Reaction Mechanisms

Mechanistic Studies of a Reaction Promoted by the [YLi_3\{tris(binaphthoxide)\}] Complex: Are Three 1,1′-Bi-2-naphthol Units in a Rare-Earth–Alkali-Metal Heterobimetallic Complex Necessary?**

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Since the early 1990s,[1a] we have reported series of rare-earth–alkali-metal heterobimetallic complexes that enable various catalytic asymmetric reactions.[1] These complexes, whose structures were determined by X-ray crystallographic analysis, mass spectrometry, and NMR spectroscopy, consist of one rare-earth metal (RE), three 1,1′-2-bi-naphtholate (binol), and three alkali metal (M) parts (Figure 1).[1b,c] Subsequently, independent studies by Aspinall et al. revealed differences in the aqua and anhydrous heterobimetallic complexes in the solid-phase structures.[2] They also reported preliminary results on the solution-phase structure of heterobimetallic complexes. More recently, Salvadori and co-workers reported a detailed spectroscopic analysis of Yb–alkali-metal heterobimetallic complexes in solution phase, raising the question as to whether the Yb/M/binol = 1:3:3 structure is really an active species or just a precatalyst (Figure 2).[3] They reported that binol in the Yb/K/binol = 1:3:3 heterobimetallic complex is labile (confirmed by an exchange spectroscopy experiment) and proposed that the active species could be generated by dissociation of one binol–Li_2 unit, as long as Yb metal was used. Furthermore, the best results in some asymmetric reactions were observed with catalysts prepared from RE/binol/M in a ratio different to 1:3:3. Yb/K/binol = 1:1:3 worked best in a nitro-Mannich-type reaction,[4] and Sc/Li/binol = 1:1:2 in a Strecker-type reaction.[5] The active species in these reactions has not yet been determined. Mechanistic studies to clarify the composition of the active species of the rare-earth–alkali-metal heterobimetallic complex would facilitate the design and application of bimetallic multifunctional asymmetric catalysis in future research. Although recent detailed spectroscopic analysis of the heterobimetallic complexes by Aspinall et al.[2] and Salvadori and co-workers[3] revealed various new and interesting properties, their behavior during catalytic cycles of asymmetric reactions have not been studied extensively. To elucidate the controversial structure of the active species, investigations based on actual catalytic asymmetric reactions as well as spectroscopic analysis of the heterobimetallic complex are essential. Herein, we report our efforts to determine the active species on the basis of mechanistic studies of a catalytic asymmetric reaction, including various kinetics studies and NMR spectroscopic analysis. Mechanistic studies of the [YLi_3\{tris(binaphthoxide)\}] complex (Figure 1, $Li_3[Y(binol)_3]$, YLB, **1**) and asymmetric 1,4-addition reaction of *O*-methylhydroxylamine catalyzed by YLB (**1**) suggested that the active species of the 1,4-addition reaction requires all three binol units in YLB, although ligand exchange of the YLB complex occurs easily under the reaction conditions (−20 °C).

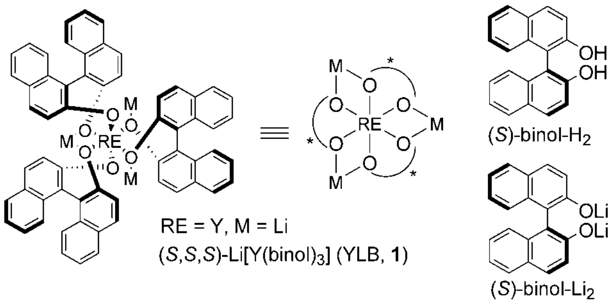


Figure 1. Structure of (*S*,*S*,*S*)-$Li_3[Y(binol)_3]$ (YLB, **1**), (*S*)-binol-H_2, and (*S*)-binol-Li_2.

