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Novel heterobimetallic asymmetric catalysis directing toward enzymatic function

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Abstract

A unique feature of multifunctional asymmetric catalysts is described. Catalytic asymmetric Michael reaction of cyclic enones with Horner–Wadsworth–Emmons reagents proceeds efficiently by use of an aluminum–lithium–BINOL complex that is activated by an addition of alkali metal reagent. In addition, rare earth–3-hydroxymethyl–BINOL complexes promote asymmetric epoxidation of *cis*-enones to afford *cis*-epoxyketones. Both of these types of reactions are believed to be realized by a synergistic cooperation of two different metals in the complexes. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Enzymatic function; Heterobimetallic asymmetric catalysis; Enones; Epoxyketones

1. Introduction

Recently, we have developed several heterobimetallic catalysts which not only activate both substrates in intermolecular reactions but also control the orientation of them [1]. The structure of representative heterobimetallic complexes are shown in Fig. 1.

Chiral lanthanoid–alkali metal–BINOL derivative complexes (LnMB, where Ln: lanthanoid, M: alkali metal, and B: BINOL derivative) efficiently promote asymmetric aldol-type reactions as well as asymmetric hydrophosphonylations of aldehydes (catalyzed by LnLB, where L: lithium), asymmetric Michael reactions (catalyzed by LnSB, where S: sodium), and asymmetric hydrophosphonylations of imines (catalyzed by LnPB, where P: potassium) to give the corresponding desired products in up to 98% ee [1]. In addition several catalytic asymmetric reactions are promoted using aluminum–lithium–BINOL (ALB, where A: aluminum, L: lithium, and B: BINOL) type catalyst [2]. For example, the first catalytic asymmetric tandem Michael–aldol reactions are performed using ALB. Most of these reactions are greatly accelerated by an addition of alkali metal reagent without a decrease in the optical purity of the products [4]. Spectroscopic analysis and computer simulations of these asymmetric reactions have proved the synergistic cooperation of the two different metals in the complexes [5]. In general, synthesis of optically active compounds is considered to be much more difficult than that of corresponding racemic compounds. Indeed, almost all developments of novel asymmetric reactions are based on the reactions for racemic compounds. However, due to this unique feature of the multifunctional catalyst several optically active compounds, which are difficult to prepare by conventional

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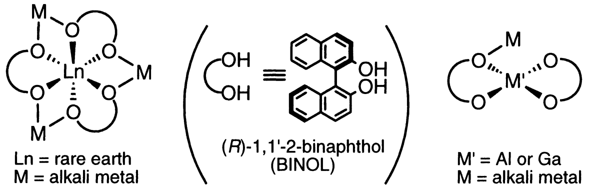


e.g.
LaLi$_3$tris((*R*)-binaphthoxide): LLB; Ln = La, M = Li
LaNa$_3$tris((*R*)-binaphthoxide): LSB; Ln = La, M = Na
LaK$_3$tris((*R*)-binaphthoxide): LPB; Ln = La, M = K

e.g.
AlLibis((*R*)-binaphthoxide): ALB; M' = Al, M = Li
GaLibis((*R*)-binaphthoxide): GaLB; M' = Ga, M = Li
GaNabis((*R*)-binaphthoxide): GaSB; M' = Ga, M = Na

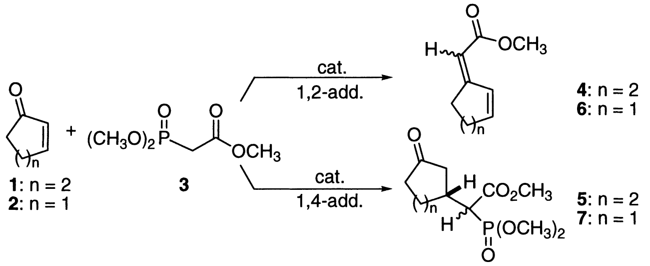
Fig. 1. Representative structure of heterobimetallic multifunctional catalysts.

catalysts, were obtained in high optical purity. In this article we introduce two kinds of such catalysis.

