J. Am. Chem. Soc. **1998,** *120,* 441−442

Regioselective Catalytic Asymmetric Reaction of Horner−Wadsworth−Emmons Reagents with Enones: The Odyssey of Chiral Aluminum Catalysts

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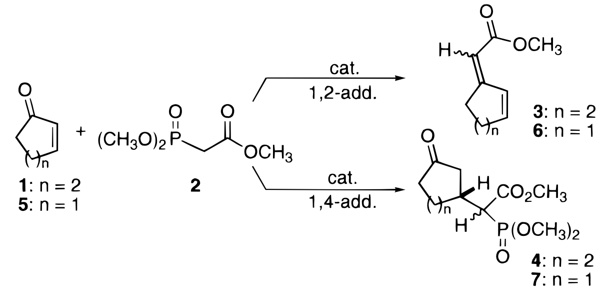
Received September 2, 1997

Horner−Wadsworth−Emmons reagents are known to be quite useful for the preparation of α,β-unsaturated carbonyl compounds from aldehydes or ketones or both.[1] These reagents, however, react with α,β-unsaturated carbonyl compounds to give either 1,2-adducts (Horner−Wadsworth−Emmons product) or 1,4-adducts (Michael product), depending on the structure of the starting compounds.[2] For example, the reaction of cyclohexenone (**1**) with Horner−Wadsworth−Emmons reagent **2** promoted by standard bases (10 mol %) such as NaO-*t*-Bu and BuLi gives the 1,2-adduct **3** in 8−9% yield (Table 1, entries 1−3). In contrast, the reaction of cyclopentenone (**5**) with **2** under similar reaction conditions gives the 1,4-adduct **7** in 90−98% yield.

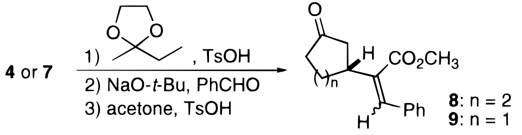
We have found that the reaction of **1** with **2** in the presence of a catalytic amount of certain heterobimetallic asymmetric complexes[3] gives **4** as a major product by way of the unusual regioselective route (entries 5, and 7−9). Although the aluminum lithium bis(binaphthoxide) complex itself (ALB)[3a] did not promote the reaction of **1** with **2** at 50 °C, the catalytic 1,4-addition promoted by the combined use of ALB (10 mol %) and BuLi (0.9 equiv to ALB)[3b] gave **4** in 58% yield with 98% ee (enantiomeric excess). More gratifyingly, the use of NaO-*t*-Bu instead of BuLi gave **4** exclusively in 64% yield with 99% ee, and no formation of **3** was detected (entry 8).[4] Moreover, **5** was also converted to **7**, even at room temperature, in 95% yield and in 95% ee (entry 10).[4] To the best of our knowledge, this is the first example of a catalytic asymmetric 1,4-addition of a Horner−Wadsworth−Emmons reagent to enones. These 1,4-adducts would be key intermediates for the catalytic asymmetric synthesis of various natural products such as strychinine,[5a] tubifolidine,[5b,c] tubifoline,[5b,c] and coronafacic acid.[5d,e] In fact, the 1,4-adduct was successfully transformed into coronafacic acid.[6]

Table 1. Regio- and Enantioselective Reaction of Horner−Wadsworth−Emmons Reagent with Enone



entry	cat.[a] (10 mol %)	temp. (°C)	time (h)	1,2-add. yield (%)	1,4-add. yield (%)	ee (%)[f] of **8** or **9**
	1 + **2** → **3** + **4**					
1	BuLi	50	120	8	0	-
2	NaO-*t*-Bu	50	120	9	0	-
3	KO-*t*-Bu	50	120	8	2	-
4[b]	La-BINOL	50	140	4	14	27
5[c]	LSB	50	140	11	19	6
6[d]	ALB	50	140	no reaction		
7[e]	ALB+BuLi	50	140	3	58	98
8[e]	ALB+NaO-*t*-Bu	50	140	0	64	99
9[e]	ALB+KO-*t*-Bu	50	140	5	27	89
	5 + **2** → **6** + **7**					
10[e]	ALB+NaO-*t*-Bu	rt	72	0	95	95

a: All chiral catalysts were prepared using (*R*)-BINOL.
b: Prepared from La(O-*i*-Pr)$_3$ and BINOL (1 : 1); see ref 3d.
c: LSB: LaNa$_3$tris(binaphthoxide); see ref 3c.
d: Prepared from LiAlH$_4$ and BINOL (1 : 2); see ref 3a.
e: Basic alkali metal reagents (0.9 mol equiv to ALB) were used; see ref 3b.
f: Compound **8** and **9** were obtained as follows. See, ref 4.



