

Asymmetric Induction

Asymmetric Autocatalysis: Triggered by Chiral Isotopomer Arising from Oxygen Isotope Substitution**

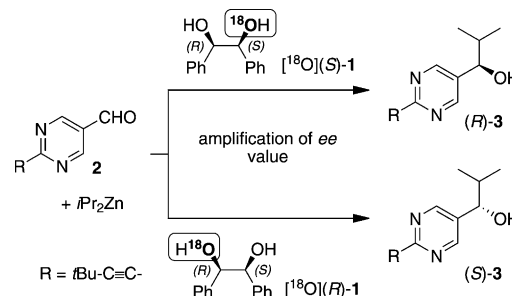
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The substitution of the atoms in the enantiotopic moiety of an achiral molecule by their isotopes makes the present molecule chiral.^[1,2] Isotopically labeled compounds^[3] have been used to elucidate structural information,^[3b] mechanisms of organic reactions,^[3c-e] and drug kinetics,^[3f] however, asymmetric synthesis using the chirality generated by isotope substitution alone is difficult because of the very low enantiomeric excess (*ee*) displayed when using deuterated chiral compounds as a source of chirality.^[4] Amplification effects of the helicity in the polyisocyanates^[5a] and supramolecular polymers^[5b] that results from hydrogen isotopes (D/H) have been reported. And discrimination of hydrogen isotope chirality using spectroscopic methods^[6] and HPLC analyses with a chiral stationary phase^[7] have been reported.

Recently, we have reported asymmetric autocatalysis with amplification of *ee* values^[8-11] that was triggered by chiral compounds resulting from hydrogen (D/H)^[12] and carbon isotope (¹³C/¹²C)^[13] substitutions. Meanwhile, the syntheses of chiral compounds resulting from oxygen isotope substitutions^[14] and oxygen kinetic isotope effects (KIEs)^[15] have been reported. However, to the best of our knowledge, there have been no reports of asymmetric synthesis or induction utilizing chiral compounds resulting from oxygen isotope substitution. Therefore, asymmetric autocatalysis initiated by chiral compounds arising from ¹⁸O/¹⁶O substitution is challenging.

We selected a *meso* compound as the oxygen isotope enantiomer (Scheme 1). Achiral *meso* hydrobenzoin forms chiral oxygen isotopomers **1** after ¹⁸O labeling of the hydroxy group in an enantioselective manner. These diols should be chiral only as a result of the oxygen isotope (¹⁸O/¹⁶O) substitution. The enantiomer whose ¹⁸O atom is bound to the *S*-configured carbon center is described as [¹⁸O](*S*)-**1**, while the opposite is described as [¹⁸O](*R*)-**1**.

Herein we report the first asymmetric induction by chiral compounds arising from oxygen isotope substitution in conjunction with asymmetric autocatalysis (Scheme 1). The



Scheme 1. Asymmetric autocatalysis in the presence of chiral isotopomer of [¹⁸O]**1**.

chiral compound created by oxygen isotope substitution serves as the chiral trigger of asymmetric autocatalysis to afford alkanol **3** with high *ee* values. The relationship between the absolute configurations of the chiral ¹⁸O-labeled hydrobenzoin ([¹⁸O]**1**) and the product alkanol **3** is reproducible.

The enantiomers of [¹⁸O]**1** were synthesized from chiral *trans*-stilbene oxide (**4**), which was obtained by resolution of its racemate by HPLC methods using a chiral stationary phase. The enantiomers of oxide **4** had *ee* values greater than 99.5% and were submitted to the epoxide-opening reaction using [¹⁸O]H₂O under basic reaction conditions (Figure 1A). By using 2-methoxyethanol as a cosolvent, the hydrolysis of the epoxide by [¹⁸O]H₂O proceeded stereoselectively to form the chiral [¹⁸O]**1** predominantly.

