Partially Hydrogenated 1,1′-Binaphthyl as Ligand Scaffold in Metal-Catalyzed Asymmetric Synthesis

Terry T.-L. Au-Yeung, Shu-Sun Chan, Albert S. C. Chan*

Open Laboratory of Chirotechnology of the Institute of Molecular Technology for Drug Discovery and Synthesis and Department of Applied Biology and Chemical Technology, The Hong Kong Polytechnic University, Hong Kong, China
Fax: (+852)-2364 – 9932, email: bcachan@polyu.edu.hk

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Abstract: Although chiral binaphthyl-type ligands are already known to be effective over a broad spectrum of reactions, they sometimes fail in providing high enantioselectivities in some catalytic asymmetric reactions. This article summarizes recent attempts to elevate their performance by partly hydrogenating the naphthyl components of the binaphthyl. The synthetic routes to some of these ligands are briefly outlined. Positive results are observed in asymmetric hydrogenation, alkylation, borane reduction, epoxidation and hetero-Diels–Alder reactions. The function of the partially reduced binaphthyl skeleton, however, can sometimes be disadvantageous or ambiguous as illustrated in reactions such as asymmetric ring-closing metathesis, 1,4-conjugate addition, epoxidation, allylic alkylation, trimethylsilylcyanation, epoxide ring-opening and hydroformylation.

Keywords: alkylation; alkynylation; allylic alkylation; asymmetric catalysis; binaphthyl; borane reduction; conjugate addition; ene-type cyclization; epoxidation; epoxide ring-opening; hetero-Diels–Alder reaction; hydroformylation; hydrogenation; octahydrobinaphthyl; ring-closing metathesis; trimethylsilylcyanation

1 Introduction

One of the core research activities in the field of asymmetric catalysis is the ongoing development of new ligands to achieve higher levels of efficiency and selectivity to meet both increasingly demanding academic and industrial needs. To embark on any modern ligand synthesis, one has to select carefully the backbone and the chelating moieties, both of which must have a high degree of modularity *via* simple means to expedite ligand optimization. Ligands embodying the binaphthyl framework, such as BINAP and BINOL, have earned a prominent status as shown by their versatility in some catalytic asymmetric reactions over the last three decades.[1] In some other reactions, however, they are less effective in inducing superior enantioselectivities. One possible modification of the original binaphthyl-type ligands to enhance their performance is by partially hydrogenating their original skeleton; and, in fact, a rising number of inves-

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Terry Tin-Lok Au-Yeung was born in Hong Kong in 1973. He completed his undergraduate study in chemistry at the University of Western Australia in 1995. Working on the development of novel methodologies for the synthesis of *P*-chiral compounds, he earned a Ph. D. degree under the supervision of Prof. Richard K. Haynes at the Hong Kong University of Science and Technology. Since graduation in 2000, he joined the group of Prof. Albert S. C. Chan as a research associate at the Hong Kong Polytechnic University. His current research interests are in asymmetric catalysis and chiral supramolecular chemistry.

Shu-Sun Chan received his B. Sc. degree in chemical technology from the Hong Kong Polytechnic in 1994. He did his M. Phil. degree at the Hong Kong Polytechnic University of late under the supervision of Dr. M. C. K. Choi in catalytic asymmetric synthesis of acetophenone cyanohydrins under high pressure. He is currently a research assistant of Prof. Albert S. C. Chan's group.

Albert Chan received his B. Sc. from International Christian University in Tokyo, Japan in 1975 and his Ph. D. from the University of Chicago in 1979. He joined the Central Research Laboratories of Monsanto Company in 1979 and worked there for 13 years. In 1992–1993 he spent a year as a Visiting Expert at National Taiwan University and six months as Reader at the Hong Kong University of Science and Technology. In 1994 he took up his current position at the Hong Kong Polytechnic University as Chair Professor and Head of the Department of Applied Biology and Chemical Technology. In 2001 he was elected to the Membership of the Chinese Academy of Sciences. His research interests are in asymmetric synthesis and catalysis, chemistry related to life sciences, and the development of new pharmaceuticals based on Chinese herbal medicines.

tigations in recent years have rightly, but not always, justified this realization.

The partial hydrogenation of the naphthyl unit(s) in a binaphthyl compound results in the formation of the tetralin unit(s). The immediate effects are as follows.

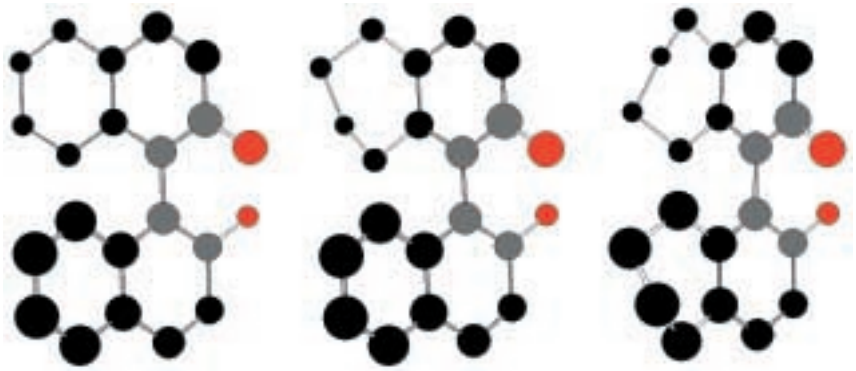
(1) The tetralin unit thus resulting becomes relatively more electron-rich than before.
(2) The tetralin unit is sterically bulkier than the naphthyl unit, and the combination of the former unit with itself or the latter unit to form the atropisomeric structure tends to create a larger dihedral angle as the degree of hydrogenation increases. As an illustration, (*R*)-1,1′-binaphthyl-2,2′-diol [**1**; (*R*)-BINOL] shows a smaller dihedral angle (-72.3°) than (*R*)-5,6,7,8-tetrahydro-1,1′-binaphthyl-2,2′-diol [**2**; (*R*)-H_4-BINOL] (-77.6°), which in turn shows a smaller dihedral angle than (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diol [**3**; (*R*)-H_8-BINOL] (-94.3°) (Figure 1). This trend is expected to apply also in cases where the 2,2′-positions are occupied by other substituents.
(3) When *pi*-electron-releasing groups are present at the 2,2′-positions of the H_8-binaphthyl, specifically regioselective activation at the 3,3′-positions is generally observed (*vide infra*).
(4) Binaphthyls comprised of the more non-polar tetralin unit(s) should be more easily solubilized in organic solvents.

This review attempts to survey the use of partially hydrogenated chiral binaphthyl ligands in metal-catalyzed asymmetric synthesis, focusing on their comparison with their parent binaphthyl analogues. Results in which direct comparison is not possible, due to difficult access to the analogous binaphthyl ligands, are also discussed.

2 Synthesis of Partially Hydrogenated Chiral 1,1′-Binaphthyl Compounds

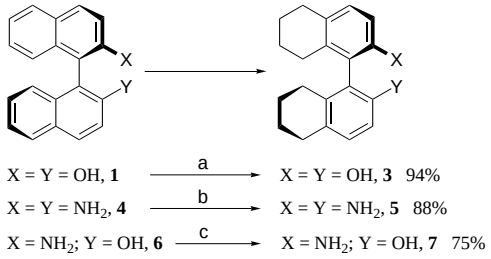
2.1 Synthesis of the Basic Skeletons

Cram et al. first successfully synthesized (*R*)-H_8-BINOL **3** in 94% yield by partial PtO_2-catalyzed hydrogenation of (*R*)-BINOL **1** in acetic acid under mild conditions (Scheme 1).[2] Chan et al. showed that the same methodology could also be applied in the synthesis of (*R*)-2,2′-diamino-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl **5**, (*R*)-H_8-BINAM (Scheme 1).[3] Recently, Ding and coworkers successfully reduced 2-amino-2′-hydroxy-1,1′-binaphthyl **6** (NOBIN) to the corresponding H_8-analogue (H_8-NOBIN **7**) with Raney Ni-Al alloy catalyst in dilute aqueous alkaline solution (Scheme 1).[4] The same research group also discovered the preparation of (*R*)-H_4-BINOL **2** by partial reduction of the *O*,*O*′-diMOM

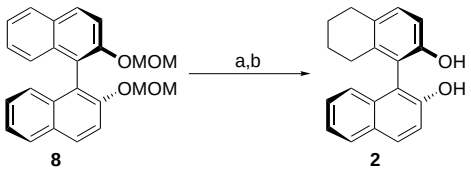


(*R*)-BINOL **1** dihedral angle = – 72.3° | (*R*)-H_4-BINOL **2** dihedral angle = – 77.6° | (*R*)-H_8-BINOL **3** dihedral angle = – 94.3°

Figure 1. Molecular structures of (*R*)-1,1′-binaphthyl-2,2′-diol [(*R*)-**1**], (*R*)-5,6,7,8-tetrahydro-1,1′-binaphthyl-2,2′-diol [(*R*)-**2**] and (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl-2,2′-diol [(*R*)-**3**]. The hydrogen atoms are omitted for the purpose of clarity. The dihedral angles of the axial biaryl groups were estimated by ChemDraw 3D calculations (MM2). (The minus sign is arbitrarily given by the program.)



Scheme 1. Synthesis of (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyls: a) PtO_2, AcOH, 3 atm H_2, 25 °C, 7 d; b) PtO_2, AcOH/H_2O, 3 atm H_2, 50 °C, 24 h; c) Raney Ni-Al alloy, *i*-PrOH/H_2O, NaOH, 90 °C, 7 h.



Scheme 2. Synthesis of (*R*)-5,6,7,8-tetrahydro-1,1′-binaphthyl-2,2′-diol **2**: a) Raney Ni-Al alloy, *i*-PrOH/H_2O, NaOH, 80 °C, 7 h; b) HCl, MeOH.

protected (*R*)-1,1′-bi-2-naphthol **8** using a similar method, and the hydroxy functionalities were recovered by an acidic work-up (Scheme 2).[5] In all the above reactions, racemization of the binaphthyls was found not to take place.

