doi:10.1246/cl.2011.320
Published on the web February 19, 2011

Editor's Choice

Enantioselective Synthesis Induced by Compounds with Chirality Arising from Partially Deuterated Methyl Groups in Conjunction with Asymmetric Autocatalysis

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Enantioselective synthesis has been achieved using chiral compounds arising from mono- and dideuterated methyl groups as chiral inducers in conjunction with asymmetric autocatalysis. The absolute configuration of the product was controlled by the small degree of chirality generated by the difference between the partially deuterated methyl groups (CDH_2 and CD_2H) and the non-deuterated methyl group (CH_3) in *N*-benzoyl-α-methylalanine.

It is known that substitution of atoms for their isotopes often generates chiral compounds.[1,2] However, enantioselective synthesis using chiral compounds arising from isotope substitution is a challenging problem.[3–5] There have been a few reports on enantioselective synthesis using chiral compounds arising from deuterium substitution.[3] However, the enantiomeric excess (ee) of the products induced by the deuterated chiral compounds was very low because the isotopes had almost the same electronic and steric structures.[6]

We studied asymmetric autocatalysis of pyrimidyl alkanols,[7–9] in which a chiral product acts as the chiral catalyst for its own production with a significant enhancement of the ee.[10] Asymmetric autocatalysis enables an amplification of the ee from extremely low ee values (ca. 0.00005% ee) to >99.5% ee during three consecutive reactions.[11,12] Chiral compounds act as chiral initiators of asymmetric autocatalysis to afford highly enantioenriched pyrimidyl alkanols with an absolute configuration corresponding to the chirality of the initiator.[13]

We have previously reported on asymmetric autocatalysis using chiral compounds arising from a deuterium substitution of the enantiotopic hydrogen atoms, i.e., for benzyl alcohol-α-*d* and glycine-α-*d*.[14] However, in these cases, the ratio of the exact mass difference between deuterium (D) and hydrogen (H) is relatively large, i.e., 99.8% of the mass of an H atom. On the other hand, the difference in mass ratio between the (partially) deuterated methyl groups (CDH_2, CD_2H, and CD_3) and CH_3 is much smaller, as shown in Figure 1. It is noteworthy that the exact difference in mass is only 6.7% between monodeuterated CDH_2 and CH_3 groups. Thus, asymmetric induction mediated using chiral compounds arising from partially deuterated enantiotopic methyl groups is a challenge. To the best of our knowledge, there have been no reports on enantioselective synthesis induced by chiral compounds arising from partially deuterated enantiotopic methyl groups.

Here, we report on a highly enantioselective synthesis induced by *N*-benzoyl-α-methyl-d_1-alanine and *N*-benzoyl-α-methyl-d_2-alanine in conjunction with asymmetric autocatalysis (Chart 1 and Scheme 1). We chose *N*-benzoyl-α-methylalanine (**1**) as our model compound, and chiral (*S*) and (*R*)-d_{1-3}-**1** having deuterated methyl groups were then synthesized.[15]

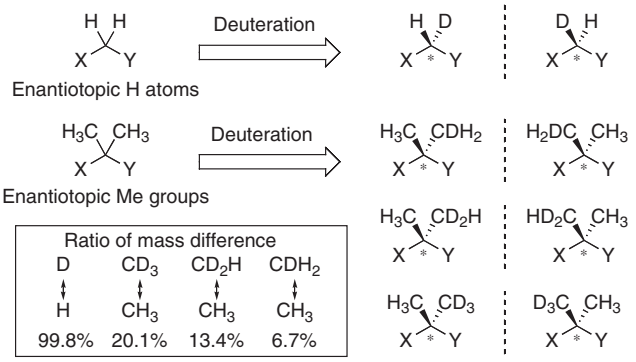


Figure 1. Generation of asymmetric carbon atom by deuterium substitution of enantiotopic hydrogen atoms and methyl groups.

