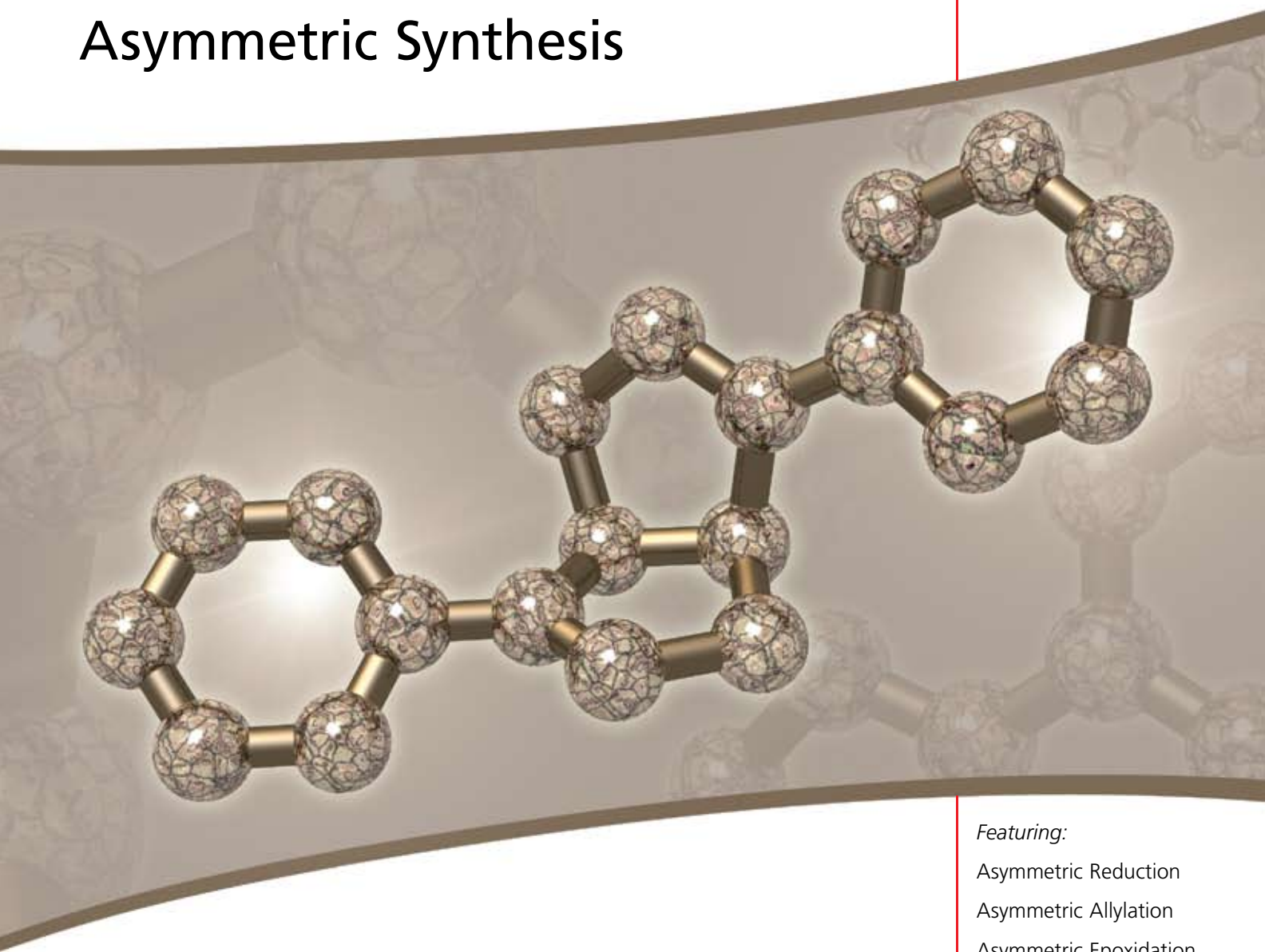
ChemFiles

Vol. 8, No. 6

ALDRICH Chemistry

Asymmetric Synthesis



New chiral diene ligand for conjugate addition

Featuring:

Asymmetric Reduction

Asymmetric Allylation

Asymmetric Epoxidation

Introduction

William Sommer
Product Manager

Asymmetric synthesis has become one of the most important tools for the synthesis of chiral molecules. The importance of this transformation is illustrated by the nearly endless discovery of chiral molecules used in various fields such as new drugs, fragrances, pesticides, etc. Since Knowles and Horner's pioneering work with the hydrogenation of prochiral olefins,[1,2] a plethora of new ligands and catalysts have been developed for new asymmetric reactions. These new transformations give access to molecules in fewer steps, high yields and high enantiopurity.

In this issue of *ChemFiles*, we are pleased to present new chiral ligands and catalysts for a variety of transformations; new chiral phosphines for hydrogenation, hydrosilylation and for the reduction of ketones; a new generation of ligands such as chiral dienes for conjugate addition from Carreira and Zhou, as well as the ligands developed by Walsh. Our different Ipc_2 boranes as well as Soderquist borabicyclodecanes are also highlighted.

If you are unable to find the catalyst or ligand for your research, "Please Bother Us" with your suggestions at *william.sommer@sial.com*.

References: (1) Knowles, W. S. et al. *Chem. Commun.* **1968**, 1445. (2) Horner, L. et al. *Angew. Chem.* **1968**, *80*, 1034.

About Our Cover

The cover graphic represents the three-dimensional structure of (3a*S*, 6a*S*)-3,6-Diphenyl-1,3a,4,6a-tetrahydropentalene (hydrogen is not represented for clarity). This ligand is used in the conjugate addition of aryl boronic acids to α,β-unsaturated carbonyl compounds.

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Vol. 8 No. 6

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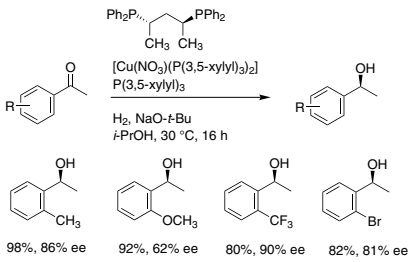
Asymmetric Reduction

Asymmetric Hydrogenation

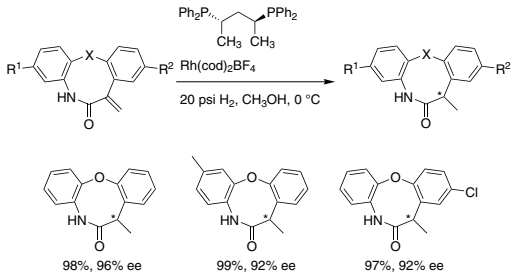
Asymmetric hydrogenation plays an important role in today's synthesis world. Knowles and Noyori pioneered this field and were rewarded with the Nobel Prize in 2001 for their work. It allows the generation of chiral centers selectively, with good yields. Furthermore, it gives access to a new pool of molecules with specific properties used in the pharmaceutical, flavors and fragrances, and agrochemical industries. However, the metal complex commonly used for these transformations is usually based on rhodium or ruthenium. The high cost and scarcity of these metal complexes make the technology prohibitive for use in large-scale synthesis. Based on the preliminary work of Stryker with copper catalysts, Shimizu et al. developed a new methodology for the hydrogenation of aryl ketones using copper complexes.[1] To achieve high enantioselectivities, (*S*,*S*)-BDPP ligand is necessary. Using a copper complex with (S,S)-BDPP, and tri(3,5-xylyl)-phosphine, a variety of aryl ketones were reduced to secondary alcohols in good to excellent yields with overall good ee's (**Scheme 1**).

