Enantiomer-Selective Activation of Racemic Catalysts

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ABSTRACT

Asymmetric catalysts can be evolved into highly activated catalysts by association with chiral activators. This asymmetric activation process is particularly useful in racemic catalysis through selective activation of one enantiomer of the racemic catalysts. Recently, a strategy whereby a racemic catalyst is selectively deactivated by a chiral additive has been reported to yield nonracemic products. However, we have reported a strategy that is an alternative to asymmetric catalysts but is conceptually opposite, in which a chiral activator selectively activates rather than deactivates one enantiomer of a racemic chiral catalyst. The advantage of this activation strategy over the deactivation counterpart is that the activated catalyst can produce a greater enantiomeric excess (x_{act}% ee) in the products than the ee attained by the enantiomerically pure catalyst on its own. Therefore, 'asymmetric activation' could provide a general and powerful strategy for the use of not only atropisomeric and, hence, racemic ligands but also chirally flexible and 'pro-atropisomeric' ligands without enantiomeric resolution!

Asymmetric catalysis of organic reactions is an important subject in modern science and technology.[1] Asymmetric catalysis enjoys this stature because it affords potentially large amounts of enantioenriched products, while producing only a small amount of waste material, through the action of a chiral catalyst.[2] Highly promising candidates for such asymmetric catalysts are metal complexes bearing chiral ligands.

In homogeneous asymmetric catalysis, Sharpless et al. have emphasized the significance of 'chiral ligand acceleration'.[3] Here, an asymmetric catalyst is formed from an achiral precatalyst via ligand exchange with an added chiral ligand (Figure 1). In heterogeneous asymmetric catalysis, the term 'chiral modification'[4] is used for the process of modifying an achiral heterogeneous catalyst, particularly on the surface with a 'chiral modifier', namely a 'chiral ligand' (Figure 1). However, modifiers are often found to interact preferentially with the substrate[5] rather than the achiral catalyst.[6]

The asymmetric catalysts thus prepared can be further evolved into highly activated catalysts with association of chiral activators (Figure 1). The term 'asymmetric activation' may be proposed for this process in an analogy to the activation process of an achiral reagent or catalyst to provide an activated but achiral one. This asymmetric activation process is particularly useful in racemic catalysis through selective activation of one enantiomer of the racemic catalysts.

While nonracemic catalysts thus developed via chiral ligand exchange can generate nonracemic products with or without the 'nonlinear relationship' in enantiomeric excesses between catalysts and products,[7] racemic catalysts inherently give only a racemic mixture of chiral products. Recently, a strategy whereby a racemic catalyst is selectively deactivated by a chiral additive has been reported to yield nonracemic products (Figure 2). However, we have reported a strategy that is an alternative to racemic catalysts but is conceptually opposite, in which a chiral activator selectively activates one enantiomer of a racemic chiral catalyst (Figure 3). The advantage of this activation strategy over the deactivation counterpart is that the activated catalyst can produce a greater enantiomeric excess (x_{act}% ee) in the products, even when a catalytic amount of activator per chiral catalyst is used, than the x% ee attained by the enantiomerically pure catalyst on its own.

'Positive Nonlinear Effect' of Nonracemic Catalysts

A chiral, nonracemic catalyst is not necessarily prepared from an enantiomerically pure ligand. Enantiomerically-pure catalysts are not needed for high enantioselectivities because of the well-known deviation from the linear relationship (Figure 4).[7−11,13] A 'nonlinear effect' (NLE) is

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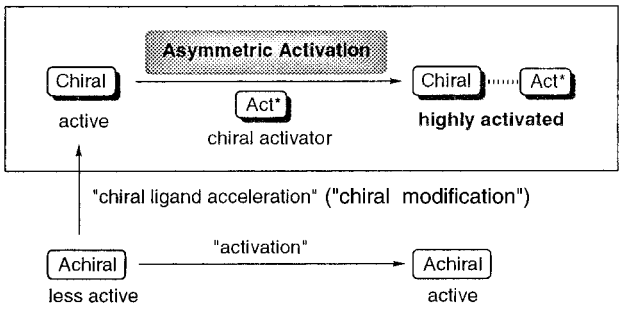


FIGURE 1. Asymmetric activation.

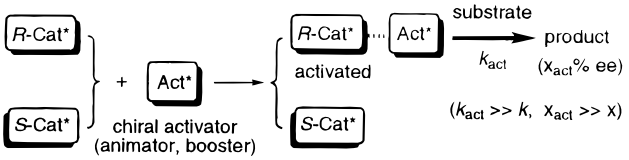


FIGURE 2. Asymmetric activation of racemic catalyst.

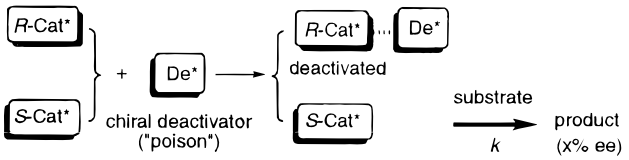


FIGURE 3. Asymmetric deactivation of racemic catalyst.

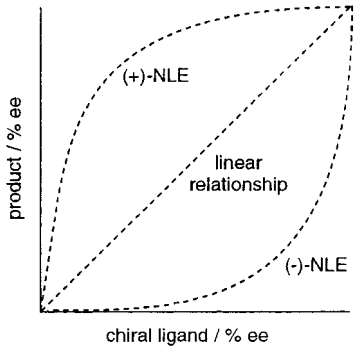


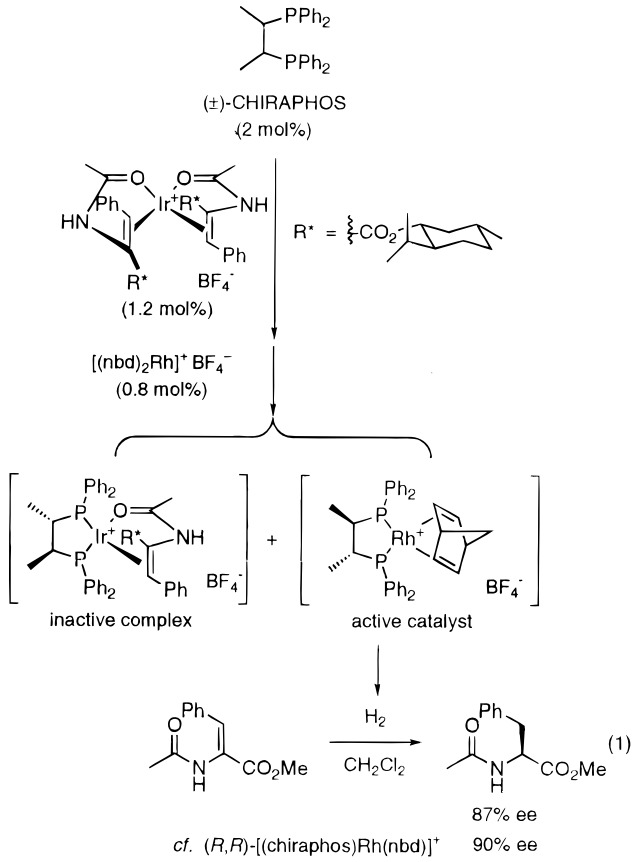
FIGURE 4. Relationship between the enantiomeric purity of chiral ligands and the optical yield of products.

sometimes observed between the enantiomeric purity of asymmetric catalysts and that of the products. The convex deviation which Kagan[8] and Mikami[9] independently refer to as 'the positive nonlinear effect' [abbreviated as (+)-NLE] has attracted attention to the achievement of a higher level of asymmetric induction than the enantiomeric purity of the nonracemic (partially resolved) catalysts might otherwise offer.

