1
BINAP

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1.1
Introduction: Structural Consideration

BINAP (2,2′-diphenylphosphino-1,1′-binaphthyl), which was devised by Ryoji Noyori (winner of the Nobel Prize in Chemistry 2001), is typical among chiral diphosphine ligands [1–3]. BINAP chemistry has contributed notably the development of the field of asymmetric catalysis [1, 4]. This ligand with transition metallic elements forms C_2-symmetric chelate complexes. Figure 1.1 indicates the chiral structure created by an (*R*)-BINAP–transition metal complex. The naphthalene rings of BINAP are omitted in the side view (right-hand side) for clarity. As illustrated in the top view, the axial-chirality information of the binaphthyl backbone is transferred through the *P*-phenyl rings to the four coordination sites shown by □ and ■. The coordination sites □ placed in the P^1–M–P^2 plane are sterically influenced by the "equatorial" phenyl rings, whereas the out-of-plane coordination sites, ■, are affected by the "axial" phenyl groups (side view). Consequently, the two kinds of quadrant of the chiral structure (first and third versus second and forth in the side view) are clearly discriminated spatially, where the second and fourth quadrants are sterically crowded, while the first and third ones are open for approach of substrates and reagents. This chiral structure realizes excellent enantiodifferentiation in various asymmetric catalytic reactions. The flexibility of the binaphthyl backbone appears to enable a wide scope of substrate.

The great success of BINAP chemistry has encouraged researchers to develop BINAP derivatives and related chiral biaryl diphosphines [5]. Figure 1.2 illustrates representative examples. As shown in Figure 1.1, substitution manner of *P*-aryl rings of BINAP ligands obviously affects the chiral structure of metal complexes. TolBINAP, which has *P*-4-tolyl groups, shows similar enantioselective features to those of BINAP, although the solubility of the metal complexes in organic solvents is increased [6]. XylBINAP and DTBM-BINAP bearing 3,5-dialkyl groups on the *P*-phenyl rings give better enantioselectivity than that with the original ligand in some cases [6]. The bulkier *P*-aryl groups seem to make the contrast of congestion in the chiral structure clearer. Diphosphines with a relatively small P^1–M–P^2 angle in the complexes, that is, MeO-BIPHEP [7], SEGPHOS [8], SYNPHOS

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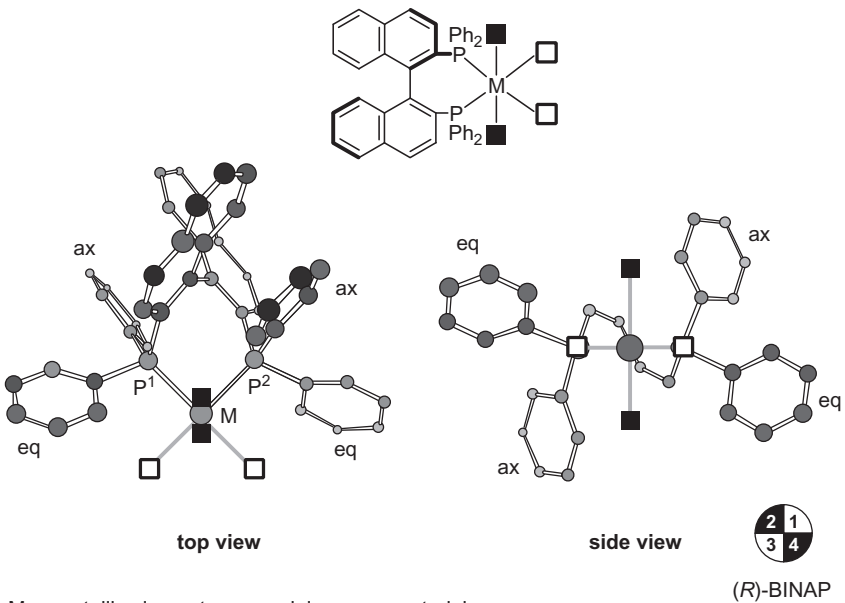
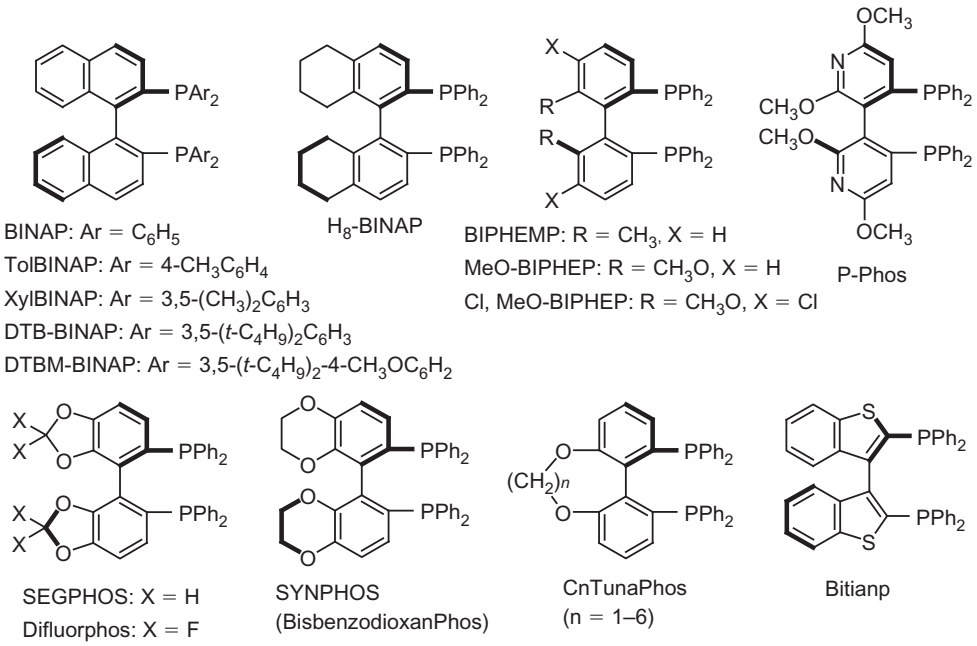


M = metallic element, ax = axial, eq = equatorial
□ = coordination site in the P^1-M-P^2 plane
■ = coordination site out of the P^1-M-P^2 plane

Figure 1.1 Molecular models of an *(R)*-BINAP–transition metal complex.



BINAP: Ar = C_6H_5
TolBINAP: Ar = 4-$CH_3C_6H_4$
XylBINAP: Ar = 3,5-$(CH_3)_2C_6H_3$
DTB-BINAP: Ar = 3,5-(t-$C_4H_9)_2C_6H_3$
DTBM-BINAP: Ar = 3,5-(t-$C_4H_9)_2$-4-$CH_3OC_6H_2$

H_8-BINAP

BIPHEMP: R = CH_3, X = H
MeO-BIPHEP: R = CH_3O, X = H
Cl, MeO-BIPHEP: R = CH_3O, X = Cl

P-Phos

SEGPHOS: X = H
Difluorphos: X = F

SYNPHOS
(BisbenzodioxanPhos)

CnTunaPhos
(n = 1–6)

Bitianp

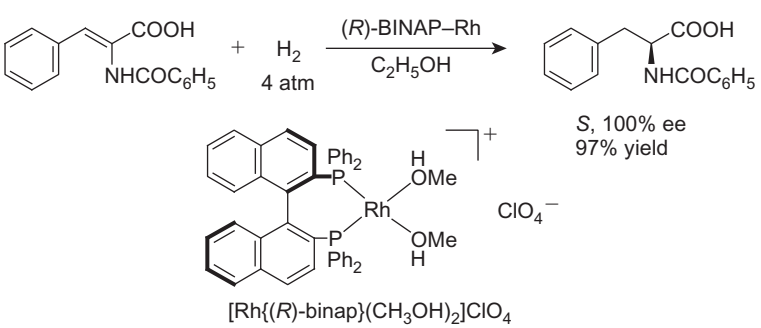
Figure 1.2 *(R)*-BINAP and selected chiral biaryl diphosphines.

(BisbenzodioxanPhos) [9], P-Phos [10], and Difluorphos [11], place the "equatorial" phenyl groups in forward regions, providing highly contrasted chiral structures. The chiral structures are varied by the size of the P^1–M–P^2 angle. C*n*Tunaphos ($n = 1$–6) can control the angle by changing the number of CH_2 moieties [12]. H_8-BINAP [13] and BIPHEMP [14], which are alkylated biphenyl diphosphines, exhibit some unique stereoselective characters. Heteroaromatic biaryl ligands, Bitianp [15] and P-Phos, as well as fluorinated diphosphine, Difluorphos, are expected to add some electronic perturbation in the catalytic systems.

In this chapter we introduce typical, but not comprehensive, asymmetric reactions catalyzed by the BINAP–metal complexes, achieving excellent enantioselectivity. Mechanistic considerations for some reactions are commented on with molecular models.

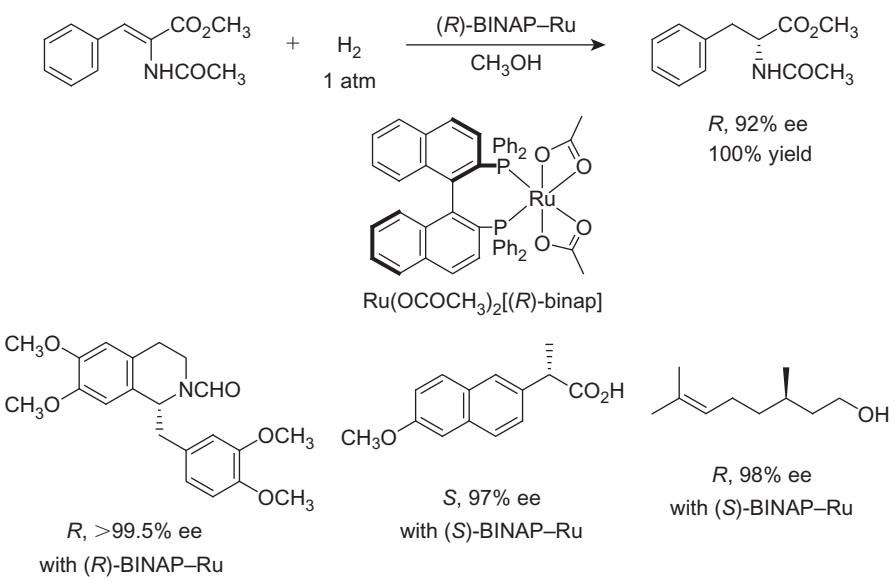
1.2
Hydrogenation of Olefins

In 1980, highly enantioselective hydrogenation of α-(acylamino)acrylic acids and esters catalyzed by the cationic BINAP–Rh(I) complexes was reported [16–18]. For example, *(Z)*-α-(benzamido)cinnamic acid is hydrogenated with [Rh{(*R*)-binap}$(CH_3OH)_2$]ClO_4 to afford *(S)*-*N*-benzoylphenylalanine in 100% enantiomeric excess (ee) and 97% yield [substrate/catalyst molar ratio (S/C) = 100, 4 atm H_2, room temperature), 48 h, in C_2H_5OH] (Scheme 1.1). In terms of enantioselectivity this hydrogenation appears to be excellent; however, very careful choice of reaction parameters, such as low substrate concentration and low hydrogen pressure, is required [19–22]. The scope of the olefinic substrates is insufficiently wide.



Scheme 1.1 Hydrogenation of *(Z)*-α-(benzamido)cinnamic acid with a BINAP–Rh catalyst.

BINAP–Ru(II) catalysis resolved the above problems. Methyl *(Z)*-α-(acetamido) cinnamate is hydrogenated in the presence of $Ru(OCOCH_3)_2$[(*R*)-binap] (S/C = 200) in CH_3OH (1 atm H_2, 30 °C, 24 h) to give methyl *(R)*-α-(acetamido)cinnamate in 92% ee and 100% yield (Scheme 1.2) [17, 23, 24]. Various olefinic substrates,



Scheme 1.2 Hydrogenation of functionalized olefins catalyzed by BINAP–Ru complexes.

including enamides, α,β- and β,γ-unsaturated carboxylic acids, and allylic and homoallylic alcohols, are converted into the desired products in high ee [25]. About 300 tons per year of optically active citronellol is produced by this hydrogenation [26]. The citronellol synthesis, by the use of a Ru(II) catalyst with a MeO-BIPHEP derivative, is applied to the production of vitamin E [27]. The H_8-BINAP–Ru (II) catalyst reduces α,β-unsaturated carboxylic acids with even higher enantioselectivity [28].

Figure 1.3 illustrates a mechanism for the hydrogenation of methyl *(Z)*-α-acetamidocinnamate catalyzed by the BINAP–Ru(II) complex [19, 20, 23]. Precatalyst $Ru(OCOCH_3)_2$[(*R*)-binap] [(*R*)-**1**] was converted into the $RuH(OCOCH_3)$ complex **2,** which is an active species, under a H_2 atmosphere with release of CH_3CO_2H. The enamide substrate reversibly coordinates to the Ru center in bidentate fashion, forming **3.** Migratory insertion gives **4,** followed by Ru–C bond cleavage largely by H_2, but also by CH_3OH solvent to some extent, resulting in the chiral product and regenerating the catalytic species **2.** The stereochemistry of the product is determined at the irreversible step (**4** → **2**). Because the reactivities of the two diastereomers of **4** are similar, the enantioselectivity of the product corresponds well to the relative stability (population) of the diastereomeric enamide–$RuH(OCOCH_3)$ intermediates [not transition states (TSs)], *Si*-**3** and *Re*-**3** (Figure 1.4). The *Si*-**3** is more favored over the diastereomeric isomer *Re*-**3**, because the latter suffers nonbonded repulsion between an equatorial phenyl ring of the *(R)*-BINAP and the methoxycarbonyl group of substrate. Therefore, the major (favored) intermediate *Si*-**3** is converted into the *(R)* hydrogenation product via **4.**

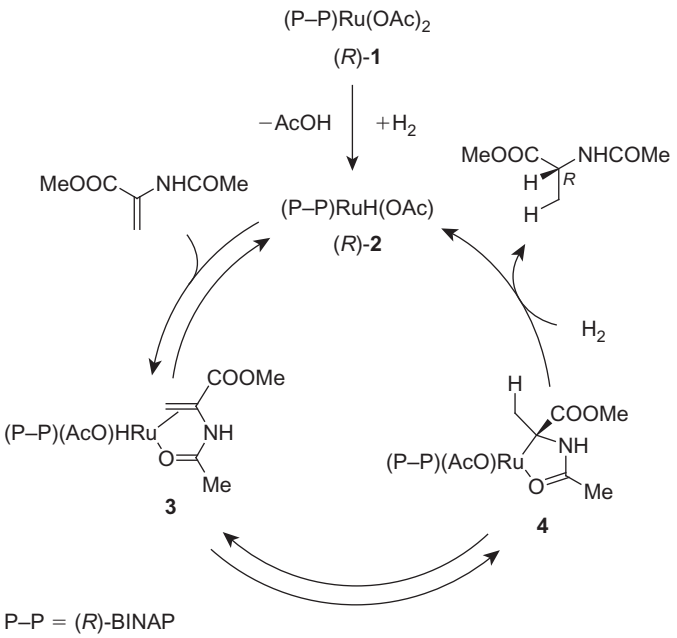


Figure 1.3 Catalytic cycle of BINAP–Ru catalyzed hydrogenation of methyl *(Z)*-α-acetamidocinnamate. (For clarity the β-substituents in the substrates are omitted.)

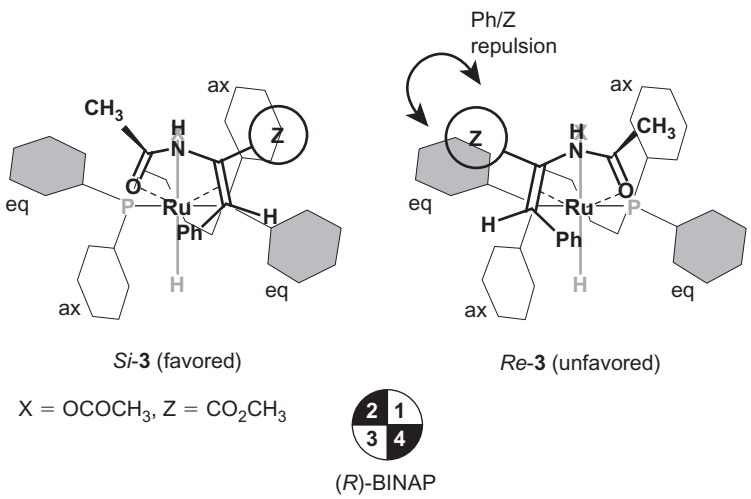
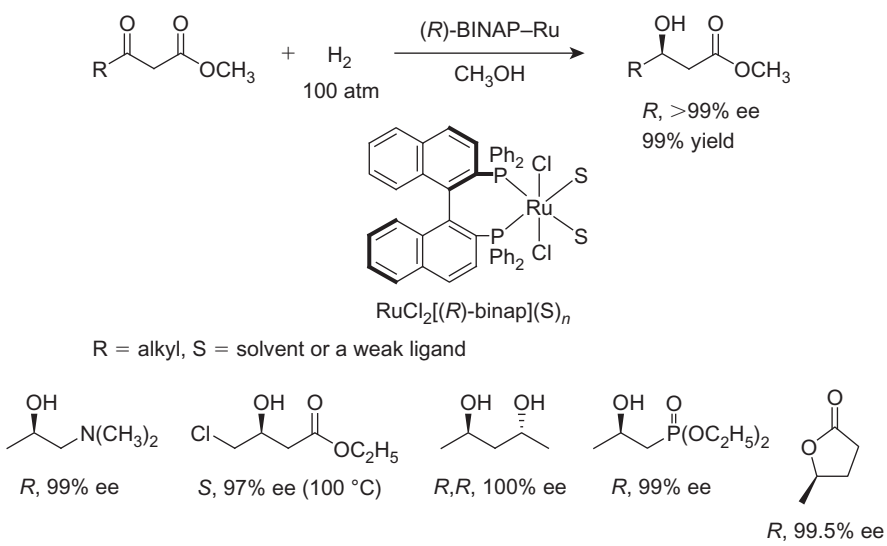


Figure 1.4 Molecular models of diastereomeric *(R)*-BINAP/enamide Ru complexes **3** (not transition state).