The versatility of (*S*,*S*)-BDPP was demonstrated in the work done by Lu and Alper.[2] In their quest to synthesize chiral heterocycles, they investigated a number of catalysts and ligands for the asymmetric hydrogenation of terminal alkenes. Common ruthenium and iridium complexes were used with limited success. Furthermore, several chiral bidentate ligands such as BINAP, Monophos, DIOP, Duphos or Josiphos were tested in the transformation with little success. The best catalytic system was found to be (*S*,*S*)-BDPP with $Rh(cod)_2BF_4$. A variety of tricyclic lactams were synthesized with excellent enantioselectivity. The procedure typically involves the use of 1 mol% of rhodium complex and ligand in methanol at 0 °C under 20 psi of H_2. It is important to note that these heterocyclic motifs are encountered in many biologically active natural products as well as drug candidates.

References: (1) Shimizu, H. et al. *Org. Lett.* **2007**, *9*, 1655. (2) Lu, S. -M. et al. *J. Am. Chem. Soc.* **2008**, *130*, 6451.



Scheme 1

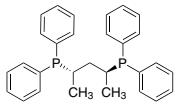


Scheme 2

(2*S*,4*S*)-2,4-Bis(diphenylphosphino)pentane, 97%

NEW

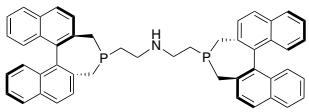
[(1*S*,3*S*)-1,3-Dimethyl-1,3-propanediyl] bis[diphenylphosphine]; (*S*,*S*)-BDPP
[77876-39-2]
$C_{29}H_{30}P_2$
FW 440.50



693618-500MG	500 mg
693618-1G	1 g

2,2′-Bis[(*R*-1,1′-binaphthyl-2,2′-dimethyl)phosphino]diethylamine

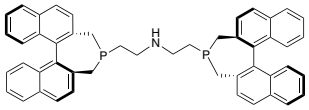
Bis(*R*-2-(4,5-dihydro-3*H*-binaphtho[1,2-c;2′,1′-*e*]-phosphepino)ethyl)amine
$C_{48}H_{41}NP_2$
FW 693.79



665002-250MG	250 mg

2,2′-Bis[(*S*-1,1′-binaphthyl-2,2′-dimethyl)phosphino]diethylamine, 97%

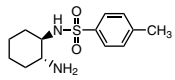
Bis(*S*-2-(4,5-dihydro-3*H*-binaphtho[1,2-c;2′,1′-*e*]-phosphepino)ethyl)amine
$C_{48}H_{41}NP_2$
FW 693.79



665010-250MG	250 mg

(1*R*,2*R*)-(–)-*N*-*p*-Tosyl-1,2-cyclohexanediamine, 97%

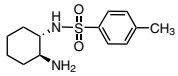
N-Toluenesulfonyl-(1*R*,2*R*)-(–)-1,2-diamino-cyclohexane; (–)-TsCYDN
$C_{13}H_{20}N_2O_2S$
FW 268.38



677302-1G	1 g

(1*S*,2*S*)-(+)-*N*-*p*-Tosyl-1,2-cyclohexanediamine, 97%

N-Toluenesulfonyl-(1*S*,2*S*)-(+)-1,2-diamino-cyclohexane; (+)-TsCYDN
$C_{13}H_{20}N_2O_2S$
FW 268.38

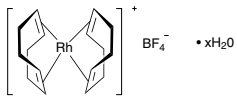


677310-1G	1 g

Bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate hydrate

NEW

[207124-65-0]
$C_{16}H_{24}BF_4Rh \cdot xH_2O$
FW 406.07 (Anh)



683140-500MG	500 mg
683140-2G	2 g

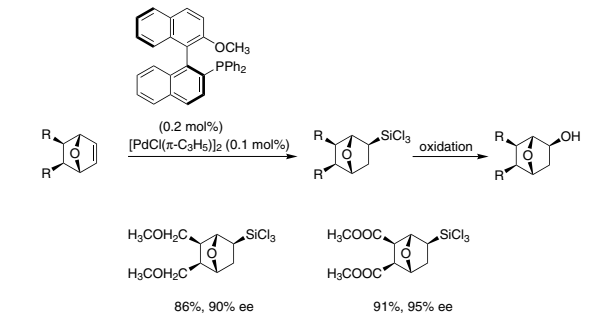
Asymmetric Hydrosilylation

The asymmetric hydrosilylation of olefins has proven to be a useful method to access a variety of chiral alcohols.[1] The introduction of the silica moiety allows further transformation of the molecule before converting it to the alcohol analogue. However, this particular reaction proved to be particularly challenging. To overcome this challenge Hayashi and co-workers synthesized a new chiral monodentate phosphine ligand using 1,1′-binaphtyl as a backbone.[1] This ligand, when used with palladium showed excellent stereoselectivities for the asymmetric hydrosilylation of 2,5-dihydrofurans.[2] The versatility of this ligand was showcased in the hydrosilylation of a variety of meso bicyclic olefins containing 2,5-dihydrofuran skeleton, with enantioselectivities as high as 95% (**Scheme 1**). In a typical reaction, 0.1 mol% of palladium allyl chloride dimer, with 0.2 mol% of MOP ligand is used. A reaction time of 24 hours is required to achieve good yields.

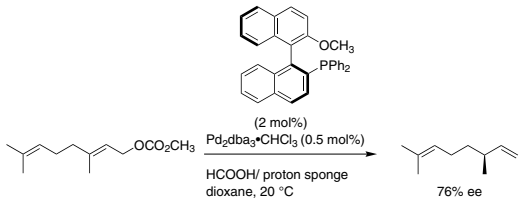
Palladium-Catalyzed Reduction of Allylic Esters

The palladium catalyzed reduction of allylic esters provides a convenient method to access chiral olefins.[3] Hayashi et al. studied the activity of the MOP ligand with palladium toward the reduction of allylic esters.[4] Mechanistic studies of the reaction have showed that a monodentate phosphine ligand is essential to achieve high selectivity. Reacting geranyl methyl carbonate with $Pd_2(dba)_3$ and MOP (1 mol% respectively), quantitatively yielded (*S*)-3,7-dimethyl-1,6-octadiene with 76%ee (**Scheme 2**). It is important to note that a low catalyst and ligand loading with mild conditions is necessary for good selectivity.

References: (1) Hayashi, T. *Acc. Chem. Res.* **2000**, *33*, 354. (2) Uozomi, Y. et al. *Tetrahedron Lett.* **1993**, *34*, 2335. (3) Tsuji, J. *Palladium Reagents and Catalysts*; Wiley: New York, 1995. (4) Hayashi, T. et al. *J. Am. Chem. Soc.* **1994**, *116*, 775. Hayashi, T. et al. *Synthesis* **1994**, 526.