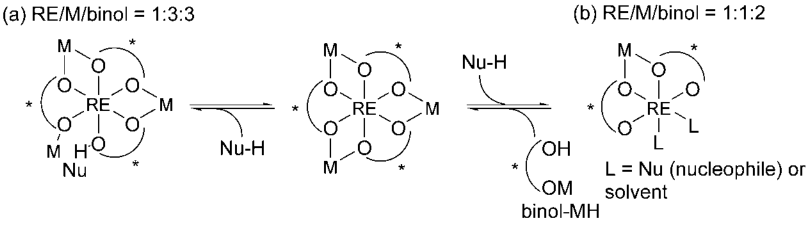
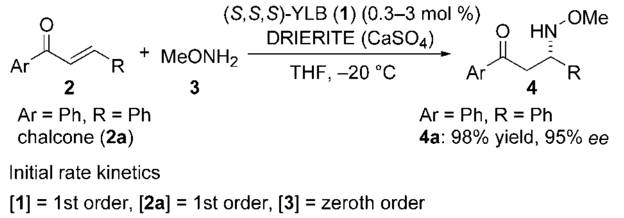


Figure 2. Debated structures of active species of rare-earth–alkali-metal heterobimetallic complexes. a) RE/M/binol = 1:3:3; b) RE/M/binol = 1:1:2. Nu = nucleophile.

We selected an asymmetric 1,4-addition of *O*-methylhydroxylamine (**3**) catalyzed by **1** as a target for the mechanistic studies (Scheme 1).[6] Because Aspinall et al. reported detailed spectroscopic data for both the solid-phase and solution-phase structures of YLB (**1**),[2] this reaction was most



Scheme 1. Catalytic asymmetric 1,4-addition of *O*-methylhydroxylamine (**3**) promoted by YLB (**1**) and results of initial rate kinetic experiments.

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suitable to investigate the behavior during the reaction pathway.[7] We first examined the reaction profile of the catalytic asymmetric 1,4-addition of amine **3** to chalcone (**2a**). Initial rate-kinetics studies revealed that several properties of the reaction:

1) first-order dependence on the YLB complex **1**;
2) first-order dependence on chalcone (**2a**);
3) zeroth order dependence on amine **3** (Scheme 1);[8]
4) negligible retro-1,4-addition;
5) only slight product inhibition (the reaction rate decreased by 34 % in the presence of as much as 100 equiv of product **4e** (relative to **1**), and the results suggested that product inhibition at the initial stage of the reaction was negligible);
6) retardation of reaction rate upon addition of H_2O;
7) strong, positive, nonlinear effects[9] (Figure 3).

A catalyst with 33 % *ee* afforded products with 95 % *ee*, which was comparable with that obtained in the presence of 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 catalyst with 33 % *ee* was only 1/34 ($v_{33\%\,ee} = 2.98 \times 10^{-4}\,\mathrm{M\,h^{-1}}$) of that observed with optically pure catalyst ($v_{100\%\,ee} = 1.01 \times 10^{-2}\,\mathrm{M\,h^{-1}}$). The reaction rate with 0 % *ee* catalyst was 1/199 ($v_{0\%\,ee} = 5.07 \times 10^{-5}\,\mathrm{M\,h^{-1}}$) of that with optically pure catalyst.[8]