2.2 Synthesis of H_8-Binaphthyl Ligands

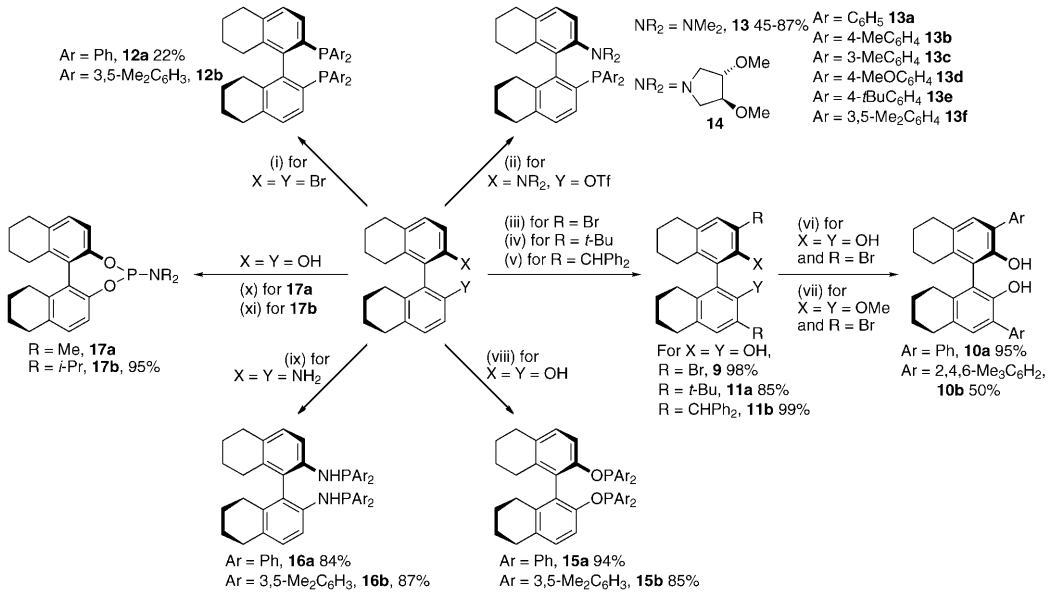
2.2.1 Synthesis of H_8-BINOL Derivatives

The above partially hydrogenated compounds either serve as ligands in their own right or as precursors for further elaborations by straightforward organic transformations. Special mention, however, should be given to **3**. It is particularly worth noting that electrophilic aromatic substitutions occur exclusively at the 3,3′-positions in this compound. For example, treatment of **3** with Br_2 at – 30 °C introduces the bromine atoms exclusively at the 3,3′-positions (Scheme 3, **9**);[2] whereas when **1** is treated with bromine, the bromine atoms end up at the distant 6,6′-positions. (A lengthier synthetic route is necessary to gain access to 3,3′-disubstituted-BINOL.) Aromatic substituents could be introduced at 3,3′-positions by further manipulating **9** or its dimethoxy derivative through the key step of a Pd-catalyzed Suzuki reaction or Ni-catalyzed coupling with boronic acids or Grignard reagents, respectively, to give compounds such as **10**.[6,51c]

In the same vein, acid-catalyzed Friedel–Crafts alkylations take place at the 3,3′-positions of **3** to furnish products such as **11**[51b,51c] (Scheme 3) whose binaphthyl analogues, again, are otherwise unobtainable by simple means. (Note, however, that **11a** was purified and isolated as its dipotassium dialkoxide after treatment with 2 equivalents of potassium hydride.) This unique chemical property renders **3** an additional ease of modularity at places in the vicinity of the reaction site.

2.2.2 Synthesis of Phosphorus Ligands

Phosphinyl groups are attached to the H_8-binaphthyl scaffold in a similar fashion as for the preparations of their binaphthyl analogues (Scheme 3). Thus, Takaya et al.[7] and Sayo et al.[8] showed that the synthesis of H_8-BINAP **12a** and H_8-DM-BINAP **12b** could be accomplished by generating the Grignard reagent at the 2,2′-positions from racemic 2,2′-dibromo-5,5,6,6′,7,7′,8,8′-



Scheme 3. Synthesis of (*R*)-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-binaphthyl ligands: (i) a. Mg, THF/$PhCH_3$, b. $Ph_2P(O)Cl$, c. resolution with (+)- or (−)-DBTA, d. $HSiCl_3$, TEA, xylene; (ii) a. $Pd(OAc)_2$, dppp, $(i\text{-}Pr)_2NEt$, $Ar_2P(O)H$. DMSO, 100 °C, b. $CeCl_3$-$LiAlH_4$, THF, 40 °C; or $HSiCl_3$, TEA, xylene; (iii) Br_2, CH_2Cl_2, −30 °C; (iv) 1 atm isobutylene, 9:1 AcOH:H_2SO_4, 70 °C; (v) Ph_2CHCl, TsOH, $ClCH_2CH_2Cl$, 65 °C; (vi) $Pd(PPh_3)_4$, K_2CO_3, $PhB(OH)_2$, $PhCH_3/H_2O$; (vii) a. *t*-BuLi, Et_2O, −78 °C, b. I_2, c. MesMgBr, $(PPh_3)_2NiCl_2$, ether, reflux, d. BBr_3, CH_2Cl_2, 0 °C; (viii) TEA, DMAP (cat.), Ar_2PCl, Et_2O, room temp.; (ix) a. *n*-BuLi, THF, −30 °C, b. Ar_2PCl, −30 °C; (x) $P(NMe_2)_3$, $PhCH_3$, reflux; (xi) a. PCl_3, TEA, $PhCH_3$, −60 °C, b. LDA, −40 °C to room temp.

octahydro-1,1′-binaphthyl, followed by the treatment with diarylphosphinoyl chloride. Subsequent resolution with (+)- or (−)-*O*,*O*′-dibenzoyltartaric acid and reduction afforded the diphosphines **12** (Scheme 3).

A series of P,N-ligands (H_8-MAP **13**[9] and **14**[10]) has been prepared by Ding et al. The overall route is characterized by the $Pd(OAc)_2$/dppp [dppp = 1,3-bis(diphenylphosphino)propane] promoted coupling of the *O*-triflate of 2-amino-2′-hydroxy-1,1′-5,5′,6,6′,7,7′,8,8′-octahydrobinaphthyl derivative with diarylphosphine oxide. The resulted triarylphosphine oxides were eventually reduced either with $CeCl_3$-$LiAlH_4$ or $HSiCl_3$ to provide the phosphine-amine ligands.

Chan and coworkers synthesized bis(diarylphosphinites) **15** and bis(diarylphosphinamidites) **16** by reacting **3** and **5**, respectively, with diarylphosphine chloride in the presence of an organic base (Scheme 3).[3,11]

Following the protocol of Feringa et al.,[12] Jiang et al. synthesized a monodentate phosphorus ligand, (*R*)-H_8-Monophos **17a**, by treating hexamethylphosphorus triamide with (*R*)-**3** in refluxing toluene.[13] Feringa et al.[14] also provided the inspiration for the synthesis of **17b** by Chan and coworkers[15] in a reaction whereby chlorophosphite of (*S*)-**3** was treated with LDA.

All the analogous chiral phosphorus-containing binaphthyl ligands could be synthesized using the aforementioned methodologies.

3 Asymmetric Hydrogenation

Asymmetric hydrogenation has become an indispensable tool in providing chiral drugs, feed stocks, agrochemicals, health supplements, intermediates and materials. It is also the most studied reaction in relation to our current discussion.

3.1 Hydrogenation of Ketones

The earliest application of H_8-binaphthyl-type ligand was in the area of asymmetric hydrogenation. Takaya et al. first prepared an iridium catalyst **18** (Figure 2) for the asymmetric hydrogenation of 1,2-benzocycloalkanones and β-thiacycloalkanones in the co-presence of a mixed P,N-donor ligand, bis[*o*-(*N*,*N*-dimethylamino)phenyl]-phenylphosphine **20**.[16] According to the authors, hydrogenation using (*R*)-**18** − **20** led to higher conversions and ees than (*R*)-**19-20** for ketonic substrates **21a – f, i** and **22** whilst both systems gave comparable results for ketones **21 g, h** (83 – 84% ee) (Table 1). Catalyst (*R*)-**19-20** was more suitable for ketones **23** whose product [(*R*)-**24a**] is an important synthetic intermediate for β-lactam antibacterials.[17] The same catalytic system was also employed in the hydrogenation of acyclic ketone **25**.[18] However, catalyst (*R*)-**19-20** was only marginally better (1%) than (*R*)-**18-20**, yet, at the expense of reaction time and yield.

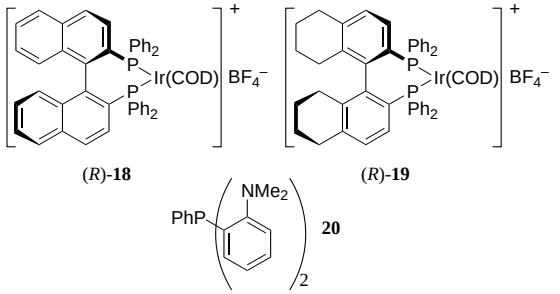


Figure 2. Iridium complexes (*R*)-**18**, (*R*)-**19** and P,N-donor ligand **20**.

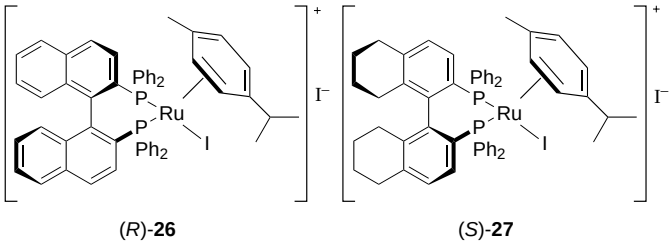
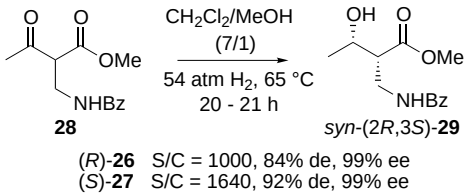


Figure 3. Ru complexes (*R*)-**26** and (*S*)-**27**.



Scheme 4. Hydrogenation of (±)-**28** via dynamic kinetic resolution.

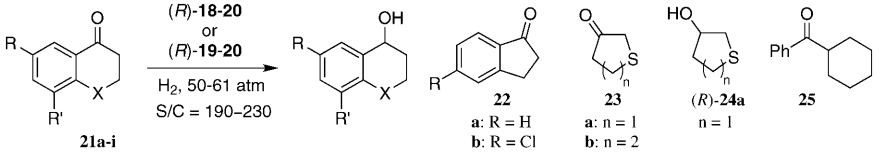
Takaya et al. later synthesized cationic Rh(I) complexes (*R*)-**26** and (*S*)-**27** and these complexes were used in the stereoselective hydrogenation of racemic methyl 2-(benzamidomethyl)-3-oxobutanoate (±)-**28** *via* dynamic kinetic resolution (Scheme 4).[7] Up to 92% de and 99% ee have been obtained. In a side-by-side comparison, the use of (*S*)-**27** was found to apply well even in non-purified commercial solvents and exhibit superior or favorably comparable selectivity than complex (*R*)-**26** which, in contrast, must be used in dried, distilled solvents.

