

Hexafluoroisopropanol-Enabled Copper-Catalyzed Asymmetric Halogenation of Cyclic Diaryliodoniums for the Synthesis of Axially Chiral 2,2'-Dihalobiaryls

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of enantiopure chiral ligands that could be potentially useful in asymmetric catalysis.

A xially chiral compounds are ubiquitous in many important organic molecules, such as natural products, biologically

Scheme 1. Significance and Synthesis of 2,2'-Dihalobiaryls



active compounds, optically pure materials, and privileged chiral ligands, which have attracted increasing attention over the past decade.¹ Among these elegant and useful axially chiral structural skeletons, 2,2'-diiodobiaryls display significant and

valuable properties in asymmetric catalysis owing to their unique structures and characteristics. Axially chiral 2,2'diiodobiaryls are widely used as hypervalent iodine catalyst precursors, which has led to their broad applications in many asymmetric transformations, such as the enantioselective α functionalization of ketones, dearomatization, the difunctionalization of alkenes, as well as oxidative rearrangement and oxidative coupling (Scheme 1a, left).² In addition, the versatile aromatic C-I bonds in 2,2'-diiodobiaryls can easily be elaborated, conveniently delivering a variety of privileged C2symmetic chiral ligands or catalysts (Scheme 1a, right).³ Given the importance of this structural motif, strategies for the efficient construction of axially chiral 2,2'-diiodobiaryls are highly desirable. However, methods to access such compounds have been rather limited to date and have mainly relied on the Sandmeyer reaction from axially chiral 2,2'-diaminobiaryls (usually BINAM),⁴ or the resolution of racemate via a chiral preparative column.⁵ As a result, catalytic approaches for the asymmetric synthesis of axially chiral 2,2'-diiodobiaryls have remained underdeveloped.

In 2015, the Yoshikai group reported an elegant copper/ diamine-catalyzed iodinative ring-opening reaction of cyclic diaryliodonium salts toward 2,2'-diiodobiaryls (Scheme 1b).⁶ Compared with the previous procedures, which underwent metathesis with KI, followed by pyrolysis at 200–250 °C,⁷ this copper-catalyzed process provides a more efficient and convenient way for the synthesis of 2,2'-diiodobiaryls in

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Letter



Cul (5 mol%), chiral ligand (10 mol%) ŌTf nBu₄NI (1.0 equiv) solvent (1.0 mL), rt, 24 h, Ar 2a L1. R = Ph**L4**. n = 1 L2. R = Bn **L5**. n = 3 **L3**, R = *i*Pr Me Ph Ph L8 16 17 yield (%)^b entry chiral ligand solvent ee (%)^c 1 L1 CH₃CN 98 -182 L1 CH₂Cl₂ 98 -8L1 toluene 99 3 -131,4-dioxane 4 L1 98 -11HFIP 5 L1 99 -97HFIP 6 L2 99 -847 HFIP 99 L3 -868 L4 HFIP 99 95 9 L5 HFIP 99 97 10 L6 HFIP 99 -96 L7HFIP 99 (93) 99 11 12 L8 HFIP 31 24 13^d L7 HFIP 98 (1.27 g) 94 (99)

Table 1. Reaction Development⁴

^aStandard conditions: **1a** (0.1 mmol), CuI (5 mol %), ligand (10 mol %), nBu_4NI (1.0 equiv), solvent (1.0 mL), room temperature, 24 h, Ar. ^bGC yield with dodecane as a standard. Isolated yield in parentheses. ^cHPLC conditions: Chiralpak OD-3, isopropanol/hexanes 0.1:99.9, flow: 0.5 mL/min. ^dGram-scale conditions: **1a** (3.0 mmol), CuI (2.5 mol %), L7 (5 mol %), nBu_4NI (1.0 equiv), HFIP (30 mL), room temperature, 24 h, Ar. *ee* of **2a** after a single recrystallization in parentheses.

