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Structure tuning of lithium amide for asymmetric 1,4-addition to cinnamate and subsequent demasking

Takeo Sakai, Hirohisa Doi, Yoshito Kawamoto, Ken-ichi Yamada and Kiyoshi Tomioka*

Graduate School of Pharmaceutical Sciences, Kyoto University, Yoshida, Sakyo-ku, Kyoto 606-8501, Japan

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Abstract—Systematic structure tuning of lithium amides derived from benzyl-*N*-TMS-, allyl-*N*-TBDMS-, and diisopropylamines lead to several candidates including anthracen-9-ylmethanamine which provided high performance in the enantioselective 1,4-addition (91% ee) and following hydrogenolysis with 10% Pd/C-H_2 in methanol to afford β-amino ester.

We have been engaged in the chiral diether **1**[1]-controlled asymmetric conjugate addition reaction of *N*-trialkylsilyl lithium amides derived from **2**[2,3] and **3**[4] with enoates, affording β-aminoalkanoates[5] with high enantioselectivity (Fig. 1).[6] The total scheme constitutes two processes; the first is asymmetric conjugate addition and the second is the demasking of *N*-silyl and *N*-organic groups from the adducts, for example, **6** to primary amines **7** ($R^1 = R^2 = H$) (Scheme 1). A trialkylsilyl group was readily removed from **6** during purification by silica gel column chromatography or by HF treatment. However, the benzyl-type group of **6** ($R^1 = CH_2Ph$) sometimes suffered from the cleavage of undesired C–N bond by hydrogenolysis to result in the formation of 3-phenylpropanoate, although an allyl-type group (R^1 = allyl) was removed by rhodium-catalyzed isomerization. As part of our continuing effort to broaden the scope of the asymmetric conjugate addition of lithium amide, we are interested in the possibility of developing other amines, thereby providing an alternative for benzyl- and allylamines.

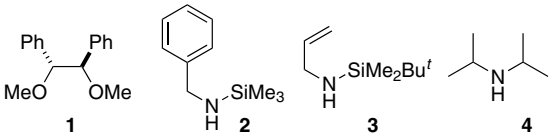
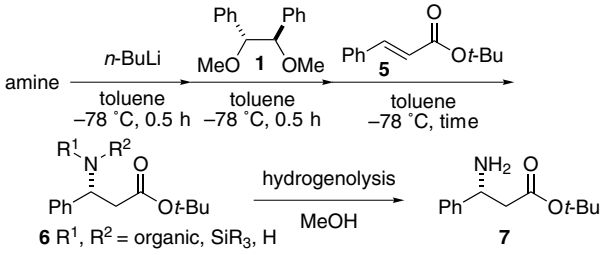


Figure 1. Chiral ligand **1** and amides **2**–**4**.



Scheme 1. Asymmetric addition to **5** and following demasking of **6** to **7**.

In order to extract amine candidates for asymmetric conjugate addition and hydrogenolytic or isomerization demasking, we set up the structure **8** that contains structural features of **2**–**4**.[7] New amine structures **9** and **10** contain the two and three aromatic units of A–C of **8**, which might increase bulkiness for asymmetric induction and hydrogenolysis activity for selective cleavage. Dibenzylamine **11** corresponds to the open version of **10**, which was proven to be less satisfactory.[2] The structure **12** is positioned between **2** and **3**. The structures **13** and **14** contain both features, A and D, of **2** and **4**, and are expected to be much more easily cleaved by hydrogenolysis than the simple benzyl group.[8] PMP-amine **15** is the aromatic version of **4** and it is possible to be cleaved by oxidation.[9] These *N*-TMS amines with reasonably high purity were prepared from the corresponding amine[10] by the standard silylation procedure in high yields[2,4] (see Fig. 2).