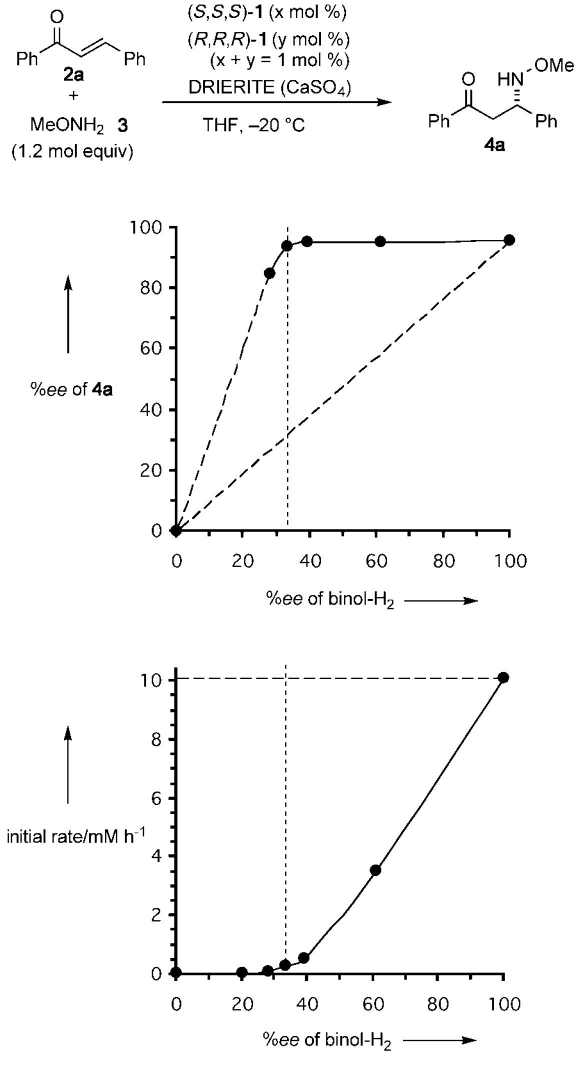

Figure 3. Positive nonlinear effects in catalytic asymmetric 1,4-addition of **3** to **2a** promoted by YLB **1**.

Possible catalytic cycles of the reaction to explain the observed kinetic properties 1)–5) are summarized in Figures 4A–C. In Figure 4A, the active species is postulated to be the Y/Li/binol = 1:3:3 complex coordinated by amine **3**. Formation of active species **A-II** from an amine-free YLB complex **I** should be fast, and the rate-determining step (rds) of the reaction is the 1,4-addition to **2a**. In Figures 4B and C, the active species is postulated to be the Y/Li/binol = 1:1:2 complex. Although the latter complex is thermodynamically unstable,[10] it might exist because of stabilization with amine **3** and/or chalcone (**2a**). In Figure 4B, the amine coordinates to the Y/Li/binol = 1:1:2 complex (**B-II**). The rate-determining step of the reaction is the 1,4-addition to **2a**. In Figure 4C, the active species is postulated to be the Y/Li/binol = 1:1:2 complex coordinated by **2a**. Formation of the active species by replacing one binol-Li_2 unit of YLB with chalcone should be the rate-determining step, and the 1,4-addition of amine is fast. We evaluated the validity of these three possible reaction mechanisms with additional mechanistic experiments.

First, we evaluated the mechanism in Figure 4B. The results of initial rate kinetic studies 1–3 listed above suggested that the formation of active species **B-II** by releasing one binol-Li_2 unit should be favorable ($K_{B1}[\mathbf{3}]/[\mathbf{B\text{-}II}] = [\text{binol-Li}_2]/[\mathbf{I}] \gg 1$) if the mechanism shown in Figure 4B is correct.[11] Thus, the active species would be observed by spectroscopic analysis on the basis of kinetic experiments. NMR spectroscopic analysis of the YLB complex under various conditions (a) (*S,S,S*)-**1**, b) (*S,S,S*)-**1** + (*S*)-binol-Li_2 (1 equiv), c) (*S,S,S*)-**1** + (*S*)-binol-Li_2 (3 equiv), d) (*S*)-binol-Li_2, e) (*S,S,S*)-**1** + **3** (10 equiv), and f) (*S,S,S*)-**1** + **3** (10 equiv) + binol-Li_2 (1 equiv) were examined (in b–f, equiv with respect to **1**; NMR spectra are available in the Supporting Information). In b, c, and f, binol-Li_2 was observed independently from peaks derived from YLB. Binol-Li_2, however, was not observed in e). These observations do not support the proposed mechanism in Figure 4B, thus the mechanism in Figure 4B is unlikely. There was no difference in the reaction rate when using 1 mol % of YLB with or without additional binol-Li_2 (1–3 mol %) (Figure 5).[8] The enantioselectivities observed for the product **4a** were 96 % *ee* (**1** alone), 96 % *ee* (**1** + 1 mol % binol-Li_2), 96 % *ee* (**1** + 2 mol % binol-Li_2), 96 % *ee* (**1** + 3 mol % binol-Li_2), and 17 % *ee* (3 mol % binol-Li_2). The results in Figure 5 also suggested that the mechanism in Figure 4B is incorrect.