1.3
Hydrogenation of Ketones

1.3.1
Functionalized Ketones

$Ru(OCOCH_3)_2$(binap) is feebly active for the hydrogenation of ketones, although it shows remarkable catalytic efficiency for the reaction of functionalized olefins. This problem is resolved simply by replacing the carboxylate ligands with halides. For instance, β-keto esters (R = alkyl) are hydrogenated with $RuCl_2$(binap) (polymeric form; S/C = 2000) in CH_3OH (100 atm H_2, 30 °C, 36 h) to give the β-hydroxy esters in >99% ee quantitatively (Scheme 1.3) [29, 30]. A turnover number (TON) of 10 000 is achieved in the best cases. Several related complexes exhibit comparable catalytic efficiency, including $RuCl_2$(binap)$(dmf)_n$ (oligomeric form) [31], [RuCl(binap)(arene)]Cl [6, 32], $[NH_2(C_2H_5)_2][\{RuCl(binap)\}_2(\mu\text{-}Cl)_3]$ [24, 33], and other *in situ* prepared halogen-containing BINAP–Ru complexes [34]. A range of α-, β-, and γ-hetero substituted ketones as well as difunctionalized ketones and diketones is converted into the chiral alcohols in high ee (Scheme 1.3) [17, 35, 36]. Ruthenium(II) complexes with biaryldiphosphines that have smaller dihedral angles (MeO-BIPHEP [37], P-Phos [10], SEGPHOS [8], and SYNPHOS [9]) hydrogenate an aromatic β-keto ester (R = C_6H_5) in high stereoselectivity [38]. For the reaction of an analogue with trifluoromethyl group (R = CF_3), the Difluorphos–Ru(II) complex exhibits fine enantioselectivity [11]. The electronic deficient character of this ligand is supposed to be important.



Scheme 1.3 Hydrogenation of functionalized ketones catalyzed by BINAP–Ru complexes.

Figure 1.5 shows a plausible catalytic cycle of hydrogenation of β-keto esters mediated by BINAP–Ru(II) complexes [19, 20]. The *(R)*-BINAP–$RuCl_2$ precatalyst [*(R)*-**5**] and H_2 generate the active catalytic RuHCl species **6** with release of HCl. The β-keto ester reversibly coordinates to the Ru center of **6**, forming the σ-type chelate complex **7**. Protonation at the carbonyl oxygen of the substrate increases electrophilic ability of the carbonyl carbon, and induces a change in chelate fashion from σ to π. Therefore, the subsequent migration of hydride on the Ru to the keto-ester carbonyl carbon occurs smoothly, resulting in the hydroxy-ester complex **8.** Replacement of the *(R)* hydroxy ester with solvent molecules gives the cationic species **9.** Heterolytic cleavage of H_2 by **9** regenerates **6** along with proton. Enantioface selection of the substrate occurs in the first irreversible hydride migration step, **7**→**8**. Protonation of the carbonyl oxygen with a strong acid (HCl) in **7** is crucial for conversion into **8**. Hydrogenation with the BINAP–$Ru(OCOCH_3)_2$ complex releases CH_3CO_2H instead of HCl, however, the acidity of CH_3CO_2H is insufficient to activate the keto-ester substrate.

Figure 1.6 illustrates molecular models of diastereomeric TSs, *Si*-**10** and *Re*-**10**, in the hydride transfer step (**7**→**8** in Figure 1.5) in the hydrogenation of β-keto esters catalyzed by the *(R)*-BINAP–Ru(II) complex [19, 20]. The protonated

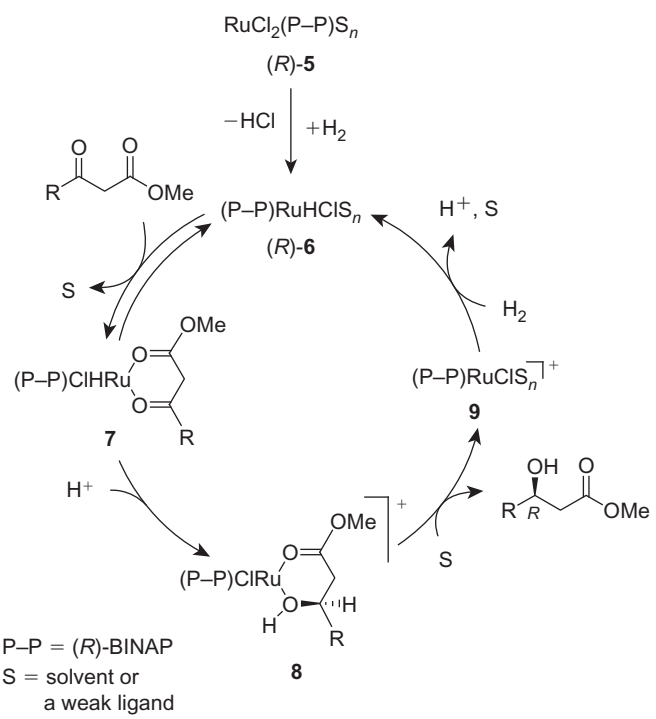


Figure 1.5 Catalytic cycle of BINAP–Ru catalyzed hydrogenation of β-keto esters.

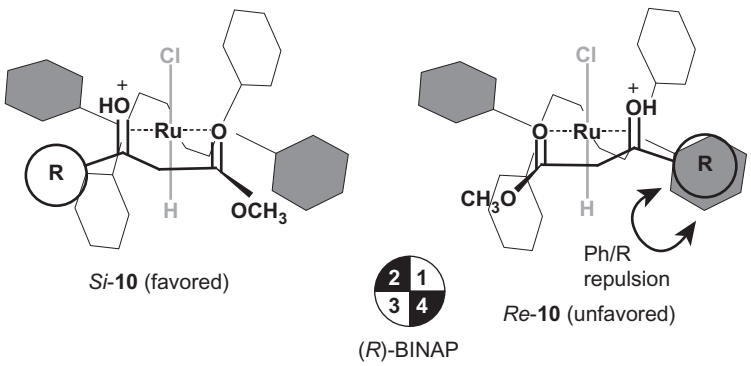
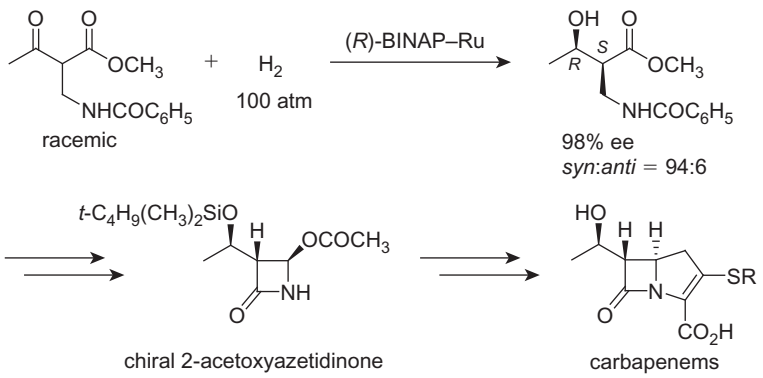


Figure 1.6 Molecular models of diastereomeric transition states in *(R)*-BINAP–Ru catalyzed hydrogenation of β-keto esters.

carbonyl moiety of substrate, C=O$^+$H, coordinates parallel to the H–Ru bond in a π fashion. Thus, the "R" group connecting to the carbonyl is placed close to the *P*-phenyl group of the *(R)*-BINAP ligand. The TS *Re*-**10** producing the *(S)* alcohol is disfavored due to the notable R/Ph repulsion in the crowded region of the fourth quadrant. Therefore, the *(R)* product is predominantly obtained via the TS *Si*-**10.**

BINAP–Ru(II) catalyzed hydrogenation of functionalized ketones is used for the production of useful chiral compounds in the chemical industry. Scheme 1.4 shows an example for the synthesis of carbapenems, a class of β-lactam antibiotics (>100 tons per year) [1, 17]. The racemic α-substituted β-keto ester is hydrogenated in the presence of BINAP–Ru catalyst with a stereo-mutation at the α position [39]. The chiral structure of the BINAP complex as well as intramolecular asymmetric induction of the substrate efficiently control the contiguous two chiral centers of the product. Therefore, the (2*S*,3*R*) alcoholic product is obtained

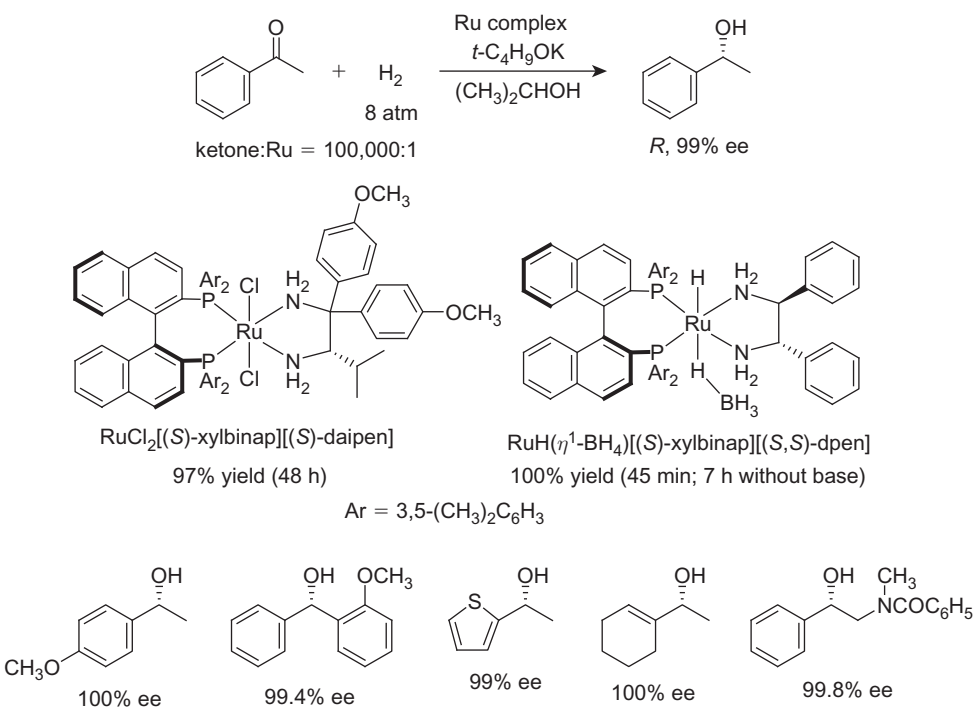


Scheme 1.4 Synthesis of a carbapenem intermediate by BINAP–Ru catalyzed hydrogenation of an α-substituted β-keto ester.

selectively among four possible stereoisomers through the dynamic kinetic resolution [40]. The use of DTBM-SEGPHOS–Ru(II) complex for this reaction affords exclusively the (2*S*,3*R*) product [8].

1.3.2 Simple Ketones

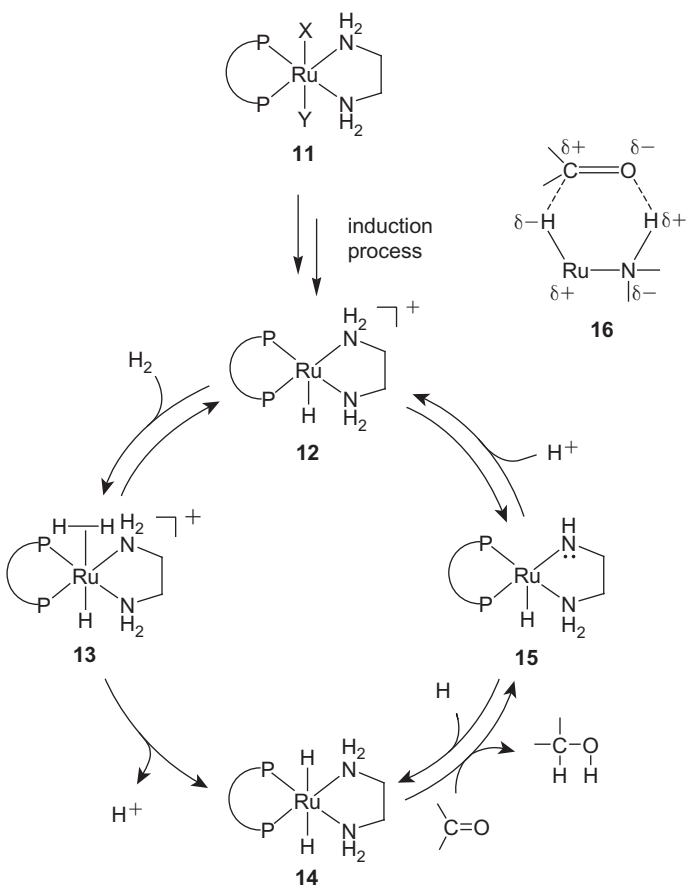
The BINAP–$RuCl_2$ catalyst hydrogenates functionalized ketones with high enantioselectivity through TSs stabilized by the substrate–Ru chelate structure (Figure 1.6). However, this catalyst is totally inert in hydrogenation of simple (unfunctionalized) ketones, because the chelate-stabilization in the TS is not available. High reactivity and enantioselectivity for this reaction is achieved by the use of a combined catalyst system of $RuCl_2$(xylbinap)(daipen) and alkaline base or RuH(η^1-BH_4)(xylbinap)(dpen) with or without a base (Scheme 1.5) [41, 42]. For example, hydrogenation of acetophenone with RuH(η^1-BH_4)[*(S)*-xylbinap][(*S*,*S*)-dpen] at an S/C of 100 000 (8 atm H_2, 45 °C) in *t*-C_4H_9OK (0.014 M, 400 equiv to Ru) containing 2-propanol is completed in 45 min to afford *(R)*-1-phenylethnol in 99% ee. The average turnover frequency (TOF_{av} = TON min^{-1}) is about 2200. The ee



Scheme 1.5 Hydrogenation of simple ketones catalyzed by XylBINAP/1,2-dimaine–Ru complexes.

value is decreased to 80–82% when BINAP or TolBINAP is used instead of XylBINAP [43]. A series of simple ketones, including alkyl aryl ketones, unsymmetrical benzophenones, hetero-aromatic ketones, α,β-unsaturated ketones, α-amino ketones, and some aliphatic ketones, is hydrogenated in high enantioselectivity [44, 45]. The analogous catalyst systems using chiral biaryl diphosphines with *P*-3,5-xylyl groups exhibit similar efficiency [30, 46].

Figure 1.7 illustrates a proposed catalytic cycle for the hydrogenation of simple ketones with the *(S)*-TolBINAP/(*S*,*S*)-DPEN–Ru(II) complex [42, 47]. The precatalyst **11** (X, Y = Cl, Cl or η^1-BH_4, H) is converted into the cationic complex **12** in 2-propanol under reductive conditions with or without base. Species **12** and H_2 reversibly forms the molecular hydrogen complex **13**, followed by deprotonation to



P–P = (*S*)-TolBINAP, NH_2–NH_2 = (*S*,*S*)-DPEN, X, Y = Cl, Cl or η^1-BH_4, H

Figure 1.7 Catalytic cycle of TolBINAP/DPEN–Ru catalyzed hydrogenation of simple ketones.

give the active RuH_2 complex **14.** A ketone is readily reduced by **14**, affording the alcoholic product and the 16-electron Ru–amide complex **15.** The cationic complex **12** is promptly regenerated by protonation of **15** in an alcoholic medium; **15** is partly converted into **14** by the addition of H_2. The reaction of RuH_2 species **14** and a ketonic substrate proceeds thorough the pericyclic six-membered TS **16.** The $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H^{\delta+}$ quadrupole on the catalyst and the $C^{\delta+}$=$O^{\delta-}$ dipole of the substrate effectively interact to reduce the activation energy. Therefore, presence of an "NH" moiety on the diamine ligand is crucial to achieve high catalytic activity.

The mode of enantioface-selection is explained by the use of TS molecular models shown in Figure 1.8 [42, 47]. These are completely different from the TSs in the hydrogenation of β-keto esters catalyzed by the BINAP–Ru(II) complex without diamine ligand (Figure 1.6). The *(S)*-TolBINAP/(*S,S*)-DPEN–RuH_2 complex **14** has a C_2-symmetric structure, in which the skewed five-membered DPEN chelate-ring appropriately arranges the amino protons. The axially directed proton, H_{ax}, is more reactive than the equatorial one (H_{eq}), because the $H^{\delta-}$–$Ru^{\delta+}$–$N^{\delta-}$–$H_{ax}^{\delta+}$ quadrupole forming a smaller dihedral angle preferentially interacts with the $C^{\delta+}$=$O^{\delta-}$ dipole of the ketone. Acetophenone approaches the reaction site

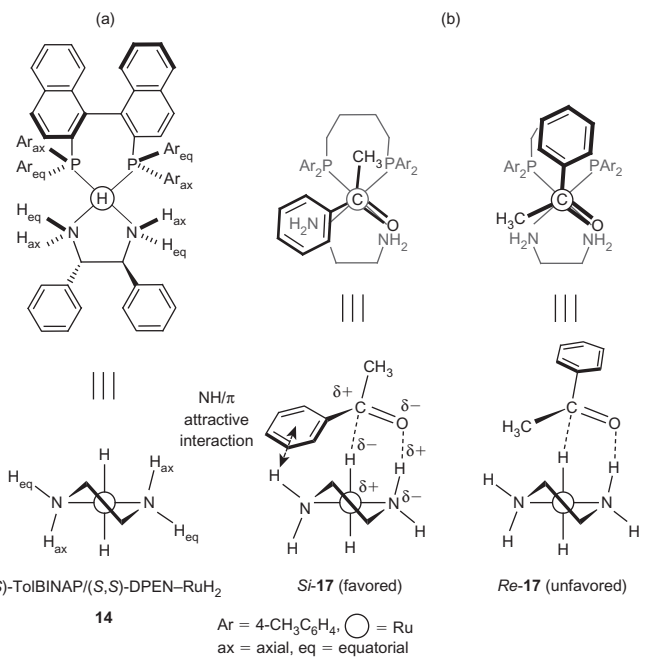


Figure 1.8 *(S)*-TolBINAP/(*S,S*)-DPEN–RuH_2 species (left) and diastereomeric transition states in the hydrogenation of acetophenone. (For clarity the equatorially oriented phenyl substituents in the DPEN ligands are omitted in the molecular models.)

with the *Si*-face (*Si*-**17**) or *Re*-face (*Re*-**17**) forming the pericyclic TS. The TS *Re*-**17** suffers significant nonbonded repulsive interaction between the phenyl ring of substrate and the aromatic groups of the *(S)*-TolBINAP. Therefore, the reaction selectively proceeds via the TS *Si*-**17** to give the *(R)* product. The secondary NH/π attractive interaction between the NH_{eq} and the phenyl of acetophenone appears to further stabilize the TS *Si*-**17**. This interpretation is supported by the result that the catalyst with the sterically more demanding XylBINAP instead of TolBINAP exhibits higher enantioselectivity (Scheme 1.5).

