Highly Enantioselective Synthesis Induced by Chiral Primary Alcohols Due to Deuterium Substitution

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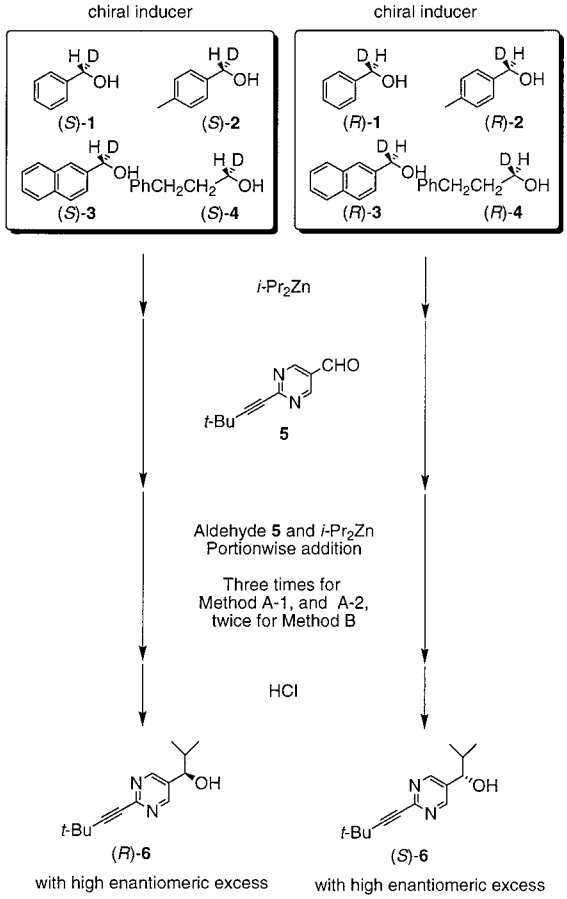
Steric isotope effects have attracted considerable attention.[1] For example, a structural steric isotope effect in deuterated tetracyanoanthraquinodimethane,[2a] conformational kinetic isotope effects in the racemization of a 9,10-dihydrophenanthrene derivative[2b] and in the flipping of [2.2]metaparacyclophanes,[2c] and a steric isotope effect in the reduction of a 4-piperidone derivative have been reported.[2d]

Chiral compounds whose chirality is due to the replacement of hydrogen by deuterium are important from the standpoint of organic stereochemistry and biochemistry.[3] The chirality of these enantiomers is mainly due to the very small difference between the lengths of carbon−deuterium and carbon−hydrogen bonds; the time-averaged carbon−deuterium bond length (0.1099 nm) is shorter than the carbon−hydrogen bond by only 0.0004 nm.[4] Thus, unlike other usual enantiomers whose chirality is due to the difference in the number of protons in the atomic nucleus, these isotopic enantiomers are considered to show only very small differences in asymmetric reactions and recognition. In fact, isotopic enantiomers were only quite recently separated analytically using HPLC with a chiral stationary phase (csp).[5]

On the other hand, despite the recent advances in asymmetric catalysis,[6] it is unclear whether any isotopic enantiomer can act as a chiral inducer in highly enantioselective synthesis. The enantioselectivities that have been reported so far in asymmetric synthesis[7] and kinetic resolution[8] induced by isotopic enantiomers have been extremely low. Enantioselective addition of MeOH to a ketene in the presence of a chiral deuterated quinuclidine derivative gave a product with an optical purity of only 0.13% based on the optical rotation, and only one enantiomer of the chiral inducer was investigated.[7] Kinetic resolution of racemic α-phenylbutyric anhydride with enantiomerically deuterated alcohols gives, after hydrolysis, α-phenylbutyric acid with an optical purity of only 0.1−0.6%.[8] Thus, highly enantioselective synthesis induced by isotopic enantiomers is a challenging problem.

We report here an unprecedented highly enantioselective synthesis of a chiral compound induced by the isotopic enantiomer of primary alcohol-α-*d*.