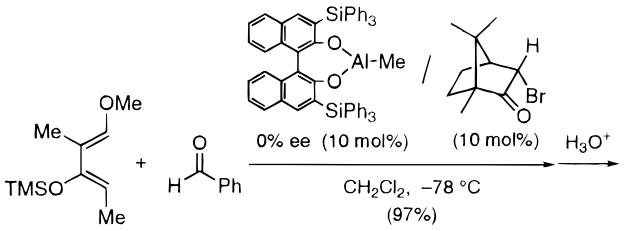
Oguni termed the (+)-NLE 'asymmetric amplification', in an asymmetric carbonyl addition reaction of dialkylzinc reagents catalyzed by chiral amino alcohols such as 1-piperidino-3,3-dimethyl-2-butanol (PDB).[10] Noyori et al. have reported the use of a highly efficient amino alcohol catalyst, (2*S*)-3-*exo*-(dimethylamino)isoborneol (DAIB).[11] In an elegant mechanistic investigation on the origin of asymmetric amplification, Noyori et al. identified the stability of the heterochiral dimer of the zinc amino alcohol catalyst compared to the homochiral dimer. We have also reported a positive nonlinear effect in a carbonyl-ene reaction[12] with glyoxylate catalyzed by a binaphthol (BINOL)-derived chiral titanium complex.[9] Significantly, the mode of preparation of a catalyst sometimes determines not only the presence or the absence of a nonlinear effect (NLE) but also the direction (positive or negative) thereof.[13]

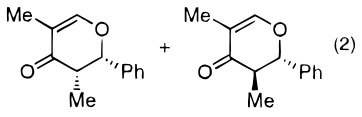
'Asymmetric Deactivation' of Racemic Catalysts

While nonracemic catalysts can generate nonracemic products with or without the NLE, racemic catalysts inherently produce only racemic products. A strategy whereby a racemic catalyst is enantiomer-selectively deactivated by a chiral molecule as a 'catalyst poison' has recently been shown to yield nonracemic products (Figure 3).[14−16] A unique resolution of racemic CHIRAPHOS has been attained with a chiral iridium complex to give a deactivated form, leading to a chiral rhodium complex in association with the remaining enantiomer of CHIRAPHOS (eq 1).[14] This process eventually results in an



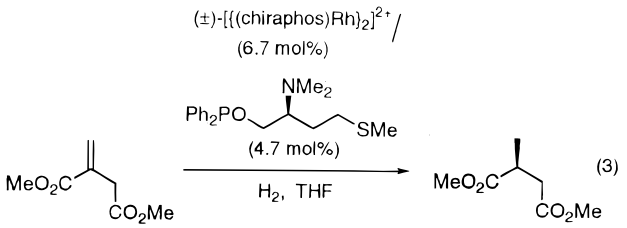
enantiomerically enriched hydrogenation product. More recently, the name 'chiral poisoning'[15,16] has been used for such a *deactivating* strategy in the context of a similar hydrogenation reaction by the asymmetric catalysis of the same CHIRAPHOS-Rh complex (eq 3).[15a,b] A racemic aluminum reagent has been treated to give a poisoned





80 (82% ee) : 20

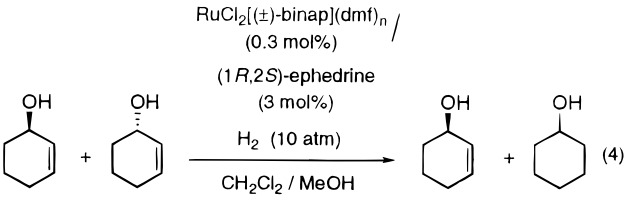
cf. (*S*)-cat. 90 (95% ee) : 10



49% ee

cf. (*R*,*R*)-[{(chiraphos)Rh}$_2$]$^{2+}$ >98% ee

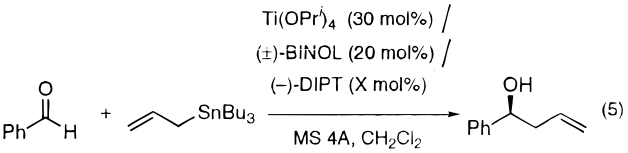
enantiomer using chiral unreactive ketones to yield hetero Diels–Alder products with the remaining enantiomer of the aluminum reagent (eq 2).[17] A chiral amino alcohol, (1*R*,2*S*)-ephedrine, may also be employed as a poison in the kinetic resolution of cyclic allylic alcohols using racemic BINAP (eq 4).[16b,c] However, the level of asymmetric induction does not exceed the level attained by the enantiopure catalyst (Figure 3).



>95% ee (23%) (77%)

cf. RuCl$_2$[(*S*)-binap](dmf)$_n$ >95% ee (40%) (60%)

Enantiomerically pure diisopropoxytitanium tartrate can also be used as a poison for racemic binaphthol-derived titanium complexes (eqs 5 and 6).[16d,e] The % ee of the product increases with an increase in the amount of DIPT employed.

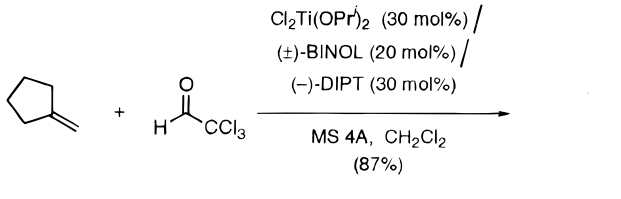


(–)-DIPT

15 mol% 39% ee (40%)

20 mol% 81% ee (47%)

30 mol% 91% ee (63%)



64% ee 24% ee

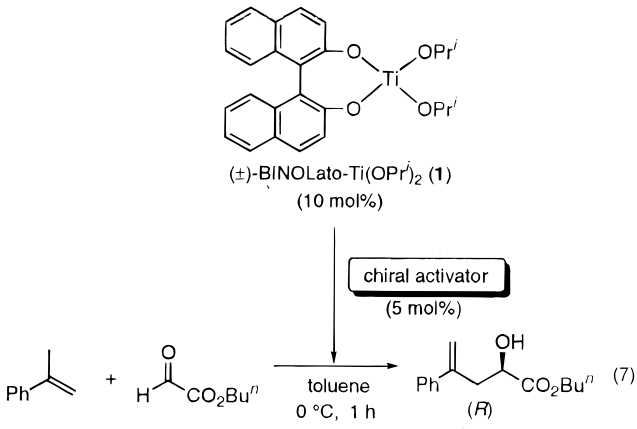
91 : 9

'Asymmetric Activation' of Racemic Catalysts

An alternative but conceptually opposite strategy has been reported for asymmetric catalysis by racemic catalysts. A *chiral activator* selectively activates one enantiomer of a racemic chiral catalyst. A higher level of catalytic efficiency might be attained (possibly by more than 2 orders of magnitude, $k_{act} > k \times 10^2$), in addition to a higher enantioselectivity than that achieved by an enantiomerically pure catalyst (x_{act}% ee > x% ee) (Figure 2).