good yields under mild conditions. Despite the fact that this facile transformation generates 2,2'-diiodobiaryls with high efficiency, no axially chiral example is shown there. Because the overarching goal is to access axially chiral 2,2'-diiodobiaryls, we questioned whether we could expand the toolbox and develop an asymmetric halogenation reaction of cyclic diaryliodonium salts via chiral transition-metal catalysis. The feasibility of the hypothesis can be supported by the recent enantioselective ring-opening of cyclic diaryliodonium salts with N, S, and O nucleophiles reported by the Gu and the Zhang groups.⁸ The key to the success of these reactions is the use of appropriate chiral copper-oxazoline type complexes that discriminates the two conformers of cyclic diaryliodonium salts and affords the ring-opening products with high enantiomeric excess. Herein we present the development of an asymmetric halogenation of cyclic diaryliodonium salts, which gives access to a wide range of axially chiral 2,2'-dihalobiaryls in good to excellent yields and with excellent enantioselectivities under mild conditions (Scheme 1c). Crucial to the successful outcome of this reaction is the use of chiral copper-bisoxazoline catalysts in the unique solvent of HFIP (hexafluoroisopropanol).

Given the superior performance of the chiral Cu/Box catalytic system in the enantioselective ring-opening of cyclic diaryliodonium salts,⁸ we commenced our studies of the

asymmetric iodination of cyclic diaryliodonium salt 1a with the iodide source nBu₄NI in the presence of CuI as the catalyst and bisoxazoline L1 as the chiral ligand in common solvents, such as CH₃CN, CH₂Cl₂, toluene, and 1,4-dioxane. To our surprise, the desired 2,2'-diiodobiaryl product 2a was obtained in quantitative yield but with very poor enantiomeric excess (ee) (Table 1, entries 1-4).⁹ Further screening of the solvent disclosed that the ee of 2a could be tremendously improved to 97% in quantitative yield in the solvent of HFIP (Table 1, entry 5). HFIP has recently been shown to display unique properties as a solvent or cosolvent in synthetic chemistry, especially in asymmetric catalysis.¹⁰ The role of HFIP in this enantioselective reaction was preliminarily studied by density functional theory (DFT) calculations. (See Supporting Information Section 6.) Next, various chiral bisoxazoline-type ligands were also tested. Replacing the phenyl group of L1 with a benzyl (L2) or isopropyl (L3) group gave 2a with lower ee (Table 1, entries 6 and 7). Spirobis(oxazoline) ligands L4, L5, and L6 did not greatly affect the enantioselectivity, whereas L7 afforded the product 2a with 99% ee and in 93% isolated yield (Table 1, entries 8–11). PyBox ligand L8 significantly reduced both the yield and the ee (Table 1, entry 12). Moreover, the reaction could also proceed smoothly on the gram scale with only a slight loss of enantioselectivity; even the loadings of CuI and L7 were reduced by half (Table 1, entry 13).

With the optimal conditions in hand, we next examined the scope for the substituted cyclic diaryliodonium salts (Scheme 2). A regioselective problem always existed in the ring-opening reactions of the cyclic diaryliodonium salts with N, S, and O nucleophiles. This problem limited the scope of the cyclic diaryliodonium salts to be symmetric structures or to contain a substituent group at one ortho position of the iodonium ions, increasing the steric hindrance. In this iodination procedure, no regioselective problem arose, which certainly enlarged the diversity of the scope of cyclic diaryliodonium salts. We found that 6,6'-dimethyl cyclic diaryliodonium salts with substituents at the para, meta, and ortho positions of the aromatic ring all provided the desired products in high yields with excellent enantioselectivities (2b-2k). Various substituted groups on the aromatic ring were well tolerated, such as fluoro, chloro, cyano, tosylate, ester, difluoromethyl, -CH2OAc, and $-CH_2Nphth$ groups (2b-2i). The substituted groups at the 6,6'-positions of cyclic diaryliodonium salts for restraining the rotation were investigated next. Substrates displaying not only alkyl substituents (such as ethyl and isopropyl) but also electron-withdrawing substituted groups (such as trifluoromethyl, -OBz, tosylate, fluoro, chloro, and bromo) could also be introduced, smoothly giving the corresponding iodination product (21-2s). It is worth mentioning that axially chiral 2,2',6,6'-tetrahalobiaryls (2q-2s) could be obtained in 90-93% yield with 99% ee and could be used as chiral synthons for the construction of numerous interesting and useful biaryl atropoisomers via the transformation of carbon-halogen bonds. Furthermore, the reaction was not limited to 1,1'biphenyl substrates; compounds bearing 1,1'-binaphthalene, naphthyl-phenyl, and phenyl-heterocyclic skeletons could all be isolated in 84–92% yields with 99% ee (2t-2v). In addition, this asymmetric ring-opening reaction was also applied to the other halogen anions, such as nBu₄NBr and nBu₄NCl, which gave access to the corresponding 2,2'-iodobromobiaryl and 2,2'-iodochlorobiaryl products without any difficulties (2w-2y).

