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Stable, Storable, and Reusable Asymmetric Catalyst: A Novel La-linked-BINOL Complex for the Catalytic Asymmetric Michael Reaction

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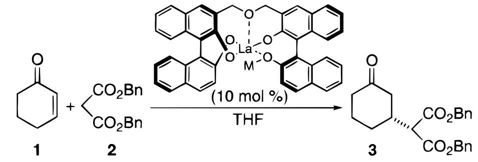
The development of efficient methods to facilitate the recovery and reuse of asymmetric catalysts remains an important goal in organic chemistry. To address this issue, intensive efforts have been devoted to develop soluble and insoluble polymer-supported asymmetric catalysts,[1] which often result in lower enantioselectivities or efficiencies than non-polymer-supported catalysts with a few excellent exceptions.[2,3] However, only a few reusable non-polymer-supported homogeneous asymmetric catalysts[4] have been accomplished due to the difficulty of recovery for recycling. In addition, reusable asymmetric Lewis acid catalysts[2b−d,4] are quite rare because of their high reactivity to moisture despite their usefulness in catalysis.[5] Therefore, an increasingly important objective within this area is the development of highly stable asymmetric Lewis acid catalysts that can be recovered and reused. Recently, we reported the oxygen-containing linked-BINOL **5**, which effectively stabilized the Ga−Li-complex against ligand exchange with a nucleophile under the reaction conditions.[6] In terms of catalyst stability itself, however, group XIII metal complexes such as Al and Ga complexes are unsatisfactory. We expected that rare earth metals could be useful as a Lewis acidic center metal in the linked-BINOL complex. This should lead to much more stable complexes, because of not only its stability against moisture but also its longer ionic radius so that the oxygen in the linker would coordinate to the rare earth metal in contrast to the Ga−Li-linked-BINOL complex.[7] We report here that the La-linked-BINOL complex **4** is indeed a highly stable, storable and reusable homogeneous catalyst for the asymmetric Michael reaction. This reaction is notable not only for its high enantioselectivity and the synthetic utility[8] of its products but also for its facility in handling of the catalyst.

Table 1. Catalytic Asymmetric Michael Reaction Promoted by (*R*,*R*)-La-M-linked-BINOL Complexes



entry	M	temp. (°C)	time (h)	yield (%)[a]	ee (%)[b]
1	Li	0	24	21	35
2	Na	0	24	41	43[c]
3	K	−20	24	16	54[c]
4	H (**4**)	0	45	53	85

[a] Isolated yield. [b] Determined by HPLC analysis. [c] The mirror image enantiomer was formed.

Table 2. Catalytic Asymmetric Michael Reaction Promoted by Stock (*R*,*R*)-La-linked-BINOL Complex **4**

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{DME, rt, 72 h}]{(R,R)\text{-La-linked-BINOL } \mathbf{4}\ (10\text{ mol }\%)} \mathbf{3}$$

storage time (week)[a]	0	1	2	3	4
yield (%)[b]	94	93	94	94	95
ee (%)[c]	>99	>99	>99	>99	>99

[a] (*R*,*R*)-La-linked-BINOL complex **4** was stored under air. [b] Isolated yield. [c] Determined by HPLC analysis.

In recent years, the catalytic asymmetric Michael reaction promoted by chiral metal complexes has been recognized as an efficient method for enantioselective carbon−carbon bond formations. Although efficient catalytic asymmetric Michael reactions have been achieved by our group[8b,9] and by others,[10−12] there is still a big demand for improvement in terms of generality and stability of the catalyst, for instance, AlLibis(binaphthoxide) complex (ALB)[8b] is applicable only to cyclic enones and it is also moisture-sensitive. In an attempt to prepare an efficient linked BINOL complex, lanthanum was chosen as a Lewis acidic center metal. Asymmetric Michael reaction of 2-cyclohexen-1-one (**1**) with dibenzyl malonate (**2**) was examined with monometallic (La only) and heterobimetallic (La−Li, La−Na, La−K) complexes. The results are summarized in Table 1. The best result was obtained using alkali-metal free La-linked-BINOL complex **4** (entry 4), in which lanthanum metal should work as a Lewis acid and lanthanum naphthoxide moiety should work as a Brønsted base to promote the reaction. After optimization of the reaction conditions, we finally found that the use of DME as a solvent afforded **3** in 94% yield and >99% ee even at room temperature (Table 2, 0 week). As we expected, the novel La-linked-BINOL complex **4** was very stable even under air and storable over a long time. The complex **4** was easily prepared from La(O-*i*-Pr)$_3$[13]

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[1] For a recent review, see: *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York; 1999; Chapter 38.