The enantioenrichment of the synthesized compound **1** was confirmed by ¹³C NMR spectroscopic analysis of its diastereomeric bis[(*S*)-MTPA] esters **6** and **7** (MTPA = α -methoxy- α -(trifluoromethyl)phenylacetyl; Figure 1B). The chemical shift differences for the pair of carbon atoms bound to normal and ¹⁸O-labeled groups can be observed. We have determined the *ee* value of [¹⁸O](*S*)-**1** and [¹⁸O](*R*)-**1** to be greater than 95%. This arises because a) the *ee* value of **4** is very high (>99.5% *ee*), and b) the epoxide-opening reaction proceeds in highly stereoselective manner. Additionally, the signals that would arise from the opposite form were not detected in the ¹³C NMR spectra of **6** and **7**. Several samples of chiral isotopomers **1** were prepared in a different reaction batches using different apparatus, and they were then submitted to the asymmetric autocatalysis reaction as chiral triggers.

We found that the isotopic chirality in [¹⁸O]**1** was successfully utilized as a chiral trigger of asymmetric autocatalysis (Table 1). When *i*Pr₂Zn addition to the pyrimidine-5-carbaldehyde **2** was performed in the presence of [¹⁸O](*S*)-**1**^[6] that was synthesized from the resolved **4**, the enantioenriched (*R*)-**3** was formed (entry 1). When [¹⁸O](*R*)-**1** was used as the

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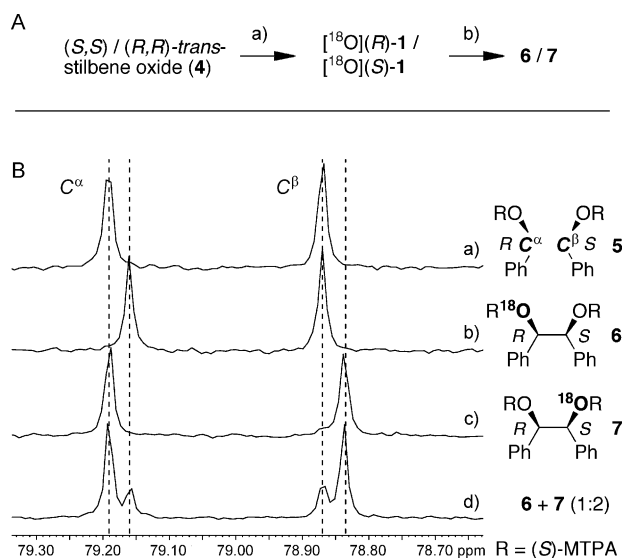


Figure 1. Synthesis of ^{18}O -(*R*)-**1** and ^{18}O -(*S*)-**1**. A) Enantioselective synthesis of ^{18}O -labeled hydrobenzoin **1**. a) Na^{18}OH , H_2^{18}O , 2-methoxyethanol, 95°C (46%, d.r. = 100:0); b) (*R*)-(-)-MTPACl, DMAP, pyridine. B) ^{13}C NMR (150 MHz, $[\text{D}_8]\text{THF}$) spectra of bis[(*S*)-MTPA] esters **5–7** without apodization. a) Compound **5**: derived from nonlabeled *meso*-**1** (signal-to-noise (S/N) ratio for these signals is ca. 22); b) compound **6**: derived from ^{18}O -(*R*)-**1** (S/N \approx 26); c) compound **7**: derived from ^{18}O -(*S*)-**1** (S/N \approx 28); and d) 1:2 mixture of **6** and **7** (S/N \approx 35). DMAP = 4-dimethylaminopyridine.

chiral trigger, (*S*)-**3** was obtained with 89% *ee* (entry 2). These stereochemical relationships between ^{18}O -labeled **1** and the resulting alkanol **3** were highly reproducible using samples No. 1 and 2 (entries 3 and 4), which were from the same batches as those used in entries 1 and 2, respectively. When other synthetic samples of compound ^{18}O **1** (samples No. 3–10; prepared using different reaction apparatus) were used in 22 additional experiments, the same stereochemical correlation results were obtained (entries 5–12 and Table S1, entries 1–14 in the Supporting Information).

