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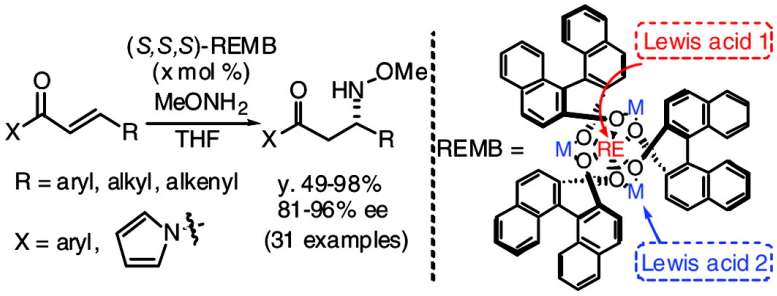

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Lewis Acid−Lewis Acid Heterobimetallic Cooperative Catalysis: Mechanistic Studies and Application in Enantioselective Aza-Michael Reaction

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Abstract: The full details of a catalytic asymmetric aza-Michael reaction of methoxylamine promoted by rare earth−alkali metal heterobimetallic complexes are described, demonstrating the effectiveness of Lewis acid−Lewis acid cooperative catalysis. First, enones were used as substrates, and the 1,4-adducts were obtained in good yield (57−98%) and high ee (81−96%). Catalyst loading was successfully reduced to 0.3−3 mol % with enones. To broaden the substrate scope of the reaction to carboxylic acid derivatives, α,β-unsaturated *N*-acylpyrroles were used as monodentate, carboxylic acid derivatives. With β-alkyl-substituted *N*-acylpyrroles, the reaction proceeded smoothly and the products were obtained in high yield and good ee. Transformation of the 1,4-adducts from enones and α,β-unsaturated *N*-acylpyrroles afforded corresponding chiral aziridines and β-amino acids. Detailed mechanistic studies, including kinetics, NMR analysis, nonlinear effects, and rare earth metal effects, are also described. The Lewis acid−Lewis acid cooperative mechanism, including the substrate coordination mode, is discussed in detail.

Introduction

The recent development and use of various types of cooperative catalyses in asymmetric reactions have received much attention.[1] Since the early 1990s,[2a] we reported a series of rare earth−alkali metal heterobimetallic complexes that enable various catalytic asymmetric reactions.[2] The structure of the rare earth−alkali metal heterobimetallic complexes, determined by X-ray, mass spectrometry, and NMR analysis, consisted of one rare earth metal (RE), three 1,1′-bi-2-naphthol (BINOL), and three alkali metals (M) (REMB, Figure 1).[2b,c] The asymmetric environment of REMB is finely tunable by varying the combination of rare earth metals and alkali metals. Mechanistic studies of asymmetric reactions with the REMB complex revealed that REMB functions as a cooperative Lewis acid−Brønsted base catalyst. The REMB catalyst functions not only as a Lewis acid to activate electrophiles but also as a Brønsted base to deprotonate nucleophiles to form activated metal nucleophiles. In previous reports of the REMB heterobimetallic catalysts, only nucleophiles with protons with a relatively low pK_a value (ca. 10−19 in H_2O), such as nitroalkane, malonate, ketone, and thiol, were used due to the limitation of the Brønsted basicity of the catalysts.[1c] Nucleophiles with a higher pK_a value were not applicable to REMB catalysts. To broaden the substrate scope of nucleophiles in REMB catalysis, we planned to use the same REMB heterobimetallic catalysts in a different reaction mode: Lewis acid−Lewis acid cooperative catalysis.[3,4]

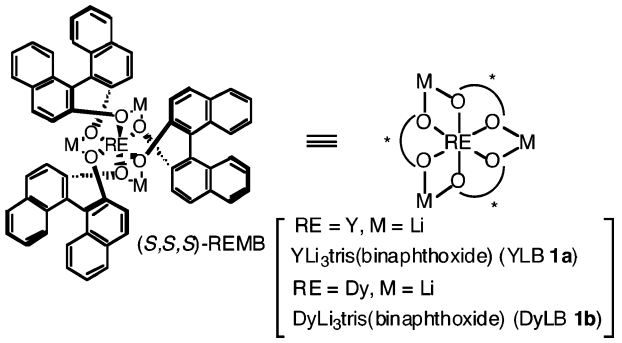


Figure 1. Structures of (*S*,*S*,*S*)-REMB, (*S*,*S*,*S*)-YLB **1a**, and (*S*,*S*,*S*)-DyLB **1b**.

We hypothesized that if the Lewis acidic part of the chiral catalyst controls both the orientation of the electrophile and nucleophile properly, with only a little, if any, deactivation of nucleophiles, high enantio-induction would be achieved (Figure 2). To evaluate this concept, we chose catalytic asymmetric 1,4-addition of *O*-alkylhydroxylamines. 1,4-Addition of amines to

(1) Reviews on bifunctional asymmetric catalysis: (a) Ma, J.-A.; Cahard, D. *Angew. Chem., Int. Ed.* **2004**, *43*, 4566. (b) Rowlands, G. J. *Tetrahedron* **2001**, *57*, 1865. (c) Kanai, M.; Kato, N.; Ichikawa, E. Shibasaki, M. *Synlett* **2005**, 1491.

(2) (a) Sasai, H.; Suzuki, T.; Arai, S.; Arai, T.; Shibasaki, M. *J. Am. Chem. Soc.* **1992**, *114*, 4418. (b) Sasai, H.; Suzuki, T.; Itoh, N.; Tanaka, K.; Date, T.; Okamura, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1993**, *115*, 10372. Reviews on rare earth−alkali metal bifunctional catalysts: (c) Shibasaki, M.; Yoshikawa, N. *Chem. Rev.* **2002**, *102*, 2187. (d) Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236.

(3) Review for combined acid catalysis including Lewis acid−assisted Lewis acid catalysis, see: (a) Yamamoto, H.; Futatsugi, K. *Angew. Chem., Int. Ed.* **2005**, *44*, 1924. For representative examples of Lewis acid−assisted Lewis acid catalysis, see: (b) Ishihara, K.; Kobayashi, J.; Inanaga, K.; Yamamoto, H. *Synlett* **2001**, 394 and references therein. (c) Hanawa, H.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2003**, *125*, 1708. (d) Ooi, T.; Takahashi, M.; Yamada, M.; Tayama, E.; Omoto, K.; Maruoka, K. *J. Am. Chem. Soc.* **2004**, *126*, 1150 and references therein. For other examples, see review (ref 3a).

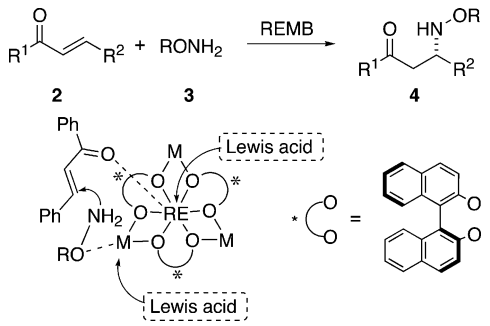
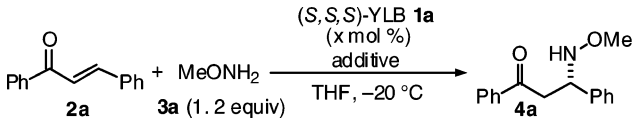


Figure 2. Working hypothesis of Lewis acid−Lewis acid cooperative catalysis in enantioselective 1,4-addition of alkoxylamine.

α,β-unsaturated carbonyl compounds provides a direct and attractive strategy for the construction of optically active β-amino carbonyl compounds,[5−8] which are often found in biologically interesting compounds. Among them, a few highly enantioselective Lewis acid catalyses for 1,4-additions of *O*-alkylhydroxylamines were recently reported,[7] providing versatile chiral building blocks. The products were readily transformed into chiral aziridines. We hypothesized that the oxygen atom of *O*-alkylhydroxylamine would coordinate to the alkali metal of a heterobimetallic complex without a significant decrease in the nucleophilicity of nitrogen (Figure 2). Here we report the complete details of our trials to utilize the heterobimetallic complex in Lewis acid−Lewis acid cooperative catalysis for enantioselective 1,4-addition of methoxylamine. The (*S*,*S*,*S*)-YLi$_3$tris(binaphthoxide) complex (YLB **1a**, Figure 1) efficiently promoted the addition of methoxylamine to enones. The substrate scope was further broadened to α,β-unsaturated carboxylic acid derivatives using α,β-unsaturated *N*-acylpyrroles as substrates. The mechanistic studies of the reaction to verify the Lewis acid−Lewis acid bifunctional reaction mode are also described in detail.

