Introduction

The quest for novel, efficient chiral transition metal catalysts has been an ongoing endeavor for the past 40 years. Leading this quest is the need from the pharmaceutical, flavors and fragrances, and agrochemical industries for enantiopure molecules. Nearly 85% of new drugs in the market are chiral. This need has led to developments in asymmetric synthesis of chiral ligands and metal complexes. In 2001, the Nobel Prize rewarded the pioneering work of Knowles, Noyori, and Sharpless in the development of catalytic asymmetric synthesis, highlighting the importance of chiral synthesis in chemistry. The pioneering work of Noyori in the 1980s with BINAP ligands began an era where catalysts and ligands became more effective and selective.

Highly effective asymmetric catalytic systems give access to arrays of chiral building blocks used in the synthesis of natural products and drugs. Among the plethora of chiral ligands, a few stand out because of their versatility. The common feature of these “privileged” ligands is their C2 symmetry, reducing the number of possible isomeric metal complexes and number of different substrates. Among the most recognized family of chiral ligands, BINAP, salens, bixoazolines, tartrate ligands, and cinchona alkaloids represent the original “privileged ligands” classes that affect a wide variety of transformations under outstanding enantiocontrol and with high yield. A second wave of privileged ligands has surfaced with the DuPhos phospholanes, DSM phosphoramidites, Solvias Josiphos families, the Reetz and Trost ligands, and ChiralQuest phosphines. These outstanding ligand families have proven their success in industrially useful reactions such as hydrogenations, aldol reactions, and asymmetric allylic alkylations, and gained much attention from the synthetic community due to the ready accessibility and modular nature of their design.

For each of the privileged ligands, representative examples are presented.

At Sigma-Aldrich®, we are committed to providing unprecedented accessibility to chiral, state-of-the-art “privileged ligands” used in a wide variety of C–H, C–C, C–N, and C–O bond-forming transformations. For a complete listing of products related to privileged ligands, please visit sigma-aldrich.com/privileged. If you cannot find a product for your research efforts in organic synthesis or drug discovery, we welcome your input. “Please Bother Us.” with your suggestions at william.sommer@sial.com or daniel.weibel@sial.com, or contact your local Sigma-Aldrich office.

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About Our Cover

The cover graphic represents the three-dimensional structure of BINAP. The phosphorus atoms are represented in blue. This chiral ligand proved to be one of the most popular, for a variety of asymmetric transformations.

ChemFiles Vol. 8 No. 2

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BINAP/SEGPHOS® Ligands and Complexes

Since the development of BINAP by Noyori 20 years ago, extensive research has been accomplished using this chiral ligand. BINAP proved to be one of the most versatile ligands, catalyzing a wide range of reactions, from hydrogenations to Heck cyclizations. The research team at Takasago International Corporation developed a series of ligands and complexes for a plethora of catalyzed asymmetric reactions. Based on a biphenyl architecture, several phosphine ligands have been synthesized. Two large families of ligands can be distinguished, BINAP and SEGPHOS (Figure 1). BINAP is based on a bisnaphthalene backbone with different phosphine derivatives. SEGPHOS is based on a bis(1,3-benzodioxole) backbone with different phosphine substituents. BINAP and SEGPHOS are highly reactive and selective in a variety of asymmetric hydrogenations. In conjunction with ruthenium, rhodium, palladium and copper complexes, these ligands allow for enantioselectivities of up to 99%.

Rhodium-Catalyzed 1,4-Addition of Arylboronic Acids to Coumarins
Chen et al. presented the asymmetric synthesis of arylated coumarins. The importance of this transformation with coumarin precursors is illustrated with the synthesis of (-)-toiletoreine, a urological drug that can be readily obtained following the asymmetric arylation. Using SEGPHOS and CuF2⋅H2O with DTBM-SEGPHOS, the aryl aldehyde is reacted with a variety of trimethoxysilane derivatives (Scheme 1). Copper-Catalyzed Asymmetric Alkenylation and Phenylation
Tomita et al. developed a new catalytic enantioselective method for chiral alcohol and dialkylmethyl synthesis. This new method is a great alternative to the kinetic resolution using the Sharpless epoxidation or the asymmetric addition of allylalcohol to carboxyl compounds, for the synthesis of chiral aliphatic alcohols. Furthermore, the transformation can be achieved using air- and moisture-stable alkenylsilanes. Using CuF2⋅H2O with DTBM-SEGPHOS, the aryl aldehyde is reacted with a variety of trimethoxysilane derivatives (Scheme 2). Excellent enantioselectivities were obtained from a wide range of aldehydes.

Copper-Catalyzed Asymmetric Hydroisilylations
Lipshutz et al. developed a new method for asymmetric hydroisilylations of various ketones using a preformed DTBM-SEGPHOS - CuH complex, a variety of amino esters were obtained in one step from the corresponding ketoesters in highly enantioselective fashion (up to 99% ee (Scheme 3)). To illustrate the relevance of this new catalyst, Okuma et al. synthesized a series of known molecules used in drug synthesis.

Ruthenium-Catalyzed Asymmetric Hydrogenation of Amino Ketones
Ohkuma et al. reported a practical asymmetric hydrogenation reaction using mild hydrogen pressure with a wide scope. The access to chiral alcohols from amino ketones is important for the synthesis of physiologically active compounds. In this new process, a diphosphine/diamine Ru catalyst is utilized. This complex is based on DM-BINAP and 1,1-di-4-arylsulfonyl-2-isopropyl-1,2-ethylenediamine (DAIPEN) and a ruthenium complex. Using a loading as low as 0.01 mol% of catalyst, the hydrogenation of various amino ketones was conducted with up to 99% yield and up to 99.8% ee (Scheme 4). To illustrate the relevance of this new catalyst, Okuma et al. synthesized a series of known molecules used in drug synthesis.

Ruthenium-Catalyzed Asymmetric Reductive Amination
Shimizu et al. developed a new catalytic en route to chiral amino acid derivatives via reductive amination. Using Ru-DM-SEGPHOS complexes, a variety of amino esters were obtained in one step from the corresponding ketoesters in highly enantioselective fashion (up to 99% ee (Scheme 5)).

References:
(S)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene, 97%

(S)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene-2,2'-diyl/dibis (diphenylphosphine) [76189-56-5]

C_{64}H_{38}P_{2}

FW 622.67

295825-250MG 250 mg
295825-1G 1 g
295825-5G 5 g

(S)-BINAP

(S)-(−)-2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene; (S)-(−)-1,1'-Binaphthalene-2,2'-diyl (diphenylphosphine) [76189-55-4]

FW 622.67

693057-100MG 100 mg
693057-500MG 500 mg

(R)-BINA

(R)-(+-)2,2'-Bis(diphenylphosphino)-1,1'-binaphthalene; (R)-(+-)1,1'-Binaphthalene-2,2'-diyl/dibis (diphenylphosphine); (R)-(+-)BINAP [76189-55-4]

FW 622.67

693065-100MG 100 mg
693065-500MG 500 mg

(R)-H_{8}-BINAP

(R)-H_{8}-BINAP; 5',6',6',7',8',8'-octahydro-1,1'-binaphthalene; 5',6',6',7',8',8'-octahydro-1,1'-binaphthalene-2,2'-diyl/dibis (diphenylphosphine) [139139-86-9]

FW 630.74

692387-50MG 50 mg
692387-100MG 100 mg

Scheme 5

Scheme 4
(5)-H₂-BINAP

(5)-(-)-2,2’-Bis(diphenylphosphino)-5,5’,6,6’,7,7’,8,8’-octahydro-1,1’-binaphthyl
[C₆H₄P₂]
FW 630.74

693014-50MG  50 mg
693014-100MG  100 mg

(5)-T-BINAP

(5)-(-)-2,2’-p-tolylphosphino)-1,1’-binaphthyl
[100165-88-6]
[C₆H₄P₂]
FW 678.78

693030-100MG  100 mg
693030-500MG  500 mg

(5)-T-BINAP

(5)-(+)-2,2’-Bis(di-p-tolylphosphino)-1,1’-binaphthyl; (S)-Tol-BINAP
[C₆H₄P₂]
FW 734.89

668966-250MG  250 mg
668966-1G  1 g

(5)-DM-BINAP

(5)-(-)-2,2’-Bis(diphenylphosphino)-5,5’,6,6’,7,7’,8,8’-octahydro-1,1’-binaphthyl
[C₆H₄P₂]
FW 678.78

693049-100MG  100 mg
693049-500MG  500 mg

(5)-Tol-BINAP

(5)-(-)-2,2’-Bis(di-p-tolylphosphino)-1,1’-binaphthyl
[C₆H₄P₂]
FW 678.78

693022-50MG  50 mg
693022-100MG  100 mg

(5)-SEGPHOS®

(5)-(+)-5,5’-Bis(diphenylphosphino)-4,4’-bi-1,3-benzodioxole; (4)/(R)-4,4’-bi-1,3-benzodioxole-5,5’-diyl[biis[diphenylphosphino]
[C₆H₄P₂]
FW 610.57

692395-50MG  50 mg
692395-100MG  100 mg

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Phosphino)-5,5'-6,7,7',8,8'-octahydro-1,1'-binaphthyl[500 mg]

Dimethylammonium dichlorotri(μ-chloro)bis[(S)-(−)-2,2'-bis(diphenylphosphino)-5,5'-6,7,7',8,8'-octahydro-1,1'-binaphthyl]diruthenate(II) C_{98}H_{88}Cl_{5}NP_{4}Ru_{2}
FW 1686.97
693324-50MG 50 mg
693324-100MG 100 mg

FW 1783.05
C_{90}H_{88}Cl_{5}NP_{4}Ru_{2}
Dimethylammonium dichlorotri(μ-chloro)bis[(R)+(−)-2,2'-bis(di(3,5-xylyl)phosphino)-1,1'-binaphthyl]diruthenate(II) C_{106}H_{104}Cl_{5}NP_{4}Ru_{2}
FW 1895.27
692204-100MG 100 mg
692204-50MG 50 mg

FW 1646.64
C_{78}H_{64}Cl_{5}NO_{8}P_{4}Ru _2
Dimethylammonium dichlorotri(μ-chloro)bis[(S)-(+)-5,5'-6,7,7',8,8'-octahydro-1,1'-binaphthyl]diruthenate(II) C_{34}H_{34}Cl_{5}NP_{4}Ru_{2}
FW 1783.05
693154-50MG 50 mg
693154-100MG 100 mg

FW 1895.27
C_{106}H_{104}Cl_{5}NP_{4}Ru_{2}
Dimethylammonium dichlorotri(μ-chloro)bis[(R)-(+)-5,5'-6,7,7',8,8'-octahydro-1,1'-binaphthyl]diruthenate(II) C_{34}H_{34}Cl_{5}NP_{4}Ru_{2}
FW 1783.05
693324-50MG 50 mg
693324-100MG 100 mg

FW 1686.97
C_{98}H_{88}Cl_{5}NP_{4}Ru_{2}
Dimethylammonium dichlorotri(μ-chloro)bis[(S)-(−)-2,2'-bis(diphenylphosphino)-5,5'-6,7,7',8,8'-octahydro-1,1'-binaphthyl]diruthenate(II) C_{98}H_{88}Cl_{5}NP_{4}Ru_{2}
FW 1686.97
693324-50MG 50 mg
693324-100MG 100 mg

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<td>228120-95-4</td>
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<td>228120-95-4</td>
<td>50 mg</td>
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<td>1028.98</td>
<td>228120-95-4</td>
<td>50 mg</td>
<td>692425-50MG</td>
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</tbody>
</table>
BINAP/SEGPHOS® Ligands and Complexes

(S)-RuCl([p-cymene](DTBM-SEGPHOS®))Cl

Dichloro([S]-(+)-5,5'-bis[di(3,5-di-tert-butyl-4-methoxyphenyl)phosphino]-(4,4'-bi-1,3-benzo-dioxole)(p-cymene)ruthenium(II)) chloride

FW 1485.72

C₆₅H₇₀Cl₂N₂O₂P₂Ru

693073-50MG 50 mg
693073-100MG 100 mg

RuCl₂((R)-DM-BINAP)[(R)-DAIPEN]

Dichloro((R)−2,2'−bis[di(3,5−xylyl)phosphino]−1,1'−binaphthyl][((R)−1,1'−bis(4−methoxyphenyl)−3−methyl−1,2−butanediamine)ruthenium(II)]

FW 1221.28

C₈₄H₁₁₄Cl₂O₈P₂Ru

692301-50MG 50 mg
692301-100MG 100 mg

RuCl₂((S)-[DM-BINAP])[S]-DAIPEN]

Dichloro((S)-(−)−2,2'−bis[di(3,5−xylyl)phosphino]−1,1'−binaphthyl][((S)−1,1'−bis(4−methoxyphenyl)−3−methyl−1,2−butanediamine)ruthenium(II)]

FW 1199.15

C₈₄H₁₁₄Cl₂O₈P₂Ru

692351-50MG 50 mg
692351-100MG 100 mg

RuCl₂((R)-DM-SEGPHOS®)[(R)-DAIPEN]

Dichloro((R)−5,5'−bis[di(3,5−xylyl)phosphino]−4,4'−bi−1,3−benzodioxole] 
[(R)−1,1'−bis(4−methoxyphenyl)−3−methyl−1,2−butanediamine)ruthenium(II)]

FW 1145.19

C₈₄H₁₁₄Cl₂O₈P₂Ru

692328-50MG 50 mg
692328-100MG 100 mg

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Dichloro[(5,5′-bis(di(3,5-xylyl)(phenylphosphino)-4,4′-bi-1,3-benzodioxole) ruthenium(II)]
C₅₂H₄₆O₄P₂Ru
FW 1107.05

RuCl₂[(S)-(DM-SEGPHOS®)]|[(S)-(DAIPEN)]

Dichloro[(S)-5,5′-bis(di(3,5-xylyl)(phenylphosphino)-4,4′-bi-1,3-benzodioxole)[(2S,2′R)-1,1-bis(4-methoxyphenyl)-3-methyl-1,2-butanediamine]]
ruthenium(II)]
C₅₄H₅₈O₄P₂Ru
FW 1209.18

RuCl₂[(R)-(DM-SEGPHOS®)]|[(R),(R)-(DPEN)]

Dichloro[(R)-5,5′-bis(di(3,5-xylyl)(phenylphosphino)-4,4′-bi-1,3-benzodioxole)[(1R,2R)-1,2-
diphenylethlyenediamine)]ruthenium(II)]
C₅₂H₄₆O₄P₂Ru
FW 1075.05

RuCl₂[(S)-(DM-SEGPHOS®)]|[(S),(S)-DPEN)]

Dichloro[(S)-5,5′-bis(di(3,5-xylyl)(phenylphosphino)-4,4′-bi-1,3-benzodioxole)[(15,23)-1,2-
diphenylethlyenediamine)]ruthenium(II)]
C₅₂H₄₆O₄P₂Ru
FW 1107.05

(S)-Ru(OAc)₂(BINAP)
Diacetato[(S)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl]ruthenium(II)
FW 841.83

RuCl₂[(R)-(DM-SEGPHOS®)]|[(R),(R)-(BINAP)]

Dichloro[(R)-5,5′-bis(di(3,5-xylyl)(phenylphosphino)-4,4′-bi-1,3-benzodioxole)]
C₅₄H₅₈O₄P₂Ru
FW 897.94

R: 36/37 S: 26
Diaceto[(R)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II)

\[ \text{C}_{50}\text{H}_{50}\text{O}_{8}\text{P}_{2}\text{Ru} \]

FW 954.04

692158-50MG 50 mg
692158-100MG 100 mg

Diaceto[(S)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl]ruthenium(II)

\[ \text{C}_{50}\text{H}_{50}\text{O}_{8}\text{P}_{2}\text{Ru} \]

FW 954.04

692158-50MG 50 mg
692158-100MG 100 mg

Diaceto[(S)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II)

\[ \text{C}_{56}\text{H}_{54}\text{O}_{4}\text{P}_{2}\text{Ru} \]

FW 941.94

693286-50MG 50 mg
693286-100MG 100 mg

Diaceto[(R)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II)

\[ \text{C}_{56}\text{H}_{54}\text{O}_{4}\text{P}_{2}\text{Ru} \]

FW 941.94

693286-50MG 50 mg
693286-100MG 100 mg

Diaceto[(S)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II)

\[ \text{C}_{56}\text{H}_{54}\text{O}_{4}\text{P}_{2}\text{Ru} \]

FW 941.94

693286-50MG 50 mg
693286-100MG 100 mg

Diaceto[(R)-5,5'-bis(diphenylphosphino)-4,4'-bi-1,3-benzodioxole]ruthenium(II)

\[ \text{C}_{56}\text{H}_{54}\text{O}_{4}\text{P}_{2}\text{Ru} \]

FW 941.94

693286-50MG 50 mg
693286-100MG 100 mg
Chiral Chromatography Products

- HPLC Columns
- GC Columns
- Screening and Purification Services

For more information on chiral chromatography products, email us at techservice@sial.com or visit us at sigma-aldrich.com/astec
Today's Solvias Ligand Portfolio has its roots in the development of the Josiphos ligands and the successful implementation in the (S)-metolachlor process—the largest industrial enantioselective manufacturing process—in the former Ciba-Geigy. Over the last decade, several additional ligand families have been added, either via Solvias' own research or via licensing from other companies. The central concept for all Solvias ligands is their modularity, usually via the introduction of different phosphino moieties in the very last stages of their synthesis. This allows the easy tuning of the steric and electronic properties and, thereby, the adaptation to the needs of a specific reaction. All ligands in the Solvias portfolio are available on a research scale with very short lead times; several ligands are being produced regularly in multikilogram quantities. The number of ligands within the portfolio varies between 10 to >100; therefore, it is not practical to have all of them available in a catalog. For this reason the members offered via Sigma-Aldrich® are a selection representing different steric and electronic properties. Further derivatives for optimization or fine tuning are usually available on request from Solvias.

MeOBIPHEP

In many respects, the catalytic profile of the MeOBIPHEP ligands is rather similar to that of other atropisomeric diphosphines such as BINAP and its many analogs. The nature of the PLz group strongly influences the catalytic performance of the metal complexes, and the ligands available have different steric bulk. MeOBIPHEP complexes are highly effective for the hydrogenation of α- and β-functionalized ketones (Figure 1), the hydrogenation of allylic alcohols and α,β-unsaturated esters (Figure 2), the hydrogenation of heteroarenes (Figure 3) and a variety of synthetically useful C–C coupling reactions (Figure 4).

