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Racemic catalysis through asymmetric activation*

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Abstract: "Asymmetric activation" provides a general strategy for the use of racemic catalysts not only with atropos but also tropos ligands without enantiomer resolution.

Asymmetric catalysis of organic reactions by metal complexes bearing chiral ligands is an important subject in modern science and technology. In homogeneous asymmetric catalysis, Sharpless *et al*. have emphasized the significance of "ligand accelerated catalysis" [1]. Here, an asymmetric catalyst is formed from an achiral "pre-catalyst" and chiral ligand. In heterogeneous asymmetric catalysis, the term "chiral modification" [2] is coined for modifying an achiral heterogeneous catalyst, particularly on the surface with a "chiral modifier", namely a "chiral ligand". The asymmetric catalysts thus prepared can be further evolved into highly activated catalysts with association of "chiral activators". "Asymmetric activation" is particularly useful in racemic catalysis through selective activation of one enantiomer of the racemic catalysts (Fig. 1). The advantage of this activation strategy is that the activated catalyst can produce a greater enantiomeric excess (x_{act}% ee) in the products, even using a catalytic amount of activator per chiral catalyst, than the x% ee attained by the enantiomerically pure catalyst on its own.

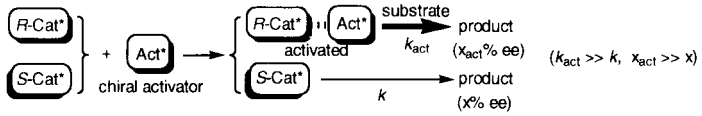

Fig. 1 Asymmetric activation of racemic catalyst.

ASYMMETRIC ACTIVATION OF RACEMIC CATALYSTS

Catalysis of asymmetric carbonyl–ene reactions [3] with racemic BINOLato-Ti(OPr^i)$_2$ (**1**) can achieve extremely high enantioselectivity by adding another diol (eq. 1, Table 1) [4]. Significantly, a high enantioselectivity can be achieved by adding just 5 mol% or even a catalytic amount (2.5 mol%) (Table 1, Runs 3, 4) of (*R*)-BINOL activator to a *racemic* (±)-BINOLato-Ti(OPr^i)$_2$ complex (**1**) (10 mol%).

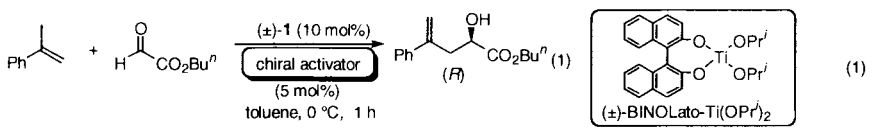

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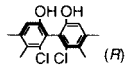
Table 1. Asymmetric activation of racemic BINOL-Ti catalyst.

run	chiral activator	yield (%)	% ee
1	none	5.9	0
2		38	80.8
3	(*R*)-BINOL	52	89.8
4		35*	80.0

* 2.5 mol% of (*R*)-BINOL was employed.

The activation of the enantiomerically pure (*R*)-BINOLato-Ti(OPr^i)$_2$ catalyst (**1**) can also be made by further addition of (*R*)-BINOL (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. 1). Comparing the results of enantiomer-selective activation of the racemic catalyst (89.8% ee, *R*) (Table 1; Run 3) with those of the enantiopure 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. 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 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 addition of (*S*)-BINOL activates the (*R*)-**1** to a smaller degree (Run 3), thus providing the product in lower optical (86.0% ee, *R*) and chemical (48.0%) yields than (*R*)-BINOL does.

Table 2 Asymmetric activation of (*R*)-BINOL-Ti catalyst.

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

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 [5]. We thus examined a variety of amines for asymmetric activation of a *racemic* BINAP-RuCl$_2$ catalyst (**2**) (eq. 2) [6].

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, (*S*,*S*)-1,2-diphenylethylenediamine [(*S*,*S*)-DPEN] or the (*R*,*R*)-enantiomer in particular, and KOH in a ratio of 1:1:2 (Table 3). The asymmetric activation of the *racemic* RuCl$_2$(tolbinap) catalyst (**2a**) by the enantiopure diamine affords higher levels of asymmetric induction and catalytic activity than those attained by the enantio-pure catalyst (**2a**) alone (Runs 1 vs. 3). 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 (Runs 4 vs. 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 (Runs 10 vs. 11).

