extreme versatility of the products which can be considered precursors of aldols, saturated alcohols, 1,3- and 1,4-diols etc. Previously, our group has reported an efficient protocol for the enantioselective allylation of aldehydes using catalytic amount of a chiral indium(III) complex prepared from (*S*)-BINOL and $InCl_3$. This method has proven to be practical and convenient, furnishing a wide variety of homoallylic alcohols in good yields and excellent enantioselectivities. The extension of this novel chiral (*S*)-BINOL-In(III) catalytic system to ionic liquid was very attractive which endeavor to recover and recycle the ionic liquid layer containing the chiral indium catalyst after a simple extraction of the product.

Ionic liquids are a new class of solvents which present interesting properties such as non-volatility, high stability and easy recyclability. They have been found to be potential and viable solvents for organic synthesis and had shown promising results in the investigations of many organic reactions, such as hydrogenation,[44] hydroformylation,[45] Friedel-Crafts acylation,[46] Diels-Alder reaction,[47] enantioselective allylation reactions,[48] enantioselective epoxidation of alkenes,[49] and enantioselective ring-opening of epoxides.[50]

Recently, our group has developed an L-proline catalyzed enantioselective direct aldol reaction in ionic liquids (Scheme 1.33).[51] The direct aldol reaction of benzaldehyde and propanone in different ionic liquids ([hmim]BF_4, [omim]BF_4, [omim]Cl, and [bmim]PF_6 were examined. The desired aldol product was obtained in all cases and [bmim]PF_6 proves to be superior in this series which preludes the formation of undesirable competing elimination product. Moreover, the enantiomeric excess obtained were comparable or higher than those obtained in DMSO, which was used as the reference solvent. Extension of the aldol reaction in [bmim][PF_6^-] to

[44] Some examples for the hydrogenation using ionic liquids: (a) Chauvin, Y.; Mussman, L.; Olivier, H. *Angew. Chem. Int., Ed. Engl.* **1995**, *34*, 2698. (b) Suarez, P. A. Z.; Dullins, J. E. L.; Einloft, S.; de Souza, R. F.; Dupont, J. *Polyhedron* **1996**, *15*, 1217. (c) Dyson, P. J.; Ellis, D. J.; Parker, D. G.; Welton, T. *Chem. Commun.* **1999**, 25. (d) Monteiro, A. L.; Zinn, F. K.; de Souza, R. F.; Dupont, J. *Tetrahedron: Asymmetry* **1997**, *8*, 177. (e) Brown, R. A.; Pollet, P.; McKoon, E.; Eckert, C. A.; Liotta, C. L.; Jessop, P. G. *J. Am. Chem. Soc.* **2001**, *123*, 1254.

[45] Some examples for the hydroformylation in ionic liquids: (a) Kuntz, E. G. *CHEMTECH* **1987**, 570. (b) Knifton, E. G. *J. Mol. Catal.* **1987**, *43*, 65. (c) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, 100. (d) Favre, F.; Olivier-Bourbigou, H.; Commereuc, D.; Saussine, L. *Chem. Commun.* **2001**, 1360. (e) Keim, W.; Vogt, D.; Waffenschmidt, H.; Wasserscheid, P. *J. Catal.* **1999**, *186*, 481.

[46] Some examples for the Friedel-Crafts acylation in ionic liquids: (a) Boon, J. A.; Levisky, A.; Pflug, J. L.; Wilkes, J. S. *J. Org. Chem.* **1986**, *51*, 480. (b) Qiao, K.; Deng, Y. *J. Mol. Catal. A: Chemical* **2001**, *171*, 81. (c) DeCastro, C.; Sauvage, E.; Valkenberg, M. H.; Hölderich, W. F. *J. Catal.* **2000**, *196*, 86. (d) Adams, C. J.; Earle, M. J.; Roberts, G.; Seddon, K. R. *Chem. Commun.* **1998**, 2097.

[47] Some examples for the Diels-Alder reaction in ionic liquids: (a) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785. (b) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.

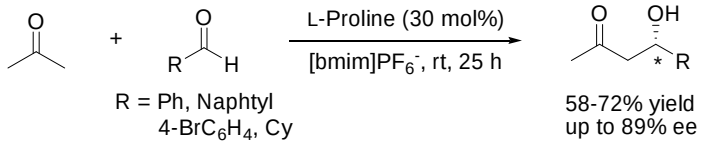
[48] McCluskey, A.; Garner, J.; Young, D. J.; Caballero, S. *Tetrahedron Lett.* **2000**, *41*, 8147.

[49] Song, C.-E.; Roh, E. J. *Chem. Commun.* **2000**, 837.

[50] Song, C.-E.; Oh, C. R.; Roh, E. J. Choo, D. J. *Chem. Commun.* **2000**, 1743.

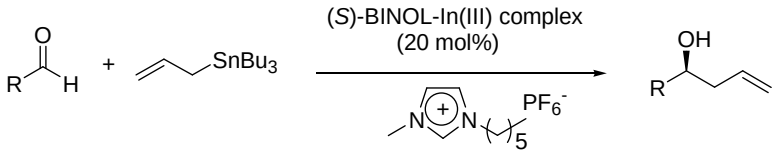
[51] Loh, T.-P.; Feng, L.-C.; Yang, H.-Y.; Yang, J.-Y. *Tetrahedron Lett.* **2002**, *43*, 8741.

various aldehydes (aromatic and aliphatic derivatives) afforded the products in good yields with moderate to excellent ee values (69 to 89% ee). In addition, the ionic liquid containing the L-proline can be recycled and reused for up to four times without significant decreased in yields and enantioselectivities.



Scheme 1.33 Direct aldol reaction catalyzed by L-Proline in $[bmim]PF_6^-$

In this chapter, the successful application of the chiral BINOL-In(III) catalyst for the enantioselective allylation of aldehydes in ionic liquid $[hmim][PF_6^-]$ as an environmentally friendly reaction media will be described (Scheme 1. 34).

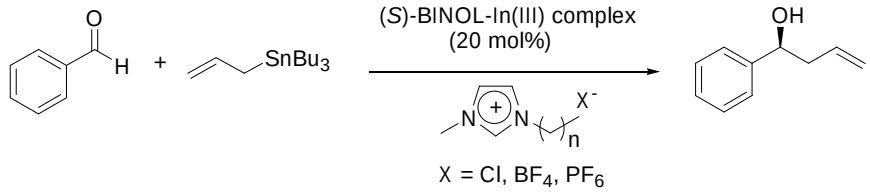


Scheme 1.34 Enantioselective allylation of aldehydes in ionic liquid $[hmim][PF_6^-]$

1.3.2 RESULTS AND DISCUSSIONS

In our initial study, we investigated the enantioselective allylation of benzaldehyde in a series of ionic liquids using the following standardized protocol. The catalyst was prepared by mixing (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in dichloromethane at room temperature. After 2 h of stirring, the ionic liquid was added to the pre-formed catalyst followed by removal of the organic solvent *in vacuo*. Subsequent addition of allyltributylstannane (2.0 equiv) and benzaldehyde (1.0 equiv) afforded the corresponding homoallylic alcohol which was isolated by a simple extraction protocol. The results evaluating the merits of various ionic liquids are shown in Table 6.

Table 6. Evaluation of various ionic liquid for the asymmetric enantioselective allylation reaction[a]



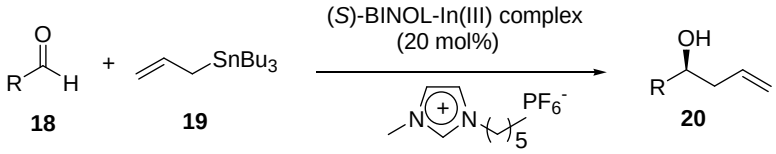
Entry	Ionic Liquid	Yield (%)[b]	ee (%)[c]
1	[bmim][PF_6^-], *n* = 3	35	64
2	[hmim][PF_6^-], *n* = 5	62	70
3	[bmim][BF_4^-], *n* = 3	26	11
4	[hmim][BF_4^-], *n* = 5	28	20
5	[hmim][Cl^-], *n* = 5	42	0
6	[omim][Cl^-], *n* = 7	62	0

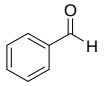
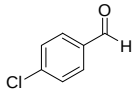
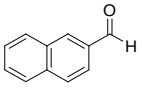
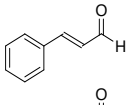
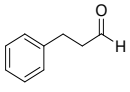
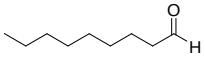
[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) using the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in 1.0 mL of ionic liquid. [b]Isolated yield. [c]Determined by HPLC analysis.

Among the ionic liquids investigated, [hmim][PF_6^-] was shown to be the best solvent system which afforded the homoallylic alcohol in moderate yield and relatively good enantioselectivity whereas the [Cl^-]-type ionic liquids did not exhibit any enantioselectivity.

Having optimized the reaction parameters, we extended the catalytic enantioselective addition of allyltributylstannane to a wide variety of aldehydes using [hmim][PF_6^-] as the solvent system. The results are shown in Table 7.

Table 7. Enantioselective allylation of various aldehydes catalyzed by (*S*)-BINOL-In(III) complex in [hmim][PF_6^-][a]



Entry	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1		**20a**	62	70
2		**20j**	42	72
3		**20c**	46	78
4		**20d**	60	92
5		**20e**	40	74
6		**20f**	72	26[d]

[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) using the chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in 1.0 mL [hmim][PF_6^-]. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Determined by ^1H NMR analysis after conversion to its Mosher ester.

The allylation of benzaldehyde and 4-chlorobenzaldehyde under the influence of the chiral indium catalyst furnished homoallylic alcohols with comparable enantioselectivities of 70% and 72%, respectively (Table 7, entries 1 and 2). In addition, 2-naphthylaldehyde also underwent the allylation reaction affording the product in 46% yield and 78% ee. Allylation of a representative conjugated enone gave exclusively 1,2-allylation in good yield and with high enantioselectivity (entry 4). Interestingly, while *trans*-4-phenyl-3-buten-2-one underwent allylation with 92% ee, the saturated derivative reacted to give the homoallylic alcohol with 74% ee (entry 5). However, the reaction of nonanal under the influence of the chiral catalyst gave the homoallylic alcohol in good yield but with low selectivity (entry 6).

Next, we continued our study by exploring the recyclability of the chiral indium catalyst which is important from the viewpoint of cost-effectiveness. We carried out our study by using the reaction of benzaldehyde and allyltributylstannane in [hmim][PF_6^-] as a model study. After the reaction was completed, the reaction mixture was extracted with ether (15 mL x 4) to give the ionic liquid residue. Use of this residue for subsequent addition of the aldehyde and allyltributylstannane resulted in no product formation even after 72 h. Investigations into this problem revealed the presence of the BINOL ligand in the ether extracts as observed in the ^{1}H NMR spectra. This suggests that the erosion of the catalytic activity was most likely due to catalyst hydration leading to deactivation of the chiral complex.

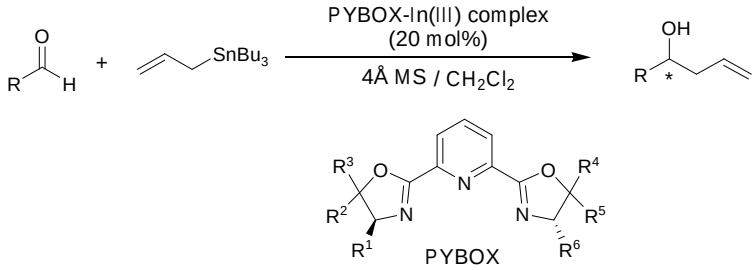
1.3.3 CONCLUSIONS

In conclusion, we have demonstrated an efficient catalytic enantioselective allylation of aldehydes using the ionic liquid [hmim][PF_6^-] as solvent at room temperature. The mild reaction and the simplicity of the reaction procedure should attract interest among organic chemists. The combinatorial synthesis of other ionic liquids for this asymmetric allylation reaction to increase conversion and enantioselectivity are in progress.

1.4 CATALYTIC ENANTIOSELECTIVE ALLYLATION OF ALDEHYDES VIA A CHIRAL PYBOX-INDIUM(III) COMPLEX

1.4.1 INTRODUCTION

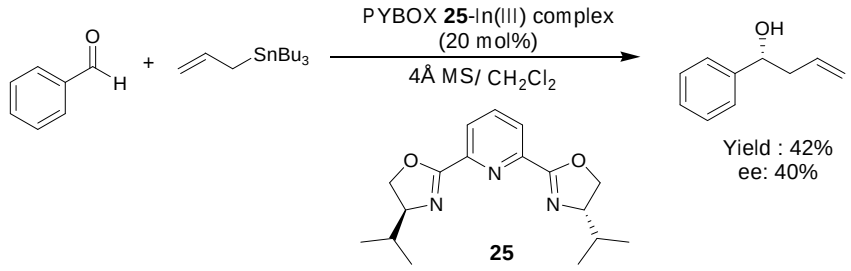
In recent years, there has been intense research in the development of chiral catalysts, especially chiral Lewis acid-catalyzed for the addition of the allyl transfer reagents to carbonyl functionality. However, enantioselective allylation using chiral indium(III) catalyst has been relatively unexplored, although indium(III) complexes have gained widespread application as efficient Lewis acid catalysts for various synthetic transformations. In this chapter, we describe a new procedure for the synthesis of optically pure homoallylic alcohols by the reaction of aldehydes with allyltributylstannane catalyzed by a novel chiral (*S*,*S*)-PYBOX-In(OTf)$_3$ complex (Scheme 1.35).



Scheme 1.35 Enantioselective allylation of aldehydes catalyzed by (*S*,*S*)-PYBOX-In(III) complex

1.4.2 RESULTS AND DISCUSSIONS

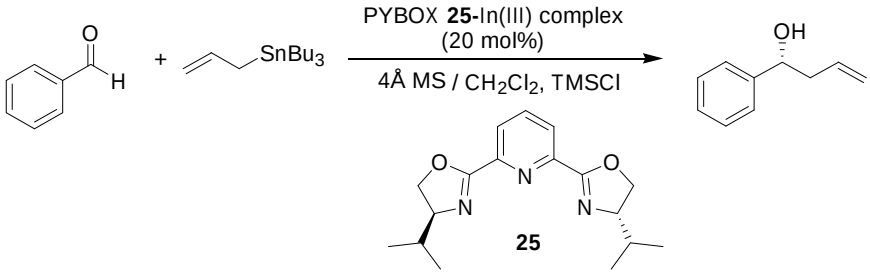
In the preliminary chiral ligand screening reported in chapter 1.2, the enantioselective addition of allyltributylstannanes to benzaldehyde catalyzed by the complex generated from $InCl_3$ and (*S,S*)-*i*-Pr-PYBOX ligand **25** afforded the allylation adducts in 42% yield and 40% ee (Scheme 1.36). With this encouraging result, a study was initiated to explore various indium salts and PYBOX ligands to increase both the enantioselectivity and chemical yield.



Scheme1.36 Enantioselective allylation catalyzed by (*S,S*)-*i*-Pr-PYBOX **25**-In(III) complex

In our initial study, we investigated the merits of various indium salts for the enantioselective allylation of benzaldehyde using a standardized protocol previously described. The chiral complex was prepared by reacting the indium salts (0.2 equiv) and (*S,S*)-*i*-Pr-PYBOX **25** (0.22 equiv) in dichloromethane at room temperature in the presence of 4Å MS. After stirring for 2 hours, benzaldehyde (1.0 equiv) and TMSCl (1.2 equiv) was added followed by allyltributylstannane (1.2 equiv). The homoallylic alcohol was then obtained by aqueous workup and column chromatography. The results are shown in Table 8.

Table 8. Evaluation of various indium reagents for the enantioselective allylation reaction[a]



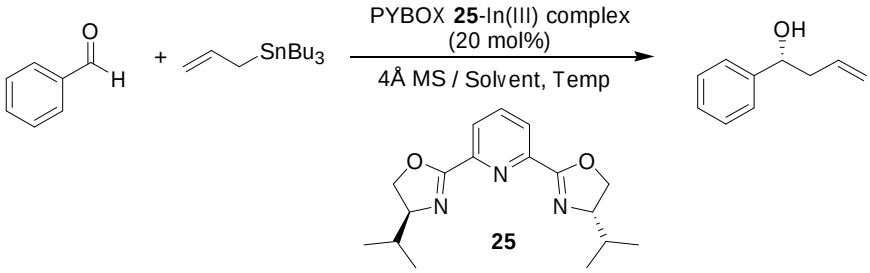
Entry	Indium salt	Yield (%)[b]	ee (%)[c]
1	$InCl_3$	42	40[d]
2	$InCl_3$	84	46
3	$In(OTf)_3$	81	22[e]
4	$In(OTf)_3$	80	85
5	$InBr_3$	12	31

[a] Unless otherwise stated, the reaction was carried out with allyltributylstannane (1.2 equiv), benzaldehyde (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium (III) catalyst prepared from PYBOX **25** (0.22 equiv), indium salt (0.2 equiv) and activated 4Å MS in CH_2Cl_2. The reaction mixture was kept for 30 h at –60 ^oC. [b] Isolated yield. [c] Determined by HPLC analysis. [d,e] Reaction carried out without TMSCl.

Among them, the reaction catalyzed by the (*S*,*S*)-*i*-Pr-PYBOX **25**-$In(OTf)_3$ complex exhibited the best conversion and enantiomeric excess (Table 8, entry 4). The corresponding halide complexes were inferior catalyst for the reaction and results in low enantioselectivity. Interestingly, the addition of TMSCl as addictives to the allylation process provided superior levels of asymmetric induction for the (*S*,*S*)-PYBOX **25**-$In(OTf)_3$ catalyzed reaction.

Next, we proceeded to investigate the effects of solvent and temperature on the (*S*,*S*)-*i*-Pr-PYBOX **25**-In(III) catalyzed enantioselective allylation of benzaldehyde. The results are shown in Table 9.

Table 9. Optimization studies for the (*S*,*S*)-*i*-Pr-PYBOX **25**-In(III) catalyzed enantioselective allylation reaction[a]



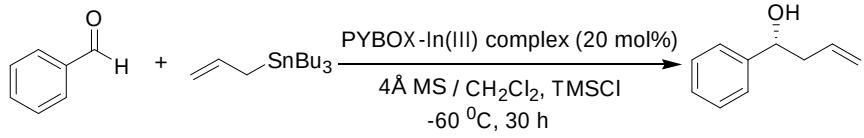
Entry	Solvent	Temperature (^oC)	Yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	rt	75	59
2	CH_2Cl_2	rt	68	12[d]
3	Toluene	rt	70	42
4	ACN	rt	65	54
5	CH_2Cl_2: ACN 1:1	rt	62	55
6	CH_2Cl_2	-10	78	78
7	CH_2Cl_2	-40	81	84
8	CH_2Cl_2	-60	80	85
9	CH_2Cl_2	-78	69	81

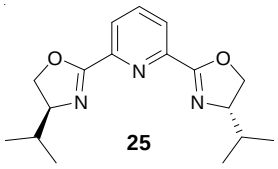
[a] Unless otherwise stated, the reaction was carried out with allyltributylstannane (1.2 equiv), benzaldehyde (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium (III) catalyst prepared from PYBOX **25** (0.22 equiv), $In(OTf)_3$ (0.2 equiv) and activated 4Å MS in solvent. The reaction mixture was kept for 30 h at –60 ^oC. [b] Isolated yield. [c]Determined by HPLC analysis. [d] Reaction carried out without TMSCl.

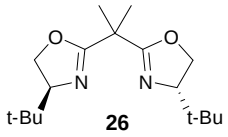
The allylation reaction carried out at room temperature in dichloromethane afforded the product in 59% ee (Table 9, entry 1). The enantioselectivity decreases significantly to 12% ee without the addition of TMSCl (entry 2). The use of other solvents led to lower enantioselectivities for the homoallylic alcohols [42% ee in toluene (entry 3), 54% ee in acetonitrile (entry 4), 55% ee in 1:1 dichloromethane : acetonitrile (entry 5)]. Having optimized the solvent system, the reaction was carried out at various temperatures in dichloromethane. The best result was obtained when the reaction was carried out at -60 ^oC which afforded the product in 80% yield and 85% ee (entry 8). [78% ee at -10 ^oC (entry 6), 84% ee at -40 ^oC (entry 7), and 81% ee at -78 ^oC (entry 9)].

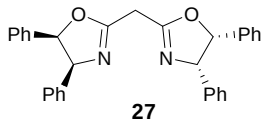
After optimizing the reaction parameters, a study was initiated to evaluate various PYBOX chiral ligands for their merits in the catalytic enantioselective allylation process. The results are shown in Table 10.

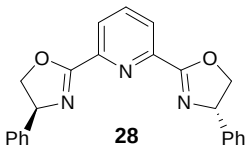
Table 10. Evaluation of various PYBOX ligands for the enantioselective allylation reaction[a]

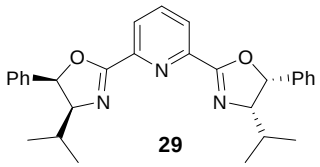


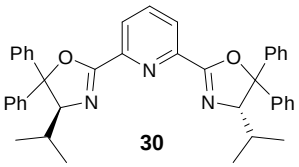












Entry	Chiral ligand	Yield (%)[b]	ee (%)[c]
1	**25**	80	85
2	**26**	0	0
3	**27**	0	0
4	**28**	96	52
5	**29**	84	63
6	**30**	81	92

[a] Unless otherwise stated, the reaction was carried out with allyltributylstannane (1.2 equiv), benzaldehyde (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium(III) catalyst prepared from PYBOX ligand (0.22 equiv), $In(OTf)_3$ (0.2 equiv) and activated 4Å MS in CH_2Cl_2. The reaction mixture was kept for 30 h at –60 ^oC. [b] Isolated yield. [c] Determined by HPLC analysis.

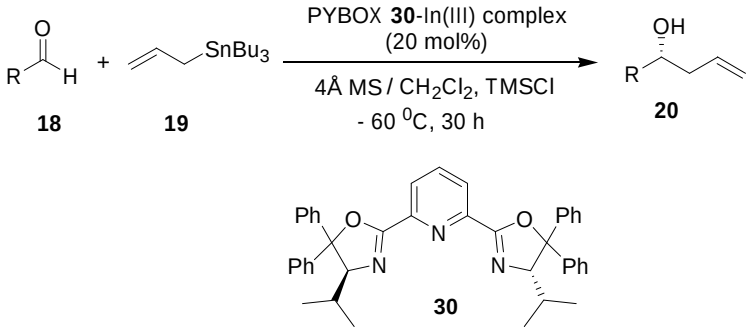
Investigation into the utility of the PYBOX-In(III) complexes demonstrated that tridentate bis(oxazolinyl)pyridine (PYBOX) (Table 10, entries 1 and 4-6) are effective catalyst for the enantioselective allylation reaction. Variation of the ligand

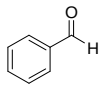
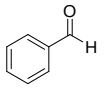
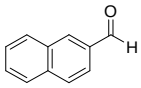
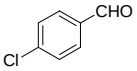
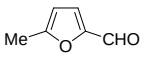
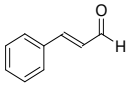
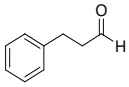
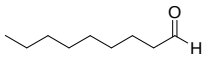
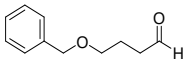
substituent revealed that tetra-phenyl-substituted (*S,S*)-*i*-Pr-PYBOX **30**-In(III) complex was the optimal catalyst in this series, affording the (*R*)-configuration homoallylic alcohol in 92% ee and 81% yield. The bidentate (*S,S*)-PYBOX ligands **26** and **27** were ineffective catalysts for this reaction (entries 2 and 3).

The followings are some of the conclusions obtained from the screening studies: (1) The chemical yields and enantioselectivities of the homoallylic alcohols were dependent on the properties of the indium salts. The triflate salts afforded the highest enantiocontrol for the allylation process while the bromide counterpart gave the lowest ee; (2) As a "promoter" for the enantioselective allylation reaction, TMSCl was more superior than TESCl, TBSCl and TIPSCl in augmenting both the conversion yield and enantioselectivity; (3) The complex generated from tetraphenyl substituted (*S,S*)-*i*-Pr-PYBOX **30** and $In(OTf)_3$ gave superior levels of asymmetric induction, affording the homoallylic alcohol in 81% yield and 92% ee (4) The use of tridentate bis(oxazolinyl)pyridine (PYBOX) gave the homoallylic alcohols in good yields with moderate to high enantioselectivities.

Having optimized the reaction conditions, we extended the catalytic enantioselective allylation to a wide variety of aldehydes in the presence of the (*S,S*)-*i*-Pr-PYBOX **30**-In(III) complex. The results are shown in Table 11.

Table 11. Enantioselective allylation of various aldehydes catalyzed by (*S*,*S*)-PYBOX **30**-In(III) complex[a]

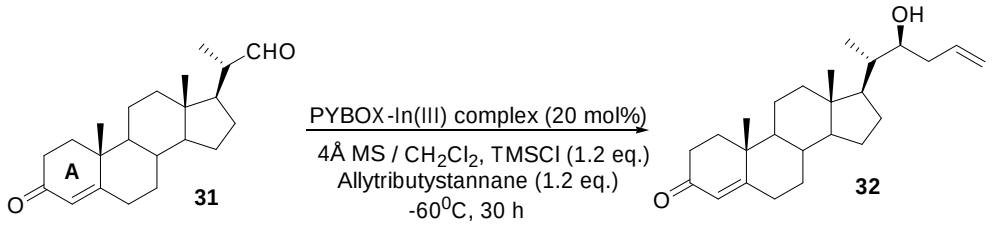


Entry	Aldehyde	Product	Yield (%)[b]	ee (%)[c]
1		**20a**	81[d]	92
2		**20a**	85	91[e]
3		**20c**	86	94
4		**20j**	61	90
5		**20l**	80	94
6		**20d**	91	86
7		**20e**	81	84
8		**20f**	68	85[f]
9		**20i**	78	91

[a]Unless otherwise, stated, the reaction was carried out with allyltributylstannane (1.2 equiv), aldehyde (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium(III) catalyst prepared from (*S*,*S*)-*i*-Pr-PYBOX **30** (0.22 equiv), $In(OTf)_3$ (0.2 equiv) and activated 4Å MS in CH_2Cl_2. The reaction mixture was kept for 30 h at –60 °C. [b]Isolated yield. [c]Determined by HPLC analysis. [d]88% of chiral ligand was recovered. [e]Recovered (*S*,*S*)-*i*-Pr-PYBOX **30** was used for the reaction. [f]Determined by HPLC analysis after conversion to its Mosher ester.

In all cases, the homoallylic alcohols were obtained in good yields and high enantioselectivities (up to 94% ee) not only with aromatic aldehydes but also with α,β-unsaturated and aliphatic aldehydes. In the reaction with α,β-unsaturated aldehydes, the 1,2-addition reaction proceeded exclusively. Furthermore, the chiral ligand (*S*,*S*)-*i*-Pr-PYBOX **30** could be easily recovered in 88% yield without racemization (Table 11, entry 1), and could be reused to afford the product in comparable yield and enantioselectivity (entry 2). This makes the cost of the chiral catalyst irrelevant and the allylation process cost-effective.

A demonstration of the synthetic value of this chiral indium complex was realized via the allylation of the steroidal aldehyde **31** to gave the steroidal alcohol **32** with excellent enantioselectivity (22*S* : 22*R* = 96 : 4) (Scheme 1.37). Moreover, the reaction was highly chemoselective with the allylation occurring exclusively at the aldehyde functionality and precluding attack at the enone ring A. Interestingly, the use of (*R*,*R*)-*i*-Pr-PYBOX **33** also afforded the 22*S*-product as a single isomer.



(*S*.*S*)-*i*-PrPYBOX **30** : 46% yield (22*S*:22*R* = 96:4)
(*R*,*R*)-*i*-PrPYBOX **33** : 62% yield (22*S*:22*R* = 100:0)

Scheme 1.37 Application of the PYBOX **30**-In(III) catalytic system to steroid side-chain synthesis.

1.4.3 CONCLUSIONS

In conclusion, we have demonstrated a highly catalytic enantioselective allylation of aldehydes to give enantiomerically enriched homoallylic alcohols in good yields and excellent enantiomeric excess in the presence of a catalytic amount of (*S*,*S*)-*i*-Pr-PYBOX **30**-$In(OTf)_3$ complexes. Further work on redesigning high affinity chiral PYBOX applicable to the allylation reaction as well as for other organic transformations is in progress.

CHAPTER 2

Catalytic Enantioselective Allylation of Ketones

2.1 OVERVIEW OF CATALYTIC ENANTIOSELECTIVE ALLYLATION OF KETONES

The catalytic enantioselective allylation of carbonyl functionality to furnish enantiopure homoallylic alcohols has acquired a major role among the organic synthetic methodologies due to the versatility and good chemical stability of the target product.[52] Moreover, the functionalized alcohols can also serve as versatile synthetic building blocks since they can be easily transformed into many other useful derivatives. As such, there has been intense research activity in this area in recent years, leading to the development of a large and diverse array of chiral catalysts, especially chiral Lewis acid-catalyzed addition of the allyl transfer reagent to the carbonyl functionality. The development of enantioselective catalytic processes for obtaining secondary homoallylic alcohols from aldehydes and allyltrialkylstannanes[53] or allyltrialkylsilanes[54] greatly enhances the potential of this synthetic tool. In particular, the catalytic enantioselective allylation of ketones[55] represent an important and efficient strategy to provide chiral tertiary homoallylic alcohols, synthons for the synthesis of pharmaceuticals.

---

[52] *(a) Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, 2000. (b) Marshall, J. A.; *Chem. Rev.* **1996**, *96*, 31. (c) Yanagisawa, A. *Comprehensive Asymmetric Catalysis*, Vol. 2 (Eds.: Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H.; Springer, Berlin, **1999**, 965-979.

[53] For Reviews, see (a) Denmark, S. C.; Fu, J.-P. *Chem. Rev.* **2003**, *103*, 2752 and references therein. For representative examples see (a) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001. (b) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (c) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umani-Ronchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897. (d) Weigand, S.; Bruckner, R. *Chem. Eur. J.* **1996**, *2*, 1077. (e) Yanagisawa, A.; Nakaahima, H.; Ishiba, A.; Yamamoto, H. *J. Am. Chem. Soc.* **1996,** *118*, 4723. (f) Casolari, S.; Cozzi, P. G.; Orioli, P.; Tagliavini, E.; Umani-Ronchi, A. *Chem. Commun.* **1997**, 2123. (g) Yu, C.-M.; Choi, H.-S.; Jung, W.-H.; Kim, H.-J.; Shin, J. *Chem. Commun.* **1997**, 761. (h) Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Back, K. *Chem. Commun.* **1997**, 763.

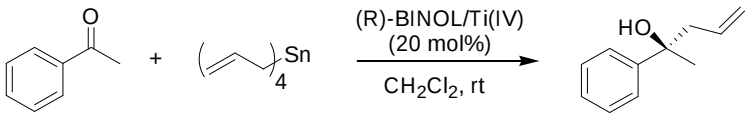
[54] Ishiara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 11490. (b) Gauthier, D. R. J.; Carreira, E. M. *Angew. Chem. Int. Ed.* **1996**, *35*, 2363.

[55] For representative examples of enantioselective allylation of ketones see (a) Tieze, L. F.; Schiemann K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851. (b) Tieze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J*, **1998**, *4*, 1862. (c) Loh, T.-P.; Zhou, J.-R.; Li, X.-R. *Tetrahedron Lett.* **1999**, *40*, 9333. (d) Yamasaki, S.; Fujii, K.; Wada, R.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 6536. (e) Satoshi, K.; Keiji, M. *Chirality*, **2003**,*15*, 68.

However, the catalytic enantioselective allylation of ketones to furnish enantiopure tertiary homoallylic alcohols has proven to be a more challenging transformation owing to the significant difference in reactivity between aldehydes and ketones. Accordingly, most catalysts that promote the enantioselective allylation of aldehydes fail to catalyze the analogous reaction with ketones. In general, the enantioselective formation of quaternary stereocenters generated from the asymmetric allylation of ketones, is of considerable difficulty.[56] As is anticipated by the lesser reactivity of ketones toward nucleophilic addition, the number of methods for enantioselective construction of tertiary alcohols by this approach is very limited.

Catalytic Enantioselective Allylation with Allylic Stannanes

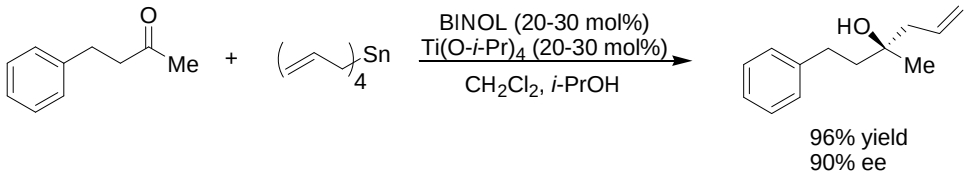
In extension of their studies on the BINOL/Ti(IV)-catalyzed allylation, Tagliavini *et al*. developed a procedure that allows the allylation of ketones with tetraallylstannane as the nucleophile.[57] With 20 mol% of this complex, the addition of tetraallylstannane to ketones provides the adducts in good yields, albeit with modest enantioselectivities (Scheme 2.1).



Scheme 2.1 Enantioselective allylation of ketones catalyzed by BINOL-Ti complex

[56] (a) Corey, E. J.; Perez, A. G. *Angew. Chem, Int. Ed. Engl.*. **1998,** *110,* 402. (b) Christoffers, J.; Mann, J. *Angew. Chem., Int. Ed. Engl.* **2001,** *40*, 4591.
[57] Casolari, S.; Addario, D.; Tagliavini, E. *Org. Lett.* **1999,** *1*, 1061.

The enantioselectivity of this process is significantly enhanced when 2-propanol is used as an additive as reported by Walsh and co-workers.[58] Under the influence of this modified catalytic system, tetraallylstannane reacted with both aromatic and olefinic ketones to afford homoallylic alcohols with high enantioselectivities (Scheme 2.2).



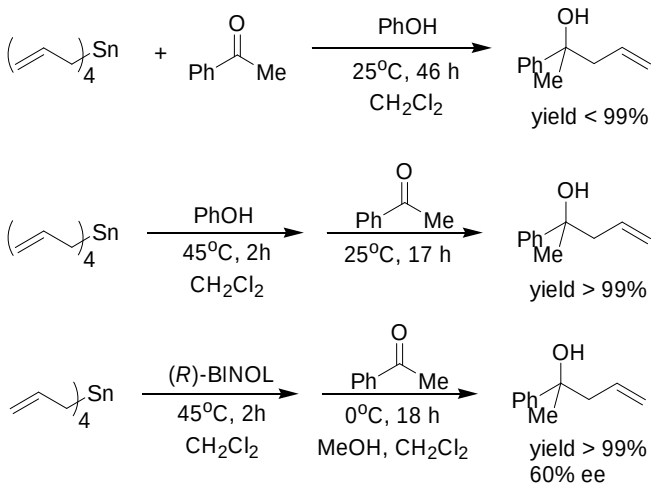
Scheme 2.2 Enantioselective allylation of ketones catalyzed by BINOL-Ti complex

Maruoka has applied the use of "dimerizing ligands' to the allylation of aryl ketones using the BINOL/Ti(IV) complex.[59] With 30 mol% of the catalyst and 1.0 equivalent of tetraallylstannane, the allylation of methyl aryl and alkyl ketones afforded the adducts with up to 98% yield and 92% ee.

Chiral alcohols have been employed as promoters for the addition of allylic stannanes to ketones without the need for other Lewis acidic activators. The addition of tetraallylstannane to acetophenone is significantly accelerated by premixing with alcohols such as phenol (Scheme 2.3).[60] An enantioselective variant of this reaction has been developed using (*R*)-BINOL as the chiral promoter. Under optimized condition with a 3:1:2 ratio of tetraallylstannane: ketone: (*R*)-BINOL and 2 equivalent

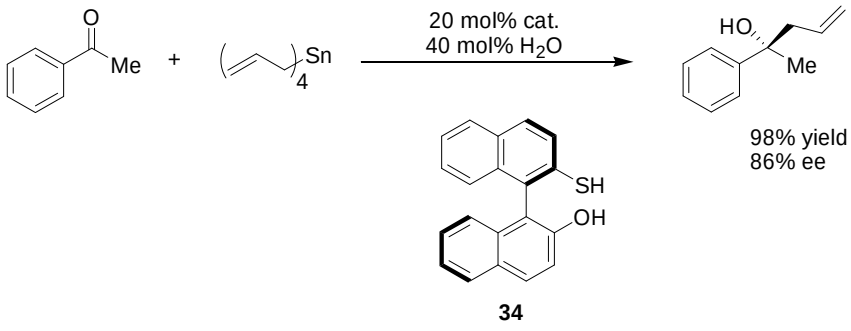
[58] Waltz, K. M.; Gavenois, J.; Walsh, P. J. *Angew. Chem., Int. Ed*. **2002**, *41*, 3697.
[59] Kii, S.; Maruoka, K. *Chirality* **2003,** *15*, 68.
[60] Yasuda, M.; Kitahara, N.; Fujibayashi, T.; Baba, A. *Chem. Lett.* **1998,** *8*, 743.

of MeOH, the allylation product was obtained in high yield albeit with modest enantioselectivity.



Scheme 2.3 Enantioselective allylation of ketones using chiral alcohols as promoters

Important improvements in enantioselectivity and chiral modifier loading are observed with the use of 1,1'-binapthalen-2'-mercapto-2-ol **34**.[61] With 20 mol% of the catalyst and 40 mol% water, a number of aryl ketones are allylated to provide the adducts in high yields and enantioselectivities (Scheme 2.4).



Scheme 2.4 Enantioselective allylation ketones catalyzed by 1,1'-binapthalen-2'-mercapto-2-ol

[61] Cunningham, A.; Woodward, S. *Synlett* **2002**, 43.

Finally, a method for the allylation of ketones with allyltrimethylsilane as well as (*E*)- and (*Z*)- crotyltrimethylsilane that employs stoichiometric modification of the ketone with a ephedrine derivative deserves mention because of the high selectivities obtained.[62]

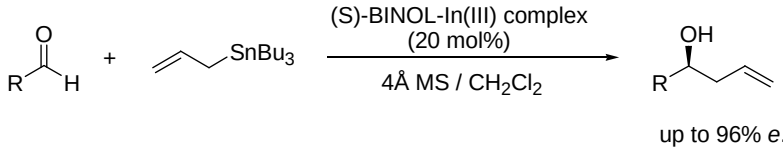
In this part, the successful application of the two novel chiral indium(III) complexes, (*S*)-BINOL-$InCl_3$ and (*S,S*)-PYBOX-$In(OTf)_3$ to catalytic enantioselective allylation of ketones will be described.

[62] Tietze, L. F.; Johnson, K.; Schafer, M. *Chem. Eur. J.* **2001,** *7*, 1304.

2.2 CATALYTIC ENANTIOSELECTIVE ALLYLATION OF KETONES VIA A CHIRAL BINOL-INDIUM(III) COMPLEX

2.2.1 INTRODUCTION

In the preceding chapter, we have demonstrated a practical catalytic asymmetric allylation of aldehydes with allyltributylstannanes in the presence of BINOL-In(III) as a chiral Lewis acid.[63] This system has proved to be remarkably efficient and especially convenient (Scheme 2.5).



Scheme 2.5 Enantioselective allylation of aldehydes catalyzed by (*S*)-BINOL-$InCl_3$ complex

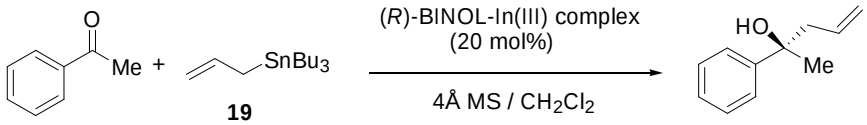
Although we have yet to study the catalyst structure or the mechanism of the allylation reaction in detail, preliminary experiment show that the addition of equimolar of allyltributylstannane to a pre-stirred solution of (*S*)-BINOL and $InCl_3$ facilitated the transmetalation reaction to afford the formation of a chiral BINOL-In-allyl complex which probably acts as the chiral Lewis acid for the enantioselective allylation reaction. Since the enantioselectivities exhibited in these reactions appear to be derived solely from the structure of the chiral indium complex, we proceeded to examine the possibility of realizing the catalytic enantioselective allylation of ketones.

[63] Teo, Y.-C.; Tan, K.-T.; Loh, T.-P. *Chem. Commun.* **2005,** 1318.

2.2.2 RESULTS AND DISCUSSIONS

The chiral indium(III) catalyst was prepared as described previously by simply mixing (*R*)-BINOL with $InCl_3$ in dichloromethane at room temperature for 2 h. The reaction of acetophenone with allyltributylstannane using the optimized conditions previously described for the corresponding allylstannane reaction afforded the homoallylic alcohol in low yield but with good enantiomeric excess (Table 1, entry 1). This result prompted us to utilize other allylstannane and indium reagents in an attempt to increase the yield and enantioselectivity of the allylation reaction. The results are shown in Table 12.

Table 12. Enantioselective allylation of acetophenone catalyzed by (*R*)-BINOL-In(III) complex.[a]



Entry	Indium Reagent	**19** (equiv)	Yield (%)[b]	ee (%)[c]
1	$InCl_3$	2.0	25	81
2	$InCl_3$	3.0	46	81
3	$InCl_3$[d]	3.0	47	10
4	$InBr_3$[e]	3.0	76	82

[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane (1.5 mmol) and acetophenone (0.5 mmol) using the chiral indium(III) catalyst prepared from (*R*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and 15 mg activated 4Å MS in 1.0 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at –78 °C and then 72 h at rt. [b]Isolated yield. [c]Determined by HPLC analysis. [d]Tetraallylstannane was used as the allylation reagent. [e]Reaction stirred at rt for 72 h.

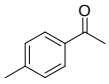
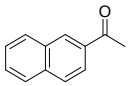
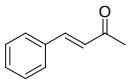
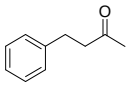
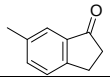
The reaction carried out using 3.0 equivalent of allyltributylstannane leads to an increase in conversion with retention of enantiomeric excess (Table 12, entry 2). To compensate for the reduced reactivity of ketones, we attempted to use more

reactive allylating reagents such as tetraallylstannane and found out that the reaction proceeded with moderate yield but very low enantiomeric excess (entry 3). Next, we attempted to use $InBr_3$ as the indium reagent for the catalytic allylation reaction due to its higher Lewis acidity. The reaction proceeded at ambient temperature and the homoallylic alcohol was isolated in 76% yield and 82% ee (entry 4). It is noteworthy that the chiral ligand, (*R*)-BINOL can be easily recovered by silica gel chromatography in almost quantitative yield (94%), making the amount of the chiral (*R*)-BINOL used in this reaction irrelevant and the allylation process cost effective.

Having optimized the reaction parameters for the allylation process, we extended the catalytic enantioselective addition of allyltributylstannane to a selection of ketones. The results are shown in Table 13.

Table 13. Enantioselective allylation of various ketones catalyzed by (*R*)-BINOL-In(III) complex[a]

35 **19** **36**

Entry	Ketone	Product	Yield (%)[b]	ee (%)[c]
1		**36a**	74	82
2		**36b**	41	84
3		**36c**	80	84
4		**36d**	82	90
5		**36e**	60	80
6		**36f**	61	90
7		**36g**	50	92

[a]Unless otherwise specified, the reaction was carried out with allyltributylstannane(1.5 mmol) and ketone (0.5 mmol) using the chiral indium(III) catalyst prepared from (*R*)-BINOL (22 mol%), $InBr_3$ (20 mol%) and 15 mg activated 4Å molecular sieves in 1.0 mL of CH_2Cl_2. The reaction mixture was stirred at rt for 72h. [b]Isolated yield. [c]Determined by HPLC analysis.