Scheme 1

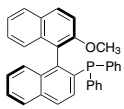


Scheme 2

R-MOP

NEW

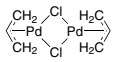
(*R*)-(+)-2-(Diphenylphosphino)-2′-methoxy-1,1′-binaphthyl
[145964-33-6]
$C_{33}H_{25}OP$
FW 468.52



693537-50MG	50 mg
693537-100MG	100 mg

Allylpalladium(II) chloride dimer, 98%

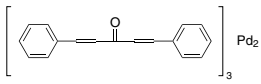
[12012-95-2]
$C_6H_{10}Cl_2Pd_2$
FW 365.89



222380-100MG	100 mg
222380-500MG	500 mg
222380-5G	5 g

Tris(dibenzylideneacetone)dipalladium(0)

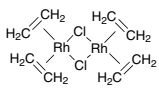
[51364-51-3]
$C_{51}H_{42}O_3Pd_2$
FW 915.72



328774-500MG	500 mg
328774-1G	1 g
328774-5G	5 g
328774-50G	50 g
328774-100G	100 g

μ-Dichlorotetraethylene dirhodium(I)

[12081-16-2]
$C_8H_{16}Cl_2Rh_2$
FW 388.93

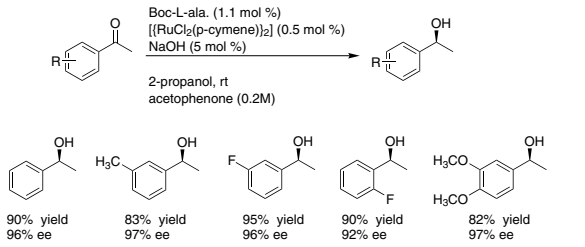


656763-100MG	100 mg
656763-1G	1 g

Asymmetric Reduction of Ketones

The enantioselective reduction of ketones to alcohols gives access to a pool of chiral building blocks that can be used for the synthesis of natural products. Adolfsson and co-workers reported a novel class of ligands, based on a pseudo-dipeptide,[1] for the mild and efficient reduction of ketones using 2-propanol as a hydrogen source. The ligand is used with $[\{RuCl_2(p\text{-cymene})\}_2]$ in presence of NaOH for the asymmetric reduction of a variety of acetophenone derivatives. Excellent yields and ee's were reported (**Scheme 1**).

Reference: (1) Bøgevig, A. et al. *Chem. Eur. J.* **2004,** *10*, 294.; Västilä, P. et al. *Chem. Commun.* **2005**, 4039.

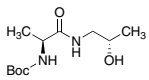


Scheme 1

Boc-L-alanine (2*S*)-2-hydroxylpropylamide, 97%

NEW

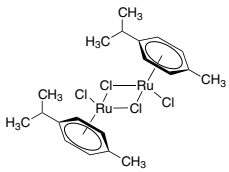
$C_{11}H_{22}N_2O_4$
FW 246.30



684414-100MG	100 mg
684414-500MG	500 mg

Dichloro(*p*-cymene)ruthenium(II) dimer

[52462-29-0]
$C_{20}H_{28}Cl_4Ru_2$
FW 612.39



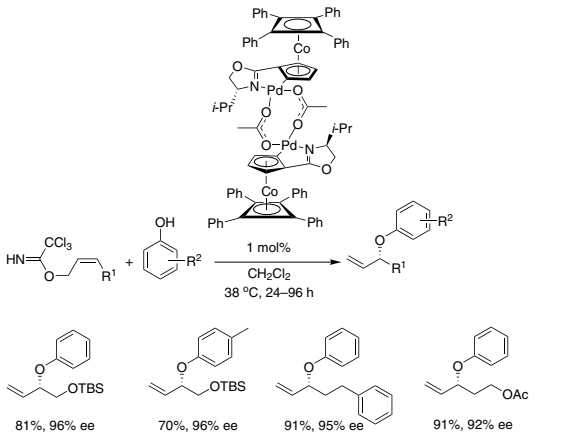
343706-1G	1 g
343706-5G	5 g

Asymmetric Allylation

Asymmetric Allylation Using COP Catalysts

Chiral allylic aryl esters are valuable building blocks for the synthesis of natural products and drug candidates. In recent years, several research groups developed new catalysts to synthesize chiral allylic esters from phenols and prochiral allylic precursors.[1] Overman and co-workers developed a new method to synthesize chiral 3-aryloxy-1-alkenes using COP-OAc catalysts.[2] This reaction only requires 1 mol% of catalyst producing the desired product in high yields and high ee's (**Scheme 1**). A library of alllylic trichloroacetimidates and phenols were screened. This new method is compatible with the presence of base-labile functionality.

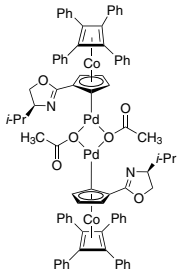
References: (1)(a) Trost, B. et al. *J. Am. Chem. Soc.* **2005**, *127*, 7014. (b) Mbaye, M. D. Et al. *Chem. Commun.* **2004**, 1870. (c) Shekhar, S. et al. *J. Am. Chem. Soc.* **2006**, *128*, 11770. (2) Kirsch, S. F. Et al. *Org. Lett.* **2007**, *9*, 911.



Scheme 1

(*S*)-(+)-COP-OAc Catalyst, 95%

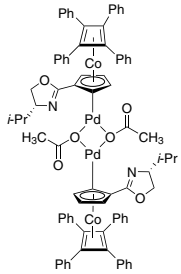
Di-μ-acetatobis[η⁵-(*S*)-(ₚ*R*)-2-(2′-(4′-methylethyl) oxazolinyl)cyclopentadienyl,1-*C*,3′-*N*)(η⁴-tetra-phenylcyclobutadiene)cobalt]dipalladium; [Bis[μ-(acetato-κO: κO′)]dipalladium] bis[1,1′,1″,1‴-(η⁴-1,3-cyclobutadiene-1,2,3,4-tetrayl)tetrakis[benzene]]bis[μ-[(1-η:1,2,3,4,5-η)-2-[(4*S*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl-κN³]-2,4-cyclopentadien-1-ylidene]]dicobalt
[222400-03-5]
$C_{82}H_{72}O_6N_2Co_2Pd_2$
FW 1512.17



661716-250MG	250 mg
661716-1G	1 g

(*R*)-(–)-COP-OAc Catalyst, 95%

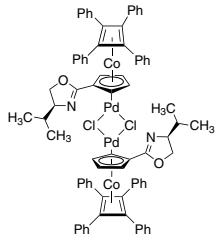
Di-μ-acetatobis[η⁵-(*R*)-(ₚ*R*)-2-(2′-(4′-methylethyl) oxazolinyl)cyclopentadienyl,1-*C*,3′-*N*)(η⁴-tetra-phenylcyclobutadiene)cobalt]dipalladium
[849592-74-1]
$C_{82}H_{72}O_6N_2Co_2Pd_2$
FW 1512.17



661708-250MG	250 mg
661708-1G	1 g

(*S*)-(+)-COP-Cl Catalyst

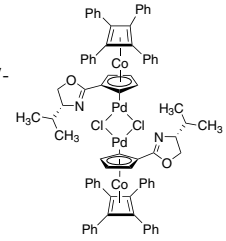
[612065-01-7]
$C_{78}H_{66}Cl_2Co_2N_2O_2Pd_2$
FW 1464.98



646636-250MG	250 mg
646636-1G	1 g

(*R*)-(–)-COP-Cl Catalyst

Di-μ-chlorobis[η⁵-(*R*)-(ₚ*R*)-2-(2′-(4′-methylethyl) oxazolinyl)cyclopentadienyl,1-*C*,3′-*N*)(η⁴-tetra-phenylcyclobutadiene)cobalt]dipalladium; [Bis[μ-(chloro-κO:κO′)]dipalladium]bis[1,1′,1″,1‴-(η⁴-1,3-cyclobutadiene-1,2,3,4-tetrayl) tetrakis[benzene]]bis[μ-[(1-η:1,2,3,4,5-η)-2-[(4*R*)-4,5-dihydro-4-(1-methylethyl)-2-oxazolyl-κN³]-2,4-cyclopentadien-1-ylidene]]dicobalt
[612065-00-6]
$C_{78}H_{66}Cl_2Co_2N_2O_2Pd_2$
FW 1464.98



661791-100MG	100 mg
661791-500MG	500 mg

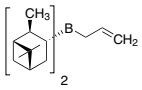
Asymmetric Allylboration Using $Ipc_2B(allyl)$

Asymmetric allylboration of aldehydes is an extremely important method for preparation of homoallylic alcohols, as evidenced in numerous complex natural product syntheses.[1] Although a variety reagents have been developed to execute this reaction, the most broadly adopted have been Brown's α-pinene-derived (–)- and (+)-β-allyldiisopinocampheylboranes (i.e., $Ipc_2B(allyl)$).[2] Typically the allylboration reagents are generated in situ and used immediately at –78 to –100 °C, since they are not stable for extended periods at ambient temperature (**Scheme 1**).