The chiral environment of the BINAP/diamine–Ru(II) complexes is readily modified by changing the combination of the diphosphine and diamine ligands (Figure 1.9). For example, the *(S)*-TolBINAP/*(R)*-DMAPEN–Ru(II) catalyst hydrogenates phenylglyoxal diethyl acetal and *(E)*-chalcone to afford the corresponding alcohols in 96% and 97% ee [48]. The same products in only 36% and 45% ee, respectively, are obtained by the use of the *(S)*-XylBINAP/*(S)*-DAIPEN–Ru(II) catalyst, which gives the highest ee (99%) of product in the reaction of acetophenone (Scheme 1.5). The combination of *(S)*-TolBINAP and *(R)*-IPHAN, a chiral 1,4-diamine, achieves high reactivity and enantioselectivity in the hydrogenation of 1-tetralones, a class of cyclic aromatic ketones, and substituted 2-cyclohexenones [49]. With the use of TolBINAP/PICA–Ru(II) catalyst, sterically

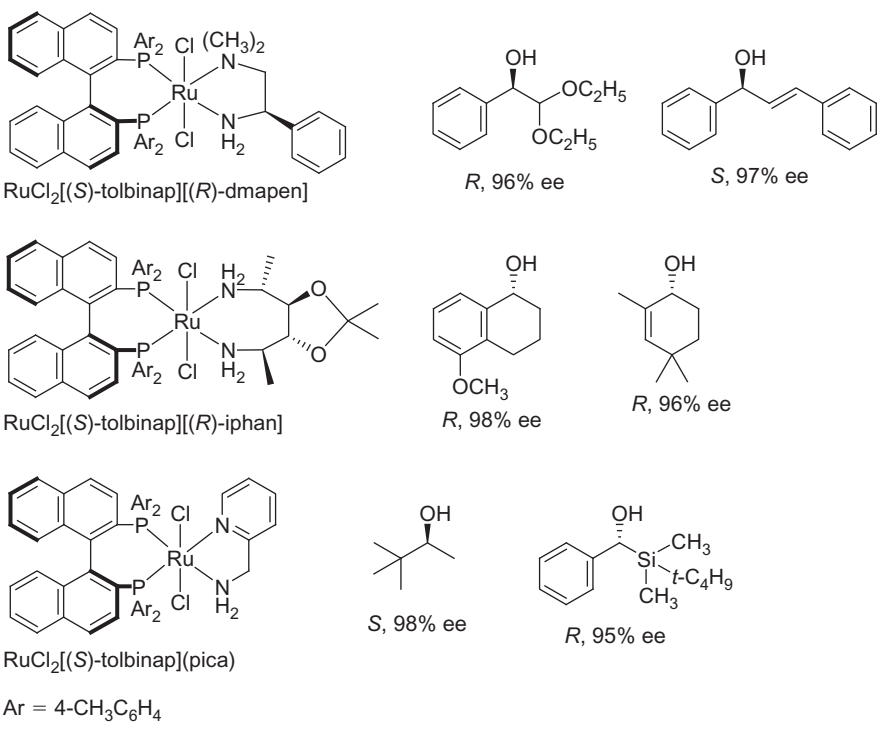
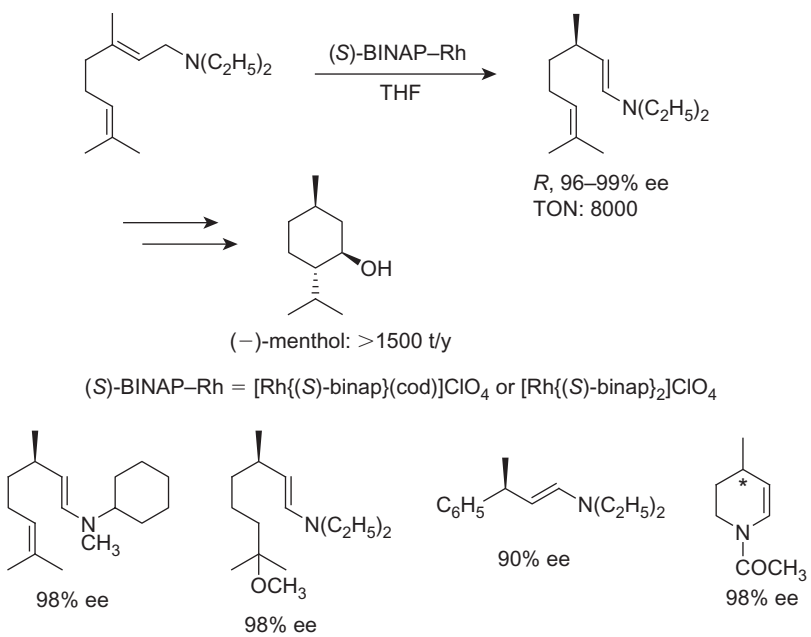


Figure 1.9 TolBINAP/amine ligand–Ru complexes and alcoholic products.

very crowded *tert*-alkyl ketones and acyl silanes are smoothly hydrogenated to quantitatively afford the chiral products in high ee [50]. Custom catalyst design notably expands the scope of substrates. This method is utilized in chemical industries on a productive scale [51, 52].

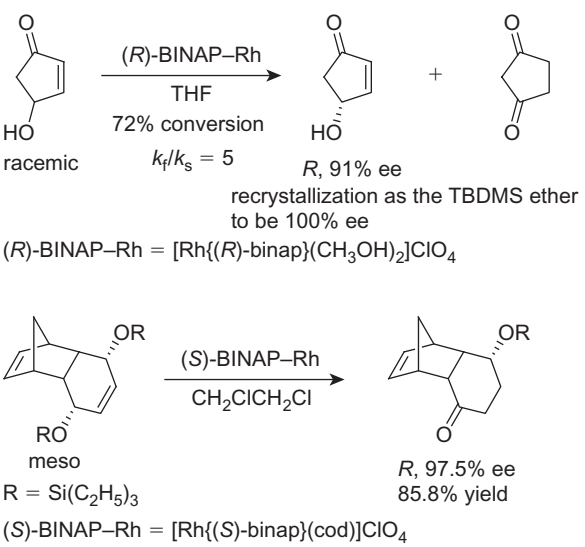
1.4 Isomerization of Allylamines and Allylalcohols

Asymmetric isomerization of allylamines is a simple and atom-economical reaction by which to obtain optically active enamines [53]. Scheme 1.6 shows a representative example for the BINAP–Rh(I) catalyzed isomerization of diethylgeranylamine to citronellal diethylenamine. [Rh{*(S)*-binap}(cod)]ClO_4 promotes the reaction in THF (60–120 °C) to afford the chiral enamine in 96–99% ee [54]. The TON approaches 8000 within 7 h. The catalyst can be recycled, so that the total chiral-multiplication number reaches 400 000. [Rh(binap)$_2$]ClO_4 acts at higher reaction temperature, but the robustness of this complex leads to its preferred practical use. More than 1500 tons of (–)-menthol are produced per year by this method [53]. Several allylamine substrates with different *N*-substituents, alkoxy alkyl groups, aromatic moieties, and cyclic skeletons are also converted into the desired compounds in high ee.



Scheme 1.6 Isomerization of allylamines catalyzed by BINAP–Rh complexes and the industrial application to the synthesis of (–)-menthol.

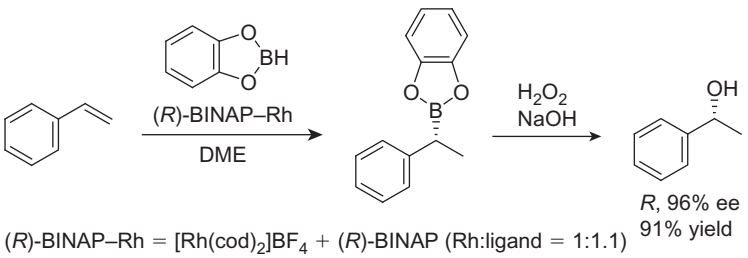
The BINAP–Rh(I) catalyzed isomerization of allylalcohols is less successful in terms of enantioselectivity. Nevertheless, some useful reactions are reported [53]. When racemic 4-hydroxy-2-cyclopentenone is subjected to isomerization conditions in the presence of [Rh{*(R)*-binap}$(CH_3OH)_2$]ClO_4 (S/C = 200, 0 °C, 14 days), the *(R)*-hydroxy enone in 91% ee is recovered at 72% conversion (Scheme 1.7) [55]. The relative reaction rate between the two enantiomers (k_f/k_s) is calculated to be 5. The *(R)* product can be optically purified by recrystallization after conversion into the *tert*-butyldimethylsilyl ether. Desymmetrization of meso allylic 1,4-enediol di-triethylsilyl ether by enantioselective isomerization is achieved by the use of [Rh{*(S)*-binap}(cod)]ClO_4 (S/C = 50, CH_2ClCH_2Cl reflux, 16 h) [56]. The desired *(R)*-mono-silyloxy-ketone is obtained in 97.5% ee and 85.8% yield.



Scheme 1.7 Isomerization of allylic alcohol and allylic ether catalyzed by BINAP–Rh complexes.

1.5 Hydroboration, Hydrosilylation, Hydroacylation, and Hydroamination

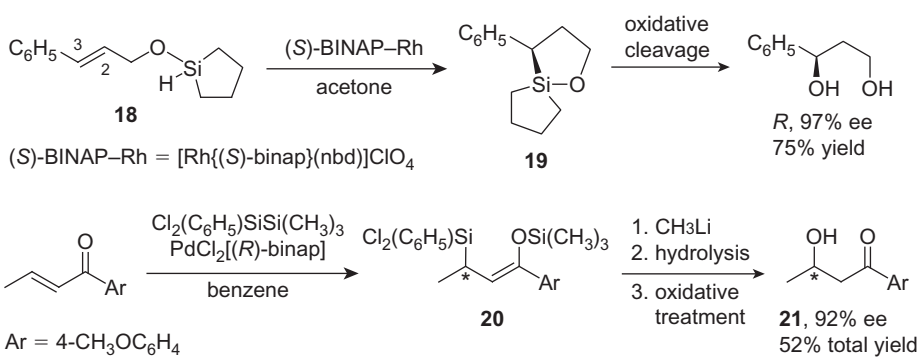
Enantioselective hydroboration of olefins is a reliable procedure for the synthesis of chiral alcohols in combination with an oxidation procedure [57]. Styrene and catechol borate (1.1 equiv) react in DME with an *in situ* prepared catalyst from [$Rh(cod)_2$]BF_4 and *(R)*-BINAP (S/C = 50, −78 °C, 2 h), followed by a treatment with H_2O_2 under basic conditions, to give *(R)*-1-phenylethanol in 96% ee and 91% yield (Scheme 1.8) [58]. The regioisomeric 2-phenylethanol, which is a major isomer in the reaction without a catalyst, is not detected. Aromatic substituted



Scheme 1.8 Hydroboration of styrenes with a BINAP–Rh catalyst.

styrenes also react with high stereoselectivity. The reactivity and enantioselectivity are decreased in the hydroboration of α- or β-substituted styrenes.

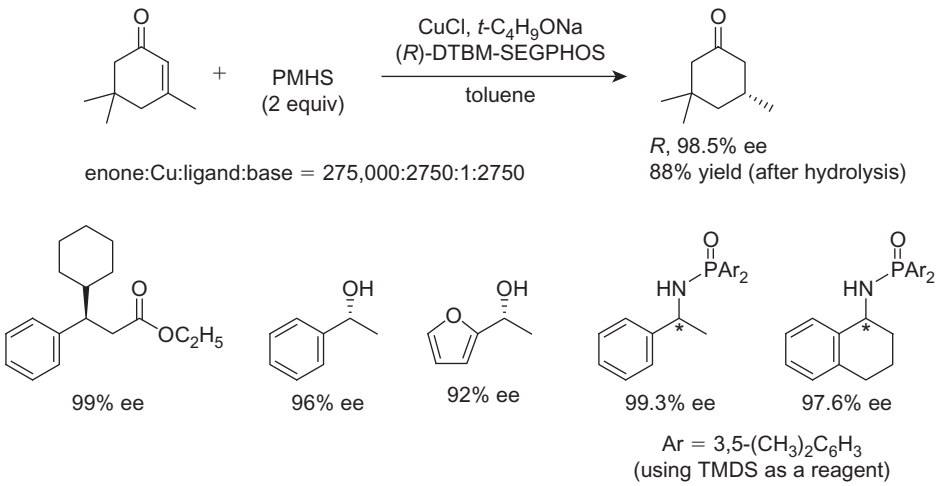
The BINAP–Rh complex efficiently catalyzes asymmetric intramolecular hydrosilylation of allylic alcohol silylethers [59]. As shown in Scheme 1.9, a cinnamyl alcohol silylether (**18**) is converted into the cyclic silylether **19** in acetone with [Rh{*(S)*-binap}(nbd)]ClO_4 (S/C = 50, 25 °C, 5 min) [60]. The competitive intermolecular reaction is observed at less than 1%. Treatment of **19** under oxidative conditions afforded *(R)*-1-phenyl-1,3-propanediol in 97% ee and 75% yield.



Scheme 1.9 Enantioselective hydrosilylation of olefins and disilylation of enones.

The cyclic silane structure of **18** is crucial for efficient enantioselection. Several 2- and 3-substituted compounds are converted into the desired products in high ee. Enantioselective 1,4-disilylation of 4′-methoxybenzalacetone using $Cl_2(C_6H_5)SiSi(CH_3)_3$ (1.5–2 equiv) as a reagent catalyzed by $PdCl_2$[*(R)*-binap] (S/C = 200, 80 °C, 0.5 h) gives the silylation compound **20**, which is converted into the β-hydroxy ketone **21** in 92% ee through treatment with CH_3Li, acidic hydrolysis, and oxidative cleavage of the C−Si bond [61]. The symmetric disilane reagents do not react with the enone. Aliphatic and aromatic enones react with good to high enantioselectivity.

Enantioselective hydrosilylation of α,β-unsaturated ketones catalyzed by Cu(I) complexes with TolBINAP and DTBM-SEGPHOS affords the chiral β-substituted

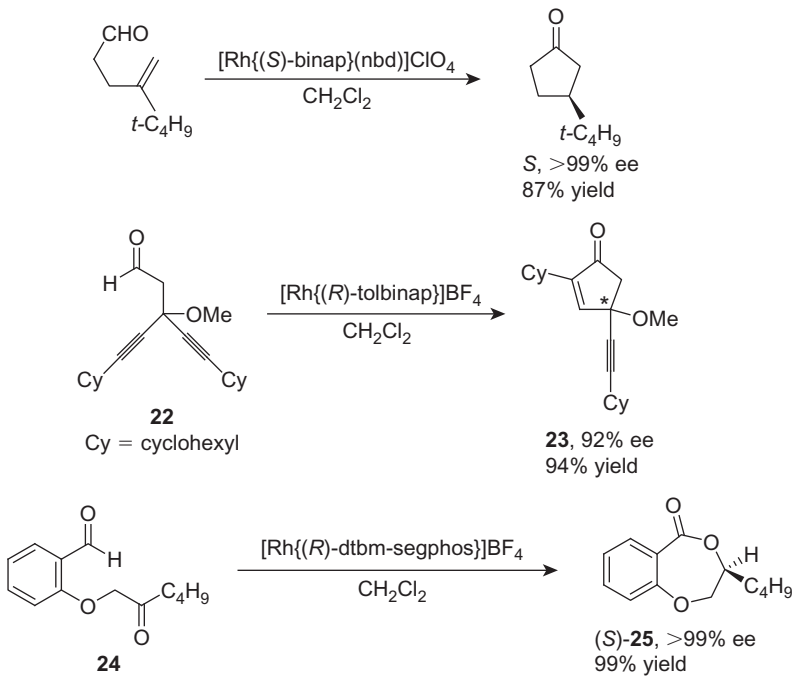


Scheme 1.10 Asymmetric hydrosilylation of enones, ketones, and imines with DTBM-SEGPHOS–Cu catalysts.

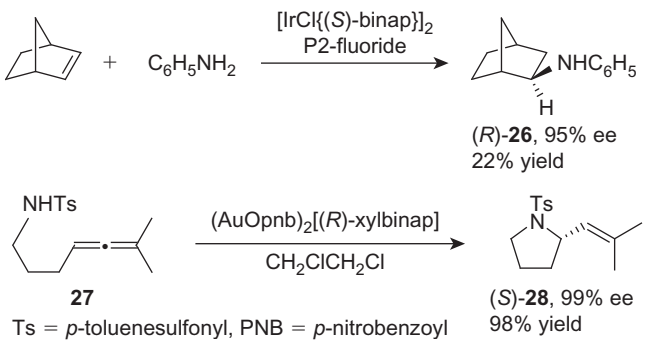
ketones in high ee. Scheme 1.10 illustrates an example using the DTBM-SEGPHOS–Cu(I) system [62]. The safe and inexpensive polymethylhydrosiloxane (PMHS) is used as a reducing agent. The reaction of isophorone is carried out with an *in situ* prepared catalyst from CuCl (S/C = 100), the *(R)* ligand (S/ligand = 275 000), and *t*-C_4H_9OK in toluene (−35 °C, 3 days) to give the *(R)* ketone in 98.5% ee and 88% yield after hydrolysis. The chiral multiplicity is remarkably high. In a similar manner, α,β-unsaturated esters [63], aromatic ketones [64], and aromatic imines [65] are also reduced with high levels of enantioselection. The use of tetramethyldisiloxane (TMDS) under modified conditions gives better stereoselectivity for the reaction of imines. Hydrosilylation of ketones with an air-stable BINAP–CuF_2 catalyst system is also reported [66].

Intramolecular hydroacylation of 4-*tert*-butyl-4-pentenal catalyzed by the cationic *(S)*-BINAP–Rh(I) complex (S/C = 20–25) in CH_2Cl_2 (25 °C, 2–4 h) gives *(S)*-3-*tert*-butylpentanone in >99% ee in high yield (Scheme 1.11) [67]. Desymmetrization of a meso 3,3-dialkynylpropanal **22** by hydroacylation with the TolBINAP–Rh(I) catalyst (S/C = 10, 10 °C, 2 h) gives the 2-cyclopentenone with a quaternary carbon center at the 4 position of **23** in 92% ee [68]. A keto aldehyde **24** is quantitatively converted into the seven-membered lactonic compound *(S)*-**25** in >99% ee by the DTBM-SEGPHOS–Rh(I) catalyzed hydroacylation (S/C = 20, room temperature, 2 days) [69]. A series of substrates with aliphatic and aromatic moieties reacts with high enantioselectivity.

A catalyst system consisting of [IrCl{*(S)*-binap}]$_2$ and a fluoride source (F/C = 4) effects the asymmetric reaction of norbornene and aniline without solvent (S/C = 50, 75 °C, 72 h), leading to the hydroamination product *(R)*-**26** in 95% ee and 22% yield (Scheme 1.12) [70]. Fluoride appears to act as a π-donating anionic ligand accelerating the N–H oxidative addition to Ir. Intramolecular



Scheme 1.11 Chiral diphosphine–Rh catalyzed intramolecular hydroacylation.