In all cases, the homoallylic alcohols were obtained in good enantioselectivities (up to 92% ee) not only with aromatic ketones but also with aliphatic and cyclic aromatic ketones. The allylation reaction of acetophenone and 4-methylacetophenone under the influence of the chiral indium catalyst furnished the homoallylic alcohols with 82% and 84% ee, respectively (Table 13, entries 1 and 2). Moreover, 2'-acetonaphthone also underwent the allylation reaction affording the product in 80% yield and 84% ee. (entry 3).

The allylation of a representative conjugated enone gave exclusively 1,2-allylation product in good yield with high enantioselectivity (entry 4). Interestingly, while *trans*-4-phenyl-3-buten-2-one underwent allylation with 90% ee, the saturated derivative reacted to give the homoallylic alcohol with 80% ee (entry 5). The ketones, 1-indanone and 6-methyl-1-indanone both underwent the allylation reaction to afford the homoallylic alcohols in excellent enantioselectivity of 90% and 92% ee, respectively though the yield of 6-methyl-1-indanone was only moderate (entries 6 and 7).

The absolute configuration of the tertiary homoallylic alcohol (Table 13, entry 1) was determined by comparing the sign of the optical rotation with the literature value.[64] The *re* face of the ketone is attacked when the (*R*)-catalyst is used, in agreement with the constant preference shown by BINOL-based catalysts.[8]

It is worthy to note that the catalytic allylation of ketones mediated by the chiral indium complex can be accomplished simply by using allyltributylstannane. This is unlike other catalytic enantioselective system which require stronger allylation reagent such as tetraallylstannanes. As such, this is the first example of catalytic enantioselective allylation of ketones using allyltributylstannanes as the allylation reagent.

[64] Ishizaki, M.; Soai, K.; Yokoyama, S. *Chem. Lett.* **1987**, 341.

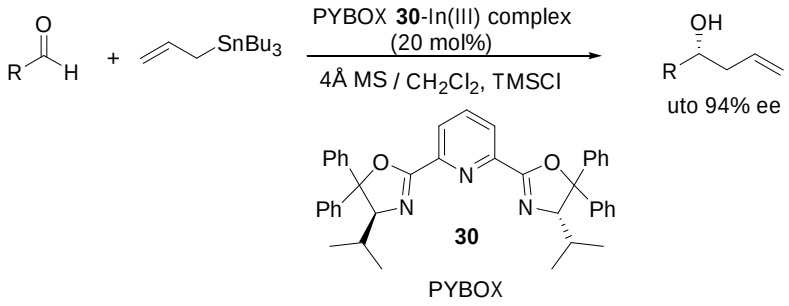
2.2.3 CONCLUSIONS

In conclusion, we have demonstrated the first highly catalytic enantioselective allylation of ketones using a chiral indium(III) complex prepared from (*R*)-BINOL and $InBr_3$. The main features of this reaction are as follows: (1) the procedure is operationally simple and can furnish a wide variety of homoallylic alcohols in good yields with high levels of enantioselectivities; (2) the allylation can be performed simply by using allyltributylstannanes and commercially available chemicals (3) the chiral ligand can be recovered in high yield thus, making this method attractive for scale-up preparation of homoallylic alcohols with high enantioselectivities; (4) the enantiomeric form for the homoallylic alcohols can be easily obtained by changing the chiral source. Continuing investigations in this laboratory will attempt to extend this catalytic system to other enantioselective carbon-carbon bond transformations.

2.3 CATALYTIC ENANTIOSELECTIVE ALLYLATION OF KETONES VIA A CHIRAL PYBOX -INDIUM(III) COMPLEX

2.3.1 INTRODUCTION

Previous work from our laboratory has demonstrated that (*S*,*S*)-*i*-Pr-PYBOX-In(III) complexes[65] can function as effective chiral Lewis acid catalysts in the enantioselective allylation of aldehydes (Scheme 2.6).



Scheme 2.6 Enantioselective allylation of aldehydes catalyzed by (*S*,*S*)-PYBOX-In(III) complex

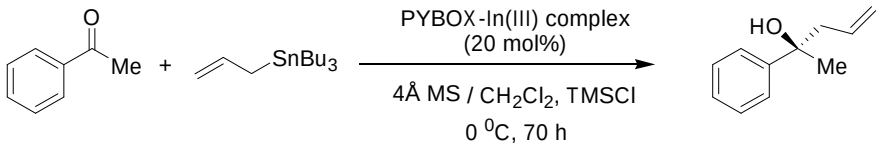
Based on our precedent experience in this enantioselective allylation reaction of aldehydes, an investigation was initiated to extend this chiral indium(III) complexes to the allylation of ketones. This process is an attractive target for enantioselective catalysis since it would provide access to the production of chiral tertiary alcohols which are present in numerous natural products.

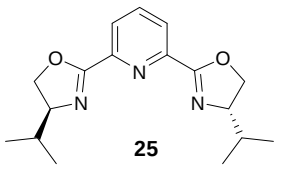
[65] Jun, L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005,** *7*, 159.

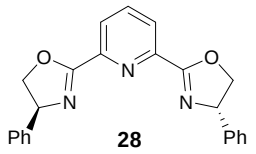
2.3.2 RESULTS AND DISCUSSIONS

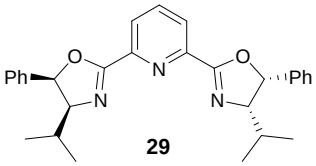
The various chiral PYBOX ligands were initially evaluated for their merits in the allylation of acetophenone using a standardized protocol previously described. To an oven dried 5mL round-bottom flask equipped with a magnetic stirring bar was added $In(OTf)_3$ (0.20 equiv) and 4Å molecular sieves (120 mg). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1 mL of dichloromethane. Chiral PYBOX ligand (0.22 equiv) was added and the mixture was stirred under nitrogen at room temperature for 2 h to afford a white suspension. A mixture of acetophenone (0.15 mmol, 1.0 equiv) and TMSCl (1.2 equiv) in dichloromethane (0.2 mL) was added to the resulting suspension and stirred for 10 min. The mixture was then cooled to $0\ ^0C$ for 15 minutes followed by addition of allyltributylstannane (1.2 equiv). The reaction mixture was stirred at $0\ ^0C$ for 70 hours and quenched with 2 mL saturated sodium bicarbonate solution at room temperature for 30 min. The aqueous residue was extracted with dichloromethane (3 x 10 mL). The combined organic extracts were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified by silica gel chromatography to afford the homoallylic alcohol and the enantioselectivity was determined by chiral High Performance Liquid Chromatography. The results are shown in Table 14.

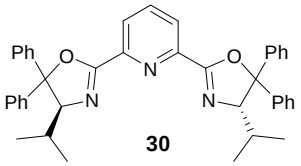
Table 14. Evaluation of various chiral indium(III) complexes for the enantioselective allylation reaction[a]











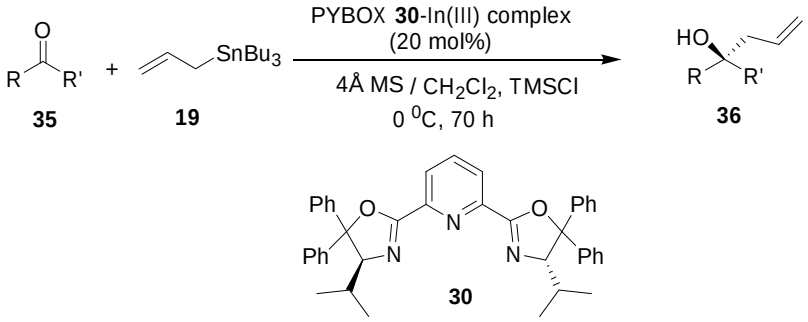
Entry	PYBOX	Yield (%)[b]	ee (%)[c]
1	**25**	34	31
2	**28**	30	27
3	**29**	10	26
4	**30**	80	62

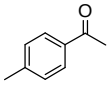
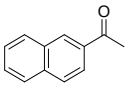
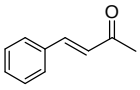
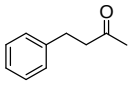
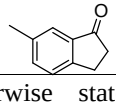
[a] Unless otherwise stated, the reaction was carried out with allyltributylstannane (1.2 equiv), acetophenone (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium(III) catalyst prepared from PYBOX ligand (0.22 equiv), $In(OTf)_3$ (0.2 equiv) and activated 4Å MS in CH_2Cl_2. The reaction mixture was kept for 70 h at 0 °C. [b] Isolated yield. [c] Determined by HPLC analysis.

Investigation into the utility of the PYBOX-In(III) complexes demonstrated that these complexes are also effective catalysts for the enantioselective allylation of acetophenone. Variation of the ligand substituent revealed that the complex formed from (*S*,*S*)-*i*-Pr-PYBOX **30** and $In(OTf)_3$ was the optimal catalyst in this series, affording the (*R*)-configuration homoallylic alcohol in 80% yield and 62% ee (Table 14, entry 4).

The extension of the optimized allylation reaction parameters catalyzed by the (*S*,*S*)-*i*-Pr-PYBOX **30**-In(III) complex to a variety of ketones was undertaken. The results are shown in Table 15.

Table 15. Enantioselective allylation of ketones catalyzed by (*S*,*S*)-PYBOX **30**-In(III) complex[a]



Entry	Ketone	Product	Yield (%)[b]	ee (%)[c]
1		**36a**	80	62[d]
2		**36a**	79	63[e]
3		**36b**	85	67
4		**36c**	74	62
5		**36d**	71	54
6		**36e**	80	55
7		**36f**	90	95
8		**36g**	40	90

[a]Unless otherwise stated, the reaction was carried out with allyltributylstannane (1.2 equiv), ketone (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium(III) complex prepared from (*S*,*S*)-*i*-Pr-PYBOX **30** (0.22 equiv), $In(OTf)_3$ (0.2 equiv) and activated 4Å MS in CH_2Cl_2. The reaction mixture was kept for 70 h at 0 °C. [b]Isolated yield. [c] Determined by HPLC analysis. [d]85% of the chiral ligand was recovered. [e]Reaction performed using recovered (*S*,*S*)-*i*-Pr-PYBOX **30**.

The reactions of various ketones with allytributylstannanes under the influence of the catalyst proceeded readily to provide the corresponding chiral homoallylic alcohols with moderate to good yields (40-90%) and moderate to high enantioselectivities (up to 95% ee). The conjugated enone undergoes exclusively 1, 2-addition reaction to afford the product in good yield with moderate enantiomeric excess (Table 15, entry 5). Moreover, the corresponding saturated derivative also reacted under the influence of the chiral In(III) catalyst to give the homoallylic alcohol with comparable enantiomeric excess (entry 6). The ketones, 1-indanone and 6-methyl-1-indanone both underwent the allylation reaction to afford the homoallylic alcohols in excellent enantioselectivity of 95% and 90% ee, respectively (entries 7 and 8). It is noteworthy that the chiral ligand could be easily recovered in a good yield of 85% without racemization (entry 1) and could be reused to afford the product in comparable yield and enantioselectivities (entry 2).

Interestingly, the absence of TMSCl in the reaction mixture leads to a significant decrease in both the enantioselectivity and chemical yield of the reaction. This result revealed that TMSCl function as a beneficial additive/promoter in chiral induction and conversion yield for the allylation process. This augmentation in enantioselectivity and chemical yield of the products via the addition of TMSCl to the catalytic process was also evident in the catalytic enantioselective allylation of aldehydes previously described.

2.3.3 CONCLUSIONS

In conclusions, we have successfully demonstrated a practical enantioselective catalytic system for the allylation of ketones that provides tertiary homoallylic alcohols with moderate to high enantiomeric excess using a catalytic amount of chiral (*S*,*S*)-*i*-Pr-PYBOX **30**-In(III) complex. Further efforts are being directed towards the utility of this novel approach to other organic transformations and mechanistic studies to investigate the origin of enantioselectivties for this chiral (*S*,*S*)-*i*-Pr-PYBOX-In(III) catalytic system.

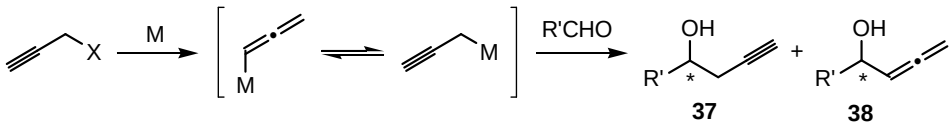
CHAPTER 3

Catalytic Enantioselective Propargylation and Allenylation of Aldehydes

3.1 OVERVIEW OF PROPARGYLATION AND ALLENYLATION OF ALDEHYDES

Optically active allenic and homopropargylic alcohols constitute an interesting class of compounds,[66] which frequently serve as important building blocks in natural products syntheses.[67] Therefore, many strategies have been developed for the enantioselective syntheses of this class of compounds.[68]

The most common method involves the enantioselective addition of homopropargylic or allenylic metals to carbonyl compounds to give the propargylic **37** and allenic **38** alcohols (Scheme 3.1).[69]



Scheme 3.1 Enantioselective propargylation and allenylation of aldehydes

[66] (a) Carreira, E. M.; Frantz, D. E.; Fassler, R. *J. Am. Chem. Soc.* **2000**, *122*, 1806. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Schuster, H. F.; Coppola, G. M. In *Allenes in Organic Synthesis*, Willey, New York, 1984. (d) Landor, S. R. (ed.), In *The Chemistry of the Allenes*, Academic Press, New York, 1982. (e) Kobayashi, S.; Nishio, K. *J. Am. Chem. Soc.* **1995**, *117*, 6392.

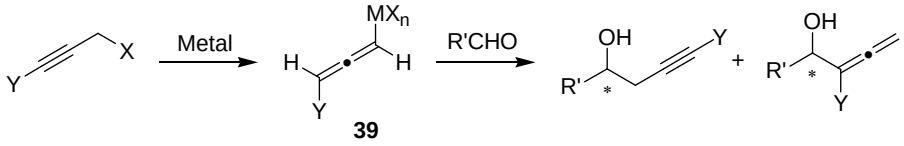
[67] (a) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2915. (b) Yamamoto, H. In *Comprehensive Organic Synthesis*, *vol. 2*, Heathcock, C. H., ed. Pergamon Press: Oxford, 1991, Chap. 1.3, p81-98. (c) R. Epsztein, In *Comprehensive Carbanion chemistry*, ed. E. Buncel and T. Durst, Elsevier, Amsterdam, 1984, part B, p. 107. (d) Helal, C. J.; Magriotis, P. A.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 10938. (c) Matsummura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. J. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

[68] (a) Moreau, J. L. In *The Chemistry of Ketenes, Allenes and Related Componds*, ed. S. Patai, Wiley, New York, 1978, p. 343. (b) Brandsma, L. H.; Verkruijsse, D. in *Synthesis of Acetylenes, Allenes and Cumulenes*, Elseviver, Amsterdam, 1981.

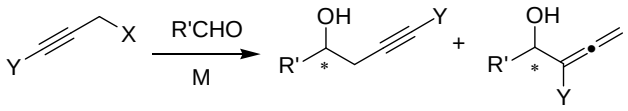
[69] (a) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667. (c)Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew. Chem., Int. Ed. Engl.*, **1998**, *37*, 2392. (d) Yu, C.-M.; Yoon, S.-K.; Choi, H.-S.; Beak, K. *Chem. Commun.* **1997**, 763. (e) Iseki, K.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1998**, *9*, 2889.

Enantioselective Homopropargylation and Allenylation

The traditional method to synthesize chiral propargylic and allenic alcohols is using chiral aldehydes or allenyl/propargylic reagent. Asymmetric synthesis of homopropargylic and allenic alcohols from aldehydes has been accomplished mainly by two methods. The first method entails the synthesis of allenylmetal compounds **39** from corresponding propargylic reagents and addition of the former to aldehydes (Scheme 3.2). The second method is the reaction of the propargylic reagents with aldehydes (Scheme 3.3).



Scheme 3.2 Addition of allenylmetal compounds and aldehydes



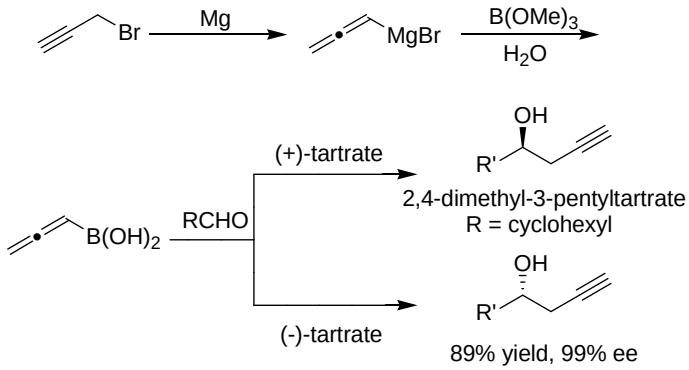
Scheme 3.3 Direct reaction of propargylic reagents with aldehydes

Allenyl Reagents

Reactions of allenylmetals with aldehydes have been the subject of a number of investigations over the past half-century. Allenylborane, allenylstannane and allenylsilane have been widely studied.

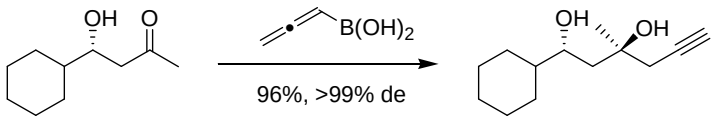
Allenylborane Reagents

Yamamoto reported that treatment of the propargyl Grignard reagent with trimethyl borate followed by acid work-up gave the crystalline allenylboronic acid. Reaction of this compound with cyclohexanecarbaldehyde in the presence of various tartrate esters gave the chiral homopropargyl alcohols. The greatest enantioselectivity was those with the tartrates of 2,4-dimethyl-3-pentanol or cyclododecanol (Scheme 3.4).[70, 71]



Scheme 3.4 Allenylborane reagents

In addition, it was found that reaction of allenylboronic acid with β-hydroxyl ketones in anhydrous ether at room temperature in the presence of 5Å molecular sieves for 20 h, followed by treatment with basic hydrogen peroxide, yielded 1,3-diol with high 1,3-asymmetric induction (>99%) (Scheme 3.5).[72]

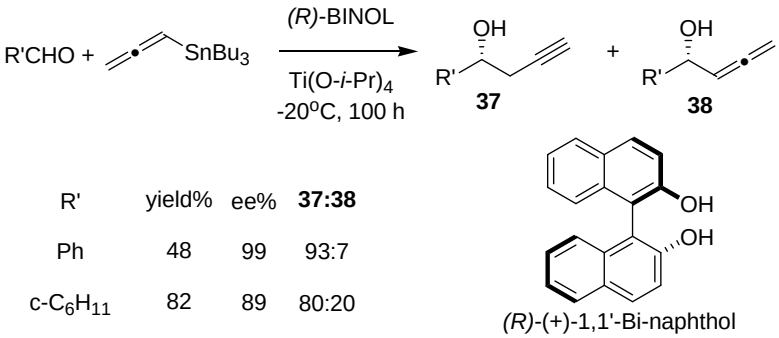


Scheme 3.5 Reaction of allenylboronic acid with β-hydroxyl ketones

[70] Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667.
[71] Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483.
[72] Ikeda, N.; Omori, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1175.

Allenylstannane Reagents

An effective asymmetric homopropargylation using allenyltributylstannane from *(R)*-BINOL and Ti(O-*i*-Pr)$_4$ was reported by Keck *et al*. The enantioselectivities was good and the regioselectivities was moderate to good, depending on the structure of aldehydes (Scheme 3.6).[73]

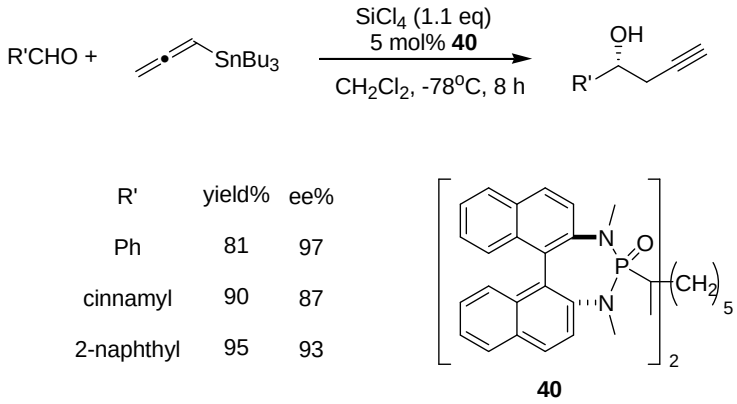


R'	yield%	ee%	**37:38**
Ph	48	99	93:7
c-C_6H_{11}	82	89	80:20

Scheme 3.6 Enantioselective homopropargylation with allenyltributylstannane

Recently, Denmark *et al*. found that chiral binaphthyl bis-phosphoramide-$SiCl_4$ system could catalyze the addition of allenylstannanes to aldehydes to give homopropargylic alcohols. When the *bis*-phosphoramide bearing a five methylene linker **40** was used in the reaction, the highest enantioselectivity of 97% was observed (Scheme 3.7).[74]

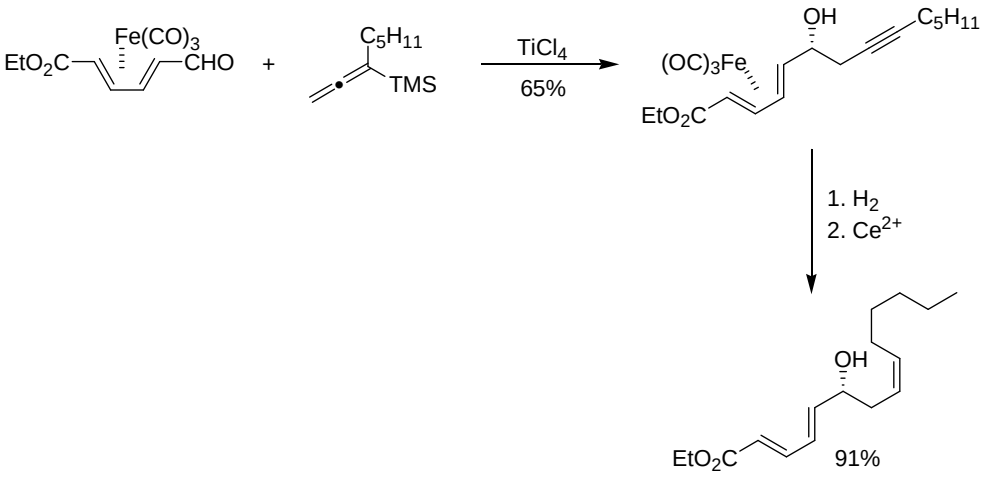
[73] Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett.* **1994**, *35*, 8323.
[74] Denmark, S. E.; Wynn, T. *J. Am. Chem. Soc.* **2001**, *123*, 6199.



Scheme 3.7 Asymmetric homopropargylation with *bis*-phosphoramide

Allenylsilane Reagents

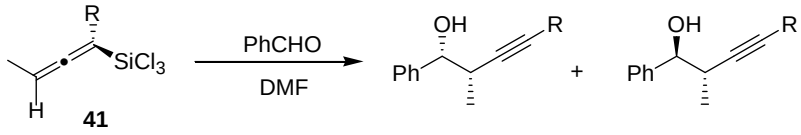
It is well known that allenylsilanes are useful intermediates in organic synthesis, reacting with a variety of electrophiles in a regiospecific manner. Reaction of allenylsilanes with the easily accessible iron tricarbonyl complex in the presence of $TiCl_4$ at -78^oC gives the homopropargyl alcohol in 65% yield, and leads only to the *endo* derivative with the *(R)*-configuration at the secondary alcohol functionality (Scheme 3.8). It is noteworthy that $Fe(CO)_3$ here acts as an efficient protecting group.[75]



Scheme 3.8 Reaction of allenylsilanes with the iron tricarbonyl complex

[75] Nunn, K.; Mosset, P.; Gree, R.; Saalfrank, R. W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1188.

Recently, considerable attention has been given to the preparation of axially chiral allenylsilane and their use for the enantioselective synthesis of homopropargylic alcohols.[76] An axially chiral allenylsilanes **41** was successfully prepared from palladium-mediated hydrosilylation by Hayashi.[77] The reaction of the allenylsilane with aldehyde afforded corresponding homopropargylic alcohol without the loss of enantiomeric purity (Scheme 3.9).



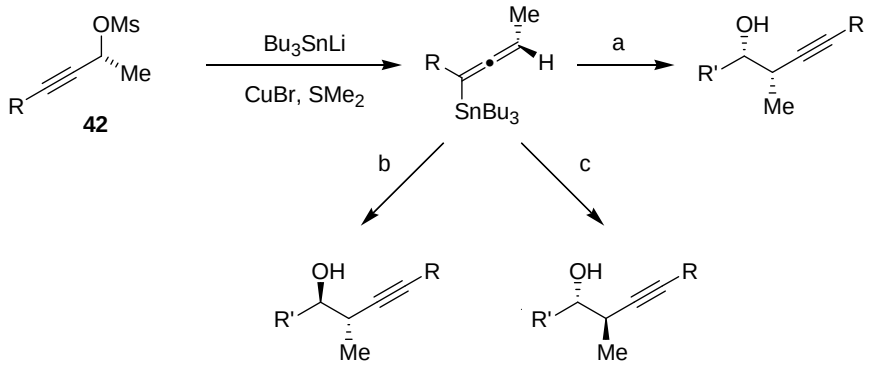
(S)-**41,** R = 2,4,6-$Me_3C_6H_2$ 80 : 20

Scheme 3.9 Asymmetric homopropargylation with chiral allenylsilanes

Allenyl Reagents Prepared from Mesylates

The allenyl reagents prepared from mesylates is especially noteworthy. During the past several years, Marshall *et al*. have contributed much in the approach that entails propargylic mesylates **42** with metals to afford allenylmetal intermediates in high ee. These asymmetric reagents undergo addition to aldehydes yielding optical active propargylic alcohols (Scheme 3.10).[78]

[76] Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630.
[77] Han, J.-W.; Tokunaga, N.; Haayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915.
[78] (a) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696. (c) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

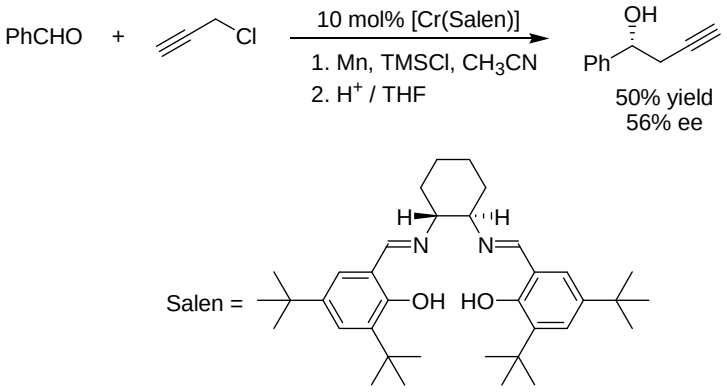


a) R'CHO, BF_3 OEt_2; b) InX_3, R'CHO; c) $SnCl_4$ or $BuSnCl_3$, R'CHO

Scheme 3.10. Asymmetric homopropargylation with propargylic mesylates

Addition of Propargylic Reagents to Aldehydes

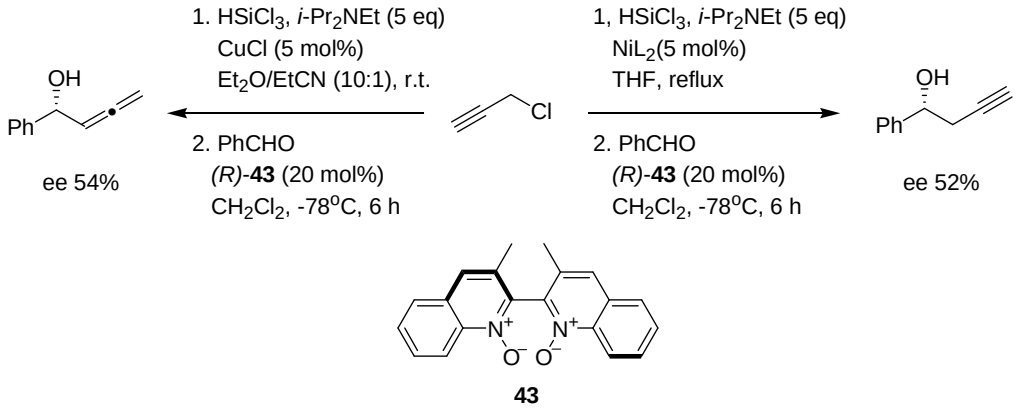
A recent method developed by Umani-Ronchi *et al.* using chiral [Cr(Salen)] complex has afforded homopropargylic alcohols with moderate enantioselectivities (Scheme 3.11).[79]



Scheme 3.11 Asymmetric homopropargylation with chiral [Cr(Salen)] complex

[79] Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Tino, R.; Umani-Ronchi, A. *Tetrahedron:Asymmetry* **2001**, *12*, 1063.

Most recently, Nakajima found that optically active allenic and homopropargylic alcohols could be obtained selectively by the chiral *N*-oxide-catalyzed **43** reaction of aldehydes from propargyl chloride (Scheme 3.12).[80]



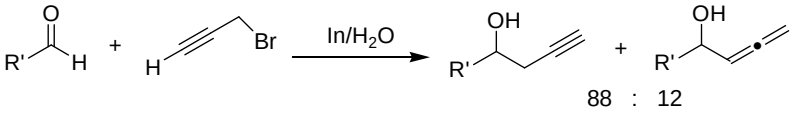
Scheme 3.12 Asymmetric homopropargylation with chiral *N*-oxide-catalyst

Indium-mediated propargylation and allenylation

Among the many methods employed, indium-mediated propargylation has attracted much attention due to its mild reaction conditions as well as wide functional group compatibility.[81] However, compared to the well-established allylic indium chemistry, the synthetic potential of homopropargylic indiums has not been fully exploited. This is because homopropargylic indium equilibrates in solution to give a mixture of homopropargylic and allenylic indium species.[82] This metallotropic rearrangement often results in poor regioselectivity since both organometallic species can react with aldehydes.

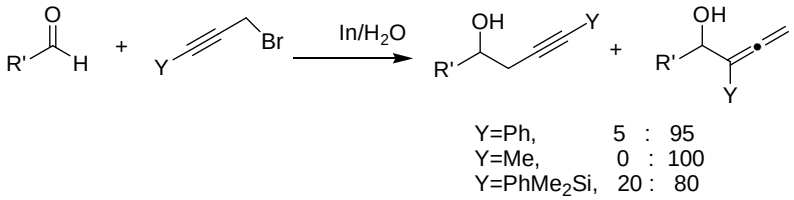
[80] Nakajima, M.; Saito, M.; Hashimoto, S. *Tetrahedron:Asymmetry* **2002**, *13*, 2449.
[81] Chan, T.-H.; Isaac, M. B. *Pure & Appl. Chem.* **1996**, *68*, 919.
[82] (a) Ogoshi, S.; Fukunishi, Y.; Tsutsumi, K.; Kurosawa, H. *Chem. Commun.* **1995**, 2485. (b) Doherty, S.; Corrigan, J. F.; Carty, A. J.; Sappa, E. *Adv. Organoment. Chem.* **1995**, *37*, 39. (c) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589. (d) Hoffmann, R. W.; Lanz, J.; Metternich, R.; Tarava, G.; Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1145.

The metal mediated reactions of aliphatic aldehydes with simple propargyl bromide exhibited lower selectivity than those of aromatic aldehydes in most cases, except for those mediated by tin or zinc. On the other hand, the reaction of terminal-substituted propargyl bromides with aldehydes mediated by indium showed a high regioselectivity in forming the allenylation products in aqueous media (Scheme 3.13).[83]



Scheme 3.13 Indium-mediated propargylation and allenylation

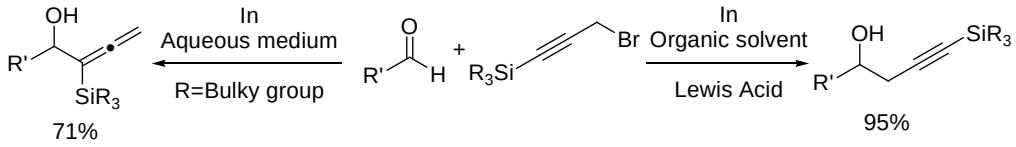
When γ-substituted propargyl bromides are used, allenyl alcohols are the major products (Scheme 3.14).[84]



Scheme 3.14 Reaction of γ-substituted propargyl bromides with aldehydes

[83] Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472.
[84] Isaac, M. B.; Chan, T.-H. *Chem. Commun.* **1995**, 1003.

Our group developed a novel method for the regioselective allenylation and homopropargylation of aldehydes (Scheme 3.15).[85]

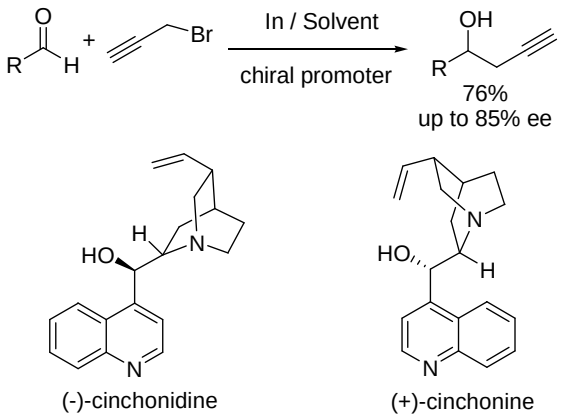


Scheme 3.15 Indium-mediated regioselective propargylation and allenylation

By varying the silyl groups and the reaction conditions, both the allenic and homopropargylic alcohols can be obtained in high regioselectivities. Furthermore, mechanistic studies have revealed that silicon plays an important role in the regioselectivities. These studies pave the way for the design of asymmetric version for the synthesis of allenic alcohols and homopropargylic alcohols respectively.

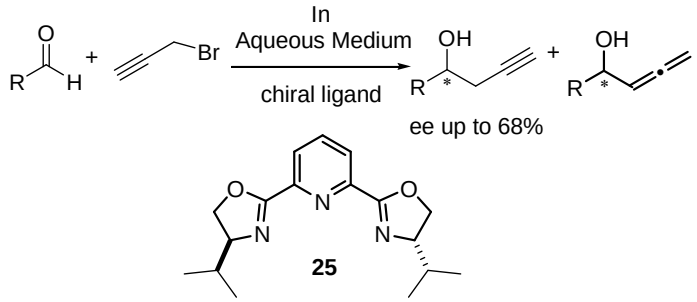
Asymmetric indium-mediated propargylation of aldehydes using two cinchona alkaloids, (-)-cinchonidine and (+)-cinchonine, as the chiral sources was also successfully accomplished (Scheme 3.16). High regioselectivity was observed in this reaction, affording the homopropargylic alcohols without any detectable amounts of the allenic alcohols.

[85] Lin, M.-J.; Loh, T.-P. *J. Am. Chem.. Soc.* **2003**, *125*, 13042.



Scheme 3.16 Enantioselective indium-mediated propargylation and allenylation

An aqueous medium enantioselective indium-mediated propargylation and allenylation of aldehydes was also developed in our group. The highest enantioselectivity of 68% ee was observed when benzaldehyde and unsubstituted propargyl bromide were used for the reaction (Scheme 3.17).



Scheme 3.17 Enantioselective indium-mediated propargylation and allenylation in aqueous media

Although regioselectively obtaining either the homopropargylic alcohol or the allenic alcohol by varying the substrate or solvent has been achieved with success,[86] there is no report on the catalytic enantioselective homopropargylation and allenylation of aldehydes using a chiral indium complex.

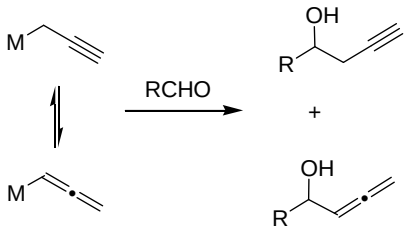
[86](a) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. (c) Yoo, B.-W.; Lee, S.-J.; Choi, K.-H.; Keum, S.-R.; Ko, J.-J.; Choi, K.-I.; Kim, J.-H. *Tetrahedron Lett.* **2001**, *42*, 7287.

In this chapter, the successful application of the (*S*)-BINOL-$InCl_3$ and the (*S*,*S*)-PYBOX-$In(OTf)_3$ to the enantioselective propargylation and allenylation of aldehydes will be described.

3.2 CATALYTIC ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF ALDEHYDES VIA A CHIRAL BINOL-INDIUM(III) COMPLEX

3.2.1 INTRODUCTION

The availability of efficient synthetic methods for achieving absolute stereoselectivity by catalytic processes in the production of optically active compounds is of considerable current interest because such products could be used as chiral building blocks for the synthesis of valuable chiral substances. Recent progress in organic synthesis suggests that the optically active homopropargylic and allenic alcohols are versatile building blocks for the enantioselective synthesis of many biologically active compounds. Hence, many methods have been developed for the enantioselective synthesis of this class of compounds. The asymmetric addition of propargyl or allenyl metals to carbonyl compounds provides a practical method for the synthesis of these important intermediates. This process often leads to both the homopropargylic and allenic alcohols at the same time due to the metallotropic rearrangement between propargyl and allenyl species (Scheme 3.18). Among the many metals employed, indium-mediated propargylation has attracted much attention due to its mild reaction conditions as well as wide functional group compatibility.



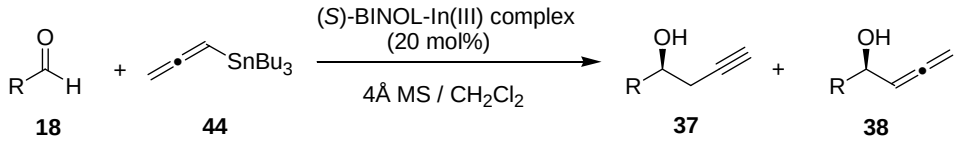
Scheme 3.18 Metallotropic rearrangement between propargyl and allenyl species

In view of our interest in the application of indium-mediated propargylation and allenylation to the syntheses of complex molecules, efforts were directed towards the application of the (*S*)-BINOL-In(III) catalytic system to the enantioselective propargylation and allenylation of aldehydes.

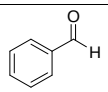
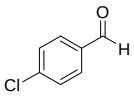
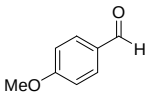
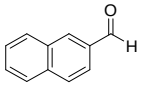
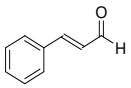
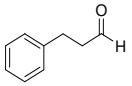
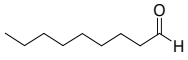
3.2.2 RESULTS AND DISCUSSIONS

Previous work from our laboratory has demonstrated that the (*S*)-BINOL-$InCl_3$ catalytic system can function as effective chiral Lewis acids in the enantioselective allylation of aldehydes and ketones. To evaluate the (*S*)-BINOL-$InCl_3$ catalyst for the asymmetric propargylation and allenylation of aldehydes, the reaction of benzaldehyde and allenyltributylstannane in the presence of the chiral BINOL-In(III) complex was carried out. The chiral indium(III) catalyst was prepared as described previously by simply mixing (*S*)-BINOL with $InCl_3$ in CH_2Cl_2 at room temperature for 2 h. The reaction afforded the propargylic and allenylic alcohol in a ratio of 45 : 55 and enantiomeric excess of 72% and 64%, respectively (Table 16, entry 1). Extension of the catalytic enantioselective propargylation and allenylation to a variety of aldehydes were investigated with the results shown in Table 16.

Table 16. Enantioselective propargylation and allenylation of various aldehydes catalyzed by (*S*)-BINOL-In(III) complex[a]



18 **44** **37** **38**

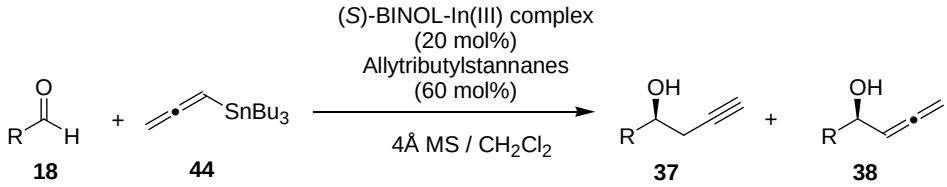
Entry	Aldehyde	Yield (%)[b]	Product	**37 : 38**[c]	ee (%)[d]	
					37	**38**
1		71	**37a : 38a**	45 : 55	72 *S*	64 *S*
2		72	**37b : 38b**	52 : 48	58 *S*	65 *S*
3		41	**37c : 38c**	32 : 68	72 *S*	75 *S*
4		76	**37d : 38d**	46 : 54	60 *S*	60 *S*
5		61	**37e : 38e**	44 : 56	46 *S*	64 *R*
6		76	**37f : 38f**	45 : 55	40 *R*	64*R*
7		62	**37g : 38g**	42 : 58	65 *R*	52 *R*

[a]Unless otherwise specified, the reaction was carried out with allenyltributylstannane (1.0 mmol) and aldehyde (0.5 mmol) in the presence of chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%) and $InCl_3$ (20 mol%) in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at –78 °C and then 18 h at rt. [b] Combined isolated yield. [c]Determined by ^1H NMR analysis. [d]Detemined by HPLC analysis. [e]Determined by HPLC analysis after conversion to its benzoate.

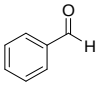
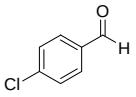
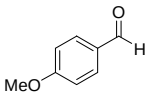
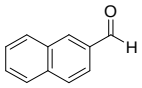
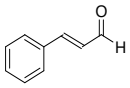
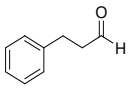
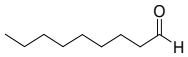
As shown in Table 16, a variety of aldehydes including aromatic, α,β-unsaturated and aliphatic underwent the catalytic process to afford the propargylic and allenylic alcohols in moderate enantioselectivities and good yields, with the exception of 4-methoxybenzaldehyde, which gave relatively low yield (Table 16, entry 3).

In Chapter 1.2, we have demonstrated that the addition of allyltributylstannane to a pre-stirred solution of (*S*)-BINOL and $InCl_3$ facilitated the transmetalation reaction to afford the formation of a chiral BINOL-In-allyl complex which probably channels the allylation of aldehydes in an enantioselective fashion. We envision the addition of allyltributylstannane to the precatalyst might promote the generation of a more potent chiral Lewis acid thus facilitating greater enantiocontrol in the asymmetric homopropargylation and allenylation process. Indeed, an important enhancement in enantioselectivity of the catalytic system was made when the precatalyst was treated with 3.0 equivalent of allyltributylstannanes (relative to $InCl_3$) prior to the addition of the allenyltributylstannanes and aldehyde. With this modification, the ee of the propargylic and allenylic alcohols formed from benzaldehyde rose to 90% and 80%, respectively. This result suggested that the allyltributylstannane had a beneficial impact on the enantiocontrol of the allylation process probably due to a more effective transmetalation reaction with the indium, affording a superior catalytic system. The result of this new catalytic system is presented in Table 17.

Table 17. Enantioselective propargylation and allenylation of various aldehydes catalyzed by (*S*)-BINOL-In(III) complex[a]



18 **44** **37** **38**

Entry	Aldehyde	Yield (%)[b]	Product	**37 : 38**[c]	ee (%)[d]	
					37	**38**
1		72	**37a : 38a**	44 : 56	90 *S*	80 *S*
2		70	**37b : 38b**	43 : 57	76 *S*	90 *S*
3		51	**37c : 38c**	36 : 64	80 *S*	88 *S*
4		78	**37d : 38d**	46 : 54	82 *S*	82 *S*
5		64	**37e : 38e**	48 : 52	80 *S*	88 *R*
6		74	**37f : 38f**	51:49	72*R*	62*R*
7		62	**37g : 38g**	74 : 26	92 *R*	88 *R*[e]

[a]Unless otherwise specified, the reaction was carried out with allenyltributylstannane(1.0 mmol) and aldehyde (0.5 mmol) in the presence of chiral indium(III) catalyst prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%) in 1.5 mL of CH_2Cl_2. The reaction mixture was kept for 4 h at –78 °C and then 18 h at rt. [b] Combined isolated yield. [c]Determined by ^1H NMR analysis. [d]Detemined by HPLC analysis. [e]Determined by HPLC analysis after conversion to its benzoate.