In the case of the mechanism shown in Figure 4C, the formation of active species **C-II** by releasing one binol-Li_2 unit should be slow, based on the observed initial rate kinetic properties 1–3 (see list above).[11] Thus, NMR spectroscopic analysis of the active species would be difficult to obtain, because the existence of the active species would be minor and the majority would be in the resting state (Y/Li/binol =

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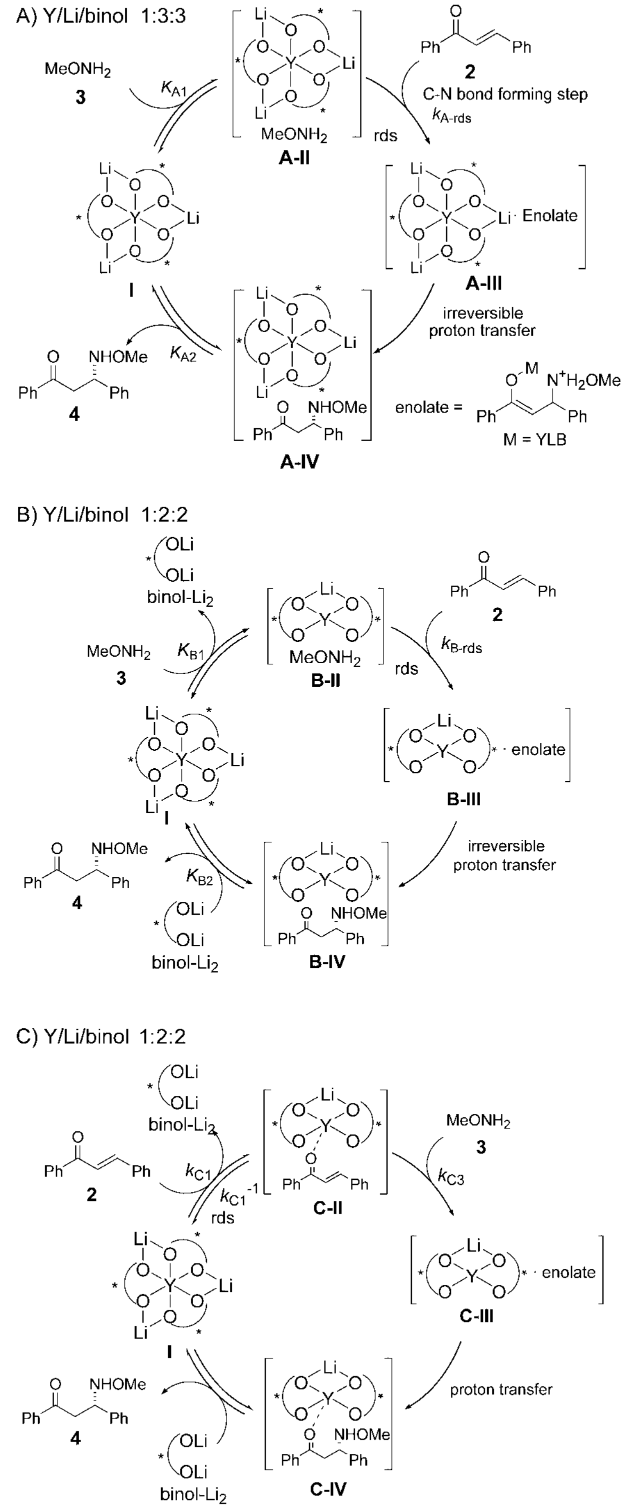


Figure 4. Possible catalytic cycles of catalytic asymmetric 1,4-addition with YLB (**1**). A) with Y/Li/binol = 1:3:3; B) and C) with Y/Li/binol = 1:1.2.