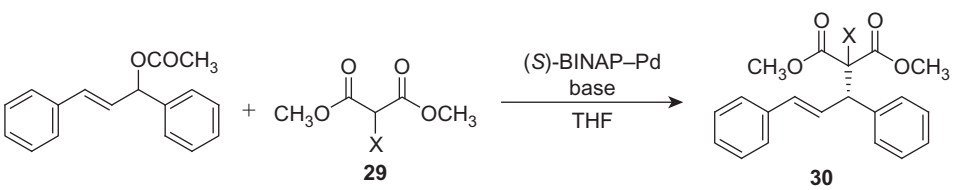


Scheme 1.12 Enantioselective hydroamination of olefins and allenes.

hydroamination of an *N*-tosyl allenic compound (**27**) is carried out in CH_2ClCH_2Cl with $(AuOpnb)_2$[*(R)*-xylbinap], a unique bimetallic complex (S/C = 33, 23 °C, 15 h), to quantitatively yield the cyclic amine product *(S)*-**28** in 99% ee [71]. Choice of *p*-nitrobenzoate as an anionic ligand is crucial to achieve a high yield and ee of the product. A range of substrates with linear and cyclic alkyl substituents at the allenic moiety gives the desired products in equally high ee. The BINAP–Pd catalyzed reaction of styrenes and anilines has also been reported [72].

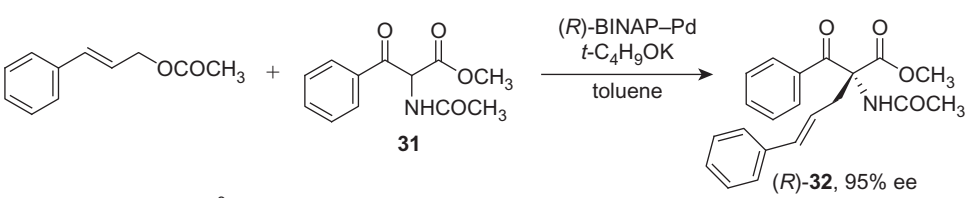
1.6
Allylic Alkylation

Allylic alkylation of 3-acetoxy-1,3-diphenyl-1-propene with the sodium salt of dimethyl 2-acetamidomalonate (**29a**) in the presence of a catalyst formed *in situ* from $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ and *(S)*-BINAP (S/C = 100, 25 °C, 120 h) affords the *(S)* adduct *(S)*-**30a** in 95% ee and 92% yield (Scheme 1.13) [73, 74]. When this reaction is conducted with the sodium salt of simple dimethyl malonate **29b** the enantioselectivity is decreased drastically. This problem is solved by using $Zn(C_2H_5)_2$ as a base to generate the malonate [75]. The desired product **30b** is obtained in 99% ee (S/C = 25, room temperature, 20 h). The reaction of a prochiral nucleophile prepared from an α-acetamide-β-keto ester **31** and $t\text{-}C_4H_9OK$ with cinnamyl acetate in the presence of the *(R)*-BINAP–Pd(II) complex (S/C = 50, −30 °C, 48 h) gives the *(R)* adduct *(R)*-**32** in 95% ee [76]. The bulky γ substituent of the allylic acetate (C_6H_5 in this case) is crucial to achieve high enantioselectivity.



(*S*)-BINAP–Pd = $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ + (*S*)-BINAP (Pd:ligand = 1:1.2–2)

29, X	base	% ee	% yield
a, $NHCOCH_3$	NaH	95	92
b, H	$Zn(C_2H_5)_2$	99	84



(*R*)-BINAP–Pd = $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ + (*R*)-BINAP (Pd:ligand = 1:1.05)

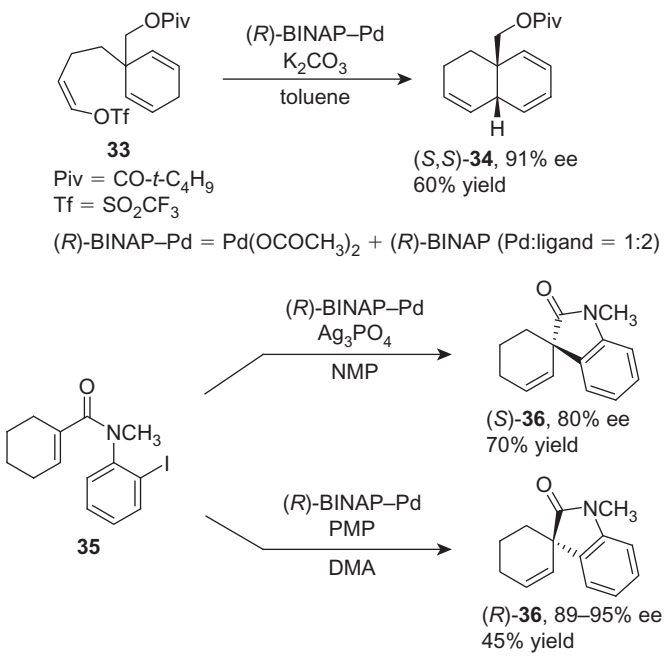
Scheme 1.13 Enantioselective allylic substitution with BINAP–Pd catalyst.

1.7
Heck Reaction

1.7.1
Intramolecular Reaction

Asymmetric Heck-type cyclization of various vinyl halides and enol triflates is catalyzed by BINAP–Pd complexes [77]. Synthetically useful chiral cyclic

compounds with functionalities are produced by this reaction. For example, a prochiral enol triflate **33** is cyclized with $Pd(OCOCH_3)_2$, *(R)*-BINAP, and K_2CO_3 in toluene (S/C = 20, 60 °C, 27 h) to afford (*S,S*)-**34** in 91% ee and 60% yield (Scheme 1.14) [78]. Spirooxindols **36** are prepared from the aryl iodide **35** in up to 95% ee [79]. Both enantiomers of **36** can be selectively synthesized from the single enantiomer of the catalyst. Thus, **35** reacts with the *(R)*-BINAP–Pd catalyst in the presence of Ag_3PO_4 (2 equiv) in *N*-methylpyrrolidine (NMP) (S/C = 10, 60 °C, 25 h) to afford *(S)*-**36** in 80% ee. When the reaction is conducted with the *(R)*-BINAP–Pd catalyst and 1,2,2,6,6-pentamethylpiperidine (PMP; 5 equiv) in *N,N*-dimethylacetamide (DMA) (S/C = 10, 100 °C, 1.5 h), the *(R)* product is selectively obtained. These results suggest that the reaction mechanism with a cationic Pd catalyst is different from that catalyzed by the neutral species.

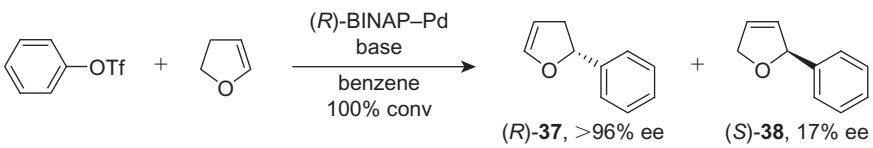


Scheme 1.14 Intramolecular Heck reaction with BINAP–Pd catalysts.

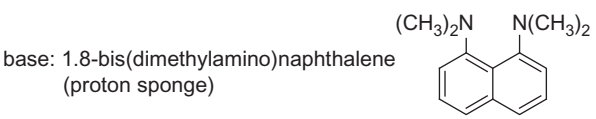
1.7.2 Intermolecular Reaction

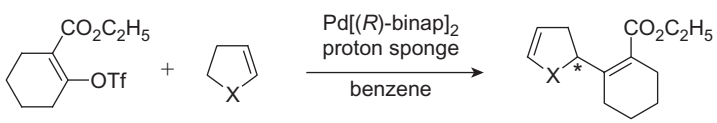
The BINAP–Pd catalyst exhibits high enantioselectivity in the intermolecular Heck reaction [77a, d]. When phenyl triflate reacts with 2,3-dihydrofuran (5 equiv) in the presence of an *in situ* formed *(R)*-BINAP–Pd complex and 1,8-bis(dimethylamino)naphthalene (proton sponge; 3 equiv) in benzene (S/C = 33, 40 °C,

9 days), *(R)*-2-phenyl-2,3-dihydrofuran [*(R)*-**37**] in >96% ee and *(S)*-2-phenyl-2,5-dihydrofuran [*(S)*-**38**] in 17% ee are obtained in a 71 : 29 ratio (Scheme 1.15) [80]. The choice of base is important to attain high enantioselectivity. The high basicity and bulkiness of the proton sponge appears to fit with the reaction. Several substituted phenyl triflates and 2-naphthyl triflates have been used successfully under the optimized conditions. When the reaction of phenyl triflate and 2,3-dihydrofuran is carried out with the DTB-MeO-BIPHEP–Pd catalyst (DTB; see Figure 1.2) using $N(C_2H_5)(i\text{-}C_3H_7)_2$ as a base, **37** is obtained in 99% ee and 70% yield [81]. The BITIANP–Pd catalyzed reaction gives exclusively **37** in 91% ee [82].



(*R*)-BINAP–Pd = $Pd(OCOCH_3)_2$ + (*R*)-BINAP (Pd:ligand = 1:2) **37:38** = 71:29





39 **40**

X	% ee	% yield
O	>96	62
NCO_2CH_3	>99	95

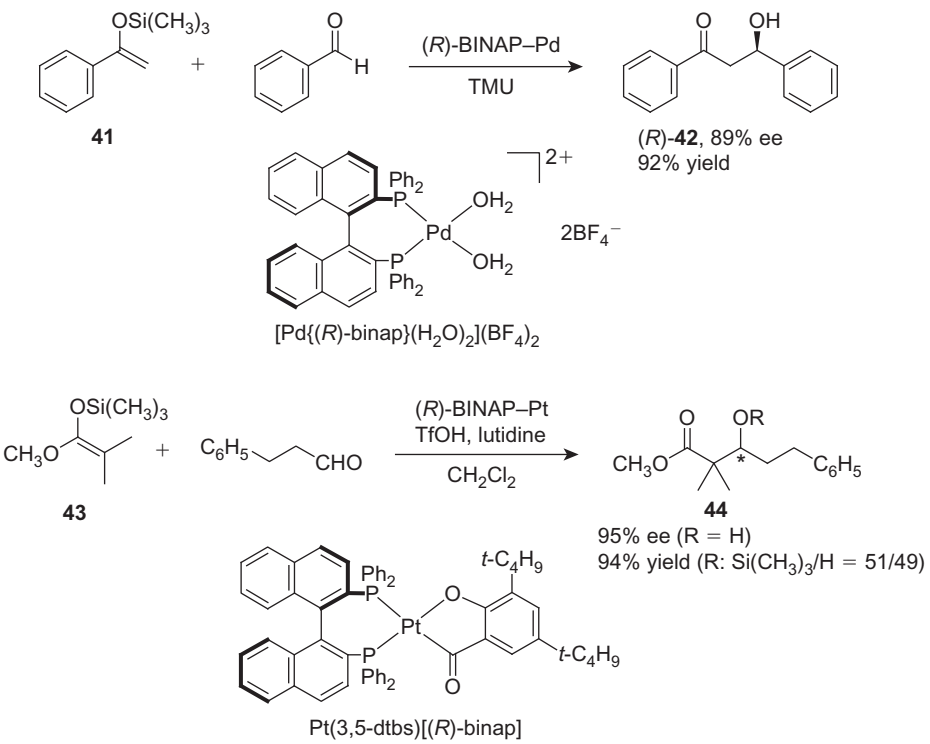
Scheme 1.15 Intermolecular Heck-type arylation and alkenylation with BINAP–Pd catalysts.

The Heck-type alkenylation of olefins is also catalyzed by the BINAP–Pd complex. The reaction of 2-ethoxycarbonyl-1-cyclohexenyl triflate (**39**) and 2,3-dihydrofuran (4 equiv) in the presence of $Pd(binap)_2$ (S/C = 33) and proton sponge (2 equiv) in benzene (40 °C, 56 h) affords the chiral product **40** (X = O) in >96% ee [83]. The use of preformed complex $Pd(binap)_2$ restrains formation of the regioisomeric products. When the reaction is conducted using 1-methoxycarbonyl-2-pyrroline instead of dihydrofuran (S/C = 33, 60 °C, 20 h), the desired product **40** ($X = NCO_2CH_3$) is obtained in >99% ee and 95% yield. The BITIANP–Pd catalyst exhibits similar efficiency [84].

1.8
Aldol and Mannich-Type Reactions

1.8.1
Aldol Reaction

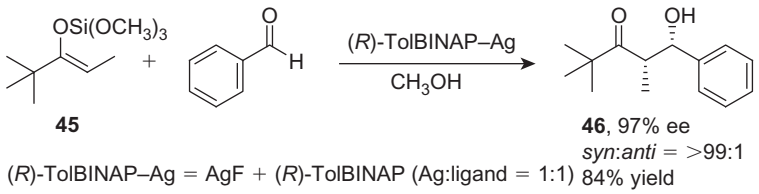
The asymmetric aldol reaction is a reliable method to produce synthetically useful chiral β-hydroxy carbonyl compounds [85]. Benzaldehyde and a silyl enolate of acetophenone (**41**) (1.5 equiv) react with [Pd{*(R)*-binap}$(H_2O)_2$]$(BF_4)_2$ (S/C = 20) in 1,1,3,3-tetramethylurea (TMU) (0 °C, 24 h) to afford *(R)*-3-hydroxy-1,3-diphenyl-1-propanone [*(R)*-**42**] in 89% ee and 92% yield (Scheme 1.16) [86]. The structure of the BINAP–Pd(II) complex has been determined by a X-ray crystallographic analysis. A chelating acyl Pt(II) complex Pt(3,5-dtbs)[*(R)*-binap] that can be handled in the open air is activated as a catalyst by treatment with *p*-toluenesulfonic acid (acid : Pt = 1 : 1) [87]. The BINAP–Pt species catalyzes the aldol reaction of 3-phenylpropanal and a ketene silyl acetal (**43**) (1.5 equiv) with 2,6-lutidine (amine : Pt = 1 : 1) in CH_2Cl_2 (S/C = 20, −25 °C, 168 h) to give the chiral product **44** in 95% ee. Primary alkyl aldehydes react with high enantioselectivity. Aromatic



Scheme 1.16 Asymmetric aldol reaction catalyzed by BINAP–Pd and BINAP–Pt complexes.

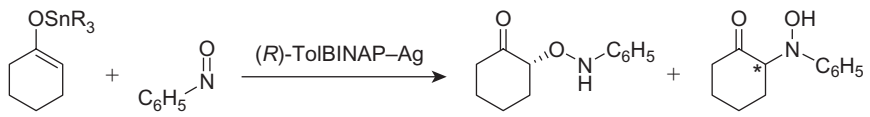
aldehydes show higher reactivity, but the ee of the products is significantly lower. A Pt cationic complex appears to be the active species.

An *in situ* prepared complex from AgF and *(R)*-BINAP in a 1 : 1 ratio catalyzes the asymmetric aldol reaction of trimethoxysilyl enolates and aromatic aldehydes (Scheme 1.17) [88]. When the silyl enolate of *tert*-butyl ethenyl ketone **45** reacts with benzaldehyde in the presence of the BINAP–Ag catalyst in CH_3OH (S/C = 10, −78 to −20 °C, 6 h), the aldol product **46** is obtained in 97% ee (*syn* : *anti* = >99 : 1) [89]. Regardless of *(E/Z)* stereochemistry of the enolate the *syn* diastereo isomer is preferably formed. The reactivity is significantly decreased in the reaction with aliphatic aldehydes. The related catalyst prepared from AgOTf and BINAP promotes the aldol reaction of aldehydes with tributyltin enolates [90]. An enantioselective nitroso aldol reaction has been achieved by the use of the BINAP–Ag chemistry. The reaction of the trimethyltin enolate of cyclohexanone (**47**) and nitrosobenzene (1 equiv) with Ag(OTf)[*(R)*-tolbinap] (S/C = 10) in THF (−78 °C, 2 h) gives exclusively the *(R)* *O*-adduct *(R)*-**48** in 99% ee [91]. In contrast, the tributyltin enolate and nitrosobenzene react in the presence of a bimetallic complex $[Ag(OTf)]_2$[*(R)*-tolbinap] (S/C = 25) in ethylene glycol diethyl ether (−78 °C, 2 h) to afford selectively the *N*-adduct **49** in >99% ee. Thus, a series of *N*- and *O*-nitroso aldol products is synthesized in high chemo- and enantioselectivity.



45 **46**, 97% ee
syn:*anti* = >99:1
84% yield

(*R*)-TolBINAP–Ag = AgF + (*R*)-TolBINAP (Ag:ligand = 1:1)



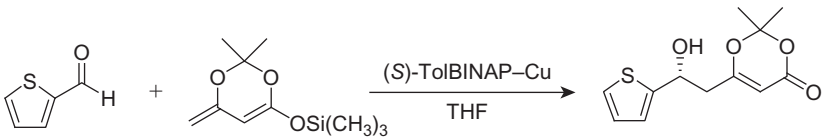
47 (*R*)-**48** **49**

R	(*R*)-TolBINAP–Ag	solvent	% yield	**48:49**	% ee
CH_3	Ag(OTf)[(*R*)-tolbinap]	THF	88	>99:1	99 (**48**)
n-C_4H_9	$[Ag(OTf)]_2$[(*R*)-tolbinap]	$C_2H_5O(CH_2)_2OC_2H_5$	95	4:96	>99 (**49**)

Scheme 1.17 BINAP–Ag catalyzed aldol reactions.

Asymmetric addition of silyl dienolates to aldehydes can be performed with the BINAP–Cu catalyst. For example, thiophene-2-carbaldehyde reacts with **50** catalyzed by a species formed *in situ* from $Cu(OTf)_2$, *(S)*-TolBINAP, and $[(n\text{-}C_4H_9)_4N](C_6H_5)_2SiF_2$ (TBAT) (S/C = 50) in THF (−78 °C, 6–8 h) to afford the *(R)*-adduct *(R)*-**51** in 95% ee almost quantitatively (Scheme 1.18) [92]. A range of aromatic and α,β-unsaturated aldehydes reacts with high enantioselectivity. The

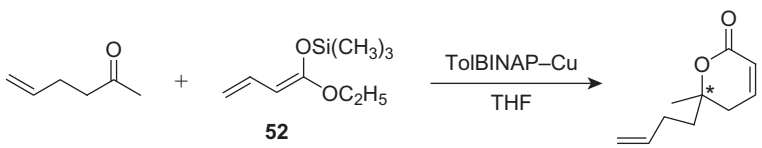
Cu(I) dienolate prepared in this system appears to be a catalytic cycle species. Usually, the aldol reaction of ketones is difficult because of their lower reactivity than that of aldehydes. However, the reaction of methyl primary alkyl ketones and a silyl dienolate (**52**) is successfully catalyzed by a ternary system consisting of $Cu(OTf)_2$, TolBINAP, and TBAT (S/C = 10) at ambient temperature to give the cyclized product **53** in 90% ee and 81% yield [93]. Aryl methyl ketones also react with medium to high enantioselectivity.