In all cases, the homoallylic alcohols were obtained in good yields and moderate to high enantioselectivities (up to 90% ee) not only with the more reactive aromatic aldehydes but also with the less reactive α,β-unsaturated and aliphatic aldehydes. 4-Chlorobenzaldehyde exhibited a marginal influence from the electronic properties of the substituent, affording the homopropargylic and allenylic alcohols in 76% and 90% ee, respectively (Table 17, entry 2) while 2-methoxybenzladehyde gave

both products in comparable enantioselectivities but with lower yields (entry 3). In addition, the reaction of 2-napthaldehyde gave the corresponding homopropargylic and allenylic alcohols both with 82% ee (entry 4).

The allylation of a representative conjugated enone gave exclusively 1,2-allylation product in high yield and excellent enantioselectivity (entry 5) while the corresponding saturated derivative afforded the homopropargylic and allenylic alcohols in lower enantioselectivities of 72% and 62% ee, respectively (entry 6). Moreover, the allylation of nonanal under the influence of the chiral indium(III) complex afforded the propargylic and allenylic alcohols in 92% and 88% ee, respectively.

The low regioselectivity exhibited by the homopropargylic and allenylic alcohols in this catalytic system could be explained by an equilibrium between the allenyl- and propargyltributylstananne reagents under the reaction conditions. This metallotropic rearrangement between the propargyl and allenyl species eventually leads to poorer regioselectivity since both organometallic species can react with the aldehydes to afford the corresponding propargylic and allenic alcohols respectively.

The absolute configuration of the propargylic and allenylic alcohols was determined by the comparison of the sign of the optical rotation and HPLC results with the literature value.[80]

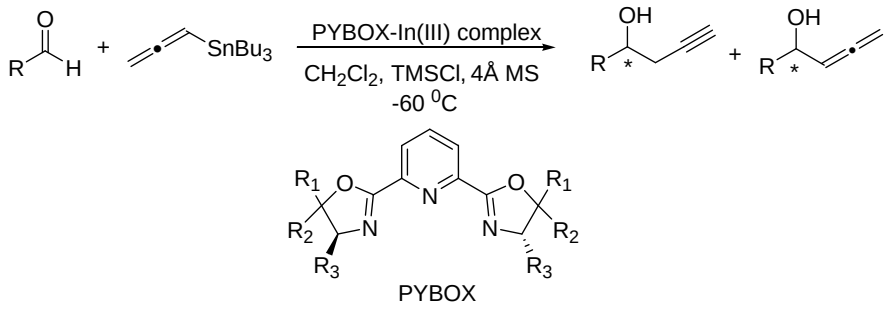
3.2.3 CONCLUSIONS

In conclusion, we have demonstrated a highly enantioselective addition of homopropargylic and allenylic moiety to aldehydes using a catalytic amount of the (*S*)-BINOL-In(III) complex. The main features of this reaction are as follows: (1) the procedure is operationally simple and can furnish a wide variety of homopropargylic and allenylic alcohols in good yields with moderate to high levels of enantioselectivities (up to 90% ee); (2) the allylation can be performed exclusively by using commercially available chemicals; (3) the addition of allyltributylstannane as activator to pre-catalyst resulted in enhancement of enantioselectivity; (4) the low regioselectivity exhibited by the catalytic system was due tometallotrophic rearrangement. Hence this catalytic procedure could be broadly applicable to many synthetic procedures. The application of this chiral BINOL-In(III) complex to other catalytic enantioselective synthesis is currently underway in our laboratory.

3.3 CATALYTIC ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF ALDEHYDES VIA A CHIRAL PYBOX-INDIUM(III)-COMPLEX

3.3.1 INTRODUCTION

Previous work from our laboratory has demonstrated the successful application of the novel chiral PYBOX-In(III) complex as a Lewis acid catalyst for the enantioselective allylation of carbonyl compounds with allyltributylstannane. Based on precedent experience, we envision that this catalytic system should also prove to be effective for the asymmetric synthesis of homopropargylic and allenic alcohols (Scheme 3.19).

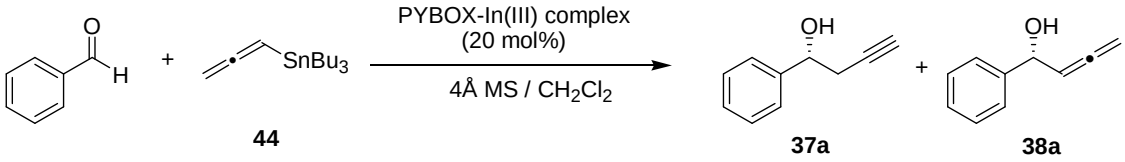


Scheme 3.19 Enantioselective propargylation and allenylation of aldehydes via the PYBOX-In(III) complex

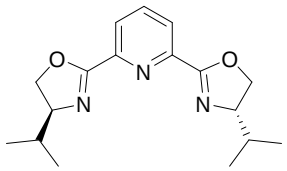
3.3.2 RESULTS AND DISCUSSIONS

To evaluate the (*S*,*S*)-*i*-Pr-PYBOX-In(OTf)$_3$ catalyst for the enantioselective propargylation and allenylation of aldehydes, the reaction of benzaldehyde and allenyltributylstannane in the presence of the chiral complex prepared from (*S*,*S*)-*i*-Pr-PYBOX **25** and In(OTf)$_3$ was investigated. The reaction afforded both the propargylic and allenylic alcohol in a ratio of 67 : 33 and enantiomeric excess of 43% and 63% respectively (Table 18, entry 1). With this encouraging result, a study was initiated to evaluate a series of chiral PYBOX ligands for the enantioselective propargylation and allenylation of benzaldehyde using the standardized protocol previously described. The results are displayed in Table 18.

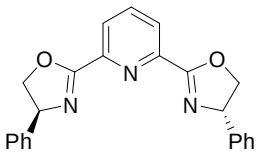
Table 18. Evaluation of various PYBOX ligands for the asymmetric propargylation and allenylation reaction[a]



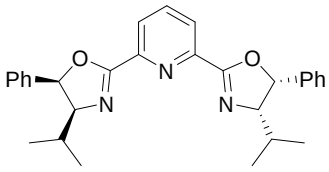
44 **37a** **38a**



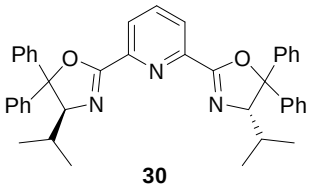
25



28



29



30

Entry	PYBOX	Yield (%)[b]	**37a : 38a**[c]	ee (%)[d]	
				37a	**38a**
1	**25**	78	67 : 33	43	63
2	**28**	75	89 : 11	39	0
3	**29**	81	31 : 69	18	47
4	**30**	86	62 : 38	88	90

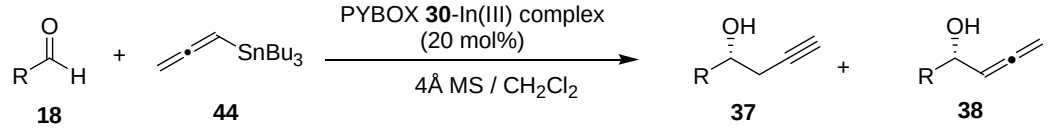
[a]Unless otherwise stated, the reaction was carried out with allenyltributylstannane (1.2 equiv), benzaldehyde (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium(III) complex prepared from PYBOX ligand (0.22 equiv), $In(OTf)_3$ (0.20 equiv) and activated 4Å MS in CH_2Cl_2. The reaction mixture was kept for 30 h at –60 °C. [b]Combined isolated yield. [C]Determined by ^1H NMR analysis. [d]Determined by HPLC analysis.

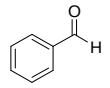
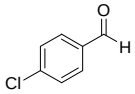
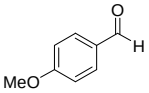
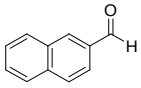
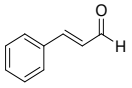
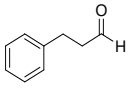
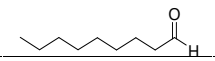
Investigation into the utility of the PYBOX-In(III) complexes demonstrated that tridentate bis(oxazolinyl)pyridine (PYBOX) are effective catalyst for the enantioselective propargylation and allenylation of benzaldehyde. In all cases, the reactions proceeded smoothly to afford both the homopropargylic and allenic alcohols. Variation of the ligand substituent revealed that tetra-phenyl-substituted (*S*,*S*)-*i*-Pr-PYBOX **30**-In(III) complex was the optimal catalyst in this series, affording

the homopropargylic and allenylic alcohol in 88% ee and 90%, respectively (Table 18, entry 4).

After optimizing this reaction conditions, extension of the catalytic system to a variety of aldehydes for the enantioselective synthesis of propargylic and allenic alcohols in the presence of (*S*,*S*)-*i*-Pr-PYBOX **30**-In(III) was investigated. The results are shown in Table 19.

Table 19. Enantioselective propargylation and allenylation of various aldehydes catalyzed by (*S*,*S*)-PYBOX **30**-In(III) complex[a]

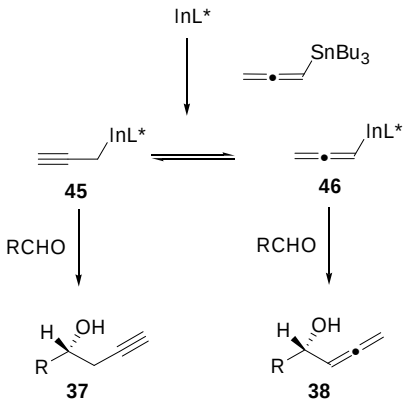


Entry	Aldehyde	Yield (%)[b]	Product	**37 : 38**[c]	ee (%)[d]	
					37	**38**
1		73	**37a : 38a**	62 : 38	88 *R*	90 *R*
2		88	**37b : 38b**	38 : 38	80 *R*	78 *R*
3		68	**37c : 38c**	52 : 48	80 *R*	70 *R*
4		85	**37d : 38d**	37 : 63	88 *R*	84 *R*
5		54	**37e : 38e**	29 : 71	84 *R*	86 *S*
6		71	**37f : 38f**	58 : 42	88 *S*	82 *S*
7		70	**37g : 38g**	35 : 65	60 *S*	66 *S*[e]

[a]Unless otherwise stated, the reaction was carried out with allenyltributylstannane (1.2 equiv), aldehyde (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium(III) complex prepared from PYBOX **30** ligand (0.22equiv), $In(OTf)_3$ (0.20 equiv) and activated 4Å MS in CH_2Cl_2. The reaction mixture was kept for 30 h at –60 °C. [b]Combined isolated yield. [C]Determined by ^1H NMR analysis. [d]Determined by HPLC analysis.

As shown in Table 19, various aldehydes including aromatic, α,β-unsaturated aromatic and aliphatic aldehydes underwent the reaction to afford the propargylic and allenic alcohols with moderate to high enantioselectivities (up to 90% ee) and good yields under the standardized conditions. The reaction of 4-chlorobenzaldehyde under the influence of the chiral indium(III) complex afforded the propargylic and allenylic alcohols in excellent yield with 80% and 78% ee, respectively (Table 19, entry 2). In contrast, an electron donating substituent at the *para*-position of benzaldehyde resulted in significant decrease in chemical yield and enantioselectivities (entry 3).

In general, allenyl reagents lead to the formation of predominantly propargylic adducts, and propargylic reagents to allenyl adducts both through S_E2' addition to the aldehydes. These apparent contradictions exhibited by the alcohol products formed in this catalytic system could be explained by the equilibrium between allenyl- and propargyltributylstananne reagents under the reaction conditions (Scheme 3.20). The chiral PYBOX-In(III) complex probably underwent transmetalation with propargyltributylstannane to form two new chiral indium species **45** and **46** in equilibrium, which subsequently reacted with the aldehydes to afford the corresponding propargylic and allenic alcohols respectively.



Scheme 3.20 Metallotropic rearrangement between indium propargyl and allenyl species

3.3.3 CONCLUSIONS

In conclusion, we have developed a highly catalytic enantioselective propargylation of aldehydes to give enantiomerically enriched propargylic and allenic alcohols in good yield and moderate to good enantiomeric excess in the presence of a catalytic amount of PYBOX **30**-$In(OTf)_3$ complex.

CHAPTER 4

Catalytic Enantioselective Diels-Alder Reaction

4.1 OVERVIEW OF CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTION

The Diels-Alder reaction is one of the most useful structural transformations in organic synthesis, serving as a reliable tool for the synthesis of complex molecules.[87] It allows in principle the formation of up to four contiguous asymmetric centers. Since the control of absolute stereochemistry is very important for natural products synthesis and drug design, where enantiopurity is often critical to biological activity[88], the development of new methods for the asymmetric induction of Diels-Alder reaction is of considerable interest.[89] There are numerous methods to achieve this goal, but the greatest potential efficiency is held by enantioselective reactions using chiral catalysts.[90] With a selective chiral catalyst, large quantities of enantiomerically pure compounds can be generated from small quantities of enantiomerically pure materials. Ideally, for a catalytic system to have excellent practical potential, it should operate to give a high enantioselectivity and predictability of absolute configuration and utilizing an inexpensive, easily recoverable and reusable chiral ligand. The focus of research in this chapter is on the application of a chiral indium Lewis acid for catalytic enantioselective Diels-Alder reactions.

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[87] Danishefsky, S. *Aldrichimica Acta* 1986, 59.
[88] Stinson, S. C. Chiral drugs in *Chem. Eng. News.* 28, **1992**, p46; Stinson, S. C ibid, Dept 27, 1993, p38
[89] For recent reviews, see (a) Paquette, L. A. *Asymmetric Synthesis*; Morrison, J. D., Academic Press: Orlando, FL**, 1854,** Vol. 3B, p455-501. (b) Oppolzer, W. *Angew. Chem., Int. Ed. Engl.* **1984,** *23*, 876. (c) For a recent review on the Diels-Alder reaction emphasizing stoichiometric reagents see : Oppolzer, W. *Comprehensive Organic Synthesis;* Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, **1991,** vol. 5., p315.
[90] Corey, E. J. Proceedings of the 31st National Organic Synposium, American Chemical Society, **1989,** p1 for an overview of some of theses enantioselective methods.

Catalytic Enantioselective Diels-Alder Reaction

The asymmetric Diels-Alder reaction was first investigated more than 25 years ago by introducing a removable chiral auxiliary on the dienophile.[91] A useful development became possible when it was found that Lewis acid catalyzed the Diels-Alder reaction, allowing it to occur under very mild conditions.[92] Recently, much attention has been focused on the use of chiral catalysts.[93] Prior work in the field of catalytic enantioselective Diels-Alder has produced a number of catalysts with varying degrees of selectivity, generality and efficiency.[94] Some representative examples of catalytic enantioselective Diels-Alder reactions are summarized below.

---

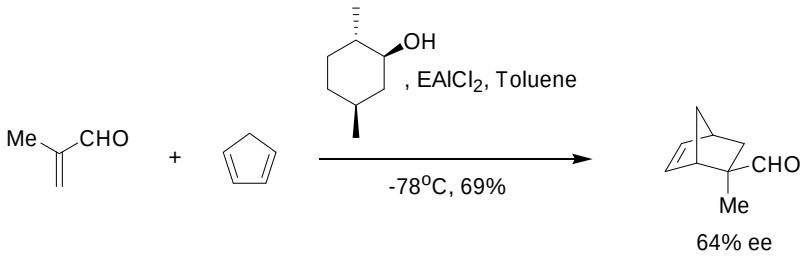
[91] (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions;* Prentice Hall: Engelwood Cliffs, NJ, **1971,** p252. (b) For the first example of asymmetric Diels-Alder reaction using a chiral dienophile see : Walborsky, H. M; Barash, L. *J. Org. Chem.* **1961,** *26*, 4478. (c) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods* 1986; Sheffold, R., Ed.; Springer Verlag: New York, **1986;** Vol. 4, p242.

[92] (a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436. (b) Hartmann, H.; Hady, A. F. A.; Sartor, K.; Weetman, J.; Helmechen, G. *Angew. Chem., Int. Ed. Engl.* **1987**, *43*, 1969.

[93] For reviews see : (a) Corey, E. J. *Angew. Chem., Int. Ed.* **2002,** *41*, 1650. (b) Evans, D. A.; Johnson, J. S. *In Comprehensive Asymmetric Catalysis*; Jacobson, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol.3, p1177. (c) Diaz, L. C. *J. Brz. Chem. Soc.* **1997**, *2*, 289. (d) Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 488. (e) Ishihara, K.; Yamamoto, H. *Euro. J. of Org. Chem.* **1999**, 527. (f) Narasaka, K. *Stereocontrolled Organic Synthesis*, 1994 17. For representative examples on catalytic enantioselective Diels-Alder see : (g) Ryu, D. H.; Zhou, G.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 4800. (h) Sprott, K. T.; Corey, E. J. *Org. Lett.* **2003**, *5*, 2465. (i) Ryu, D. H.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 6388. (j) Nakano, H.; Suzuki, Y.; Kabuto, C.; Fujita, R.; Hongo, H. *J. Org. Chem.* **2002**, *67*, 5011. (k) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002** *124*, 2458. (l) Corey, E. J.; Shibata, T.; Lee, T.-W. *J. Am. Chem. Soc.* **2002**, *124*, 3808. (m) Ryu, D. H.; Lee, T.-W.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 9992. (n) Breuning, M.; Corey, E. J. *Org. Lett.* **2001**, *3*, 1559. For more examples see : (o) Evans, D. A.; Miller, S. C.; Thomas; von Matt, P. *J. Am. Chem. Soc.* **1999**, *121*, 7559. (p) Evans, D. A.; Olhava, E. J.; Johnson, J. S.; Janey, J. M. *Angew. Chem., Int. Ed.* **1998,** *37*, 3372. (q) Loh, T.-P.; Wang, R.-B., Sim, K.-Y. *Tetrahedron Lett.* **1996**, *37*, 2989. (r) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. (s) Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 1561. (t) Ishihara, K.; Gao, Q.-Z.; Yamamoto, H. *J. Org. Chem.* **1993**, *58*, 6917. (u) Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460. (v) Corey, E. J.; Loh, T.-P.; Toper, T. D.; Azinioara, M. D.; Noe, M. C. *J. Am. Chem. Soc.* **1992**, *114*, 8290. (w) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966. (x) Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* **1991,** *64*, 387. (y) Furuta, K.; Shimizu, S.; Miwa, Y.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 1481. (z) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987,** *12*, 2409.

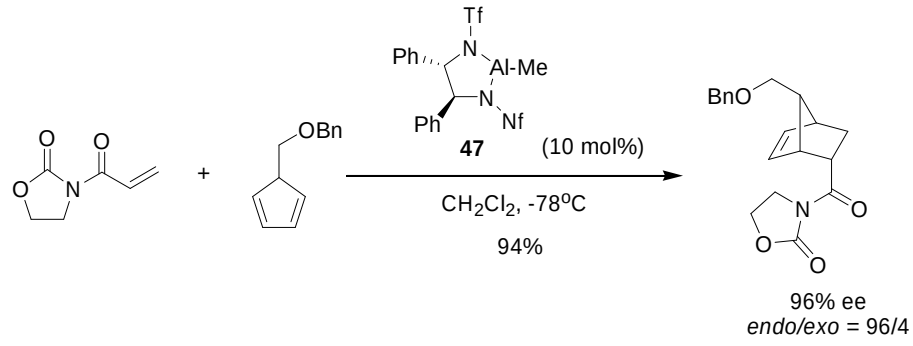
[94] Review on the Catalytic Asymmetric Diels-Alder Reactions: Kagan, H. B.; Tlant, O. *Chem. Rev.* **1992,** *92*, 1007.

The first positive asymmetric catalytic Diels-Alder reaction was reported by Koga and Komeshima in 1979. They performed the cycloaddition of methacrolein to cyclopentadiene under the catalysis of menthoxydichloroaluminum[95] (Scheme 4.1).



Scheme 4.1 Enantioselective Diels-Alder catalyzed by menthoxydichloroaluminum

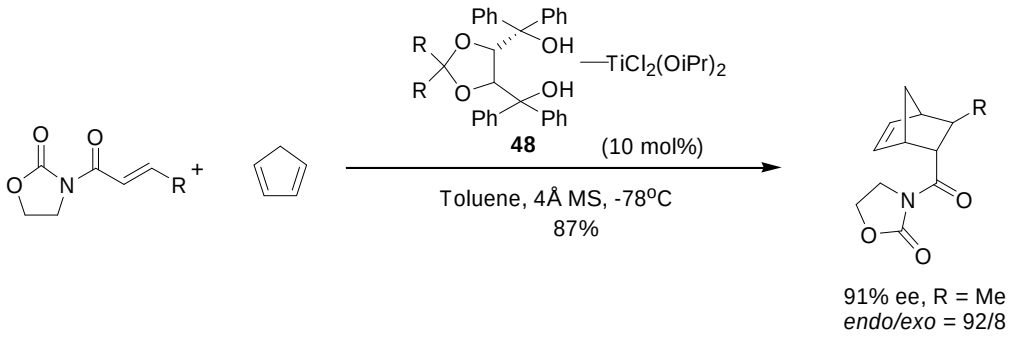
A highly selective asymmetric Diels-Alder reaction was reported by Corey *et al.*[96], using a chiral aluminum reagent prepared *in situ* by the reaction of chiral bis(sulfonamides) with trimethylaluminum or diisobutylaluminum hydride. The chiral aluminum complex **47** (10 mol%) formed acts as a catalyst for the cycloadditions of *N*-acryloyl- or *N*-crotonyl-1,3-oxazolidin-2-ones with substituted cyclopentadienes, to give the cycloadducts which are important synthetic intermediates of prostaglandin (Scheme 4.2). Hence this methodology is clearly of outstanding practical utility.



Scheme 4.2 Enantioselective Diels-Alder catalyzed by chiral aluminum reagent

[95] Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.
[96] Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y.-B. *J. Am. Chem. Soc.* **1989,** *111,* 5493. (b) Corey, E. J.; Yu, C.-M.; Kim, S. S. *J. Am. Chem. Soc.* **1989,** *111,* 5495. (c) Corey, E. J.; Imai, N.; Pikul, S. *Tetrahedron Lett.* **1991**, *32*, 7517.

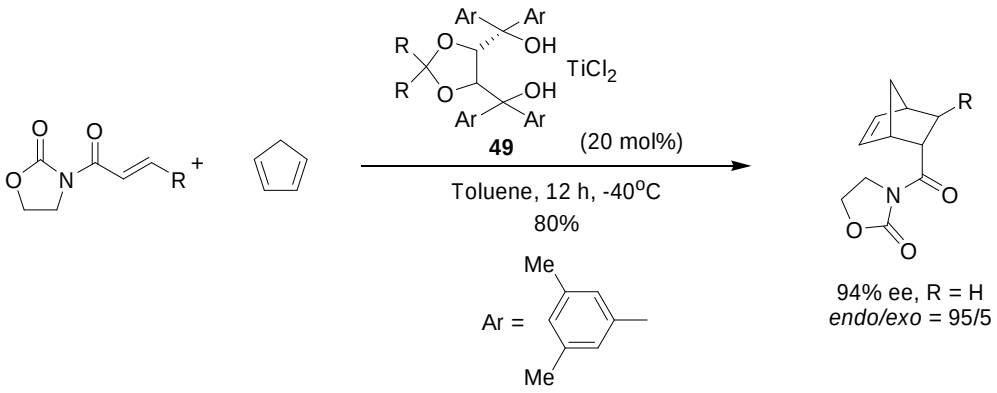
Narasaka *et al*. have found that a chiral titanium complex can be readily prepared by mixing chiral 1,4-diol derived from tartrate and $TiCl_2(O\text{-}i\text{-}Pr)_2$ **48** at room temperature[97]. The reaction between n-crotonyl-1,2-oxazolin-2-one and cyclopentadiene was also found to proceed using a catalytic amount of the chiral titanium complex to afford the adduct with 91% ee in the presence of molecular sieves 4Å (Scheme 4.3).



Scheme 4.3 Enantioselective Diels-Alder catalyzed by chiral titanium complex

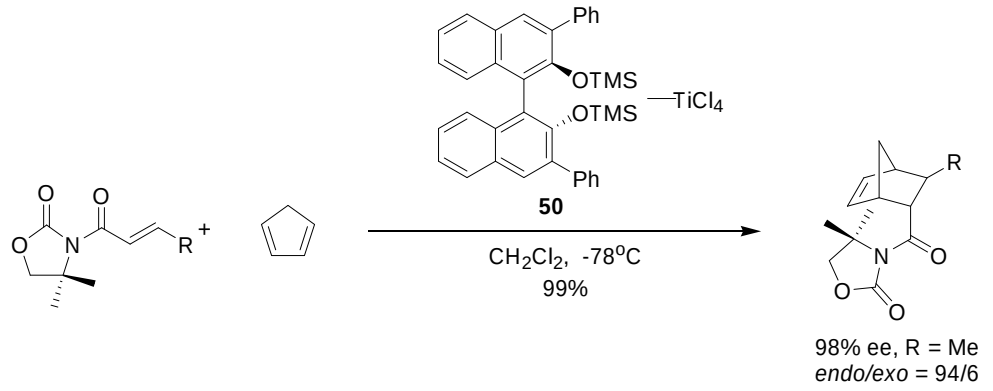
Subsequently, Corey and Matsumura investigated the modified titanium complexes **49** to elucidate the origin of the high enantioselectivity observed by Narasaka *et al.*. They found that the selectivity is influenced by groups at the *meta* positions of aromatic rings.[98] The high enantioselectivity is rationalized by the attractive interactions between the "electron-rich" aromatic rings of the ligand and the "electron-deficient' double bond of the dienophile (with *s*-trans geometry). This results in the suitability of only one face of the olefin for the reaction with cyclopentadiene as depicted in Scheme 4.4.

[97] (a) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986,** 1109. (b) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986,** 1967. (c) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, 2409. (d) Narasaka, K.; Inoue, M.; Okada, N.; Amada, T.; Nakasima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989,** *111*, 5340.
[98] Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991,** *32*, 6289.



Scheme 4.4 Enantioselective Diels-Alder catalyzed by chiral titanium complex

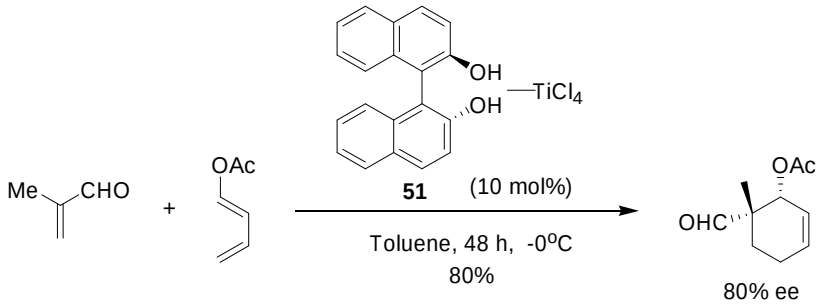
Chapius and Jurczak used a similar chelating crotonamide **50** with cyclopentadiene in the presence of 1 mole equivalent of chiral titanium complex to yield a cycloadduct with very high enantiomeric excess (Scheme 4.5).[99]



Scheme 4.5 Enantioselective Diels-Alder catalyzed by chiral titanium complex

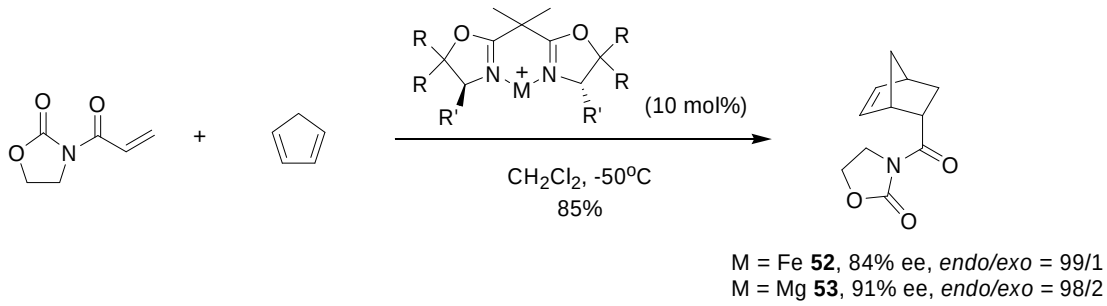
Mikami *et al.* found that the chiral titanium complex **51** derived from BINOL catalyzed the Diels-Alder reaction of 1-acetoxy butadiene and methacrolein to give the cycloadduct in high enantioselectivity (Scheme 4.6).[100]

[99] Chapius, C.; Matsumura, Y. *Tetrahedron Lett.* **1991,** *32,* 6289.
[100] Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991,** *2,* 643.



Scheme 4.6 Enantioselective Diels-Alder catalyzed by chiral titanium complex

Another class of catalyst developed by Corey *et al.* used ionic species of chiral magnesium **52** and iron **53** complexes derived from chiral bisoxazolines (R' = Ph). These complexes catalyze Diels-Alder reaction between cyclopentadiene and a bidentate dienophile to afford the cycloadduct with excellent enantioselectivity. Further studies by Corey *et al.* have also shown that the use of ionic species of Cu(II) catalyzes the same reaction leading to fairly selective formation of the enantiomer.[101] Evans *et al*. have also found that an ionic copper species derived from chiral bis-oxazolines (R' = *t*-Bu) gives high enantioselectivity between cyclopentadiene and bidentate dienophiles (scheme 4.7).[102]

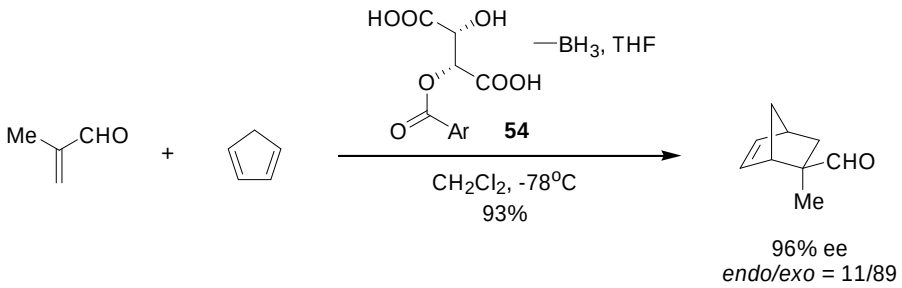


Scheme 4.7 Enantioselective Diels-Alder catalyzed by chiral bis-oxazolines complex

[101] (a) Corey, E. J.; Imai, N.; Zhang, H.-Y. *J. Am. Chem. Soc.* **1991,** *113*, 728. (b) Corey, E. J.; Ishihara, K. *Tetrahedron Lett*. **1992**, *33*, 6807.
[102] Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460.

Various mono- and di-isopinocamphenylhaloboranes have been synthesized and their abilities to act as chiral catalysts in asymmetric Diels-Alder reactions have been investigated for the reaction of 2-methyl-2-propenal with cyclopentadiene. Only catalytic amounts of the catalyst are required for the reaction to proceed, but the enantioselectivity obtained is not high.[103]

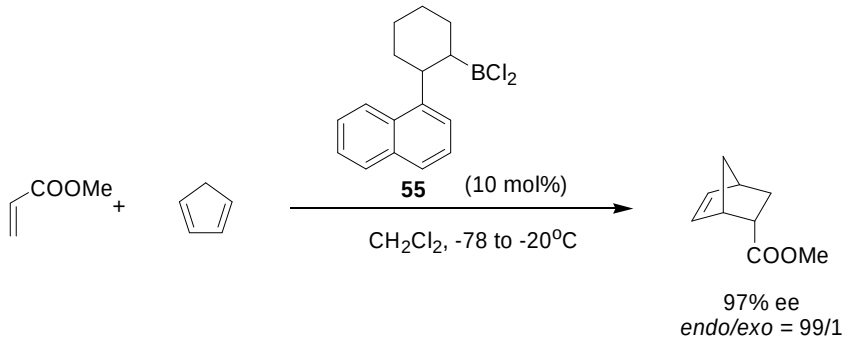
Yamamoto *et al.* have found that acyloxyborane prepared from monoacylated (*R*)-tartaric acids and diborane was successfully employed as a catalyst **54** in the reaction of methacrolein with cyclopentadiene (Scheme 4.8).[104]



Scheme 4.8 Enantioselective Diels-Alder catalyzed by chiral boron complex

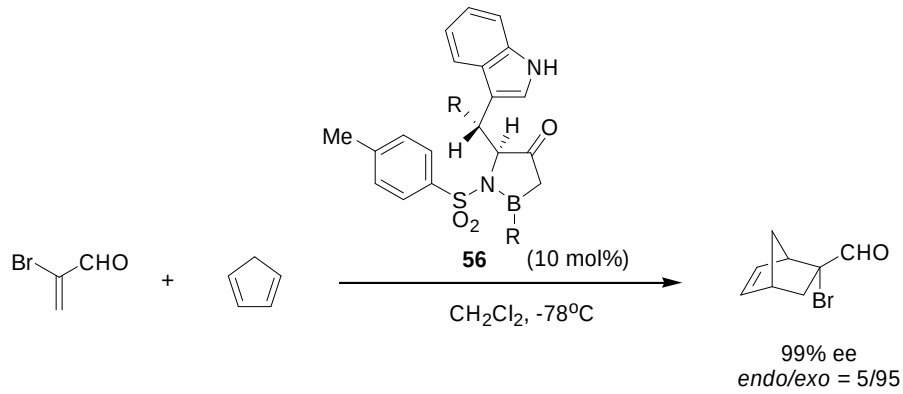
A chiral dichloroborane complex **55** has been designed by Hawkins *et al.* catalyzed the Diels-Alder reaction of methyl crotonate and cyclopentadiene to afford the product in high enantioselectivity (Scheme 4.9).[105] A model based on X-ray structure complex has been proposed to explain the observed enantioselectivity.

[103] Bir, G.; Kaufmann, D. *Tetrahedron Lett.* **1987,** *28*, 777.
[104] (a) Furuta, K.; Miwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **1988,** *110*, 6254 (b) Furuta, K.; Kanematsu, A.; Yamamoto, H.; Takaoka, S. *J. Org. Chem.* **1989**, *54*, 1481.
[105] Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991,** *112*, 7794.



Scheme 4.9 Enantioselective Diels-Alder catalyzed by chiral dichloroborane complex

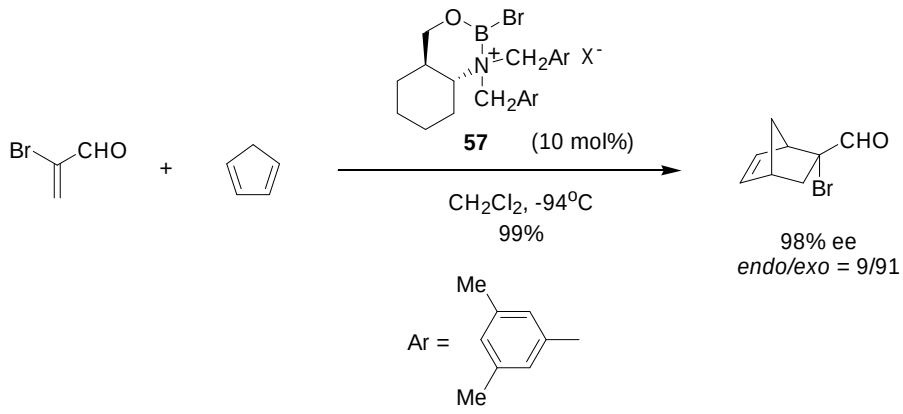
An elegant chiral oxazoborolidinone catalyst **56** has been designed by Corey and Loh in 1992. The catalyst is especially efficient in the asymmetric Diels-Alder reaction between 2-bromoacrolein and various dienes (>90-95% ee) (Scheme 4.10).[106] A transition state based on the attractive interactions between the π-basic indole moiety and the π-acidic dienophile shielded one face of the dienophile has been proposed to explain the observed absolute stereochemistry. This effect is well supported by the discovery of the replacement of the indole portion by a cyclohexyl; or isopropyl group which gives the cycloadduct with the opposite configuration of 70% ee.



Scheme 4.10 Enantioselective Diels-Alder catalyzed by chiral boron complex

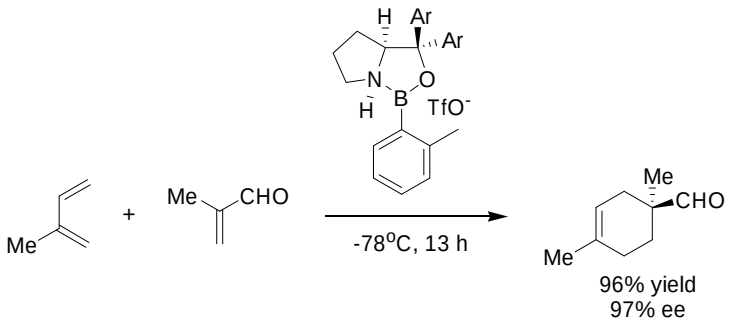
[106] Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.

Promising results have been reported by Corey using cationic oxazaborinane complex **57** as an aldehyde-diene cycloaddition catalyst. α-Substituted aldehydes and various dienes are reported to undergo low-temperature (-94° C) Diels-Alder reaction to give adducts in high *exo* selectivity and excellent enantioselectivity (Scheme 4.11).[107] The catalyst is prepared in seven steps and ligand recovery after the reaction is 85%.



Scheme 4.11 Enantioselective Diels-Alder catalyzed by chiral cationic oxazaborinane complex

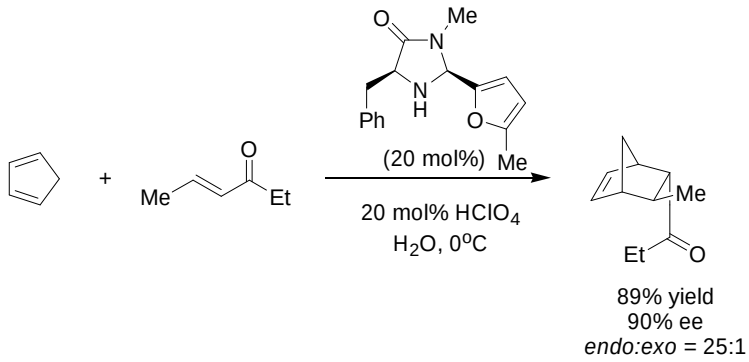
Corey *et al*. demonstrated that the cationic Lewis acid generated from the oxazaborolidines by protonation by trifluoromethanesulfonic (triflic) acid are excellent catalysts for enantioselective reaction of 2-substituted acroleins with a variety of dienes (Scheme 4.12).[108]



Scheme 4.12 Enantioselective Diels-Alder catalyzed by chiral cationic oxazaborinane complex

[107] Hayashi, Y.; Rhode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996,** *118*, 5502.
[108] Corey, E. J.; Shibata, T.; Lee, T.-W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.

MacMillan *et al.* documented an enantioselective Diels-Alder reaction using an organocatalytic strategy involving the activation of α,β-unsaturated ketones catalyzed by a chiral amine catalyst (Scheme 4.13).[109]



Scheme 4.13 Enantioselective Diels-Alder catalyzed by chiral amine organocatalyst

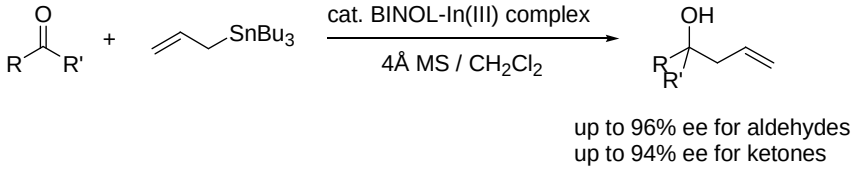
[109] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

4.2 CATALYTIC ENANTIOSELECTIVE DIELS-ALDER VIA A CHIRAL BINOL-INDIUM(III) COMPLEX

4.2.1 INTRODUCTION

The Diels-Alder reaction is one of the most useful and powerful of the known structural transformations in organic synthesis for the construction of six-membered rings. The application of DA reactions encompasses compounds of biological and medicinal significance. Accordingly, much attention has been focused on the development of enantioselective versions, including most recently the use of chiral catalysts. Although the use of catalytic amount of chiral Lewis acid to channel the Diels-Alder reaction in an enantioselective fashion has been well documented by many groups, the development of a novel method for the control of absolute stereochemistry in the Diels-Alder adduct using chiral indium complex has never been reported. Moreover, efforts to develop a chiral indium complex for enantioselective Diels-alder have so far been unsuccessful. Henceforth, the development of an chiral indium Lewis acid catalyst for enantioselective Diels-Alder reaction has been a key focus in our research group.

In previous chapters, we have reported reaction protocols for the catalytic asymmetric allylation of aldehydes and ketones with allyltributylstannanes using chiral indium(III) complex prepared from (*S*)- or (*R*)-BINOL and $InCl_3$ (Scheme 4.14). These procedures have proven remarkably efficient and especially convenient, since the chiral catalyst is prepared very simply in ca. 2 h from commercially available reagents.



Scheme 4.14 Enantioselective allylation of aldehyde catalyzed by BINOL-In(III) complex

Since the enantioselectivity exhibited in these reactions appear to be derived from the structure of the chiral indium-aldehyde complex, we proceed to extend this catalytic system to enantioselective Diels-Alder reaction. To the best of our knowledge, asymmetric Diels-Alder reaction using chiral indium(III) catalyst has never been reported. In this chapter, we report the first successful enantioselective Diels-Alder reaction which employs a chiral (*S*)-BINOL-In(III) complex as precatalyst and allyltributylstannane as activator to generate a potent Lewis acid.

4.2.2 RESULTS AND DISCUSSIONS

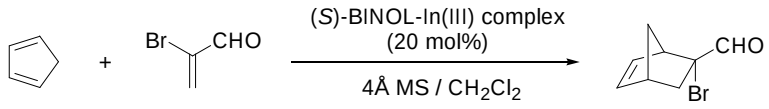
In our initial study, we reacted 2-bromoacrolein with cyclopentadiene using the optimized conditions previously described for the corresponding allylstannane reaction in which the catalyst was prepared by stirring $InCl_3$, (*S*)-BINOL and 4Å MS at rt for 2 h. However, reaction using 20 mol% of this pre-formed catalyst at –78 ^oC afforded a racemic product in 32% yield (Table 20, entry 1). This prompted us to investigate further the active catalytic species of the chiral (*S*)-BINOL-In(III) complex. Previously, we postulated that indium trichloride underwent transmetalation with allyltributylstannane (excess) to facilitate the formation of a chiral BINOL-In-allyl complex, which probably acts as the chiral Lewis acid for the asymmetric allylation reaction.

Indeed, the addition of 0.6 equivalent of allyltributylstannane to a pre-stirred solution of $InCl_3$, (*S*)-BINOL and 4Å MS solution prior to the addition of the dienophile and diene at –78 ^oC afforded the Diels-Alder adduct in 36% yield and 82% ee (Table 20, entry 2). This encouraging result demonstrated that allyltributylstannane was critical for the generation of the active catalytic species, which catalyzed the Diels-Alder reaction in an enantioselective fashion.

Optimization studies on the application of the chiral indium(III) complex as a catalyst for enantioselective Diels-Alder reaction to determine the most favorable reaction parameters were carried out with the results that are summarized in Table 20. Attempt to increase the reaction time using 10 mol% catalyst loading afforded the Diels-Alder adduct in 40% yield with 90% ee (entry 3). We also attempted to

increased the catalyst loading to 20 mol% and found out that the reaction proceeded at –40 °C with a good yield and high enantiomeric excess (entry 5). It is worthy to note that the sequence for the addition of allyltributylstannane during the catalyst preparation was critical for the asymmetric Diels-Alder reaction. When allyltributylstannane was added to a stirred solution of $InCl_3$ prior to the addition of (*S*)-BINOL and 4Å MS, the reaction proceeded with a significant decrease in enantioselectivity (entry 6).

