

**PART I : DESIGN OF CHIRAL INDIUM COMPLEXES
FOR ENANTIOSELECTIVE CARBON-CARBON BOND
FORMATION REACTIONS**

**PART II : SYNTHETIC STUDIES TOWARDS THE
TOTAL SYNTHESIS OF RK-397**

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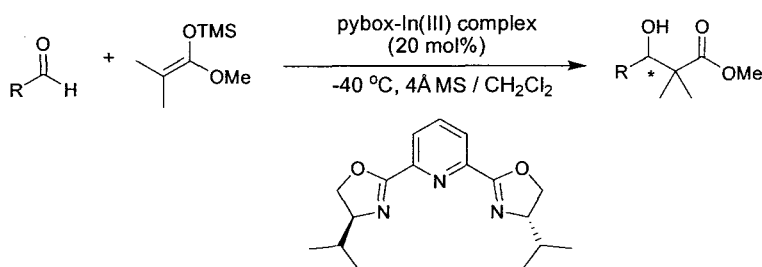
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SUMMARY

First part of this thesis describes the design and application of two novel chiral indium complexes, namely (*S,S*)-*i*Pr-PYBOX-In(OTf)₃ and (*S*)-BINOL-InCl₃ complex for various catalytic enantioselective organic transformations. The second part involves the synthetic studies towards the total synthesis of the antibiotic RK-397.

I. CATALYTIC ENANTIOSELECTIVE MUKAIYAMA ALDOL REACTION

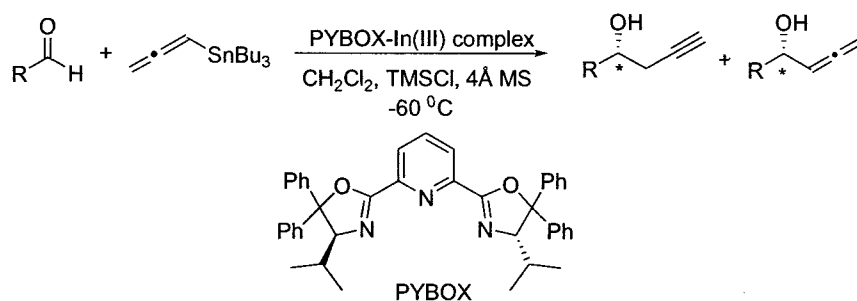
A chiral indium(III) complex prepared from indium triflate and (*S,S*)-*i*-Pr-pybox ligand has been developed to afford good yields and enantioselectivities (up to 92% ee) in the addition of (1-methoxy-2-methyl-propenyloxy)-trimethylsilane to various aromatic and aliphatic aldehydes via the Mukaiyama aldol reaction.



II. CATALYTIC ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF ALDEHYDES

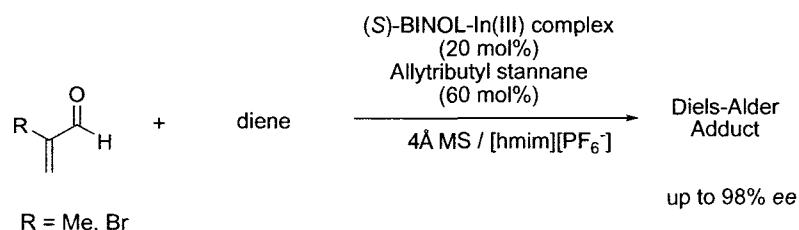
The second chapter describes the application of the newly developed chiral (*S,S*)-PYBOX-In(III) complex for the catalytic enantioselective propargylation and allenylation of aldehydes. The complex was effective in catalyzing the enantioselective addition of

allenyltributylstannane to a variety of aromatic, α,β -unsaturated and aliphatic aldehydes. The corresponding homopropargylic and allenylic alcohols were isolated in good yields and moderate to high enantioselectivities (up to 88% ee for homopropargylic alcohol and 90% ee for allenylic alcohol). A simple and practical approach to separate homopropargylic alcohol from allenic alcohol mixture in excellent yields with the retention of enantiomeric excess has also been developed.



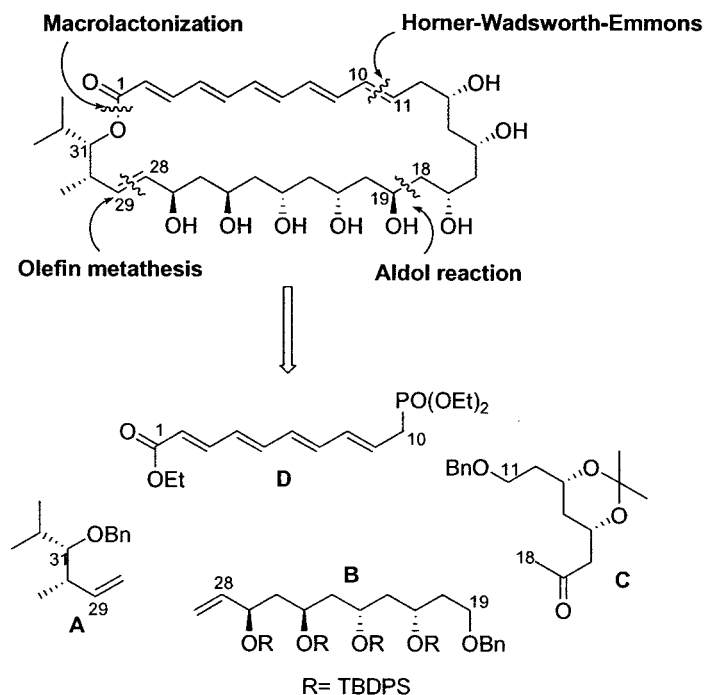
III. CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTION IN IONIC LIQUID VIA A CHIRAL IN(III)-BINOL COMPLEX

A recyclable, air- and moisture-stable chiral indium complex in [hmim][PF₆⁻] ionic liquid has been developed. 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). Moreover, the chiral In(III) complex can be reused for seven successive cycles with comparable enantioselectivities and yields without loss of catalytic activity.



IV. SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF RK-397

In the final part of this thesis, C1 to C31 fragment of RK-397 was synthesized via a convergent synthetic strategy that features the use of asymmetric Brown's allylation and crotylation, catalytic enantioselective hetero-Diels–Alder protocol employing the Cr(III)-Salen complex, and a 1,5-*anti*-stereo induction by substrate-controlled dibutylboron enolate aldol addition for absolute control of the 10 chiral centres in the polyol chain. The synthesis also demonstrated a successful intermolecular cross-metathesis between two elaborate molecular fragments. As excellent enantio- and diastereo-control was achieved during the synthesis, a single isomer was isolated towards the end of the synthesis.



INDEX OF ABBREVIATIONS

*Aux	chiral auxiliary
Ac	acetyl
AcOH	acetic acid
anhyd.	anhydrous
AllylBr	allylbromide
Ar	aryl
aq	aqueous
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-Bi-2-naphthol
Bn	benzyl
b.p.	boiling point
brs	broad singlet
BuLi	butyl lithium
<i>c</i>	concentration
CAB	(acyloxy)borane
Cacl _d	calculated
cat.	catalyst
CDCl ₃	chloroform
CH ₂ Cl ₂	dichloromethane
COSY	correlated spectroscopy
CSA	camphorsulfonic acid
°C	degree centigrade
cm ⁻¹	Inverse centimeter
cy	cyclohexane; cyclohexanyl
<i>d</i>	Density
d	Doublet
dd	doublet of doublet

ddd	doublet of a doublet of a doublet
de	diastereomeric excess
dr	diastereomeric ratio
DCC	1,3-dicyclohexylcarbodiimide
DIBAL	Diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPBr	B-bromodiisopinocampheylborane
DMAP	4- <i>N,N</i> -dimethylamino pyridine
DMF	<i>N,N</i> -dimethylformamide
DMP	Dess-Martin periodinane
DMSO	dimethyl sulfoxide
dt	doublet of triplets
ee	enantiomeric excess
EI	electron-impact ionization
equiv.	equivalent(s)
ESI	electrospray ionization
Et	Ethyl
Et ₃ N	triethylamine
ether	Diethyl ether
EtOAc	Ethyl acetate
EtOH	ethanol
FAB	Fast atomic bombardment
FGI	Functional group interconversion
FTIR	fourier transform infrared spectrometry
g	Gram
h	hour(s)
HDA	hetero Diels-Alder
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HMQC	Heteronuclear multiple quantum correlation
Hz	Hertz

<i>i</i> -Pr	Isopropyl
IPC	isopinocampheyl
IR	Infrared
IUPAC	International Union of Pure and Applied Chemistry
<i>J</i>	coupling constant
LiDBB	lithium 4,4'-di- <i>tert</i> -butylbiphenyl
LiHMDS	lithium hexamethyldisilazide
LDA	Lithium diisopropylamide
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
<i>n</i> -Bu	<i>n</i> -butyl
nm	nanometres
NMO	4-methylmorpholine <i>N</i> -oxide
NOSEY	Nuclear Overhauser enhancement spectroscopy
NMR	Nuclear magnetic resonance
Nu	nucleophile
OTf	trifluoromethane sulfonate (triflate)
<i>p</i>	Para
PBr	Phosphorous tribromide

PCC	Pyridinium chlorochromate
Pd/C	Palladium on carbon
Ph	Phenyl
PMB	<i>p</i> -methoxybenzyl
ppm	parts per million
Pr	Propyl
Py	Pyridine
PYBOX	bis(oxazoliny)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	<i>tert</i> -but(yl)
TBAF	tetrabutylammonium fluoride
TBDPS	<i>tert</i> -butyldiphenylsilyl
td	triplet of doublets
<i>tert</i>	Tertiary
temp.	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSCl	trimethylsilyl chloride
Tf	trifluoromethanesulfonyl
Ts	<i>p</i> -toluenesulfonyl (tosyl)
tt	triplet of triplets
UV	Ultraviolet
vol.	volume

CHAPTER 1

Catalytic Enantioselective Mukaiyama aldol Reaction

1.1 OVERVIEW OF ENANTIOSELECTIVE MUKAIYAMA ALDOL REACTION

The aldol reaction is one of the most powerful methods for the construction of 1, 3-dioxygenated carbon skeletons, which is a common feature in numerous natural products such as RK-397, roxaticin and callipeltoside A etc (Figure 1.1). The Lewis acid-catalyzed addition of enol silyl ether to aldehydes, commonly known as the Mukaiyama aldol reaction,¹ is an important variant of the general aldol process. The ability to control the absolute configurations of the newly formed stereogenic centres during the carbon-carbon bond formation process is of paramount importance for the synthesis of natural products and medicinal agents.

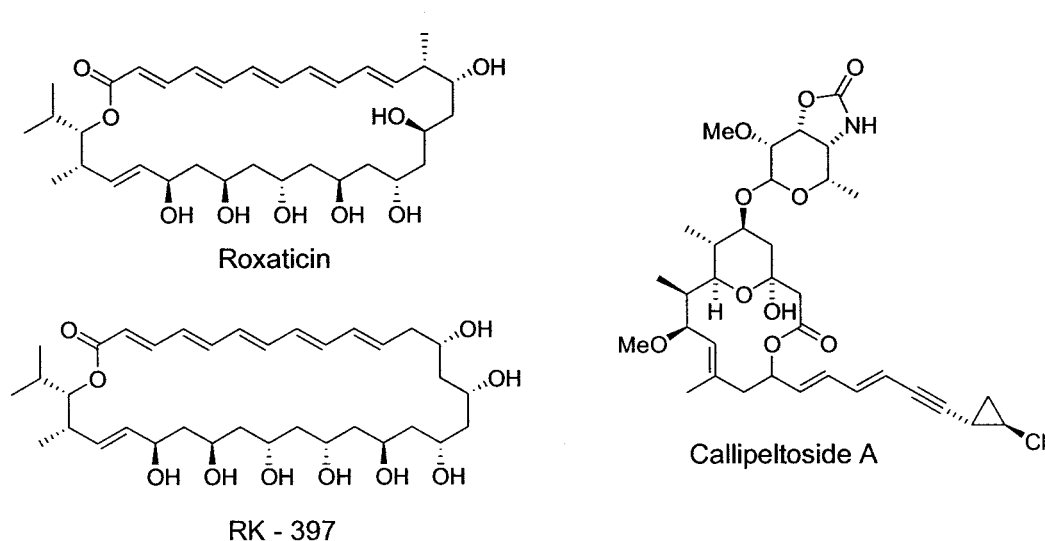


Figure 1.1 1,3 dioxygenated carbon skeletons in natural products

In general, control of stereochemistry can be accomplished diastereomerically through the use of either chiral aldehydes or stoichiometric chiral auxiliaries attached

¹ (a) Mukaiyama, T.; Narasaka, K.; Banno, K. *Chem. Lett.* **1973**, 1011-4. (b) Mukaiyama, T.; Banno, K.; Narasaka, K. *J. Am. Chem. Soc.* **1974**, *96*, 7503-9. (c) Gennari, C. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 2.4. (d) Heathcock, C. H. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: San Diego, CA, 1984; Vol. 3, Chapter 2. (e) Evans, D.A. *Aldrichimica Acta* **1982**, *15*, 23-32.

to the donor enolate. The control of stereochemistry using chiral aldehydes as substrates has some limitations. While chiral aldehydes undergo stereospecific addition in a very predictable fashion, the formation of all the possible stereoisomers from a single chiral aldehyde is not possible. The use of chiral auxiliaries has solved this problem, however, while this approach has been quite successful, it requires additional steps to introduce and remove the chiral auxiliary. The search for methods that predictably transfer chirality efficiently and catalytically by reagent has been a challenging goal in organic synthesis. Therefore, the development of chiral catalysts that promote asymmetric Mukaiyama aldol reaction in a highly stereocontrolled fashion has attracted much attention² and examples of several chiral catalysts developed over the years are discussed below.

Chiral titanium(IV) complexes

Development of the asymmetric aldol reaction based on chiral titanium(IV) complexes was reported independently by the groups of Mikami,³ Keck,⁴ and Carreira⁵.

Excellent enantioselectivities up to 96% have been obtained with Mikami's catalyst based on the $\text{Ti}(\text{O}-i\text{Pr})_2\text{Cl}_2$ and (*R*)-BINOL complex. His work covered a broad range of functionalized aldehydes and thioester-derived ketene silyl acetals (Scheme 1.1).^{2a} Moreover, the Mikami's system also able to catalyze the

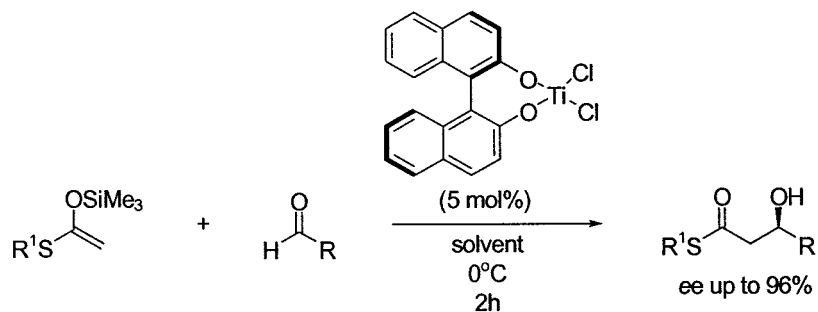
² (a) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137. (b) Machajewski, T. D.; Wong, C. H. *Angew. Chem. Int. Ed.* **2000**, *39*, 1352.

³ (a) Mikami, K.; Matsukawa, M.; *J. Am. Chem. Soc.* **1994**, *116*, 4077. (b) Mikami, K.; Matsukawa, S.; *ibid.* **1993**, *115*, 7039. (c) Mikami, K.; *Pure Appl. Chem.* **1996**, *68*, 639.

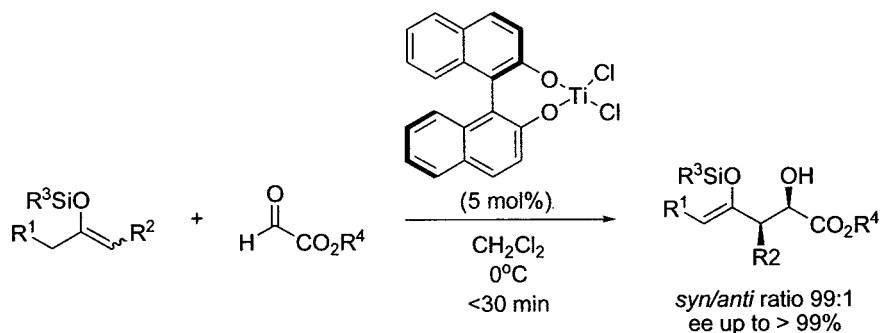
⁴ Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363.

⁵ (a) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837. (b) Singer, R. A.; Carreira, E. M.; *ibid.* **1995**, *117*, 12360. (c) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

diastereoselective and enantioselective aldol reaction of ketone enol silyl ethers with glyoxylates (*syn/anti* ratio 99:1; ee (*syn*) up to > 99%) (Scheme 1.2).^{2b}



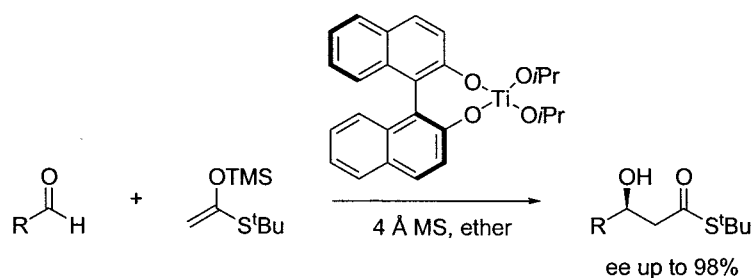
Scheme 1.1 Reaction of aldehydes with thioester-derived ketene silyl acetals



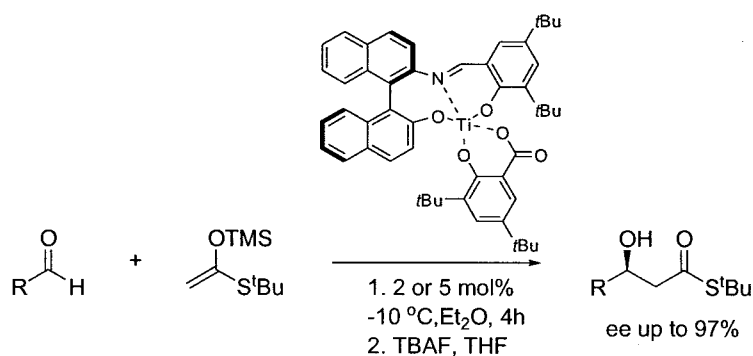
Scheme 1.2 Diastereoselective and enantioselective aldol reaction

The second titanium(IV) system was reported by Keck *et al.*, who used $\text{Ti}(\text{O}-i\text{Pr})_4$ instead of $\text{Ti}(\text{O}-i\text{Pr})_2\text{Cl}_2$ as the titanium source. High enantioselectivities between 89% and >98% ee could be achieved by using the thioester derivatives with a various aldehydes (Scheme 1.3).^{3,6}

⁶ Keck, G. E.; Krishnamurthy, D.; Grier, M. C. *J. Org. Chem.* **1993**, *58*, 6543.

Scheme 1.3 Aldol reaction reported by Keck *et al.*

A new BINOL-based ligand (with an imine functionality) was developed by Carreira *et al.*, leading to a further extension of the titanium(IV) catalyst. The Mukaiyama aldol reaction proceeded smoothly with excellent enantioselectivities between 94% and 97% in the presence of only 2 - 5 mol % of the corresponding catalyst (Scheme 1.4).

Scheme 1.4 A new BINOL-based ligand by Carreira *et al.*

Chiral copper(II) complexes

The family of copper(II) box and pybox catalyst⁷ was developed by Evans *et al.* for the Mukaiyama aldol reaction. The catalysts function by activating α -keto esters and α -alkyloxy aldehydes respectively through bidentate coordination with copper. Various aldol adducts were achieved with up to 99% ee and 100% yield even in the presence of only 0.5 mol % catalyst (eqn (I) Scheme 1.5).^{7a,7c}

A five-membered catalyst-substrate chelate is a requirement for high stereoselectivity (Scheme 1.5). The geometry around copper has been reported to be square planar and square pyramidal in the case of Cu(II)-box complex and Cu(II)-pybox derivatives respectively from experimental results and ESR spectroscopic experiments.

Moreover high *syn* selectivity (*syn/anti* ratio up to 98:2) with excellent enantioselectivities (*syn* up to 99% ee) was also achieved with substituted enolsilanes. It is noteworthy that (*Z*)- and (*E*)-enolsilane isomers react in a stereoconvergent manner.^{7e,7f}

Interestingly, formation of the *anti* adducts in remarkable *anti/syn* ratio up to 99:1 and enantioselectivities up to 99% ee (eqn (IV) Scheme 1.5) was achieved just by replacing Cu(II) by Sn(II) as center ion in box and pybox complexes.^{7d}

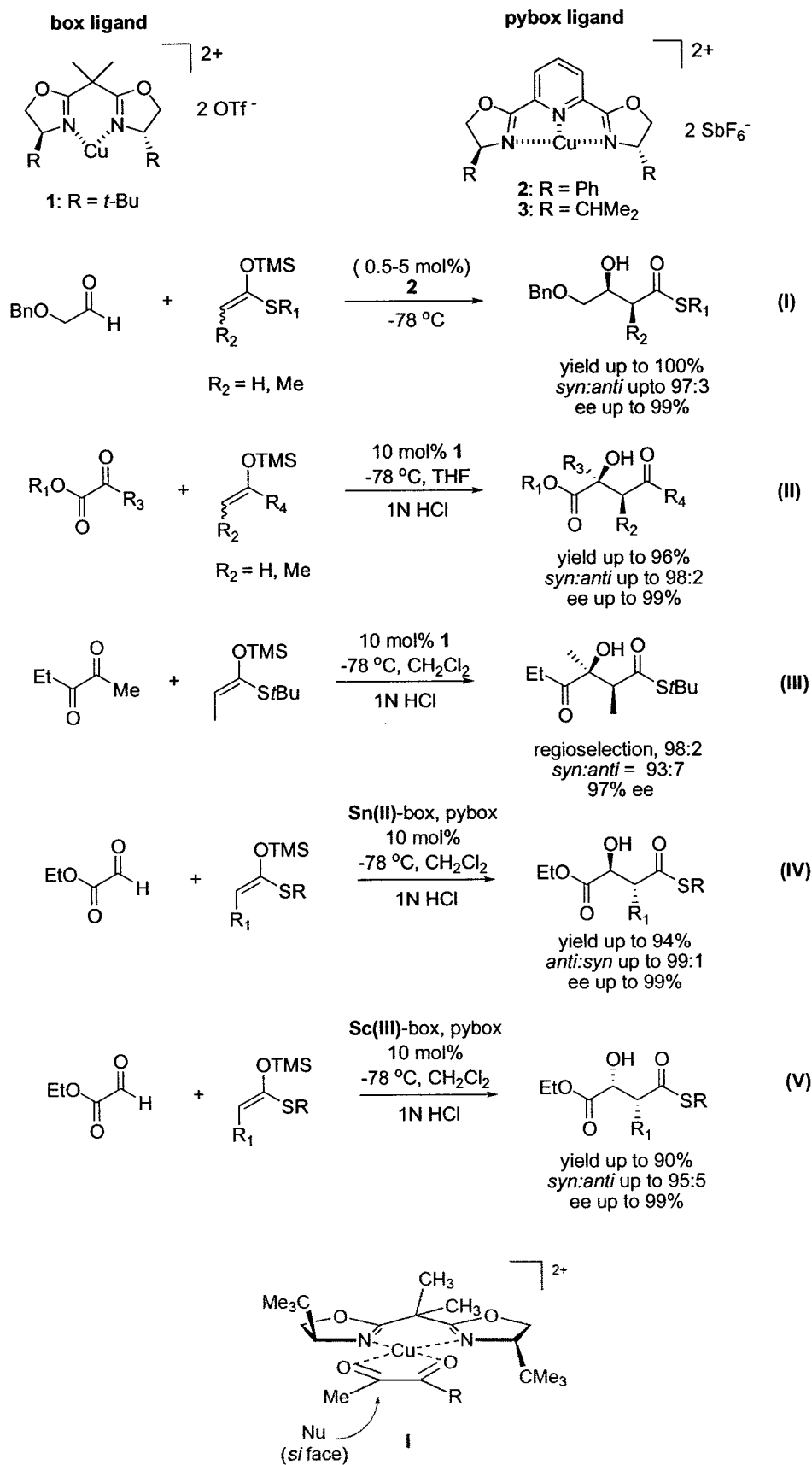
⁷ (a) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814. (b) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1997**, *42*, 7481. (c) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893. (d) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859. (e) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Connell, B. T. *J. Am. Chem. Soc.* **1999**, *121*, 669. (f) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686. (g) Evans, D. A.; Masse, C. E.; Wu, J. *Org Lett.* **2002**, *4*, 3375.

The corresponding *syn* aldol process with glyoxylate esters was achieved through the use of Sc(III) box and pybox derived complexes in the *syn*-selective aldol addition reactions between enolsilanes and ethyl glyoxylate (eqn (V) Scheme 1.5).^{7g}

Thus, very efficient diastereo- and enantioselective approaches to *syn* as well as *anti* aldol adducts are accessible by Evans' catalytic bichelating concept. Kobayashi *et al.* also reported similar Cu(II) box and pybox complexes that could function in aqueous systems such as water and water/alcohol, although the enantiofacial selectivity and efficiency were lower than that in aprotic solvents.⁸

⁸ Kobayashi, S.; Nagayama, S.; Busujima, T. *Tetrahedron*. **1999**, *55*, 8739.

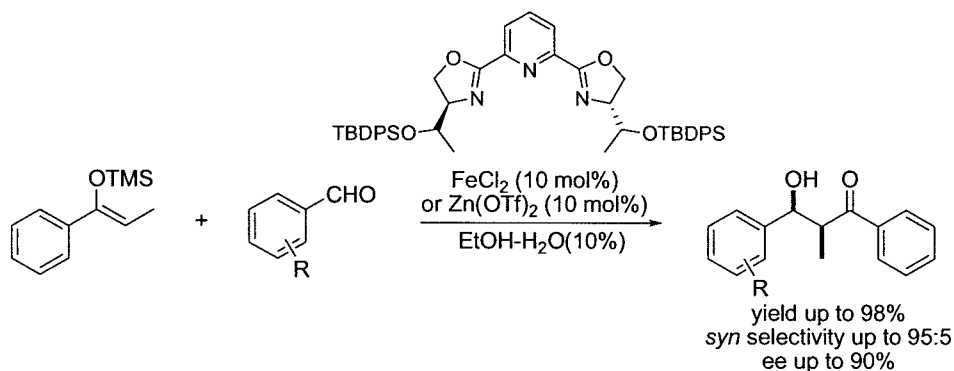
CATALYTIC ENANTIOSELECTIVE MUKAIYAMA ALDOL REACTION



Scheme 1.5 Catalytic aldol reaction with α -alkyloxy aldehydes and α -keto esters

Chiral iron(II) and zinc(II) complexes

Recently, Mlynarski and co-workers reported the use of an Fe(II) complex with a hindered hydroxyethyl-pybox (he-pybox) ligand which shows improved catalytic activity and enantioselectivity for asymmetric Mukaiyama-aldol reactions in aqueous media. This water-stable chiral Lewis acid promotes condensation of aromatic silyl enol ethers with a range of aldehydes with good yields, excellent *syn*-diastereoselectivity and enantioselectivities up to 90% ee. The combination of the same ligand with Zn(II) salt is also demonstrated as a remarkably efficient and water-compatible chiral Lewis acid (Scheme 1.6).⁹

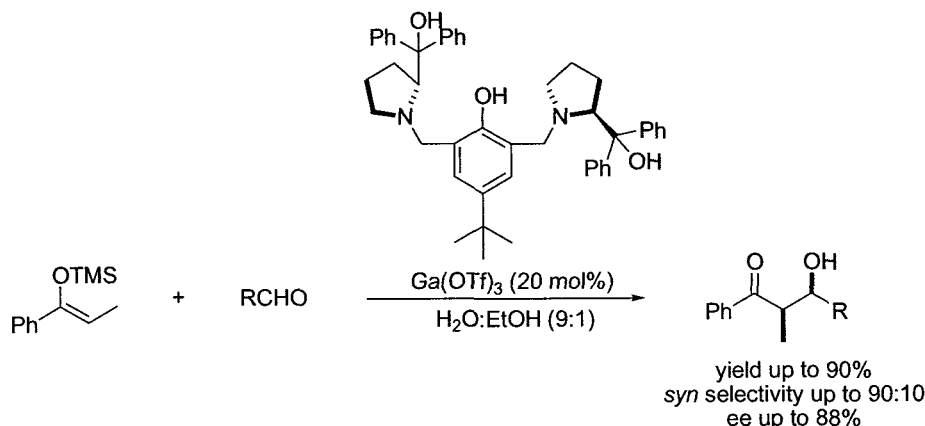


Scheme 1.6 Aldol reaction with Fe(II) and Zn(II) he-pybox complexes

⁹ (a) Jankowska, J.; Mlynarski, J. *J. Org. Chem.* **2006**, *71*, 1317. (b) Jankowska, J.; Paradowska, J.; Mlynarski, J. *Tetrahedron Lett.* **2006**, *47*, 5281. (c) Jankowska, J.; Paradowska, J.; Rakiel, B.; Mlynarski, J. *J. Org. Chem.* **2007**, *72*, 2228.

Chiral gallium(III) complex

Li and co-workers reported a novel chiral gallium catalysts ($\text{Ga}(\text{OTf})_3$ or GaCl_3) with chiral semi-crown ligands as highly effective chiral Lewis acid catalysts for catalytic aqueous Mukaiyama aldol reaction that give good yields, diastereo- and enantioselectivities (Scheme 1.7).¹⁰



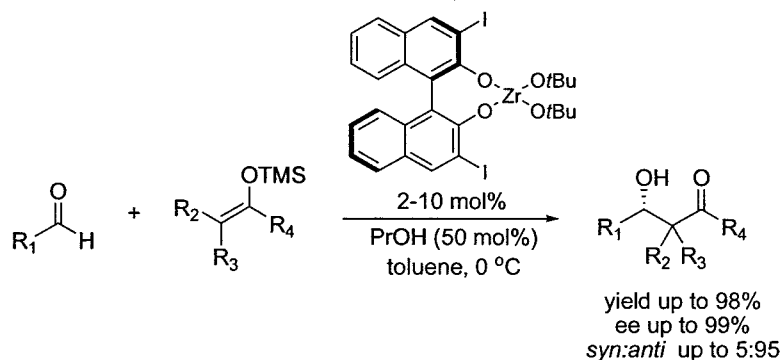
Scheme 1.7 Asymmetric Mukaiyama aldol with chiral Ga(III) complex

Chiral zirconium(IV) complexes

In year 2000, Kobayashi and co-workers reported a highly *anti*-selective catalytic asymmetric aldol reactions using a novel chiral zirconium catalyst prepared from $\text{Zr}(\text{O}i\text{Bu})_4$ and (*R*)-3,3'-dibromo-1,1'-bi-2-naphthol ((*R*)-3,3'- Br BINOL). It is noteworthy that while most previous catalytic asymmetric aldol reactions required temperatures of -20 to -78 °C under anhydrous conditions, high yields and selectivities (up to 98% yield and 99% ee with various aldehydes) were obtained even at 0 °C to room temperature in the presence of free alcohols with this novel zirconium complex. Moreover, *anti*-aldol adducts were obtained in the reactions of silyl enolates of propionate derivatives with several aldehydes in high selectivities. It was also

¹⁰ Li, H. J.; Tian, H. Y.; Chen, Y. J.; Wang, D.; Li, C. J. *Chem. Commun.*, **2002**, 2994.

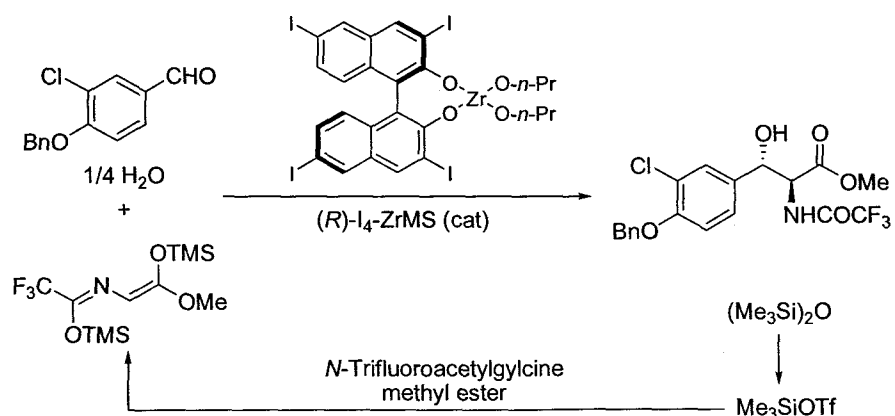
confirmed that the selectivities were independent of the geometry of the silyl enolates. Namely, *anti*-selectivities were obtained using both (*E*)- and (*Z*)-silyl enolates (Scheme 1.8).



Scheme 1.8 Asymmetric Mukaiyama aldol with Chiral Zr complex

Recently, they also reported an industrial scale synthesis of *anti*-(2*S*,3*S*)- β -(*p*-benzyloxy-*m*-chloro)-phenyl-*N*-trifluoroacetyl-l-serine methyl ester, a key building block of the antibacterial vancomycin through the use of the air-stable zirconium molecular sieves combined catalyst [(*R*)-I₄-ZrMS] with (*R*)-3,3',6,6'-I₄-BINOL. The product was obtained in high yield with high diastereo- and enantioselectivities (94%, *anti/syn* = 89/11, *anti* = 94% ee) on a 100g scale production. Moreover, this is the first example of the complete recovery of the silicon source in a Mukaiyama aldol reaction (Scheme 1.9).¹¹

¹¹ (a) Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192. (b) Ueno, M.; Ishitani, H.; Kobayashi, S. *Org. Lett.* **2002**, *4*, 3395. (c) Kobayashi, S.; Saito, S.; Ueno, M.; Yamashita, Y. *Chem. Commun.* **2003**, 2016. (d) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Yamashita, Y. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 5476. (e) Ishitani, H.; Yamashita, Y.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2000**, *122*, 5403. (f) Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292.

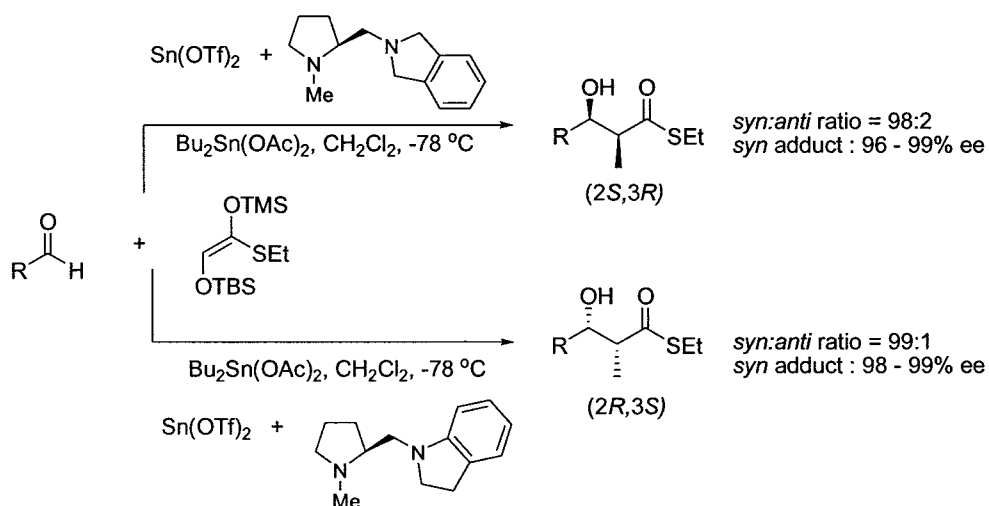


Scheme 1.9 Reaction scheme of a key building block of the antibacterial vancomycin

Chiral tin(II) complexes

Recently, Kobayashi *et al.* managed to obtain both enantiomers of the *syn* aldol adduct by using the same initial source of chirality with stoichiometric amounts of Sn(II) diamine complexes as chiral Lewis acids. The diamine ligand was based on the L-proline framework. Both *syn* enantiomers of the resulting dihydroxythioester derivatives can be obtained in high enantioselectivity (*syn/anti* ratio up to > 99:1; *syn* up to > 99% ee) by modifying the position of the nitrogen around the bicyclic system (Scheme 1.10).¹²

¹² Kobayashi, S.; Horibe, M. *Chem. Eur. J.* **1997**, *3*, 1472.

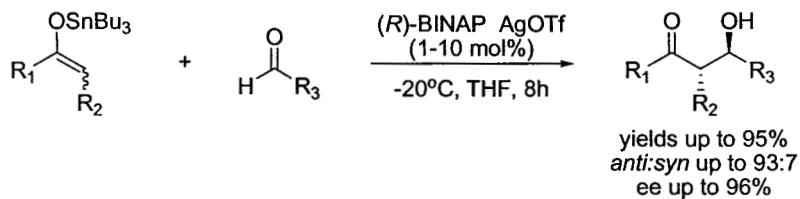


Scheme 1.10 Asymmetric Mukaiyama aldol with chiral Sn(II) complexes

Chiral silver(I) complex

Yamamoto *et al.* found that other than classic silyl enolates, tributyltin enolates can act as alternative nucleophiles when a chiral BINAP-containing silver(I) complex was utilized as catalyst (ee up to 95%).¹³ The catalytic system afforded the *anti* adduct as major diastereomer in high ee, with (*E*)-enolates as starting materials (*anti/syn* ratio up to 93:7; *anti* up to 96% ee; Scheme 7). The *syn* adducts were obtained with (*Z*)-enolates achieving *syn/anti* ratios of up to > 99:1 (*syn* up to 95% ee) (Scheme 1.11).

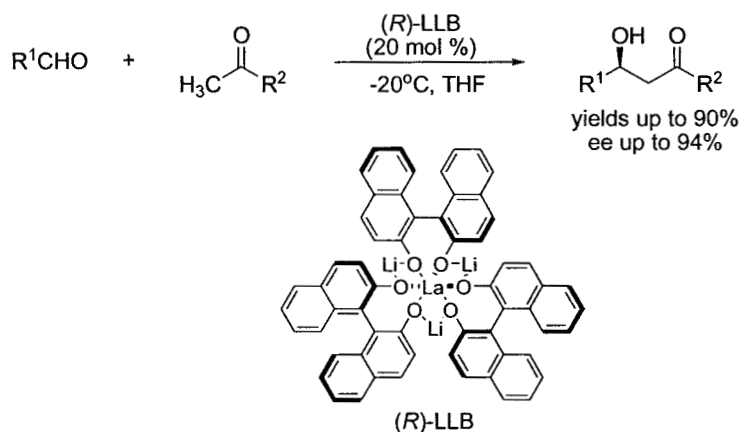
¹³ Yanagisawa, A.; Matsumoto, Y.; Nakashima, H.; Asakawa, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1997**, *119*, 9319.



Scheme 1.11 Asymmetric Mukaiyama aldol with chiral Ag(I) complex.

Chiral lanthanum(III) complex

The direct asymmetric aldol reaction between unmodified ketones and aldehydes has been achieved up to 94% ee by Shibasaki *et al.*¹⁴ through the employment of multifunctional Shibasaki catalyst LLB, containing both Lewis acidic and Bronsted basic properties similar to the corresponding aldolases (Scheme 1.12). The central lanthanum(III) ion functioned as a Lewis acid, by means activating the aldehyde, whereas the lithium binaphthoxide moiety acted as a Bronsted base. As a result of the synergetic effect of both functional groups, there is no need for activation of the starting materials.

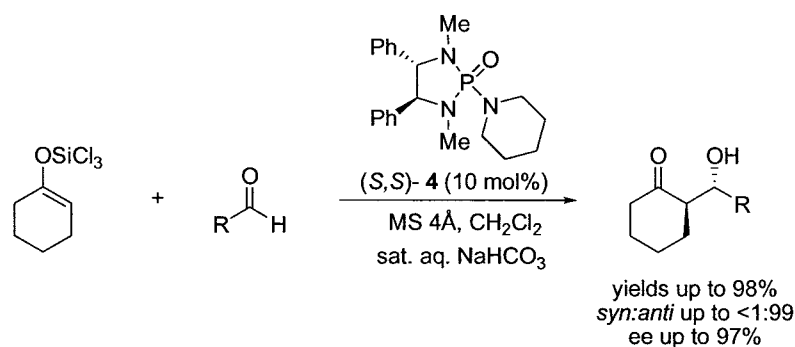


Scheme 1.12 Asymmetric Mukaiyama aldol with chiral La(III) complex

¹⁴ Yamada, Y. M. A.; Yoshikawa, N.; Sasai, H.; Shibasaki, M. *Angew. Chem.* **1997**, *109*, 1942; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1871.

Chiral nonmetallic Lewis bases

Denmark *et al.* demonstrated that chiral phosphoramides can act as effective catalyst for the aldol reaction. 10 mol % of (*S,S*)- **4** was found to afford the aldol adducts in enantioselectivities up to 97% in nearly quantitative yields. This concept utilizes chiral bases instead Lewis acids¹⁵ of which seem to coordinate temporarily to the silicon atom of trichlorosilyl enolates. Such enolates constitute strongly activated carbonyl group and react spontaneously with a number of aldehydes at -80 °C (Scheme 1.13).¹⁶



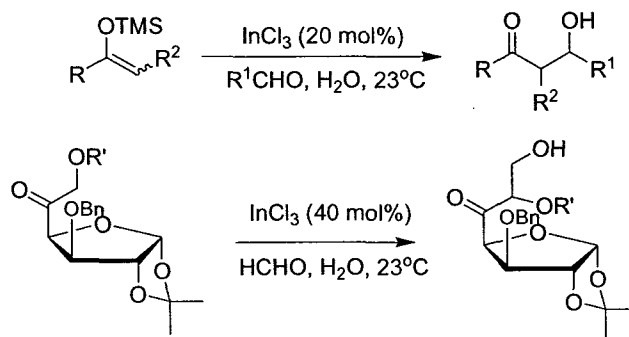
Scheme 1.13 Chiral nonmetallic Lewis bases as catalyst

¹⁵ Corey, E. J.; Cywin, C. L.; Roper, T. D. *Tetrahedron Lett.* **1992**, 33, 6907.

¹⁶ a) Denmark, S. E.; Winter, S. B. D.; Su, X.; Wong, K.-T. *J. Am. Chem. Soc.* **1996**, 118, 7404. (b) Denmark, S. E.; Wong, K.-T.; Stavenger, R. A. *J. Am. Chem. Soc.* **1997**, 119, 2333.

Chiral In(III) complex

Our laboratory has been interested in developing water tolerant reactions since its establishment. For this purpose, we initially chose indium salts for their low toxicities and stability in air and water, properties that matched our research goal. Our group observed that indium(III) chloride can be an efficient catalyst in Mukaiyama type reactions of silyl enol ethers with aldehydes in water as well as in ionic liquids at room temperature to yield the corresponding aldol products in good yields.¹⁷ The reaction has been successfully applied to the carbon-chain elongation of a glucose derivative.¹⁸ In addition, indium triflate also proved its catalytic efficiency in this reaction.

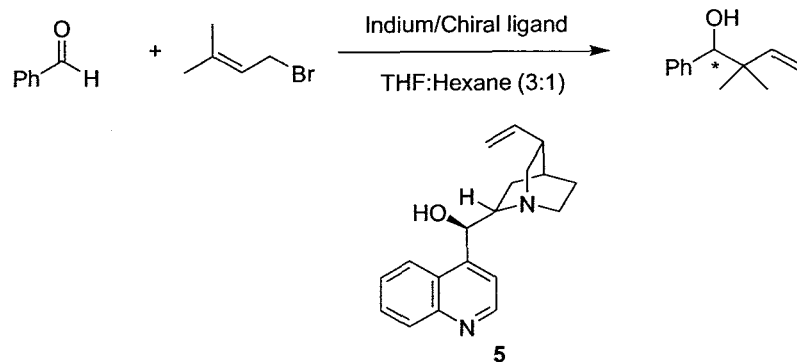


Scheme 1.14 Indium catalyzed Mukaiyama-Aldol reaction

¹⁷ (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. (d) Chen, S.L.; Ji, S.J.; Loh, T.P. *Tetrahedron Lett.* **2004**, *45*, 375.

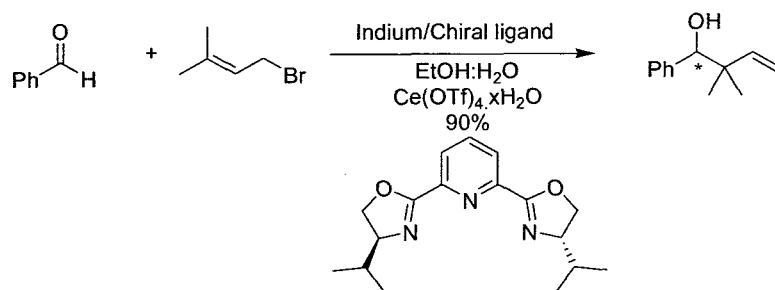
¹⁸ Loh, T.-P.; Chua, G.-L.; Vittal, J. J.; Wong, M.-W. *J. Chem. Soc., Chem. Commun.* **1998**, 861.

In the presence of cinchonidine **5** or cinchonine, indium mediated allylation of aldehydes proceeded in anhydrous organic solvents with high enantioselectivity (Scheme 1.15).¹⁹



Scheme 1.15 Enantioselective allylation of aldehydes with (-)-cinchonidine

An enantioselective version indium-mediated allylation of aldehydes in aqueous media has also been achieved by employing (*S,S*)-*i*Pr-pybox as the chiral source, with observed enantioselectivities up to 92% when used in conjunction with hydrated cerium (IV) trifluoromethanesulfonate as Lewis acid (Scheme 1.16).²⁰

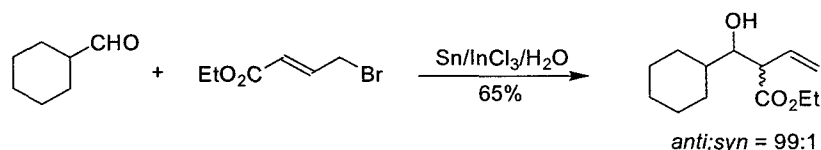


Scheme 1.16 Enantioselective allylation of aldehydes with (*S,S*)-*i*Pr-pybox

¹⁹ (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.

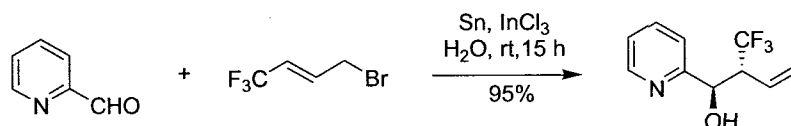
²⁰ Loh, T.-P.; Zhou, J.-R. *Tetrahedron Lett.* **2000**, *40*, 9115.

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 1.17).²¹



Scheme 1.17 Transmetalation in water

In aqueous media, fluorinated containing allylindium generated *in situ* from a catalytic amount of indium(III) chloride and tin (Scheme 1.18) reacted with aldehydes to give high regio- and diastereoselectivities.²² This one pot reaction furnishes the β -trifluoromethylated allylic alcohols in high yields.



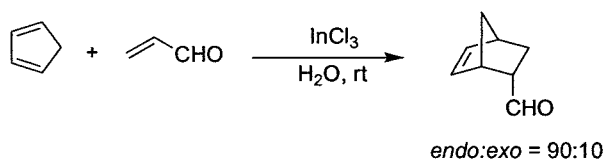
Scheme 1.18 Transmetalation with allylic stannanes in water

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.

²¹ Li, X.-R.; Loh, T.-P. *Tetrahedron Asymmetry* **1996**, *7*, 1535.

