Pergamon

Tetrahedron Letters 41 (2000) 209–213

TETRAHEDRON LETTERS

# Catalytic asymmetric protonation of achiral lithium enolates mediated by a chiral tetraamine ligand with water as a proton source

Yasuhiro Yamashita, Yoshihiro Emura, Kazunori Odashima and Kenji Koga *,†

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

Received 9 September 1999; revised 29 September 1999; accepted 1 October 1999

**Abstract**

Catalytic protonation of achiral lithium enolates (derived from 2-substituted-1-tetralones), mediated by a chiral tetraamine ligand [(*R*,*R*)-*N*,*N*′-bis[1-phenyl-2-(1-piperidinyl)ethyl]-1,3-propanediamine (0.10 equiv.)], was achieved with high enantioselectivity (up to 93% ee) by using water (10% aqueous citric acid) as a proton source. A possible mechanism of highly efficient catalytic turnover of the chiral tetraamine ligand is discussed. 

*Keywords:* asymmetric reactions; enantioselection; protonation; catalysis; enolates; cyclic ketones.

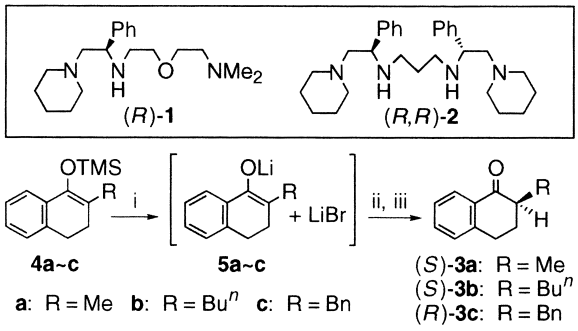
Asymmetric protonation of achiral enolates affords a method of high synthetic versatility for converting racemic α-substituted carbonyl compounds to the optically active ones.[1] Following the pioneering work by Duhamel et al.,[2] many examples including catalytic approaches[3] have been reported to date. We have made efforts for enantioselective protonation which featured the use of chiral multidentate ligands in the presence of LiBr.[4a,b] By using ligand (*R*)-**1**, protonation of lithium enolates **5a**–**c** derived from the corresponding 2-substituted-1-tetralones (**3a**–**c**) via the trimethylsilyl (TMS) enol ethers (**4a**–**c**) (Scheme 1) was achieved with high enantioselectivities, not only under stoichiometric conditions (up to 91% ee)[4a] but also under catalytic conditions (up to 83% ee with 0.2 equiv. of **1**).[4b] Meanwhile, in the course of our study on catalytic enantioselective alkylation (quaternization) of **5a** by using ligand (*R*,*R*)-**2** (0.10 equiv.),[5] we frequently observed high asymmetric induction (72–91% ee) for the recovered ketones (**3a**) after aqueous workup, showing the possibility of using water as an effective proton source for catalytic enantioselective protonation. The versatility of such a system as well as fundamental interest prompted us to carry out detailed investigation of catalytic enantioselective protonation mediated by

* Corresponding author. Tel: +81-743-72-6170; fax: +81-743-72-6179; e-mail: kkoga@ms.aist-nara.ac.jp

† Present address: Research and Education Center for Materials Science, Nara Institute of Science and Technology, Takayama-cho, Ikoma-shi, Nara 630-0101, Japan.

0040-4039/00/$ - see front matter 
*PII:* S0040-4039(99)01912-7

(*R*,*R*)-**2**. Highly efficient enantioselective protonation with a large excess of water as a proton source was achieved in upto 93% ee under catalytic conditions [0.10 equiv. of (*R*,*R*)-**2**].




Scheme 1. Enantioselective protonation. (i) MeLi-LiBr (1.0 equiv.), $Et_2O$, rt, 1.5 h; (ii) chiral amine [+achiral additive (2.0 equiv.)], toluene, −20°C, 40 min; (iii) achiral proton source, −45°C→room temperature

Table 1 shows the results of enantioselective protonation of lithium enolates (**5a**–**c**), derived from **3a**–**c** (racemate) via **4a**–**c**, to give the corresponding optically active ketones under stoichiometric and catalytic conditions (Scheme 1).[6,7] The reactions were carried out in the presence of 1.0 equiv. of LiBr at the initial stage of the reaction.[8]