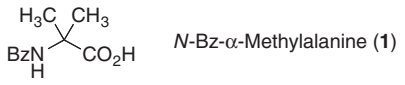
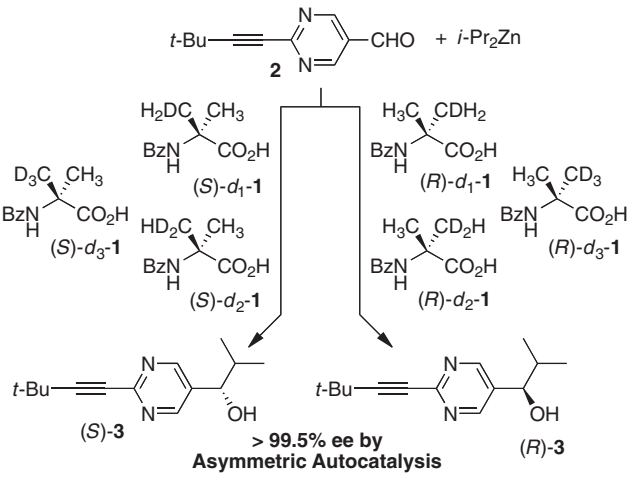


Chart 1.



Scheme 1. Asymmetric autocatalysis triggered by isotopically (D/H) chiral *N*-benzoyl-α-methylalanine (**1**).

When pyrimidine-5-carbaldehyde **2** and diisopropylzinc (*i*-Pr_2Zn) were reacted in the presence of (*R*)-*N*-benzoyl-α-methyl-d_1-alanine **1**, (*R*)-pyrimidyl alkanol **3** with an 87% ee was obtained (Table 1, Entry 1). On the other hand, the reaction using (*S*)-d_1-**1** afforded (*S*)-**3** with an 85% ee (Entry 2). The correlation between the absolute configurations of the chiral initiator and alkanol **3** produced exhibited a nice reproducibility, i.e., (*R*)- and (*S*)-d_1-**1** afforded (*R*)- and (*S*)-**3** (84%–90% ee), respectively (Entries 3 and 4). When a smaller amount

Table 1. Asymmetric autocatalysis induced by chiral *N*-benzoyl-α-methylalanine arising from deuterium substitution

Entry[a]	Initiator[b]	5-Pyrimidyl alkanol **3**		
		Yield[c]/%	ee[d]/%	Config.
1	(*R*)-d_1-**1**	85	87	*R*
2	(*S*)-d_1-**1**	80	85	*S*
3	(*R*)-d_1-**1**	87	84	*R*
4	(*S*)-d_1-**1**	92	90	*S*
5	(*R*)-d_1-**1**[e]	83	69	*R*
6	(*S*)-d_1-**1**[e]	85	55	*S*
7[f]	(*R*)-d_1-**1**	95	>99.5	*R*
8[f]	(*S*)-d_1-**1**	97	>99.5	*S*
9	(*S*)-d_2-**1**	90	80	*S*
10	(*R*)-d_2-**1**	94	88	*R*
11	(*S*)-d_2-**1**	92	84	*S*
12	(*S*)-d_2-**1**	87	86	*S*
13[f]	(*R*)-d_2-**1**	94	>99.5	*R*
14[f]	(*S*)-d_2-**1**	99	>99.5	*S*
15	(*R*)-d_3-**1**	92	91	*R*
16	(*S*)-d_3-**1**	96	89	*S*
17	(*R*)-d_3-**1**	76	77	*R*
18	(*S*)-d_3-**1**	85	86	*S*
19	(*R*)-d_3-**1**	90	87	*R*
20	(*S*)-d_3-**1**	90	82	*S*
21[f]	(*R*)-d_3-**1**	97	>99.5	*R*
22[f]	(*S*)-d_3-**1**	98	>99.5	*S*