²² (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 has also been used as a catalyst for Diels-Alder reactions in water (Scheme 1.19).²³



Scheme 1.19 Diels-Alder reaction

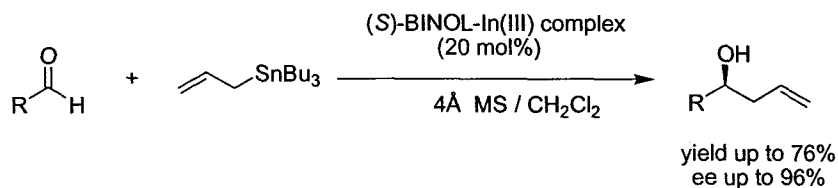
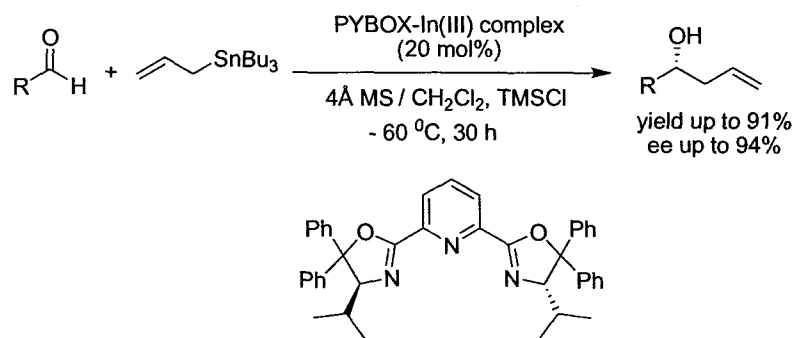
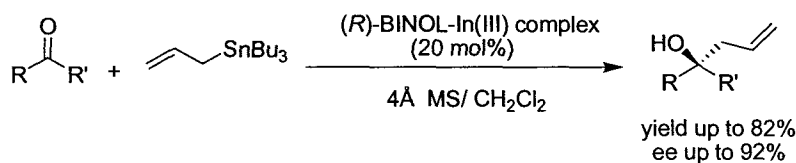
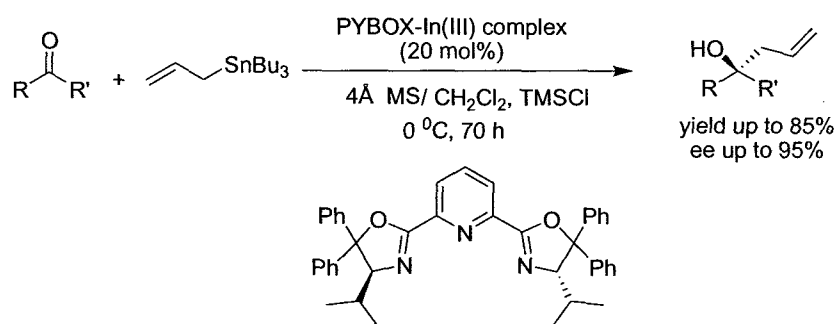
Our laboratory had been studying the feasibility of a water-tolerant chiral catalyst and recently, we had developed two catalytic chiral indium complexes that are capable of catalyzing the allylation of aldehydes and ketones. Our initial work on a chiral indium complex was developed through the study on the asymmetric allylation of carbonyl compounds. We found that both (*S*)-BINOL-In(III) complex²⁴ and (*S,S*)-PYBOX-In(III) complex²⁵ can catalyze the allylation of a variety of aromatic, aliphatic and α, β -unsaturated aldehydes in a highly enantioselective manner with excellent yields and enantioselectivities (Scheme 1.20).

²³ Loh, T.-P.; Pei, J.; Lin, M. *J. Chem. Soc., Chem. Commun.* **1996**, 2315.

²⁴ (a) Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 6209. (b) Teo, Y.-C.; Goh, E.-L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 4573. (c) Teo, Y.-C.; Goh, J.-D.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2743. (d) Teo, Y.-C.; Tan, K.-T.; Loh, T.-P. *Chem. Commun.* **2005**, *10*, 1318.

²⁵ (a) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 7435. (b) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Chem. Commun.* **2005**, *33*, 4217. (c) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159. (d) Lu, J.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, *18*, 2345. (e) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, *8*, 1010.

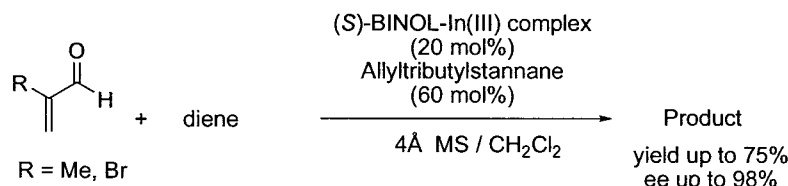
CATALYTIC ENANTIOSELECTIVE MUKAIYAMA ALDOL REACTION

Catalytic enantioselective allylation with (S) -BINOL-In(III) complexCatalytic enantioselective allylation with (S,S) -PYBOX-In(III) complexCatalytic enantioselective allylation of ketones with (S) -BINOL-In(III) complexCatalytic enantioselective allylation of ketones with (S,S) -PYBOX-In(III) complex.

Scheme 1.20 Chiral indium complexes for the allylation reaction

An important aspect of the above protocol is the tolerance of the formed chiral (*S*)-BINOL–In(III) complex to small amounts of water. In addition, due to the lesser reactivities of ketones, such allylations are normally carried out using the more reactive tetra-allyl stannanes. However, we are able to carry out the allylation process with allyltributyl stannane.

Since the enantioselectivity exhibited in these reactions appear to be derived from the structure of the chiral indium-aldehyde complex, we proceed to extend the (*S*)-BINOL–In(III) catalytic system to enantioselective Diels-Alder reaction.²⁶ Indeed, this 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 (Scheme 1.21).

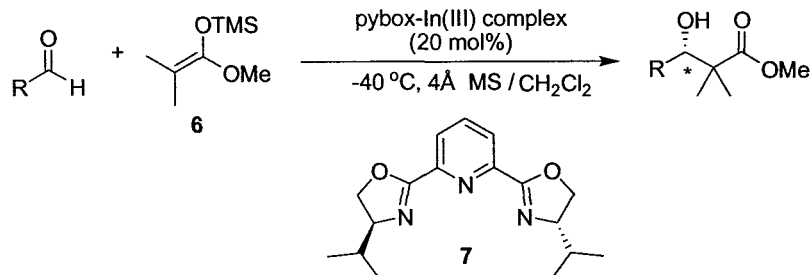


Scheme 1.21 Catalytic enantioselective Diels-alder reaction with (*S*)-BINOL–In(III) complex

Indium chemistry has constantly obtained unprecedented triumph in the past decade. However, the design of a chiral indium Lewis acid for the Mukaiyama aldol reaction 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.

²⁶ Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539.

In this part of the thesis, the successful application of a novel chiral indium complex based on $\text{In}(\text{OTf})_3$ and (S,S) -*iPr*-pybox for catalytic enantioselective Mukaiyama aldol reaction will be described (Scheme 1.22).



Scheme 1.22 Enantioselective Mukaiyama aldol reaction with (S,S) -*iPr*-pybox-In(III) complex

1.2 CATALYTIC ENANTIOSELECTIVE MUKAIYAMA ALDOL REACTION VIA A CHIRAL INDIUM(III)-PYBOX COMPLEX

1.2.1 INTRODUCTION

The asymmetric Mukaiyama aldol²⁷ reaction between enolsilane derivatives and aldehydes constitutes one of the most versatile synthetic methodologies for the stereoselective construction of optically active β -hydroxy carbonyl units which are important building blocks for the construction of many natural products and pharmaceuticals.²⁸ Therefore, intense research in this area has been carried out in recent years leading to the development of numerous Lewis acid catalysts bound to chiral ligands.²⁹ However, to the best of our knowledge, enantioselective Mukaiyama aldol reactions employing a chiral indium(III) catalyst have not been reported. Herein, we report the first asymmetric Mukaiyama aldol reaction between (1-methoxy-2-methyl-propenyloxy)-trimethylsilane and various aldehydes catalyzed by a chiral indium(III)-pybox complex.

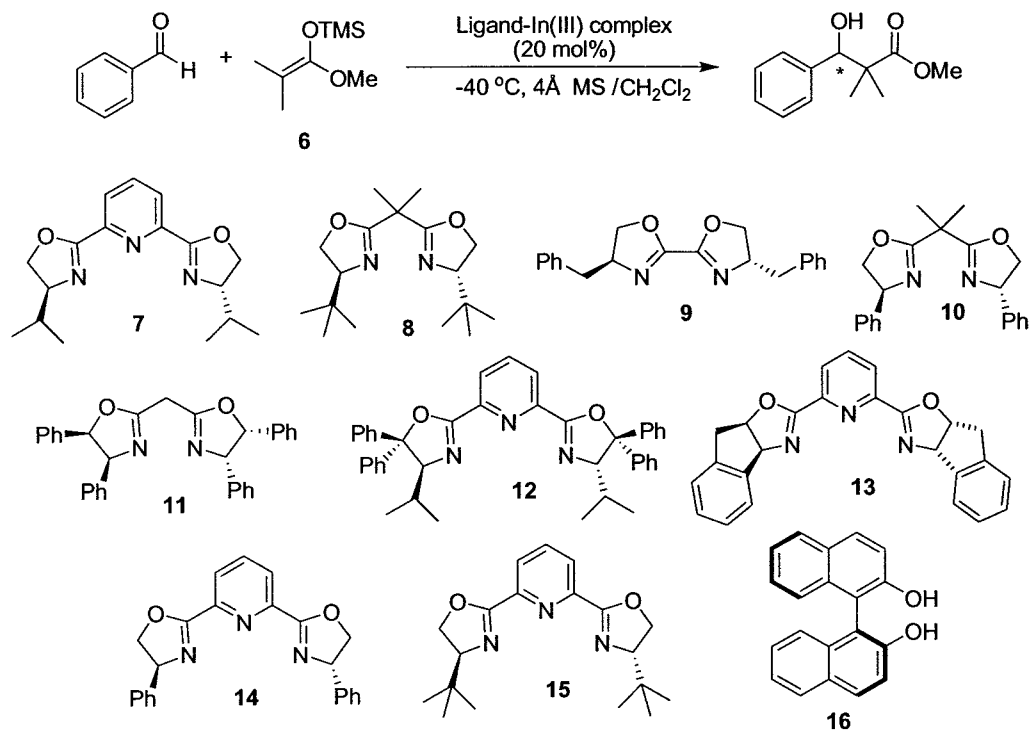
²⁷ Kobayashi, S.; Fujishita, B. Y.; Mukaiyama, T. *Chem. Lett.* **1990**, 1455.

²⁸ Review: Comprehensive Organic Synthesis; Trost, B. M., Ed.; Pergamon Press: Oxford, **1991**; Vol. 2, Chapter 1.

²⁹ For representative examples, see: (a) Kobayashi, S.; Furuya, M.; Ohtsubo, A.; Mukaiyama, T. *Tetrahedron: Asymmetry* **1991**, *2*, 635; (b) Kobayashi, S.; Uchiro, H.; Shiina, I.; Mukaiyama, T. *Tetrahedron* **1993**, *49*, 1761; (c) Evans, D. A.; Murry, J. A.; Kozlowski, M. C. *J. Am. Chem. Soc.* **1996**, *118*, 5814; (d) Evans, D. A.; Kozlowski, M. C.; Tedrow, J. S. *Tetrahedron Lett.* **1997**, *42*, 7481; (e) Evans, D. A.; Kozlowski, M. C.; Burgey, C. S.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7893; (f) Evans, D. A.; MacMillan, D. W. C.; Campos, K. R. *J. Am. Chem. Soc.* **1997**, *119*, 10859; (g) Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connel, B. T.; Staples, R. *J. Am. Chem. Soc.* **1999**, *121*, 669; (h) Evans, D. A.; Burgey, C. S.; Kozlowski, M. C.; Tregay, S. W. *J. Am. Chem. Soc.* **1999**, *121*, 686; (i) Mikami, K.; Matsukawa, M. *J. Am. Chem. Soc.* **1994**, *116*, 4077; (j) Mikami, K.; Matsukawa, S. *J. Am. Chem. Soc.* **1993**, *115*, 7039; (k) Mikami, K. *Pure Appl. Chem.* **1996**, *68*, 639; (l) Keck, G. E.; Krishnamurthy, D. *J. Am. Chem. Soc.* **1995**, *117*, 2363; (m) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1994**, *116*, 8837; (n) Singer, R. A.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 12360; (o) Carreira, E. M.; Singer, R. A.; Lee, W. *J. Am. Chem. Soc.* **1995**, *117*, 3649.

1.2.2 RESULTS AND DISCUSSIONS

In our initial study, we investigated the merits of various chiral ligands for their ability to promote the catalytic enantioselective Mukaiyama aldol reaction of benzaldehyde with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane **6** using a standard protocol. The chiral indium complexes were prepared by reacting indium salts (0.2 equiv) and a series of ligands **7–16** (0.22 equiv) in dichloromethane at room temperature in the presence of 4Å MS. After stirring for 1 h, benzaldehyde (1.0 equiv) was added followed by (1-methoxy-2-methyl-propenyloxy)-trimethylsilane **6** (1.2 equiv). The product was obtained by aqueous work-up and column chromatography. The results are shown in Table 1.

Table 1. Evaluation of various bis-oxazoline ligands and (*S*)-BINOL ligand for the enantioselective Mukaiyama aldol reaction^a

Entry	Indium salt	Ligand	Yield (%) ^b	ee (%) ^c
1	In(OTf) ₃	7	86	65
2	In(OTf) ₃	8	68	0
3	In(OTf) ₃	9	56	0
4	In(OTf) ₃	10	33	0
5	In(OTf) ₃	11	24	0
6	In(OTf) ₃	12	11	11
7	In(OTf) ₃	13	14	15
8	In(OTf) ₃	14	12	20
9	In(OTf) ₃	15	65	34
10	InCl ₃	16	52	0
11	InCl ₃	16	56	0 ^d
12	InBr ₃	16	60	0
13	In(OTf) ₃	16	50	0

^aUnless otherwise specified, the reaction was carried out with (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (0.6 mmol) and benzaldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from chiral ligands (22 mol %) and In(OTf)₃ (20 mol %) in the presence of 15 mg powdered activated 4 Å molecular sieves in 1.5 mL of CH₂Cl₂. The reaction mixture was kept for 24 h at -40 °C.

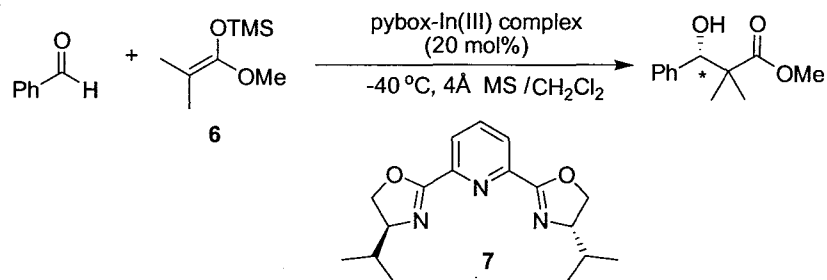
^b Isolated yield.

^c Determined by HPLC analysis.

^d 60 mol% allyltributyl stannane added.

Investigation into the utility of the In(III)–pybox complexes demonstrated that tridentate bis(oxazolanyl)pyridines (pybox) ligands (Table 1, entries 1 and 6 - 9) were effective catalysts for the enantioselective Mukaiyama aldol reaction. Variation of the ligand substituent revealed that the (*S,S*)-*i*-Pr-pybox–In(III) complex **7** was the optimal catalyst in this series, affording the (*S*)- β -hydroxy ester in 65% ee and 86% yield (entry 1). The bidentate (*S,S*)- bis-oxazoline ligands **8–11** were ineffective catalysts for enantiocontrol of this reaction (entries 2–5) probably due to ineffective binding of the ligand to indium. The chiral complex formed between (*S*)-BINOL and various indium salts were also ineffective catalyst for the Mukaiyama aldol reaction in regardless of the addition of allyltributyl stannane for the formation of the active (*S*)-BINOL–In(III) complex (entries 10-13).

With these encouraging results, an optimization study to enhance both the enantiomeric excess and yield of the reaction was initiated. The merits of various indium salts, temperature and the effects of additives were investigated. The results are shown in Table 2.

Table 2 Optimization studies for the enantioselective Mukaiyama aldol reaction catalyzed by chiral (*S,S*)-*i*-Pr-pybox-In(III) complex.^a

Entry	Indium reagent	Temp (°C)	Yield (%) ^b	ee (%) ^c
1	In(OTf) ₃	-40	86	65
2	InF ₃	-40	0	-
3	InCl ₃	-40	23	0
4	InBr ₃	-40	19	5
5	In(OTf) ₃	-20	84	50
6	In(OTf) ₃	-60	<10	-
7	In(OTf) ₃	-40	85	0 ^d
8	In(OTf) ₃	-40	72	62 ^e
9	In(OTf) ₃	-40	82	63 ^f

^a Unless otherwise specified, the reaction was carried out with (1-methoxy-2-methylpropenyloxy)-trimethylsilane **6** (0.6 mmol) and benzaldehyde (0.5 mmol) in the presence of a chiral indium(III) catalyst prepared from (*S,S*)-*i*-Pr-pybox-**7** (22 mol %) and In(OTf)₃ (20 mol %) in the presence of 15 mg powdered activated 4Å molecular sieves in 1.5 mL of CH₂Cl₂. The reaction mixture was kept for 24 h at -40 °C.

^b Isolated yield.

^c Determined by HPLC analysis.

^d The reaction was carried out with 1.2 equiv of TMSCl.

^e The reaction was carried out with 1.2 equiv of 2,6-*di-tert*-butyl-4-methylpyridine.

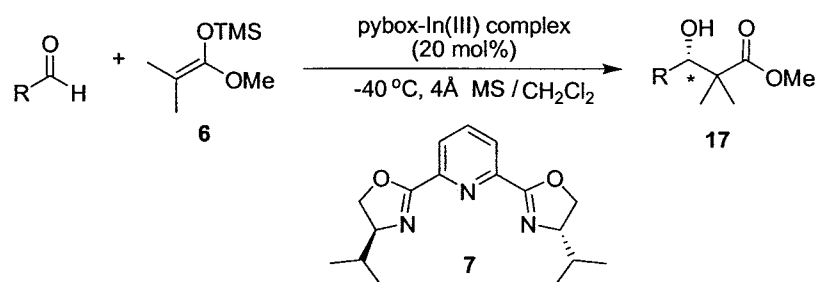
^f The reaction was carried out with 1.2 equiv of isopropanol.

The reaction catalyzed by the (*S,S*)-*i*-Pr-pybox-**7**-In(OTf)₃ complex exhibited the best conversion and enantiomeric excess (Table 2, entry 1). The corresponding halide complexes were inferior catalysts for the reaction and resulted in low yields and enantioselectivities. Moreover, a temperature study revealed that the reaction carried out at -60 °C afforded a very low yield (entry 6) while a significant decrease in enantioselectivity was observed at -20 °C (entry 5). Attempts to increase the yield and enantioselectivity through the employment of additives were also unsuccessful. The addition of TMSCl probably results in the formation of a catalytically active silicon

intermediate (Me_3SiX), which affords an avenue for a competing achiral catalytic process hence leading to a loss of enantioselectivity (entry 7).³⁰ Attempts to quench any HOTf present (which initiates the formation of Me_3SiOTf) through the use of a hindered base 2,6-di-tert-butyl-4-methylpyridine proves to be futile as neither the yield nor the selectivity was improved (entry 8). Moreover, the addition of isopropanol also did not afford any significant increase in enantioselectivity or yield (entry 9).

Having optimized the reaction parameters, we extended this catalytic enantioselective Mukaiyama aldol reaction to a series of aldehydes. The results are shown in Table 3.

³⁰ Hollis, T. K.; Bosnich, B. *J. Am. Chem. Soc.* **1995**, *117*, 4570.

Table 3. Enantioselective Mukaiyama aldol reaction of various aldehydes catalyzed by chiral (*S,S*)-*i*-Pr-pybox (**7**)-In(III) complex^a

Entry	R	Product	Yield (%) ^b	ee (%) ^c
1	Ph	17a	86	65
2	4-NO ₂ C ₆ H ₄	17b	75	92
3	4-OMeC ₆ H ₄	17c	71	57
4	4-MeC ₆ H ₄	17d	73	65
5	1-naphthyl	17e	50	77
6	2-naphthyl	17f	56	76
7	PhCH ₂ CH ₂	17g	40	51

^aUnless otherwise specified, the reaction was carried out with (1-methoxy-2-methylpropenyloxy)-trimethylsilane **6** (0.6 mmol) and aldehyde (0.5 mmol) in the presence of the chiral indium(III) catalyst prepared from pybox (**7**) (22 mol %) and In(OTf)₃ (20 mol %) in the presence of 15 mg powdered activated 4Å molecular sieves in 1.5 mL of CH₂Cl₂. The reaction mixture was kept for 24 h at -40 °C.

^b Isolated yield.

^cDetermined by HPLC analysis.

Among the aromatic aldehydes employed, 4-nitro-benzaldehyde underwent the catalytic process to afford the β -hydroxy ester with an excellent enantiomeric excess of 92% and a yield of 75% (Table 3, entry 2). In addition, the Mukaiyama aldol reaction of 1-naphthyl and 2-naphthylaldehyde under the influence of the chiral indium catalyst **7** furnished the products in comparable enantiomeric excesses of 77% and 76%, respectively (entries 5 and 6). The reaction of 3-phenyl-propionaldehyde under the influence of the chiral indium catalyst also afforded the product in 51% ee

(entry 7). The absolute configuration of the β -hydroxy esters was determined by comparison of the sign of optical rotation and the HPLC data with literature values.³¹

³¹ Yamashita, Y.; Ishitani, H.; Shimizu, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2002**, *124*, 3292.

1.3 CONCLUSION

In conclusion, we have demonstrated an enantioselective Mukaiyama aldol reaction between (1-methoxy-2-methyl-propenyloxy)-trimethylsilane **6** and various aldehydes using a catalytic amount of (*S,S*)-*iPr*-pybox-**7**-In(III) complex. The main features of this reaction are as follows: (1) the procedure is operationally simple and can furnish a variety of β -hydroxy esters in good yields and enantioselectivities; (2) the reaction can be performed exclusively using commercially available chemicals. Continuing investigations into the identity of the catalytic species and further extension of the catalytic system to other enantioselective organic transformations are in progress.

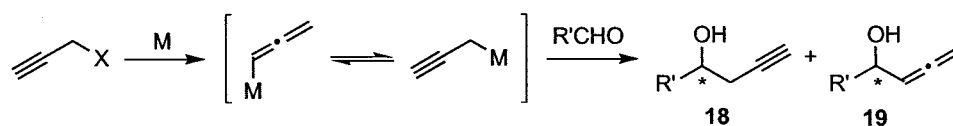
CHAPTER 2

Catalytic Enantioselective Propargylation and Allenylation of Aldehydes

2.1 OVERVIEW OF PROPARGYLATION AND ALLENYLATION OF ALDEHYDES

Optically active allenic and homopropargylic alcohols constitute an interesting class of compounds,³² which frequently serve as important building blocks in natural products syntheses.³³ Therefore, many strategies have been developed for the enantioselective syntheses of this class of compounds.³⁴

The most common method involves the enantioselective addition of homopropargylic or allenic metals to carbonyl compounds to give the homopropargylic and allenic alcohols **18** and **19** (Scheme 2.1).³⁵



Scheme 2.1 Enantioselective propargylation and allenylation of aldehydes

³² (a) Carreira, E. M.; Frantz, D. E.; Fessler, 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*, Wiley, 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.

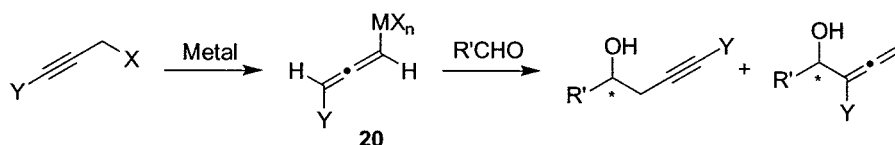
³³ (a) O'Malley, S. J.; Leighton, J. L. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 2915. (b) Yamamoto, H. In *Comprehensive Organic Synthesis*, vol. 2, Heathcock, C. H., ed. Pergamon Press: Oxford, 1991, Chap. 1.3, p81-98. (c) R. Epsztein, In *Comprehensive Carbanion chemistry*, ed. E. Buncl and 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. (e) Matsumura, K.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1997**, *119*, 8738.

³⁴ (a) Moreau, J. L. In *The Chemistry of Ketenes, Allenes and Related Compounds*, ed. S. Patai, Wiley, New York, 1978, p. 343. (b) Brandsma, L. H.; Verkruijse, D. in *Synthesis of Acetylenes, Allenes and Cumulenes*, Elsevier, Amsterdam, 1981.

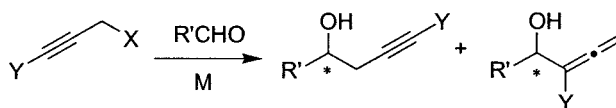
³⁵ (a) Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095. (b) Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667. (c) Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew. Chem., Int. Ed. Engl.*, **1998**, *37*, 2392. (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 **20** from corresponding propargylic reagents and addition of the former to aldehydes (Scheme 2.2). The second method is the reaction of the propargylic reagents with aldehydes (Scheme 2.3).



Scheme 2.2 Addition of allenylmetal compounds and aldehydes



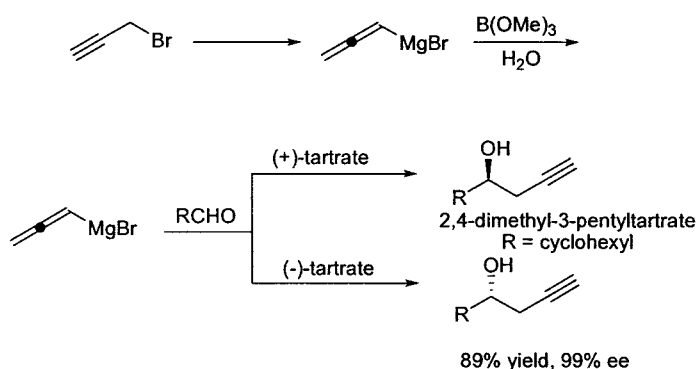
Scheme 2.3 Direct reaction of propargylic reagents with aldehydes

Allenyl Reagents

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

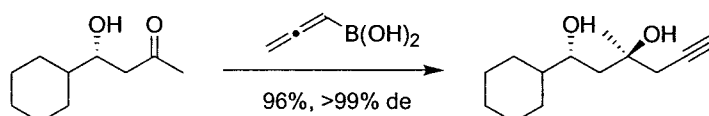
Allenylborane Reagents

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 2.4).^{36, 37}



Scheme 2.4 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 2.5).³⁸



Scheme 2.5 Reaction of allenylboronic acid with β -hydroxyl ketones

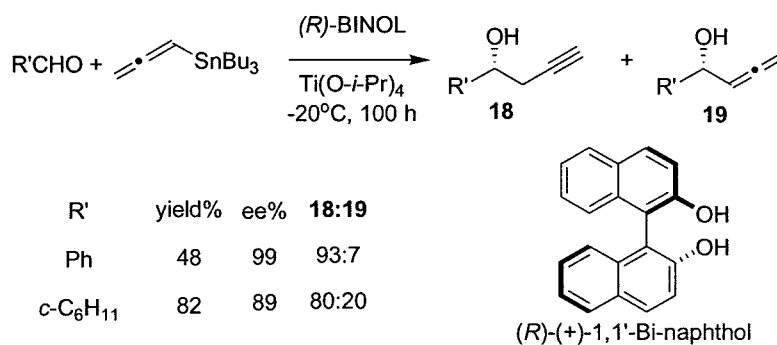
³⁶ Haruta, R.; Ishiguro, M.; Ikeda, N.; Yamamoto, H. *J. Am. Chem. Soc.* **1982**, *104*, 7667.

³⁷ Ikeda, N.; Arai, I.; Yamamoto, H. *J. Am. Chem. Soc.* **1986**, *108*, 483.

³⁸ Ikeda, N.; Omori, K.; Yamamoto, H. *Tetrahedron Lett.* **1986**, *27*, 1175.

Allenylstannane Reagents

An effective asymmetric homopropargylation using allenyltributylstannane from (*R*)-BINOL and $\text{Ti}(\text{O-}i\text{-Pr})_4$ was reported by Keck *et al.* The enantioselectivities was good and the regioselectivities was moderate to good, depending on the structure of aldehydes (Scheme 2.6).³⁹

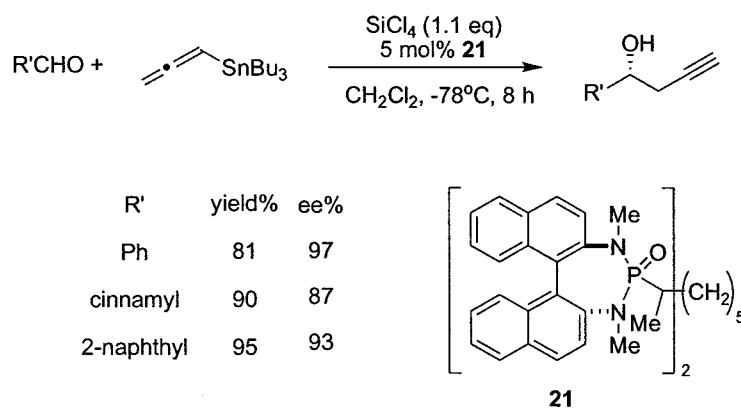


Scheme 2.6 Enantioselective homopropargylation with allenyltributylstannane

Recently, Denmark *et al.* found that chiral binaphthyl bis-phosphoramidate- SiCl_4 system could catalyze the addition of allenylstannanes to aldehydes to give homopropargylic alcohols. When the *bis*-phosphoramidate bearing a five methylene linker **21** was used in the reaction, the highest enantioselectivity of 97% was observed (Scheme 2.7).⁴⁰

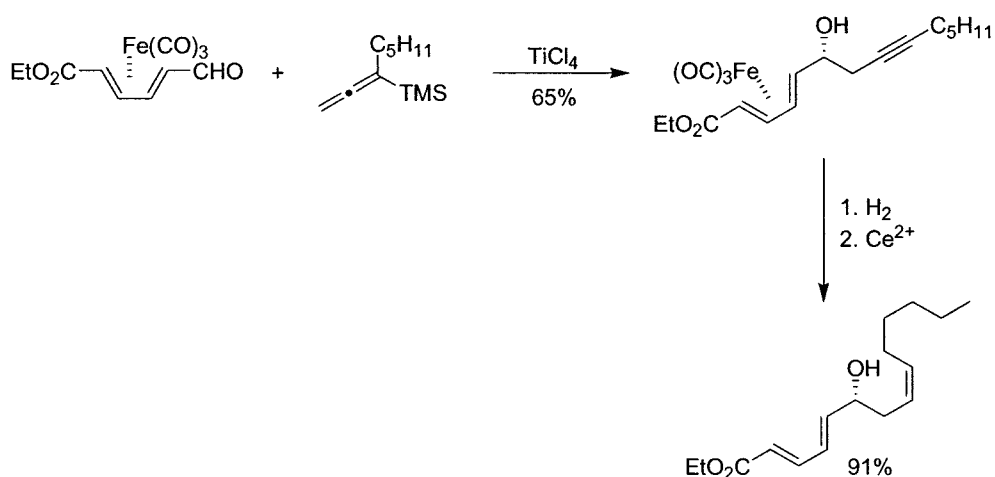
³⁹ Keck, G. E.; Krishnamurthy, D.; Chen, X. *Tetrahedron Lett.* **1994**, 35, 8323.

⁴⁰ Denmark, S. E.; Wynn, T. J. *Am. Chem. Soc.* **2001**, 123, 6199.

Scheme 2.7 Asymmetric homopropargylation with *bis*-phosphoramidate

Allenylsilane Reagents

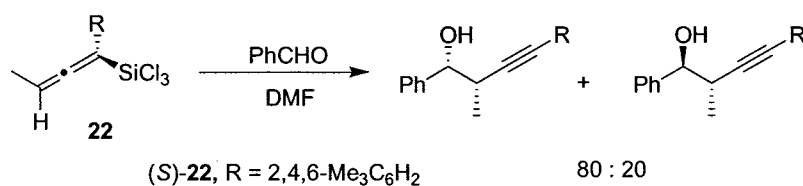
It is well known that allenylsilanes are useful intermediates in organic synthesis, reacting with a variety of electrophiles in a regioselective manner. Reaction of allenylsilanes with the easily accessible iron tricarbonyl complex in the presence of TiCl_4 at -78°C gives the homopropargyl alcohol in 65% yield, and leads only to the *endo* derivative with the (*R*)-configuration at the secondary alcohol functionality (Scheme 2.8). It is noteworthy that $\text{Fe}(\text{CO})_3$ here acts as an efficient protecting group.⁴¹



Scheme 2.8 Reaction of allenylsilanes with the iron tricarbonyl complex

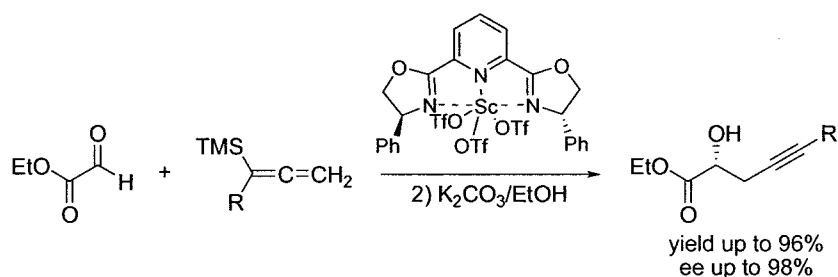
⁴¹ Nunn, K.; Mosset, P.; Gree, R.; Saalfrank, R. W. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1188.

Recently, considerable attention has been given to the preparation of axially chiral allenylsilane and their use for the enantioselective synthesis of homopropargylic alcohols.⁴² An axially chiral allenylsilane **22** was successfully prepared from palladium-mediated hydrosilylation of 1,3-enynes by Hayashi.⁴³ The reaction of the allenylsilane with aldehyde afforded corresponding homopropargylic alcohol without the loss of enantiomeric purity (Scheme 2.9).



Scheme 2.9 Asymmetric homopropargylation with chiral allenylsilanes

Evans *et al* reported a highly enantioselective scandium triflate catalyzed addition of allenylsilanes with ethyl glyoxylate. Trimethylsilylallenes function as propargylic anion equivalents in addition reactions to aldehyde however if the silicon center is sterically congested, the normal addition pathway is suppressed and functionalized dihydrofurans are produced (Scheme 2.10).⁴⁴



Scheme 2.10 Asymmetric homopropargylation with chiral Sc(OTf)₃ complex

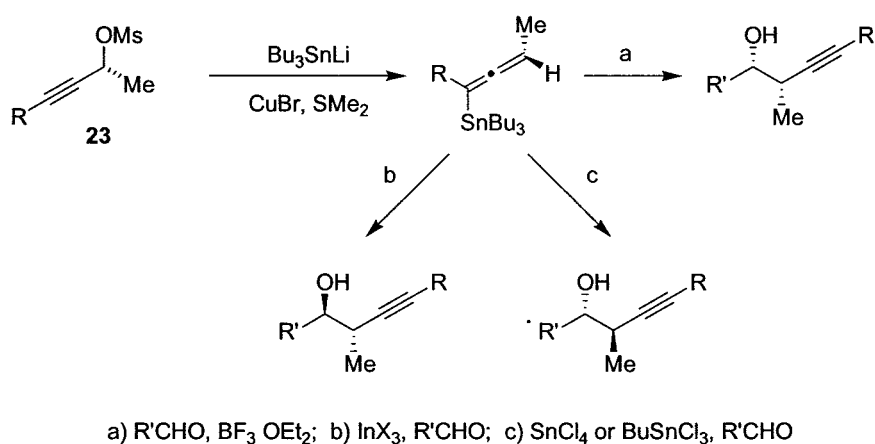
⁴² Marshall, J. A.; Maxson, K. *J. Org. Chem.* **2000**, *65*, 630.

⁴³ Han, J.-W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915.

⁴⁴ Evans, D. A.; Sweeney, Z. K.; Rovis, T.; Tedrow, J. S. *J. Am. Chem. Soc.* **2001**, *123*, 12095.

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 **23** with metals to afford allenylmetal intermediates in high ee. These asymmetric reagents undergo addition to aldehydes yielding optical active propargylic alcohols (Scheme 2.11).⁴⁵



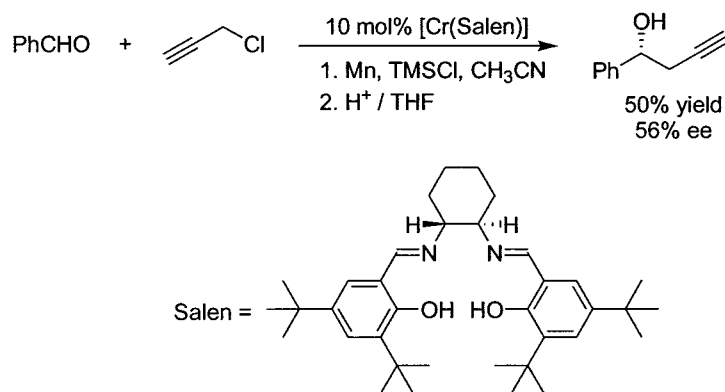
Scheme 2.11. Asymmetric homopropargylation with propargylic mesylates

Addition of Propargylic Reagents to Aldehydes

A recent method developed by Umani-Ronchi *et al.* using chiral [Cr(II)-(Salen)] complex has afforded homopropargylic alcohols with moderate enantioselectivities (Scheme 2.12).⁴⁶

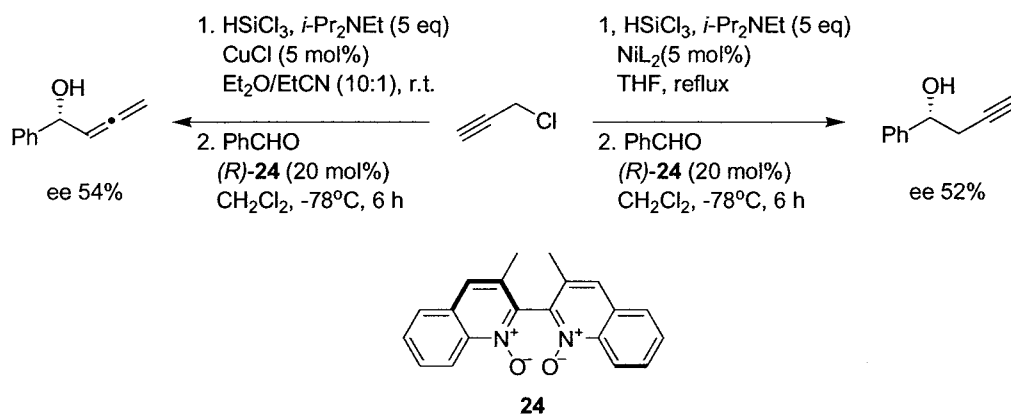
⁴⁵ (a) Marshall, J. A.; Perkins, J. F.; Wolf, M. A. *J. Org. Chem.* **1995**, *60*, 5556. (b) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 696. (c) Marshall, J. A. *Chem. Rev.* **2000**, *100*, 3163.

⁴⁶ Bandini, M.; Cozzi, P. G.; Melchiorre, P.; Tino, R.; Umani-Ronchi, A. *Tetrahedron: Asymmetry* **2001**, *12*, 1063.



Scheme 2.12 Asymmetric homopropargylation with chiral [Cr(Salen)] complex

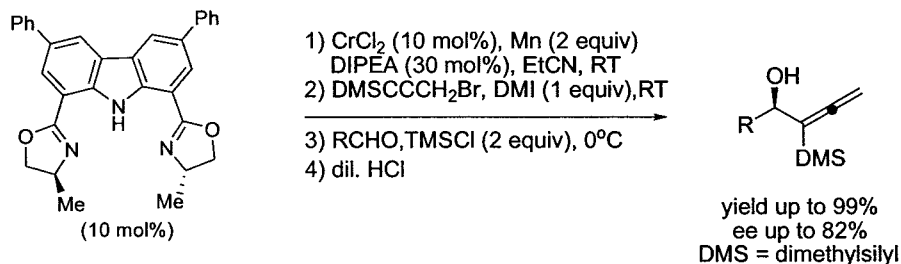
Nakajima also found that optically active allenic and homopropargylic alcohols could be obtained selectively by the chiral *N*-oxide-catalyzed **24** reaction of aldehydes from propargyl chloride (Scheme 2.13).⁴⁷

Scheme 2.13 Asymmetric homopropargylation with chiral *N*-oxide-catalyst

Nakada *et al* recently reported asymmetric catalysis of the Nozaki–Hiyama allenylation of various aldehydes with terminally silylated propargyl halides, affording the 2-silylated secondary allenic alcohol in good yield and selectivity (Scheme 2.14).⁴⁸

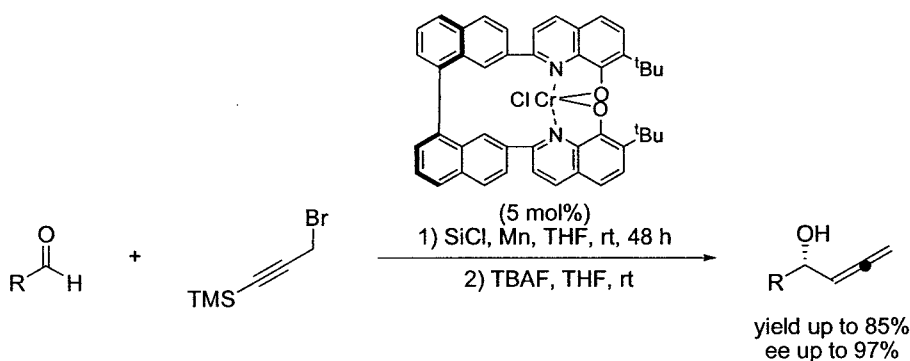
⁴⁷ Nakajima, M.; Saito, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2449.

⁴⁸ Inoue, M.; Nakada, M. *Angew. Chem., Int. Ed. Engl.* **2006**, *45*, 252.



Scheme 2.14 Asymmetric allenylation with chiral chromium complex

Most recently, Yamamoto *et al.* developed a tethered bis(8-quinolinolato) (TBOx) chromium catalyst for the asymmetric allenylation reaction between various aldehydes and commercially available 1-trimethylsilyl-3-bromopropyne to afford allenic alcohols exclusively as the only product in excellent yield and selectivity (Scheme 2.14).⁴⁹



Scheme 2.14 Asymmetric allenylation with bis(8-quinolinolato) (TBOx) chromium catalyst

Indium-mediated propargylation and allenylation

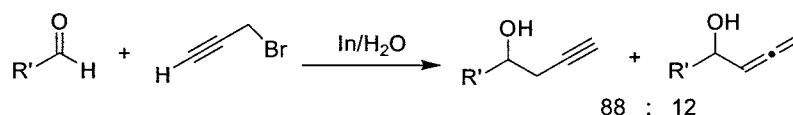
Among the many methods employed, indium-mediated propargylation has attracted much attention due to its mild reaction conditions as well as wide functional group compatibility.⁵⁰ However, compared to the well-established allylic indium chemistry, the synthetic potential of propargylic indiums has not been fully exploited. This is because propargylic indium equilibrates in solution to give a mixture of

⁴⁹ Xia, G.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 496.

⁵⁰ Chan, T.-H.; Isaac, M. B. *Pure & Appl. Chem.* **1996**, *68*, 919.

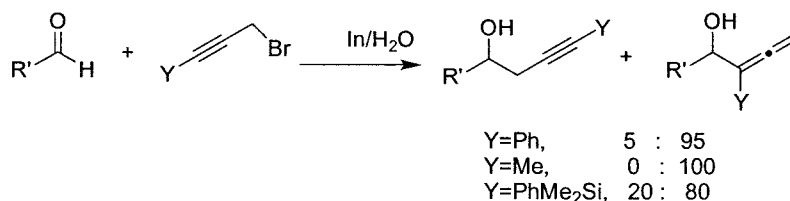
homopropargylic and allenyllic indium species.⁵¹ This metallotropic rearrangement often results in poor regioselectivity since both organometallic species can react with aldehydes.

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 2.15).⁵²



Scheme 2.15 Indium-mediated propargylation and allenylation

When γ -substituted propargyl bromides are used, allenyl alcohols are the major products (Scheme 2.16).⁵³



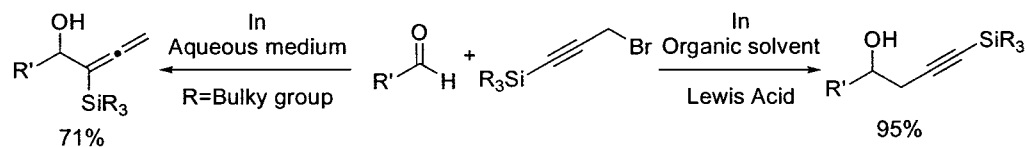
Scheme 2.16 Reaction of γ -substituted propargyl bromides with aldehydes

⁵¹(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. Organomet. 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.

⁵² Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472.

⁵³ 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 2.17).⁵⁴

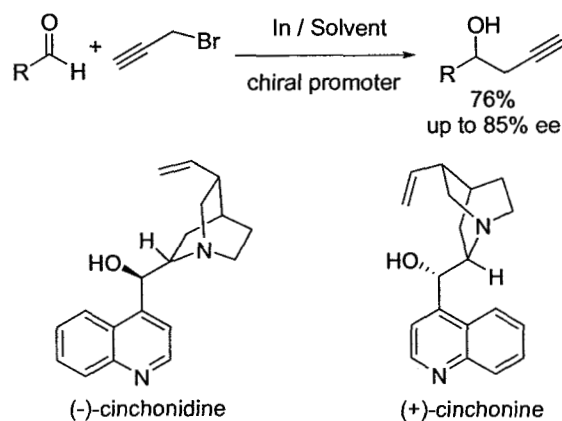


Scheme 2.17 Indium-mediated regioselective propargylation and allenylation

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.

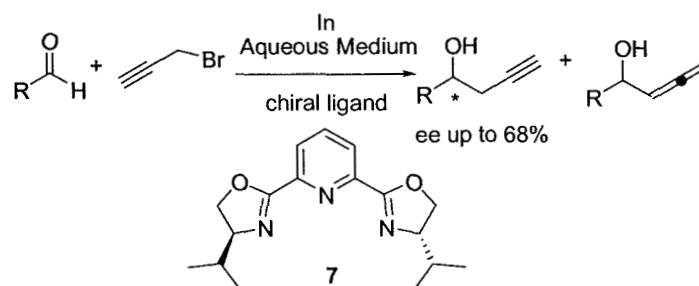
Asymmetric indium-mediated propargylation of aldehydes using two cinchona alkaloids, (-)-cinchonidine and (+)-cinchonine, as the chiral sources was also successfully accomplished^{54b} (Scheme 2.18). High regioselectivity was observed in this reaction, affording the homopropargylic alcohols without any detectable amounts of the allenic alcohols.

⁵⁴ Lin, M.-J.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 13042. (b) Loh, T.-P.; Lin, M.-J.; Tan, K.-L. *Tetrahedron Lett.* **2003**, *44*, 507.



Scheme 2.18 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 2.19).

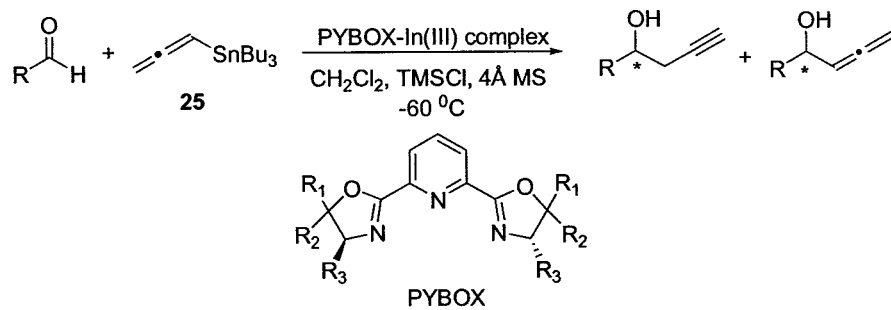


Scheme 2.19 Enantioselective indium-mediated propargylation and allenylation in aqueous media

Although regioselectively obtaining either the homopropargylic alcohol or the allenic alcohol by varying the substrate or solvent has been achieved with success,⁵⁵ there is no report on the catalytic enantioselective homopropargylation and allenylation of aldehydes using a chiral indium complex.

⁵⁵(a) Yi, X.-H.; Meng, Y.; Hua, X.-G.; Li, C.-J. *J. Org. Chem.* **1998**, *63*, 7472. (b) 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.

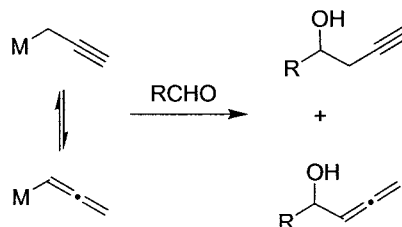
In this chapter, the successful application of the (*S,S*)-PYBOX-In(OTf)₃ to the enantioselective homopropargylation and allenylation of aldehydes will be described.



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

2.2.1 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 2.20). 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.