(R)-(+)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine), ≥97.0% (CHN)

FW 1151.56  
C₇₄H₁₀₄O₆P₂

(S)-(-)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine), ≥97.0% (CHN)

FW 1151.56  
C₇₄H₁₀₄O₆P₂

(R)-(3,5-di-tert-butyl-4-methoxyphenyl)phosphine), ≥97.0% (CHN)

FW 694.82  
C₄₆H₄₈O₂P₂

(S)-(-)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(diphenylphosphine), ≥97.0% (CHN)

FW 694.82  
C₄₆H₄₈O₂P₂

(S)-(-)-(2,2'-Bis(di-2-furylphosphino)-6,6'-dimethoxy-1,1'-biphenyl; SL-A108-2, (S)-2-Furyl-MeOBIPHEP [145214-59-1]

FW 542.46  
C₃₈H₳₂O₂P₂

(S)-(-)-(2,2'-Bis(di-2-furylphosphino)-6,6'-dimethoxy-1,1'-biphenyl; SL-A108-2, (S)-2-Furyl-MeOBIPHEP

FW 542.46  
C₃₈H₳₂O₂P₂

(R)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphine), ≥97.0% (CHN)

FW 1151.56  
C₄₆H₄₈O₂P₂

(S)-(-)-(2,2'-Bis(di-2-furylphosphino)-6,6'-dimethoxy-1,1'-biphenyl; SL-A108-2, (S)-2-Furyl-MeOBIPHEP

FW 542.46  
C₃₈H₳₂O₂P₂

(R)-(6,6'-Dimethoxybiphenyl-2,2'-diyl)bis(3,5-di-tert-butyl-4-methoxyphenyl)phosphine), ≥97.0% (CHN)

FW 1151.56  
C₄₆H₄₈O₂P₂

(S)-(-)-(2,2'-Bis(di-2-furylphosphino)-6,6'-dimethoxy-1,1'-biphenyl; SL-A108-2, (S)-2-Furyl-MeOBIPHEP

FW 542.46  
C₃₈H₳₂O₂P₂
Josiphos

The Josiphos ligands arguably constitute one of the most versatile and successful ligand families, second probably only to the BINAP ligands. Since the two phosphine groups are introduced in consecutive steps with very high yields, a variety of ligands are readily available with widely differing steric and electronic properties. Up to now, only the (R,S,S)-family (and its enantiomers) but not the (R,R,R)-diastereomers have led to high enantioselectivities. At present, about 150 different Josiphos ligands have been prepared and 40 derivatives are available in a ligand kit (12000) for screening and on a multikilogram scale for production.3

Catalytic applications of the Josiphos ligand family were reviewed up to 2002.4 Until now, Josiphos ligands have been applied in 4 production processes and about 5 or 6 pilot and bench scale processes involving Rh, Ir, and Ru catalyzed hydrogenation reactions of C=C and C=N bonds.4 Selected applications are summarized in Figure 1. The most important application undoubtedly is the ICI005-1 catalyzed hydrogenation of a hindered N-aryl imine of methoxyacetone, the largest known enantioselective process operated for the enantioselective production of the herbicide (S)-metolachlor.5,6 The hydrogenation of tetrastubstituted olefins was the key step for two production processes developed for the synthesis of biotin by Lonza and of methyl dihydrojasmonate by Firmenich.7 Pilot processes were developed by Lonza for a building block of crevixan and for dextromethorphan.8 Recently, MSD Sharp & Dome GmbH chemists reported the unprecedented hydrogenation of unprotected dehydro β-amino acid derivatives catalyzed by Rh-Josiphos with ee’s up to 97.9%. It was shown that not only simple derivatives but also the complex intermediate for MK-0431 depicted in Figure 1 can be hydrogenated successfully. Regular production on a multiton/year scale with ee’s up to 98% has been started in 2006.9

Rh and Ir complexes with chiral Josiphos ligands are highly selective, active, and productive catalysts for various enantioselective reductions. Very high enantioselectivities were described for the enantioselective hydrogenation of enanamines, tetraconic acid derivatives, acetoacetics as well as N-aryl imines (in presence of acid and iodide) and phosphinylamines.10 Josiphos J001 is the ligand of choice for the Cu catalyzed reduction of activated C=C bonds with polyethylene glycol succinate (PIMHS) (Figure 2) with very high enantioselectivities for nitro alkenes,11 α,β-unsaturated ketones,12a esters,13β and nitriles.13c Very recently, it was disclosed that Ru-Josiphos-pyrindyl-alkylamines complexes (best ligands J001 and J007) are extraordinarily effective for the enantioselective transfer hydrogenation of aryl ketones with turnover frequencies for full conversion exceeding 20,000 h⁻¹ (Figure 3).14

Josiphos complexes have been successfully applied to various asymmetric catalytic coupling reactions such as allylic amination or hydroformylation.15 Selected recent examples are depicted in Figure 4. Feringa’s group reported high ee’s for the Cu catalyzed Michael addition of Grignard reagents to α,β-unsaturated esters,16a thioesters,16b and for selected cyclic enones.16c The preferred ligands were J001 and J004. The Ru/J001 was very effective for the nuclophilic ring opening of various oxabicyclic substrates leading to interesting new tetrahydro-naphthalene and cyclohexene derivatives.17 This reaction was scaled up to the kilogram scale.18 The Pd catalyzed opening of various cyclic anhydrides with Ph2Zn was described by Bercot and Floris to occur with very high ee’s in presence of J001.19 Lorman et al.17 reported up to 95% ee for an intermolecular Heck reaction using a Pd J001 catalyst.

Josiphos ligands were not only applied to enantioselective reactions but also were shown to be useful for Pd catalyzed coupling reactions with very high activities. Hartwig’s group reported that Pd/J009 (B8733 and B8734) complexes were effective catalysts for the amination of aryl halides or sulphonamides with ammonia,10b coupling of aryl halides or sulphonates with thiol,16d and Kumada coupling of aryl or vinyl tosylates with Grignard reagents.16e

References:

**Figure 1**

$\text{R} = \text{NO}_2, \text{COMe}, \text{CN}$

$\text{X} = \text{NO}_2, \text{COMe}, \text{CN}$

$0.1 - 3 \text{ mol}\%$ Cu/I001

85 - 99% ee

60 - >95%

**Figure 2**

$\text{R} = \text{NO}_2, \text{COMe}, \text{CN}$

$\text{X} = \text{NO}_2, \text{COMe}, \text{CN}$

$0.1 - 3 \text{ mol}\%$ Cu/I001

85 - 99% ee

60 - >95%

**Figure 3**

$\text{I} = \text{NO}_2, \text{COMe}, \text{CN}$

95 - >99% ee

95 - >99% cv

**Figure 4**

(RS)-1-[(5S)-2-(Diphenylphosphino)ferrocenyl]ethylcyclohexylphosphine

(RS)-1-[(5S)-2-(Dicyclohexylphosphino)ethylcyclohexylphosphine]

ferrocene (acc. to CAS). Josphos SL-J001-1 [155806-35-2]

C$_3$H$_6$P$_2$Fe$_2$-C$_6$H$_{12}$OH

FW 640.60

>97.0% (CHN)

88718-1G

1 g

88718-5G

5 g

500 mg

100 mg

**(S)-1-[(R)-2-(Diphenylphosphino)ferrocenyl]ethylcyclohexylphosphine**

(S)-1-[(R)-2-(Diphenylphosphino)ethylcyclohexylphosphine]

ferrocene (acc. to CAS). Josphos SL-J001-2 [162291-02-8]

C$_3$H$_6$P$_2$Fe$_2$-C$_6$H$_{12}$OH

FW 640.60

>97.0% (CHN)

88718-100MG

100 mg

88718-500MG

500 mg

88718-1G

1 g

88718-5G

5 g

C36H44FeP$_2$·C$_2$H$_5$OH (FW 640.60) ferrocene (acc to CAS); Josiphos SL-J001-1

C36H44FeP$_2$·C$_2$H$_5$OH (FW 640.60) phosphino)ethyl)-2-(diphenylphosphino)ferrocenyl
dicyclohexylphosphine

Josiphos; (2R)-1-[(1R)-1-(Dicyclohexylphosphino)ethyl]-2-(diphenylphosphino)ferrocene

FW 640.60

100 mg

5 g

100 mg

5 g

FW 640.60

5 g

FW 640.60
(R)-1-[(S)-2-(Diphenylphosphino)ferroceny]ethylid-tert-butylphosphine, ≥97.0% (CHN)

FW 606.62 C_{36}H_{56}FeP_{2}

88719-1G 1 g
88719-5G 5 g
88719-100MG 100 mg
88719-500MG 500 mg
88719-1000MG 1000 mg

(S)-1-[(R)-2-(Diphenylphosphino)ferroceny]ethylid-tert-butylphosphine, ≥97.0% (CHN)

FW 594.53 C_{36}H_{44}FeP_{2}

88720-1G 1 g
88720-5G 5 g
88720-100MG 100 mg
88720-500MG 500 mg
88720-1000MG 1000 mg

(R)-1-[(S)-2-(Dicyclohexylphosphino)ferroceny]ethylid-diphenylphosphine

FW 638.54 C_{40}H_{40}FeP_{2}

88721-1G 1 g
88721-5G 5 g
88721-100MG 100 mg
88721-500MG 500 mg
88721-1000MG 1000 mg

(S)-1-[(R)-2-(Dicyclohexylphosphino)ferroceny]ethylid-diphenylphosphine, ≥97.0% (CHN)

FW 594.53 C_{36}H_{44}FeP_{2}

88722-1G 1 g
88722-5G 5 g
88722-100MG 100 mg
88722-500MG 500 mg
88722-1000MG 1000 mg

(R)-1-[(S)-2-(Dicyclohexylphosphino)ferroceny]ethylid-[3,5-xyl]phosphine, ≥97.0% (CHN)

FW 638.54 C_{40}H_{40}FeP_{2}

88723-1G 1 g
88723-5G 5 g
88723-100MG 100 mg
88723-500MG 500 mg
88723-1000MG 1000 mg

(S)-1-[(R)-2-(Dihexylphosphino)ferroceny]ethylid[3,5-xyl]phosphine, ≥97.0% (CHN)

FW 638.54 C_{40}H_{40}FeP_{2}

88724-1G 1 g
88724-5G 5 g
88724-100MG 100 mg
88724-500MG 500 mg
88724-1000MG 1000 mg

(R)-1-[(S)-2-(Diphenylphosphino)ferroceny]ethylid-[3,5-xyl]phosphine, ≥97.0% (CHN)

FW 638.54 C_{40}H_{40}FeP_{2}

88725-1G 1 g
88725-5G 5 g
88725-100MG 100 mg
88725-500MG 500 mg
88725-1000MG 1000 mg

(S)-1-[(R)-2-(Diphenylphosphino)ferroceny]ethylid-[3,5-xyl]phosphine, ≥97.0% (CHN)

FW 638.54 C_{40}H_{40}FeP_{2}

88726-1G 1 g
88726-5G 5 g
88726-100MG 100 mg
88726-500MG 500 mg
88726-1000MG 1000 mg

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(R)-1-((S)-2-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]ferroceny)ethyl)dicyclohexylphosphine, ≥97.0% (19F-NMR)

(1R)-1-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]-2-{(1R)-1-[dicyclohexylphosphino]ethyl}ferrocene (acc to CAS); Josiphos SL-J006-1
BF3·FeCl2
FW 866.52
BB77-100MG 100 mg
BB77-500MG 500 mg
BB77-1G 1 g
BB77-5G 5 g

(S)-1-((R)-2-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]ferroceny)ethyl)dicyclohexylphosphine, ≥97.0% (19F-NMR)

(1S)-1-[Bis[3,5-bis(trifluoromethyl)phenyl]phosphino]-2-{(1S)-1-[bis(3,5-dimethylphenyl)phosphino]ethyl}ferrocene (acc to CAS); Josiphos SL-J008-1
BF3·FeCl2
FW 910.53
BB79-100MG 100 mg
BB79-500MG 500 mg
BB79-1G 1 g
BB79-5G 5 g

[292638-88-1]
C40H40F12FeP2
FW 88727
88727-100MG 100 mg
88727-500MG 500 mg
88727-1G 1 g
88727-5G 5 g

[849923-15-5]
C40H40F12FeP2
FW 88728
88728-100MG 100 mg
88728-500MG 500 mg
88728-1G 1 g
88728-5G 5 g

[360048-63-1]
C40H40F12FeP2
FW 88731
88731-100MG 100 mg
88731-500MG 500 mg
88731-1G 1 g
88731-5G 5 g

[166172-63-0]
C40H40F12FeP2
FW 88732
88732-100MG 100 mg
88732-500MG 500 mg
88732-1G 1 g
88732-5G 5 g

20
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(R)-1-{[(S)-2-(Dicyclohexylphosphino)ferroceny]ethyldi-tert-butylphosphine, ≥97.0% (CHN)

(2R)-1-{[(R)-1{-[Bis(1,1-dimethylphenyl)phosphino]ethyl}-2-(dicyclohexylphosphino)ferrocene (acc to CAS); Josiphos SL-J009-1 [158923-11-6] C₃₂H₅₂FeP₂ FW 554.55

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(S)-1-{[(R)-2-(Dicyclohexylphosphino)ferroceny]ethyldi-tert-butylphosphine, ≥97.0% (CHN)

(2S)-1-{[(S)-1{-[Bis(1,1-dimethylphenyl)phosphino]ethyl}-2-(dicyclohexylphosphino)ferrocene (acc to CAS); Josiphos SL-J009-2 C₃₂H₅₂FeP₂ FW 554.55

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(R)-1-{[(S)-2-[Bis(4-trifluoromethyl)phenyl]phosphino]ferroceny]ethyldi-tert-butylphosphine, ≥97.0% (¹⁹F-NMR)

(2R)-1-{[(R)-1{-[Bis(1,1-dimethylphenyl)phosphino]ethyl}-2-[bis(4-trifluoromethyl)phenyl]phosphino]ferrocene (acc to CAS); Josiphos SL-J011-1 [246231-79-8] C₃₆H₃₆FeO₂P₂ FW 618.46

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(S)-1-{[(R)-2-[Bis(4-trifluoromethyl)phenyl]phosphino]ferroceny]ethyldi-tert-butylphosphine, ≥97.0% (¹⁹F-NMR)

(2S)-1-{[(S)-1{-[Bis(1,1-dimethylphenyl)phosphino]ethyl}-2-[bis(4-trifluoromethyl)phenyl]phosphino]ferrocene (acc to CAS); Josiphos SL-J013-1 [187733-50-2] C₃₈H₅₂FeO₂P₂ FW 658.61

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(R)-1-{[(S)-2-[Di(2-furyl)phosphino]ferroceny]ethyldi(3,5-xyl)phosphine, ≥97.0% (CHN)

(2R)-1-{[(R)-1{-[Bis(3,5-dimethylphenyl)phosphino]ethyl}-2-[di-2-furylphosphino]ferrocene (acc to CAS); Josiphos SL-J015-1 [649559-65-9] C₃₀H₂₆FeO₂P₂ FW 682.49

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(R)-1-{[(S)-2-[Di(3,5-dimethylphenyl)phosphino]ethyl]-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocene (acc to CAS); Josiphos SL-J013-2 [849924-60-9] C₃₂H₃₂FeO₂P₂ FW 658.61

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(R)-1-{[(S)-2-{Bis(4-methoxy-3,5-dimethyl[phenyl]phosphino)ferroceny]ethyldi-tert-butylphosphine, ≥97.0% (CHN)

(2R)-1-{[(R)-1{-[Bis(1,1-dimethylphenyl)phosphino]ethyl}-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocene (acc to CAS); Josiphos SL-J013-1 [187733-50-2] C₃₈H₅₂FeO₂P₂ FW 658.61

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(S)-1-(R)-2-[Di(2-furyl)phosphino]ferroceny]ethyldi(3,5-xylyl)phosphine, ≥97.0% (CHN)

(2S)-1-[(1S)-1-{Bis(3,5-dimethylphenyl)phosphino]ethyl}-2-(di-2-furany1-phosphino)ferrocene (acc to CAS); Josiphos SL-J015-2
[C₄₀H₃₇FeP₂]
FW: 618.46

BB740-100MG  100 mg
BB740-500MG  500 mg
BB740-1G  1 g
BB740-5G  5 g

(R)-1-(S)-2-[Di(2-furyl)phosphino]ferroceny]ethyldi-tert-butylphosphine, ≥97.0% (CHN)

(2R)-1-[(1R)-1-{Bis(1,1-dimethylethyl)phosphino]ethyl}-2-(di-2-furany1-phosphino)ferrocene (acc to CAS); Josiphos SL-J012-1
[C₄₀H₃₇FeP₂]
FW: 522.38

BB741-100MG  100 mg
BB741-500MG  500 mg
BB741-1G  1 g
BB741-5G  5 g

(S)-1-[(R)-2-[Di(2-furyl)phosphino]ferroceny]ethyldi-tert-butylphosphine, ≥97.0% (CHN)

(2S)-1-[(1S)-1-{Bis(1,1-dimethylethyl)phosphino]ethyl}-2-(di-2-furany1-phosphino)ferrocene (acc to CAS); Josiphos SL-J012-2
[C₄₀H₃₇FeP₂]
FW: 522.38

BB742-100MG  100 mg
BB742-500MG  500 mg
BB742-1G  1 g
BB742-5G  5 g

(R)-1-[(S)-2-[Di(1-naphthyl)phosphino]ferroceny]ethyldi-(3,5-xylyl)phosphine, ≥97.0% (CHN)

(2R)-1-[(1R)-1-{Bis(3,5-dimethylphenyl)phosphino]ethyl}-2-(di-1-naphthylphosphino)ferrocene (acc to CAS); Josiphos SL-J014-1
[C₄₀H₃₇FeP₂]
FW: 738.66

BB745-100MG  100 mg
BB745-500MG  500 mg
BB745-1G  1 g
BB745-5G  5 g

(S)-1-[(R)-2-[Di(1-naphthyl)phosphino]ferroceny]ethyldi-(3,5-xylyl)phosphine, ≥97.0% (CHN)

(2S)-1-[(1S)-1-{Bis(3,5-dimethylphenyl)phosphino]ethyl}-2-(di-1-naphthylphosphino)ferrocene (acc to CAS); Josiphos SL-J014-2
[C₄₀H₃₇FeP₂]
FW: 738.66

BB746-100MG  100 mg
BB746-500MG  500 mg
BB746-1G  1 g
BB746-5G  5 g

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(S)-1-(S,S)-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocenyl-ethyl(3,5-xyllyl)phosphine, ≥97.0% (CHN)

FW 726.64
\(\text{C}_{44}\text{H}_{48}\text{FeO}_{2}\text{P}_{2}\)

Josiphos SL-J425
5g
88749-5G
1g
88749-1G
500 mg
88749-500MG
100 mg
88749-100MG

(2R)-1-{[1R]-1-[Bis(3,5-dimethylphenylphosphino)ethyl]-2-[bis(4-methoxy-3,5-dimethylphenylphosphino)ferrocene (acc to CAS); Josiphos SL-J41B-1

FW 754.70
\(\text{C}_{46}\text{H}_{52}\text{FeO}_{2}\text{P}_{2}\)

Josiphos SL-J502-1
5g
88753-5G
1g
88753-1G
500 mg
88753-500MG
100 mg
88753-100MG

(5S)-1-[(R,S)-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocenyl]-ethyl(3,5-xyllyl)phosphine, ≥97.0% (CHN)

FW 754.70
\(\text{C}_{46}\text{H}_{52}\text{FeO}_{2}\text{P}_{2}\)

Josiphos SL-J452-1
5g
88748-5G
1g
88748-1G
500 mg
88748-500MG
100 mg
88748-100MG

(2S)-1-[(S,S)-1-[Bis(3,5-dimethylphenylphosphino)ethyl]-2-[bis(4-methoxy-3,5-dimethylphenylphosphino)ferrocene (acc to CAS); Josiphos SL-J41B-2

FW 590.41
\(\text{C}_{34}\text{H}_{32}\text{FeO}_{2}\text{P}_{2}\)

Josiphos SL-J502-1
5g
88751-5G
1g
88751-1G
500 mg
88751-500MG
100 mg
88751-100MG

(2R)-1-[(S,S)-2-[Bis(2-furyl)phosphino]ferrocenyl]ethyl(2-methylphosphino)phosphine, ≥97.0% (CHN)

FW 542.45
\(\text{C}_{32}\text{H}_{40}\text{FeP}_{2}\)

Josiphos SL-J502-1
5g
88750-5G
1g
88750-1G
500 mg
88750-500MG
100 mg
88750-100MG

(2S)-1-[[1S]-1-[Bis(3,5-dimethylphenylphosphino)ethyl]-2-[bis(2-methylphenyl)phosphino]di(2-methylphenyl)ferrocene (acc to CAS); Josiphos SL-J425-2
849924-52-3

FW 726.64
\(\text{C}_{44}\text{H}_{48}\text{FeO}_{2}\text{P}_{2}\)

Josiphos SL-J502-1
5g
88755-5G
1g
88755-1G
500 mg
88755-500MG
100 mg
88755-100MG

(1R)-1-[(R,S)-2-[Bis(4-methoxy-3,5-dimethylphenyl)phosphino]ferrocene (acc to CAS); Josiphos SL-J502-1

FW 590.41
\(\text{C}_{34}\text{H}_{32}\text{FeO}_{2}\text{P}_{2}\)

Josiphos SL-J502-1
5g
88754-5G
1g
88754-1G
500 mg
88754-500MG
100 mg
88754-100MG

(1R)-1-[Bis(1,1-dimethylethyl)phosphino]-2-[(1R)-1-(diphenylphosphino)ethyl]ferrocene (acc to CAS); Josiphos SL-J502-1

FW 542.45
\(\text{C}_{32}\text{H}_{40}\text{FeP}_{2}\)

Josiphos SL-J502-1
5g
88753-5G
1g
88753-1G
500 mg
88753-500MG
100 mg
88753-100MG

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(5S)-1-[[Rh]-2-(Di-tert-butylphosphino)ferrocenylerithydiphenylphosphine, ≥97.0% (CHN)]

(1S)-1-[bis(1,1-dimethylphosphino)2-[(1S)-1-diphenylphosphino]ethylerhodocene (acc to CAS); Josiphos SL-J505-2

