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Inversion of the axial information during oxidative aromatization in the synthesis of axially chiral biaryls using organocatalyst as a key step

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In memory of the late Professor Dieter Enders

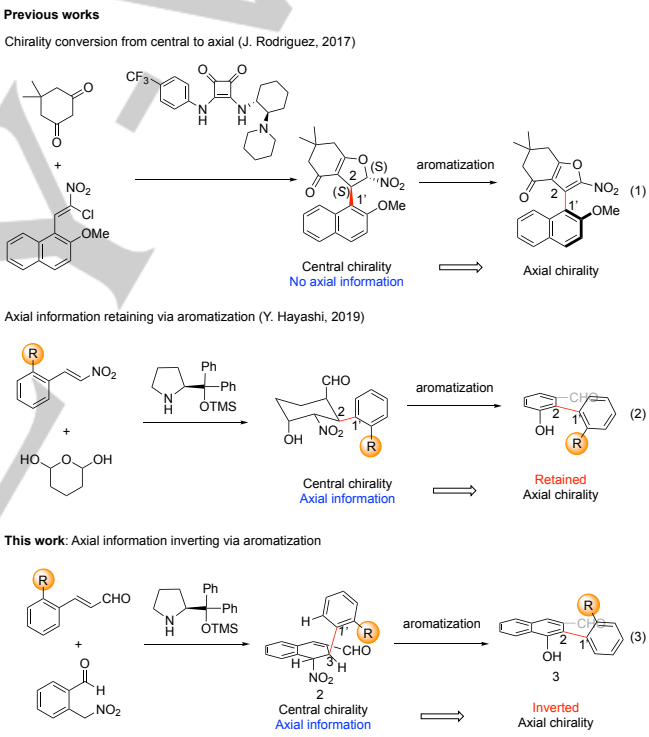
Abstract: The pot economical highly enantioselective synthesis of axially chiral biaryls was developed using one-pot reactions of organocatalyst mediated domino reaction and aromatization as key steps. The axial information of the precursor, which possesses also the central chirality, was completely inverted in the final biaryls. The inversion of the axial information occurred in the conversion of the central chirality to the axial chirality of an oxidative aromatization step.

Introduction

Recently there has been a great interest in axially chiral molecules due to their use in many different scientific areas. In enantioselective reactions, for instance, they are used as ligands in organometallic reactions[1] and catalysts in organocatalytic reactions.[2] A large number of natural products are found to possess axial chirality. Axial chirality influences biological activities,[3] and some drugs are enantiomers of axially chiral molecules.[4] Axial chirality also affects physical properties in material science.[5] Thus, the stereoselective construction of axially chiral molecules is important not only in the synthetic organic chemistry but also in other scientific fields.

Many synthetic methods for the construction of axially chiral biaryls have been developed due to their importance.[6] One of the most representative methods is the enantioselective coupling of two aryl units.[7] Other methods include axial selective desymmetrization[8] and enantioselective biaryl construction.[9] Besides these methods, "chirality conversion from central to axial" is another strategy, in which central chirality is converted into axial chirality.[10] A recent example is Rodriguez's highly stereoselective synthesis of axially chiral biaryls from naphthol derivatives (Eq. 1).[10f] While the intermediate possesses central chirality, it does not possess a defined configuration of a stereogenic axis because of free rotation around the C2-C1' axis.

Scheme 1. Relationship of the chirality of the intermediate and the axial chirality of the product



In some of the reactions, however, the intermediate possesses not only central chirality but also a defined configuration of a stereogenic axis.[11] The defined configuration of the stereogenic axis of the precursor is retained in the final axially chiral molecules, in which the axial information of the intermediate and that of the final product are identical. There is no reaction as far as we were aware that the axial information of the precursor inverts completely with excellent enantioselectivity. For instance, Thomson reported the synthesis of chiral bisphenols via oxidative aromatization, during which a defined configuration of a stereogenic axis has been retained.[10d] Chen also successfully synthesized axially chiral 3-aryl pyrrole, which retains the axial information of the precursor.[10i] Recently we prepared axially chiral biphenyls from the domino product of *o*-substituted nitrostyrene and succinaldehyde using diphenylprolinol silyl ether (Eq. 2).[11b] The domino product exists