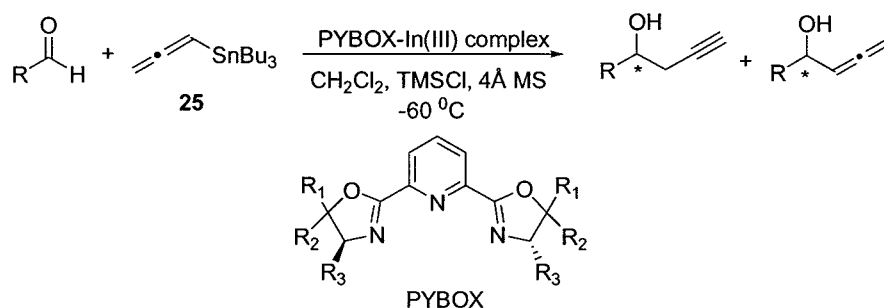


Scheme 2.20 Metallotropic rearrangement between propargyl and allenyl species

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,S)*-*iPr*-PYBOX-In(OTf)₃ catalytic system to the enantioselective propargylation and allenylation of aldehydes.

2.2.2 RESULTS AND DISCUSSIONS

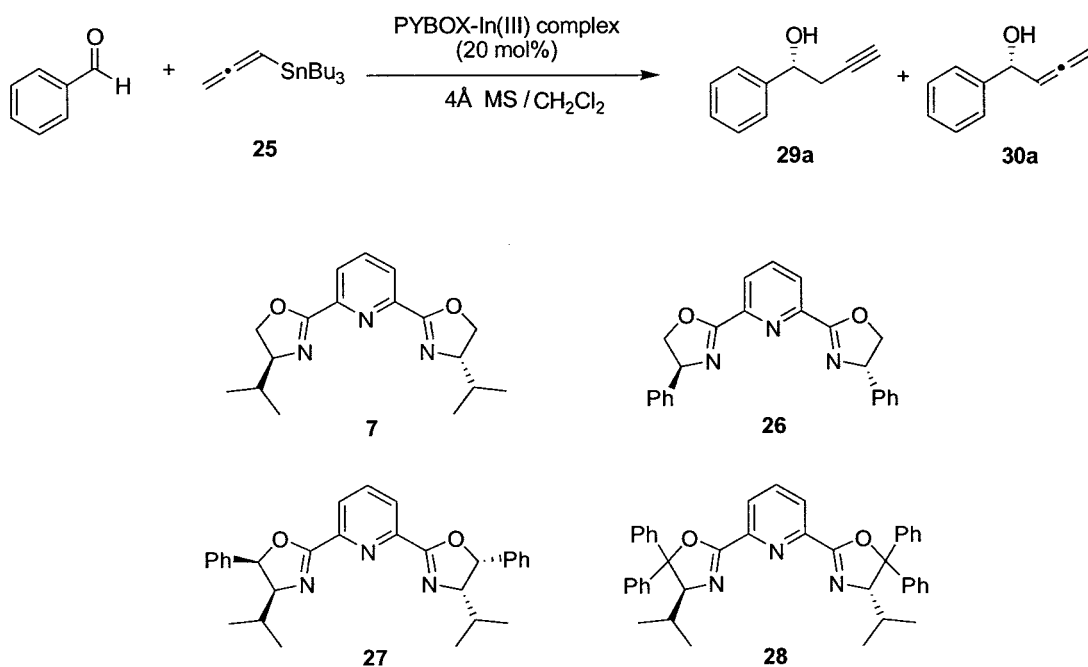
Previous work from our laboratory has demonstrated the successful application of the novel chiral (*S,S*)-*iPr*-pybox-In(III) complex as a Lewis acid catalyst for the enantioselective Mukaiyama aldol reaction as well as the allylation of carbonyl compounds with allyltributylstannane.⁵⁶ Based on precedent experience, we envision that this catalytic system should also prove to be effective for the asymmetric synthesis of homopropargylic and allenic alcohols (Scheme 2.21).



Scheme 2.21 Enantioselective propargylation and allenylation of aldehydes via the PYBOX-In(III) complex

To evaluate the (*S,S*)-*iPr*-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*)-*iPr*-pybox **7** and In(OTf)₃ was investigated. The reaction afforded both the propargylic and allenic alcohol in a ratio of 67:33 and enantiomeric excess of 43% and 63% respectively (Table 1, 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 1.

⁵⁶ (a) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 7435. (b) Lu, J.; Hong, M.-L.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Chem. Commun.* **2005**, *33*, 4217. (c) Lu, J.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, *18*, 2345. (d) Lu, J.; Hong, M.-L.; Ji, S.-J.; Loh, T.-P. *Chem. Commun.* **2005**, *8*, 1010. (e) Lu, J.; Ji, S.-J.; Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 159.

Table 1. Evaluation of various PYBOX ligands for the asymmetric propargylation and allenylation reaction^a

Entry	PYBOX	Yield (%) ^b	29a : 30a ^c	ee (%) ^d	
				29a	30a
1	7	78	67 : 33	43	63
2	26	75	89 : 11	39	0
3	27	81	31 : 69	18	47
4	28	86	62 : 38	88	90

^aUnless otherwise stated, the reaction was carried out with allenyltributylstannane **25** (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 CH₂Cl₂. The reaction mixture was kept for 30 h at -60 °C.

^bCombined isolated yield. ^cDetermined by ¹H NMR analysis.

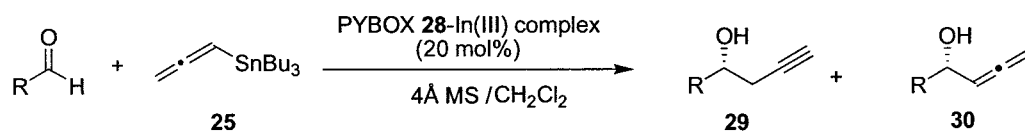
^dDetermined by HPLC analysis.

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*)-*iPr*-

PYBOX **28**-In(III) complex was the optimal catalyst in this series, affording the homopropargylic and allenyl alcohol in 88% and 90% ee respectively (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 **28**-In(III) was investigated. The results are shown in Table 2.

Table 2. Enantioselective propargylation and allenylation of various aldehydes catalyzed by (*S,S*)-*i*Pr-PYBOX **28**-In(III) complex^a



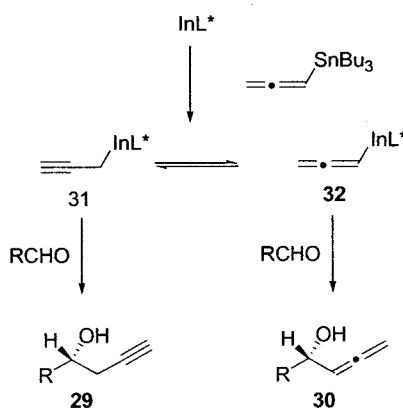
Entry	Aldehyde	Yield (%) ^b	Product	29 : 30 ^c	ee (%) ^d	
					29	30
1		73	29a : 30a	62 : 38	88 <i>R</i>	90 <i>R</i>
2		88	29b : 30b	38 : 62	80 <i>R</i>	78 <i>R</i>
3		68	29c : 30c	52 : 48	80 <i>R</i>	70 <i>R</i>
4		85	29d : 30d	37 : 63	88 <i>R</i>	84 <i>R</i>
5		54	29e : 30e	29 : 71	84 <i>R</i>	86 <i>S</i>
6		71	29f : 30f	58 : 42	88 <i>S</i>	82 <i>S</i>
7		70	29g : 30g	35 : 65	60 <i>S</i>	66 <i>S</i> ^e

^aUnless otherwise stated, the reaction was carried out with allenyltributylstannane **25** (1.2 equiv), aldehyde (1.0 equiv) and TMSCl (1.2 equiv) using the chiral indium(III) complex prepared from PYBOX **28** ligand (0.22 equiv), In(OTf)₃ (0.20 equiv) and activated 4Å MS in CH₂Cl₂. The reaction mixture was kept for 30 h at -60 °C.

^bCombined isolated yield. ^cDetermined by ¹H NMR analysis. ^dDetermined by HPLC analysis.

As shown in Table 2, 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 allenic alcohols in excellent yield with 80% and 78% ee, respectively (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 propargyltributylstannane reagents under the reaction conditions (Scheme 2.22). The chiral (*S,S*)-*iPr*-PYBOX **28**-In(III) complex probably underwent transmetalation with propargyltributylstannane to form two new chiral indium species **31** and **32** in equilibrium, which subsequently reacted with the aldehydes to afford the corresponding homopropargylic and allenic alcohols respectively.



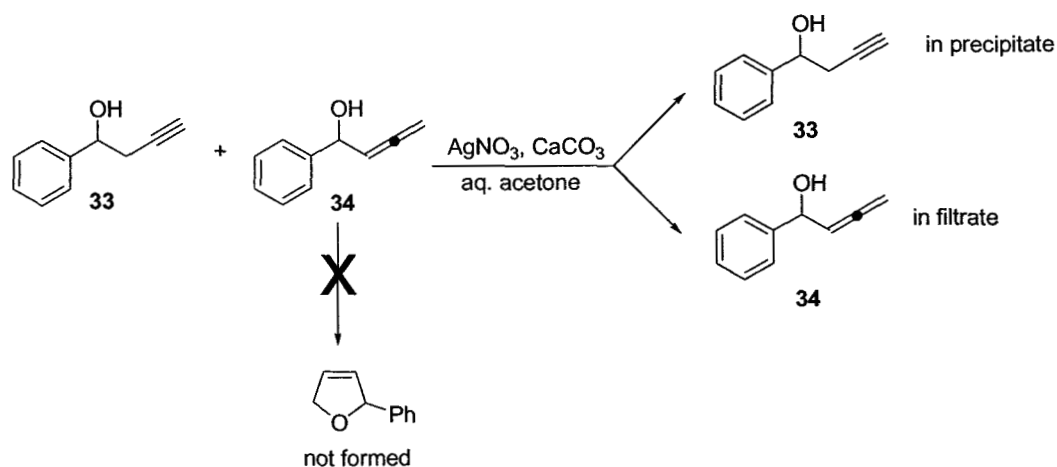
Scheme 2.22 Metallo-tropic rearrangement between indium propargyl and allenyl species

Although good yields and selectivities are achieved with the chiral (*S,S*)-*iPr*-PYBOX **28**-In(III) complex, the homopropargylic and allenic alcohols mixture are of little synthetic value if they are inseparable via the usual chromatographic separation. Previous work by Claesson *et al* reported the synthesis of 2,5-dihydrofurans⁵⁷ via cyclization of allenic alcohols catalyzed by silver(I) nitrate. With an interest in this report, we attempt to convert the allenic alcohols in the mixture into 2,5-dihydrofurans with the homopropargylic alcohols remaining intact. The 2,5-dihydrofurans can be separated from homopropargylic alcohols via column chromatography as they have different R_f value.

In our initial study, we added 1:1 ratio of 1-Phenylbut-3-yn-1-ol **33** and 1-Phenyl-buta-2,3-dien-1-ol **34** (0.5 mmol) to a mixture of silver(I) nitrate (0.5 mmol) and calcium carbonate (0.5 mmol) in acetone: water (0.4 mL: 0.6 mL). The reaction mixture was stirred in the dark for six hours and a brown suspension was formed. The brown precipitate was removed via suction filtration and the filtrate was dried with $MgSO_4$ before removal of excess solvent. Surprisingly, the heterocyclic-forming reaction essentially did not proceed as intended. The 1H NMR spectrum showed no traces of the homopropargylic alcohol and the 2,5-dihydrofurans, only the allenic alcohol was isolated in the filtrate. However, when we proceeded to treat the brown precipitate isolated earlier with 1M HCl, the homopropargylic alcohol was isolated cleanly after extraction with ether. It is noteworthy that the homopropargylic alcohol was trapped in the precipitate and can only be isolated by extraction with ether after treatment with 1M HCl (Scheme 2.23).

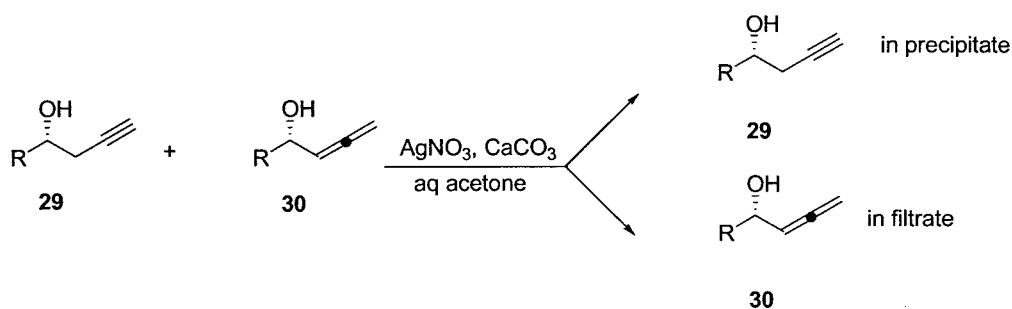
⁵⁷ Olsson, L.-I.; Claesson, A. *Synthesis* **1979**, 743.

CATALYTIC ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF ALDEHYDES



Scheme 2.23 Separation of homopropargylic alcohols and allenic alcohol using AgNO₃ and CaCO₃

Having optimized the separation protocol, we extended this procedure to a series of enantiomeric enriched aromatic, α,β unsaturated and aliphatic homopropargylic and allenic alcohols mixture. The results are shown in Table 3.

Table 3. Separation of homopropargylic alcohols and allenic alcohol using AgNO₃ and CaCO₃.

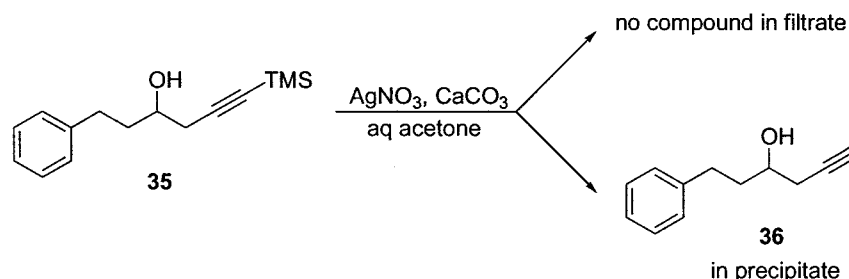
Entry	Aldehyde	Product	Yield (%) ^a	ee (%) ^b	
				29	30
1		29a : 30a	81 : 93	88 <i>R</i>	90 <i>R</i>
2		29b : 30b	81 : 95	80 <i>R</i>	78 <i>R</i>
3		29c : 30c	94 : 93	80 <i>R</i>	70 <i>R</i>
4		29d : 30d	98 : 97	88 <i>R</i>	84 <i>R</i>
5		29e : 30e	80 : 96	84 <i>R</i>	86 <i>S</i>
6		29f : 30f	81 : 98	88 <i>S</i>	82 <i>S</i>
7		29g : 30g	92 : 95	60 <i>S</i>	66 <i>S</i> ^e

^aYield is determined based on the amount of material recovered after the separation using AgNO₃ and CaCO₃. ^bDetermined by HPLC analysis.

The various aromatic, α,β unsaturated and aliphatic allenic alcohols were separated from the homopropargylic alcohols cleanly with excellent yields and retention of enantiomeric excess.

Earlier successful separations suggested that acidic terminal hydrogen atom in homopropargylic alcohol might play a role in the separation. In order to test the above assumption, we employed this reaction to 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-ol **35**. However, we managed to isolate 1-phenylhex-5-yn-3-ol **36** instead of 1-phenyl-6-

(trimethylsilyl)hex-5-yn-3-ol **35** from the precipitate after treatment with 1M HCl and no compound was isolated from the filtrate (Scheme 2.24).



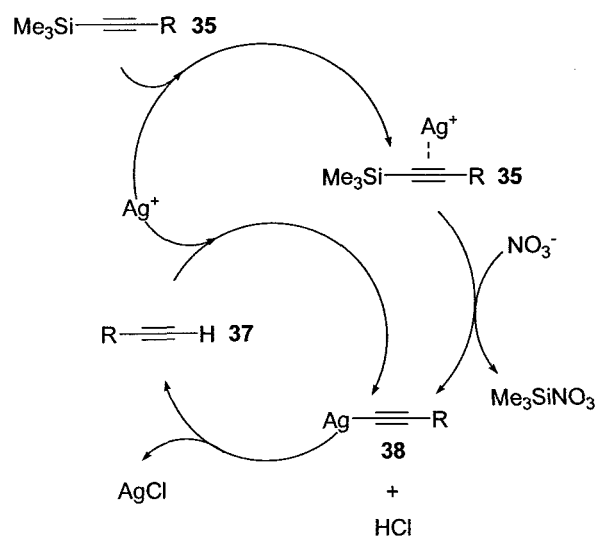
Scheme 2.24 Reaction of 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-ol with AgNO₃

The mechanism probably involves the formation of a complex between silver nitrate and calcium carbonate which reacts with alkynes **37** to afford the corresponding silver acetylide **38** that precipitated (Scheme 2.25). This silver acetylide precipitate can be isolated by filtration. In the presence of a proton source such as HCl, the silver acetylide species would be hydrolyzed, generating back the alkynes species **37**.

Previous work by Pale and co-workers⁵⁸ suggested that in the reaction of silver with 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-ol **35**, the first step was the formation of a π -complex between the silver salt and **35**. This coordination would induce activation of the TMS group toward nucleophilic attack by either the silver counter-ion (NO₃⁻) or a nucleophilic solvent (Scheme 2.25). This cascade of events would lead to the formation of a silver acetylide species **38** which precipitated. This silver acetylide **38** can be separated through a simple filtration. In the presence of a proton source such as

⁵⁸ (a) Viterisi, A.; Orsini, A.; Weibel, J-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 2779. (b) Orsini, A.; Viterisi, A.; Bodlener, A.; Weibel, J-M.; Pale, P. *Tetrahedron Lett.* **2005**, *46*, 2259.

HCl, the silver acetylide species would similarly be hydrolyzed, generating back 1-phenylhex-5-yn-3-ol **37**.



Scheme 2.25 Mechanistic hypothesis for Ag-catalyzed reaction with alkynes.

2.3 CONCLUSIONS

In conclusion, we have developed a highly enantioselective catalytic addition of homopropargylic and allenyl moiety to 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 (*S,S*)-*iPr*-PYBOX 28-In(OTf)₃ 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 allenyl alcohols in good yields with moderate to high levels of enantioselectivities (up to 90% ee); (2) the reaction can be performed exclusively by using commercially available chemicals; (3) the low regioselectivity exhibited by the catalytic system was due to metallotropic rearrangement; (4) a simple and practical approach to separate homopropargylic alcohol from allenic alcohol has been developed. It involves the formation of an insoluble silver acetylide species in aqueous acetone which can be separated from the allenic alcohol through a simple filtration. The homopropargylic alcohol can subsequently be recovered by hydrolysis with 1N HCl. This approach is operationally simple and can separate a wide variety of homopropargylic and allenic alcohol mixtures in excellent yields with the retention of enantiomeric excess. Hence this catalytic procedure could be broadly applicable to many synthetic procedures.

CHAPTER 3

***Catalytic Enantioselective Diels-Alder Reaction in
Ionic Liquid via a Recyclable Chiral In(III)
Complex***

3.1 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.⁵⁹ 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 activity⁶⁰, the development of new methods for the asymmetric induction of Diels-Alder reaction is of considerable interest.⁶¹ There are numerous methods to achieve this goal, but the greatest potential efficiency is held by enantioselective reactions using chiral catalysts.⁶² 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.

⁵⁹ Danishefsky, S. *Aldrichimica Acta* **1986**, 59.

⁶⁰ Stinson, S. C. Chiral drugs in *Chem. Eng. News*. 28, **1992**, p46; Stinson, S. C. *ibid*, Dept 27, 1993, p38

⁶¹ For recent reviews, see (a) Paquette, L. A. *Asymmetric Synthesis*; Morrison, J. D., Academic Press: Orlando, FL, **1984**, 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.

⁶² Corey, E. J. Proceedings of the 31st National Organic Symposium, American Chemical Society, **1989**, p1 for an overview of some of these 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.⁶³ 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.⁶⁴ Recently, much attention has been focused on the use of chiral catalysts.⁶⁵ Prior work in the field of catalytic enantioselective Diels-Alder has produced a number of catalysts with varying degrees of selectivity, generality and efficiency.⁶⁶ Some representative examples of catalytic enantioselective Diels-Alder reactions are summarized below.

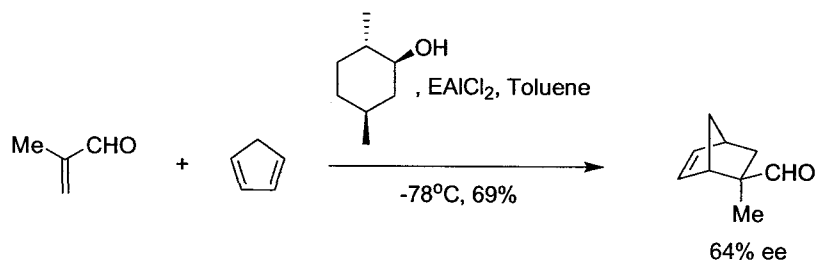
⁶³ (a) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; Prentice Hall: Engelwood Cliffs, NJ, 1971, p252. (b) For the first example of asymmetric Diels-Alder reaction using a chiral dienophile see : Walborsky, H. M; Barash, L. *J. Org. Chem.* 1961, 26, 4478. (c) Helmchen, G.; Karge, R.; Weetman, J. In *Modern Synthetic Methods* 1986; Sheffold, R., Ed.; Springer Verlag: New York, 1986; Vol. 4, p242.

⁶⁴ (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.

⁶⁵ 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.

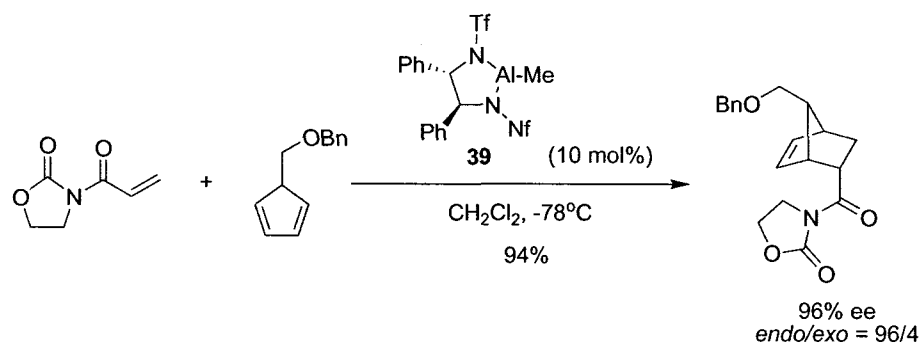
⁶⁶ Review on the Catalytic Asymmetric Diels-Alder Reactions: Kagan, H. B.; Tlant, O. *Chem. Rev.* 1992, 92, 1007.

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 menthoxydichloroaluminum⁶⁷ (Scheme 3.1).



Scheme 3.1 Enantioselective Diels-Alder catalyzed by menthoxydichloroaluminum

A highly selective asymmetric Diels-Alder reaction was reported by Corey *et al.*⁶⁸, using a chiral aluminum reagent prepared *in situ* by the reaction of chiral bis(sulfonamides) with trimethylaluminum or diisobutylaluminum hydride. The chiral aluminum complex **39** (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 3.2). Hence this methodology is clearly of outstanding practical utility.

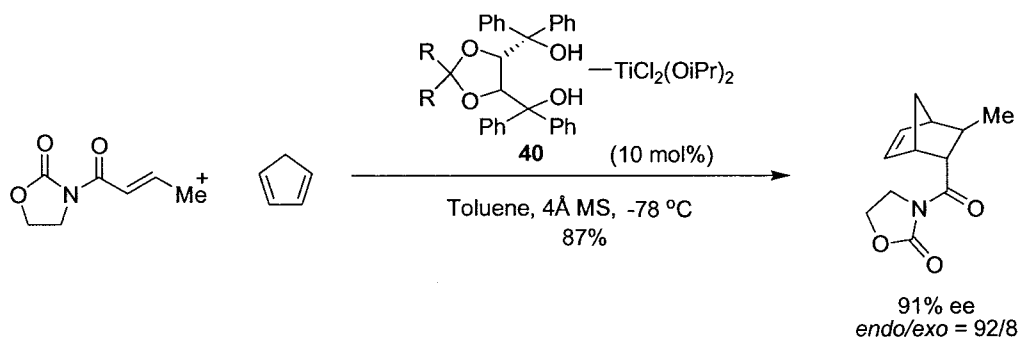


Scheme 3.2 Enantioselective Diels-Alder catalyzed by chiral aluminum reagent

⁶⁷ Hashimoto, S.; Komeshima, N.; Koga, K. *J. Chem. Soc., Chem. Commun.* **1979**, 437.

⁶⁸ 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 **40** can be readily prepared by mixing chiral 1,4-diol derived from tartrate and $\text{TiCl}_2(\text{O-}i\text{-Pr})_2$ at room temperature⁶⁹. 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 3.3).

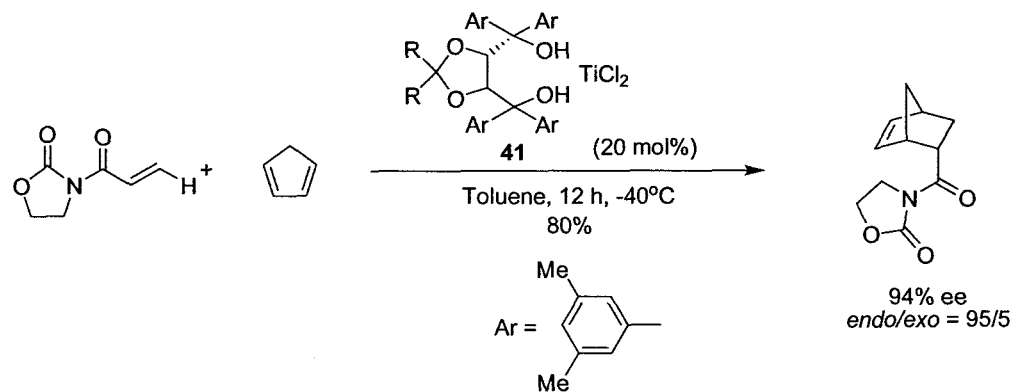


Scheme 3.3 Enantioselective Diels-Alder catalyzed by chiral titanium complex

Subsequently, Corey and Matsumura investigated the modified titanium complexes **41** 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.⁷⁰ 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 3.4.

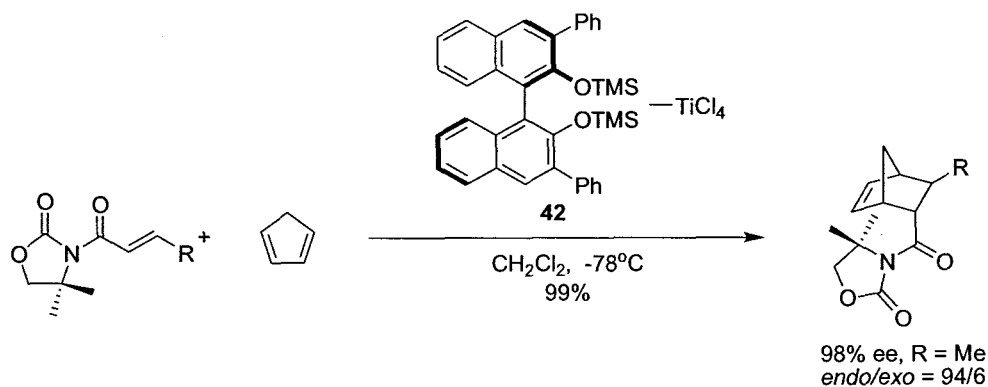
⁶⁹ (a) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1109. (b) Narasaka, K.; Inoue, M.; Okada, N. *Chem. Lett.* **1986**, 1967. (c) Narasaka, K.; Inoue, M.; Yamada, T.; Sugimori, J.; Iwasawa, N. *Chem. Lett.* **1987**, 2409. (d) Narasaka, K.; Inoue, M.; Okada, N.; Amada, T.; Nakasima, M.; Sugimori, J. *J. Am. Chem. Soc.* **1989**, *111*, 5340.

⁷⁰ Corey, E. J.; Matsumura, Y. *Tetrahedron Lett.* **1991**, *32*, 6289.



Scheme 3.4 Enantioselective Diels-Alder catalyzed by chiral titanium complex

Chapius and Jurczak used a similar chelating crotonamide **42** with cyclopentadiene in the presence of 1 mole equivalent of chiral titanium complex to yield a cycloadduct with very high enantiomeric excess (Scheme 3.5).⁷¹



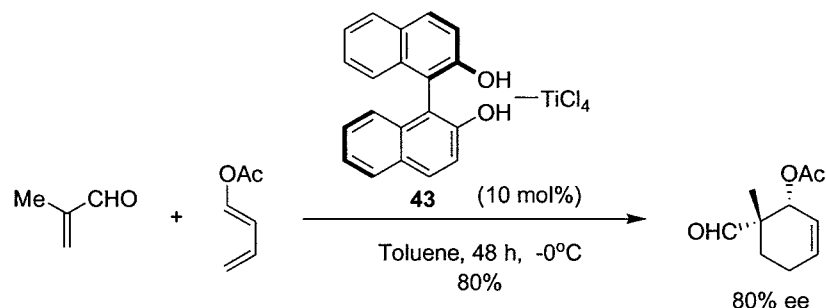
Scheme 3.5 Enantioselective Diels-Alder catalyzed by chiral titanium complex

Mikami *et al.* found that the chiral titanium complex **43** derived from BINOL catalyzed the Diels-Alder reaction of 1-acetoxy butadiene and methacrolein to give the cycloadduct in high enantioselectivity (Scheme 3.6).⁷² Recently, Corey *et al.* applied this catalyst to the Diels-Alder reaction of 1,4-quinone monoketals with

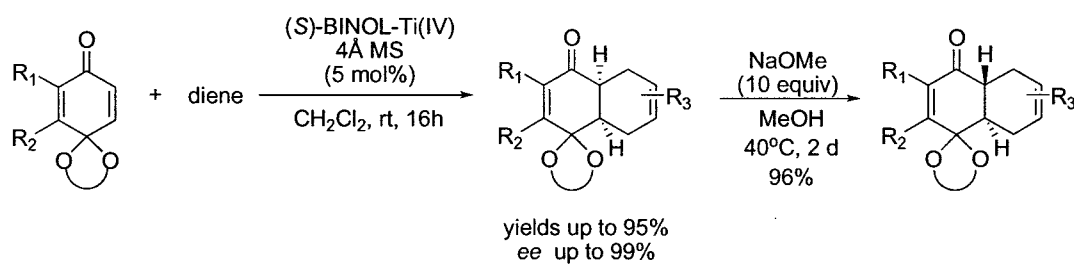
⁷¹ Chapius, C.; Matsumura, Y. *Tetrahedron Lett.* **1991**, 32, 6289.

⁷² Mikami, K.; Terada, M.; Motoyama, Y.; Nakai, T. *Tetrahedron: Asymmetry* **1991**, 2, 643.

various dienes to provide a straightforward route to *trans*-decalins as well as *cis*-decalins found in numerous natural products (Scheme 3.7).⁷³



Scheme 3.6 Enantioselective Diels-Alder catalyzed by chiral titanium complex



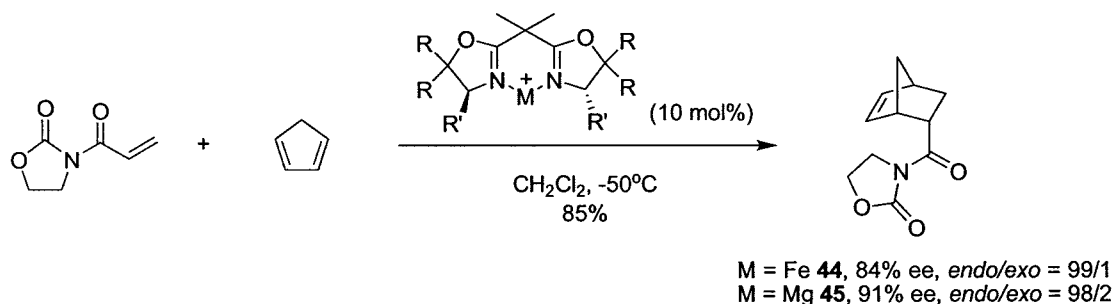
Scheme 3.7 Enantioselective Diels-Alder of 1,4-quinone monoketals with various dienes

Another class of catalyst developed by Corey *et al.* used ionic species of chiral iron **44** and magnesium **45** complexes derived from chiral bisoxazolines ($R' = \text{Ph}$). 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.⁷⁴ Evans *et al.* have also found that an ionic copper species derived from chiral bis-

⁷³ Breuning, M.; Corey, E. J. *Org Lett.* **2001**, *3*, 1559.

⁷⁴ (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.

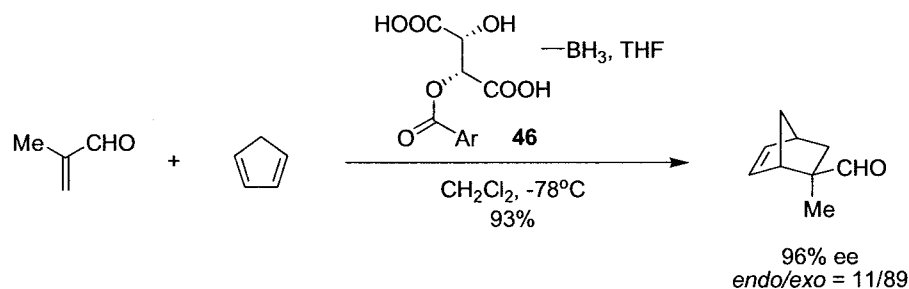
oxazolines ($R' = t\text{-Bu}$) gives high enantioselectivity between cyclopentadiene and bidentate dienophiles (scheme 3.8).⁷⁵



Scheme 3.8 Enantioselective Diels-Alder catalyzed by chiral bis-oxazolines complex

Various mono- and di-isopinocampheylhaloboranes 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.⁷⁶

Yamamoto *et al.* have found that acyloxyborane prepared from monoacylated (*R*)-tartaric acids and diborane was successfully employed as a catalyst **46** in the reaction of methacrolein with cyclopentadiene (Scheme 3.9).⁷⁷



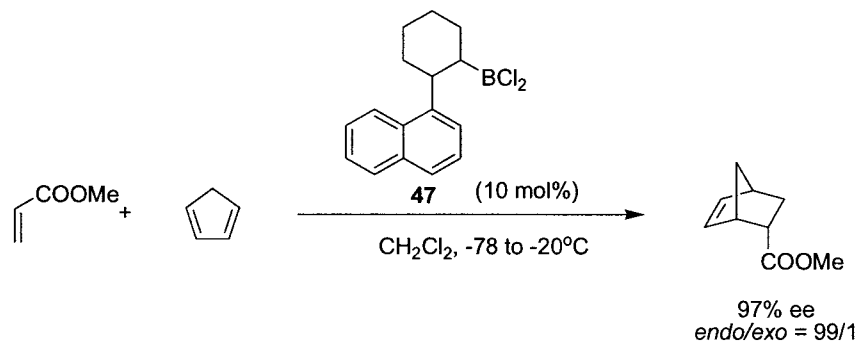
Scheme 3.9 Enantioselective Diels-Alder catalyzed by chiral boron complex

⁷⁵ Evans, D. A.; Miller, S. J.; Lectka, T. *J. Am. Chem. Soc.* **1993**, *115*, 6460.

⁷⁶ Bir, G.; Kaufmann, D. *Tetrahedron Lett.* **1987**, *28*, 777.

⁷⁷ (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.

A chiral dichloroborane complex **47** 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 3.10).⁷⁸ A model based on X-ray structure complex has been proposed to explain the observed enantioselectivity.

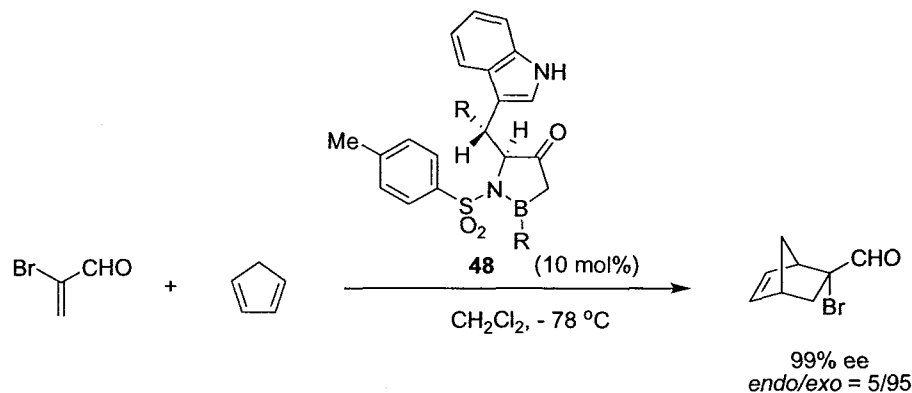


Scheme 3.10 Enantioselective Diels-Alder catalyzed by chiral dichloroborane complex

An elegant chiral oxazaborolidinone catalyst **48** 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 3.11).⁷⁹ 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.

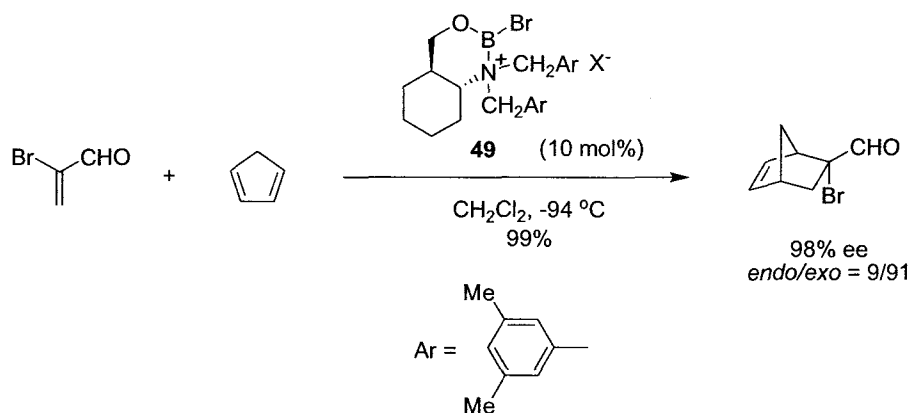
⁷⁸ Hawkins, J. M.; Loren, S. *J. Am. Chem. Soc.* **1991**, *113*, 7794.

⁷⁹ Corey, E. J.; Loh, T.-P. *J. Am. Chem. Soc.* **1991**, *113*, 8966.



Scheme 3.11 Enantioselective Diels-Alder catalyzed by chiral boron complex

Promising results have been reported by Corey using cationic oxazaborinane complex **49** as an aldehyde-diene cycloaddition catalyst. α -Substituted aldehydes and various dienes are reported to undergo low-temperature ($-94\text{ }^\circ\text{C}$) Diels-Alder reaction to give adducts in high *exo* selectivity and excellent enantioselectivity (Scheme 3.12).⁸⁰ The catalyst is prepared in seven steps and ligand recovery after the reaction is 85%.

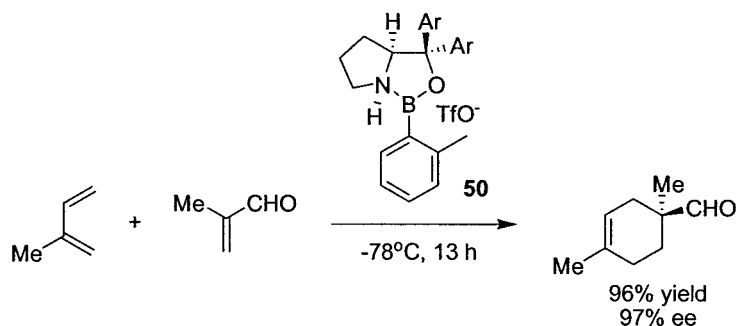


Scheme 3.12 Enantioselective Diels-Alder catalyzed by chiral cationic oxazaborinane complex

Corey *et al.* demonstrated that the cationic Lewis acid generated from the oxazaborolidines by protonation by trifluoromethanesulfonic (triflic) acid **50** are excellent catalysts for enantioselective reaction of 2-substituted acroleins with a

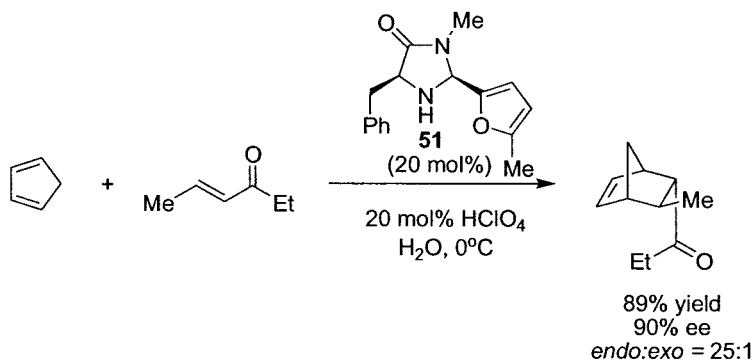
⁸⁰ Hayashi, Y.; Rhode, J. J.; Corey, E. J. *J. Am. Chem. Soc.* **1996**, *118*, 5502.

variety of dienes (Scheme 3.13).⁸¹ Recently, he applied the catalyst successfully to the Diels–Alder reactions of furans and 1,1,1-trifluoroethyl acrylate to give adducts in high *exo* selectivity and excellent enantioselectivity.⁸²



Scheme 3.13 Enantioselective Diels-Alder catalyzed by chiral cationic oxazaborinane complex

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 **51** (Scheme 3.14).⁸³



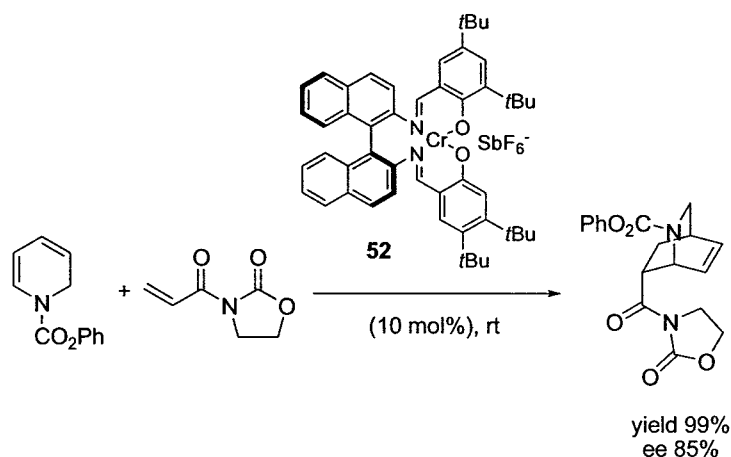
Scheme 3.14 Enantioselective Diels-Alder catalyzed by chiral amine organocatalyst

⁸¹ Corey, E. J.; Shibata, T.; Lee, T.-W. *J. Am. Chem. Soc.* **2002**, *124*, 3808.

⁸² Ryu, D. H.; Kim, K. H.; Sim, J. Y.; Corey, E. J. *Tetrahedron Lett.* **2007**, *48*, 5735.

⁸³ Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

Rawal *et al.* described the first catalysed enantioselective Diels–Alder reactions of 1,2-dihydropyridine. A family of BINAM based Cr(III) salen complexes **52** were developed specifically for these cycloadditions. Under optimised reaction conditions, the cycloaddition between the dihydropyridine and acryloyloxazolidinone proceeded in excellent yield (99%) and good ee (up to 85%) (Scheme 3.15).⁸⁴

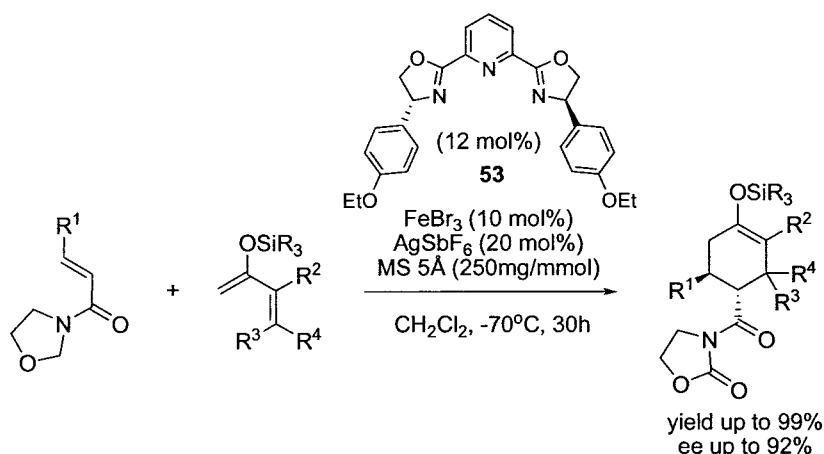


Scheme 3.15 Enantioselective Diels-Alder catalyzed by BINAM based Cr(III) salen complexes

Shibasaki *et al.* developed a catalytic enantioselective Diels-Alder reaction using a cationic Fe^{3+} -Ar-pybox complex **53** as a catalyst. This reaction is the first catalytic enantioselective Diels-Alder reaction of acyclic 4,4-disubstituted 1,3-dienes. It allowed for an efficient and rapid synthesis of chiral polysubstituted cyclohexanones with good yields and high enantioselectivities (Scheme 3.16).⁸⁵

⁸⁴ Takenaka, N.; Huang, Y.; Rawal, V. H. *Tetrahedron*. **2002**, *58*, 8299.

⁸⁵ Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org Lett*. **2004**, *6*, 4387.



Scheme 3.16 Enantioselective Diels-Alder catalyzed by a cationic Fe³⁺-Ar-pybox complex

Diels-Alder Reaction in Ionic Liquids

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,⁸⁶ hydroformylation,⁸⁷ Friedel-Crafts acylation,⁸⁸ Diels-Alder reaction,⁸⁹ enantioselective allylation reactions,⁹⁰ enantioselective epoxidation of alkenes,⁹¹ and enantioselective ring-opening of epoxides.⁹²

⁸⁶ 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.

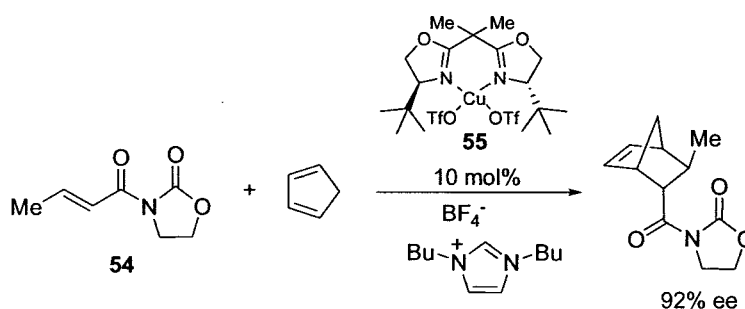
⁸⁷ Some examples for the hydroformylation in ionic liquids: (a) Kuntz, E. G. *CHEMTECH* **1987**, 570. (b) Knifton, E. G. *J. Mol. Catal.* **1987**, *43*, 65. (c) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, 100. (d) Favre, F.; Olivier-Bourbigou, H.; Commereuc, D.; Saussine, L. *Chem. Commun.* **2001**, 1360. (e) Keim, W.; Vogt, D.; Waffenschmidt, H.; Wasserscheid, P. *J. Catal.* **1999**, *186*, 481.

⁸⁸ 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.

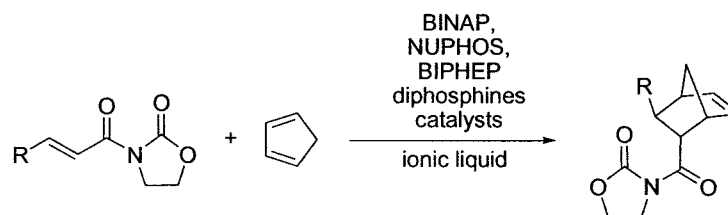
⁸⁹ Some examples for the Diels-Alder reaction in ionic liquids: (a) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785. (b) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793.

⁹⁰ McCluskey, A.; Garner, J.; Young, D. J.; Caballero, S. *Tetrahedron Lett.* **2000**, *41*, 8147.

