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Mixed La−Li Heterobimetallic Complexes for Tertiary Nitroaldol Resolution

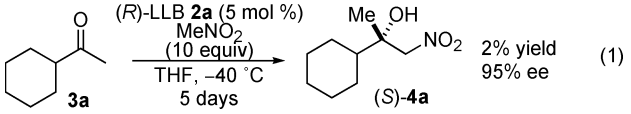
Shin-ya Tosaki, Keiichi Hara, Vijay Gnanadesikan, Hiroyuki Morimoto, Shinji Harada, Mari Sugita, Noriyuki Yamagiwa, Shigeki Matsunaga,* and Masakatsu Shibasaki*

Graduate School of Pharmaceutical Sciences, The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

Received July 8, 2006; E-mail: mshibasa@mol.f.u-tokyo.ac.jp; smatsuna@mol.f.u-tokyo.ac.jp

Catalytic asymmetric nitroaldol (Henry) reactions[1] of ketones lead to synthetically versatile chiral tertiary nitroaldols. Enantioselective nitroaldol reactions of α-keto esters have been achieved using chiral Cu[2a−d] and Mg complexes[2e] and cinchona alkaloids;[2f] however, there are no reports on the asymmetric synthesis of tertiary nitroaldols derived from simple ketones.[3] Even for a racemic version, only a few methodologies with limited substrate scope are available.[4] The difficulty arises from the attenuated reactivity of ketones and the strong tendency toward a retro-nitroaldol reaction under basic conditions. Therefore, the synthesis of tertiary nitroaldols with chirality control is in high demand. Herein, we describe a kinetic resolution approach using BINOL **1a**−H_2/biphenol **1b**−H_2 mixed La−Li heterobimetallic complexes (Figure 1). Tertiary nitroaldols were obtained in 80−97% ee.

Initial trials revealed that (*R*)-LLB **2a** (Figure 1)[5] promoted a reaction of **3a** with 10 equiv of nitromethane at −40 °C to afford (*S*)-**4a** in 95% ee, albeit in poor yield (2%), after 5 days (eq 1). Excess nitromethane was essential to obtain product **4a**. Further trials to improve the yield failed, however, possibly because the nitroaldol reaction of **3a** is thermodynamically unfavorable.[6,7] Good conversion is difficult to achieve in the absence of stoichiometric amounts of trapping reagents, such as silylating reagent, to make the reaction irreversible or stoichiometric amounts of chelating metals to stabilize the product.



The nitroaldol reaction is reversible under basic conditions; therefore, we planned to use (*R*)-LLB **2a** for a kinetic resolution of racemic tertiary nitroaldols via a retro-nitroaldol reaction.[8,9] On the basis of the high enantioselectivity achieved (eq 1), we hypothesized that (*R*)-LLB **2a** would preferentially convert the matched enantiomer (*S*)-**4a** into **3a** and nitromethane, while the mismatched enantiomer (*R*)-**4a** would remain unchanged and be recovered in an enantiomerically enriched form. Kinetic resolution of (±)-**4a** using 5 mol % of (*R*)-LLB **2a** proceeded at −40 °C. As expected, **4a** was recovered in 76% yield and 30% ee [(*R*)-**4a** major][10] after 24 h, together with ketone **3a** and nitromethane. To enhance the reaction rate, the reaction was performed at −20 °C, giving good enantioselectivity (86% ee) in 48% recovery yield of (*R*)-**4a** (Table 1, entry 1, 24 h, selectivity factor: $s = 23.8$).[11] To further improve selectivity, we investigated various chiral ligands, such as BINOL derivatives and biphenol derivatives. Inspired by recent reports of a mixed-ligand chiral catalyst screening strategy,[12] we also examined the mixture of two chiral ligands. The best selectivity was obtained when using (*R*)-LLB **2a** and (*R*)-LLB* **2b** (Figure 1)[13] in a ratio of 2:1 (entry 2, 90% ee, 50% yield, $s = 58.4$). Neither **2a**/**2b** = 1:2 ratio nor **2b** alone had satisfactory

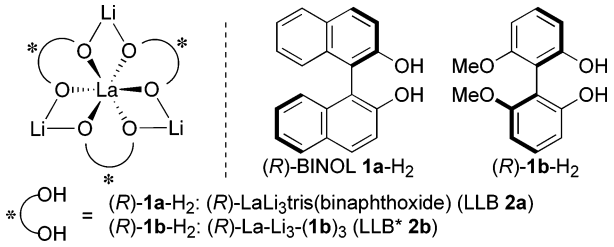
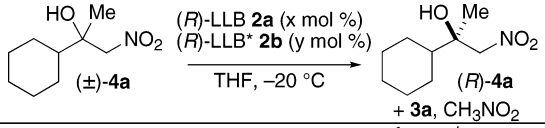


Figure 1. Structures of (*R*)-BINOL **1a**−H_2, biphenol (*R*)-**1b**−H_2, and La−Li heterobimetallic complexes LLB **2a** and LLB* **2b**.