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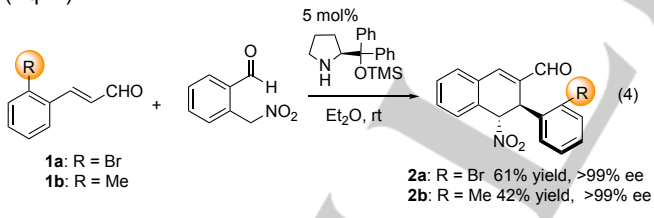
as a single conformer, possessing the central chirality with the axial information along the C2-C1' axis, and the removal of the central chirality afforded the axially chiral biphenyls that retain the axial information with excellent enantioselectivity. During the investigation to synthesize the axial chiral molecule, we found that the axial information of the intermediates was completely inverted during the removal of central chirality (Eq. 3), which we will describe in this paper.

Results and Discussion

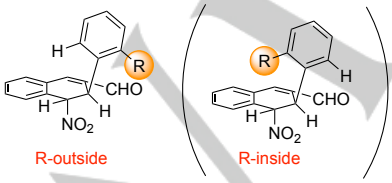
The enantio-enriched dihydronaphthalenes **2** were selected as chiral starting materials, because they can be converted into synthetically useful chiral biaryls in short steps. Two examples of dihydronaphthalenes **2** with 2-substituted phenyl moiety (R = NO_2 **2g**, OMe **2h**, Eq. 3) are known to be prepared by the enantioselective domino Michael–aldol condensation reaction catalyzed by diphenylprolinol silyl ether reported by Enders.[12]

First, the domino reactions of 3-(2-bromophenyl)-propenal (**1a**) and 3-(2-methylphenyl)propenal (**1b**) with 2-(nitromethyl)–benzaldehyde were investigated in the presence of a catalytic amount of diphenylprolinol silyl ether[13] to afford the corresponding dihydronaphthalene derivatives **2a**, **2b** with excellent enantioselectivity (Eq. 4). We determined the absolute configuration and the conformation in the solid state of bromo substrate **2a** by X-ray crystallography (Figure 1a),[14] while Enders' group determined the relative configuration of methoxy substrate **2h** by X-ray analysis.[12] It was found that, in the both crystals of bromo and methoxy substrates **2a** and **2h**, the phenyl ring stands approximately vertically on the dihydro-naphthalene ring, in which the dihedral angles between the H(3)(benzylic proton)–C(3)–C(4)–H(4)(α-position of nitro group) were 80.4° and 77.8°, respectively. It was also observed that the *o*-substituent of phenyl ring overhangs, avoiding the dihydronaphthalene skeleton, which we call as Br-outside and OMe-outside conformers in this paper (Eq. 4).[15]



1a: R = Br
1b: R = Me

2a: R = Br 61% yield, >99% ee
2b: R = Me 42% yield, >99% ee



In order to investigate the conformational information in the solution phase, the NMR experiments were performed on dihydronaphthalene having *o*-tolyl substituent **2b**, which would provide more NMR information than that of bromo and methoxy substituted ones. The coupling constant between the H(3) and H(4) is almost 0 Hz, indicating that the dihedral angle between H(3)–C(3)–C(4)–H(4) is similar with that of the solid state of **2a** and **2h**. NOE correlation between H(3)–H(Me) was observed, while NOE correlation between H(3)–H(6') was not detected (Figure 1b). These results suggest that **2b** exists as a single axial conformer, in which the Me substituent at *o*-position of phenyl ring exists outside of dihydronaphthalene ring, Me-outside. Thus, the conformations in the solid state and the solution phase are similar, and dihydronaphthalene possesses central chirality with axial information along the C3–C1' bond.