Recently, two asymmetric Diels-Alder reactions performed in ionic liquid have been reported. Meracz and Oh⁹³ observed an ee of 92% for the Diels-Alder reaction of oxazolidinone **54** and cyclopentadiene at room temperature using a rigid copper bisoxazoline-based chiral Lewis acid **55** with a yield of 65% in 1,3-dibutylimidazolium tetrafluoroborate (Scheme 3.17). This was compared with dichloromethane which showed only 76% ee with a yield of only 4%. Moreover, Doherty⁹⁴ *et al* also found that ionic liquids provide an ideal medium in which to perform the room temperature Diels-Alder reaction between oxazolidinone and cyclopentadiene (Scheme 3.18) catalyzed by platinum complexes of conformationally rigid (BINAP) and flexible (NUPHOS, BIPHEP) diphosphines.



Scheme 3.17 Diels-Alder in ionic liquid catalyzed by chiral Cu(II) bisoxazoline



Scheme 3.18 Diels-Alder in ionic liquid catalyzed by chiral diphosphines

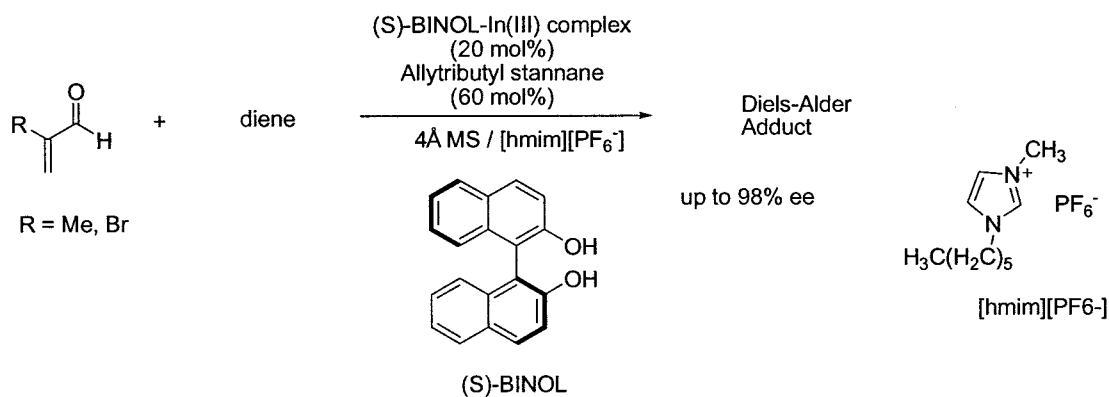
⁹¹ Song, C.-E.; Roh, E. J. *Chem. Commun.* **2000**, 837.

⁹² Song, C.-E.; Oh, C. R.; Roh, E. J.; Choo, D. J. *Chem. Commun.* **2000**, 1743.

⁹³ Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465.

⁹⁴ Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.-K.; Rooney, D.W.; Seddon, K. R.; Styring, P. *Green Chem.* **2004**, *6*, 63.

In this chapter, the successful application of the chiral BINOL-In(III) catalyst for the enantioselective Diels-Alder reaction in ionic liquid [hmim][PF₆⁻] as an environmentally friendly reaction media will be described (Scheme 3.19).



Scheme 3.19 Catalytic enantioselective Diels-Alder reaction in ionic liquid

3.2 CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTION IN IONIC LIQUID VIA A RECYCLABLE CHIRAL INDIUM(III) COMPLEX

3.2.1 INTRODUCTION

The application of ionic liquids (IL) as potential “green” alternatives to conventional solvents for a wide range of organic transformations has sparked an increasing interest among organic chemists. In particular, they have been demonstrated to effect large increases in reaction rates in asymmetric Diels-Alder reactions. To the best of our knowledge, only two asymmetric catalytic Diels-Alder reactions performed in ionic liquids have been reported.⁹⁵ However, the application of chiral catalytic systems to the asymmetric Diels-Alder reaction in ionic liquids using a variety of dienes, in particular, open chained dienes, has yet to be explored. In this chapter, we report an efficient asymmetric Diels-Alder reaction of both cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein catalyzed by a chiral (*S*)-BINOL-In(III) complex in [hmim][PF₆].

⁹⁵ Examples of asymmetric catalytic Diels-Alder reactions in ionic liquids: (a) Doherty, S.; Goodrich, P.; Hardacre, C.; Luo, H.-K.; Rooney, D.W.; Seddon, K. R.; Styring, P. *Green Chem.* **2004**, *6*, 63. (b) Meracz, I.; Oh, T. *Tetrahedron Lett.* **2003**, *44*, 6465. Other examples of Diels-Alder reactions in ionic liquids: (c) Jaeger, D. A.; Tucker, C. E. *Tetrahedron Lett.* **1989**, *30*, 1785. (d) Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* **1999**, *40*, 793. (e) Nobuoka, K.; Kitaoka, S.; Kunimitsu, K.; Iio, M.; Harran, T.; Wakisaka, A.; Ishikawa, Y. *J. Org. Chem.* **2005**, *70*, 10106. (f) Silvero, G.; Arevalo, M. J.; Bravo, J. L.; Avalos, M.; Jimenez, J. L.; Lopez, I. *Tetrahedron* **2005**, *61*, 7105. (g) Xiao, Y.; Malhotra, S. V. *Tetrahedron Lett.* **2004**, *45*, 8339. (h) Abbott, A. P.; Capper, G.; Davies, D. L.; Rasheed, R. K.; Tambyrajah, V. *Green Chem.* **2002**, *4*, 24. (i) Song, C. E.; Shim, W. H.; Roh, E. J.; Lee, S.-G.; Choi, J. H. *Chem. Commun.* **2001**, 1122.

3.2.2 RESULTS AND DISCUSSIONS

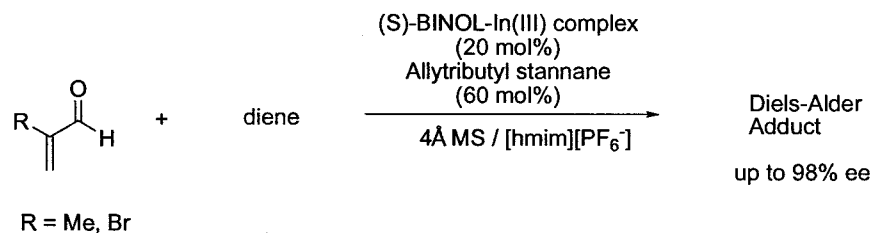
Recently, we have demonstrated an efficient protocol for the asymmetric Diels-Alder reaction in dichloromethane, which employs a chiral (*S*)-BINOL-In(III) as precatalyst and allyltributylstannane as activator to generate the potent Lewis acid.⁹⁶ This method has proven to be practical and convenient, furnishing a variety of cycloadducts in good yields and excellent enantioselectivities. However, the catalyst was not able to be recycled and reused.⁹⁷ In this chapter, we demonstrate that the chiral BINOL-In(III) catalytic system can be extended to the asymmetric Diels-Alder reaction using ionic liquids with increased chemical yields of the cycloadducts. In addition, the chiral catalyst can be recovered and reused through a simple extraction protocol. This system in ionic liquid was also found to work using 5 mol % catalyst.

In our initial study, we carried out the catalytic enantioselective Diels-Alder reaction using a standardized protocol. The catalyst was prepared by mixing (*S*)-BINOL, 4 Å molecular sieve (MS), and InCl₃ in dichloromethane at room temperature. After 2 h of stirring, allyltributylstannane was added and stirred for 10 min followed by the addition of [hmim][PF₆⁻] to the preformed catalyst. The organic solvent was removed under reduced pressure followed by subsequent addition of cyclopentadiene and 2-bromoacrolein. This preliminary study afforded the Diels-Alder adduct in a good yield of 92% and excellent enantiomeric excess of 98%. Having achieved the optimum reaction parameters for the catalytic process, we extended the asymmetric Diels-Alder reaction of a selection of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein. The results are shown in Table 1.

⁹⁶ Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539.

⁹⁷ Teo, Y.-C.; Goh, E. L.; Loh, T.-P. *Tetrahedron Lett.* **2005**, *46*, 4573.

CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTION IN IONIC LIQUID

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

Entry	Diene	Product, 56	Condt. (°C, h)	Yield (%) ^b	ee (%) ^c
1		56a	rt, 20	89	98
2		56b	rt, 20	92	98
3		56b	0,20	89	92 ^d
4		56c	rt, 20	78	88 ^e
5		56d	rt, 20	90	96 ^f
6		56e	rt, 20	88	97
7		56f	rt, 20	90	94
8		56g	rt, 20	89	92

^a Unless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol %), InCl₃ (20 mol %), and allyltributylstannane (60 mol %) in the presence of activated 4 Å MS. ^b Isolated yield. ^c Enantioselectivities were determined by reduction to the primary alcohol (NaBH₄), conversion to the Mosher ester, and ¹H NMR analysis, or conversion to the benzoate and HPLC analysis. ^d Reaction carried out using 5 mol % catalyst loading. ^e Diels-Alder adduct contains ca. 23% of its regioisomer. ^f Diels-Alder adduct contains ca. 16% of its regioisomer.

The reaction of 2-methacrolein and 2-bromoacrolein with cyclopentadiene afforded both Diels-Alder adducts in 98% ee (*exo:endo* 97:3) and yields of 89% and 92%, respectively (Table 1, entries 1 and 2). Moreover, the Diels-Alder adduct of cyclopentadiene with 2-bromoacrolein can also be obtained with an enantiomeric excess of 92% (*exo:endo* 96:4) and a yield of 89% with as low as 5 mol % catalyst loading (entry 3). The reaction of 2-methyl-1,3-butadiene with 2-methacrolein and 2-bromoacrolein afforded the cycloadducts in 88% and 96% ee, respectively (entries 4 and 5). In addition, the cycloaddition of 2,3-dimethyl-1,3-butadiene to 2-methacrolein and 2-bromoacrolein catalyzed by the (*S*)-BINOL-In(III) complex also afforded both adducts with excellent enantioselectivities of 97% and 94%, respectively (entries 6 and 7). It is noteworthy that the yields obtained for the asymmetric Diels-Alder adducts in ionic liquid were significantly higher as compared to that in dichloromethane. In conjunction with an interest in the application of this system to the synthesis of steroids, we also tested the reaction on the complex open-chain diene, 7-methoxy-4-vinyl-1,2-dihydronaphthalene (entry 8). The cycloadduct was obtained with an enantiomeric excess of 92% and chemical yield of 89%.

The absolute configurations of the Diels-Alder products shown in Table 1 have been assigned by measurement of optical rotation and comparison with known substances.⁹⁸

The stereochemical course of the Diels-Alder reaction catalyzed by the chiral (*S*)-BINOL-In(III) complex can be envisaged in terms of the catalyst-aldehyde pre-transition state assembly **57** depicted in Figure 1. In assembly **57**, 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

⁹⁸ Teo, Y.-C.; Loh, T.-P. *Org. Lett.* **2005**, *7*, 2539.

to the *si* face (front) of the α,β -double bond leading to the enantiomers shown in Table 1.

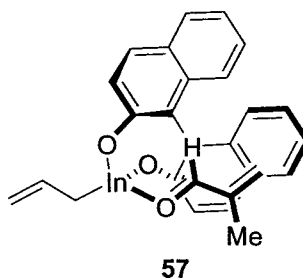


Figure 1. Proposed BINOL-In(III)-aldehyde pre-transition state

Next, we continued our study by exploring the recyclability of the chiral indium complex which is important from the viewpoint of cost-effectiveness. We carried out the model study by using the cycloaddition of cyclopentadiene and 2-bromoacrolein in [hmim][PF₆]. After the reaction was completed, the reaction mixture was extracted with hexanes (10 mL x 5) to afford the cycloadduct. The ionic liquid residue was then azeotroped with THF to facilitate removal of solvent remnants prior to subsequent addition of the diene and dienophile in the next cycle. The results are shown in Table 2.

Table 2. Recyclability of (*S*)-BINOL-In(III) complex in hmin[PF₆]

no. of cycles	% yield ^b	% ee ^c
1 st	92	98
2 nd	89	98
3 rd	88	92
4 th	89	90
5 th	88	90
6 th	86	90
7 th	87	86

^aUnless otherwise specified, the chiral indium(III) catalyst was prepared from (*S*)-BINOL (22 mol %), InCl₃ (20 mol %) and allyltributyl stannane (60 mol %) in the presence of activated 4 Å MS. Reaction mixture was stirred at room temperature for 20 h. ^bIsolated yield. ^cEnantioselectivities were determined by reduction to the primary alcohol (NaBH₄), conversion to the Mosher ester, and ¹H NMR analysis

It was noteworthy that the chiral In(III) complex can be reused for seven successive cycles with comparable enantioselectivities and yields without loss of catalytic activity. Moreover, the extraction process was operationally simple and convenient to execute, which precludes the need for stringent anhydrous conditions. This extraction process further demonstrated the moisture-tolerance and stability of the chiral indium complex with retention of catalytic activity throughout the recyclability studies.

3.3 CONCLUSIONS

In conclusion, a highly catalytic In(III) complex was developed to give enantiomerically enriched Diels-Alder adducts with high enantiomeric excess in ionic liquid. The main features of this reaction are as follows: (1) the procedure is operationally simple, and the catalyst can be easily prepared from commercially available chemicals; (2) the cycloaddition of a variety of cyclic and open-chained dienes to 2-methacrolein and 2-bromoacrolein resulted in good yields and high enantioselectivities without the need to recourse to low temperatures; (3) good enantiomeric excess and yield of cyclopentadiene and 2-bromoacrolein adduct can be achieved with as low as 5 mol % catalyst loading in ionic liquid; (4) the catalyst can be recycled up to seven cycles with comparable yields and enantioselectivities; and (5) stringent anhydrous condition during workup for recycling the catalyst is not required. This contribution should provide a convenient and practical synthetic strategy for the construction of six-membered rings for complex molecules with medicinal and biological significance.

CHAPTER 4

Synthetic Studies towards the Total Synthesis of

RK-397

4.1 BACKGROUND OF RK-397

The new antibiotic RK-397, a member of a large family of polyene macrolides, was isolated from a strain of soil bacteria *Streptomyces sp. 87-397*, from a soil sample collected in Saku city, Nagano prefecture of Japan (Figure 4.1). This antibiotic exhibits antifungal and antibacterial activity as well as promising anticancer activity. It was isolated and structurally characterized by Osada *et al.* in 1993.⁹⁹

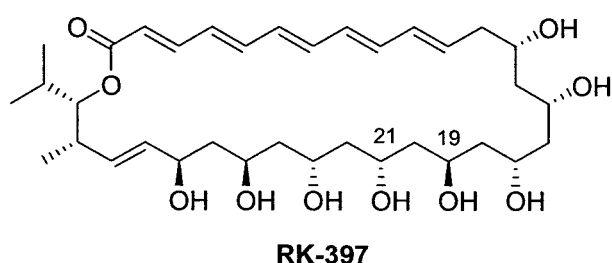


Figure 4.1 RK-397

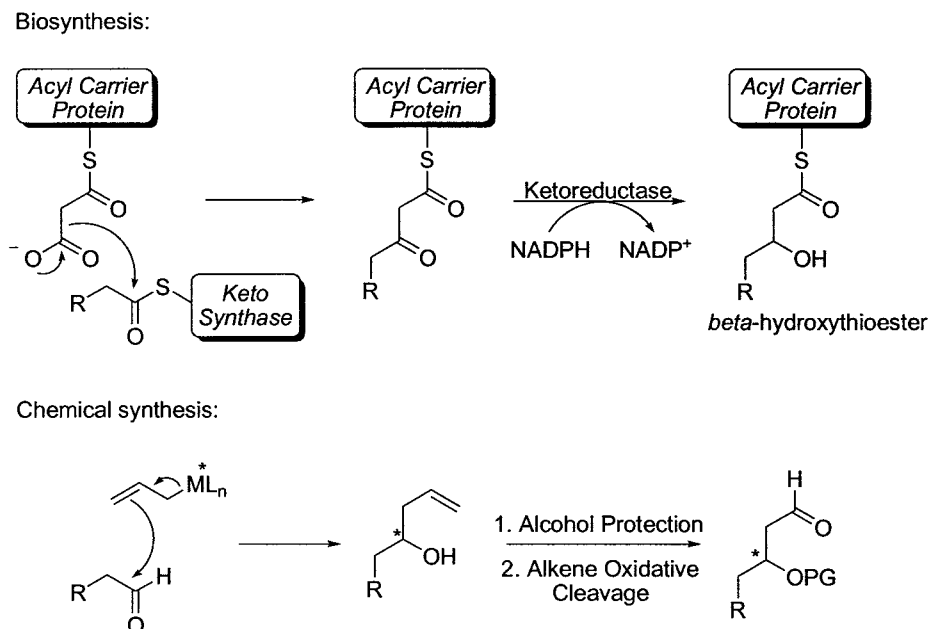
The large family of polyene macrolides includes amphotericins, nystatin, mycoticins, as well as roxaticins¹⁰⁰ and all of them contain a highly conjugated polyene and a long 1,3-polyol chain. The alternating 1,3,5-... polyol chains in polyacetate compounds are biosynthesized through the use of simple acetate and propionate building blocks.¹⁰¹ In this respect, the Schreiber chemical synthesis of mycoticin based on iterative aldol equivalent addition to aldehydes mimics the

⁹⁹(a) Kobinata, K.; Koshino, H.; Kudo, T.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1616. (b) Koshino, H.; Kobinata, K.; Isono, K.; Osada, H. *J. Antibiot.* **1993**, *46*, 1619.

¹⁰⁰(a) Maehr, H.; Yang, R.; Hong, L. N.; Liu, C. M.; Hatada, M. H.; Todaro, L. J. *J. Org. Chem.* **1989**, *54*, 3816. (b) Wasserman, H. H.; Van Verth, J. E.; McCaustland, D. J.; Borowitz, I. J.; Kamber, B. *J. Am. Chem. Soc.* **1967**, *89*, 1535. (c) Schreiber, S. L.; Goulet, M. T. *J. Am. Chem. Soc.* **1987**, *109*, 8120. (d) Lancelin, J. M.; Beau, J. M. *Tetrahedron Lett.* **1989**, *30*, 4521. (e) Suenaga, T.; Nakamura, H.; Koshino, H.; Kobinata, K.; Osada, H.; Nakata, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1997**, *39*, 607 (*Chem. Abstr.* **1997**, *131*, 129786).

¹⁰¹(a) *Enzymatic Reaction Mechanisms*, Walsh, C., Ed.; W. H. Freeman: San Francisco, 1979; pp 909-916. (b) Staunton, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1302. (c) Cortes, J.; Haydock, S. F.; Roberts, G. A.; Bevitt, D. J.; Leadlay, P. F. *Nature* **1990**, *348*, 176. (d) Donadio, S.; Staver, M. J.; McAlpine, J. B.; Swanson, S. J.; Katz, L. *Science* **1999**, *252*, 675. (e) Tsoi, C. J.; Khosla, C. *Chem. Biol.* **1995**, *2*, 355. (f) Rohr, J. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 881. (g) Bailey, J. E. *Nat. Biotechnol.* **1999**, *17*, 616. (h) Cane, D. E.; Walsh, C. T.; Khosla, C. *Science* **1998**, *282*, 63. (i) Carreras, C. W.; Santi, D. V. *Curr. Opin. Biotechnol.* **1998**, *9*, 403.

biosynthetic pathway (Scheme 4.1).¹⁰² It is noteworthy that 16 carbon-carbon bond-forming steps is required for a linear synthesis of a 34-carbon chain from two-carbon synthons.



Scheme 4.1 Construction of polyacetates from two-carbon synthons: biosynthesis vs chemical synthesis.

Significant changes in biological activities can result from minor structural differences in the macrolides. For example, minor structural difference between amphotericin B and nystatin resulted in toxicity in amphotericin B although it is used for severe systemic and potentially fatal fungal infections,¹⁰³ whereas nystatin has virtually no human toxicity and is much milder in activity.¹⁰⁴ In addition, considering the minor structural differences between RK-397 and mycoticin, specifically the additional methyl group at C14 of mycoticin and differing relative stereochemistry of the C19 and C21 alcohols (Figure 4.2) resulted in the anticancer activity for RK-397

¹⁰² Poss, C. S.; Rychnovsky, S. D.; Schreiber, S. L. *J. Am. Chem. Soc.* **1993**, *115*, 3360. (b) Roush, W. R.; Palkowitz, A. D.; Ando, K. *J. Am. Chem. Soc.* **1990**, *112*, 6348. (c) Andersen, M. W.; Hildebrandt, B.; Dahmann, G.; Hoffmann, R. W. *Chem. Ber.* **1991**, *124*, 2127.

¹⁰³ Bolard, J. *Biochim. Biophys. Acta* **1988**, *864*, 257.

¹⁰⁴ *Drug Facts and Comparisons*; Wolters Kluwer: St Louis, 1996; pp 2174, 2180.

verses the absence of activity reported for mycoticin. Both macrolides exhibit broad antimicrobial activities against filamentous fungi, yeast, and bacteria at 50-100 $\mu\text{g/mL}$, yet only RK-397 is reported to have in vitro anticancer activity, inhibiting human leukemia cell lines HL-60 and K-562 at 25 $\mu\text{g/mL}$ and 50 $\mu\text{g/mL}$ respectively. However, the mode of action of RK-397 is yet to be resolved. Due to their potent biological activity and structural complexity, these polyene macrolides have attracted much interest as targets for total synthesis.¹⁰⁵

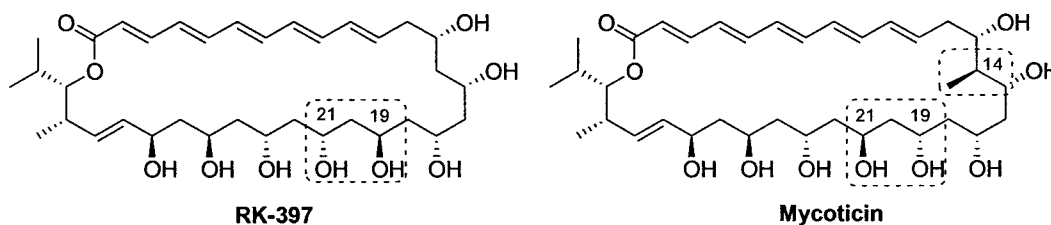


Figure 4.2 Structural difference between RK-397 and Mycoticin.

There has been three total syntheses of RK-397 reported so far, the first pioneered by McDonald *et al.*, second by Denmark *et al.* and third by Sammakia *et al.*, and two asymmetric syntheses of the polyol fragment by Vogel *et al.* and Schneider *et al.* respectively.

The first asymmetric total synthesis of the natural product RK-397 by Burova and McDonald¹⁰⁶ in year 2004, is based on a new synthetic strategy for assembling polyacetate structures, by efficient cross-coupling of nucleophilic terminal alkyne modules with electrophilic epoxides bearing another alkyne at the opposite terminus. Their elegant approach involves coupling larger building blocks with six or more

¹⁰⁵ Rychnovsky, R. D. *Chem. Rev.* **1995**, *95*, 2021.

¹⁰⁶ (a) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2002**, *124*, 8188. (b) Burova, S. A.; McDonald, F. E. *J. Am. Chem. Soc.* **2004**, *126*, 2495.

carbons in a linear chain, further reducing the number of carbon-carbon bond-forming steps required for polyacetate synthesis.

The natural product is constructed from four principal modules: a polyene precursor for carbons 3-9, and three alkyne-terminated modules for carbons 10-16, 17-22, and 23-33 (Figure 4.3). Each module is prepared with control of all stereochemical elements, and the alkynyl alcohols obtained from alkyne-epoxide couplings are converted into 1,3-diols by a sequence of hydroxyl-directed hydrosilylation, C-Si bond oxidation, and stereoselective ketone reduction with induction from the β -hydroxyl group. The highly convergent nature of their synthetic pathway and the flexibility of the modular synthesis strategy for virtually any stereoisomer can provide access to other members of the polyene-polyol macrolides, including stereoisomers of RK-397.

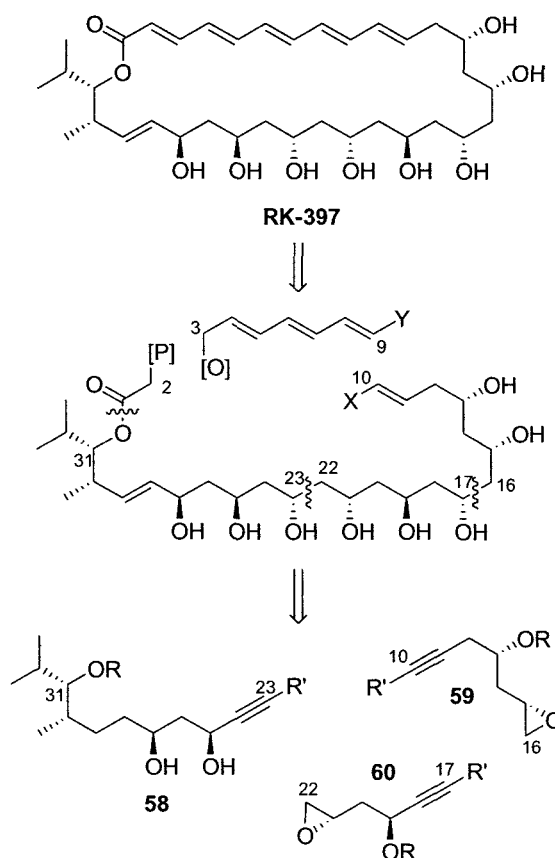
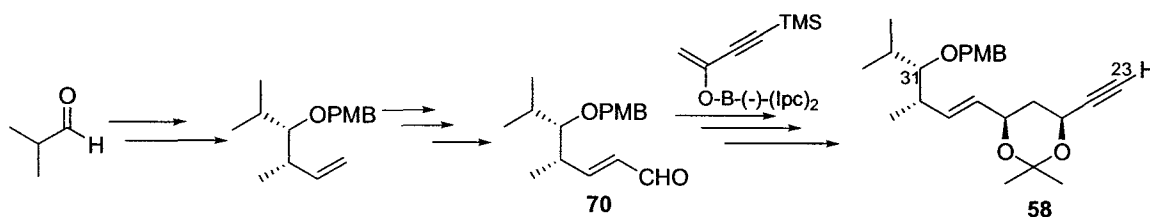


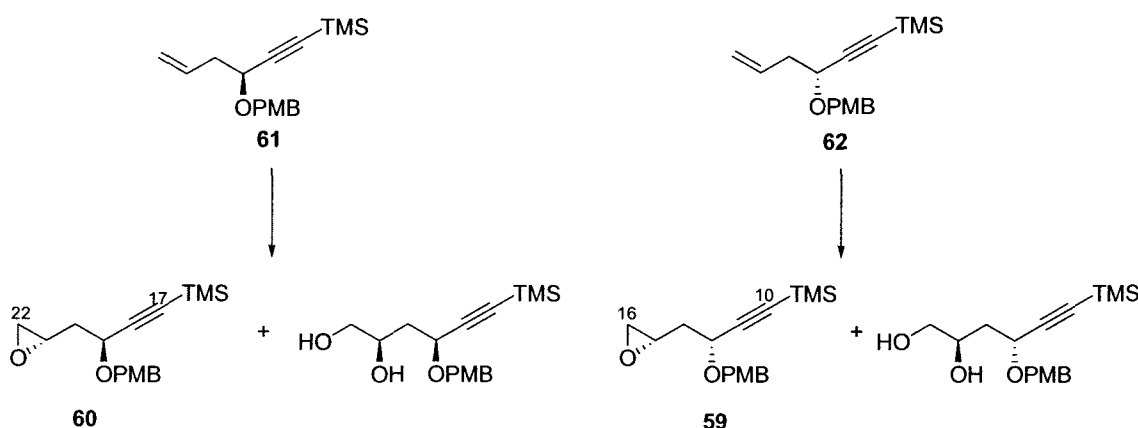
Figure 4.3 Retrosynthetic analysis of RK-397 by McDonald.

The synthesis of the C23-C31 module **58** began with synthesis of homoallylic alcohol from the reaction of isobutyraldehyde with (*Z*)-crotyldiisopinocampheylborane followed by an olefin methathesis and subsequently a one-pot boron aldol addition and stereoselective reduction of the intermediate boron chelate with NaBH₄ to provide the acetonide protected *syn*-diol **58** as an 4:1 mixture of diastereomers in excellent yield.



Scheme 4.2 Synthesis of C23-C31 module.

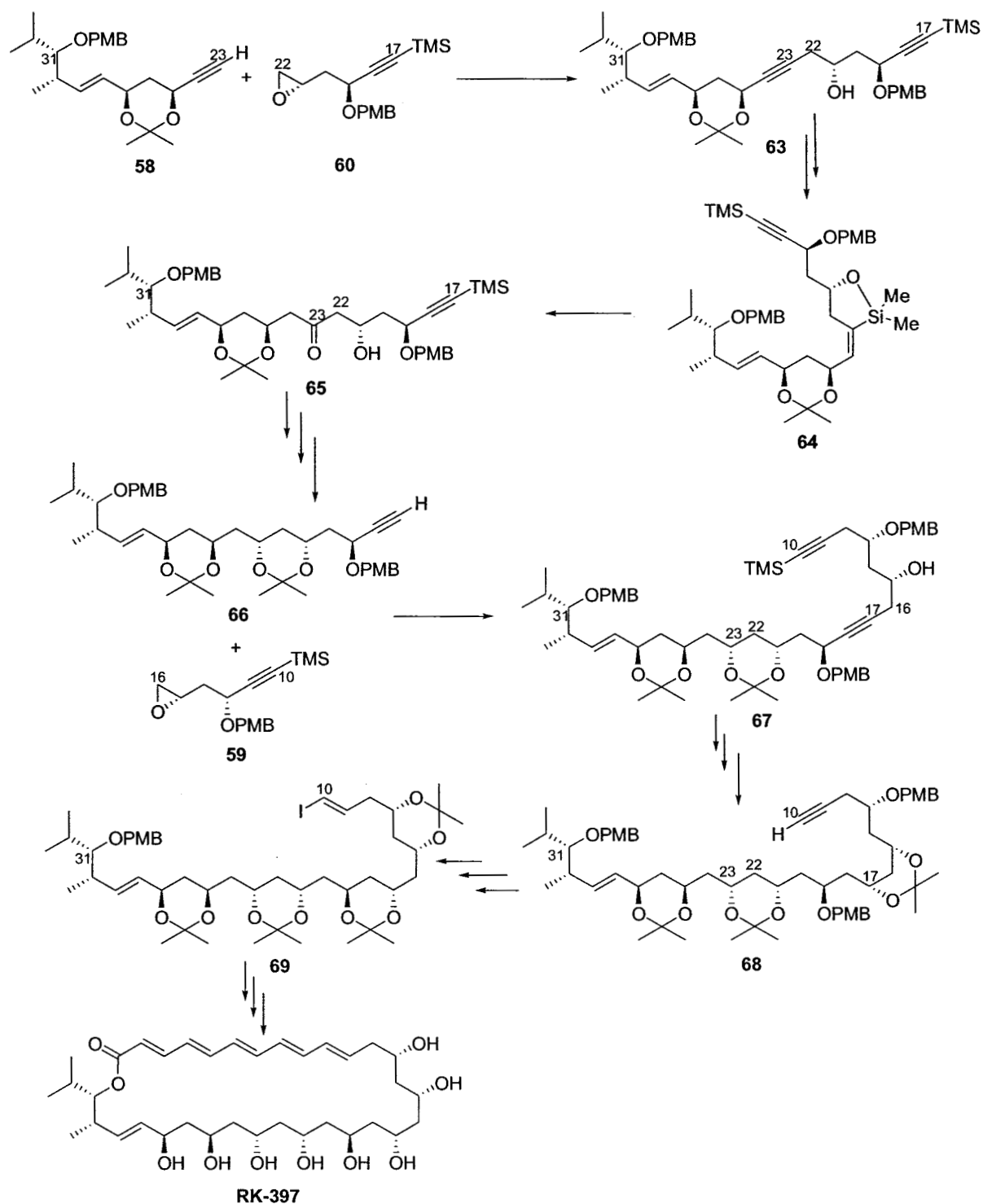
Their approach to the C10-C16 module **59** and C17-C22 module **60** involves preparation of the protected six-carbon epoxyalkynol **61** and **62** by enzyme-catalyzed resolution followed by a sequence of virtually nonstereoselective epoxidation and Jacobsen's hydrolytic kinetic resolution procedure (Scheme 4.3).



Scheme 4.3 Synthesis of C10-C16 module and C17-C22 module

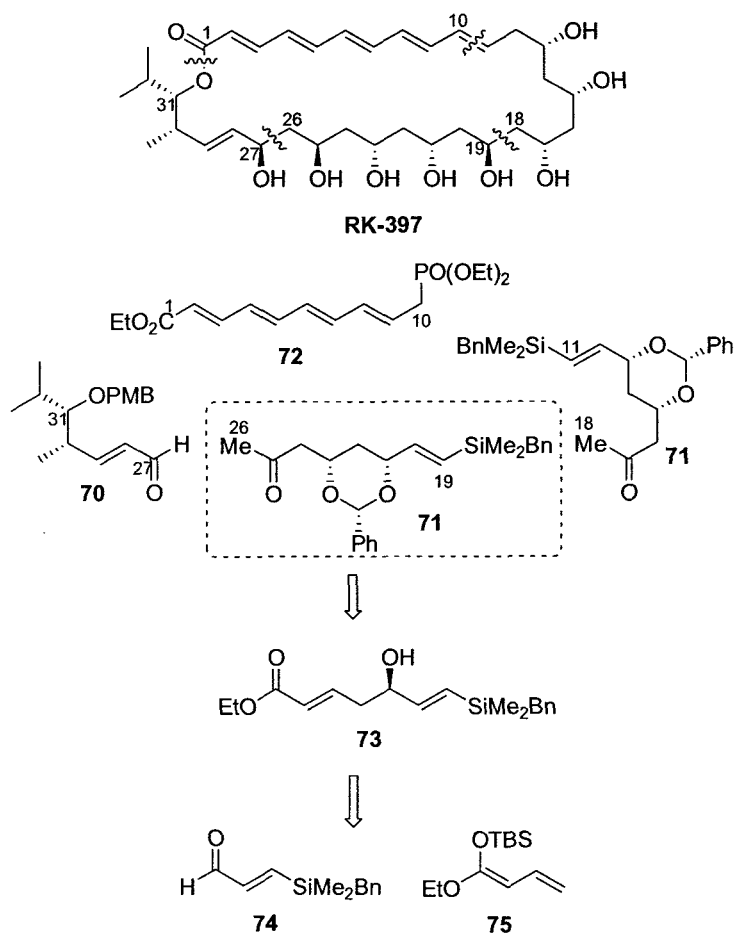
Cross-coupling of the lithium acetylide from **58** with electrophilic epoxide **60** could be accomplished with $\text{BF}_3 \cdot \text{OEt}_2$ to provide the corresponding homopropargylic alcohols **63**. Hydration of the C23-C24 alkyne **64** was achieved by hydroxyl-directed hydrosilylation/Si-C bond oxidation. Hydroxyl-directed reduction of the mixture of β -hydroxyketone **65** with $\text{NaBH}_4/\text{Et}_2\text{BOMe}$ and sequential acetylenic TMS deprotection and acetonide formation, gave product **66** in good yield. The coupling of terminal alkyne **66** and the C10-C16 epoxyalkyne module **59** proceeded smoothly to afford diyne **67**, which underwent the identical sequence of hydrosilylation-oxidation to **68** and chelation-controlled reduction to provide regio- and stereoselective introduction of the C17-alcohol, protected as the acetonide **69**.

The substrate **69** further undergoes esterification with diethylphosphonoacetic acid, Stille coupling with *all-trans*-7-(tributylstannyl)-2,4,6-heptatrien-1-ol and Horner-Emmons macrocyclization to provide the known tetraacetonide derivative of RK-397. Acidic methanolysis of the acetonide protective groups provided the final synthetic RK-397 (Scheme 4.4).



Scheme 4.4 Coupling of C10-C31 to polyene and completion of RK-397 synthesis

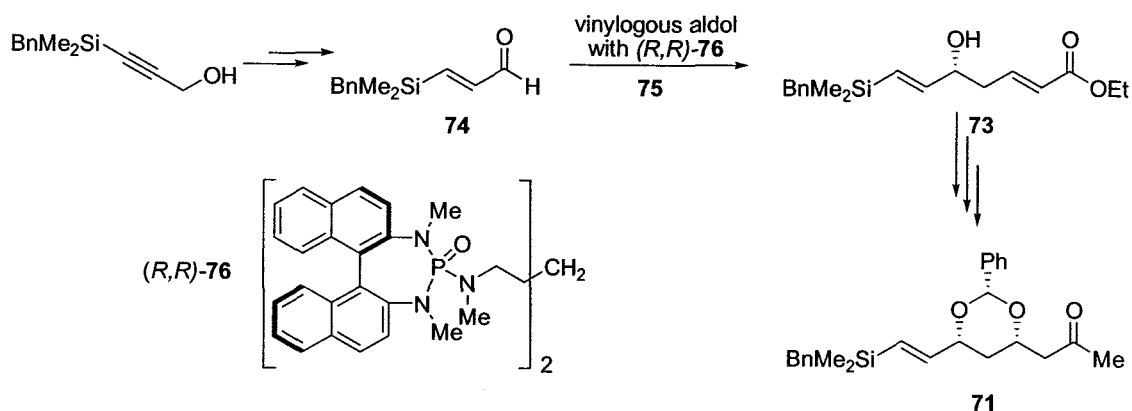
The second total synthesis by Fujimori and Denmark was published a year later.¹⁰⁷ To maximize synthetic convergency, the target was divided into four modules, the known C1-C10 polyene phosphonate fragment, C11-C18 and C19-C26 fragments as an identical building block and the same module **70** which was also employed by McDonald (Scheme 4.5).



Scheme 4.5 Denmark's retrosynthetic analysis of RK-397

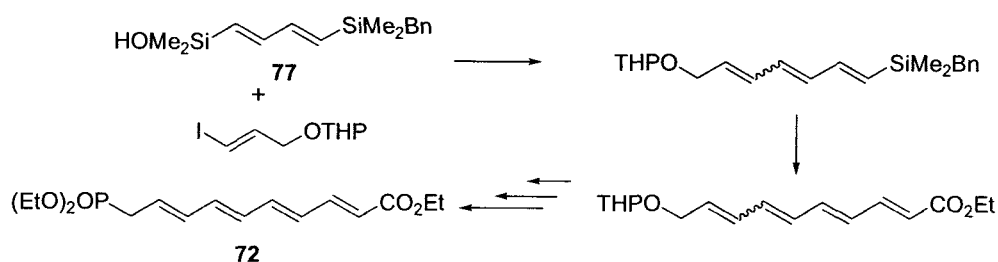
¹⁰⁷ Denmark, S.E.; Fujimori, S. *J. Am. Chem. Soc.* **2005**, *127*, 8971.

The key building block **71** was envisioned to arise from vinylogous aldol addition of ketene acetal **75** to aldehyde **74** using chiral bisphosphoramidate (*R,R*)-**76** which provided **73** smoothly in good yield with excellent γ -selectivity and enantioselectivity. Finally, the synthesis of building block **71** was completed by conversion of the ester group into a methyl ketone in excellent yield (58%, three steps) via the Weinreb amide (Scheme 4.6).

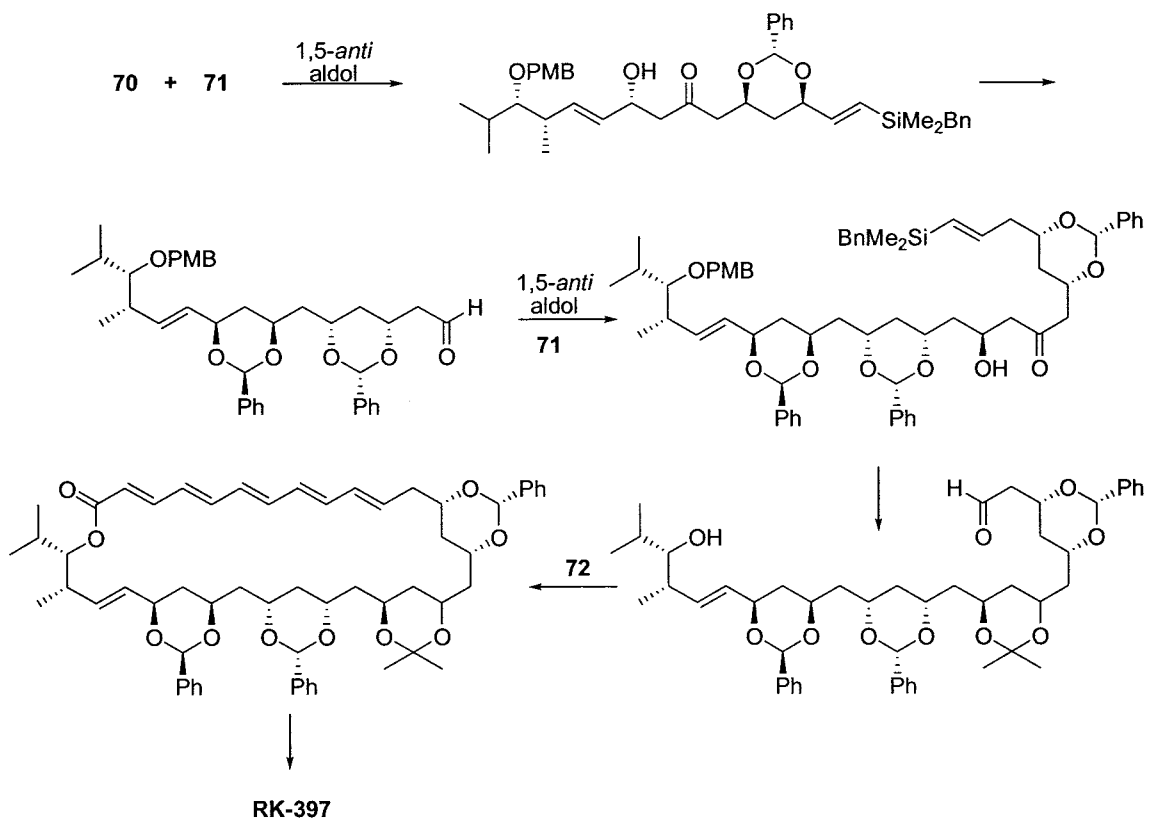


Scheme 4.6 Synthesis of C11-C18 and C19-C26 key intermediate

Their elegant approach utilizes two 1,5-anti stereo induction by substrate-controlled dibutylboron enolate aldol addition for coupling of fragment **70** with two **71** fragments (Scheme 4.7) and silicon-based sequential palladium-catalyzed, cross-coupling of 1,4- bisilyl-1,3-butadiene **77** for the construction of the tetraene moiety **72** (Scheme 4.8).

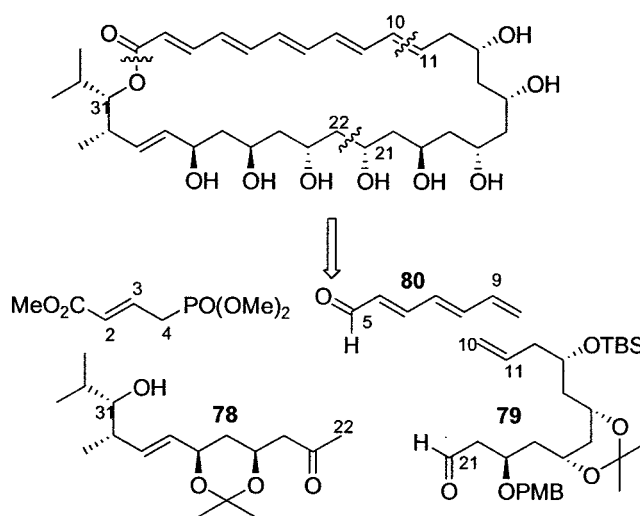


Scheme 4.7 Synthesis of polyene phosphonate

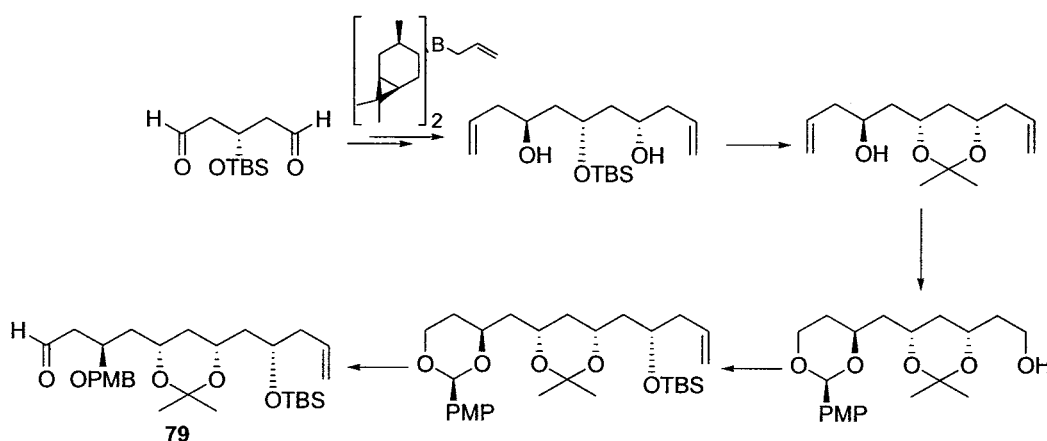


Scheme 4.8 Assembly of all fragments

Sammakia¹⁰⁸ *et al* reported a convergent total synthesis of RK-397 recently which utilizes remote asymmetric induction (for C22-C31) **78** and a two-directional chain synthesis (for C10-C21) **79** to prepare the polyol portion of the molecule (Scheme 4.10), as well as a cross-metathesis reaction of a trienal **80** with a terminal alkene **79** to append the polyene to the polyol (Scheme 4.9).



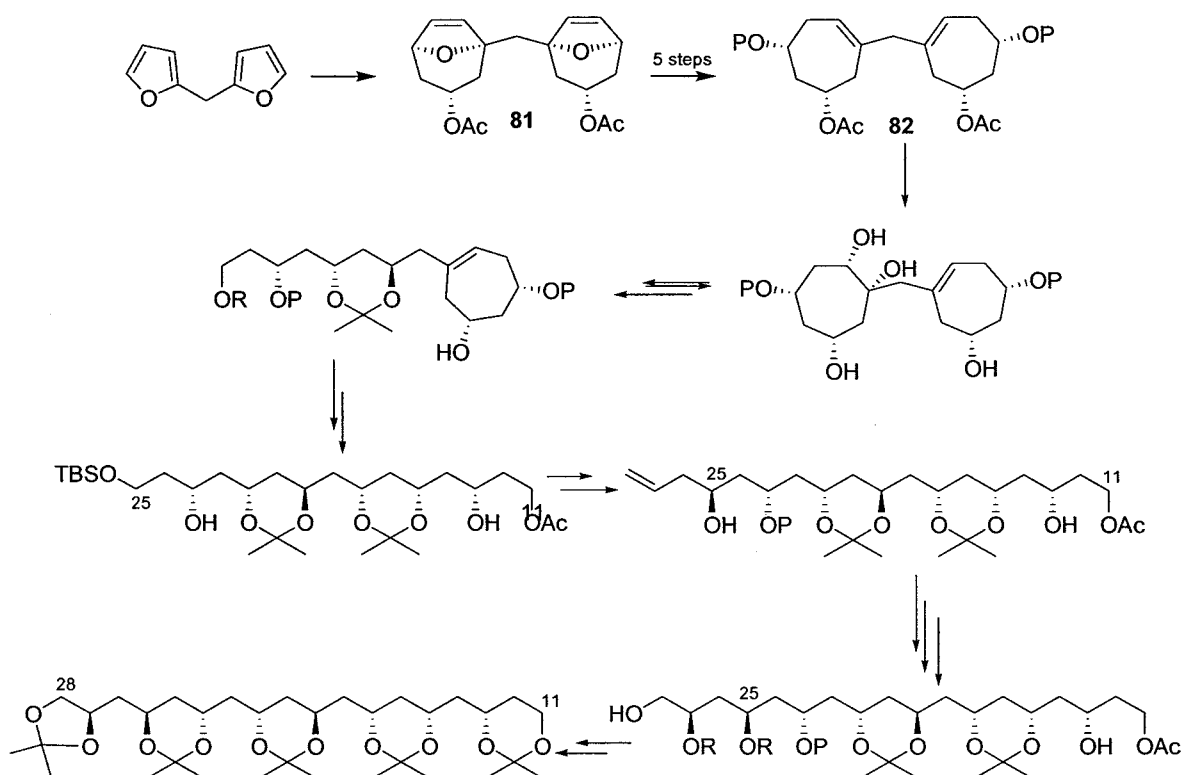
Scheme 4.9 Retrosynthetic analysis of RK-397



Scheme 4.10 Two-directional chain synthesis of C10-C21 fragment

¹⁰⁸ Mitton-Fry, M. J.; Cullen, A. J.; Sammakia, T. *Angew. Chem. Int. Ed.* **2006**, *45*, 1.