Under the conditions similar to those employed previously for (*R*)-**1** in the reaction from **4a** to (*S*)-**3a** (91% ee by quenching with acetic acid at −78°C),[4a] tetraamine ligand (*R*,*R*)-**2** gave a comparatively high enantioselectivity (91% ee, data not shown in Table 1). However, to our surprise, essentially the same result was obtained with a large excess of water (10% aqueous citric acid), added in one portion (ca. 3 s) as a proton source in place of acetic acid. Furthermore, when the chiral ligand (*R*,*R*)-**2** was reduced to substoichiometric amounts, the enantioselectivity did not decrease substantially, showing an efficient catalytic turnover with water as a proton source (entries 1–3).[9,10] An examination of the effect of added achiral bidentate ligands (entries 4–8) revealed that the enantioselectivity could be retrieved to nearly that attained under the stoichiometric conditions (entry 1, 93% ee) by carrying out the reactions in the presence of appropriate bidentate ligands (**7b**–**d**). The highest enantioselectivity was obtained with ligand **7c** having a tetramethylene bridge (entry 7, 89% ee). The enantioselectivity was mostly retained when neutral water was used as a proton source (entry 9, 86% ee) but decreased substantially when acetic acid was used (entry 10, 56% ee). The enantioselectivity was slightly improved by adding the achiral diamine before the chiral tetraamine (entry 7 versus 11). The amount of the chiral tetraamine could be reduced to 0.025 equiv. without substantial decrease in the enantioselectivity (entry 11–14). For other substrates, an enantioselectivity comparable to that for **4a** (R=Me; entry 11, 93% ee) was observed for **4b** (R=Bu$^n$; entry 15, 90% ee) but not for substrate **4c** with a benzyl substituent (entry 16, 54% ee). In all cases, the preferred direction of protonation was the same as that in the protonation mediated by (*R*)-**1**[4a,b] and opposite from that in the alkylation mediated by (*R*)-**1**,[4a,7c,11a] (*R*,*R*)-**2**[5] or related ligands.[11a,b]

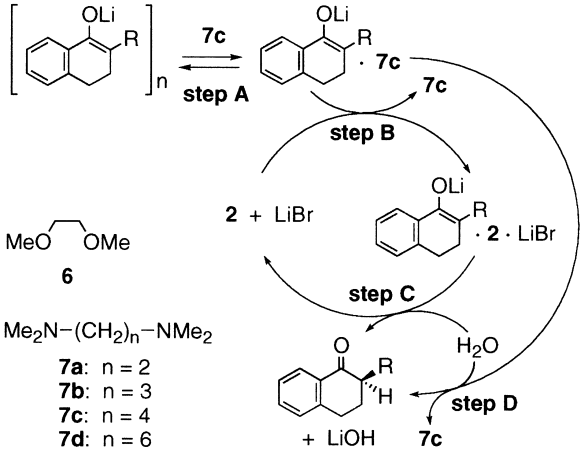
A possible mechanism of catalytic turnover of the chiral ligand is shown in Scheme 2. Of the two protonation processes, step D (nonenantioselective process) will be suppressed substantially in a two-phase system compared to a homogeneous system using acetic acid as a proton source. In contrast, step C (enantioselective process) in a two-phase system may not be suppressed as markedly as step D because the more hydrophilic nature of the chiral tetraamine ligand compared to the achiral diamine ligand makes the complex with the former more favorable for an interfacial protonation process that may predominate in a two-phase system. A possible role of achiral bidentate ligand such as **7c** is deaggregation of unreacted lithium enolates by complexation (step A), facilitating the ligand exchange

Table 1
Enantioselectivities of protonation mediated by chiral tetraamine ligand (*R*,*R*)-**2**[a]