New, salt-free, $Ipc_2B(allyl)$ reagents have been developed as stable solutions in pentane or dioxane. Under refrigerator storage, no appreciable decreases in selectivity are observed after several months. They exhibit excellent reactivity and reactions can be performed at 5 °C, even in water.

References: (1)(a) Furstner, A. et al., *Angew. Chem. Int. ed.* **2006**, *45*, 5506. (b) Smith, A. B. et al. *J. Am. Chem. Soc.* **2003**, *125*, 350. (2) For a review of allylborane reagents, see: Ramachandran, P. V. Aldrichimica Acta 2002, 35, 23.

(-)-$Ipc_2B(allyl)$borane solution

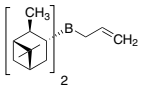


(-)-*B*-Allyldiisopinocampheylborane solution
[85116-38-7]
$C_{23}H_{39}B$
FW 326.37

▸ **1 M in dioxane**

678546-5ML	5 mL
678546-25ML	25 mL

(-)-$Ipc_2B(allyl)$borane solution

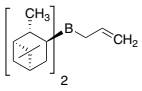


(-)-*B*-Allyldiisopinocampheylborane solution
[85116-38-7]
$C_{23}H_{39}B$
FW 326.37

▸ **1 M in pentane**

678538-5ML	5 mL
678538-25ML	25 mL

(+)-$Ipc_2B(allyl)$borane solution



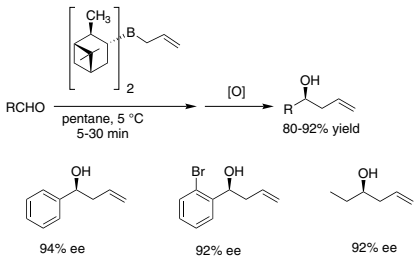
(+)-*B*-Allyldiisopinocampheylborane solution
[106356-53-0]
$C_{23}H_{39}B$
FW 326.37

▸ **1 M in dioxane**

678511-5ML	5 mL
678511-25ML	25 mL

▸ **1 M in pentane**

678503-5ML	5 mL
678503-25ML	25 mL

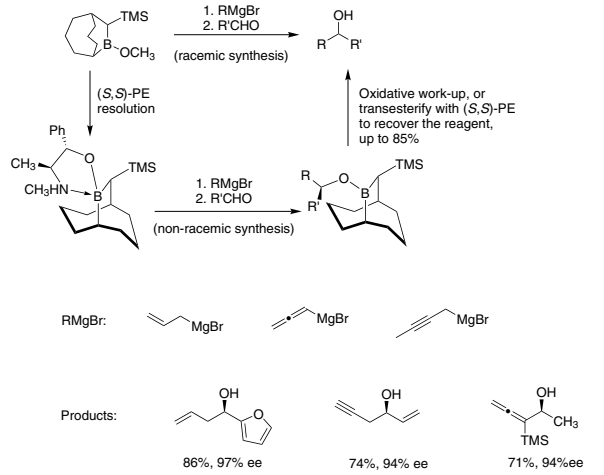


Scheme 1

Soderquist Borabicyclodecanes

In the past 20 years, the asymmetric allylboration of aldehydes has become an essential reaction for the synthesis of homoallylic or homopropargylic alcohols. Soderquist et al. developed a robust, versatile and recyclable pseudoephedrine reagent improving the reaction performance and selectivity. Treatment of these air stable crystalline pseudoephedrine borinic acid complexes with the appropriate Grignard reagent gives access to homoallylic or homopropargylic alcohols and -allenyl carbinols via symmetric allyl-, propargyl-, and allenylboration reactions. Allyboration reactions occur rapidly, can be performed in the presence of Mg salts, and the degree of asymmetric induction is only minimally affected by temperature. Moreover, the reagents are easily recycled in good yield. The reagents also perform well in asymmetric crotylborations,[1] allylborations of imines,[2] and the alkynylboration of *N*-acylimines to give chiral *N*-propargylamides (**Scheme 1**).[3]

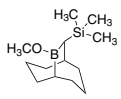
References: (1) Burgos, C. H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8044. (2) Hernandez, E. et al. *Pure Appl. Chem.* **2006**, *78*, 1389. (3) Gonzales, A. Z. et al. *Org. Lett.* **2006**, *8*, 3331.



Scheme 1

B-Methoxy-10-trimethylsilyl-9-borabicyclo(3.3.2)decane, 95%

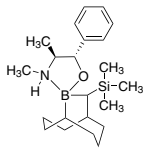
9-Methoxy-10-trimethylsilanyl-9-borabicyclo(3.3.2)decane
$C_{13}H_{27}BOSi$
FW 238.25



676667-5G	5 g
676667-25G	25 g

(+)-9-(1*S*, 2*S*-Pseudoephedrinyl)-(10*R*)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane

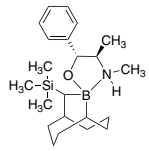
N,α-Dimethyl-β-[[(10*R*)-10-(trimethylsilyl)-9-borabicyclo[3.3.2]dec-9-yl]oxy]-(αS,βS)-benzeneethanamine
[848618-13-3]
$C_{22}H_{38}BNOSi$
FW 371.44



676675-1G	1 g
676675-5G	5 g

(–)-9-(1*R*,2*R*-Pseudoephedrinyl)-(10*S*)-(trimethylsilyl)-9-borabicyclo[3.3.2]decane

$C_{22}H_{38}BNOSi$
FW 371.44

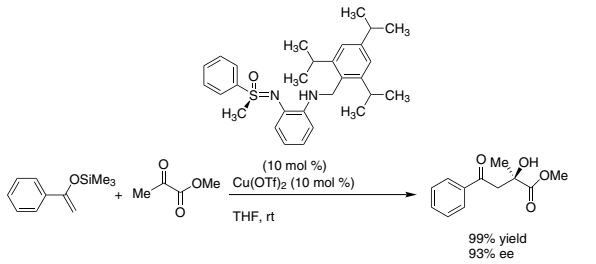


676683-1G	1 g
676683-5G	5 g

Asymmetric Aldol-Type Reactions

Asymmetric Addition Reaction Using Sulfoximine Ligands

Chiral sulfoximine ligands have been studied for the past 15 years for catalytic asymmetric reactions. The Bolm group developed a new class of sulfoximine used with copper salts for asymmetric aldol reactions.[1] Using these bidentate ligands, Bolm and co-workers reported up to 93% ee and 99% yield for the Mukaiyama-type aldol reaction of 1-phenyl-1-(trimethylsilyloxy)ethylene and methyl pyruvate (**Scheme 1**).

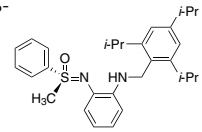


Scheme 1

Reference: (1) Okamura, H. et al. *Chem. Lett.* **2004**, *33*, 482.