Table 1. Optimization of Catalytic Asymmetric Aza-Michael Reaction of **2a** with **3a**



entry	additive	catalyst (*x* mol %)	time (h)	yield (%)	ee (%)
1	none	10	24	94	97
2	H_2O[b]	10	24	29	93
3	MS 3 Å	10	24	85	96
4	MS 4 Å	10	24	67	96
5	MS 5 Å	10	24	44	97
6	Drierite	10	24	94	97
7	Drierite	5	42	94	96
8	Drierite	3	42	97	95
9	Drierite	1	48	95	96
10	Drierite	0.5	80	96	96
11	Drierite	0.3	80	96	92
12[a]	Drierite	1	48	98	95

[a] Reaction was performed in 10 g scale at 2.1 M. [b]30 mol % of H_2O was added.

Results and Discussion

A. Addition to Enones.[9] Initially, we screened various heterobimetallic complexes containing rare earth metals and alkaline metals for the addition of **3a** to **2a**, and YLB **1a** gave the best reactivity and enantioselectivity.[10] The reaction proceeded smoothly with 10 mol % of **1a** at −20 °C to give **4a** in 94% yield and 97% ee (Table 1, entry 1). In contrast to the catalytic asymmetric ethoxycarbonylation reaction of aldehydes using the YLB−H_2O complex,[11,12] the addition of H_2O somewhat retarded the reaction. Anhydrous conditions gave the best reaction rate, although H_2O had no adverse effects on enantioselectivity (entry 1 vs entry 2).[10] We speculated that even a small amount of H_2O derived from a possible side reaction (oxime formation) would be problematic for reducing the catalyst loading. Thus, various desiccants were screened (entries 3−6), and Drierite ($CaSO_4$) gave the best results (entry 6).[13] The low chemical yield produced using molecular sieves (entries 3−5) is due to the absorption of methoxylamine to the molecular sieves.[13] Under the optimal conditions (YLB, **3a**: 1.2 equiv, Drierite), catalyst loading was reduced. As summarized in entries 7−11, the reaction proceeded without any problem with as little as 0.5−1 mol % of **1a**, giving **4a** in good yield and ee (entry 9,

(4) For selected recent examples of other bifunctional chiral metal catalysis, see: (a) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206. (b) Knudsen, K. R.; Jørgensen, K. A. *Org. Biomol. Chem.* **2005**, *3*, 1362. (c) Kanemasa, S.; Ito, K. *Eur. J. Org. Chem.* **2004**, 4741. (d) Evans, D. A.; Seidel, D.; Rueping, M.; Lam, H. W.; Shaw, J. T.; Downey, C. W. *J. Am. Chem. Soc.* **2003**, *125*, 12692. (e) Sammis, G. M.; Danjo, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2004**, *126*, 9928. (g) Josephsohn. N. S.; Kuntz, K. W.; Snapper, M. L.; Hoveyda, A. M. *J. Am. Chem. Soc.* **2001**, *123*, 11594. (h) Trost, B. M.; Terrell, L. R. *J. Am. Chem. Soc.* **2003**, *125*, 338 and references therein. (i) Matsunaga, S.; Yoshida, T.; Morimoto, H.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8777 and references therein. For other examples, see review in refs 1−3.

(5) Reviews for enantioselective conjugate addition: (a) Sibi, M. P.; Manyem, S. *Tetrahedron* **2000**, *56*, 8033. (b) Krause, N.; Hoffmann-Röder, A. *Synthesis* **2001**, 171.

(6) Review for aza-Michael reaction: Xu, L.-W.; Xia, C.-G. *Eur. J. Org. Chem.* **2005**, 633.

(7) Alkoxyamines as nucleophiles: (a) Sibi, M. P.; Shay, J. J.; Liu, M.; Jasperse, C. P. *J. Am. Chem. Soc.* **1998**, *120*, 6615. (b) Jørgensen, K. A.; Falborg, L. *J. Chem. Soc., Perkin Trans. 1* **1996**, 2823. (c) Sugihara, H.; Daikai, K.; Jin, X. L.; Furuno, H.; Inanaga, J. *Tetrahedron Lett.* **2002**, *43*, 2735. (d) Jin, X. L.; Sugihara, H.; Daikai, K.; Takeishi, H.; Jin, Y. Z.; Furuno, H.; Inanaga, J. *Tetrahedron* **2002**, *58*, 8321. (e) Cardillo, G.; Gentilucci, L.; Gianotti, M.; Kim, H.; Perciaccante, R.; Tolomelli, A. *Tetrahedron: Asymmetry* **2001**, *12*, 2395.

(8) For recent highly enantioselective catalytic asymmetric 1,4-additions of other nitrogen nucleophiles to afford β-amino carbonyl compounds, see: *N*-Benzylhydroxylamine: (a) Sibi, M. P.; Prabagaran, N.; Ghorpade, S. G.; Jasperse, C. P. *J. Am. Chem. Soc.* **2003**, *125*, 11796 and references therein. Aromatic amine: (b) Zhuang, W.; Hazell, R. G.; Jørgensen, K. A. *Chem. Commun.* **2001**, 1240. (c) Fadini, L.; Togni, A. *Chem Commun.* **2003**, 30. (d) Li, K.; Hii, K. K. *Chem Commun.* **2003**, 1132. (e) Li, K.; Cheng, X.; Hii, K. K. *Eur. J. Org. Chem.* **2004**, 959. (f) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861. Azide ion: (g) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959. (h) Guerin, D. J.; Miller, S. J. *J. Am. Chem. Soc.* **2002**, *124*, 2134. Carbamate: (i) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188. For ligand-controlled asymmetric addition of lithium amide, see: (j) Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.-i.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886 and references therein.

(9) A part of this article (addition to enones, section A) was reported previously as a preliminary communication. Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178.

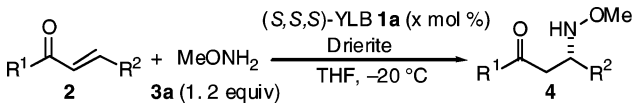
(10) Effects of rare earth metals and alkali metals on the reaction rate and enantioselectivity are described in detail in section D. Adverse effects of H_2O are also discussed in detail in section D.

(11) In the asymmetric cyanation reaction, YLB−H_2O complex was essential to achieve good reactivity and enantioselectivity. Anhydrous YLB **1a** complex gave cyanation adducts in poor ee; see: (a) Yamagiwa, N.; Tian, J.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 3413. (b) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 3636. (c) Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021. (d) Abiko, Y.; Yamagiwa, N.; Sugita, M.; Tian, J.; Matsunaga, S.; Shibasaki, M. *Synlett* **2004**, 2434.

(12) For preparation and characterization of the structure of anhydrous YLB: (a) Aspinall, H. C.; Dwyer, J. L. M.; Greeves, N.; Steiner, A. *Organometallics* **1999**, *18*, 1366. (b) Aspinall, H. C.; Bickley, J. F.; Dwyer, J. L. M.; Greeves, N.; Kelly, R. V.; Steiner, A. *Organometallics* **2000**, *19*, 5416.

(13) Ability of Drierite as desiccant toward THF was checked by Karl Fisher experiment. See Supporting Information. Absorption of methoxylamine **3a** to molecular sieves was confirmed by NMR analysis of methoxylamine solution in THF using 2,4,6-trimethylbenzene as an internal standard.