| entry | substrate/product[b] | (*R*,*R*)-**2** (equiv) | additive[c] | proton source[d] | ee (%) |
|---|---|---|---|---|---|
| 1 | **4a**/(*S*)-**3a** | 1.0 | – | A | 93 |
| 2 | **4a**/(*S*)-**3a** | 0.20 | – | A | 85 |
| 3 | **4a**/(*S*)-**3a** | 0.10 | – | A | 76 |
| 4 | **4a**/(*S*)-**3a** | 0.10 | **6** | A | 18 |
| 5 | **4a**/(*S*)-**3a** | 0.10 | **7a** | A | 20 |
| 6 | **4a**/(*S*)-**3a** | 0.10 | **7b** | A | 82 |
| 7 | **4a**/(*S*)-**3a** | 0.10 | **7c** | A | 89 |
| 8 | **4a**/(*S*)-**3a** | 0.10 | **7d** | A | 86 |
| 9 | **4a**/(*S*)-**3a** | 0.10 | **7c** | B | 86 |
| 10 | **4a**/(*S*)-**3a** | 0.10 | **7c** | C | 56 |
| 11 | **4a**/(*S*)-**3a** | 0.10 | **7c** | A | 93 |
| 12 | **4a**/(*S*)-**3a** | 0.050 | **7c** | A | 91 |
| 13 | **4a**/(*S*)-**3a** | 0.025 | **7c** | A | 88 |
| 14 | **4a**/(*S*)-**3a** | 0.010 | **7c** | A | 81 |
| 15 | **4b**/(*S*)-**3b** | 0.10 | **7c** | A | 90 (92)[e] |
| 16 | **4c**/(*R*)-**3c** | 0.10 | **7c** | A | 54 (76)[e] |

[a] See note 6 for a typical experimental procedure. The protonation temperature was -45 °C in all entries. The isolated chemical yields of ketones **3a**, **3b** and **3c** were 85~91%, 85% and 81%, respectively.
[b] For the absolute configurations of ketones **3a~c**, see note 7.
[c] In entries 1~10, (*R*,*R*)-**2** was added first, followed by the addition of the achiral additive (2.0 equiv). In entries 11~16, the achiral additive (2.0 equiv) was added before the addition of (*R*,*R*)-**2**.
[d] A, 10% aqueous citric acid (large excess); B, water (large excess); or C, acetic acid (1.2 equiv) was added in one portion (*ca.* 3 s).
[e] The ee's obtained with 1.0 equiv of (*R*,*R*)-**2**.

(step B) and making the formation (regeneration) of a highly reactive chiral complex[8] faster than the nonenantioselective protonation process (step D).




Scheme 2. A proposed catalytic cycle

In conclusion, highly enantioselective *catalytic* protonation of lithium enolates was achieved in upto 93% ee with *a large excess of water* as a *proton source* by chiral tetraamine (*R*,*R*)-**2**, particularly when used together with achiral diamine **7c**. As interesting examples in view of this point, catalytic enantioselective protonation using a limited amount of water as a proton source[3a] as well as that using two-phase systems composed of a tetrahydrofuran/fluorocarbon media[3c] have been reported recently. Compared to these examples, the present protonation system is quite unusual in the sense that high enantioselectivities can be achieved with a large excess of water as a proton source in a usual workup procedure. This characteristic aspect may provide a new possibility of ligand design for efficient catalytic turnover in protonation.

## Acknowledgements

This work was supported by Grants from CREST and from the Ministry of Education, Science, Sports and Culture, Japan.