What is then the actual structure of the activated catalyst generated from ALB and standard bases? Treatment of ALB with a base such as MeLi, BuLi, and the Li enolate of **2** (1.0 equiv to ALB, respectively) in THF (0.01 mM of ALB) was found to give a stable colorless crystal (43% based on ALB). Surprisingly, 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 (Figure 1).[7,8] The mechanism for the formation of **10** is proposed as shown in Scheme 1.[9] But is AlLi$_3$tris(binaphthoxide)(thf)$_6$ (**10**) the actual structure of the activated ALB-type catalyst? It soon became clear that treatment of **1** with **2** in the presence of **10** (10 mol %) in THF at 50 °C for

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(1) For reviews on the Horner−Wadswarth−Emmons reaction, see: (a) Maryanoff, B. E.; Reize, A. B. *Chem. Rev.* **1989**, *89*, 863−927. (b) Kelly, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 755−782.

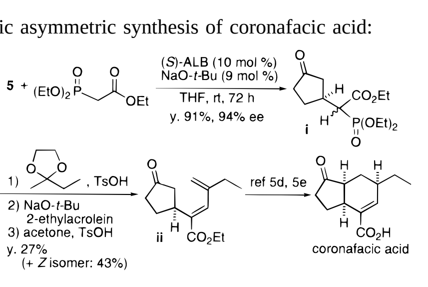
(2) (a) Ruder, S. M.; Kulkarni, V. R. *J. Chem. Soc., Chem. Commun.* **1994**, 2119−2200. (b) Yuan, C.; Li, C.; Ding, Y. *Synthesis*, **1991**, 854−857. (c) Bergmann, E. D.; Solomonovici, A. *Tetrahedron* **1971**, *27*, 2675−2678 and references therein.

(3) (a) Arai, T.; Sasai, H.; Aoe, K.; Okamura, K.; Shibasaki, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 104−106. (b) Arai, T.; Yamada, Y. M. A.; Yamamoto, N.; Sasai, H.; Shibasaki, M. *Chem. Eur. J.* **1996**, *2*, 1368−1372. (c) Sasai, H.; Arai, T.; Satow, Y.; Houk, K. N.; Shibasaki, M. *J. Am. Chem. Soc.* **1995**, *117*, 6194−6198. Although alkali-metal-free La-BINOL is not the heterobimetallic complex, this catalyst is also effective for the catalytic asymmetric 1,4-addition: (d) Sasai, H.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1994**, *116*, 1571−1572. For a review, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236−1256 and references therein.

(4) The ee of the 1,4-adduct was determined by chiral HPLC assay after the transformation to **8** or **9**. The absolute configurations of **8** and **9** were determined by comparison with authentic samples derived from enones and dimethyl malonate (ref 3a).

(5) (a) Angl, S. R.; Fevig, J. M.; Knight, S. D.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 3966−3976. (b) Fevig, J. M.; Marquis, R. W., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1991**, *113*, 5085−5086. (c) Magnus, P.; Sear, N.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70−78. (d) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron Lett.* **1996**, *37*, 6745−6748. (e) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron* **1997**, *53*, 9509−9524.

(6) Catalytic asymmetric synthesis of coronafacic acid:



S0002-7863(97)03064-3 CCC: $15.00

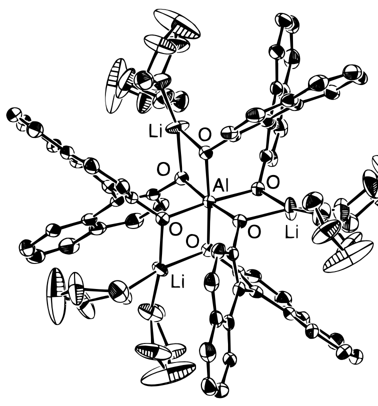


Figure 1. X-ray structure of AlLi$_3$tris(binaphthoxide) complex **10**.

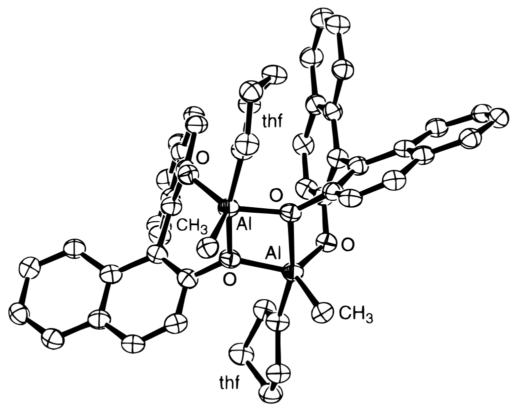
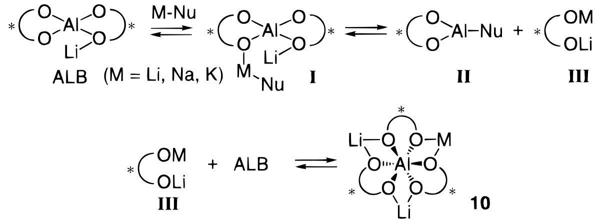


Figure 2. X-ray structure of $(CH_3)_2Al_2$(binaphthoxide)$_2$(thf)$_2$ complex **11**.

Scheme 1. Proposed Mechanism for the Generation of AlLi$_3$tris(binaphthoxide) Complex **10**



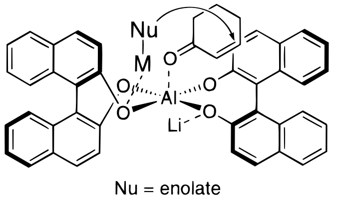


Figure 3. Working model for the mode of enantioface selection.