Optically active pantolactone was prepared by asymmetric hydrogenation of ketopantolactone in the presence of $Ru_2Cl_4(L^*)_2(NEt_3)$, (1*S*,2*S*)-diphenylethylenediamine and potassium hydroxide in a mixture of 2-propanol and THF under 50 atm hydrogen at 50 °C for 20 h. The best results, 77% conversion and 92% ee, were obtained by using (*S*)-DM-H_8-BINAP **12b** (Scheme 5).[8]

3.2 Hydrogenation of α,β-Unsaturated Carboxylic Acids

Takaya et al. demonstrated that $Ru(OAc)_2(H_8$-BINAP) **32** was a more effective catalyst than the BINAP analogue **31** in the asymmetric hydrogenation of a

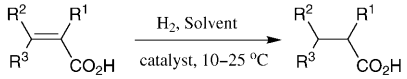
Table 1. Asymmetric hydrogenation of cyclic and acyclic ketones catalyzed by (*R*)-**18-20** and (*R*)-**19-20** systems.



Substrate	X	R	R′	Catalyst	Solvent[a]	Temp. [°C]	Time [h]	Yield [%]	ee [%]	Config.	Ref.
21a	CH_2	H	H	(*R*)-**18-20**	A	90	75	88	95	(*R*)-(−)	[16]
21b	CH_2	OMe	H	(*R*)-**18-20**	A	90	69	74	95	(−)	[16]
21c	CH_2	Me	Me	(*R*)-**18-20**	A	90	60	78	95 (100)[b]	(−)	[16]
21d	CH_2	NO_2	H	(*R*)-**18-20**	A	90	68	64	94	(−)	[16]
21e	O	H	H	(*R*)-**18-20**	B	90	64	89	93 (>99)[b]	(*R*)-(+)	[16]
21f	O	F	H	(*R*)-**18-20**	B	90	68	77	92 (100)[b]	(+)	[16]
21 g	O	Cl	H	(*S*)-**18-20**	B	90	68	91	84 (96)[b]	(−)	[16]
21h	S	H	H	(*S*)-**18-20**	B	90	40	87	84 (100)[b]	(*S*)-(−)	[16]
21i	S	Cl	H	(*R*)-**18-20**	B	90	68	91	87 (100)[b]	(+)	[16]
22a	–	–	–	(*S*)-**18-20**	B	90	22	72	86	(*S*)-(+)	[16]
22b	–	–	–	(*R*)-**18-20**	B	90	40	81	84 (100)[b]	(−)	[16]
23a	–	–	–	(*R*)-**19-20**	A	90	13	87	75	(*R*)-(+)	[16]
23b	–	–	–	(*S*)-**19-20**	A	90	13	94	70	(*S*)-(−)	[16]
25	–	–	–	(*S*)-**18-20**	A	120	74	74	76	(*R*)-(+)	[18]
25	–	–	–	(*S*)-**19-20**	A	90	166	27	80	(*R*)-(+)	]18]

[a] A = Dioxane-MeOH (5:1) as solvent; B = THF-MeOH (5:1) as solvent.
[b] Values in parentheses were obtained after one to two recrystallizations of the alcoholic products.

Table 2. Asymmetric hydrogenation of α,β-unsaturated carboxylic acids catalyzed by BINAP- and H_8-BINAP-Ru(II) complexes.



Ru(OAc)$_2$[(*R*)-BINAP] (*R*)-**31**
Ru(OAc)$_2$[(*S*)-H$_8$-BINAP] (*S*)-**32**

Entry	R^1	R^2	R^3	Catalyst	S/C	Solvent	pH_2 [atm]	Time [h]	Conv. [%]	Yield [%]	ee [%]	Ref.
1	Me	Me	H	(*R*)-**31**	160	MeOH	4.0	12	100	85	92 (*R*)	[19a]
2	Me	Me	H	(*S*)-**32**	200	MeOH	1.5	20	100	85	97 (*S*)	[19c]
3	Me	Et	H	(*R*)-**31**	220	MeOH	1.5	24	75	69	84 (*R*)	[19c]
4	Me	Et	H	(*S*)-**32**	213	MeOH	1.5	24	100	89	96 (*S*)	[19c]
5	Me	*n*-Pr	H	(*R*)-**31**	1000	[a, b]	4.0	4	100	86	82 (*R*)	[19b]
6	Me	*n*-Pr	H	(*S*)-**32**	209	[a, b]	4.0	3	100	83	94 (*S*)	[19b]
7	Et	*n*-Pr	H	(*R*)-**31**	203	MeOH	1.5	37	100	95	88 (*R*)	[19c]
8	Et	*n*-Pr	H	(*S*)-**32**	197	MeOH	1.5	20	100	80	95 (*S*)	[19c]
9	Me	Ph	H	(*R*)-**31**	200	MeOH	1.5	48	30	29	30 (*R*)	[19c]
10	Me	Ph	H	(*S*)-**32**	200	MeOH	1.5	48	95	87	89 (*S*)	[19c]
11	H	CF_3	Me	(*R*)-**31**	207	MeOH	100	8	100	83	75 (+)	[19b]
12	H	CF_3	Me	(*S*)-**32**	200	MeOH	100	8	100	86	93 (−)	[19b]
13	H	Ph	Me	(*R*)-**31**	200	MeOH	100	7	89	–	27 (*R*)	[19c]
14	H	Ph	Me	(*S*)-**32**	200	MeOH	100	7	100	90	70 (*S*)	[19c]
15	H	Me	Ph	(*R*)-**31**	200	MeOH	4.0	25	100	98	92 (*S*)	[19c]
16	H	Me	Ph	(*S*)-**32**	200	MeOH	4.0	25	100	93	92 (*R*)	[19c]
17	Me	Me	Me	(*R*)-**31**	600	THF	100	44	100	–	82 (*R*)	[19c]
18	Me	Me	Me	(*S*)-**32**	600	THF	100	3	100	95	88 (*S*)	[19c]
19	Me	Ph	Me	(*R*)-**31**	200	THF	100	19	50	–	53[d]	[19c]
20	Me	Ph	Me	(*S*)-**32**	200	THF	100	18	100	–	58[e]	[19c]
21	Me	Me	H	(*R*)-**31**	150	$scCO_2$[a, c]	33	15	–	50	37 (*R*)	[20]
22	Me	Me	H	(*S*)-**32**	150	$scCO_2$[a, c]	33	15	–	99	81 (*S*)	[20]

[a] Reaction performed at 50 °C.
[b] Solvent system was MeOH-H_2O (10:1).
[c] Reaction performed in supercritical carbon dioxide.
[d] ee for the diastereomer (2*R*,3*R*).
[e] ee for the diastereomer (2*S*,3*S*).

variety of unsaturated carboxylic acids, free from any other ancillary chelating group, in methanol (Table 2, entries 1–20).[19] Gratifying result has been obtained for tiglic acid in 97% ee and 85% yield (entries 1 and 2). Furthermore, the non-steriodal anti-inflammatory (NSAI) drug (*S*)-ibuprofen **34** was produced in as high as 97% ee by the catalytic use of **32**, comparable with the use of **31** (Scheme 6).

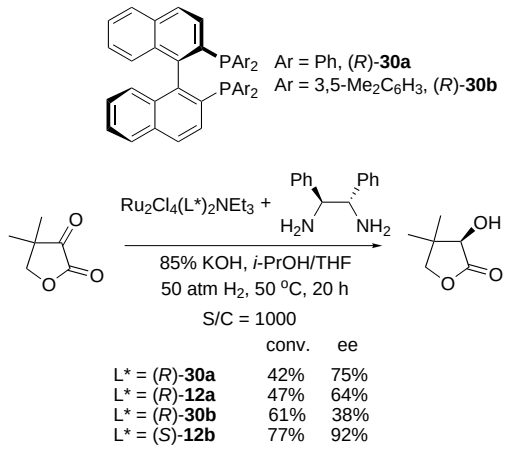
Noyori et al. reported the asymmetric hydrogenation of tiglic acid in supercritical carbon dioxide catalyzed by (*R*)-**31** and (*S*)-**32** complexes.[20] The corresponding adduct was obtained in 99% yield and 89% ee in the presence of $CF_3(CF_2)_6CH_2OH$ under 5 atm of H_2 (Table 2, entries 21 and 22).

Among all the ligands examined by Hiyama et al. under identical conditions,[21] (*S*)-**32** displayed the highest activity and enantioselectivity for the reduction of benzazepine precursor (*E*)-**35** to **36**, a useful building block for non-peptide vasopressin receptor antagonists and agonists (Scheme 6).[22] Further, (*S*)-**32** was able to convert a mixture of the (*E*)-, (*Z*)- and *endo*-isomers of **35** to **36** in 76% ee. The latter can be readily recrystallized from MeOH to its enantiopure form and is now commercially produced on a 40 kg scale.[21]

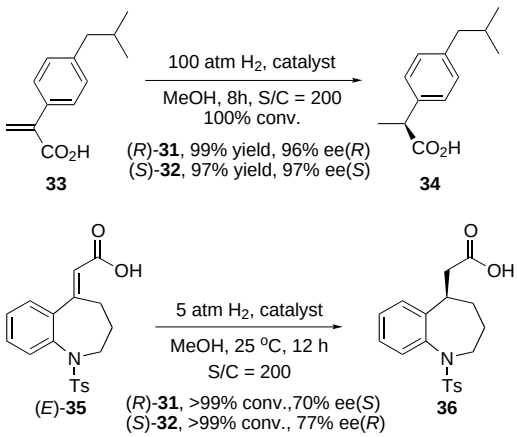
3.3 Hydrogenation of C=C Bonds with Allylic Functional Groups

Besides α,β-unsaturated systems, **31** and **32** have also been employed in the hydrogenation of β,γ-unsaturated carboxylic acids. Again, **32** proved to be better than **31** in terms of both ee and rate of reaction (Scheme 7, Equation 1).[19b]

Ru-catalysts **31** and **32**, were found to be equally enantioselective in the asymmetric hydrogenation of geraniol. Nonetheless, the catalyst loading required for **32** was ten times less than that required for **31** (Scheme 7, Equation 2).[7]



Scheme 5. Asymmetric hydrogenation of ketopantolactone.