50

(*R*)-**51**, 95% ee
98% yield

(*S*)-TolBINAP–Cu = $Cu(OTf)_2$ + (*S*)-TolBINAP + TBAT (Cu:ligand:TBAT = 1:1:2)
TBAT = $[(n\text{-}C_4H_9)_4N](C_6H_5)_3SiF_2$



52

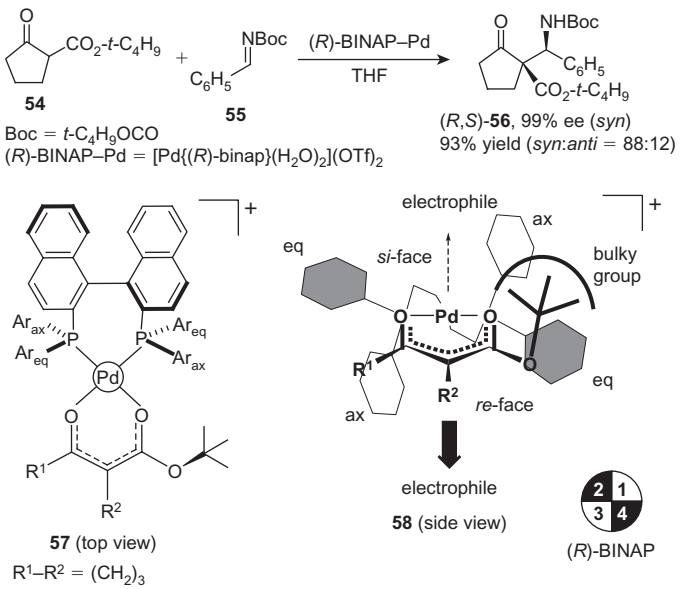
53, 90% ee
81% yield

TolBINAP–Cu = $Cu(OTf)_2$ + TolBINAP + TBAT (Cu:ligand:TBAT = 1:1.1:2)

Scheme 1.18 BINAP–Cu catalyzed aldol reactions with silyl dienolates.

1.8.2
Mannich-Type Reaction

The Mannich-type reaction of a β-keto ester **54** and *N*-Boc-protected imine of benzaldehyde **55** is catalyzed by $[Pd\{(R)\text{-binap}\}(H_2O)_2](OTf)_2$ (S/C = 20) in THF (0 °C, 5 h) to afford the adduct (*R*,*S*)-**56** (*syn* : *anti* = 88 : 12) in 99% ee and 93% yield (Scheme 1.19) [94]. The reaction appears to proceed through the cationic Pd enolate **57**, illustrated in the scheme, with release of H_2O and TfOH from the precatalyst. The bulky *tert*-butyl group of the enolate preferably locates in the first quadrant to avoid the crowded second quadrant with the equatorial *P*-phenyl ring of *(R)*-BINAP (see side view); the *tert*-butyl group then shields the *Si*-face of the enolate. Therefore, the enolate predominantly reacts with the electrophile at the *Re*-face to give the desired enantiomer of product. The chiral structure of BINAP indirectly controls the approach of the electrophile. The *in situ* formed protic acid, TfOH, is presumed to activate the imino substrate. A series of aromatic and α,β-unsaturated imines as well as α-imino esters reacts with high enantioselectivity.

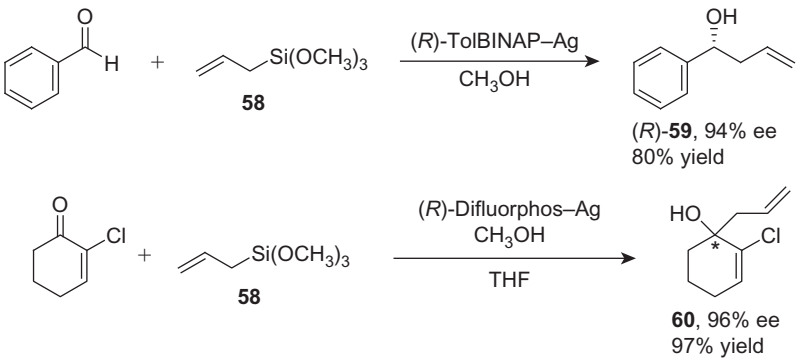


Scheme 1.19 Mannich-type reaction catalyzed by BINAP–Pd complex, and molecular models of the Pd-enolate intermediate.

1.9
Nucleophilic Additions to Carbonyl and Imino Compounds

1.9.1
Allylation

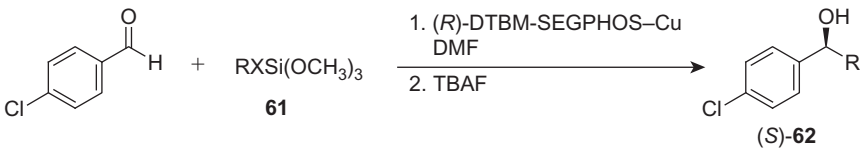
Enantioselective addition of allyltrimethoxysilane (**58**) to aldehydes is performed by the use of BINAP–Ag catalysts (Scheme 1.20) [88, 95]. When benzaldehyde reacts with **58** (1.5 equiv) in the presence of a complex formed *in situ* from AgF and *(R)*-TolBINAP (S/C = 33) in CH_3OH (−20 °C, 4 h), the homoallylic alcohol *(R)*-**59** is obtained in 94% ee and 80% yield [96]. Several aromatic and α,β-unsaturated aldehydes react with good to high enantioselectivity. The allylation of ketones is catalyzed by the chiral Ag complex. Thus, 2-chloro-2-cyclohexenone and **58** (2 equiv) react with the *(R)*-Difluorphos–AgF catalyst (S/C = 20) and CH_3OH (1 equiv) in THF (−78 °C, 12 h) to produce predominantly the 1,2-addition product **60** in 96% ee and 97% yield [97]. This reaction does not proceed in CH_3OH solution, while a stoichiometric amount of CH_3OH in THF improves the product yield. This is because the protonation of a Ag-alkoxide intermediate with CH_3OH occurs smoothly. The reaction of cyclic and acyclic aromatic ketones also proceeds with high enantioselectivity.



Scheme 1.20 Addition of allyltrimethoxysilane to aldehydes and ketones with chiral Ag catalysts.

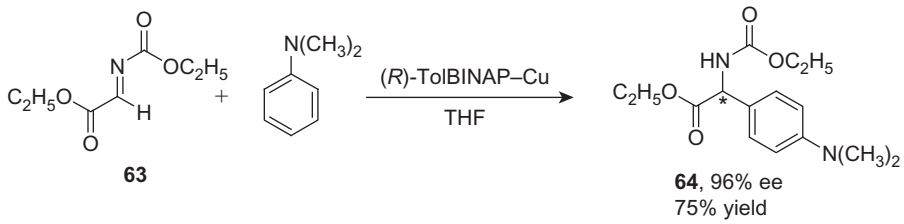
1.9.2
Alkenylation and Arylation

A chiral catalyst generated *in situ* from CuF_2 and *(R)*-DTBM-SEGPHOS (ligand and also reductant) effects asymmetric vinylation and arylation to aldehydes (Scheme 1.21). The reaction of 4-chlorobenzaldehyde and trimethoxyvinylsilane (**61a**; R = CH_2=CH, X = OCH_3; 2 equiv) with the *(R)*-DTBM-SEGPHOS–Cu



61	R	X	% yield	% ee
a	CH_2=CH	OCH_3	99	97
b	C_6H_5	C_6H_5	81	92

TBAF = tetrabutylammonium fluoride
(*R*)-DTBM-SEGPHOS–Cu = CuF_2•$2H_2O$ + (*R*)-DTBM-SEGPHOS (Cu:ligand = 1:2)



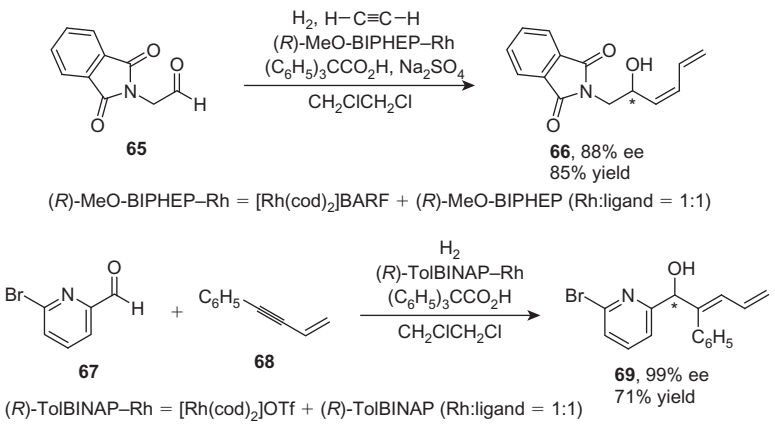
(*R*)-TolBINAP–Cu = $CuPF_6$•$4CH_3CN$ + (*R*)-TolBINAP (Cu:ligand = 1:1.1)

Scheme 1.21 Vinylation and arylation to aldehydes and α-imino esters with chiral Cu catalysts.

catalyst (S/C = 33) in DMF (40 °C, 2 h) affords quantitatively the allylic alcohol *(S)*-**62a** (R = CH_2=CH) in 97% ee [98]. Several aromatic, aliphatic, and α,β-unsaturated aldehydes react with good to excellent levels of enantioselectivity. When the reaction is carried out using dimethoxydiphenylsilane (**61b**; R = X = C_6H_5) (S/C = 33, 40 °C, 1 h), the diaryl methanol *(S)*-**62b** (R = C_6H_5) is obtained in 92% ee. The asymmetric Friedel–Crafts type arylation of imines is catalyzed by a complex prepared *in situ* from $CuPF_6$ and *(R)*-TolBINAP. An *N*-protected α-imino ester (**63**) reacts with *N*,*N*-dimethylaniline in the presence of the *(R)*-TolBINAP–Cu catalyst (S/C = 20) in THF at −78 °C to afford the aromatic α-amino-acid derivative **64** in 96% ee [99]. Only the *para*-substituted compound is detected. A series of aniline analogues can be converted into the desired products in high regio- and enantioselectivity.

1.9.3 Dienylation

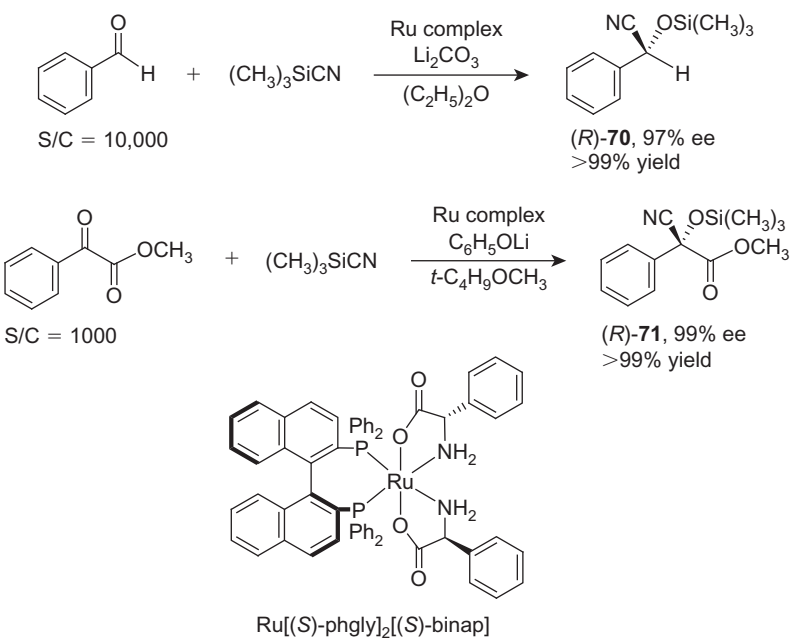
The carbonyl dienylation using acetylene and hydrogen gas is achieved with a cationic Rh catalyst (Scheme 1.22) [100]. Thus, an α-substituted aldehyde **65**, acetylene (1 atm), and H_2 (1 atm) react with a complex formed *in situ* from $[Rh(cod)_2]BARF$ (BARF = $B[3,5\text{-}(CF_3)_2C_6H_3]_4$) and *(R)*-MeO-BIPHEP (S/C = 20) in the presence of triphenylacetic acid (7.5 mol%) and Na_2SO_4 (2 equiv) in CH_2ClCH_2Cl (25 °C, 72 h) to exclusively afford the *(Z)*-dienylation product **66** in 88% ee and 85% yield [101]. This reaction is suggested to proceed through the carbonyl insertion of a rhodacyclopentadiene that is formed by acetylene dimerization. When 6-bromopyridine-2-carboxaldehyde (**67**) reacts with an enyne **68** (2 equiv) and H_2 (1 atm) in the presence of the *(R)*-TolBINAP–$[Rh(cod)_2]OTf$ complex (S/C = 25) and triphenylacetic acid (2 mol%) at 40 °C, the *(E)*-dienylation product **69** is obtained in 99% ee [102]. Many heterocyclic aromatic aldehydes as well as ketones are converted into the desired products in high ee.



Scheme 1.22 Dienylation of aldehydes catalyzed by chiral Rh complexes.

1.9.4
Cyanation

The combined catalyst system of Ru[*(S)*-phgly]$_2$[*(S)*-binap] (phgly = phenylglycinate) and Li_2CO_3 in a 1 : 1 ratio effects asymmetric cyanosilylation of aldehydes (Scheme 1.23). The reaction of benzaldehyde and $(CH_3)_3SiCN$ (1.2 equiv) with the Ru[*(S)*-phgly]$_2$[*(S)*-binap]–Li_2CO_3 system (S/C = 10 000) in diethyl ether (−78 °C, 12 h) affords the cyanohydrin product *(R)*-**70** quantitatively with 97% ee [103]. The Ru complex alone does not show substantial reactivity. The combined system can complete the reaction with an S/C of 100 000 at −40 °C to give **70** in 90% ee. A series of aromatic, heteroaromatic, and α,β-unsaturated aldehydes reacts with high enantioselectivity. Methyl benzoylformate reacts with $(CH_3)_3SiCN$ (2 equiv) catalyzed by the Ru[*(S)*-phgly]$_2$[*(S)*-binap]–C_6H_5OLi system (S/C = 1000) in *t*-$C_4H_9OCH_3$ (−60 °C, 18 h) to give the adduct *(R)*-**71** quantitatively with 99% ee [104]. The reaction is completed with an S/C of 10 000 at −50 °C to afford the product in 98% ee. A range of aromatic, aliphatic, and α,β-unsaturated keto esters can be converted into the silylated products with high enantioselectivity.

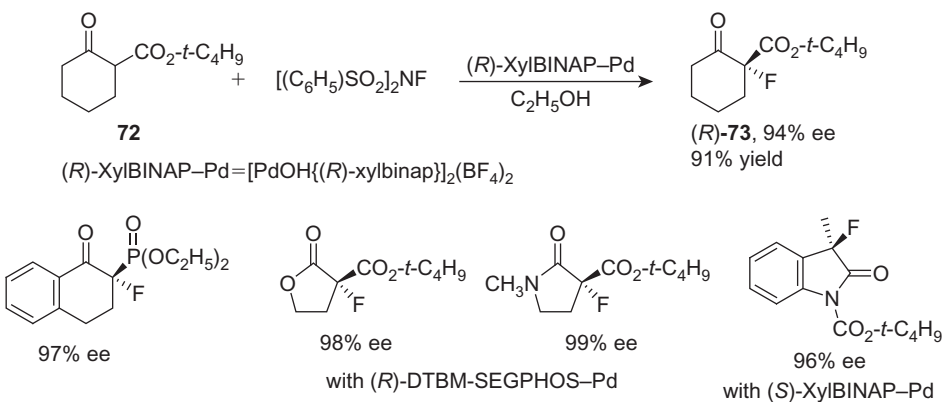


Scheme 1.23 Cyanosilylation of aldehydes and α-keto esters with a chiral Ru · Li catalyst.

1.10
α-Substitution Reactions of Carbonyl Compounds

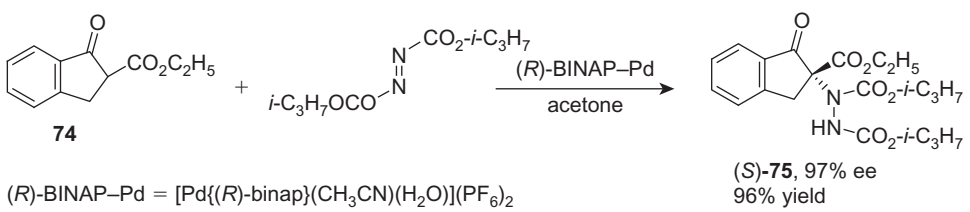
1.10.1
Fluorination and Amination

The α-fluorination of 1,3-dicarbonyl compounds is successfully catalyzed by the XylBINAP– and DTBM-SEGPHOS–Pd complexes [105]. For example, β-keto ester **72** reacts with *N*-fluorobenzenesulfonimide (NFSI; 1.5 equiv) in the presence of [Pd{*(R)*-xylbinap}$(OH)_2$]$(BF_4)_2$ (S/C = 40) in C_2H_5OH (−10 °C, 20 h) to afford the α-fluorinated product *(R)*-**73** in 94% ee and 91% yield (Scheme 1.24) [106]. The mode of enantioface selection is similar to that of the BINAP–Pd catalyzed Mannich-type reaction (Scheme 1.19). The more stereo-demanding XylBINAP is preferable for this reaction. C_2H_5OH is the solvent of choice, because the alcohol appears to facilitate the formation of a Pd-enolate intermediate. This chemistry is applicable to the reaction of β-keto phosphonates and α-*tert*-butoxycarbonyl lactones and lactams as well as *N*-(*tert*-butoxycarbonyl)oxindols [107].



Scheme 1.24 α-Fluorination of carbonyl compounds with chiral Pd catalysts.

The BINAP–Pd catalyst effects the asymmetric reaction of β-keto esters and azodicarboxylates (Scheme 1.25). Thus, cyclic β-keto ester **74** reacts with diisopropyl

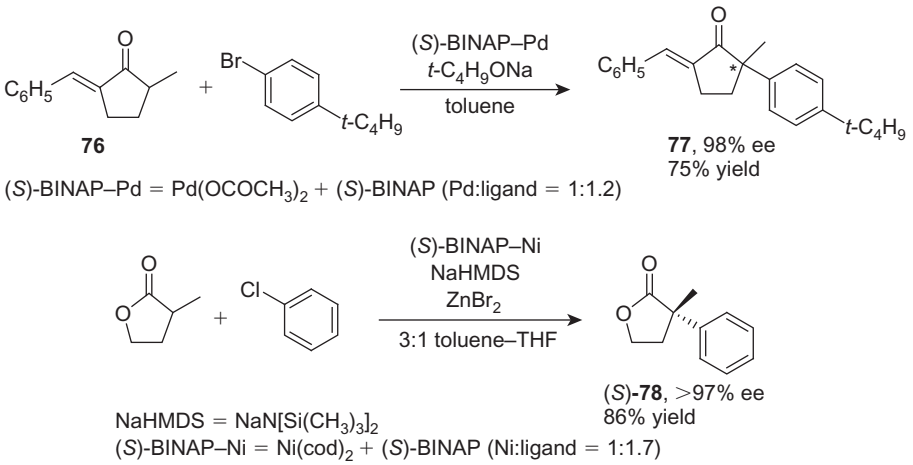


Scheme 1.25 α-Amination of β-keto esters catalyzed by BINAP–Pd complex.

azodicarboxylate using [Pd{*(R)*-binap}(CH_3CN)(H_2O)](PF_6)$_2$ (S/C = 1000) in acetone (room temperature, 70 h) to give the α adduct *(S)*-**75** in 97% ee and 96% yield [108]. The mechanism is closely related to that of α fluorination. α-Cyanoketones can also be used as substrates [109].