2. Results and discussion

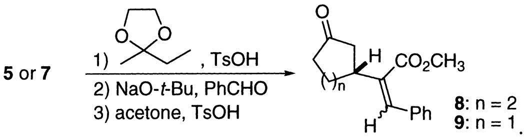
Horner–Wadsworth–Emmons reagents are known to be quite useful for the preparation of α,β-unsaturated carbonyl compounds from aldehydes and/or ketones. These reagents, however, react with α,β-unsaturated carbonyl compounds to give Horner–Wadsworth–Emmons products or 1,4-adducts (Michael product), depending on the structure of the starting compounds [6–8]. For example, the reaction of cyclohexenone (**1**) with Horner–Wadsworth–Emmons reagent **3** promoted by standard bases (10 mol%) such as NaO-*t*-Bu

Table 1
Regio- and enantioselective reaction of Horner–Wadsworth–Emmons reagent **3** with enones



Entry	Catalyst[a] (10 mol%)	Temperature (°C)	Time (h)	1,2-adduct yield (%)	1,4-adduct yield (%)	ee (%) of **8** of **9**
1 + **3** → **4** + **5**						
1	BuLi	50	120	8	0	–
2	NaO-*t*-Bu	50	120	9	0	–
3	KO-*t*-Bu	50	120	8	2	–
4	LSB	50	140	11	19	6
5	ALB	50	140	No reaction		
6	ALB + BuLi	50	140	3	58	98
7	ALB + NaO-*t*-Bu	50	140	0	64	99
8	ALB + KO-*t*-Bu	50	140	5	27	89
2 + **3** → **6** + **7**						
9	ALB + NaO-*t*-Bu	RT	72	0	95	95

[a] All chiral catalysts were prepared using (*R*)-BINOL



and/or BuLi gives the 1,2-adduct **4** in 8–9% yield (Table 1, entries 1–3).

In contrast, the reaction of cyclopentenone (**2**) with **3** under similar reaction conditions gives the 1,4-adduct **7** in 90–98% yield.

We have found that the reaction of **1** with **3** in the presence of a catalytic amount of certain heterobimetallic asymmetric complexes [1–5] gives **5** as a major product by way of the unusual regioselective route (entries 4, 6–8). Although the AlLibis(binaphthoxide) complex itself (ALB) [3] did not promote the reaction of **1** with **3** at 50°C (entry 5), the catalytic 1,4-addition promoted by the combined use of ALB (10 mol%) and BuLi (0.9 equivalent to ALB) [4] gave **5** in 58% yield with 98% ee. More gratifyingly, the use of NaO-*t*-Bu instead of BuLi gave **5** exclusively in 64% yield with 99% ee, and no formation of **4** was detected (entry 7).[2] Moreover, **2** was also converted to **7**, even at room temperature, in 95% yield and in 95% ee (entry 9).[3] This is the first example of a catalytic asymmetric 1,4-addition of a Horner–Wadsworth–Emmons reagent to enones. These 1,4-adducts are key intermediates for the catalytic asymmetric synthesis of various natural products [2].

Then, what is the actual structure of the activated catalyst generated from ALB and standard bases? Although we could obtain a stable colorless crystal from a mixture of ALB and standard bases such as CH_3Li, the X-ray structural analysis revealed that this product was $AlLi_3$tris(binaphthoxide)$(thf)_6$ (**10**) which has a hexacoordinated aluminum as the center metal.[4] The structure is shown in Fig. 2.