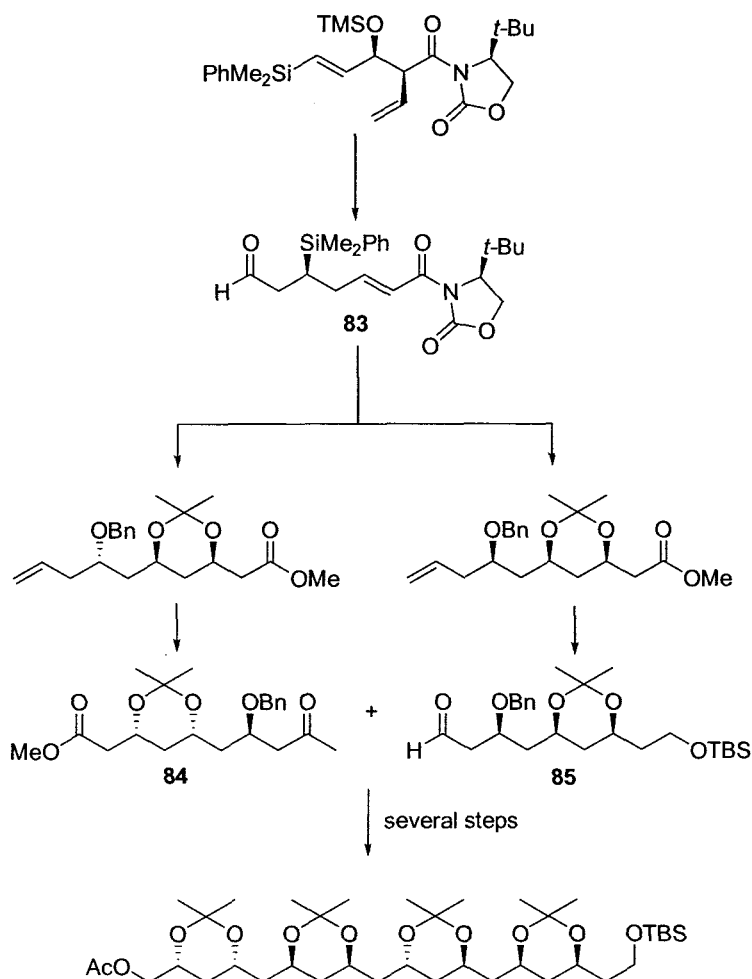
As for the asymmetric synthesis of the polyol subunit of the polyene macrolide, Vogel¹⁰⁹ *et al.* developed a new, noniterative asymmetric synthesis of octahydroxypentadecanols. The dimeric *meso* derivative **82**, accessible via a five-step synthesis starting from the oxabicyclic dimer *meso*-**81**, was desymmetrized using Sharpless asymmetric dihydroxylation. Subsequent ring-opening of the carbocycles, diastereoselective reductions, and further transformations yielded the polyol fragment of RK-397 (Scheme 4.11).



Scheme 4.11 Vogel's synthesis of polyol fragment of RK-397

¹⁰⁹ Gerber-Lemaire, S.; Carmona, A. T.; Meilert, K. T.; Vogel, P. *Eur. J. Org. Chem.* **2006**, 891.

Finally, Schneider¹¹⁰ *et al.* assembled the polyol fragment from two triol building blocks of similar complexity (**84** and **85**), which in turn were derived from the same chiral key compound **83**. The key step in their asymmetric polyol synthesis also featured a 1,5-anti stereo induction by substrate-controlled dibutylboron enolate aldol addition (Scheme 4.12).



Scheme 4.12 Asymmetric synthesis of polyol fragment by Schneider

¹¹⁰ Schneider, C.; Tolksdorf, F.; Rehfeuter, M. *Synlett* **2002**, 2098.

4.2 RETROSYNTHETIC ANALYSIS OF RK-397

The principal challenge in the synthesis of RK-397 is the stereocontrolled assembly of the polyol chain. We felt that the challenge could be efficiently addressed by employing two asymmetric allylation¹¹¹, a catalytic asymmetric hetero-Diels-Alder¹¹² protocol and a 1,5-*anti* stereo induction by substrate-controlled dibutylboron enolate aldol addition¹¹³ in the control of the absolute stereochemistry of the polyol fragment. The pentaenoate backbone would be constructed using known procedures. Herein, we report an efficient, enantioselective synthesis of C1 to C31 fragment of RK-397 utilizing these developed methods as key strategic steps.

To maximize synthetic convergency, the polyene macrolide was divided into four modules (Scheme 4.13). Disconnections at the lactone linkage and the C10-C11 bond afforded the known polyene phosphonate fragment **D**. Careful examination of

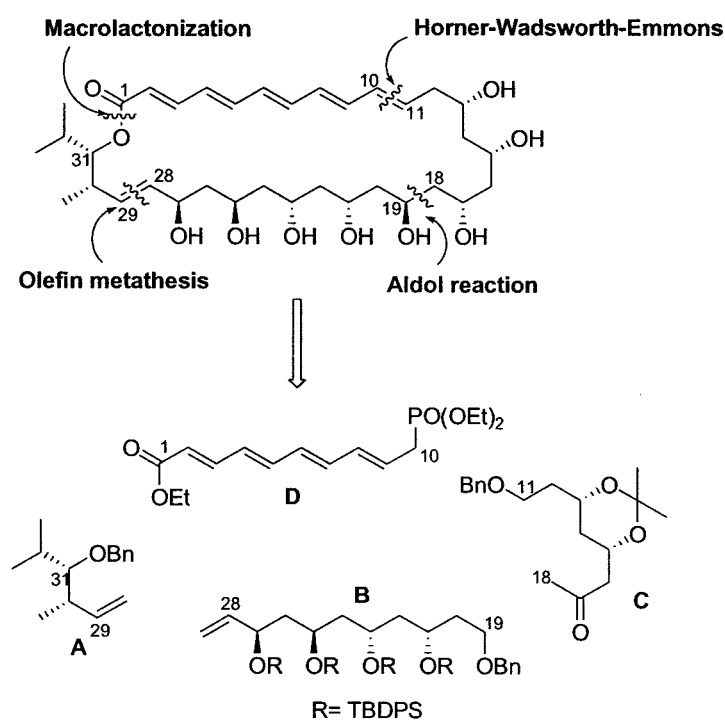
¹¹¹ (a) Gung, B. W.; Xue, X.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 10692. (b) Roush, W. R.; Walts, A. E.; Hoong, L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186. (c) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467. (d) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001.

¹¹² For comprehensive reviews on HDA reactions, see: (a) Danishefsky, S. J.; Deninno, M. P. *Angew. Chem., Int. Ed.* **1987**, *26*, 15. (b) Jorgensen, K. A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3558. (c) Maruoka, K. In *Catalysis Asymmetric Synthesis*; Ojima, I., Ed. 2nd ed.; Wiley-VCH: New York, 2000. (d) Ooi, T.; Maruoka, K. In Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; *Comprehensive Asymmetric Catalysis*; Springer: Berlin, 1999; Vol. III, Chapter 4, pp 1237–1254. (e) Jorgensen, K. A. In *Cycloaddition Reactions in Organic Synthesis*; Kobayashi, S., Jorgensen, K. A., Eds.; Wiley-VCH: Weinheim, 2002. For more recent examples, see: (f) Fan, Q.; Lin, L.; Liu, J.; Huang, Y.; Feng, X.; Zhang, G. *Org. Lett.* **2004**, *6*, 2185. (g) Fu, Z.; Gao, B.; Yu, Z.; Yu, L.; Huang, Y.; Feng, X.; Zhang, G. *Synlett* **2004**, 1772. (h) Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* **2003**, *125*, 3793. (i) Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* **2002**, *4*, 4349. (j) Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* **2002**, *67*, 2175. (k) Long, J.; Hu, J.; Shen, X.; Ji, B.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 10. (l) Kii, S.; Hashimoto, T.; Maruoka, K. *Synlett* **2002**, 931. (m) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 1333. (n) Liu, P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 10772. (o) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974. (p) Doyle, M. P.; Phillips, I. M.; Hu, W. *J. Am. Chem. Soc.* **2001**, *123*, 5366–5367. (q) Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Chem. Lett.* **2000**, 824. (r) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (s) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **1999**, *38*, 2398. (t) Wang, B.; Feng, X.; Cui, X.; Liu, H.; Jiang, Y. *Chem. Commun.* **2000**, 1605. (u) Du, H.; Ding, K. *Org. Lett.* **2003**, *5*, 1091. (v) Du, H.; Zhang, X.; Wang, Z.; Ding, K. *Tetrahedron* **2005**, *61*, 9465. (w) Yuan, Y.; Long, J.; Sun, J.; Ding, K. *Chem. Eur. J.* **2002**, *8*, 5033. (x) Yuan, Y.; Li, X.; Sun, J.; Ding, K. *J. Am. Chem. Soc.* **2002**, *124*, 14866. (y) Doyle, M. P.; Valenzuela, M.; Huang, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5391. (z) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2002**, *41*, 3059.

¹¹³ Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.

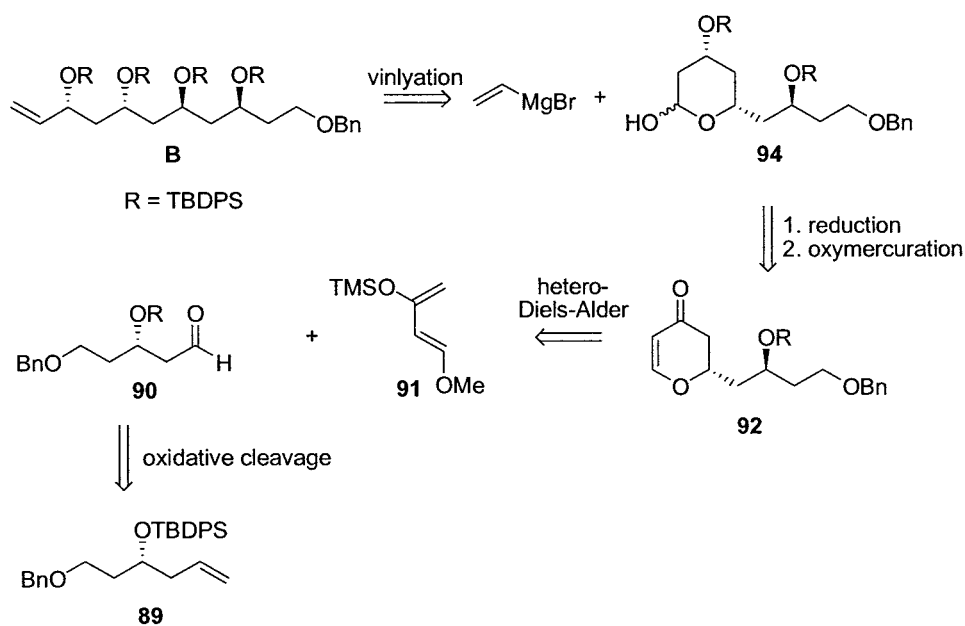
the stereogenic centers pattern on the polyol chain lead us to propose that an efficient synthesis might be achieved by the disconnections at C18-C19 and C28-C29 bonds, affording fragment **B** and **C** which started out with similar building blocks.

In the forward synthesis, these disconnections require an aldol addition with 1,5-*anti* stereoiduction from the methyl ketone **C** and fragment **B**. The aldehyde functionality at C11 and C19 was masked with benzyl ether for functional group robustness. An olefin metathesis step would join fragment **A**, **B** and **C** together. The light- and air-sensitive polyene **D** will be connected to the rest of the molecule at the end of the synthesis via the Horner-Wadsworth-Emmons followed by macrolactonization to close up the ring. The remaining homoallylic alcohol **A** would be synthesized from the reaction of asymmetric crotylation.



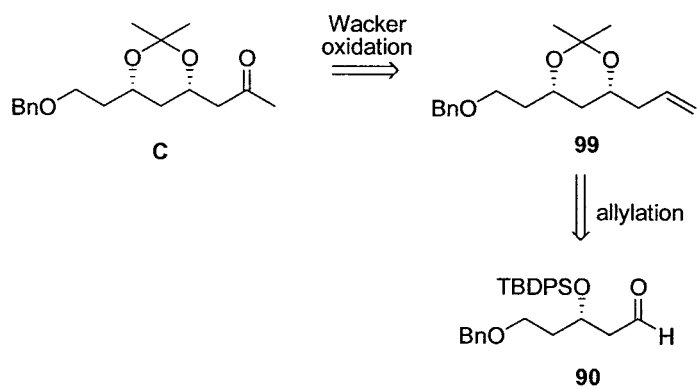
Scheme 4.13 Our retrosynthetic analysis of RK-397

The key building block **B** has five 1, 3 diol array with a vinyl group at the terminal. It was envisioned to arise from vinyl Grignard addition to lactol **94**, which was constructed from the hetero-Diels-Alder adduct **92** between aldehyde **90** and Danishefsky's diene **91**. Aldehyde **90** can subsequently be obtained from the oxidative cleavage of di-protected homoallylic alcohol **89** (Scheme 4.14).



Scheme 4.14 Retrosynthetic analysis of fragment **B**

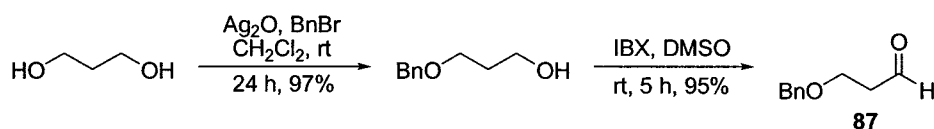
Fragment **C** is a *syn* 1,3-diol with a masked aldehyde functionality as a benzyl ether at one end and a methyl ketone at the opposite terminal. It can be seen to arise from an additional diastereoselective allylation to aldehyde **90**, (a key intermediate in the synthesis of fragment **B**) followed by Wacker oxidation of terminal olefin **99** (Scheme 4.15).



Scheme 4.15 Retrosynthetic analysis of fragment **C**

4.3.2 Synthesis of Fragment B

The preparation of key building block **B** began with the mono benzyl ether protection of 1,3-propanediol followed by 2-iodoxybenzoic acid (IBX) oxidation¹¹⁷ to afford 3-(benzyloxy)propanal **87** in excellent yield of 95% (only 2% of benzaldehyde was detected). Previous attempt to oxidize 3-(benzyloxy)propan-1-ol with pyridinium chlorochromate¹¹⁸ resulted in lower yields (60%) due to substantial acidic cleavage of the benzyl ether protecting group and subsequent oxidation to benzaldehyde.



Scheme 4.17 Synthesis of 3-(benzyloxy)propanal

The introduction of the first chiral centre was attempted using the chiral (*R*)-BINOL-InCl₃ complex and the chiral (*R,R*)-PYBOX-In(OTf)₃ complex¹¹⁹ developed in our laboratory for the asymmetric allylation of 3-(benzyloxy)propanal **87**. The yields and enantioselectivities of the allylation product (*R*)-1-(benzyloxy)hex-5-en-3-ol **88** obtained were 64% and 88% ee (Table 4.1 entry 1) and 70% and 80 % ee (entry 2) for the (*R*)-BINOL-InCl₃ complex and the chiral (*R,R*)-PYBOX-In(OTf)₃ complex respectively. Unfortunately, when we attempt to carry the asymmetric allylation on a larger scale (10 mmol), the yield remained the almost same, however, the enantioselectivity was reduced to 51% ee with the (*R*)-BINOL-InCl₃ complex (entry 3). Similar result was also obtained for the (*R,R*)-PYBOX-In(OTf)₃ complex (entry 4).

¹¹⁷ (a) Frigerio, M.; Santagostino, M. *Tetrahedron Lett.* **1994**, 35, 8019. (b) Frigerio, M.; Santagostino, M.; Sputore, S. *J. Org. Chem.* **1999**, 64, 4537.

¹¹⁸ (a) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647. (b) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 2641.

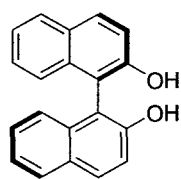
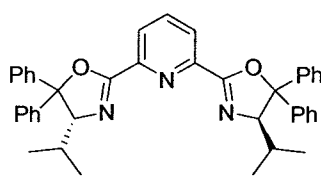
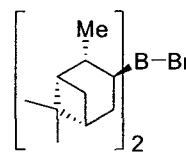
¹¹⁹ Teo, Y. C.; Tan, K. T.; Loh, T. P. *Chem Commun.* **2005**, 1318. (b) Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, 7, 2539. (c) Lu, J.; Ji, S. J. Teo, Y. C.; Loh, T. P. *Org. Lett.* **2005**, 7, 159.

Eventually, we found Brown's allylation,¹²⁰ employing the bromide derivative to be most desirable protocol, yielding 60% of the homoallylic alcohol with 98% ee (entry 6). Moreover, the reaction can be carried on a large scale (20 mmol).

¹²⁰ (a) Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc.* **1983**, *105*, 2092. (b) Brown, H. C.; Jadhav, P. K. *J. Org. Chem.* **1984**, *49*, 4089. (c) Brown, H. C.; Jadhav, P. K.; Bhat, K. S.; Perumal, T. *J. Org. Chem.* **1986**, *51*, 432. (d) Brown, H. C.; Bhat, K. S.; Randad, R. S. *J. Org. Chem.* **1987**, *52*, 319. (e) Brown, H. C.; Randad, R. S.; Bhat, K. S. *J. Org. Chem.* **1989**, *54*, 1570. (f) Brown, H. C.; Randad, R. S.; Bhat, K. S.; Zaidlewicz, M.; Racherla, U. S. *J. Am. Chem. Soc.* **1990**, *112*, 2389.

Table 4.1 Various allylation methods to synthesize (*R*)-homoallylic alcohol.

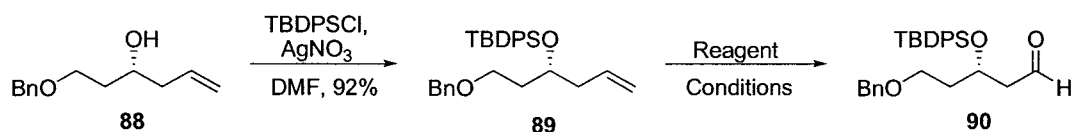
Entry	Reagent	Conditions	Yield (%)	Ee (%)
1	InCl ₃ (20mol%), allyltributylstannane (2 equiv), (<i>R</i>)-BINOL ^c (22mol%), 4Å MS	-78 °C to rt	64	88 ^a
2	In(OTf) ₃ (20mol%), allyltributylstannane (1.2 equiv), (<i>R,R</i>)-PYBOX ^d (22mol%), TMSCl (1.2equiv.), 4Å MS	-60 °C	70	80 ^a
3	InCl ₃ (20mol%), allyltributylstannane (2 equiv), (<i>R</i>)-BINOL (22mol%), 4Å MS	-78 °C to rt	57	51 ^b
4	In(OTf) ₃ (20mol%), allyltributylstannane (1.2 equiv), (<i>R,R</i>)-PYBOX ^d (22mol%), TMSCl (1.2equiv.), 4Å MS	-60 °C	61	46 ^b
5	(+)-DIP-OMe ^e , allylMgBr, THF	-78 °C	62	75 ^a
6	(+)-DIP-Br ^e , allylMgBr, THF	-78 °C	60	98 ^g

^aReaction was carried out on 0.5 mmol scale.^bReaction was carried out on 10 mmol scale.^gReaction was carried out on 20 mmol scale.^d(*R*)-BINOL^e(*R,R*)-PYBOX^f(+)-DIP-Br

The protection of (*R*)-1-(benzyloxy)hex-5-en-3-ol **88** proceeded smoothly with silver(I) nitrate and *tert*-butyldiphenylsilylchloride (TBDPSCl), however the subsequent ozonolysis of the protected alkene **89** upon treatment with ozone and

dimethyl sulfide reduction yielded only 50% of product **90** (Table 4.2 entry 1) together with small amounts of starting material and other side products. Several attempts to improve the yield with other reducing agents like triphenylphosphine (entry 3) and zinc (entry 4) was not met with success either. Moreover, the use of triphenylphosphine as reducing agent proved to be a problem at the purification stage of the aldehyde **90**. Albeit after flash chromatography, the aldehyde was often contaminated with some remnant triphenylphosphine residues. The low yield at this early stage of the synthesis prompted us to focus our attention to the one pot osmium tetroxide-catalyzed dihydroxylation¹²¹ followed by oxidative cleavage with sodium periodate (entry 5). This method was much cleaner and gave the desired aldehyde **90** with an excellent yield of 95%.

Table 4.2 Oxidative cleavage of terminal double bond with various reagents.



Entry	Reagent	Condition	Yield (%) ^a
1	O ₃ , Me ₂ S (5 equiv), CH ₂ Cl ₂	-78 °C to rt	51
2	O ₃ , Me ₂ S (10 equiv), CH ₂ Cl ₂	-78 °C to rt	53
3	O ₃ , PPh ₃ (5 equiv), CH ₂ Cl ₂	-78 °C to rt	56
4	O ₃ , Zn (3 equiv), CH ₂ Cl ₂	-78 °C to rt	54
5	OsO ₄ (0.7 mol %), NMO (2 equiv), NaIO ₄ (2 equiv), acetone/water	rt	95

^aThe reaction was monitored using TLC to ensure most of the starting material has reacted prior to addition of the reducing agents except entry 5.

¹²¹ For reviews, see (a) Bayer, A. *Comprehensive Asymmetric Catalysis* **2004**, 2, 21. (b) Donohoe, T. J. *Synlett* **2002**, 8.

With the desired aldehyde **90** in hand, we attempted to introduce the second chiral alcohol into the molecule via the asymmetric hetero-Diels-Alder reaction between Danishefsky's diene **91** and aldehyde **90** to afford the 2,3-dihydropyran-4-one **92**. There are many chiral catalyst reported in literatures for the catalytic asymmetric hetero-Diels-Alder reaction¹²², one of the most well-known being Jacobson's (salen)Cr(III) complex **I** and **II** and the tridentate Schiff base-Cr(III) complexes **III** and **IV** which are all reactive and effective catalyst for asymmetric hetero-Diels-Alder reaction. We decided to focus on Jacobson's chiral catalysts¹²³ as complex **I** and **II** is commercially available and complexes **III** and **IV** can be synthesize easily from commercially available starting materials in three steps.

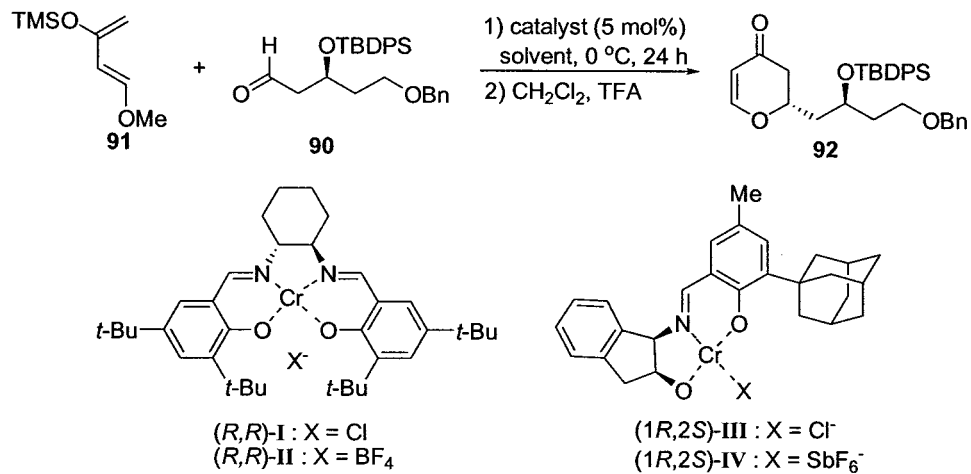
The cycloaddition between Danishefsky's diene **91** and aldehyde **90** with complexes **I-IV** was investigated and the results are shown in Table 4.3. Excellent yields and diastereoselectivities were obtained with complexes **I-IV**, in particular complex **I**, which gave the highest diastereomeric ratio of 97: 3 (Table 4.3, entry 1). The optimum reaction condition was established with 1.2 equiv. of aldehyde **90** and 1 equiv of diene **91**. Replacing the Cl⁻ counterion with BF₄⁻ counterion in complex **II**

¹²² (a) Wang, H.; Liu, X.; Xia, H.; Liu, Peng.; Gao, J.; Ying, P.; Xiao, J.; Li, C. *Tetrahedron*. **2006**, *62*, 1025. (b) Rajaram, S.; Sigman, M. S. *Org. Lett.* **2005**, *7*, 5473. (c) Du, H.; Zhang, Xue.; Wang, Z.; Ding, K. *Tetrahedron*. **2005**, *61*, 9465. (d) Zhuang, W.; Poulsen, T. B. and Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 3284. (e) Gao, B.; Fu, Z.; Yu, Z.; Yu, L.; Huang, Y.; Feng, X. *Tetrahedron*. **2005**, *61*, 5822. (f) Kwiatkowski, P.; Asztemborska, M.; Jurczak, J. *Tetrahedron: Asymmetry*. **2004**, *15*, 3189. (g) Fu, Z.; Gao, B.; Yu, Z.; Yu, L.; Huang, Y.; Feng, X.; Zhang, G. *Synlett*. **2004**, *10*, 1772. (h) Anada, M.; Washio, T.; Shimada, N.; Kitagaki, S.; Nakajima, M.; Shiro, M.; Hashimoto, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 2665. (i) Kobayashi, S.; Ueno, M.; Saito, S.; Mizuki, Y.; Ishitani, H.; Yamashita, Y. *PNAS*, **2004**, *101*, 5476. (j) Ji, B.; Yuan, Y.; Ding, K.; Meng, J. *Chem. Eur. J.* **2003**, *9*, 5989. (k) Furuno, H.; Hayano, T.; Kambara, T.; Sugimoto, Y.; Hanamoto, T.; Tanaka, Y.; Yong, Z. J. Kagawa, T.; Inanaga, J. *Tetrahedron* **2003**, *59*, 10509. (l) Bolm, C.; Verrucci, M.; Simic, O.; Cozzi, P. G.; Raabe, G.; Okamura, H. *Chem. Commun.* **2003**, 2826. (m) Hayano, T.; Sakaguchi, T.; Furuno, H.; Ohba, M.; Okawa, H.; Inanaga, J. *Chem. Lett.* **2003**, *32*, 608. (n) Du, H.; Ding, K. *Org. Lett.* **2003**, *5*, 1091. (o) Roberson, M.; Jepsen, A. S.; Jørgensen, K. A. *Tetrahedron* **2001**, *57*, 907. (p) Aikawa, K.; Irie, R.; Katsukip, T. *Tetrahedron* **2001**, *57*, 845. (q) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487.

¹²³ (a) Lucas, B. S.; Luther, L. M.; Burke, S. D. *J. Org. Chem.* **2005**, *70*, 3757. (b) Joly, G. D.; Jacobsen, E. N. *Org. Lett.* **2002**, *4*, 1795. (c) Dossetter, A. G.; Jamison, T. F.; Jacobsen, E. N. *Angew. Chem. Int. Ed.* **1999**, *38*, 2398. (d) Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749. (e) Schaus, S. E. Brånalt, J.; and Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403. (f) Thompson, C. F.; Jamison, T. F.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2001**, *123*, 9974. (g) Kwiatkowski, P.; Asztemborska, M.; Jurczak J. *Synlett*. **2004**, *10*, 1755.

gave similar diastereoselectivity (entry 3). Complexes **III** and **IV** gave slightly inferior diastereoselectivity compared to complex **I** (entry 6 and 7). Insignificant changes in diastereoselectivity were observed, when different solvents were used for the reaction with complex **III** (entries 4-6). It has been established by Jacobson *et al.* that the mechanism of the hetero-Diels-Alder reaction catalyzed by the (salen)Cr(III)-Cl complex proceeds via a concerted [4 + 2] cycloaddition pathway on the contrary to Mukaiyama aldol condensation followed by cyclization under the influence of acid catalysis.¹²⁴

¹²⁴ Schaus, S. E.; Brånalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 403.

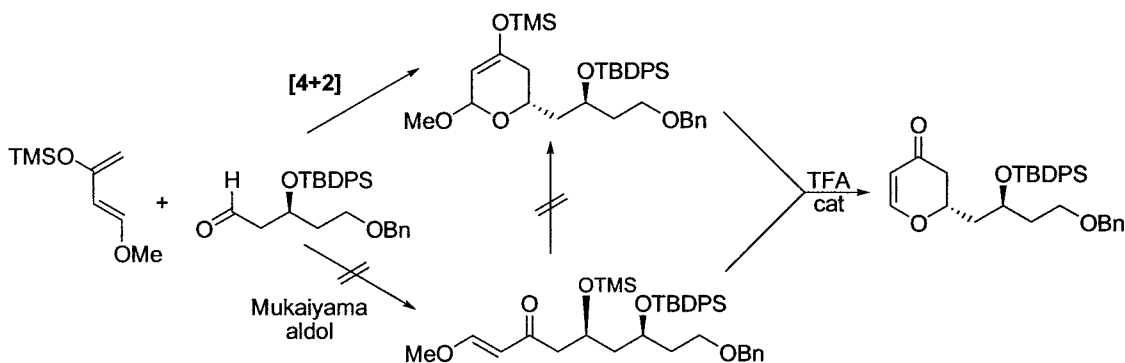
Table 4.3 Cycloaddition between Danishefsky's diene **91** and aldehyde **90** with complexes **I-IV**.

Entry	Catalyst	Solvent	Yield (%)	<i>dr</i> ^a
1	I	TBME	89	97: 3
2	I	TBME	75	85: 15 ^b
3	II	TBME	77	96: 4
4	III	Et ₂ O	76	93: 7
5	III	TBME	80	94: 6
6	III	EtOAc	83	93: 7
7	IV	TBME	86	92: 8

^aAll reactions were done with 1.2 equiv. aldehyde **90** and 1 equiv diene

91. ^bReaction was done with 1 equiv. aldehyde **90** and 1.2 equiv. diene

91.



Scheme 4.18 [4 + 2] cycloaddition pathway on the contrary to Mukaiyama aldol condensation

Luche reduction¹²⁵ with CeCl_3 is known to be efficient for the regioselective 1,2–instead of 1,4–reduction of α -enones by NaBH_4 in methanol solution. As excellent stereo-control was achieved in the hetero-Diels-Alder step ($dr = 97:3$), the *syn* isomer was obtained exclusively in the reduction step. The reaction mixture was quenched and the crude alcohol was immediately subjected to protection with TBDPSCl to afford dihydropyran **93**.

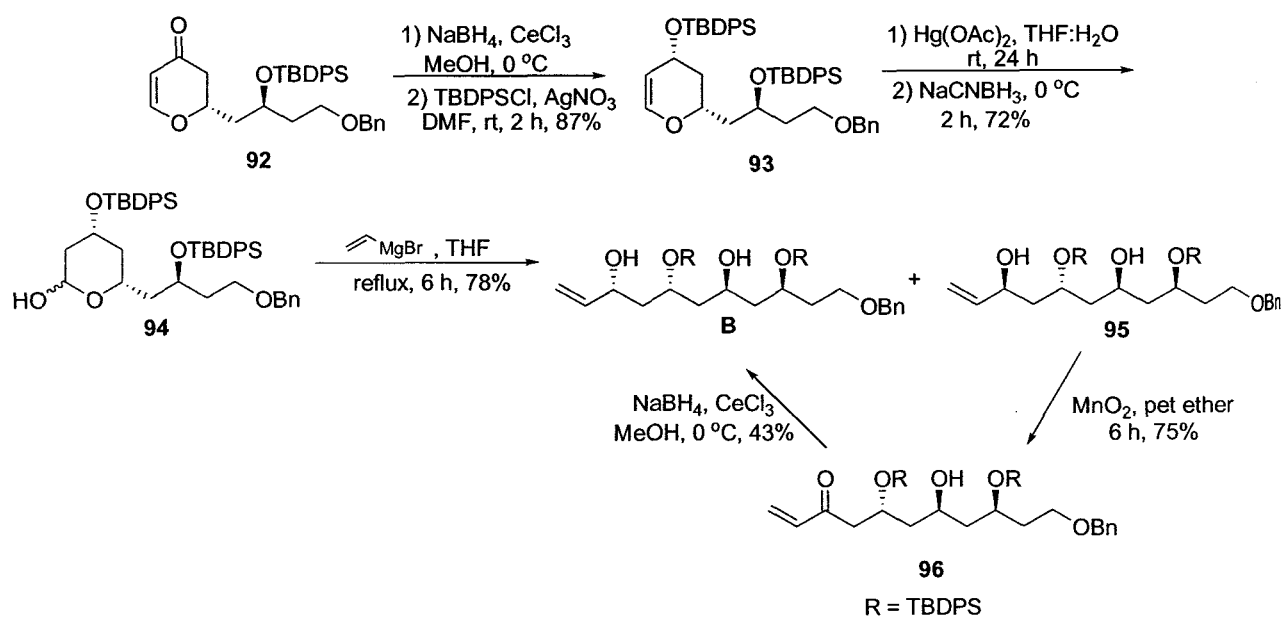
Danishefsky first reported the oxymercuration of dihydropyrene in methanol to afford β -methoxy ketone.¹²⁶ Using this strategy, oxymercuration of the functionalized dihydropyran **93** in THF: H_2O (1:1) was carried out to afford the corresponding lactol **94**. The oxymercuration reaction with mercuric(II) acetate proceeded smoothly and the intermediate was subsequently demercurated with sodium cyanoborohydride via a radical process to afford the corresponding lactol **94**. Vinylation with vinyl magnesium bromide gave the allylic alcohol as a one to one mixture of the desired fragment **B** and the undesired isomer **95**. The two isomers can be separated via flash chromatography and undesired isomer can be converted to the

¹²⁵ (a) Gemal, A. L.; Luche, J. -L. *J. Am. Chem. Soc.* **1981**, *103*, 5454. (b) Luche, J. L.; Gemal, A. L. *J. Am. Chem. Soc.* **1979**, *101*, 5848. (c) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226. (d) Luche, J. L., Rodriguez-Hahn, L.; Crab, M. P. *Chem. Commun.* **1978**, 601. (e) Gemal, A. L.; Luche, J. L. *J. Org. Chem.* **1979**, *44*, 4187.

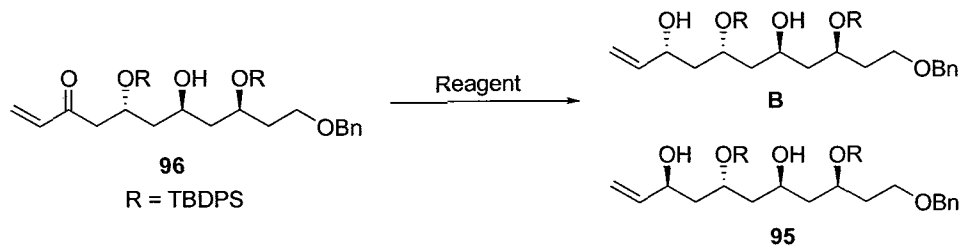
¹²⁶ Danishefsky, S.; Maring, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 2455.

desired isomer via an allylic oxidation to the α,β unsaturated ketone and a regioselective 1,2-reduction back to the alcohol **B** (Scheme 4.19).

In the attempts to improve the selectivity of the 1,2-reduction of the α,β -unsaturated ketone **96**, we screened various reducing agents like diisobutylaluminium hydride, lithium aluminium hydride and Luche reagent. The reduction proceeded sluggishly with diisobutylaluminium hydride while substantial side products were observed with lithium aluminium hydride reduction. Luche reduction proceeded rapidly and cleanly, however, no selectivity was observed with all the reducing agents (Table 4.4). The 1,3 bulky *O*-TBDPS protecting group is probably too far away to cause any steric facial blocking and it prevents 1,3-chelation, hence, leading to no selectivity.



Scheme 4.19 Synthesis of Fragment **B**

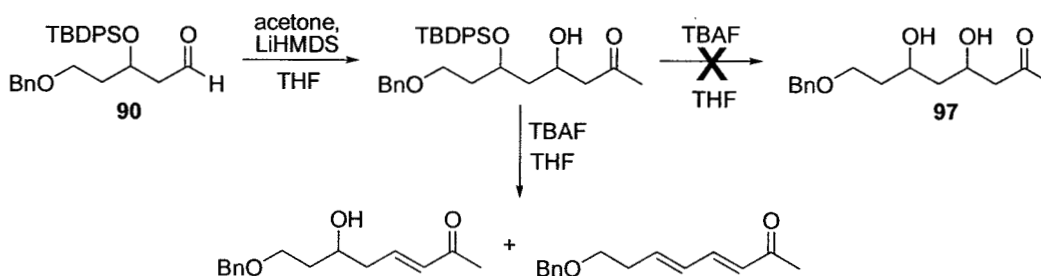
Table 4.4 1,2-reduction with various reagent.

Entry	Reagent	Selectivity ^a B : 95	Yield (%)
1	DIBAL-H, CH ₂ Cl ₂	1:1	54
2	LiAlH ₄ , THF	1:1	66
3	CeCl ₃ , NaBH ₄ , MeOH	1:1	86

^aDetermine by ¹³C NMR.

4.3.3 Synthesis of Fragment C

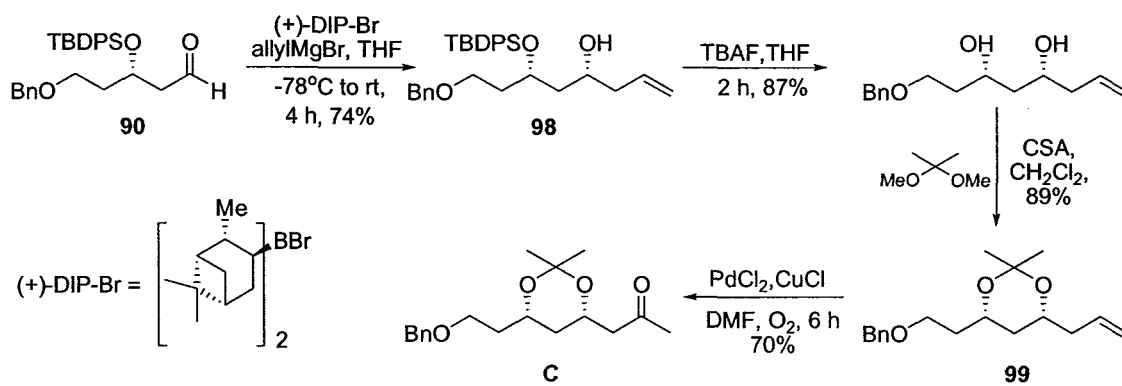
The racemic synthesis of fragment **C** proceeded smoothly via a direct aldol reaction with acetone to aldehyde **90**, which was previously employed in the synthesis of fragment **B**. However, when we attempt to remove the *tert*-butyldiphenylsilyl protecting group in the second step, elimination products were always obtained instead of the desired diol **97** (Scheme 4.20). The *tert*-butyldiphenylsilyl removal proceeded sluggishly with HF-pyridine and the elimination products were always obtained with either tetrabutylammonium fluoride (TBAF) or TBAF/acetic acid to afford the undesired α,β unsaturated ketone. Hence, we decided to abandon this strategy and adopt the alternative route (shown in Scheme 4.21) instead.



Scheme 4.20 Elimination products obtained instead of the desired diol

Excellent diastereomeric ratio of 96:4 was achieved when aldehyde **90** was subjected to a second Brown's allylation. The homoallylic alcohol **98** was further subjected to TBAF for the removal of the secondary TBDPS protected alcohol. This time no elimination product was obtained. The 1,3 diol was subsequently protected as an acetonide **99** followed by Wacker oxidation¹²⁷ to afford the desired Fragment **C** as a single isomer (Scheme 4.22).

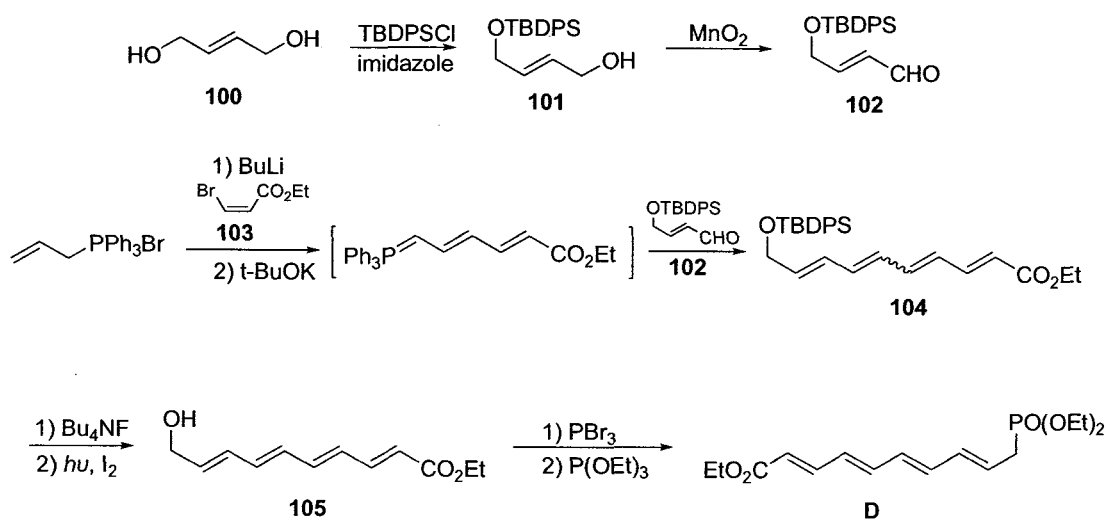
¹²⁷ (a) Tsuji, J. *Synthesis* **1983**, 369.



Scheme 4.21 Alternative synthesis of fragment C

4.3.4 Synthesis of Fragment D

As for the synthesis of fragment **D**, we elected to employ the synthetic route designed by Mori *et al* (Scheme 4.22).¹²⁸ Monoprotection of *trans*-butene-1,4-diol **100**¹²⁹ with *tert*-butyldiphenylchlorosilane and oxidation with MnO₂ gave the unsaturated aldehyde **102**. The Wittig reaction of **102** with Vedejs reagent **103**¹³⁰ gave the unstable tetraene ester **104** as a mixture of *E* and *Z* isomers after quick purification by flash chromatography. The tetraene gradually decomposed on standing to liberate *tert*-butyldiphenylsilanol. Immediate desilylation and subsequent photochemical isomerization provided the all-*trans* tetraene alcohol **105** in 63% overall yield. Finally, bromination of the alcohol with PBr₃ and reaction with triethyl phosphite gave the desired tetraene phosphonate **D**.

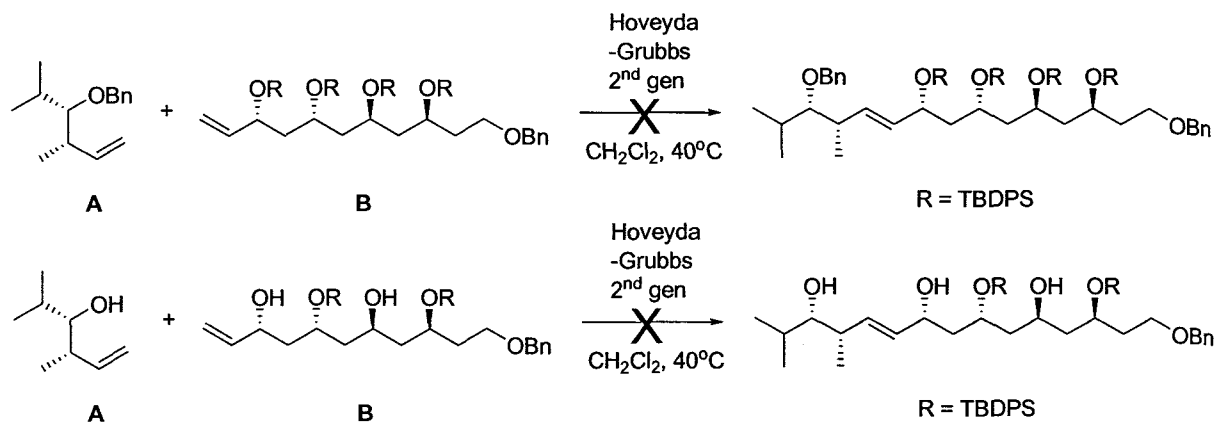
Scheme 4.22 Synthesis of fragment **D**¹²⁸ Mori, Y.; Asai, M.; Kawade, J.-I.; Furukawa, H. *Tetrahedron* **1995**, *51*, 5315¹²⁹ Miller, A. E. G.; Biss, J. W.; Schwartzman, L. H. *J. Org. Chem.* **1969**, *24*, 627.¹³⁰ Vedejs, E.; Bershas, J. P. *Tetrahedron Lett.* **1975**, *16*, 1359.

4.3.5 Coupling of Fragment A and B

With the four individual fragments in hand, we began coupling of the modules together for the synthesis of RK-397. The first coupling involves the assembly of fragment **A** with **B** via an intermolecular cross-metathesis. Since the development of ruthenium-carbene complexes¹³¹, intermolecular cross-metathesis has exhibited tremendous applicability on total synthesis of complex molecule. It is true for large molecular fragments, there may be several limitations such as poor reactivity, steric hinderance, self coupling and polymerization. Nevertheless, this direct method of forming the cross metathesis product is still a worthy attempt because of its ease of use and its elegance in using lesser number of steps to obtain the desired product.

Our initial strategy was to couple fragment **A** with the fully protected form of **B**. However, no desired coupled product was obtained. We rationalized it was probably due to the steric bulk of the TBDPS which prevented the two fragments from coupling together. We also tried to couple the unprotected form of homoallylic alcohol **A** with **B** as well. To our dismay, the second strategy did no work either (Scheme 4.23).

¹³¹ (a) Chatterjee, A. K.; Choi, T. -L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360. (b) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. *J. Organomet. Chem.* **2001**, *634*, 216. (c) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Busmann, D. A.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 58. (d) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939. (e) Chatterjee, A. K.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 1751.



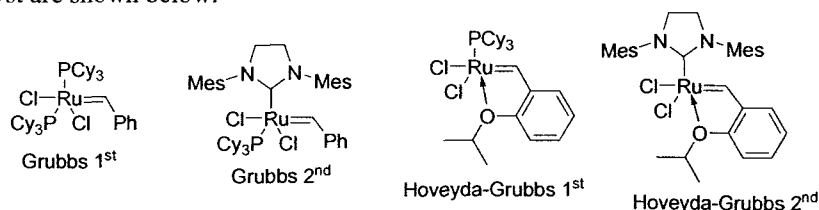
Scheme 4.23 Unsuccessful attempts with intermolecular cross-metathesis

We realized that in order to do a cross metathesis successfully, careful choice of substrate is required. The most selective cross metathesis involves the coupling of a more reactive type I olefin with a less reactive type II olefin.¹³² Hence, we decided to carry out the cross metathesis with fragment A (type I olefin: terminal alkene) and the unprotected secondary allylic alcohol B (type II olefin: secondary allylic alcohol) with a series of different catalyst and reaction conditions. The results are shown in Table 4.5.

All the catalyst¹³³ failed to give any cross metathesis product **106** (Table 4.5, entries 1-4) except for the Hoveyda-Grubbs 2nd generation catalyst which gave the best yield of 52% when the catalyst was dissolved in dichloromethane and added dropwise to the refluxing reaction mixture over 30 minutes (entry 7). The low yield was caused by significant amounts of self-coupled and polymerized side products. An attempt to reduce the amount of undesired side products by carrying out the reaction at room

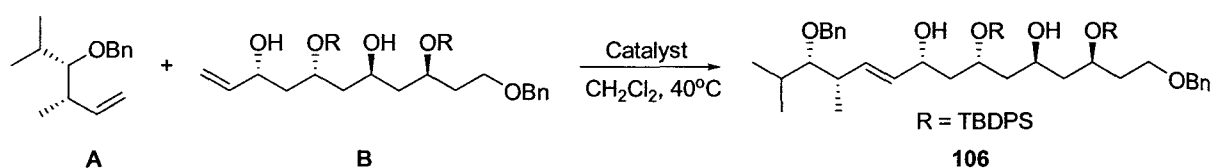
¹³² Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. *J. Am. Chem. Soc.* **2003**, *125*, 11360.

¹³³ The catalyst are shown below:



temperature only resulted in low conversion, with significant amounts of unreacted starting materials remaining (entry 6). We tried to accelerate the cross metathesis by operating at higher reaction concentration (entry 9) and higher catalyst loading (entry 11), however, it led to formation of more undesired side products. Beneficial effect was observed when the catalyst was added slowly in portions instead of one portion at the beginning (entry 5) probably due to slower rate of catalyst decomposition. Attempts to increase the yield with ruthenium scavengers to quench the catalyst after the reaction did not meet with any success either (entry 10).