FW 570.51
C₃₄H₄₄FeP₂
88755-1G
100 mg
88755-500MG
500 mg
88755-100MG
500 mg

(5R)-1-[(5S)-2-(Di-tert-butylphosphino)ferrocenylerithylibis(2-methylphenylphosphine, ≥97.0% (CHN)]

(1R)-1-[bis(1,1-dimethylphosphino)2-[(1R)-1-bis(2-methylphosphino)ethylerhodocene (acc to CAS); Josiphos SL-J505-1

FW 570.51
C₃₄H₄₄FeP₂
88755-1G
100 mg
88755-500MG
500 mg

Walphos

Like Josiphos, Walphos ligands are modular but form 8-membered metalacycles due to the additional phenyl ring attached to the cyclopentadiene ring. There are noticeable electronic effects but the scope of this ligand family is still under investigation; several derivatives are available from Solvias on a research scale. Walphos ligands show promise for various enantioselective hydrogenations and pertinent transformations were reported to be catalyzed by Rh/Walphos complexes with high enantioselectivities (Figure 1): the 4+2-addition of 4-alkyls with an acyl amide by Tanaka and co-workers5 and the reductive coupling of enynes with α-keto esters by Kreische’s group.6

The first industrial application has just been realized in collaboration with Speedel/Novartis for the hydrogenation of SPP100-SyA, a sterically demanding α,β-unsaturated acid intermediate of the renin inhibitor SPP100.7 The process has already been operated on a multiton scale. Lilly’s chemists7 developed a process of a PPAR agonist using the Rh-catalyzed asymmetric hydrogenation of 2α-cinnamic acid as key step. A screen of over 250 catalysts and conditions revealed Rh-W001 as the most effective ligand, giving the product in 92% ee.
(R)-1-[(R)-2-[(Diphenylphosphino)phenyl]ferroceny]ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine, ≥97.0% (19F-NMR)

1S₁-1-[(S)-1-[(S)-2-[(Diphenylphosphino)phenyl]ferroceny]ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine, ≥97.0% (19F-NMR)

Solvias® Ligand Portfolio

CF8.2 Extract 4 cd XML 032508 PGD UNP ed0423
(R)-1-((R)-2-[2-(Diphenylphosphino)phenyl]ferrocenyl)ethyl-di(3,5-xylyl)phosphine, ≥97.0% (CHN)

(S)-1-((S)-2-[2-(Dicyclohexylphosphino)phenyl]ferrocenyl)ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine, ≥97.0% (NMR)

(CA)-1-((CA)-2-[2-(Dicyclohexylphosphino)phenyl]ferrocenyl)ethyl-di(3,5-xylyl)phosphine, ≥97.0% (CHN)

(S)-1-((S)-2-[2-(Dicyclohexylphosphino)phenyl]ferrocenyl)ethylbis[3,5-bis(trifluoromethyl)phenyl]phosphine, ≥97.0% (NMR)

(R)-1-((R)-2-[2-(Dicyclohexylphosphino)phenyl]ferrocenyl)ethyl-di(3,5-xylyl)phosphine, ≥97.0% (CHN)

(S)-1-((S)-2-[2-(Dicyclohexylphosphino)phenyl]ferrocenyl)ethyl-di(3,5-xylyl)phosphine, ≥97.0% (NMR)
Compared to Josiphos, the Taniaphos ligands developed by the Knochel group1 have an additional phenyl ring inserted at the α-position of the Ugi amine. Besides the two-phosphine moieties, the substituent at the stereogenic center can also be varied and, up to now, three generations of Taniaphos ligands with different substituents at the α-position have been prepared. Several Taniaphos ligands are being marketed by Solvias in collaboration with Umicore and selected derivatives are being produced on a multikilogram scale.

A variety of Taniaphos ligands are very selective in a number of model hydrogenation reactions.1,2-4 Both the nature of two phosphine moieties, as well as the substituent and the configuration of the stereogenic center at the α-position, have strong effects on the catalytic performance, sometimes even on the sense of induction. Taniaphos complexes are highly active and stereoselective for the Rh catalyzed hydrogenation of methyl acrylate and of methyl ketones to methyl acrylate.4b

Recently, a variety of highly enantioselective transformations were described using Taniaphos complexes.3,4 Selected reactions are depicted in Figure 1. T001 was found to be very selective for the Rh catalyzed nucleophilic ring opening of an azabicycle.2 Cu Taniaphos complexes were also very effective for the reductive addition of aldehydes5 to methyl acrylate and of methyl ketones to methyl acrylate.4b

References:

Figure 1

(R)-1-Dicyclohexylphosphino-2-((R)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl)ferrocene, >97.0% (CHN)

References:

Figure 1

(R)-1-Dicyclohexylphosphino-2-((R)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl)ferrocene, >97.0% (CHN)

References:

Figure 1

(R)-1-Dicyclohexylphosphino-2-((R)-α-(dimethylamino)-2-(dicyclohexylphosphino)benzyl)ferrocene, >97.0% (CHN)

References:
Mandyphos (Ferriphos)

Ferriphos was first prepared by Itô and coworkers as a bidentate analog of PPh₂A. In 1998, Knochel developed a general synthesis for a highly modular ligand family which was later called Mandyphos in which not only the PR₃ moieties but also the substituents at the side chain can be used for fine-tuning purposes. Selected Mandyphos derivatives are commercialized by Solvias in collaboration with Umicore. Even though the scope of this family is not yet fully explored, screening results indicate high enantioselectivities as well as high activity for several Mandyphos derivatives in the Rh catalyzed hydrogenation of dehydroamino acid derivatives (preferred ligand M004, 95–99% ee, sc up to 20,000) and the Ru catalyzed hydrogenation of tiglic acid (M004, 97% ee). M004 was also the ligand of choice for the Rh catalyzed hydrogenation of various methyl 2-furyl acrylates while RuFerriphos is highly selective for Rh catalyzed ring opening of azabicycles with amines (see Figure 1). Several Mandyphos derivatives are being produced on a multikilogram scale.

References:
(R,S)-1,1'- Bis(dicyclohexylphosphino)-2,2'- bis((S)-α- (dimethylamino)benzyl)ferrocene, ≥97.0% (CHN)

FW 1364.74
C₆₀H₄₂F₂₄FeN₂P₂

73466-100MG  100 mg
73466-500MG  500 mg
73466-1G      1 g
73466-5G      5 g

(S,R)-1,1'- Bis[3,5-bis(trifluoromethyl)phenyl]phosphino)-2,2'- bis((S)-α- (dimethylamino)benzyl)ferrocene, ≥97.0% (¹⁹F-NMR)

FW 1053.08
C₆₄H₇₄FeN₂O₄P₂

73469-100MG  100 mg
73469-500MG  500 mg
73469-1G      1 g
73469-5G      5 g

(R,R')-1,1'- Bis[4-methoxy-3,5-dimethylphenyl]phosphino)-2,2'-bis((R)-α- (dimethylamino)phenylmethyl)ferrocene, ≥97.0% (CHN)

FW 1053.08
C₆₄H₇₄FeN₂O₄P₂

73470-100MG  100 mg
73470-500MG  500 mg
73470-1G      1 g
73470-5G      5 g

(R,S)-1,1'- Bis[4-methoxy-3,5-dimethylphenyl]phosphino)-2,2'- bis((S)-α- (dimethylamino)benzyl)ferrocene, ≥97.0% (CHN)

FW 1053.08
C₆₄H₇₄FeN₂O₄P₂

73471-100MG  100 mg
73471-500MG  500 mg
73471-1G      1 g
73471-5G      5 g
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<th>Chemical Structure</th>
<th>Formula</th>
<th>CAS Number</th>
<th>Description</th>
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<tr>
<td>(S,P)-1,1'-Bis[(R)-α-(dimethylamino)benzyl]-2,2'-bis[di(3,5-xylyl)phosphino]ferrocene, ≥97.0% (CHN)</td>
<td>C_{60}H_{66}FeN_{2}P_{2}</td>
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<td>73471-5G</td>
<td>5 g</td>
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<tr>
<td>(R,P)-1,1'-Bis[(S)-α-(dimethylamino)benzyl]-2,2'-bis[di(3,5-xylyl)phosphino]ferrocene, ≥97.0% (CHN)</td>
<td>C_{60}H_{66}FeN_{2}P_{2}</td>
<td>73472-100MG</td>
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<tr>
<td>(R,P)-1,1'-Bis[(R)-α-(dimethylamino)benzyl]-2,2'-bis[di(3,5-xylyl)phosphino]ferrocene, ≥97.0% (CHN)</td>
<td>C_{60}H_{66}FeN_{2}P_{2}</td>
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Naud Catalyst

Complexes prepared in situ from RuCl₂(PPh₃)₃ and chiral phosphate-oxazoline ligands (Naud catalysts) are effective catalysts for the hydrogenation of various aryl ketones with up to 99% ee’s and substrate to catalyst ratios of 10,000–50,000. The reaction tolerates high substrate concentrations,¹ and several derivatives are being produced on a multikilogram scale. A pilot process has been developed for the hydrogenation of 3,5-bistrifluoromethyl acetophenone.² The reaction was carried out twice on a 140 kg scale at 20 bar and 25 °C with substrate to catalyst ratios of 20,000 with an enantiomeric excess of >95%. After crystallization, (R)-3,5-bistrifluoromethyl phenyl ethanol was obtained with an ee between 97.7 and 98.6% in 70% chemical yield (Figure 1). A feasibility study was reported by MSD Sharp & Dome GmbH for the reduction of a highly functionalized aryl ketone.³


Butaphene

In many respects the catalytic profile of the Butaphene ligands¹ P005-1 (53361) and P005-2 (53362) is rather similar to that of other phospholine diphosphines such as DuPhos and its many analogs.² Up to now, the potential of the ligand has only been demonstrated in the Rh catalyzed hydrogenation of dehydroamino acid derivatives, enamides, and itaconates, achieving ee values of up to 98.7%.³

**Kit**

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**Components**

- (R)-2-(4-Chlorophenyl)phosphinomethylferrocene (Aldrich 73460)
- (R)-2-(4-Methoxy-3,5-dimethylphenyl)phosphinomethylferrocene (Aldrich 73461)
- (R)-2-(4-Methoxyphenyl)phosphinomethylferrocene (Aldrich 73462)
- (R)-2-(4-Methylphenyl)phosphinomethylferrocene (Aldrich 73463)
- (R)-2-(3,4-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73464)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73465)
- (R)-2-(3,5-Dimethylxylyl)phosphinomethylferrocene (Aldrich 73466)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73467)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73468)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73469)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73470)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73471)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73472)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73473)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73474)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73475)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73476)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73477)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73478)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73479)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73480)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73481)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73482)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73483)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73484)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73485)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73486)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73487)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73488)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73489)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73490)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73491)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73492)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73493)
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- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73502)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73503)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73504)
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- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73511)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73512)
- (R)-2-(3,5-Dimethylphenyl)phosphinomethylferrocene (Aldrich 73513)

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DuPhos and BPE Phospholane Ligands and Complexes

In the early 1990s, Burk and coworkers developed new electron-rich C₂ symmetric bis(phospholane) ligands. The modular nature of these ligands allowed for variation of both phosphane substituent and backbone structures, leading to an extensive library of ligands for enantioselective catalytic reactions. The large-scale capacity of these robust catalysts is observed in the efficiency (substrate-to-catalyst (S/C) ratios up to 50,000) and the high activities (TOF >5,000 h⁻¹) in a myriad of enamine and ketone reductions. Under optimized conditions, (R,R)-Me-BPE-Rh reduced N-acetyl-enynamides in >95% ee to yield valuable α,β-unsaturated enamines (Scheme 1).¹

It should be noted that Me-DuPhos-Rh complexes were equally effective in asymmetric reductions of prochiral enamides. The general utility of these phospholane ligands is illustrated in the incredible diversity-oriented production of a vast array of amino acid derivatives (Scheme 2).²

Asymmetric Hydrogenation of the C=N Group

Burk and co-workers exploited the high activity of the Ethyl-DuPhos ligand via a powerful catalytic reductive amination process.³ The procedure exhibits general applicability in the reduction of a wide variety of N-arylamides, yielding enantioselectivities for most substrates >90% (Scheme 3). Additionally this (Et-DuPhos)-Rh catalyst system displays exceptionally high chemoselectivities, yielding little or no reduction of unfunctionalized amines, alkenes, ketones, aldehydes, and imines in competition experiments. The synthetic utility of these asymmetric hydrazone reductions is enhanced by their facile reaction at ambient temperature with samarium diiodide, which proceed with no observable loss of optical purity.

Catalytic Hydrogenation of Enamides

Burk has also pioneered the asymmetric hydrogenation of various enamido olefins affording highly enantioselective unsaturated amino acid products.² The (S,S)-Et-DuPhos-Rh catalyst system controls the reactivity of conjugated substrates with high regioselectivies as well. Under the standard hydrogenation conditions (S/C =500, H₂ pressures ranging from 60 to 90 psi, and 0.5–3 h), this catalyst gave less than 2% overreduction, with all products isolated in better than 95% yield. The authors elaborated upon this outstanding catalyst reactivity by demonstrating a concise and highly selective synthesis of the natural product (R)-bulgecine, preceded by formation of the key chiral intermediate in 99% yield with 99.3% ee (Scheme 4).

Preparation of Chiral Organics with C–O Stereogenic Centers

Neil Boaz has also utilized rhodium(I)-(R,R)-Me-DuPhos) catalyst 1 to produce chiral alcohols via the asymmetric hydrogenation of enol esters (Scheme 5). Aliphatic alcohol derivatives are desirable organic building blocks in diversity-oriented synthesis, because the olefin can be further functionalized after the stereochemistry has been set in the hydrogenation.² Under asymmetric hydrogenation conditions, the initially formed propargylic acetate was subsequently reduced to yield the 2-allylic acetate. Impressively, the enantioselectivity observed in this reaction was very high among the general substrate class 2a-c.²

Burk and co-workers have also designed highly effective catalysts for the asymmetric reduction of C=O bonds under hydrogenation conditions.³ In this case, the methodology proceeded via use of a chiral Ru(III)(Br₂)-(C₃Pr-BPE) complex, which was prepared by reacting [(COD)Ru(2-methylallyl)₂] with the BPE ligand followed by treatment with methanolic HBr. A variety of ketones were highly hydrogenated as mediated by this catalyst to the hydroxyl esters with very high enantioselectivities >98% ee for the alkyl-substituted substrates (Scheme 6).
Enantioselective Hydrogenation of Alkenes and Imines

The use of gold complexes to effect catalytic transformations is on the rise, with numerous reports of catalytically active gold species. Sanchez and co-workers have now reported the first example of a gold hydrogenation catalyst utilized in asymmetric transformations. The authors found that the bulkiest substrate, which incorporates a diethyl 2-naphthylidene succinate group, proceeds under the reaction conditions to afford the highest enantioselectivities due to reactant control (Scheme 7). Future plans in gold-mediated asymmetric hydrogenation involve substantial modifications to the ligand structure to provide higher levels of enantiocontrol in this reaction paradigm.

Enantioselective Allylboration of Ketones

The Shibasaki research group has also championed the use of the DuPhos ligand system for asymmetric catalysis. They have now reported the first general catalytic, enantioselective allylation reaction with ketones, which employs copper salts and a rare-earth lanthanide additive. Impressively, a diverse array of aromatic, heteroaromatic, ketones, which employs copper salts and a rare-earth lanthanide additive.

Enantioselective Addition of Dialkylzinc to β-Nitroalkenes

The use of chiral bis(phosphine) monoxide ligand has found widespread applications in catalysis. Côté et al. reported the use of Me-DuPhos monoxide in the addition of dialkylzinc to nitroalkanes. Various chiral nitroalkanes were synthesized with excellent yields and selectivities (Scheme 9).

References:

(-)-1,2-Bis(2R,5R)-2,5-dimethylphospholano[2,1-b:3,4-b']benzene
(2R,2'S,5'R,5'S)-2',5'-Tetramethyl-1,1'-o-phenylene) diphospholane; (R,R)-Methyl-DUPHOS; (R,R)-Me-DUPHOS [147253-67-6] C22H36P2 FW 306.36
S: 22-2425
665258-100MG 100 mg
665258-250MG 250 mg
665258-500MG 500 mg
665258-2G 2 g

(-)-1,2-Bis(2R,5R)-2,5-diethylphospholano[2,1-b:3,4-b']benzene
(2R,2'R,5'R,5'S)-2',5'-Tetraethyl-1,1'-o-phenylene) diphospholane; (R,R)-Ethyl-DUPHOS [136705-64-1] C22H36P2 FW 362.47
Fp: 110 °C (230 °F)
668494-100MG 100 mg
668494-500MG 500 mg
668494-2G 2 g

(-)-1,2-Bis(2S,5S)-2,5-dimethylphospholano[2,1-b:3,4-b']benzene
(2S,2'S,5'S,5'S)-2',5'-Tetramethyl-1,1'-o-phenylene) diphospholane; (S,S)-Methyl-DUPHOS; (S,S)-Me-DUPHOS [136735-95-0] C22H36P2 FW 306.36
665266-100MG 100 mg
665266-500MG 500 mg
665266-2G 2 g

(-)-1,2-Bis(2S,5S)-2,5-diethylphospholano[2,1-b:3,4-b']benzene
(2S,2'S,5'S,5'S)-2',5'-Tetraethyl-1,1'-o-phenylene) diphospholane; (S,S)-Ethyl-DUPHOS [136772-28-7] C22H36P2 FW 362.47
Fp: 110 °C (230 °F)
668486-100MG 100 mg
668486-500MG 500 mg
668486-2G 2 g
(±)-1,2-Bis(2R,5R)-2,5-diisopropylphospholano]benzene
donor
(R,R)-Pr-DUPHOS
FW 418.58

(-)-1,2-Bis(2S,5S)-2,5-diisopropylphospholano]benzene
(RR)-i-Pr-DUPHOS
FW 418.58

1,2-Bis(2R,5R)-2,5-diisopropylphospholano]benzene monooxide
FW 418.58

1,2-Bis(2S,5S)-2,5-diisopropylphospholano]benzene monooxide
FW 418.58

1,2-Bis(2S,5S)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate
FW 660.36

1,2-Bis(2R,5R)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate
FW 660.36

1,2-Bis(2R,5R)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate
FW 722.62

1,2-Bis(2S,5S)-2,5-diethylphospholano]benzene(1,5-cyclooctadiene)rhodium(I) trifluoromethanesulfonate
FW 722.62

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1,2-Bis[(2R,5R)-2,5-diisopropylphospholano]benzene (1,5-cyclooctadiene)rhodium(II) tetrafluoroborate

FW 716.47

698342-50MG 50 mg
698342-250MG 250 mg

1,2-Bis[(2S,5S)-2,5-diisopropylphospholano]benzene (1,5-cyclooctadiene)rhodium(II) tetrafluoroborate

FW 604.25

675520-100MG 100 mg
675520-500MG 500 mg

1,2-Bis[(2S,5S)-2,5-dimethylphospholano]benzene (1,5-cyclooctadiene)rhodium(II) tetrafluoroborate

FW 370.53

668443-100MG 100 mg
668443-500MG 500 mg
668443-2G 2 g

1,2-Bis[(2R,5R)-2,5-diisopropylphospholano]benzene (1,5-cyclooctadiene)rhodium(II) trifluoromethanesulfonate, ≥97%

FW 314.43

668435-100MG 100 mg
668435-500MG 500 mg
668435-2G 2 g
(+)-1,2-Bis[(2R,5R)-2,5-dimethylphospholano]ethane

(R,R)-Me-BPE

[C2H5P2]

FW 258.32

R: 11-17

665231-100MG

100 mg

665231-500MG

500 mg

665231-2G

2 g

(-)-1,2-Bis[(2S,5S)-2,5-dimethylphospholano]ethane

(S,S)-Me-BPE

[C2H5P2]

FW 258.32

R: 11-17

665207-100MG

100 mg

665207-500MG

500 mg

665207-2G

2 g

(+)-1,2-Bis[(2R,5R)-2,5-diphenylphospholano]ethane

(C8H17P2)

FW 506.60

R: 36/37/38 S: 26

698350-50MG

50 mg

698350-250MG

250 mg

1,2-Bis[(2R,5R)-2,5-diphenylphospholano]ethane(cyclooctadiene)rhodium(I) tetrafluoroborate