Treatment of **1** with **3** in the presence of **10** (10 mol%) in THF at 50°C for 92 h afforded **4** in 13% yield accompanied by **5** (28, 57% ee), strongly indicating that **10** is not the actual activated catalyst generated from ALB. It seems likely that a cycloalkenone cannot coordinate to the aluminum in **10** anymore, resulting in lower ees and lower regioselectivity. The mechanism for the formation of **10** is proposed as shown in Scheme 1.[5]

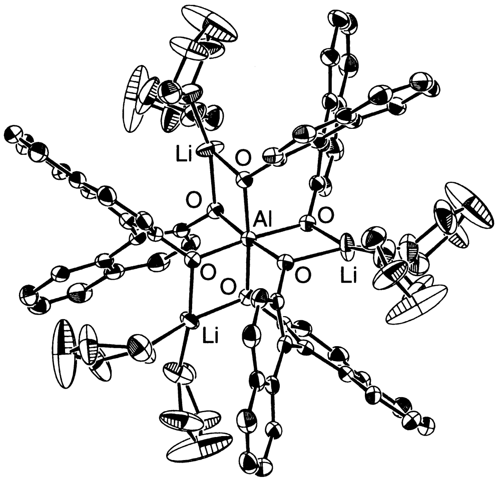
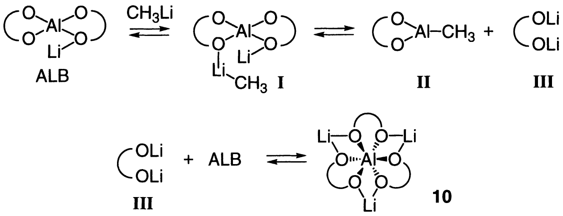


Fig. 2. X-ray structure of $AlLi_3$tris(binaphthoxide)$(thf)_6$ complex **10**.



Scheme 1. Proposed mechanism for the generation of $AlLi_3$-tris(binaphthoxide) complex **10**.

We next paid attention to the aluminum complex **II** probably generated from ALB and the basic compound. Actually we succeeded in preparing **II** from $Al(CH_3)_3$ and BINOL (1 equivalent) in THF, and the structure was unequivocally determined by X-ray analysis, revealing the dimeric structure **11**, which was a unique pentacoordinated aluminum complex (Fig. 3).[6]

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[2] The enantiomeric excess of the 1,4-adduct was determined by chiral HPLC assay after the transformation to **8** or **9**. The absolute configuration of **8** and **9** was determined by comparing with authentic samples derived from enones and dimethyl malonate [3].

[3] See Footnote 2.

[4] Crystal data for the $AlLi_3$tris(binaphthoxide)$(thf)_6$ complex **10** (m.p. 104–114°C, decomposition) collected at 291 K: $C_{84}H_{84}-AlLi_3O_{12} = 1235.47$, $a = b = 14.5874(1)$ Å, $c = 19.6798(2)$ Å, $\alpha = \beta = 90°$, $\gamma = 120°$, $U = 3626.2(6)$ Å^3, hexagonal, $P6_3$ ($Z = 2$), $Dx = 1.23\,g/cm^3$, $R(F) = 0.074$.

[5] The reaction of ALB with the dilithium salt of BINOL gave **10** as a crystal.

[6] Crystal data for the $(CH_3)_2Al_2$(binaphthoxide)$_2$(thf)$_2$ complex **11** (m.p. 85–89°C, decomposition, unstable) collected at 100 K: $C_{33}H_{39}AlO_5 = 542.65$, $a = 30.21(3)$ Å, $b = 11.064(8)$ Å, $c = 8.519(7)$ Å, $\beta = 101.30(5)°$, $U = 2792(3)$ Å^3, monoclinic, C2 ($Z = 4$), $Dx = 1.29\,g/cm^3$, $R(F) = 0.050$.

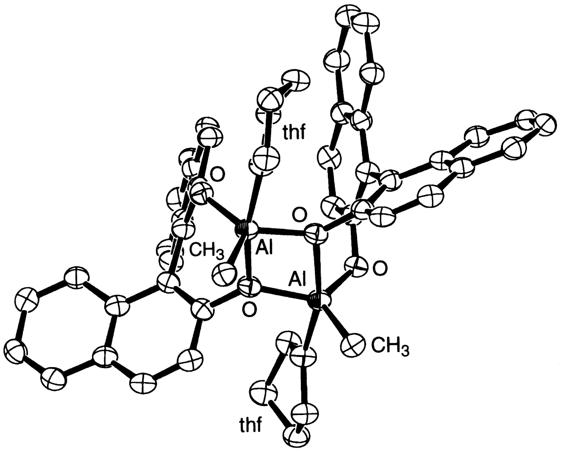


Fig. 3. X-ray structure of $(CH_3)_2Al_2(binaphthoxide)_2(thf)_2$ complex **11**.