Table 2. Catalytic Asymmetric Aza-Michael Reaction of Various Enones



entry	enone R¹	enone R²	product		YLB (mol %)	time (h)	yield (%)	ee (%)
1	Ph	Ph	**2a**	**4a**	3	42	97	95
2	Ph	Ph	**2a**	**4a**	1	48	95	96
3	4-Cl−C_6H_4	Ph	**2b**	**4b**	3	42	96	96
4	4-Cl−C_6H_4	Ph	**2b**	**4b**	1	46	92	96
5[a]	4-F−C_6H_4	Ph	**2c**	**4c**	3	54	97	96
6[a]	4-F−C_6H_4	Ph	**2c**	**4c**	1	65	91	96
7	4-Me−C_6H_4	Ph	**2d**	**4d**	3	48	96	94
8[a]	4-MeO−C_6H_4	Ph	**2e**	**4e**	3	74	91	96
9	3-Me−C_6H_4	Ph	**2f**	**4f**	3	48	96	92
10	2-furyl	Ph	**2g**	**4g**	3	48	95	94
11	2-thienyl	Ph	**2h**	**4h**	3	78	96	93
12[a]	Ph	4-Cl−C_6H_4	**2i**	**4i**	3	48	92	92
13	Ph	4-Cl−C_6H_4	**2i**	**4i**	1	78	97	93
14[a]	Ph	4-Me−C_6H_4	**2j**	**4j**	3	48	96	96
15	Ph	4-MeO−C_6H_4	**2k**	**4k**	3	82	85	95
16[a]	Ph	4-MeO−C_6H_4	**2k**	**4k**	1	74	85	95
17[a]	Ph	3-NO_2−C_6H_4	**2l**	**4l**	3	42	98	81
18[a]	Ph	3-ClC_6H_4	**2m**	**4m**	3	48	95	92
19	Ph	2-Cl−C_6H_4	**2n**	**4n**	3	122	92	82
20[a]	Ph	2-furyl	**2o**	**4o**	3	84	80	92
21[b]	Ph	2-thienyl	**2p**	**4p**	3	48	96	95
22	Ph	4-pyridyl	**2q**	**4q**	3	60	91	85
23	Ph	*n*-C_5H_{11}	**2r**	**4r**	3	84	96	84
24	Ph	*i*-$PrCH_2$	**2s**	**4s**	3	48	95	93
25	Ph	*i*-Pr	**2t**	**4t**	3	78	97	86
26	Ph	*cyclo*-hexyl	**2u**	**4u**	3	48	98	82
27	Ph	*t*-Bu	**2v**	**4v**	3	96	57	82
28	Ph	*trans*-PhCH=CH	**2w**	**4w**	3	84	91	95

[a] 2 equiv of **3a** were used. [b] 3 equiv of **3a** were used.

95% yield and 96% ee; entry 10, 96% yield and 96% ee). The reaction also proceeded with 0.3 mol % of **1a**, although the enantiomeric excess was slightly decreased (92% ee, entry 11). In entry 12, the reaction was performed on a 10 g scale at 2.1 M. **4a** was obtained without any problem in large scale under concentrated conditions.

We then examined the substrate scope of the reaction. For convenience, most reactions were performed with 3 mol % of **1a**. For selected substrates, including **2k** with an electron donating substituent on the aromatic ring, reactions were also performed with 1 mol % of **1a**, and similar results were obtained (Table 2, entries 1, 3, 5, 12, 15 vs 2, 4, 6, 13, 16). β-Aryl substituted enones with various substituents (entries 1−19) afforded 1,4-adducts in 81−96% ee and 85−97% yield. For the less reactive substrate, 2 to 3 equiv of **3a** were used. β-Heteroaromatic- (entries 20−22) and β-aliphatic- (entries 23−27) enones and dienone (entry 28) also gave products in good ee.[14]

B. Addition to α,β-Unsaturated *N*-Acylpyrroles. To broaden the substrate scope to α,β-unsaturated carboxylic acid derivatives, we investigated α,β-unsaturated *N*-acylpyrroles as electrophiles. The concept for the use of α,β-unsaturated *N*-acylpyrrole as a monodentate ester surrogate is summarized in Figure 3.[15,16] Because the lone electron pair of the nitrogen in the pyrrole ring is delocalized in an aromatic system, the property of a carbonyl group is similar to that of a phenyl ketone.[16a] We supposed that the relatively low LUMO energy of α,β-unsaturated *N*-acylpyrrole due to the aromaticity of pyrrole

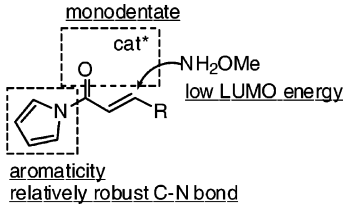


Figure 3. Property of *N*-acylpyrrole.

would facilitate the 1,4-addition of **3a**. In addition, the monodentate coordination mode of *N*-acylpyrrole is the same as that of enones. Thus, we hypothesized that the chiral environment optimized for enones would also be effective for *N*-acylpyrroles.

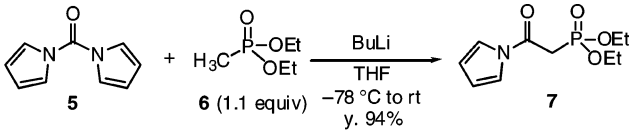
Although we previously reported the efficient synthesis of various α,β-unsaturated *N*-acylpyrroles using the Wittig reaction,[15a] the method was not suitable for the preparation of β-alkyl-substituted α,β-unsaturated *N*-acylpyrroles due to modest *E*/*Z* selectivity. Thus, we first developed an improved synthetic procedure for β-alkyl-substituted α,β-unsaturated *N*-acylpyrroles, utilizing the HWE reaction. The HWE reagent was readily synthesized by the reaction of carbonyl dipyrrole **5**[16a] with lithiated **6** (Table 3). HWE reaction under Masamune−Roush

(14) Aliphatic ketones (R^1 = alkyl) are not suitable substrates for the present system. For example, no reaction proceeded with benzalacetone.

(15) Use of α,β-unsaturated *N*-acylpyrrole in catalytic asymmetric 1,4-additions: (a) Matsunaga, S.; Kinoshita, T.; Okada, S.; Harada, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 7559. (b) Mita, T.; Sasaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2005**, *127*, 514. Application to diastereoselective 1,4-addition reactions: (c) Arai, Y.; Kasai, M.; Ueda, K.; Masaki, Y. *Synthesis* **2003**, 1511.

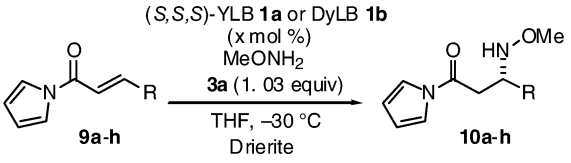
(16) Properties of *N*-acylpyrroles and carbonyl dipyrrole **5** were reported by Evans and co-workers in detail. (a) Evans, D. A.; Borg, G.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 3188. (b) Evans, D. A.; Johnson, D. S. *Org. Lett.* **1999**, *1*, 595. (c) Evans, D. A.; Scheidt, K. A.; Johnston, J. N.; Willis, M. C. *J. Am. Chem. Soc.* **2001**, *123*, 4480.

Table 3. Synthesis of β-Alkyl-Substituted α,β-Unsaturated *N*-Acylpyrroles



entry	aldehyde R	product		time(h)	yield(%)	*E*/*Z*
1	$(CH_3)_2CHCH_2$—	**8a**	**9a**	13	96	>20/1
2	*n*-Pr	**8b**	**9b**	12	90	>20/1
3	$PhCH_2CH_2$-	**8c**	**9c**	22	89	>20/1
4	CH_2=$CH(CH_2)_8$—	**8d**	**9d**	15	94	>20/1
5	*i*-Pr	**8e**	**9e**	10	90	>20/1

Table 4. Catalytic Asymmetric Aza-Michael Reaction of Various α,β-Unsaturated *N*-Acylpyrroles