Keywords: Asymmetric conjugate addition; Lithium amide; Chiral ligand; Hydrogenolysis; Amino acid.
* Corresponding author. Tel.: +81 757534553; fax: +81 757534604; e-mail: tomioka@pharm.kyoto-u.ac.jp

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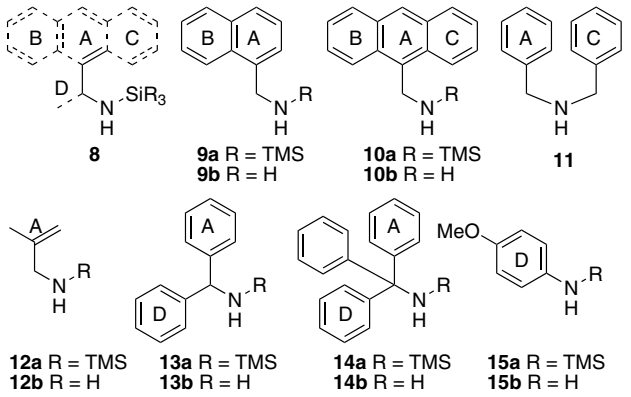


Figure 2. Structures **9**–**15** extracted systematically from the structure **8**.

The asymmetric conjugate addition reaction of these lithium amides with *tert*-butyl cinnamate **5** was conducted using 3 equiv of an amine and 3.6 equiv of **1** in toluene (Scheme 1).[11] The reaction of **9a** and **10a** proceeded smoothly at −78 °C within a reasonable time. Purification by silica gel column chromatography gave the corresponding desilylated adducts **6** with 87% ee and 91% ee in reasonably high yields (Table 1, runs 1 and 2). The ee of **6** was determined by a chiral stationary phase HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 100/1, 1.0 mL/min, 254 nm). The absolute configuration was determined by converting to the known primary amine **7**.[12] Isobutenylamine **12a** gave **6** with 50% ee in 73% yield, being less satisfactory than the corresponding allylamine **3** (run 3). Contrary to our expectation TMS-amines **13a**, **14a** and **15a** did not give the products **6** even under the enforced higher temperature conditions, probably due to too much bulkiness and poor nucleophilicity (runs 4–6).

Other than TMS-amines, amines themselves were also examined with respect to their reactivities. Benzylamine **2b** underwent the reaction at −78 °C to afford **6** (R^1, R^2 = Bn, H) in 64% yield, although ee was as low as 16% (run 7). Unfortunately, lithium amide prepared from **9b** was insoluble in toluene. Interestingly, **10b** gave *ent*-**6** (R^1, R^2 = anthracen-9-ylmethyl, H) with 27% ee in 72% yield (run 8). Diphenylmethylamine **13b** recovered its reactivity by removing an electron-withdrawing and bulky TMS group to afford **6** (R^1, R^2 = Ph_2CH, H) with 57% ee in 73% yield (run 9). Triphenylmethylamine **14b** did not give the conjugate adduct **6**, recovering **5** in 65% yield, together with the corresponding cinnamamide as an isolable by-product in 34% yield (run 10). PMP-amine **15b** was found to give **6** (R^1, R^2 = PMP, H) with 14% ee in 36% yield, together with the corresponding cinnamamide in 38% yield and its conjugate adduct in 17% yield (run 11). These results indicated that a balance of steric and electronic features is the key to high reactivity and enantioselectivity.

Handling of **10a** is easier than **2** because **10a** is needles of mp 69.5–70.5 °C. The product amine **6** (R^1 = 9-anthra-CH_2, R^2 = H) is also needles of mp 109–111 °C, which is enantioenriched by recrystallization from methanol to give the amine of mp 114–115 °C with >99% ee in 70% recovery yield. These are practical merits of **10a** in the use of asymmetric amination.

Since the reasonably high enantioselectivity in the reaction with 1-naphthylmethyl- and anthracen-9-ylmethylamines **9a** and **10a** was obtained, the demasking of the products **6** was examined. Hydrogenolysis of **6** (R^1 = Bn, 1-naphCH_2, 9-anthraCH_2, Ph_2CH, R^2 = H) was conducted in methanol at room temperature to find out efficiency and selectivity in C–N cleavage (Table 2). A benzyl group in **6** (R^1 = Bn, R^2 = H) was a good masking one to be selectively cleaved giving **7** in high yields under the conditions of $Pd(OH)_2$–7 atm of hydrogen[2] as well as 10% Pd/C–ordinary hydrogen atmosphere (runs 1 and 2). 1-Naphthylmethyl group was easily cleaved to give **7** in 92% yield (run 3). Anthracen-9-ylmethyl group of **6** with 90% ee was also cleaved readily to give **7** with 90% optical purity in reasonable yields (runs 4 and 5). However, by-product **16** was obtained in less than 5% yield (Scheme 2). It is noteworthy