First, the reaction of **1** with **3** in the presence of **11** (5 mol%) was found not to promote the reactions at all. On the other hand, we were very pleased to find that treatment of **1** with **3** in the presence of a mixture of **10** (10 mol%) and **11** (5 mol%) in THF at 50°C for 92 h gave **5** in 96% ee and 54% yield. Likewise, **2** was also converted to **7** in 92% ee and in 83% yield. From these results, we can now conclude that there is an equilibrium between the tetracoordinated aluminum catalyst (ALB) and the hexacoordinated aluminum complex **10** in the reaction medium, and the actual structure of the activated ALB-type catalyst is probably the self-assembled complex **I** of ALB and a standard base. Actually, the addition of an alkali metal enolate such as the Na enolate generated from **3** and NaH (0.9 equivalent to ALB) instead of standard bases gives similar results.

Regardless of the structure of the activated ALB-type catalyst (the self-assembled complex of ALB and a standard base or alkali metal enolate), the working model for the mode of enantioface selection is shown in Fig. 4.

It is clear that the actual asymmetric catalysts show stronger Brønsted basicity than ALB itself. In addition, the nearly perfect enantioselection as well as the perfect regioselection appears to indicate the efficient coordination of **1** to the aluminum atom even in the case of the activated ALB-type asymmetric catalysis [3,4]. The change of coordination number for aluminum from 4 to 6, caused by the nucleophilic attack on the aluminum center, would reasonably support the coordination of the enone to aluminum. This working model convincingly explains very well the high regioselectivity and enantioselectivity as well as the absolute configuration of the product.

The above-mentioned heterobimetallic catalysts contained two different kinds of metals in the catalyst. In addition to these types of catalysts, we have found that an alkali metal free–rare earth–BINOL derivative complexes also act as multifunctional catalysts, promoting epoxidation of enones (α,β-unsaturated ketones) with hydroperoxides to give epoxyketones [9–11]. Among the catalysts examined, we found that use of the ytterbium–(*R*)-3-hydroxymethyl–BINOL

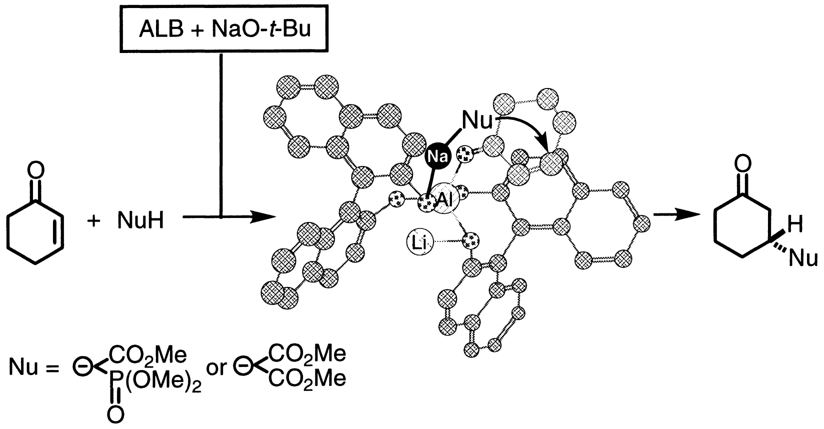
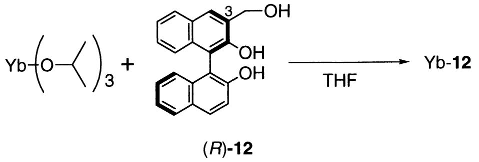


Fig. 4. Working model for the enantioface selection.