The ene reaction converts readily available olefins with 'C–H bond activation' at an allylic site and allylic transposition of the C=C bond into more functionalized products. The ene reaction encompasses a vast number of variants in terms of the enophile used.[12b,18] Among these, the ene reactions of carbonyl enophiles (aldehydes in particular), which we refer to as 'carbonyl-ene reactions',[12] can constitute an alternative to the carbonyl addition reaction of allylmetals for stereocontrol.[19]

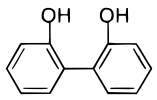
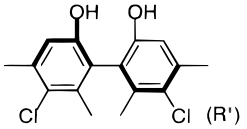
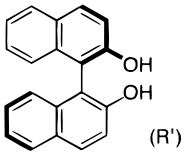
Catalysis of the carbonyl-ene reaction with racemic BINOLato-Ti(OPr^i)$_2$ (**1**) can achieve extremely high enantioselectivity with addition of another diol for the enantiomer-selective activation (eq 7) (Table 1).[20] Significantly,



a high enantioselectivity (89.8% ee, *R*) can be achieved by adding just 5 mol % of (*R*)-BINOL activator to a *racemic* (±)-BINOLato-Ti(OPr^i)$_2$ complex (**1**) (10 mol %).

The activation of the enantiomerically pure (*R*)-BINOLato-Ti(OPr^i)$_2$ catalyst (**1**) can also be made synthetically useful by further addition of (*R*)-BINOL (eq 8) (Table 2). The reaction proceeded quite smoothly to provide the carbonyl-ene product in higher chemical yield (82.1%) and enantioselectivity (96.8% ee) than those without additional BINOL (94.5% ee, 19.8%) (run 2 vs run 1). Comparing the

Table 1. Enantiomer-Selective Activation of Racemic BINOLato-Ti(OPr^i)$_2$ (1)

run	chiral activator	yield (%)	% ee
1	none	5.9	0
2		20	0
3		38	80.8
4		52	89.8
5 [a]		35	80.0

[a] 2.5 mol % of (*R*)-BINOL was used as a chiral activator.

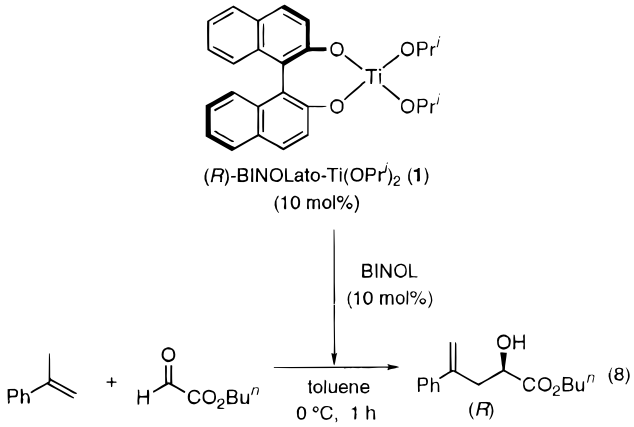


Table 2. Asymmetric Activation of Enantiopure (*R*)-BINOLato-Ti(OPr^i)$_2$ (1')

run	BINOL	yield (%)	ee (%)
1	none	19.8	94.5
2	(*R*′)-BINOL	82.1	96.8
3	(*S*′)-BINOL	48.0	86.0
4	(±)-BINOL	69.2	95.7

results of enantiomer-selective activation of the racemic catalyst (89.8% ee, *R*) (Table 1, run 4) with those of the enantiomerically pure catalyst (with (96.8% ee, *R*) or without activator (94.5% ee, *R*)), the reaction catalyzed by the (*R*)-BINOLato-Ti(OPr^i)$_2$/(*R*′)-BINOL complex ((*R*),(*R*′)-**1**′) is calculated to be 26.3 times as fast as that catalyzed by the (*S*)-BINOLato-Ti(OPr^i)$_2$ (**1**) in the racemic case (Figure 5a). Indeed, kinetic studies show that the reaction catalyzed by the (*R*)-BINOLato-Ti(OPr^i)$_2$/(*R*′)-BINOL complex ((*R*),(*R*′)-**1**′) is 25.6 ($=k_{act}/k$) times as fast as that catalyzed by the (*R*)-BINOLato-Ti(OPr^i)$_2$ (**1**). These results imply that the racemic (±)-BINOLato-Ti(OPr^i)$_2$ (**1**) and half-molar amount of (*R*′)-BINOL assemble preferentially

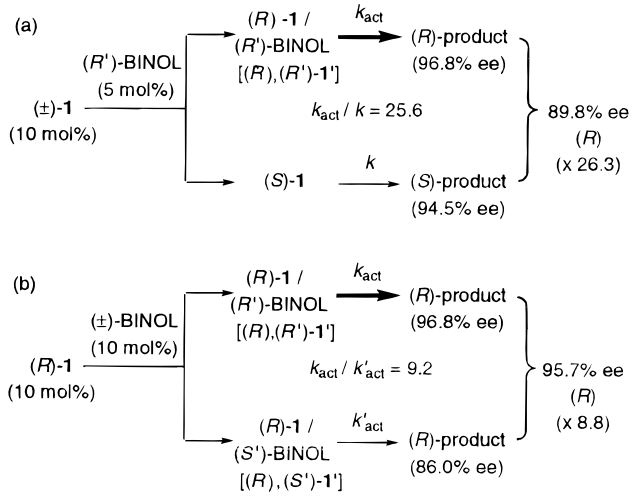
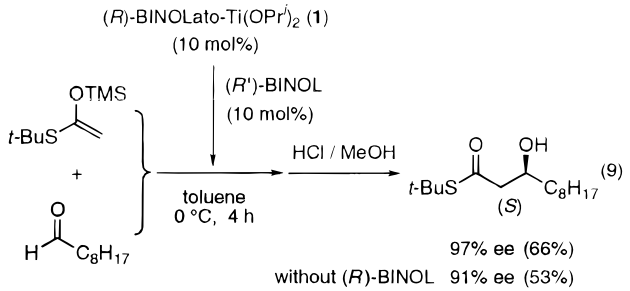


FIGURE 5. Kinetic feature of asymmetric activation of BINOLato-Ti(OPr^i)$_2$.

