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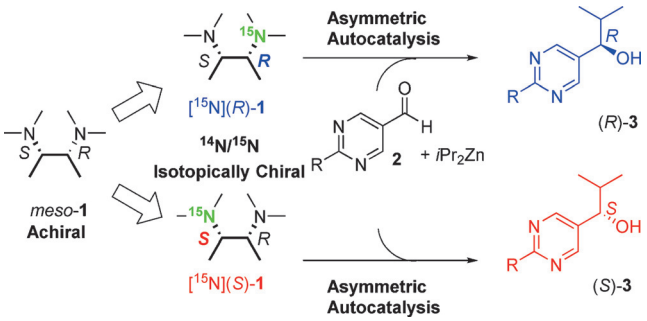
Asymmetric Induction by a Nitrogen $^{14}N/^{15}N$ Isotopomer in Conjunction with Asymmetric Autocatalysis

Arimasa Matsumoto, Hanae Ozaki, Shunya Harada, Kyohei Tada, Tomohiro Ayugase, Hitomi Ozawa, Tsuneomi Kawasaki, and Kenso Soai**

Abstract: *Chirality arising from isotope substitution, especially with atoms heavier than the hydrogen isotopes, is usually not considered a source of chirality in a chemical reaction. An N^2,N^2,N^3,N^3-tetramethyl-2,3-butanediamine containing nitrogen ($^{14}N/^{15}N$) isotope chirality was synthesized and it was revealed that this isotopically chiral diamine compound acts as a chiral initiator for asymmetric autocatalysis.*

Most of the chemical elements have stable isotopes. Isotope-substituted compounds (isotopomers) have almost the same chemical reactivity, isotope substitution and isotope effect, therefore they are widely used for studies of reaction mechanisms and tracing compounds.[1] However, isotope substitution sometimes breaks the molecular symmetry and produces hidden chirality in usually achiral molecules. Usually, this hidden chirality does not receive much attention because the difference between these isotopically chiral compounds is very small and negligible in asymmetric induction. Although the chirality arising from isotope substitution was discussed after the finding of stable isotopomers,[2–4] the isotope effect in chirality has mainly been studied on hydrogen isotopes because the almost double relative mass ratio of H and D produces relatively large isotope effects compared with other element isotopomers.[5] Thus, chirality induction in a reaction arising from heavier atoms[6] is a highly challenging and interesting topic, especially in the study of the origin of homochirality.[7]

We have been studying asymmetric autocatalysis of pyrimidyl alkanol,[8] which causes significant amplification of enantiomeric excess (*ee*) during the progress of a reaction. This reaction can recognize the various chiral environments[9] and attracts wide attention from the viewpoint of symmetry breaking[10] and its unique reaction mechanism.[11] Recently, we demonstrated that a subtle difference of isotopic chirality can induce asymmetric induction in an asymmetric autocatalysis reaction.[12] Chiral compounds (as the result of hydrogen (H/D),[13] carbon ($^{12}C/^{13}C$),[14] and oxygen ($^{16}O/^{18}O$)[15] isotopes) act as chiral initiators for asymmetric autocatalysis. Herein, we report the first example of asymmetric induction by chiral nitrogen ($^{14}N/^{15}N$) isotopomers with a smaller relative mass difference compared to previously reported isotopomers (Scheme 1).



Scheme 1. Asymmetric autocatalysis of pyrimidyl alkanol **3** triggered by a nitrogen ($^{14}N/^{15}N$) isotopically chiral diamine.

Nitrogen is one of the abundant atoms in the construction of various bioorganic molecules, and the coordinating ability of nitrogen atoms is widely exploited in various ligands. ^{15}N is a useful NMR-active isotope and the isotope ratio of $^{14}N/^{15}N$ is also used in the study of the origin of meteorites.[16] However, to our knowledge, isotopically chiral compounds arising from nitrogen isotope ($^{14}N/^{15}N$) substitution have not been synthesized and studied as a chiral initiator. Herein, we demonstrate the synthesis of compounds that are isotopically chiral by nitrogen isotope substitution and their chiral induction of asymmetric autocatalysis (Scheme 1).