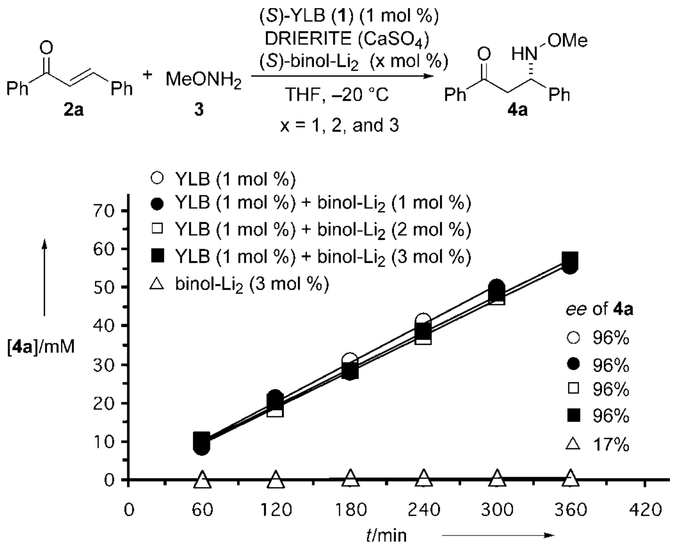


Figure 5. Initial rate kinetics using 1 mol% of (*S,S,S*)-**1** with additional (*S*)-binol-Li$_2$. (0–3 mol%).

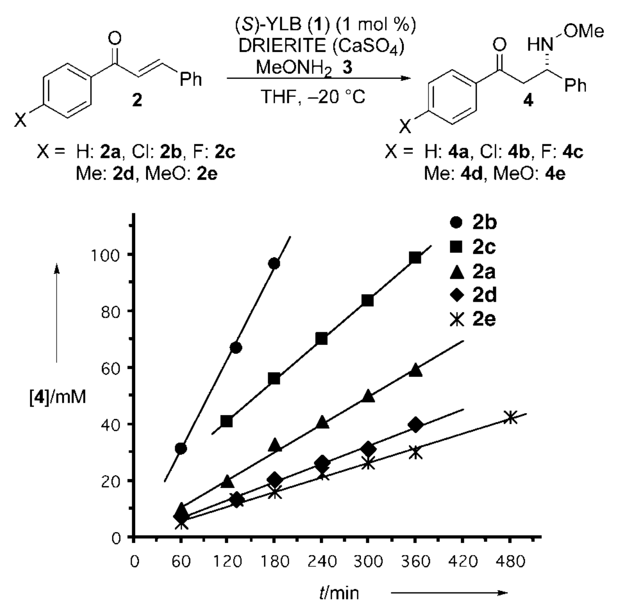
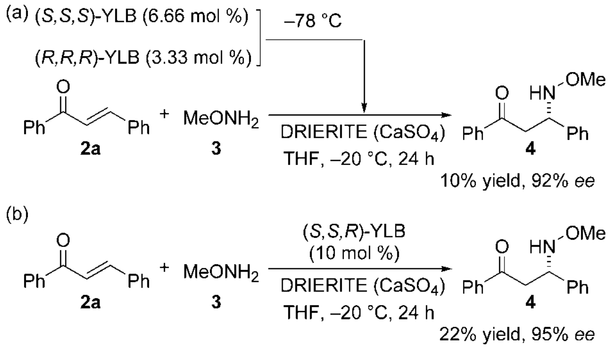


Figure 6. Substituents effects of chalcone **2** on initial rate.

1:3:3). On the other hand, the 1,4-addition step is fast in this mechanism. This mechanism was ruled out, however, when substituent effects on the reaction rate were examined (Figure 6).[8] If the mechanism in Figure 4C were correct, then introduction of an electron-donating group on chalcone **2** would accelerate the reaction, because electron-rich chalcone would accelerate the exchange with binol-Li$_2$. The tendency shown in Figure 6, however, suggests that the rate-determining step is the 1,4-addition step and not the formation of active species **II-C**.