Table 4.5 Cross metathesis with fragment A and B.



Entry	Catalyst	Conditions	Yield (%) ^a
1	Grubbs 1 st	40 °C, 12 h Catalyst added in 1 portion	0
2	Grubbs 2 nd	40 °C, 12 h Catalyst added in 1 portion	0
3	Grubbs 2 nd	40 °C, 36 h Catalyst added in 1 portion	< 10 % conversion
4	Hoveyda-Grubbs 1 st	40 °C, 12 h Catalyst added in 1 portion	0
5	Hoveyda-Grubbs 2 nd	40 °C, 12 h Catalyst added in 1 portion	33
6	Hoveyda-Grubbs 2 nd	rt, 24 h Catalyst added in 1 portion	15
7	Hoveyda-Grubbs 2 nd	40 °C, 6 h Catalyst added over ½ h	52
8	Hoveyda-Grubbs 2 nd	40 °C, 6 h Catalyst added over 1 h	48
9	Hoveyda-Grubbs 2 nd	40 °C, 12 h Catalyst added over ½ h 0.5 M reaction conc.	40
10	Hoveyda-Grubbs 2 nd	40 °C, 6 h Catalyst added over ½ h 10 mol % catalyst	44

^aUnless otherwise specified, all reactions were carried out in oven dried glassware with 1 equiv of **B** and 2 equiv of **A** with 5 mol % catalyst loading. Dichloromethane was degassed with argon. The reaction was quenched when all of **B** has reacted. *Cis/trans* ratio of 10:90 was obtained.

With the coupling of fragment **A** and **B** successfully completed, we turned our attention to the next key aldol reaction with fragment **C**. However, before we proceed with this aldol coupling, there is a need to selectively deprotect the primary *O*-benzyl ether at C19 instead of the secondary benzyl ether at C31, revealing the primary alcohol for Dess-martin oxidation to the aldehyde function at C19. The cross metathesis product **106** was therefore subjected to alcohol protection with *tert*-butyldiphenylsilyl chloride. The selective deprotection of the primary benzyl ether of **107** proved to be more tedious than usual. Unsuccessful attempts were made with BCl_3 ¹³⁴, $\text{BF}_3 \cdot \text{OEt}_2 / \text{NaI}$ ¹³⁵ and Li/naphthalene ¹³⁶, with majority starting material remaining (Table 4.6, entries 1-3).

Eventually, we decided to focus on lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)¹³⁷ (entry 4). Careful control in the course of the reaction has to be made to ensure cleavage of the primary benzyl ether but not the secondary. After the substrate **107** was dissolved in anhydrous THF and cooled to $-78\text{ }^\circ\text{C}$, the 1 M forest green LDBB solution was added dropwise very slowly to the reaction mixture. Each drop of LDBB would turn the colorless reaction mixture green which changes to red on vigorous stirring. The reaction mixture was monitored by TLC with every equiv. of LDBB added until there is little starting material remaining and quenched with saturated aq NH_4Cl and saturated aq NaHCO_3 solution. There is usually a very small amount of the di-deprotected alcohol isolated, despite the dilute reaction condition. After purification of the product **108** with flash column chromatography, Dess

¹³⁴ Williams, D. R.; Brown, D. L.; Benbow, J. W. *J. Am. Chem. Soc.* **1989**, *111*, 1923.

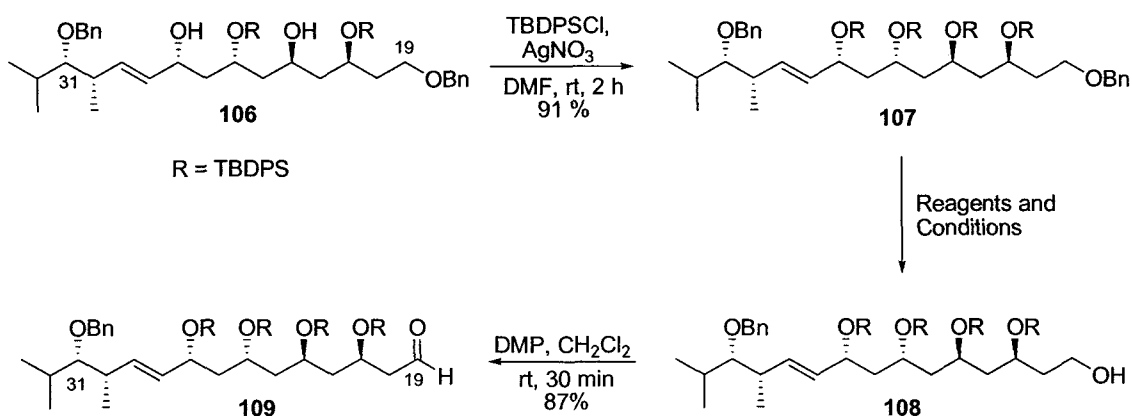
¹³⁵ Vankar, Y. D.; Rao, C. T. *Chem. Res. Synop.* **1985**, 232.

¹³⁶ Alonso, E.; Ramon, D. J.; Yus, M. *Tetrahedron* **1997**, *53*, 14355.

¹³⁷ (a) Shimshock, S. J.; Waltermire, R. E.; DeShong, P. *J. Am. Chem. Soc.* **1991**, *113*, 8791. (b) Cohen, T.; Jeong, I. -H.; Mudryk, B.; Bhupathy, M.; and Awad, M. M. A. *J. Org. Chem.* **1990**, *55*, 1528. (c) Smith, A. B., III; Safonov, I. G.; Corbett, R. M. *J. Am. Chem. Soc.* **2002**, *124*, 11102.

Martin¹³⁸ oxidation proceeded smoothly with the primary alcohol to afford the aldehyde **109** in excellent yield.

Table 4.6 Selective removal of primary benzyl ether.



Entry	Reagents	Conditions	Yield (%)
1	BCl ₃ , CH ₂ Cl ₂	-78 °C, 24 h	10 ^a
2	BF ₃ OEt ₂ /NaI, CH ₂ Cl ₂	-78 °C, 24 h	12 ^a
3	Li/naphthalene, THF	-78 °C, 24 h	23 ^a
4	LiDBB, THF	-78 °C	70 ^b

^aSubstantial amounts of starting material remains even though more than 5 equiv of reagents are added.

^bReaction was monitored by TLC to ensure most of the starting material has reacted before the reaction was quenched.

¹³⁸ (a) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277. (b) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899. (c) Meyer, S. D.; Schreiber, S. L. *J. Org. Chem.* **1994**, *59*, 7549.

4.3.6 Coupling to Fragment C and D

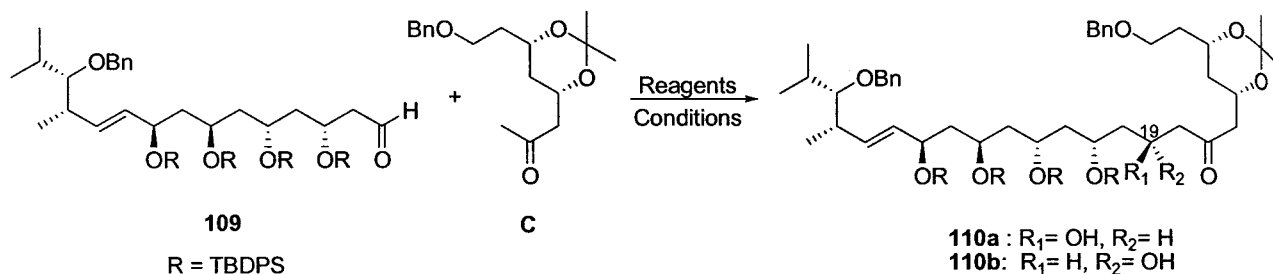
The use of boron enolates of methyl ketones for asymmetric aldol reactions has become a powerful tool for the total synthesis of polyketide natural products, particularly those of propionate origin. High levels of asymmetric 1,5-*anti* aldol induction has been observed with methyl ketone enolates that contain a β -alkoxy substituent. The nature of the β -alkoxy substituent is critical in determining the level of induction as, usually, the use of benzylic (OBn, OPMB), acetonide or benzyldiene acetal gave the highest selectivity whereas the use of silicon protecting groups often give rise to little or no selectivity.

The choice of β -alkoxy substituent in our methyl ketone fragment C, in this case, the acetonide protecting group seemed appropriate enough and we would expect high levels of selectivity to be achieved in our 1,5-*anti* aldol coupling with C. Unfortunately, the selectivity of the *anti*-aldol adduct **110a** could not be improved beyond 75: 25. We allow the reaction to proceed overnight at -78 °C as there were still substantial amounts of unreacted starting material if we were to quench the reaction prematurely. The choice of bases and solvents were irrelevant in this case as both made no difference to the selectivity (Table 4.7 entries 1-4). The aldol reaction of the lithium enolate of C, generated by LiHMDS in THF afforded the aldol adduct in very low yield, hence, the selectivity was not determined (entry 5). Despite the excellent selectivity achieved with chiral boron enolate generated from (+)-DIP-Br (entry 6) and (-)-DIP-Br (entry 7) *via* triple asymmetric induction,¹³⁹ the yields were very low, especially with (-)-DIP-Br which gives the desired isomer **110a** in only 15 % yield. Therefore, we decided to keep to the original *n*-Bu₂BOTf reagent

¹³⁹ (a) Duplantier, A. J.; Nantz, M. H.; Roberts, J. C.; Short, R. P.; Somfai, P.; Masamune, S. *Tetrahedron Lett.* **1989**, *30*, 7357. (b) Roush, W. R. *J. Org. Chem.* **1991**, *56*, 4151.

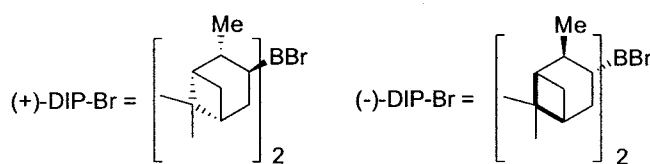
although it gives a better yield with poorer selectivity. The desired isomer can be separated cleanly from the undesired isomer via flash column chromatography.

Table 4.7 Aldol coupling with various reagents



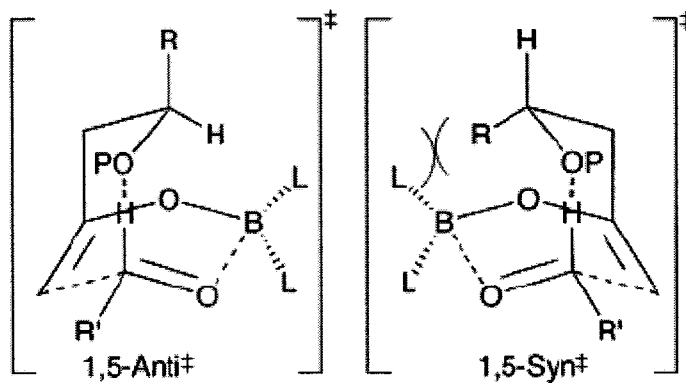
Entry	Reagents	Condition	110a : 110b	Yield (%)
1	<i>n</i> -Bu ₂ BOTf, <i>i</i> -Pr ₂ NEt CH ₂ Cl ₂	-78 °C, 16 h	75:25	73
2	<i>n</i> -Bu ₂ BOTf, <i>i</i> -Pr ₂ NEt Et ₂ O	-78 °C, 16 h	75:25	69
3	<i>n</i> -Bu ₂ BOTf, Et ₃ N CH ₂ Cl ₂	-78 °C, 16 h	75:25	66
4	<i>n</i> -Bu ₂ BOTf, Et ₃ N Et ₂ O	-78 °C, 16 h	75:25	67
5	LiHMDS, THF	78 °C for 16 h, 0 °C for 2h	-	19
6	(+)-DIP-Br, Et ₃ N Et ₂ O	-78 °C for 16 h, 0 °C for 2h	> 5:95	35
7	(-)-DIP-Br, Et ₃ N Et ₂ O	-78 °C for 16 h, 0 °C for 2h	> 95:5	15

^aReactions were carried out with 1 equiv. of aldehyde and 1.2 equiv of methyl ketone.



The configuration at C19 was confirmed to be *S* by comparing the results of the chiral boron enolates (entry 6 and 7) where the aldol product from (-)-DIP-Br¹⁴⁰ corresponds to the major diastereomer **110a** obtained from the reaction with *n*-Bu₂BOTf. Stereochemical outcome of similar systems have also been confirmed by Evans *et al.*¹⁴¹

The origins of remote asymmetric induction in the boron aldol reactions of β -alkoxy methyl ketones has recently been discussed by Goodman¹⁴² *et al* through theoretical studies which showed the boron aldol reactions of methyl ketones proceed via a boat transition structure. A stabilizing hydrogen bond between the alkoxy oxygen and formyl proton leads to preferential formation of the 1,5-adduct, by minimizing steric interactions between the β -alkyl group and one of the ligands on boron. On the contrary, 1,5-*syn* adduct is disfavored due to significant steric interactions between the β -alkyl group and one of the ligands on boron.

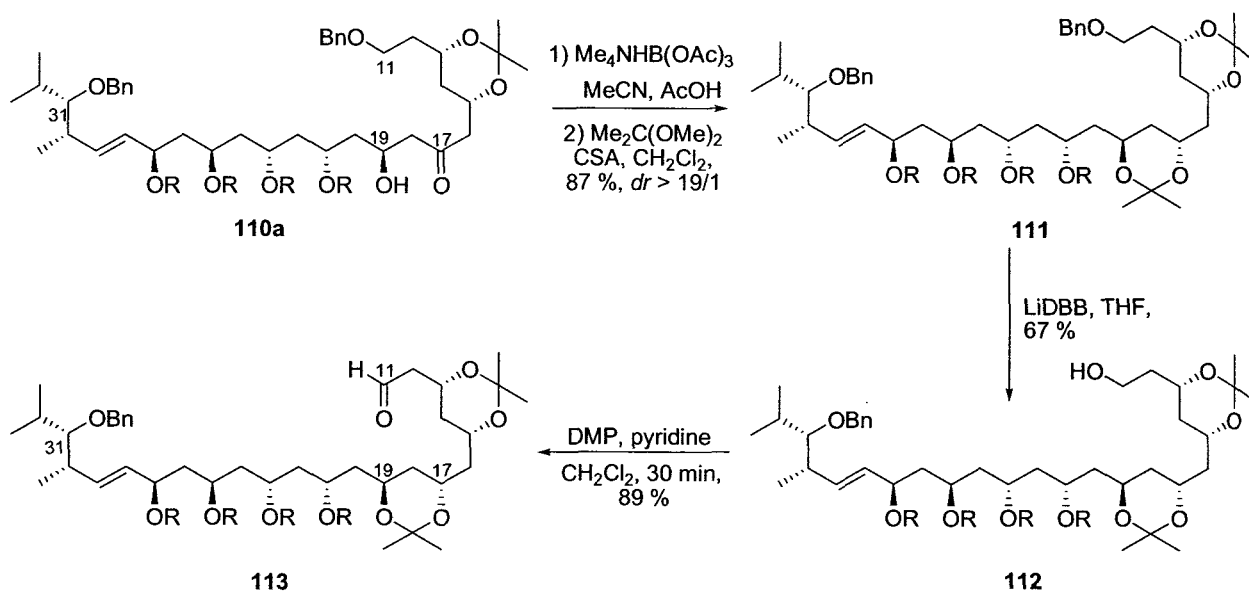


¹⁴⁰ (a) Paterson, I; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512. (c) Seco, J. M.; Quinoa, E.; Riguera, R. *Chem. Rev.* **2004**, *104*, 17.

¹⁴¹ Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.

¹⁴² (a) Paton, R. S.; Goodman, J. M. *Org. Lett.* **2006**, *8*, 4299. (b) Stocker, B. L.; Teesdale-Spittle, P.; Hoberg, J. O. *Eur. J. Org. Chem.* **2004**, 330.

The carbonyl group at C17 was reduced using tetramethylammonium triacetoxyborohydride, and the resulting *anti*-diol was protected as an acetonide **111**.¹⁴³ The stage was now set to introduce the polyene fragment which required unveiling the primary benzyl ether protecting group to reveal the aldehyde **113** at C11 as described previously, via a selective deprotection to **112** and oxidation by DMP reagent to aldehyde **113** (Scheme 4.24).

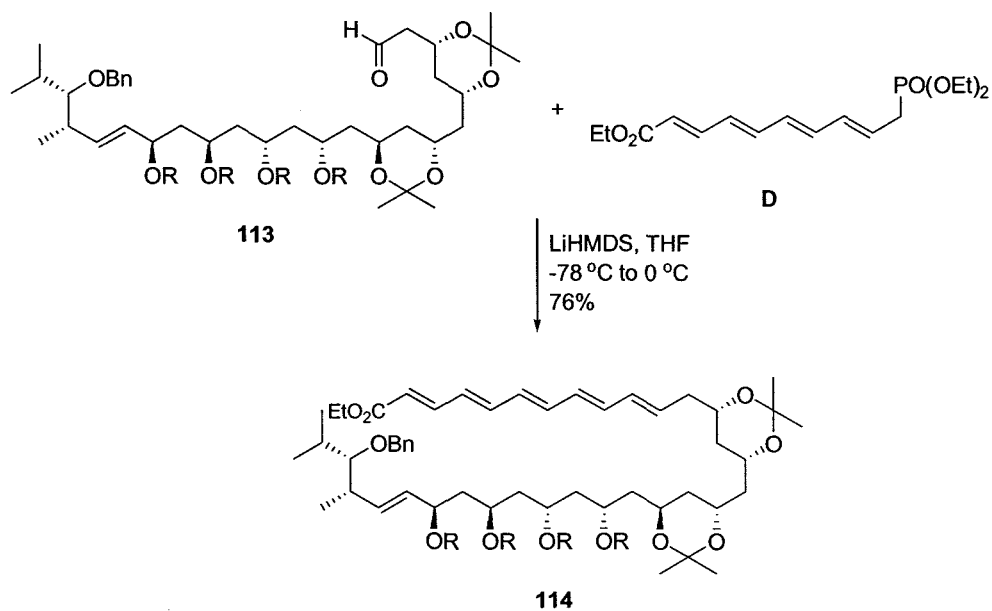


Scheme 4.24 Synthesis of C11 to C31 polyol subunit of RK-397

Removal of the secondary benzyl ether protected alcohol with LiDBB failed to afford the desired hydroxyl aldehyde. The presence of the aldehyde functionality probably caused complication in the reaction and a series of close spots were seen on the TLC, rendering isolation and identification of the product impossible. Hence, we decided to bring the final fragment coupling of the polyene phosphonate **D** and the polyol chain **113** together using the standard Horner-Wadsworth-Emmons olefination protocol before removal of the secondary benzyl ether protecting group. The olefination proceeded smoothly with the aid of LiHMDS to afford pentaenoate **114** in

¹⁴³ (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.

good yield (Scheme 4.25). However, when we tried to remove the secondary benzyl protecting group in **114** with LiDBB, the substrate decomposed under the reaction conditions probably due to the presence of the conjugated polyene chain.



Scheme 4.25 Coupling of the phosphonate and the polyol chain

4.4 CONCLUSION

In conclusion, C1 to C31 fragment of RK-397 was synthesized via a convergent synthetic strategy that features the use of asymmetric Brown's allylation and crotylation, catalytic enantioselective hetero-Diels–Alder protocol employing the Cr(III)-Salen complex, and a 1,5 *anti*-stereo induction by substrate-controlled dibutylboron enolate aldol addition for absolute control of the 10 chiral centres in the polyol chain. The synthesis also demonstrated a successful intermolecular cross-metathesis between two elaborate molecular fragments. As excellent enantio- and diastereo-control was achieved during the synthesis, including isolation of desired isomer via column chromatography, a single isomer of **114** was isolated towards the end of the synthesis. Future work for RK-397 will include the use of an alternative alcohol protecting group such as *p*-methoxy benzyl ether at C31 to facilitate suitable deprotection conditions at the end for the total synthesis of RK-397. An alternative strategy will be the removal of both benzyl ether protecting group at C31 and C11 followed by a selective oxidation of the primary alcohol at C11 with TEMPO-mediated oxidation. With the aldehyde at C11 and alcohol functionality at C31 in hand, standard Horner-Wadsworth-Emmons olefination followed by Yamaguchi macrolactonization protocol can be performed. Final deprotection of the TBDPS protected alcohol and the acetonides can be carried out with TBAF and HCl respectively to afford the final RK-397 antibiotic.

CHAPTER 5

Experimental Section

5.1 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. Reaction 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 °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 °C using Büchi rotary evaporator cooled with circulating ethylene glycol / water mixture (1:1) at -5 °C.

Materials

Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.¹⁴⁴ 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

¹⁴⁴ Perrin, D. D. and Armarego, W. L. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford, 1988.

from sodium and benzophenone. Anhydrous dichloromethane was distilled 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 °C and re-distilled. 2-Bromoacrolein,¹⁴⁵ 7-methoxy-4-vinyl-1,2-dihydro-naphthalene¹⁴⁶ and 3-vinyl-1*H*-indene was prepared according to literature procedures.¹⁴⁷

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. 3M sodium hydroxide solution was prepared from sodium hydroxide pearls. 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 F₂₅₄ pre-coated silica gel plates (0.25 mm thickness). Visualization was accomplished with UV light (254 nm) and iodine crystals, KMnO₄ or ceric molybdate solution followed by heating on a hot plate.

¹⁴⁵ (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.

¹⁴⁶ Woski, S. A.; Koreeda, M. *J. Org. Chem.* **1992**, *57*, 5736.

¹⁴⁷ 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/CH₂Cl₂ 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 Shimadzu IR Prestige-21 FT-IR Spectrometer. Solid samples were analyzed as a KBr pressed-disk while liquid samples were either examined neat between NaCl salt plates or as a solution in dichloromethane using NaCl liquid cells.

Optical Rotation

Optical rotation was measured using a JASCO P-1030 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 spectrometry was performed by the staffs in the Division of Chemistry and Biological Chemistry of Nanyang Technological University. MS (EI) spectra were

recorded on a Thermo Finnigan Polaris Q GCMS. MS (ESI and APCI) spectra were recorded on a Thermo Finnigan LCQ Deca XP Max. HRMS (EI, ESI, FAB) spectra were recorded on a Thermo Finnigan MAT 95 XP. MS and HRMS were reported in units of mass of charge ratio (m/z).

Nuclear Magnetic Resonance Spectroscopy

Proton nuclear magnetic resonance (^1H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) spectroscopy were performed on Bruker Avance NMR spectrometers.

Chemical shifts were reported as δ in units of parts per million (ppm) downfield from tetramethylsilane (δ 0.00), using the residual solvent signal as an internal standard: deuterio chloroform-*d*, CDCl_3 (^1H 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 $n\text{H}$.

Nomenclature

Systematic nomenclature for the compounds would follow the numbering system as defined by IUPAC. Compounds were named with assistance from CS Chemdraw Ultra 9.0 software.

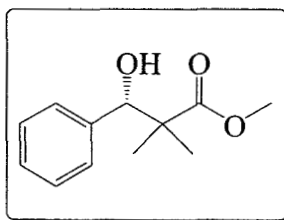
5.2 CATALYTIC ENANTIOSELECTIVE MUKAIYAMA ALDOL REACTION

Catalytic Enantioselective Mukaiyama aldol reaction of Aldehydes via a Chiral (*S,S*)-*iPr*-pybox-In(OTf)₃ complex

Representative procedure for asymmetric Mukaiyama aldol reaction of aldehydes:

Preparation of (*S*)- Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate

To an oven dried 10 mL round-bottom flask equipped with a magnetic stirring bar was added In(OTf)₃ (56.2 mg, 0.1 mmol, 0.2 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,S*)-*iPr*-pybox (**7**) (33.2 mg, 0.11 mmol, 0.22 equiv.) was added to the mixture and stirred under nitrogen at room temperature for 1 h. Benzaldehyde (0.05 mL, 0.5 mmol, 1 equiv.) was added to the resulting mixture and stirred for 10 min to afford a white suspension. The reaction mixture was then cooled to -40 °C for 15 min followed by slow addition of (1-methoxy-2-methyl-propenyloxy)-trimethylsilane (0.12 mL, 0.6 mmol, 1.2 equiv.). The reaction mixture was stirred at -40 °C for 24 h and then quenched with 5 mL saturated sodium bicarbonate solution. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic extracts was concentrated *in vacuo* and treated with a mixture of THF : 1M HCl (5ml : 1ml) solution for 20 min. The mixture was extracted with ether (3 x 10 mL), dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo*. The residual crude product was purified via silica gel chromatography to afford the β -hydroxy ester as colorless oil.

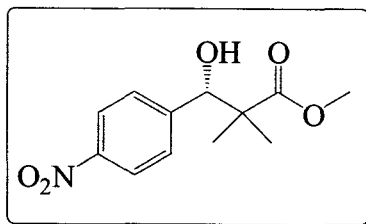
Characterization of β -hydroxyl esters**(S)-Methyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (17a)**

(65% ee)

Colorless oil (86%); $R_f = 0.28$ (EA/Hexane = 1/6). $^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.32–7.28 (m, 5H, Ar), 4.90 (d, $J = 3.81$ Hz, 1H, CHOH), 3.72 (s, 3H, OCH_3), 3.05 (d, $J = 3.81$ Hz, CHOH), 1.15 (s, 3H, CH_3), 1.12 (s, 3H, CH_3). $^{13}\text{C NMR}$ (75.4 MHz, CDCl_3): δ 178.0 (C=O), 148.0 (C), 128.7 (CH x 2), 127.6 (CH x 2), 125.3 (CH), 78.5 (CH), 51.9 (CH_3), 47.7 (C), 22.8 (CH_3), 19.0 (CH_3).FTIR (NaCl, neat): 1722, 1257, 705 cm^{-1} .HRMS (EI) Calcd. for $\text{C}_{12}\text{H}_{16}\text{O}_3$ [M^+]: 208.1099. Found: 208.1103. $[\alpha]_{\text{D}} = +13.43^\circ$ ($c = 8.43$, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 98:2, 1 mL/min: $t_1 = 13.8$ min for *S* enantiomer , $t_2 = 16.67$ for *R* enantiomer). It had been established from literature that the *S* enantiomer elutes first.¹⁴⁸

¹⁴⁸ Y.Yamashita, H.Ishitani, H. Shimizu, S. Kobayashi, *J. Am. Chem. Soc.* **2002**, *124*, 3292-3302.

(S)-Methyl 3-hydroxy-2,2-dimethyl-3-(4-nitrophenyl)propanoate (17b)

(92% ee)

Pale yellow oil (75%); ($R_f = 0.22$ (EA/Hexane = 1/4).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 8.23 (d, 2H, $J = 8.8$ Hz, Ar), 7.53 (d, 2H, $J = 8.8$ Hz, Ar), 5.01 (d, 1H, CHOH), 3.74 (s, 3H, OCH_3), 1.15 (s, 3H, CH_3), 1.13 (s, 3H, CH_3).

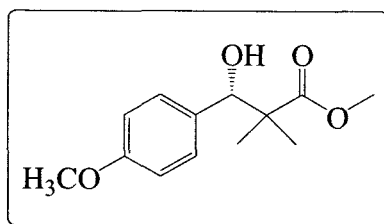
$^{13}\text{C NMR}$ (75.4 MHz, CDCl_3): δ 177.7 (C=O), 147.6 (C), 147.3 (C), 128.6 (CH x 2), 122.9 (CH x 2), 77.7 (CH), 52.3 (CH₃), 47.6 (C), 22.7 (CH₃), 19.2 (CH₃).

FTIR (NaCl, neat): 3495, 2952, 1728, 1606, 1531, 1470, 1052, 854 cm^{-1} .

HRMS (ESI) Calcd. for $\text{C}_{12}\text{H}_{16}\text{NO}_5$ $[\text{M}+\text{H}]^+$: 254.0848. Found: 254.0849.

$[\alpha]_D = +2.43^\circ$ ($c = 1.02$, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel AD-H column (Hexane : *i*-propanol 95:5, 1 mL/min: $t_1 = 14.87$ min for major enantiomer, $t_2 = 16.63$ for *minor* enantiomer).

(S)-Methyl 3-hydroxy-3-(4-methoxyphenyl)-2,2-dimethylpropanoate (17c)

(57% ee)

Colorless oil (71), $R_f = 0.15$ (EA/Hexane = 1/4).

^1H NMR (300 MHz, CDCl_3): δ 7.22 (d, $J = 8.71$ Hz, 2H, Ar), 6.86 (d, $J = 8.71$ Hz, 2H, Ar), 4.85 (s, 1H, CHOH), 3.80 (s, 3H, OCH_3), 3.72 (s, 3H, OCH_3), 1.14 (s, 3H, CH_3), 1.10 (s, 3H, CH_3).

^{13}C NMR (75.4 MHz, CDCl_3): δ 178.2 (C=O), 159.1 (C), 132.1 (C), 128.7 (CH x 2), 113.2 (CH x 2), 78.3 (CH), 55.2 (CH_3), 52.1 (CH_3), 47.8 (C), 23.0 (CH_3), 19.0 (CH_3).

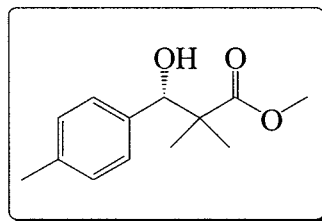
FTIR (NaCl, neat): 3448, 2977, 2952, 1703, 1515, 1254, 839, 797 cm^{-1} .

HRMS (EI) Calcd. for $\text{C}_{13}\text{H}_{15}\text{O}_4$ $[\text{M}]^+$: 238.1205. Found: 238.1204.

$[\alpha]_{\text{D}} = +16.31^\circ$ ($c = 8.41$, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel OD column (Hexane : *i*-propanol 95:5, 1 mL/min: $t_1 = 9.63$ min for major enantiomer, $t_2 = 12.80$ for *minor* enantiomer).

(S)-Methyl 3-hydroxy-3-(4-methylphenyl)-2,2-dimethylpropanoate (17d)



(65% ee)

Colorless oil (73%); $R_f = 0.35$ (EA/Hexane = 1/4).

^1H NMR (300 MHz, CDCl_3): δ 7.22 (dd, $J = 8.4$ Hz, 2H, Ar), 7.15 (dd, $J = 8.4$ Hz, 2H, Ar), 4.86 (d, $J = 4.02$ Hz, 1H, CHOH), 3.72 (s, 3H, OCH_3), 2.96 (d, $J = 4.41$ Hz, 1H, CHOH), 2.34 (s, 3H, CH_3), 1.14 (s, 3H, CH_3), 1.10 (s, 3H, CH_3).

^{13}C NMR (75.4 MHz, CDCl_3): δ 177.9 (C=O), 137.0 (C), 136.9 (C), 128.1 (CH x 2), 127.3 (CH x 2), 78.1 (CH), 51.7 (CH_3), 47.6 (C), 22.5 (CH_3), 20.8 (CH_3), 18.9 (CH_3).

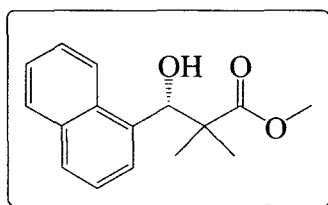
FTIR (NaCl, neat): 3444, 1716 cm^{-1} .

HRMS (EI) Calcd. for $\text{C}_{13}\text{H}_{18}\text{O}_3$ $[\text{M}]^+$: 222.1256. Found: 222.1250.

$[\alpha]_{\text{D}} = +13.82^\circ$ ($c = 6.98$, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 98:2, 1 mL/min: $t_1 = 12.63$ min for major enantiomer , $t_2 = 15.71$ for *minor* enantiomer).

(S)-Methyl 2,2-dimethyl-3-hydroxy-3-(1-naphthyl)propionate (17e)



(77% ee)

Pale yellow oil (50%); $R_f = 0.38$ (EA/Hexane = 1/4).

^1H NMR (300 MHz, CDCl_3): δ 8.15-8.17 (d, 1H, Ar), 7.79-7.86 (m, 2H, Ar), 7.66-7.69 (d, 1H, Ar), 7.43-7.52 (m, 3H, Ar), 5.92 (s, 1H, CHOH), 3.72 (s, 3H, OCH_3), 1.24 (s, 3H CH_3), 1.07 (s, 3H CH_3).

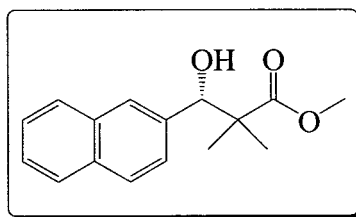
^{13}C NMR (75.4 MHz, CDCl_3): δ 178.24 (C=O), 137.45 (C), 132.97 (C), 132.79 (C), 128.01 (CH), 127.57 (CH), 127.28 (CH), 126.67 (CH), 126.04 (CH), 125.91 (CH), 125.64 (CH), 78.78 (CH), 52.15 (CH_3), 47.89 (C), 23.15 (CH_3), 19.12 (CH_3).

FTIR (KBr, neat): 3471, 2946, 1720 cm^{-1} .

HRMS (EI) Calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_3$ $[\text{M}]^+$: 258.1301. Found: 258.1241.

$[\alpha]_D = +10.21^\circ$ ($c = 6.55$, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OJ column (Hexane : *i*-propanol 98:2, 1 mL/min: $t_1 = 22.54$ min for major enantiomer , $t_2 = 29.03$ for *minor* enantiomer).

(S)-Methyl 2,2-dimethyl-3-hydroxy-3-(2-naphthyl)propionate (17f)

(76% ee)

Pale yellow oil (56%); $R_f = 0.34$ (EA/Hexane = 1/4).

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.75–7.86 (m, 4H, Ar), 7.42–7.50 (m, 3H, Ar), 5.07 (d, 1H, $J = 3.8$ CHOH), 3.74 (s, 3H, OCH_3), 3.29 (d, 1H, $J = 3.8$, OH), 1.20 (s, 3H CH_3), 1.16 (s, 3H CH_3).

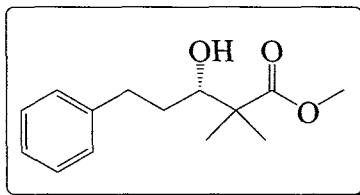
$^{13}\text{C NMR}$ (75.4 MHz, CDCl_3): δ 178.24 (C = O), 137.45 (C), 132.97 (C), 132.79 (C), 128.01 (CH), 127.57 (CH), 127.28 (CH), 126.67 (CH), 126.04 (CH), 125.91 (CH), 125.64 (CH), 78.78 (CH), 52.15 (CH_3), 47.89 (C), 23.15 (CH_3), 19.12 (CH_3).

FTIR (KBr, neat): 3350–3700, 2800–3100, 1735 cm^{-1} .

HRMS (EI) Calcd. for $\text{C}_{16}\text{H}_{18}\text{O}_3$ $[\text{M}]^+$: 258.1301. Found: 258.1241.

$[\alpha]_D = +10.03^\circ$ ($c = 6.25$, CH_2Cl_2).

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 98:2, 1 mL/min: $t_1 = 31.06$ min for major enantiomer, $t_2 = 37.64$ for *minor* enantiomer).

(S)-Methyl 3-hydroxy-2,2-dimethyl-5-phenylpentanoate (17g)

(51% ee)

Colorless oil (40%); $R_f = 0.28$ (EA/Hexane = 1/4) ^1H NMR (300 MHz, CDCl_3): δ 7.31–7.16 (m, 5H, Ar), 3.68 (s, 3H, OCH_3), 3.65–3.59 (m, 1H, CHOH), 2.70–2.55 (m, 2H, PhCH_2), 1.82–1.72 (m, 2H, PhCH_2CH_2), 1.18 (s, 3H, CH_3), 1.16 (s, 3H, CH_3). ^{13}C NMR (75.4 MHz, CDCl_3): δ 178.2 (C=O), 142.1 (C), 128.5 (CH_2), 128.4 (CH_2), 125.8 (CH), 76.1 (CH), 51.9 (CH_3), 47.1 (C), 33.6 (CH_2), 32.9 (CH_2), 22.5 (CH_3), 20.3 (CH_3).FTIR (NaCl, neat): 3497, 1722 cm^{-1} .HRMS (EI, m/z): $[\text{M}]^+$, Calcd. for $\text{C}_{14}\text{H}_{20}\text{O}_3$: 236.1412. Found: 236.1412. $[\alpha]_D = -15.06$ ($c = 3.53$, CH_2Cl_2).The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OD-H column (Hexane : *i*-propanol 98:2, 1 mL/min: $t_1 = 12.94$ min for major enantiomer, $t_2 = 21.40$ for *minor* enantiomer).

5.3 CATALYTIC ENANTIOSELECTIVE PROPARGYLATION AND ALLENYLATION OF ALDEHYDES

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 (*R*)-1-Phenylbut-3-yn-1-ol and (*R*)-1-Phenyl-buta-2,3-dien-1-ol

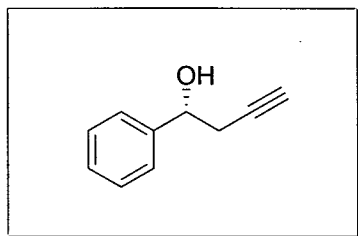
To an oven dried 5 mL round-bottom flask equipped with a magnetic stirring bar was added In(OTf)₃ (16.9 mg, 0.03 mmol, 0.20 equiv) and 4Å molecular sieve (120 mg). The solid was azeotropically dried with anhydrous tetrahydrofuran twice (2 mL x 2) prior to the addition of 1.0 mL of dichloromethane. (*S,S*)-2,6-bis(4-isopropyl-2-oxazolin-2-yl)-pyridine (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 °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 °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 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 homopropargylic and allenylc alcohols mixture as a colorless oil.

Representative procedure for separation of homopropargylic and allenylc alcohols :

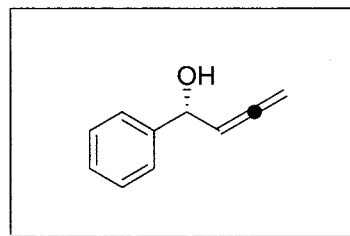
To an 8 mL sample vial equipped with a stirring bar was added AgNO_3 (1.2 equiv) and CaCO_3 (1.2 equiv) in acetone:water (0.6 mL to 0.4 mL). The homopropargylic and allenylc alcohol mixture (1 equiv) was added and the mixture was stirred in the dark for 6 h to afford a brown precipitate in solution. The precipitate was separated via suction filtration and the filtrate was dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the pure allenylc alcohol. The precipitate was treated with 1M HCl (3 mL) and stirred vigorously for 5 min prior to extraction of the aqueous layer with diethyl ether (3 x 10 mL). The combined organic extracts was washed with brine, dried over anhydrous magnesium sulphate, filtered and concentrated *in vacuo* to afford the pure homopropargylic alcohol.

Characterization of Homopropargylic and Allenylic Alcohols

(R)-1-Phenylbut-3-yn-1-ol (29a)

(88 % ee)

62

(R)-1-Phenylbuta-2,3-dien-1-ol (30a)

(90 % ee)

38

Colorless oil (Combined yield : 73%); $R_f = 0.43$ (4:1 Hexane/EA)**(R)-1-phenylbut-3-yn-1-ol (29a)**

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.25-7.63 (m, 5H, aromatic), 4.88 (t, $J = 6.3$ Hz, 1H, CH_2CHOH), 2.66-2.63 (dd, $J = 6.6, 2.6$ Hz, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.45 (s, 1H, CHOH), 2.07 (t, $J = 2.5$ Hz, 1H, $\text{CH}_2\text{C}\equiv\text{CH}$).

$^{13}\text{C NMR}$ (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 $\text{C}_{10}\text{H}_{12}\text{O}$ [M^+]: 146.0732. Found: 146.0733.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel 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-phenylbuta-2,3-dien-1-ol (30a)

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 7.45-7.27 (m, 5H, aromatic), 5.45 (q, $J = 6.5$ Hz, 1H, $\text{CH}=\text{C}=\text{CH}_2$), 5.31-5.21 (br, 1H, CHOH), 4.98-4.90 (m, 2H, $\text{CH}=\text{C}=\text{CH}_2$), 2.11 (d, $J = 3.5$ Hz, 1H, CHOH).

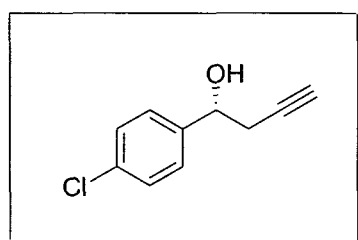
$^{13}\text{C NMR}$ (75.4 MHz, CDCl_3): δ 207.1, 142.9, 128.4, 127.8, 126.1, 95.2, 78.2, 71.9.

FTIR (neat): 3356, 1613, 1484, 758, 749 cm^{-1} .

HRMS Calcd for $C_{10}H_{12}O$ [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 = 18.29 min for *R* enantiomer, t_2 = 19.35 for *S* enantiomer).¹⁴⁹

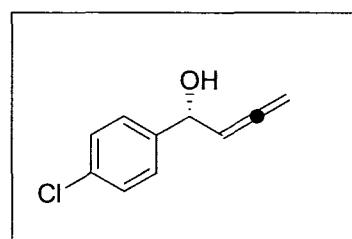
**(*R*)-1-(4-chloro-phenyl)-
but-3-yn-1-ol (29b)**



(80 % ee)

38

**(*R*)-1-(4-chloro-phenyl)-
buta-2,3-dien-1-ol (30b)**



(78 % ee)

62

Colorless oil (Combined yield : 88 %); R_f = 0.42 (4:1 Hexane/EA)

(*R*)-1-(4-chloro-phenyl)-but-3-yn-1-ol (29b)

1H NMR (300 MHz, $CDCl_3$): δ 7.32 (m, 4H, aromatic), 4.88-4.81 (m, 1H, CH_2CHOH), 2.60-2.50 (m, 2H, $CH_2C\equiv CH$), 2.27-2.26 (m, 1H, $CHOH$), 2.07 (t, J = 2.8 Hz, 1H, $CH_2C\equiv CH$).

^{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).

¹⁴⁹ Nakajima, M.; Saito, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2002**, *13*, 2449.

(R)-1-(4-chloro-phenyl)-buta-2,3-dien-1-ol (30b)

^1H NMR (300 MHz, CDCl_3): δ 7.32 (m, 4H, aromatic), 5.39 (q, $J = 6.8$ Hz, 1H, $\text{CH}=\text{C}=\text{CH}_2$), 5.26-5.24 (m, 1H, CHOH), 4.94-4.91 (m, 2H, $\text{CH}=\text{C}=\text{CH}_2$).

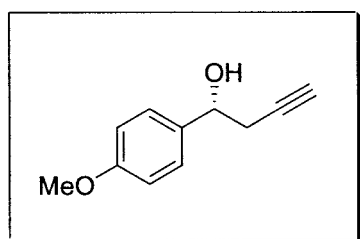
^{13}C NMR (75.4 MHz, CDCl_3): δ 207.2, 140.9, 133.5, 128.6, 127.2, 95.0, 78.4, 71.6.

FTIR (neat): 3351, 1624, 1490, 749 cm^{-1} .

HRMS Calcd for $\text{C}_{10}\text{H}_9\text{ClO}$ [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).

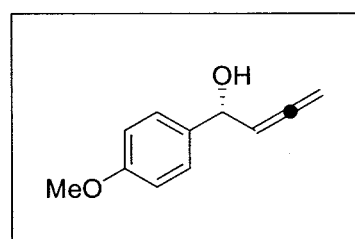
**(R)-1-(4-methoxy-phenyl)-
but-3-yn-1-ol (29c)**



(80 % ee)

52

**(R)-1-(4-methoxyphenyl)-
buta-2,3-dien-1-ol (30c)**



(70 % ee)

48

Colorless oil (Combined yield : 68 %); $R_f = 0.31$ (4:1 Hexane/EA)

(R)-1-(4-methoxy-phenyl)-buta-3-yn-1-ol (29c)

^1H 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_2CHOH), 3.81 (s, 3H, OCH_3), 2.65-2.61 (m, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.05 (t, $J = 2.6$ Hz, 1H, $\text{CH}_2\text{C}\equiv\text{CH}$).

^{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 $\text{C}_{11}\text{H}_{12}\text{O}_2$ [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).

(*R*)-1-(4-methoxy-phenyl)-buta-2,3-dien-1-ol (30c)

^1H 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, $\text{CH}=\text{C}=\text{CH}_2$), 5.23 (br, 1H, CHOH), 4.94-4.91 (m, 2H, $\text{CH}=\text{C}=\text{CH}_2$), 3.84 (s, 3H, OCH_3).

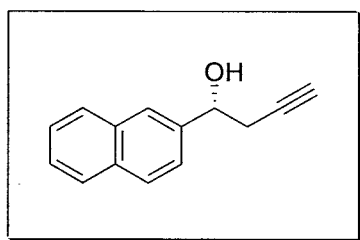
^{13}C NMR (75.4 MHz, CDCl_3): δ 207.1, 159.3, 135.1, 127.5, 113.9, 95.3, 78.2, 71.6, 55.3.

FTIR (neat): 3330, 1636, 1429, 715 cm^{-1} .

HRMS Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$ [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).

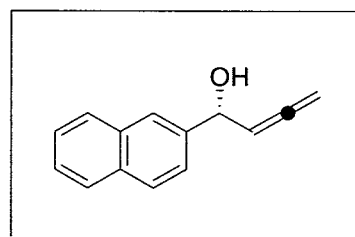
**(*R*)-1-Naphthalen-2-yl-
but-3-yn-1-ol (29d)**



(88 % ee)

37

**(*R*)-1-Naphthalen-2-yl-
buta-2,3-dien-1-ol (30d)**



(84 % ee)

63

Colorless oil (Combined yield : 85 %); $R_f = 0.39$ (4:1 Hexane/EA)

(R)-1-Naphthalen-2-yl-but-3-yn-1-ol (29d)

^1H 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_2CHOH), 2.71-2.63 (m, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.05 (t, $J = 2.8$ Hz, 1H, $\text{CH}_2\text{C}\equiv\text{CH}$).

^{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 $\text{C}_{14}\text{H}_{12}\text{O}$ [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).

(R)-1-Naphthalen-2-yl-buta-2,3-dien-1-ol (30d)

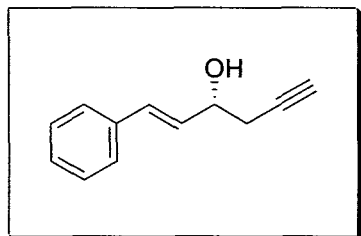
^1H NMR (300 MHz, CDCl_3): δ 7.85-7.82 (m, 4H, aromatic), 7.52-7.46 (m, 3H, aromatic), 5.51 (q, $J = 6.4$ Hz, 1H, $\text{CH}=\text{C}=\text{CH}_2$), 5.44-5.43 (br, 1H, CHOH), 5.06-5.00 (m, 2H, $\text{CH}=\text{C}=\text{CH}_2$).

^{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} .

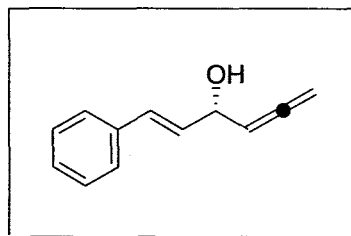
HRMS Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_2$ [M^+]: 196.0888. Found: 196.0887.

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).

(R)-1-Phenyl-hex-1-en-5-yn-3-ol**(29e)**

(84 % ee)

29

(S)- 1-Phenyl-hexa-1,4,5-trien-3-ol**(30e)**

(86 % ee)

71

Colorless oil (Combined yield : 54 %); $R_f = 0.43$ (4:1 Hexane/EA)**(R)-1-Phenyl-hex-1-en-5-yn-3-ol (29e)**

^1H NMR (300 MHz, CDCl_3): δ 7.32 (m, 5H, aromatic), 6.67 (d, $J = 16.0$ Hz, 1H, $\text{PhCH}=\text{CH}$), 6.29 (dd, $J = 16.0, 6.3$ Hz, 1H, $\text{PhCH}=\text{CH}$), 4.48 (m, 1H, CH_2CHOH), 2.56 (m, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.32 (bs, 1H, OH), 2.10 (t, $J = 2.6$ Hz, 1H, $\text{CH}_2\text{C}\equiv\text{CH}$)

^{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, 1038 cm^{-1} .

HRMS Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$ [M^+]: 172.0888. Found: 172.0888.