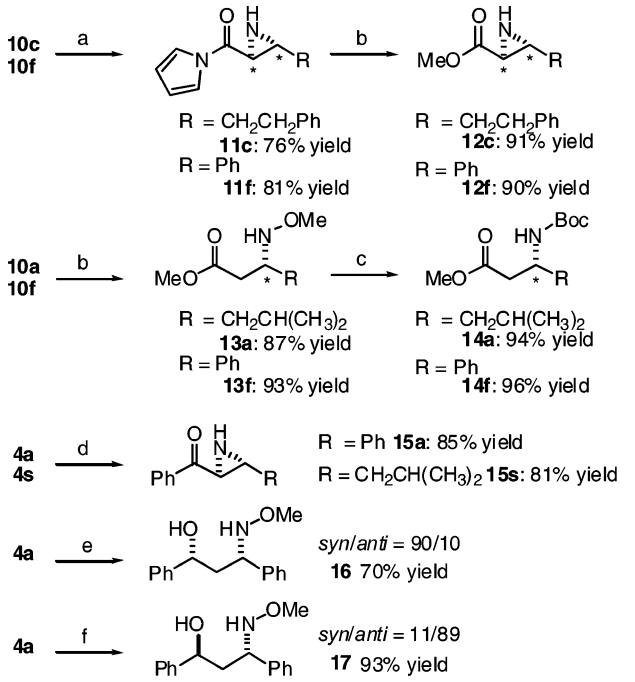
entry	*N*-acylpyrrole R		catalyst (*x* mol %)	time (h)	yield (%)	ee (%)
1	$(CH_3)_2CHCH_2$—	**9a**	YLB **1a** (5)	38	92	92
2		**9a**	YLB **1a** (10)	38	96	94
3		**9a**	DyLB **1b** (10)	62	92	94
4	$CH_3CH_2CH_2$—	**9b**	YLB **1a** (10)	38	91	83
5		**9b**	DyLB **1b** (10)	38	97	86
6	$PhCH_2CH_2$-	**9c**	YLB **1a** (10)	38	86	83
7		**9c**	DyLB **1b** (10)	38	94	85
8	CH_2=$CH(CH_2)_5CH_2$—	**9d**	YLB **1a** (10)	38	84	89
9		**9d**	DyLB **1b** (10)	62	89	89
10	$(CH_3)_2CH$—	**9e**	YLB **1a** (10)	106	94	86
11		**9e**	DyLB **1b** (10)	114	91	84
12	Ph—	**9f**	DyLB **1b** (10)	165	53	81
13	*m*-Cl—C_6H_4—	**9 g**	DyLB **1b** (10)	107	63	80
14	*p*-CF_3—C_6H_4—	**9h**	DyLB **1b** (10)	107	49	82

conditions[17] gave various β-alkyl substituted α,β-unsaturated *N*-acylpyrroles in good yield and high *E*-selectivity.

The reaction conditions for the aza-Michael reaction were optimized with substrate **9a** (Table 4). YLB **1a** (5 mol %) promoted the reaction of **9a** using 1.03 equiv of **3a** at −30 °C, and the product **10a** was obtained in 92% yield and 92% ee after 38 h (entry 1). Ee increased to 94% when using 10 mol % of YLB (entry 2). $DyLi_3$tris(binaphthoxide) (DyLB **1b**, Figure 1) gave comparable results (92% yield, 94% ee; entry 3). Other substrates with alkyl substituents were also applicable, and products were obtained in high yield and good ee (entries 4−11). For *N*-acylpyrroles **9b** and **9c**, DyLB **1b** gave better enantioselectivity than YLB **1a**. The reactivity of β-aryl-substituted substrates was only modest (entries 12−14). Products were obtained in modest yield using 10 mol % of DyLB **1b**.[18]

C. Transformation of 1,4-Adducts. To demonstrate the utility of aza-Michael adducts, several transformations were performed (Scheme 1). **4** and **10** were readily converted into chiral aziridines without loss of enantiomeric excess. Treatment of **10c** and **10f** with $TiCl_4$ and Et_3N afforded **11c** and **11f** in 76% and 81% yield, respectively.[19] The *N*-acylpyrrole unit was converted into methyl ester by treatment with NaOMe for 10 min at 4 °C. The N−O bond in **13a** and **13f** was easily cleaved with Pd/C under H_2 (1 atm) in MeOH. After protection with a Boc group, **14a** and **14f** were isolated in 94% and 96% yield, respectively (two steps). For the aza-Michael adducts from

Scheme 1. Transformations of aza-Michael Adducts[a]



[a] Reagents and conditions: (a) $TiCl_4$, CH_2Cl_2; then Et_3N, −30 °C to −10 °C. (b) NaOMe, MeOH, 4 °C, 10 min. (c) Pd/C, H_2 (1 atm), MeOH, rt; then Boc_2O. (d) NaO*t*-Bu, THF, rt. (e) $Zn(BH_4)_2$, Et_2O, −78 °C. (f) K-Selectride, THF, −78 °C.

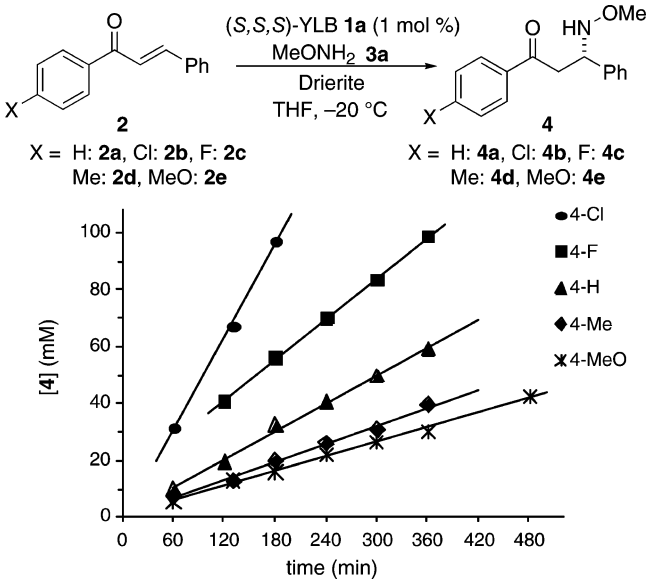


Figure 4. Substituent effects of chalcones **2a**−**e** on initial rate.

(17) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essefeld, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(18) Similar tendency that β-aryl substituted carboxylic acid derivatives are much less reactive than β-alkyl substrates was observed in asymmetric aza-Michael reactions of alkoxylamines. See ref 7a and 7b. Trials to activate substrates by introducing an electron-withdrawing group on a pyrrole ring failed.

(19) For aziridine formation using $TiCl_4$ and amine, see: Bongini, A.; Cardillo, G.; Gentilucci, L.; Tomasini, C. *J. Org. Chem.* **1997**, *62*, 9148. For the use of NaO*t*-Bu, see ref 7d. No loss of enantiomeric excess was observed during transformations in Scheme 1 as confirmed by HPLC analysis.

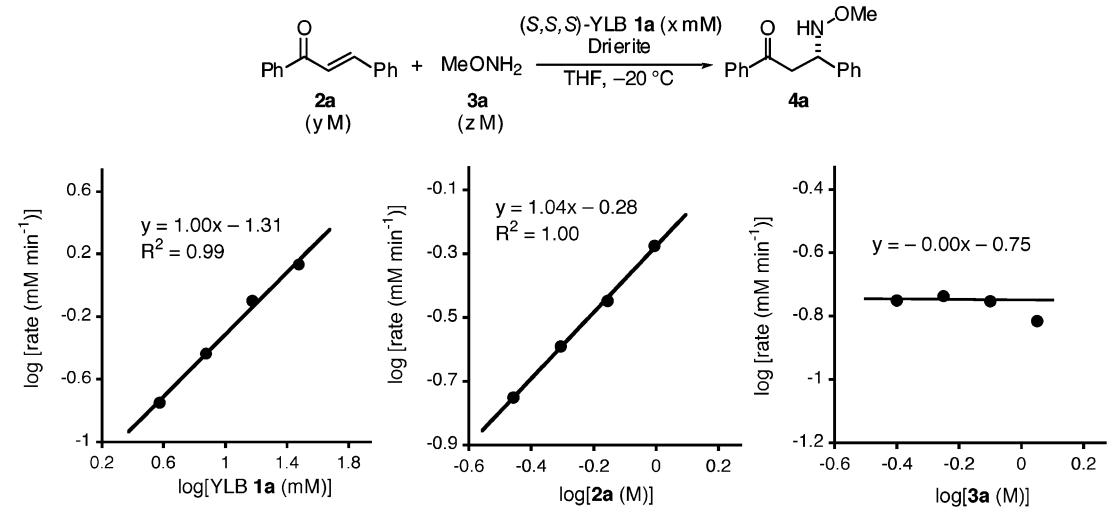


Figure 5. Initial reaction rate kinetics of YLB **1a**, chalcone (**2a**), and amine **3a**.