## References

1. For recent reviews, see: (a) Fehr, C. *Angew. Chem., Int. Ed. Engl*. **1996**, *35*, 2566–2587. (b) Yanagisawa, A.; Ishihara, K.; Yamamoto, H. *Synlett* **1997**, 411–420.
2. (a) Duhamel, L.; Plaquevent, J.-C. *Tetrahedron Lett*. **1977**, 2285–2288. (b) Duhamel, L.; Plaquevent, J.-C. *J. Am. Chem. Soc*. **1978**, *100*, 7415–7416.
3. In addition to the literatures cited in Ref. 1a,b, see the following examples for recent studies of *catalytic* enantioselective protonation: (a) Sugiura, M.; Nakai, T. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2366–2368. (b) Vedejs, E.; Kruger, A. W. *J. Org. Chem*. **1998**, *63*, 2792–2793. (c) Takeuchi, S.; Nakamura, Y.; Ohgo, Y.; Curran, D. P. *Tetrahedron Lett*. **1998**, *39*, 8691–8694.
4. (a) Yasukata, T.; Koga, K. *Tetrahedron: Asymmetry* **1993**, *4*, 35–38. (b) Riviere, P.; Koga, K. *Tetrahedron Lett*. **1997**, *38*, 7589–7592.
5. Yamashita, Y.; Odashima, K.; Koga, K. *Tetrahedron Lett*. **1999**, *40*, 2803–2806.
6. The general experimental procedure for enantioselective protonation is as follows: Under argon atmosphere, TMS enol ether **4a**–**c** (1.0 mmol) was treated with a solution of methyllithium (MeLi) (1.0 mmol) in diethyl ether containing LiBr (1.1 mmol) (purchased from Kanto Chemical, Tokyo, Japan) at room temperature for 1.5 h. Toluene (11.5 mL) was added, and the reaction mixture was cooled to −20°C and stirred for 10 min. Then a solution of chiral amine (1.0 mmol or catalytic amount) in toluene [3.0 mL; added dropwise within 2 min and rinsed with toluene (1.0 mL×2)] and achiral additive (2.0 mmol; added neat) were added, and the mixture was stirred for an additional 40 min at this temperature. After the whole was cooled to −45°C and stirred for 20 min, the proton source [10% aqueous citric acid (10 mL), water (10 mL), or AcOH (1.2 equiv.)], without precooling, was added in one portion (ca. 3 s), and the mixture was allowed to warm to room temperature. The organic layer was separated and the aqueous layer was extracted with diethyl ether (20 mL×2). The combined organic layers were washed successively with sat. aq. $NaHCO_3$ (20 mL×2) and brine (20 mL×1), dried over anhyd $MgSO_4$, filtered and concentrated in vacuo to give a crude oil, which was purified by column chromatography (silica gel 15 g, hexanes:ether=50:1) to afford the target compound as a pale yellow oil. This oil was analyzed by HPLC (Daicel Chiralcel OJ or OD-H) to determine the enantiomeric excess.
7. The absolute configurations of chiral ketones (*S*)-**3a**,[7a,b] (*S*)-**3b**,[4a] and (*R*)-**3c**[7c] are known. (a) Jaouen, G.; Meyer, A. *J. Am. Chem. Soc*. **1975**, *97*, 4667–4672. (b) Meyers, A. I.; Williams, D. R.; Erickson, G. W.; White, S.; Druelinger, M. *J. Am. Chem. Soc*. **1981**, *103*, 3081–3087. (c) Murakata, M.; Nakajima, M.; Koga, K. *J. Chem. Soc., Chem. Commun*. **1990**, 1657–1658.
8. Such a condition has been shown to be essential for obtaining high enantioselectivities in protonation[4a,b] as well as in other types of reactions[8a,b] mediated by related ligands. The effect of lithium salt is possibly due to the formation of a highly reactive ternary complex composed of the chiral ligand, lithium enolate and LiBr.[8a–f] For related discussions, see the following review articles and references cited therein: (a) Koga, K. *Pure Appl. Chem*. **1994**, *66*, 1487–1492. (b) Koga, K.; Shindo, M. *J. Synth. Org. Chem., Jpn*. **1995**, *53*, 1021–1032. (c) Seebach, D. *Angew. Chem., Int. Ed. Engl*. **1988**, *27*,

1624–1654. (d) Juaristi, E.; Beck, A. K.; Hansen, J.; Matt, T.; Mukhopadhyay, T.; Simson, M.; Seebach, D. *Synthesis* **1993**, 1271–1290. See also: (e) Yanagisawa, A.; Kikuchi, T.; Kuribayashi, T.; Yamamoto, H. *Tetrahedron* **1998**, *54*, 10253–10264. (f) Asensio, G.; Aleman, P.; Gil, J.; Domingo, L. R.; Medio-Simon, M. *J. Org. Chem*. **1998**, *63*, 9342–9347.

9. The reproducibility of the protonation experiments under the catalytic conditions of entry 7 was that, although the ee ranged from 80 to 89%, the values close to 89% ee were obtained in most cases.
10. An additional fact supporting the effectiveness of water as a proton source is that the catalytic protonation with (*R*)-**1** in place of (*R*,*R*)-**2** under the catalytic condition of entry 11 also induced a moderate enantioselectivity (74% ee).
11. (a) Murakata, M.; Yasukata, T.; Aoki, T.; Nakajima, M.; Koga, K. *Tetrahedron* **1998**, *54*, 2449–2458. (b) Imai, M.; Hagihara, A.; Kawasaki, H.; Manabe, K.; Koga, K. *J. Am. Chem. Soc*. **1994**, *116*, 8829–8830.