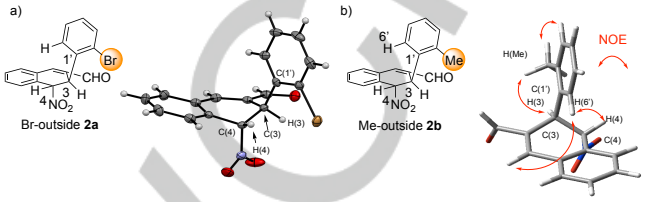


Figure 1. Structural analysis of dihydronaphthalene **2** a) ORTEP of **2a**. Thermal ellipsoids are set at 50 % probability. b) NOE correlation of **2b**

Next, density function theory (DFT) calculation was conducted to investigate why dihydronaphthalene existed as a single axial conformer (Figure 2). Calculations were carried out for the substrate **2a** possessing bromo substituent. The rotational barrier of the C(3)–C(1') axis was calculated to be 49.29 kJ/mol. This indicates that the two axial conformers such as Br-outside and Br-inside can be easily interconverted at room temperature. The potential energy of Br-inside conformer is higher in 15.38 kJ/mol than that of Br-outside conformer, indicating that Br-outside conformer is favored and the ratio of abundance would be over 500 vs 1. Therefore, the axial information of the dihydronaphthalenes is controlled by thermodynamic stability of the substrate.[16]

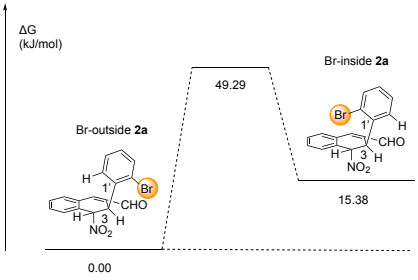


Figure 2. The free energy potential profile of the interconversion between two axial conformers of **2a**

As dihydronaphthalene **2a** possesses two central chiralities and one axial information, the removal of the two central chiralities without distorting the axial information was investigated to provide the chiral biaryl **3a**. After various investigations, it was found that **2a** can be converted into **3a** via one-pot operation over five reaction steps (1. acetalization, 2. formation of nitronate, 3. Nef reaction, 4. keto-enol isomerization, 5. deprotection of acetal) in 89% yield with 99% ee (Eq. 5). The synthetic sequence will be explained *vide infra*. The rotation barrier of **3a** is measured to be 148.5 kJ/mol, which is high enough to have an axial chirality at room temperature. The absolute configuration of **3a** was

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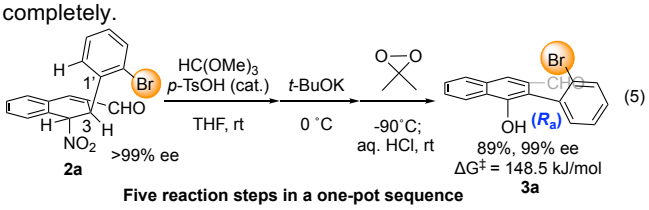
determined by X-ray single crystal analysis,[17] and was expected to be *Sa* because of the retention of the conformation of the stereogenic axis during the transformation from **2a** to **3a**. However, it was found to be *Ra*, which indicates that the axial information of C3–C1' bond of dihydronaphthalene was inverted completely.



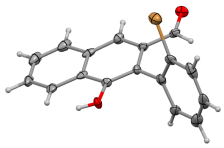
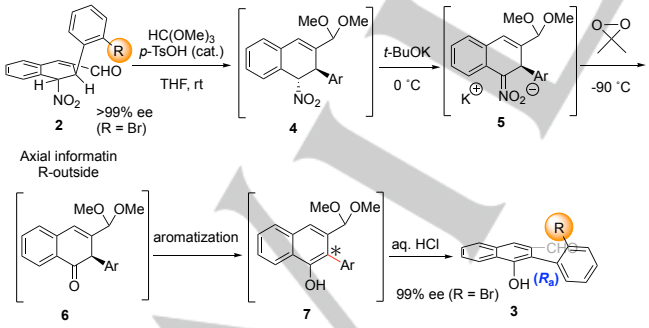


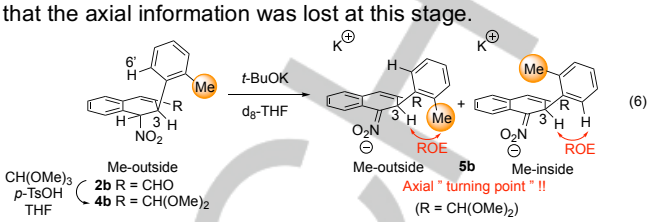
Figure 3. ORTEP of **3a**. Thermal ellipsoids are set at 50 % probability.