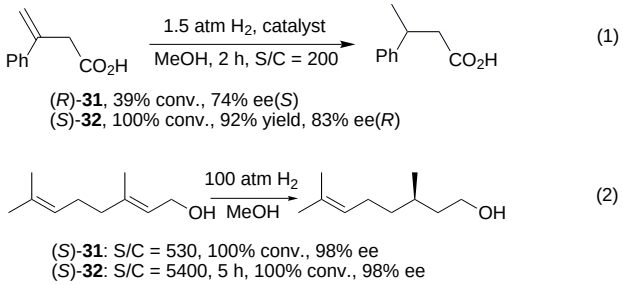
Scheme 6. Synthesis of some pharmaceutically important carboxylic acids by asymmetric hydrogenation.

Although an X-ray structural comparison between **31** and **32** is not available from the literature, the structures from the **30a**- and **12a**-Rh(I) complexes could be used as models. The P-M-P natural bite angles for [(*S*)-**30a**-Rh(NBD)]ClO_4,[23] $Ru(OAc)_2$[(*S*)-**30a**][24] and [(*S*)-**12a**-Rh(COD)]ClO_4 are 91.8°, 90.6° and 90.6°, respectively. As one can see, the bite angles do not differ much when **30a** or **12a** coordinates to either Rh or Ru; and thus, the change of bite angle cannot account for the difference in the stereochemical outcome. The dihedral angles between the naphthalene rings of **30a** in a number of [(*S*)-**30a**-Rh(diene)]X complexes fall in the range of 71.0–75.5°[25] as opposed to the dihedral angle between the two tetralin units found for **12a** in [(*S*)-**12a**-Rh(COD)]-ClO_4 (80.3°),[7] a significant variation. In turn, an increase in the dihedral angle of the axial biaryl groups on going from **30a**- to **12a**-Ru(II) or -Rh(I) complexes could be anticipated. Therefore, enantioselectivity appears to be more of a function of dihedral angle.

In addition, since the alicyclic moiety of the tetralin unit is rather remote from the site of reaction (i.e., the metal center), its direct effect on the stereoselectivity should be negligible. Rather, it is believed that the tetralin indirectly exerts an influence on the orientations or dispositions of the phenyl groups on the phosphorus, and hence the stereochemical course of the reaction.

3.4 Hydrogenation of α-Dehydroamino Acids and Their Derivatives

Phosphinamidites and phosphinities are attractive ligands because they are relatively easy to prepare and a huge multitude of chiral diols or amines can serve as the scaffold. Chan et al.[11a] showed that binaphthyl- or H_8-binaphthyl-based phosphinamidites and phosphinites are very effective in the synthesis of α-amino acids *via* enantioselective hydrogenation. Under the optimal conditions and regardless of the (*Z*)-acetamido-3-aryl-

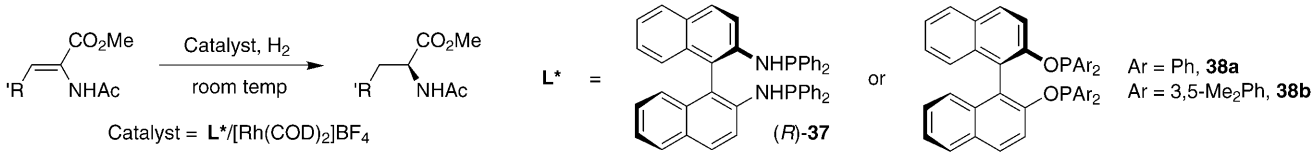


Scheme 7. Hydrogenation of C=C bonds with allylic functional groups.

acrylic esters, when either the diphosphinite **15a** or the diphosphinamidite **16a** containing the diphenylphosphinyl groups was used, the H_8-binaphthyl analogues always performed better than the corresponding binaphthyl ligands **37** or **38** (Table 3). When the PPh_2 groups were replaced with $P(3,5\text{-}Me_2C_6H_3)_2$ groups (ligand **15b**), sharp increases in ees were further observed.[11b, c] For example, **15b** (97% ee) outperformed **15a** (81% ee) by a substantial margin in the hydrogenation of methyl acetamidoacrylic ester. In all instances, irrespective of the diarylphosphinyl moiety, H_8-binaphthyl-based ligands always excel their parent compounds. The same trend was noticed for the hydrogenation of (*Z*)-acetamido-3-arylacrylic acids (Table 4).

Feringa and coworkers were among the recent chemists to redress the usefulness of monodentate phosphorus ligands as effective auxiliaries by showing (*S*)-Monophos **39** to be effective in the asymmetric hydrogenation of substrates bearing prochiral carbon-carbon double bonds.[27] Jiang et al. later synthesized a stable and easily prepared phosphoramidite analogue, (*R*)-H_8-MonoPhos **17a**, and higher than 99.9% ee was obtained when **17a** was applied in the rhodium-catalyzed hydrogenation of α-dehydroamino acids and their derivatives.[13] Ligand **17a** was equally competent as

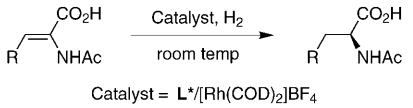
Table 3. Enantioselective hydrogenation of α-dehydroamino acid α-derivatives by **L***/[Rh(COD)$_2$]BF$_4$.[a]



L*	R′, ee [%]										Ref.
	Ph	*p*-MeOC$_6$H$_4$	*p*-MeC$_6$H$_4$	*p*-AcOC$_6$H$_4$	*o*-ClC$_6$H$_4$	*m*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	*p*-NO$_2$C$_6$H$_4$	2-furanyl	H	
38a	64[b], 76[c, d, e]					55[f]				76[c]	[11a], [26]
15a	84		84		85	78	81		64	81[g]	[11a]
38b	92	91	92	90	90		91	89	89	94	[11c]
15b	94	94	94	93	93		93	91	92	97	[11c]
37	90		90		90	90	88			93	[11a]
16a	96	93	94		97	94	94	91	91	97	[11a]

[a] 100% conversion unless otherwise stated.
[b] 86% conversion.
[c] **L***/[Rh(COD)Cl]$_2$ in a 1:1 mixture of acetone and toluene at 0 °C; see Ref.[26]
[d] Hydrogenation of (*E*)-acetamido-3-arylacrylic esters.
[e] 41% conversion.
[f] 70% conversion.
[g] 49% conversion.

Table 4. Enantioselective hydrogenation of α-dehydroamino acid derivatives by **L***/[Rh(COD)$_2$]BF$_4$.[a]

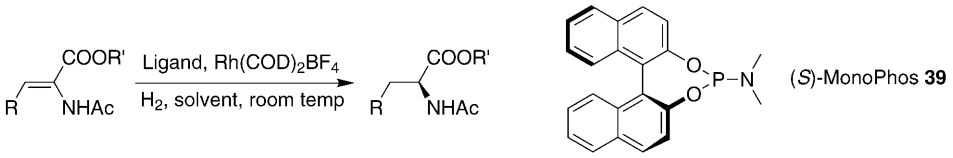


L*	R, ee [%]						Ref.
	Ph	*m*-MeOC$_6$H$_4$	*o*-ClC$_6$H$_4$	*m*-ClC$_6$H$_4$	*p*-ClC$_6$H$_4$	H	
38a	18[b], 9[c, d, e]			11[f]		6[e, g]	[11a], [26]
15a	74[h]			37[i]			[11a]
38b						86	[11c]
15b						90	[11c]
37	90		90	88	86	94	[11a]
16a	94	93	94	93	93	99	[11a]

[a] 100% conversion unless otherwise stated.
[b] 71% conversion.
[c] **L***/[Rh(COD)Cl]$_2$ in toluene with 50% conversion.
[d] Hydrogenation of (*E*)-acetamido-3-arylacrylic esters, see Ref.[26]
[e] Ref.[26]
[f] 56% conversion.
[g] **L***/[Rh(COD)Cl]$_2$ in a 1:1 mixture of acetone and toluene at 0 °C.
[h] 82% conversion.
[i] 88% conversion.

compared to the parent ligand **39** in most solvents to provide comparable ees (Table 5). Moreover, there was little difference between them in the rate of hydrogenation under similar conditions.[27d] In one exceptional instance, unlike the Rh(I)/(*S*)-**39** complex (entry 5), Rh(I)/(*R*)-**17a** was solubilized quite comfortably by

Table 5. Asymmetric hydrogenation of α-dehydroamino acid derivatives by MonoPhos **39**- and H_8-MonoPhos **17a**-containing Rh-complexes.



Entry	R	R′	Ligand	S/C	pH_2 [bar]	Time [h]	Solvent	Conv. [%]	ee [%]	Ref.
1	Ph	Me	(*S*)-**39**	20	1	20	CH_2Cl_2	100	95.0	[27a]
2	Ph	Me	(*S*)-**39**	200	5	0.67	CH_2Cl_2	100	95.0	[27a, b]
3	Ph	Me	(*R*)-**17a**	100	5	0.15	CH_2Cl_2	100	98.0	[27b]
4	Ph	Me	(*R*)-**17a**	100	20	0.5	CH_2Cl_2	99.3	94.4	[13]
5	Ph	Me	(*S*)-**39**	20	1	20	$PhCH_3$	[a]	93.0	[27a]
6	Ph	Me	(*R*)-**17a**	100	20	2	$PhCH_3$	99.1	94.9	[13]
7	Ph	Me	(*S*)-**39**	20	1	20	$ClCH_2CH_2Cl$	100	89.0	[27a]
8	Ph	Me	(*R*)-**17a**	100	20	0.5	$ClCH_2CH_2Cl$	99.7	95.0	[13]
9	Ph	Me	(*S*)-**39**	20	1	20	THF	100	93.0	[27a]
10	Ph	Me	(*R*)-**17a**	100	20	0.5	THF	90.2	94.2	[13]
11	Ph	Me	(*S*)-**39**	20	1	20	EtOAc	100	93.0	[27a]
12	Ph	Me	(*R*)-**17a**	100	20	0.5	EtOAc	96.9	95.7	[13]
13	Ph	Me	(*S*)-**39**	20	1	20	acetone	100	92.0	[27a]
14	Ph	Me	(*R*)-**17a**	100	20	1	acetone	99.3	95.4	[13]
15	H	Me	(*S*)-**39**	20	1	20	CH_2Cl_2	100	99.0	[27a]
16	H	Me	(*S*)-**39**	20	1	20	EtOAc	100	99.6	[27a]
17	H	Me	(*S*)-**39**	200	5	0.167	EtOAc	100	97.0	[27a]
18	H	Me	(*R*)-**17a**	100	20	0.5	acetone	99.9	99.9	[13]
19	H	Me	(*R*)-**17a**	500	20	8	acetone	99.9	99.9	[13]

[a] Slow and incomplete reaction due to poor solubility of the Rh(I)/(*S*)-**39** complex.

toluene and gave almost quantitative conversion in a comparatively shorter period of time (entry 6).