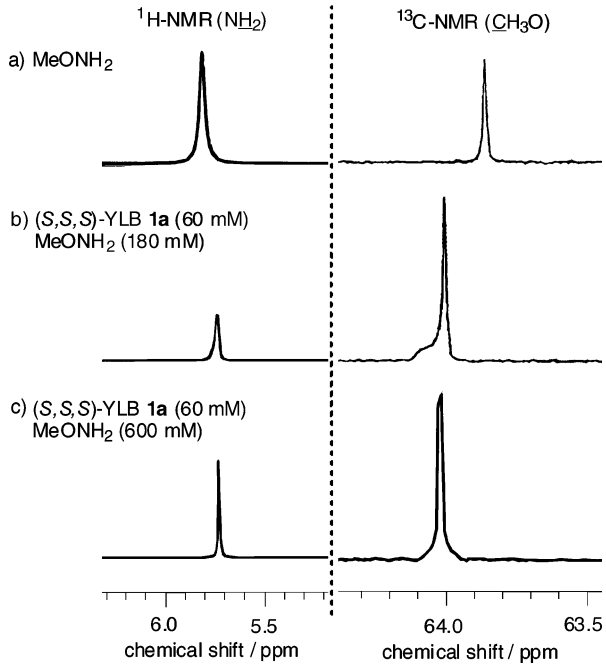


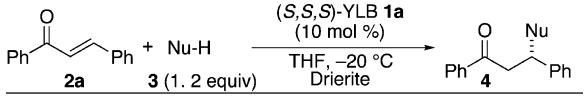
Figure 6. NH_2 region {left (a−c)} ^1H NMR spectra and CH_3O region {right (a−c)} ^{13}C NMR spectra of methoxylamine **3a** with and without YLB **1a** in THF at −20 °C; (a) without YLB **1a**; (b) YLB **1a** (60 mM), $MeONH_2$ **3a** (180 mM); (c) YLB **1a** (60 mM), $MeONH_2$ **3a** (600 mM).

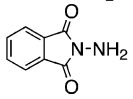
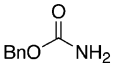
enones, NaO*t*-Bu was effective to afford aziridines **15a** and **15s** in 85% and 81% yield, respectively.[19] Diastereoselective synthesis of *syn*- or *anti*-1,3-amino alcohols **16** and **17** was also achieved. Treatment of **4a** with in situ generated $Zn(BH_4)_2$ afforded *syn*-1,3-methoxyamino alcohol **16** in 70% yield (syn/anti = 9/1), and treatment of **4a** with K-Selectride afforded *anti*-1,3-methoxyamino alcohol **17** in 93% yield (syn/anti = 1/9).[20]

D. Mechanistic Studies. After developing synthetically useful methods to provide optically active aziridines and β-amino carbonyl compounds, we investigated the reaction mechanism to evaluate whether the hypothetical Lewis acid−Lewis acid cooperative mechanism functions.

Substituent effects of chalcone derivatives on initial rate were examined (**2a**, **2b**, **2c**, **2d**, and **2e**) to determine the rate-determining step in the catalytic cycle. The initial reaction profiles of chalcone derivatives are summarized in Figure 4. Chalcones **2** with an electron-withdrawing group were more reactive ($\rho > 1$), indicating that the carbon−nitrogen bond-forming step is the rate-determining step. Initial rate kinetic studies using **2a** revealed that the reaction had (i) first-order dependency on YLB **1a**, (ii) first-order dependency on chalcone **2a**, and (iii) zeroth-order dependency on amine **3a** (Figure 5). Results in Figures 4 and 5 indicated that the carbon−nitrogen bond-forming step is the rate-determining step, while the free amine **3a** is not involved in the rate-determining step. Thus, the active species is speculated to be a YLB−$(MeONH_2)_n$ complex. Formation of the postulated active YLB−$(MeONH_2)_n$ complex was supported by NMR analysis (Figure 6).[21,22] A high field shift of the amine proton indicated that the amine proton interacted with the oxygen atom of YLB **1a**. The low field shift in the ^{13}C NMR of **3a** indicated coordination of the oxygen atom of **3a** with YLB **1a**. Only one amine proton peak was

Table 5. Effects of Structures of Amines **3** on Yield and Enantiomeric Excess



entry	Nu-H		time (h)	yield (%)	ee (%)
1	CH_3ONH_2	**3a**	24	94	96
2	$PhCH_2ONH_2$	**3b**	26	91	91
3	Ph_2CHONH_2	**3c**	48	50	66
4	$CH_3CH_2NH_2$	**3d**	48	no reaction	
5	$(CH_3)_2NNH_2$	**3e**	120	79	23
6	$TsHN-NH_2$	**3f**	24	no reaction	
7		**3g**	24	no reaction	
8		**3h**	24	no reaction	

(20) Pilli, R. A.; Russowsky, D.; Dias, L. C. *J. Chem. Soc., Perkin Trans. 1* **1990**, 1213.

(21) Active species of the aza-Michael reaction was proved to have three BINOL units through preliminary kinetic studies. In the preliminary mechanistic studies, however, the reaction mode (Lewis acid−assisted Lewis acid) and coordination mode of substrates remained unclear; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4493.

(22) For the full details of NMR analysis of YLB−**3a** complex, including YLB **1a** region, see Supporting Information.

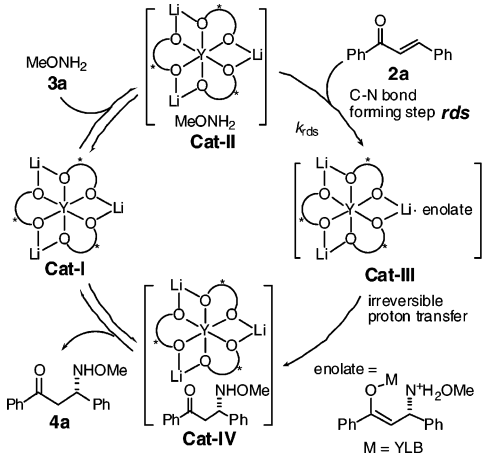


Figure 7. Supposed catalytic cycle of the aza-Michael reaction.

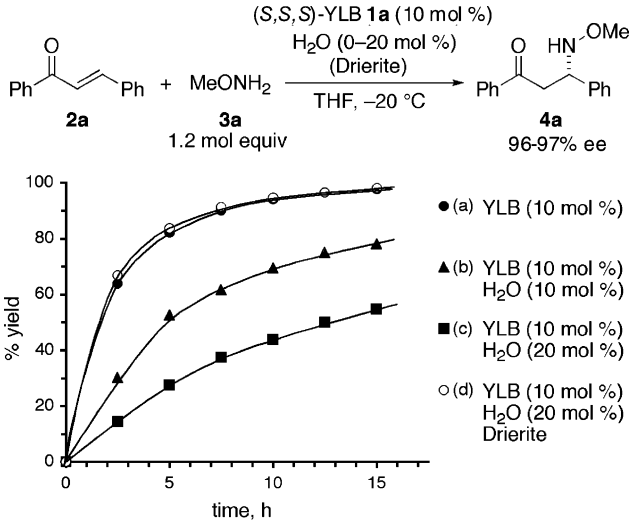


Figure 8. Water effects on the reaction rate.

observed even in the presence of an excess amount of amine **3a** at −20 °C (Figure 6c), indicating the rapid and reversible coordination of **3a** to YLB **1a** at −20 °C. The adverse effects of sterically crowded amines on reactivity and enantioselectivity (Table 5, entries 1−3) also indicate that the complexation of the YLB-amine nucleophile is important.[23] Amines without the oxygen group also gave poor results (entries 4−8), suggesting that the interaction between the oxygen atom in **3a** and YLB **1a** is important.