We focused on an achiral diamine, *meso*-N^2,N^2,N^3,N^3-tetramethyl-2,3-butanediamine **1**. This diamine is a derivative of the frequently used achiral ligand, tetramethylethylenediamine, and has mirror symmetry. However, replacing one nitrogen atom with the ^{15}N isotope breaks the symmetry and affords the isotopically chiral diamine, [^{15}N](*S*)-**1** or [^{15}N](*R*)-**1**. We synthesized these isotopically chiral diamines **1** and

[*] Dr. A. Matsumoto, H. Ozaki, S. Harada, K. Tada, T. Ayugase, H. Ozawa, Prof. Dr. K. Soai
Department of Applied Chemistry, Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
E-mail: soai@rs.kagu.tus.ac.jp
matsumoto@rs.tus.ac.jp
Dr. A. Matsumoto, Prof. Dr. T. Kawasaki, Prof. Dr. K. Soai
Research Institute for Science and Technology
Tokyo University of Science
Kagurazaka, Shinjuku-ku, Tokyo 162-8601 (Japan)
Prof. Dr. T. Kawasaki
Department of Materials Science and Engineering
Faculty of Engineering, University of Fukui
Bunkyo, Fukui, 910-8507 (Japan)

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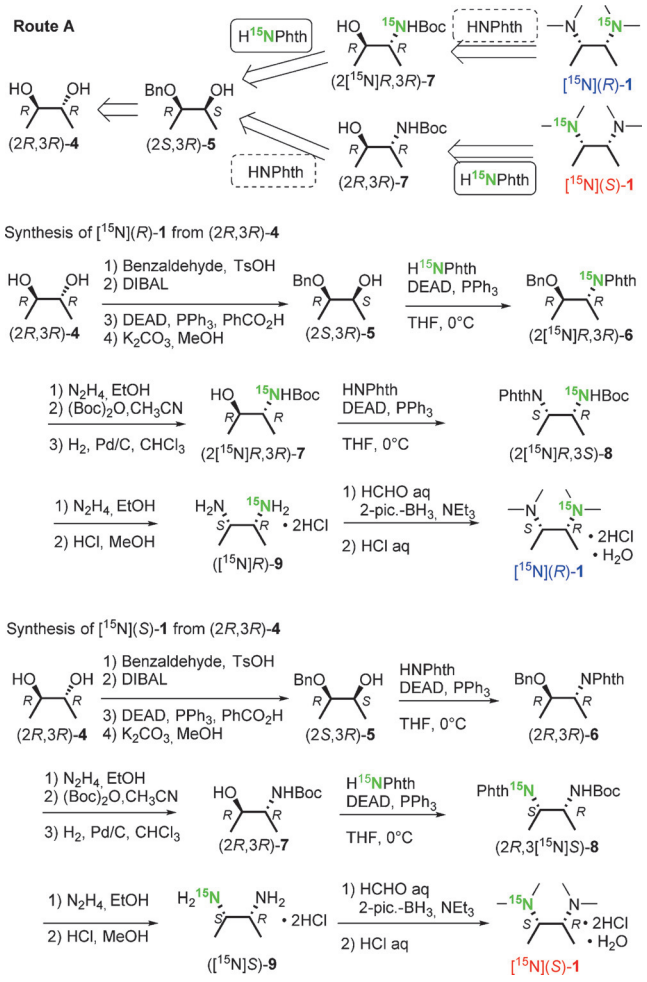
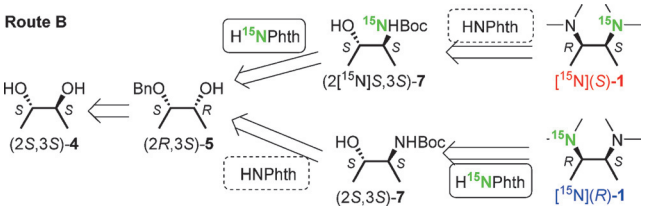
achieved asymmetric induction in the asymmetric autocatalytic reaction of pyrimidine-5-carbaldehyde **2** and iPr_2Zn to give pyrimidyl alkanol chiral compounds **3** with high *ee*.

The nitrogen ($^{14}N/^{15}N$) isotopically chiral diamine was synthesized from (2*R*,3*R*)-butane-2,3-diol **4** using ^{15}N-phthalimide as a ^{15}N source (Scheme 2). First, one alcohol in (2*R*,3*R*)-butane-2,3-diol **4** was protected with a benzyl group, followed by stereoinversion of the remaining alcohol by the Mitsunobu reaction to give the alcohol (2*S*,3*R*)-**5**. A Mitsunobu reaction of (2*S*,3*R*)-**5** with ^{15}N-phthalimide afforded ^{15}N-amine (2[^{15}N]*R*,3*R*)-**6**. After deprotection of the phthalimide by hydrazine, the obtained amine was protected with a *tert*-butoxycarbonyl (Boc) group. The benzyl group was removed with hydrogen and Pd/C to give (2[^{15}N]*R*,3*R*)-**7**. A Mitsunobu reaction with non-labeled phthalimide, followed by reduction and deprotection, afforded the isotopically chiral diamine [^{15}N](*R*)-**9**. The methylation reaction was performed with formaldehyde and picoline borane, and the tetramethylated diamine [^{15}N](*R*)-**1** isolated as the diammonium chloride salt and purified by recrystallization from ethanol.[17]



Scheme 2. Synthesis of nitrogen ($^{14}N/^{15}N$) isotopically chiral diamine **1** (Route A). Key: phthalimide (HNPhth), diisobutylaluminum hydride (DIBAL), diethyl azodicarboxylate (DEAD), 2-picoline-borane (2-pic.-BH_3).