(*S*)-*S*-Methyl-*S*-phenyl-*N*-{2-[(2,4,6-triisopropylphenyl) methylamino]phenyl}sulfoximine, ≥97.0% (HPLC)

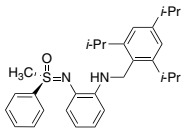
(*S*)-*N*-[2-(2,4,6-Triisopropylbenzylamino)phenyl]-*S*-methyl-*S*-phenylsulfoximine
[825612-43-9]
$C_{29}H_{38}N_2OS$
FW 462.69



669970-100MG	100 mg
669970-500MG	500 mg

(*R*)-*S*-Methyl-*S*-phenyl-*N*-{2-[(2,4,6-triisopropylphenyl) methylamino]phenyl}sulfoximine, ≥97.0% (HPLC)

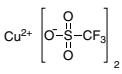
(*R*)-*N*-[2-(2,4,6-Triisopropylbenzylamino)-phenyl]-*S*-methyl-*S*-phenylsulfoximin
[948831-14-9]
$C_{29}H_{38}N_2OS$
FW 462.69



669857-100MG	100 mg
669857-500MG	500 mg

Copper(II) trifluoromethanesulfonate, 98%

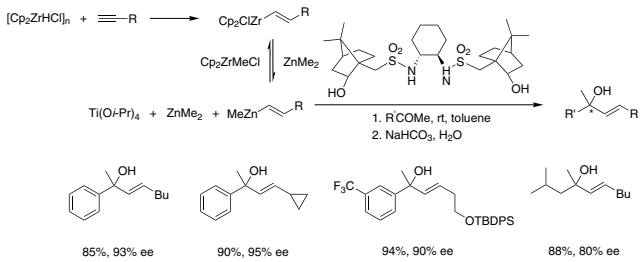
Copper(II) triflate; Trifluoromethanesulfonic acid copper(II) salt; Cupric trifluoromethanesulfonate
[34946-82-2]
$C_2CuF_6O_6S_2$
FW 361.68



283673-5G	5 g
283673-25G	25 g

Asymmetric Aldol Reaction Using Chiral Sulfonamide Ligands

Walsh and co-workers developed a chiral diamine ligand used in the alkylation, arylation and vinylation of ketones under high enantiocontrol.[1] The activity of this new ligand toward the vinylation of ketones has been demonstarted using a variety of vinylzinc intermediates. These vinylzinc reagents are generated by the hydrozirconation of terminal alkynes with Schwartz's reagent, followed by transmetallation to zinc. This intermediate is then reacted with the aldehyde in the presence of the Ti(O*i*-Pr)$_4$, $ZnMe_2$ and the chiral diamine ligand. The final chiral vinyl alcohol is generated with good to excellent yields and good enantioselectivities. This new ligand affords several distinct advantages over the prior art in the field including: low catalyst loading (up to 1 mol%), room temperature reactions complete in 24–36 h and high ee's generated in gram scale reactions.

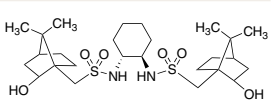


Scheme 1

Reference: (1) Li, H. et al. *J. Am. Chem. Soc.* **2005**, *127*, 8355

N,*N*′-(1*R*,2*R*)-(–)-1,2-cyclohexanediylbis[2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptane-1-methanesulfonamide], 97%

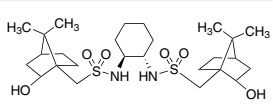
$C_{26}H_{46}N_2O_6S_2$
FW 546.78



673315-250MG	250 mg

N,*N*′-(1*S*,2*S*)-(+)-1,2-cyclohexanediylbis[2-hydroxy-7,7-dimethyl-bicyclo[2.2.1]heptane-1-methanesulfonamide], 97%

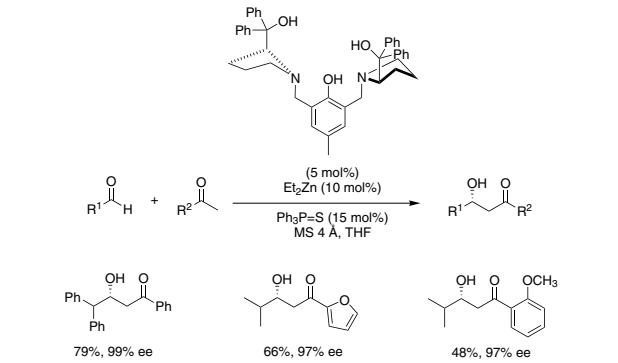
$C_{26}H_{46}N_2O_6S_2$
FW 546.78



673382-100MG	100 mg
673382-1G	1 g

Asymmetric Aldol Reaction Using Bis-ProPhenol Ligands

The aldol reaction is an important tool for the synthesis of complex molecules. However, the chemo- and regioselectivity of this reaction is usually poor. In view of these challenges, Trost and co-workers developed a new ligand capable of performing aldol reactions enantioselectively.[1] The approach taken by the researchers was to look at the different requirements for a good catalyst for asymmetric transformations. The final structure of the catalyst is a semi-crown complex which allows good chiral recognition as well as a path for easy exchange of product. The ligand structure is based on a p-cresol backbone. To probe the activity of the ligand, various aldehydes were reacted with various aryl ketones with overall good yields and excellent selectivity (**Scheme 1**).

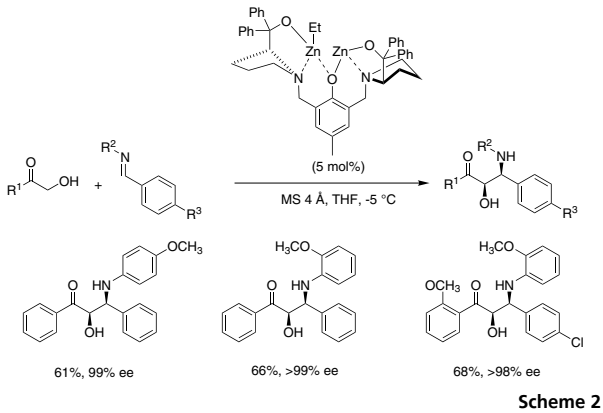


Scheme 1

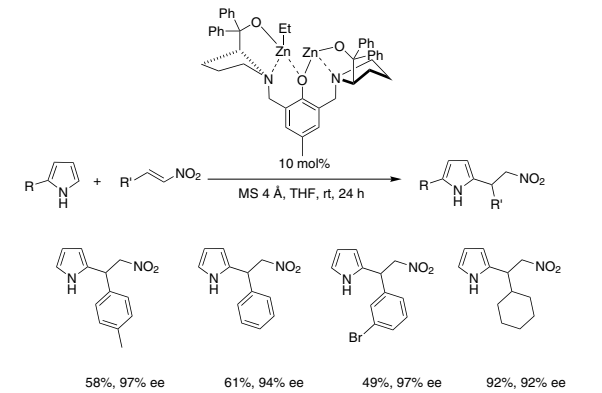
Asymmetric Mannich-Type Reaction Using Bis-ProPhenol Ligands

The Mannich reaction has become an essential tool for the synthesis of nitrogen-containing compounds. Trost and co-workers utilized the semi-crown ligand that they developed for asymmetric aldol reaction in an asymmetric imine-aldol reaction generating syn 1,2-amino alcohols.[2] A series of hydroxyacetophenone derivatives were reacted with different glyoxalate imines in the presence of a zinc complex in THF (**Scheme 2**). It was noted that more electron-rich aromatic hydroxy ketones required higher catalyst loading. Good yields and selectivity were reported for the synthesis of a variety of amino alcohols. It is important to note that these imine alcohols are important synthons that can be reacted further to yield different α-hydroxyl-β-amino acids.