The postulated catalytic cycle of the reaction to explain the above observation is shown in Figure 7. Amine **3a** reversibly coordinates to YLB **1a** (**Cat-I**) to form an active YLB−$(MeONH_2)_n$ complex (**Cat-II**). Zeroth-order dependency on amine **3a** (Figure 5) implies that amine **3a** coordinated to YLB **1a** reacts with chalcone **2a**. YLB−$(MeONH_2)_n$ complex (**Cat-II**) is a dominant species among all the catalyst species (**Cat-I**, **Cat-II**, **Cat-III**, and **Cat-IV**). **2a** interacts with **Cat-II**, and subsequent carbon−nitrogen bond formation affords an enolate intermediate (**Cat-III**). The step from **Cat-II** to **Cat-III** is rate-determining. Irreversible proton transfer affords **Cat-IV**.[24]

(23) The tendency observed in Table 5, entries 1−3 is different from results obtained by Inanaga and co-workers using Sc chiral Lewis acid catalysis. In their report, sterically crowded amine **3c** gave the best enantioselectivity. See ref 7d.

(24) The irreversibility of the present aza-Michael reaction was experimentally confirmed. See Supporting Information for detail results.

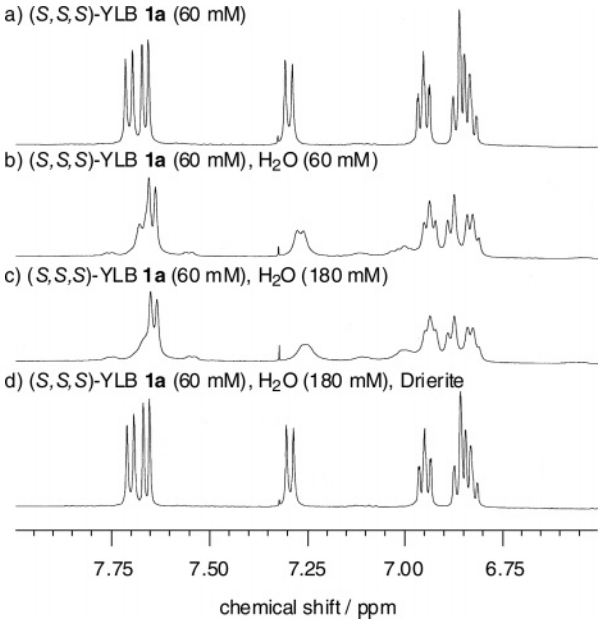


Figure 9. NMR spectra of (*S*,*S*,*S*)-YLB (60 mM in d_8-tetrahydrofuran) at −20 °C: (a) without H_2O, (b) with H_2O (60 mM), (c) with H_2O (180 mM), (d) with H_2O (180 mM) and Drierite ($CaSO_4$: 200 mg/mL d_8-tetrahydrofuran).

Exchange between 1,4-adduct **4a** and amine **3a** regenerates the active YLB−$(MeONH_2)_n$ complex (**Cat-II**).

The addition of H_2O decreased the reaction rate, while still maintaining similar enantioselectivity (Table 1, entry 2). Adverse effects of H_2O on the reaction rate were investigated in detail (Figure 8). The tendency is in striking contrast to the asymmetric cyano-ethoxycarbonylation using the same YLB complex,[11] in which the YLB−H_2O complex was essential for high reactivity and enantioselectivity. In the present aza-Michael reaction, the initial rate was decreased to approximately half in the presence of 10 mol % H_2O and to a quarter with 20 mol % H_2O. On the other hand, reactivity recovered when Drierite ($CaSO_4$) was added. NMR spectroscopy revealed a reversible interaction between YLB and H_2O in solution (Figure 9). NMR spectra of anhydrous YLB in THF at −20 °C showed six sharp signals (Figure 9a), implying that the YLB complex has a C_3-symmetric structure in solution. The signals gradually broadened, however, by adding H_2O to YLB (Figure 9b and 9c). In Figure 9d, Drierite ($CaSO_4$) was added to the mixture of YLB and 3 equiv of H_2O, and the sharp signals of YLB **1a** were observed again. These observations suggested that there is equilibrium between anhydrous-YLB and the YLB−H_2O complex. Aspinall et al. reported the X-ray crystallographic structure of both $[Li(Et_2O)]_3[Eu(binol)_3]$ (anhydrous-EuLB) and $[Li(Et_2O)]_3[Eu(binol)_3(H_2O)]$ (EuLB−H_2O).[12] We assumed that H_2O would coordinate with the yttrium center in a similar manner as observed for the europium complex. Considering the coordination number (six or seven) of rare earth−alkali metal heterobimetallic complexes *observed in crystal structures*,[2d,12] only one substrate other than tris(binaphthoxide) would coordinate with the yttrium center. The H_2O-induced deceleration is due to a reversible and competitive occupation of the seventh coordination site of the yttrium center. In other words, a vacant coordination site on yttrium metal is essential to promote the conjugate addition reaction.

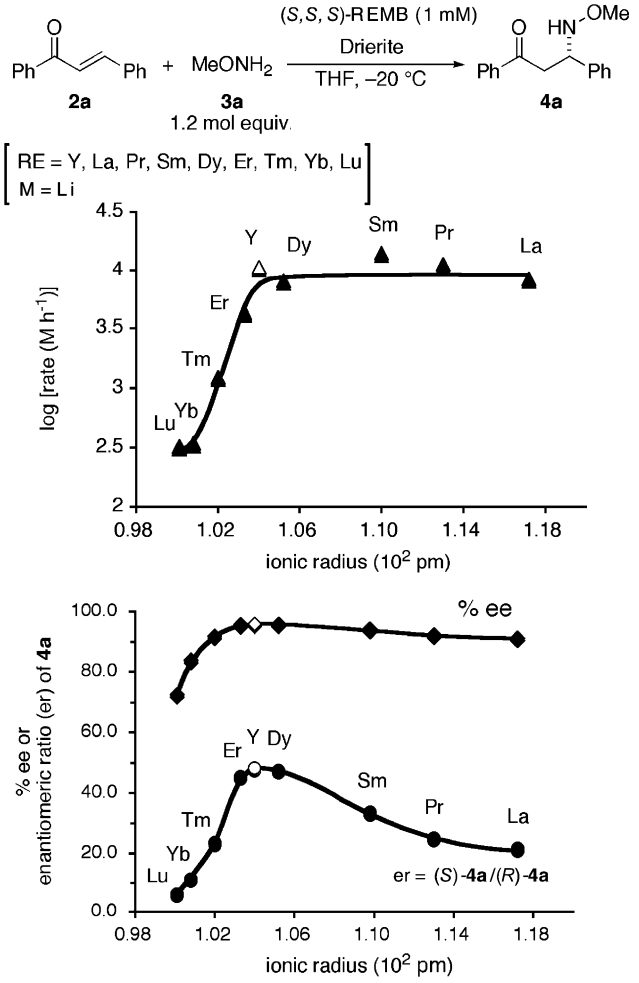


Figure 10. Rare earth metal effects on reaction rate and enantioselectivity.

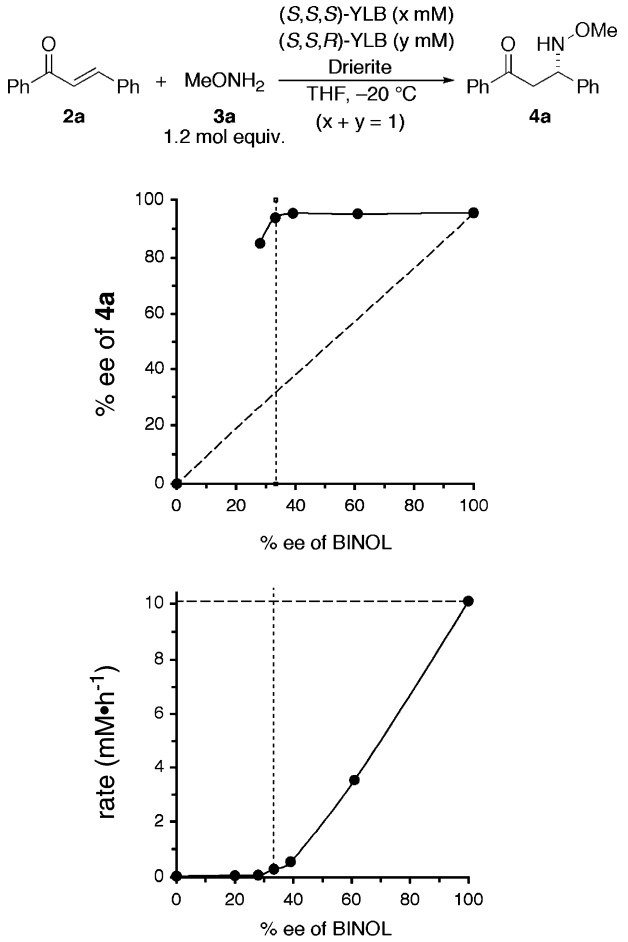


Figure 11. Nonlinear effects on the catalytic asymmetric 1,4-addition reaction of **3a** to **2a**.