To further establish reproducibility, we carried out an additional 24 asymmetric autocatalyses in the presence of chiral isotopically labeled **1**, which was prepared by H_2^{18}O hydrolysis of (*S,S*)- and (*R,R*)-**4** derived from commercially available (*S,S*)- and (*R,R*)-hydrobenzoin, respectively (entries 13–17 and Table S1, entries 15–33 in the Supporting Information). The results show the same induction sense without exception; that is, ^{18}O -(*S*)-**1** acted as a chiral trigger for (*R*)-**3** and ^{18}O -(*R*)-**1** promoted the formation of enantioenriched (*S*)-**3**. The direction of the asymmetric induction is correlated strongly with the chirality of ^{18}O -(*S*)-**1** and ^{18}O -(*R*)-**1**. Notably, the sequential increase in the *ee* value of **3** was measured through sequential addition of **2** (entry 17); the enantioenrichment of (*R*)-**3** after the initial addition of aldehyde **2** and $i\text{Pr}_2\text{Zn}$ in the presence of ^{18}O -(*S*)-**1** was below the detectable level,^[17] and then after two consecutive reactions^[8b] the *ee* value was amplified to 87% *ee*. Therefore, the enantioenrichment of the product **3** is enhanced by the addition of aldehyde **2** and $i\text{Pr}_2\text{Zn}$.

These results show clearly that the extremely small chiral effect caused by the oxygen isotope substitution of **1**^[18] could

Table 1: Enantioselective synthesis of 5-pyrimidyl alkanol **3** initiated by ^{18}O **1**.

Entry ^[a]	Sample No. ^[b]	Chiral trigger ^[c]	5-Pyrimidyl alkanol 3 yield [%] ^[d]	<i>ee</i> [%] ^[e]	config.
Series I ^[f]					
1	1	^{18}O -(<i>S</i>)- 1	97	97	<i>R</i>
2	2	^{18}O -(<i>R</i>)- 1	96	89	<i>S</i>
3	1	^{18}O -(<i>S</i>)- 1	85	93	<i>R</i>
4	2	^{18}O -(<i>R</i>)- 1	93	91	<i>S</i>
5	3	^{18}O -(<i>S</i>)- 1	82	93	<i>R</i>
6	4	^{18}O -(<i>R</i>)- 1	94	96	<i>S</i>
7	5	^{18}O -(<i>S</i>)- 1	93	94	<i>R</i>
8	6	^{18}O -(<i>R</i>)- 1	92	93	<i>S</i>
9	7	^{18}O -(<i>S</i>)- 1	93	89	<i>R</i>
10	8	^{18}O -(<i>R</i>)- 1	93	95	<i>S</i>
11	9	^{18}O -(<i>S</i>)- 1	93	85	<i>R</i>
12	10	^{18}O -(<i>R</i>)- 1	93	77	<i>S</i>
Series II ^[g]					
13	11	^{18}O -(<i>S</i>)- 1	92	97	<i>R</i>
14	12	^{18}O -(<i>R</i>)- 1	99	98	<i>S</i>
15	13	^{18}O -(<i>S</i>)- 1	91	90	<i>R</i>
16	14	^{18}O -(<i>R</i>)- 1	90	92	<i>S</i>
17 ^[h]	15	^{18}O -(<i>S</i>)- 1	92	87	<i>R</i>

[a] The molar ratios used were ^{18}O **1**/2/ $i\text{Pr}_2\text{Zn}$ = 0.05:1.05:2.2. [b] Each sample of isotopically chiral hydrobenzoin **1** was prepared in a different reaction batch using different apparatus. [c] The *ee* value of **1** was > 95% *ee*. See also Figure 1. [d] Yield of isolated product. [e] The *ee* value was determined by HPLC using a chiral stationary phase. [f] Chiral initiators **1** were prepared from resolution of **4** using HPLC with a chiral stationary phase. [g] Chiral triggers ^{18}O **1** were prepared by hydrolysis of **4**, which was derived from commercially available (*S,S*)- and (*R,R*)-hydrobenzoin (see the Supporting Information). [h] The *ee* values of the product **3** were below the detectable level^[17] (after the initial dropwise addition of **2** and $i\text{Pr}_2\text{Zn}$); 42% *ee* (after the second addition), and then 87% *ee* (after the third addition).

be responsible for the initial enantioselection of the addition of $i\text{Pr}_2\text{Zn}$ to aldehyde **2** to induce the small bias in the *ee* value of the isopropylzinc alkoxide of **3**. The enantiomeric imbalance could be enhanced to achieve high *ee* values by the subsequent asymmetric autocatalysis that leads to amplification of the *ee* value. The absolute configuration of product **3** was correlated to that of the chiral oxygen isotopomer **1**.