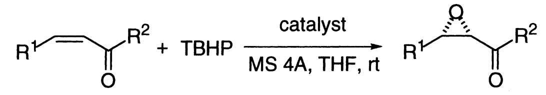
Scheme 2. Preparation of Yb–3-hydroxymethyl–BINOL complex.

complex [9–11] (Yb–3-CH_2OH–BINOL; Yb-**12**), prepared from Yb(O-*i*-Pr)$_3$ and **12** in a ratio of 1:1.4 (Scheme 2) gave *cis*-epoxides quite efficiently.

With the hitherto known method, the stereoselective construction of *cis*-epoxyketones from acyclic *cis*-enones is difficult due to the tendency of *cis*-enones to afford the corresponding more stable *trans*-derivatives during the oxidation process. For example, treatment of *cis*-**13** with TBHP in the presence of BuLi (10 mol%) provided a mixture of *cis*- and *trans*-epoxyketones in 8 and 43% yield, respectively (Table 2, entry 1).

Although the structural elucidation of the Yb-**12** catalyst is extremely difficult [9–11], the amphoteric rare earth atom(s) in the catalyst could control the orientation of *cis*-enone and the peroxide anion to furnish *cis*-epoxide, avoiding the side reactions that form *trans*-derivatives. It is noteworthy that the reaction proceeds at room temperature without special care to remove moisture. As shown in Table 2, the Yb-**12** catalyst gave *cis*-epoxyketone of a higher ee than the La-**12** catalyst and/or the BINOL derived catalysts. By use of the Yb-**12** catalyst, aliphatic *cis*-enones were converted into *cis*-epoxyketones in a highly enantioselective manner (93∼96% ee) [12]. The absolute configuration of the β-position of *cis*-epoxyketones was determined to be *S* when (*R*)-**12** was utilized for the catalyst preparation. This was in direct contrast to what was seen in the epoxidation of the corresponding *trans*-enones, in which the major enantiomer was (α*S*, β*R*) [10]. Attempts to prepare racemic authentic samples with Ln(O-*i*-Pr)$_3$ resulted in the formation of

Table 2
Catalytic asymmetric epoxidation of *cis*-enones

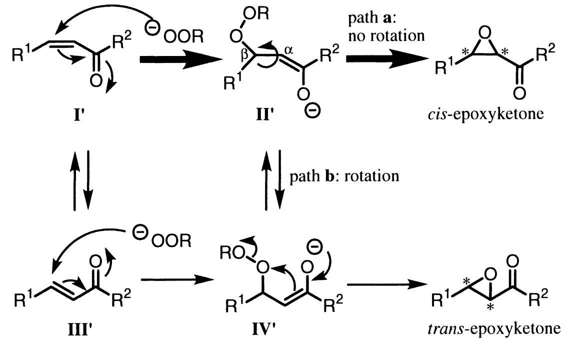


13: $R^1 = C_5H_{11}$, $R^2 = CH_3$
15: $R^1 = C_3H_7$, $R^2 = (CH_2)_2Ph$
17: $R^1 = C_5H_{11}$, $R^2 = C_3H_7$
19: $R^1 = CH_3$, $R^2 = Ph$
21: $R^1 = C_3H_7$, $R^2 = Ph$

cis-**14**: $R^1 = C_5H_{11}$, $R^2 = CH_3$
cis-**16**: $R^1 = C_3H_7$, $R^2 = (CH_2)_2Ph$
cis-**18**: $R^1 = C_5H_{11}$, $R^2 = C_3H_7$
cis-**20**: $R^1 = CH_3$, $R^2 = Ph$
cis-**22**: $R^1 = C_3H_7$, $R^2 = Ph$