Table 1. The chiral diether **1**-controlled asymmetric conjugate addition of amines to cinnamate **5** giving **6**[a]

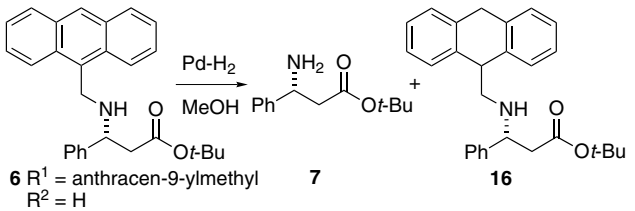
Run	Amine	Temp (°C)	Time (h)	Yield (%)	ee (%)[c]
1	**9a**	−78	0.2	94	87
2	**10a**	−78	1.5	90	91
3	**12a**	−78	1.5	73	50
4	**13a**	−78 to rt	6	0	nd
5	**14a**	−78 to rt	5	0	nd
6	**15a**	−78 to rt	3	0	nd
7	**2b**[b]	−78	0.5	64	16
8	**10b**	−78	2	72	*ent*-27
9	**13b**	−78	1	73	57
10	**14b**	−78 to reflux	3	0	nd
11	**15b**	−78 to 20	3	36	14

[a] Amines (3 equiv) and **1** (3.6 equiv) were used.
[b] Benzylamine was used instead of TMS-amine.
[c] nd: Not determined.

Table 2. Hydrogenolysis of **6** (R^2 = H) in MeOH at rt giving **7**[a]

Run	**6** R^1 (R^2 = H)	Pd	H_2 (atm)	Time (h)	Yield (%)
1	$PhCH_2$	20% $Pd(OH)_2$	7	24	94
2	$PhCH_2$	10% Pd/C	1	40	92
3	1-naphCH_2	20% $Pd(OH)_2$	7	24	92
4	9-anthraCH_2	20% $Pd(OH)_2$	7	24	69
5	9-anthraCH_2	10% Pd/C	1	24	81
6	Ph_2CH	10% Pd/C	1	41	84

[a] The 0.1–0.2 equiv (20–30% w/w) of palladium catalyst was used.



Scheme 2. Hydrogenolysis of **6** giving **7** and **16**.

that the hydrogenolysis was possible with 10% Pd/C under hydrogen balloon conditions for 24 h shorter than the hydrogenation time, 40 h, required for the benzyl group-come off (runs 2 and 5). Expectedly, a diphenylmethyl group was cleaved easily to give **7** in a good yield (run 6). These hydrogenolysis reactions indicated that 10% Pd/C–ordinary atmosphere of hydrogen in methanol is the conditions of choice. It is also important to note that no racemization was observed in these hydrogenolysis reactions of **6**, indicating potential utility of these *N*-masking groups in the synthetic manipulation of **6**.

In conclusion, systematic survey of lithium amide structures lead to anthracen-9-ylmethylamine potentially applicable in asymmetric conjugate addition to cinnamate and following hydrogenolytic demasking to β-amino ester. Since β-amino esters are constituents of organic compounds with promising function,[13] the journey in this line will be continued in our laboratories.[14,15]