The enantiomer of this diamine [^{15}N](*S*)-**1** was also synthesized from the (2*R*,3*R*)-butane-2,3-diol **4** starting material, by changing the order of ^{15}N-labeled and non-labeled phthalimide in the synthetic Scheme 2; that is, by introducing non-labeled phthalimide first and introducing ^{15}N-labeled phthalimide second. Thus, both enantiomers of [^{15}N]-**1** were synthesized in a stereoselective manner from the same (2*R*,3*R*)-butane-2,3-diol. By employing this procedure, preservation of chirality was assured even when chiral contaminants from (2*R*,3*R*)-butan-2,3-diol **4** or its derivative are present in the final diamine **1**. Therefore, even when chiral contaminants (instead of chiral diamine isotopomer **1**) trigger the asymmetric autocatalysis, pyrimidyl alkanol **3** with the same absolute configuration should be formed. Furthermore, to eliminate the possibility of chiral contamination from the synthetic route, we synthesized both [^{15}N](*S*)-**1** and [^{15}N](*R*)-**1** from the opposite enantiomer (2*S*,3*S*)-**4** (Scheme 3).



Scheme 3. Synthesis of nitrogen ($^{14}N/^{15}N$) isotopically chiral diamine from (2*S*,3*S*)-**4** (Route B).

Nitrogen isotope incorporation can be observed in the ^{13}C NMR spectrum. Non-labeled *meso*-tetramethylbutane-2,3-diamine **1** afforded one resonance for the 2,3-position of the carbon atom. In the case of ^{15}N-labeled diamine the observed ^{13}C NMR resonance resulted in two signals 1.5 C:0.5 C. It seems that there is a high-field shift for one carbon resonance that is directly connected to the ^{15}N atom. This signal becomes a doublet because of ^{15}N-^{13}C coupling, and one resonance of the doublet overlaps with that of the carbon atom bonded to ^{14}N (Figure 1). Nitrogen isotope substitution was also signaled by a change in the N-H stretching region of the IR spectrum (Supporting Information). Nitrogen isotope incorporation was also confirmed by high-resolution ESI-TOF-MS. Although the *ee* of the final

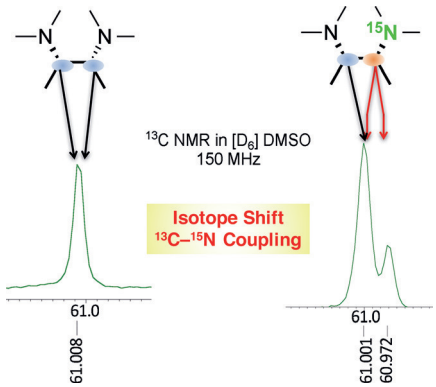
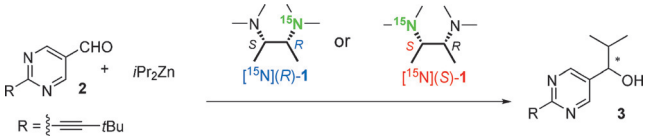


Figure 1. ^{13}C NMR of ^{15}N-substituted diamine **1**.

isotopically chiral diamine **1** cannot be directly determined because of the lack of optical activity and chiral interaction with the chiral HPLC column, the *ee* of the product was determined for the precursor **8**. Chiral HPLC analysis of **8** showed that the compound has a high *ee* (>98% *ee*) and there are no other detectable diastereomers.

To examine asymmetric induction with nitrogen isotopically chiral diamine, the addition of diisopropylzinc to the pyrimidin-5-carbaldehyde **2** was performed in the presence of diamine **1** (a chiral trigger) in pursuit of asymmetric autocatalysis of pyrimidyl alkanol **3**. The results are summarized in Table 1. The addition of diisopropylzinc (iPr$_2$Zn) to

Table 1: Asymmetric autocatalysis initiated by nitrogen (^{14}N/^{15}N) isotopically chiral diamine.