The importance of the rare earth metal as a Lewis acid was also supported by the results shown in Figure 10. aza-Michael reaction of **2a** was performed with various rare earth−Li−BINOL = 1/3/3 complexes (REMB, Figure 1, RE = Y, La, Pr, Sm, Dy, Er, Tm, Yb, Lu and M = Li). Rare earth metals had drastic effects on both reaction rate and enantioselectivity of the reaction. The reaction rate and enantioselectivity correlated with the ionic radius of the rare earth metals used. Initial reaction rates were similar with metals larger than yttrium and drastically dropped with smaller metals (Er, Tm, Yb, and Lu). Metals with a small ionic radius (Tm, Yb, and Lu) had low enantioselectivity and low reactivity. The best enantioselectivity was achieved with Y and Dy metals. Metals with a large ionic radius (Sm, Pr, and La) gave products with lower selectivity, although the reaction proceeded smoothly. The observed rare earth metal effects are explained nicely by considering the difference in coordination number. Various investigations of rare earth−alkali metal heterobimetallic complexes indicated that the coordination number of central rare earth metals is different depending on the ionic size of the rare earth metals.[2,12,21] Salvadori and co-workers reported that the $YbLi_3$tris(binaphthoxide) (YbLB) complex does not accept a seventh ligand for steric reasons, which was suggested by NMR analysis of YbLB in the presence of H_2O.[25] Based on their reports, rare earth metals with a small ionic radius (Tm, Yb, and Lu) would not accept a seventh ligand for steric reasons. Thus, the desirable Lewis acid−Lewis acid cooperative reaction would not proceed with Tm, Yb, and Lu metals, resulting in a low reaction rate and low enantioselectivity. In other words, coordination of the substrate to the center metal of the REMB catalyst is essential to promote the reaction. In contrast to Tm, Yb, and Lu metals, REMB complexes with a large ionic radius are known to have the seventh coordination site as confirmed by X-ray crystal analysis.[26] When using Y, Dy, Sm, Pr, and La, the seventh coordination site of the rare earth metal center is available. Thus, the reaction proceeds smoothly. Enantioselectivity depends on the size of the chiral space ascribed to the ionic size of central metals.

Positive nonlinear effects[27] for enantioselectivity and negative nonlinear effects on reaction rate were observed for the present aza-Michael reaction (Figure 11). A catalyst with 33% ee of BINOL afforded products in 95% ee, which was comparable to that obtained by an optically pure catalyst (96% ee). The reaction rate, however, differed greatly depending on the optical purity of the catalyst. For example, the reaction rate with a catalyst with 33% ee was only 1/34 ($v_{33\%\ ee} = 2.98 \times 10^{-4}$ Mh^{-1}) of that observed with an optically pure catalyst ($v_{100\%\ ee}$

(25) Bari, L. D.; Lelli, M.; Pintacuda, G.; Pescitelli, G.; Marchetti, F.; Salvadori, P. *J. Am. Chem. Soc.* **2003**, *125*, 5549.

(26) The crystal structures of La, Pr, Nd, Eu heterobimetallic complexes with H_2O as the seventh ligand are reported. See refs 2, 12 and references therein.

(27) Reviews: (a) Girard, C.; Kagan, H. B. *Angew. Chem., Int. Ed.* **1998**, *37*, 2922. (b) Kagan, H. B. *Adv. Synth.* Catal. **2001**, *343*, 227. For a review discussing kinetic aspects of nonlinear effects, see: (c) Blackmond, D. G. *Acc. Chem. Res.* **2000**, *33*, 402.

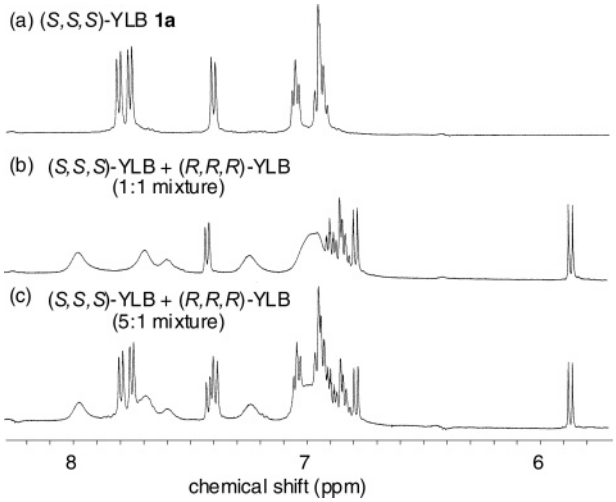
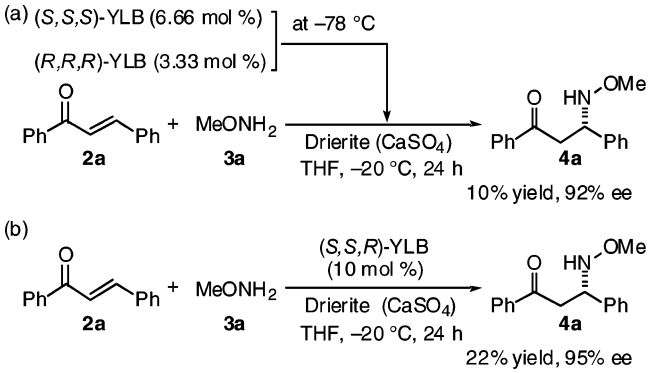


Figure 12. NMR spectra of homochiral (*S*,*S*,*S*)-YLB and heterochiral-YLB; (a) (*S*,*S*,*S*)-YLB **1a**, (b) (*S*,*S*,*S*)-YLB + (*R*,*R*,*R*)-YLB (1:1 mixture), (c) (*S*,*S*,*S*)-YLB + (*R*,*R*,*R*)-YLB (5:1 mixture).

Scheme 2. Aza-Michael Reaction (a) with (*S*,*S*,*S*)-YLB (6.66 mol %) + (*R*,*R*,*R*)-YLB (3.33 mol %) and (b) with Preformed (*S*,*S*,*R*)-YLB (10 mol %)



$= 1.01 \times 10^{-2}$ Mh^{-1}). The reaction rate with 0% ee catalyst was 1/199 ($v_{0\%\ ee} = 5.07 \times 10^{-5}$ Mh^{-1}) of that with an optically pure catalyst.

To explain the observed nonlinear effects, we continued spectroscopic analysis of YLB. Aspinall et al. reported that the (*S*,*S*,*R*)-heterochiral YLB complex is thermodynamically more stable than the (*S*,*S*,*S*)-YLB complex due to the C−H to π hydrogen bond.[12] Because they synthesized the (*S*,*S*,*R*)-heterochiral YLB [together with the (*S*,*R*,*R*)-complex] from racemic-BINOL, it was uncertain whether ligand exchange occurred under the 1,4-addition reaction conditions at −20 °C. To observe the lability of BINOL in YLB under the reaction conditions, we performed NMR analysis of a YLB solution prepared from 1 equiv of (*S*,*S*,*S*)-YLB and 1 equiv of (*R*,*R*,*R*)-YLB. NMR analysis of the mixture solution revealed only the heterochiral (*S*,*S*,*R*)-and (*S*,*R*,*R*)-YLB complex (Figure 12b) [no (*S*,*S*,*S*)-YLB was detected by ^{1}H NMR]. The spectrum was identical to that reported by Aspinall et al.[12] The mixture of (*S*,*S*,*S*)-YLB and (*R*,*R*,*R*)-YLB in a 5:1 ratio resulted in an approximately 1:1 mixture of (*S*,*S*,*S*)-YLB and (*S*,*S*,*R*)-YLB (Figure 12c). The results clearly indicated that the ligand exchange between (*S*,*S*,*S*)-YLB and (*R*,*R*,*R*)-YLB occurred smoothly to exclusively form a thermodynamically more stable (*S*,*S*,*R*)-YLB-type complex. On the other hand, the reaction rate using 6.66 mol % of (*S*,*S*,*S*)-YLB and 3.33 mol % of (*R*,*R*,*R*)-YLB mixed at −78 °C was as slow as that performed with 10 mol % of the