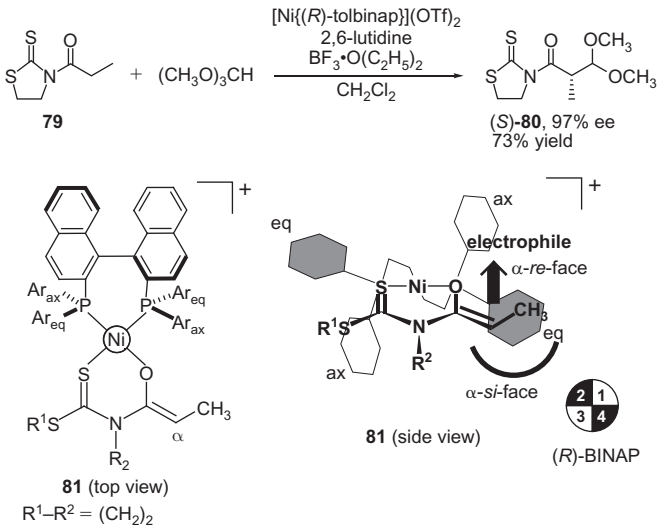
1.10.2 Arylation and Orthoester Alkylation

Asymmetric α-arylation of substituted carbonyl compounds has been developed for the construction of all-carbon chiral quaternary centers. The chiral catalyst formed from Pd($OCOCH_3$)$_2$ and *(S)*-BINAP (S/C = 5) promotes the reaction of an α-methyl ketone (**76**) and 4-*tert*-butylbromobenzene (2 equiv) in the presence of *t*-C_4H_9ONa (2 equiv) at 100 °C to afford the arylation product **77** in 98% ee and 75% yield (Scheme 1.26) [110]. Some specific substrates react with high stereoselectivity. The BINAP–Ni complex effectively catalyzes asymmetric arylation of α-substituted γ-butyrolactones. For example, the reaction of α-methyl-γ-butyrolactone and chlorobenzene (1 equiv) is catalyzed by the *(S)*-BINAP–Ni(cod)$_2$ system (S/C = 20) with NaHMDS (2.3 equiv) and $ZnBr_2$ (15 mol%) in a toluene–THF mixture (60 °C, 17–20 h) to produce the α phenylation product *(S)*-**78** in >97% ee [111]. Addition of the Zn salt significantly increases the reaction rate and yield of products. A range of optically active α-alkyl α-aryl γ-butyrolactones can be synthesized by this method.



Scheme 1.26 α-Arylation of carbonyl compounds with BINAP–Pd and –Ni catalysts.

Asymmetric α alkylation of carbonyl compounds is difficult. However, the reaction of *N*-propionylthiazolidinethione (**79**) and trimethyl orthoformate (3 equiv) is catalyzed by [Ni{*(R)*-tolbinap}](OTf)$_2$ (S/C = 20) with 2,6-lutidine (3 equiv) and $BF_3 \cdot O(C_2H_5)_2$ (3 equiv) in CH_2Cl_2 (−78 °C, 0.5 h) to afford the α adduct *(S)*-**80** in



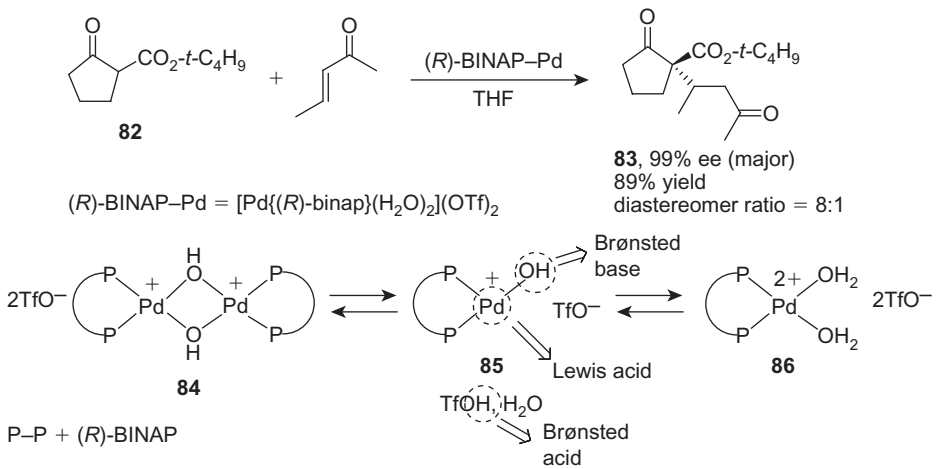
Scheme 1.27 α-Orthoester alkylation catalyzed by TolBINAP–Ni complex, and molecular models of the Ni enolate intermediate.

97% ee and 73% yield (Scheme 1.27) [112]. A series of acyl derivatives of **79** reacts with high enantioselectivity. The corresponding oxazolidinone does not give the desired product. This addition reaction is suggested to proceed via a Ni-enolate intermediate (**81**), the conformation of which is fixed by the S–Ni–O chelate structure. The electrophile (CH_3O^+=$CHOCH_3$) approaches the α-carbon of the enolate from the α-*Re*-face side or α-*Si*-face side (see the side view in Scheme 1.27). The C–C bond formation predominantly occurs at the side of α-*Re*-face [first quadrant of *(R)*-BINAP–Ni complex], because the α-*Si*-face of the enolate is covered by the equatorial *P*-phenyl ring of *(R)*-BINAP at the fourth quadrant. Thus, the *(S)* addition product is obtained in high ee.

1.11
Michael-Type Reactions

1.11.1
Michael Reaction

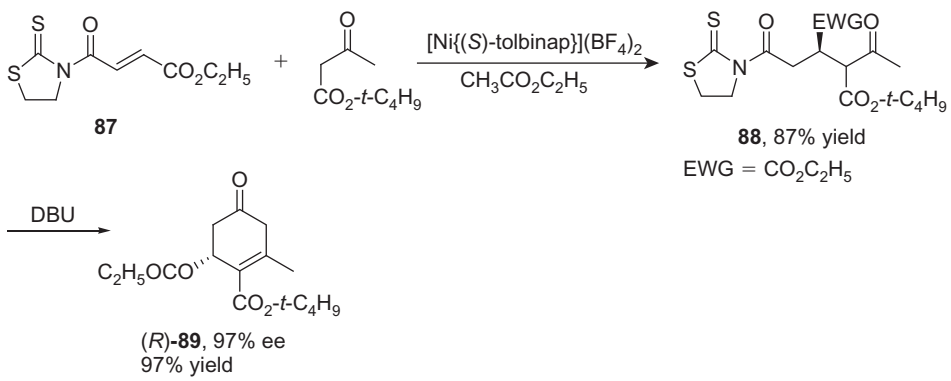
The asymmetric Michael reaction [113] of 1,3-dicarbonyl compounds with α,β-unsaturated ketones proceeds without addition of strong acid or base when $[Pd(binap)(H_2O)_2](OTf)_2$ is used as the catalyst (Scheme 1.28). For instance, cyclic β-keto ester **82** reacts with 3-penten-2-one using the *(R)*-BINAP–Pd aqua complex (S/C = 20) in THF (−20 °C, 24 h) to afford the conjugate addition product **83** in 89% yield (diastereomer ratio = 8 : 1) [114]. The ee value of the major diastereomer is 99%. The aqua Pd complex appears to be in equilibrium among three



Scheme 1.28 Michael reaction catalyzed by BINAP–Pd complex.

species: **84** (a dimer), **85** (a hydroxo complex), and **86** (an aqua complex). Species **85**, which includes a Lewis acidic Pd center and a Brønsted basic OH, is suggested to behave as the catalyst. The acid–base bifunctionality cooperatively forms the Pd-enolate intermediate. The enone substrate is activated by a protonation with TfOH formed in this system. The enantioselective manner is similar to that shown in Section 1.8.2 (Mannich-type reaction) (Scheme 1.19).

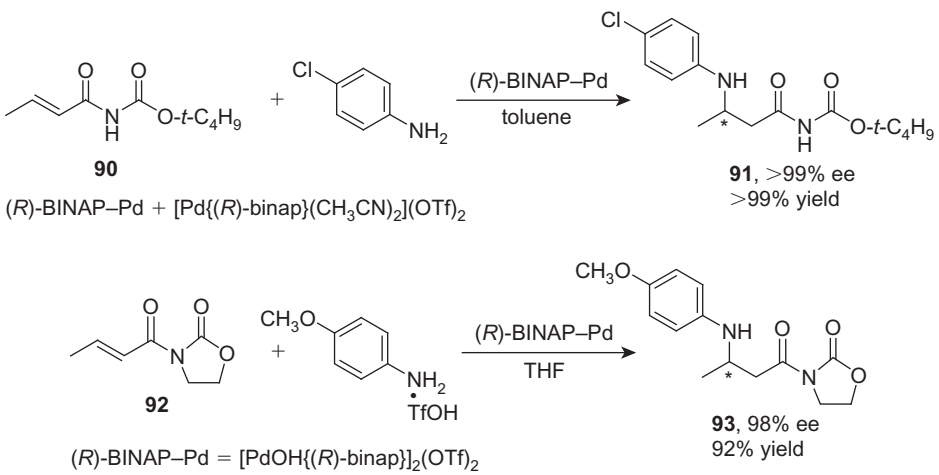
The addition reaction of a fumarate derivative of thiazolidinethione (**87**) and *tert*-butyl 3-oxobutanoate (1.5 equiv) is catalyzed by [Ni{*(S)*-tolbinap}]$(BF_4)_2$ (S/C = 10) in ethyl acetate (0 °C, 12 h) to give the Michael product **88** in 87% yield (Scheme 1.29) [115]. Treatment of **88** with DBU (0.05 equiv) affords quantitatively the dihydropyrone *(R)*-**89** in 97% ee. The nickel catalyst is presumed to activate both the thione Michael acceptor **87** and the nucleophilic β-keto ester.



Scheme 1.29 Michael reaction catalyzed by TolBINAP–Ni complex.

1.11.2
Aza-Michael Reaction

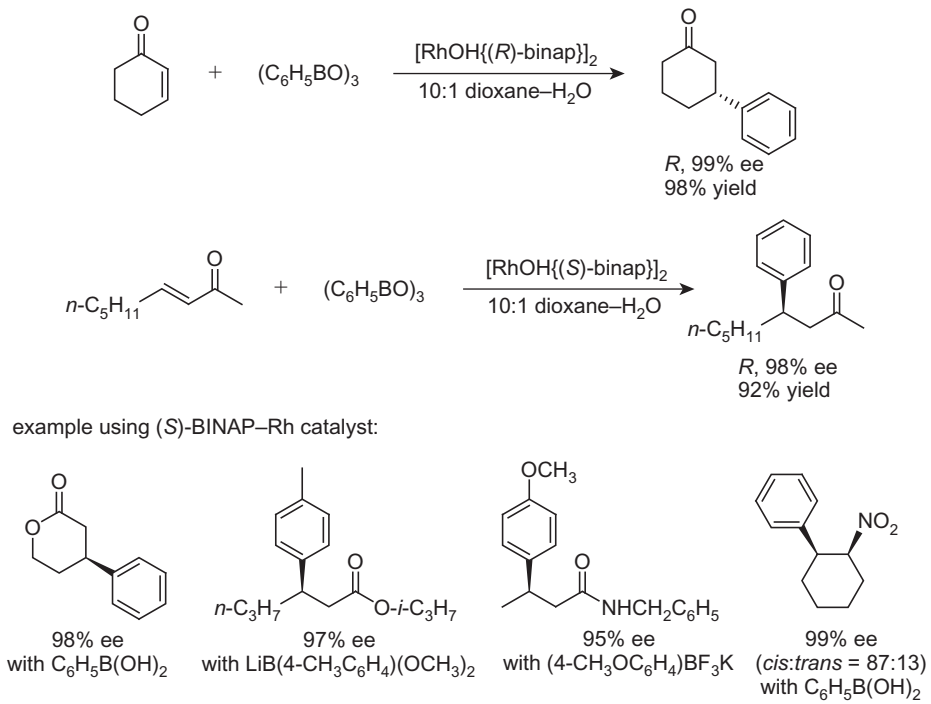
Conjugate addition of primary aromatic amines to *N*-alkenoyl carbamates is catalyzed by the BINAP–Pd complex (Scheme 1.30). The reaction of 4-chloroaniline and a *tert*-butyl alkenoyl carbamate **90** (1.5 equiv) with [Pd{*(R)*-binap}(CH_3CN)]-($OTf)_2$ (S/C = 50) proceeds in toluene (25 °C, 18 h) to give the amination product **91** in >99% ee quantitatively [116]. The reactivity and enantioselectivity depend on the electronic character of the anilines. Alkenoyl oxazolidinone **92** reacts with a salt of 4-methoxyaniline and TfOH (1.5 equiv) in the presence of [PdOH{*(R)*-binap}]$_2$($OTf)_2$ (S/C = 50) in THF (room temperature, 12 h) to afford the β-amination product **93** in 98% ee and 92% yield [117]. A catalytic amount of the basic PdOH complex reacts with the aniline salt to generate the appropriate amount of the free amine, so that the uncatalyzed addition reaction with the aniline is inhibited. The reaction using aniline analogues substituted by electron-rich and -deficient groups also shows high enantioselectivity.



Scheme 1.30 Aza-Michael reactions catalyzed by BINAP–Pd complexes.

1.12
Conjugate Additions Using Organoboron and Grignard Reagents

Asymmetric 1,4-addition reactions of α,β-unsaturated carbonyl compounds are versatile procedures for the synthesis of useful chiral β-substituted carbonyl compounds [118, 119]. The reaction of 2-cyclohexenone and phenylboroxine (2.5 equiv) is catalyzed by [RhOH{*(R)*-binap}]$_2$ (S/C = 33) in a 10 : 1 mixture of dioxane and H_2O (35 °C, 3 h) to afford *(R)*-3-phenylcyclohexanone in 99% ee



Scheme 1.31 Conjugate addition reactions using arylboron reagents catalyzed by BINAP–Rh complexes.

quantitatively (Scheme 1.31) [120]. Under the same conditions 3-nonen-2-one, an acyclic enone, is converted into the *(R)* phenylation product in 98% ee. This method is applied to various cyclic and acyclic esters and amides as well as 1-alkenylphosphonates and nitroalkenes by appropriate use of the borane reagents, such as arylboronic acids, $LiBAr(OCH_3)_3$, and $ArBF_3K$ [121]. Arylsiloxanes are also used for this reaction [122].

Figure 1.10a illustrates a plausible reaction mechanism for the 1,4-addition of aryl boronic acids to α,β-unsaturated carbonyl compounds catalyzed by the *(R)*-BINAP–Rh complex [120]. The [Rh]OH complex **94** is converted into the [Rh]Ar species **95** by transmetallation of an aryl group from boron to rhodium. An enone substrate is inserted into the Rh–Ar bond to form an oxa-π-allyl-rhodium intermediate **96**. Hydrolysis of **96** by H_2O releases the arylation product along with regeneration of the catalyst species **94.** Therefore, an addition of H_2O in the reaction media is necessary. The configuration of the products is determined at the insertion of the enone into the Rh–Ar bond (**95**→**96**). At this step an enone substrate (e.g., 2-cyclohexenone) coordinates with the α-*Re*-face to avoid steric hindrance caused by an equatorial *P*-phenyl ring of the *(R)*-BINAP at the second quadrant (Figure 1.10b; **97**). Therefore, migration of an Ar group from the Rh center to the β-carbon of 2-cyclohexenone forms the β-*(R)* configuration in the intermediate **96.**

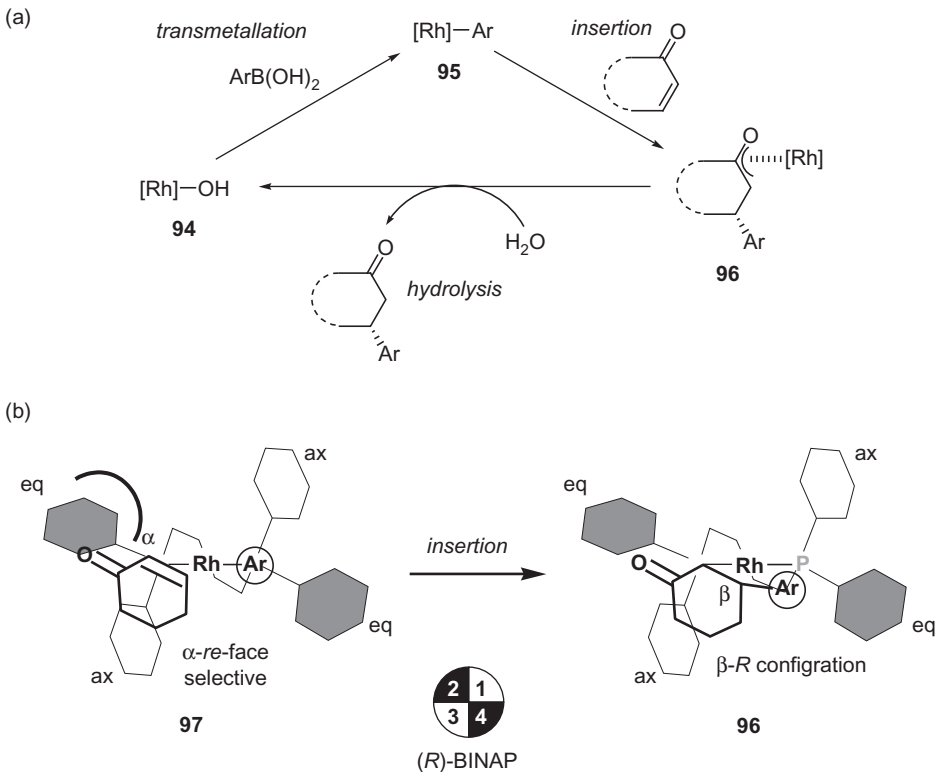
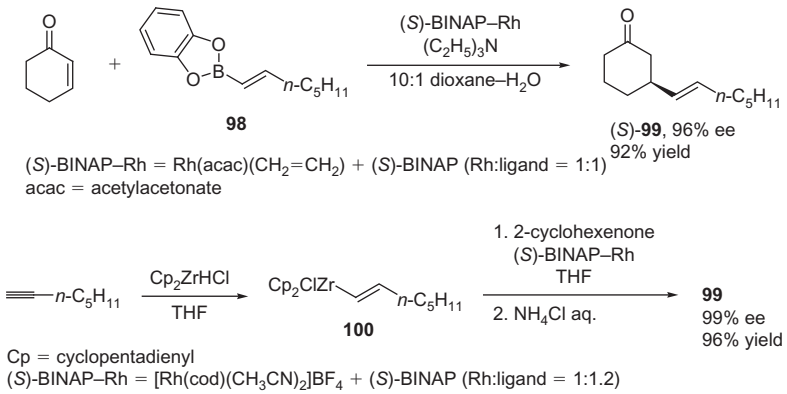


Figure 1.10 (a) Plausible 1,4-addition reaction mechanism catalyzed by *(R)*-BINAP–Rh complex; (b) molecular models of the stereo-determining step.