Acknowledgements

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References and notes

1. (a) Tomioka, K. *Synthesis* **1991**, 541–549; (b) Tomioka, K.; Shindo, M.; Koga, K. *J. Am. Chem. Soc.* **1989**, *111*, 8266–8268; (c) Shindo, M.; Koga, K.; Tomioka, K. *J. Am. Chem. Soc.* **1992**, *114*, 8732–8733; (d) Shindo, M.; Koga, K.; Tomioka, K. *J. Org. Chem.* **1998**, *63*, 9351–9357.
2. Doi, H.; Sakai, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *J. Am. Chem. Soc.* **2003**, *125*, 2886–2887.
3. (a) Uyehara, T.; Asano, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1987**, 1410–1411; (b) Yamamoto, Y.; Asano, N.; Uyehara, T. *J. Am. Chem. Soc.* **1992**, *114*, 5427–5429.
4. Doi, H.; Sakai, T.; Yamada, K.; Tomioka, K. *Chem. Commun.* **2004**, 1850–1851.
5. Our approaches to asymmetric synthesis of β-amino alkanoate by the Mannich-type reaction of a lithium ester enolate: (a) Fujieda, H.; Kanai, M.; Kambara, T.; Iida, A.; Tomioka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2060–2061; (b) Kambara, T.; Hussein, M. A.; Fujieda, H.; Iida, A.; Tomioka, K. *Tetrahedron Lett.* **1998**, *39*, 9055–9058; (c) Hussein, M. A.; Iida, A.; Tomioka, K. *Tetrahedron* **1999**, *55*, 11219–11228; (d) Kambara, T.; Tomioka, K. *J. Org. Chem.* **1999**, *64*, 9282–9285; (e) Tomioka, K.; Fujieda, H.; Hayashi, S.; Hussein, M. A.; Kambara, T.; Nomura, Y.; Kanai, M.; Koga, K. *Chem. Commun.* **1999**, 715–716; (f) Hata, S.; Iguchi, M.; Iwasawa, T.; Yamada, K.; Tomioka, K. *Org. Lett.* **2004**, *6*, 1721–1724; (g) Hata, S.; Iwasawa, T.; Iguchi, M.; Yamada, K.; Tomioka, K. *Synthesis* **2004**, 1471–1475.
6. For the leading reference of asymmetric conjugate addition of chiral lithium amide, see: Davies, S. G.; Garner, A. C.; Nicholson, R. L.; Osborne, J.; Savory, E. D.; Smith, A. D. *Chem. Commun.* **2003**, 2134–2135.
7. Although the reaction of 2.2 equiv of LDA derived from **4** was reported to give the adduct with 68% ee, 4 equiv of LDA was found to improve the enantioselectivity up to 83% ee.
8. Greene, T. W.; Wuts, P. G. *Protective Groups in Organic Synthesis*; John Wiley & Sons: New York, 1999.
9. (a) Tomioka, K.; Inoue, I.; Shindo, M.; Koga, K. *Tetrahedron Lett.* **1990**, *31*, 6681–6684; (b) Taniyama, D.; Hasegawa, M.; Tomioka, K. *Tetrahedron Lett.* **2000**, *41*, 5533–5536; (c) Hasegawa, M.; Taniyama, D.; Tomioka, K. *Tetrahedron* **2000**, *56*, 10153–10158.
10. These amines are commercially available except **10b**, which was prepared according to the reported procedure. (a) Rai, R.; Katzenellenbogen, J. A. *J. Med. Chem.* **1992**, *35*, 4297–4305; (b) Stack, D. E.; Hill, A. L.; Diffendaffer, C. B.; Burns, N. M. *Org. Lett.* **2002**, *4*, 4487–4490.
11. The use of 3 equiv of lithium amide gives the comparable level of selectivity with the reaction in the presence of TMSCl.
12. Davies, S. G.; Garrido, N. M.; Ichihara, O.; Walters, I. A. S. *J. Chem. Soc., Chem. Commun.* **1993**, 1153–1155.
13. (a) Drey, C. N. C. *Chemistry and Biochemistry of the Amino Acids*; Chapman and Hall: London, 1985; (b) Hecht, S. M. *Acc. Chem. Res.* **1986**, *19*, 383–391; (c) *Enantioselective Synthesis of β-Amino Acids*; Juaristi, E., Ed.; Wiley-VCH: New York, 1997.
14. Recently reported is a fascinating asymmetric amination and its equivalent: (a) Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178–16179; (b) Hamashima, Y.; Somei, H.; Shimura, Y.; Tamura, T.; Sodeoka, M. *Org. Lett.* **2004**, *6*, 1861–1864; (c) Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 9188–9189.
15. Recently reported application of Davis protocol[6] to the asymmetric synthesis of a pharmaceutical by Merck group: Yasuda, N.; Hsiao, Y.; Jensen, M. S.; Rivera, N. R.; Yang, C.; Wells, K. M.; Yau, J.; Palucki, M.; Tan, L.; Dormer, P. G.; Volante, R. P.; Hughes, D. L.; Reider, P. J. *J. Org. Chem.* **2004**, *69*, 1959–1966.