Entry	Substrate	Catalyst (mol%)	TBHP (equivalent)	Time (h)	*cis*-Epoxide[a]		*trans*-Epoxide[b]	
					y (%)	ee (%)	y (%)	ee (%)
1[c]	**13**→**14**	BuLi (10)	3	22	8	ND	43	ND
2[c]	**13**→**14**	La–BINOL[d] (5)	1.5	72	31	5	<10	ND
3[c]	**13**→**14**	Yb–BINOL[d] (5)	1.5	72	60	4	<10	ND
4[c]	**13**→**14**	La-**12** (10)	3	72	58	58	<10	ND
5	**13**→**14**	Yb-**12** (10)	3	72	74	94	Trace	ND
6[c]	**15**→**16**	Yb–BINOL[d] (10)	3	146	56	21	<10	ND
7	**15**→**16**	Yb-**12** (10)	3	146	78	93	Trace	ND
8[c]	**17**→**18**	Yb–BINOL[d] (10)	3	127	75	27	Trace	ND
9	**17**→**18**	Yb-**12** (10)	3	127	80	96	Trace	ND
10	**19**→**20**	Yb-**12** (10)	3	81	60	82	32	10[e]
11	**21**→**22**	Yb-**12** (10)	3	96	51	88	19	58[e]

[a] Absolute configurations of the major enantiomer were determined to be (α*S*, β*S*) other than entries 3, 6, 8 (α*R*, β*R*).
[b] ND: Not determined.
[c] The starting material was retained.
[d] Prepared from lanthanoid 2-propoxide and BINOL in a ratio of 1:1.
[e] Absolute configurations of the major enantiomer were determined to be (α*S*, β*R*).



Scheme 3. Proposed mechanism for the epoxidation of *cis*-enones.

a mixture of *cis*- and *trans*-epoxyketones, suggesting the importance of the multifunctional character of the Yb-**12** catalyst. For aromatic *cis*-enones, which isomerize readily to *trans*-enones, 10 mol% of the Yb-**12** catalyst was effective to obtain *cis*-epoxides, though a small amount of *trans*-epoxyketones were also formed. We also examined asymmetric epoxidation of trisubstituted enone $(CH_3)_2C{=}CHCOPh$ (**23**). The Yb-**12** catalyst (10 mol%) was also effective, giving 78% of corresponding epoxide **24** in 87% ee (120 h).[7]

In the absence of TBHP, treatments of *cis*-enones by base catalysts, including Yb-**12**, afforded *trans*-enones.[8] This fact indicates the possibility of isomerization of *cis*-enones to *trans*-enones in Yb-**12** catalyzed epoxidation. If the *trans*-epoxyketones were only obtained from *trans*-enones generated via isomerization of *cis*-enones, the ee of the *trans*-epoxyketone should be as high as that obtained from *trans*-enones as a starting material [9].[9] However, the *trans*-epoxyketones obtained from *cis*-enones have low optical purity. These results clearly indicate that two kinds of pathways to afford *trans*-epoxyketones are involved in the epoxidation of *cis*-enones. The proposed mechanism for *trans*-epoxyketones from *cis*-enones is shown in Scheme 3.

The epoxidation of enones by hydroperoxides proceeds via conjugate addition of peroxide anion to enones. In the intermediary enolate **II**′, single bond rotation between the α and β position occurs to form *trans*-epoxyketone through the enolate **IV**′. Meanwhile, isomerization of *cis*-enones to *trans*-enones competes with this pathway.

3. Conclusions

Efficient catalyses utilizing heterobimetallic catalysts like ALB and alkali metal free–rare earth–BINOL derivative complexes have been developed. These catalysts function both as Brønsted bases and as Lewis acids, making possible the formation of unique optically active products which are difficult to obtain even in a racemic form.

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[7] Yield and ee of **24** using another catalyst: La–BINOL (5 mol%, 92 h) 46% (42% ee), Yb–BINOL (5 mol%, 97 h) 75% (8% ee) La-**12** (10 mol%, 190 h) 51% (27% ee).

[8] Treatment of **15** with Yb-**12** (10 mol%) in the absence of TBHP at RT for 78 h gave *cis*- and *trans*-**15** in a ratio of 6:1.

[9] Epoxidation of *trans*-**19** and *trans*-**21** with Yb-**12** catalyst (10 mol%) gave *trans*-**20** and *trans*-**22** in 80% ee (87% yield) and 71% ee (81% yield), respectively.