3.5 Hydrogenation of Enamides

Chan and coworkers introduced a chiral bisphosphinamidite **16a** for the Rh(I)-catalyzed hydrogenation of enamides which gave amine derivatives of up to 99% ee.[3] The results are shown in Table 6. The hydrogenation of the enamide (Ar = Ph) with a Rh catalyst containing (*R*)-**16a** gave an excellent ee value (97% ee) for the product and the reaction was complete within 30 min (entry 2). Only 93% ee was obtained with the Rh catalyst containing (*R*)-BDPAB **37** under the same reaction conditions (entry 1). It was clearly observed that the enantioselectivities of the hydrogenation catalyzed by Rh-(*R*)-**16a** were consistently higher than those from the same reaction with Rh-(*R*)-**37** (entries 5 – 12).

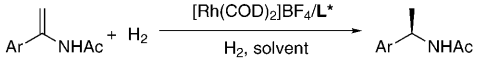
In an alternative study, again, monodentate phosphoramidite **17a** conveyed better chiral information than **39** in this same hydrogenation reaction (entry 4 *vs.* 3). It was argued that the result was attributed to the larger biaryl torsional angle of **17a** carving out a more efficient stereodifferentiating space around the Rh atom.[28]

4 Alkylation of Prochiral Carbonyl Compounds

4.1 Diethylzinc Additions to Aldehydes

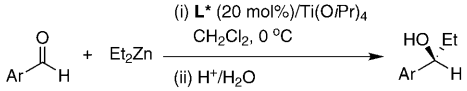
The addition of dialkylzinc or diarylzinc reagents to prochiral carbonyl compounds is an important C-C bond forming reaction to furnish a great variety of chiral secondary or tertiary alcohols or amines.[29] Seebach et al. were the first to have developed a diol/Ti catalytic system to bring about such carbonyl additions.[30] Chan et al., Nakai et al. and Ding et al. capitalized on this finding and showed that **1**,[31,32] **2**[5] and **3**[33] in combination with Ti(O-*i*-Pr)$_4$ were all capable of producing high yields and high ees in the diethylzinc addition to aldehydes in dichloromethane at 0 °C; although a 7:1 Ti:diol and an excess of Et_2Zn had to be used under the optimal conditions. Among these ligands, **3** was the most effective chiral inducer, affording up to 98% ee and 100% conversion.

Table 6. Asymmetric hydrogenation of enamides catalyzed by L*/[Rh(COD)$_2$]BF$_4$.



Entry	Ar	L*	S/C	pH_2 [atm]	Time [h]	Solvent	Conv. [%]	ee [%]	Ref.
1	Ph	(*R*)-**37**	200	1	0.5	THF	100	93	[3]
2		(*R*)-**16a**	200	1	0.5	THF	100	97	[3]
3		(*S*)-**39**	100	10	12	toluene	100	93	[28]
4		(*S*)-**17a**	100	10	12	toluene	100	96	[28]
5	*p*-$CF_3C_6H_4$	(*R*)-**37**	200	1	0.5	THF	100	95	[3]
6		(*R*)-**16a**	200	1	0.5	THF	100	99	[3]
7	*p*-MeC_6H_4	(*R*)-**37**	200	1	0.5	THF	98	95	[3]
8		(*R*)-**16a**	200	1	0.5	THF	100	97	[3]
9	*p*-ClC_6H_4	(*R*)-**37**	200	1	0.5	THF	100	95	[3]
10		(*R*)-**16a**	200	1	0.5	THF	100	97	[3]
11	*p*-FC_6H_4	(*R*)-**37**	200	1	0.5	THF	86	90	[3]
12		(*R*)-**16a**	200	1	0.5	THF	100	96	[3]
13	*m*-MeC_6H_4	(*R*)-**37**	200	1	0.5	THF	93	95	[3]
14		(*R*)-**16a**	200	1	0.5	THF	100	98	[3]
15	2-furanyl	(*R*)-**37**	200	1	0.5	THF	100	96	[3]
16		(*R*)-**16a**	200	1	0.5	THF	100	98	[3]

Table 7. The effect of ligands (*S*)-**1**, (*R*)-**2** and (*S*)-**3** on the addition of diethylzinc to arylaldehydes.



Ar	L*[a]	Conv. [%]	Yield [%]	ee [%]	Ref.
Ph	(*S*)-**1**	100	–	92/87	[31]/[5]
	(*R*)-**2**	–	96	91	[5]
	(*S*)-**3**	100	–	98/93	[33]/[5]
m-$MeOC_6H_4$	(*S*)-**1**	100	–	94/81	[31]/[5]
	(*R*)-**2**	–	95	88	[5]
	(*S*)-**3**	100	–	96	[33]
p-ClC_6H_4	(*S*)-**1**	86	–	88/84	[31]/[5]
	(*R*)-**2**	–	96	91	[5]
	(*S*)-**3**	89	–	97	[33]
p-$MeOC_6H_4$	(*S*)-**1**	100	–	79/81	[31]/[5]
	(*R*)-**2**	–	95	90	[5]
	(*S*)-**3**	99	–	97	[33]
α-naphthyl	(*S*)-**1**	100	–	94/88	[31]/[5]
	(*R*)-**2**	–	97	93	[5]
	(*S*)-**3**	100	–	98	[33]
β-naphthyl	(*S*)-**1**	100	–	81/55	[31]/[5]
	(*R*)-**2**	–	92	75	[5]
	(*S*)-**3**	100	–	95	[33]

[a] Ti(O-*i*-Pr)$_4$:L* = 7:1.

4.2 Alkylation of Aldehydes with Trialkylaluminum

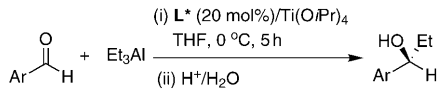
An alternative route to the ethylation of aldehydes has been introduced by Chan and coworkers by reacting the economically prepared triethylaluminum with an aldehyde in the presence of Ti complexes formed *in situ* between Ti(O-*i*-Pr)$_4$ and (*R*)-**1** or (*S*)-**3**.[34] A wide range of arylaldehydes was smoothly alkylated, and the results are illustrated in Table 8. For the (*R*)-**1**/Ti(O-*i*-Pr)$_4$ system, the enantioselectivity is sensitive to changes of the steric and electronic properties of the substituted benzaldehyde. But, for the (*S*)-**3**/Ti(O-*i*-Pr)$_4$ system, the substituent effect is less significant, partly because the ee values were already quite high. Not only did (*S*)-**3** confer stereochemical information more efficiently than (*R*)-**1**, higher selectivity was also observed. Unfortunately, switching the alkylating reagent to trimethylaluminum led to the desired products in disappointingly poor ees even though the chemical yields were still excellent.

4.3 Alkynylation

Propargylic compounds enjoy extensive applications in chemical synthesis and materials science.[35] In spite of their importance, it is surprising that the development of catalytic asymmetric alkynylation of aldehydes,[36] aldimines[37] and enamines[38] has only very recently come of age. In a separate development, Chan et al.[39] and Pu et al.[40] extended the above diol/Ti catalyst system to perform highly enantioselective alkynylation of numerous aldehydes (Table 9).

The first step is the generation of the zinc phenylacetylide nucleophile by treating phenylacetylene with a dialkylzinc reagent, followed by the addition of a premixed solution of the diol/Ti(O-*i*-Pr)$_4$ and the aldehyde at a specified temperature. It is intriguing that the use of R_2Zn had a significant effect on yield and enantioselectivity. With the use of the slow reacting Me_2Zn, no side product was observed; whereas with the

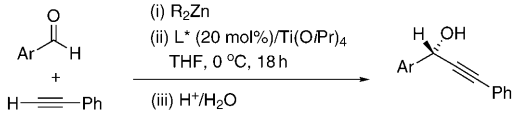
Table 8. The effect of ligands (*R*)-**1** and (*S*)-**3** on the addition of triethylaluminum to arylaldehydes.



Ar	(*R*)-**1**[a]			(*S*)-**3**[a]		Ref.
	Conv. [%]	Selectivity [%]	ee [%]	Conv. [%][b]	ee [%]	
Ph	100	100	81	100	96	[34]
o-FC_6H_4	91	93	52	96	91	[34]
o-ClC_6H_4	95	92	62	96	91	[34]
p-FC_6H_4	92	98	78	98	94	[34]
p-ClC_6H_4	93	100	81	59	90	[34]
p-MeC_6H_4	85	85	76	92	93	[34]
p-$MeOC_6H_4$	93	80	67	98	92	[34]
m-ClC_6H_4	97	100	86	98	94	[34]
m-$MeOC_6H_4$	93	100	71	99	94	[34]

[a] $Ti(O\text{-}i\text{-}Pr)_4$:**L*** = 7:1.
[b] 100% product selectivity.

Table 9. The effect of ligands (*R*)-**1** and (*R*)-**3** on the addition of zinc phenylacetylide to arylaldehydes.



R	**L***[a]	Yield [%]	ee [%]	Ref.
Ph	(*R*)-**1**	84 (77)	90 (96)	[39] ([40b])
	(*R*)-**3**	85	92	[39]
o-ClC_6H_4	(*R*)-**1**	88	64	[39]
	(*R*)-**3**	90	76	[39]
m-ClC_6H_4	(*R*)-**1**	88 (79)	92 (92)	[39] ([40b])
	(*R*)-**3**	87	95	[39]
p-ClC_6H_4	(*R*)-**1**	87 (81)	92 (92)	[39] ([40b])
	(*R*)-**3**	91	94	[39]
p-MeC_6H_4	(*R*)-**1**	83	86	[39]
	(*R*)-**3**	84	86	[39]

[a] $Ti(O\text{-}i\text{-}Pr)_4$:**L*** = 7:1.

more reactive Et_2Zn, the alkynylated as well as the ethylated products were both isolated. To avoid the latter problem, heating Et_2Zn and $PhC\equiv CH$ in toluene at 60 °C was carried out to ensure complete generation of the zinc nucleophile. Even then, the yields were lower than those obtained with the Me_2Zn method. Again, (*R*)-**3** showed better stereoselectivity in general.