(C34H36P2RhBF4)

FW 804.49

R: 36/37/38 S: 26-36/37

698369-50MG

50 mg

698369-250MG

250 mg

1,1′-Bis[(2R,5R)-2,5-diethylphospholano]ferrocene

(C26H40FeP2)

FW 470.39

680990-100MG

100 mg

680990-500MG

500 mg

1,1′-Bis[(2S,5S)-2,5-diethylphospholano]ferrocene

(S,S)-Et-Ferrocelane™

FW 470.39

681008-100MG

100 mg

681008-500MG

500 mg

1,2-Bis[(2R,5R)-2,5-dimethylphospholano]ethane(cyclooctadiene)rhodium(I) tetrafluoroborate

(C21H24BF4P2Rh)

FW 556.21

R: 36/37/38 S: 26

675547-100MG

100 mg

675547-500MG

500 mg

1,2-Bis[(2S,5S)-2,5-dimethylphospholano]ethane(cyclooctadiene)rhodium(I) tetrafluoroborate

(C21H24BF4P2Rh)

FW 556.21

R: 36/37/38 S: 26

675555-100MG

100 mg

675555-500MG

500 mg

1,2-Bis[(2R,5R)-2,5-diphenylphospholano]ethane(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate

(C42H48BF4P2Rh)

FW 804.49

R: 36/37/38 S: 26

698350-50MG

50 mg

698350-250MG

250 mg

1,2-Bis[(2S,5S)-2,5-diphenylphospholano]ethane(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate

(C42H48BF4P2Rh)

FW 804.49

R: 36/37/38 S: 26

698350-50MG

50 mg

698350-250MG

250 mg

1,1′-Bis[(2R,5R)-2,5-diethylphospholano]ferrocene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate

(S,S)-Et-Ferrocelane™

FW 470.39

681008-100MG

100 mg

681008-500MG

500 mg

1,1′-Bis[(2S,5S)-2,5-diethylphospholano]ferrocene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate

(S,S)-Et-Ferrocelane™

FW 470.39

681008-100MG

100 mg

681008-500MG

500 mg
**Components**

1.1-Bis[(2R,5R)-2,5-diisopropylphospholano]ferrocene (DuPhos and BPE) 100 mg

FW: 526.49

**Components**

(2R,5S)-(+) -1-(2-(1,3-Dioxolan-2-yl)phenyl)-2,5-diethylphospholane

S,S-Et-RajPhos™

C₇H₁₀O₂P

FW: 292.35

**Components**

(2R,5R)-1-(2-(1,3-Dioxolan-2-yl)phenyl)-2,5-dimethylphospholane

R,R-Me-RajPhos™

C₉H₁₈O₂P

FW: 264.30

**Components**

(2R,5S)-(+) -1-(2-(1,3-Dioxolan-2-yl)phenyl)-2,5-diethylphospholane

S,S-Me-RajPhos™

C₉H₁₈O₂P

FW: 264.30

DuPhos/BPE Ligands Kit I

**Components**

(+) -1,2-Bis(25,5S)-2,5-dimethylphospholano)ethane (Aldrich 665207) 100mg

FW: 526.49

(+) -1,2-Bis(25,5S)-2,5-diethylphospholano)ethane (Aldrich 667854) 100mg

FW: 526.49

(+) -1,2-Bis(25,5S)-2,5-diphenylphospholano)benzene (Aldrich 668176) 100mg

FW: 526.49

(+) -1,2-Bis(25,5S)-2,5-diisopropylphospholano)ethane (Aldrich 668435) 100mg

FW: 526.49

(+) -1,2-Bis(25,5S)-2,5-diethylphospholano)ethane (Aldrich 668451) 100mg

FW: 526.49

(+) -1,2-Bis(25,5S)-2,5-diethylphospholano)benzene (Aldrich 668486) 100mg

FW: 526.49

(+) -1,2-Bis(25,5S)-2,5-diisopropylphospholano)benzene (Aldrich 675598) 100mg

FW: 526.49

FW: 526.49

100 mg

FW: 526.49

FW: 526.49

1 kit
catASium®—Essential Elements for Asymmetric Hydrogenations

Renat Kadyrov, Jürgen Krauter
Evonik Degussa GmbH, Rodenbacher Chaussee 4, D-63457 Hanau-Wolfgang, Germany

Transition metal catalyzed enantioselective hydrogenation has been established as one of the most favorable strategies for the synthesis of optically active compounds in academia and on the industrial scale. In particular, chiral ligands bearing trivalent phosphorus as the ligating atom for “soft” metals like rhodium(II), ruthenium(II), or iridium(III) play a pivotal role in this area. Among electron-rich chiral phosphines, chiral phospholanes have emerged as one of the most efficient classes of ligands in metal catalyzed enantioselective reactions. Prominent examples are bisphospholanes. Ligands like DuPHOS and BPE. In general, these compounds are synthesized by a linear approach, where the phospholane is constructed by condensation of a primary phosphine with the sulfate or sulfonates derived from the appropriate chiral diols in the presence of strong bases. This tedious approach is restricted by low tolerance of the functional groups and, therefore, strongly limits the possible variations of the backbone.

Evonik Degussa GmbH has developed a modular synthesis of diverse arrays of chiral vicinal bisphospholanes in collaboration with the Leibniz-Institute of Organic Catalysis in Rostock.¹ These ligands, which are now commercially available on a multikilogram scale under the trademark catASium M, are characterized by varied “bite-angle” and electronic properties of the bridging unit.² The new ligands can be advantageously employed in the fine-tuning of those enantioselective hydrogenations, where the results obtained with traditional phospholane ligands require optimization.

A rhodium(II) catalyst based on the new chiral bisphospholane ligand is one of the most effective catalytic systems for the hydrogenation of non-substituted and β-substituted itaconic acid derivatives known.³ The selected results (Table 1) show that this ligand displays a higher performance as compared to the known systems. The excellent enantioselectivities (up to 99%) are combined with a high catalytic activity (TOF up to 40,000 h⁻¹).⁴

Exciting results were also observed in the hydrogenation of β-acylamido acrylates (Table 2). These are important intermediates in the synthesis of enantiopure β-amino acids. Particularly, when the hydrogenation of the challenging Z-configured substrates bearing bulky substituents in the 3-position (for example i-Pr) were tested, a catASium M[Rh]-catalyst showed the highest enantioselectivities known for these substrates. A new class of atropisomeric ligands based on camphor catASium were developed in close collaboration with Russian researchers. The new ligand system combines the features of central chirality derived from a natural product with axial chirality like in the biaryl type ligands. In addition to this, the two phosphorus groups are introduced sequentially leading to a large variety of tuneable ligands.⁵

The selected results of hydrogenation of β- and (E)-methyl-3-acetylamino-2-butenoates are summarized in Table 2. Excellent enantiomeric excesses of 99% were reached by hydrogenation of the E-isomer. Noteworthy is the 94% ee achieved using catASium T2 catalyst in the hydrogenation of the Z-isomer. It is one of the best optical inductions achieved in the hydrogenation of the Z-β-enamides. These ligands also show interesting properties in the hydrogenation of challenging simple α-enamides (Table 3).

Whereas applying catalysts based on catASium T ligands to electron-rich substrates induce only moderate enantiomeric excesses, the hydrogenation of the substrate with electron-withdrawing groups surprisingly leads to near complete enantioselectivity.

Caticonic catalyst catASium DH, with a ligand well known under the old name Deguphos, was successfully utilized in the first highly enantioselective reductive amination of keto acids, where several chiral α-amino acids were produced in good yield and very high ee’s (up to 98%) (Table 4).

References

Table 1. Hydrogenation of β-substituted itaconic acid derivatives

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Configuration</th>
<th>R</th>
<th>R’</th>
<th>Solvent</th>
<th>TON</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>catASium® M[Rh]</td>
<td>E</td>
<td>Me</td>
<td>Me</td>
<td>CH₂Cl₂</td>
<td>10,000</td>
<td>99</td>
</tr>
<tr>
<td>catASium® M[Rh]</td>
<td>Z</td>
<td>Me</td>
<td>Me</td>
<td>CH₂Cl₂</td>
<td>4,000</td>
<td>99</td>
</tr>
<tr>
<td>catASium® M[Rh]</td>
<td>i-Pr</td>
<td>Me</td>
<td>Me</td>
<td>CH₂Cl₂</td>
<td>500</td>
<td>98</td>
</tr>
<tr>
<td>catASium® M[Rh]</td>
<td>i-Pr</td>
<td>Me</td>
<td>Me</td>
<td>CH₂OH</td>
<td>500</td>
<td>98</td>
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</tbody>
</table>

Table 2. Enantioselective hydrogenations of β-enamides using catASium® ligands

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Configuration</th>
<th>R</th>
<th>R’</th>
<th>Solvent</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>catASium® M[Rh]</td>
<td>E</td>
<td>Me</td>
<td>Me</td>
<td>CH₂Cl₂</td>
<td>99.5</td>
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<tr>
<td>catASium® M[Rh]</td>
<td>Z</td>
<td>Me</td>
<td>Me</td>
<td>CH₂OH</td>
<td>89.9</td>
</tr>
<tr>
<td>catASium® M[Rh]</td>
<td>E</td>
<td>i-Pr</td>
<td>Et</td>
<td>CH₂Cl₂</td>
<td>99.7</td>
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<tr>
<td>catASium® M[Rh]</td>
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<td>i-Pr</td>
<td>Et</td>
<td>CH₂Cl₂</td>
<td>89.6</td>
</tr>
<tr>
<td>catASium® T2[Rh]</td>
<td>E</td>
<td>Me</td>
<td>Me</td>
<td>CH₂OH</td>
<td>99.3</td>
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<tr>
<td>catASium® T2[Rh]</td>
<td>Z</td>
<td>Me</td>
<td>Me</td>
<td>CH₂Cl₂</td>
<td>94</td>
</tr>
</tbody>
</table>

Table 3. Enantioselective hydrogenation of enamides using Rh(II)-complexes of catASium® T

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Product</th>
<th>Isolated Yield</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>catASium® D[Rh]</td>
<td>Me</td>
<td>43</td>
<td>78</td>
</tr>
<tr>
<td>catASium® D[Rh]</td>
<td>PhCH₂</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>catASium® D[Rh]</td>
<td>MeCH₂</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>catASium® D[Rh]</td>
<td>Me₂CH₂</td>
<td>94</td>
<td>86</td>
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</table>

Table 4. Yields and enantioselectivities of the reductive amination of α-keto acids with benzylamine using catASium® D[Rh]

<table>
<thead>
<tr>
<th>Product</th>
<th>Isolated Yield</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-Bn-Ala</td>
<td>43</td>
<td>78</td>
</tr>
<tr>
<td>N-Bn-Phe</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>N-Bn-Leu</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td>N-Bn-tBu-Ala</td>
<td>94</td>
<td>86</td>
</tr>
</tbody>
</table>

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D-type

(+)-N-Benzyl-[3R,4R]-bis(diphenylphosphino)pyrrolidine, 98%
(+)-3R,4R-1,4-Bis(diphenylphosphino)-1-benzyl-pyrrolidine; catASium® D(R)
FW 529.59
≥98% (31P-NMR)

(3R)-trans-3,4-Bis(diphenylphosphino)-1-(phenylmethyl)pyrrolidine rhodium complex; catASium® D(R)Rh
FW 827.48
≥98% (31P-NMR)

M-type

2,3-Bis[(2R,5R)-2,5-dimethylphospholano]-N-benzyl-
maleimide(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 95%
3,4-Bis[(2R,5R)-2,5-dimethylphospholany]-1-[benzyl-1H-pyrrol-2,5-dione(1,5-cyclooctadiene)rhodium(I)] tetrafluoroborate; catASium® MNXyl(R)Rh
FW 713.34
≥95% (31P-NMR)

2,3-Bis[(2R,5R)-2,5-dimethylphospholano]-N-[3,5-bis
(trifluoromethyl)phenyl]maleimide, 98%
3,4-Bis[(2R,5R)-2,5-dimethylphospholany]-1-[3,5-bis(trifluoromethyl)phenyl]-1H-pyrrol-2,5-dione; catASium® MNXyl(R)P2
FW 537.41
≥98% (31P-NMR)

(-)-2,3-Bis[(2R,5R)-2,5-dimethylphospholano]-N-[3,5-bis(trifluoromethyl)phenyl]maleimide(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 98%
3,4-Bis[(2R,5R)-2,5-dimethylphospholany]-1-[3,5-di(trifluoromethyl)phenyl]-1H-pyrrol-2,5-dione(1,5-cyclooctadiene)rhodium(I)] tetrafluoroborate; catASium® MNXylF(R)Rh
FW 835.31
≥98% (31P-NMR)

(-)-4,5-Bis[(2R,5R)-2,5-dimethylphospholano]-1,2-dihydro-1,2-dimethyl-3,6-pyridazinedione(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 95%
[4,5-Bis[(2R,5R)-2,5-dimethylphospholany]-1,2-dimethyl-1,2-dihydropyridazine-3,6-dione(1,5-cyclooctadiene)rhodium(I)] tetrafluoroborate; catASium® MNXyl(R)Rh
FW 666.28
≥95% (31P-NMR)

2,3-Bis[(2R,5R)-2,5-dimethylphospholano]-N-[3,5-
dimethylphenyl]maleimide, 98%
3,4-Bis[(2R,5R)-2,5-dimethylphospholany]-1-[3,5-
dimethylphenyl]-1H-pyrrol-2,5-dione; catASium® MNXyl(R)P2
FW 429.47
≥98% (31P-NMR)

(-)-2,3-Bis[(2R,5R)-2,5-dimethylphospholano]-N-[3,5-
dimethylphenyl]maleimide(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 95%
3,4-Bis[(2R,5R)-2,5-dimethylphospholany]-1-[3,5-
dimethylphenyl]-1H-pyrrol-2,5-dione(1,5-cyclooctadiene)rhodium(I)] tetrafluoroborate; catASium® MNXyl(R)Rh
FW 727.36
≥95% (31P-NMR)

(-)-2,3-Bis[(2R,5R)-2,5-dimethylphospholano]-N-[3,5-
dimethylphenyl]maleimide(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 95%
3,4-Bis[(2R,5R)-2,5-dimethylphospholany]-1-[3,5-
dimethylphenyl]-1H-pyrrol-2,5-dione(1,5-cyclooctadiene)rhodium(I)] tetrafluoroborate; catASium® MNXyl(R)Rh
FW 727.36
≥95% (31P-NMR)

(+)-1-Benzyl-[3R,4R]-bis(diphenylphosphino)pyrrolidine(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 98%
3,4-Bis[(2R,5R)-2,5-dimethylphospholany]-1-[3,5-di(trifluoromethyl)phenyl]-1H-pyrrol-2,5-dione(1,5-cyclooctadiene)rhodium(I)] tetrafluoroborate; catASium® MNXylF(R)Rh
FW 835.31
≥98% (31P-NMR)
(−)-2,3-Bis([2R,5R]-2,5-dimethylphospholano)maleic anhydride, 98%

3,4-Bis([2R,5R]-2,5-dimethylphospholano)[furan-2,5-dione], catASium® M(R)

C₆H₄O₂P₂
FW 326.31
≥98% (31P-NMR)
670693-100MG 100 mg
670693-500MG 500 mg

(−)-2,3-Bis([2R,5R]-2,5-dimethylphospholano)maleic anhydride(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 98%

2,3-Bis([2R,5R]-2,5-dimethylphospholano)maleic anhydride(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, catASium® M(R)Rh

C₂₄H₃₆BF₄O₃P₂Rh
FW 624.20
≥98% (31P-NMR)
670804-100MG 100 mg
670804-500MG 500 mg

(−)-2,3-Bis([2R,5R]-2,5-dimethylphospholano)-N-(4-methoxyphenyl)maleimide(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 98%

3,4-Bis([2R,5R]-2,5-dimethylphospholano)-1-(4-methoxyphenyl)-1H-pyrole-2,5-dione(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, catASium® MNAn(R)Rh

C₃₁H₄₃BF₄NO₃P₂Rh
FW 729.34
≥98% (31P-NMR)
670251-100MG 100 mg
670251-500MG 500 mg

1,2-Bis([2R,5R]-2,5-dimethylphospholano)-3,3,4,4-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, 95%

1,2-Bis([2R,5R]-2,5-dimethylphospholano)3,3,4,4-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate, catASium® MQF(R)Rh

C₂₅H₃₉BF₄NO₂P₂Rh
FW 637.24
≥98% (31P-NMR)
669598-100MG 100 mg
669598-500MG 500 mg

669598-100MG 100 mg
669598-500MG 500 mg

670472-100MG 100 mg
670472-500MG 500 mg

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T-type

(1R,αR)-3-Diphenylphosphino-2-(4-bis(3,5-dimethyl-phenyl)phosphino-2,5-dimethyl-3-thienyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene, 99%

3-[Bis(3,5-dimethylphenylphosphanyl)-4-[(1R,4S)-3-diphenylphosphanyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene]-2,5-dimethylphosphine, catASium® T1(R)

≥99% (31P-NMR)

671258-100MG 100 mg
671258-500MG 500 mg

(1R,αR)-3-[Bis(3,5-dimethylphenylphosphino)-2-(4-diphenylphosphino-2,5-dimethyl-3-thienyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene, 99%

3-[(1R,4S)-3-Bis(3,5-dimethylphosphanyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene-2-y1)-4-diphenylphosphanyl-2,5-dimethylphosphine, catASium® T1(R)

≥99% (31P-NMR)

671142-100MG 100 mg
671142-500MG 500 mg

(1R,αR)-3-Diphenylphosphino-2-(4-diphenylphosphino-2,5-dimethyl-3-thienyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene, 99%

3-Diphenylphosphanyl-4-[(1R,4S)-3-diphenylphosphanyl-1,7,7-trimethylbicyclo[2.2.1]hept-2-en-2-yl]-2,5-dimethylphosphine, catASium® T1(R)

≥99% (31P-NMR)

671029-100MG 100 mg
671029-500MG 500 mg

Kit

Evonik Ligand Kit for Asymmetric Hydrogenations
catASium® Ligand Toolbox

Components

(+)-N-Benzyl-C3R,4R-bis(diphenylphosphino)pyrrolidine (Aldrich 672653)
(+)-1-Benzyl-(C3R,4R-bis(diphenylphosphino)pyrrolidine)(1,5-cyclooctadiene)rhomodium(tetrafluoroborate (Aldrich 672777)
(1R,αR)-3-Diphenylphosphino-2-(4-bis(3,5-dimethylphenyl)phosphino-2,5-dimethyl-3-thienyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (Aldrich 671258)
(1R,αR)-3-(Bis(3,5-dimethylphenyl)phosphino)-2-(4-diphenylphosphino-2,5-dimethyl-3-thienyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (Aldrich 671142)
(1R,αR)-3-Diphenylphosphino-2-(4-diphenylphosphino-2,5-dimethyl-3-thienyl)-1,7,7-trimethylbicyclo[2.2.1]hept-2-ene (Aldrich 671029)
(+)-(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,6-epoxyzinedione(1,5-cyclooctadiene)(hodium)(tetrafluoroborate (Aldrich 670472)
(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,5-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)(hodium)(tetrafluoroborate (Aldrich 670367)
(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,5-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)(hodium)(tetrafluoroborate (Aldrich 670154)
(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,5-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)(hromium)(tetrafluoroborate (Aldrich 670030)
(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,5-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)(hromium)(tetrafluoroborate (Aldrich 669938)
(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,5-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)(hromium)(tetrafluoroborate (Aldrich 669914)
(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,5-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)(hromium)(tetrafluoroborate (Aldrich 669709)
(2S,5R)-2,5-Dimethylphospholano[1,2-b]pyrrolidinone, 1,2-dihydridro-1,2-dimethyl-3,5-tetrafluoro-1-cyclobutene(1,5-cyclooctadiene)(hromium)(tetrafluoroborate (Aldrich 669958)

672556-1KT 1 kit

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**P-Phos, PhanePhos and BoPhoz™ Ligands**

The P-Phos ligand family was developed by Professor Chan of Hong Kong Polytechnic University and licensed to JM CCT in 2002. P-Phos is an atropisomeric biaryl bisphosphine with the unique feature of incorporating two methoxy-substituted pyridine rings in the backbone. This family of ligands often presents higher activity and selectivity than the analogous BINAP ligands in a series of reactions such as ruthenium-catalyzed hydrogenation of β-ketoesters (Scheme 1) and rhodium- and ruthenium-catalyzed hydrogenation of dehydroamino acids (Scheme 2). Ru-catalyzed hydrogenation of non-functionalized ketones is also highly effective using P-Phos ligands. Moreover, JM has further developed the scope of P-Phos Ru diamine complexes in ketone hydrogenation by the application of less traditional 1,3- and 1,4-diamines (Scheme 3). Iridium-P-Phos catalysts have been recently used for the asymmetric hydrogenation of C=N bonds in quinolines (Scheme 4).