In order to clarify the reason of the complete inversion of the axial information, we investigated each step in detail. In the following investigations, NMR experiments were carried out for the methyl substrates, in which more NMR information can be obtained, while DFT calculations were performed for bromo substrates in order to reduce the calculation time. In the transformation from **2** to **3**, the following reaction steps are involved (Scheme 2): Aldehyde **2** is protected as its acetal **4**, which is treated with *t*-BuOK to generate nitronate **5**. Nef reaction by the addition of dimethyldioxirane (DMDO) afforded ketone **6**, which isomerizes to naphthol **7**. Deprotection of acetal afforded biaryl **3**. It should be noted that all these transformations from **2** to **3** over five reaction steps can be carried out in a single vessel after the careful optimization of all the reaction steps based on the pot economy.[18]

Scheme 2. The synthetic scheme and intermediates from **2** to **3**



As already described, the compound **2b** (R = Me) exists as a single axial conformer (Me-outside, Eq. 6). Dimethyl acetal **4b** was also found to exist as a single axial conformer (Me-outside), which was revealed by the NOE experiments. NOE between H(C3)–H(Me) was observed with no NOE between H(C3)–H(C6'). On the other hand, after treating the dimethyl acetal **4b** with *t*-BuOK in d_8-THF, the ROE correlations for resulted nitronate **5b** was observed not only between H(C3)–H(Me) but also between H(C3)–H(C6'). This indicates that the nitronate **5b** existed as a mixture of two axial conformers, Me-outside and Me-inside, and that the axial information was lost at this stage.



As chiral biaryl **3a** with opposite axial chirality is obtained, the next questions are when and how the axial information is redefined as completely opposite. The next intermediate after the Nef reaction would be ketone **6** (Scheme 2), which cannot be detected because of the facile keto-enol tautomerization to afford naphthol **7** immediately. Thus, the DFT calculation of the ketone **6a** was performed, and it indicated that the rotation barrier between the two axial conformers is small ($\Delta G^{\ddagger}$=41.54 kJ/mol), and that each conformer can be easily interconverted (Figure 4). It also discloses that Br-outside conformer is 1.68 kJ/mol more stable than Br-inside conformer, indicating that the abundance ratio of both conformers was estimated to be about 2:1. Thus, the complete inversion of the axial information does not occur at the ketone stage.

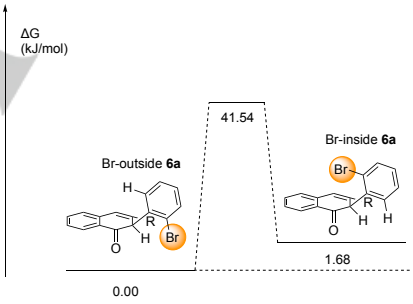


Figure 4. The Free energy potential profile of the interconversion between two axial conformers of **6a** (R = CHO)

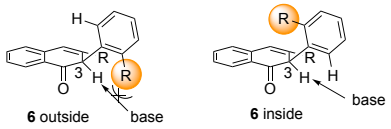


Figure 5. Reaction of ketone **6** with base

Based on the above findings, the complete inversion of axial information would occur during the aromatization step from ketone **6** to naphthol **7** as follows (Figure 5): Although the R-inside conformer is thermodynamically unstable, the deprotonation of a proton at C3 by base proceeds preferentially from the R-inside conformer as it is difficult to deprotonate a proton at C3 of R-outside conformer due to the steric hindrance caused by base and bulky substituent. If so, the size of the base would affect the enantioselectivity. In fact, a bulky base such as KHMDS gave excellent enantioselectivity (96% ee), while a lower