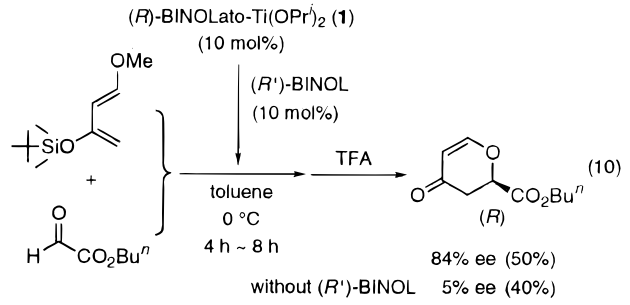
into the (*R*)-BINOLato-Ti(OPr^i)$_2$/(*R*′)-BINOL complex ((*R*),(*R*′)-**1**′) and unchanged (*S*)-BINOLato-Ti(OPr^i)$_2$ (**1**). In contrast, the enantiomeric form of the additional chiral ligand ((*S*′)-BINOL) activates the (*R*)-BINOLato-Ti(OPr^i)$_2$ (**1**) to a smaller degree (run 3), thus providing the carbonyl-ene product in lower optical (86.0% ee, *R*) and chemical (48.0%) yields than (*R*′)-BINOL does.

Another possibility is explored using racemic BINOL as an activator (Table 2, run 4). Racemic BINOL is added to the (*R*)-BINOLato-Ti(OPr^i)$_2$ (**1**), giving higher yield and enantioselectivity (95.7% ee, 69.2%) than those obtained by the original catalyst (*R*)-BINOLato-Ti(OPr^i)$_2$ (**1**) (94.5% ee, 19.8%) (run 4 vs run 1). Comparing the results (95.7% ee, *R*) obtained with the racemic activator with those of enantiomerically pure catalyst, (*R*)-BINOLato-Ti(OPr^i)$_2$/(*R*′)-BINOL ((*R*),(*R*′)-**1**′) (96.8% ee, *R*) or (*R*)-BINOLato-Ti(OPr^i)$_2$/(*S*′)-BINOL ((*R*),(*S*′)-**1**′) (86.0% ee, *R*) (run 4 vs runs 2 and 3), the reaction catalyzed by the (*R*)-BINOLato-Ti(OPr^i)$_2$/(*R*′)-BINOL complex ((*R*),(*R*′)-**1**′) is calculated to be 8.8 times as fast as that catalyzed by the (*R*)-BINOLato-Ti(OPr^i)$_2$/(*S*′)-BINOL ((*R*),(*S*′)-**1**′) (Figure 5b). Kinetic studies show that the reaction catalyzed by the (*R*)-BINOLato-Ti(OPr^i)$_2$/(*R*′)-BINOL complex ((*R*),(*R*′)-**1**′) is 9.2 ($=k_{act}/k'_{act}$) times as fast as that catalyzed by the (*R*)-BINOLato-Ti(OPr^i)$_2$/(*S*′)-BINOL ((*R*),(*S*′)-**1**′).

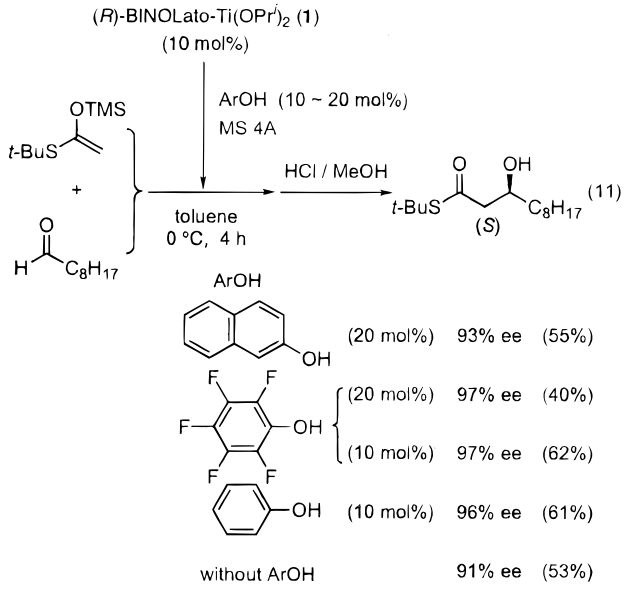
The great advantage of asymmetric activation of the racemic BINOLato-Ti(OPr^i)$_2$ complex (**1**) is highlighted in a catalytic version (Table 1, run 5). High enantioselectivity (80.0% ee) is obtained by adding less than the stoichiometric amount (0.25 equiv per (±)-**1**) of additional (*R*′)-BINOL. A new but otherwise similar phenomenon of enantiomer-selective activation has been observed in aldol (eq 9)[21] and hetero Diels−Alder reactions (eq 10)[22] catalyzed not only by a racemic but also by an enantiomerically pure BINOLato-Ti(OPr^i)$_2$ catalyst (**1**). Asymmetric activation of the (*R*)-BINOLato-Ti(OPr^i)$_2$ (**1**) by (*R*′)-BINOL is essential to provide higher levels of enantioselectivity than those attained by the enantiomerically pure BINOL-



ato-Ti(OPr^i)$_2$ catalyst (**1**) (5% ee) in the hetero Diels−Alder reaction of glyoxylates with the Danishefsky diene (eq 10).

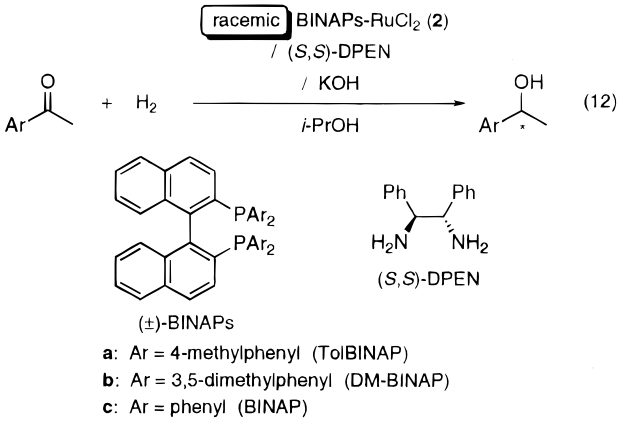


Activation of the (*R*)-BINOLato-Ti(OPr^i)$_2$ (**1**) by acidic, sterically demanding achiral alcohols is also effective. The phenols shown in eq 11 provide higher levels of enantioselectivity than the parent enantiomerically pure BINOLato-Ti(OPr^i) catalyst (**1**) in the Mukaiyama aldol reaction of silyl enol ethers.[23]

