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First atroposelective Chan–Lam coupling for the synthesis of C–N linked biaryls†

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The first atroposelective Chan–Lam coupling for the synthesis of C–N axial enantiomers is reported with good yields and ee. MnO_2 additive is crucial for the success of the coupling. The longstanding problem of the lack of enantioselective synthesis to make chiral C–N linked atropisomers is solved.

C–N axially chiral biaryls are found in many biologically active compounds, functional molecules, and chiral ligands (Fig. 1).[1] Particularly, drugs targeted for human use should consist of a single enantiomer because one of the enantiomers can be more biologically active than the other in many cases. In some cases, like that of thalidomide, the other enantiomer can cause serious side effects.[2,3] However, the construction of axially chiral C–N bonds is rather a difficult process. This is because the rotational barrier of the biaryls bearing C–N bonds connecting two aromatic rings is relatively low, which eventually results in racemization during synthesis and/or storage.[3] Accordingly, these compounds have been synthesized by the resolution of racemic mixtures, leading to considerable industrial waste.

C–N coupling reactions have been long studied because of the wide variety of nitrogen-containing aromatic compounds with C–N bonds.[4–6] Copper-catalyzed couplings between aryl halides and nitrogen nucleophiles have been long-used for synthesizing biaryl compounds with C–N bonds. However, the reactions require high temperatures, and sterically congested C–N bonds are difficult to construct using copper catalysts.[5] Palladium-catalyzed couplings using bulky electron-rich ligands are powerful tools for synthesizing these compounds.[6] The copper- and palladium-catalyzed couplings are complementary in many ways for C–N bond formation. Another method for the copper-catalyzed C–N coupling between boronic acids and nitrogen nucleophiles under mild conditions is the Chan–Lam coupling.[7,8] This coupling reaction can be applied to substrates bearing halogen atoms on the aromatic rings.

The pioneering stereoselective synthesis of C–N axially chiral biaryls was reported by Kamikawa and Uemura *et al.* in 2006 (Scheme 1, eqn (1)).[9c,d] In their original method, they conducted diastereoselective nucleophilic substitution of enantiomerically pure chromium-bound fluoarenes prepared by resolution using chiral HPLC. Although several methods have been developed for the selective synthesis of C–N axially chiral biaryls,[9–11] the first enantioselective catalytic construction of the C–N axis for the direct one-step synthesis of axially chiral biaryls was accomplished by Tan *et al.* in 2020 (eqn (2)).[9b] The C–H amination of 2-diazonaphthalenes with indoles proceeded in high yields and enantioselectivities using a chiral phosphoric acid catalyst. However, the substrates scope was limited, and the reactions required two to three days to reach completion. Herein, we report the first enantioselective Chan–Lam coupling of imidazole derivatives **1** with various arylboronic acids **2** for the synthesis of C–N axially chiral biaryls **3** (eqn (3)).[10,11]

Motivated by the copper-catalyzed *N*-arylation of sterically hindered substrates presented by Kozlowski *et al.*,[8e] we investigated the enantioselective Chan–Lam couplings of imidazole derivatives. Initially, the reaction was conducted in MeOH under an O_2 atmosphere for 24 h using $Cu(NO_3)_2$ and TMEDA (Table 1). However, the coupling reactions between 2-substituted

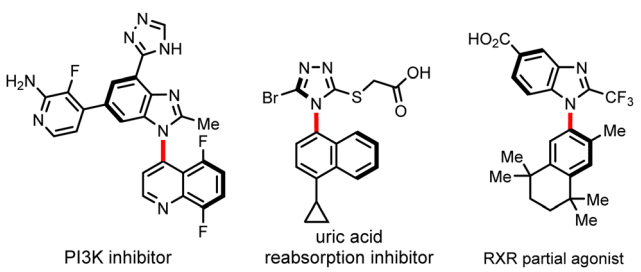

Fig. 1 Biologically-active C–N axially chiral biaryls.

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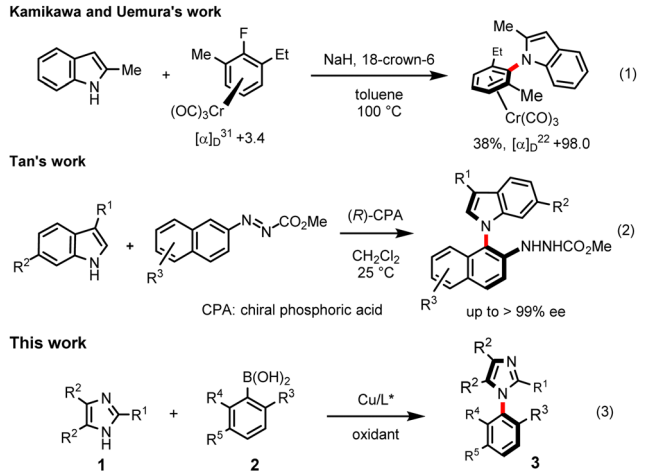
‡ These authors contributed equally.