[a]Unless otherwise noted, asymmetric autocatalysis was performed as follows. A 1 M toluene solution of *i*-Pr_2Zn (0.075 mL) was added to 0.5 mL of (*R*)-d_1-**1** (0.025 mmol) in toluene at 0 °C. After the mixture was stirred for a period of 30 min at 0 °C, a toluene solution (0.2 mL) of pyrimidine-5-carbaldehyde **2** (4.7 mg, 0.025 mmol) was added to the mixture over a period of 1.5 h. The mixture was then stirred for 12 h, and toluene (1.1 mL), a 1 M toluene solution of *i*-Pr_2Zn (0.2 mL) and aldehyde **2** (18.8 mg, 0.10 mmol) in toluene (0.5 mL) were added. After a period of 3 h, toluene (7.2 mL), a 1 M toluene solution of *i*-Pr_2Zn (0.80 mL), and **2** (75.3 mg, 0.4 mmol) were then added over a period of 1 h at 0 °C, and the mixture was stirred for a period of 1.5 h. The reaction was quenched using a mixture of 30% aqueous ammonia and a saturated aqueous ammonium chloride (2/1, v/v) solution (10 mL). The mixture was extracted three times using ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated in vacuo. Purification of the residue using silica gel column chromatography (hexane/ethyl acetate = 3/1, v/v) gave (*R*)-5-pyrimidyl alkanol **3** with an 85% ee in an 87% yield. [b]As to the ee of the initiators, see the Supporting Information and refs. 14b, 15, and 16. [e]Isolated yield. [d]The ee value was determined by HPLC on a chiral stationary phase (Daicel Chiralcel IB). [e]Reduced amount of chiral initiator (0.0025 mmol) was submitted to the reaction. [f]Additional rounds of asymmetric autocatalysis were performed for the purpose of further amplification of ee. See also ref. 11.

(10 mol %) of (*R*)- or (*S*)-d_1-**1** was used as the chiral initiator, the same stereochemical correlation was observed, although the ee of the product was moderate (Entries 5 and 6). It should be noted that further asymmetric autocatalysis amplified the ee to >99.5% ee (Entries 7 and 8).

In the same manner, (*R*)- and (*S*)-*N*-benzoyl-α-methyl-d_2-alanine **1** afforded the (*R*)- and (*S*)-pyrimidyl alkanols **3** with a high ee (80%–88% ee), respectively (Entries 9–12). Again, the ee reached >99.5% after an additional asymmetric autocatalysis (Entries 13 and 14). In addition, *N*-benzoyl-α-methyl-d_3-alanines, (*R*)- and (*S*)-d_3-**1**, were employed as the chiral initiators. The same correlation was observed as with the *d* and d_2 analogs (Entries 15–22).

In summary, we have demonstrated the first example of asymmetric induction, in conjunction with asymmetric autocatalysis, using chiral compounds arising from the partial deuteration of enantiotopic methyl groups.

This work was supported by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science.