[2] For examples of recycling of the polymer-supported asymmetric catalysts itself, see: (a) Nozaki, K.; Itoi, Y.; Shibahara, F.; Shirakawa, E.; Ohta, T.; Takaya, H.; Hiyama, T. *J. Am. Chem. Soc.* **1998**, *120*, 4051. (b) Annis, D. A.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 4147. (c) Sellner, H.; Seebach, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1918. (d) Heckel, A.; Seebach, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 163. (e) Vachal, P.; Jacobsen, E. N. *Org. Lett.* **2000**, *2*, 867.

[3] For a example of recycling of the polymer-supported metal and the chiral ligand independently, see: Kobayashi, S.; Endo, M.; Nagayama, S. *J. Am. Chem. Soc.* **1999**, *121*, 11229.

[4] (a) Martínez, L. E.; Leighton, J. L.; Carsten, D. H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1995**, *117*, 5897. (b) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936.

[5] For a recent review, see: *Lewis Acid Reagents. A Practical Approach*; Yamamoto, H., Ed.; Oxford University Press: New York; 1999.

[6] Matsunaga, S.; Das, J.; Roels, J.; Vogl, E. M.; Yamamoto, N.; Iida, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 2252.

[7] The X-ray data of LiCl free Ga−Li-linked-BINOL complex showed that there was no coordination between oxygen in the linker and gallium. See ref 6.

[8] (a) Magnus, P.; Sear, N. L.; Kim, C. S.; Vicker, N. *J. Org. Chem.* **1992**, *57*, 70. (b) Shimizu, S.; Ohori, K.; Arai, T.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1998**, *63*, 7547. (c) Ohori, K.; Shimizu, S.; Ohshima, T.; Shibasaki, M. *Chirality*, in press.

[9] For a review, see: Shibasaki, M.; Sasai, H.; Arai, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1236.

[10] For recent reviews, see: (a) *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: New York; 1999; Chapter 31. (b) Tye, H. *J. Chem. Soc., Perkin Trans. 1* **2000**, 275.

[11] For a representative example of the catalytic asymmetric Michael reactions of enones with malonates, see: Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* **1996**, *61*, 3520.

[12] For representative examples of other catalytic asymmetric Michael reactions, see: (a) Feringa, B. L.; Pineschi, M.; Arnold, L. A.; Imbos, R.; de Vries, A. H. M. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2620. (b) Takaya, Y.; Ogasawara, M.; Hayashi, T.; Sakai, M.; Miyaura, N. *J. Am. Chem. Soc.* **1998**, *120*, 5579. (c) Corey, E. J.; Noe, M. C.; Xu, F. *Tetrahedron Lett.* **1998**, *39*, 5347. (d) Evans, D. A.; Rovis, T.; Kozlowski, M. C.; Tedrow, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 1994. (e) Ji, J.; Barnes, D. M.; Zhang, J.; King, S. A.; Wittenberger, S. J.; Morton, H. E. *J. Am. Chem. Soc.* **1999**, *121*, 10215 and references therein.

[13] La(O-*i*-Pr)$_3$ can be purchased from Kojundo Chemical Laboratory Co., Ltd., 5-1-28, Chiyoda, Sakado-shi, Saitama 350-0214, Japan (Fax: +(81)-492-84-1351).

10.1021/ja001036u CCC: $19.00

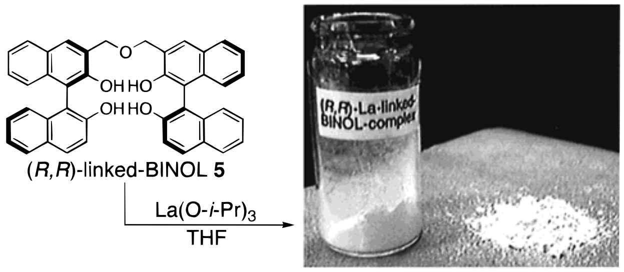
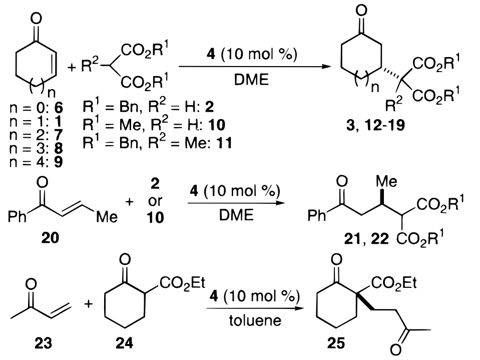


Figure 1. Stock air-stable powdered (*R*,*R*)-La-linked-BINOL complex **4**, which has no deliquescent property.