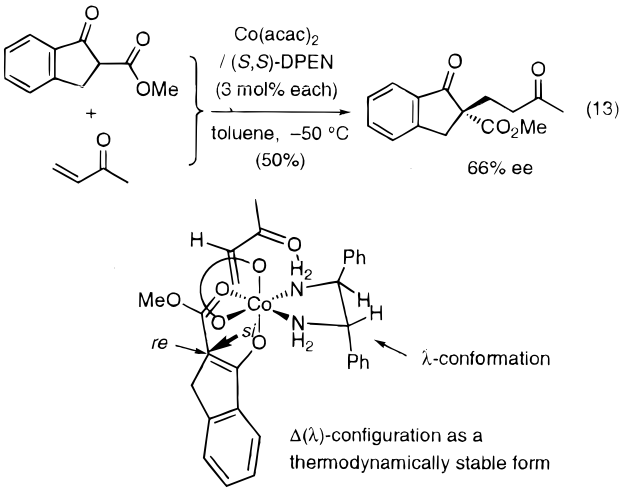


Catalytic asymmetric hydrogenation has been shown to be one of the most efficient processes for the asymmetric functional group transformation of organic molecules. Noyori et al. have reported the use of *enantiomerically pure* RuCl$_2$(binap)(dmf)$_n$ complex (**2**) together with an enantiomerically pure diamine and KOH to provide hydrogenation products of carbonyl compounds with high enantioselectivity.[24] This provided an opportunity for us to examine an asymmetric activation of a *racemic* BINAP-RuCl$_2$ catalyst (**2**) for the enantioselective catalysis of the carbonyl reduction of the carbonyl compounds (eq 12).[25]

The hydrogenation was performed in a mixture of

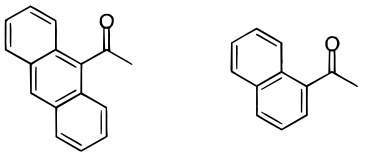


racemic RuCl$_2$(tolbinap)(dmf)$_n$ (**2a**) or RuCl$_2$(dmbinap)(dmf)$_n$ (**2b**), an enantiomerically pure diamine such as (*S*,*S*)-1,2-diphenylethylenediamine [(*S*,*S*)-DPEN] or the (*R*,*R*)-enantiomer, and KOH in a ratio of 1:1:2 (Table 3).



A chiral diamine leads to a nonracemic hydrogenation product, supporting the importance of chirality in the diamine activator for selective activation of one enantiomer of the (±)-RuCl$_2$(tolbinap) catalyst (**2a**) (run 2 vs run 3). Thus, the asymmetric activation of the chiral RuCl$_2$(tolbinap) catalyst (**2a**) by the chiral diamine affords higher levels of asymmetric induction and catalytic activity than those attained by the enantiopure catalyst (**2a**) alone (run 1 vs run 3), even when starting from the *racemic* mixture of **2a**. The enantioselectivity thus obtained by the (±)-RuCl$_2$(tolbinap) complex (**2a**) and (*S*,*S*)-DPEN is very close to that obtained by the matched pair of (*R*)-RuCl$_2$(tolbinap) (**2a**)/(*S*,*S*)-diamine complex, as exemplified by (*R*)-BINAPs-RuCl$_2$(**2**)/(*S*,*S*)-DPEN (**A**) (run 4 vs runs 5 and 6). However, the matched pair is dramatically changed on going from 9-acetylanthracene (**AA**) to 1′-acetonaphthone (**AN**) (runs 7−11); in the latter case, (*S*)-BINAPs-RuCl$_2$(**2**)/(*S*,*S*)-diamine complex (**B**) is a more enantioselective combination than (*R*)-BINAPs-RuCl$_2$(**2**)/(*S*,*S*)-DPEN (**A**) to provide (*R*)-(+)-product in higher % ee (run 10 vs run 11) (Figure 6).

Table 3. Asymmetric Activation of Racemic BINAPs-RuCl$_2$ Catalyst (2) by Enantiopure DPEN[a]



AA **AN**

run	**2**	ketone	*T* (°C)	*t* (h)	yield (%)	ee (%)
1[b]	(*R*)-**2a**	**AA**	28	18	2	29 (*S*)
2[b]	(±)-**2a**	**AA**	28	18	<1	0
3	(±)-**2a**	**AA**	28	18	28	80 (*R*)
4	(±)-**2a**	**AA**	80	10	99	80 (*R*)
5	(*R*)-**2a**	**AA**	80	10	99	81 (*R*)
6	(*S*)-**2a**	**AA**	80	10	91	40 (*R*)
7	(±)-**2b**	**AN**	28	4	99	80 (*R*)
8	(±)-**2b**	**AN**	−35	7	95	90 (*R*)
9[c]	(±)-**2b**	**AN**	−35	7	90	90 (*R*)
10	(*S*)-**2b**	**AN**	28	4	99	>99 (*R*)
11	(*R*)-**2b**	**AN**	28	4	99	56 (*S*)

[a] Under H_2 (8 atm) atmosphere. Ketone:**2**:(*S*,*S*)-DPEN:KOH = 250:1:1:2. [b] In the absence of (*S*,*S*)-DPEN. [c] A 0.5 molar amount of (*S*,*S*)-DPEN per (±)-**2b** was used. **AN**:**2b**:DPEN:KOH = 250:1:0.5:2.

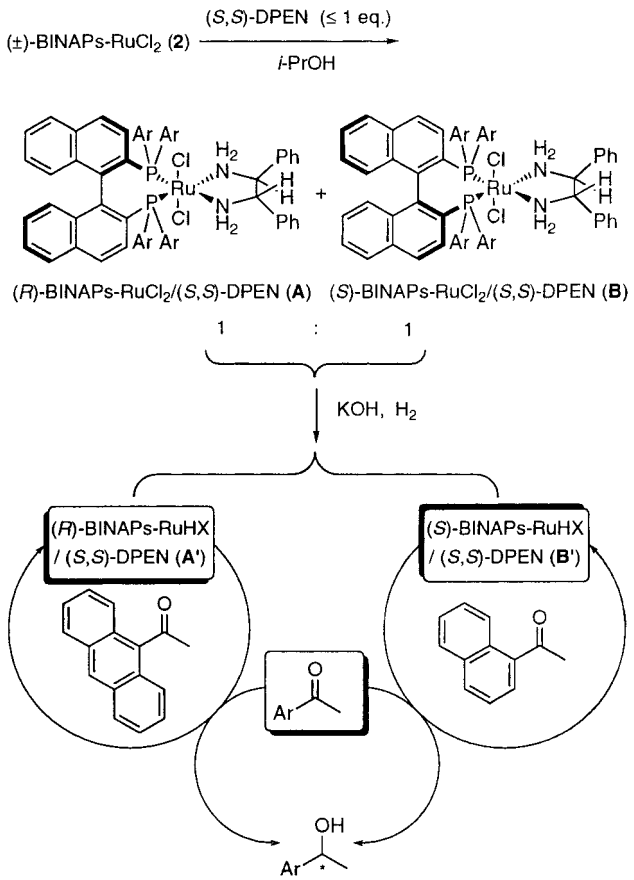


FIGURE 6. Dichotomous sense in enantioselectivity by diastereomeric BINAPs-RuHX (X = H or Cl)/DPEN complexes (**A′** and **B′**).