A recent example of the use of Bis-ProPhenol ligands is the Friedel–Crafts alkylation of pyrroles with nitroalkenes. The Friedel–Crafts reaction has been extensively studied and used for the past 100 years. Recently, several research groups focused their attention on asymmetric Friedel–Crafts alkylation with very good success.[3] Trost et al. reported a dinuclear zinc-bis-ProPhenol complex to efficiently catalyze the asymmetric Friedel–Crafts alkylation of unprotected pyrroles with nitroalkenes.[4] The resulting products are 2-alkyl-substituted and 2,5-dialkyl-substituted pyrroles containing a chiral center at C–1 of the alkyl substituent. The significance of this transformation lies in the fact that pyrroles are relatively unstable in the acidic environment of the classical Friedel–Crafts reaction and that unprotected pyrroles can be used directly in the reaction. Furthermore, pyrroles are important motifs present in numerous natural products and medicinal reagents. The current alkylation is carried out at room temperature in THF and gives rise to moderate-to-high yields and enantioselectivities (**Scheme 3**).



Scheme 2



Scheme 3

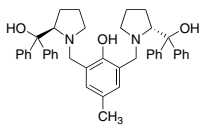
References: (1) Trost, B. M. et al. *J. Am. Chem. Soc.* **2000**, *122*, 12003. (2) Trost, B. M. et al. *J. Am. Chem. Soc.* **2003**, *125*, 338. (3)(a) Bandini, M. et al. *Eur. J. Org. Chem.* **2006**, 3527. (b) Jia, Y. X. et al. *J. Org. Chem.* **2006**, *71*, 75. (4) Trost, B. M. et al. *J. Am. Chem. Soc.* **2008**, *130*, 2438.

(*R*,*R*)-(–)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinylmethyl]-4-methylphenol, 95%

(*R*,*R*)-2,6-Bis((2-(hydroxydiphenylmethyl) pyrrolidin-1-yl)methyl)-4-methylphenol; Trost (*R*,*R*)-Bis-ProPhenol Ligand

$C_{43}H_{46}N_2O_3$

FW 638.84



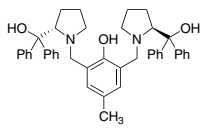
667625-1G	1 g
667625-5G	5 g

(*S*,*S*)-(+)-2,6-Bis[2-(hydroxydiphenylmethyl)-1-pyrrolidinylmethyl]-4-methylphenol, 95%

(*S*,*S*)-2,6-Bis[2-(hydroxydiphenylmethyl) pyrrolidin-1-ylmethyl]-4-methylphenol; Trost (*S*,*S*)-Bis-ProPhenol Ligand

$C_{43}H_{46}N_2O_3$

FW 638.84



668370-1G	1 g
668370-5G	5 g

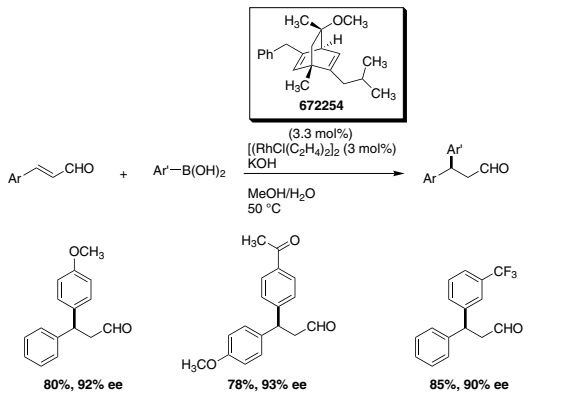
Asymmetric Conjugate Addition

In the past 5 years, chiral diene ligands have surfaced for a variety of asymmetric transformations. Hayashi[1] and Carreira[2] pioneered this field by synthesizing chiral diene ligands that formed stable complexes with metals and exerted high catalytic activity as well as high enantioselectivity. Carreira and co-workers reported the asymmetric synthesis of 3,3-diarylpropanals using a chiral bicyclo[2.2.2]octadiene as a ligand with a rhodium complex.[3] This new synthesis provides access to important building blocks that are otherwise not readily available. The reaction offers a general synthesis of a wide variety of diaryl propanals. This rhodium catalyzed conjugate addition of aryl boronic acids is both chemo- and regio-selective wherein conjugate addition is favored over 1,2-addition. In a typical reaction, 3.3 mol% of the ligand and 3 mol% of the rhodium complex in a mixture of methanol and water is required. Good yields and selectivity were reported with both electron rich and electron poor boronic acids and various cinamaldehydes (**Scheme 1**).

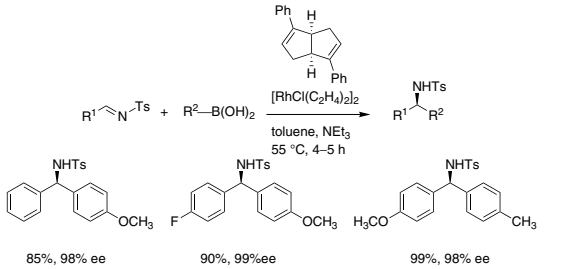
Following on the work of Carreira and Hayashi, Feng et al. developed a new type of diene ligand based on a nonbridged bicyclo[3.3.0]octadiene framework.[4] The two cis-fused cyclopentadiene rings generate a wedge structure providing a chiral environment giving excellent enantiocontrol in the reaction when coordinated to the metal. The activity of the ligand was evaluated in the asymmetric arylation of *N*-tosylarylimines with aryl boronic acids. Using 3 mol% of $[RhCl(C_2H_4)_2]_2$ and 3.3 mol% of the ligand, a variety of aryl boronic acids and *N*-tosylarylimines were screened. It is important to note that the reactants screened had diverse steric and electronic properties and showed little influence on the yield and enantioselectivity of the reaction (**Scheme 2**).

To expand the scope of this new ligand, Feng et al. investigated the asymmetric 1,4-addition of aryl boronic acids to α,β-unsaturated carbonyl compounds.[5] Using 2.5 mol% of $[RhCl(C_2H_4)_2]_2$ and 5.5 mol% of the ligand, a variety of sterically hindered, electron donating and electron withdrawing substituted aryl boronic acids were screened (**Scheme 3**). The nature of the substituant on the aryl boronic acid had no influence on the yield and the enantioselectivity.

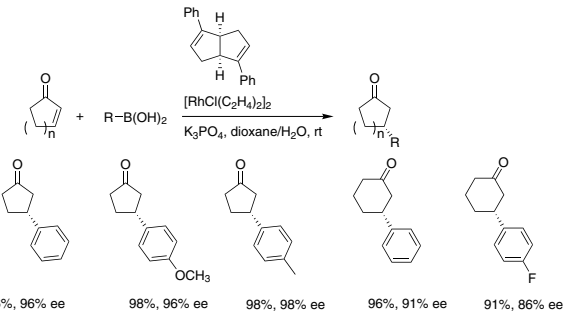
References: (1) Hayashi, T. et al. *J. Am. Chem. Soc.* **2003**, *125*, 11508. (2) Fischer, C. et al. *J. Am. Chem. Soc.* **2004**, *126*, 1628. (3) Paquin, J. -F. et al. *J. Am. Chem. Soc.* **2005**, *127*, 10850. (4) Wang, Z., -Q. Et al. *J. Am. Chem. Soc.* **2007**, *129*, 5336. (5) Feng, C. -G. Et al. *Chem. Asian. J.* **2008**, ASAP



Scheme 1



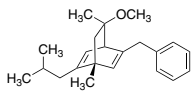
Scheme 2



Scheme 3

(1*R*,4*R*,8*R*)-5-Benzyl-8-methoxy-1,8-dimethyl-2-(2′-methylpropyl)-bicyclo[2.2.2]octa-2,5-diene, ≥98%

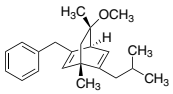
(1*R*,4*R*,8*R*)-5-Benzyl-2-isobutyl-8-methoxy-1,8-dimethyl-2-bicyclo[2.2.2]octa-2,5-diene; (1*R*,4*R*,8*R*) Carreira DOLEFIN Ligand
[948594-95-4]
$C_{22}H_{30}O$
FW 310.47



