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

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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 $^{14}\text{N},^{14}\text{N},^{14}\text{N},^{15}\text{N}$-tetramethyl-2,3-butanediamine containing nitrogen ($^{14}\text{N}/^{15}\text{N}$) 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 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 ($^{12}\text{C}/^{13}\text{C}$),[14] and oxygen ($^{16}\text{O}/^{18}\text{O}$)[15] isotopes) act as chiral initiators for asymmetric autocatalysis. Herein, we report the first example of asymmetric induction by chiral nitrogen ($^{14}\text{N}/^{15}\text{N}$) isotopomers with a smaller relative mass difference compared to previously reported isotopomers (Scheme 1).

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. $^{14}\text{N}$ is a useful NMR-active isotope and the isotope ratio of $^{14}\text{N}/^{15}\text{N}$ is also used in the study of the origin of meteorites.[16] However, to our knowledge, isotopically chiral compounds arising from nitrogen isotope ($^{14}\text{N}/^{15}\text{N}$) 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, $\text{meso-}^{14}\text{N},^{14}\text{N},^{14}\text{N},^{15}\text{N}$-tetramethyl-2,3-butanediamine 1. This diamine is a derivative of the frequently used achiral ligand, tetramethylthelyenediamine, and has mirror symmetry. However, replacing one nitrogen atom with the $^{15}\text{N}$ isotope breaks the symmetry and affords the isotopically chiral diamine, $^{15}\text{N}(S)$ or $^{15}\text{N}(R)$-1. We synthesized these isotopically chiral diamines 1 and...
achieved asymmetric induction in the asymmetric autocatalytic reaction of pyrimidine-5-carbaldehyde and \(iPr_2Zn\) to give pyrimidyl alkanol chiral compounds with high ee.

The nitrogen \((^{14}\text{N}/^{15}\text{N})\) isotopically chiral diamine was synthesized from \((2R,3R)-\text{butane-2,3-diol}\) using \(^{15}\text{N}\)-phthalimide as a \(^{15}\text{N}\) source (Scheme 2). First, one alcohol in \((2R,3R)-\text{butane-2,3-diol}\) was protected with a benzyl group, followed by stereoinversion of the remaining alcohol by the Mitsunobu reaction to give the alcohol \((2S,3R)-5\). A Mitsunobu reaction of \((2S,3R)-5\) with \(^{15}\text{N}\)-phthalimide afforded \(^{15}\text{N}\)-amine \((2S)^{15}\text{N}(R,3S)-6\). 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 \((2S)^{15}\text{N}(R,3S)-7\). A Mitsunobu reaction with non-labeled phthalimide, followed by reduction and deprotection, afforded the isotopically chiral diamine \([^{15}\text{N}](R)-1\) isolated as the diammonium chloride salt and purified by recrystallization from ethanol.\(^{[17]}\)

The enantiomer of this diamine \([^{15}\text{N}](S)-1\) was also synthesized from the \((2R,3R)-\text{butane-2,3-diol}\) starting material, by changing the order of \(^{15}\text{N}\)-labeled and non-labeled phthalimide in the synthetic Scheme 2; that is, by introducing non-labeled phthalimide first and introducing \(^{15}\text{N}\)-labeled phthalimide second. Thus, both enantiomers of \([^{15}\text{N}]-1\) were synthesized in a stereoselective manner from the same \((2R,3R)-\text{butane-2,3-diol}\). By employing this procedure, preservation of chirality was assured even when chiral contaminants from \((2R,3R)-\text{butane-2,3-diol}\) 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 \([^{15}\text{N}](S)-1\) and \([^{15}\text{N}](R)-1\) from the opposite enantiomer \((2S,3S)-4\) (Scheme 3).

Nitrogen isotope incorporation can be observed in the \(^{13}\text{C}\) 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 \(^{15}\text{N}\)-labeled diamine the observed \(^{13}\text{C}\) NMR resonance resulted in two signals 1.5C:0.5C. It seems that there is a high-field shift for one carbon resonance that is directly connected to the \(^{15}\text{N}\) atom. This signal becomes a doublet because of \(^{15}\text{N}-^{13}\text{C}\) coupling, and one resonance of the doublet overlaps with that of the carbon atom bonded to \(^{15}\text{N}\) (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

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**Scheme 2.** Synthesis of nitrogen \((^{14}\text{N}/^{15}\text{N})\) isotopically chiral diamine 1 (Route A). Key: phthalimide (HNPhth), diisobutylaluminum hydride (DIBAL), diethyl azodicarboxylate (DEAD), 2-picoline-borane (2-pic.-BH3).

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

**Figure 1.** \(^{13}\text{C}\) NMR of \(^{15}\text{N}\)-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 disopropylzinc to the pyrimidine-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 disopropylzinc (iPr₂Zn) to the pyrimidine-5-carbaldehyde 2 in the presence of [N(N)]-1 afforded (S)-pyrimidyl alkanol 3. In contrast, (R)-alkanol 3 was obtained from the reaction with [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 ([N(N)]- substitution from a diol, by stepwise synthesis with [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 15N/14N 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 15N-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 [N(N)]-1 (5.5 mg, 0.025 mmol, 1 equiv) was placed in a dried flask under argon. To this flask, a toluene solution of disopropylzinc (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 disopropylzinc 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), disopropylzinc (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 NH₄Cl aq and 30% NH₃ aq (2/1, v/v, 10 mL) and extracted with EtOAc three times. The combined organic layers were dried over anhydrous Na₂SO₄ 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).

**Acknowledgements**

This work was financially supported by a Grant-in-Aid for Scientific Research from Japan Society for the Promotion of Science (JSPS KAKENHI Grant Numbers 23685012, 26810026, and 15H03781) and MEXT-Supported Program for the Strategic Research Foundation at Private Universities, 2012–2016.

**Keywords:** asymmetric amplification · asymmetric autocatalysis · chirality · isotopes · nitrogen isotopes

**How to cite:** Angew. Chem. Int. Ed. 2016, 55, 15246–15249

Angew. Chem. 2016, 128, 15472–15475

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**Table 1:** Asymmetric autocatalysis initiated by nitrogen ([N(N)]-15N) isotopically chiral diamine.

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

[a] Reaction conditions: 1, 2, and iPr₂Zn (1:1:6) in toluene 0°C, additional aldehyde 2 (4 equiv and 8 equiv) and iPr₂Zn (16 equiv and 32 equiv) were added stepwise. [b] After scale-up by additional autocatalytic reaction with isolated alkanol.
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According to the thermogravimetric (TG) analysis of meso-diamine 1, the obtained amine contained crystallization water even after recrystallization from ethanol.