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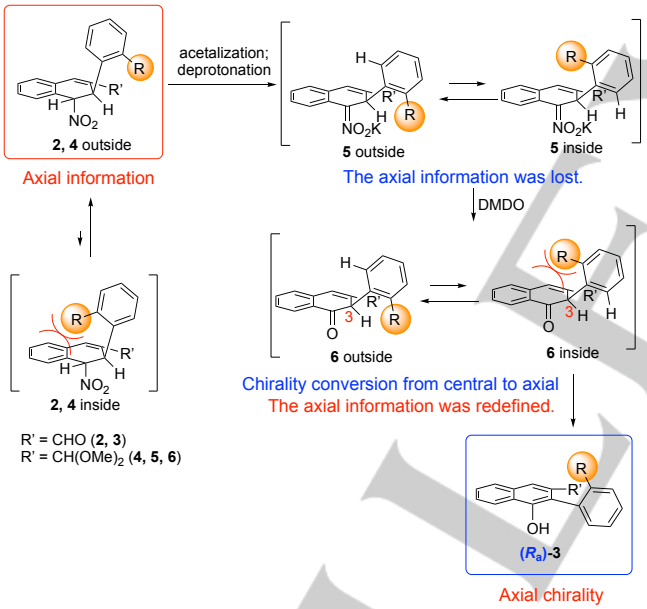
enantioselectivity (89% ee) was observed in the case of a smaller base such as KOMe. Thus, the deprotonation proceeds from R-inside conformer selectively, affording biaryl **7** with the *Ra* axial chirality.[6j, 10b, 10e, 10f, 15b]

Thus, the plausible reaction mechanism of the inversion of the axial information would be as follows (Scheme 3): The axial information of dihydronaphthalene **2** reflects thermodynamic stability between two axial conformers, existing as a single conformer R-outside. Acetal **4** also exists as a single axial conformer, R-outside. The axial information was lost at nitronate **5**, in which two conformers are observed by ROE experiments. Oxidation with DMDO afforded ketone **6**, which also exists as a mixture of two axial conformers revealed by the calculation. Although R-inside conformer of **6** is less stable, the keto-enol tautomerization would selectively proceed from this conformer because of the easy access of base to a proton at C3. Thus, the axial information is redefined with the complete inversion to afford *Ra* axial enantiomer. This phenomenon essentially belongs to a strategy of chirality conversion from central to axial, although it seems that there is no free rotation in dihydronaphthalene **2**.

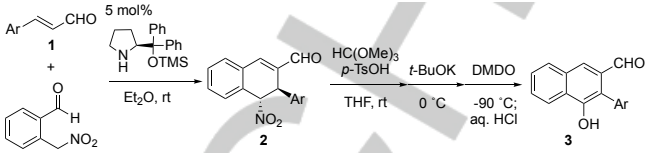
Scheme 3. The reaction mechanism of the inversion of axial chiral information from **2** to **3**

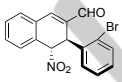
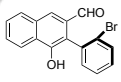
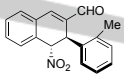
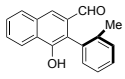
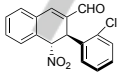
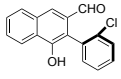
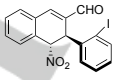
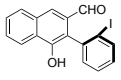
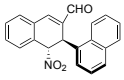
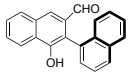
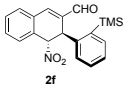
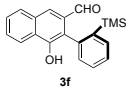
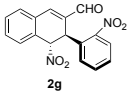
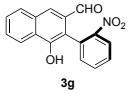
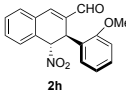
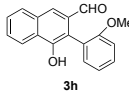
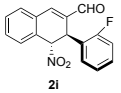
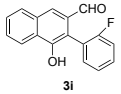


The generality of the two-pot synthesis of axially chiral biaryls was investigated (Table 1). The first domino Michael-aldol condensation reactions catalyzed by diphenylprolinol silyl ether proceeded well with all the substrates examined, affording excellent enantioselectivities. All dihydronaphthalenes **2** exist as a single axial conformer around the C3-C1' axis. In the second pot reaction, all axially chiral biaryls **3** were obtained in good yield over five reaction steps in a one-pot operation. Excellent enantioselectivity was observed in the substrates having a sufficiently bulky substituent at the *o*-position of aromatic ring such as Me, Cl, Br and I (entries 1-4). The substrate with naphthyl substituent is a suitable substrate, affording bis-naphthyls with excellent enantioselectivity (entry 5). Even the substrate with the much bulkier trimethylsilyl group is also suitable to afford the chiral biaryl **3f** with excellent enantioselectivity (entry 6).