Table 3. Catalytic Asymmetric Michael Reactions Promoted by (*R*,*R*)-La-linked-BINOL **4**



entry	enone	β-dicarbonyl compounds	temp. (°C)	time (h)	produce	yield[a] (%)	ee[b] (%)
1	**6**	**2**	4	85	**12**	85	>99
2	**6**	**10**	4	85	**13**	96	>99
3	**1**	**2**	rt	72	**3**	94	>99
4	**1**	**2**	4	85	**3**	98	>99
5	**1**	**10**	rt	72	**14**	95	>99
6[c]	**1**	**11**	rt	84	**15**	84	98
7	**7**	**2**	4	85	**16**	96	>99
8	**7**	**10**	4	85	**17**	97	>99
9[c]	**8**	**10**	rt	96	**18**	82	99
10	**9**	**2**	4	120	**19**	61	82
11	**20**	**2**	−40	56	**21**	97	78
12	**20**	**10**	−40	56	**22**	95	74
13[d]	**23**	**24**	−30	36	**25**	97	75

[a] Isolated yield. [b] Determined by HPLC analysis. [c] The reaction was carried out in DME/THF (9:1). [d] **24** was added dropwise over 24 h.

and 1.0 equiv of linked-BINOL **5**, which were mixed in THF followed by removal of solvent under reduced pressure to afford **4** as a pale-yellow powder (Figure 1). This air-stable complex **4** is storable without any care at ambient temperature for at least 4 weeks. As shown in Table 2, no change in catalytic activity, in terms of both chemical yield and ee, was observed using stock catalyst. After 4 weeks storage, **3** was obtained in 95% yield and >99% ee. Although the structure of complex **4** has not yet been unequivocally elucidated, we propose on the basis of the previous structural investigation on Ga−Li-linked-BINOL that the complex **4** would be monomer.[14]

Having succeeded in developing a novel stable and storable catalyst, we examined the scope and limitations of different substrates. As shown in Table 3, the complex **4** promoted the Michael reaction of a variety of cyclic enones ($n = 0-4$) with various malonates to afford Michael adducts[15] with good to excellent ee's. The complex **4** was also effective for the Michael reaction of acyclic enones such as **20** with **2** (97%, 78% ee) and **10** (95%, 74% ee).[15] In addition, the Michael reaction of **23** with **24** gave **25** in 97% yield and 75% ee, where a newly formed chiral center was induced by the Michael donor moiety. To the best of our knowledge no efficient catalytic Michael reaction of eight- and nine-membered ring enones with malonates has been reported to date, and this is the first example of a Michael reaction where the catalyst shows such broad generality.

Table 4. Catalytic Asymmetric Michael Reaction with Catalyst Recycling

$$\mathbf{1} + \mathbf{2} \xrightarrow[\text{DME, 4 °C, 110 h}]{(R,R)\text{-La-linked-BINOL } \mathbf{4}\ (10\ \text{mol}\ \%)} \mathbf{3}$$

cycle	1	2	3	4
yield (%)[a]	82	94	68	50
ee (%)[b]	>99	>99	99	98

[a] Isolated yield. [b] Determined by HPLC analysis.

Finally, we were very pleased to demonstrate that complex **4** could be recovered from the reaction mixture due to the large difference of solubility between the complex **4** and product **3** and reused. The successful implementation of this strategy is shown in Table 4. After completion of the reaction, the complex **4** was precipitated by addition of pentane at 0 °C. Supernatant liquid, which contained product **3** and only trace amounts of **4**, was simply separated via cannula. The residual precipitate was dried under reduced pressure to afford the powdered complex **4** again.[16] The recovered complex **4** was reused several times. Although slight loss of activity was observed, the recovered complex **4** promoted the Michael reaction to afford the desired product **3** in very high ee even after the fourth use.

In conclusion, we have successfully developed the stable, storable, and reusable La-linked-BINOL complex **4** for the asymmetric Michael reaction (up to >99% ee) with broader generality compared to any reported catalysts. Even after 4 weeks storage, this powdered complex **4** was highly effective in the catalytic asymmetric Michael reaction. Furthermore, recovering and recycling of the complex **4** has been accomplished, and the recovered complex **4** still gave the desired product in very high ee even after fourth cycle.

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Supporting Information Available: Experimental procedures for the preparation of the La-linked-BINOL complex **4**, general procedures for the Michael reaction and spectral and analytical data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Computational optimization of a model compound (La-linked-biphenol complex) using molecular mechanics calculation followed by ab initio calculation indicated that the distance between lanthanum and oxygen in the linker should be 2.62−2.69 Å, which is nearly equal to that between lanthanum and phenolic oxygen (2.58−2.65 Å). It seems reasonable to consider that the oxygen atom in the linker would also function as coordinative moiety and thus linked-BINOL would function as pentadentate ligand toward La, thus making the La-linked-BINOL complex **4** unusually stable. See Supporting Information for details and references of the calculation.

(15) The absolute configurations of **3**, **12**−**17**, and **25** have already been determined. See Supporting Information. The absolute configurations of **18**, **19**, **21**, and **22** were tentatively determined on the basis of the previous results. See ref 9.

(16) The recovered powdered complex **4** contained $\sim$10−15% of **3**.