5 Hetero-Diels–Alder Reaction

In a recent patent, Inanaga et al. revealed that scandium phosphate complexes **40** and **41** (Figure 4) could be readily prepared and applied to the hetero-Diels–Alder reaction of Danishefsky's diene with various aldehydes.[41] The (*R*)-**3** derived phosphate complex **41** showed both higher enantioselectivity and reactivity under otherwise identical conditions (Table 10, entries 1–3).

Jiang and coworkers used the previously described Lewis acidic catalyst system, (*R*)-**3**/$Ti(O\text{-}i\text{-}Pr)_4$, to mediate the same cycloaddition.[42] The results were much improved in most instances when compared with those performed by Keck et al.[43] with (*R*)-**1** (Table 10, entries 4–16). In one case, (*R*)-**2** (entry 6) was more efficient than (*R*)-**1** (entry 5), but less so than (*R*)-**3** (entry 7).

Ding et al. generated a large combinatorial library of chiral diol/Ti/diol complexes for the synthesis of chiral dihydropyrones *via* high-throughput screening.[44] The approach, based on the concept of molecular self-assembly,[45] involved the mingling of a preformed diol/$Ti(O\text{-}i\text{-}Pr)_4$ mixture with another diol to form the most efficient catalyst species. Of the 13 diols tested, the combination of (*R*)-**2** and (*R*)-**3** gave the most pleasing results (Table 11). Unlike the use of 10–20 mol % of catalyst by Jiang et al. and Keck et al., an extraordinary use of merely 0.005 mol % of the catalyst was enough to promote the reaction, in the case of furfural (entry 12), to give the product in 63% yield but a remarkable 96% ee. Another outstanding feature was that the reaction proceeded well in the absence of a solvent at a relatively low catalyst loading in general (S/C = 20,000) to furnish excellent product ees. This approach thus set a good example for the development of green asymmetric catalysis.

It is extremely difficult to elucidate the catalytically active species owing to the presence of a range of thermodynamically equilibrating polynuclear alkoxide complexes in the diol/Ti system.[45a,46] A number of reports have appeared on the isolated X-ray solid-state structures of certain BINOLate-Ti aggregates and allowed us to peek at the possible conformations of the binaphthyls. A trimeric complex $[(BINOLate)Ti(O\text{-}i\text{-}Pr)_2]_3 \cdot CHCl_3$, formed from a 1:1 reaction of BINOL and $Ti(O\text{-}i\text{-}Pr)_4$, shows binaphthyl dihedral angles of 58–60°,[47] as compared with the biaryl dihedral angles of 80–88° for the similarly prepared tetranuclear titanium oxo-octahydrobinaphtholate complex.[48] These findings, coupled with the results

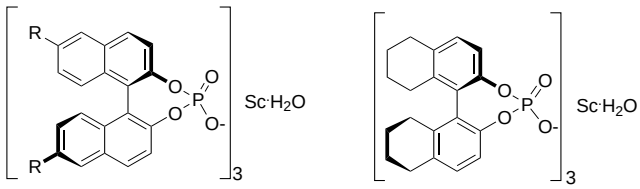
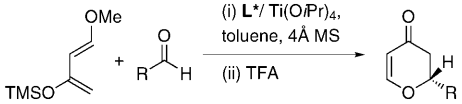


Figure 4. Sc-BINOLate and Sc-H_8-BINOLate complexes.

Table 10. Hetero-Diels–Alder reactions of Danishefsky's diene with aldehydes.[a]



Entry	R	L*	Temp. [°C]	Time [h]	Yield [%]	ee [%]	Ref.
1	Ph	**40a**[b, c]	rt	24	82	23	[41]
2		**40b**[b, c]	rt	24	83	52	[41]
3		**41**[b, c]	rt	16	95	96	[41]
4		(*R*)-**1**[d]	−20	12	83	75	[43]
5		(*R*)-**1**	0	24	60	87	[42b]
6		(*R*)-**2**	0	24	64	95	[42b]
7		(*R*)-**3**	0	24	92	97	[42]
8		(*R*)-**1**[b, d]	−20	40	40	55	[43]
9		(*R*)-**3**[b]	0	12	75	73	[42]
10	2-Furyl	(*R*)-**1**[d]	−20	40	61	97	[43]
11		(*R*)-**3**	0	30	78	96	[42]
12	(*E*)-MeCH=CH	(*R*)-**1**[d]	−20	72	50	86	[43]
13		(*R*)-**3**	12–14	92	35	98	[42a]
14	*n*-C_8H_{17}	(*R*)-**1**[d]	−20	72	88	97	[43]
15		(*R*)-**3**	12–14	92	76	94	[42a]
16		(*R*)-**3**	23–25	72	57	96	[42b]

[a] 20 mol % catalyst (**L***/Ti(O-*i*-Pr)4 = 1.1/1.0) and toluene as solvent unless otherwise stated.
[b] 10 mol % catalyst.
[c] CH_2Cl_2 as solvent.
[d] Et_2O as solvent.

Table 11. Solvent-free hetero-Diels–Alder reactions of Danishefsky's diene with aldehydes catalyzed by a molecular self-assembly system.[a]

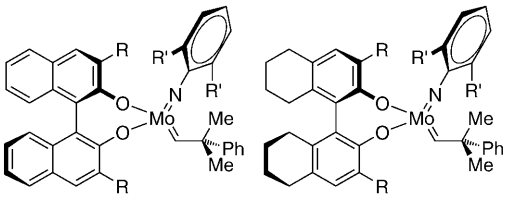
Entry	R	(*R*)-**2**/Ti/(*R*)-**2**[b]				(*R*)-**2**/Ti/(*R*)-**3**[b]				Ref.
		S/C [mol/mol]	Time [h]	Yield [%]	ee [%]	S/C [mol/mol]	Time [h]	Yield [%]	ee [%]	
1	Ph	2000	24	>99	99	2000	24	82	99	[44]
2	*o*-$MeOC_6H_4$	2000	48	95	75	2000	48	>99	95	[44]
3	*m*-$MeOC_6H_4$	2000	48	81	97	2000	48	83	>99	[44]
4	*m*-MeC_6H_4	1000	48	95	99	2000	48	92	>99	[44]
5	*m*-BrC_6H_4	1000	48	>99	97	2000	48	98	98	[44]
6	*p*-$MeOC_6H_4$	2000	48	>99	91	2000	48	>99	98	[44]
7	*p*-BrC_6H_4	2000	48	>99	98	2000	48	>99	98	[44]
8	*p*-ClC_6H_4	2000	48	>99	91	2000	48	>99	99	[44]
9	*p*-NCC_6H_4	1000	48	>99	93	2000	48	98	98	[44]
10	*p*-$NO_2C_6H_4$	2000	48	>99	97	2000	24	>99	99.4	[44]
11	α-Naphthyl	2000	48	55	86	2000	48	65	99	[44]
12	2-Furyl	2000	48	>99	99	2000	48	>99	>99	[44]
		10000	96	37	95	10000	96	>99	98	[44]
						20000	144	63	96	[44]
13	(*E*)-PhCH=CH	1000	96	82	98	2000	96	57	97	[44]
14	$PhCH_2CH_2$	2000	96	>99	98	2000	96	>99	98	[44]

[a] Reaction carried out at room temperature.
[b] Ratio = 1 : 1 : 1.

discussed above, correlate well with the idea that a larger dihedral angle of the H_8-BINOL appears to be inherently endowed with the ability to communicate the stereochemical information better with the substrates in this reaction.

6 Asymmetric Ring Closing Metathesis (ARCM)

Ring-closing olefin metathesis is a powerful strategy to construct carbocycles or heterocycles of any ring size.[49] In recent years, an increasing number of publications have been devoted to the development of an asymmetric version.[50] Some of the most effective catalysts for this reaction class are composed of modified H_8-BINOLate units **11** as shown by Hoveyda and Schrock et al. (Figure 5).[51] As mentioned earlier, introduction of sterically hindered substituents at the 3,3′-positions of the H_8-binaphthyl framework is both exclusive and facile, and their presence is essential to prevent bimolecular decomposition of the Mo catalysts. These catalysts appear to be more air-stable than their parent BINOL analogues and have demonstrated the same or better levels of efficiency and selectivity. For example, **43e** can be used in a regular fume cupboard and handled without the requirement of Schlenk techniques.



R = 2,4,6-$Me_3C_6H_2$; R' = *i*-Pr, **42a**
R = 2,4,6-*i*-$Pr_3C_6H_2$; R' = *i*-Pr, **42b**
R = 2,4,6-*i*-$Pr_3C_6H_2$; R' = Cl, **42c**
R = 2,4,6-$Me_3C_6H_2$; R' = *i*-Pr, **43a**
R = 2,4,6-$Me_3C_6H_2$; R' = Cl, **43b**
R = $CHPh_2$; R' = *i*-Pr, **43c**
R = $CHPh_2$; R' = Cl, **43d**
R = *t*-Bu; R' = *i*-Pr, **43e**

Figure 5. Binolate-containing Mo catalysts for ARCM.