Scheme 1. Enantioselective Addition of Diisopropylzinc to Aldehyde 5 Using Chiral α-Deuterated Alkohols as Chiral Inducers



2-(*tert*-Butylethynyl)pyrimidine-5-carbaldehyde **5**[9] was reacted with diisopropylzinc (*i*-Pr_2Zn) in the presence of chiral deuterated alcohol (Scheme 1).[10] The results are shown in Table 1. When aldehyde **5** was reacted with *i*-Pr_2Zn in the presence of chiral (*S*)-benzyl alcohol-α-*d* **1** (>95% ee, 1.6 mol % against the total amount of aldehyde **5**) and aldehyde **5** and *i*-Pr_2Zn were successively added in three portions, (*R*)-2-pyrimidyl alkanol **6** with 96% ee was obtained in an isolated yield of 95% (Method A-1, Table 1, run 1). On the other hand, in the presence of (*R*)-**1** (>95% ee) instead of (*S*)-**1**, (*S*)-2-pyrimidyl alkanol **6** with 95% ee was obtained in 98% yield (run 2). Thus, (*S*)- and (*R*)-benzyl alcohol-α-*d* **1** acted as chiral inducers to give (*R*)- and (*S*)-pyrimidyl alkanol **6** with high ee's, respectively.

Even in the presence of a decreased amount of (*S*)- or (*R*)-**1** (0.5 mol % relative to the total amount of **5**), (*R*)-**6** and (*S*)-**6** with 93% ee were obtained in isolated yields of 98 and 95%, respectively (Method A-2, runs 3 and 4). Thus, the (*S*)- and (*R*)-enantiomers of **1** based on the substitution of hydrogen with deuterium act as chiral inducers in the highly enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **5**.

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(10) (*S*)-Alcohols-α-*d* **1**−**4** were synthesized by enantioselective reduction of the corresponding aldehydes-1-*d* using (*R*)-2-methyl-CBS-oxazaborolidine [Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275−6278]. (*R*)-Alcohols were prepared by Mitsunobu inversion of the resulting (*S*)-alcohols [Mitsunobu, O. *Synthesis* **1981**, 1−28]. The ee's of (*S*)- and (*R*)-alcohols were determined to be >95% by NMR analyses of their (*S*)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) esters. Absolute configurations of **2**−**4** were assigned by analogy to **1**.

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Table 1. Enantioselective Synthesis of Pyrimidyl Alkanol **6** Using Chiral α-Deuterated Alcohols as Chiral Inducers

			pyrimidyl alkanol **6**	
run[a]	chiral α-deuterated alcohol RCHDOH (ee (%))	method[b,c]	isolated yield (%)	ee (%) (configuration)[d]
1	(*S*)-PhCHDOH **1** (>95)	A-1	95	96 (*R*)
2	(*R*)-**1** (>95)	A-1	98	95 (*S*)
3	(*S*)-**1** (>95)	A-2	98	93 (*R*)
4	(*R*)-**1** (>95)	A-2	95	93 (*S*)
5	(*S*)-**1** (56)	A-1	90	91 (*R*)
6	(*S*)-*p*-TolylCHDOH **2** (>95)	B	92	96 (*R*)
7	(*R*)-**2** (>95)	B	94	95 (*S*)
8	(*S*)-2-NaphthylCHDOH **3** (>95)	B	96	95 (*R*)
9	(*R*)-**3** (>95)	B	92	90 (*S*)
10	(*R*)-**3** (>95)	A-1	96	92 (*S*)
11	(*S*)-$PhCH_2CH_2CHDOH$ **4** (>95)	A-1	98	94 (*R*)
12	(*R*)-**4** (>95)	A-1	95	92 (*S*)