92 h afforded **3** in 13% yield accompanied by **4** (28%, 57% ee). Moreover, the reaction of **5** with **2** (1.0 equiv) in the presence of **10** (10 mol %) in THF at room temperature for 56 h gave **7** in 78% yield and in only 12% ee, strongly indicating that **10** is not the actual activated catalyst generated from ALB. It seems likely that a cycloalkenone cannot coordinate to the hexacoordinated aluminum in **10** anymore, resulting in lower ee values and lower regioselectivity. We next paid attention to the aluminum complex **II** probably generated from ALB and the basic compound. Actually, we succeeded in preparing **II** (Nu = CH_3) from $Al(CH_3)_3$ and BINOL (1 equiv) in THF, and the structure was unequivocally determined by X-ray analysis, revealing the dimeric structure **11**, which was a unique pentacoordinated aluminum complex (Figure 2).[10] First, the reaction of **1** with **2** in the presence of **11** (5 mol %) was found to not promote the reactions at all. On the other hand, we were very pleased to find that treatment of **1** with **2** in the presence of a mixture of **10** (10 mol %) and **11** (5 mol %) in THF at 50 °C for 92 h gave **4** in 96% ee and 54% yield. Likewise, **5** 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)[11] and the hexacoordinated aluminum complex **10** in the reaction medium,[12] and the actual structure of the activated ALB-type catalyst is probably the self-assembled complex **I** of ALB and a standard base or an alkali metal enolate.[13] Actually, the addition of an alkali metal enolate such as the Na enolate generated from **2** and NaH (0.9 equiv 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),[14] the working model for the mode of enantioface selection is shown in Figure 3. 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.[3a,b,13] 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.[15]

In conclusion, we have reported here a highly effective catalytic asymmetric 1,4-addition of a Horner–Wadsworth–Emmons reagent to an enone, in which both the regioselectivity and enantioselectivity have been perfectly controlled for the first time by utilizing a heteropolymetallic multifunctional asymmetric complex. Further studies are currently under investigation.[16]

Acknowledgment. We thank the Rigaku Corporation and Tanabe Seiyaku Co. Ltd. for the X-ray structure determination of **10**.

Supporting Information Available: Experimental procedures and crystallographic details (42 pages). See any current masthead page for ordering and Internet access instructions.

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(7) Crystal data for the AlLi$_3$tris(binaphthoxide)(thf)$_6$ complex **10** (mp 104–114 °C, dec.) 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), D_x = 1.23 g/cm^3, *R*(*F*) = 0.074.

(8) The structure of **10** has a structure similar to the LnM$_3$tris(binaphthoxide) complex (Ln = rare earth), expect for the distance of the central metal–oxygen bond and coordinating H_2O (ref 3).

(9) The reaction of ALB with the dilithium salt of BINOL gave **10** as a crystal.

(10) Crystal data for the $(CH_3)_2Al_2$(binaphthoxide)$_2$(thf)$_2$ complex **11** (mp 85–89 °C, dec., 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, *C*2 (*Z* = 4), D_x = 1.29 g/cm^3, *R*(*F*) = 0.050. Although H. Yamamoto et al. have reported the elegant use of CH_3Al(3,3′-disubstituted-binaphthoxide) complexes for the hetero-Diels–Alder reaction and Claisen rearrangement, the structure of their catalysts has not been determined unequivocally. (a) Maruoka, K.; Itoh, T.; Shirasaka, T.; Yamamoto, H. *J. Am. Chem. Soc.* **1988**, *110*, 310–312. (b) Maruoka, K.; Banno, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1990**, *112*, 7791–7793.

(11) The tetracoordinated aluminum structure of ALB was unequivocally determined by X-ray analysis (ref 3a,b). In addition, ^{13}C NMR spectrum of ALB (10 peaks) revealed that ALB exsisted as a single species in THF solution.

(12) For the reaction of **1** with dimethyl malonate, **10** gave the 1,4-adduct with high ee. This would also suggest the regeneration of ALB from **10**.

(13) The reaction of **1** and **2** promoted by the dilithium salt of BINOL gives only the 1,2-adduct **3**.

(14) It appears that the self-assembled complex of ALB and a standard base is readily converted to the self-assembled complex of ALB and an alkali metal enolate.

(15) For examples of the 1,4-addition to enones controlled by aluminum Lewis acids, see: (a) Maruoka, K.; Imoto, H.; Saito, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 4131–4132. (b) Ooi, T.; Kondo, Y.; Maruoka, K. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1183–1185 and references therein.

(16) After the submission of this manuscript, Feringa et al. published asymmetric Michael reactions of α-nitroesters with enones using ALB as a catalyst. They also isolated the hexacoordinated aluminum complex **10**. Keller, E.; Veldman, N.; Spek, A. L.; Feringa, B. L. *Tetrahedron: Asymmetry* **1997**, *8*, 3403–3413.