Table 1. Effects of LLB **2a**/LLB* **2b** Ratio on Kinetic Resolution of Tertiary Nitroaldol (±)-**4a**



entry	LLB (x mol %)	LLB* (y mol %)	time (h)	recov. of **4a**[a] (%)	ee[b] (%)	*s*
1	5	0	24	48	86	23.8
2	3.33	1.67	23	50	90	58.4
3	1.67	3.33	24	51	52	5.5
4	0	5	48	58	14	1.7

[a] Determined by ^{1}H NMR analysis using mesitylene as an internal standard. [b] Determined by chiral HPLC analysis.

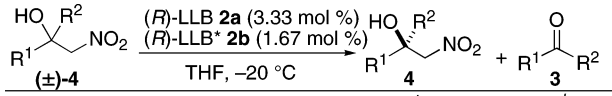
selectivity (entries 3 and 4). Other chiral ligands gave less satisfactory results.

The substrate scopes and limitations of the present kinetic resolution are summarized in Table 2.[14] Retro-nitroaldol reactions of methyl ketone-derived substrates **4a**−**e** with aliphatic substituents proceeded smoothly to afford chiral **4a**−**e** with good enantioselectivity (entries 1−6). For each substrate, the reaction time was optimized to achieve both a good recovery yield of **4** and high enantiomeric excess. With **4b**, catalyst loading was successfully reduced to 2.5 mol % (**2a**: 1.67 mol %, **2b**: 0.83 mol %), still affording good selectivity (entry 3, 90% ee and 40% yield). In the case of acetophenone-derived substrate **4f** and ethyl ketone-derived substrate **4g**, higher conversion (entry 7, 69% conversion, 30% recovery yield of **4f**; entry 8, 65% conversion, 33% recovery yield of **4g**) was required to achieve good enantioselectivity (**4f**, 88% ee; **4g**, 88% ee).

In the present reaction, a combination of (*R*)-LLB **2a** and (*R*)-LLB* **2b** in a ratio of 2:1 gave the best results (Table 1). We speculate that ligand exchange between **2a** and **2b** would occur to generate a mixed-ligand La−Li_3−(**1a**)$_2$/(**1b**) complex in equilibrium,[15] which would be the most enantioselective and reactive catalyst. ESI-MS supported the ligand exchange in situ. Analysis of the **2a**/**2b** = 2:1 mixture revealed major peaks corresponding to La−Li_3−(**1a**)$_2$/(**1b**) and La−Li_3−(**1a**)/(**1b**)$_2$ complexes and minor peaks corresponding to **2a** and **2b** (Figure 2).[16] Further investigation to unequivocally determine the structure of the active species is ongoing.

10.1021/ja064858l CCC: $33.50

Table 2. Kinetic Resolution of *tert*-Nitroaldols **4a**−**g**[a]



entry	substrate R¹	R²		time (h)	conv.[b] (%)	yield of 4[c] (%)	ee[d] (%)	*s*
1	cyclohexyl	Me	**4a**	23	50	47	90	58.4
2	*i*-Bu	Me	**4b**	15	58	40	97	23.1
3[e]	*i*-Bu	Me	**4b**	48	57	40	90	15.7
4		Me	**4c**	24	58	41	85	11.0
5		Me	**4d**	15	58	40	95	19.3
6[f]	$Ph(CH_2)_2$	Me	**4e**	19	60	40	80	7.7
7[g]	Ph	Me	**4f**	26	69	30	88	6.1
8	*i*-Bu	Et	**4g**	13	65	33	88	7.6

[a] Reaction was performed in THF (0.4 M) at −20 °C using 3.33 mol % of (*R*)-LLB **2a** and 1.67 mol % of (*R*)-LLB* **2b** unless otherwise noted. [b] Determined by ^{1}H NMR analysis using mesitylene as an internal standard. [c] Isolated yields after column chromatography. The theoretical maximum is (100% − conversion)%. [d] Determined by chiral HPLC analysis. [e] (*R*)-LLB **2a** (1.67 mol %) and (*R*)-LLB* **2b** (0.83 mol %) were used. [f] (*R*)-LLB **2a** (6.67 mol %) and (*R*)-LLB* **2b** (3.33 mol %) were used. [g] Reaction was run at −40 °C.