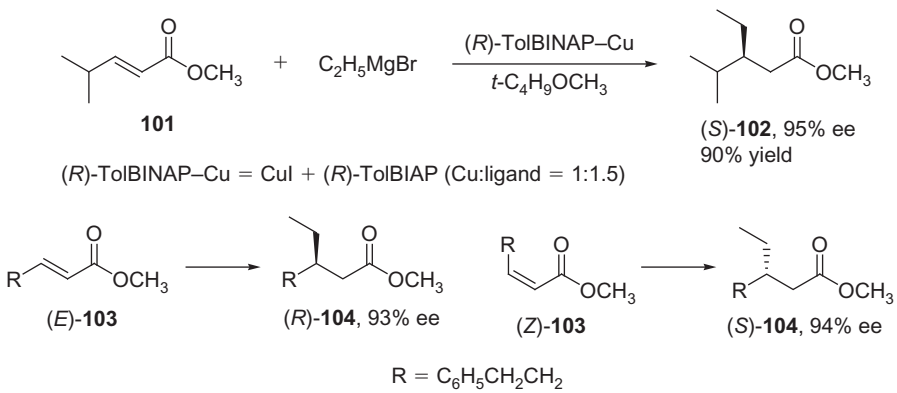
The BINAP–Rh complexes also catalyze the asymmetric 1,4-addition of alkenyl groups (Scheme 1.32). 2-Cyclohexenone reacts with an alkenylcatecholborane **98** (5 equiv) using the *(S)*-BINAP–Rh(acac)(CH_2=CH_2) system as a catalyst (S/C = 33) and $(C_2H_5)_3N$ (10 equiv) (100 °C, 3 h) to furnish the alkenylation product *(S)*-**99** in 96% ee and 92% yield [123]. Addition of a base is necessary to trap acidic alkenylboronic acid and catechol generated during the reaction. The conjugate alkenylation of 2-cyclohexenone with an alkenyl Zr reagent (**100**) (1.2 equiv), which is prepared by hydrozirconation of 1-heptyne with Cp_2ZrHCl (room temperature, 0.5 h), can be carried out with the *(S)*-BINAP–[Rh(cod)-$(CH_3CN)_2$]BF_4 system (S/C = 20) in an aprotic media (room temperature, 5 h) to give the adduct **99** in 99% ee and 96% yield after usual workup [124]. The enantioselectivity is somewhat decreased in the reaction of acyclic enones.

Asymmetric 1,4-addition of alkyl groups by Grignard reagents to α,β-unsaturated esters is catalyzed by the BINAP–Cu complex. For example, unsaturated ester **101** and C_2H_5MgBr (5 equiv) react with the *(R)*-TolBINAP–CuI system (S/C = 100) in *t*-$C_4H_9OCH_3$ (−40 °C, 2–3 h) to afford the β-substituted ester *(S)*-**102** in 95% ee and 90% yield (Scheme 1.33) [125]. The absolute configuration of



Scheme 1.32 Conjugate addition reactions using alkenyl metal reagents catalyzed by BINAP–Rh complexes.

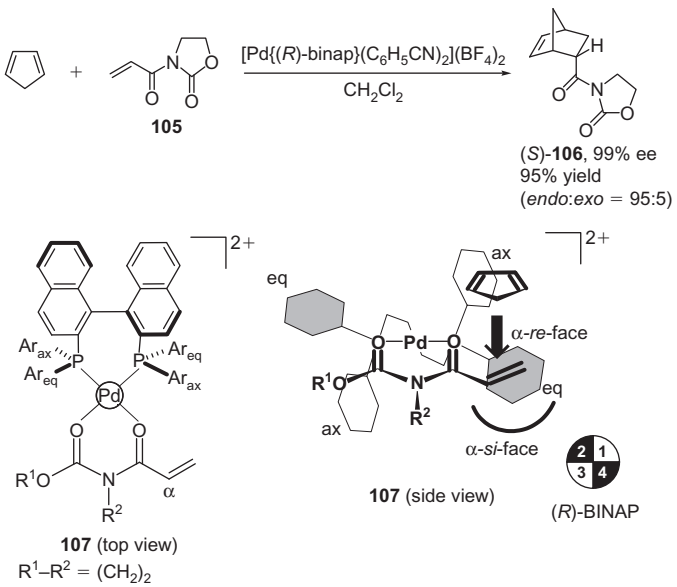
product is reversed by using the geometrical isomer. Thus, methyl *(E)*-5-phenyl-2-pentenoate [*(E)*-**103**] is converted into the *(R)* product *(R)*-**104** in 93% ee with the *(R)*-TolBINAP–Cu catalyst. On the other hand, the reaction of *(Z)*-**103** results in the *(S)* adduct *(S)*-**104** in 94% ee catalyzed by the same complex.



Scheme 1.33 1,4-Addition of alkyl groups using Grignard reagents catalyzed by TolBINAP–Cu complex.

1.13 Diels–Alder Reaction

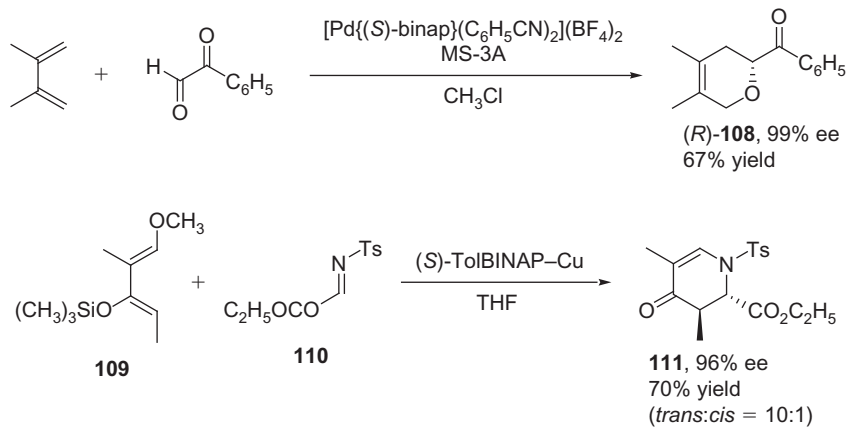
A dicationic BINAP–Pd complex acts as an efficient Lewis-acidic catalyst for asymmetric Diels–Alder cyclization [126]. The reaction of *N*-acryloyloxazolidinone (**105**) and cyclopentadiene (5 equiv) with [Pd{*(R)*-binap}(C_6H_5CN)](BF_4)$_2$ (S/C = 10) in CH_2Cl_2 (−50 °C, 24 h) affords the cyclization product *(S)*-**106** in



Scheme 1.34 Diels–Alder reaction catalyzed by BINAP–Pd complex, and molecular models of the reaction intermediate.

99% ee and 95% yield (*endo* : *exo* = 95 : 5) (Scheme 1.34) [127]. The enantioselectivity depends on the nature of the counter anion (77% ee with the PF_6^- complex). The reaction appears to proceed through the intermediate **107**, which has a six-membered Pd–**105** chelate-ring structure. The diene approaches the dienophile from the side of α-*Re*-face to avoid repulsive interaction with the *(R)*-BINAP's equatorial *P*-phenyl ring at the fourth quadrant (see the side view of **107**), exclusively forming the *(S)* chiral center.

The BINAP–Pd has been applied successfully to the asymmetric hetero-Diels–Alder reaction [128]. Thus, phenylglyoxal reacts with 2,3-dimethyl-1,3-butadiene (1.5 equiv) in the presence of $[Pd\{(S)\text{-binap}\}(C_6H_5CN)](BF_4)_2$ (S/C = 50) in CH_3Cl (0 °C, 24 h) to give the cycloadduct *(R)*-**108** in 99% ee and 67% yield (Scheme 1.35) [129]. An addition of MS-3A increases the enantioselectivity. A trace amount of H_2O existing in the reaction system may react with the Pd complex to generate acidic impurities, causing an achiral pathway of the reaction. The corresponding Pt complex under the same conditions also exhibits high enantioselectivity [130]. The Pd-catalyzed asymmetric 1,3-dipolar cyclization of nitrones and *N*-alkenoyloxazolidinones is also studied [131]. The asymmetric cyclization of a kind of Danishefsky's diene (**109**) and an *N*-tosyl-α-imino ester **110** (1.25 equiv) with the *(S)*-TolBINAP–$CuClO_4 \cdot 4CH_3CN$ system (S/C = 100) in THF at −78 °C produces the aza-cyclization product **111** in 96% ee and 70% yield (trans : cis = 10 : 1) [132]. The use of several other solvents decreases both diastereoselectivity and enantioselectivity. The SEGPHOS–Cu catalyzed nitroso Diels–Alder reaction proceeds in a highly diastereo- and enantioselective



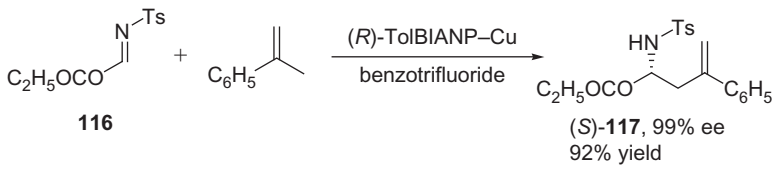
Scheme 1.35 Hetero-Diels–Alder reactions and a molecular model of the reaction intermediate with *(R)*-SEGPHOS–Cu catalyst.

manner. Thus, 6-methylnitrosopyridine (**113**) and a diene (**112**) (1.2 equiv) react with the *(R)*-SEGPHOS–$[Cu(CH_3CN)_4]PF_6$ system (S/C = 10) in CH_2Cl_2 (−85 to −20 °C, 6 h) to afford quantitatively the adduct **114** in 97% ee as a single diastereomer [133]. A methyl group at the 6 position of nitrosopyridine is essential to attain high enantioselectivity. The reaction is supposed to proceed through a tetrahedral intermediate (**115**) with a Cu–**113** chelate ring. The diene horizontally approaches the nitroso N=O from the *Re*-face direction at the first

quadrant, because the opposite side is blocked by the equatorial *P*-phenyl ring of *(R)*-SEGPHOS at the second quadrant, resulting in **114** predominantly.

1.14 Ene Reaction

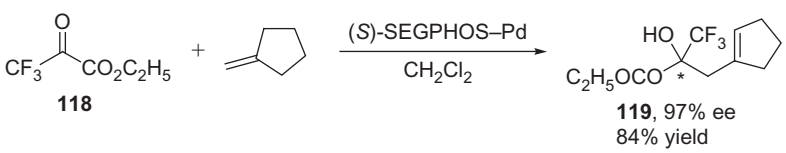
Under appropriate Lewis-acidic conditions alkenes react with imino and carbonyl compounds [134]. An *N*-toluenesulfonyl-α-imino ester (**116**) and α-methylstyrene (2 equiv) react with the *(R)*-TolBINAP–$[Cu(CH_3CN)_4]ClO_4$ system (S/C = 20) in benzotrifluoride, a polar aromatic solvent, (room temperature, 18 h) to afford the α-amino ester *(S)*-**117** in 99% ee and 92% yield (Scheme 1.36) [135]. Hetero-substituted alkenes are applicable to this reaction. A carbonyl-ene reaction is carried out with the SEGPHOS–Pd catalyst. Thus, methylenecyclopentane and ethyl trifluoropyruvate (**118;** 1.5 equiv) react, using a dicationic catalyst prepared *in situ* from $PdCl_2$[*(S)*-segphos] and $AgSbF_6$ (S/C = 20) in CH_2Cl_2 (room temperature, 15 min), to give the ene-adduct **119** in 97% ee and 84% yield [136]. Several mono- and di-substituted alkenes have been used for this reaction. The corresponding Pt complexes also exhibit high catalytic efficiency [130, 137].



116

(*S*)-**117**, 99% ee
92% yield

(*R*)-TolBIANP–Cu = $[Cu(CH_3CN)_4]ClO_4$ + (*R*)-TolBINAP (Cu:ligand = 1:1.04)



118

119, 97% ee
84% yield

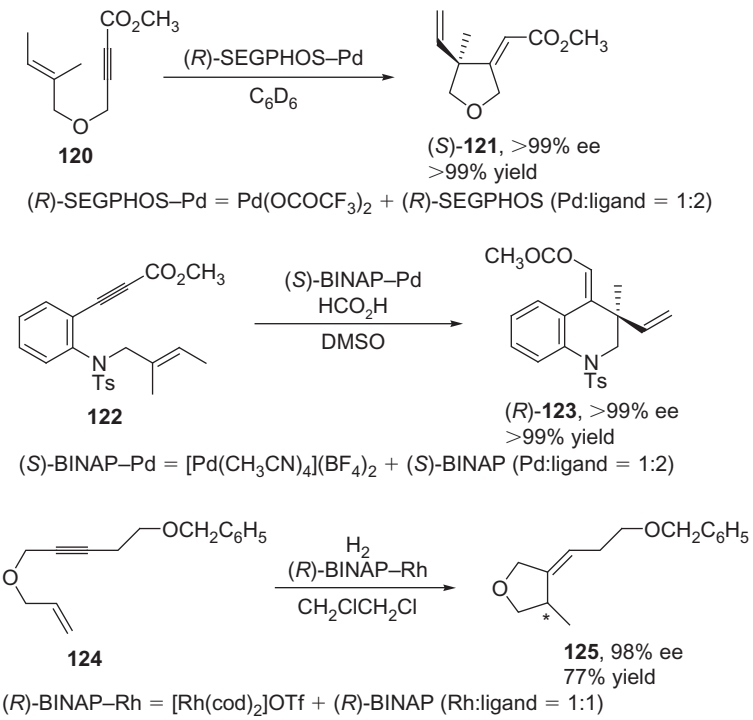
(*S*)-SEGPHOS–Pd = $PdCl_2$[(*S*)-segphos] + $AgSbF_6$ (Pd:Ag = 1:2.2)

Scheme 1.36 Imine- and carbonyl-ene reactions catalyzed by Cu and Pd complexes.

1.15 Cyclization

1.15.1 Intramolecular Reactions of Enynes

A SEGPHOS–Pd complex effectively catalyzes the asymmetric ene-type cyclization of a 1,6-enyne (**120**, Scheme 1.37) [138]. The reaction with the *(R)*-SEGPHOS–Pd-$(OCOCF_3)_2$ system (S/C = 20) proceeds in C_6D_6 (100 °C, 37 h) to give the

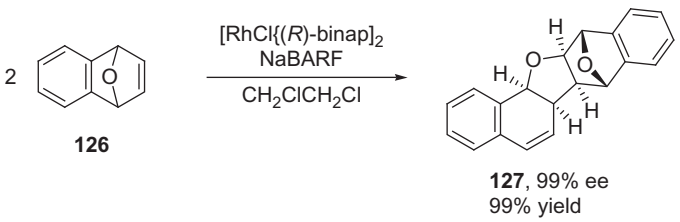


Scheme 1.37 Cyclization of 1,6- and 1,7-enynes catalyzed by chiral Pd and Rh complexes.

cyclization product *(S)*-**121** in pure form. The reactivity and enantioselectivity depend on the solvent polarity, which closely relates to the reaction mechanism. When a 1,7-enyne (**122**) reacts with the *(S)*-BINAP–$[Pd(CH_3CN)_4](BF_4)_2$ system (S/C = 20) and HCO_2H (1 equiv) in DMSO (100 °C, 3 h) the quinoline derivative *(R)*-**123** is obtained in >99% ee quantitatively [139]. The spiro compound is formed from the substrate with a cyclic alkene moiety. A BINAP–Rh complex also catalyzes the reaction of related 1,6-enynes with nearly perfect enantioselectivity [140]. Reductive cyclization of 1,6-enyne **124** with the *(R)*-BINAP–$[Rh(cod)_2]OTf$ system (S/C = 20) under a H_2 atmosphere (1 atm) in CH_2ClCH_2Cl (25 °C, 2–3 h) affords the desired cyclization product **125** in 98% ee and 77% yield [141]. The reaction is suggested to proceed via a Rh-metallocycle intermediate. A series of carbo- and heterocyclic compounds has been synthesized by this method.

1.15.2
[3+2] and [5+2] Cycloaddition Reactions

Cyclodimerization of oxabenzonorbornadienes is catalyzed by the BINAP–Rh complex in a highly enantioselective manner (Scheme 1.38). When the reaction of **126** is carried out with $[RhCl\{(R)\text{-binap}\}]_2$ and NaBARF (S/C = 100,



Scheme 1.38 BINAP–Rh catalyzed [3 + 2] cycloaddition reaction.

Rh : Na = 1 : 2) in CH_2ClCH_2Cl (40 °C, 1 h), the polycyclic tetrahydrofuran derivative **127** is obtained in 99% ee quantitatively [142]. The reaction of **126** and dimethyl 2-butynedioate gives the cross-cycloaddition product in high ee.

Figure 1.11a illustrates a proposed reaction mechanism of the cyclodimerization of **126** [142]. A cationic BINAP–Rh(I) species **128** is generated in this system; **128** reacts with two **126** molecules to form the rhodacyclopentane intermediate **129,** which is converted into the alkoxorhodium(III) species **130** by β-oxygen elimination. Then, reductive elimination of the sp^3 C–O bond from **130** produces the product **127** with regeneration of **128.** The stereochemistry of **127** is determined at the formation of the intermediate **129.** Figure 1.11b shows two diastereomeric molecular models of **129.** Two **126** molecules approach the Rh center via the open space of the *(R)*-BINAP–Rh species **128** (first and third quadrants) to form the favored intermediate **131,** which is then converted into the product **127.** In contrast, the diastereomeric intermediate **132** suffers notable steric repulsion between the *(R)*-BINAP's equatorial *P*-phenyl rings and oxabenzonorbornadiene moieties at the second and fourth quadrants of the complex.