Table 20. Optimization of enantioselective Diels Alder reactions[a]

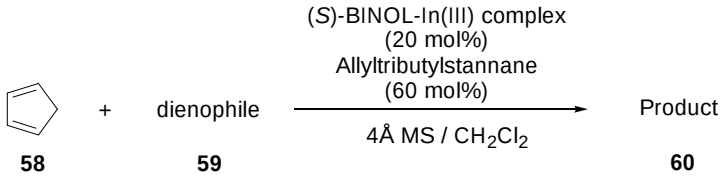


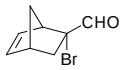
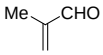
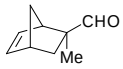
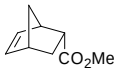
Entry	Cat. (mol%)	Condt. (°C, h)	Yield (%)[b] (*exo:endo*)	ee (%)[c]
1	20	-78, 7	32(89:11)	0
2	10	-78, 7	36 (99:1)	82
3	10	-40, 20	40 (99:1)	90
4	20	-78, 7	38 (98:2)	92
5	20	-40, 20	74 (99:1)	98
6	20[d]	-40, 20	62 (96:4)	54

[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%) in the presence of activated 4Å MS. [b]Isolated yield. [c]Enantioselectivities were determined by reduction ($NaBH_4$) to the primary alcohol, conversion to the Mosher ester, and ^1H NMR analysis. [d]Allyltributylstannane was added to $InCl_3$ prior to addition of (*S*)-BINOL and 4Å MS.

Having optimized the most favorable parameters for the Diels- Alder reactions catalyzed by the chiral In(III) complex, the scope for the reactions of cyclopentadiene with various dienophiles were studied with the results shown in Table 21.

Table 21. Diels-Alder reaction of cyclopentadiene with dienophiles catalyzed by (*S*)-BINOL-In(III) complex[a]

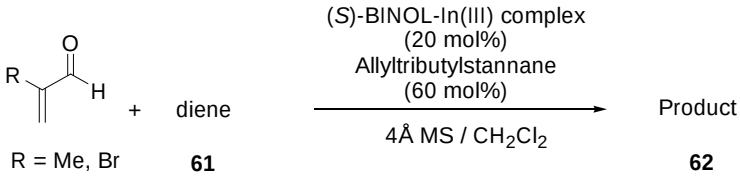


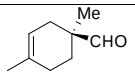
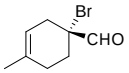
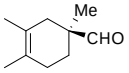
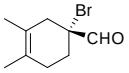
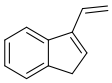
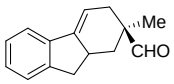
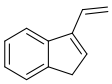
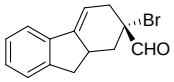
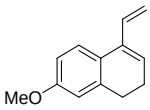
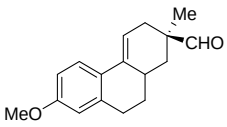
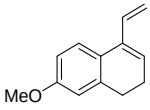
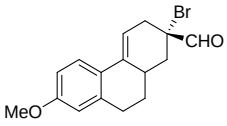
Entry	Dienophile	Product		Condt. (^{o}C, h)	Yield (%)[b] (*exo:endo*)	ee (%)[c]
1		**60a**		-40, 20	74 (99:1)	98
2		**60b**		-20, 20	70 (99:1)	98
3		**60c**		-20, 20	-	-

[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%) in the presence of activated 4Å MS. [b]Isolated yield. [c]Enantioselectivities were determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and ^{1}H NMR analysis.

The reaction of 2-methacrolein and 2-bromoacrolein with cyclopentadiene afforded both Diels-Alder adducts in 98% ee and yield of 70% and 74%, respectively Table 21, entries 1 and 2). However, no product was obtained when cyclopentadiene was reacted with methyl acrylate under the optimized condition (entry 3). Extension of the Diels-Alder reactions to open-chain dienes using 2-methacrolein and 2-bromoacrolein were investigated with the results shown in Table 22.

Table 22. Diels-Alder reaction of open chain 1,3-dienes with 2-methacrolein and 2-bromoacrolein catalyzed by (*S*)-BINOL-In(III) complex[a]



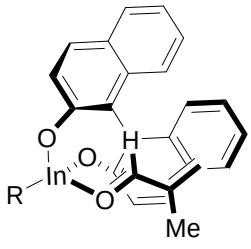
Entry	Diene	Product, **62**	Condt. (°C, h)	Yield (%)[b]	ee (%)[c]
1		**62a** 	rt, 20	35	90
2		**62b** 	-20, 20	70	96
3		**62c** 	rt, 20	63	98
4		**62d** 	-20, 20	74	98
5		**62e** 	-20, 20	71	98
6		**62f** 	-20, 20	72	98
7		**62g** 	-20, 20	75	97
8		**62h** 	-20, 20	77	94

[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%) in the presence of activated 4Å MS. [b]Isolated yield. [c]Enantioselectivities were determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and ^1H NMR analysis, or conversion to the benzoate and HPLC analysis.

This newly developed catalyst exhibited a broad applicability for the reactions of 2-methacrolein and 2-bromoacrolein with a variety of dienes including both cyclic and open-chain dienes, affording the respective Diels-Alder adducts with good yields

and excellent enantioselectivities. The reaction of 2-methyl-1,3-butadiene with 2-methacrolein and 2-bromoacrolein afforded the cycloadducts in 90% and 96% ee, respectively (Table 22, entries 1 and 2). Moreover, the cycloaddition of 2,3-dimethyl-1,3-butadiene to 2-methacrolein and 2-bromoacrolein catalyzed by the BINOL-In(III) complex also afforded both adducts with an excellent enantioselectivity of 98%. (entries 3 and 4). It is noteworthy that the BINOL-In(III) complex also exhibited superior catalytic activity and enantiocontrol in the cycloaddition of dienes containing cyclic structure to both 2-methacrolein and 2-bromoacrolein (entries 5-8). The absolute configurations of the Diels-Alder products shown in Table 21 and 22 have been assigned by measurement of optical rotation and comparison with known substances.[93l]

The stereochemical course of the Diels-Alder reactions catalyzed by the chiral (*S*)-BINOL-In(III) complex can be envisaged in terms of the catalyst-aldehyde pre-transition state assembly **63** depicted in Figure 9**.** In assembly **63,** the aromatic rings of the (*S*)-BINOL effectively screens the rear face of the complexed *s-trans*-α-β-enal from attack by the diene component. As such, this facilitated the addition of the diene to the *si* face (front) of the α-β-double bond leading to the enantiomers shown in Table 21 and 22.

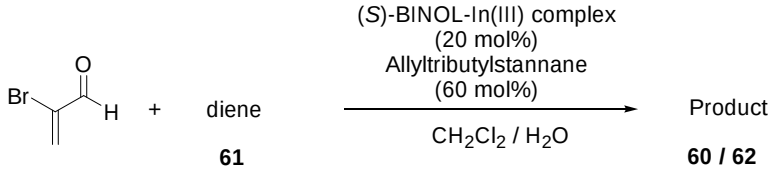


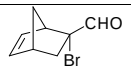
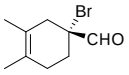
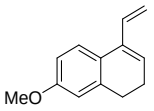
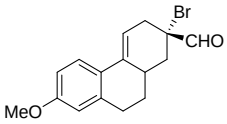
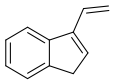
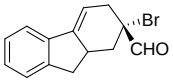
63

Figure 9. Proposed BINOL-In(III)-aldehyde pre-transition state

Next, we proceed to examine the possibility of realizing the catalytic enantioselective Diels-Alder reaction in aqueous media. The preliminary aqueous media reaction was carried out by adding 7.4 equiv water (relative to $InCl_3$) previously reported for the enantioselective aldehyde allylation reaction to a stirred solution of the pre-formed catalyst. Thereafter, 2-bromoacrolein was added to the reaction mixture followed by slow addition of cyclopentadiene at room temperature. Interestingly, the water-tolerant chiral indium complex was able to catalyze the reaction affording the cycloadduct in 64% yield and 94% ee (*exo:endo* = 98:2). On the contrary, no product was obtained when water was added before the formation of the active catalytic indium species. These results suggested that the sequence of water addition was critical for the chiral indium complex to function in aqueous media. The scope for the reaction of 2-bromoacrolein with various dienes was investigated with the results shown in Table 23.

Table 23. Diels-Alder reaction of 2-bromoacrolein with various dienes catalyzed by (*S*)-BINOL-In(III) complex in aqueous media[a]



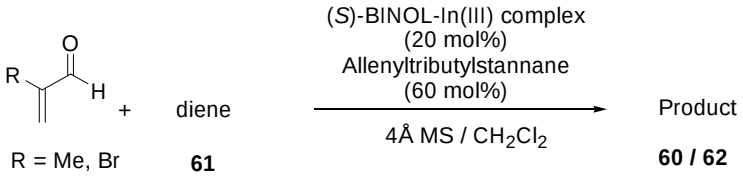
Entry	Diene	Product		Condt. (°C, h)	Yield (%)[b] (exo:endo)	ee (%) [c]
1		**60a**		-20, 20	64 (98:2)	94
2		**62b**		rt, 20	70	80
3		**62h**		-20, 20	61	94
4		**62f**		rt, 20 -20, 20	72 68	66 66

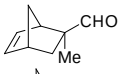
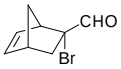
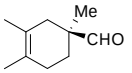
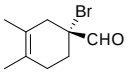
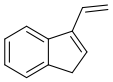
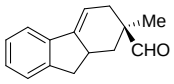
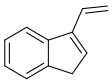
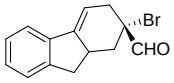
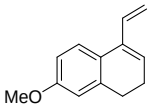
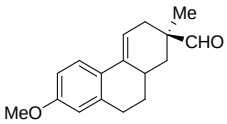
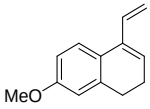
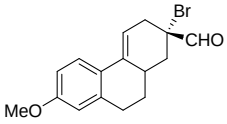
[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%). [b]Isolated yield. [c]Enantioselectivities were determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and ^1H NMR analysis, or conversion to the benzoate and HPLC analysis.

These results suggested that the addition of 4Å MS is important for high asymmetric induction and provide insights into the design of better chiral ligands that may have stronger complexation with indium in order to function in a fully aqueous media.

Previous work in our laboratory has also demonstrated that the BINOL-In(III) complex can function as effective chiral Lewis acid catalysts in the enantioselective propargylation and allenylation of aldehydes using allenyltributylstannanes. Based on this experience, we envision that indium underwent a transmetalation reaction with allenyltributylstannanes to form an indium allenylic species which complexes with (*S*)-BINOL to afford the active chiral catalytic species. These results revealed that allenyltributylstannanes can also act as a potential 'activator' for the chiral indium complex. A study was initiated to investigate the use of allenyltributylstannanes as alternative activators for the BINOL-In(III) system for the enantioselective Diels-Alder reaction. The results are displayed in Table 24.

Table 24. Enantioselective Diels-Alder reaction catalyzed by (*S*)-BINOL-In(III) complex using allenyltributylstannanes as activators[a]



Entry	Diene	Product		Condt. (°C, h)	Yield (%)[b]	ee (%)[c]
1		**60a**		-20, 20	62	45
2		**60b**		rt, 20	70	96
3		**62c**		rt, 20	12	-[d]
4		**62d**		-20, 20	52	35
5		**62e**		-20, 20	36	32
6		**62f**		-20, 20	65	90
7		**62g**		-20, 20	35	30
8		**62h**		-20, 20	72	94

[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22mol%), $InCl_3$ (20 mol%) and allenyltributylstannane (60 mol%). [b]Isolated yield. [c]Enantioselectivities were determined by reduction to the primary alcohol ($NaBH_4$), conversion to the Mosher ester, and ^1H NMR analysis, or conversion to the benzoate and HPLC analysis. [d]Enantioselectivity not determined.

Investigation into the utility of allenyltributylstannanes as activators for the pre-catalyst revealed that the enantiocontrol facilitated by the resultant BINOL-In(III) complex was less superior to using allyltributylstannanes. As shown in Table 24, the

enantioselective Diels-Alder reaction using 2-methacrolein as the dienophile with both cyclic and open-chain dienes gave the corresponding cycloadducts in low chemical yields and enantioselectivities (Table 24, entries 1, 3, 5 and 7). It is noteworthy that the reaction of 2-bromoacrolein with cyclic diene (entry 2) and dienes containing cyclic structure (entries 6 and 8) gave the respective cycloadducts in excellent enantioselectivity except for 2,3-dimethyl-1,3-butadiene which afforded the product in moderate yield and low ee. (entry 4). Therefore, allyltributylstannanes proves to be a superior candidate as activators for the chiral indium pre-catalyst compared to allenyltributylstannanes.

4.2.3 CONCLUSIONS

In conclusion, we have developed the first chiral indium complex for catalytic asymmetric Diels-Alder reaction by designing the novel catalyst containing $InCl_3$, (*S*)-BINOL and allyltributylstannane. The main features of this reaction are as follows: (1) the procedure is operationally simple and the catalyst can be simply prepared from commercially available chemicals at ambient temperature; (2) the cycloaddition of a wide variety of cyclic and open-chain dienes to 2-methacrolein and 2-bromoacrolein resulted in good yield and high enantioselectivities; (3) preliminary studies have also shown that this reaction can be carried out in aqueous media; (4) allyltributylstannanes as activators for the pre-catalyst was more efficient compared to allenyltributylstannanes for the reaction. Since the Diels-Alder reaction is one of the most powerful structural transformations in organic synthesis, this contribution should provide a new synthetic strategy for the construction of six-membered rings for complex molecules with medicinal and biological significance.

4.3 APPLICATION OF THE BINOL-INDIUM(III) CATALYTIC ENANTIOSELECTIVE PROCESS FOR THE CONSTRUCTION OF STEROIDAL SCAFFOLD

4.3.1 INTRODUCTION

Interest in the total synthesis of steroids has been widespread ever since the start of the extensive researches of Windaus and Wieland on the earliest known steroids. The members of cholesterol and cholic acid groups have received added impetus as the recognition of the great importance of steroids in medicine has grown.[110] Steroids play vital roles in a broad range of physiological processes across both plant and animal kingdoms. In recent years, the isolation of interesting steroids such as insect molting hormone ecodysterone **64**, withaferin **65** and other withanolides with anti-tumour activity, the sex stimulating steroids antheridiol **66** and the plant growth promoter brassinolide **67**, together with various marine steroids, have stimulated chemists to explore new methodologies for the stereoselective construction of steroidal scaffold (Figure 10).

[110] Woodward, R. B.; Franz, S.; David, T.; Karl, H.; McLamore, W. M. *J. Am. Chem. Soc.* **1952**, *74*, 4223.

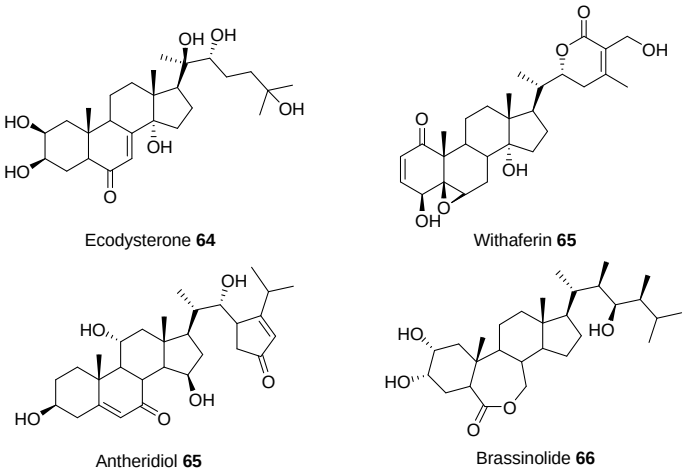


Figure 10. Representative biologically active steroids

The steroidal skeleton **68** comprises four core ring structure denoted A, B, C and D shown in Figure 11.

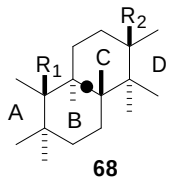
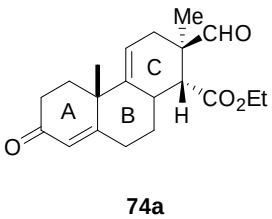


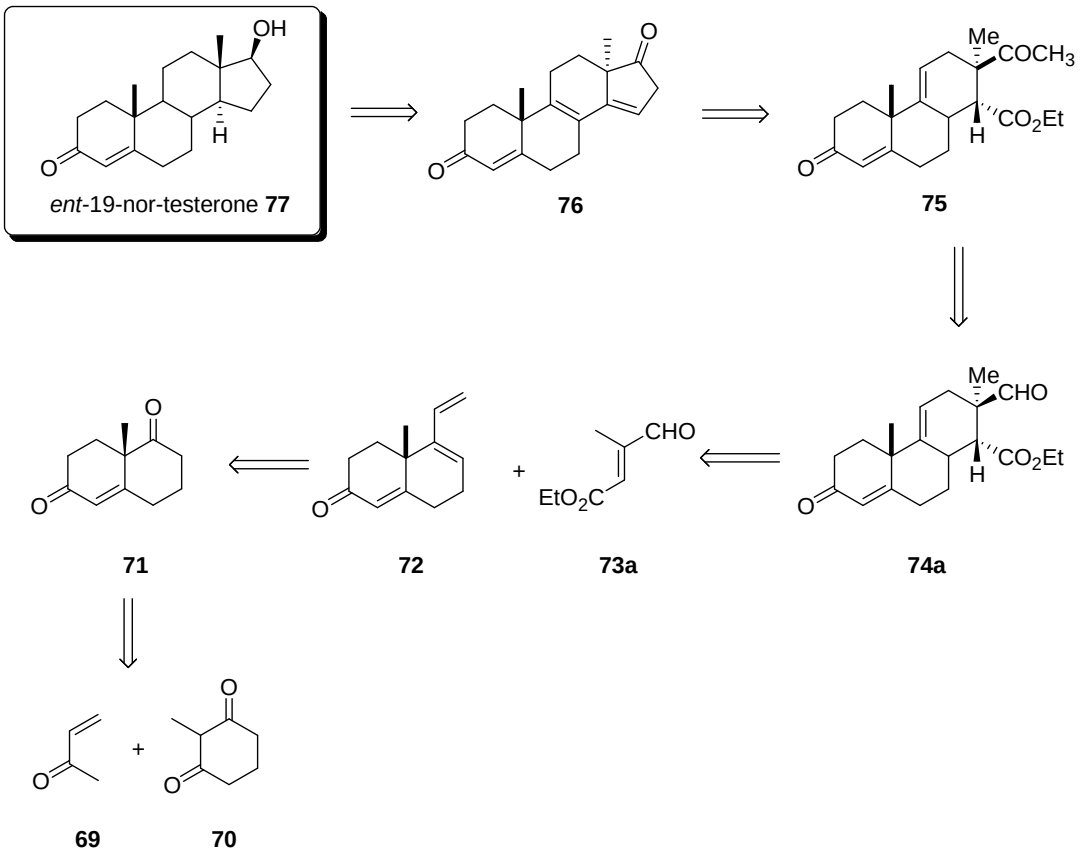
Figure 11. Steroid skeleton comprising 4 core ring structure

In this part, the synthetic studies towards the steroidal skeleton **74a** which encompasses the construction of ring A, B and C will be described. The application of the novel (*S*)-BINOL-In(III) catalyzed asymmetric Diels-Alder reaction for the construction of ring C in the steroidal skeleton **74a** will be the emphases in this part of the thesis.



4.3.2 RESULTS AND DISCUSSIONS

The steroidal precursor **74a** was envisioned to be a key intermediate in the total synthesis of *ent*-19-nor-testosterone **77** (Scheme 4.15). The synthetic approach to the steroidal scaffold **74a** is outlined as shown in Scheme 15. The Wieland-Miescher ketone **71**, (*S*)-3,4,8,8a-tetrahydro-8a-methylnaphthalene-1,6(2H,7H)-dione was foreseen to arise by the L-proline catalyzed Robinson annulation between methyl vinyl ketone **69** and 2-methyl-1,3-cyclohexanedione **70**. Subsequent vinylation on the carbonyl functionality followed by a dehydration step afforded the diene precursor **72**, 4a-Methyl-5-vinyl-4,4a,7,8-tetrahydro-3H-naphthalen-2-one. The construction of the ring C was planned around the Diels-Alder reaction between the diene precursor **72** and the dienophile **73a** affording the steroidal scaffold **74a** with control of stereochemistry. Two notable features of this synthetic plan include the L-proline catalyzed Robinson annulation reactions to produce the Wieland Miescher ketone and the application of the novel (*S*)-BINOL-In(III) catalyzed asymmetric Diels-Alder reaction to control the stereochemistry of the steroidal skeleton.



Scheme 4.15 Retrosynthetic analysis of *ent*-19-nor-testosterone

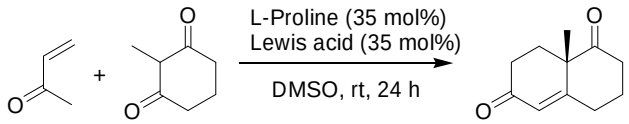
Synthesis of the Wieland Miescher Ketone 84, *(S)*-3,4,8,8a-tetrahydro-8a-methylnaphthalene-1,6(2H,7H)-dione

The first step in the synthetic approach towards the target steroidal scaffold involves the application of the L-Proline catalyzed Robinson annulation to afford the enantiopure Wieland-Miescher ketone, **71**. The Wieland Miescher (W.M.) ketone has been employed on countless occasions in the synthesis of natural products, notably steroids and terpenoids. For this, as well as other applications, the availability of the enantiopure version of the Wieland Miescher ketone is enormously helpful. In practice, however, the enantioselection is on the order of 70% enantiomeric excess using catalytic amount of L-proline as organocatalyst and either DMSO or DMF as solvents. Towards the aim of obtaining a higher enantiopurity of the Wieland Miescher ketone, we envision the addition of equimolar of Lewis acid metal(III) halides catalyst to the L-proline catalyzed Robinson annulation reaction might achieve this purpose.

A study was initiated to investigate the asymmetric Robinson annulation reaction catalyzed by L-proline in the presence of various Lewis acid metal(III) halides, MX_3 as additives using a standardized protocol. A solution of L-proline (0.35 equiv), 2-methyl-1,3-cyclohexandione **70** and $M(III)Cl_3$ (0.35 equiv) in anhydrous DMSO was stirred under nitrogen at room temperature until complete dissolution of the reagents. To this solution, freshly distilled methyl vinyl ketone **69** was slowly added dropwise (1.51 equiv). The reaction was vigorously stirred at this temperature for 24 h and then quenched with saturated NH_4Cl / ethyl acetate. The organic layer and aqueous layer were separated with an addition of saturated NaCl. The aqueous

phase was extracted with ethyl acetate (10 mL x 3) and the combined extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo* to afford the residual crude product which was purified by silica gel chromatography. The results are shown in Table 25.

Table 25. L-proline catalyzed asymmetric Robinson Annulation reaction with Lewis acid M(III)Cl_3 as additives



69 **70** **71**

Entry	Lewis acid	Yield (%)[a]	ee (%)[b]
1	-	49	76[111]
2	$InCl_3$	66	86
3	$InBr_3$	28	80
4	$ScCl_3$	21	78
5	YCl_3	42	4
6	$LaCl_3$	73	38
7	$CeCl_3$	53	18
8	$PrCl_3$	53	38
9	$NdCl_3$	38	26
10	$EuCl_3$	60	8
11	$GdCl_3$	30	36
12	$TbCl_3$	29	11
13	$DyCl_3$	30	12
14	$HoCl_3$	32	4
15	$TmCl_3$	40	15
16	$YbCl_3$	45	26
17	$LuCl_3$	62	28

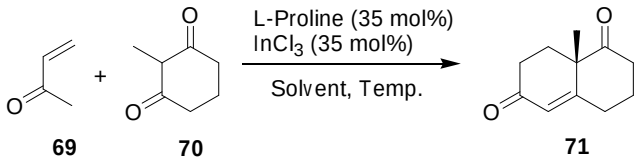
[a]Isolated yield. [b]Enantioselectivities were determined by HPLC analysis.

Investigation into the effect of utilizing equimolar Lewis acid and L-proline for the Robinson annulation reaction revealed that $InCl_3$ (Table 6, entry 1) was the best additive affording the Wieland-Miescher ketone in 86% ee and 61% yield. It is noteworthy that this is of higher yield and enantiopurity than that cited in the literature

(entry 1, 76% ee).[111] The bromide counterpart (entry 2) and $ScCl_3$ (entry 3) afforded the product in 80% ee and 78% ee respectively but with lower yields.

With these encouraging results, the effects of solvent and temperature on the L-proline/$InCl_3$ catalyzed Robinson annulation were surveyed and the results are shown in Table 26.

Table 26. Optimization studies on the L-proline/$InCl_3$ catalyzed Robinson annulation



Entry	Solvent	Temp.(°C)	Yield (%)[a]	ee (%)[b]
1	DMSO	rt	66	86
2	DMSO	18	42	85
3	DMSO	35	66	80
4	*i*-PrOH/DMSO 5 :1	rt	36	66
5	Ether/DMSO 5:1	rt	54	74
6	Hexane/DMSO 5:1	rt	40	74
7	ACN/DMSO 5: 1	rt	26	78
8	CH_2Cl_2	rt	-	-
9	DMF	rt	61	80
10	THF	rt	-	-
11	EtOH	rt	-	-
12	MeOH	rt	15	24

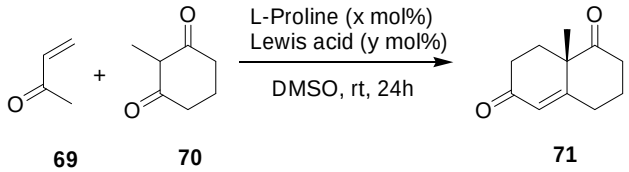
[a]Isolated yield. [b]Enantioselectivities were determined by HPLC analysis.

[111] Tommy, B.; Barbas, C. F. *Tetrahedron Lett.* **2000**, *41*, 5573.

Investigation into the temperature and solvent system for the asymmetric Robinson annulation reaction shows that using DMSO as solvent and executing the reaction at room temperature gave the best result in this series, affording the ketone product in 62% yield and 86% ee (Table 26, entry 1).

Next, the effect of the molar ratio of L-proline and $InCl_3$ on the yield and enantiomeric excess of the reaction was investigated. The results are shown in Table 27.

Table 27. Asymmetric Robinson annulation reaction at various molar ratio of L-proline and $InCl_3$

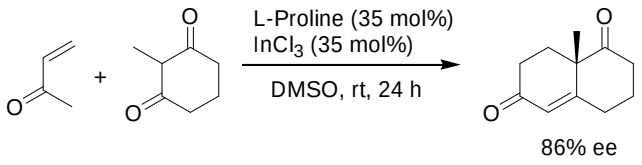


Entry	L-proline (x mol%)	$InCl_3$ (y mol%)	Mole ratio L-proline : $InCl_3$	Yield (%)[a]	ee (%)[b]
1	35.0	35.0	1 : 1	66	86
2	35.0	70.0	1 : 2	49	86
3	35.0	100.0	1 : 2.8	31	86
4	35.0	10.0	3.5 : 1	43	85
5	35.0	4.0	8.8 : 1	47	82

[a]Isolated yield. [b]Enantioselectivities were determined by HPLC analysis.

Investigation into the molar ratio of the L-proline catalyst and $InCl_3$ additive for the Robinson annulation reaction revealed that equimolar of L-proline and $InCl_3$ was the optimal ratio affording the ketone product in 66% yield and 85% ee (Table 27, entry 3). Note that other combination of molar ratio of L-proline and $InCl_3$ can only affect the reaction rate significantly but not the ee value (entries 2-5).

Henceforth, we have successfully increased the enantiopurity of the Wieland-Miescher ketone in the Robinson annulation process (Scheme 4.16) via the addition of $InCl_3$ as metal catalyst in DMSO as organic solvent.

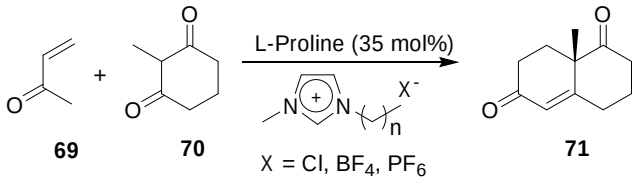


Scheme 4.16 Robinson annulation catalyzed by L-proline/$InCl_3$

Next, we proceed to realize the enantioselective Robinson annulation reaction in ionic liquid which endeavor to recover and recycle the ionic liquid layer containing the L-proline catalyst after a simple extraction of the product.

In our initial study, we investigated the asymmetric L-proline catalyzed Robinson annulation in a series of ionic liquids (a moderate ee value of 76% in DMSO has been reported in the literature[111]) using a standardized protocol. A solution of L-proline (0.35 equiv) and 2-methyl-1,3-cyclohexandione (1.0 equiv) in 1.0 mL of the ionic liquid was stirred under nitrogen at room temperature for 30 min. To this solution, freshly distilled methyl vinyl ketone was slowly added dropwise (1.5 equiv). The reaction was vigorously stirred at this temperature for 48 h and then decanted using diethyl ether (10 mL x 4). The combined organic layers were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residual crude product was purified via silica gel chromatography affording the product as a yellowish oil. The results are shown in Table 28.

Table 28. L-proline catalyzed asymmetric Robinson annulation in various ionic liquid



69 **70** **71**

Entry	Ionic Liquid	Yield (%)[a]	ee (%)[b]
1	[bmim][PF_6^-], *n* = 3	-	-
2	[hmim][PF_6^-], *n* = 5	-	-
3	[bmim][BF_4^-], *n* = 3	76	78
4	[hmim][BF_4^-], *n* = 5	21	48
5	[hmim][Cl^-], *n* = 5	-	-
6	[omim][Cl^-], *n* = 7	-	-
7	[bmim][BF_4^-], *n* = 3	-[c]	-

[a]Isolated yield. [b]Enantioselectivities were determined by HPLC analysis. [c]35 mol% of $InCl_3$ was added as additives to the reaction mixture.

Investigation into the utility of the ionic liquids demonstrated that the [BF_4^-]-counterion type ionic liquid are effective non-conventional solvents for the Robinson annulation. The [bmim][BF_4^-] was the optimal ionic liquid in this series, affording the ketone in 78% ee and 76% yield (Table 28, entry 3) . The corresponding [hmim][BF_4^-] were inferior for this reaction affording the product in poor yield and lower enantioselectivity (entry 4). The [PF_6^-] and [Cl^-] counterion type ionic liquid also proved to be unsuitable solvent for the Robinson annulation. However, the addition of equimolar of $InCl_3$ as a metal catalyst directed towards increasing the enantioselectivity of the reaction in [bmim][BF_4^-] proves to be futile (entry 7). This result indicated that the addition of $InCl_3$ to the reaction in ionic liquid was not feasible as opposed to that conducted in DMSO which exhibited a significant yield and enantioselectivity enhancement in the preceding section.

With the success of the above reactions, we continued our study by exploring the recyclability of the catalyst. We carried out our study by using the reaction of 2-methyl-1,3-cyclohexanedione and methyl vinyl ketone in [bmim][BF_4^-] as a model study. After the reaction was completed, the reaction mixture was extracted with diethyl ether (15 mL x 4) to give the ionic liquid residual that contain the L-proline catalyst. The crude ^{1}H NMR of the crude product indicates the absence of L-proline. To the residue was added 2-methyl-1,3-cyclohexanedione and methyl vinyl ketone and the reaction mixture was stirred at room temperature. This process was repeated five times and it was found that the desired Wieland-Miescher ketone could still be obtained with a comparable yield and ee values. The results are shown in Table 29.

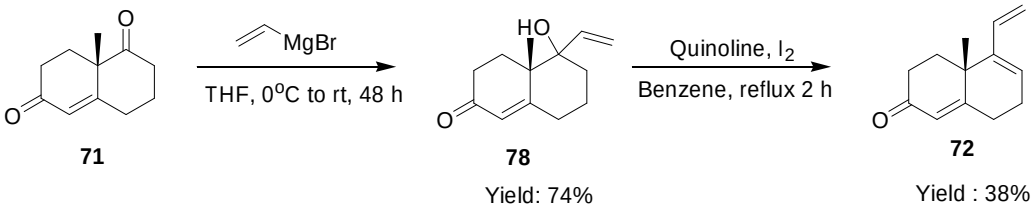
Table 29. Recycling study of the L-proline catalyzed Robinson annulation reaction

Times	Yield (%)[a]	ee (%)[b]
1	80	76
2	72	72
3	70	76
4	70	72
5	68	72

[a]Isolated yield. [b]Enantioselectivities were determined by HPLC analysis.

Synthesis of steroidal diene precursor 85, *(S)*-4,4a,7,8-tetrahydro-4a-methyl-5-vinylnaphthalen-2(3H)-one (b)

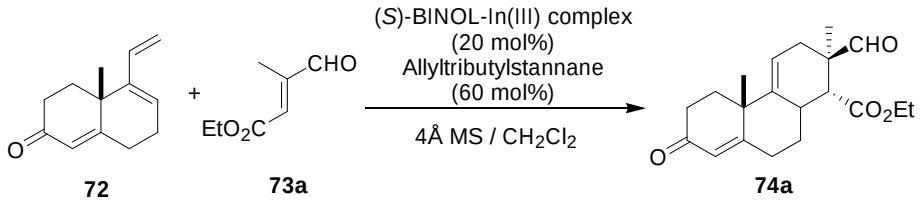
The Wieland-Miescher ketone **71** was reacted with vinylmagnesium bromide in THF to afford the corresponding vinylic alcohol **78** in 74% yield. Subsequent dehydration of the crude alcohol via quinoline and iodine with reflux afforded the diene precursor, **72** in 38% yield (Scheme 4.17).



Scheme 4.17 Synthesis of diene precursor

Application of the BINOL-In(III) catalytic system for the construction of Ring C in 87a

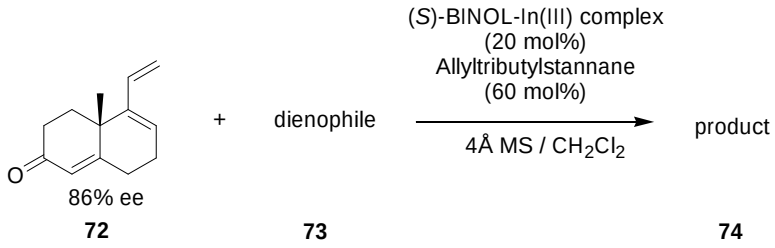
The ring C of the steroidal scaffold **74a** can be realized via an asymmetric Diels-Alder reaction between the diene precursor **72** and the dienophile **73a**. In this section, the application of the BINOL-In(III) chiral complex for the control of stereochemistry in **74a** will be discussed (Scheme 4.18).

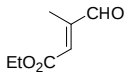
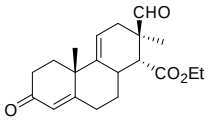
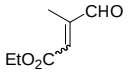
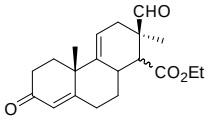
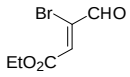
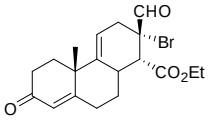
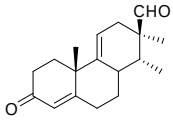
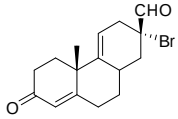
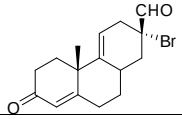


Scheme 4.18 Synthesis of steroidal scaffold via enantioselective Diels-Alder reaction

The application studies of the asymmetric Diels-Alder reaction between the diene precursor **72**, *(S)*-4,4a,7,8-tetrahydro-4a-methyl-5-vinylnaphthalen-2(3H)-one and a variety of dienophile, **73a - e** to generate steroidal skeleton cycloadducts **74a - e** was investigated and the results shown in Table 30.

Table 30. Enantioselective Diels-Alder reaction of diene **72** with various dienophile catalyzed by (*S*)-BINOL-In(III) complex[a]



Entry	Dienophile	**74**	Product	Yield (%)[b]	de (%)[c]
1		**74a**		-	-
2		**74b**		-	-
3		**74c**		-	-
4		**74d**		-	-
5		**74e**		10	88
6		**74e**		52[d]	90

[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%) in the presence of activated 4Å MS. [b]Isolated yield. [c]Diastereoselectivities were determined by HPLC analysis. [d]$InBr_3$ was used as the reagent for the complex formation.

The reaction of the aldehyde-dienophile containing the ester functionality at the β-position, employing either the *E*- or mixture of *E*-and *Z*-isomers (74 : 36) with the diene precursor **72** under the influence of the chiral (*S*)-BINOL-In(III) catalyst did not afford the cycloadducts **74a - b** (Table 30, entries 1 and 2). Attempt to use the bromide counterpart of the aldehyde-dienophile (*E*-isomer) for the enantioselective Diels-Alder reaction was also unsuccessful (entry 3). Moreover, the reaction employing β-substituted methyl group on the aldehyde-dienophile for the formation of cycloadduct **74d** also proves to be futile (entry 4). The ester and the methyl substituent at the β-position of the dienophile probably lower the reactivity of the dienophile and prelude the coordination with the indium and hence subsequent activation for the catalyzed Diels-Alder reaction.

To support this hypothesis, we carried out a model study involving the reaction of the diene precursor **72** and 2-bromoacrolein. Indeed, 2-bromoacrolein underwent cycloaddition with **72** to afford the cycloadduct **74e** in low yield (12%) and high enantioselectivity (88% ee) (entry 5). The absence of β-substituent on 2-bromoacrolein proves to be a critical factor for the proper function of the catalytic system. This prompted us to further investigate the Diels-Alder reaction by using $InBr_3$ as the indium reagent for the complex preparation directed towards obtaining a higher chemical yield and enantioselectivity for the reaction. Interestingly, the Diels-Alder reaction catalyzed by the chiral complex prepared from (*S*)-BINOL and $InBr_3$ afforded the cycloadduct **74e** in 52% yield with excellent enantiomeric excess (90% ee) (entry 6). It is interesting to note that the cyclic α,β-unsaturated enone being a less reactive dienophile did not facilitated self-cycloaddition to afford any products under the influence of the chiral indium complex.

4.3.3 CONCLUSIONS

In conclusion, the application of the (*S*)-BINOL-In(III) catalyzed Diels-Alder reaction for the construction of ring C of the target steroidal skeleton **74a** was not feasible. Nevertheless, the following pertaining to the catalytic system can be concluded: (1) The presence of β-substituent on the aldehyde-dienophile lowers the reactivity of the dienophile and prelude the coordination by the chiral indium(III)-(S)-BINOL complex and hence proves to be ineffective for the catalyzed Diels-Alder reaction; (2) $InBr_3$ as the indium reagent for the complex formation afforded the adduct in higher conversion yield with retention of enantioselectivity; (3) In the model study, 2-bromoacrolein underwent the Diels Alder reaction to afford the adduct **74e** in excellent enantiomeric excess. In this context, the application of the L-proline / $InCl_3$ catalyzed Robinson annulation and (*S*)-BINOL-$InBr_3$ catalyzed Diels-Alder reaction effect the control of absolute stereochemistry in the steroidal scaffold **74e** of 86% ee and 90% ee respectively (Figure 12). Continuing investigations in the laboratory will be directed towards the design of other chiral ligands for the asymmetric Diels-Alder for the synthesis of the potential target steroidal scaffold **74a.**

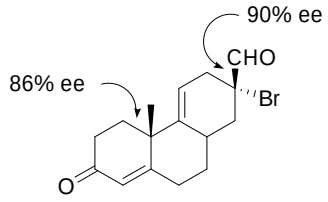


Figure 12. Stereochemical control synthesis of steroidal scaffold **74e**

The goal towards obtaining Wieland Miescher ketone with higher enantiopurity for the construction of biologically active compounds including steroids and terpenoids was realized via the introduction of the equimolar of $InCl_3$ as additives to the L-proline catalyzed Robinson annulation reaction. In practice, however, the enantioselection is in the order of 70% enantiomeric excess, but through the addition of $InCl_3$, the enantioselection improved to 86%. This higher enantiopurity of Wieland Miescher ketone contributes greatly in obtaining higher enantiopurity natural products, notably steroids. The design of other L-proline derivative directed towards the preparation of higher enantiopure Wieland Miescher ketone is currently in progress.

The first L-proline catalyzed Robinson annulation in imidazolium-based ionic liquid [bmim][BF_4^-] has been successfully realized with good enantioselectivity. Further study regarding the recycling of the catalyst has revealed that the L-proline in ionic liquid can be reused at least five times with comparable yields and ee values. The use of a chiral catalyst in an ionic liquid enhances the synthetic value of ionic liquids as green reaction media.

4.4 CATALYTIC ENANTIOSELECTIVE DIELS-ALDER VIA A CHIRAL PYBOX -INDIUM(III) COMPLEX

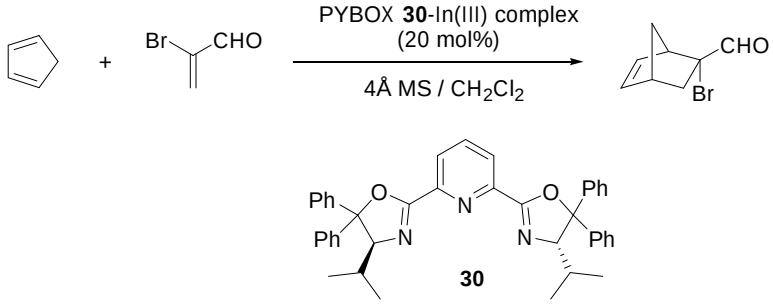
4.4.1 INTRODUCTION

In the previous chapters, we have demonstrated the successful application of the novel chiral PYBOX-In(III) complex as a Lewis acid catalyst for the enantioselective allylation of aldehydes and ketones with allyltributylstannane and enantioselective propargylation and allenylation of aldehydes using allenyltributylstannanes. Based on precedent experience, we proceed to extend this catalytic system to enantioselective Diels-Alder reaction.

4.4.2 RESULTS AND DISCUSSIONS

To evaluate the PYBOX-In(III) catalytic system for the enantioselective Diels-Alder reaction, we carry out the reaction of 2-bromoacrolein and cyclopentadiene in the presence of 20 mol% of the chiral indium(III) complex. The catalyst was prepared as described previously by simply mixing the chiral ligand (*S*,*S*)-PYBOX **30** with $In(OTf)_3$ in CH_2Cl_2 at room temperature for 2 h. Thereafter, the catalyst solution was pre-cooled to -40^oC followed by the slow addition of the dienophile and diene. The product was then isolated by aqueous work up and column chromatography. However, this initial study afforded the cycloadduct in 61% yield and 8% ee. The addition of allyltributylstannane and TMSCl to the catalyst preparation directed towards enhancing the enantioselectivity was attempted and the results shown in Table 31.

Table 31. Optimization of enantioselective Diels Alder reactions catalyzed by (*S*,*S*)-PYBOX **30**-In(III) complex[a]



Entry	Condt. (°C, h)	Yield (%)[b] (*exo:endo*)	ee (%)[c]
1	-40, 20	61 (82:18)	8
2	-40, 20	72 (87:13)	10[d]
3	-40,20	64 (88:12)	6[e]
4	-40, 20	65 (90:10)	12[f]

[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*,*S*)-PYBOX **30** (22 mol%), $In(OTf)_3$ (20 mol%) and activated 4Å MS. [b]Isolated yield. [c]Enantioselectivities were determined by reduction ($NaBH_4$) to the primary alcohol, conversion to the Mosher ester, and ^1H NMR analysis. [d]Allyltributylstannane (0.6 equiv) was added. [e]TMSCl (1.2 equiv) was added. [f]Allyltributylstannane (0.6 equiv) and TMSCl (1.2 equiv) was added.

As shown in Table 31, the addition of either allyltributylstannane or TMSCl as activators for the catalyst generation step was futile since the cycloadducts were isolated with enantiomeric excess of 10% and 6% ee, respectively (Table 31, entries 2 and 3). Moreover, the addition of both allyltributylstannanes (0.6 equiv) and TMSCl (1.2 equiv) as activators for the pre-catalyst also revealed poor enantioselectivity of the cycloadduct (entry 4).