Scheme 2. Substrate Scope^a



^aStandard conditions: 1 (0.1 mmol), CuI (5 mol %), L7 (10 mol %), *n*Bu₄NX (1.0 equiv), HFIP (1.0 mL), room temperature, 24 h, Ar; isolated yields. ^bL1 was used as ligand. ^cCuBr (5 mol %) was used as catalyst. ^dCuCl (5 mol %) was used as catalyst.

To further demonstrate the utility of these axially chiral 2,2'diiodobiaryls, compound 2a was then converted into various privileged C2-symmetic chiral ligands or catalysts by diversityoriented transformations (Scheme 3). First, the consecutive treatment of 2a with nBuLi and nitrobenzene successfully delivered the corresponding 6,6'-dimethyl biphenol 3 in 63% yield with 96% ee. Compared with the widely used BINOL scaffold, the 6,6'-dimethyl groups made the biphenol more configurationally stable,¹¹ which found unique applications in the asymmetric Mannich-type reactions.¹² It is noteworthy that previously, the preparation of chiral 6,6'-dimethyl biphenol relied on a four-step resolution synthesis, which obviously limited its further applications in asymmetric catalysis.¹³ The lithiation of 2a with tBuLi and trapped with benzophenone afforded BAMOL (1,1'-biaryl-2,2'-dimethanol) derivatives 4 in 68% yield with 97% ee, which have displayed excellent performance in the hetero-Diels-Alder reaction as a hydrogen bonding catalyst.¹⁴ Moreover, axially chiral bisphenylsulfane 5 and BIPHEMP 6 could be easily obtained by simple nucleophilic substitution between the lithium intermediate of 2a and phenyl disulfide and chlorodiphenylphosphine,

respectively. Further consecutive treatment of **2a** with *n*BuLi and CO₂ smoothly produced the chiral dicarboxylic acid 7 in 80% yield with 97% *ee*, which has been exploited in a wide range of enantioselective transformations.¹⁵ Finally, the replacement of CO₂ into *N*,*N*-dimethylformamide (DMF) for the synthesis of the axially chiral dialdehyde **8** also proceeded without any problems. This dialdehyde **8** could be further transformed into the axially chiral dibenz[*c*,*e*]azepine **9** by simple reductive amination.

In summary, we have developed a highly efficient coppercatalyzed asymmetric halogenation of cyclic diaryliodonium salts with simple tetrabutylammonium halides, which gives access to a wide range of axially chiral 2,2'-dihalobiaryls in good to excellent yields with excellent enantioselectivities. Crucial to the successful outcome of this reaction is the use of CuI with the chiral bisoxazoline ligand in the solvent of HFIP. We also demonstrated that the axially chiral 2,2'-dihalobiaryl products can be further smoothly transformed into a number of enantiopure chiral ligands, which could be potentially useful in asymmetric catalysis.

Scheme 3. Application of Axially Chiral 2,2'-Diiodobiaryls



^ai. *n*BuLi, Et₂O, PhNO₂, -78 °C; ii. MeOH, rt. ^btBuLi, THF, PhCOPh, -78 °C. ^c*n*BuLi, Et₂O, PhSSPh, -78 °C. ^d*n*BuLi, Et₂O, Ph₂PCl, -78 °C. ^e*n*BuLi, Et₂O, CO₂, -78 °C. ^f*n*BuLi, THF, DMF, -78 °C. ^gBnNH₂, NaBH₃CN, CH₃CN, rt.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03833.

Materials and methods, experimental procedures, characterization data, computational studies, ¹H, ¹³C, and ¹⁹F NMR spectral data, HPLC spectra, and mass spectrometry data of new compounds (PDF)

Accession Codes

CCDC 2002852 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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Organic Letters

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Letter