The dichotomous sense of enantioselectivity attained by (*S*)-BINAPs-RuCl$_2$/(*S*,*S*)-DPEN and (*R*)-BINAPs-RuCl$_2$/(*S*,*S*)-DPEN complexes in naphthyl (**AN**) and anthryl (**AA**) cases, respectively is

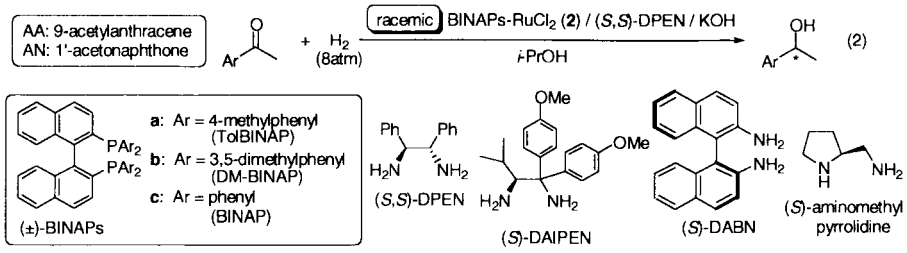


Table 3 Asymmetric activation of racemic BINAPs-$RuCl_2$ catalyst (**2**)[a].

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]Ketone : **2** : (*S*,*S*)-DPEN : KOH = 250:1:1:2.
[b]In the absence of (*S*,*S*)-DPEN.
[c]0.5 molar amount of (*S*,*S*)-DPEN per (±)-**2b** was used.

determined by the ratio and catalytic activity (turnover frequency) of mono- or dihydrido BINAPs-RuHX/DPEN complexes (X = H or Cl), **A'** and **B'** (Fig. 2). Interestingly, the use of a catalytic amount of diamine affords an equally high level of enantioselectivity to that obtained by an equimolar amount of diamine (Runs 9 vs. 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).

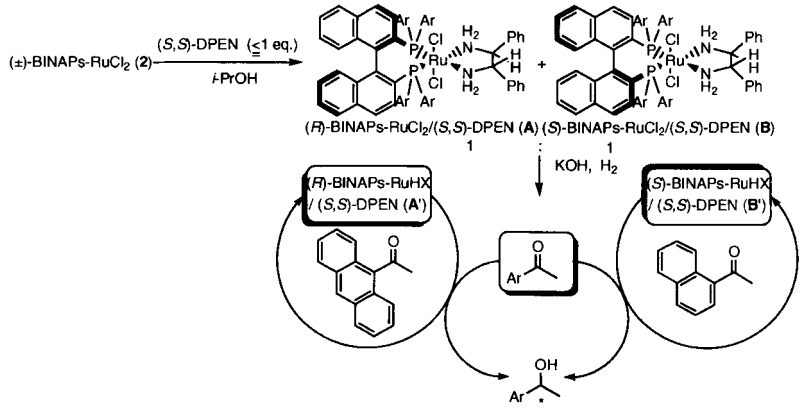


Fig. 2 Dichotomous sense in enantioselectivity by diastereomeric BINAPs-RuHX (X = H or Cl)/DPEN complexes (**A'** and **B'**).

ASYMMETRIC ACTIVATION OF CHIRALLY DYNAMIC CATALYSTS

An advanced strategy for asymmetric activation can be seen in using chirally dynamic (tropos) ligands that achieves higher enantioselectivity than that attained by chirally static (atropos) 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 static BINAP is replaced by a dynamic BIPHEPs, diastereomeric complexes are formed, in principle, in unequal amounts (Fig. 3) [7]. When the major diastereomer shows higher chiral efficiency, this strategy becomes more effective.

The initial 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 (Fig. 3).

The significant effect of chirally dynamic 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 chirally static (±)-$RuCl_2$(dmbinap) (**2b**)/(*S*,*S*)-dpen complex (Run 2).

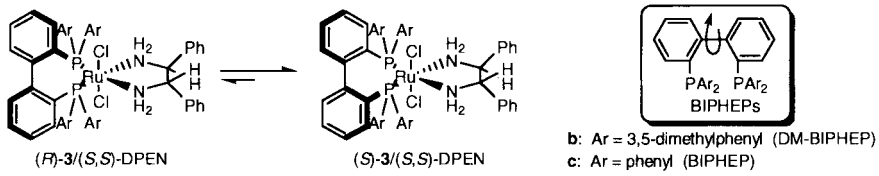


Fig. 3 Stereomutation of BIPHEPs-$RuCl_2$/DPEN complexes.

Table 4 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

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

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 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

These examples clearly illustrate that chirally rigid ligands can be replaced by dynamic ligands to give preferentially the thermodynamically favorable diastereomer with higher chiral efficiency than does the minor isomer.

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