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiralcel 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 (30e)

^1H NMR (300 MHz, CDCl_3): δ 7.34 (m, 5H, aromatic), 6.68 (d, $J = 16.0$ Hz, 1H, $\text{PhCH}=\text{CH}$), 6.27 (dd, $J = 15.7, 6.3$ Hz, 1H, $\text{PhCH}=\text{CH}$), 5.38 (dd, $J = 12.9, 6.3$ Hz, 1H, $\text{CH}=\text{C}=\text{CH}_2$), 4.94 (dd, $J = 6.6, 2.43$ Hz, 2H, $\text{CH}=\text{C}=\text{CH}_2$), 4.87 (bs, 1H, CHOH)

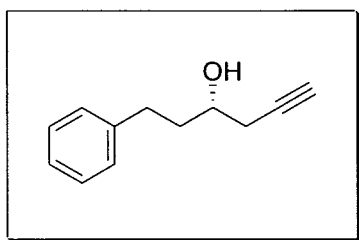
^{13}C NMR (75.4 MHz, CDCl_3): δ 207.1, 136.6, 134.1, 131.7, 130.7, 127.8, 118.5, 94.0, 78.2, 70.5.

FTIR (neat): 3556, 3321, 2139, 1825, 1589, 1087, 1021 cm^{-1} .

HRMS Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$ [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).

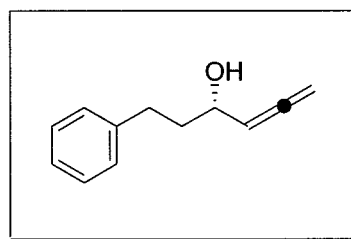
(S)-1-Phenyl-hex-5-yn-3-ol (29f)



(88 % ee)

58

(S)-1-Phenyl-hexa-4,5-dien-3-ol (30f)



(82 % ee)

42

Colorless oil (Combined yield : 71 %); $R_f = 0.40$ (4:1 Hexane/EA)

(S)-1-Phenyl-hex-5-yn-3-ol (29f)

^1H NMR (300 MHz, CDCl_3): δ 7.27 (m, 5H, aromatic), 3.80 (m, 1H, CH_2CHOH), 2.76 (m, 2H, PhCH_2CH_2), 2.40 (m, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.07 (t, $J = 2.6$ Hz, 1H, $\text{CH}_2\text{C}\equiv\text{CH}$), 1.94 (brd, 1H, CHOH), 1.87 (m, 2H, PhCH_2CH_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 $\text{C}_{12}\text{H}_{14}\text{O}$ [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).

(S)- 1-Phenyl-hexa-4,5-dien-3-ol (30f)

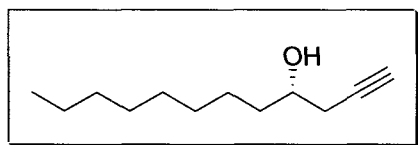
^1H NMR (300 MHz, CDCl_3): δ 7.38-7.11 (m, 5H, aromatic), 5.26 (q, $J = 6.6$ Hz, 1H, $\text{CH}=\text{C}=\text{CH}_2$), 4.86 (q, $J = 2.4$ Hz, 2H, $\text{CH}=\text{C}=\text{CH}_2$), 4.21 (br, 1H, CHOH), 2.83-2.68 (m, 2H, PhCH_2CH_2), 1.98-1.81 (m, 2H, PhCH_2CH_2).

^{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} .

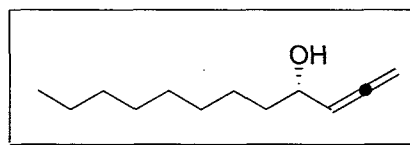
HRMS Calcd for $\text{C}_{12}\text{H}_{14}\text{O}$ [M^+]: 174.1045. Found: 174.1047.

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).

(S)-Dodec-1-yn-4-ol (29g)

(60 % ee)

35

(S)-Dodeca-1,2-dien-4-ol (30g)

(66 % ee)

65

Colorless oil (Combined yield : 70 %); $R_f = 0.51$ (4:1 Hexane/EA)

(S)-Dodec-1-yn-4-ol (29g)

^1H NMR (300 MHz, CDCl_3): δ 3.76 (m, 1H, CH_2CHOH), 2.38 (m, 2H, $\text{CH}_2\text{C}\equiv\text{CH}$), 2.05 (t, $J = 2.6$ Hz, 1H, $\text{CH}_2\text{C}\equiv\text{CH}$), 1.62-1.27 (m, 14H, aliphatic (CH_2) $_7$), 0.88 (t, $J = 6.6$ Hz, 3H, CH_2CH_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 $\text{C}_{14}\text{H}_{22}\text{O}$ [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).

(S)-Dodeca-1,2-dien-4-ol (30g)

^1H NMR (300 MHz, CDCl_3): δ 5.24 (dd, $J = 12.8, 6.4$ Hz, 1H, $\text{CH}=\text{C}=\text{CH}_2$), 4.85 (dd, $J = 6.4, 2.5$ Hz, 2H, $\text{CH}=\text{C}=\text{CH}_2$), 4.19-4.15 (m, 1H, CHOH), 1.61-1.27 (m, 14H, $(\text{CH}_2)_7$), 0.88 (t, $J = 6.5$ Hz, 3H, CH_2CH_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 $\text{C}_{11}\text{H}_{12}\text{O}_2$ [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).

5.4 CATALYTIC ENANTIOSELECTIVE DIELS-ALDER REACTION

Catalytic Enantioselective Diels-Alder reaction in ionic liquid via a recyclable chiral In(III)-Binol Complex

Representative procedure for enantioselective Diels-Alder reaction : Preparation of (1R,2R,4R)-2-bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

To an oven dried 10mL round-bottom flask equipped with a magnetic stirring bar was added InCl₃ (22 mg, 0.1 mmol, 0.2 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 hours. Allyltributyl stannane (0.093 mL, 0.3 mmol, 0.6 equiv) was added to the resulting mixture and stirred for 10 minutes followed by addition of 1 mL of hmim[PF₆⁻] to the pre-formed catalyst. The organic solvent was removed *in vacuo* and subsequent dropwise addition of 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv.) along side of the flask were carried out. The reaction mixture stirred at room temperature for 20 h. The mixture was extracted with ether (10 mL x 3). The combined organic extracts was washed with brine, dried over anhydrous MgSO₄, 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 (92% yield).

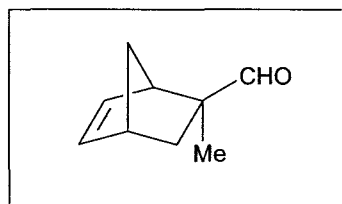
Procedure for Asymmetric Diels Alder Reaction in Ionic Liquid (recyclability)Representative procedure for enantioselective Diels-Alder reaction: Preparation of (1R,2R,4R)-2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde

To an oven dried 10mL round-bottom flask equipped with a magnetic stirring bar was added InCl_3 (22 mg, 0.1 mmol, 0.2 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 hours. Allyltributyl stannane (0.093 mL, 0.3 mmol, 0.6 equiv.) was added to the resulting mixture and stirred for 10 minutes followed by addition of 1 mL of hmim[PF₆⁻] to the pre-formed catalyst. The organic solvent was removed in vacuo and subsequent dropwise addition of 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv.) along side of the flask were carried out. The reaction mixture stirred at room temperature for 20 h. The rubber septum was removed and the mixture was extracted with hexane (10 mL x 5). The round bottom flask was resealed with a rubber septum and anhydrous THF (2 mL x 2) was added to the hmim[PF₆⁻] containing chiral In(III) complex mixture for the removal of residual hexane and moisture *in vacuo*. The mixture was purge with nitrogen prior to addition of 2-bromoacrolein (67.5 mg, 0.5 mmol, 1.0 equiv) and cyclopentadiene (0.10 mL, 1.5 mmol, 3.0 equiv.) for subsequent cycles of Diels-Alder reaction. The combined organic extracts was washed with brine, dried over anhydrous MgSO₄, 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.

Characterization of Diels-Alder adduct

(1*R*, 2*S*, 4*R*)-2-Methyl-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (56a)



(98 % ee)

Colorless oil (89%); $R_f = 0.64$ (4:1 hexane/ethyl acetate)

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.68 (s, 1H, -CHO), 6.28 (dd, $J = 3.1, 5.6$ Hz, 1H, =CH), 6.09 (dd, $J = 3.1, 5.6$ Hz, 1H, =CH), 2.88 (bs, 1H, -CH), 2.80 (bs, 1H, -CH), 2.24 (dd, $J = 3.8, 11.9$ Hz, 1H, -CH), 1.38 (m, 2H, -CH₂), 1.00 (s, 3H, -CH₃), 0.75 (bd, $J = 11.8$ Hz, 1H, -CH).

$^{13}\text{C NMR}$ (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} .

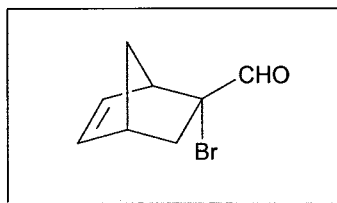
HRMS Calcd for $\text{C}_9\text{H}_{12}\text{O}$ [M^+]: 136.0888. Found: 136.0895.

$[\alpha]_D = +13.5^\circ$ ($c = 3.10$, CH_2Cl_2)

Diastereoselectivity (*exo-endo* ratio) was determined by $^1\text{H NMR}$ analysis of the crude mixture: δ 9.68 (s, 1H, *exo*, major), 9.38 (s, 1H, *endo*, minor). Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and $^1\text{H NMR}$ integration (500 MHz, CDCl_3): 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.¹⁵⁰

¹⁵⁰ Corey, E. J.; Shibata, T.; Lee, T. W. *J. Am. Chem. Soc.* **2002**, *124*, 3808

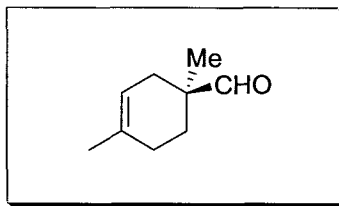
(1*R*, 2*R*, 4*R*)-2-Bromo-bicyclo[2.2.1]hept-5-ene-2-carbaldehyde (56b)

(98 % ee)

Colorless oil (92%); $R_f = 0.65$ (4:1 hexane/ethyl acetate) ^1H NMR (300 MHz, CDCl_3): δ 9.54 (s, 1H, -CHO, *exo*), 6.45 (dd, $J = 3.1, 5.6$ Hz, 1H, =CH), 6.14 (dd, $J = 3.1, 5.6$ Hz, 1H, =CH), 3.25 (bs, 1H, -CH), 2.97 (bs, 1H, -CH), 2.65 (dd, $J = 3.5, 13.6$ Hz, 1H, -CH), 1.59-1.42 (m, 2H, -CH₂), 1.32 (d, $J = 9.4$ Hz, 1H, -CH). ^{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 $\text{C}_8\text{H}_{10}\text{BrO}$ [M^+]: 199.9837. Found: 199.9834. $[\alpha]_D = +9.6^\circ$ ($c = 1.37$, CH_2Cl_2)

Diastereoselectivity (*exo-endo* ratio) was determined by ^1H NMR analysis of the crude mixture: δ 9.56 (s, 1H, -CHO, *exo*, major), 9.34 (s, 1H, -CHO, *endo*, minor). Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^1H NMR integration (500 MHz, CDCl_3): 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.

(S)-1,4-Dimethyl-cyclohex-3-enecarbaldehyde (56c)

(88% ee)

Colorless oil (78%); $R_f = 0.68$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 9.47 (s, 1H, -CHO), 5.37 (bs, 1H, =CH), 2.32 (bd, $J = 17.1$ Hz, 1H, ring -CH), 1.96 (m, 2H, ring - CH_2), 1.83 (m, 2H, ring - CH_2), 1.68 (s, 3H, - CH_3), 1.49 (m, 1H, ring -CH), 1.03 (s, 3H, - CH_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.

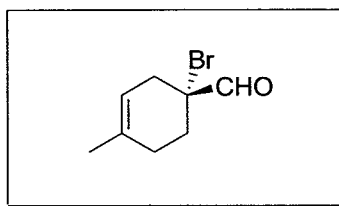
FTIR (neat): 2924, 1725, 1633 cm^{-1} .

$[\alpha]_D = +42.0^\circ$ ($c = 3.28$, CH_2Cl_2)

Enantioselectivity was determined by reduction with NaBH_4 to the corresponding alcohol, conversion to the (*R*)-MTPA ester derivative and ^1H NMR integration (500 MHz, CDCl_3): δ 4.14 (d, 1H, major), 4.09 (d, 1H, minor), 4.03 (d, 1H, minor), 3.98 (d, 1H, major).¹⁵¹

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances and by analogy with (*R*)-1-bromo-4-methylcyclohex-3-enecarbaldehyde.

¹⁵¹ Diels-Alder adduct contains ca. 23% of its regioisomer.

(R)-1-Bromo-4-methyl-cyclohex-3-enecarbaldehyde (56d)

(96% ee)

Colorless oil (90%); $R_f = 0.67$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 9.36 (s, 1H- CHO), 5.33 (bs, 1H, =CH), 2.79 (bd, 1H, $J = 18.1$ Hz, ring -CH), 2.62 (bd, 1H, $J = 18.0$ Hz, ring -CH), 2.28-2.09 (m, 4H, ring - $(\text{CH}_2)_2$), 1.67 (bs, 3H, - CH_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} .

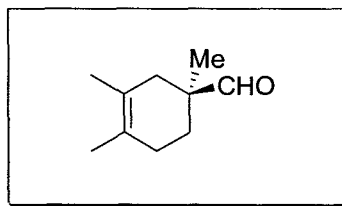
HRMS Calcd for $\text{C}_8\text{H}_{11}\text{O}$ [M-Br]: 123.0810. Found: 123.0810

$[\alpha]_D = +67.7^\circ$ ($c = 1.50$, 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).¹⁵²

The absolute configuration was assigned by measurement of optical rotation and comparison with known substances.

¹⁵² The Diels-Alder adduct contains ca. 16% of its regioisomer.

(S)-1,3,4-Trimethyl-cyclohex-3-enecarbaldehyde (56e)

(97% ee)

Colorless oil (88%); $R_f = 0.68$ (4:1 hexane/ethyl acetate)

^1H NMR (300 MHz, CDCl_3): δ 9.45 (s, 1H, -CHO), 2.25 (bd, $J = 17.4$ Hz, 1H, ring -CH), 1.97 (bs, 2H, ring - CH_2), 1.85-1.73 (m, 2H, ring - CH_2), 1.64 (s, 3H, - CH_3), 1.59 (s, 3H), 1.50-1.41 (m, 1H, ring -CH), 1.02 (s, 3H, - CH_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.

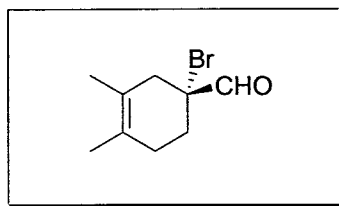
FTIR (neat): 2918, 1726 cm^{-1} .

HRMS Calcd for $\text{C}_{10}\text{H}_{16}\text{O}$ [M^+]: 152.1201. Found: 152.1198.

$[\alpha]_D = +48.0^\circ$ ($c = 4.60$ 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 ^1H NMR integration (500 MHz, CDCl_3): 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-methylcyclohex-3-enecarbaldehyde.

(R)-1-Bromo-3,4-dimethyl-cyclohex-3-enecarbaldehyde (56f)

(94% ee)

Colorless oil (90%); $R_f = 0.67$ (4:1 hexane/ethyl acetate)

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.34 (s, 1H, -CHO), 2.74 (bd, $J = 17.4$ Hz, 1H, ring -CH), 2.56 (bd, $J = 17.8$ Hz, 1H, ring -CH), 2.27-2.08 (m, 4H, ring-(CH_2)₂), 1.65 (s, 3H, - CH_3), 1.62 (s, 3H, - CH_3).

$^{13}\text{C NMR}$ (75.4 MHz, CDCl_3): δ 192.2, 125.4, 122.2, 67.7, 40.0, 31.2, 29.9, 19.0, 18.6.

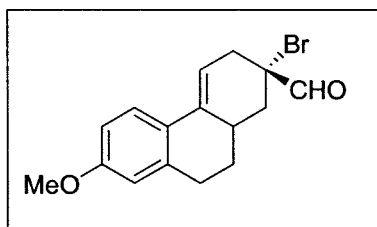
FTIR (neat): 2916, 1726, 1641 cm^{-1} .

HRMS Calcd for $\text{C}_{19}\text{H}_{13}\text{BrO}$ [M^+]: 216.0150. Found: 216.0141.

$[\alpha]_D = +62.3^\circ$ ($c = 3.19$, 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.

(2S)-2-Bromo-7-methoxy-1,2,3,9,10,10a-hexhydro-phenanthrene-2-carbaldehyde**(56g)****(92% ee)**

Light yellow solid (89%); $R_f = 0.51$ (4:1 hexane/ethyl acetate)

$^1\text{H NMR}$ (300 MHz, CDCl_3): δ 9.52 (s, 1H, -CHO), 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, =CH), 3.80 (s, 3H, -OCH₃), 3.10-2.93 (m, 2H, ring CH₂), 2.90-2.71 (m, 3H, ring CH₂ and -CH), 2.37-2.02 (m, 1H, ring CH), 2.06-2.02 (m, 1H, ring CH), 1.68-1.52 (m, 2H, ring CH₂).

$^{13}\text{C NMR}$ (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 $\text{C}_{16}\text{H}_{17}\text{BrO}_2$ [M^+]: 320.0412. Found: 320.0408.

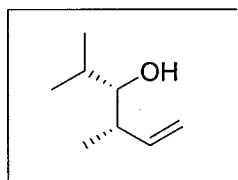
$[\alpha]_D = -58.2^\circ$ ($c = 2.0$, CH_2Cl_2)

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.

5.5 SYNTHETIC STUDIES TOWARDS THE TOTAL SYNTHESIS OF RK-397

(3*S*,4*S*)-2,4-dimethylhex-5-en-3-ol (86)



To a stirred mixture of potassium *tert*-butoxide (3.4 g, 28.8 mmol, 1 equiv.) and *cis*-2-butene (3.2 g, 57.5 mmol, 2 equiv.) in dry THF (20 mL) at $-78\text{ }^{\circ}\text{C}$ was added 1.4 M *n*-BuLi in hexanes (20.6 mL, 28.8 mmol, 1 equiv.). The mixture was allowed to warm to $-45\text{ }^{\circ}\text{C}$ and stirred at that temperature for 10 min. After this period, the mixture was recooled to $-78\text{ }^{\circ}\text{C}$ and to it was added (+)-*B*-methoxy-diisopinocampheyl borane (9.1 g, 28.8 mmol, 1 equiv.) in dry THF (30 mL) over a period of 10 min. The resulting mixture was stirred for another 40 min and then $\text{BF}_3\cdot\text{OEt}_2$ (5.5 g, 38.5 mmol, 1.3 equiv.) was added dropwise over a period of 5 min. Isobutyraldehyde (2.9 g, 40.3 mmol, 1.4 equiv) in dry THF (10 mL) was added and the resulting reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for additional 3 h. The reaction was quenched at $-78\text{ }^{\circ}\text{C}$ with 3N aqueous NaOH (20 mL) and 30% aqueous H_2O_2 solution (17 mL) and then allowed to warm to $23\text{ }^{\circ}\text{C}$. The mixture was heated at reflux for 15 min and the layers were separated. The aqueous layer was extracted with diethyl ether and the combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4 . Evaporation of the solvents followed by purification of the residue by flash column chromatography furnished the product as an oil.

Colourless oil (76%, 92% ee)

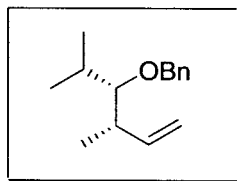
^1H NMR (400 MHz, CDCl_3): δ 5.29 (m, 1H), 5.06 (m, 2H), 3.15 (dd, $J = 5.8\text{ Hz}$, 1H), 2.35 (m, 1H), 1.75 (m, 1H), 1.5 (br s, 1H), 1.02 (d, 3H, $J = 6.7\text{ Hz}$), 0.91 (d, $J = 7.1$, 6H).

^{13}C NMR (100 MHz, CDCl_3): δ 141.7, 114.5, 79.4, 40.5, 30.3, 19.5, 16.9, 13.4.

FTIR (neat): 3404, 2960, 2913, 1703, 1470, 1385, 1105, 1024 cm^{-1} .

HRMS (CI) Calcd for $\text{C}_8\text{H}_{16}\text{O}$ [M^+]: 128.1201. Found: 128.1198.

$[\alpha]_{\text{D}} = +5.91^{\circ}$ ($c = 2.59$, CHCl_3)

Fragment A: (((3*S*,4*S*)-2,4-dimethylhex-5-en-3-yloxy)methyl)benzene

To a suspension of sodium hydride (0.64 g, 16 mmol, 2 equiv.) in dry THF (20 mL) was added homoallylic alcohol **86** (1.02 g, 8 mmol, 1 equiv.) and stirred for 1 h at room temperature. Benzyl bromide (1.14 ml, 9.6 mmol, 1.2 equiv.) was added and the resulting mixture was stirred for additional 2 h. The reaction mixture was quenched with ice water and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 1% ethyl acetate: hexane solvent mixture.

Colourless oil (90%)

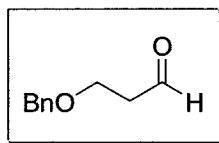
¹H NMR (400 MHz, CDCl₃): δ 7.47-7.41 (m, 5H), 5.99-5.91 (m, 1H), 5.19-5.07 (m, 2H), 4.72 (d, *J* = 11.1 Hz, 1H), 4.66 (d, *J* = 11.1 Hz, 1H), 3.11 (dd, *J* = 5.7 Hz, 1H), 2.60-2.55 (m, 1H), 2.05-1.95 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 1.08 (d, *J* = 6.8 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 142.5, 139.1, 128.2 (2C), 127.5 (2C), 127.3, 113.6, 88.6, 75.1, 41.1, 30.9, 20.4, 17.5, 15.4.

FTIR (neat): 2958, 2929, 2870, 1637, 1470, 1455, 1110, 1066, 975, 910, 732, 696 cm⁻¹.

HRMS (CI) Calcd for C₁₅H₂₃O [M+H]⁺: 219.1743. Found: 219.1749.

[α]_D = +12.6° (*c* = 7.49, CH₂Cl₂)

3-(benzyloxy)propanal (87)

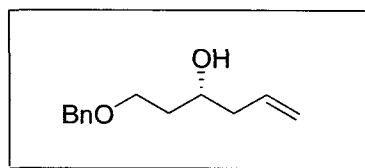
To a mixture of silver(I) oxide (27.8 g, 120 mmol, 1.2 equiv.) in dichloromethane (250 mL) in a 500 mL round-bottom flask was added 1, 3–propanediol (36 mL, 500 mmol, 5 equiv.) under nitrogen. The mixture was cooled to 0 °C prior to slow addition of benzyl bromide (11.9 mL, 100 mmol, 1 equiv.) and subsequently stirred at room temperature for 24 h. The black suspension was filtered through a pad of celite and flushed with copious diethyl ether (500 ml). The filtrate was washed with water, brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was dissolved in DMSO (200 mL) and cooled to 0 °C prior to addition of 2-iodoxybenzoic acid (56 g, 200 mmol, 2 equiv.). The reaction mixture was stirred at room temperature for 5 h before cooling to 0 °C and quenched with water (200 mL). The aqueous mixture was extracted with diethyl ether and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 10 % ethyl acetate: hexane solvent mixture.

Colourless oil (95%)

¹H NMR (400 MHz, CDCl₃): δ 9.80 (t, *J* = 1.6 Hz, 1H), 7.37-7.29 (m, 5H), 4.54 (s, 2H), 3.81 (t, *J* = 6.1 Hz, 2H), 2.70 (dt, *J* = 4.4, 1.7 Hz, 2H).

¹³C NMR (100 MHz, CDCl₃): δ 201.1, 137.8, 128.4 (2C), 127.8 (2C), 127.7, 73.3, 63.8, 43.8.

HRMS (ESI) Calcd for C₁₀H₁₂O₂Na [M+Na]⁺: 187.0735. Found: 187.0744.

(R)-1-(benzyloxy-hex-5-en-3-ol (88)

(98 % ee)

To an oven dried 500 mL round bottom flask equipped with a magnetic stirring bar was added (+)-DIP-Br (10 g, 27.4 mmol, 1 equiv.) and dry THF (250 mL). The solution was cooled to -78 °C prior to dropwise addition of allylmagnesium bromide (1.0 M in ether, 24.6 ml, 0.9 equiv.) over 30 min. The mixture was allowed to stir at -78 °C for an hour and was allowed to warm up to room temperature over 1 h. The mixture was cooled to -78 °C again and was treated with a solution of aldehyde **87** (3.37 g, 20.5 mmol, 0.75 equiv.) in THF (20 mL) dropwise over 30 min. The reaction mixture was stirred at -78 °C for 1 h and was allowed to warm gradually to room temperature and stirred for another hour. The solution was cooled to 0 °C and quenched with a pre-formed mixture of 3M NaOH (30 mL) and 30% H₂O₂ (10 mL) for 30 min. The aqueous layer was extracted with diethyl ether (3 x 30 mL), and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 5 % ethyl acetate: hexane solvent mixture.

Colorless oil (60 %, 98% ee)

¹H NMR (300 MHz, CDCl₃): δ 7.36-7.31 (m, 5H), 5.88-5.78 (m, 1H), 5.13-5.08 (m, 2H), 4.52 (s, 2H), 3.89-3.86 (m, 1H), 3.74-3.69 (m, 1H), 3.67-3.62 (m, 1H), 2.26-2.23 (m, 2H), 1.79-1.74 (m, 2H).

¹³C NMR (75.4 MHz, CDCl₃): δ 137.8, 134.8, 128.4, 127.6, 126.9, 117.5, 73.2, 70.2, 68.9, 41.8, 35.8.

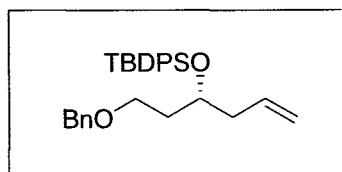
FTIR (neat): 3469, 2920, 2864, 1642, 1452, 1098, 915, 698 cm⁻¹.

HRMS (CI) Calcd for C₁₃H₁₈O₂ [M⁺]: 206.1307. Found: 206.1316.

[α]_D = +3.4° (c = 7.43, CH₂Cl₂)

The enantiomeric excess was determined by HPLC analysis employing a Daicel Chiracel OB-H column (Hexane : *i*-propanol 95:5, 1.0 mL/min: $t_1 = 16.51$ min for the *R* enantiomer, $t_2 = 20.00$ min for the *S* enantiomer).

(*R*)-(1-(benzyloxy)hex-5-en-3-yloxy)(*tert*-butyl)diphenylsilane (89)



To a cooled solution of homoallylic alcohol **88** (7.31 g, 35.5 mmol, 1 equiv.) in anhydrous *N,N*-dimethylformamide (50 mL) at 0 °C was added *tert*-butyldiphenylsilylchloride (10.71 g, 39 mmol, 1.1 equiv) and silver(I) nitrate (6.62 g, 39 mmol, 1.1 equiv). The brown suspension was stirred at 0 °C for 2 h and filtered through a pad of celite. The celite was flushed with copious diethyl ether (500 mL) and the filtrate was washed with water, followed by brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 2 % ethyl acetate: hexane solvent mixture.

Pale yellow oil (92%)

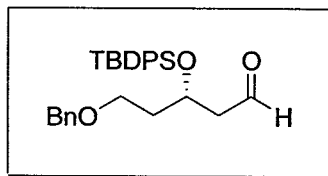
¹H NMR (300 MHz, CDCl₃): δ 7.69-7.65 (m, 4H), 7.41-7.21 (m, 11H), 5.75-5.64 (m, 1H), 4.96-85 (m, 2H), 4.33 (s, 2H), 4.01-3.94 (m, 1H), 3.53-3.42 (m, 2H), 2.28-2.11 (m, 2H), 1.82-1.76 (m, 2H), 1.05 (s, 9H).

¹³C NMR (75.4 MHz, CDCl₃): δ 138.5, 135.9 (2C), 135.8 (2C), 134.5, 134.4, 134.2, 129.5 (2C), 128.2 (2C), 127.5 (2C), 127.5(2C), 127.4(2C), 127.3, 117.1, 72.7, 70.3, 66.9, 41.5, 36.1, 27.0 (3C), 19.4.

FTIR (neat): 3070, 2954, 2929, 2858, 1644, 1420, 1111, 821, 736, 700 cm⁻¹.

HRMS (CI) Calcd for C₂₉H₃₇O₂Si [M+H]⁺: 445.2557. Found: 445.2501.

[α]_D = -6.1° (*c* = 11.06, CH₂Cl₂)

(S)-5-(benzyloxy)-3-(tert-butylidiphenylsilyloxy)pentanal (90)

To a solution of alkene **89** (9.75 g, 22 mmol, 1 equiv.) and 4-methylmorpholine *N*-oxide (5.9 g, 44 mmol, 2 equiv.) in aqueous acetone (220 mL, 3:1 acetone: water) was added OsO₄ (4% w/w in water, 0.9 mL, 0.7 mol %). The mixture was stirred at room temperature for 16 h and subsequently treated with NaIO₄ (9.4 g, 44 mmol, 2 equiv.) and stirred for 1 h. The reaction mixture was quenched with saturated ammonium chloride solution and the aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 5 % ethyl acetate: hexane solvent mixture.

Brown oil (95%)

¹H NMR (400 MHz, CDCl₃): δ 9.69 (t, *J* = 2.5 Hz, 1H), 7.72-7.69 (m, 4H), 7.47-7.24 (m, 11H), 4.46 (m, 1H), 4.39 (d, *J* = 12 Hz, 1H), 4.35 (d, *J* = 12 Hz, 1H), 3.55-3.44 (m, 2H), 2.61 (ddd, *J* = 16.1, 5.7, 2.1 Hz, 1H), 2.53 (ddd, *J* = 16.1, 5.7, 2.8 Hz, 1H), 1.99-1.92 (m, 2H), 1.08 (s, 9H).

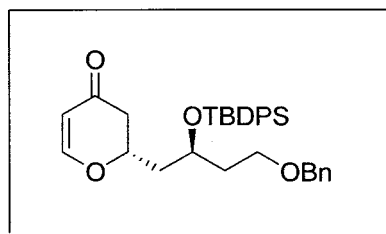
¹³C NMR (100 MHz, CDCl₃): δ 201.8, 138.1, 135.8(2C), 133.6, 133.4, 129.8, 129.7, 128.3, 127.7 (2C), 127.6(2C), 127.5 (2C), 127.5(2C), 127.4(2C), 72.7, 67.0, 66.3, 50.5, 37.1, 26.9 (3C), 19.2.

FTIR (neat): 2956, 2931, 2856, 1720, 1361, 1263, 1111, 999, 821, 738, 702 cm⁻¹.

HRMS (ESI) Calcd for C₂₈H₃₄O₃SiNa [M+Na]⁺: 469.2175. Found: 469.2183.

[α]_D = +5.3° (*c* = 22.98, CH₂Cl₂)

(S)-2-((S)-4-(benzyloxy)-2-(*tert*-butyldiphenylsilyloxy)butyl)-2,3-dihydropyran-4-One (92)



A 50 mL oven-dried round bottomed flask equipped with a magnetic stir bar was charged with 3.85 g of oven dried powdered 4Å molecular sieves and (*R,R*)-(salen)Cr(III)-Cl complex **I** (0.45 g, 0.70 mmol, 5 mol %). The flask was sealed with a rubber septum and purged with N₂ for 5 min. Aldehyde **90** (6.945 g, 15.55 mmol, 1.2 equiv.) was added followed by TBME (15.5 mL). The flask was further sealed with Teflon tape and parafilm. This mixture was stirred at room temperature for 10 min and then it was cooled to 0 °C and stirred an additional 10 min. 1-methoxy-3-[(trimethylsilyl)oxy]butadiene **91** (2.43 g, 14.13 mmol, 1 equiv.) was added and the reaction was stirred at this temperature for 24 h. Dichloromethane (5 mL) was added followed by 5 drops of TFA. The reaction was allowed to warm to room temperature and stirred for 10 min. The reaction was then filtered through a plug of silica gel on celite with copious diethyl ether (300 mL). The filtrate was concentrated *in vacuo* and the crude residue was purified by flash chromatography (10 % to 15% ethyl acetate: hexane) to afford the product as a bright yellow oil. The isolated material was determined have a diastereomeric ratio of 97:3 by chiral HPLC.

Bright yellow oil (89%)

¹H NMR (400 MHz, CDCl₃): δ 7.65- 7.63 (m, 4H), 7.44-7.21 (m, 11H), 7.16 (d, *J* = 5.9 Hz, 1H), 5.30 (d, *J* = 5.9 Hz, 1H), 4.56-4.48 (m, 1H), 4.35 (d, *J* = 12 Hz, 1H), 4.34 (d, *J* = 12 Hz, 1H), 4.14-4.08 (m, 1H), 3.53 (ddd, *J* = 9.3, 6.3 Hz, 1H), 3.46 (ddd, *J* = 9.3, 6.3 Hz, 1H), 2.25 (dd, *J* = 16.7, 13.1 Hz, 1H), 2.14 (dd, 16.7, 3.7 Hz, 1H), 1.98 (ddd, *J* = 14.1, 7.9, 5.1 Hz, 1H), 1.86 (ddd, *J* = 22.3, 14.1, 7.7 Hz, 2H), 1.73 (ddd, *J* = 14.1, 5.8, 5.2 Hz, 1H), 1.04 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 192.1, 162.8, 138.2, 135.8 (2C), 135.7 (2C), 133.7, 133.7, 129.7, 129.6, 128.2 (2C), 127.6 (2C), 127.5 (2C), 127.5 (2C), 127.4, 106.8, 76.4, 72.7, 67.5, 66.4, 41.7, 40.9, 36.3, 26.9 (3C), 19.23.

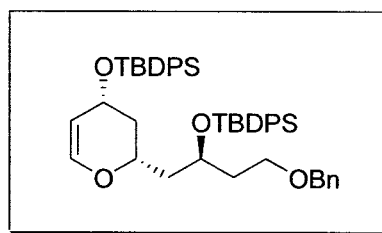
FTIR (neat): 2956, 2931, 2856, 1681, 1600, 1273, 1215, 1111, 997, 736, 701 cm^{-1} .

HRMS (CI) Calcd for $\text{C}_{32}\text{H}_{38}\text{O}_4\text{Si}$ [M^+]: 514.2539. Found: 514.2532.

$[\alpha]_{\text{D}} = -27.3^\circ$ ($c = 4.94$, CH_2Cl_2)

The diastereomeric ratio was determined by HPLC analysis employing a Daicel Chiracel OD column (Hexane : *i*-propanol 99:1, 1.0 mL/min: $t_1 = 26.84$ min for the major diastereomer, $t_2 = 38.33$ min for the minor diastereomer).

((*S*)-4-(benzyloxy)-1-((2*S*,4*R*)-4-(*tert*-butyldiphenylsilyloxy)-3,4-dihydro-2H-pyran-2-yl)butan-2-yloxy)(*tert*-butyl)diphenylsilane (93)



To a solution of dihydropyranone **92** (10 g, 18 mmol, 1 equiv.) in methanol (100 mL) at 0 °C was added cerium(III) chloride (4.43 g, 18 mmol, 1 equiv.). Sodium borohydride (0.68 g, 18 mmol, 1 equiv) was added slowly in portions due to vigorous effervescence evolved during the reduction. The reaction was quenched with saturated sodium sulphate solution after 15 minutes. The white suspension was filtered through a sintered glass funnel and the residue was flushed with copious ethyl acetate (200 mL). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was immediately dissolved in anhydrous *N,N*-dimethylformamide (50 mL) and cooled to 0 °C followed by addition of *tert*-butyldiphenylsilylchloride (4.95 g, 18 mmol, 1 equiv.) and silver(I) nitrate (3.05 g, 18 mmol, 1 equiv.). The suspension was stirred at 0 °C for 2 h and filtered through a pad of celite. The celite was flushed with copious ether (300 mL) and the filtrate was washed with water, followed by brine, dried

over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 2 % ethyl acetate: hexane solvent mixture.

Pale yellow oil (87%)

¹H NMR (400 MHz, CDCl₃): δ 7.70-7.62 (m, 8H), 7.47-7.22 (m, 17H), 6.15 (d, *J* = 6.2 Hz, 1H), 4.56 (dd, *J* = 6.2, 1.5 Hz, 1H), 4.35 (m, 1H), 4.34 (s, 2H), 4.11-4.08 (m, 1H), 3.93-3.92 (m, 1H), 3.48 (ddd, *J* = 9.3, 6.7 Hz, 1H), 3.41 (ddd, *J* = 9.3, 6.7 Hz, 1H), 1.89 (ddd, *J* = 14, 8.1, 4.9 Hz, 1H), 1.81 (dd, *J* = 12.5, 6.3 Hz, 2H), 1.75-1.70 (m, 1H), 1.66-1.60 (m, 2H), 1.06 (s, 9H), 1.03 (s, 9H).

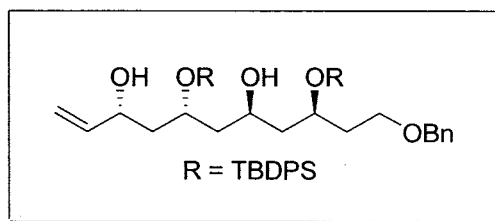
¹³C NMR (100 MHz, CDCl₃): δ 144.1, 138.5, 135.8 (2C), 135.8, 135.7, 134.2, 134.2 (2C), 134.1, 129.6 (2C), 129.6 (2C), 129.5 (2C), 128.2 (2C), 127.6 (2C), 127.6 (2C), 127.5 (2C), 127.5 (2C), 127.5 (2C), 127.4, 105.5, 72.7, 71.4, 68.1, 66.8, 63.9, 41.7, 37.7, 36.1, 27.0 (3C), 26.9 (3C), 19.3, 19.0.

FTIR (neat): 2956, 2931, 2856, 1643, 1446, 1240, 1111, 881, 738, 700 cm⁻¹.

HRMS (CI) Calcd for C₄₈H₅₈O₄Si₂ [M⁺]: 754.3874. Found: 754.3881.

[α]_D = +0.15° (*c* = 5.76, CH₂Cl₂)

Fragment B: (3*S*,5*S*,7*R*,9*R*)-11-(benzyloxy)-5,9-bis-(tert-butylidiphenylsilyloxy)undec-1-ene-3,7-diol



To a solution of dihydropyran **93** (9.07 g, 11.7 mmol, 1 equiv.) in aqueous THF (30 mL, 1:1 THF:H₂O) was added mercury(II) acetate (4.10 g, 12.87 mmol, 1.1 equiv.) and stirred at room temperature for 24 h. The mixture was cooled to 0 °C prior to addition of sodium cyanoborohydride (0.36 g, 4.68 mmol, 0.4 equiv.) and stirred for 1 h at that temperature. The grey mixture was passed through a pad of celite and flushed with copious ethyl acetate (250 mL). The filtrate was washed with brine, dried over MgSO₄, filtered and

concentrated *in vacuo*. The crude lactol **94** was subsequently dissolved in anhydrous THF (10 mL) and vinylmagnesium bromide in THF (1.0 M, 70 mL, 6 equiv.) was added. The mixture was refluxed for 6 h and stirred at room temperature for 12 h. Saturated ammonium chloride solution was added to the cooled mixture at 0 °C. The aqueous layer was extracted with ethyl acetate (3 x 150 mL) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product (1:1 diastereomeric ratio) was purified *via* flash column chromatography using 10 % ethyl acetate: hexane solvent mixture. The desired isomer was further isolated from the undesired isomer *via* a second flash column chromatography.

Pale yellow oil (87%)

¹H NMR (400 MHz, CDCl₃): δ 7.71-7.66 (m, 8H), 7.45-7.29 (m, 15H), 7.22-2.20 (m, 2H), 5.71-5.62 (m, 1H), 5.10-4.97 (m, 2H), 4.29 (s, 2H) 4.14-4.09 (m, 2H), 4.06-4.03 (m, 1H), 3.77-3.73 (m, 1H), 3.39 (ddd, *J* = 12.9, 6.5 Hz, 1H), 3.29 (ddd, *J* = 12.9, 6.4 Hz, 1H), 1.77-1.65 (m, 6H), 1.55-1.47 (m, 2H), 1.07 (s, 9H), 1.03 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 141.1, 138.3, 135.9 (2C), 135.9 (2C), 135.8 (2C), 135.8 (2C), 134.2, 133.9, 133.8, 133.7, 129.8, 129.7, 129.7, 129.6, 128.3 (2C), 127.7 (2C), 127.7 (2C), 127.6 (2C), 127.6(2C), 127.5 (2C), 127.5, 113.7, 72.7, 70.4, 70.3, 69.7, 66.8, 66.5, 44.3, 43.7, 43.6, 36.5, 27.0 (6C), 19.3, 19.3.

FTIR (neat): 3412, 2956, 2931, 2856, 1643, 1446, 1240, 1111, 881, 738, 700 cm⁻¹.

HRMS (ESI) Calcd for C₅₀H₆₄O₅Si₂Na [M+Na]⁺: 823.4190. Found: 823.4183.

[α]_D = +4.9° (*c* = 0.43, CH₂Cl₂)

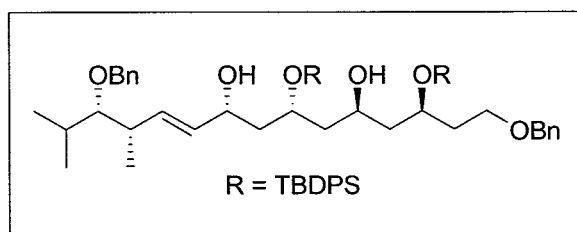
Recycling of the undesired diastereomer

To a solution of the undesired diastereomer **95** (1 equiv.) in petroleum ether was added manganese(IV) oxide (20 equiv.) and stirred for 6 h at room temperature. The black suspension was filtered through a pad of celite. The filtrate was concentrated *in vacuo* and the crude product was immediately dissolved in methanol at 0 °C prior to addition of cerium(III) chloride (1 equiv.). Sodium borohydride (1 equiv) was added slowly in portions due to vigorous effervescence evolved during the reduction. The reaction was quenched with saturated sodium potassium tartrate solution after 15 minutes. The

aqueous layer was extracted with ethyl acetate (3 x 30mL) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product (1:1 diastereomeric ratio) was purified *via* flash column chromatography using 10 % ethyl acetate: hexane solvent mixture. The desired isomer **B** was further isolated from the undesired isomer **95** *via* a second flash column chromatography.

Coupling of Fragment A and B

Olefin (106)



To a heated solution of **B** (0.731 g, 0.91 mmol, 1 equiv.) and **A** (0.39 g, 1.82 mmol, 2 equiv.) in 10 mL of argon degassed CH₂Cl₂ was added a solution of Hoveyda Grubb's 2nd generation catalyst (0.028 g, 0.05 mmol, 5 mol %) in CH₂Cl₂ (1 mL) over a period of 30 min. The reaction was heated to reflux (45 °C) for 6 h at which time NMR analysis revealed that all of substrate **B** has been consumed. The reaction was deemed complete, and was cooled to room temperature and concentrated under reduced pressure. Purification of the residue by flash column chromatography 10% ethyl acetate: hexane furnished the product as a 9:1 mixture of isomers.

Pale yellow oil (52%)

¹H NMR (400 MHz, CDCl₃): δ 7.72-7.68 (m, 8H), 7.44-7.28 (m, 20H), 7.24-7.22 (m, 2H), 5.47 (dd, *J* = 7.8, 15.5 Hz, 1H), 5.32 (dd, *J* = 5.9, 15.5 Hz, 1H), 4.58 (s, 2H), 4.30 (s, 2H), 4.12-4.06 (m, 3H), 3.37 (m, 1H), 3.40 (ddd, *J* = 12.8, 6.4 Hz, 1H), 3.31 (ddd, *J* = 12.8, 6.4 Hz, 1H), 2.97 (dd, *J* = 5.0, 6.3 Hz, 1H), 2.41-2.38 (m, 1H), 1.85-1.80 (m, 1H), 1.74-1.71 (m, 8H), 10.8 (s, 9H), 1.04 (s, 9H), 1.06 (d, *J* = 6.8 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H)

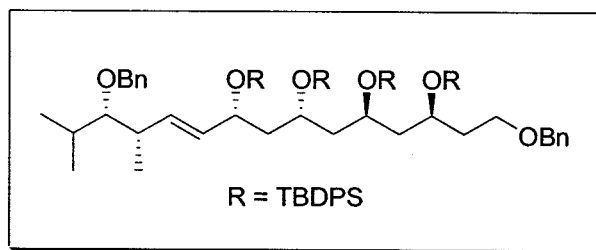
^{13}C NMR (100 MHz, CDCl_3): δ 139.1, 138.4, 136.0 (2C), 135.9 (2C), 135.9 (2C), 135.8 (2C), 134.2, 134.0, 133.9, 133.8, 133.8, 132.2, 129.8, 129.8, 129.7, 129.6, 128.3 (2C), 128.3 (2C), 127.7 (2C), 127.6 (4C), 127.6 (4C), 127.6 (2C), 127.5, 127.4, 88.7, 75.3, 72.7, 70.5, 70.3, 69.5, 66.8, 66.5, 44.4, 44.0, 43.7, 39.7, 36.5, 30.9, 27.0 (6C), 20.6, 19.3, 19.3, 17.3, 15.9.

FTIR (neat): 3412, 2956, 2931, 2856, 1643, 1462, 1427, 1265, 1111, 1070, 975, 920, 821, 738, 720, 700 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{63}\text{H}_{82}\text{O}_6\text{Si}_2\text{Na}$ $[\text{M}+\text{Na}]^+$: 1013.5548. Found: 1013.5556.

$[\alpha]_{\text{D}} = +4.8^\circ$ ($c = 1.64$, CH_2Cl_2)

Olefin 107



To a solution of olefin **106** (0.392 g, 0.395 mmol, 1 equiv.) in anhydrous *N,N*-dimethylformamide (2 mL) was added *tert*-butyldiphenylsilylchloride (0.434 g, 1.58 mmol, 4 equiv) and silver(I) nitrate (0.268 g, 1.58 mmol, 4 equiv). The brown suspension was stirred at 0 °C for 2 h and filtered through a pad of celite. The celite was flushed with copious diethyl ether (3 x 10 mL) and the filtrate was washed with water, followed by brine, dried over MgSO_4 , filtered and concentrated in *vacuo*. The crude product was purified *via* flash column chromatography using 2 % ethyl acetate: hexane solvent mixture.

Pale yellow oil (91%)

^1H NMR (400 MHz, CDCl_3): δ 7.81-7.75 (m, 10H), 7.62-7.36 (m, 38H), 7.33-7.28 (m, 2H), 5.3 (dd, $J = 15.6, 6.8$ Hz, 1H), 5.2 (dd, $J = 15.5, 7.1$ Hz, 1H), 4.64 (d, $J = 11.1$ Hz, 1H), 4.59 (d, $J = 11.1$ Hz, 1H), 4.56-4.54 (m, 1H), 4.48 (d, $J = 11.9$ Hz, 1H), 4.43 (d, $J = 11.9$ Hz, 1H), 4.43-4.40 (m, 1H), 3.61-3.52 (m, 3H), 3.44-3.40 (m, 1H), 2.82 (dd, $J = 3.1, 8.3$ Hz, 1H), 2.36-2.2.31 (m, 1H), 1.75-1.67 (m, 3H), 1.45-1.43 (m, 4H), 1.22-1.21 (m,

2H), 1.22 (s, 9H), 1.21 (s, 9H), 1.08 (d, $J = 6.8$ Hz, 3H) 1.04 (d, $J = 7$ Hz, 3H), 0.99 (d, $J = 6.5$ Hz, 3H), 0.92 (s, 18H).

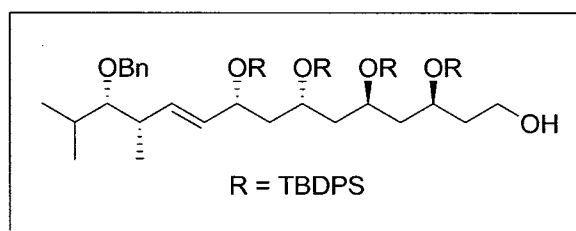
^{13}C NMR (100 MHz, CDCl_3): δ 139.0, 138.5, 135.9 (4C), 135.9 (4C), 135.7 (4C), 135.6 (2C), 135.6 (2C), 135.5, 135.3, 134.6, 134.4, 134.4, 134.3, 134.3, 134.1, 133.4, 131.6, 129.7, 129.5 (2C), 129.4 (2C), 129.2, 128.3 (2C), 128.2 (2C), 127.6 (2C), 127.6 (2C), 127.6 (3C), 127.5 (4C), 127.4 (4C), 127.4 (4C), 127.3 (2C), 127.2 (2C), 119.9, 88.4, 75.5, 72.7, 71.3, 68.4, 68.1, 67.9, 66.7, 46.4, 44.8, 43.3, 40.0, 34.9, 30.9, 27.1 (3C), 27.0 (3C), 26.7 (6C), 20.9, 19.4, 19.2, 19.0, 18.9, 17.0, 15.9.