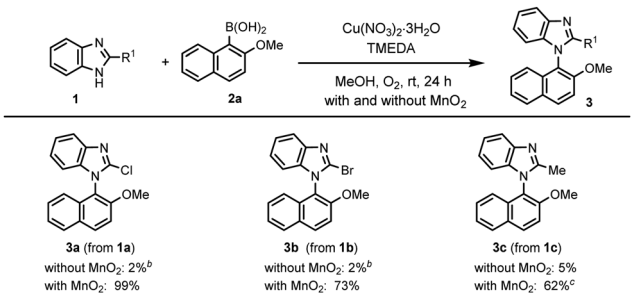


Scheme 1 Construction of the C–N bond in axially chiral biaryls.

benzimidazole **1a–c** (R = Cl, Br, and Me) and 2-methoxynaphthalene-1-boronic acid **2a** afforded coupling products **3a–c**, which have high rotational barriers, in only 2–5% yields indicating that the coupling reactions of hindered substrates such as **1a–c** need to be promoted to a much higher extent for developing meaningful enantioselective reactions. Therefore, a wide variety of additives, especially oxidants, were explored to accelerate the coupling between **1c** and **2a**. Among these, MnO_2[12] could dramatically accelerate the reactions of **1a**, **1b** and **1c** with **2a**, affording **3a**, **3b**, and **3c** in 99%, 73%, and 62% yields as racemic mixtures, respectively.

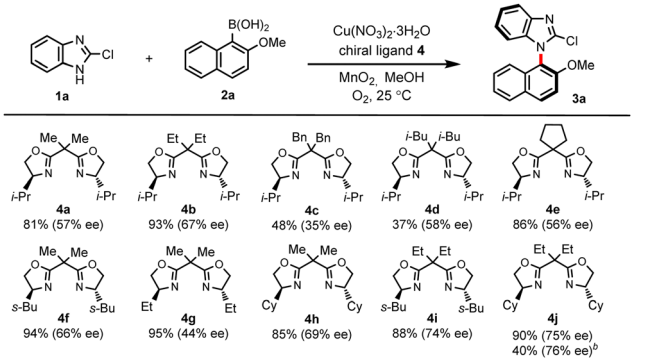
The enantioselective $Cu(NO_3)_2$-catalyzed coupling between **1a** and **2a** in MeOH under O_2 atmosphere in the presence of MnO_2, using chiral ligands instead of TMEDA was investigated. The use of the C2-symmetric bisoxazoline ligand **4a** bearing isopropyl groups (i-Pr) on oxazolines and two methyl groups (diMe) on the methylene linker afforded **3a** in high yield and enantioselectivity (81% yield and 57% ee, Table 2). The effect of bridged methylene substituents linking two bisoxazolines was studied using **4a–e**. Changing the substituents on the methylene from diMe (**4a**) to diEt (**4b**) improved both the yield and enantioselectivity (93% yield and 67% ee), whereas the

Table 1 Effect of MnO_2 additive on copper-catalyzed *N*-arylation of imidazoles[a]



[a] Conditions: **1** (0.20 mmol), **2a** (2 equiv.), $Cu(NO_3)_2{\cdot}3H_2O$ (25 mol%), TMEDA (50 mol%) in MeOH at rt for 24 h with and without MnO_2 (10 equiv.) [b] Determined by GC analysis. [c] MnO_2 (100 equiv.)

Table 2 Optimization of chiral bisoxazoline ligand[a]