Entry	Chiral diamine **1**		Pyrimidyl alkanol **3**		
	Config.	Synthetic route	Yield [%]	*ee* [%]	Config.
1	[^{15}N](*R*)	A	84 (82[b])	45 (>99.5[b])	*R*
2	[^{15}N](*S*)	A	85 (82[b])	35 (>99.5[b])	*S*
3	[^{15}N](*R*)	A	58	38	*R*
4	[^{15}N](*S*)	A	71	37	*S*
5	[^{15}N](*R*)	A	86	26	*R*
6	[^{15}N](*S*)	A	81	18	*S*
7	[^{15}N](*R*)	A	54	12	*R*
8	[^{15}N](*S*)	A	79	18	*S*
9	[^{15}N](*R*)	B	69	40	*R*
10	[^{15}N](*S*)	B	67	54	*S*
11	[^{15}N](*R*)	B	75	24	*R*
12	[^{15}N](*S*)	B	69	41	*S*
13	[^{15}N](*R*)	B	77	16	*R*
14	[^{15}N](*S*)	B	73	22	*S*

[a] Reaction conditions: **1**, **2**, and iPr$_2$Zn (1:1:6) in toluene 0 °C, additional aldehyde **2** (4 equiv and 8 equiv) and iPr$_2$Zn (16 equiv and 32 equiv) were added stepwise. [b] After scale-up by additional autocatalytic reaction with isolated alkanol.

the pyrimidine-5-carbaldehyde **2** in the presence of [^{15}N](*S*)-**1** afforded (*S*)-pyrimidyl alkanol **3**. In contrast, (*R*)-alkanol **3** was obtained from the reaction with [^{15}N](*R*)-**1**. The *ee* was amplified by further asymmetric autocatalytic reaction with the obtained pyrimidyl alkanol (Table 1, entries 1 and 2). The selectivity has good reproducibility and diamines with nitrogen isotope chirality, synthesized from different starting material, also show the same selectivity in the asymmetric autocatalytic reaction of pyrimidyl alkanol **3** (Table 1, entries 9–14). These results support the contention that the sense of enantioselectivity actually came from the nitrogen-isotope-substituted chiral diamine **1**. Thus, a diamine with nitrogen isotope chirality can act as a chiral initiator in asymmetric autocatalysis.

In summary, we have synthesized a diamine arising from nitrogen isotope (^{14}N/^{15}N) substitution from a diol, by stepwise synthesis with ^{15}N-substituted and non-substituted phthalimide. Using this isotopically chiral diamine, asymmetric induction of asymmetric autocatalysis can be achieved. This result is the first example of enantioselective induction by chirality using only the nitrogen isotope ^{14}N/^{15}N difference. This is an important demonstration that the chiral effect of nitrogen isotope substitution can affect the reaction selectivity of asymmetric induction.

Experimental Section

Experimental details pertaining to the synthesis and characterization of ^{15}N-substituted compounds are described in the Supporting Information.

Typical procedure for asymmetric autocatalysis initiated by a diamine containing isotopically chiral nitrogen (Table 1, entry 1): Isotopically chiral diamine [^{15}N](*R*)-**1** (5.5 mg, 0.025 mmol, 1 equiv) was placed in a dried flask under argon. To this flask, a toluene solution of diisopropylzinc (1.0 M, 0.15 mL, 0.15 mmol, 6 equiv) was added at 0 °C and stirred for 20 min. Subsequently, pyrimidine-5-carbaldehyde **2** (4.7 mg, 0.025 mmol, 1 equiv) in toluene (0.15 mL) was added dropwise over 1 h at 0 °C. After 2 h stirring at 0 °C, one-pot scale-up of asymmetric autocatalysis was performed by adding toluene (0.4 mL) and a diisopropylzinc toluene solution (1 M, 0.2 mL, 0.2 mmol), followed by dropwise addition of aldehyde **2** (18.8 mg, 0.1 mmol) in toluene (0.5 mL) over 1 h. After an additional 2 h of stirring, a second scale-up of asymmetric autocatalysis was performed by adding toluene (3.6 mL), diisopropylzinc (1 M, 0.8 mL, 0.8 mmol), and aldehyde **2** (75.3 mg, 0.4 mmol) in toluene (2 mL) in a similar manner. After 2 h, the reaction was quenched with a mixture of saturated NH_4Cl aq and 30% NH_3 aq (2/1, v/v, 10 mL) and extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na_2SO_4 and the volatiles were removed under reduced pressure. The crude products were purified by silica gel column chromatography (eluent: hexane/EtOAc = 2/1) to give the (*R*)-alkanol **3** in 84% yield (103.2 mg) with 45% *ee*. The *ee* value was determined by HPLC analysis on a chiral stationary phase (Daicel Chiralpak IB: ϕ 4.6 mm × 250 mm, 254 nm UV detector, RT, 5% 2-propanol in hexane, 1.0 mL min^{-1}. Retention times: 10.9 min for (*S*)-**3** and 15.5 min for (*R*)-**3**).

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[17] According to the thermogravimetric (TG) analysis of *meso*-diamine **1**, the obtained amine contained crystallization water even after recrystallization from ethanol.

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