The dichotomous sense with enantioselectivity attained by (*S*)-BINAPs-RuCl$_2$/(*S*,*S*)-DPEN and (*R*)-BINAPs-RuCl$_2$/(*S*,*S*)-DPEN complexes in naphthyl (**NA**) and anthryl (**AA**) cases, respectively, is determined by the ratio and catalytic activity (turnover frequency) of mono- or dihydrido BINAPs-RuHX/DPEN complexes (X = H or Cl),[25,26] **A′** and

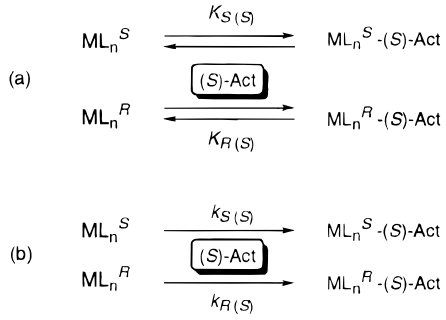


FIGURE 7. Formation of activated diastereomeric catalysts under thermodynamic (a) or kinetic (b) conditions.

B′ (Figure 6), which are derived from diastereomeric complexes, **A** and **B**, respectively, under the hydrogenation conditions. It should be noted here that the catalytic activity critically depends on the nature of the carbonyl substrates. Interestingly, the use of a catalytic amount of diamine affords an equally high level of enantioselectivity as compared to that obtained by an equimolar amount of diamine (run 9 vs run 8). Indeed, the ^{31}P NMR spectrum of a mixture of (±)-RuCl$_2$(tolbinap) (**2a**) and a catalytic amount of (*S*,*S*)-DPEN (0.5 molar amount per Ru) is identical to that of the 1:1 mixture, except for the remaining (±)-RuCl$_2$(tolbinap) complex (**2a**) (run 2).

Continuum from Preferential Activation to Substrate-Dependent Activation

The asymmetric activation phenomena can be interpreted as a continuum from the preferential complexation with the one enantiomer of a catalyst selectively giving the single activated diastereomer to 1:1 complexation giving the activated diastereomeric mixture (1:1). The catalyst efficiency (turnover frequency) depends critically on the substrates employed.

For the sake of simplicity, the formation of the activated complexes can be discussed starting from the complexation of the chiral activator with racemic parent catalyst in monomeric form using the thermodynamic and/or kinetic features (Figure 7). (1) Under equilibrium conditions between the activated catalyst and the parent catalyst (Figure 7a), the ratio of the activated diastereomeric catalysts depends on their thermodynamic stability. (2) Under nonequilibrium conditions, the ratio reflects the relative rate of the reaction of the enantiomeric catalyst with the chiral activator (Figure 7b). Of course, the use of 1.0 equiv of the activator per parent catalyst gives a 1:1 mixture of the activated diastereomeric complexes. The kinetic or thermodynamic features described above are more significant under the treatment with less than 1.0 equiv of the activator (vide infra). However, once a 1:1 mixture is formed even with 0.5 equiv of the activator, the relative activity of these activated diastereometic catalysts with the substrate is the factor that determines the outcome in terms of enantioselectivity of the asymmetric reaction. In other words, the turnover efficiency of these activated diastereomers should be dependent on the reactivity of complex with the substrate used.

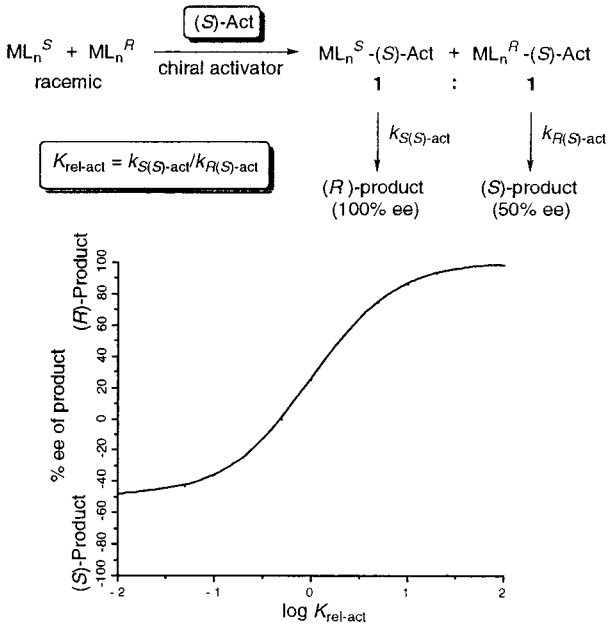


FIGURE 8. Asymmetric reaction catalyzed by activated 1:1 diastereomeric mixtures.

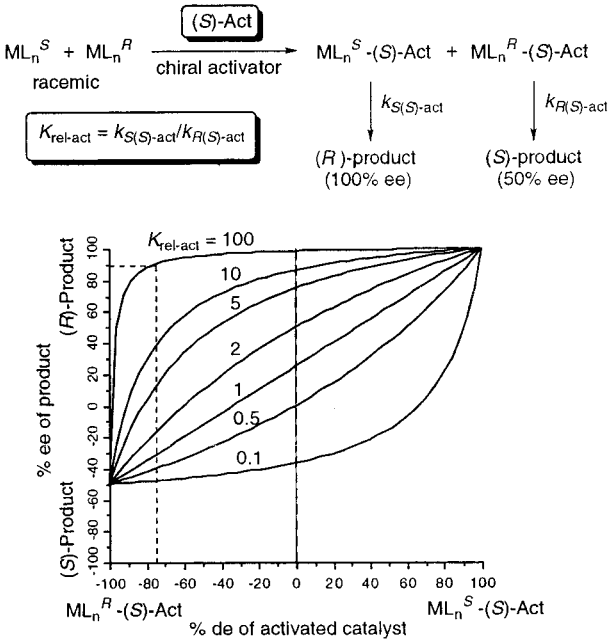


FIGURE 9. Asymmetric reaction catalyzed by activated diastereomeric complexes.

Therefore, the most crucial step determining the overall enantioselectivity is the catalytic asymmetric reaction with the substrate. The logarithum of the relative rate is varied from, for example, 0.01 to 100 (Figure 8). Let us examine the case in which one activated diastereomeric complex provides the product in 100% ee (*R*) and the other diastereomer provides the opposite enantiomeric product in 50% ee (*S*). Even when two activated diastereomer complexes are formed in a 1:1 ratio, more than 98% ee of the product can be obtained in the case in which the relative rate of the two activated diastereomers is 100 (log $K_{rel-act} = 2$).