4.4.3 CONCLUSIONS

The extension of the chiral (*S*,*S*)-PYBOX **30**-In(III) complex to catalytic enantioselective Diels-Alder reaction revealed that the catalytic system was unable to function as an chiral Lewis acid for the reaction. Continuing investigations in this laboratory will attempt to elucidate the catalytic species of the chiral indium complex and further extend the scope to other enantioselective organic transformation reactions.

CHAPTER 5

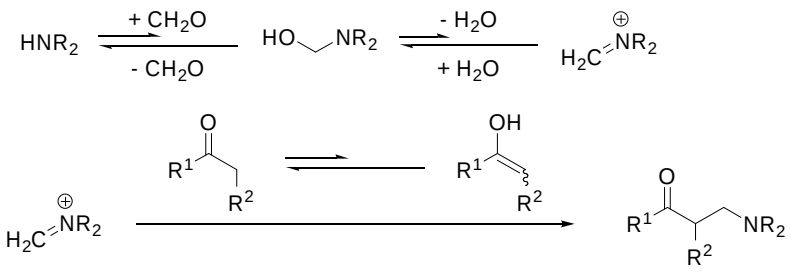
Catalytic Enantioselective Mannich-Type Reaction and Imine Allylation

5.1 OVERVIEW OF CATALYTIC ENANTIOSELECTIVE MANNICH-TYPE REACTION

Enantioselective Mannich-Type Reaction

In 1912, the enormous significance of the aminoalkylation of CH-acidic compounds was first recognized by Carl Mannich which referred to as the Mannich reaction. It is one of the most important classical methods for the preparation of β-amino ketones and aldehydes (Mannich bases). This reaction has since developed into one of the most important C–C bond formation reaction in organic chemistry. It is often used as the key step in numerous pharmaceutical production processes and in the synthesis of natural products. It is also well established in macromolecular chemistry.[112]

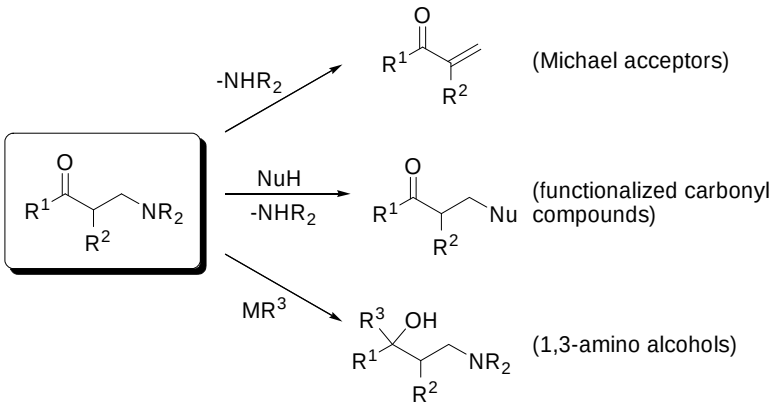
The classical Mannich reaction is a three-component condensation whereby a compound containing an active hydrogen atom, usually an enolizable aldehyde or ketone, is allowed to react with formaldehyde and a secondary amine in a protic solvent. A simplified mechanism is given in Scheme 5.1.



Scheme 5.1 Simplified mechanism of the classical Mannich reaction

[112] Tramontini, M.; Angiolini, L. *Mannich Bases: Chemistry and User*; CRC press: Florida, 1994 and *references therein.*

The formation of both a C–C bond and a C–N bond enables three different molecules to be bonded together in one step. This makes the Mannich reaction an extremely useful transformation. Furthermore, Mannich bases are also versatile synthetic building blocks, since they can be easily converted into a wide range of useful and valuable derivatives as shown in Scheme 5.2.



Scheme 5.2 Mannich bases as synthetic building blocks

Mannich bases and their derivatives have many attractive applications in many industries. Among them, the most important application is in the field of pharmaceutical research.[113] These include drugs like Tramadol (analgesic), Osnervan (anti-parkinsonic), Moban (neuroleptic), Falicain (anaesthetic) and Be-2254 (anti-hypertensive), as presented in Figure 13, and also the synthesis of pharmacologically active derivatives and modification of known drugs.[114]

[113] Arend, M.; Wester, B.; Rish, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044.
[114] (a) Traxler, P.; Trinks, U.; Buchdunger, E.; Mett, H.; Meyer, T.; Müller, M.; Regenass, U.; Rösel, J.; Lydon, N. *J. Med. Chem.* **1995**, *38*, 2441. (b) Dimmock, J. R.; Sidhu, K. K.; Chen, M.; Reid, R. S.; Allen, T. M.; Kao, G. Y.; Truitt, G. A. *Eur. J. Med. Chem.* **1993**, *28*, 313.

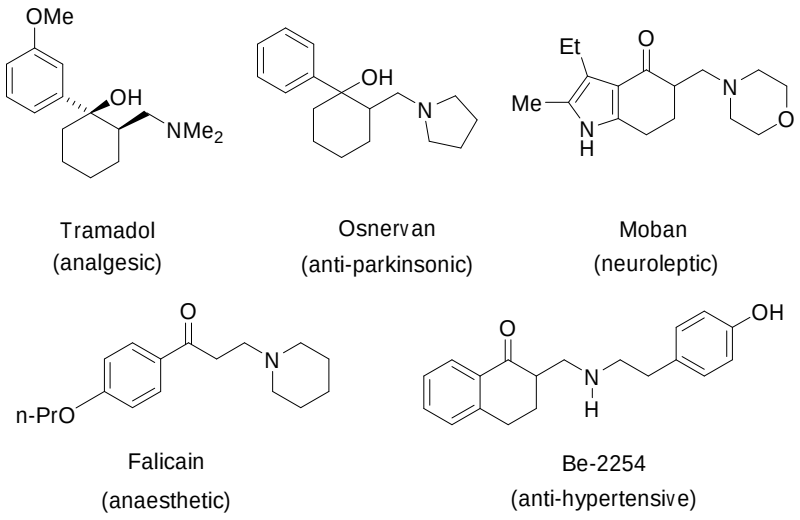


Figure 13. Application of Mannich bases and their derivatives in medicine

Hence, the versatility of the Mannich reaction, along with the potential of Mannich bases in producing further derivatives, makes it possible to attain readily the most varied chemical structures with the practical requirements and applications needed in industry.

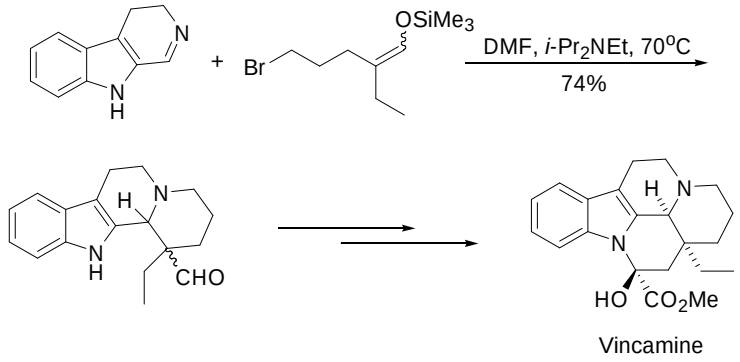
To date, there have been two major advances in the syntheses of Mannich bases, these being the development of extremely mild reaction conditions and the effective control of regio- and stereoselectivities.[115]

Modern versions of the Mannich reaction usually involve the use of pre-formed Mannich reagent such as iminium salts, imines[116] and enol ethers.[117] As compared to the classical Mannich reaction conditions, these pre-formed reagents

[115] Volkmann, R. A.; In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Schreiber, S. L.; Eds: Pergamon Press: Oxford, 1991, vol. 1, chapter 1, p355.
[116] Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H. Eds.: Pergamon Press: Oxford, 1991, vol. 2, chapter 4, p893.
[117] (a) Hooz, J.; Oudenes, J.; Roberts, J. L.; Benderly, A. *J. Org. Chem.* **1987**, *52*, 1347. (b) Hooz, J.; Bridson, J. N. *J. Am. Chem. Soc.* **1973**, *95*, 602. (d) Kobayashi, S.; Ishitani, H. *J. Chem. Soc. Chem. Commun.* **1995**, 1379.

provide a higher concentration of the electrophile, leading to lower reaction temperatures and shorter experimental times. Thus, many undesired side reactions and the use of protic solvents can be avoided. This allows the carbonyl component to be replaced with a more reactive synthetic equivalent such as an enolate. This widely extends the application spectrum of the reaction to include sterically demanding substrates or carboxylic acid derivatives, normally impossible to undergo condensation under the classical conditions. Moreover, the reaction is no longer restricted to aminomethylation, as the more encompassing aminoalkylation is also possible.

The first report of silyl enol ethers participating in a Mannich reaction was found in Oppolozer *et al.* report on the synthesis of (±)-vincamine (Scheme 5.3).[118,119]

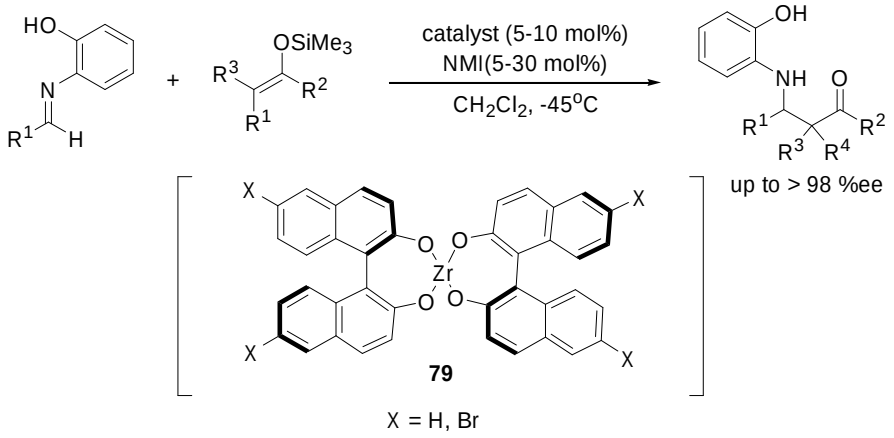


Scheme 5.3 Synthesis of (±)-vincamine

In 1997, Kobayashi *et al.* reported the first catalytic enantioselective Mannich-type reactions of aldimines with silyl enolates using a novel zirconium catalyst **79**

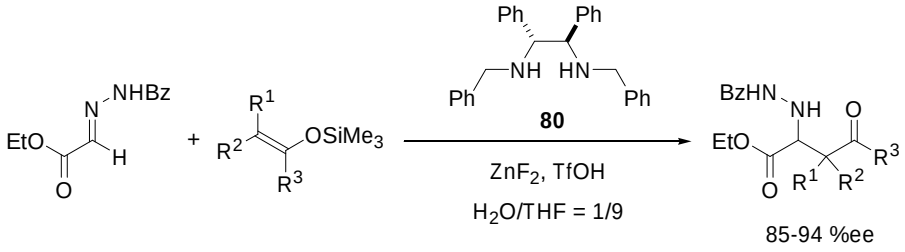
[118] Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H.; Eds.: Pergamon Press: Oxford, 1991, vol. 2, chapter 4, p1015.
[119] Oppolozer, W.; Hauth, H.; Pfaffli, P.; Wenger, R. *Helv. Chim. Acta.* **1977**, *60*, 1801.

(Scheme 5.4).[120] High enantioselectivities in the synthesis of β-amino ester derivatives have been achieved using small amounts of *N*-methlimidazole (NMI) additive. The zirconium catalyst **79** has been shown to be effective for the catalytic activation of aldimines.



Scheme 5.4 Catalytic enantioselective Mannich-type reactions using a novel chiral zirconium catalyst

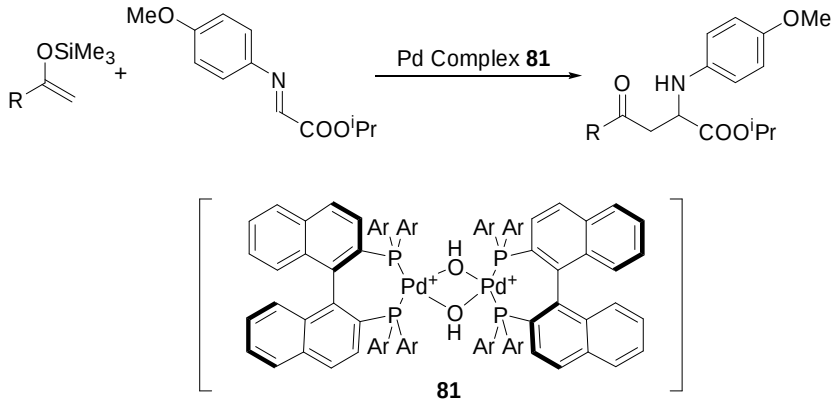
Recently, a catalytic asymmetric Mannich-type reaction in aqueous media was achieved using the combination of zinc fluoride and a chiral diamine ligand **80** (Scheme 5.5).[121] High enantioselectivities were obtained ranging from 85–94% ee. In addition, the use of water and a small amount of TfOH were essential for this reaction to proceed in high yield.



Scheme 5.5 The catalytic asymmetric Mannich-type reaction in aqueous media.

[120] (a) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **1997**, *119*, 7154. (b) Ishitani, H.; Ueno, M.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 8180.
[121] Kobayashi, S.; Hamado, T.; Manabe, K. *J. Am. Chem. Soc.* **2002**, *124*, 5640.

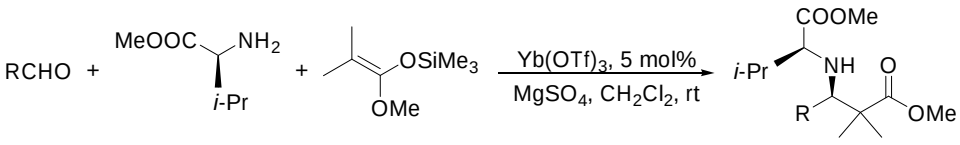
Optically active palladium complexes were also used to catalyze the asymmetric addition of enol silyl ethers to imines. Sodeoka *et al.* developed an enantioselective Mannich-type reaction of silyl enol ethers with imines catalyzed by the chiral binuclear μ-hydroxo palladium(II) complex **81** to obtain highly optically active acylalanine derivatives (up to 90% ee) (Scheme 5.6).[122]



Scheme 5.6 Enantioselective addition of enol silyl ethers to imines catalyzed by palladium complexes.

Using Lewis acids as catalysts, Kobayashi *et al*. reported the discovery of a highly efficient one-pot preparation of β-amino esters using lanthanide triflates in the presence of active 4Å molecular sieves or anhydrous magnesium sulfate.[123] Cozzi *et al.* further applied this methodology to the reaction between silyl enolates and chiral imines with satisfactory results, obtaining the Mannich base products in high diastereoselectivities[124] (Scheme 5.7). In both works, the imines were generated *in situ* from their respective aldehydes and amines and reacted immediately with the silyl enolates in the one-pot reaction.

[122] (a) Hagiwara, E.; Fujii, A.; Sodeoka, M. *J. Am. Chem. Soc.* **1998**, *120*, 2474. (b) Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.***1999**, *121*, 5450.
[123] Kobayashi, S.; Araki, M.; Yasuda, M. *Tetrahedron Lett.* **1995**, *36*, 5773.
[124] Cozzi, P. G.; Simone, B. D.; Umani-Ronchi, A. *Tetrahedron Lett.* **1996**, *37*, 1691.



Scheme 5.7 Mannich reaction using lanthanide triflate with high diastereoselectivity.

The Lewis acid-catalyzed condensation of silyl enol ethers or silyl ketene acetals to preformed imines is an excellent variant of the classical intermolecular Mannich reaction.[125]

In this chapter, the extension of the chiral BINOL-$InCl_3$ catalytic system to the Mannich-type reaction and imine allylation will be discussed.

[125] (a) Ishihara, O.; Funahashi, M.; Hanaki, N.; Miyata, M.; Yamamoto, H. *Synlett* **1994**, 963. (b) Onaka, M.; Ohno, R.; Yanagiya, N.; Izumi, Y. *Synlett* **1993**, 141. (c) Mukaiyama, T.; Akamatsu, H.; Han, J. S. *Chem. Lett.* **1990**, 889. (d) Mukaiyama, T.; Kashiwagi, K.; Matsui, S. *Chem. Lett.* **1989**, 1397. (e) Guanti, G.; Narisano, E.; Banfi, L. *Tetrahedron Lett.* **1998**, *28*, 4331.

5.2 CATALYTIC ENANTIOSELECTIVE MANNICH-TYPE REACTION AND IMINE ALLYLATION VIA A CHIRAL BINOL-INDIUM(III) COMPLEX

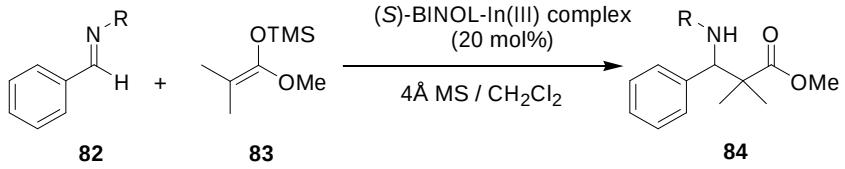
5.2.1 RESULTS AND DISCUSSIONS

To evaluate the (*S*)-BINOL-$InCl_3$ catalytic system for the enantioselective Mannich-type reaction, the reaction of benzylidene-(4-methoxy-phenyl)-amine prepared from benzaldehyde and 4-methoxy-phenylamine with 1-methoxy-1-trimethylsilyloxypropene **83** in the presence of the chiral In(III)-BINOL complex was initiated. The chiral indium(III) catalyst was prepared as described previously by simply mixing (*S*)-BINOL with $InCl_3$ in CH_2Cl_2 at room temperature for 2 h. Based on our previous experience with the Diels-Alder reaction, allyltributylstannane was also added as activator for the pre-catalyst. Thereafter, the catalyst solution was pre-cooled to –78^{o}C followed by the slow addition of the imine and 1-methoxy-1-trimethylsilyloxypropene **83**. The amino ester was then isolated by aqueous work up and column chromatography. The enantioselectivity was determined by chiral HPLC. However, this preliminary reaction resulted in a racemic product with 54% yield.

In order to realize the enantiocontrol of the Mannich-type reaction catalyzed by the chiral indium complex, efforts were directed towards the modification of the R group on the amine counterpart in the imine substrate **82**. The R group on the amine moiety probably played a role in modulating the electronic properties of the nitrogen atom and henceforth promoting successful complexation of the imine to the indium metal, directing the reaction in an enantioselective fashion. A study was initiated to investigate the effects of a variety of imine substrates on the enantioselectivity of the

Mannich-type reaction using a standardized protocol. In this screening process, a series of amine functionality with different R groups was reacted with benzaldehyde to generate the imine substrate **82a - h** prior to reaction with the 1-methoxy-1-trimethylsilyloxypropene **83**. The results are shown in Table 32.

Table 32. Enantioselective Mannich-type reaction of various imine catalyzed by the (*S*)-BINOL-In(III) complex[a]



82 **83** **84**

Entry	R	Product	Yield (%)[b]	ee (%)[c]
1	Ph	**84a**	38	0
2	4-OMePh	**84b**	54	0
3	OMe	**84c**	-	-
4	$CH_2CH=CH_2$	**84d**	35	0
5	2-OHPh	**84e**	-	-
6	$OCOCH_3$	**84f**	-	-
7	NHCOPh	**84g**	-	-
8	$NHCOCH_3$	**84h**	-	-

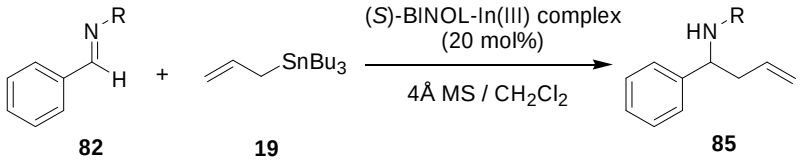
[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%). [b]Isolated yield. [c]Enantioselectivities were determined by HPLC analysis.

Investigation into the R group on the imine revealed that the chiral indium complex was unable to function as an effective chiral Lewis acid for the enantioselective Mannich-type reaction. In all cases, the reaction either gave no desired product or a racemic mixture (Table 32, entries 1, 2 and 4). The electronic properties of the nitrogen atom and the bulkiness of the R group might probably preclude the complexation of the imine substrate to the indium metal. In addition, the Lewis acid property of the indium atom in the chiral complex might have lower affinity for the nitrogen donor in the imine substrate as opposed to the oxygen donor

previously observed in the allylation of carbonyl functionality. Moreover, the 1-methoxy-1-trimethylsilyloxypropene reagent **83** might be an ineffective reagent for this catalytic system. These factors might account for the low reactivity and lack of enantiocontrol for the Mannich-type reaction catalyzed by the chiral indium complex. The products obtained in entries 1, 2 and 4 might be due to some other achiral pathway that are operating under the reaction condition.

Despite the futile results obtained from the Mannich reactions described, we proceed to extend the (*S*)-BINOL-In(III) catalytic system to imine allylation in our attempts to study this catalyst further. A series of imine previously synthesized from the Mannich-type reaction was subjected to allylation using allyltributylstannane **19** under the influence of catalytic amounts of the chiral indium complex. The results are shown in Table 33.

Table 33. Enantioselective imine allylation catalyzed by the (*S*)-BINOL-In(III) complex[a]



82 **19** **85**

Entry	R	Product	Yield (%)[b]	ee (%)[c]
1	Ph	**85a**	-	-
2	4-OMePh	**85b**	12	0
3	4-OMePh	**85b**	15[d]	0
4	OMe	**85c**	-	-
5	OMe	**85c**	-[e]	-
6	$CH_2CH=CH_2$	**85d**	-	-
7	$CH_2CH=CH_2$	**85d**	-[f]	-
9	NHCOPh	**85e**	-	-
10	$NHCOCH_3$	**85f**	-	-

[a]Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol%), $InCl_3$ (20 mol%) and allyltributylstannane (60 mol%). [b]Isolated yield. [c]Enantioselectivities were determined by HPLC analysis. [d,e,f] Tetraallylstannane was used as the allylation reagent.

Investigation into the application of the (*S*)-BINOL-In(III) complex to catalytic imine allylation revealed that most of the reaction does not afford any desired product except for entries 2 and 4 (Table 33) which gave a racemic mixture. This lack of reactivity and enantiocontrol of the chiral complex for the imine allylation might be attributed to the electronic properties of the imine and the Lewis acidity of the indium metal as previously described for the Mannich-type reaction.

5.2.2 CONCLUSIONS

In conclusions, the extension of the chiral (*S*)-BINOL-In(III) complex to catalytic enantioselective Mannich-type and imine allylation revealed that the catalytic system was unable to function as an chiral Lewis acid for both reactions. Continuing investigations in this laboratory will attempt to explore other chiral ligands for successful complexation with indium(III) salts for catalyzing these type of enantioselective organic transformations.

CHAPTER 6

Experimental Section

6.1 GENERAL INFORMATION

Experiments involving moisture and/or sensitive compounds were performed under a positive pressure of nitrogen in flame-dried glassware equipped with a rubber septum inlet. Solvents and liquid reagents were transferred by oven-dried syringes cooled in a dessicator or via double-tipped cannular needles. Reactions mixtures were stirred with Teflon-coated magnetic stirring bars unless otherwise stated. Moisture in non-volatile reagents/compounds was removed by the addition of the stated amount of anhydrous THF, followed by the removal of the solvent and traces of moisture *in vacuo* by means of an oil pump (~30 mmHg, 23-50 ^{o}C) and subsequent purging with nitrogen.

All experiments were monitored by analytical thin layer chromatography (refer to section under "Chromatography"). Solvents were removed *in vacuo* under ~30 mmHg and heated with a water bath at 23 ^{o}C using Büchi rotary evaporator cooled with running water at 0 ^{o}C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[126] Solvents such as hexane, ethyl acetate, dichloromethane and water were freshly distilled prior to use. Anhydrous THF was obtained by distillation under nitrogen atmosphere from a deep purple solution resulting from sodium and benzophenone. Anhydrous dichloromethane was distilled

[126] Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford. 1988.

over calcium hydride under nitrogen atmosphere. Azeotropic drying of starting materials or reagents was performed by the addition of the stated amount of anhydrous tetrahydrofuran, ensued by azeotropic removal of tetrahydrofuran with traces of moisture *in vacuo* followed by subsequent purging with nitrogen. 2-methacrolein was freshly distilled prior to usage. 1,3-cyclopentadiene was cracked at 170 ^{o}C and re-distilled. 2-bromoacrolein[127], 7 -Methoxy-4-vinyl-1,2-dihydro-napthalene[128] and 3-Vinyl-1H-indene was prepared according to literature procedures.[129]

Both triethylamine and dimethyl sulfoxide were distilled over calcium hydride and stored over molecular sieves to maintain dryness. Hydrochloric acid was diluted from concentrated 37% solution. Saturated solutions of ammonium chloride, sodium chloride, sodium bicarbonate, and sodium carbonate were prepared from their respective solids.

Chromatography

Analytical thin layer chromatography was performed using Merck 60 F_{254} pre-coated silica gel plates (0.25 mm thickness). Visualization was accomplished with UV light (254 nm) and iodine crystals, $KMnO_4$ or ceric molybdate solution followed by heating on a hot plate.

[127] (a) Corey, E. J.; Snider, B. B. *J. Am. Chem. Soc.* **1972**, *94*, 2549. (b) Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.
[128] Woski, S. A.; Koreeda, M. *J. Org. Chem.* **1992**, *57*, 5736.
[129] Louis, D. Q.; Alan, N. H.; Franklin, L.; Annette, L. G. *Tetrahedron* **1983**, *39*, 401.

Flash column chromatography was performed using Merck Silica Gel 60 (0.010-0.063 nm) and freshly distilled solvents. Columns were packed as slurry of silica gel in hexane/CH_2Cl_2 and equilibrated with the appropriate solvent/solvent mixture prior to use. The analyte was loaded neat or as a concentrated solution using the appropriate solvent system. The elution was assisted by applying pressure with an air pump.

Instruments & Equipments

Infrared Spectroscopy

Infrared spectra were recorded on a Bio-RAD FTS 165 FT-IR Spectrometer. Solid samples were analyzed as a KBr pressed-disk while liquid samples were either examined neat between KBr salt plates or as a solution in dichloromethane using NaCl liquid cells.

Optical Rotation

Optical rotation was measured using a JASCO DIP-1000 Digital Polarimeter equipped with a sodium vapour lamp at 589 nm. Concentration is denoted as *c* and was calculated as grams per milliliters (g/100 mL) whereas the solvent was indicated in parentheses (*c*, solvent).

Mass Spectroscopy

Mass spectrometries were performed by the staff from the Chemical and Molecular Analysis Center of the National University of Singapore (http://www.chemistry.nus.edu.sg/cmac/ms/MS_Instrument.html). MS (EI) spectra

were recorded on a Hewlett-Packard 5890A gas chromatogram, and HRMS (EI) spectra were recorded on a V>G> Micromass 7035. MS and HRMS (ESI) spectra were recorded on a Finnigan/MAT LCQ quadrupole ion trap mass spectrometer, coupled with the TSP4000 HPLC system and the Crystal 310 CE system. HRMS (FAB) spectra were recorded on a Finnigan MAT 95XL-T. MS and HRMS were reported in units of mass of charge ratio (*m/z*).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on a 300 MHz Bruker ACF 300, 300 MHz Bruker DPX 300 and 500 MHz Bruker AMX 500 NMR spectrometer.

Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethysilane (δ 0.00), using the residual solvent signal as an internal standard: deuterio chloroform-*d*, $CDCl_3$ (^{1}H NMR, δ 7.26, singlet; ^{13}C NMR, δ 77.04, triplet).

Multiplicities were given as: s (singlet), d (doublet), t (triplet), q (quartet), qn (quintet), m (multiplets), br (broad), dd (doublet of doublets), dt (doublet of triplets), ddd (doublet of doublet of doublets) and ddt (doublet of doublet of triplets). Coupling constants (*J*) were recorded in Hertz (Hz). The number of protons (n) for a given resonance was indicated by nH.

Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 8.0 software.

6.2 CATALYTIC ENANTIOSELECTIVE ALLYLATION OF ALDEHYDES

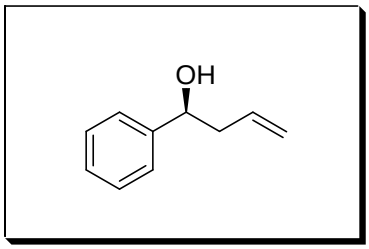
6.2.1 Catalytic Enantioselective Allylation of Aldehydes via a Chiral (*S*)-BINOL-In(III) Complex

Representative procedure for asymmetric allylation of aldehydes : Preparation of (*S*)-1-phenylbut-3-en-1-ol

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) and 4Å molecular sieve (15 mg) were added and the mixture was stirred under nitrogen at room temperature for 2 h to afford a white suspension. Allyltributylstannane (0.31 mL, 1.0 mmol, 2.0 equiv) was added to the resulting suspension and stirred for 10 min. The mixture was then cooled to -78 ^{o}C for 15 min followed by slow addition of benzaldehyde (53 mg in 0.5 mL dichloromethane, 0.5 mmol, 1.0 equiv). The reaction mixture was stirred at -78 ^{o}C for 4 h and then for 16 h at room temperature and then quenched with 5 mL saturated sodium bicarbonate solution at room temperature for 30 min. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as a colorless oil.

Characterization of Secondary Homoallylic Alcohols

(*S*)-1-phenylbut-3-en-1-ol (20a)



(92 % ee)

Colorless oil (76 %); R_f = 0.38 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37-7.27 (m, 5H, aromatic,), 5.89-5.75 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.20-5.13 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.75 (t, *J* = 5.6 Hz, 1H, $CH_2C\mathbf{H}OH$), 2.54-2.49 (m, 2H, $C\mathbf{H_2}CH=CH_2$), 2.20 (br, 1H, CHO**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 143.9, 134.5, 128.4, 127.6, 125.8, 118.4, 73.3, 43.8.

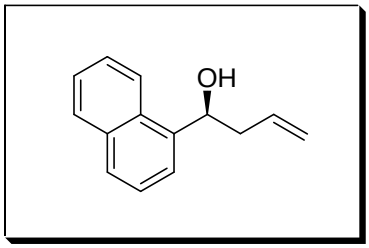
FTIR (neat): 3468, 2932, 1707, 1642, 1494, 1452, 1051, 999, 916, 758, 701 cm^{-1}.

HRMS Calcd for $C_{10}H_{12}0$ [M^+]: 148.0888. Found: 148.0899.

$[\alpha]_D$ = -42.7 ^{o} (*c* = 1.69, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 9.72 min for *R* enantiomer, t_2 = 12.78 min for *S* enantiomer). It has been established that the *R* enantiomer elutes first.[43]

(*S*)-1-Naphthalen-1-yl-but-3-en-1-ol (20b)



(90 % ee)

Colorless oil (55 %); R_f = 0.41 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 8.10-7.46 (m, aromatic, 7H), 6.01-5.87 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.55-5.52 (m, 1H, $CH_2C\mathbf{H}OH$), 5.29-5.17 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 2.82-2.73 (m, 1H, $C\mathbf{H_2}CH=CH_2$), 2.66-2.56 (m, 1H, $C\mathbf{H_2}CH=CH_2$), 2.22 (br, 1H, CHO**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 139.4, 134.7, 133.7, 130.2, 128.9, 127.9, 126.0, 125.5, 125.4, 122.9, 122.8, 118.3, 69.9, 42.8.

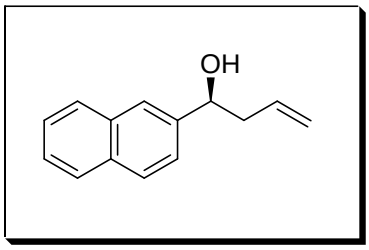
FTIR (neat): 3399cm^{-1}.

HRMS Calcd for $C_{14}H_{14}0$ [M^+]: 198.1047. Found: 198.1052.

$[\alpha]_D$ = - 31.4^o (*c* = 1.61, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column (Hexane : *i*-propanol 95:5, 0.8 mL/min: t_1 = 14.21 min (major), t_2 = 22.81 min (minor). The configuration was assigned by analogy with (*S*)-1-phenylbut-3-en-1-ol assuming a constant preference for the *Si* face of the aldehyde.

(*S*)-1-Naphthalen-2-yl-but-3-en-1-ol (20c)



(90 % ee)

Colorless oil (58 %); R_f = 0.40 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.81 (m, 4H, aromatic), 7.50-7.45 (m, 3H, aromatic), 5.91-5.77 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.22-5.13 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.91 (t, *J* = 6.4 Hz, 1H, $CH_2C\mathbf{H}OH$), 2.68-2.53 (m, 2H, $\mathbf{CH_2}CH=CH_2$), 2.14 (br, 1H, CHO**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 141.2, 134.3, 133.2, 132.9, 128.1, 127.9, 127.6, 126.0, 125.7, 124.4, 123.9, 118.4, 73.3, 43.6.

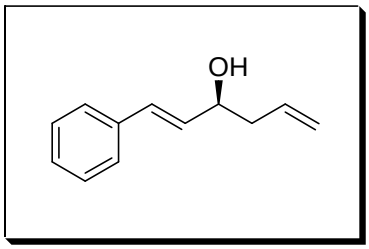
FTIR (neat): 3380cm^{-1}.

HRMS Calcd for $C_{14}H_{14}0$ [M^+]: 198.1047. Found: 198.1054.

$[\alpha]_D$ = -31.1 ^{o} (*c* = 1.40, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column (Hexane : *i*-propanol 95:5, 0.8 mL/min: t_1 = 15.68 min (major), t_2 = 18.12 min (minor). The configuration was assigned by analogy with (*S*)-1-phenylbut-3-en-1-ol assuming a constant preference for the *Si* face of the aldehyde.

(*S*)-1-phenylhexa-1,5-dien-3-ol (20d)



(96 % ee)

Colorless oil (72 %); R_f = 0.40 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40-7.21 (m, 5H, aromatic), 6.60 (d, *J* = 15.9 Hz, 1H, PhC**H**=CH), 6.25 (dd, *J* = 15.9, 6.3 Hz, 1H, PhCH=C**H**), 5.93-5.79 (m, 1H, CH_2C**H**=CH_2), 5.21-5.15 (m, 2H, CH_2CH=C**H$_2$**), 4.37-4.35 (m, 1H, CH_2C**H**OH), 2.48-2.33 (m, 2H, C**H$_2$**CH=CH_2), 1.80 (br, 1H, CHO**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 136.6, 134.0, 131.5, 130.3, 128.5, 127.6, 126.4, 118.4, 71.6, 42.0.

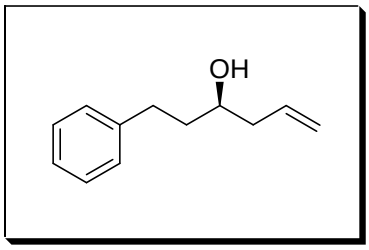
FTIR (neat): 3414 cm^{-1}.

HRMS Calcd for $C_{12}H_{16}0$ [M^+]: 174.1045. Found: 176.1040.

$[\alpha]_D$ = -15.1 (*c* = 1.54, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 13.80 min for *R* enantiomer, t_2 = 23.17 min for *S* enantiomer). It has been established that the *R* enantiomer elutes first.[43]

(*R*)-1-phenylhex-5-en-3-ol (20e)



(90 % ee)

Colorless oil (64 %); R_f = 0.49 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.16 (m, 5H, aromatic), 5.89-5.75 (m, 1H, CH_2CH=CH_2), 5.17-5.12 (m, 2H, CH_2CH=C**H$_2$**), 3.68 (m, 1H, CH_2CHOH), 2.72-2.76 (m, 2H, PhCH_2CH_2), 2.36-2.14 (m, 2H, CH_2CH=CH_2), 1.81-1.76 (m, 2H, PhCH_2CH_2).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.0, 134.6, 128.40, 128.38, 125.8, 118.2, 70.0, 42.0, 38.4, 32.0.

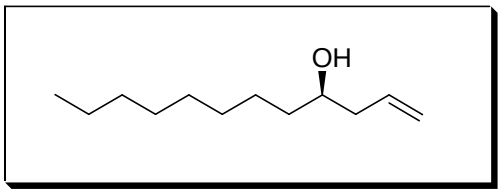
FTIR (neat): 3377, 2928, 1495 cm^{-1}.

HRMS Calcd for $C_{12}H_{16}0$ [M^+]: 176.1201. Found: 176.1199.

$[\alpha]_D$ = +15.9 ^{o} (*c* = 2.15, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 11.35 min for *S* enantiomer, t_2 = 18.52 min for *R* enantiomer). It has been established that the *S* enantiomer elutes first.[43]

(*R*)-dodec-1-en-4-ol (20f)



(94 % ee)

Colorless oil (72 %); R_f = 0.53 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90-5.76 (m, 1H, CH_2CH=CH_2), 5.17-5.11 (m, 2H, CH_2CH=C**H$_2$**), 3.64 (m, 1H, CH_2CHO**H**), 2.36 (m, 2H, C**H$_2$**CH=CH_2), 1.48-1.43 (m,

2H, C**H₂**CHOH), 1.33-1.25 (m, 12H, aliphatic (C**H₂**)$_6$), 0.88 (t, *J* = 6.3 Hz, 3H, CH_2C**H₃**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 134.9, 118.0, 70.7, 41.9, 36.8, 31.9, 29.67, 29.58, 29.3, 25.7, 22.7, 14.1.

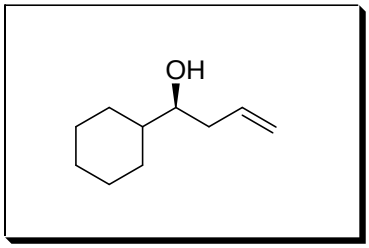
FTIR (neat): 3557, 2924, 2855, 1642, 1464, 995, 913 cm^{-1}.

HRMS Calcd for $C_{12}H_{24}0$ [M^+]: 184.1827. Found: 184.1830.

$[\alpha]_D$ = +6.4^o (*c* = 1.56, CH_2Cl_2)

Chiral resolution using *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mosher acid). The enantiomeric excess was found to be 94 % by 500 MHz ^{1}H NMR analysis of its Mosher derivative at δ 2.40 for the *R* enantiomer and 2.33 for the *S* enantiomer.

(*S*)-1-cyclohexyl-but-3-en-1-ol (20g)



(94 % ee)

Colorless oil (53 %); R_f = 0.43 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90-5.76 (m, 1H, CH_2C**H**=CH_2), 5.15-5.10 (m, 2H, CH_2CH=C**H₂**), 3.43-3.37 (m, 1H, CH_2CHO**H**), 2.33-2.28 (m, 2H, C**H₂**CH=CH_2), 2.18-2.08 (m, 1H, C**H**CHOH), 1.94-1.26 (m, 10H, cyclohexyl C**H₂**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 135.5, 117.9, 74.8, 43.1, 38.8, 29.1, 28.1, 26.5, 26.1, 25.4.

FTIR (neat) 3469, 2923, 2853, 1641, 1449, 1036, 986, 911 cm^{-1}.

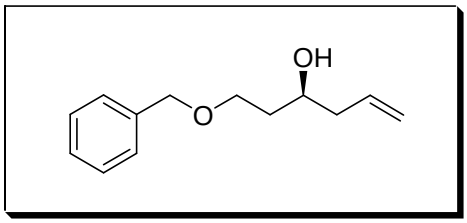
HRMS Calcd for $C_{10}H_{18}0$ [M^+]: 154.1358. Found: 154.1358.

$[\alpha]_D$ = -5.4^o (*c* = 1.13, CH_2Cl_2)

Product was derivatized with 2,4-dinitrobenzolic chloride before the enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column

(Hexane : *i*-propanol 99:1, 0.3 mL/min: t_1 = 42.32 min for the *R* enantiomer, t_2 = 46.07 min for the *S* enantiomer).

(*S*)-1-(benzyloxy-hex-5-en-3-ol (20h)



(94 % ee)

Colorless oil (70 %); R_f = 0.44 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35-7.31 (m, 5H aromatic), 5.90-5.77 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.15-5.08 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.52 (s, $PhC\mathbf{H_2}$, 2H), 3.92-3.84 (m, 1H, $CH_2C\mathbf{H}OH$), 3.76-3.61 (m, 2H, $OC\mathbf{H_2}CH_2$), 2.28-2.22 (m, 2H, $C\mathbf{H_2}CH=CH_2$), 1.80-1.74 (m, 2H, $OCH_2C\mathbf{H_2}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.0, 134.9, 128.5, 127.8, 127.7, 117.6, 73.3, 70.3, 68.9, 41.9, 35.9.

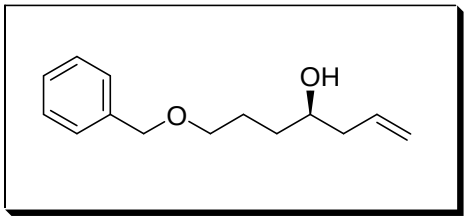
FTIR (neat): 3469, 2920, 2864, 1642, 1452, 1098, 915, 698 cm^{-1}.

HRMS Calcd for $C_{14}H_{20}0_2$ [M^+]: 206.1307. Found: 206.1316.

$[\alpha]_D$ = +9.4 ^{o} (*c* = 1.52, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OB column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 21.71 min for the *R* enantiomer, t_2 = 29.01 min for the *S* enantiomer).

(*R*)-7-(benzyloxy)hept-1-en-4-ol (20i)



(94 % ee)

Colorless oil (70 %); R_f = 0.38 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39-7.28 (m, aromatic, 5H), 5.90-5.77 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.17-5.09 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.52 (s, 2H, $PhC\mathbf{H_2}$), 3.71-3.61 (m, 1H, $CH_2C\mathbf{H}OH$), 3.52 (t, *J* = 5.9 Hz, 2H, $OC\mathbf{H_2}CH_2CH_2$), 2.32-2.13 (m, 2H, $C\mathbf{H_2}CH=CH_2$), 1.78-1.63 (m, 2H, $OCH_2C\mathbf{H_2}CH_2$), 1.53-1.41 (m, 2H, $OCH_2CH_2C\mathbf{H_2}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 138.2, 135.0, 128.4, 127.7, 127.6, 117.7, 73.0, 70.6, 70.4, 42.0, 34.0, 26.2.

FTIR (neat): 3451, 2928, 2862, 1641, 1452, 1097, 1026, 998, 915, 740, 699 cm^{-1}.

HRMS Calcd for $C_{14}H_{20}0_2$ [M^+]: 220.1463. Found: 220.1465.

$[\alpha]_D$ = +7.4 ^{o} (*c* = 1.63, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OB column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 18.84 min for the *R* enantiomer, t_2 = 27.00 min for the *S* enantiomer).

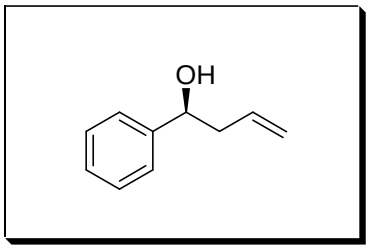
6.2.2 Catalytic Enantioselective Allylation of Aldehydes via a Water-Tolerant Chiral (*S*)-BINOL-In(III) Complex

Representative procedure for asymmetric allylation of aldehydes : Preparation of (*S*)-1-phenylbut-3-en-1-ol

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (33 mg, 0.15 mmol, 0.30 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (47 mg, 0.17 mmol, 0.33 equiv) was added to the mixture and stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min followed by addition of water (20.0 μL, 1.1 mmol, 2.2 equiv) to afford a white suspension. The pre-formed catalyst was further treated with allyltributylstannane (0.22 mL, 0.7 mmol, 1.4 equiv) and stirred for 10 minutes followed by benzaldehyde (53 mg, 0.50 mmol, 1.0 equiv). The reaction mixture was stirred for 20 h at room temperature and then quenched with 5 mL saturated sodium bicarbonate solution at room temperature for 30 min. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as a colorless oil.