FTIR (neat): 3070, 3047, 2958, 2929, 2891, 2856, 1462, 1427, 1386, 1361, 1265, 1188, 1111, 1087, 1072, 937, 821, 738, 700, 611 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{95}\text{H}_{119}\text{O}_6\text{Si}_4$ $[\text{M}+\text{H}]^+$: 1467.8084. Found: 1467.8091.

$[\alpha]_{\text{D}} = +1.6^\circ$ ($c = 6.27$, CH_2Cl_2)

Alcohol (108)



Several pieces of lithium metal (1.5 g in total) were dipped one by one into methanol until shiny then immediately transferred into diethyl ether. The shiny lithium metal were then dried and added into a nitrogen purge, oven-dried 50-mL round-bottomed flask equipped with a magnetic stirring bar, containing 4,4'-*di-tert*-butylbiphenyl (DBB) (4 g, 15 mmol, 15 equiv.) in 15 mL of dry THF. The mixture was sonicated at 0 °C, and the resultant deep forest green color of the radical anion solution appeared within 1-5 min. After 3 h of vigorous stirring at 0 °C, the resulting 1.0 M solution of LDBB in THF was added dropwise very slowly to a solution of the alkene **107** (1.46 g, 1 mmol, 1 equiv.) in dry THF (10 ml) at -78 °C, with vigorous stirring after each drop of LDBB added. The initial colourless solution turned deep forest green with every drop of LDBB added and

eventually turned deep maroon on vigorous stirring. The reaction was monitored closely with TLC with every equivalent of LDBB added until most of the starting material has disappeared. The deep maroon mixture was quenched by dropwise addition of saturated ammonium chloride solution at $-78\text{ }^{\circ}\text{C}$, with stirring, until the reaction becomes pale orange. Saturated sodium bicarbonate solution was then added, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 3% ethyl acetate: hexane solvent mixture.

Pale yellow oil (70%)

^1H NMR (500 MHz, CDCl_3): δ 7.61-7.58 (m, 9H), 7.40-7.21 (m, 34H), 7.17-7.14 (m, 2H), 5.12-5.10 (m, 2H), 4.46 (d, $J = 11.1$ Hz, 1H), 4.41 (d, $J = 11.1$ Hz, 1H), 4.42-4.36 (m, 1H), 4.24 (m, 1H), 3.46-3.45 (m, 2H), 3.31 (m, 1H), 3.22 (m, 1H), 2.66 (dd, $J = 3.3, 7.9$ Hz, 1H), 2.19-2.15 (m, 1H), 1.84-1.83 (m, 1H), 1.51 (m, 2H), 1.33-1.21 (m, 4H), 1.16-1.12 (m, 2H), 1.05 (s, 9H), 1.04 (s, 9H), 0.91 (d, $J = 6.6$ Hz, 3H), 0.85 (d, $J = 6.8$ Hz, 3H), 0.81 (d, $J = 6.7$ Hz, 3H), 0.75 (s, 9H), 0.73 (s, 9H).

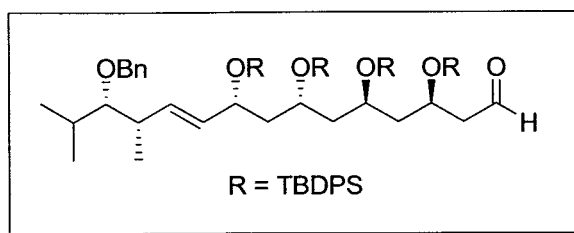
^{13}C NMR (100 MHz, CDCl_3): δ 139.1, 136.0 (4C), 135.9 (4C), 135.9 (4C), 135.8 (2C), 135.7 (2C), 135.6 (2C), 135.3, 134.6, 134.5, 134.3, 134.2, 134.0, 134.0, 133.9, 133.9, 133.4, 131.4, 129.8, 129.7, 129.7, 129.6, 129.5 (3C), 129.3, 128.2 (2C), 127.6 (2C), 127.6(4C), 127.6(4C), 127.5, 127.4 (4C), 127.3, 88.5, 75.4, 71.3, 69.3, 68.3, 68.1, 59.2, 46.6, 45.0, 42.3, 39.8, 36.0, 30.8, 27.2 (3C), 27.1 (3C), 26.8 (6C), 20.9, 19.3 (2C), 19.1, 19.0, 16.7, 16.1.

FTIR (neat): 3446, 3070, 3049, 2968, 2929, 2893, 2856, 1462, 1427, 1265, 1111, 1068, 1039, 1028, 939, 821, 738, 702, 688, 611 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{88}\text{H}_{112}\text{O}_6\text{Si}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 1399.7434. Found: 1399.7421.

$[\alpha]_{\text{D}} = -20.2^{\circ}$ ($c = 5.63$, CH_2Cl_2)

Aldehyde (109)



To a cooled solution of primary alcohol **108** (0.1 g, 0.07 mmol, 1 equiv.) in dry dichloromethane (2 mL) at 0 °C was added Dess–Martin periodinane (0.196 g, 0.7 mmol, 10 equiv.). The reaction was monitored by TLC after 15 min to ensure all of the alcohol has been oxidized to the aldehyde. Saturated sodium thiosulphate solution and saturated sodium bicarbonate solution in 1:1 ratio were added slowly to the stirring reaction mixture at 0 °C and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 mL) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 2% ethyl acetate: hexane solvent mixture.

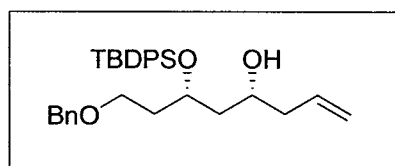
White foam (87%)

¹H NMR (500 MHz, CDCl₃): δ 9.41 (m, 1H), 7.69-7.67 (m, 5H), 7.62-7.60 (m, 5H), 7.48-7.30 (m, 30H), 7.25-7.21 (m, 5H), 5.22 (dd, *J* = 7.5, 15.7 Hz, 1H), 5.14 (dd, *J* = 7.5, 15.7 Hz, 1H), 4.52 (d, 11.1, Hz, 1H), 4.47 (d, 11.1, Hz, 1H), 4.46-4.44 (m, 2H), 3.34-3.29 (m, 2H), 2.70 (dd, *J* = 6.6 Hz, 1H), 2.24-2.21 (m, 1H), 2.06-2.03 (m, 1H), 1.95-1.92 (m, 1H), 1.57 (m, 1H), 1.37-1.22 (m, 6H), 1.10 (s, 9H), 1.08 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.85 (d, *J* = 6.7, 3H), 0.82 (s, 9H), 0.79 (s, 9H).

¹³C NMR (100 MHz, CDCl₃): δ 202.1, 139.1, 135.9 (2C), 135.9 (4C), 135.8 (4C), 135.7 (4C), 135.6 (2C), 135.5 (2C), 135.4, 134.6, 134.4, 134.2, 134.2, 133.6, 133.6, 133.6, 133.2, 131.5, 129.8 (2C), 129.7, 129.6, 129.5, 129.4, 129.3, 128.2 (2C), 127.7 (2C), 127.6 (2C), 127.6 (2C), 127.5 (2C), 127.4 (2C), 127.4 (2C), 127.3 (4C), 127.3 (2C), 88.4, 75.5, 71.3, 67.9, 67.9, 66.9, 48.2, 46.4, 44.9, 43.3, 39.9, 30.8, 27.0 (3C), 26.9 (3C), 26.8 (3C), 26.7 (3C), 20.9, 19.3, 19.2, 19.0, 18.9, 16.9, 15.9.

FTIR (neat): 3070, 3049, 2958, 2929, 2891, 2856, 1722, 1589, 1462, 1427, 1388, 1361, 1265, 1111, 1085, 1039, 1028, 937, 821, 738, 702, 688, 611 cm⁻¹.

HRMS (ESI) Calcd for C₈₈H₁₁₀O₆Si₄Na [M+Na]⁺: 1397.7277. Found: 1397.7281.

$[\alpha]_D = -5.87^\circ$ ($c = 5.77$, CH_2Cl_2)**(4*R*,6*S*)-8-(benzyloxy)-6-(tert-butyldiphenylsilyloxy)oct-1-en-4-ol (98)**

To an oven dried 100 mL round bottom flask equipped with a magnetic stirring bar was added (+)-DIP-Br (2.5 g, 6.84 mmol, 1 equiv.) and dry THF (70 mL). The solution was cooled to -78°C prior to dropwise addition of allylmagnesium bromide (1.0 M in ether, 6.2 mL, 0.9 equiv.) over 30 min. The mixture was allowed to stir at -78°C for an hour and was allowed to warm up to room temperature over 1 hour. The mixture was cooled to 78°C again and was treated with a solution of aldehyde **90** (2.23 g, 5.13 mmol, 0.75 equiv.) in THF (10 mL) dropwise over 30 min. The reaction mixture was stirred at -78°C for 1 h and was allowed to warm gradually to room temperature and stirred for another hour. The solution was cooled to 0°C and quenched with a pre-formed mixture of 3M NaOH (30mL) and 30% H_2O_2 (10 mL) for 30 min. The aqueous layer was extracted with diethyl ether (3 x 30 mL), and the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 5 % ethyl acetate: hexane solvent mixture.

Colorless oil (74 %, dr = 96:4)

^1H NMR (400 MHz, CDCl_3): δ 7.75-7.72 (m, 4H), 7.46-7.23 (m, 11H), 5.79-5.72 (m, 1H), 5.10-5.05 (m, 2H), 4.34 (s, 2H), 4.19-4.16 (m, 1H), 3.87-3.85 (m, 1H), 3.46 (dt, $J = 12.6$, 6.3 Hz, 1H), 3.37 (dt, $J = 12.6$, 6.3 Hz, 1H), 2.53 (d, $J = 3.4$ Hz, 1H, OH), 2.14-2.10 (m, 2H), 1.86-1.82 (m, 2H), 1.76-1.67 (m, 2H), 1.09 (s, 9H).

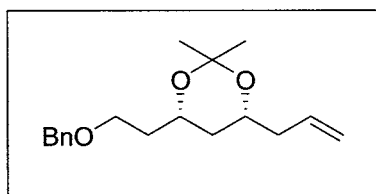
^{13}C NMR (100 MHz, CDCl_3): δ 138.2, 135.8 (4C), 134.7, 134.1, 133.7, 129.7, 129.6, 128.2 (2C), 127.6 (2C), 127.5 (4C), 127.4, 117.6, 72.6, 70.7, 68.6, 66.7, 43.1, 42.1, 36.8, 26.9 (3C), 19.3.

FTIR (neat): 3425, 2929, 2856, 1441, 1111, 914, 642, 821, 736, 702, 611 cm^{-1} .

HRMS (ESI) Calcd for C₃₁H₄₀O₃SiNa [M+Na]⁺: 511.2644. Found: 511.2653.

[α]_D = +2.71° (*c* = 5.42, CH₂Cl₂)

(4*R*,6*S*)-4-allyl-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxane (99)



To a solution of homoallylic alcohol **98** (1.95 g, 4 mmol, 1 equiv.) in dry THF (10 mL) was added 1.0 M TBAF in THF (12 mL, 12 mmol, 3 equiv.) and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the crude residue was passed through a short plug of silica gel. The eluted diol was concentrated under reduced pressure and immediately taken to the next step. In a 25-mL, round-bottom flask were placed the crude diol, dichloromethane (10 mL), 2,2-dimethoxypropane (4.9 mL, 40 mmol, 10.0 equiv) and *dl*-camphorsulfonic acid (5 mg). The solution was stirred at room temperature for 6 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (30 mL) and the biphasic mixture was transferred to a 250-mL separatory funnel. The aqueous layer was extracted with dichloromethane (30 mL) and the combined organic extracts were washed with saturated aqueous NaHCO₃ solution (30 mL) and brine (30 mL). The extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography using 10% ethyl acetate: hexane solvent mixture.

Colorless oil (89%)

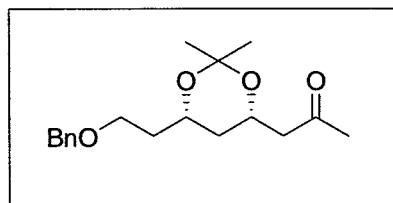
¹H NMR (400 MHz, CDCl₃): δ 7.70-7.31 (m, 5H), 5.89-5.78 (m, 1H), 5.14-5.08 (m, 2H), 4.54 (d, *J* = 12 Hz, 1H), 4.53 (d, *J* = 12 Hz, 1H), 4.08-4.05 (m, 1H), 3.94-3.88 (m, 1H), 3.66-3.54 (m, 2H), 2.34 (dt, 13.9, 6.2 Hz, 1H), 2.18 (dt, 13.9, 6.2 Hz, 1H), 1.84-1.75 (m, 2H), 1.56 (dt, *J* = 2.43, 12.9 Hz, 1H), 1.47 (s, 3H), 1.42 (s, 3H), 1.19 (q, *J* = 12.7 Hz, 1H).
¹³C NMR (100 MHz, CDCl₃): δ 138.4, 134.1, 128.3 (2C), 127.5 (2C), 127.4, 116.9, 98.4, 72.8, 68.5, 66.1, 65.9, 40.7, 46.5, 36.4, 30.1, 19.8

FTIR (neat): 2991, 2928, 2860, 1641, 1372, 1265, 1101, 908, 729 cm^{-1} .

HRMS (CI) Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_3$ $[\text{M}+\text{H}]^+$: 291.1955. Found: 291.1918.

$[\alpha]_{\text{D}} = -9.6^\circ$ ($c = 5.84$, CH_2Cl_2)

Fragment C: 1-((4*S*,6*S*)-6-(2-(benzyloxy)ethyl)-2,2-dimethyl-1,3-dioxan-4-yl)propan-2-one



In a 25 mL round bottomed flask fitted with a magnetic stirring bar, and a rubber balloon filled with oxygen was placed a mixture of palladium(II) chloride (0.017 g, 0.1 mmol, 20 mol %) and copper(I) chloride (0.545 g, 0.55 mmol, 1 equiv.) in water (1 mL) and DMF (7 mL). Oxygen was bubbled into the stirring mixture for 1 h and alkene **99** (0.145 g, 0.5 mmol, 1 equiv.) dissolved in DMF (2 mL) was subsequently added to the mixture slowly with constant bubbling of O_2 . The reaction was stirred under O_2 atmosphere for 4 h and monitored by TLC to ensure all the starting material has been consumed. The reaction was then quenched with ice cold 1.0 M HCl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 30 mL) and the combined organic extracts were washed with brine, dried over MgSO_4 , filtered and concentrated *in vacuo*. The crude product was purified *via* flash column chromatography using 10 % ethyl acetate: hexane solvent mixture.

Colorless oil (70%)

^1H NMR (400 MHz, CDCl_3): δ 7.36-7.28, (m, 5H), 4.53 (d, $J = 12$ Hz, 1H), 4.49 (d, $J = 12$ Hz, 1H), 4.36-4.31 (m, 1H), 4.11-4.05 (m, 1H), 3.62-3.48 (m, 2H), 2.68 (dd, $J = 7.1, 15.9$ Hz, 1H), 2.44 (dd, $J = 5.3, 15.9$ Hz, 1H), 2.18 (s, 3H), 1.79-1.73, (m, 2H), 1.59-1.56 (m, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.24-1.16 (m, 1H).

^{13}C NMR (100 MHz, CDCl_3): δ 206.9, 138.4, 128.3 (2C), 127.6 (2C), 127.5, 98.67, 72.9, 66.1, 65.8, 65.6, 50.0, 36.7, 36.4, 31.0, 30.0, 19.7

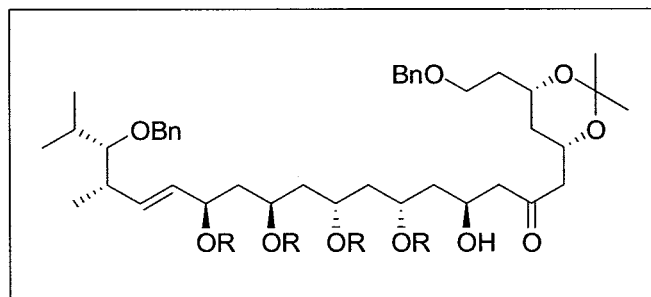
FTIR (neat): 2997, 2360, 2090, 1633, 1305, 1263, 1199, 1168, 1095, 873, 736, 698 cm^{-1} .

HRMS(CI) Calcd for $\text{C}_{18}\text{H}_{27}\text{O}_4$ $[\text{M}+\text{H}]^+$: 307.1854. Found: 307.1904.

$[\alpha]_{\text{D}} = -17.8^\circ$ ($c = 2.04$, CH_2Cl_2)

Coupling to Fragment C

Aldol adduct (110a)



In a 25-mL Schlenk flask were placed ketone **C** (0.116 g, 0.38 mmol, 1.5 equiv) and dry ether (1.5 ml). The solution was cooled to $-78\text{ }^{\circ}\text{C}$. To the reaction mixture were added diisopropylethylamine (0.095 ml, 0.55 mmol, 1.45 equiv. to ketone) followed by a 1.0 M solution of dibutylboron triflate (0.5 mL, 0.5 mmol, 1.32 equiv. to ketone) dropwise. The reaction mixture was stirred for 1 h before the addition of solution of aldehyde **109** (0.348 g, 0.25 mmol, 1 equiv.) in dichloromethane (1 ml) dropwise over 1 h whereupon the reaction mixture was stirred for 16 h. To the reaction mixture was added a 6/1 mixture MeOH/pH 7 phosphate buffer solution (7 mL). The resulting emulsion was allowed to warm to $0\text{ }^{\circ}\text{C}$ using an ice bath. To the reaction mixture was added dropwise a 3/1 mixture of MeOH/30% H_2O_2 solution (6 mL). The reaction mixture was stirred for 30 min and was poured into a 100-mL separatory funnel. The solution was diluted with ethyl acetate (10 mL) and was washed with water (10 mL), saturated aqueous NaHCO_3 solution (10 mL) and brine (10 mL). The solution was dried over Na_2SO_4 and was concentrated under reduced pressure. The crude product was purified *via* flash column chromatography using 2% ethyl acetate: hexane solvent mixture to afford the product in 3:1 diastereomeric ratio.

White foam (73%)

^1H NMR (500 MHz, CDCl_3): δ 7.63-7.59 (m, 8H), 7.47-7.45 (m, 2H), 7.39-7.36 (m, 10H), 7.34-2.27 (m, 24H), 7.24-7.21 (m, 4H), 7.14-7.11 (m, 2H), 5.14 (dd, $J = 7.6, 15.6$ Hz, 1H), 5.03 (dd, $J = 7.6, 15.6$ Hz, 1H), 4.50 (d, $J = 12.1$ Hz, 1H), 4.46 (d, $J = 12.1$ Hz, 1H), 4.45 (d, $J = 11.2$ Hz, 1H), 4.39 (d, $J = 11.2$ Hz, 1H), 4.36-4.34 (m, 2H), 4.30-4.27 (m, 1H), 4.11-4.09 (m, 1H), 4.03-4.00 (m, 1H), 3.58-3.44 (m, 3H), 3.33-3.31 (m, 1H), 3.05 (d,

$J = 1.8$ Hz, 1H, OH), 2.62 (dd, $J = 3.2, 8.4$ Hz, 1H), 2.54 (dd, $J = 7.5, 15.9$ Hz, 1H), 2.46 (dd, $J = 7.2, 16.9$ Hz, 1H), 2.33-2.24 (m, 2H), 2.17-2.13 (m, 1H), 1.74-1.69 (m, 3H), 1.51-1.49 (m, 2H), 1.35 (s, 3H), 1.29 (s, 3H), 1.25-1.13 (m, 8H), 1.06 (s, 9H), 1.03 (s, 9H), 0.90 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H), 0.72 (s, 9H), 0.71 (s, 9H).

^{13}C NMR (100 MHz, CDCl_3): δ 207.0, 139.1, 138.5, 135.9 (4C), 135.9 (4C), 135.9 (2C), 135.7 (2C), 135.7 (2C), 135.6 (2C), 135.6 (2C), 135.4, 134.7, 134.4, 134.4, 134.2, 134.2, 133.7, 133.6, 133.4, 131.6, 129.7, 129.7, 129.7, 129.4, 129.3, 129.2, 128.3 (2C), 128.2 (2C), 127.6 (2C), 127.6 (6C), 127.5 (2C), 127.5 (2C), 127.4 (2C), 127.3 (4C), 127.2 (4C), 98.6, 88.4, 75.4, 72.9, 71.6, 69.4, 68.2, 68.1, 66.1, 65.9, 65.8, 64.1, 51.4, 49.6, 46.4, 44.7, 42.2, 40.1, 39.7, 36.8, 36.5, 30.8, 30.0, 27.1 (3C), 27.0 (3C), 26.7 (6C), 20.9, 19.7, 19.3 (2C), 19.0, 18.9, 16.8, 15.9.

FTIR (neat): 3070, 3047, 3032, 2995, 2956, 2929, 2893, 2856, 1712, 1469, 1427, 1379, 1361, 1265, 1111, 1068, 821, 738, 700, 611 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{106}\text{H}_{136}\text{O}_{10}\text{Si}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 1703.9108. Found: 1703.9117.

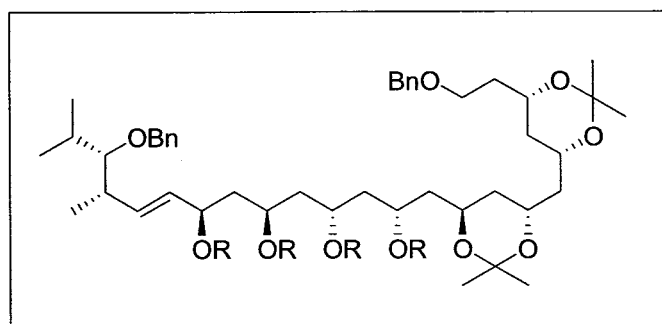
$[\alpha]_{\text{D}} = -13.7^\circ$ ($c = 5.69$, CH_2Cl_2)

The stereochemistry was confirmed by comparing the results of the chiral boron enolates where the aldol product from (-)-DIP-Br¹⁵³ corresponds to the major diastereomer obtained from the reaction with *n*-Bu₂BOTf. Stereochemical outcome of similar systems have also been confirmed by Evans *et al.*¹⁵⁴

¹⁵³ Paterson, I.; Goodman, J. M.; Lister, M. A.; Schumann, R. C.; McClure, C. K.; Norcross, R. D. *Tetrahedron* **1990**, *46*, 4663.

¹⁵⁴ Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. T. *J. Am. Chem. Soc.* **2003**, *125*, 10893.

Acetonide (111)



In a 100-mL, round-bottom flask were placed aldol adduct **110a** (0.191 g, 0.113 mmol), acetonitrile (5 mL) and acetic acid (5 mL). The solution was cooled to 0 °C. To the solution was added tetramethylammonium triacetoxyborohydride (0.15 g, 0.57 mmol, 5.0 equiv), and the reaction mixture was stirred at 0 °C for 10 h. The reaction was quenched with saturated aqueous sodium potassium tartrate (10 mL) and the mixture was transferred to a 125- mL separatory funnel and then was extracted with dichloromethane (2 x 30 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution (20 mL) and brine (20 mL), then was dried over Na₂SO₄ and concentrated under reduced pressure to afford a crude diol. In a 25-mL, round-bottom flask were placed the crude diol, dichloromethane (10 mL), 2,2-dimethoxypropane (0.15 ml, 1.13 mmol, 10.0 equiv) and *dl*-camphorsulfonic acid (5 mg). The solution was stirred at rt for 6 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (30 mL) and the biphasic mixture was transferred to a 250-mL separatory funnel. The aqueous layer was extracted with dichloromethane (30 mL) and the combined organic extracts were washed with saturated aqueous NaHCO₃ solution (30 mL) and brine (30 mL). The extracts were dried over Na₂SO₄ and concentrated under reduced pressure. The crude product was purified *via* flash column chromatography using 10% ethyl acetate: hexane solvent mixture to afford the product in greater than 19:1 diastereomeric ratio.

White foam (87%)

¹H NMR (500 MHz, CDCl₃): δ 7.70-7.65 (m, 4H), 7.62-7.59 (m, 6H), 7.47-7.45 (m, 2H), 7.42-7.32 (m, 34H), 7.22-7.19 (m, 2H), 7.17-7.13 (m, 2H), 5.05-5.03 (m, 2H), 4.55 (d, *J* = 12, 1H), 4.51 (d, *J* = 12, 1H), 4.48 (d, *J* = 11.1 Hz, 1H), 4.43 (d, *J* = 11.1 Hz, 1H),

4.34 (m, 2H), 4.05-4.03 (m, 1H), 3.96-3.94 (m, 2H), 3.87-3.85 (m, 1H), 3.65-3.60 (m, 1H), 3.58-3.54 (m, 1H), 3.37-3.33 (m, 1H), 3.32-3.27 (m, 1H), 2.64 (dd, $J = 3.3, 8.2$, 1H), 2.16-2.11 (m, 1H), 1.79-1.74 (m, 4H), 1.52-1.49 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 1.38-1.25 (m, 5H), 1.29-1.25 (m, 4H), 1.24 (s, 3H), 1.07-1.05 (m, 2H), 1.06 (s, 9H), 1.04 (s, 9H), 1.00 (s, 3H), 0.90 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.82 (s, 9H), 0.74 (s, 9H).

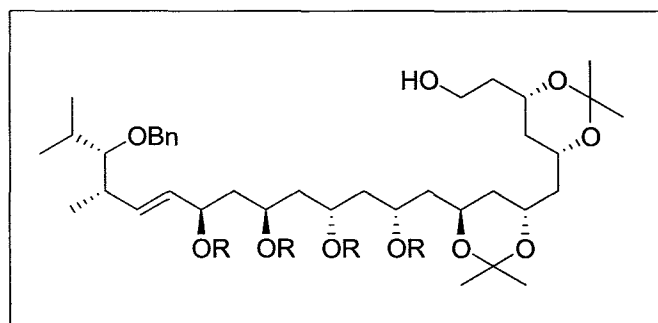
^{13}C NMR (100 MHz, CDCl_3): δ 139.0, 138.5, 125.9 (2C), 135.9 (4C), 135.9 (4C), 135.7, 135.6, 135.1, 134.8, 134.6 (2C), 134.4 (2C), 134.3 (2C), 133.2, 131.5, 129.8, 129.5, 129.4 (4C), 129.3, 129.3, 128.4 (4C), 128.3 (4C), 127.7 (2C), 127.6 (2C), 127.5 (2C), 127.5 (4C), 127.4 (2C), 127.3 (4C), 127.3 (4C), 127.2 (2C), 99.9, 98.4, 88.4, 75.5, 73.1, 71.2, 68.5, 68.4, 68.2, 66.3, 65.9, 65.7, 63.4, 62.6, 46.2, 45.0, 44.9, 44.2, 42.2, 39.9, 39.3, 36.7 (2C), 30.8, 30.3, 27.2 (3C), 27.1 (3C), 27.0 (3C), 26.8 (3C), 25.2, 24.8, 20.9, 19.9, 19.5, 19.3, 19.2, 19.0, 16.9, 16.1.

FTIR (neat): 3070, 3049, 3032, 2995, 2956, 2931, 2893, 2856, 1454, 1427, 1379, 1361, 1265, 1111, 1087, 1068, 939, 821, 738, 700, 611 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{109}\text{H}_{142}\text{O}_{10}\text{Si}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 1745.9578. Found: 1745.9567.

$[\alpha]_{\text{D}} = -7.8^\circ$ ($c = 4.27$, CH_2Cl_2)

Alcohol (112)



Several pieces of lithium metal (1 g) were dipped one by one into methanol until shiny then immediately transferred into diethyl ether. The shiny lithium metal were then dried and added into a nitrogen purge, oven-dried 50-mL round-bottomed flask equipped with a magnetic stirring bar, containing 4,4'-*di-tert*-butylbiphenyl (DBB) (1.34 g, 5mmol) in 10 mL of dry THF. The mixture was sonicated at 0 °C, and the resultant deep forest green color of the radical anion solution appeared within 1-5 min. After 3 h of vigorous stirring at 0 °C, the resulting 1.0 M solution of LDBB in THF was added dropwise very slowly to a solution of the acetonide **111** (39.8 mg, 0.023 mmol, 1 equiv.) in dry THF (3 ml) at -78 °C, with vigorous stirring after each drop of LDBB added. The initial colourless solution turned deep forest green with every drop of LDBB added and eventually turned deep maroon on vigorous stirring. The reaction was monitored closely with TLC with every equivalent of LDBB added until most of the starting material has disappeared. The deep maroon mixture was quenched by dropwise addition of saturated ammonium chloride solution at -78 °C, with stirring, until the reaction becomes pale orange. Saturated sodium bicarbonate solution was then added, the layers were separated, and the aqueous phase was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in *vacuo*. The crude product was purified *via* flash column chromatography using 3% ethyl acetate: hexane solvent mixture.

Pale yellow oil (67%)

¹H NMR (400 MHz, CDCl₃): δ 7.68-7.64 (m, 4H), 7.60-7.57 (m, 4H), 7.47-7.44 (m, 2H), 7.40-7.28 (m, 31H), 7.20-7.17 (m, 2H), 7.15-7.12 (m, 2H), 5.03-5.01 (m, 2H), 4.46 (d, *J*

= 11.1 Hz, 1H), 4.42 (d, $J = 11.1$ Hz, 1H), 4.34-4.32 (m, 2H), 4.09 (m, 1H), 3.94-3.91 (m, 2H), 3.85-3.80 (m, 1H), 3.79-3.76 (m, 2H), 3.36-3.31 (m, 2H), 2.63 (dd, $J = 3.2, 8.2$ Hz, 1H), 2.13 (m, 1H), 1.76-1.73 (m, 4H), 1.52-1.49 (m, 2H), 1.44 (s, 3H), 1.39 (s, 3H), 1.37-1.28 (m, 5H), 1.29-1.27 (m, 4H), 1.23 (s, 3H), 1.17-1.11 (m, 2H), 1.05 (s, 9H), 1.03 (s, 9H), 0.99 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H), 0.86 (s, 3H), 0.83 (s, 9H), 0.73 (s, 9H).

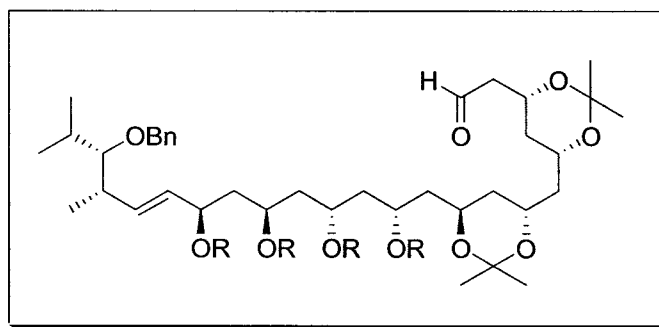
^{13}C NMR (100 MHz, CDCl_3): δ 138.9, 135.9 (4C), 135.8 (4C), 135.7 (2C), 135.6, 135.1, 134.6, 134.6, 134.5, 134.3, 134.2, 133.2, 131.5, 129.8, 129.5 (2C), 129.4, 129.3, 129.3, 128.2 (2C), 128.3 (2C), 127.7 (2C), 127.6 (2C), 127.5 (4C), 127.5 (4C), 127.4 (4C), 127.3 (4C), 127.3 (4C), 127.2 (2C), 99.9, 98.5, 88.3, 75.4, 71.1, 69.5, 68.4, 68.3, 68.2, 65.6, 63.4, 62.6, 60.9, 46.2, 45.0, 44.9, 44.2, 42.1, 39.9, 39.3, 38.0, 36.2, 30.8, 30.2, 27.2 (3C), 27.0 (3C), 26.9 (3C), 26.7 (3C), 25.1, 24.8, 20.9, 19.9, 19.5, 19.2, 19.1, 18.9, 16.9, 16.1.

FTIR (neat): 3487, 3070, 3049, 3032, 2995, 2956, 2931, 2893, 2856, 1454, 1427, 1379, 1361, 1265, 1111, 1087, 1068, 939, 821, 738, 700, 611 cm^{-1} .

HRMS Calcd for $\text{C}_{102}\text{H}_{136}\text{O}_{10}\text{Si}_4\text{Na}$ $[\text{M}+\text{Na}]^+$: 1655.9108. Found: 1655.9127.

$[\alpha]_{\text{D}} = -2.1^\circ$ ($c = 0.75$, CH_2Cl_2)

Aldehyde (113)



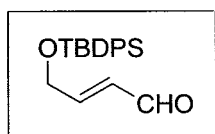
To a cooled solution of primary alcohol **112** (28.8 mg, 0.0176 mmol, 1 equiv.) in dry dichloromethane (3 mL) at 0°C was added Dess Martin periodinane (0.09 g, 0.211 mmol, 12 equiv.). The reaction was monitored by TLC after 15 min to ensure all of the alcohol has been oxidized to the aldehyde. Saturated sodium thiosulphate solution and saturated sodium bicarbonate solution in 1:1 ratio were added slowly to the stirring reaction

mixture at 0 °C and the layers were separated. The aqueous phase was extracted with ethyl acetate (3 x 10 ml) and the combined organic extracts were washed with brine, dried over MgSO₄, filtered and concentrated in *vacuo*. The crude product was purified *via* flash column chromatography using 2% ethyl acetate: hexane solvent mixture and immediately subjected to the next step.

White foam (89%)

Synthesis of Fragment D

(*E*)-4-(*tert*-butyldiphenylsilyloxy)but-2-enal (101)

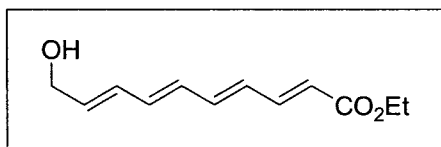


A mixture of (*E*)-2-butene-1,4-diol (1.29 g, 14.66 mmol), imidazole (2.19 g, 32.25 mmol), and *tert*-butyldiphenylchlorosilane (3.63 g, 13.19 mmol) was stirred at 0 °C for 15 h. The mixture was extracted with ether, and the extract was washed with water and brine, dried, and concentrated. The crude mixture was passed through a plug of silica gel to afford the mono protected alcohol which was immediately taken to the next step. A mixture of the alcohol and activated MnO₂ (19.67 g, 226 mmol) in petroleum ether (100 mL) was stirred vigorously for 6 h at room temperature. The mixture was filtered and the filtrate was concentrated. The crude product was purified *via* flash column chromatography using 24% ethyl acetate: hexane solvent mixture.

White solid (74%)

¹H NMR (300 MHz, CDCl₃): δ 9.60 (d, *J* = 8.1 Hz, 1H), 7.36-7.48 (m, 6H), 7.64-7.73 (m, 4H), 6.85 (dt, *J* = 15.5, 3.0, Hz, 1H), 6.57 (ddt, *J* = 15.5, 8.1, 2.0, Hz, 1H), 4.45 (dd, *J* = 3.0, 2.0 Hz, 2H), 1.08 (s, 9H).

FTIR (CHCl₃): 1690, 1435, 1120, 970 cm⁻¹.

(2E,4E,6E,8E)-ethyl 10-hydroxydeca-2,4,6,8-tetraenoate (105)

A stirred suspension of allyltriphenylphosphonium bromide (5.75 g, 15 mmol, 1.2 equiv) in dry THF (10 mL) was treated with 1.6M *n*-BuLi in hexane (12 mL, 19.5 mmol, 1.5 equiv.) at 0 °C under a nitrogen atmosphere. After being stirred at 0°C for 25 min, ethyl (*Z*)-3-bromoacrylate **103** (1.81 mL, 15 mmol, 1.2 equiv.) was added and the mixture was stirred at room temperature for 90 min. The reaction mixture was cooled to 0 °C and a solution of potassium *tert*-butoxide (15 mL, 15 mmol, 1.2 equiv.) was added. The mixture was allowed to stir at 0 °C for 30 min and then a solution of aldehyde **102** (4.1 g, 12.6 mmol, 1 equiv.) in dry THF (15 mL) was added. After being stirred at room temperature for 17 h, the reaction was quenched with saturated aqueous NH₄Cl and the whole was concentrated. The residue was extracted with ether, and the extract was washed with water and brine, dried, and concentrated. The crude product was purified *via* flash column chromatography using 7% ethyl acetate: hexane solvent mixture to afford polyene **104** in 33 % yield as a 1:1.5 mixture of *E* and *Z* isomers which was immediately taken to the next step. To a solution of polyene **104** (0.439 g, 0.983 mmol, 1 equiv.) in THF (5 mL) was added 1M Bu₄NF in THF (2.9 mL, 2.9 mmol, 3 equiv.), and the solution was stirred at room temperature for 1 h. The reaction mixture was extracted with EtOAc. The extract was washed with water and brine, dried, and evaporated to give a mixture of hydroxy esters **105**. A solution of this mixture and a trace amount of I₂ in CH₂Cl₂ (10 mL) was irradiated with a 300-W sunlamp for 1.5 h. The solution was diluted with CH₂Cl₂ (20 mL), washed with aqueous Na₂S₂O₃, dried, and concentrated. The crude product was purified *via* flash column chromatography using 9% ethyl acetate: hexane solvent mixture.

Yellow solid 82%

¹H NMR (400 MHz, CDCl₃): δ 7.31 (dd, *J* = 15.4, 11.5 Hz, 1H), 6.58 (dd, *J* = 14.4, 10.7 Hz, 1H), 6.41 (dd, *J* = 14.4, 10.5 Hz, 1H), 6.34 (m, 2H), 6.29 (dd, *J* = 14.4, 10.7 Hz, 1H),

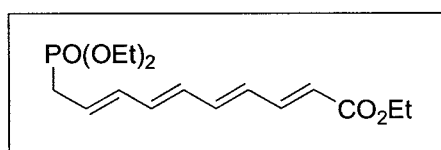
5.96 (dt, $J = 14.4, 5.6$ Hz, 1H), 5.87 (d, $J = 15.4$ Hz, 1H), 4.24 (d, $J = 5.6$ Hz, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 1.94 (br, OH, 1H), 1.29 (t, $J = 7.1$ Hz, 3H).

^{13}C NMR (100 MHz, CDCl_3): δ 167.14, 144.26, 140.36, 136.13, 135.02, 131.89, 130.52, 130.20, 120.83, 63.06, 60.30, 14.26.

FTIR (CHCl_3): 3600, 3470, 1695, 1620, 1595, 1365, 1300, 1240, 1120, 1005 cm^{-1} .

HRMS (FAB) Calcd for $\text{C}_{12}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 209.1178. Found: 209.1186.

Fragment D: (2E,4E,6E,8E)-ethyl 10-(diethoxyphosphoryl)deca-2,4,6,8-tetraenoate



To a solution of hydroxyl polyene **105** (0.17 g, 0.816 mmol, 1 equiv.) in CH_2Cl_2 (5 ml) at 0 °C were added pyridine (6 μL) and PBr_3 (0.115 mL, 1.22 mmol, 1.5 equiv.). The mixture was stirred for 30 min and then water was added. The whole was extracted with ether, and the extract was washed with saturated aqueous NaHCO_3 and brine, dried, and concentrated. The bromide thus obtained was employed without further purification. A solution of the bromide and triethyl phosphite (0.35 ml, 2.04 mmol, 2.5 equiv.) in toluene (5mL) was refluxed for 8h. After cooling the reaction to ambient temperature, the solution was extracted with EtOAc. The extract was washed with water and brine, dried, and concentrated. The crude product was purified *via* flash column chromatography using 25% ethyl acetate: hexane solvent mixture.

Yellow solid (75%)

^1H NMR (400 MHz, CDCl_3): δ 7.31 (dd, $J = 15.1, 11.5$ Hz, 1H), 6.57 (dd, $J = 14.9, 11.0$ Hz, 1H), 6.39 (dd, $J = 14.9, 10.8$ Hz, 1H), 6.20-6.36 (m, 3H), 5.87 (d, $J = 15.1$ Hz, 1H), 5.77 (m, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 4.10 (q, $J = 7.1$ Hz, 2H), 4.09 (q, $J = 7.1$ Hz, 2H), 2.69 (dd, $J_{\text{H-P}} = 23.0, J_{\text{H-H}} = 7.6$ Hz, 2H), 1.31 (t, $J = 7.1$ Hz, 6H), 1.30 (t, $J = 7.1$ Hz, 3H).

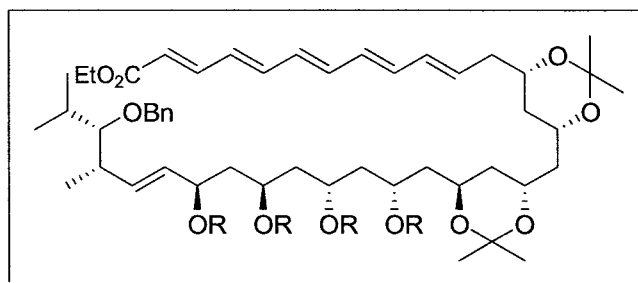
^{13}C NMR (100 MHz, CDCl_3): δ 167.05, 144.18, 140.29, 136.05 (d, $J_{\text{C-P}} = 4.9$ Hz), 134.69 (d, $J_{\text{C-P}} = 16.1$ Hz), 131.43 (d, $J_{\text{C-V}} = 5.8$ Hz), 125.13 (d, $J_{\text{C-P}} = 13.2$ Hz), 120.83, 62.08, 62.01, 60.25, 31.08 (d, $J_{\text{C-P}} = 40.9$ Hz), 16.44, 16.39, 14.26.

FTIR (CHCl_3): 1700, 1620, 1595, 1370, 1300, 1250, 1025, 965 cm^{-1} .

HRMS (FAB) Calcd for $\text{C}_{16}\text{H}_{26}\text{O}_5\text{P}$ $[\text{M}+\text{H}]^+$: 329.1516. Found: 329.1552.

Coupling to Fragment D

Product 114



In a 50-mL Schlenk flask was placed **D** (59.1 mg, 0.18 mmol, 2.5 equiv) and tetrahydrofuran (15 mL). The solution was cooled to -78 $^{\circ}\text{C}$. To the solution was added dropwise a 0.2 M solution of LiHMDS in THF (0.9 mL, 0.18 mmol, 2.5 equiv). The dark blue solution was stirred for 15 min before the addition of a solution of aldehyde **113** (58 mg, 0.072 mmol) in tetrahydrofuran (5 mL). The reaction mixture was stirred at -72 $^{\circ}\text{C}$ for 15 min, then was allowed to warm to 0 $^{\circ}\text{C}$ using an ice bath and was stirred for 45 min at 0 $^{\circ}\text{C}$. The reaction mixture was quenched with saturated aqueous NaHCO_3 solution (20 mL). The biphasic mixture was transferred to a 125-mL separatory funnel. The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic layers were washed with brine (20 mL). The extracts were dried over Na_2SO_4 and then were concentrated under reduced pressure. The crude product was purified *via* flash column chromatography using 2% ethyl acetate: hexane solvent mixture.

Yellow foam (71%)

^1H NMR (500 MHz, CDCl_3): δ 7.66-7.71 (m, 4H), 7.58-7.55 (m, 4H), 7.43-7.42 (m, 2H), 7.33-7.27 (m, 31H), 7.18-7.15 (m, 2H), 7.13-7.10 (m, 2H), 6.58 (dd, $J = 11.1$ 14.6 Hz, 1H), 6.40 (dd, $J = 10.9$, 14.7 Hz, 1H), 6.33-6.27 (m, 3H), 6.26-6.24 (m, 1H), 6.22-6.13

(m, 2H), 5.86 (d, $J = 15.2$ Hz, 1H), 5.81-5.76 (m, 1H), 5.01-4.99 (m, 2H), 4.44 (d, $J = 11.1$ Hz, 1H), 4.40 (d, $J = 11.1$ Hz, 1H), 4.31 (m, 2H), 4.20 (q, $J = 7.1$ Hz, 2H), 3.90-3.83 (m, 4H), 3.34-3.29 (m, 2H), 2.61 (dd, $J = 3.3, 8.3$ Hz, 1H), 2.37-2.35 (m, 1H), 2.25-2.22 (m, 1H), 2.10-2.09 (m, 1H), 1.89-1.84 (m, 1H), 1.76-1.72 (m, 3H), 1.62-1.59 (m, 3H), 1.50-1.45 (5H), 1.42 (s, 3H), 1.39 (s, 3H), 1.38-1.34 (m, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.21 (s, 3H), 1.03 (s, 9H), 1.02 (s, 9H), 0.99 (s, 3H), 0.86- 0.84 (m, 9H), 0.78 (s, 9H), 0.70 (s, 9H)

^{13}C NMR (100 MHz, CDCl_3): δ 167.2, 144.4, 140.7, 139.0, 137.2, 135.9 (4C), 135.9 (4C), 135.9 (4C), 135.7, 135.6, 135.4, 135.1, 134.6, 134.6, 134.5, 134.3, 134.2, 133.2, 132.7, 132.1, 131.5, 131.4, 130.9, 129.8, 129.7 (2C), 129.5, 129.4, 129.3, 128.2 (4C), 127.7 (4C), 127.5 (4C), 127.5 (4C), 127.5 (2C), 127.4 (2C), 127.3 (2C), 127.3 (2C), 127.2 (2C), 127.2 (2C), 120.4, 99.9, 98.5, 88.4, 75.5, 71.1, 68.7, 68.4, 68.3, 68.2, 65.6, 63.4, 62.6, 60.2, 46.3, 45.0, 44.9, 44.2, 42.1, 39.9, 39.9, 39.2, 36.1, 30.8, 30.2, 27.2 (3C), 27.0 (3C), 26.9 (3C), 26.7 (3C), 25.1, 24.8, 20.9, 19.9, 19.5, 19.2, 19.1, 18.9, 16.9, 16.1, 14.3.

FTIR (neat): 3070, 3049, 3032, 2995, 2956, 2931, 2893, 2856, 1620, 1595, 1454, 1427, 1379, 1361, 1300, 1265, 1111, 1087, 1068, 1025, 965, 939, 821, 738, 700, 611 cm^{-1} .

HRMS (ESI) Calcd for $\text{C}_{114}\text{H}_{148}\text{O}_{11}\text{Si}_4\text{Na}$ [$\text{M} + \text{Na}$] $^+$: 1827.9996. Found: 1828.0009.

$[\alpha]_{\text{D}} = -0.99^\circ$ ($c = 0.96$, CH_2Cl_2)

LIST OF PUBLICATIONS

International Refereed Papers:

1. Fan Fu, Yong-Chua Teo and Teck-Peng Loh, *Tetrahedron Lett.* **2006**, *47*, 4267.
Catalytic Enantioselective Mukaiyama aldol reaction via a chiral indium(III)–pybox complex..
2. Fan Fu, Yong-Chua Teo, and Teck-Peng Loh, *Org Lett*, **2006**, *8*, 5999.
Catalytic Enantioselective Diels-Alder Reaction in Ionic Liquid via a Recyclable Chiral In(III) Complex.
3. Fan Fu, Jun Lu, Yong-Chua Teo and Teck-Peng Loh.
Catalytic enantioselective propargylation and allenylation of aldehydes via a chiral PYBOX-In(III) Complex. Submitted for publication.
4. Yong-Chua Teo, Show-Mun Wong, Fan Fu and Teck-Peng Loh.
Catalytic enantioselective propargylation and allenylation of aldehydes via a chiral BINOL-In(III) Complex. Submitted for publication.
5. Fan Fu and Teck-Peng Loh.
Asymmetric Synthesis of the Polyol Fragment of the Polyene Macrolide antibiotic RK-397. Submitted for publication.

6. Fan Fu, Le Mai Hoang Kim, Teck-Peng Loh.

A simple approach to separate a mixture of homopropargylic and allenic alcohols. *Submitted for publication.*

Conference Papers:

7. Fan Fu, Yong-Chua Teo, and Teck-Peng Loh. **Catalytic enantioselective Diels-Alder reaction in ionic liquid via a recyclable chiral In(III) complex.** Abstracts of Papers, 234th ACS National Meeting, Boston, MA, United States, August 19th -23rd, 2007.
8. Fan Fu, Yong-Chua Teo and Teck-Peng Loh. **Catalytic enantioselective Mukaiyama aldol reaction via a chiral indium(III)-pybox complex.** Singapore International Chemical Conference 3, Shangri-La Hotel, Singapore, December 15th -17th 2005.