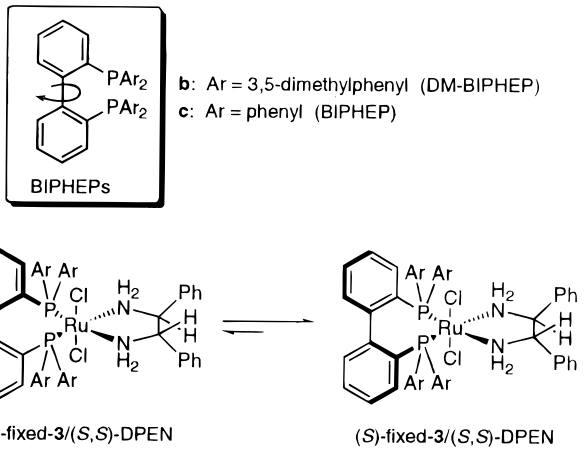


FIGURE 10. Stereomutation of BIPHEPs-$RuCl_2$/DPEN complexes.

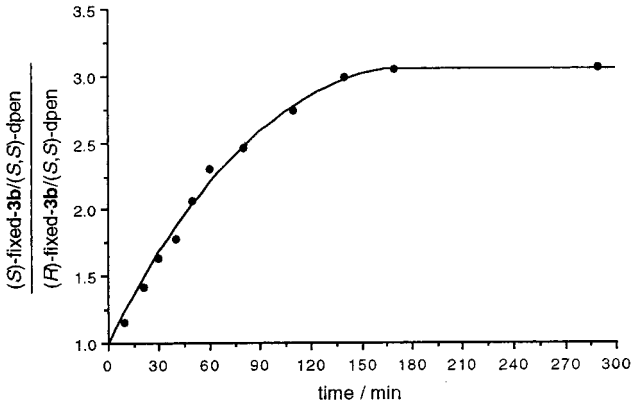


FIGURE 11. Stereomutation of $RuCl_2$(dmbiphep) (**3b**)/dpen diastereomers in a 1:2 $CDCl_3$ and $(CD_3)_2CDOD$ mixture at room temperature.

In a similar case (Figure 9), wherein the relative rate of the two activated diastereomers is 100, more than 90% ee product can be obtained, even with −75% de (12.5%) presence of the favorable diasteromer (dotted line); thermodynamically unstable and hence catalytically more active complexes may be found.[27] Similar phenomena can be drawn in a different way for the 1:1 formation of diasteromers. The relative rate of 14 (log $K_{rel-act} = 1.15$) is sufficiently high to provide more than 90% ee of the desired product (Figure 8).

Asymmetric Activation of Chirally Flexible Catalysts

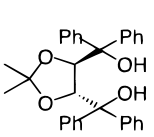
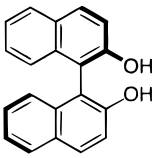
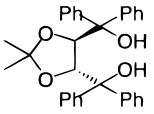
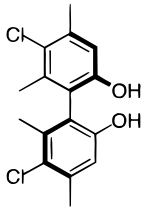
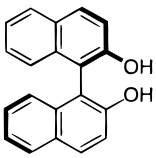
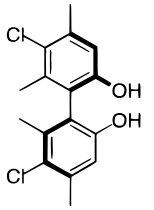
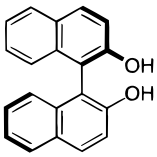
An advanced strategy for 'asymmetric activation' can be seen in using chirally dynamic ligands that achieve higher enantioselectivity than that attained by chirally rigid and hence racemic ligands. As described above, combination of a racemic BINAP-$RuCl_2$ (**2**) species even with a 0.5 equimolar amount of an enantiomerically pure diamine gives a 1:1 mixture of two diastereomeric BINAP-$RuCl_2$ (**2**)/DPEN complexes. When the chirally rigid BINAP is replaced by a flexible[28] and 'pro-atropisomeric' BIPHEPs,[29] diastereomeric complexes are formed, in principle, in unequal amounts (Figure 10).[30] When the major diaste-

Table 4. Pro-Atropisomeric BIPHEP Ligand for Enantioselective Hydrogenation[a]

run	ketone	**3** or **2**	H_2 (atm)	*T* (°C)	*t* (h)	yield (%)	ee (%)
1	**AN**	**3b**	8	28	4	>99	84
2[b]	**AN**	(±)-**2b**	8	28	4	>99	80
3	**AN**	**3b**	40	−35	12	>99	92
4[b]	**AN**	(±)-**2b**	40	−35	7	>99	89
5	**AA**	**3c**	8	80	10	>99	70
6[b]	**AA**	(±)-**2c**	8	80	10	>99	78

[a] BIPHEPs-$RuCl_2$ (**3**)/(*S*,*S*)-DPEN in 2-propanol was preheated at 80 °C for 30 min. Ketone:(**3** or **2**):(*S*,*S*)-DPEN:KOH = 250:1:1:2. [b] Without preheating operation.

Table 5. Asymmetric Catalysis by Multicomponent Ligand Cooperation

Run	$R^{1*}(OH)_2$	$R^{2*}(OH)_2$	yield (%)	% ee
1			50	91
2		none	0	–
3			66	97
4		none	13	75
5		none	20	95

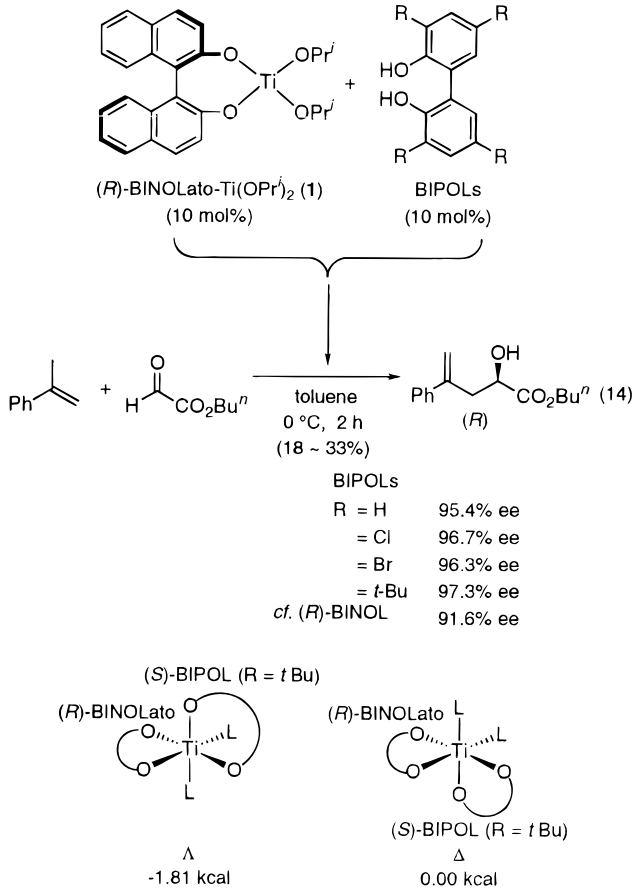
reomer shows higher chiral efficiency than does the minor isomer, this strategy becomes more effective than the use of similar but chirally rigid analogues.