The mechanism shown in Figure 4A is therefore the most probable of the three.[11] The mechanism shown in Figure 4A fits all the observed kinetic profiles 1–6 (see list above) and additional mechanistic studies (NMR spectroscopic analysis, Figure 5, and Figure 6). ^{13}C and ^{1}H NMR spectra of **1** alone and **1** with amine did show small differences, suggesting that amine **3** coordinates to the Y complex without breaking the Y/Li/binol = 1:3:3 framework.[12] Inhibition of the reaction with H_2O (kinetic data 6) is explained by the reversible coordination of H_2O to YLB. H_2O would compete with chalcone. NMR spectroscopic analysis supported the reversible coordination of H_2O to **1**.[13] Thus, the properties of **1** are quite different to those of the Yb heterobimetallic complexes reported by Salvadori and co-workers.[3] The mechanism shown in Figure 4 A involving a seventh axial ligand would be reasonable in the case of **1**.

To explain the observed nonlinear effects of the present 1,4-addition reaction (Figure 3), we further analyzed YLB complex spectroscopically. Aspinall et al. reported that the (*S,S,R*)-YLB-type complex is thermodynamically more stable than the (*S,S,S*)-YLB complex owing to the C−H–π hydrogen bond. Because they synthesized the (*S,S,R*)-YLB-type complex (together with the (*S,R,R*)-complex) from racemic-binol, it was uncertain as to whether or not ligand exchange occurs under the 1,4-addition reaction conditions. To observe the lability of binol in **1** under the reaction conditions, we analyzed a YLB solution prepared from (*S,S,S*)-**1** (2 equiv) and (*R,R,R*)-**1** (1 equiv) by NMR spectroscopy. The mixed solution revealed only the (*S,S,R*)-YLB-type complex (>30:1 ratio when taking the resolution of NMR analysis in consideration: no (*S,S,S*)-YLB was detected). The spectrum was identical to that reported by Aspinall et al.[2] The results clearly indicated that the ligand exchange between (*S,S,S*)-**1** and (*R,R,R*)-**1** occurred smoothly to form a thermodynamically more stable (*S,S,R*)-YLB-type complex exclusively. On the other hand, the reaction rate when using (*S,S,S*)-**1** (6.66 mol %) and (*R,R,R*)-**1** (3.33 mol %) mixed at −78 °C was as slow as that performed with 10 mol % of the 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*)-**1**. The results indicated that ligand exchange occurs smoothly at least under the 1,4-addition reaction conditions at −20 °C. On the basis of these results, the nonlinear effects and the observed reaction rate tendency in Figure 3 are explained as follows: The (*S,S,R*)-YLB-type complex is thermodynamically more stable than (*S,S,S*)-YLB. On the other hand, equilibrium between the (*S,S,R*)-YLB-type complex and (*S,S,S*)-YLB would occur under the reaction conditions. The (*S,S,R*)-YLB-type complex is not active for 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*.[14] The *ee* value of the product was same with ligands with over 33 % *ee*, whereas the reaction rate increased drastically by increasing the *ee* value of the ligands from 33 to >99 % *ee*, because the amount of (*S,S,S*)-**1** increased accordingly (Figure 3).



Scheme 2. 1,4-Addition reaction: a) with (*S,S,S*)-YLB (6.66 mol%) + (*R,R,R*)-YLB (3.33 mol%); b) with preformed (*S,S,R*)-YLB (10 mol%).

In summary, various kinetics studies and NMR spectroscopic analysis revealed that the active species in the asymmetric 1,4-addition reaction with YLB as a catalyst is Y/Li/binol = 1:3:3 coordinated with amine **3**, although the binol unit in YLB is labile under the reaction conditions. Our conclusion is different from that proposed by Salvadori and co-workers,[3] probably because the active species differs, depending on the combination of rare earth metal, alkali metal, and nucleophile used. The results reported herein do not necessarily extend to the active species in other reactions. In particular, the active species when using more-acidic nucleophiles such as nitroalkanes and phosphonates, which may or may not be replaced with binol, is the future target of investigation. Further studies based on kinetic studies of other asymmetric reactions are essential to clarify the active species. This project is currently in progress.