669490-100MG	100 mg

(1*S*,4*S*,8*S*)-5-Benzyl-8-methoxy-1,8-dimethyl-2-(2′-methylpropyl)-bicyclo[2.2.2]octa-2,5-diene, ≥98%

(1*S*,4*S*,8*S*)-5-Benzyl-2-isobutyl-8-methoxy-1,8-dimethyl-2-bicyclo[2.2.2]octa-2,5-diene; (1*S*,4*S*,8*S*) Carreira DOLEFIN Ligand
[862499-50-1]
$C_{22}H_{30}O$
FW 310.47

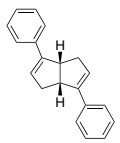


672254	

(3a*R*,6a*R*)-3,6-Diphenyl-1,3a,4,6a-tetrahydro-pentalene, 97%

NEW

(3a*R*,6a*R*)-1,3a,4,6a-tetrahydro-3,6-diphenylpentalene
[947503-81-3]
$C_{20}H_{18}$
FW 258.36

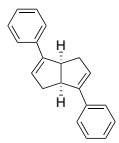


698725-50MG	50 mg

(3a*S*,6a*S*)-3,6-Diphenyl-1,3a,4,6a-tetrahydro-pentalene, 97%

NEW

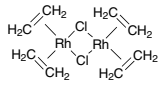
(3a*S*,6a*S*)-1,3a,4,6a-tetrahydro-3,6-diphenylpentalene
[940280-80-8]
$C_{20}H_{18}$
FW 258.36



698733-50MG	50 mg

μ-Dichlorotetraethylene dirhodium(I)

[12081-16-2]
$C_8H_{16}Cl_2Rh_2$
FW 388.93



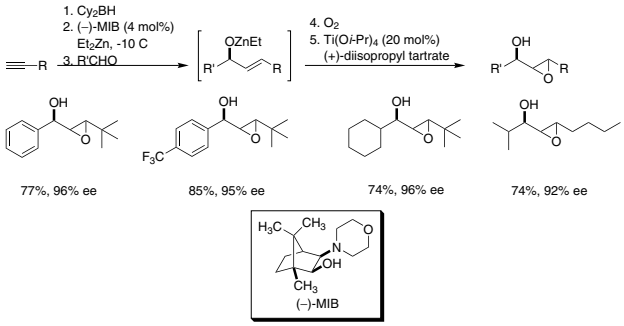
656763-100MG	100 mg
656763-1G	1 g

Asymmetric Epoxidation

Asymmetric Epoxidation Reaction Using MIB

Chiral epoxy alcohols are essential building blocks extensively used in the synthesis of natural products. However, the synthesis of these molecules proved to be challenging, especially allylic alcohols containing (*E*)-olefins. To access a plethora of chiral epoxy alcohols Professor Walsh and coworkers have invented a novel methodology,[1,2] which complements the Sharpless asymmetric epoxidation. This process is mediated by a zinc catalyst built around Nugent's (–)-MIB ligand. Starting with a substituted terminal alkyne, the one pot reaction yields the desired epoxy alcohols with excellent levels of enantiocontrol, as well as yielding moderate to excellent diastereomeric ratios for a wide array of substrates.

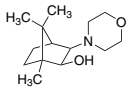
References: (1) Jeon, S. -J. et al. *Org. Lett.* **2005**, *7*, 1729. (2) Lurain, A. E. et al. *J. Org. Chem.* **2005**, *70*, 1262.



Scheme 1

(2*S*)-3-*exo*-(Morpholino)isoborneol, 96%

[(–)-MIB]
[287105-48-0]
$C_{14}H_{25}NO_2$
FW 239.35



676942-1G	1 g
676942-5G	5 g

Asymmetric Epoxidation Using Shi Catalyst

Catalytic asymmetric epoxidation of alkenes has been the focus of many research efforts over the past two decades, the best known methods probably being those developed by Sharpless[1] and Jacobsen-Katsuki.[2] Shi has also developed a very efficient method for asymmetric epoxidation, using a ketone-derived organocatalyst based on D-fructose.[3] This organocatalyst is able to epoxidize *trans* alkenes and certain *cis* alkenes with good to excellent yields and selectivities. More recently, Shi has achieved excellent results using hydrogen peroxide as an oxidant instead of Oxone, which allows a significant reduction in the amount of additional salts introduced and solvent used in the reaction (**Scheme 1**).[4]

Other groups have used of Shi's methodology in pursuit of a number of unique structural moieties. For example, McDonald and co-workers recently reported a robust and selective synthesis of 2-amino-3,5-diols that employs the Shi epoxidation in a key step (**Scheme 2**).[5] These 2-amino-3,5-diols are 1-deoxy-5-hydroxysphingosine analogues, which show promise as anticancer agents.

A recent example of the use of the Shi catalyst is the synthesis of thiosulfonate. Chiral sulfinyl derivatives have been of interest for the past three decades.[6] This interest stemmed from the use of these molecules as chiral controllers in asymmetric synthesis, as chiral ligands and as Lewis bases. Khiar et al. reported a new method to synthesize enantiomerically pure, functionalized, sterically demanding thiosulfonates.[7] Investigating several catalysts for the oxidation of disulfides diesters and diethers, Khiar et al. determined that a particular chiral pyranone derived from D-glucose, the Shi catalyst, yielded the best yields and stereoselectivities. Using the Shi catalyst in combination with oxone in acetonitrile and dimethoxymethane, the authors reported up to 89% yield and up to 96% ee's for the oxidation of disulfides (**Scheme 3**).

References: (1) Johnson, R. A.; Sharpless, K. B. In *Catalytic Asymmetric Synthesis* (2nd Ed.); Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 6A. (2) Jacobsen, E. N. In *Catalytic Asymmetric Synthesis* (1st Ed.); Ojima, I., Ed.; VCH: New York, 1993; Chapter 4.2. (3)(a) Shi, Y. *Acc. Chem. Res.* **2004**, *37*, 488. (b) Frohn, M.; Shi, Y. *Synthesis* **2000**, 1979. (c) Wang, Z.-X. et al. *J. Am. Chem. Soc.* **1997**, *119*, 11224. (d) Tu, Y. et al. *J. Am. Chem. Soc.* **1996**, *118*, 9806. (4) Shu, L.; Shi, Y. *Tetrahedron* **2001**, *57*, 5213. (5) Wiseman, J. M. et al. *Org. Lett.* **2005**, *7*, 3155. (6) Fernandez, I; Khiar, N. Chem. Rev. 2003, 95, 1717. (7) Khiar, N. et al. *Org. Lett.* **2007**, *9*, 1255.