PhanePhos was first reported in 1997, and since then it has found applications in the rhodium-catalyzed hydrogenation of dehydroamino acids (Scheme 5) and the ruthenium-catalyzed hydrogenation of β-ketoesters (Scheme 6). Both rhodium and ruthenium catalysts bearing the PhanePhos ligand show an exceptionally high activity in most homogeneous hydrogenation reactions.
The BoPhoz class of ligands, based on the ferrocene backbone, have proven to be exceptionally active in many rhodium-catalyzed hydrogenations as well as being used in a number of ruthenium-catalyzed reactions. More recently Johnson-Matthey has developed new variants of BoPhoz ligands that offer increased structural and electronic diversity that may be required for the desired transformation. MeBoPhoz has shown excellent activity in many rhodium-catalyzed asymmetric hydrogenation of C=C bonds in dehydroaminoacids and \( \alpha,\beta \)-unsaturated acids and esters (S/C up to 100,000) (Scheme 7).1,2

The \( \Phi \)-Cy-Me-BoPhoz ligand has been shown to catalyze the asymmetric reduction of \( \alpha \)-ketoesters, which is unusual for a rhodium catalyst (Scheme 8).

References:

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**((R))-N-Methyl-N-diphenylphosphino-1-[(S)-2-diphenylphosphino]ferrocenyl)ethylamine**

Methyl-BoPhoz; (1R)-1-(Diphenylphosphino)-2-[(1R)-1-[(diphenylphosphino)methylamino]ethyl]ferrocene

\[ \text{C}_{37} \text{H}_{35} \text{FeNP}_2 \]  
FW 611.47

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**((S))-N-Methyl-N-diphenylphosphino-1-[(R)-2-diphenylphosphino]ferrocenyl)ethylamine**

Methyl-BoPhoz; (1S)-1-(Diphenylphosphino)-2-[(1S)-1-[(diphenylphosphino)methylamino]ethyl]ferrocene

\[ \text{C}_{37} \text{H}_{35} \text{FeNP}_2 \]  
FW 611.47

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**((R)-)2,2',6,6'-Tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, 97%**

((R)-)P-Phos

\[ \text{C}_{26} \text{H}_{26} \text{N}_2 \text{O}_4 \text{P}_2 \]  
FW 644.64

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**((S)-)2,2',6,6'-Tetramethoxy-4,4'-bis(di(3,5-xylyl)phosphino)-3,3'-bipyridine, 97%**

((S)-Xylyl-P-Phos

\[ \text{C}_{46} \text{H}_{50} \text{N}_2 \text{O}_4 \text{P}_2 \]  
FW 756.85

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\[ \text{C}_{46} \text{H}_{50} \text{N}_2 \text{O}_4 \text{P}_2 \]  
FW 756.85

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((S)-Xylyl-P-Phos

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FW 756.85

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**((R))-2,2',6,6'-Tetramethoxy-4,4'-bis(diphenylphosphino)-3,3'-bipyridine, 97%**

((R)-)P-Phos

\[ \text{C}_{26} \text{H}_{26} \text{N}_2 \text{O}_4 \text{P}_2 \]  
FW 644.64

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**((S))-2,2',6,6'-Tetramethoxy-4,4'-bis(di(3,5-xylyl)phosphino)-3,3'-bipyridine, 97%**

((S)-Xylyl-P-Phos

\[ \text{C}_{46} \text{H}_{50} \text{N}_2 \text{O}_4 \text{P}_2 \]  
FW 756.85

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ChiralQuest Phosphine Ligands and Complexes

Professor Xumu Zhang at Penn State has made remarkable advances by creating a toolbox of chiral phosphines which can be used on a variety of substrates, some of which have been historically resistant to facile hydrogenation. Furthermore, an additional benefit in some reductions is reduced catalyst loading, due to increased turnover numbers (TON).^1

(5)-C3-TunePhos
C3-TunePhos, a member of the atropisomeric aryl bisphosphine ligand family with tunable dihedral angles, provides comparable or superior enantioselectivities and catalytic abilities to BINAP in Ru-catalyzed asymmetric hydrogenation of β-keto esters (Scheme 1),^4 cyclic β-(acylamino)acrylates (Scheme 2),^5 and α-phthalimide ketones (Scheme 3).^6

(15,15″,2R,2′R)-TangPhos
A highly electron-donating, low molecular weight, and rigid P-chiral bisphosphine ligand, TangPhos proved to be incredibly efficient in the rhodium-catalyzed hydrogenation of a variety of functionalized olefins such as α-dihydroxyaminocids,^5 arenemides,^3 β-(acylamino)acrylates,^5 itaconic acids,^3 and N-tosylamines^5 (Scheme 4).

This P-chiral phosphorus ligand represents a superior ligand for asymmetric catalysis including hydrogenation because of its ability to force the chiral environment to encompass the substrate in close proximity to the reactive metal center. TangPhos exhibits substantial conformational rigidity allowing for high enantioselectivities in the hydrogenation of a wide variety of densely functionalized prochiral olefins, with some reaction examples approaching 100% ee.

(5)-BINAPINE
BINAPINE, a highly electron-donating rigid ligand, demonstrates excellent enantioselectivity and reactivity, with TON up to 10,000 for the asymmetric hydrogenation of 2′-β-aryl(β-acylamino) acrylates (Scheme 5).^7 Interestingly, BINAPINE is a rare example of a binaphthophosphine ligand with P-chiral phosphine atoms. High enantioselectivities have been obtained with substrates that contain diverse substituents ranging from electron-rich and electron-poor aryl groups to heteroaryl components. This catalyst system illustrates the incredible effects of rigidity on the stereoccontrol in the hydrogenation reaction.

(R)-BINAPHANE
BINAPHANE incorporates a bisphosphinite backbone that displays restricted orientation of the aromatic groups proximate to the phosphines. Zhang and co-workers can tune BINAPHANE by modifying the groups on the aromatic and/or the phosphine, thus creating a general catalytic system useful for obtaining high enantioselectivities in the asymmetric hydrogenation reaction. This ligand demonstrated excellent enantioselectivity (up to >99% ee) for hydrogenation of EZ-isomeric mixtures of β-substituted arenes. (Scheme 6)^10

BINAPHANE also proved to be a very good ligand for the palladium catalyzed enantioselective cyclization of silyloxy-1,6-enynes. ^11 This novel reaction allows for the synthesis of precursors for naturally occurring molecules. Using mild conditions and 5 mol% of catalyst, Toste et al. reported good yields and good selectivities (Scheme 7).

(1R,1″R,2S,2′S)-DuanPhos
DuanPhos is more rigid than the related TangPhos ligand, due to the fused phenyl rings on the phospholine architecture. This self-imposed conformational stability improves the enantioselectivity in the hydrogenations of a diverse array of functionalized olefins. Furthermore, Zhang and co-workers have successfully synthesized both enantiomers of this electron-rich ligand through a trivial resolution process. Even highly electron-rich prochiral olefins are readily hydrogenated with exceptional stereoccontrol by this productive Rh-catalyst system (Scheme 8).

**Scheme 5**

(R,R)-1,2-Bis( (R)-4,5-di-hydro-3H-binaphtho(1,2-c:2',1'-e)phosphepin) benzene

FW 698.77

**(S)-BINAPINE**

FW 734.89

**Scheme 6**

(R)-Binaphane-Pd(OH2)2(OTf)2

Et2O / AcOH

83%, 89% ee

91%, 87% ee

80%, 98% ee

79%, 80% ee

**Scheme 7**

(R,R)-DuanPhos

H2 (20 psi), rt, MeOH, 2 h

TON = 10,000

TOF = 5,000

96% ee

**Scheme 8**

[(S)-BINAPINE(cyclooctadiene)rhodium(I)] tetrafluoroborate

FW 1032.78

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(1R,1′R,2S,2′S)-DuanPhos
(1R,1′R,2S,2′S)-Di-tert-butyl-2,3,2′,3′-tetrahydro-1H, 1′H-1,1′]biisophosphindolyl
FW 382.46

(1R,1′R,2S,2′S)-DuanPhos-rhodium complex, 96%
((1R,1′R,2S,2′S)-DuanPhos (cyclooctadiene) rhodium) tetrafluoroborate
FW 680.35

(S,S,R,R)-TangPhos
(1S,1′S,2R,2′R)-1,1′-Di-tert-butyl-(2,2′)-diphospholane
FW 286.37

(S,S,R,R)-TangPhos-rhodium complex
((S,S,R,R)-TangPhos(cyclooctadiene)rhodium) tetrafluoroborate
FW 584.26

(R,C3-TunePhos
(R)-1,13-Bis(diphenylphosphino)-7,8-dihydro-6f-dibenzo[f,h][1,5]dioxin
FW 594.62

(R)-C3-TunePhos-ruthenium complex
[Chloro(R)-C3-TunePhos(p-cymene) ruthenium(II)] chloride
FW 900.81

(S,S)-f-Binaphane
1,1′-Bis((11b)-3,5-dihydro-4H-dinaphtho[2,1-c:1′,2′-e]phosphapin-4yl] ferrocene, 1,1′-Bis((5-S)-4,5-dihydro-3H-binaphtho[2,1-c:1′,2′-e]phosphapin-4yl] ferrocene
FW 806.69

Chiral Quest Ligands Kit I
Components
(R)-Binaphane (Aldrich 650854) 100 mg
(S,S)-Binaphane (Aldrich 685925) 100 mg
(S)-Binaphane (Aldrich 650870) 100 mg
(1R,1′R,2S,2′S)-DuanPhos (Aldrich 657697) 100 mg
(5)-Me-f-KetalPhos (Aldrich 650889) 100 mg
(R)-C3-TunePhos (Aldrich 650862) 100 mg
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- Prof. Benjamin List (MPI) TRIP—A Powerful Brønsted Acid Catalyst for Asymmetric Synthesis
- Prof. Jik Chin (U. of Toronto) Designer Chiral Diamines by the Diaza-Cope Rearrangement
- Prof. M. Christina White (UIUC) Skip the Oxygen: Allylic Esterifications and Aminations Directly from C-H Bonds
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DSM MonoPhos™ Family

Feringa and co-workers have developed a diverse array of chiral, monodentate phosphoramidites based on the privileged BINOL platform.1 The MonoPhos™ family has exhibited high levels of enantiocontrol in synthetic transformations ranging from metal-catalyzed asymmetric 1,4-additions of organometallic reagents to allylic alkylations to desymmetrization of meso-cycloalkene oxides.²

Asymmetric 1,4-Additions of Organometallic Reagents

Feringa and co-workers have showcased the high activity of the (S,R,R)-phosphoramidite ligand in copper-catalyzed 1,4-additions of organozinc reagents to cyclohexenones.1 Interestingly, the in situ formed zinc species originating from the cyclohexenone is readily trapped via a palladium-catalyzed allylation. It was followed by a formal annihilation process through a palladium-catalyzed Wacker oxidation, and finally by an aldol cyclization. The high (96%) enantioselectivity of this methodology is completely retained throughout this synthetic strategy (Scheme 1).

Highly Asymmetric Rhodium-Catalyzed Hydrogenation

Feringa has also gone to great lengths to develop structurally varied MonoPhos ligands in industrially useful transformations such as asymmetric hydrogenation.³ Impressively, the (S)-aryl-benzyl-N-methyl-MonoPhos derivative shown has been utilized in highly selective hydrogenations of (E)-vinylcyclohexene by affording the corresponding enantiopure α-amino acid derivatives (Scheme 2).⁴ The authors found that this ligand, after being screened versus related chiral phosphoramidites, afforded the highest enantiocontrol in hydrogenations, albeit at slightly slower reaction times.

The Feringa research group has broadened the substrate scope of the asymmetric hydrogenation reaction by generating another chiral center on the amine moiety of the phosphoramidite ligand. Amazingly, this fine ligand tuning produces a very active and productive catalyst, which efficiently hydrogenates a wide range of acetamido derivatives in less time than the corresponding Me-DuPhos analogs.⁵ Note that the chiral (S,R,R)-phosphoramidite ligand is the only ligand known to afford greater than 90% enantioselectivities for the substrate shown (Scheme 3).

Recently, Feringa’s R&D group prepared additional structurally varied phosphoramidite ligands for rhodium-catalyzed asymmetric hydrogenations. The aptly named PipPhos and MorPhos ligands contain piperidinyl and morpholinyl amine subunits, respectively, and are examples of easily synthesized chiral ligands for highly effective enantioselective transformations. Under mild reaction conditions including low H₂ pressure, this catalyst system yields unprecedented enantioselectivities for several substrates such as dimethyl itaconate and α-dehydroamino ester derivatives (Scheme 4).⁵

Asymmetric Regioselective Allylic Aminations

Hartwig and co-workers have succeeded in developing highly selective iridium catalysts with the (R,R,R)-phosphoramidite L.⁶ The allylic aminations of a wide variety of achiral allylic esters proceeded with total conversion and superb regioselectivity in many cases. The reaction clearly shows the power of this methodology; wherein, cinnamyl acetate was converted to the allylic benzyl amine in excellent yield and enantiopurity (Scheme 5). The authors mentioned that these valuable amination reactions were mediated by air-stable Ir complexes at ambient temperatures, which should lead to wide acceptance of this catalyst in bench-top organic synthesis.

References:
(5S)-(−)-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']
dinaphthalen-4-yl)methylamine, 97%

(+)-N-Benzyl-N-methyl-dinaphtho[2,1-d′:1′,2′-d]
dioxaphosphepin-4-amine, (11bS)
C_{22}H_{20}NO_2P
FW 361.37

665347-100MG 100 mg
665347-500MG 500 mg
665347-2G 2 g

(5S,5,S)-(−)-(3,5-dioxa-4-phospha-cyclohepta[2,1-a;3,4-a']
dinaphthalen-4-yl)bis(1-phenylethyl)amine, 97%

(+)-N,N,N′-tris(1-phenylethyl)-dinaphtho[2,1-d′:1′,2′-d]
dioxaphosphepin-4-amine, (11bS)
C_{36}H_{30}NO_2P
FW 539.60

665363-100MG 100 mg
665363-500MG 500 mg
665363-2G 2 g

(11bR)-2,6-Bis(diphenylphosphino)-N,N-dimethyldi-
naphtho[2,1-d:1′,2′-f]-1,3,2-dioxaphosphepin-4-amine

C_{46}H_{36}NO_2P_3
FW 727.70

683248-100MG 100 mg
683248-500MG 500 mg

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Chiral vicinal diamines are of tremendous interest to the synthetic chemist as they are found in many chiral catalysts and pharmaceuticals.

Currently, there is no unified approach to making these chiral vicinal diamines, and they are often challenging to synthesize, especially if unsymmetrically substituted. Jik Chin and co-workers have recently reported some preliminary theoretical and experimental studies for converting a parent diamine (1) into other chiral vicinal diamines.1 These diamines can be used as ligands for chiral catalysts, or they can be further elaborated to produce chiral heterocyclic rings and β-lactams via ring closure.

**References:**
Reetz Ligands

In 1998, Reetz et al. reported the synthesis of a new generation of ligand for enantioselective, catalyzed hydrogenation. Based on BINOL-derived diphosphonite molecules, these ligands showed good enantioselectivities for the asymmetric hydrogenation of terminal alkenes, ketones, and \( \beta \)-keto esters,\(^1\)\(^2\) and the asymmetric conjugate addition of arylboronic acid derivatives to \( \alpha,\beta \)-unsaturated carbonyls.\(^3\)

**Enantioselective Hydrogenation of Olefins**

Reetz et al. reported the hydrogenation of two different olefins with Rh(cod)BF\(_4\) and \( R,R \)-Reetz F-Diphosphonite. Outstanding yields and selectivity were reported (Scheme 1).\(^4\)

Used with a RuCl\(_2\)(p-cymene): Complex, the \( R,R \)-Reetz X-Diphosphonite converts a variety of ketones into secondary alcohols with yields and ee's up to 100% and 98%, respectively (Scheme 2).\(^1\)

**References:**


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**Scheme 1**

**Scheme 2**

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BINOL and Derivatives

BINOL and its derivatives are one of the mostly widely used classes of ligands in asymmetric synthesis; being utilized in a broad array of reactions including: Diels–Alder, carbonyl addition and reductions, Michael additions, as well as many others. While tremendous success has been obtained with the BINOL platform, other C₂ symmetric diol ligands have attracted considerable attention. Among these are the vaulted biaryl ligands developed by Wulff and co-workers. Both vaulted 3,3’-biphenanthrol (VAPOL) and vaulted 2,2’-binaphthol (VANOL) have proven to be excellent ligands in catalytic asymmetric Diels–Alder, imine aldol, and aziridination reactions (Figure 1). Recently the phosphoric acid derivative of VAPOL was shown to be effective as a chiral Brønsted acid catalyst. In many of the examples illustrated herein, the vaulted biaryls give both higher yields and higher inductions than the same reactions using a BINOL ligand.

Asymmetric Diels–Alder Reaction

Very early on, a catalyst generated from Et₃AlCl and VAPOL was shown to be an effective catalyst for the asymmetric Diels–Alder reaction. As shown in Scheme 1, the cycloaddition of acrolein with cyclopentadiene in the presence of the VAPOL-derived catalyst gave high conversions and excellent stereoselectivities for the exo isomer in very high optical purity. Analogous reactions with the BINOL-derived catalyst provided the cycloadduct in high yield, but in very low enantiomeric excess (13–41%).

Asymmetric Aziridination Reaction

Aziridines are important building blocks in organic synthesis because they allow for convenient access to amines, amino alcohols, diamines, and other useful nitrogen-containing molecules. Most contemporary methods of chiral aziridine preparation have relied on the chiral pool. Recently, the Wulff group has developed a robust catalytic asymmetric aziridination reaction providing optically active aziridines in high yields and selectivities. The reaction relies on the addition of commercially available ethyl diazoacetate (EDA) to benzhydryl imines in the presence of arylborate catalysts prepared from vaulted aryl ligands and B(OPh)₃. Analogous reactions with the BINOL-derived catalyst provided the cycloadduct in high yield, but in very low enantiomeric excess (13–41%).

Asymmetric Aldol Reaction

Asymmetric imine aldol reactions are also catalyzed by vaulted biaryl-derived catalysts, providing an important method for the synthesis of chiral β-amino esters. The addition of styryl ketene acetics to ary imines in the presence of either Zr-VANOL or Zr-VAPOL catalysts proceeds with high asymmetric induction and in excellent yield (Scheme 4, Table 3). Significantly, both catalysts exhibit substantially higher levels of induction over the analogous BINOL-derived catalyst.

Chiral Bronsted Acid

Antilla and co-workers demonstrated VAPOL hydrogenphosphate to be a useful chiral Bronsted acid catalyst in the addition of sulfonamides to Boc-activated aryl imines (Scheme 5). The resultant N,N-aminal products were prepared in high yields with impressive enantiopurities. The identical reaction with a BINOL-derived Bronsted acid catalyst gave an excellent yield (95%), but a dismal level of asymmetric induction (<5% ee) was obtained. A variety of sulfonamides and aryl imines are active in the imine amidation reaction, and the resultant protected amines are shelf-stable compounds.

References:

Scheme 1

Figure 1

Scheme 2

Table 1

The asymmetric synthesis of leukointerin LFA-1 antagonist BRT-377 utilized an aziridination/alkylation methodology to provide the hydantoin target in excellent overall yield.

The highly expedient synthesis of the antibacterial agent (–)-chloramphenicol utilized the asymmetric aziridination reaction, followed by a nucleophilic ring opening of the aziridine with dichloroacetic acid with a subsequent acyl group migration (Scheme 3, Table 2). Both VANOL and VAPOL gave higher yields and stereoselectivities than the BINOL-derived catalyst.