6.1 Desymmetrization of 1,6- and 1,7-Trienes

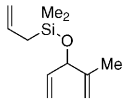
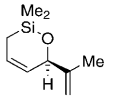
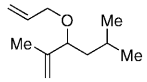
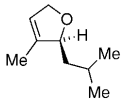
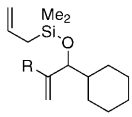
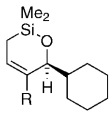
In the desymmetrization of unsaturated amines **44**, **43a** effected asymmetric ring-closing metathesis at room temperature to provide the unsaturated chiral piperidine in 95% chemical yield and 80% ee versus 84% yield and 51% ee with **42a** (Scheme 8).[51e] When employed in the desymmetrization of the test substrates **45**, some of the Mo-catalysts **43a–d** performed relatively effectively compared with catalysts such as **42c**, which is already known to give good results in other metathesis reactions. Enantioselectivity and conversion up to 98% and 99%, respectively, were obtained.[51b, c]

In separate experiments, of all the atropisomeric diolate Mo catalysts tested, only **43a** gave the desired **47** in an appreciable enantioselectivity of 50% ee in the ring closure of triene **46**. The desymmetrization process was always accompanied with the unwanted side-product **48**.[51e]

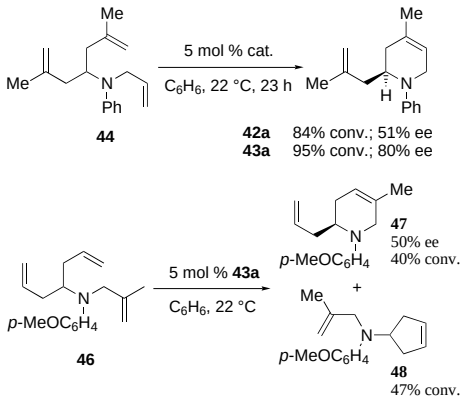
6.2 Kinetic Resolution of Polyenes through ARCM

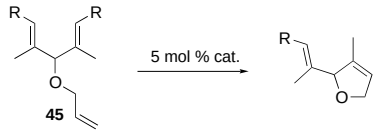
Catalyst **43e** was also shown to be more reactive and a better chiral inducer than **42b** in the kinetic resolution of certain polyenes as indicated in Table 12;[51b] although the latter catalyst was found to be very efficient with other substrates.[52] A relatively small amount of homo-coupled dimeric side-product was detected in all reactions, except for entries 2 and 8. Remarkably, **43e** exhibited $k_{rel} \geqslant 20$ and represented the best catalyst in

Table 12. Mo-catalyzed kinetic resolutions through ARCM.

Entry	Substrate	Product	R	Cat.	S/C	Time	k_{rel}[a]	Conv.	Ref.
1			-	**42b**	20	30 min	5.0	41	[51b]
2			-	**43e**	20	5 min	20	42[b]	[51b]
3			-	**42b**	20	6 h	< 2.0	44	[51b]
4			-	**43e**	20	1 h	23	58	[51b]
5			R = H	**42b**	20	5 min	3.0	63	[51b]
6			R = H	**43e**	20	2 min	> 25	58	[51b]
7			R = Me	**42b**	20	1 h	> 25	60	[51b]
8			R = Me	**43e**	20	1 h	> 25	65[c]	[51b]

[a] Relative rate determined based on the recovered substrate.[53]
[b] 18% dimer detected.
[c] 45% dimer detected.





	R = H		R = Me	
	conv.	ee	conv.	ee
43a	84%	93%	83%	98%
43b	99%	90%	95%	96%
43c	95%	93%		
43d	99%	95%	95%	91%
43e	58%	92%		
42c	99%	86%	99%	91%

Scheme 8. Desymmetrization of trienes *via* Mo-catalyzed ARCM.

the study. Nevertheless, it is not possible to generalize the effectiveness of **43e** because of the sensitivity of enantioselectivity to subtle changes in the substrate structure for any given Mo catalyst.

7 1,4-Addition to α,β-Unsaturated Compounds

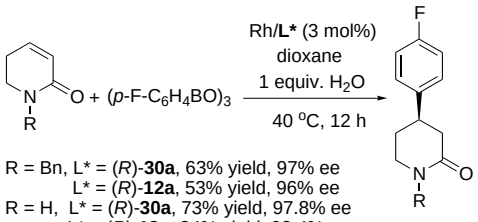
The asymmetric nucleophilic 1,4-conjugate addition to α,β-unsaturated compounds is an invaluable method to generate a *C*-chiral center, and is one of the prime strategies to synthesize compounds of medicinal interest.[54,55]

7.1 1,4-Addition of Arylboron Reagents

Hayashi and coworkers found that α,β-unsaturated lactams underwent rhodium-catalyzed 1,4-addition of arylboron reagents.[56] The asymmetric addition of 4-fluorophenylboroxine with 5,6-dihydro-2(1*H*)-pyridinones proceeded with high enantioselectivity in the presence of either Rh/(*R*)-**30a** or (*R*)-**12a** catalyst (Scheme 9). The resulting chiral (*R*)-4-(4-fluorophenyl)-2-piperidone could serve as a key intermediate for the synthesis of (−)-paroxetine.

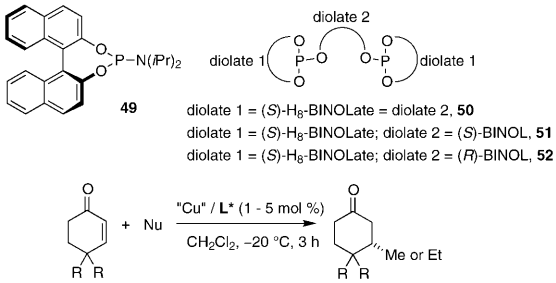
7.2 Nucleophilic 1,4-Addition to Cyclic Enones

Using a previously published method of Pringle et al.,[57] Chan's group recently synthesized some new bidentate phosphites by *in situ* formation of the chlorophosphite of (*S*)-**3** followed by the treatment with a solution of (*R*)-**1**, (*S*)-**1** or (*S*)-**3** in toluene. The ligand with an (*S*)-H_8-BINOLate bridge (**50**) was found to be less effective than the other two ligands (**51** and **52**), which contain BINOLate bridges, in the copper-catalyzed 1,4-conjugate addition of trimethylaluminum to 2-cyclohexenone in CH_2Cl_2 at 0 °C for 6 h. Up to 96% ee was reported (Table 13).[58]



Scheme 9. 1,4-Addition of boroxine to α,β-unsaturated β-lactams.

Table 13. Asymmetric 1,4-diethylzinc addition to cyclohexenones.



L*	"Cu"	Nu	R	Conv. [%]	ee [%]	Ref.
50	$Cu(OTf)_2 \cdot C_6H_6$	Me_3Al	H	85	68	[58]
51	$Cu(OTf)_2 \cdot C_6H_6$	Me_3Al	H	83	69	[58]
52	$Cu(OTf)_2 \cdot C_6H_6$	Me_3Al	H	83	91	[58]
52	$Cu[(MeCN)_4]BF_4$	Me_3Al	H	81	96	[58]
52	$Cu(OTf)_2$	Me_3Al	H	60	95	[58]
49	$Cu(OTf)_2$	Et_2Zn	H	100	68	[15]
(*S*)-**17b**	$Cu(OTf)_2$	Et_2Zn	H	100	82	[15]
49	$Cu(OTf)_2$	Et_2Zn	Me	91	81	[15]
(*S*)-**17b**	$Cu(OTf)_2$	Et_2Zn	Me	92	88	[15]

Chan et al. explored the usage of a copper catalyst involving a monodentate chiral phosphoramidite ligand with an H_8-binaphthoxy moiety **17b**, and higher ees were obtained in the asymmetric conjugate addition of

diethylzinc to cyclic enones than those by using the parent ligand **49**.[15]

8 Miscellaneous Reactions

8.1 Borane Reduction

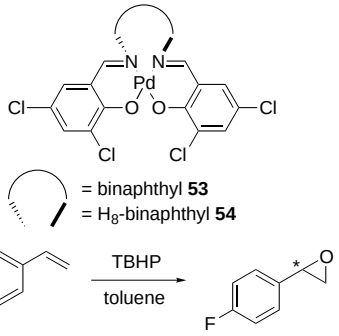
Uang et al. employed BINOL derivatives as the chiral ligand in the aluminum-catalyzed borane reduction of aromatic ketones. As a test reaction, (*R*)-**3** was found to give a higher ee for the rapid reduction of acetophenone and a variety of aromatic ketones were subsequently reduced under the optimized conditions to afford the secondary alcohols in up to 99% yield and 90% ee (Table 14).[59]

8.2 Epoxidation

Che et al. synthesized two palladium(II) binaphthyl Schiff base complexes, **53** and **54**, and the catalytic activities of these two complexes were examined in the asymmetric epoxidation of unfunctionalized alkenes. Complex **54** was purported to be superior and up to 71% ee was obtained in the epoxidation of *p*-fluorostyrene in toluene by TBHP (Scheme 10).[60]

8.3 Allylic Alkylation

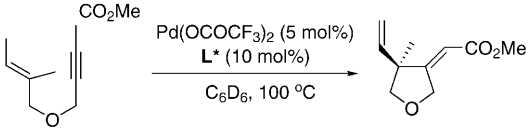
Ding et al. synthesized a series of novel chiral aminophosphine ligands, H_8-MAPs **13** and their parent compounds (Figure 6), and their effectiveness in palladium-catalyzed asymmetric allylic substitutions of dimethyl malonate with racemic 1,3-diphenylprop-2-en-1-yl acetate was probed (Table 15). Generally, H_8-MAPs **13** gave higher ees than MAP **55** (entry 2 *vs.* 1).[9] Under the optimized conditions, 91% ee was obtained with **13f**. With the utilization of **14**, a ligand type possessing both axial and central chirality, the effect of the H_8-binaphthyl was much diminished, probably due to the operation of a mismatching synergy (**56** *vs.* **14**).[10]



Scheme 10. Epoxidation of *p*-fluorostyrene with **53** and **54**.

8.4 Enyne Cycloisomerization

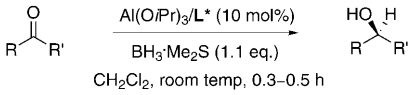
Mikami et al. developed a number of highly effective palladium(II)-diphosphine complexes for enantioselective ene-type cyclization of a 1,6-enyne leading to enantio-enriched furans.[61] The effects of palladium precursors, solvents, weak acid, reaction temperature and ligands were examined and >99% yield with



L* = (*R*)-**30a**; 24 h; >99% yield, 93% ee (*S*)
L* = (*S*)-**12a**; 48 h; >99% yield, 95% ee (*R*)

Scheme 11. Pd-catalyzed ene-type cyclization.

Table 14. Al(O-*i*-Pr)$_3$/(*R*)-**3** catalyzed borane reduction of ketones.