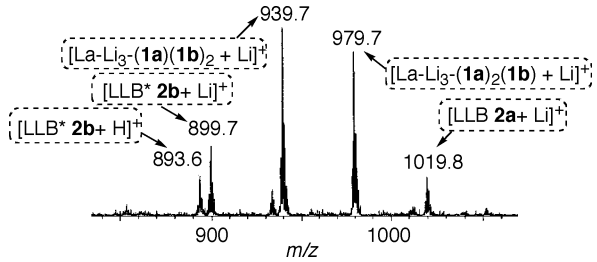
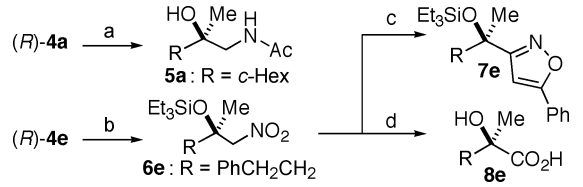


Figure 2. ESI-MS chart of LLB **2a**/LLB* **2b** = 2:1 mixture [*m*/*z* 840−1060].[15]

Scheme 1. Transformations of *tert*-Nitroaldols[a]



[a] Reagents and conditions: (a) cat. Pd−C, H_2 (1 atm), MeOH, rt; Ac_2O, Et_3N, CH_2Cl_2, 86% (2 steps); (b) cat. $B(C_6F_5)_3$, Et_3SiH, CH_2Cl_2, rt, 90%; (c) Ph−acetylene, PhNCO, cat. Et_3N, benzene, reflux, 84%; (d) $NaNO_2$, AcOH, DMSO, rt to 40 °C, 99%.

Scheme 1 illustrates the synthetic utility of tertiary nitroaldols as chiral building blocks. Hydrogenation of **4a**, followed by acetylation, gave *N*-Ac amine **5a** in 86% yield. Silylated adduct **6e** was successfully converted into isoxazole **7e** (84%) and α-hydroxy carboxylic acid **8e** (99%).[17]

In summary, we achieved a kinetic resolution of tertiary nitroaldols (±)-**4** derived from simple ketones. Mixed La−Li heterobimetallic complexes had the best selectivity (80−97% ee with 30−47% recovery yield). Further investigation of the structure of the active species and application of the present mixed heterobimetallic catalyst system to other asymmetric reactions are in progress.

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Supporting Information Available: Experimental procedures, spectral data of the new compounds, and ESI-MS data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) In the nitroaldol reaction in eq 1, excess nitromethane was required to suppress undesired retro-nitroaldol reaction and to obtain kinetically controlled product. We speculate that excess nitromethane was also important due to a low equilibrium constant. Generally, equilibrium constants for aldol(-type) reactions of ketone electrophiles are much lower than those of aldehydes. For example, an equilibrium constant for aldol reaction of benzaldehyde and acetone is 11.7 M^{-1}, while that of acetophenone and acetone is 1.89×10^{-3} M^{-1}. (a) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 7249. (b) Guthrie, J. P. Wang, X.-P. *Can. J. Chem.* **1992**, *70*, 1055 and references therein.

(7) (*R*)-LLB **2a** also promoted nitroaldol reactions of other simple ketones in high enantioselectivity, albeit in poor yields. Ketone **3d** (90% ee, 5% yield); **3e** (89% ee, 20% yield).

(8) For an elegant kinetic resolution of tertiary aldols via retro-aldol reaction with a catalytic antibody, see: (a) List, B.; Shabat, D.; Zhong, G.; Turner, J. M.; Li, A.; Bui, T.; Anderson, J.; Lerner, R. A.; Barbas, C. F., III. *J. Am. Chem. Soc*. **1999**, *121*, 7283 and references therein. For a retro-nitroaldol reaction with a catalytic antibody, see: (b) Flanagan, M. E.; Jacobsen, J. R.; Sweet, E.; Schultz, P. G. *J. Am. Chem. Soc*. **1996**, *118*, 6078.

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(10) The absolute configurations of **4a**, **4e**, and **4f** were determined to be *R* after conversion into known compounds. See Supporting Information.

(11) The *s* values in this paper were calculated based on conversion and ee of recovered **4** assuming first-order kinetic dependence on **4**. Kinetic studies are required to determine accurate *s* values. For discussion on the validity of calculated *s* values, see: Keith, J. M.; Larrow, J. F.; Jacobsen, E. N. *Adv. Synth. Catal*. **2001**, *343*, 5. See also ref 9a.

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(14) Because the known synthetic methods of racemic tertiary nitroaldols did not afford satisfactory yield for **4f**, we developed a new synthetic method. See Supporting Information for details.

(15) Ligand liability of related rare earth−alkali metal heterobimetallic complexes was reported. (a) Bari, L. D.; Lelli, M.; Salvadori, P. *Chem.*−*Eur. J.* **2004**, *10*, 4594. See also: (b) Horiuchi, Y.; Gnanadesikan, V.; Ohshima, T.; Masu, H.; Katagiri, K.; Sei, Y.; Yamaguchi, K.; Shibasaki, M. *Chem.*−*Eur. J.* **2005**, *11*, 5195.

(16) For full details of ESI-MS data [*m*/*z* 200−1300] of LLB **2a**, LLB* **2b**, **2a**/**2b** = 2:1, and **2a**/**2b** = 1:2, see Supporting Information. Although it is impossible to discuss quantitatively using MS, we believe the ESI-MS data at least suggested the presence of mixed-ligand La−Li complexes in the mixture of LLB **2a** and LLB* **2b**. NMR analysis only resulted in a complex mixture spectrum.

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