Figure 1

Scheme 1
Scheme 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand, Loading</th>
<th>X</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>cis:trans</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-BINOL, 10 mol %</td>
<td>H</td>
<td>3</td>
<td>61</td>
<td>17:1</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>(S)-VANOL, 10 mol %</td>
<td>H</td>
<td>0.5</td>
<td>85</td>
<td>&gt;50:1</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>(S)-VAPOL, 2 mol %</td>
<td>H</td>
<td>48</td>
<td>77</td>
<td>&gt;50:1</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>(S)-VAPOL, 1 mol %</td>
<td>4-Br</td>
<td>20</td>
<td>87</td>
<td>&gt;50:1</td>
<td>94 (&gt;99% ee recryst.)</td>
</tr>
</tbody>
</table>

Table 1

Scheme 3

Scheme 4

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand, Loading</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-BINOL</td>
<td>CH₂Cl₂</td>
<td>25</td>
<td>4</td>
<td>100</td>
<td>28</td>
</tr>
<tr>
<td>2</td>
<td>(S)-VAPOL</td>
<td>Toluene</td>
<td>25</td>
<td>15</td>
<td>94</td>
<td>89</td>
</tr>
<tr>
<td>3</td>
<td>(S)-VAPOL</td>
<td>Toluene</td>
<td>40</td>
<td>6</td>
<td>100</td>
<td>86</td>
</tr>
</tbody>
</table>

Table 2

Scheme 5

Table 3

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### BINOL and Derivatives

<table>
<thead>
<tr>
<th>Formula</th>
<th>Description</th>
<th>CAS Number</th>
<th>Molecular Weight</th>
<th>RTECS Number</th>
<th>Packaging</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>((R)-,(+)-(1,1')-Bi(2'-naphthol), 99%)</td>
<td>((R)-)BINOL; ((+)-(2'-2'')-Dihydroxy-1',1''-dinaphthyl; ((R)-,(+)-(1,1')-)Binaphthalene-2,2''-diol</td>
<td>[18531-94-7]</td>
<td>C_{10}H_{14}O_{2}</td>
<td>286.32</td>
<td>DU3106100</td>
<td>1g</td>
</tr>
<tr>
<td>((S)-,-(1,1')-Bi(2'-naphthol), 99%)</td>
<td>((S)-)BINOL; ((-)-(2'-2'')-Dihydroxy-1',1''-dinaphthyl; ((S)-,-(1,1')-)Binaphthalene-2,2''-diol</td>
<td>[18531-99-2]</td>
<td>C_{10}H_{14}O_{2}</td>
<td>286.32</td>
<td>DU3106100</td>
<td>1g</td>
</tr>
<tr>
<td>((R)-,(+)-(1,1')-Bi(2'-naphthol) bis(trifluoromethanesulfonate), 97%)</td>
<td>((R)-1,1'-Binaphthalene-2,2''-diyl bis(trifluoromethanesulfonate); ((R)-,(+)-(1,1')-)Bi(2'-naphthol) bis(trifluoromethanesulfonate)</td>
<td>[126613-06-7]</td>
<td>C_{12}H_{12}F_{6}O_{6}S_{2}</td>
<td>550.45</td>
<td>DU3106100</td>
<td>1g</td>
</tr>
<tr>
<td>((S)-,(+)-(1,1')-Bi(2'-naphthol) bis(trifluoromethanesulfonate), 97%)</td>
<td>((S)-1,1'-Bi(2'-naphthol) bis(trifluoromethanesulfonate); ((S)-,(+)-(1,1')-)Bi(2'-naphthol) bis(trifluoromethanesulfonate)</td>
<td>[128544-06-9]</td>
<td>C_{12}H_{12}F_{6}O_{6}S_{2}</td>
<td>550.45</td>
<td>DU3106100</td>
<td>1g</td>
</tr>
</tbody>
</table>

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**BINOL and Derivatives**

**(R)**-(+)-3,3′-Bis(3,5-bis(trifluoromethyl)phenyl)-1,1′-bi-2-naphthol, 95%  
[756491-54-0]  
C₉₃H₉₁F₁₂O₂  
FW 710.51

**R:** 36/37/38  
S: 26

67491-100MG  
100 mg

**(S)**-(−)-3,3′-Bis(3,5-bis(trifluoromethyl)phenyl)-1,1′-bi-2-naphthol, 95%  
(1S)-3,3′-Bis(3,5-bis(trifluoromethyl)phenyl)-1,1′-bi-2-naphthol-2,2′-diol  
[849939-13-5]  
C₉₃H₉₁F₁₂O₂  
FW 710.51

**R:** 36  
S: 26

681539-100MG  
100 mg

**((R))-(−)-3,3′-Bis(3,5-dimethylphenyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol, 97%**  
(R)-3,3′-Bis(3,5-dimethylphenyl)-5,5′,6,6′,7,7′,8,8′-octahydro[1,1′]binaphthalenyl-2,2′-diol  
C₅₆H₄₂O₂Si₂  
FW 803.10

669180-100MG  
100 mg

**((S))-(−)-3,3′-Bis(3,5-dimethylphenyl)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2-naphthol, 97%**  
(S)-3,3′-Bis(3,5-dimethylphenyl)-5,5′,6,6′,7,7′,8,8′-octahydro[1,1′]binaphthalenyl-2,2′-diol  
C₅₆H₄₂O₂Si₂  
FW 803.10

669172-100MG  
100 mg

**((R))-(+)-3,3′-Bis(triphenylsilyl)-1,1′-bi-2-naphthol, 96%**  
(R)-3,3′-Bis(triphenylsilyl)[1,1′]binaphthalenyl-2,2′-diol  
C₅₆H₄₂O₂Si₂  
FW 803.10

669172-100MG  
100 mg

**((S))-(−)-3,3′-Bis(triphenylsilyl)-1,1′-bi-2-naphthol, 96%**  
(S)-3,3′-Bis(triphenylsilyl)[1,1′]binaphthalenyl-2,2′-diol  
C₅₆H₄₂O₂Si₂  
FW 803.10

669172-100MG  
100 mg

**((R))-(+)-3,3′-Dibromo-1,1′-bi-2-naphthol, 97%**  
[R]-3,3′-Dibromo[1,1′]binaphthalenyl-2,2′-diol  
C₁₀₈H₈O₂Br₂  
FW 444.12

595721-250MG  
250 mg

595721-1G  
1 g

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(R)-(−)-6,6′-Dibromo-1,1′-bi-2-naphthol, 98%

\[ \text{C}_{20}\text{H}_{12}\text{Br}_2\text{O}_2 \]
FW 444.12

R: 36/37/38  S: 26-36
482617-500MG  500 mg

(S) (+)-6,6′-Dibromo-1,1′-bi-2-naphthol, 98%

\[ \text{C}_{20}\text{H}_{12}\text{Br}_2\text{O}_2 \]
FW 444.12

R: 36/37/38  S: 26-36
482625-250MG  250 mg
482625-500MG  500 mg

(S) (−)-3,3′-Dibromo-1,1′-bi-2-naphthol, 96%

\[ \text{C}_{20}\text{H}_{12}\text{Br}_2\text{O}_2 \]
FW 444.12

R: 36/37/38  S: 26-36
595837-250MG  250 mg
595837-1G  1 g

(R)-(+)-6,6′-Dibromo-2,2′-bis(methoxymethoxy)-1,1′-binaphthalene, 97%

\[ \text{C}_{22}\text{H}_{18}\text{O}_2 \]
FW 314.38

R: 41  S: 25-26/36/39
631604-250MG  250 mg

(S)-(-)-3,3′-Dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-bi-2,2′-naphthalenediol, 97%

\[ \text{C}_{20}\text{H}_{20}\text{Br}_2\text{O}_2 \]
FW 452.18

R: 36/37/38  S: 26-36
595403-250MG  250 mg

(R)-(+)-2,2′-Dimethoxy-1,1′-binaphthalene, 97%

\[ \text{C}_{22}\text{H}_{18}\text{O}_2 \]
FW 314.38

R: 41  S: 26-36
595403-250MG  250 mg

(R)-(+)-2,2′-Dimethoxy-1,1′-binaphthyldimethyl ether

\[ \text{C}_{22}\text{H}_{18}\text{O}_2 \]
FW 314.38

R: 41  S: 26-36
595519-250MG  250 mg

(R)(−)-Dimethyl-2,2′-dihydroxy-1,1′-binaphthalene-3,3′-dicarboxylate, 98%

\[ \text{C}_{24}\text{H}_{18}\text{O}_6 \]
FW 402.40

R: 36/37/38  S: 26-36
579343-2G  2 g

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(S)-(−)-Dimethyl-2,2-dihydroxy-1,1′-binaphthalene-3,3′-dicarboxylate

[C₂₈H₁₈O₆] 402.40

(+)−Dimethyl-2,2′-dihydroxy-1,1′-binaphthalene-3,3′-dicarboxylate 98%

R: 36/37/38  S: 26-36
579971-2G  2 g

(1R,2R,3S,4R,5R)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-2-naphthol 97%

[C₂₀H₂₂O₂] 294.39

(1R,2R,3S,4R,5R)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-2-naphthol 100 mg
540579-100MG
675156-250MG
675210-100MG
675210-250MG
675210-500MG

BINOL Ligands Kit I

Components

(S)-(−)-1,1′-Bi(2-naphthol) (Aldrich 346956) 1g
(S)-(−)-6,6′-Dibromo-1,1′-bi-2-naphthal (Aldrich 482625) 250mg
(S)-(−)-5,5′,6,6′,7,7′,8,8′-Octahydro-1,1′-2-bi-1-naphthol (Aldrich 540579) 100mg
(S)-(−)-3,3′-Dibromo-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-2-bi-2,2′-naphthalenediol (Aldrich 540595) 100mg
(S)-(−)-2,2′-Dimethoxy-1,1′-binaphthalene (Aldrich 595719) 250mg
(S)-(−)-3,3′-Dibromo-1,1′-bi-2-naphthal (Aldrich 595837) 250mg

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TADDOL

The chiral auxiliaries TADDOLs (α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanol) developed by Seebach’s group have found numerous applications in asymmetric synthesis ranging from utilization as stoichiometric chiral reagents or in Lewis acid mediated reactions, to roles in catalytic hydrogenation and stereoregular metathesis polymerization.

Nucleophilic Addition

The principal field of application of TADDOLs to date is in Ti-catalyzed, enantioselective reactions. Nucleophilic additions of organometallic compounds to aldehydes are depicted in Scheme 1. The preparation of the Ti-TADDOLate complex used in such transformations is critical with respect to reproducibility.

Enantioselective Transesterification

Several examples of enantioselective transesterifications were reported for ring openings of lactones and cyclic anhydrides using Ti-TADDOLate of 393762 (Scheme 3). The observed selectivity in this desymmetrization step is largely independent of structure. The half esters obtained are readily converted into the corresponding γ-lactones.

It is worth mentioning that TADDOL 395242 bearing 1-naphthyl groups infrequently differs in its reactivity from the other TADDOLs (a dramatic loss in enantioselectivity is observed in Ti-TADDOLate catalyzed addition reactions described previously). This change in reactivity could be explained with the higher steric hindrance around the chiral pocket of the active site.

Enantioselective Protonation

Nevertheless, surprisingly stereoselective examples using TADDOL 395242 were found in enantioselective protonation reactions (Scheme 4). The first example of a catalytic enantioselective fluorination reaction reported by Hintermann and Togni used the Cl2Ti-complex of polymeric 1.

The principal field of application of TADDOLs to date is in Ti-catalyzed, enantioselective hetero-Diels-Alder reaction using 395242 (reaction reported by Hintermann and Togni used the Cl2Ti-complex of polymeric 1.)

References:

**BOX**

C$_2$-symmetric chiral bisoxazolines (BOX) are privileged structures because they promote a great number of transformations with unprecedented selectivity. In 1991, in the same Journal of American Chemistry issue, two communications appeared by Evans and Corey. These two publications have paved the way for a rapidly and ever-growing number of examples where BOX ligands find success as chiral ligands.

Evans described the cyclopropanation of alkenes using diazo esters catalyzed by a complex formed of 406147 and Cu(II)OTf. With the ester derived from 2,6-di-tert-butyl-4-methylphenol (BHT) it was found that the increased steric demand displays increased trans selectivity (Scheme 1).

In a related experiment, Evans announced the first catalytic enantioselective aziridination of styrene. Two years later, he reported on an extension of this preliminary work in a full communication (Scheme 2). Using BOX ligand 405000, complexed to Cu(II)OTf, in the catalytic enantioselective aziridination of styrene, the BOX ligand having phenyl substituents proved to be superior to the one bearing sterically demanding R-Bu groups (Scheme 2).

Recently, Reiser et al. discovered a general route to disubstituted γ-butyrolactones. In an Cu(I)-catalyzed asymmetric cyclopropanation of furans with diazo esters, brs(4-isopropylxoxazoline) 680192 was used as chiral ligand (Scheme 3). This transformation was carried out on a 50–100 g scale without a detectable loss of enantioselectivity.

In his 1991 Journal of American Chemical Society communication, Corey used BOX ligand 405000 in an Fe(III)-catalyzed enantioselective Diels–Alder reaction (Scheme 4). Two years later, Evans described the Cu(I)-catalyzed version of the enantioselective Diels–Alder reaction of unsubstituted acrylonitriles using BOX ligand 406147 as a chiral Lewis acid. The reaction proceeded in good yield exhibiting excellent enantioselectivity for the endo diastereoisomer (Scheme 5). From further investigations by Evans et al., it appears that the best combination is BOX 406147 and Cu(II), and the best countercations are OTf and SbF$_6$.

4-Aryl- and 4-alkylsubstituted BOX-based catalysts were widely used in a large number of reactions and their behavior can provide a good representation of their efficiency. But BOX ligands with other structural motifs have been successfully used too. BOX ligand 405981 has been used in the Cu(I)-catalyzed highly enantioselective Mannich reactions to efficiently produce highly functionalized 4-oxo-glutamic acid derivatives (Scheme 6).

Recently, Ma et al. reported on the enantioselective Cu(II)-bisoxazoline)-catalyzed addition of propionate and terminal yrones to 4-acylpyridinium salt to afford highly functionalized dihydropyridines with excellent enantioselectivity using 1464155 (Scheme 7). It is found that the carbonyl group adjacent to the alkyne moiety is essential for the enantioselectivity of the addition.

2.2'-Bis(4S,4S)-4-isopropyl-2-oxazoline)propane, 96%
S-4,5-Dihydro-2-(2-(4S,5S)-4,5-dihydro-4-isopropyl-oxazol-2-yl)propan-2-yl-4-isopropyl-2-oxazoline
C13H26N2O2
FW 266.38

β: 36° S: 26° Fp: 230 °F
680192-500MG 500 mg

2.2'-Isopropylidenebis(4S,4S)-4-tert-butyl-2-oxazoline), 99%
(S,5S,5S,5S)-2,2'-Isopropylidenebis(4-tert-butyl-2-oxazoline)
[131833-93-7] C23H26N2O2 FW 294.43

β: 36/37/38° S: 26-36
406147-500MG 50 mg
406147-250MG 250 mg

2.2'-Methylenebis(4S,4S)-4-tert-butyl-2-oxazoline), 99%
(S,5S,5S,5S)-2,2'-Methylenebis(4-tert-butyl-2-oxazoline)
[132098-54-5] C24H28N2O2 FW 266.38

β: 36/37/38° S: 26-36
405965-500MG 500 mg

(+)-2.2'-Isopropylidenebis(4R,4R)-4-phenyl-2-oxazoline), 97%
(R,R,R,R)-2,2'-Isopropylidenebis(4-phenyl-2-oxazoline)
[150529-93-4] C28H33N3O2 FW 334.41

β: 23/24/25° S: 26-36-45
406961-250MG 250 mg
406961-1G 1 g

(-)-2.2'-Isopropylidenebis(4S,4S)-4-phenyl-2-oxazoline), 97%
(S,S,S,S)-2,2'-Isopropylidenebis(4-phenyl-2-oxazoline); (S,S,S,S)-2,2'-Isopropylidenebis(4-phenyl-2-oxazoline)-propane
[131457-46-0] C28H33N3O2 FW 334.41
β: 22-24/25° Fp: 110 °C (230 °F)
405000-250MG 250 mg
405000-1G 1 g

(+)-2.2'-Isopropylidenebis(4R,4R)-4-benzyl-2-oxazoline), 98%
[R,R,R,R]+(+)-2,2'-Isopropylidenebis(4-benzyl-2-oxazoline)
[143162-77-8] C20H20N2O2 FW 282.46
β: 36/37/38° S: 26-36
495301-250MG 250 mg
495301-1G 1 g

2.2'-Methylenebis(4S,4S)-4-phenyl-2-oxazoline), 97%
(S,S)-2,2'-Methylenebis(4-phenyl-2-oxazoline)
[132098-59-0] C24H28N2O2 FW 306.36

β: 36/37/38° S: 26-36 Fp: 110 °C (230 °F)
416428-250MG 250 mg
416428-1G 1 g

2.2'-Bis(4S,4S)-4-benzyl-2-oxazoline), 98%
(S,S)-2,2'-Bis(4-benzyl-2-oxazoline); (S,S)-4,4'-Dibenzyldi(2-oxazoline)
[133463-88-4] C20H20N2O2 FW 320.39

β: 36/37/38° S: 26-36
405973-250MG 250 mg
405973-1G 1 g

2.2'-Methylenebis(4R,5S,5S,5S)-4,5-diphenyl-2-oxazoline), 99%
(4R,5S,5S,5S)-2,2'-Methylenebis(4,5-diphenyl-2-oxazoline)
[139021-82-2] C20H20N2O2 FW 458.55

β: 36/37/38° S: 26-36
405981-250MG 250 mg
405981-1G 1 g

(4S)-4-[4-(tert-butyl)phenyl]-cyclo-(4S)-4-[4-(tert-butyl)phenyl]-2-oxazolidinylidene]-2-oxazolineacetonitrile, 97%
Bis(4S)-4-[4-(tert-butyl)phenyl]-4,5-dihydro-2-oxazolyl)acetonitrile
C28H33N3O2 FW 443.58

β: 36/37/38° S: 26
682772-250MG 250 mg

(4S,4'S)-(−)-2,2'-Bis(3-Pentylidene)bis(4-isopropyl-2-oxazoline), 97%
(4S,4'S)-(−)-2,2'-Bis(3-Pentylidene)bis(4-isopropyl-2-oxazoline)
[160191-65-1] C16H28N2O2 FW 394.43

β: 36/37/38° S: 26-36 Fp: 82 °C (180 °F)
650897-500MG 500 mg
650897-1G 1 g
(4S,4')-Phenyl-α-(4-phenyloxazolidin-2-ylidene)-2-oxazoline-2-acetonitrile, 97%

C₂₀H₁₇N₃O₂
FW 331.37

S: 26-36
L: R: 36/37/38

417068-250MG 250 mg
417068-1G 1 g

(15.95)-1,9-Bis[(tert-butyldimethylsiloxyl)methyl]-5-cyanosemicorrin, ≥97.0% (HPLC)

C₂₄H₄₅N₃O₂Si₂
FW 463.80

S: 26-36
L: R: 36/37/38

14556-10MG 10 mg

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PYBOX

The PYBOX ligand, consisting of a pyridine ring flanked by two oxazoline groups, was introduced in 1989 by Nishiyama. PYBOX evolved directly from the BOX ligands. In comparing them, two points merit to be mentioned: (1) the binding site of PYBOXes is big enough to complex even lanthanide cations and (2) the rigidity of the tridentate PYBOX scaffold is increased.

In his very first application, Nishiyama showed that isopropyl-PYBOX rhodium(III) catalyst effectively promotes the asymmetric hydrosilylation of ketones giving extremely high enantioselectivities (Scheme 1).

Li and Wei reported in 2002 the copper(I)-catalyzed enantioselective direct-addition of terminal alkynes to imines. The most successful ligand tested was PYBOX bearing phenyl groups (Scheme 2). Recently, Shibasaki’s group reported on lanthanum aryl oxide/PYBOX-catalyzed direct asymmetric Mannich-type reactions using a trichloromethyl ketone as a propionate equivalent donor. The La(OAr)3-i-Pr-PYBOX + LiOAr system gave products in 72 to >99% yield, 8:1 to >30:1 dr, and 92-98% ee (Table 1).