We determined the absolute configuration of **3a** via X-ray crystallographic analysis, and those of **3e** and **3f** based on CD

Table 1: The generality of the two-pot synthesis of biaryl **3a**



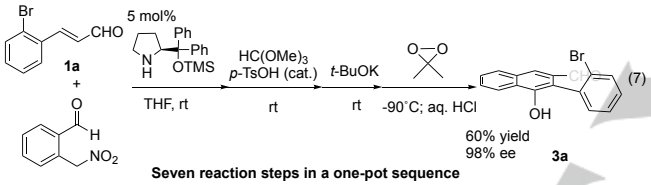
Entry [a]	2	yield of 2 [%][b] (ee of 2 [%][c])	3	yield of 3 [%][b] (ee of 3 [%][c])
1[d]	 2a	61 (>99)	 3a	89 (99)
2[e]	 2b	42 (>99)	 3b	96 (98)
3[e]	 2c	67 (>99)	 3c	66 (95)
4[e]	 2d	60 (99)	 3d	94 (>99)
5[f]	 2e	61 (97)	 3e	81 (95)
6[g]	 2f	75 (94)	 3f	75 (92)
7[e]	 2g	52 (98)	 3g	76 (50)
8[e]	 2h	52 (99)	 3h	70 (0)
9[e]	 2i	62 (99)	 3i	79 (0)

[a]For first organocatalyst mediated domino reaction: **1** (1.0 mmol), 2-(nitromethyl)benzaldehyde (1.2 mmol), catalyst (0.05 mmol), Et_2O (2.0 ml).; For oxidative aromatization: **2** (0.50 mmol), $CH(OMe)_3$ (2.50 mmol), *p*-TsOH•H_2O (0.10 mmol), *t*-BuOK (1.00 mmol), DMDO (0.60 mmol as acetone solution). [b]Isolated yield. [c]The ee values of the compounds were determined by HPLC analysis on a chiral column. [d]The absolute configuration of resulted biaryl was determined by X-ray christalography. [e]The absolute configuration was estimated from other substrates. [f]The absolute configuration of resulted biaryl was determined by CD spectra and DFT calculation. [g]The absolute configuration of resulted biaryl was determined by VCD spectra and DFT calculation

and VCD[19] with the combination of DFT calculations. In all cases of **3a** - **3f**, the axial information was completely inverted and *R*a enantiomers were obtained.

However, the stereo-selectivity of the resulting biaryl is moderate when it is sufficiently bulky but possesses a strong electron withdrawing group such as a nitro group (entry 7). This would be due to the diminishing rotational barrier along the C3–C1' axis owing to the push-pull effect between the nitro group and naphthol. On the other hand, when the substrate has a sterically less bulky substituent such as fluoro or methoxy group, despite existing as a single axial conformer in dihydronaphthalene **2**, the obtained biaryls are racemic after aromatization (entries 8 and 9). This would be because of the rotation around the axis in the final biaryl product owing to the small substituents.

In addition, we found the all reactions from the first domino reaction to the aromatization over seven reaction steps can be carried out in a single vessel, and that an axially chiral biaryl **3a** was obtained in good yield without impairing the enantioselectivity (Eq. 7). It should be noted that the yield (60%) of the one-pot procedure is higher than the total yield of the reaction using two reaction vessels (54% = 61% x 89%).