Characterization of Secondary Homoallylic Alcohols

(*S*)-1-phenylbut-3-en-1-ol (20a)

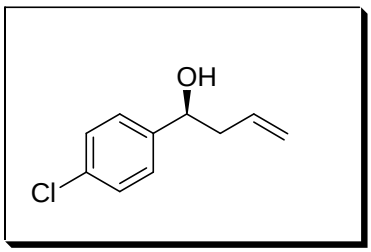


(83 % ee)

Colorless oil (53 %); $[\alpha]_D$ = -44.6 ^{o} (*c* = 2.50, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 9.72 min for *R* enantiomer, t_2 = 12.78 min for *S* enantiomer).

(*S*)-1-(4-chloro-phenyl)but-3-en-1-ol (20j)



(80% ee)

Colorless oil (65 %); R_f = 0.51 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (d, *J* = 2.7 Hz, 2H, aromatic), 7.12 (d, *J* = 2.8 Hz, 2H, aromatic), 5.84-5.70 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.19-5.11 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.70-4.65 (m, 1H, $CH_2C\mathbf{H}OH$), 2.55-2.37 (m, 2H, $C\mathbf{H_2}CH=CH_2$), 2.11 (br, 1H, CHO**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.2, 133.8, 133.0, 128.5, 127.2, 118.7, 72.5, 43.6.

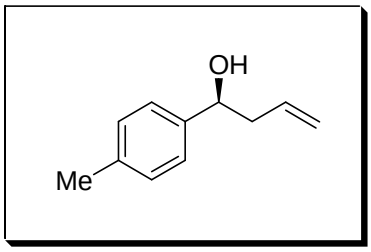
FTIR (neat): 3367,2905, 1573, 1432, 1196 cm^{-1}.

HRMS Calcd for $C_{10}H_{11}ClO$ [M^+]: 182.0498. Found: 182.0502.

$[\alpha]_D$ = -52.7 (*c* = 2.46, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 27.28min for the *S* enantiomer, t_2 = 28.95 min for the *R* enantiomer). The configuration was assigned by analogy with (*S*) 1-phenylbut-3-en-1-ol assuming a constant preference for the *Si* face of the aldehyde.

(*S*)-1-(4-methyl-phenyl)but-3-en-1-ol (20k)



(81% ee)

Colorless oil (51 %); R_f = 0.52 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25 (d, *J* = 8.0 Hz, 2H, aromatic), 7.17 (d, *J* = 8.0 Hz, 2H, aromatic), 5.88-5.74 (m, 1H, CH_2CH=CH_2), 5.20-5.12 (m, 2H, CH_2CH=C**H$_2$**), 4.70 (t, *J* = 6.6 Hz, 1H, CH_2CHOH), 2.53-2.478 (m, 2H, C**H$_2$**CH=CH_2) , 2.35 (s, 3H, aromatic ring C**H$_3$**), 2.04 (br, 1H, CHO**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 140.96, 137.17, 134.60, 129.07, 125.77, 118.15, 73.21, 43.71, 21.06.

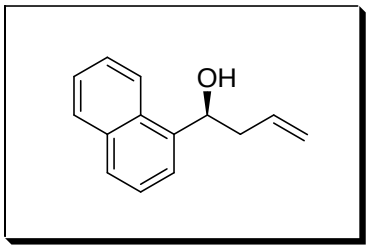
FTIR (neat): 3321, 2915, 1565, 1426, 1201 cm^{-1}.

HRMS Calcd for $C_{11}H_{14}O$ [M^+]: 162.1045 Found: 162.1043.

$[\alpha]_D$ = -54.9 (*c* = 2.84, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 9.29 min for the *R* enantiomer, t_2 = 11.40 min for the *S* enantiomer). The configuration was assigned by analogy with (*S*)-1-phenylbut-3-en-1-ol assuming a constant preference for the *Si* face of the aldehyde.

(*S*)-1-Naphthalen-1-yl-but-3-en-1-ol (20b)

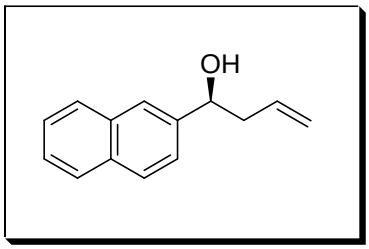


(72 % ee)

Colorless oil (51 %); $[\alpha]_D$ = - 65.1° (*c* = 2.45, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column (Hexane : *i*-propanol 95:5, 0.8 mL/min: t_1 = 14.21 min (major), t_2 = 22.81 min (minor).

(*S*)-1-Naphthalen-2-yl-but-3-en-1-ol (20c)

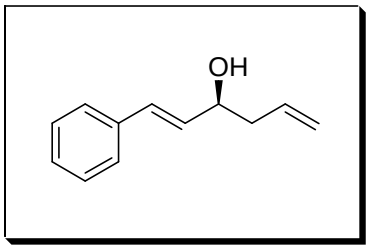


(78 % ee)

Colorless oil (47 %); $[\alpha]_D$ = -52.2 ° (*c* = 2.80, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column (Hexane : *i*-propanol 95:5, 0.8 mL/min: t_1 = 15.68 min (major), t_2 = 18.12 min (minor).

(*S*)-1-phenylhexa-1,5-dien-3-ol (20d)

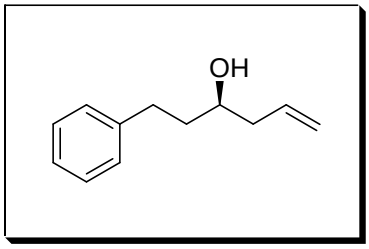


(85 % ee)

Colorless oil (76 %); $[\alpha]_D$ = -16.2 (*c* = 2.64, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 13.80 min for *R* enantiomer, t_2 = 23.17 min for *S* enantiomer).

(*R*)-1-phenylhex-5-en-3-ol (20e)

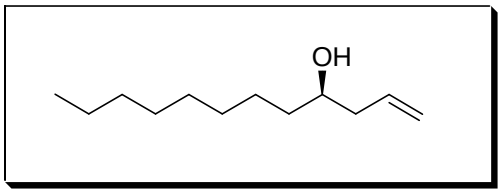


(80 % ee)

Colorless oil (57 %); $[\alpha]_D$ = +9.3 ^{o} (*c* = 4.46, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 11.35 min for *S* enantiomer, t_2 = 18.52 min for *R* enantiomer).

(*R*)-dodec-1-en-4-ol (20f)

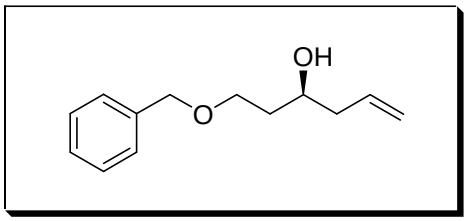


(78 % ee)

Colorless oil (75 %); $[\alpha]_D$ = +6.2^o (*c* = 1.56, CH_2Cl_2)

Chiral resolution using *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mosher acid). The enantiomeric excess was found to be 94 % by 500 MHz ^{1}H NMR analysis of its Mosher derivative at δ 2.40 for the *R* enantiomer and 2.33 for the *S* enantiomer.

(*S*)-1-(benzyloxy-hex-5-en-3-ol (20h)

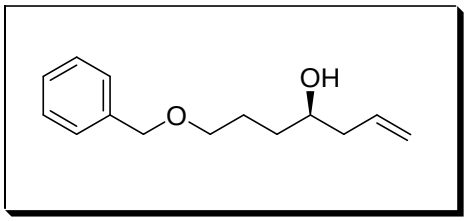


(86 % ee)

Colorless oil (46 %); $[\alpha]_D$ = +8.1 ^{o} (*c* = 1.68, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OB column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 21.71 min for the *R* enantiomer, t_2 = 29.01 min for the *S* enantiomer).

(*R*)-7-(benzyloxy)hept-1-en-4-ol (20i)



(86 % ee)

Colorless oil (42 %); $[\alpha]_D$ = +7.9 ^{o} (*c* = 1.56, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OB column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 18.84 min for the *R* enantiomer, t_2 = 27.00 min for the *S* enantiomer).

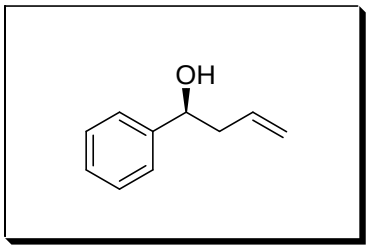
6.2.3 Catalytic Enantioselective Allylation of Aldehydes via a Chiral (*S*)-BINOL-In(III) Complex in Ionic Liquids

Representative procedure for asymmetric allylation of aldehydes : Preparation of (*S*)-1-phenylbut-3-en-1-ol

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) was added to the mixture which was stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture which was then stirred for 10 min. The solvent was removed *in vacuo* after the addition of 1.0 mL of [hmim][PF_6^-]. The pre-formed catalyst in ionic liquid was further treated with allyltributylstannane (0.22 mL, 0.70 mmol, 1.4 equiv) and stirred for 10 min followed by benzaldehyde (53 mg, 0.50 mmol, 1.0 equiv). The reaction mixture was stirred for 40 h at room temperature and then extracted with ether (5 x 10 mL). The combined organic extracts was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as a colorless oil.

Characterization of Secondary Homoallylic Alcohols

(*S*)-1-phenylbut-3-en-1-ol (20a)

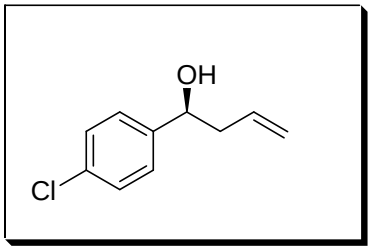


(70 % ee)

Colorless oil (62 %); $[\alpha]_D$ = -31.5 ^{o} (*c* = 1.57, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 9.72 min for *R* enantiomer, t_2 = 12.78 min for *S* enantiomer).

(*S*)-1-(4-chloro-phenyl)but-3-en-1-ol (20j)

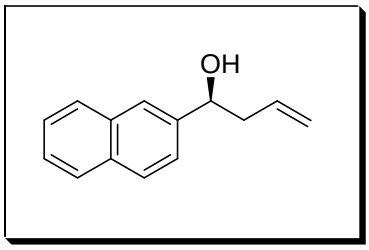


(72% ee)

Colorless oil (42 %); $[\alpha]_D$ = -29.1 (*c* = 1.23, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 27.28min for the *S* enantiomer, t_2 = 28.95 min for the *R* enantiomer).

(*S*)-1-Naphthalen-2-yl-but-3-en-1-ol (20c)

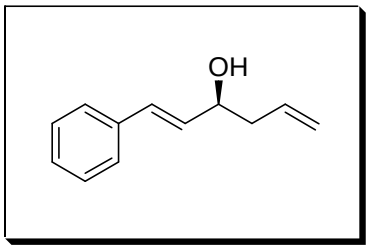


(78 % ee)

Colorless oil (46 %); $[\alpha]_D$ = -25.7 ^{o} (*c* = 1.53, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column (Hexane : *i*-propanol 95:5, 0.8 mL/min: t_1 = 15.68 min (major), t_2 = 18.12 min (minor).

(*S*)-1-phenylhexa-1,5-dien-3-ol (20d)

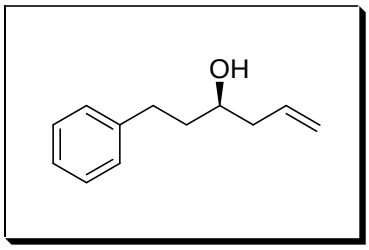


(92 % ee)

Colorless oil (60 %); $[\alpha]_D$ = -16.6 (*c* = 1.61, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 13.80 min for *R* enantiomer, t_2 = 23.17 min for *S* enantiomer).

(*R*)-1-phenylhex-5-en-3-ol (20e)

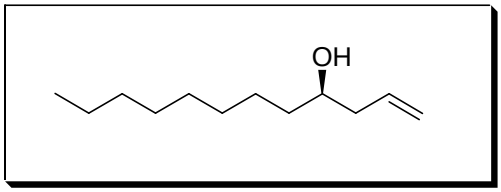


(74 % ee)

Colorless oil (40 %); $[\alpha]_D$ = +11.7 ^{o} (*c* = 1.87, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 11.35 min for *S* enantiomer, t_2 = 18.52 min for *R* enantiomer).

(*R*)-dodec-1-en-4-ol (20f)



(26 % ee)

Colorless oil (72 %); $[\alpha]_D$ = +2.3^o (*c* = 1.62, CH_2Cl_2)

Chiral resolution using *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mosher acid). The enantiomeric excess was found to be 94 % by 500 MHz ^{1}H NMR analysis of its Mosher derivative at δ 2.40 for the *R* enantiomer and 2.33 for the *S* enantiomer.[1]

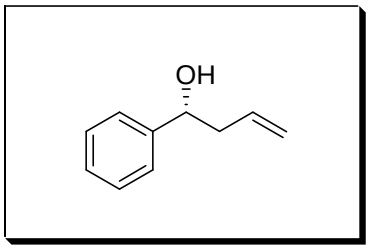
6.2.4 Catalytic Enantioselective Allylation of Aldehydes via a Chiral (*S,S*)-PYBOX-In(III) complex

Representative procedure for asymmetric allylation of aldehydes : Preparation of (*R*)-1-phenylbut-3-en-1-ol

To an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar was added $In(OTf)_3$ (16.9 mg, 0.03 mmol, 0.20 equiv) and 4Å molecular sieve (120 mg). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.0 mL of dichloromethane. (*S,S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)-pyridine (9.9 mg, 0.033 mmol, 0.22 equiv) were added and the mixture was stirred under nitrogen at room temperature for 2 h to afford a white suspension. A mixture of benzaldehyde (15.0 μL, 0.15 mmol, 1.0 equiv) and TMSCl (23.0 μL, 0.18 mmol, 1.2 equiv) in dichloromethane (0.2 mL) was added to the resulting suspension and stirred for 10 min. The mixture was then cooled to -60 ^{o}C for 15 min followed by addition of allyltributylstannane (57.0 μL, 0.18 mmol, 1.2 equiv). The reaction mixture was stirred at -60 ^{o}C for 30 h and then quenched with 2 mL saturated sodium bicarbonate solution at room temperature for 30 min. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as colorless oil.

Characterization of Secondary Homoallylic Alcohols

(*R*)-1-phenylbut-3-en-1-ol (20a)

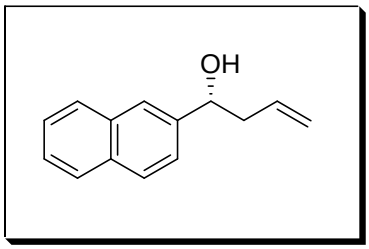


(92 % ee)

Colorless oil (81 %); $[\alpha]_D$ = +45.6^o (*c* = 0.92, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 =10.35 min for *R* enantiomer, t_2 =13.86 min for *S* enantiomer).

(*R*)-1-Naphthalen-2-yl-but-3-en-1-ol (20c)

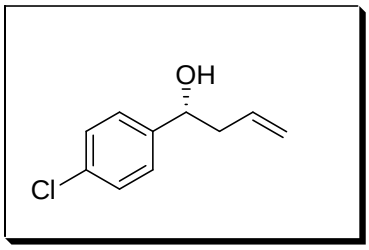


(94 % ee)

Colorless oil (86 %); $[\alpha]_D$ = +41.2 (*c* = 1.60, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column (Hexane : *i*-propanol 95:5, 0.8 mL/min: t_1 = 16.58 min (minor), t_2 = 18.62 min (major).

(*R*)-1-(4-chloro-phenyl)but-3-en-1-ol (20j)

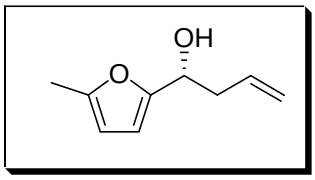


(90% ee)

Colorless oil (61 %); $[\alpha]_D$ = +38.8 (*c* =1.10, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 =27.28min for the *S* enantiomer, t_2 = 28.95 min for the *R* enantiomer).

(*R*)-1-(5-methyl-furan-2-yl)-but-3-en-1-ol (20l)



(94% ee)

Colorless oil (80 %); R_f = 0.5 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.10 (d, *J* = 3.2 Hz, 1H, aromatic), 5.90-5.75 (m, 2H, aromatic and $CH_2C\mathbf{H}=CH_2$,), 5.22-5.11 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 4.67 (q, *J* = 6.4 Hz, 1H, $CH_2C\mathbf{H}OH$), 2.63-2.58 (m, 2H, $C\mathbf{H_2}CH=CH_2$), 2.28 (d, *J* = 0.8 Hz, 3H, $C\mathbf{H_3}$), 2.01 (d, *J* = 5.3 Hz, 1H, CHO**H**,).

^{13}C NMR (75.4 MHz,$CDCl_3$): δ 154.1, 151.6, 133.9, 118.2, 106.8, 105.9, 66.8, 39.9, 13.4.

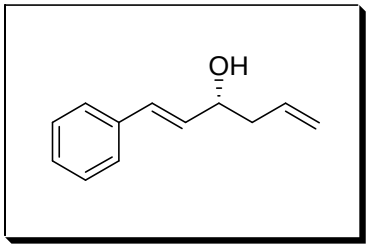
FTIR (neat): 3388, 2921, 1580, 1438 cm^{-1}.

HRMS Calcd for $C_9H_{12}0_2$ [M+]: 152.0837. Found: 152.0839.

$[\alpha]_D$ = -24.8 (*c* = 0.98, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 95:5, 1 mL/min: t_1 = 5.95 min (for the major), t_2 = 7.93 min (for the minor).

(*R*)-1-phenylhexa-1,5-dien-3-ol (20d)

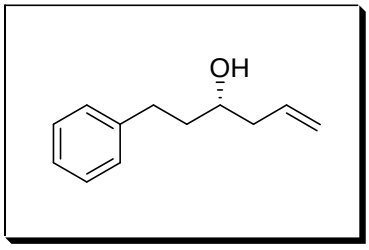


(86 % ee)

Colorless oil (91 %); $[\alpha]_D$ = +12.8 (*c* = 0.88, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 14.69 min for *R* enantiomer, t_2 = 26.58 min for *S* enantiomer).

(*S*)-1-phenylhex-5-en-3-ol (20e)

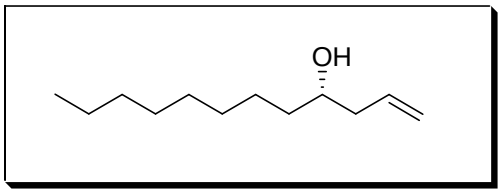


(84 % ee)

Colorless oil (81 %); $[\alpha]_D$ = -14.8 ^{o} (*c* = 1.02, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 15.02 min for *S* enantiomer, t_2 = 25.24 min for *R* enantiomer).

(*S*)-dodec-1-en-4-ol (20f)

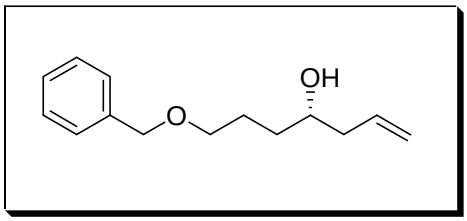


(85 % ee)

Colorless oil (68 %); $[\alpha]_D = -6.2^o$ (*c* = 1.22, CH_2Cl_2)

Chiral resolution using *R*-(+)-α-trifluoromethyl-α-methoxy-phenylacetic acid (Mosher acid). The enantiomeric excess was found to be 94 % by 500 MHz ^{1}H NMR analysis of its Mosher derivative at δ 2.40 for the *R* enantiomer and 2.33 for the *S* enantiomer.

(*S*)-7-(benzyloxy)hept-1-en-4-ol (20i)

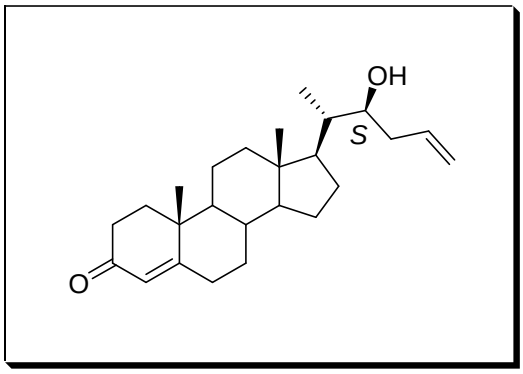


(91 % ee)

Colorless oil (78 %); $[\alpha]_D = -7.2^o$ (*c* = 1.24, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OB column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 22.24 min for the *R* enantiomer, t_2 = 28.95 min for the *S* enantiomer).

20-(1'-hydroxy-3'-buten-1'yl)-3-oxopregn-4-ene (32)



White solid, m.p.178-180 ^{o}C; R_f = 0.3 (1:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.87-5.76 (m, 1H, CH_2C**H**=CH_2), 5.72 (s, 1H), 5.14-5.08 (m, 2H, CH_2CH=C**H$_2$**), 3.72 (q, 1H, CH_2C**H**OH, *J* = 5.2 Hz), 1.18 (s, 3H, C(18)**H$_3$**), 0.92 (d, *J* = 5.6 Hz, 3H, C(21)**H$_3$**), 0.72 (s, CH_3, C(19)**H$_3$**).

^{13}C NMR (75.4MHz,$CDCl_3$): δ 199.6, 171.5, 135.7, 123.8, 117.5, 72.4, 55.8, 53.8, 52.6, 42.4, 40.2, 40.1, 39.7, 38.6, 35.7, 35.8, 34.0, 32.9, 32.0, 27.7, 24.1, 21.1, 17.4, 11.9, 11.7.

FTIR (neat): 3368, 2939, 1674, 1432, 1229, 886 cm^{-1}.

HRMS Calcd for $C_{25}H_{38}0_2$ [M^+]: 370.2872. Found: 370.2888.

Minor (22*R*)isomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.74 (s, 3H, C(19)H_3).

6.3 CATALYTIC ENANTIOSELECTIVE ALLYLATION OF KETONES

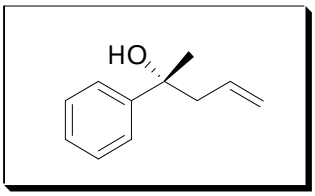
6.3.1 Catalytic Enantioselective Allylation of Ketones via a Chiral (*S*)-BINOL-In(III)Complex

Representative procedure for asymmetric allylation of ketones : Preparation of (*S*)- 2-phenyl-pent-4-en-2-ol

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InBr_3$ (0.35 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to addition of 1.0 mL of dichloromethane. *(R)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) and 4Å molecular sieve (15 mg) were added and the mixture was stirred at room temperature for 2 h to afford a white suspension. Allyltributylstannane (0.47 mL, 1.5 mmol, 3.0 equiv) was added to the resulting suspension and stirred for 10 min followed by the slow addition of acetophenone (0.06 mL in 0.5 mL dichloromethane, 0.50 mmol, 1.0 equiv). The reaction mixture was stirred for 72 h at room temperature and then quenched with 5 mL ammonium chloride. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as a colorless oil.

Characterization of Tertiary Homoallylic Alcohols

(*R*)-2-Phenyl-pent-4-en-2-ol (36a)



(82 % ee)

Colorless oil (74 %); R_f = 0.48 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48-7.21 (m, 5H, aromatic), 5.72-5.57 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.18-5.10 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 2.70 (dd, *J* = 13.9, 6.3 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 2.51 (dd, *J* = 13.6, 8.0 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 2.08 (s, 1H, O**H**), 1.56 (s, 3H, $C\mathbf{H_3}$)

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 147.6, 133.6, 128.1, 126.6, 124.7, 119.4, 73.6, 48.4, 29.8.

FTIR (neat): 3415, 3075, 2974, 1640, 1445, 914, 766, 700 cm^{-1}.

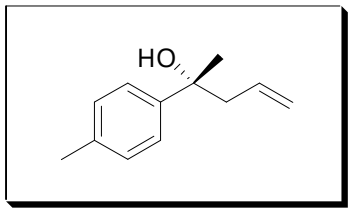
HRMS Calcd for $C_{12}H_{16}0$ [M - H_2O]: 144.0939 Found: 144.0934

$[\alpha]_D$ = +37.6^o (*c* = 1.52, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 9.96 min for major enantiomer, t_2 = 12.78 min for minor enantiomer).

The absolute configuration of the product was determined by comparison of the sign of the optical rotation with the literature value.[64] The *re* face of the ketone is attacked when the (*R*)-catalyst is used, in agreement with the constant preference shown by the BINOL-based catalyst.

(*R*)-2-*p*-Tolyl-pent-4-en-2-ol (36b)



(84 % ee)

Colorless oil (41 %); R_f = 0.49 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (d, *J* = 8.0 Hz, 2H, aromatic), 7.15 (d, *J* = 8.4 Hz, 2H, aromatic), 5.70-5.56 (m, 1H, CH_2CH=CH_2), 5.16-5.10 (m, 2H, CH_2CH=CH_2), 2.68 (dd, *J* = 13.6, 6.4 Hz, 1H, CH_2CH=CH_2), 2.49 (dd, *J* = 13.6, 8.4 Hz, 1H, CH_2CH=CH_2), 2.34 (s, 3H, aromatic ring CH_3), 2.04 (s, 1H, OH), 1.56 (s, 3H, CH_3)

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 144.8, 136.1, 133.9, 128.8, 124.7, 119.1, 73.5, 48.5, 29.8, 20.9.

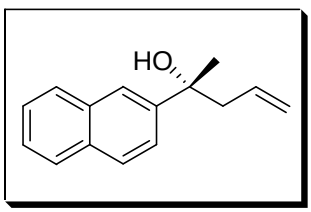
HRMS Calcd for $C_{12}H_{16}0$ [M - H_2O]: 158.1095 Found: 158.1093

$[\alpha]_D$ = +12.8^o (*c* = 2.03, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 6.98 min for major enantiomer, t_2 = 9.64 min for minor enantiomer).

The configuration was assigned by analogy with (*R*)-2-phenyl-pent-4-en-2-ol assuming a constant preference for the *re* face of the ketone.

(*R*)-2-Naphthalen-2-yl-pent-4-en-2-ol (36c)



(84 % ee)

Colorless oil (80 %); R_f = 0.54 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92 – 7.82 (m, 4H, aromatic), 7.56 – 7.45 (m, 3H, aromatic), 5.70-5.59 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.19-5.10 (m, 2H. $CH_2CH=C\mathbf{H_2}$), 2.80 (dd, *J* = 13.6, 6.3 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 2.59 (dd, *J* = 13.6, 8.4 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 2.19 (s, 1H, O**H**), 1.64 (s, 3H, $C\mathbf{H_3}$),

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.4, 131.0, 130.5, 129.6, 125.5, 125.2, 124.8, 123.4, 123.1, 120.9, 120.6, 116.9, 71.2, 45.7, 27.3.

FTIR (neat): 3433, 3058, 2929, 2923, 2851, 1638, 1600, 1376, 916, 857, 818, 748 cm^{-1}.

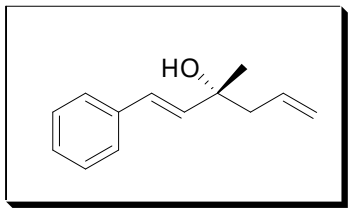
HRMS Calcd for $C_{14}H_{14}0$ [M – H_2O]: 194.1095. Found: 194.1091

$[\alpha]_D$ = +39.8^o (*c* = 0.92, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 26.28 min for minor enantiomer, t_2 = 31.30 min for major enantiomer).

The configuration was assigned by analogy with (*R)*-2-phenyl-pent-4-en-2-ol assuming a constant preference for the *re* face of the ketone.

(*R*)-3-Methyl-1-phenyl-hexa-1,5-dien-3-ol (36d)



(90% ee)

Colorless oil (82 %); R_f = 0.43 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 – 7.19 (m, 5H, aromatic), 6.60 (d, *J* = 16.1 Hz, 1H, $PhC\mathbf{H}=CH$), 6.30 (d, *J* = 16.0 Hz, 1H, $PhCH=C\mathbf{H}$), 5.91-5.77 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.19-5.14 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 2.45 (dd, *J* = 13.6, 6.4 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 2.36 (dd, *J* = 13.6, 8.0 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 1.77 (s, 1H, O**H**), 1.39 (s, 3H, $C\mathbf{H_3}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 137.0, 136.3, 133.6, 128.6, 127.5, 127.4, 126.4, 119.3, 72.4, 47.4, 28.0.

FTIR (neat): 3410, 3078, 1640, 970, 916, 748, 693 cm^{-1}.

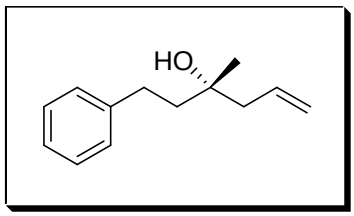
HRMS Calcd for $C_{10}H_{16}0$ [M – H_2O]: 170.1095. Found: 170.1091

$[\alpha]_D$ = +63.5^o (*c* = 1.19, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 28.92min for major enantiomer, t_2 = 33.59 min for minor enantiomer).

The configuration was assigned by analogy with (*R)*-2-phenyl-pent-4-en-2-ol assuming a constant preference for the *re* face of the ketone.

(*S*)-3-Methyl-1-phenyl-hex-5-en-3-ol (36e)



(80 % ee)

Colorless oil (60 %); R_f = 0.51 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 – 7.19 (m, 5H, aromatic), 5.96-5.82 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.19-5.12 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 2.74-2.68 (m, 2H, $PhC\mathbf{H_2}CH_2$, 2H), 2.30 (d, *J* = 7.2 Hz, 2H, $C\mathbf{H_2}CH=C\mathbf{H_2}$), 1.81-1.75 (m, $PhCH_2C\mathbf{H}_2$, 2H), 1.26 (s, 3H, $C\mathbf{H_3}$),

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.5, 133.8, 128.4, 128.3, 125.8, 118.9, 72.1, 46.5, 43.7, 30.3, 26.8.

FTIR (neat): 3429, 3415, 2977, 1640, 912, 742, 699 cm^{-1}.

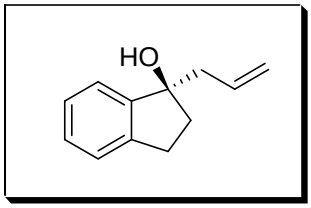
HRMS Calcd for $C_{12}H_{16}0$ [M – H_2O]: 172.1252. Found: 172.1252

$[\alpha]_D$ = +9.5 ^{o} (*c* = 4.30, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 22.76 min for major enantiomer, t_2 = 25.54 min for minor enantiomer).

The configuration was assigned by analogy with (*R)*-2-phenyl-pent-4-en-2-ol assuming a constant preference for the *re* face of the ketone.

(*R*)-1-Allyl-indan-1-ol (36f)



(90 % ee)

Colorless oil (61 %); R_f = 0.43 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 – 7.31 (m, 1H, aromatic), 7.29 – 7.21 (m, 3H, aromatic), 5.93-5.80 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.20-5.14 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 3.00 (ddd, *J* = 16.0, 8.7, 4.5 Hz, 1H, cyclopentyl $\mathbf{CH_2}$), 2.87-2.77 (m, 1H, cyclopentyl $C\mathbf{H_2}$), 2.64 (dd, *J* = 13.8, 7.3 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 2.52 (dd, *J* = 13.6, 7.0 Hz, 1H, $C\mathbf{H_2}CH=CH_2$), 2.38-2.29 (m, 1H, cyclopentyl $C\mathbf{H_2}$), 2.19 (bs, 1H, OH), 2.12-2.03 (m, 1H, cyclopentyl $C\mathbf{H_2}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 147.0, 143.0, 133.8, 128.2, 126.6, 124.9, 122.9, 118.7, 82.7, 45.0, 39.6, 29.4.

FTIR (neat): 3402, 1640, 996, 914, 760cm^{-1}.

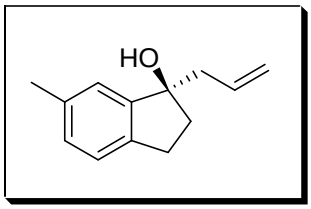
HRMS Calcd for $C_{10}H_{18}0$ [M – H_2O]: 156.0939. Found: 156.0934

$[\alpha]_D$ = -5.1^o (*c* = 4.03, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0mL/min: t_1= 8.34 min for major enantiomer, t_2= 10.48 min for minor enantiomer).

The configuration was assigned by analogy with (*R)*-2-phenyl-pent-4-en-2-ol assuming a constant preference for the *re* face of the ketone.

(*R*)-1-Allyl-6-methyl-indan-1-ol (36g)



(92 % ee)

Colorless oil (50 %); R_f = 0.41 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.15 – 7.08 (m, 3H, aromatic), 5.93-5.79 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.21-5.15 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 2.95 (ddd, *J* = 16.0, 8.7, 4.5 Hz, 1H, cyclopentyl C**H$_2$**), 2.82-2.72 (m, 1H, cyclopentyl C**H$_2$**), 2.64 (dd, *J* = 13.6, 7.7 Hz, 1H, C**H$_2$**CH=CH_2), 2.50 (dd, *J* = 13.6, 7.0 Hz, 1H, C**H$_2$**CH=CH_2), 2.36 (s, 3H, C**H$_3$**), 2.35-2.28 (m, 1H, cyclopentyl C**H$_2$**,), 2.11-2.02 (m, 1H, cyclopentyl C**H$_2$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 147.2, 140.0, 136.3, 133.9, 129.2, 124.7, 123.4, 118.8, 82.7, 45.0, 39.9, 29.0, 21.4.

FTIR (neat): 3294, 3079, 3015, 2844, 1638, 1491, 996, 913, 812cm^{-1}.

HRMS Calcd for $C_{10}H_{18}0$ [M – H_2O]: 170.1095 Found: 170.1089

$[\alpha]_D$ = -11.4^o (*c* = 3.42, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel OD column (Hexane : *i*-propanol 99:1, 0.5mL/min: t_1= 14.25 min for major enantiomer, t_2= 17.00 min for minor enantiomer).

The configuration was assigned by analogy with (*R)*-2-phenyl-pent-4-en-2-ol assuming a constant preference for the *re* face of the ketone.

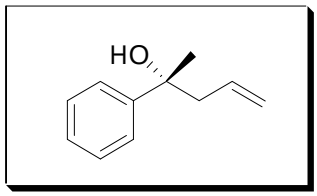
6.3.2 Catalytic Enantioselective Allylation of Ketones via a Chiral (*S,S*)-PYBOX-In(III) complex

Representative procedure for asymmetric allylation of ketones : Preparation of (*S*)- 2-phenyl-pent-4-en-2-ol

To an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar was added $In(OTf)_3$ (16.9 mg, 0.03 mmol, 0.20 equiv) and 4Å molecular sieve (120 mg). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.0 mL of dichloromethane. (*S,S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)-pyridine (9.9 mg, 0.033 mmol, 0.22 equiv) was added and the mixture was stirred under nitrogen at room temperature for 2 h to afford a white suspension. A mixture of acetophenone (18.0 μL, 0.15 mmol, 1.0 equiv) and TMSCl (23.0 μL, 0.18 mmol, 1.2 equiv) in dichloromethane (0.2 mL) was added to the resulting suspension and stirred for 10 min. The mixture was then cooled to 0 ^{o}C for 15 min followed by addition of allyltributylstannane (57.0 μL, 0.18 mmol, 1.2 equiv). The reaction mixture was stirred at 0 ^{0}C for 72 h and then quenched with 2 mL saturated sodium bicarbonate solution at room temperature for 30 min. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as colorless oil.

Characterization of Tertiary Homoallylic Alcohols

(*R*)-2-Phenyl-pent-4-en-2-ol (36a)

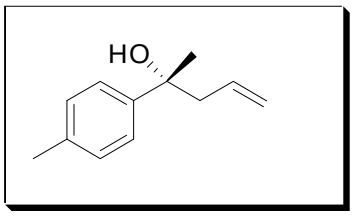


(62 % ee)

Colorless oil (80 %); $[\alpha]_D = +27.2^o$ (*c* = 1.36, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 9.96 min for major enantiomer, t_2 = 12.78 min for minor enantiomer).

(*R*)-2-*p*-Tolyl-pent-4-en-2-ol (36b)

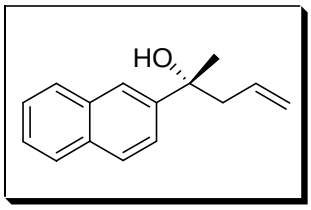


(63 % ee)

Colorless oil (79 %); $[\alpha]_D = +9.8^o$ (*c* = 1.87, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 6.98 min for major enantiomer, t_2 = 9.64 min for minor enantiomer).

(*R*)-2-Naphthalen-2-yl-pent-4-en-2-ol (36c)

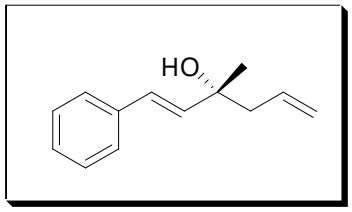


(62 % ee)

Colorless oil (74 %); $[\alpha]_D$ = +26.7^o (*c* = 1.12, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 26.28 min for minor enantiomer, t_2 = 31.30 min for major enantiomer).

(*R*)-3-Methyl-1-phenyl-hexa-1,5-dien-3-ol (36d)

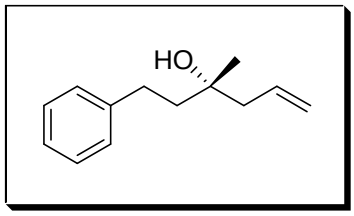


(54% ee)

Colorless oil (71 %); $[\alpha]_D$ = +38.9^o (*c* = 1.32, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 28.92min for major enantiomer, t_2 = 33.59 min for minor enantiomer).

(*S*)-3-Methyl-1-phenyl-hex-5-en-3-ol (36e)

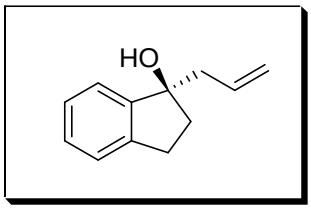


(55 % ee)

Colorless oil (80 %); $[\alpha]_D = +7.4^{o}$ (*c* = 3.98, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 0.5 mL/min: t_1 = 22.76 min for major enantiomer, t_2 = 25.54 min for minor enantiomer).

(*R*)-1-Allyl-indan-1-ol (36f)

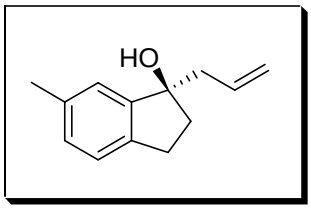


(95 % ee)

Colorless oil (90 %); $[\alpha]_D = -7.3^{o}$ (*c* = 3.75, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0mL/min: t_1= 8.34 min for major enantiomer, t_2= 10.48 min for minor enantiomer).

(R)-1-Allyl-6-methyl-indan-1-ol (36g)



(90 % ee)

Colorless oil (40 %); $[\alpha]_D = -12.9^o$ (*c* = 3.22, CH_2Cl_2)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel OD column (Hexane : *i*-propanol 99:1, 0.5mL/min: t_1= 14.25 min for major enantiomer, t_2= 17.00 min for minor enantiomer).

6.4 CATALYTIC ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF ALDEHYDES

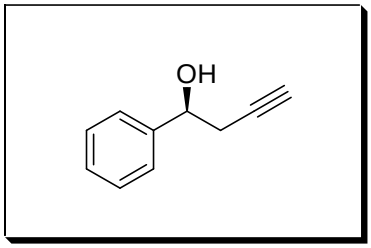
6.4.1 Catalytic Enantioselective Propargylation and Allenylation of Aldehydes via a Chiral (*S*)-BINOL-In(III) Complex

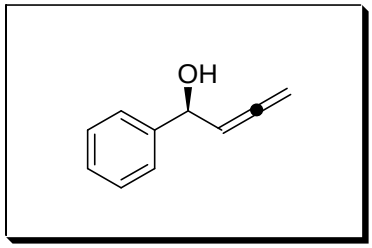
Representative procedure for asymmetric propargylation and allenylation of aldehydes : Preparation of (*S*)-1-Phenylbut-3-yn-1-ol and (*S*)-1-Phenyl-buta-2,3-dien-1-ol

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) was added to the mixture and stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min to afford a white suspension. The pre-formed catalyst was then cooled to -78 ^{o}C for 15 min followed by slow addition of allenylltributylstannane (0.30 mL, 1.0 mmol, 2.0 equiv) and benzaldehyde (53 mg, 0.50 mmol, 1.0 equiv). The reaction mixture was stirred at -78 ^{o}C for 4 h and 16 h at room temperature and then quenched with 5 mL saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated in *vacuo*. The residual crude product was purified via silica gel chromatography to afford the homopropargylic and allenylic alcohol as colorless oil.

Characterization of Homopropargylic and Allenylic Alcohols

(*S*)-1-Phenylbut-3-yn-1-ol (37a) **(*S*)-1-Phenyl-buta-2,3-dien-1-ol (38a)**





(90 % ee) (80 % ee)

44 : 56

Colorless oil (Combined yield : 72%); R_f = 0.43 (4:1 hexane/ethyl acetate)

(*S*)-1-phenylbut-3-yn-1-ol (37a)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.63 (m, 5H, aromatic), 4.88 (t, *J* = 6.3 Hz, 1H, $CH_2C\mathbf{H}OH$), 2.66-2.63 (dd, *J* = 6.6, 2.6 Hz, 2H, $C\mathbf{H_2}C{\equiv}CH$), 2.45 (s, 1H, $CHO\mathbf{H}$), 2.07 (t, *J* = 2.5 Hz, 1H, $CH_2C{\equiv}C\mathbf{H}$)

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 142.4, 128.5, 128.0, 125.7, 80.7, 72.3, 70.9, 29.4.

FTIR (neat): 3396, 3297, 3064, 3032, 2912, 1604, 1494, 1450, 1051, 757, 701 cm^{-1}.

HRMS Calcd for $C_{10}H_{12}0$ [M^+]: 146.0732. Found: 146.0733.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 95:5, 0.5 mL/min: t_1 = 18.29 min for *R* enantiomer , t_2 = 19.35 for *S* enantiomer). It had been established from literature that the *R* enantiomer elutes first.[80]

(*S*)-1-phenyl-buta-2,3-dien-1-ol (38a)

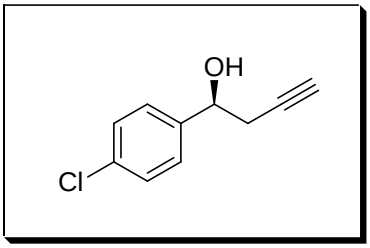
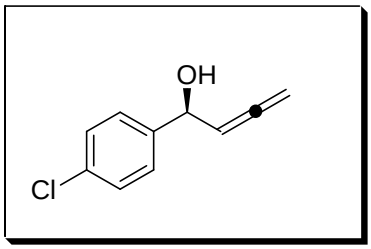
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.45-7.27 (m, 5H, aromatic), 5.45 (q, *J* = 6.5 Hz, 1H, $C\mathbf{H}{=}C{=}CH_2$), 5.31-5.21 (br, 1H, $C\mathbf{H}OH$), 4.98-4.90 (m, 2H, $CH{=}C{=}C\mathbf{H_2}$), 2.11 (d, *J* = 3.5 Hz, 1H, $CHO\mathbf{H}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.1, 142.9,128.4, 127.8, 126.1, 95.2, 78.2, 71.9.

FTIR (neat): 3356, 1613, 1484, 758, 749 cm^{-1}.