References and Notes

1 D. Arigoni, E. L. Eliel, *Top. Stereochem.* **1969**, *4*, 127.
2 B. Barabás, L. Caglioti, K. Micskei, C. Zucchi, G. Pályi, *Origins Life Evol. Biospheres* **2008**, *38*, 317.
3 a) H. Pracejus, *Tetrahedron Lett.* **1966**, *7*, 3809. b) A. Horeau, A. Nouaille, K. Mislow, *J. Am. Chem. Soc.* **1965**, *87*, 4957.
4 a) For an elegant example of spectroscopic chiral recognition of a compound due to partially deuterated methyl groups, see: J. Haesler, I. Schindelholz, E. Riguet, C. G. Bochet, W. Hug, *Nature* **2007**, *446*, 526. b) R. N. Harris, III, P. Sundararaman, C. Djerassi, *J. Am. Chem. Soc.* **1983**, *105*, 2408.
5 Formation of helical polymer using deuterium-labeled chiral pendant: M. M. Green, J.-W. Park, T. Sato, A. Teramoto, S. Lifson, R. L. B. Selinger, J. V. Selinger, *Angew. Chem., Int. Ed.* **1999**, *38*, 3138.
6 a) L. S. Bartell, E. A. Roth, C. D. Hollowell, K. Kuchitsu, J. E. Young, *J. Chem. Phys.* **1965**, *42*, 2683. b) L. S. Bartell, R. R. Roskos, *J. Chem. Phys.* **1966**, *44*, 457.
7 a) C. Bolm, F. Bienewald, A. Seger, *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1657. b) M. Avalos, R. Babiano, P. Cintas, J. L. Jiménez, J. C. Palacios, *Chem. Commun.* **2000**, 887. c) J. Podlech, T. Gehring, *Angew. Chem., Int. Ed.* **2005**, *44*, 5776. d) L. Caglioti, C. Zucchi, G. Pályi, *Chim. Oggi* **2005**, *23*, 38. e) I. D. Gridnev, *Chem. Lett.* **2006**, *35*, 148. f) B. Barabás, J. Tóth, G. Pályi, *J. Math. Chem.* **2010**, *48*, 457.
8 a) K. Soai, T. Shibata, I. Sato, *Acc. Chem. Res.* **2000**, *33*, 382. b) K. Soai, T. Shibata, I. Sato, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1063. c) K. Soai, T. Kawasaki, *Chim. Oggi* **2009**, *27* (Suppl), 3. d) T. Kawasaki, K. Soai, *J. Fluorine Chem.* **2010**, *131*, 525.
9 a) I. D. Gridnev, J. M. Serafimov, J. M. Brown, *Angew. Chem., Int. Ed.* **2004**, *43*, 4884. b) D. G. Blackmond, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5732. c) J. R. Islas, D. Lavabre, J.-M. Grevy, R. H. Lamoneda, H. R. Cabrera, J.-C. Micheau, T. Buhse, *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 13743. d) Y. Saito, H. Hyuga, *J. Phys. Soc. Jpn.* **2004**, *73*, 33. e) G. Lente, *J. Phys. Chem. A* **2005**, *109*, 11058. f) L. Schiaffino, G. Ercolani, *Angew. Chem., Int. Ed.* **2008**, *47*, 6832. g) K. Micskei, G. Rábai, E. Gál, L. Caglioti, G. Pályi, *J. Phys. Chem. B* **2008**, *112*, 9196. h) I. Sato, D. Omiya, H. Igarashi, K. Kato, Y. Ogi, K. Tsukiyama, K. Soai, *Tetrahedron: Asymmetry* **2003**, *14*, 975. i) G. Pályi, K. Micskei, L. Zékány, C. Zucchi, L. Caglioti, *Magyar Kém. Lapja* **2005**, *60*, 17.
10 K. Soai, T. Shibata, H. Morioka, K. Choji, *Nature* **1995**, *378*, 767.
11 I. Sato, H. Urabe, S. Ishiguro, T. Shibata, K. Soai, *Angew. Chem., Int. Ed.* **2003**, *42*, 315.
12 cf. L. Caglioti, K. Micskei, G. Pályi, *Viva Orig.* **2007**, *35*, 82.
13 a) K. Soai, S. Osanai, K. Kadowaki, S. Yonekubo, T. Shibata, I. Sato, *J. Am. Chem. Soc.* **1999**, *121*, 11235. b) T. Kawasaki, K. Jo, H. Igarashi, I. Sato, M. Nagano, H. Koshima, K. Soai, *Angew. Chem., Int. Ed.* **2005**, *44*, 2774. c) T. Kawasaki, K. Suzuki, Y. Hakoda, K. Soai, *Angew. Chem., Int. Ed.* **2008**, *47*, 496. d) T. Kawasaki, Y. Hakoda, H. Mineki, K. Suzuki, K. Soai, *J. Am. Chem. Soc.* **2010**, *132*, 2874.
14 a) I. Sato, D. Omiya, T. Saito, K. Soai, *J. Am. Chem. Soc.* **2000**, *122*, 11739. b) T. Kawasaki, M. Shimizu, D. Nishiyama, M. Ito, H. Ozawa, K. Soai, *Chem. Commun.* **2009**, 4396. c) For the asymmetric autocatalysis triggered by carbon isotope chiral compounds see: T. Kawasaki, Y. Matsumura, T. Tsutsumi, K. Suzuki, M. Ito, K. Soai, *Science* **2009**, *324*, 492.
15 D. Seebach, A. Fadel, *Helv. Chim. Acta* **1985**, *68*, 1243.
16 Supporting Information is available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