The chiral indium(III)-PYBOX complex prepared from indium triflate and C2-symmetric chiral PYBOX was found to be an effective chiral ligand for the enantioselective allylation reaction of aldehydes with allyltributylstannane, giving high enantioselectivities. Using this methodology, the chiral steroidal aldehyde could be allylated with excellent enantioselectivity (22S):(22R) = >99:1) and in good yield (78%). Furthermore, the reaction was highly chemoselective, reacting only with the aldehyde functionality. No reaction was observed with the enone functionality in the A ring (Scheme 3).

References:

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
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<th>% Yield</th>
<th>dr (s/c)</th>
<th>% ee (s)</th>
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<td>96</td>
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<td>2</td>
<td>4-Cl-C6H4</td>
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<td>3</td>
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<td>i-Pr</td>
<td>74</td>
<td>&gt;30:1</td>
<td>97</td>
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2,6-Bis[(4R)-(+)–isopropyl-2-oxazolin-2-yl]pyridine, 99%

\[\text{FW: } 301.38\]

<table>
<thead>
<tr>
<th>Code</th>
<th>Quantity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>477494-250MG</td>
<td>250 mg</td>
<td>(4R)-2,6-Bis[(4R)-(+)–isopropyl-2-oxazolin-2-yl]pyridine</td>
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<td>477494-1G</td>
<td>1 g</td>
<td>(4R)-2,6-Bis[(4R)-(+)–isopropyl-2-oxazolin-2-yl]pyridine</td>
</tr>
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</table>

2,6-Bis[(4S)-(−)–isopropyl-2-oxazolin-2-yl]pyridine, 99%

\[\text{FW: } 301.38\]

<table>
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<tr>
<th>Code</th>
<th>Quantity</th>
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<tr>
<td>407151-250MG</td>
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<td>(4S)-2,6-Bis[(4S)-(−)–isopropyl-2-oxazolin-2-yl]pyridine</td>
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<tr>
<td>407151-1G</td>
<td>1 g</td>
<td>(4S)-2,6-Bis[(4S)-(−)–isopropyl-2-oxazolin-2-yl]pyridine</td>
</tr>
</tbody>
</table>

2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine, 98%

\[\text{FW: } 369.42\]

<table>
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<tr>
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<tr>
<td>496065-500MG</td>
<td>500 mg</td>
<td>(4R)-2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine</td>
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<td>496065-2G</td>
<td>2 g</td>
<td>(4R)-2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine</td>
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2,6-Bis[(4S)-4-phenyl-2-oxazolinyl]pyridine, 98%

\[\text{FW: } 369.42\]

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<tr>
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<td>(4S)-2,6-Bis[(4S)-4-phenyl-2-oxazolinyl]pyridine</td>
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<td>496073-2G</td>
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<td>(4S)-2,6-Bis[(4S)-4-phenyl-2-oxazolinyl]pyridine</td>
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2,6-Bis[(4R,5R)-4-methyl-5-phenyl-2-oxazolinyl]pyridine, 97%

\[\text{FW: } 397.47\]

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<tr>
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<tr>
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<tr>
<td>496081-2G</td>
<td>2 g</td>
<td>(4R,5R)-2,6-Bis[(4R,5R)-4-methyl-5-phenyl-2-oxazolinyl]pyridine</td>
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2,6-Bis[(4S,5S)-4-methyl-5-phenyl-2-oxazolinyl]pyridine, 98%

\[\text{FW: } 397.47\]

<table>
<thead>
<tr>
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<th>Quantity</th>
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<tr>
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<td>(4S,5S)-2,6-Bis[(4S,5S)-4-methyl-5-phenyl-2-oxazolinyl]pyridine</td>
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</table>

2,6-Bis[(4S,8aR)-3a,8a-dihydro-8H-indeno[1,2-d]oxazolin-2-yl]pyridine

\[\text{FW: } 393.44\]

<table>
<thead>
<tr>
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<td>250 mg</td>
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<tr>
<td>673978-1G</td>
<td>1 g</td>
<td>(4S,8aR)-2,6-Bis[(4S,8aR)-3a,8a-dihydro-8H-indeno[1,2-d]oxazolin-2-yl]pyridine</td>
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</table>

2,6-Bis[(3aS,3′aS)-3a,8a-dihydro-8H-indeno[1,2-d]oxazolin-2-yl]pyridine

\[\text{FW: } 393.44\]

<table>
<thead>
<tr>
<th>Code</th>
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<tr>
<td>673986-250MG</td>
<td>250 mg</td>
<td>(3aS,3′aS)-2,6-Bis[(3aS,3′aS)-3a,8a-dihydro-8H-indeno[1,2-d]oxazolin-2-yl]pyridine</td>
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<tr>
<td>673986-1G</td>
<td>1 g</td>
<td>(3aS,3′aS)-2,6-Bis[(3aS,3′aS)-3a,8a-dihydro-8H-indeno[1,2-d]oxazolin-2-yl]pyridine</td>
</tr>
</tbody>
</table>

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PHOX

Of the thousands of chiral ligands used in asymmetric synthesis a relatively large number exhibit C2-symmetry. More recently, non-symmetrical modular P,N-ligands have been introduced independently by Pfaltz, Helmchen, and Williams and applied successfully in various metal-catalyzed reactions. These phosphinooxazolines (PHOX) are a highly versatile class of ligands.2

PHOX ligand 43158 was successfully used in Pd-catalyzed asymmetric allylic alkylation reactions. Racemic allyl acetates were transformed into their Pd allyl complex, which is subsequently attacked by a nucleophile to give the corresponding addition adduct (Scheme 1).3

Phosphinooxazoline 688495 can induce very high enantioselectivities in the Heck reaction.4 In contrast to analogous reactions with diphosphine-Pd catalysts, virtually no C=C double bond migration is observed in the primary product. Hence, particularly in cases where double bond migration leads to undesired products or mixtures of isomers, phosphinooxazolines are the ligands of choice (Scheme 2).5

Cationic iridium-phosphinooxazoline complexes have proved to be effective catalysts for the enantioselective hydrogenation of imines and trisubstituted olefins (Scheme 3).6 In a systematic study, PHOX ligand with a bis(o-tolyl)phosphanyl moiety gave highest enantioselectivities (up to 97% ee).

The cationic iridium complex with PHOX ligand 91716 is an efficient catalyst for the enantioselective intramolecular Pauson-Khand reaction.5 Under optimized conditions, enantioselectivities of >90% ee were obtained with 9 mol% of catalyst (Table 1). The anion proved to be important, as it had a significant influence on the enantioselectivity and yield. Best results obtained with relatively small, weakly coordinating anions such as tetrafluoroborate and hexafluorophosphate, but also triflate.

Recently, Rovis et al. used PHOX ligand 688495 in a rhodium(I)-catalyzed enantioselective desymmetrization reaction of meso-3,5-dimethyl glutaric anhydride, providing rapid access to substituted syn-deoxypolypropionate fragments in a single transformation (Scheme 4).6

References:

Table 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Z</th>
<th>R</th>
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<th>solvent</th>
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<td>H</td>
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<td>DME</td>
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<tr>
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<td>O</td>
<td>H</td>
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</tr>
<tr>
<td>6</td>
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<td>H</td>
<td>BF4</td>
<td>THF</td>
<td>76</td>
<td>91</td>
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<tr>
<td>7</td>
<td>C(CO2CH3)2</td>
<td>H</td>
<td>PF6</td>
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<td>8</td>
<td>O</td>
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<td>O</td>
<td>CH3</td>
<td>BF4</td>
<td>THF</td>
<td>6</td>
<td>64</td>
</tr>
</tbody>
</table>

Scheme 1

Scheme 2

Scheme 3

Scheme 4

PHOX
Dynamic Kinetic Resolution (DKR) catalysis is an essential methodology for the conversion of racemic substrates into single enantiomeric products. Kim et al. reported the (S)-selective DKR of a variety of alcohols by utilizing the combination of substilisin and an aminocyclopentadienylruthenium complex. High yields and selectivities were obtained for a variety of secondary alcohols.

Salen Ligands

Salen molecules have been studied for more than six decades. However, in 1990 Jacobsen and Katsuki independently published the first reports of salen used as ligands with manganese for asymmetric epoxidation reactions. Since these first reports, the area of metal-salen catalysis has expanded greatly. A plethora of metal-salen complexes have been synthesized and used in a variety of catalyzed asymmetric transformations. For example, chromium and cobalt salen complexes catalyze the epoxidation of unfunctionalized olefins with high levels of enantioselectivity.5 Aluminum salen complexes catalyze the conjugate addition of azide to unsaturated imides.6 The easy synthesis and modifications of the salen ligand framework made it the platform of choice for the discovery of new catalysts and reactions.

Examples of the versatility of the salen complexes are illustrated in Scheme 1.


(R,R)-(−)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine, 98%

(R,R)-Jacobsen’s ligand
[C₃₆H₅₂AlClN₂O₂]
FW 607.24
E: 36/37/38 S: 26

(R,R)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminoaluminum chloride

(R,R)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminoaluminum(III) chloride
[C₃₆H₅₂AlClN₂O₂]
FW 607.24
E: 36/37/38 S: 26-36

(S,S)-(−)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediamine, 98%

(S,S)-Jacobsen’s ligand
[C₃₆H₅₂N₂O₂]
FW 546.83
E: 36/37/38 S: 26-36

(S,S)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminoaluminum chloride

(S,S)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminoaluminum(III) chloride
[C₃₆H₅₂AlClN₂O₂]
FW 607.24
E: 36/37/38 S: 26-36

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(R, R)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminochromium(III) chloride

\[
\begin{align*}
\text{FW} & = 632.26 \\
\text{L} & = \text{R}: 20/21/22 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{531944-1G} & = 1 \text{ g} \\
\text{531944-5G} & = 5 \text{ g}
\end{align*}

(S, S)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminomanganese(III) chloride

\[
\begin{align*}
\text{FW} & = 635.20 \\
\text{L} & = \text{R}: 36/37/38 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{404454-1G} & = 1 \text{ g} \\
\text{404454-5G} & = 5 \text{ g} \\
\text{404454-25G} & = 25 \text{ g}
\end{align*}

(S, S)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediminochromium(III) chloride

\[
\begin{align*}
\text{L} & = \text{R}: 20/21/22 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{531944-1G} & = 1 \text{ g} \\
\text{531944-5G} & = 5 \text{ g}
\end{align*}

(R, R)-(−)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediminochromium(III) chloride

\[
\begin{align*}
\text{FW} & = 632.26 \\
\text{L} & = \text{R}: 20/21/22 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{474606-1G} & = 1 \text{ g} \\
\text{474606-5G} & = 5 \text{ g} \\
\text{474606-25G} & = 25 \text{ g}
\end{align*}

Jacobsen's catalyst; (R,R)-Jacobsen's catalyst

\[
\begin{align*}
\text{FW} & = 635.20 \\
\text{L} & = \text{R}: 36/37/38 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{404446-1G} & = 1 \text{ g} \\
\text{404446-5G} & = 5 \text{ g} \\
\text{404446-25G} & = 25 \text{ g}
\end{align*}

(R, R)-Jacobsen's catalyst

\[
\begin{align*}
\text{FW} & = 635.20 \\
\text{L} & = \text{R}: 36/37/38 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{404446-1G} & = 1 \text{ g} \\
\text{404446-5G} & = 5 \text{ g} \\
\text{404446-25G} & = 25 \text{ g}
\end{align*}

(S, S)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediminochromium(III) chloride

\[
\begin{align*}
\text{L} & = \text{R}: 20/21/22 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{531944-1G} & = 1 \text{ g} \\
\text{531944-5G} & = 5 \text{ g}
\end{align*}

(R, R)-(−)-N,N′-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediminochromium(III) chloride

\[
\begin{align*}
\text{L} & = \text{R}: 20/21/22 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{474606-1G} & = 1 \text{ g} \\
\text{474606-5G} & = 5 \text{ g} \\
\text{474606-25G} & = 25 \text{ g}
\end{align*}

Josephson's catalyst; (R,R)-Josephson's catalyst

\[
\begin{align*}
\text{FW} & = 635.20 \\
\text{L} & = \text{R}: 36/37/38 \\
\text{S} & = 26-36
\end{align*}
\]

\begin{align*}
\text{404446-1G} & = 1 \text{ g} \\
\text{404446-5G} & = 5 \text{ g} \\
\text{404446-25G} & = 25 \text{ g}
\end{align*}
The use of chiral diene as ligands for asymmetric synthesis has been growing for the past 5 years. Paquin et al. reported the asymmetric synthesis of 3,3-diarylpropanals using a chiral bicyclo[2.2.2]octadiene as a ligand with a rhodium complex. This new synthesis provides access to building blocks that are otherwise not readily available. Good yields and selectivity were reported with a variety of boronic acids and cinnamaldehydes.

Cinchona Alkaloids

Cinchona alkaloids and their derivatives have proven to catalyze an astonishing array of enantioselective transformations, providing access to chiral products of high enantiopurity. The presence of the tertiary quinuclidine nitrogen renders them effective ligands for a variety of metal-catalyzed processes. Of these reactions, the osmium-catalyzed asymmetric dihydroxylation of olefins (Scheme 1), developed by Sharpless in 1988, has had the greatest impact in synthetic chemistry.

Bis-(cinchona alkaloid) ligands (which are generally the better catalysts) catalyze the formation of diols of high enantiopurity from a very broad range of olefins. A recent example stems from O’Doherty et al. where (E,E)- and (Z,Z)-1,3-dienoates were dihydroxylated regioselectively in good yields and excellent enantioselectivities using (DHQD)2PHAL 392731 (Scheme 2).

Subsequently, these cinchona alkaloids were used for the osmium-catalyzed asymmetric aminohydroxylation of olefins. The significance of this reaction is immediately apparent as the asymmetric aminohydroxylation provides straightforward access to the formation of quaternary asymmetric centers with high enantiomeric excesses. Using the (DHQD)2AQN (Scheme 3) to form a diverse range of highly functionalized amine compounds (Scheme 5).

Jørgensen et al. have developed the first catalytic enantioselective conjugate addition to alkynones using (DHQ)2PHAL (392723). For both aromatic and aliphatic alkynes, the addition of β-diketones proceeds in high yields and enantioselectivity giving a mixture of (E)- and (Z)-enones (Scheme 6).

Dimeric (DHAD)2AQN catalyzes the enantioselective desymmetrization of meso anhydrides with methanol by a nucleophilic mechanism (Scheme 7). The scope of the reaction was found to be very general, with excellent enantioselectivity obtained in the desymmetrization of monocyclic, bicyclic, and tricyclic prochiral and meso anhydrides.

The metal-free, allylic amination reaction provides a useful extension to the conventional palladium catalyzed π-allylic methodology. Amination with dimides at the remote γ-position can be carried out using (DHQ)2PYR (418978) to form a diverse range of highly functionalized amine compounds (Scheme 5).

References:

References:
Scheme 4

Scheme 5

Scheme 6

(+)-Cinchonine, 85%

Cinchonidine, 96%

Cinchonine monohydrochloride hydrate, 99%

Cinchona Alkaloids
**Quinidine, ≥98.0% (NT, dried material)**

[C20H24N2O2]  
FW 324.42

R: 22  S: 36  EC No. 200-279-0  RTECS # VA4725000

- 22600-10G-F  10 g
- 22600-50G-F  50 g

**Quinine, 90%**

[C20H24N2O2]  
FW 324.42

R: 22  S: 36  EC No. 205-003-2  RTECS # VA6020000

- 145904-10G  10 g
- 145904-50G  50 g

**Quinine hemisulfate salt monohydrate, 90%**

[C20H24N2O2 · 0.5H2SO4 · H2O]  
FW 391.47

R: 22  EC No. 207-621-8  RTECS # MX3018000

- 341320-1G  1 g
- 341320-5G  5 g

**Hydroquinidine, 95%**

[Dihydroquinidine]  
[C20H26N2O2 · HCl]  
FW 362.89

R: 22  EC No. 216-024-1  RTECS # MX3016000

- 254819-5G  5 g
- 254819-25G  25 g

**Hydroquinine, 98%**

[Dihydroquinine]  
[C20H26N2O2]  
FW 326.43

R: 22  EC No. 208-334-0  RTECS # MX3018000

- 337714-1G  1 g
- 337714-5G  5 g

**Hydrocinchonine, ≥97.0% (GC, sum of enantiomers)**

[Dihydrocinchonine]  
[C19H24N2O]  
FW 296.41

≥99.0% (NT)

R: 2021/22  S: 36/37  EC No. 213-86-9  RTECS # MH5011000

- 54060-500MG  500 mg
Hydroquinidine 4-chlorobenzoate, 98%
Dihydroquinidine 4-chlorobenzoate, O-(4-Chlorobenzoyl)hydroquinidine
\[\text{Formula: } \text{C}_{12}\text{H}_{12}\text{ClNO}_{3}\]
FW 464.98
*E: 36/37/38 S: 26-36
336483-1G 1 g
336483-5G 5 g

Hydroquinine 4-methyl-2-quinolyl ether, 98%
[135096-79-6]
\[\text{C}_{30}\text{H}_{33}\text{N}_{3}\text{O}_{2}\]
FW 467.60
*E: 36/37/38 S: 26-36
381969-1G 1 g
381969-5G 5 g

Hydroquinidine 4-methyl-2-quinolyl ether, 97%
[135042-89-6]
\[\text{C}_{30}\text{H}_{33}\text{N}_{3}\text{O}_{2}\]
FW 467.60
*E: 36/37/38 S: 26-36
381942-1G 1 g

Hydroquinidine 9-phenanthryl ether, 96%
O-(9-Phenanthryl)hydroquinidine
[135096-78-5]
\[\text{C}_{34}\text{H}_{34}\text{N}_{2}\text{O}_{2}\]
FW 502.65
*S: 22-24/25
381950-250MG 250 mg
381950-1G 1 g

Hydroquinidine 9-phenanthryl ether, 97%
O-(9-Phenanthryl)hydroquinine
[135096-78-5]
\[\text{C}_{34}\text{H}_{34}\text{N}_{2}\text{O}_{2}\]
FW 502.65
*E: 36/37/38 S: 26-36
381977-100MG 100 mg
381977-500MG 500 mg

(2R,4S,5R)-2-Aminomethyl-5-ethylquinuclidine, ≥95.0% (GC)
(2R,4S,5R)-5-Ethyl-2-quinuclidinylmethylamine
\[\text{C}_{10}\text{H}_{20}\text{N}_{2}\]
FW 168.28
*R: 22-37/38-41 S: 26-39
39867-100MG-F 100 mg
39867-500MG-F 500 mg

(2S,4S,5R)-2-Aminomethyl-5-ethylquinuclidine, ≥95.0% (GC)
(2S,4S,5R)-5-Ethyl-2-quinuclidinylmethylamine
\[\text{C}_{10}\text{H}_{20}\text{N}_{2}\]
FW 168.28
*R: 22-38-41 S: 26-39
07317-100MG-F 100 mg
07317-500MG-F 500 mg

(2R,4S,5R)-2-Hydroxymethyl-5-ethylquinuclidine, ≥99.0% (GC)
(2R,4S,5R)-5-Ethyl-2-quinuclidinylmethanol
\[\text{C}_{10}\text{H}_{19}\text{NO}\]
FW 169.26
*R: 37/38-41 S: 26-39
49463-100MG-F 100 mg
49463-500MG-F 500 mg

(2S,4S,5R)-2-Hydroxymethyl-5-ethylquinuclidine, ≥99.0% (GC)
(2S,4S,5R)-5-Ethyl-2-quinuclidinylmethanol
\[\text{C}_{10}\text{H}_{19}\text{NO}\]
FW 169.26
*R: 37/38-41 S: 26-39
51957-100MG-F 100 mg
51957-500MG-F 500 mg

(2R,5R)-(+)-5-Vinyl-2-quinuclidinemethanol, 96%
\[\text{C}_{10}\text{H}_{17}\text{NO}\]
FW 167.25
Fp: 113 °C (235 °F)
472549-250MG 250 mg
**Cinchona Alkaloids**

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<tr>
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<th>Molecular Weight</th>
<th>CAS Registry Number</th>
<th>Appearance</th>
<th>Specification</th>
<th>Availability</th>
<th>Order Information</th>
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<tbody>
<tr>
<td>(DHQ)₂AQN, 95%</td>
<td>C₄₆H₄₄N₄O₄</td>
<td>857.05</td>
<td>176097-24-8</td>
<td>Hydroquinine anthraquinone-1,4-diyl diether</td>
<td></td>
<td>36/37/38 S: 26-36</td>
<td>456705-500MG</td>
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<tr>
<td>(DHQD)₂AQN, 95%</td>
<td>C₄₆H₄₄N₄O₄</td>
<td>857.05</td>
<td>176298-44-5</td>
<td>Hydroquinidine (anthraquinone-1,4-diyl) diether</td>
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<td>36/37/38 S: 26-36</td>
<td>456713-500MG</td>
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<tr>
<td>(DHQ)₂PHAL, ≥95%</td>
<td>C₄₆H₄₄N₄O₄</td>
<td>857.05</td>
<td>140853-10-7</td>
<td>Hydroquinine 1,4-phthalazinediyl diether</td>
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<td>392731-1G</td>
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<tr>
<td>(DHQ)₂Pyr, 97%</td>
<td>C₄₆H₄₄N₄O₄</td>
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**AD-mix-α**

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<td>149725-81-5</td>
<td>Hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether</td>
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**AD-mix-β**

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<tr>
<td>AD-mix-β</td>
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<td>857.05</td>
<td>149820-65-5</td>
<td>Hydroquinine 1,4-phthalazinediyl diether</td>
<td></td>
<td>36/37/38 S: 26-36</td>
<td>392766-10G</td>
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</tbody>
</table>

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QuinoxP* Ligands

Various optically active phosphine ligands incorporating a chiral center at the phosphorus display exceptional enantioselectivities in metal-catalyzed asymmetric synthesis.1 For instance, known classes of P-Chiral phosphine ligands offer good to excellent enantiocontrol in Ru- and Rh-catalyzed hydrogenation reactions.2 The one limitation associated with these ligands is their sensitivity to air, which has impeded widespread applicability in bench-top chemistry. Imamoto and co-workers have addressed this deficiency through the invention of QuinoxP*, which contains an electron-withdrawing quinoxaline architecture.3 It is worth noting that QuinoxP* is not oxidized at the stereogenic phosphorus center on standing at ambient temperature in air for more than 9 months.