HRMS Calcd for $C_{10}H_{12}0$ [M^+]: 146.0732. Found: 146.0736.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 95:5 0.5 mL/min: t_1 = 21.50 min for *R* enantiomer, t_2 = 22.93 for *S* enantiomer).[80]

(*S*)-1-(4-chloro-phenyl)-but-3-yn-1-ol (37b)		**(*S*)-1-(4-chloro-phenyl)-buta-2,3-dien-1-ol (38b)**
		
(76 % ee)		(90 % ee)
43	:	57

Colorless oil (Combined yield : 70 %); R_f = 0.42 (4:1 hexane/ethyl acetate)

(*S*)-1-(4-chloro-phenyl)-but-3-yn-1-ol (37b)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 4H, aromatic), 4.88-4.81 (m, 1H, $CH_2C\mathbf{H}OH$), 2.60-2.50 (m, 2H, $C\mathbf{H_2}C{\equiv}CH$), 2.27-2.26 (m, 1H, $CHO\mathbf{H}$), 2.07 (t, *J* = 2.8 Hz, 1H, $CH_2C{\equiv}C\mathbf{H}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 141.3, 133.7, 128.6, 127.5, 80.2, 71.6, 71.3, 29.5.

FTIR (neat): 3392, 2902, 1442, 1614 cm^{-1}.

HRMS Calcd for $C_{10}H_9ClO$ [M^+]: 180.0342. Found: 180.0341.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel ODH and AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 60.20 min for *R* enantiomer, t_2 = 63.11 min for *S* enantiomer).

(*S*)-1-(4-chloro-phenyl)-buta-2,3-dien-1-ol (38b)

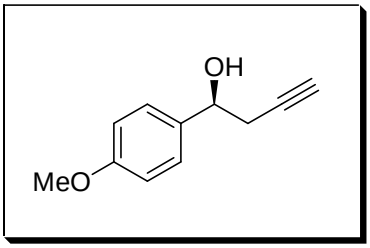
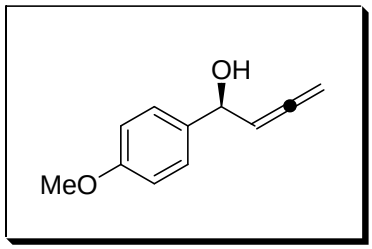
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 4H, aromatic), 5.39 (q, *J* = 6.8 Hz, 1H, $C\mathbf{H}{=}C{=}CH_2$), 5.26-5.24 (m, 1H, $C\mathbf{H}OH$), 4.94-4.91 (m, 2H, $CH{=}C{=}C\mathbf{H_2}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.2, 140.9, 133.5, 128.6, 127.2, 95.0, 78.4, 71.6.

FTIR (neat): 3351, 1624, 1490, 749 cm^{-1}.

HRMS Calcd for $C_{10}H_9ClO$ [M^+]: 180.0342. Found: 180.0344.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H and AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 47.18 min for *R* enantiomer, t_2 = 48.90 min for *S* enantiomer).

(*S*)-1-(4-methoxy-phenyl)-but -3-yn-1-ol (37c)		**(*S*)-1-(4-methoxyphenyl)-buta-2,3-dien-1-ol (38c)**
		
(80 % ee)		(88 % ee)
36	:	64

Colorless oil (Combined yield : 51 %); R_f = 0.31 (4:1 hexane/ethyl acetate)

(*S*)-1-(4-methoxy-phenyl)-buta-3-yn-1-ol (37c)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31 (d, *J* = 8.8 Hz, 2H, aromatic), 6.88 (d, *J* = 8.8 Hz, 2H, aromatic), 4.86-4.81 (m, 1H, $CH_2C\mathbf{H}OH$), 3.81 (s, 3H, $O\mathbf{CH_3}$), 2.65-2.61 (m, 2H, $C\mathbf{H_2}C{\equiv}CH$), 2.05 (t, *J* = 2.6 Hz, 1H, $CH_2C{\equiv}C\mathbf{H}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 159.3, 134.7, 127.0, 113.9, 80.9, 72.0, 70.9, 55.3, 29.4.

FTIR (neat): 3300, 2916, 1487, 1604 cm^{-1}.

HRMS Calcd for $C_{11}H_{12}O_2$ [M^+]: 176.0837. Found: 176.0838.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 90:10, 0.5 mL/min: t_1 = 19.93 min for *R* enantiomer, t_2 = 23.50 min for *S* enantiomer).

(*S*)-1-(4-methoxy-phenyl)-buta-2,3-dien-1-ol (38c)

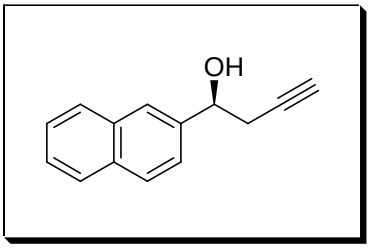
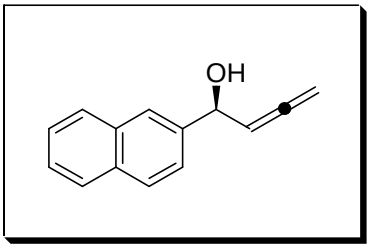
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 16.4 Hz, 2H, aromatic), 6.62 (d, *J* = 16.4 Hz, 2H, aromatic), 5.44 (q, *J* = 6.4 Hz, 1H, C**H**=C=CH_2), 5.23 (br, 1H, C**H**OH), 4.94-4.91 (m, 2H, CH=C=C**H$_2$**), 3.84 (s, 3H, O**CH$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.1, 159.3, 135.1, 127.5, 113.9, 95.3, 78.2, 71.6, 55.3.

FTIR (neat): 3330, 1636, 1429, 715 cm^{-1}.

HRMS Calcd for $C_{11}H_{12}O_2$ [M^+]: 176.0837. Found: 176.0836.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 90:10, 0.5 mL/min: t_1 = 17.08 min for *R* enantiomer, t_2 = 18.74 min for *S* enantiomer).

(*S*)-1-Napthalen-2-yl-but-3-yn-1-ol (37d)		**(*S*)-1-Naphthalen-2-yl-buta-2,3-dien-1-ol (38d)**
		
(82 % ee)		(82 % ee)
46	:	54

Colorless oil (Combined yield : 78 %); R_f = 0.39 (4:1 hexane/ethyl acetate)

(*S*)-1-Napthalen-2-yl-but-3-yn-1-ol (37d)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86-7.83 (m, 4H, aromatic), 7.48-7.45 (m, 3H, aromatic), 4.93-4.90 (m, 1H, CH_2C**H**OH), 2.71-2.63 (m, 2H, C**H$_2$**C≡CH), 2.05 (t, *J* = 2.8 Hz, 1H, CH_2C≡C**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 139.9, 133.2, 133.1, 128.3, 128.0, 127.7, 126.2, 126.0, 124.7, 124.3, 80.7, 72.5, 72.1, 29.4.

FTIR (neat): 3300, 2916, 1469, 1604 cm^{-1}.

HRMS Calcd for $C_{14}H_{12}O$ [M^+]: 196.0888. Found: 196.0883.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 38.32 min for *R* enantiomer, t_2 = 44.80 min for *S* enantiomer).

(*S*)-1-Naphthalen-2-yl-buta-2,3-dien-1-ol (38d)

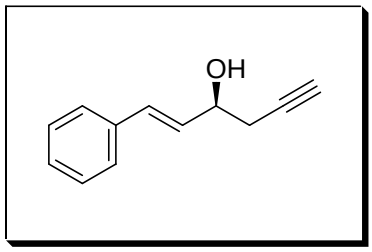
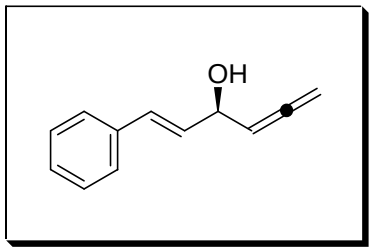
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85-7.82 (m, 4H, aromatic), 7.52-7.46 (m, 3H, aromatic), 5.51 (q, *J* = 6.4 Hz, 1H, C**H**=C=CH_2), 5.44-5.43 (br, 1H, C**H**OH), 5.06-5.00 (m, 2H, CH=C=C**H$_2$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.2, 140.2, 133.2, 133.1, 128.3, 128.1, 127.7, 126.3, 126.2, 124.7, 124.3, 95.2, 78.3, 71.1.

FTIR (neat): 3431, 1651, 1435, 726 cm^{-1}.

HRMS Calcd for $C_{11}H_{12}O_2$ [M^+]: 196.0888. Found: 196.0887.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 32.29 min for *R* enantiomer, t_2 = 36.42 min for *S* enantiomer).

(*S*)-1-Phenyl-hex-1-en-5-yn-3-ol (37e)		**(*R*)- 1-Phenyl-hexa-1,4,5-trien-3-ol (38e)**
		
(80 % ee)		(88 % ee)
48	:	52

Colorless oil (Combined yield : 64 %); R_f = 0.43 (4:1 hexane/ethyl acetate)

(*S*)-1-Phenyl-hex-1-en-5-yn-3-ol (37e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 5H, aromatic), 6.67 (d, *J* = 16.0 Hz, 1H, PHC**H**=CH), 6.29 (dd, *J* = 16.0, 6.3 Hz, 1H, PhCH=C**H**), 4.48 (m, 1H, CH_2C**H**OH), 2.56 (m, 2H, C**H$_2$**C≡CH), 2.32 (bs, 1H, O**H**), 2.10 (t, *J* = 2.6 Hz, 1H, CH_2C≡C**H**)

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 136.4, 131.3, 130.0, 128.6, 127.9, 126.6, 80.3, 71.1, 70.7, 27.7.

FTIR (neat): 3573, 3380, 3272, 3027, 2910, 2119, 1806, 1593, 1573, 1489, 1099, 1071, 1038cm^{-1}.

HRMS Calcd for $C_{12}H_{14}O$ [M^+]: 172.0888. Found: 172.0888.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 44.07 min for *S* enantiomer, t_2 = 53.47 min for *R* enantiomer).

(*R*)- 1-Phenyl-hexa-1,4,5-trien-3-ol (38e)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (m, 5H, aromatic), 6.68 (d, *J* = 16.0 Hz, 1H, PhC**H**=CH), 6.27 (dd, *J* = 15.7, 6.3 Hz, 1H, PhCH=C**H**), 5.38 (dd, *J* = 12.9, 6.3 Hz, 1H, C**H**=C=CH_2), 4.94 (dd, *J* = 6.6, 2.43 Hz, 2H, CH=C=C**H$_2$**), 4.87 (bs, 1H, C**H**OH)

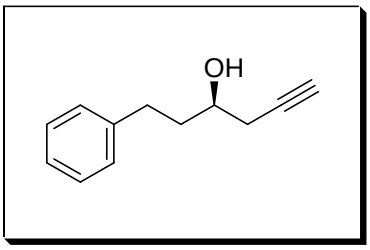
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.1, 136.6, 134.1, 131.7, 130.7, 127.8, 118.5, 94.0, 78.2, 70.5.

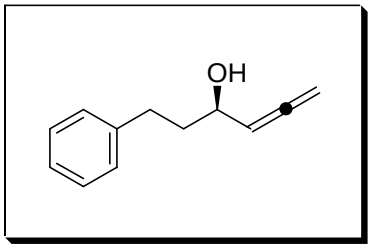
FTIR (neat): 3556, 3321, 2139, 1825, 1589, 1087, 1021cm^{-1}.

HRMS Calcd for $C_{12}H_{14}O$ [M^+]: 172.0888. Found: 172.0887.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 28.11 min for *R* enantiomer, t_2 = 32.62 min for *S* enantiomer).

(*R*)-1-Phenyl-hex-5-yn-3-ol (37f) **(*R*)-1-Phenyl-hexa-4,5-dien-3-ol (38f)**





(72 % ee) (62 % ee)

51 : 49

Colorless oil (Combined yield : 74 %); R_f = 0.40 (4:1 hexane/ethyl acetate)

(*R*)-1-Phenyl-hex-5-yn-3-ol (37f)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.27 (m, 5H, aromatic), 3.80 (m, 1H, $CH_2C\mathbf{H}OH$), 2.76 (m, 2H, $PhC\mathbf{H_2}CH_2$), 2.40 (m, 2H, $C\mathbf{H_2}C{\equiv}CH$), 2.07 (t, *J* = 2.6 Hz, 1H, $CH_2C{\equiv}C\mathbf{H}$), 1.94 (brd, 1H, $CHO\mathbf{H}$), 1.87 (m, 2H, $PhCH_2\mathbf{CH_2}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 141.7, 128.4, 128.3, 125.9, 80.7, 71.1, 69.1, 37.8, 31.9, 27.5.

FTIR (neat): 3573, 1954, 1603, 1493, 1454, 1217, 1078, 1052 cm^{-1}.

HRMS Calcd for $C_{12}H_{14}O$ [M^+]: 174.1045. Found: 174.1045.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 8.97 min for *R* enantiomer, t_2 = 9.60 min for *S* enantiomer).

(*R*)- 1-Phenyl-hexa-4,5-dien-3-ol (38f)

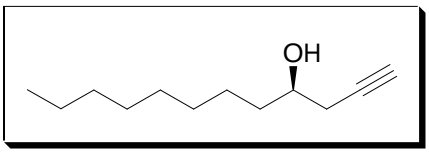
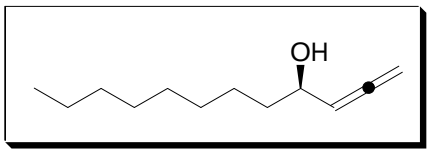
^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38-7.11 (m, 5H, aromatic), 5.26 (q, *J* = 6.6 Hz, 1H, $C\mathbf{H}{=}C{=}CH_2$), 4.86 (q, *J* = 2.4 Hz, 2H, $CH{=}C{=}C\mathbf{H_2}$), 4.21 (br, 1H, $C\mathbf{H}OH$), 2.83-2.68 (m, 2H, $PhC\mathbf{H_2}CH_2$), 1.98-1.81 (m, 2H, $PhCH_2C\mathbf{H_2}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.1, 141.8, 128.5, 128.4, 125.9, 94.7, 77.6, 68.9, 39.0, 31.7.

FTIR (neat): 3443, 1649, 1426, 732 cm^{-1}.

HRMS Calcd for $C_{12}H_{14}O$ [M^+]: 174.1045. Found: 174.1047.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 10.56 min for *R* enantiomer, t_2 = 11.35 min for *S* enantiomer).

(*R*)-Dodeca-1,2-dien-4-ol (37g)		**(*R*)-Dodeca-1,2-dien-4-ol (38g)**
		
(92 % ee)		(88 % ee)
74	:	26

Colorless oil (Combined yield : 62 %); R_f = 0.51 (4:1 hexane/ethyl acetate)

(*R*)-Dodeca-1,2-dien-4-ol (37g)

^{1}H NMR (300 MHz, $CDCl_3$): δ 3.76 (m, 1H, $CH_2C\mathbf{H}OH$), 2.38 (m, 2H, $C\mathbf{H_2}C{\equiv}CH$), 2.05 (t, *J* = 2.6 Hz, 1H, $CH_2C{\equiv}C\mathbf{H}$), 1.62-1.27 (m, 14H, aliphatic $(C\mathbf{H_2})_7$), 0.88 (t, *J* = 6.6 Hz, 3H, $CH_2C\mathbf{H_3}$)

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 81.0, 70.8, 70.0, 36.3, 31.9, 30.9, 29.6, 29.3, 27.4, 25.7, 22.7, 14.1.

FTIR (neat): 3306, 3017, 2928, 2857, 2401, 1714, 1454, 1216, 1047, 760 cm^{-1}.

HRMS Calcd for $C_{14}H_{12}O$ [M^+]: 182.1671. Found: 182.1674.

Product was derivatized with 2,4-dinitrobenzolic chloride before the enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 6.43 min for the *S* enantiomer, t_2 = 6.70 min for the *R* enantiomer).

(*R*)-Dodeca-1,2-dien-4-ol (38g)

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (dd, *J* = 12.8, 6.4 Hz, 1H, $C\mathbf{H}{=}C{=}CH_2$), 4.85 (dd, *J* = 6.4, 2.5 Hz, 2H, $CH{=}C{=}C\mathbf{H_2}$), 4.19-4.15 (m, 1H, $C\mathbf{H}OH$), 1.61-1.27 (m, 14H, $(C\mathbf{H_2})_7$), 0.88 (t, *J* = 6.5 Hz, 3H, $CH_2C\mathbf{H_3}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 207.0, 94.8, 77.6, 69.7, 37.5, 32.0, 29.6, 29.5, 29.3, 24.5, 22.8, 14.0.

FTIR (neat): 3289, 3004, 2989, 1724, 1050, 771 cm^{-1}.

HRMS Calcd for $C_{11}H_{12}O_2$ [M^+]: 182.1671. Found: 182.1673.

Product was derivatized with 2,4-dinitrobenzolic chloride before the enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 8.83 min for the *S* enantiomer, t_2 = 10.36 min for the *R* enantiomer).

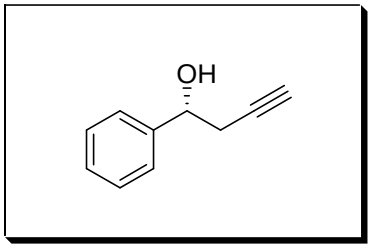
6.4.2 Catalytic Enantioselective Propargylation and Allenylation of Aldehydes via a Chiral (*S,S*)-PYBOX-In(III) complex

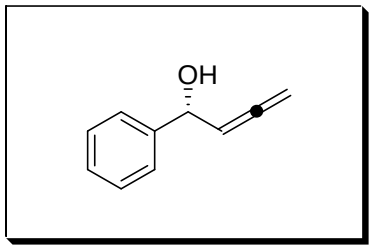
Representative procedure for asymmetric propargylation and allenylation of aldehydes : Preparation of (*S*)-1-Phenylbut-3-yn-1-ol and (*S*)-1-Phenyl-buta-2,3-dien-1-ol

To an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar was added $In(OTf)_3$ (16.9 mg, 0.03 mmol, 0.20 equiv) and 4Å molecular sieve (120 mg). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.0 mL of dichloromethane. (*S,S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)-pyridine (9.9 mg, 0.033 mmol, 0.22 equiv) was added and the mixture was stirred under nitrogen at room temperature for 2 h to afford a white suspension. A mixture of benzaldehyde (15.0 μL, 0.15 mmol, 1.0 equiv) and TMSCl (23.0 μl, 0.18 mmol, 1.2 equiv) in dichloromethane (0.2 mL) was added to the resulting suspension and stirred for 10 min. The mixture was then cooled to 0 ^{o}C for 15 min followed by addition of allenyltributylstannane (57.0 μL, 0.18 mmol, 1.2 equiv). The reaction mixture was stirred at -60 ^{o}C for 30 h and then quenched with 2 mL saturated sodium bicarbonate solution at room temperature for 30 min. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the homoallylic alcohol as a colorless oil.

Characterization of Homopropargylic and Allenylic Alcohols

(*R*)-1-Phenylbut-3-yn-1-ol (37a) **(*R*)-1-Phenyl-buta-2,3-dien-1-ol (38a)**





(88 % ee) (90 % ee)

62 : 38

Colorless oil (Combined yield : 73%); R_f = 0.43 (4:1 hexane/ethyl acetate)

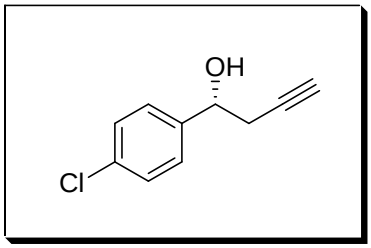
(*R*)-1-phenylbut-3-yn-1-ol (37a)

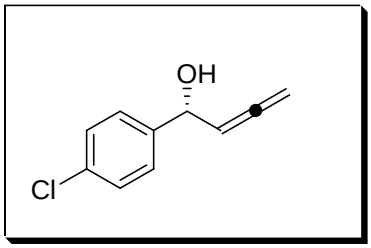
The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 95:5, 0.5 mL/min: t_1 = 18.29 min for *R* enantiomer , t_2 = 19.35 for *S* enantiomer).

(*R*)-1-phenyl-buta-2,3-dien-1-ol (38a)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 95:5 0.5 mL/min: t_1 = 21.50 min for *R* enantiomer, t_2 = 22.93 for *S* enantiomer).

(*R*)-1-(4-chloro-phenyl)-but-3-yn-1-ol (37b) **(*R*)-1-(4-chloro-phenyl)-buta-2,3-dien-1-ol (38b)**





(80 % ee) (78 % ee)

38 : 62

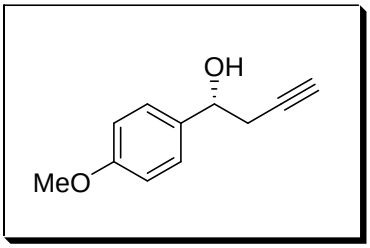
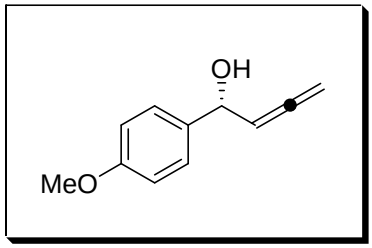
Colorless oil (Combined yield : 88 %); R_f = 0.42 (4:1 hexane/ethyl acetate)

(*R*)-1-(4-chloro-phenyl)-but-3-yn-1-ol (37b)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel ODH and AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 60.20 min for *R* enantiomer, t_2 = 63.11 min for *S* enantiomer).

(*R*)-1-(4-chloro-phenyl)-buta-2,3-dien-1-ol (38b)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H and AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 470.18 min for *R* enantiomer, t_2 = 48.90 min for *S* enantiomer).

(*R*)-1-(4-methoxy-phenyl)-but -3-yn-1-ol (37c)		**(*R*)-1-(4-methoxyphenyl)-buta-2,3-dien-1-ol (38c)**
		
(80 % ee)		(70 % ee)
52	:	48

Colorless oil (Combined yield : 68 %); R_f = 0.31 (4:1 hexane/ethyl acetate)

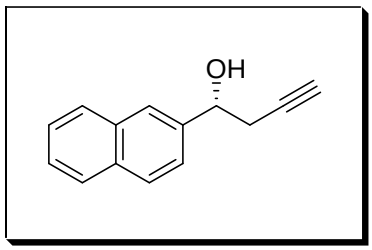
(*R*)-1-(4-methoxy-phenyl)-buta-3-yn-1-ol (37c)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 90:10, 0.5 mL/min: t_1 = 19.93 min for *R* enantiomer, t_2 = 23.50 min for *S* enantiomer).

(*R*)-1-(4-methoxy-phenyl)-buta-2,3-dien-1-ol (38c)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 90:10, 0.5 mL/min: t_1 = 17.08 min for *R* enantiomer, t_2 = 18.74 min for *S* enantiomer).

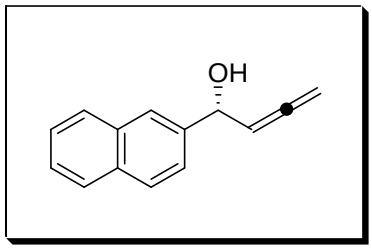
(*R*)-1-Napthalen-2-yl-but-3-yn-1-ol (37d)



(88 % ee)

37 :

(*R*)-1-Naphthalen-2-yl-buta-2,3-dien-1-ol (38d)



(84 % ee)

63

Colorless oil (Combined yield : 85 %); R_f = 0.39 (4:1 hexane/ethyl acetate)

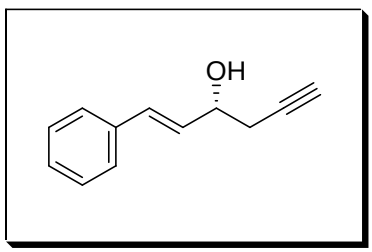
(*R*)-1-Napthalen-2-yl-but-3-yn-1-ol (37d)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 38.32 min for *R* enantiomer, t_2 = 44.80 min for *S* enantiomer).

(*R*)-1-Naphthalen-2-yl-buta-2,3-dien-1-ol (38d)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 0.5 mL/min: t_1 = 32.29 min for *R* enantiomer, t_2 = 36.42 min for *S* enantiomer).

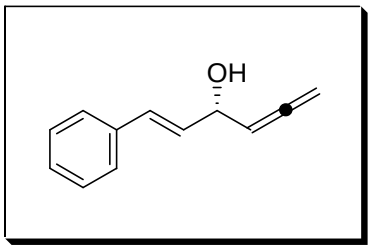
(*R*)-1-Phenyl-hex-1-en-5-yn-3-ol (37e)



(84 % ee)

29 :

(*S*)- 1-Phenyl-hexa-1,4,5-trien-3-ol (38e)



(86 % ee)

71

Colorless oil (Combined yield : 54 %); R_f = 0.43 (4:1 hexane/ethyl acetate)

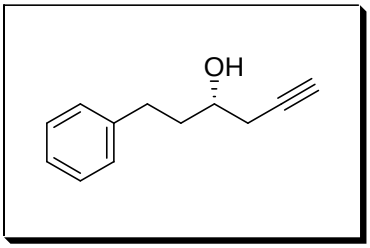
(*R*)-1-Phenyl-hex-1-en-5-yn-3-ol (37e)

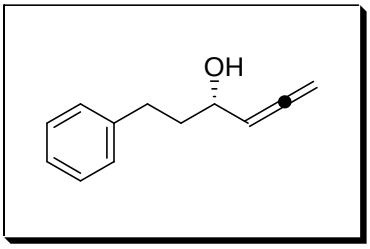
The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 44.07 min for *S* enantiomer, t_2 = 53.47 min for *R* enantiomer).

(*S*)- 1-Phenyl-hexa-1,4,5-trien-3-ol (38e)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 28.11 min for *R* enantiomer, t_2 = 32.62 min for *S* enantiomer).

(*S*)-1-Phenyl-hex-5-yn-3-ol (37f) **(*S*)- 1-Phenyl-hexa-4,5-dien-3-ol (38f)**





(88 % ee) (82 % ee)

58 : 42

Colorless oil (Combined yield : 71 %); R_f = 0.40 (4:1 hexane/ethyl acetate)

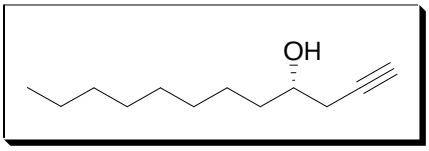
(*S*)-1-Phenyl-hex-5-yn-3-ol (37f)

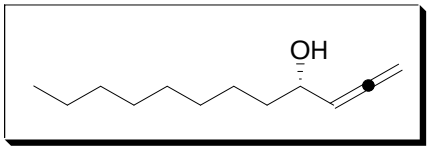
The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 8.97 min for *R* enantiomer, t_2 = 9.60 min for *S* enantiomer).

(*S*)- 1-Phenyl-hexa-4,5-dien-3-ol (38f)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AS-H column (Hexane : *i*-propanol 98:2, 1.0 mL/min: t_1 = 10.56 min for *R* enantiomer, t_2 = 11.35 min for *S* enantiomer).

(*S*)-Dodeca-1,2-dien-4-ol (37g) **(*S*)-Dodeca-1,2-dien-4-ol (38g)**





(60 % ee) (66 % ee)

35 : 65

Colorless oil (Combined yield : 70 %); R_f = 0.51 (4:1 hexane/ethyl acetate)

(*S*)-Dodeca-1,2-dien-4-ol (37g)

Product was derivatized with 2,4-dinitrobenzolic chloride before the enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 6.43 min for the *S* enantiomer, t_2 = 6.70 min for the *R* enantiomer).

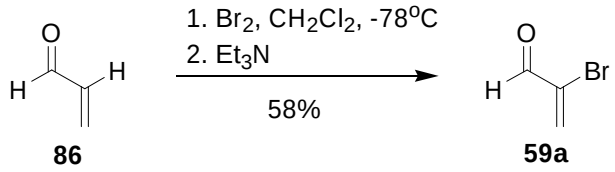
(*S*)-Dodeca-1,2-dien-4-ol (38g)

Product was derivatized with 2,4-dinitrobenzolic chloride before the enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD-H column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 8.83 min for the *S* enantiomer, t_2 = 10.36 min for the *R* enantiomer).

6.5 CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTION

6.5.1 Catalytic Enantioselective Diels-Alder via a Chiral (*S*)-BINOL-In(III) complex

2-bromoacrolein (59a)

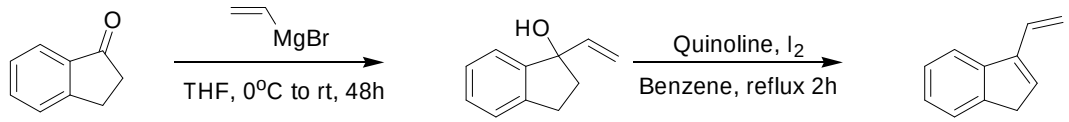


A flame-dried 250 mL three-necked flask equipped with a mechanical stirrer and an addition funnel was charged with a solution of acrolein **86** (33.5 mL, 0.5 mol) in dichloromethane (20 mL). The mixture was cooled to -78 ^{o}C and bromine (25.8 mL, 0.5 mol) was added dropwise through the addition funnel. The resulting colorless solution was treated with additional bromine, dropwise, until a reddish brown color persisted. Acrolein was then added dropwise through the addition funnel until the reddish brown color disappeared. The solution was stirred at 0 ^{o}C for 20 min. The solution was cooled to -78 ^{o}C and triethylamine (70.0 mL, 1.0 mol) was added slowly with vigorous mechanical stirring. Dropwise addition of triethylamine and efficient cooling are essential to prevent decomposition of product during the highly exothermic reaction. Copious salt precipitation was observed and the solid suspension was treated with 200 mL ether. The suspension was rapidly filtered, and the solids were repeatedly washed with 300 mL ether. The filtrate was washed once with 50 mL saturated sodium thiosulfate and twice with brine. The organic layer was dried

thoroughly with $MgSO_4$, filtered and solvent removed on a rotary evaporator with the bath temperature kept at 0 ^oC. Distillation of the crude product at 10 - 20 mmHg using an oil bath maintained at 90 ^oC and a receiver temperature at -78 ^oC yielded 39.0 g (58%) product **59a** as a pale yellow oil.

^1H NMR (500MHz, $CDCl_3$): δ 6.85 (s, 2H, **CH_2**=CHBrCHO), 9.2 (s, 1H, CH_2=CHBrC**H**O,); FTIR (neat): 1670 cm^{-1}.

Preparation of 3-Vinyl-1H-indene (66e/f)



87 **88** **61e**

Vinylmagnesium bromide (68.0 mL (1.0 M in THF), 68.0 mmol, 2.0 equiv) was added to a solution of 1-indanone **87** (4.51 g, 34.0 mmol) in 20 mL anhydrous THF via a dropping funnel at 0 ^oC under nitrogen. After the addition was completed, the mixture was allowed to warm slowly to room temperature and the resulting solution was stirred for 24 h. The solution was then cooled to 0 ^oC and quenched very slowly with saturated aqueous NH_4Cl (25 mL) followed by sufficient H_2O (about 10 mL) to dissolve any precipitated inorganic materials. The organic and aqueous layers were extracted with ether (4 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to give 4.07g (74%) of the crude alcohol **88** as a clear, yellow-orange oil.

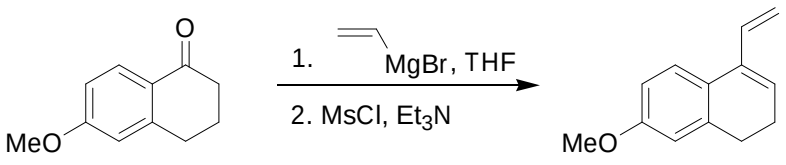
^1H NMR (300MHz, $CDCl_3$): δ 7.24-7.19 (m, 4H, aromatic), 6.22-5.93 (m, 1H, C**H**=CH_2), 5.32-5.07 (m, 2H, CH=C**H_2**), 2.87 (bs, 1H, O**H**), 3.15-2.73 (m, 2H,

cyclopentyl C**H₂**), 2.38-2.06 (m, 2H, cyclopentyl C**H₂**). Further purification of the alcohol was not attempted and it was used immediately for the preparation of 3-Vinyl-1H-indene **61e**.

Crude alcohol **88** (5.06 g, 32.0 mmol), used within 1 h of its isolation, was dissolved in dry benzene (80 mL) in which quinoline (0.25 mL) and iodine (*ca.* 0.1 g) had been dissolved. The mixture was then heated under reflux for 2 h until the evolution of H_2O had ceased as measured by a Dean and Stark apparatus. The quantity of H_2O evolved (*ca.* 0.6 mL) indicated virtually quantitative dehydration. The dark solution was cooled to room temperature and filtered through a thick pad (ca. 15 cm x 4 cm) of silica gel to remove traces of 1-indanone **87** carried through from the previous synthesis, and some dark impurity. The resulting brownish-yellow solution was then evaporated in *vacuo* to give 3.29 g (68 %) of the crude diene **61e** as a brownish-yellow viscous oil.

^{1}H NMR (300MHz, $CDCl_3$): 7.64-7.10 (m, 4H, aromatic,), 6.90-6.62 (m, 1H, ring C=C**H**), 6.45 (t, *J* = 2.1 Hz, 1H, C**H**=CH_2), 5.90-5.24 (m, 2H, CH=C**H₂**), 3.34 (bs, 2H, cyclopentyl C**H₂**).

Methoxy-4-vinyl-1,2-dihydro-napthalene (61g/h)



89 **61g**

To a solution of vinylmagnesium bromide (freshly prepared, 1.6 equiv) in 50 mL THF was added dropwise via cannula over 0.5 h a solution of 6-methoxy-1-tetralone **89**

(6.34 g, 36.0 mmol) in 30 mL THF at 0 °C. The reaction mixture was stirred for 16 h at room temperature, and then heated to reflux for 1 h. The resulting solution was cooled to 0 °C. Methanesulfonyl chloride (8.4 mL, 12.4 g, 108 mmol, 3.0 equiv) was added dropwise to the above solution. After 10 min, 30 mL of triethylamine (21.8 g, 215 mmol, 6.0 equiv) was added slowly to the reaction solution. The mixture was stirred for another 3 h at 0 °C. The reaction mixture was then poured into a separator funnel containing 100 mL water and was extracted with ether (3 x 100 mL). The combined organic extracts were washed with water (100 mL), and brine (2 x 70 mL) and were dried over anhydrous Na_2SO_4. The solvent was removed by rotary evaporation. The residue was purified by flash column chromatography (ethyl acetate-hexanes, v/v, 1 : 200), afforded the diene **61g** (3.4 g, 51% yield) as a colorless oil.[3]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 7.8 Hz, 1H, aromatic), 6.75-6.72 (m, 2H, aromatic), 6.62 (ddq, *J* = 1.1, 11.0, 17.2 Hz, 1H, ring C=C**H**) , 6.08 (t, *J* = 4.8 Hz, 1H, C**H**=CH_2), 5.53 (dd, *J* = 1.83, 17.6 Hz, 1H, CH=C**H$_2$**), 5.19 (dd, *J* = 1.83, 11.0 Hz, 1H, CH=C**H$_2$**), 3.82 (s, 3H, O**CH$_3$**), 2.75 (t, *J* = 7.7 Hz, 2H, ring C**H$_2$**), 2.34-2.27 (m, 2H, ring C**H$_2$**,).

^{13}C NMR (100.6 MHz, $CDCl_3$) δ 158.5, 138.5, 136.2, 135.7, 127.2, 125.0, 124.1, 114.9, 113.8, 110.8, 55.2, 28.7, 23.2.

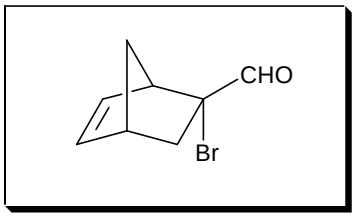
FTIR (film) 1605.7, 1495.1, 1248.7, 1140.7, 1042.1, 910.3, 824.0.

Representative procedure for asymmetric Diels-Alder reaction : Preparation of (*1R ,2R , 4R*) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) and 4Å molecular sieve (15 mg) were added and the mixture was stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min to afford a white suspension. The pre-formed catalyst was then cooled to -40 ^oC for 15 min. 2-bromoacrolein (67.5 mg, 0.50 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv, added dropwise along side of the flask) were added successively and the reaction mixture stirred at -40 ^oC for 20 h. The mixture was then quenched by addition of 5 mL of saturated $NaHCO_3$ and extracted with ether (10 mL x 3). The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the Diels - Alder adduct as a colorless solid (74% yield).

Characterization of Diels-Alder adduct

(*1R ,2R , 4R*) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (60a)



(98 % ee)

Colorless oil (74%); R_f = 0.65 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.54 (s, 1H, -C**H**O, *exo*), 6.45 (dd, *J* = 3.1, 5.6 Hz, 1H, =C**H**), 6.14 (dd, *J* = 3.1, 5.6 Hz, 1H, =C**H**), 3.25 (bs, 1H, -C**H**), 2.97 (bs, 1H, -C**H**), 2.65 (dd, *J* = 3.5, 13.6 Hz, 1H, -C**H**), 1.59-1.42 (m, 2H, -C**H$_2$**), 1.32 (d, *J* = 9.4 Hz, 1H, -C**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 191.9, 140.0, 133.8, 72.6, 49.6, 46.7, 42.4, 36.9.

FTIR (neat): 2978, 1722 cm^{-1}.

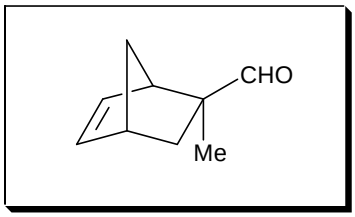
HRMS Calcd for $C_8H_{19}BrO$ [M^+]: 199.9837. Found:199.9834

$[\alpha]_D$ = +9.6^o (*c* = 1.37, CH_2Cl_2)

Diastereoselectivity *(ex*o-*endo* ratio) was determined by ^{1}H NMR analysis of the crude mixture: δ 9.56 (s, 1H, -C**H**O, *ex*o, major), 9.34 (s, 1H, -C**H**O, *end*o, minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.74 (d, 1H, minor), 4.67 (d, 1H, major), 4.61 (d,1H, major), 4.52 (d, 1H, minor).

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances.[93l]

(*1R, 2S, 4R*)-2-Methyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (60b)



(98 % ee)

Colorless oil (70%); R_f = 0.64 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.68 (s, 1H, -C**H**O), 6.28 (dd, *J* = 3.1, 5.6 Hz, 1H, =C**H**), 6.09 (dd, *J* = 3.1, 5.6 Hz, 1H, =C**H**), 2.88 (bs, 1H, -C**H**), 2.80 (bs, 1H, -C**H**), 2.24 (dd, *J* = 3.8, 11.9 Hz, 1H, -C**H**), 1.38 (m, 2H, -C**H$_2$**), 1.00 (s, 3H, -C**H$_3$**), 0.75 (bd, *J* = 11.8 Hz, 1H, -C**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.1, 138.0, 131.8, 52.3, 49.7, 45.7, 45.1, 42.7, 27.6.

FTIR (neat): 2918, 1726 cm^{-1}.

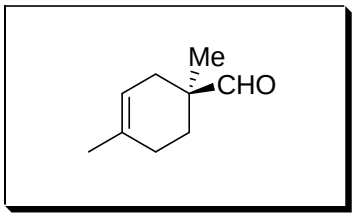
HRMS Calcd for $C_9H_{12}O$ [M^+]: 136.0888. Found: 136.0895.

$[\alpha]_D$ = +13.5^o (*c* = 3.10, CH_2Cl_2)

Diastereoselectivity *(ex*o-*endo* ratio) was determined by 1H NMR analysis of the crude mixture: δ 9.68 (s, 1H, *ex*o, major), 9.38 (s, 1H, *end*o, minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.34 (d, 1H, major), 4.31 (d, 1H minor), 4.25 (d, 1H, minor), 4.22 (d, 1H, major).

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances.[93l]

(*S*)-1,4-Dimethyl-cyclohex-3-enecarbaldehyde (62a)



(90% ee)

Colorless oil (35%); R_f = 0.68 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.47 (s, 1H, -C**H**O), 5.37 (bs, 1H, =C**H**), 2.32 (bd, *J* = 17.1 Hz, 1H, ring -C**H**), 1.96 (m, 2H, ring -C**H$_2$**), 1.83 (m, 2H, ring -C**H$_2$**), 1.68 (s, 3H, -C**H$_3$**), 1.49 (m, 1H, ring -C**H**), 1.03 (s, 3H, -C**H$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): 205.0, 133.7, 118.3, 44.3, 31.8, 29.0, 26.8, 23.4, 20.7.

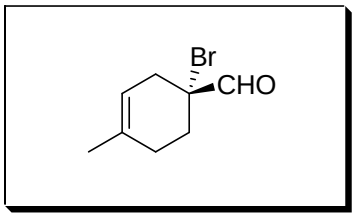
FTIR (neat): 2924, 1725, 1633 cm^{-1}.

$[\alpha]_D$ = +42.0^o (*c* = 3.28, CH_2Cl_2)

Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.14 (d, 1H, major), 4.09 (d, 1H minor), 4.03 (d, 1H, minor), 3.98 (d, 1H, major).

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances[93l] and by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde (62b)



(96% ee)

Colorless oil (70%); R_f = 0.67 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.36 (s, 1H- C**H**O), 5.33 (bs, 1H, =C**H**), 2.79 (bd, 1H, *J* = 18.1 Hz, ring -C**H**), 2.62 (bd, 1H, *J* = 18.0 Hz, ring -C**H**), 2.28-2.09 (m, 4H, ring -(C**H**$_2$)$_2$), 1.67 (bs, 3H, -C**H**$_3$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 192.2, 134.0, 117.0, 67.0, 34.4, 30.9, 28.5, 23.1.

FTIR (neat): 2916, 1726, 1638 cm^{-1}.

HRMS Calcd for $C_8H_{11}O$ [M-Br]: 123.0810. Found: 123.0810

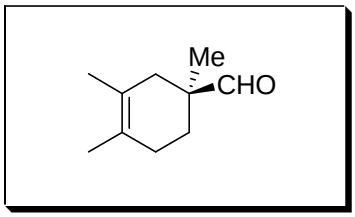
$[\alpha]_D$ = +67.7^o (*c* = 1.50, CH_2Cl_2)

Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the benzoyl ester derivative and HPLC analysis using two Daicel ADH + AD column with 1.0% *i*-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 51.31 min (minor), 52.57 min (major).[130]

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances.[93l]

[130] The Diels-Alder adduct contains ca. 8% of its regioisomer (1-bromo-3-methylcyclohex-3-ene-1-carboxaldehyde) that cannot be separated by column chromatography. (*S*)-1,4-Dimethyl-cyclohex-3-enecarbaldehyde.

(*S*)-1,3,4-Trimethyl-cyclohex-3-enecarbaldehyde (62c)



(98% ee)

Colorless oil (63%); R_f = 0.68 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.45 (s, 1H, -C**H**O), 2.25 (bd, *J* = 17.4 Hz, 1H, ring -C**H**), 1.97 (bs, 2H, ring -C**H$_2$**), 1.85-1.73 (m, 2H, ring -C**H$_2$**), 1.64 (s, 3H, -C**H$_3$**), 1.59 (s, 3H), 1.50-1.41 (m, 1H, ring -C**H**), 1.02 (s, 3H, -C**H$_3$**)

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 206.2, 125.2, 123.1, 45.3, 38.0, 29.3, 28.5, 20.7, 19.2, 18.8.

FTIR (neat): 2918, 1726 cm^{-1}.

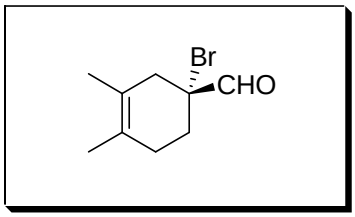
HRMS Calcd for $C_{10}H_{16}O$ [M^+]: 152.1201. Found: 152.1198.

$[\alpha]_D$ = +48.0^o (c = 4.60 g/100mL, CH_2Cl_2)

Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.12 (d, 1H, major), 4.08 (d, 1H minor), 4.01 (d, 1H, minor), 3.98 (d, 1H, major).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(*R*)-1-Bromo-3,4-dimethyl-cyclohex-3-enecarbaldehyde (62d)



(98% ee)

Colorless oil (74%); R_f = 0.67 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.34 (s, 1H, -C**H**O), 2.74 (bd, *J* = 17.4 Hz, 1H, ring -C**H**), 2.56 (bd, *J* = 17.8 Hz, 1H, ring -C**H**), 2.27-2.08 (m, 4H, ring-(C**H$_2$**)$_2$) 1.65 (s, 3H, -C**H$_3$**), 1.62 (s, 3H, -C**H$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 192.2, 125.4, 122.2, 67.7, 40.0, 31.2, 29.9, 19.0, 18.6.