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[1] a) H. Sasai, T. Suzuki, S. Arai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1992**, *114*, 4418; b) H. Sasai, T. Suzuki, N. Itoh, K. Tanaka, T. Date, K. Okamura, M. Shibasaki, *J. Am. Chem. Soc.* **1993**, *115*, 10372; for reviews, see: c) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1236; d) M. Shibasaki, N. Yoshikawa, *Chem. Rev.* **2002**, *102*, 2187.

[2] a) H. C. Aspinall, J. L. M. Dwyer, N. Greeves, A. Steiner, *Organometallics* **1999**, *18*, 1366; b) H. C. Aspinall, J. F. Bickley, J. L. M. Dwyer, N. Greeves, R. V. Kelley, A. Steiner, *Organometallics* **2000**, *19*, 5416; Review: c) H. C. Aspinall, *Chem. Rev.* **2002**, *102*, 1807.

[3] L. D. Bari, M. Lelli, G. Pintacuda, G. Pescitelli, F. Marchetti, P. Salvadori, *J. Am. Chem. Soc.* **2003**, *125*, 5549.

[4] K. Yamada, S. J. Harwood, H. Gröger, M. Shibasaki, *Angew. Chem.* **1999**, *111*, 3713; *Angew. Chem. Int. Ed.* **1999**, *38*, 3504.

[5] M. Chavarot, J. J. Byrne, P. Y. Chavant, Y. Vallée, *Tetrahedron: Asymmetry* **2001**, *12*, 1147.

[6] N. Yamagiwa, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 16178.

[7] YLB (**1**) is also most suitable to investigate the effects of H_2O on reactivity and selectivity of heterobimetallic asymmetric catalysis. Anhydrous YLB was essential for the asymmetric 1,4-addition of amine, whereas aqua YLB was essential for the catalytic asymmetric cyanoethoxycarbonylation reaction. Comparison of these two reactions to clarify the role of H_2O will be reported as a full article. For the use of aqua YLB in the cyanoethoxycarbonylation reaction, see: a) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Angew. Chem.* **2002**, *114*, 3788; *Angew. Chem. Int. Ed.* **2002**, *41*, 3636; b) J. Tian, N. Yamagiwa, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2003**, *5*, 3021.

[8] For detailed data of kinetic profiles 1–6, nonlinear effects 7, and the reaction profiles in Figures 5 6, see Supporting Information.

[9] For reviews, see: a) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922; b) H. B. Kagan,

Adv. Synth. Catal. **2001**, *343*, 227; for a review discussing kinetic aspects of nonlinear effects, see: c) D. G. Blackmond, *Acc. Chem. Res.* **2000**, *33*, 402.

[10] NMR spectroscopic analysis suggested that YLB (**1**) (1:3:3 complex) forms predominantly even when the Y–Li complex was mixed in a 1:2:2 ratio in THF. Coordination of THF would not be sufficient to stabilize the coordinatively unsaturated Y/Li/binol = 1:1:2 species. When the Y–Li complex was mixed in a 1:1:2 ratio (Y/Li/binol), a complicated NMR spectrum was observed. We speculate that **1** would form, but that other species derived from remaining $Y(HMDS)_3$ and binol-H_2 would also form, thus resulting in the complicated NMR spectrum.

[11] For a more detailed discussion evaluating mechanisms A-C in Figure 4, see Supporting Information.

[12] ^{13}C and ^{1}H NMR spectra of YLB and YLB with amine **3** are shown in the Supporting Information. The difference in chemical shifts is also summarized.

[13] ^{1}H NMR spectra of anhydrous and aqua YLB and experiments to show the reversibility between aqua and anhydrous YLB are summarized in the Supporting Information.

[14] The possibility that the (*S*,*S*,*R*)-YLB-type complex is much less reactive (1/34 of (*S*,*S*,*S*)-YLB), but as enantioselective as (*S*,*S*,*S*)-YLB (95 % *ee*) cannot be excluded. Further mechanistic studies are necessary.

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