In summary, we have demonstrated the first example of asymmetric induction, in conjunction with asymmetric autocatalysis, using chiral compounds arising from oxygen isotope substitution. The oxygen isotope chirality can be amplified to deliver enantiomerically enriched pyrimidyl alkanol **3** by asymmetric autocatalysis, which is a highly sensitive reaction for amplifying the extremely small chiral influence that arises from ^{16}O and ^{18}O substitution.

Experimental Section

Asymmetric autocatalysis in the presence of ^{18}O **1:** A 1M toluene solution of $i\text{Pr}_2\text{Zn}$ (0.2 mL, 0.2 mmol) was added to a toluene (1.0 mL) solution of ^{18}O -(*R*)-**1** (0.05 mmol) at 0°C . After the mixture was stirred for 30 min, a toluene (0.25 mL) solution of aldehyde **2** (9.4 mg, 0.05 mmol) was added to the mixture over a period of 1 h. The mixture was then stirred for 12 h, after which toluene (0.8 mL), a 1M toluene solution of $i\text{Pr}_2\text{Zn}$ (0.4 mL, 0.4 mmol), and **2** (37.6 mg, 0.2 mmol) in toluene (1.0 mL) were added over a period of 1 h. After

a period of 2 h, toluene (7.2 mL), a 1 M toluene solution of $i\text{Pr}_2\text{Zn}$ (1.6 mL, 1.6 mmol), and a toluene (6.0 mL) solution of **2** (150.6 mg, 0.8 mmol) were then added over a period of 1 h at 0 °C, and the mixture was stirred for 2 h. The reaction was quenched using a mixture of 30% aqueous ammonia and a saturated aqueous ammonium chloride (1/1, *v/v*) solution (10 mL). The mixture was extracted 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 (*n*-hexane:ethyl acetate = 2:1) gave 5-pyrimidyl alkanol **3**. The *ee* value was determined by HPLC analysis on a chiral stationary phase (Daicel Chiralcel IB: 4.6 × 250 mm, 254 nm UV detector, RT, 5% 2-propanol in hexane, 1.0 mL min⁻¹, retention time: 10.9 min for (*S*)-**3** and 15.5 min for (*R*)-**3**).

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- [16] It is known that the reaction between diethylzinc and alcohol forms ethylzinc alkoxide (EtZnOR) (See: T. Tsuruta, M. Ishimori, *Kogyo Kagaku Zasshi* **1963**, *66*, 1477–1483) at 0 °C to RT based on the evolution of ethane (M. Kitamura, S. Okada, S. Suga, R. Noyori, *J. Am. Chem. Soc.* **1989**, *111*, 4028–4036). When *meso* hydrobenzoin was treated with an excess amount of Et₂Zn, the evolution of one molar equivalent of ethane was observed (see the Supporting Information). Thus, it is reasonable to consider that mono-isopropylzinc alkoxide (see also Refs. [11a–f]) of **1** is formed from **1** and $i\text{Pr}_2\text{Zn}$.
- [17] The observed *ee* value of (*R*)-**3** was 0.19% as determined by HPLC analysis. However, because of the detection level of the HPLC instrument, an *ee* value below 1% may be more reasonably categorized as being below the detectable level.
- [18] Our working hypothesis is as follows: There may be a slight difference in the ratio of the mono-isopropylzinc alkoxide of **1** formed from the ¹⁸O-labeled hydroxy group and nonlabeled hydroxy group that results from the oxygen kinetic isotope effect (see also Ref. [15]). Thus, we postulate that this small difference would be one of the reasons for the initial induction of enantiomeric imbalance in asymmetric autocatalysis.