FTIR (neat): 2916, 1726, 1641 cm^{-1}.

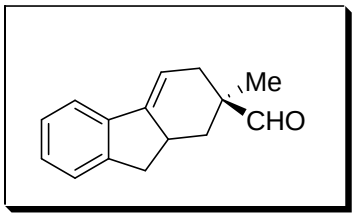
HRMS Calcd for $C_{19}H_{13}BrO$ [M^+]: 216.0150 . Found: 216.0141.

$[\alpha]_D$ = +62.3^o (*c* =3.19, CH_2Cl_2)

Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the benzoyl ester derivative and HPLC analysis using Daicel AD column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 62.39 min (minor), 65.89 min (major).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(2*R*)-2-Methyl-2,3,9,9a-tetrahydro-1*H*-fluorene-2-carbaldehyde (62e)



(98% ee)

Colorless solid (71%); R_f = 0.65 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.42-7.39 (m, 1H, aromatic), 7.27-7.18 (m, 3H, aromatic), 5.97 (dd, *J* = 7.3, 3.5 Hz, 1H, =C**H**), 3.14 (dd, *J* = 15.0, 8.4 Hz, 1H, ring -C**H**), 2.99-2.93 (m, 1H, ring -C**H**), 2.64-2.53 (m, 2H, ring-C**H$_2$**), 2.03-1.91 (m, 2H, ring-C**H$_2$**), 1.57-1.49 (m, 1H, ring -C**H**), 1.20 (s, 3H, -C**H$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.2, 144.2, 143.1, 140.6, 127.7, 126.7, 125.1, 120.1, 113.8, 45.52, 37.6, 36.7, 33.5, 31.0, 19.1.

FTIR (neat): 2923, 1712, 1454, 744 cm^{-1}.

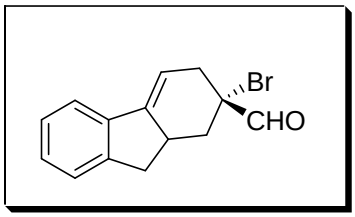
HRMS Calcd for $C_{15}H_{16}O$ [M^+]:212.1201. Found: 212.1200.

$[\alpha]_D$ = +50.5^o (*c* = 1.0, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ASH + ADH column with 1.0% *i*-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 11.03 min (major), 11.40 min (minor).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(2*S*)-2-Bromo-2,3,9,9a-tetrahydro-1*H*-fluorene-2-carbaldehyde (62f)



(98% ee)

Light yellow solid (72%); R_f = 0.60 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.54 (s, 1H, -C**H**O), 7.46-7.43 (m, 1H, aromatic), 7.22-7.16 (m, 3H, aromatic), 5.94 (dd, *J* = 7.0, 3.5 Hz, 1H, =C**H**), 3.49-3.35 (m, 1H, -C**H**), 3.24-3.14 (m, 2H, ring -C**H$_2$**), 2.87 (bd, *J* = 17.8 Hz, 1H, ring -C**H**), 2.72 (dd, *J* = 15.0, 9.0 Hz, 1H, ring -C**H**), 2.55 (ddd, *J* = 13.6, 4.9, 1.1 Hz, 1H, ring -C**H**), 1.66 (dd, *J* = 13.2. 11.2 Hz, 1H, ring -C**H**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 192.1, 144.3, 143.6, 140.0, 128.2, 126.9, 125.2, 120.5, 111.0, 68.9, 38.2, 36.8, 35.4, 34.5.

FTIR (neat): 2843, 1720, 1420, 752 cm^{-1}.

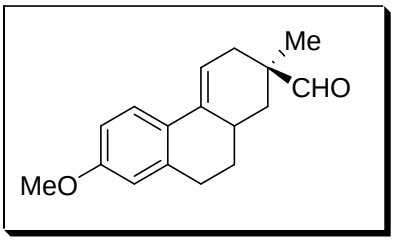
HRMS Calcd for $C_{14}H_{13}BrO$ [M^+]: 276.0150 Found: 276.0150.

$[\alpha]_D$ = +165.0^o (*c* = 2.10, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 20.28 min (major), 21.12 min (minor).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(2*R*)-2-Methyl-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde (62g)



(97% ee)

Colorless solid (75%); R_f = 0.57 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.54 (s, 1H, -C**H**O), 7.53 (d, *J* = 8.7 Hz, 1H, aromatic), 6.74 (dd, *J* = 8.7, 2.4 Hz, 1H, aromatic), 6.62 (bd, *J* = 2.4 Hz, 1H, aromatic), 6.13-6.11 (m, 1H, =C**H**), 3.79 (s, 3H, OC**H$_3$**), 3.00-2.80 (m, 2H, ring C**H$_2$**), 2.57 (bd, *J* = 18.1 Hz, 1H, ring -C**H**), 2.45-2.33 (m, 1H, ring -C**H**), 2.00-1.92 (m, 2H, ring C**H$_2$**), 1.75-1.68 (m, 1H, ring -C**H**), 1.58-1.39 (m, 2H, ring C**H$_2$**), 1.15 (s, 3H, C**H$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 205.8, 158.6, 137.7, 134.8, 126.9, 124.8, 114.4, 113.3, 112.8, 55.2, 44.5, 35.5, 31.8, 31.7, 30.8, 30.2, 18.0.

FTIR (neat): 2927, 1721, 1499, 821 cm^{-1}.

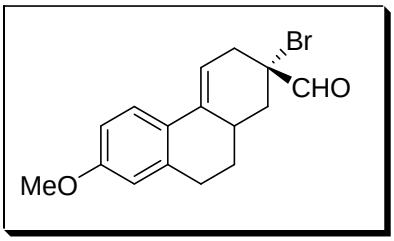
HRMS Calcd for $C_{17}H_{20}O_2$ [M^+]: 256.1463. Found: 256.1463.

$[\alpha]_D$ = -117.0 (*c* = 1.36, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 2.0% *i*-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 7.38 min (major), 8.51 min (minor).

The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

(2*S*)-2-Bromo-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde (62h)



(94% ee)

Light yellow solid (77%); R_f = 0.51 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.52 (s, 1H, -C**H**O), 7.56 (d, *J* = 8.7 Hz, 1H, aromatic), 6.75 (dd, *J* = 8.7, 2.8 Hz, 1H, aromatic), 6.63 (d, *J* = 2.4 Hz, 1H, aromatic), 6.11-6.09 (m, 1H, =C**H**), 3.80 (s, 3H, -OC**H$_3$**), 3.10-2.93 (m, 2H, ring C**H$_2$**), 2.90-2.71 (m, 3H, ring C**H$_2$** and -C**H**), 2.37-2.02 (m , 1H, ring C**H**), 2.06-2.02 (m, 1H, ring C**H**), 1.68-1.52 (m, 2H, ring C**H$_2$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 192.6, 158.9, 137.9, 135.5, 126.3, 125.2, 113.3, 112.9, 111.9, 68.2, 55.3, 37.2, 34.7, 33.9, 30.2, 30.1.

FTIR (neat): 2928, 1717, 1494, 1234, 810 cm^{-1}.

HRMS Calcd for $C_{16}H_{17}BrO_2$ [M^+]: 320.0412. Found:320.0408

$[\alpha]_D$ = -58.2^o (*c* = 2.0, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 10.65 min (major), 12.49 min (minor).

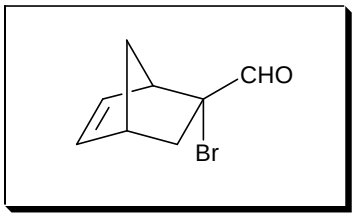
The absolute configuration was assigned by analogy with (*R*)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde.

6.5.2 Catalytic Enantioselective Diels-Alder Reaction via a Water Tolerant Chiral (S)-BINOL-In(III) Complex

Representative procedure for asymmetric Diels-Alder reaction : Preparation of (*1R ,2R , 4R*) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) was added and the mixture was stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min followed by addition of water (20.0μL, 1.11 mmol, 2.2 equiv) to afford a white suspension. The pre-formed catalyst was then cooled to -20 ^oC for 15 min. 2-bromoacrolein (67.5 mg, 0.50 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv, added dropwise along side of the flask) were added successively and the reaction mixture stirred at -20 ^oC for 20 h. The mixture was then quenched by addition of 5 mL of saturated $NaHCO_3$ and extracted with ether (10 mL x 3). The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the Diels-Alder adduct as a colorless solid (64% yield).

(*1R ,2R , 4R*) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (60a)

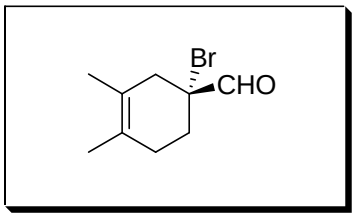


(94 % ee)

Colorless oil (64%); $[\alpha]_D = +9.3^o$ (*c* = 1.46, CH_2Cl_2)

Diastereoselectivity *(ex*o-*endo* ratio) was determined by ^{1}H NMR analysis of the crude mixture: δ 9.56 (s, 1H, *ex*o, major), 9.34 (s, 1H, *end*o, minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.74 (d, 1H, minor), 4.67 (d, 1H, major), 4.61 (d,1H, major), 4.52 (d, 1H, minor).

(*R*)-1-Bromo-3,4-dimethyl-cyclohex-3-enecarbaldehyde (62b)

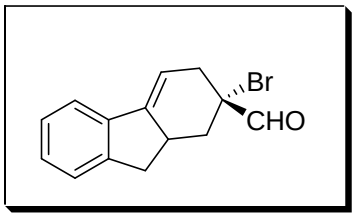


(80% ee)

Colorless oil (70%); $[\alpha]_D = +49.3^o$ (*c* =3.25, CH_2Cl_2)

Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the benzoyl ester derivative and HPLC analysis using Daicel AD column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 62.39 min (minor), 65.89 min (major).

(2*S*)-2-Bromo-2,3,9,9a-tetrahydro-1*H*-fluorene-2-carbaldehyde (62f)

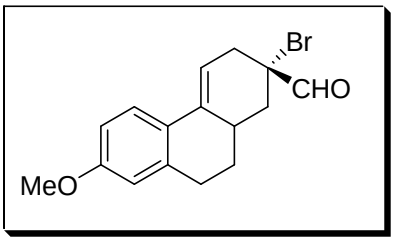


(66% ee)

Colorless solid (68%); $[\alpha]_D = +157.0^o$ (*c* = 1.96, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 20.28 min (major), 21.12 min (minor).

(2*S*)-2-Bromo-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde (62h)



(94% ee)

Light yellow solid (61%); $[\alpha]_D = -39.7^o$ (*c* = 2.15, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 10.65 min (major), 12.49 min (minor).

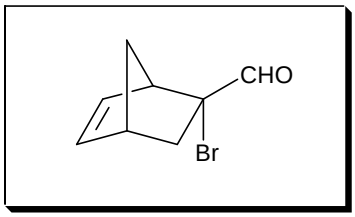
6.5.3 Catalytic Enantioselective Diels-Alder via a Chiral (*S*)-BINOL-In(III) complex using allenyltributylstannane as pre-activators

Representative procedure for asymmetric Diels-Alder reaction : Preparation of (*1R ,2R , 4R*) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) and 4Å molecular sieve (15 mg) were added and the mixture was stirred under nitrogen at room temperature for 2 h. Allenyltributylstannane (0.091 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min to afford a white suspension. The pre-formed catalyst was then cooled to -40 ^{o}C for 15 minutes. 2-bromoacrolein (67.5 mg, 0.50 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv, added dropwise along side of the flask) were added successively and the reaction mixture stirred at -40 ^{o}C for 20 h. The mixture was then quenched by addition of 5 mL of saturated $NaHCO_3$ and extracted with ether (10 mL x 3). The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the Diels-Alder adduct as a colorless solid (70% yield).

Characterization of Diels-Alder adduct

(*1R ,2R , 4R*) -2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (60a)



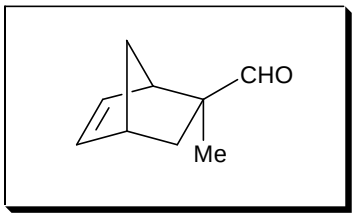
(96 % ee)

Colorless oil (70%); R_f = 0.65 (4:1 hexane/ethyl acetate)

$[\alpha]_D$ = +9.4^o (*c* = 1.49, CH_2Cl_2)

Diastereoselectivity *(ex*o-*endo* ratio) was determined by ^{1}H NMR analysis of the crude mixture: δ 9.56 (s, 1H, *ex*o, major), 9.34 (s, 1H, *end*o, minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.74 (d, 1H, minor), 4.67 (d, 1H, major), 4.61 (d,1H, major), 4.52 (d, 1H, minor).

(*1R, 2S, 4R*)-2-Methyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (60b)



(45 % ee)

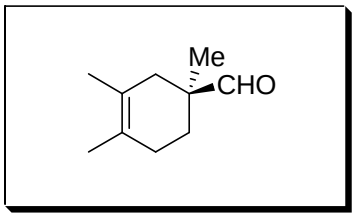
Colorless oil (62%); R_f = 0.64 (4:1 hexane/ethyl acetate)

$[\alpha]_D$ = +6.7^o (*c* = 3.03, CH_2Cl_2)

Diastereoselectivity *(ex*o-*endo* ratio) was determined by 1H NMR analysis of the crude mixture: δ 9.68 (s, 1H, *ex*o, major), 9.38 (s, 1H, *end*o, minor). Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding

alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.34 (d, 1H, major), 4.31 (d, 1H minor), 4.25 (d, 1H, minor), 4.22 (d, 1H, major).

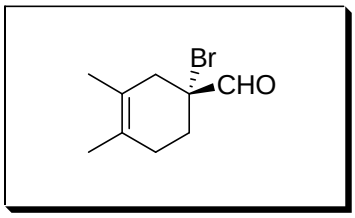
(*S*)-1,3,4-Trimethyl-cyclohex-3-enecarbaldehyde (62c)



Colorless oil (12%); R_f = 0.68 (4:1 hexane/ethyl acetate)

Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the *(*R)-MTPA ester derivative and ^{1}H NMR integration (500 MHz, CDCl3): δ 4.12 (d, 1H, major), 4.08 (d, 1H minor), 4.01 (d, 1H, minor), 3.98 (d, 1H, major).

(*R*)-1-Bromo-3,4-dimethyl-cyclohex-3-enecarbaldehyde (62d)



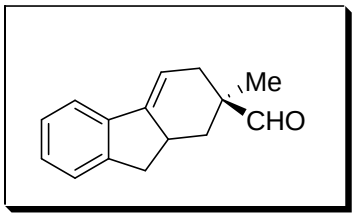
(35% ee)

Colorless oil (52%); R_f = 0.67 (4:1 hexane/ethyl acetate)

$[\alpha]_D$ = +21.3^o (*c* =2.97, CH_2Cl_2)

Enantioselectivity was determined by reduction with $NaBH_4$ to the corresponding alcohol, conversion to the benzoyl ester derivative and HPLC analysis using Daicel AD column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 62.39 min (minor), 65.89 min (major).

(2*R*)-2-Methyl-2,3,9,9a-tetrahydro-1*H*-fluorene-2-carbaldehyde (62e)



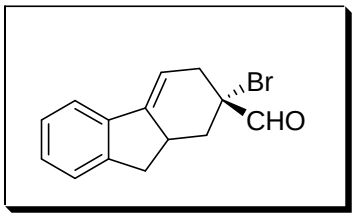
(32% ee)

Colorless solid (36%); R_f = 0.65 (4:1 hexane/ethyl acetate)

$[\alpha]_D$ = +16.8^o (*c* = 1.36, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ASH + ADH column with 1.0% *i*-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 11.03 min (major), 11.40 min (minor).

(2*S*)-2-Bromo-2,3,9,9a-tetrahydro-1*H*-fluorene-2-carbaldehyde (62f)



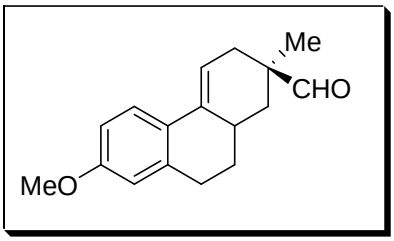
(90% ee)

Light yellow solid (65%); R_f = 0.60 (4:1 hexane/ethyl acetate)

$[\alpha]_D$ = +146.2^o (*c* = 2.32, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 0.3 mL/min; 235 nm; retention times: 20.28 min (major), 21.12 min (minor).

(2*R*)-2-Methyl-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde (62g)



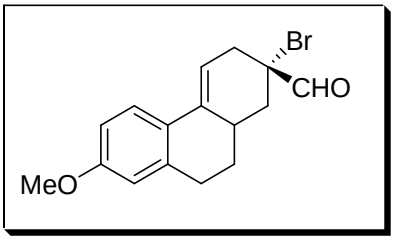
(30% ee)

Colorless solid (35%); R_f = 0.57 (4:1 hexane/ethyl acetate)

$[\alpha]_D$ = -41.2 (*c* = 1.56, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 2.0% *i*-PrOH in hexanes for elution; 1.0 mL/min; 235 nm; retention times: 7.38 min (major), 8.51 min (minor).

(2*S*)-2-Bromo-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde (62h)



(94% ee)

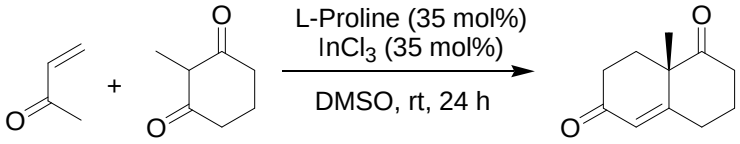
Light yellow solid (72%); R_f = 0.51 (4:1 hexane/ethyl acetate)

$[\alpha]_D$ = -52.6^o (*c* = 1.92, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% *i*-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 10.65 min (major), 12.49 min (minor).

6.5.4 Application of the (*S*)-BINOL-In(III) Catalytic Enantioselective Process for the Construction of Steroidal Scaffold

Wieland Miescher Ketone, *(S)*-3,4,8,8a-tetrahydro-8a-methylnaphthalene-1,6(2H,7H)-dione (84)



69 **70** **71**

A solution of L-proline (0.32 g, 2.8 mmol, 0.35 equiv), $InCl_3$ (0.62 g, 2.8 mmol, 0.35 equiv) and 2-methyl-1,3-cyclohexandione **70** (1.0 g, 7.9 mmol, 1.0 equiv) in 50 ml of anhydrous DMSO was stirred under nitrogen at room temperature until the ketone and proline are completely dissolved. To this solution, freshly distilled methyl vinyl ketone **69** was slowly added dropwise (0.99 mL, 11.9 mmol, 1.5 equiv). The reaction was vigorously stirred at this temperature for 24 h and then quenched with saturated NH_4Cl /ethyl acetate. The organic layer and aqueous layer were separated with addition of brine. The aqueous phase was extracted with ethyl acetate (100 mL x 3) and combined extracts were dried over magnesium sulfate, filtered and evaporated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the product **71** as a yellow oil.

Yellow oil (66%); R_f = 0.37(1:1 hexane/ethyl acetate)

1H NMR (300 MHz, $CDCl_3$): δ 5.86 (d, *J* = 1.74 Hz, 1H, =C**H**), 2.78-2.66 (m, 2H, ring -C$\mathbf{H_2}$), 2.53-2.43 (m, 4H, ring -(C$\mathbf{H_2}$)$_2$), 2.17-2.11 (m, 3H, ring C$\mathbf{H_2}$ and -C**H**), 1.79-1.65 (m, 1H, ring C**H**), 1.45 (s, 3H, -C$\mathbf{H_3}$).

^{13}C NMR (75.4 MHz, $CDCl_3$) : δ210.9, 198.2, 165.7, 125.9, 60.3, 37.6, 33.6, 31.7, 29.8, 23.3, 22.9.

FTIR (neat): 2956.2, 1713.3, 1669.4, 1620.7cm^{-1}.

HRMS Calcd for $C_{11}H_{14}O_2$ [M^+]: 178.0994. Found: 178.0994

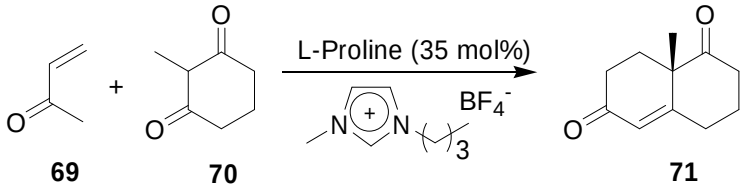
$[\alpha]_D$ = +20.9 ^{o} (*c* = 3.06, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using 2 ODH column with 1.0% *i*-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 63.10 min (major), 67.51 min (minor). The absolute configuration was assigned with references to the literature[131].

[131] Francesca, C.; Massimo, S. J. *Liquid Chromatography and related tech.* **2003**, v 26, *3*, 409

L-proline in an ionic liquid as an efficient and reusable catalyst for enantioselective Robinson annulation reaction

Representative procedure for the L-proline catalyzed Robinson Annulation in bminBF_4

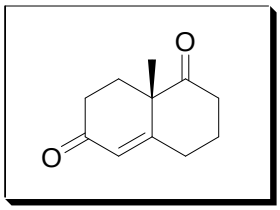


A solution of L-proline (0.032 g, 0.28 mmol. 0.35 equiv) and 2-methyl-1,3-cyclohexandione **70** (0.1 g, 0.79 mmol, 1.0 equiv) in 1.0 ml of [bmim]BF_4 was stirred under nitrogen at room temperature for 30 min. To this solution freshly distilled methyl vinyl ketone **69** was slowly added dropwise (0.099 mL, 1.19 mmol, 1.50 equiv). The reaction was vigorously stirred at this temperature for 48 h and then decanted using anhydrous diethyl ether (10 mL x 4). The combined organic layer were dried over magnesium sulfate, filtered and evaporated in *vacuo*. The residual crude product was purified via silica gel chromatography affording the product **71** as a yellowish oil.

Representative procedure for the recyclability studies of the L-proline catalyzed Robinson Annulation

A solution of L-proline (0.032 g, 0.28 mmol, 0.35 equiv) and 2-methyl-1,3-cyclohexandione **70** (0.1 g, 0.79 mmol, 1.0 equiv) in 1.0 mL of [bmim]BF_4 was stirred under nitrogen at room temperature for 30 min. To this solution freshly distilled methyl vinyl ketone **69** was slowly added dropwise (0.099 mL, 1.19 mmol, 1.5 equiv). The reaction was vigorously stirred at this temperature for 48 h and then decanted using anhydrous diethyl ether (10 mL x 4). The combined organic layer were dried over magnesium sulfate, filtered and evaporated in *vacuo*. The residual crude product was purified via silica gel chromatography. Anhydrous THF (1.5 mL) was added to the ionic liquid residue containing L-proline and the solvent removed in *vacuo* to azeotropically eliminate residual moisture. 2-methyl-1,3-cyclohexandione **70** (0.1 g, 0.79 mmol, 1.0 equiv) was added and stirred at room temperature for 30 min, followed by addition of methyl vinyl ketone **69** (0.099 mL, 1.19 mmol, 1.5 equiv). The reaction mixture was then stirred for 48 h. The recyclability process was repeated five times.

(*S*)-3,4,8,8a-tetrahydro-8a-methylnaphthalene-1,6(2H,7H)-dione (71)



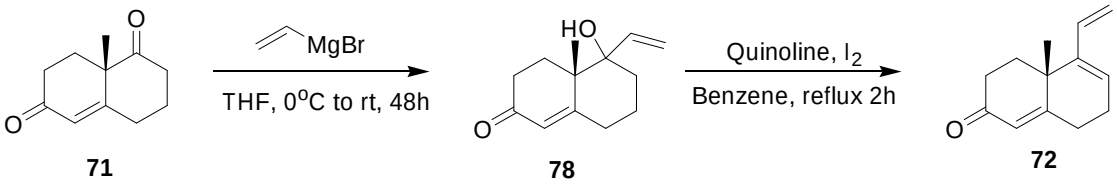
(78% ee)

Yellow oil (76%); $[\alpha]_D = +16.9^{o}$ (*c* = 2.86, CH_2Cl_2)

Enantioselectivity was determined by HPLC analysis using 2 ODH column with 1.0% *i*-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 63.10 min (major), 67.51 min (minor).

The absolute configuration was assigned with references to the literature.

Diene precursor, *(S)*-4,4a,7,8-tetrahydro-4a-methyl-5-vinylnaphthalen-2(3H)-one (85)



71 **78** **72**

Yield : 38%

Vinylmagnesium bromide (38.0 mL (1.0 M in THF), 38.0 mmol, 2.0 equiv) was added to a solution of Wieland Miescher ketone **71** (3.38 g, 19.0 mmol) in 15 mL anhydrous THF via a dropping funnel at 0 ^{o}C under nitrogen. After the addition was completed, the mixture was allowed to warm slowly to room temperature and the resulting solution was stirred for 24 h. The solution was then cooled to 0 ^{o}C and quenched very slowly with saturated aqueous NH_4Cl (25 mL) followed by sufficient H_2O (about 10 mL) to dissolve any precipitated inorganic materials. The organic and aqueous layers were extracted with ether (4 x 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated in *vacuo* to give 2.90 g (74%) of the crude alcohol **78** as a clear, yellow-orange oil.

Crude alcohol **78** (2.90 g, 14.0 mmol), used within 1 h of its isolation, was dissolved in dry benzene (50 mL) in which quinoline (0.15 mL) and iodine (*ca.* 0.5 g) had been dissolved. The mixture was then heated under reflux for 2 h until the evolution of H_2O had ceased as measured by a Dean and Stark apparatus. The quantity of H_2O evolved (*ca.* 0.3 mL) indicated virtually quantitative dehydration. The dark solution was cooled to room temperature and filtered through a thick pad (ca. 15 cm x 4 cm) of silica gel to remove traces of the ketone **71** carried through from the previous

synthesis, and some dark impurity. The resulting brownish-yellow solution was then evaporated in *vacuo* to give 1.24 g (38 %) of the steroidal diene **72** as a brownish-yellow viscous oil.

R_f = 0.71(4:1 hexane/ethyl acetate)

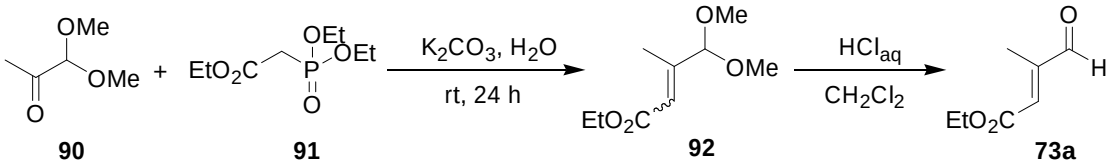
^{1}H NMR (300 MHz, $CDCl_3$): δ 6.39 (dd, *J* = 17.4, 10.8 Hz, 1H, =C**H**), 6.05 (s, 1H, =C**H**), 5.73-5.76 (t, *J* = 4.4 Hz, 1H, C**H**=CH_2), 5.26-5.04 (dd, *J* = 17.4, 10.8 Hz, 2H, CH=C**H$_2$**), 2.78-2.66 (m, 2H, ring -C**H$_2$**), 2.53-2.43 (m, 2H, ring -C**H$_2$**), 2.17-2.11 (m, 3H, ring -C**H$_2$** and -C**H**), 1.79-1.65 (m, 1H, ring -C**H**), 1.45 (s, 3H, -C**H$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$) : δ 214.9, 140.4, 138.8, 135.1, 128.5, 123.9, 112.6, 45.5, 35.5, 28.4, 24.3, 22.6, 20.6.

FTIR (neat): 3089.3, 2931.0, 2842.2, 1709.4, 1618.4, 1450.9, 894.5 cm^{-1}.

HRMS Calcd for $C_{13}H_{16}O$ [M^+]: 188.1204. Found: 188.1201.

Dienophile[132], 3-Methyl-4-oxo-but-2-enoic acid ethyl ester (73a)



A mixture of 1,1-dimethoxyacetone **90** (5.91 g, 50 mmol) and ethyl 2-(diethoxyphosphoryl)acetate **91** (13.45 g, 60 mmol) was added dropwise to a suspension of K_2CO_3 (17.28 g) in 10 mL of water at room temperature. After the addition was complete, stirring was continued at room temperature for an additional 24 h. The insoluble matter was then removed by filtration and washed with ether. The organic phase was separated and washed with brine to neutrality. After drying and

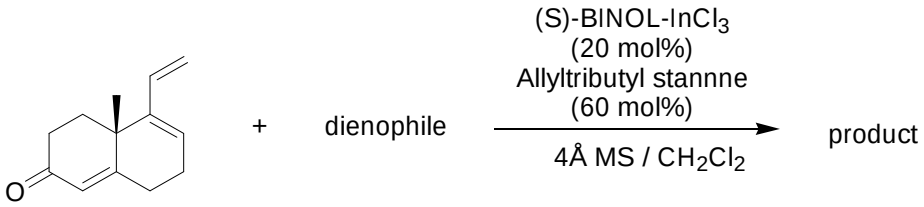
[132] Curley, R. W.; Ticoras, C. *J. Syn. Comm.* **1986,** 16, 627.

evaporation of solvent, the product was purified by distillation under vacuum, which yields a mixture of *E* and *Z* acetal esters **92** as a colorless oil.

HCl (3 N, 15 mL) was added dropwise to a solution of the above obtained *E* and *Z* acetal esters in 15 mL CH_2Cl_2 at 0 °C. The resulting mixture was stirred for another 2 h at 0 °C. The organic layer was separated and washed with a saturated aqueous solution of $NaHCO_3$ and brine, and dried over anhydrous Na_2SO_4. Solvent was removed under vacuum. The crude product was purified by vacuum distillation to yield 7.1 g of the *E* isomer of **73a** (Yield: 75%, b.p. 44-47 °C at 1 mm of Hg).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.55 (s, 1H, -C**H**O), 6.50 (q, *J* = 1.76 Hz, 1H, =C**H**), 4.28 (q, *J* = 7.03 Hz, 2H, OC**H$_2$**CH$_3$), 2.16 (d, *J* = 1.76 Hz, 3H, -C**H$_3$**), 1.34 (t, *J* = 7.03 Hz, 3H, OCH$_2$C**H$_3$**).

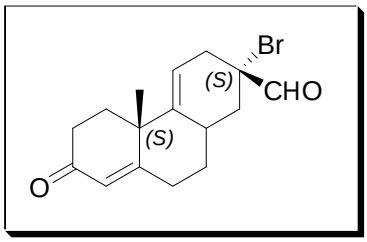
Representative procedure for the Diels-Alder Reaction catalyzed by the (*S*)-BINOL-$InCl_3$ complex



72 **73** **74**

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InBr_3$ (35 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) and 4Å molecular sieve (15 mg) were added and the mixture was stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min to afford a white suspension. The pre-formed catalyst was then cooled to -20 ^oC for 15 minutes. The corresponding dienophile **73** (0.5 mmol, 1.0 equiv) and *(S)*-4,4a,7,8-tetrahydro-4a-methyl-5-vinylnaphthalen-2(3H)-one **72** (0.10 mL, 1.5 mmol, 3.0 equiv, added dropwise along side of the flask) were added successively and the reaction mixture stirred at -20 ^oC for 20 h. The mixture was then quenched by addition of 5 mL of saturated $NaHCO_3$ and extracted with ether (10 mL x 3). The combined organic extracts was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the Diels-Alder adducts **74**.

(2*S*)-2-Bromo-(*4S*)-4b-methyl-7-oxo-1,2,3,4b,5,6,7,9,10,10a-decahydro-phenanthrene-2-carbaldehyde (74e)



Yellow oil (52%); R_f = 0.37 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$) δ 9.46 & 9.47 (s, 2H, -C**H**O), 5.98 & 5.91 (s, 2H, =C**H**), 5.43 (s, 2H, =C**H**), 2.74-2.61 (m, 4H, ring -C**H$_2$**), 2.41-2.28 (m, 10 H, ring -C**H$_2$**) 2.26-2.04 (m, 10 H, ring -C**H$_2$**), 1.94-1.92 (m, 1H, ring -C**H$_2$**), 1.89-1.87 (m, 1H, ring -C**H**), 1.43 & 1.35 (s, 6H, -C**H$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 213.63, 211.18, 192.44, 192.10, 135.97, 135.76, 124.61, 124.45, 117.21, 117.09, 68.67, 68.18, 52.49, 51.16, 38.12, 37.51, 36.89, 36.81, 36.29, 36.25, 34.32, 34.26, 31.05, 30.10, 29.67, 28.53, 26.74, 26.38, 24.88, 24.72.

FTIR (neat): 3017.9, 2936.5, 1711.8, 756.4 cm^{-1}.

HRMS Calcd for $C_{16}H_{19}BrO_2$ [M^+]: 322.0568. Found: 322.0564

Enantioselectivity was determined by HPLC analysis using ADH column with 1.0% i-PrOH in hexanes for elution; 1.0mL/min; 235 nm; retention times: 11.99 min (minor), 13.04 min (minor), 14.25min (major), 15.78 (minor).

6.6 CATALYTIC ENANTIOSELECTIVE MANNICH-TYPE REACTION AND IMINE ALLYLATION

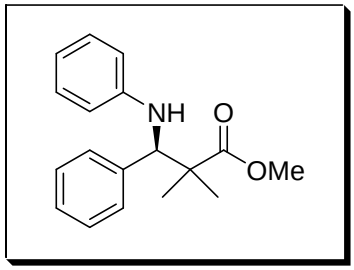
6.6.1 Catalytic Enantioselective Mannich-Type Reaction and Imine Allylation via a Chiral (*S*)-BINOL-$InCl_3$ Complex

Representative procedure for enantioselective Mannich-type Reaction: Preparation of (*R*)-3-(4-Methoxy-phenylimino)-2,2-dimethyl-3-phenyl-propionic acid methyl ester

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.22 mmol, 0.22 equiv) was added to the mixture and stirred under nitrogen at room temperature for 2 h. Allyltributylstannane (0.093 mL, 0.30 mmol, 0.60 equiv) was added to the resulting mixture and stirred for 10 min to afford a white suspension. The pre-formed catalyst was then cooled to -78 ^{o}C for 15 min followed by the slow addition of benzylidene-(4-methoxy-phenyl)-amine (0.11 g in 0.5 mL dichloromethane, 0.5 mmol, 1.0 equiv) and 1-methoxy-1-trimethylsilyloxypropene (0.20 mL, 1.0 mmol, 2.0 equiv). The reaction mixture was stirred at -78 ^{o}C for 4 h and 16 h at room temperature and then quenched with 5 mL saturated sodium bicarbonate solution. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated in *vacuo*. The residual crude product was purified via silica gel chromatography to afford the β-amino ester as a colorless oil.

Characterization of β-Amino Esters

(*R*)- 2,2-Dimethyl-3-phenyl-3-phenylamino-propionic acid methyl ester (84a)



Yellowish wet-solid (38 %); R_f = 0.61 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31-7.23 (m, 5H, aromatic), 7.10-7.03 (m, 2H, aromatic), 6.65-6.50 (m, 3H, aromatic), 4.53 (s, 1H, -C**H**), 3.67 (s, 3H, -OC**H$_3$**), 1.30 (s, 3H, -C**H$_3$**), 1.20 (s, 3H, -C**H$_3$**).

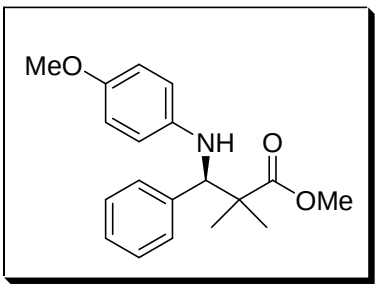
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 176.97, 146.86, 139.17, 128.95, 128.21, 127.93, 127.38, 117.22, 113.34, 64.30, 52.01, 46.95, 24.48.

FTIR (neat): 1715.8 cm^{-1}.

HRMS Calcd for $C_{18}H_{21}NO_2$ [M^+]: 283.1572. Found: 283.1568.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 9.72 min, t_2 = 12.78 min).

(*R*)- 3-(4-Methoxy-phenylamino)-2,2-dimethyl-3-phenyl-propionic acid methyl ester (84b)



Dark brown wet-solid; m.p. 92-94^{o}C (54 %); R_f = 0.50 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28-7.24 (m, 5H, aromatic), 6.66-6.44 (m, 4H, aromatic), 4.46 (br, 1H, -C**H**), 3.66 (s, 6H, $(-OCH_3)_2$), 1.25 (s, 3H, -C**H$_3$**), 1.16 (s, 3H, -C**H$_3$**).

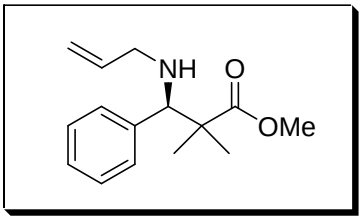
^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.03, 151.84, 141.15, 139.28, 128.26, 127.85, 127.27, 114.62, 114.59, 65.12, 55.57, 51.93, 41.04, 24.37, 20.36.

FTIR (neat): 1719.2 cm^{-1}.

HRMS Calcd for $C_{19}H_{23}NO_3$ [M^+]: 313.1678. Found: 313.1673.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 17.38 min, t_2 = 20.26 min).

(*R*)- 3-Allylamino-2,2-dimethyl-3-phenyl-propionic acid methyl ester (84d)



Dark brown wet-solid (35 %); R_f = 0.50 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H, aromatic), 5.86-5.72 (m, 1H, CH_2C**H**=CH_2), 5.08-5.00 (m, 2H, CH_2CH=C**H$_2$**), 3.92 (s, 1H, -C**H**), 3.68 (s, 3H, -OC**H$_3$**), 3.13-3.06 (m, 1H, C**H$_2$**CH=CH_2), 2.92-2.85 (m, 1H, C**H$_2$**CH=CH_2), 1.12 (s, 3H, -C**H$_3$**), 1.06 (s, 3H, -C**H$_3$**).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 177.71, 139.32, 137.03, 128.90, 128.78, 127.26, 115.48, 67.79, 51.71, 50.08, 47.45, 24.00, 19.67.

FTIR (neat): 1724.6 cm^{-1}.

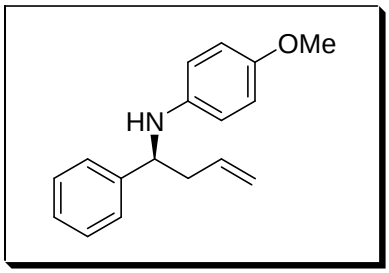
HRMS Calcd for $C_{15}H_{17}NO_2$ [M^+]: 247.1572. Found: 247.1569.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 5.66 min, t_2 = 6.62 min).

Representative procedure for enantioselective allylation of imines : Preparation of (*S*)-(4-Methoxy-phenyl)-(1-phenyl-but-3-enyl)-amine

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added $InCl_3$ (22 mg, 0.10 mmol, 0.20 equiv). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.5 mL of dichloromethane. *(S)*-BINOL (31 mg, 0.11 mmol, 0.22 equiv) and 4Å molecular sieve (15 mg) and the mixture was stirred under nitrogen at room temperature for 2 h to afford a white suspension. Allyltributylstannane (0.31 mL, 1.0 mmol, 2.0 equiv) was added to the resulting suspension and stirred for 10 min. The mixture was then cooled to -78 ^{o}C for 15 min followed by the slow addition of benzylidene-(4-methoxy-phenyl)-amine (0.11 g in 0.5 mL dichloromethane, 0.5 mmol, 1.0 equiv). The reaction mixture was stirred at -78 ^{o}C for 4 h and then for 16 h at room temperature and then quenched with 5 mL saturated sodium bicarbonate solution at room temperature for 30 min. The aqueous layer was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the product as a colorless oil.

(*S*)-(4-Methoxy-phenyl)-(1-phenyl-but-3-enyl)-amine (85b)



Dark brown wet-solid (15 %); R_f = 0.50 (4:1 hexane/ethyl acetate)

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H, aromatic), 5.86-5.72 (m, 1H, $CH_2C\mathbf{H}=CH_2$), 5.08-5.00 (m, 2H, $CH_2CH=C\mathbf{H_2}$), 3.92 (s, 1H, -C**H**), 3.68 (s, 3H, -$OC\mathbf{H_3}$), 3.13-3.06 (m, 1H, $C\mathbf{H_2}CH=CH_2$), 2.92-2.85 (m, 1H, $C\mathbf{H_2}CH=CH_2$), 1.12 (s, 3H, -$C\mathbf{H_3}$), 1.06 (s, 3H, -$C\mathbf{H_3}$).

^{13}C NMR (75.4 MHz, $CDCl_3$): δ 152.10, 143.88, 141.72, 134.83, 128.57, 126.95, 126.41, 118.16, 114.83, 114.75, 58.07, 55.78, 43.38.

FTIR (neat): 1713.7 cm^{-1}.

HRMS Calcd for $C_{17}H_{19}NO$ [M^+]: 253.1467 . Found: 253.1462.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel AD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: t_1 = 6.58 min, t_2 = 6.97 min).

LIST OF PUBLICATIONS

International Refereed Papers:

1. Yong-Chua Teo, Kui-Thong Tan and Teck-Peng Loh. **Catalytic enantioselective allylation of aldehydes via a chiral indium(III) complex.** *Chemical Communication* **2005**, *1318*.
2. Jun Lu, Shun-Jun Ji, Yong-Chua Teo and Teck-Peng Loh. **Highly enantioselective allylation of aldehydes catalyzed by indium(III)-PYBOX complex.** *Organic Letters* **2005**, *7*, 159.
3. Yong-Chua Teo, Joshua-Daniel Goh and Teck-Peng Loh. **Catalytic enantioselective allylation of ketones via a chiral indium(III) complex.** *Organic Letters* **2005**, *7*, 2743.
4. Yong-Chua Teo and Teck-Peng Loh. **Catalytic enantioselective Diels-Alder reaction via a chiral indium(III) complex.** *Organic Letters* **2005**, *7*, 2539.
5. Yong-Chua Teo, Ee-Ling Goh and Teck-Peng Loh. **Catalytic enantioselective allylation of aldehydes via a chiral indium(III) complex in ionic liquids.** *Tetrahedron Letters* **2005**, *46*, 4573.
6. Jun Lu, Mei-Ling Hong, Shun-Jun Ji, Yong-Chua Teo and Teck-Peng Loh. **Enantioselective allylation of ketones catalyzed by chiral In(III)-PYBOX complexes.** *Chemical Communication* **2005**, 4217.
7. Yong-Chua Teo, Ee-Ling Goh and Teck-Peng Loh. **Catalytic enantioselective allylation of aldehydes via a moisture-tolerant chiral BINOL-In(III) complex.** *Tetrahedron Letters* **2005**, *46*, 6209.

8. Yong-Chua Teo and Teck-Peng Loh. **Catalytic enantioselective homopropargylation and allenylation of aldehydes via a chiral (*S*)-BINOL-In(III) complex.** *Submitted for publication.*
9. Fan-Fu, Yong-Chua Teo and Teck-Peng Loh. **Catalytic enantioselective homopropargylation and allenylation of aldehydes via a chiral PYBOX-In(III) complex.** *Submitted for publication.*

Conference Papers:

1. Yong-Chua Teo and Teck-Peng Loh. **Catalytic enantioselective allylation of aldehydes via a chiral indium(III) complex.** *Singapore International Conference-2: Frontiers in Chemical Design and Synthesis,* December 18 – 20, **2001**, Marina Mandarin Singapore Hotel, Singapore.
2. Yong-Chua Teo and Teck-Peng Loh. **Catalytic enantioselective allylation of aldehydes via a chiral indium(III) complex.** *The 228th American Chemical Society (ACS) National Meeting,* August 22 – 26, **2004**, Philadelphia, PA, United States, Division of Organic Chemistry.