Highly Asymmetric Rhodium-Catalyzed Hydrogenation

Imamoto has gone to great lengths to develop enantiomerically pure P-chiral ligands for industrially useful transformations such as asymmetric hydrogenation. Impressively, a diverse array of prochiral amino acid and amine substrates were hydrogenated with great efficiency to yield highly enantiopure amine derivatives (Scheme 1). The authors carried out these experiments at room temperature in methanol under low hydrogen pressures (3 atm). Note that all hydrogenation reactions were complete in 6 hours and with enantioselectivities ranging from 96 to 99.9%. Dramatic stereocochemical reversal, consistent with the results observed with the related (S,S)-tert-Bu-BisP* ligands,4,5 was obtained when 1-acetylaminol-1-adamantylmethane was hydrogenated to afford the S configuration amine with >96% enantioselectivity (Table 1).

Asymmetric 1,4-additions of Arylboronic Acids

Imamoto and co-workers exploited the high activity of the QuinoxP* ligand in rhodium-catalyzed enantioselective 1,4-additions of arylboronic acids to α,β-unsaturated carbonyl substrates.6 High yields of the addition products were obtained via running the reactions between 40 and 50 °C (Scheme 2). The exceptional enantiocontrol exerted by this Rh(I)-catalyzed system is evident when compared to the use of BINAP as the chiral ligand.6

Asymmetric Pd-catalyzed Ring Opening

Imamoto and co-workers have also succeeded in developing a Pd-catalyzed C=C bond-forming reaction, which displays high enantioselectivities with both dimethyl- and diethylzinc (Scheme 3, Table 2). This alkylative ring-opening methodology entails simply premixing PdCl2(cod) and QuinoxP* for 2 hours at room temperature—leading to a highly active catalyst. This catalytic system affords excellent yields of the ring-opened products and selectivities that rival the highest reported for this transformation. These results, when combined with the outstanding methodologies presented, indicate that QuinoxP* is useful for a broad variety of asymmetric metal-catalyzed transformations.

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Rewarded by a Nobel Prize in 2001 for his pioneering work in asymmetric synthesis, Knowles was the first to develop a transition-metal chiral catalyst based on a chiral diphosphine ligand, DIPAMP, that could transfer chirality to a prochiral substrate with high enantiomeric excesses. He demonstrated that a chiral diphosphine chelated to rhodium could give access to catalysis mimicking enzyme selectivity. To demonstrate the activity and selectivity of this new ligand, Knowles synthesized L-DOPA, a treatment for Parkinson’s disease, requiring the selective hydrogenation of an alkene. The synthesis of L-DOPA starts with the asymmetric hydrogenation of (Z)-2-acetamido-3-(3,4-dihydroxyphenyl)acrylic acid using the Rh-DIPAMP complex followed by deprotection of the amine. This process has been scaled up at Monsanto (Scheme 1).1

Trost Ligands

Palladium-catalyzed asymmetric allylic alkylation (AAA) has proven to be an exceptionally powerful method for the efficient construction of stereogenic centers. In sharp contrast to many other catalytic methods, AAA has the ability to form multiple types of bonds (C–C, C–O, C–S, C–N) with a single catalyst system.

The Trost group at Stanford University has pioneered the use of C-2 symmetric diaminocyclohexyl (DACH) ligands in AAA, allowing for the rapid synthesis of a diverse range of chiral products with a limited number of chemical transformations. Reactions are typically high-yielding, and excellent levels of enantioselectivity are observed.1

Codified Asymmetric Allylic Alkylation

Carbon Nucleophiles

In early examples of this methodology, Trost and co-workers demonstrated diesters are competent nucleophiles for the deracemization of cyclic allylic acetates, to afford chiral malonate derivatives. Since that time, soft carbon nucleophiles such as barbituric acid derivatives, β-keto esters, nitro compounds, and many others have been employed in AAA for assembly of tertiary and quaternary asymmetric centers.

Oxygen Nucleophiles

Carbon-oxygen bond-forming reactions using palladium-catalyzed asymmetric allylic alkylation have been well-demonstrated in numerous natural product syntheses. Alcohols, carboxylates, and hydroxycarbonates have all been employed as O-nucleophiles.

Nitrogen Nucleophiles

A formidable challenge in asymmetric synthesis is the stereocontrolled construction of carbon-nitrogen bonds. Nitrogen nucleophiles such as alkylamines, azides, amides, imides, and N-heterocycles have all been employed in asymmetric allylic alkylation reactions.

Alcohol Nucleophiles

Carboxylate Nucleophiles

Nitrogen Nucleophiles

Alkylamines Nucleophiles

Azide Nucleophiles

Imide Nucleophiles
Molybdenum-Catalyzed Reactions

The mechanism of the molybdenum-catalyzed AAA reaction is presumed to be distinctly different from the analogous Pd-catalyzed reaction, and in some cases, the levels of regio-, enantio-, and diastereoselectivity are enhanced relative to the palladium-catalyzed reaction. Trost and Dogra report the total synthesis of (−)-Δ²-trans-tetrahydrocannabinol, a psychomimetic of marijuana, utilizing a molybdenum catalyst. An overall yield of 30% of enantiomerically pure (−)-Δ²-trans-tetrahydrocannabinol (Scheme 1).


Scheme 1

(R,R)-DACH-naphthyl Trost ligand, 95%

(1R,2R)-(−)-1,2-Diaminocyclohexane-N,N′-bis(2-diphenylphosphino-1-naphthoyl)
[C₂H₅N₂O₃P₂]
FW 790.87
692778-250MG 250 mg
692778-1G 1 g

(S,S)-DACH-Naphthyl Trost Ligand, 95%

(1S,2S)-(−)-1,2-Diaminocyclohexane-N,N′-bis(2-diphenylphosphino-1-naphthoyl)
[205495-66-5]
[C₂H₅N₂O₃P₂]
FW 790.87
692786-250MG 250 mg
692786-1G 1 g

(R,R)-DACH-phenyl Trost ligand, 95%

(1R,2R)-(−)-1,2-Diaminocyclohexane-N,N′-bis(2-diphenylphosphino-benzoyl)
[1-74810-09-4]
[C₂H₅N₂O₃P₂]
FW 690.75
692808-250MG 250 mg
692808-1G 1 g

(S,S)-DACH-phenyl Trost ligand, 95%

(1S,2S)-(−)-1,2-Diaminocyclohexane-N,N′-bis(2-diphenylphosphino-benzoyl)
[C₂H₅N₂O₃P₂]
FW 690.75
692794-250MG 250 mg
692794-1G 1 g

(R,R)-DACH-pyridyl Trost ligand, 95%

(−)-N,N′-(1R,2R)-1,2-Diaminocyclohexane-N,N′-bis(2-pyridinecarboxamide)
[218290-24-5]
[C₂H₅N₂O₃]
FW 324.38
692751-500MG 500 mg
692751-1G 1 g

(S,S)-DACH-pyridyl Trost ligand, 95%

(1S,2S)-(−)-1,2-Diaminocyclohexane-N,N′-bis(2-pyridinecarboxylic amino)cyclohexane, (1S,2S)-(−)-1,2-Diaminocyclohexane-N,N′-bis(2-pyridinecarboxamide); (1S,2S)-(−)-1,2-Bis(2-pyridinecarboxamido)cyclohexane; (−)-N,N′-(1S,2S)-1,2-Diaminocyclohexane-N,N′-bis(2-pyridinecarboxamide)
[172138-95-3]
[C₂H₅N₂O₃]
FW 324.38
692743-500MG 500 mg
692743-1G 1 g
Landis Ligands

The interest in asymmetric reactions has been growing for the past 40 years. To address the challenges of synthesizing chiral building blocks with high yields and high selectivities, researchers developed a broad range of catalysts. Two of the essential components for highly active and selective catalysts are the ligand and the metal. Professor Landis and co-workers developed a series of new ligands based on chiral 3,4-diazaphospholane structures (Figure 1). These ligands are highly active for enantioselective hydroformylation and enantioselective allylic alkylation reactions. These two transformations are essential to access a variety of chiral blocks for the synthesis of more complex molecules.

Synthesis of Isoxazolines and Imidazoles

The asymmetric hydroformylation reaction is a highly chemoselective transformation allowing the conversion of terminal olefins into optically active aldehydes. Despite the recognized powerful methodology of this transformation, it has been sporadically utilized on a commercial scale due to the low reaction rates, the challenges to control the region- and enantioselectivities simultaneously and the limited substrate scope. Professor Landis and coworkers developed a new family of ligands based on 2,5-disubstituted phospholane addressing these issues.

Utilizing this newly developed ligand, Thomas and coworkers synthesized a series of oxazolines and imidazoles. Reacting vinyl acetate with Rh(CO)2(acac) and (R,R,R)-Diazaphos-SPE in a reactor with CO and H2 at 400 psi yielded the corresponding chiral aldehydes with 94% conversion and 96% ee (Scheme 1). It is important to note that a catalyst loading of only 0.001 mol% is necessary to complete this transformation. Following this reaction Thomas and coworkers ensured the conservation of the enantioselectivity by synthesizing the isoxazolines and imidazoles with overall good yields.

Asymmetric Allylic Alkylation

The asymmetric allylic alkylation reaction is an attractive reaction to form a new C–C bond with a desired nucleophile enantioselectively. Professor Landis and co-workers utilized this reaction to test newly synthesized chiral 3,4-diazaphospholanes (Diazaphos-PPE). With the presence of a palladium catalyst, these new ligands yielded outstanding conversions and enantioselectivities with a variety of substrates. Using 1,3-diphenylallyl acetate and 2-penten-4-yl acetate as reactants, with dimethyl malonate as the nucleophile, Clark and Landis demonstrated that Diazaphos-PPE is surpassing other ligands with high yields and selectivities for both substrates (Scheme 2).

References:

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**Bis(1,5-cyclooctadiene)rhomodium(II) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate**

692573

**Bis(1,2,4-triazolyl)rhodium(II) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate**

693774

**Bis(1,2,4-triazolyl)iridium(II) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate**

693774

**Bis(1,2,4-triazolyl)rhodium(II) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate**

693774

**Bis(1,2,4-triazolyl)iridium(II) tetrakis[3,5-bis(trifluoromethyl)phenyl]borate**

693774

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Landis Ligands
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Aminophosphine Ligands

An increased interest in aminophosphine type ligands used for asymmetric synthesis has been witnessed. This growth in popularity of aminophosphine ligands in asymmetric synthesis is in part due to the growing number of convenient synthetic pathways leading to useful ligand sets. Several groups have been using amino acids as precursors to synthesize these ligands. Researchers at Kanata have synthesized several sets of aminophosphine ligands showing great reactivity and selectivity in a wide array of enantioselective reactions.

Ruthenium Hydrogenation Catalysts

A growing area of application for aminophosphine ligands in asymmetric synthesis is in ruthenium-catalyzed hydrogenations. This process is integral in the preparation of alcohols and amines, which are essential in the pharmaceutical, agrochemical, material, and fine chemicals industries.

Chen et al. have described the use of ferrocenylaminophosphines in the ruthenium-catalyzed asymmetric hydrogenation of acetophenone. Using precatalysts [RuCl2(benzene)]2 and the ferrocenyl based aminophosphine ligand, they found that the hydrogenation proceeded quickly with reasonable enantioselectivity (Scheme 1).

Abdur-Rashid et al. reported the synthesis of cis-2-tert-butylcyclohexyl alcohol using bis-2-(diphenylphosphino)ethylamine ruthenium dichloride as a catalyst. Excellent selectivities were reported yielding only the cis-product (Scheme 2).

References:
Aminophosphine Ligands

(15,25)-2-[N-Methylamino-1-phenylpropyl]diphenyl-phosphine

\[
(15,25)-N,1\text{-Dimethyl-2-}(\text{diphenylphosphino})\text{-2-phenyl-ethyamine}
\]

\[
\text{C}_{28}\text{H}_{34}\text{NP}
\]

FW 333.41

697397-100MG 100 mg


\[
\text{C}_{24}\text{H}_{24}\text{NP}
\]

FW 355.41

697362-100MG 100 mg

(15,25)-2-[((4R,11bS)-3H-dinaphtho[2,1-c-1',2'-e]phosphepin-4(5H)-yl)-1,2-diphenylethylamine

\[
\text{C}_{31}\text{H}_{28}\text{NP}
\]

FW 445.53

696943-100MG 100 mg

\[
(\text{R}_{p})\text{-1-}(1\text{S})\text{-}(1\text{-Aminoethyl})\text{-2-(diphenylphosphino)ferrocene}
\]

\[
\text{C}_{24}\text{H}_{24}\text{FeNP}
\]

FW 413.27

697354-100MG 100 mg

Dichlorobis(2-(di-tert-butylphosphino)ethylamine)ruthenium(II), 95%

\[
\text{C}_{20}\text{H}_{48}\text{Cl}_{2}\text{N}_{2}\text{P}_{2}\text{Ru}
\]

FW 550.53

664979-250MG 250 mg

664979-1G 1g

Chlorodihydrido[bis(2-diisopropylphosphino)ethylamine]iridium(III), mixture of isomers, 97%

\[
\text{C}_{16}\text{H}_{39}\text{ClIrNP}_{2}
\]

FW 535.11

664995-250MG 250 mg

664995-1G 1g

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- Isolation/purification of enantiomers
- Resolution of metabolites
- Establishment of minimum detection limits
- LC-MS compatible methods for clinical, stability, or dissolution studies

Typical experiments in the optimization study include modifying buffer and pH, organic modifier type and strength, and column temperature.

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3. Extreme risk of explosion by shock, friction, fire or other sources of ignition
4. Forms very sensitive explosive metallic compounds
5. Heating may cause an explosion
6. Explosive with or without contact with air
7. May cause fire
8. Contact with combustible material may cause fire
9. Explosive when mixed with combustible material
10. Flammable
11. Highly flammable
12. Extremely flammable
13. Reacts violently with water
14. Contact with water liberates extremely flammable gases
15. Explosive when mixed with oxidizing substances
16. Spontaneously flammable in air
17. In use may form flammable explosive vapor-air mixture
18. May form explosive peroxides
19. Toxic to fauna
20. Toxic to flora
21. Harmful to aquatic organisms
22. Toxic to aquatic organisms
23. Very toxic to aquatic organisms
24. May cause cancer by inhalation
25. Danger of serious damage to health by prolonged exposure if swallowed
26. Toxic to eyes, respiratory system and skin
27. May cause sensitization by skin contact
28. May cause sensitization by inhalation
29. Risk of serious damage to eyes
30. Limited evidence of a carcinogenic effect
31. Risk of serious damage to eyes
32. May cause sensitization by skin contact
33. May cause sensitization by inhalation
34. May cause serious burns
35. Causes burns
36. Irritating to the eyes
37. Irritating to the respiratory system
38. Irritating to the skin
39. Danger of very serious irreversible effects
40. Limited evidence of a carcinogenic effect
41. Risk of serious damage to eyes
42. May cause sensitization by inhalation
43. May cause sensitization by skin contact
44. Risk of explosion if heated under confinement
45. May cause cancer
46. May cause heritable genetic damage
47. Danger of serious damage to health by prolonged exposure
48. May cause cancer by inhalation
49. Very toxic to aquatic organisms
50. Toxic to aquatic organisms
51. May cause long-term adverse effects in the aquatic environment
52. Hazardous to aquatic organisms
53. May cause long-term adverse effects in the aquatic environment
54. Toxic to flora
55. Toxic to fauna
56. Toxic to soil organisms
57. Toxic to bees
58. May cause long-term adverse effects in the environment
59. Dangerous to the ozone layer
60. May impair fertility
61. May cause harm to the unborn child
62. Possible risk of impaired fertility
63. Possible risk of harm to the unborn child
64. May cause harm to breast-fed babies
65. Harmful: may cause lung damage if swallowed
66. Repeated exposure may cause skin dryness or cracking
67. Vapors may cause drowsiness and dizziness
68. Possible risk of irreversible effects

COMBINATION OF PARTICULAR RISKS:
14/15: Reacts violently with water, liberating extremely flammable gases
15/29: Contact with water liberates toxic, extremely flammable gas
20/21/22: Harmful by inhalation and in contact with skin
20/22: Harmful by inhalation and if swallowed
21/22: Harmful in contact with skin and if swallowed
23/24/25: Toxic by inhalation, in contact with skin and if swallowed
23/25: Toxic by inhalation and if swallowed
24/25: Toxic in contact with skin and if swallowed
26/27: Very toxic by inhalation and in contact with skin
26/27/28: Very toxic by inhalation, in contact with skin and if swallowed
26/28: Very toxic by inhalation and if swallowed
27/28: Very toxic in contact with skin and if swallowed
30/37: Irritating to eyes and respiratory system
36/37/38: Irritating to eyes, respiratory system and skin
36/38: Irritating to eyes and skin
37/38: Irritating to respiratory system and skin
39/23/24: Toxic: danger of very serious irreversible effects through inhalation and in contact with skin
39/23/24/25: Toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed
39/23/25: Toxic: danger of very serious irreversible effects in contact with skin and if swallowed
39/24/25: Toxic: danger of very serious irreversible effects in contact with skin and if swallowed
39/26/27: Very toxic: danger of very serious irreversible effects through inhalation and in contact with skin
39/26/27/28: Very toxic: danger of very serious irreversible effects through inhalation, in contact with skin and if swallowed
39/26/28: Very toxic: danger of very serious irreversible effects through inhalation and if swallowed
39/27: Very toxic: danger of very serious irreversible effects in contact with skin
39/27/28: Very toxic: danger of very serious irreversible effects in contact with skin and if swallowed
39/28: Very toxic: danger of very serious irreversible effects in contact with skin and if swallowed
42/43: May cause sensitization by inhalation and skin contact
48/20/21: Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin
48/20/21/22: Harmful: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed
48/20/22: Harmful: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin
48/21/22: Harmful: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed
48/22: Harmful: danger of serious damage to health by prolonged exposure if swallowed
48/23: Toxic: danger of serious damage to health by prolonged exposure through inhalation
48/23/24/25: Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin
48/23/24: Toxic: danger of serious damage to health by prolonged exposure through inhalation and in contact with skin
48/23/25: Toxic: danger of serious damage to health by prolonged exposure through inhalation and if swallowed
48/24: Toxic: danger of serious damage to health by prolonged exposure in contact with skin
48/24/25: Toxic: danger of serious damage to health by prolonged exposure in contact with skin and if swallowed
48/25: Toxic: danger of serious damage to health by prolonged exposure if swallowed
Pictograms are based on widely accepted standards.
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