Conclusion

In summary, we developed a one-pot method of the highly enantioselective synthesis of axially chiral biaryls **3** by converting the central chirality to the axial chirality from dihydronaphthalenes **2** present as single axial conformers, which are generated by the domino reaction of 3-(2-substituted-phenyl)propenals and 2-(nitromethyl)benzaldehyde catalyzed by diphenylprolinol silyl ether. Although the dihydronaphthalene **2** exists as a single axial conformer, this axial information is completely inverted during the removal of central chirality. It is a first example, as far as we are aware, where the complete inversion of the axial information was observed between the precursor, which possesses central chirality and the axial information, and the final biaryl. It was revealed that deletion and redefinition of axial information occur in the nitronate generation and keto/enol isomerization step, respectively. This result indicates that even if the precursor with central chirality exists as a single axial conformer, there is no guarantee that the axial information can be retained in the final product. During the removal of the central chirality, the rotation around the axis might occur. In the conversion from central to axial chirality in the precursor with a defined configuration of a stereogenic axis, the delicate investigation about the origin of the axial chirality would be necessary.

Experimental Section

Preparation of dihydronaphthalene 2a: To a solution of 2-nitromethyl-benzaldehyde (1.0 mmol) and 3-(2-bromophenyl)-propenal (1.2 mmol) in Et_2O (2.0 mL) was added (*S*)-diphenylprolinol TMS-ether (0.05 mmol, 5 mol%). After stirring for 4 h at ambient temperature, the generated **2a** as solid was gathered by filtration and washed with Et_2O (50% yield). The filtrate was concentrated in vacuo and purified by flash column chromatography (eluent: Ethyl acetate/Hexane = 1/3) to afford **2a** (11% yield).

Synthesis of axially chiral biaryl 3a: To a THF solution (1.0 mL) of 3,4-dihydronaphthalenes **2a** (0.50 mmol) was added trimethyl orthoformate (2.50 mmol) and *p*-toluenesulfonic acid (0.10 mmol) at ambient temperature. After stirring the reaction mixture for 2 h, *t*-BuOK (1.0 mmol) was added to the reaction mixture at –90 °C, then the reaction mixture was stirred for 30 min at 0 °C. To the reaction mixture was added dimethyldioxirane (0.60 mmol, 0.1 M solution in acetone) at –90 °C. After stirring the reaction mixture for 30 min, the reaction was quenched by sat. aq. $Na_2S_2O_3$, and then 1 N aqueous solution of hydrogen chloride (0.50 mL) was added to the reaction mixture at ambient temperature. After stirring the reaction mixture for 10 min, the organic materials were extracted with ethyl acetate (3 × 3 mL) and the organic layers were dried with Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by flash column chromatography (eluent: hexane 100% → ethyl acetate/hexane = 1/5) to afford biaryl compound **3a**.

Acknowledgements

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Conflict of interest

The authors declare no competing financial interest.

Keywords: Axial chirality, central chirality, enantioselective synthesis, organocatalyst

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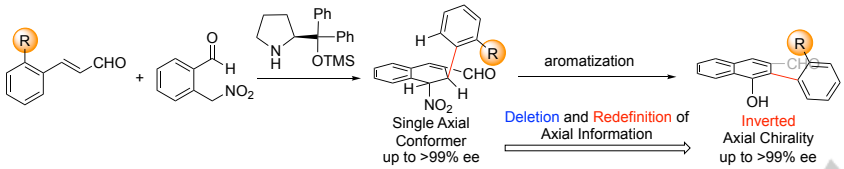

Unexpected inversion of axis: A new synthetic method of axially chiral biaryl was developed. Although the key intermediate existed as a single axial conformer, the axial information was completely inverted after aromatization. The axial inversion phenomenon was investigated in detail and an interesting "deletion and redefinition" mechanism was proposed. This study indicates the necessity of the careful investigation in the conversion of the chirality from central to axial.

*Seitaro Koshino, Akira Takikawa, Keiichi Ishida, Tohru Taniguchi, Kenji Monde, Eunsang Kwon, Shigenobu Umemiya, Yujiro Hayashi**

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Title

Inversion of the axial information during oxidative aromatization in the synthesis of axially chiral biaryls using organocatalyst as a key step