The initially formed mixture of (*S*)- and (*R*)-$RuCl_2$-(dmbiphep) (**3b**)/(*S*,*S*)-dpen in 2-propanol-d_8 ($CDCl_3$:$(CD_3)_2CDOD$ = 1:2), when allowed to stand at room temperature (or at 80 °C), was found to give a 1:3 mixture of the (*S*)-**3b**/(*S*,*S*)-dpen major diastereomers (Figure 11). The equilibration occurred readily due to the conformational flexibility of BIPHEPs-$RuCl_2$ (**3**)/diamine complexes. The dichloro complexes may be further converted to active mono- or dihydrido Ru species under hydrogenation conditions.[26]

The significant effect of the conformationally flexible BIPHEPs-$RuCl_2$ (**3**)/diamine complexes can be seen in hydrogenation (Table 4) of 1′-acetonaphthone (**AN**) (run 1) in comparison with the enantioselectivity obtained using the (±)-$RuCl_2$(dmbinap) (**2b**)/(*S*,*S*)-dpen complex (run 2).

A further increase in enantioselectivity was attained at a lower reaction temperature (run 3). The enantioselectivity given by the $RuCl_2$(dmbiphep) (**3b**)/(*S*,*S*)-dpen was higher than that given by the (±)-$RuCl_2$(dmbinap) (**2b**)/(*S*,*S*)-dpen complex at the same low temperature and high pressure (run 4). Thus, (*R*)-1-(1-naphthyl)ethanol was obtained with 92% ee in quantitative yield. $RuCl_2$-(dmbiphep) (**3b**)/(*S*,*S*)-dpen was also useful in the reduction of 2′-methylacetophenone.

Self-organization of ligands in multicomponent titanium catalysts[31] with conformationally flexible biphenols is also found in the enantioselective glyoxylate-ene reaction[20] to give high enantioselectivity (eq 14).[32] Results of



molecular modeling suggested that the hexacoordination of the titanium atom would make the central titanium atom a center of chirality and that the Λ isomer is more favorable than the Δ isomer.

Chiral *ansa*-metallocene complexes have become useful catalysts for asymmetric polymerization reactions.[33] While resolution of *ansa*-metallocene racemates cannot yield more than 50% of a particular enantiomer, the readily accessible racemate of a biphenyl-bridged metallocene complex (which we abbreviate as BIPHECp-M, M = Ti, Zr) has been reported to give enantiopure *ansa*-titanocene and -zirconocene complexes through BINOL-induced asymmetric transformation (Figure 12).[34] The

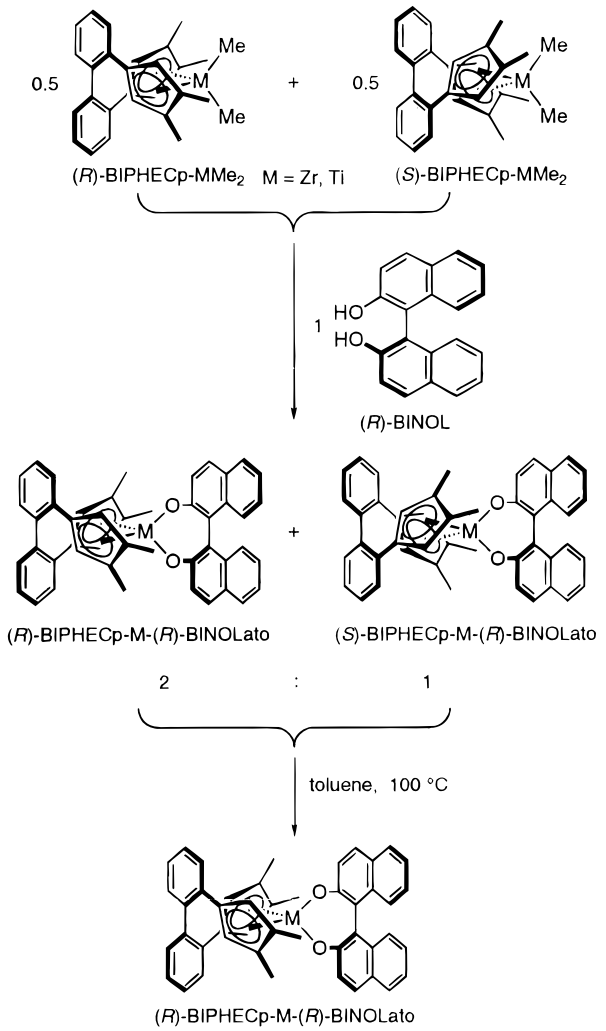
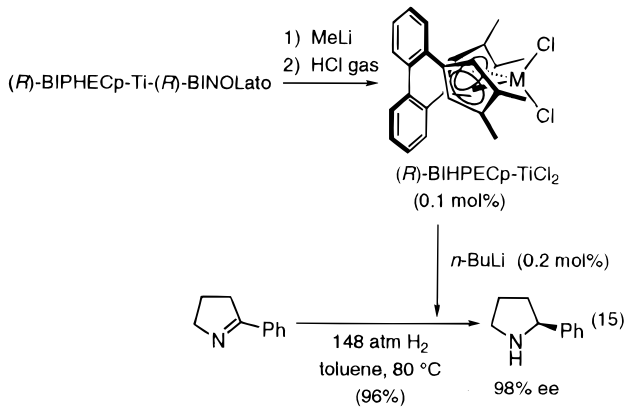


FIGURE 12. BINOL-induced asymmetric transformation of biphenyl-bridged metallocene complexes.

biphenyl-bridged complex (*R*)-BIPHECp-$TiCl_2$ in the presence of *n*-BuLi resulted in an efficient asymmetric catalyst for imine hydrogenation (eq 15).



These examples clearly illustrate that chirally rigid ligands can be replaced by flexible and hence 'pro-atropisomeric' ligands to give preferentially the thermodynamically favorable diastereomer with higher chiral efficiency than does the minor isomer. This strategy with chirally flexible and 'pro-atropisomeric' ligands becomes more effective than the use of structurally similar but chirally rigid ligands. Therefore, 'asymmetric activation' could provide a general and powerful strategy for the use of not only atropisomeric and, hence, racemic ligands but also chirally flexible and 'pro-atropisomeric' ligands without enantiomeric resolution!

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