Shi Epoxidation Oxazolidinone Methyl Catalyst, 95%

NEW

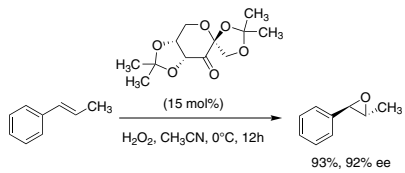
(3a*R*,5′*S*,7a*R*)-Dihydro-2,2-dimethyl-3′-(4-methylphenyl)-spiro[6*H*-1,3-dioxolo[4,5-*c*]pyran-6,5′-oxazolidine]-2′,7(4*H*)-dione
[403501-30-4]
$C_{17}H_{19}NO_6$
FW 333.34

693456-100MG	100 mg
693456-500MG	500 mg

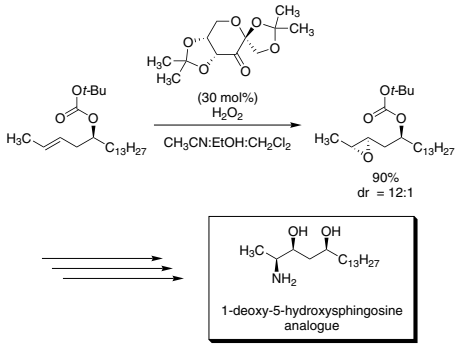
Shi Epoxidation Diketal Catalyst, 98%

1,2:4,5-Di-*O*-isopropylidene-β-D-*erythro*-2,3-hexodiulo-2,6-pyranose
[18422-53-2]
$C_{12}H_{18}O_6$
FW 258.27

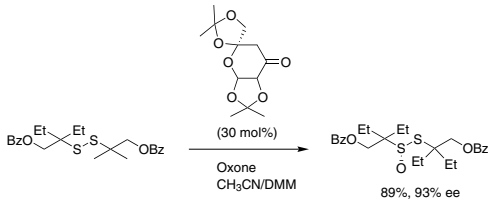
520160-5G	5 g



Scheme 1



Scheme 2



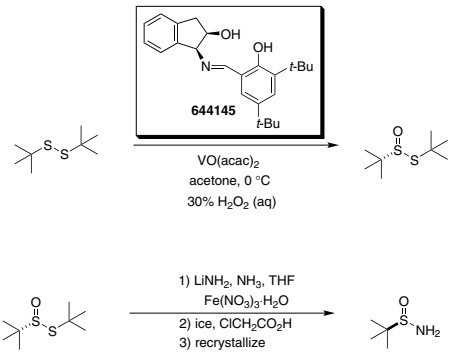
Scheme 3

Asymmetric Oxidation

Asymmetric Oxidation of Di-*tert*-butyl Disulfide

The seminal work of Ellman and coworkers provided the first example of the catalytic asymmetric oxidation of *tert*-butyl disulfide. The desymmetrization involves reaction of *tert*-butyl disulfide with catalytic $VO(acac)_2$ and a chiral indanol ligand in the presence of hydrogen peroxide as the stoichiometric oxidant (**Scheme 1**). Upon monoxidation to provide *tert*-Butyl *tert*-butanethiosulfinate, the sulfur-sulfur bond is cleaved via displacement with $LiNH_2$ to afford the sulfonamide. The sulfonamides are often reacted with aldehydes to provide upon addition of organometallic reagents and deprotection, chiral amines (one of many uses of chiral sulfinimines). This sequence has been demonstrated to be effective on a large scale, utilizes relatively non-toxic solvents such as acetone (first step), and is economically feasible.

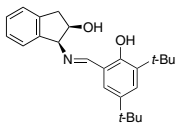
References: (1)(a) Weix, D. J.; Ellman, J. A. *Org. Lett.* **2003**, 5, 1317. (b) Weix., D. J.; Ellman, J. A. *Org. Syn.* **2005**, *82*, 157. (c) Cogan, D. A.; Liu, G.; Kim, K.; Backes, B. J.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 8011. (d) Morton, D.; Stockman, R. A. *Tetrahedron* **2006**, *62,* 8869.



Scheme 1

(1*S*,2*R*)-1-[(3,5-Di-*tert*-butyl-2-hydroxybenzylidene)amino]-2-indanol, 97%

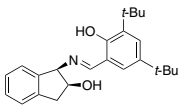
(1*S*,2*R*)-1-((2-Hydroxy-3,5-di-*tert*-butylbenzylidene)amino)indan-2-ol
[212378-89-7]
$C_{24}H_{31}NO_2$
FW 365.51



644145-1G	1 g
644145-5G	5 g

(1*R*,2*S*)-1-[(3,5-Di-*tert*-butyl-2-hydroxybenzylidene)amino]-2-indanol, 97%

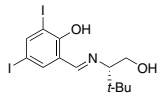
(1*R*,2*S*)-1-((2-Hydroxy-3,5-di-*tert*-butylbenzylidene)amino)indan-2-ol
[275374-67-9]
$C_{24}H_{31}NO_2$
FW 365.51



642959-1G	1 g
642959-5G	5 g

(*S*)-(–)-2-[(1-Hydroxy-3,3-dimethylbutan-2-ylimino)methyl]-4,6-diiodophenol, 97%

2-[[[(1*S*)-1-(Hydroxymethyl)-2,2-dimethylpropyl]imino]methyl]-4,6-diiodophenol
[477339-39-2]
$C_{13}H_{17}I_2NO_2$
FW 473.09



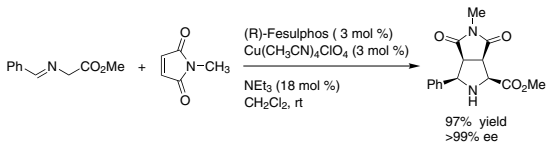
677558-100MG	100 mg
677558-500MG	500 mg

Asymmetric Cycloaddition

Asymmetric 1,3-dipolar Cycloaddition Using Fesulphos

The asymmetric 1,3-dipolar cycloaddition reaction is of the utmost importance for the enantioselective synthesis of five-membered heterocycles. Cabrera et al. introduced a new family of ligands consisting of a planar chiral P,S-ligand, named Fesulphos, for the 1,3-dipolar cycloaddition of azomethine halides.[1] The catalytic reaction is carried out with the Fesulphos ligand, a copper salt, and triethylamine in methylene chloride. This new catalytic system demonstrated complete enantiocontrol (ee >99%) with conversion up to 97% (**Scheme 1**).

Reference: (1) Cabrera, S. et al. *J. Am. Chem. Soc.* **2005,** *127*, 16394.

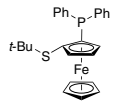


Scheme 1

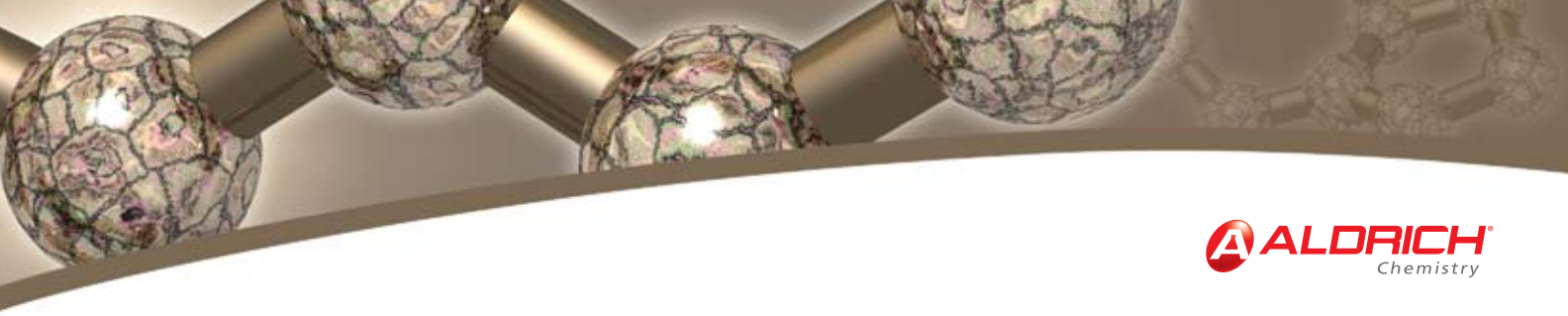
(R_p)-2-(*tert*-Butylthio)-1-(diphenylphosphino)ferrocene, 98%

NEW

(1*S*)-1-(*tert*-Butylthio)-2-(diphenylphosphino)ferrocene; (*R*)-FeSulPhos
[503859-61-8]
$C_{26}H_{27}FePS$
FW 458.38



687561-100MG	100 mg
687561-500MG	500 mg



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