The TolBINAP–Pd complex catalyzes the asymmetric cycloaddition of vinyloxiranes and carbodiimides (Scheme 1.39). For example, the reaction of a mixture of a vinyloxirane **133** and di(4-chlorophenyl)carbodiimide (**134**; 1 equiv) with the *(S)*-TolBINAP–$Pd_2(dba)_3 \cdot CHCl_3$ system (S/C = 17) in THF (room temperature, 15 h) produces the 4-vinyl-1,3-oxazolidin-2-imine *(R)*-**135** in 94% ee and 95% yield [143]. Several arylcarbodiimides react with high stereoselectivity. Cyclization of an azalactone (**136**) with *N*-phenylmaleimide (1.5 equiv) using $(AuOCOC_6H_5)_2$[*(R)*-dtbm-segphos] (S/C = 50) in acetone (room temperature, 24 h) followed by a methyl-esterification affords the cycloadduct **137** in 98% ee and 84% yield [144]. No *endo*-isomer is observed. A range of electron-deficient alkenes can be used as dipolarophiles. The Au complex is presumed to interact with the sp^2-N of **136** but not C=C-π bond.

Intramolecular [5 + 2] cycloaddition of vinylcyclopropanes tethered with alkene moieties is catalyzed by the BINAP–Rh complex (Scheme 1.40). Thus, a cyclopropyl diene (**138**) reacts with [Rh{*(R)*-binap}]SbF_6 (S/C = 10) in CH_2ClCH_2Cl (70 °C, 2 days) to afford the bicyclo[5.3.0] product **139** in 99% ee and 80% yield [145]. The enantioselectivity, notably, depends on the substrate structure. Vinylcyclopropanes with malono-diester and sulfonamide groups are converted into the corresponding products in high ee.

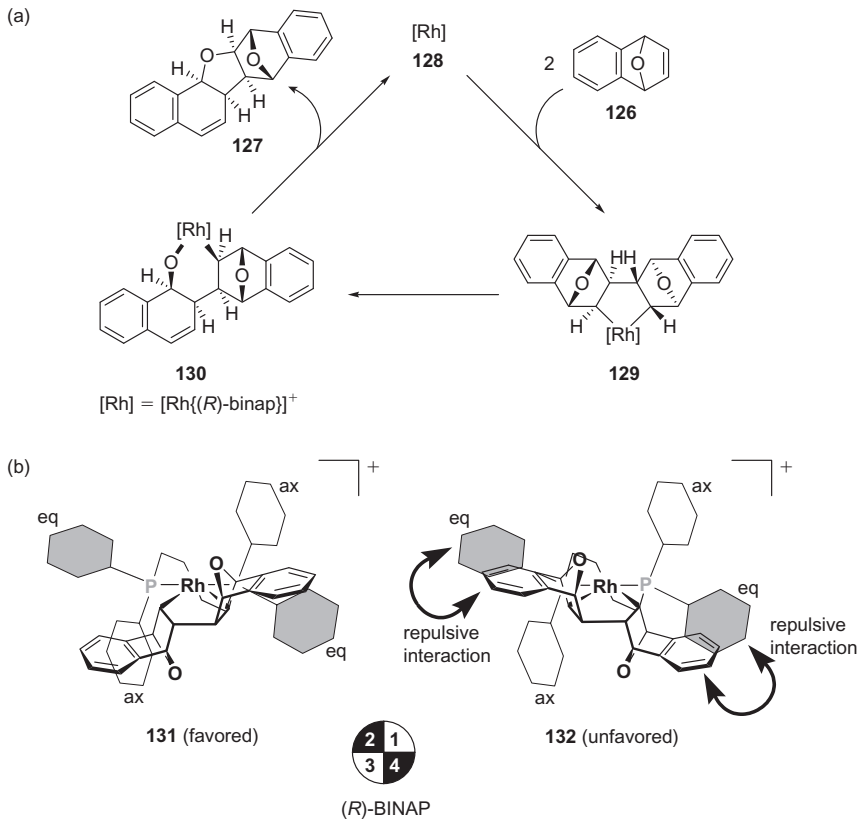
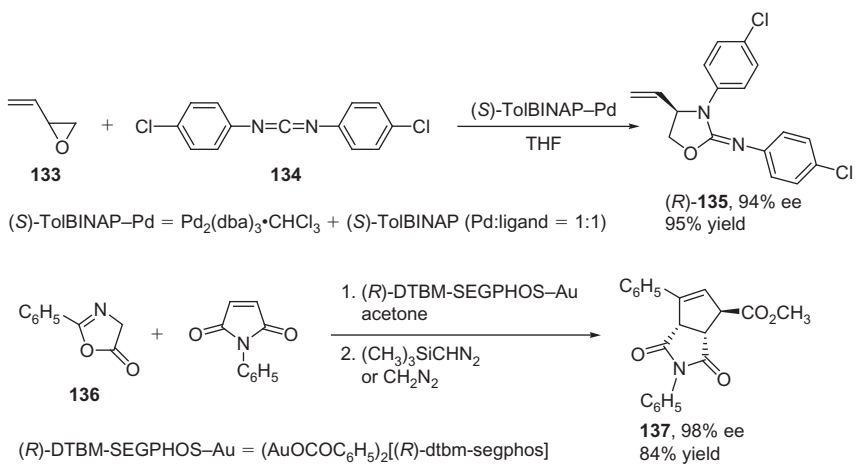
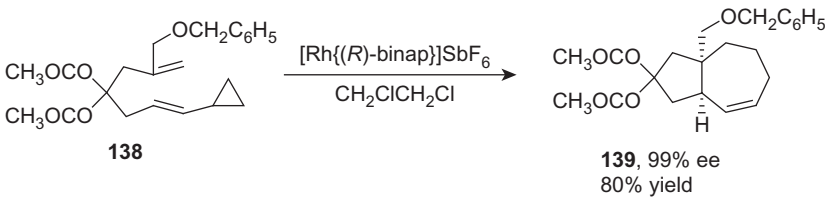


Figure 1.11 (a) Plausible [3 + 2] cycloaddition reaction mechanism catalyzed by *(R)*-BINAP–Rh complex; (b) molecular models of the diastereomeric intermediates **131** and **132**.



Scheme 1.39 [3+2] cycloaddition reactions with chiral Pd and Au catalysts.



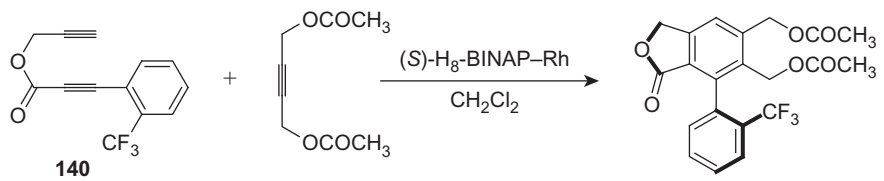
138

139, 99% ee
80% yield

Scheme 1.40 BINAP–Rh catalyzed [5+2] cycloaddition reaction.

1.15.3
[2 + 2 + 2] Cycloaddition Reactions

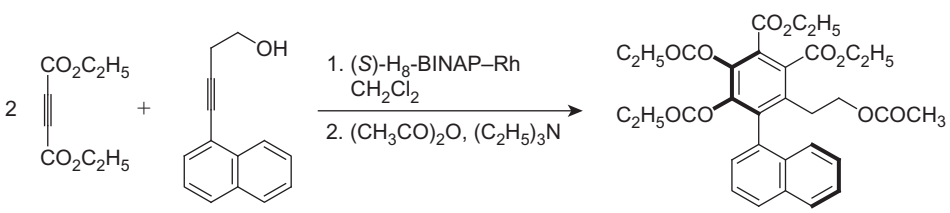
Asymmetric cyclotrimerization of α,ω-diynes and monoynes forms axially chiral biaryl compounds in the presence of the H_8-BINAP–Rh catalyst (Scheme 1.41) [146]. For example, unsymmetric diene **140** and 1,4-diacetoxy-2-butyne (5 equiv) react with the *(S)*-H_8-BINAP–$[Rh(cod)_2]BF_4$ system (S/C = 20) in CH_2Cl_2 (room temperature, 3 h) to afford the chiral phthalide derivative *(R)*-**141** in >99% ee and 73% yield [147]. The presence of an *ortho*-substituted aryl group in **140** is crucial to achieve high enantioselectivity. Terminal monoynes are also appropriate substrates for this reaction. This methodology has been applied to the intermolecular cross-cyclotrimerization of internal alkynes with two equivalents of dialkyl acetylenedicarboxylates. Thus, an internal alkynyl alcohol (**142**) and diethyl acetylenedicarboxylate (2 equiv) react with the *(S)*-H_8-BINAP–Rh catalyst (S/C = 20) followed by acetylation to give the biaryl product **143** in 96% ee and 75% yield [148].



140

(*R*)-**141**, >99% ee
73% yield

(*S*)-H_8-BINAP–Rh = $[Rh(cod)_2]BF_4$ + (*S*)-H_8-BINAP (Rh:ligand = 1:1)



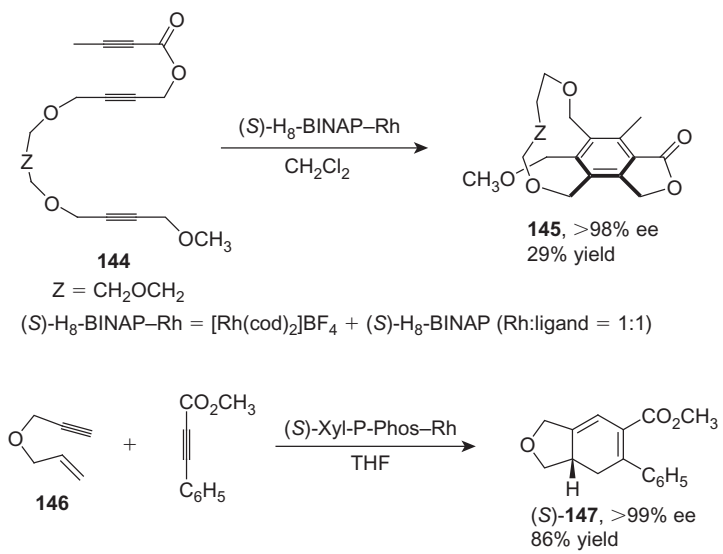
142

143, 96% ee
75% yield

(*S*)-H_8-BINAP–Rh = $[Rh(cod)_2]BF_4$ + (*S*)-H8-BINAP (Rh:ligand = 1:1)

Scheme 1.41 [2+2+2] cycloadditions of alkynes to form axially chiral biaryls.

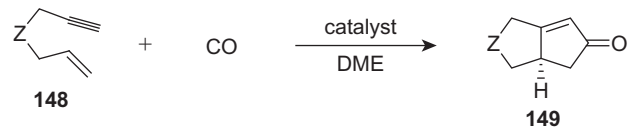
Planar-chiral metacyclophanes can be synthesized by the H_8-BINAP–Rh catalyzed cyclotrimerization of appropriate triynes (Scheme 1.42). For instance, a triyne (**144**) is cyclized with the *(R)*-H_8-BINAP–$[Rh(cod)_2]BF_4$ catalyst system (S/C = 50) in CH_2Cl_2 (room temperature, 16 h) to afford the [7]–[10]metacyclophane product **145** in an optically pure form, although the chemical yield is relatively low [149]. The corresponding [7]–[10]orthocyclophane is obtained as a by-product. The asymmetric [2 + 2 + 2] cycloaddition successfully controls the central chirality of products [150, 151]. The reaction of a 1,6-enyne (**146**) with an ether-linkage and methyl phenylpropiolate (3 equiv) is catalyzed by the *(S)*-Xyl-P-Phos–$[RhCl(cod)]_2$–$AgBF_4$ system (S/C = 10) in THF (60 °C, about 2.5 h) to produce the bicyclohexadiene *(S)*-**147** in >99% ee as a single regioisomer [150]. The steric hindrance with *P*-xylyl groups of Xyl-P-Phos leads to the high regioselectivity, and the narrower dihedral angle of this ligand increases the enantioselectivity. 1,6-Enynes tethered with NTs and $C(CO_2CH_3)_2$ moieties are also converted into the desired products in high stereoselectivity.



Scheme 1.42 [2+2+2] cycloadditions with control of planar and central chirality.

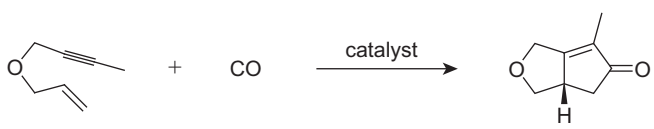
1.15.4
Pauson–Khand Type Reactions

Asymmetric cyclization of 1,6-enynes with CO in the presence of appropriate catalysts gives the corresponding 2-cyclopentenones in high stereoselectivity (Scheme 1.43) [152]. A Co complex prepared *in situ* from $Co_2(CO)_8$ and *(S)*-BINAP in a 1 : 1



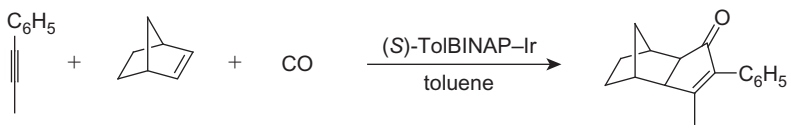
148 **149**

148	catalyst	% ee	% yield
a; Z = NTs	$Co_2(CO)_8$ + (*S*)-BINAP (Co:ligand = 2:1)	93	60
b; Z = $C(CO_2CH_3)_2$	$Co_4(CO)_{12}$ + (*S*)-TolBINAP (Co:ligand = 2:1)	96	85



150 **151**

ctsylata	solvent	% ee	% yield
$[RhCl(CO)_2]_2$ + (*S*)-BINAP + AgOTf (Rh:ligand:Ag = 1:1:2)	THF	96	40
$[IrCl(cod)]_2$ + (*S*)-TolBINAP (Ir:ligand = 1:1)	toluene	98	61



152, 93% ee

(*S*)-TolBINAP–Ir = $[IrCl(cod)]_2$ + (*S*)-TolBINAP (Ir:ligand = 1:1) 32% yield

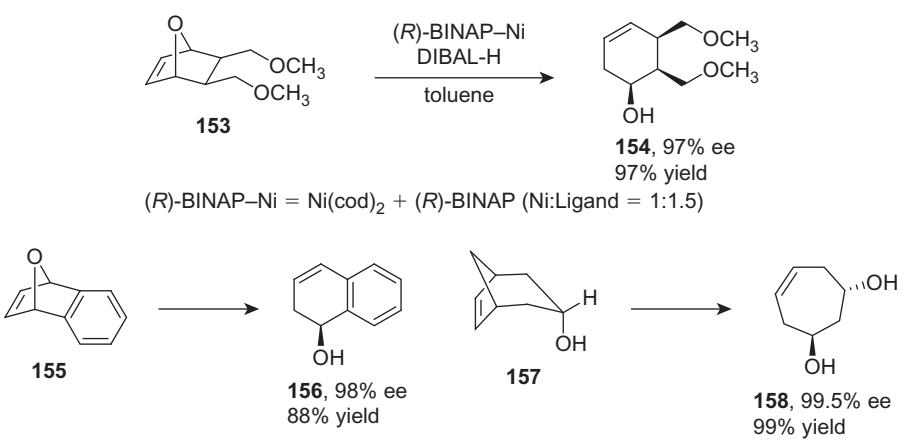
Scheme 1.43 Pauson–Khand-type cycloaddition reactions with BINAP–metal catalysts.

ratio catalyzes the cyclocarbonylation of an enyne (**148a,** Z = NTs) in DME (S/C = 5, 1 atm CO, 85 °C, 15 h) to furnish the bicyclo[3.3.0]enone **149a** in 93% ee and 60% yield [153]. The cycloaddition of **148b** [Z = $C(CO_2CH_3)_2$] with the *(S)*-TolBINAP–$Co_4(CO)_{12}$ system (S/C = 13) gives the product **149b** in 96% ee and 85% yield under similar conditions (1.05 atm CO, 75 °C, 5 h) [154]. The bimetallic complex $Co_2(binap)(CO)_6$ appears to be a key intermediate for this reaction [155]. The MeO-BIPHEP–Co complex also exhibits good catalyst performance [156]. A cationic complex formed from *(S)*-BINAP, $[RhCl(CO)_2]_2$, and AgOTf (S/C = 17) effects the asymmetric cyclocarbonylation of allyl 2-butynyl ether **150** with CO (1 atm) in THF (90 °C, 5 h) to produce the adduct **151** in 96% ee and 40% yield [157]. The same reaction is catalyzed by a neutral complex consisting of $[IrCl(cod)]_2$ and *(S)*-TolBINAP (S/C = 5) under the toluene reflux conditions (1 atm CO, 20 h) to

afford **151** in 98% ee and 61% yield [158]. This Ir system catalyzes the three-component cycloaddition of 1-phenyl-1-propyne, norbornene, and CO (S/C = 5, toluene reflux) to give the adduct **152** in 93% ee and 32% yield as a single regioisomer. Rhodium complexes bearing other chiral biaryl diphosphines, including BIPHEMP, BisbenzodioxanPhos (SYNPHOS), Difluorphos, and P-Phos also catalyze the Pauson–Khand-type reactions with high enantioselectivity [159].

1.16 Ring-Opening Reactions

Enantioselective reductive ring-opening reaction of meso oxabicyclic alkenes using DIBAL-H as a hydride source can be performed by the BINAP–Ni catalysis [160]. For example, an oxabicyclo[2.2.1] compound **153** is treated with DIBAL-H (1.1 equiv) in the presence of the *(R)*-BINAP–Ni(cod)$_2$ system (S/C = 7) in toluene (room temperature, 1 h) to afford the cyclohexenol **154** in 97% ee and 97% yield (Scheme 1.44) [161]. Slow addition of the reductant is crucial to achieve high enantioselectivity. Oxabenzonorbornadiene (**155**) and oxabicyclo[3.2.1]alkene **157** are converted into the corresponding cyclohexenol **156** and cycloheptenol **158**, respectively, in >98% ee under similar conditions [162].



Scheme 1.44 BINAP–Ni catalyzed reductive ring-opening reactions of oxabicyclic alkenes.

1.17 Concluding Remarks

BINAP has been utilized as the typical chiral ligand in a wide variety of catalytic asymmetric reactions, including hydrogenation, isomerization, C−C bond formation, cyclization, and so on. The chiral structures of the BINAP–metal

complexes, which are schematically illustrated in this text, precisely discriminate two enantiomers and enatiofaces. Owing to the clear C_2-symmetric character, the stereoselective outcome is rationally explainable and also predictable. Furthermore, the flexible binaphthyl backbone attains high generality for substrates. Recent development of BINAP analogues has notably improved the enantioselective ability in some cases. Therefore, BINAP is regarded as one of the most reliable and successful diphosphine ligands. We believe that BINAP will continue contributing to improve the chemistry of asymmetric catalysis.

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