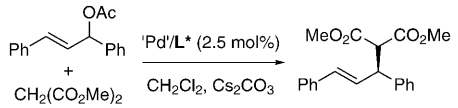


R = Ph; R′ = Me; **L*** = (*R*)-**1**, 97% yield, 60% ee
R = Ph; R′ = Me; **L*** = (*R*)-**3**, 95% yield, 71% ee

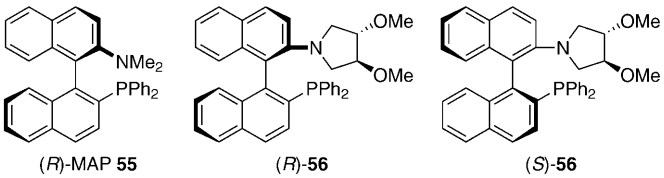
R	R′	Time [min]	Yield [%]	ee [%][a]	Ref.
Ph	Me	10	99	81 (*S*)	[59]
m-ClC_6H_4	Me	10	92	70 (*S*)	[59]
p-ClC_6H_4	Me	10	90	76 (*S*)	[59]
p-$MeOC_6H_4$	Me	10	89	52 (*S*)	[59]
p-$NO_2C_6H_4$	Me	20	94	78 (*S*)	[59]
Ph	CH_2Cl	10	92	72 (*R*)	[59]
Ph	CH_2Br	10	93	85 (*R*)	[59]
Ph	Et	10	99	90 (*S*)	[59]
Ph	*i*-Pr	120	94	50 (*S*)	[59]
Ph	*t*-Bu	720	93	32 (*S*)	[59]
Ph	*n*-Hex	10	96	78 (*S*)	[59]

[a] All the results were obtained with (*R*)-**3**.

Table 15. Pd(0)-catalyzed substitution of racemic 1,3-diphenylprop-2-en-1-yl acetate with malonate nucleophiles.



L*	'Pd'	T [°C]	Time [h]	Yield [%]	ee [%]	Ref.
(*R*)-**55**	$Pd_2(dba)_3 \cdot CHCl_3$	13	48	55	68	[9]
(*R*)-**13a**	$Pd_2(dba)_3 \cdot CHCl_3$	13	48	51	83	[9]
(*S*)-**56**	$[Pd(C_3H_5)Cl]_2$	20	24	97	83	[9]
(*R*)-**56**	$[Pd(C_3H_5)Cl]_2$	20	24	98	27	[10]
(*S*)-**14**	$[Pd(C_3H_5)Cl]_2$	20	24	90	50	[10]
(*R*)-**14**	$[Pd(C_3H_5)Cl]_2$	20	24	97	31	[10]



(*R*)-MAP **55** (*R*)-**56** (*S*)-**56**

Figure 6. Binaphthyl-based aminophosphines.

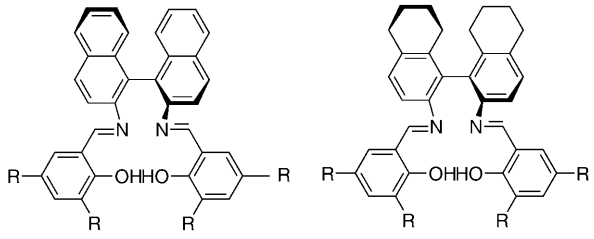


Figure 7. Binaphthyl- and H_8-binaphthyl-based Schiff bases.

> 99% ee were obtained. Similar effectiveness was displayed by BINAP **30a** and H_8-BINAP **12a** (Scheme 11).

8.5 Trimethylsilylcyanation

Che and coworkers reported the asymmetric trimethylsilylcyanation (Table 16) of some aromatic and aliphatic aldehydes catalyzed by titanium complexes formed *in situ* from Ti(O-*i*-Pr)$_4$ with a variety of Schiff bases (Figure 7).[62] Again H_8-binaphthyl derivatives offered no advantage over their parent analogues.

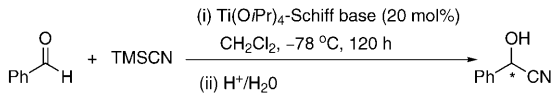
8.6 Epoxide Ring Opening

Shibasaki et al. reported the first catalytic enantioselective *meso*-epoxide ring opening reaction with 4-methoxyphenol.[63] The gallium complex **60** prepared from (*R*)-**3** showed much higher catalytic activities albeit with lower enantioselectivities than the analogous parent complex **59** (Table 17). It is unfortunate that the difference in the second metal (Li for **59** *vs.* Na for **60**) in the heterobimetallic system makes the direct comparison difficult.

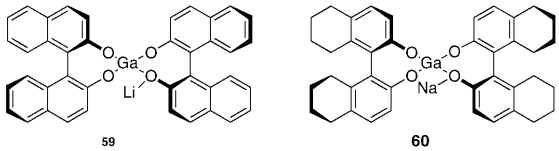
8.7 Hydroformylation

Bakos and coworkers prepared chiral diphosphites **61**–**64** (Figure 9) and their platinum and rhodium complexes were investigated in the asymmetric hydroformylation of styrene.[64,65] Generally, the platinium complexes gave better enantioselectivites than the corresponding rhodium complexes. Consistent with the X-ray crystallographic studies discussed previously, (*S*)-**62** (81.8°) shows a larger torsional angle than (*S*)-**61** (76.9°).[63] Discounting the effect due to the presence

Table 16. Enantioselective trimethylsilylcyanation of benzaldehyde.

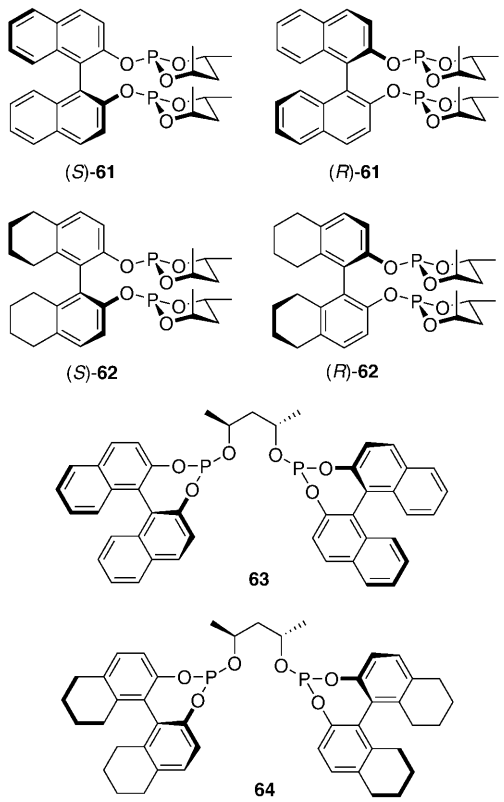


Schiff Base	Yield [%]	ee [%] (Config.)	Ref.
57a (*R*)	76	38 (*S*)	[62]
57b (*R*)	53	47 (*S*)	[62]
57c (*R*)	92	93 (*S*)	[62]
58a (*R*)	85	68 (*S*)	[62]
58b (*R*)	42	37 (*S*)	[62]
58c (*R*)	54	24 (*S*)	[62]



59 60

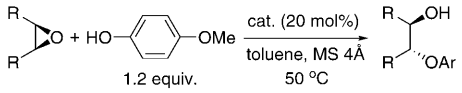
Figure 8. Heterobimetallic complexes.

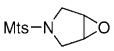
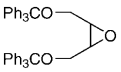


(*S*)-**61** (*R*)-**61** (*S*)-**62** (*R*)-**62** **63** **64**

Figure 9. Diphosphite ligands for hydroformylation of styrene.

Table 17. The effect of catalysts **59** and **60** on the addition of *p*-methoxyphenol to epoxides.



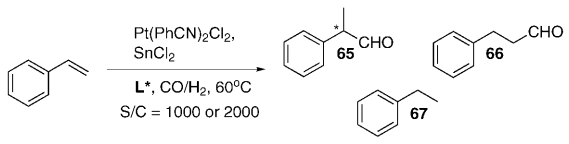
Epoxide	Catalyst	Time [h]	Yield [%]	ee [%]	Ref.
	**59**	72	75	86	[63]
	60	4	77	54	
	**59**	72	48	93	[63]
	60	4	73	56	
	**59**	72	31	67	[63]
	60	4	67	58	
	**59**	72	70	87	[63]
	60	24	90	55	
	**59**	160	51	90	[63]
	60	19	44	34	
	**59**	72	–	–	[63]
	60	7	75	50	

of an extra chiral auxiliary, ligands with the H_8-BINOLate bridge or end groups gave inferior regioselectivities and/or enantioselectivities (Table 18).

9 Conclusion

A number of research groups have realized the potential utility of partly reduced binaphthyl structures and contributed considerably to the application of these ligands in some catalytic asymmetric processes. It is noted that partial hydrogenation consequently bestows a better performance on these ligands in most metal-catalyzed asymmetric reactions.

Table 18. Hydroformylation of styrene with Pt-diphosphites complexes.



L*	Time [h]	Conv. [%]	**67** [%]	**65**/**66**	ee [%]	Ref.
(*R*)-**61**	12	100	42	70/30	23 (*R*)	[64]
(*S*)-**61**	5	65	29	84/16	39 (*S*)	[64]
(*R*)-**62**	10.5	22	50	62/38	14 (*R*)	[64]
(*S*)-**62**	10.5	60	28	66/34	21 (*R*)	[64]
(*S*)-**63**	2	100	47	59/41	71 (*R*)	[65]
(*S*)-**64**	1.5	95	32	70/30	67 (*R*)	[65]

Whilst binaphthyl ligands demonstrate a great adaptability to form stable chelates by flexibly changing the biaryl dihedral angle (58–77°), their H_8-analogues are found to be more rigid, displaying biaryl torsional angles within the range of 80–88°. These variations in the dihedral angle, in turn, have significant impact on the enantioselectivity. In the cases discussed above, asymmetric hydrogenation, hetero-Diels–Alder reaction, enantioselective alkylation of carbonyl compounds, borane reduction, allylic alkylation and epoxidation are receptive to ligands with large dihedral angles, responding favorably to deliver higher enantioselectivities.

Another advantageous aspect is that the octahydrobinaphthyl allows facile modifications at the 3,3′-positions leading to more catalytically active metal catalysts as exemplified in ring-closing olefin metathesis.

All in all, only trimethylsilylcyanation gave results in apparent disfavor of the H_8-binaphthyls. It is necessary, however, to clarify the role of the latter in reactions such as allylic alkylation, 1,4-conjugate addition and hydroformylation, since their effect is primarily masked in the presence of more than one chiral element in the ligand.

A further profound implication is whether the biaryl dihedral angle effect can be extrapolated to other atropisomeric ligands. A systematic attempt has been reported by Zhang et al.,[66] and the optimal result for the enantioselective hydrogenation of β-ketoesters was exhibited by C4-TunaPhos with a calculated dihedral angle of 88° for the free ligand, in keeping with the prevailing optimal range of dihedral angles for H_8-binaphthyls. On another note, however, better enantioselectivities were achieved with ligands having otherwise smaller dihedral angles in the asymmetric hydrogenation of different substrates.[67,68] Thus, more data are certainly required in order to generalize a trend and shed light on future ligand design for any particular reaction.

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