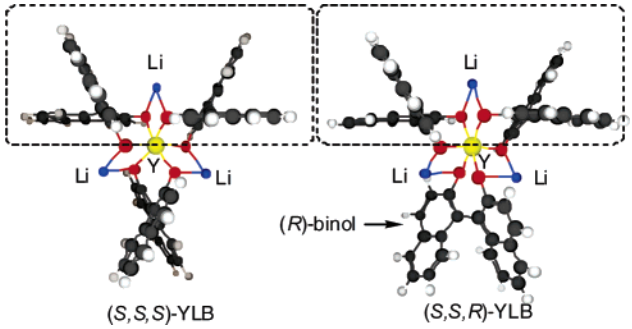
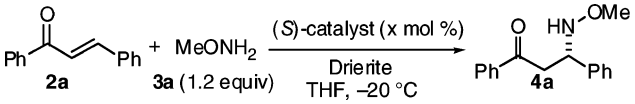


Figure 13. Structures of (*S*,*S*,*S*)-YLB and (*S*,*S*,*R*)-YLB (THF is omitted for clarity).

Table 6. Alkali Metal Effects on Aza-Michael Reaction



entry	catalyst (*x* mol %)	time (h)	yield (%)	ee (%)	config
1	none	42	trace		
2	BuLi/BINOL (9/9)	42	11	12	*R*
3	Y(HMDS)$_3$/BINOL (3/9)	42	29	16	*R*
4[a]	YPB **1c** (3)	42	19	12	*R*
5	YLB **1a** (3)	42	97	95	*S*

[a] (*S*,*S*,*S*)-YK$_3$tris(binaphthoxide)(YPB **1c**) was prepared from Y(HMDS)$_3$/KHMDS/(*S*)-BINOL in a ratio of 1/3/3.

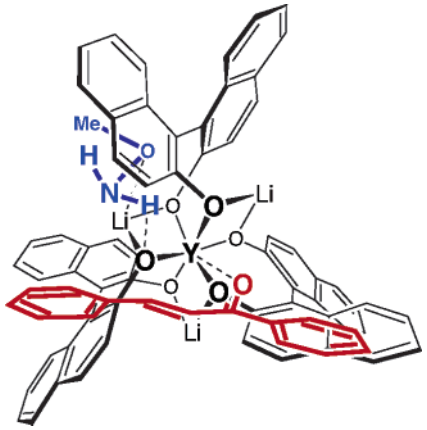


Figure 14. Proposed Lewis acid−Lewis acid cooperative transition-state model for aza-Michael reaction.

preformed (*S*,*S*,*R*)-YLB-type complex (Scheme 2). Product **4a** was obtained in only 10% yield after 24 h (92% ee). The reaction rate was much slower than that observed with (*S*,*S*,*S*)-YLB. The results in Scheme 2 indicate that ligand exchange occurs smoothly at −20 °C.[28] On the basis of these results, the nonlinear effects and the observed reaction rate tendency in Figure 11 are explained as follows. The (*S*,*S*,*R*)-heterochiral YLB complex is thermodynamically more stable than (*S*,*S*,*S*)-YLB **1a**. On the other hand, equilibrium between the (*S*,*S*,*R*)-heterochiral YLB complex and (*S*,*S*,*S*)-YLB **1a** occurs under the reaction conditions. The (*S*,*S*,*R*)-heterochiral YLB complex is not active in the 1,4-addition reaction, and only trace (*S*,*S*,*S*)-YLB formed in equilibrium and promoted the reaction, when the reaction was performed with ligands with 33% ee.The

(28) Recently, Salvadori and co-workers independently reported that binaphthoxide in YbK$_3$tris(binaphthoxide) is labile in solution phase; see: Bari, L. D.; Lelli, M.; Salvadori, P. *Chem.—Eur. J.* **2004**, *10*, 4594.

enantiomeric excess of the product was the same with ligands over 33% ee, while the reaction rate increased drastically by increasing the ee of the ligands from 33% ee to >99% ee because the amount of (*S*,*S*,*S*)-YLB increased accordingly.

A striking difference in the reaction rate between the homochiral (*S*,*S*,*S*)-YLB and the heterochiral (*S*,*S*,*R*)-YLB would also support the importance of the yttrium center. Structures of (*S*,*S*,*S*)-YLB and (*S*,*S*,*R*)-YLB are shown in Figure 13. Aspinall reported that the $[Li(THF)_2]_3[Y\{(S)\text{-binol}\}_2]$ fragment (Figure 13, dotted square) of homochiral and heterochiral YLB in crystal structures does not highlight any gross structural change.[12] Thus, it is difficult to explain the large difference in the reaction rate, if Li alone can promote the aza-Michael reaction. Based on the observation, a transition state model where only Li metal functions as a Lewis acid to activate chalcone **2a** and controls the orientation of amine **3a** is unlikely. Both Y and Li metals are required to promote the reaction. As shown in Table 6, the BuLi/BINOL complex (entry 2) and $Y(HMDS)_3$/BINOL complex (entry 3) afforded product **4a** only in poor yield and ee. (*S*,*S*,*S*)-YK_3tris(binaphthoxide) (YPB, **1c**) also gave poor results (entry 4). The reaction proceeded in high enantioselectivity only when both Y and Li were used (entry 5).

The proposed transition state model under the Lewis acid−Lewis acid cooperative mechanism is shown in Figure 14. Mechanistic studies in this section suggested that both Y and Li function as a Lewis acid. On the basis of aza-Michael reactions using conformationally rigid enones,[29] we speculate that enone **2a** would coordinate to the yttrium center in a *s*-cis form. NMR analysis of the YLB-**3a** complex (Figure 6) suggested that **3a** would coordinate with both the Li and O of YLB **1a**. Thus, the orientation of amine **3a** is controlled nicely to afford (*S*)-**4a** with high ee.[30]

In summary, we demonstrated that the rare earth−alkali metal heterobimetallic complex functions as Lewis acid−Lewis acid cooperative catalysts. The reaction mechanism is different from previous results obtained using related complexes,[2] thus broadening the utility of heterobimetallic complexes. YLB **1a** and DyLB **1b** complexes promoted catalytic asymmetric 1,4-addition of methoxylamine **3a** to enones and α,β-unsaturated *N*-acylpyrroles. Transformation of the 1,4-adducts from enones and α,β-unsaturated *N*-acylpyrroles afforded corresponding aziridines. Detailed mechanistic studies, including kinetics, NMR analysis, nonlinear effects, and rare earth metal effects, revealed the catalytic cycle. Examination for alkali metal effects and rare earth metal effects revealed that both metals are essential for catalyst activity. The results obtained in mechanistic studies support the proposed Lewis acid−Lewis acid cooperative mechanism.

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Supporting Information Available: Experimental procedures, characterization of the products, detail data for mechanistic studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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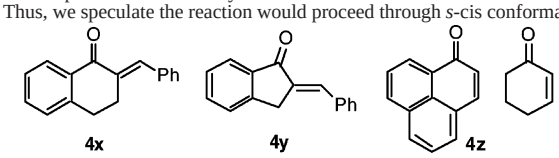
(29) Conformationally rigid enones **4x**, **4y**, **4z** and cyclohexenone were used. **4x** and **4y** with *s*-cis form afforded aza-Michael products in high ee, although the reactivity was low probably due to steric hindrance. Reaction did not proceed at all with cyclohexenone and enone **4z** with *s*-trans form. Thus, we speculate the reaction would proceed through *s*-cis conformation.



5% yield	20% yield, dr = 1/1		
84% ee	93% ee (one isomer)	no reaction	no reaction

(30) The possibility that amine **3a** coordinates to the yttrium center and enone **2a** coordinates to Li cannot be excluded completely. Considering the absolute configuration of aza-Michael products, however, we believe the transition state model in Figure 14 is more appropriate.