[a] All of the experiments were reproducible. Reactions were carried out at 0 °C. [b] Molar ratio of Method A-1 (aldehyde **5** and *i*-Pr_2Zn were added in four portions), chiral α-deuterated alcohol: aldehyde **5** (total amount): *i*-Pr_2Zn (total amount) = 0.016:1.0:2.0; Method A-2 (aldehyde **5** and *i*-Pr_2Zn were added in four portions), 0.0045:1.0:2.0; Method B (aldehyde **5** and *i*-Pr_2Zn were added in three portions), 0.047:1.0:2.5. [c] Experimental procedure for **Method A-2** (Table 1, run 3): To a toluene solution (0.5 mL) of (*S*)-benzyl alcohol-α-*d* **1** (0.8 mg, 0.0075 mmol) was added a toluene solution (1.0 M) of *i*-Pr_2Zn (0.075 mmol) at 0 °C. A toluene (0.5 mL) solution of aldehyde **5** (4.7 mg, 0.025 mmol) was then added using a syringe at a rate of one drop per 30 s, and the mixture was stirred for 12 h at 0 °C. Toluene (1.6 mL), *i*-Pr_2Zn (0.2 mmol, 0.2 mL of 1.0 M toluene solution), and a toluene solution (1.0 mL) of aldehyde **5** (18.8 mg, 0.1 mmol) were added successively, and the reaction mixture was stirred for 3.5 h. Toluene (7.2 mL), *i*-Pr_2Zn (0.8 mmol, 0.8 mL of 1. 0 M toluene solution), and a toluene (2.0 mL) solution of aldehyde **5** (75.3 mg, 0.4 mmol) were then added successively, and the mixture was stirred at 0 °C for another 2.5 h. After the addition of toluene (22 mL), *i*-Pr_2Zn (2.0 mmol, 2.0 mL of 1. 0 M toluene solution), and a toluene solution (5.0 mL) of aldehyde **5** (188 mg, 1.0 mmol), the mixture was stirred for 2 h. The reaction was quenched with hydrochloric acid (1 M, 10 mL), and satd. aq. sodium hydrogen carbonate (30 mL) was then added. The mixture was filtered using Celite, and the filtrate was extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate and evaporated under reduced pressure. Purification of the residue by silica gel thin-layer chromatography (developing solvent, hexane:ethyl acetate = 2:1 v/v) gave (*R*)-pyrimidyl alkanol **6** with 93% ee in an isolate yield of 98% (348 mg). **Method A-1:** The same as Method A-2 except that the amount of chiral α-deuterated alcohol was 0.025 mmol. **Method B:** The same as Method A-1 except that the final addition of toluene (22 mL), *i*-Pr_2Zn (2.0 mmol, 2.0 mL of 1.0 M toluene solution), and aldehyde **5** (188 mg, 1.0 mmol) in Method A-1 was omitted. [d] ee was determined by HPLC analysis using a chiral stationary phase (Chiralcel OD).

The generality of the effect of isotopic enantiomers in chiral initiation was exemplified using chiral tolyl methanol-α-d_1 **2**, 2-naphthyl methanol-α-d_1 **3** and 3-phenylpropanol-α-d_1 **4**. As shown in Table 1, (*S*)-tolyl methanol-α-d_1 **2** (>95% ee) and (*R*)-**2** induced the formation of (*R*)-**6** with 96% ee and (*S*)-**6** with 95% ee, respectively (Method B, runs 6 and 7). The enantioselective alkylation of **5** in the presence of (*S*)-2-naphthyl methanol **3** gave enantiomerically enriched (*R*)-**6** in 95% ee (run 7), while (*S*)-**6** with 90−92% ee was obtained in the presence of (*R*)-**3** (Methods B and A-1, runs 8−10). Even (*S*)-3-phenylpropanol-α-d_1 **4**, in which the asymmetric carbon atom is not bonded to the aromatic ring, acted as a chiral initiator to give (*R*)-**6** with 94% ee in a yield of 98% (run 11). On the other hand, (*S*)-**6** with 92% ee was obtained in 95% yield using (*R*)-**4** (run 12).

Furthermore, (*S*)-benzyl alcohol-α-d_1 **1**, with a moderate enantiomeric excess of 56%, acts as a chiral initiator in the enantioselective addition of *i*-Pr_2Zn to the aldehyde **5**, and pyrimidyl alkanol (*R*)-**6** with high ee (91%) was synthesized (run 5).

The very high enantiomeric excesses of the products in the above asymmetric reactions induced by chiral *primary* alcohols-α-d_1 may be explained as follows: (1) Chiral (*S*)- or (*R*)-α-deuterated alcohol readily forms chiral isopropylzinc alkoxide by reacting with *i*-Pr_2Zn. (2) The resulting isopropylzinc alkoxides of chiral (*S*)- or (*R*)-α-deuterated alcohols **1**−**4** act as chiral inducers in the enantioselective addition of *i*-Pr_2Zn to aldehyde **5**. (3) The isopropylzinc alkoxide of pyrimidyl alkanol with a certain (small) ee forms, and possesses the corresponding absolute configuration determined by the chiral inducer. (4) The ee of the isopropylzinc alkoxide of pyrimidyl alkanol increases during asymmetric autocatalysis,[11,12] and workup gives (*R*)- or (*S*)-pyrimidyl alkanol **6** with very high ee.

In summary, we have demonstrated a chemical process in which a small isotopic chirality based on the replacement of hydrogen in primary alcohols with deuterium induces chirality in the enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **5** to afford pyrimidyl alkanol **6** with very high ee. We believe that the present results are the first example of an isotopic chiral effect leading to significantly high enantiomeric excesses in enantioselective synthesis.[13]

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Supporting Information Available: Preparation and characterization data of α-deuterated chiral alcohols **1**−**4**. Representative procedure for the enantioselective addition of diisopropylzinc to aldehyde **5** induced by chiral α-deuterated alcohols (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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