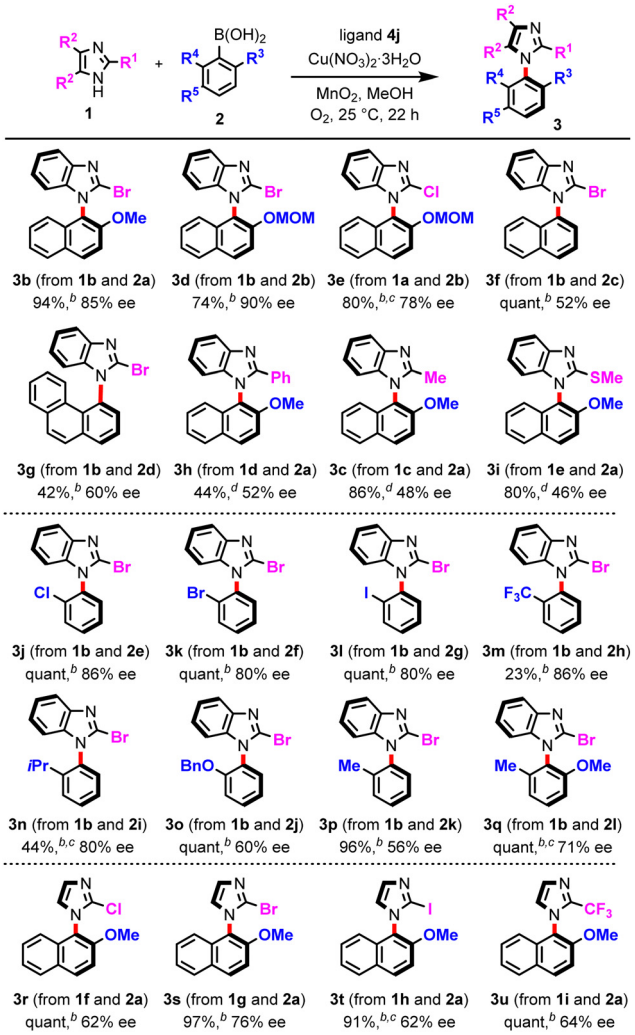


[a] Conditions: **1** (0.20 mmol), **2a** (2 equiv.), $Cu(NO_3)_2{\cdot}3H_2O$ (25 mol%), ligand **4** (50 mol%), MnO_2 (10 equiv.) in MeOH at rt for 24 h. [b] Without MnO_2.

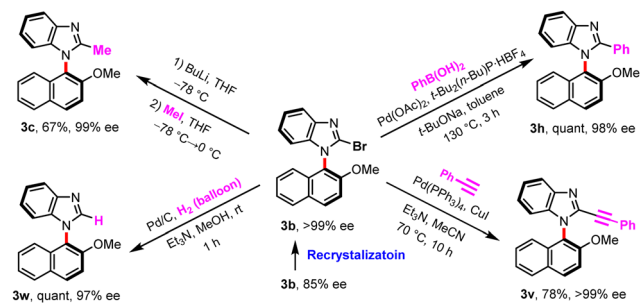
replacement with diBn, di(i-Bu), $(CH_2)_4$ gave lower yields and/or lower ee. The effect of the other substituents on the chiral center of ligand **4** was also studied, and we found that switching from i-Pr (**4a**) to the cyclohexyl group (Cy) (**4h**) improved both yield (from 81% to 85%) and enantioselectivity (from 57% to 69% ee). Finally, the use of the optimized ligand **4j** with diEt on the methylene linker and Cy on the chiral center gave the best yield (90%) and ee (75%) for **3a**. Notably, only the yield was significantly reduced from 90% to 44% in the absence of MnO_2, the high enantioselectivity was maintained (76% ee) even without MnO_2.[13]

With the optimized conditions in hand,[14–16] a wide variety of imidazole **1** and boronic acid **2** were reacted under the optimal conditions (Table 3). The coupling reaction of 2-bromobenzimidazole **1b** with **2a** gave C–N axially chiral biaryl **3b** in higher yield and enantioselectivity (94% yield and 85% ee)[17] than those of **3a** bearing a chlorine atom at the 2-position of the imidazole (90% yield and 75% ee). This can be successfully utilized for further transformations and recrystallization (*vide infra*, see Scheme 2), since the reactions of aryl bromides are generally easier than those of chlorides. The reaction of 1-naphthylboronic acid bearing a 2-methoxymethoxy group (**2b**) gave the corresponding biaryl product **3d** in 74% yield and the highest ee of 90% at the moment. The reaction of chlorine-bearing **1a** with **2b** gave **3e** with slightly lower enantioselectivity (78% ee), as expected. Instead of 2-alkoxynaphthalene-1-boronic acids (**2a** and **2b**), the use of 1-naphthalene boronic acid **2c** and 1-phenanthrene boronic acid **2d** gave **3f** in quantitative yield with 52% ee and **3g** in 42% yield with 60% ee. The substituent effects at C2 of benzimidazole were also investigated using **1c–e**. Although the enantioselectivities of the obtained C–N axially chiral biaryls **3h** (R^1 = Ph), **3c** (R^1 = Me), **3i** (R^1 = SPh) were not very high (42–56% ee), the conversion of **3b** could solve this problem (*vide infra*, see Scheme 2). The coupling reactions of 2-substituted phenylboronic acids **2e–k** with **1b** also afforded biaryls **3j–3p** with moderate to high enantioselectivities [**3j**: 86% ee (R^3 = Cl), **3k**: 80% ee (R^3 = Br), **3l**: 80% ee (R^3 = I), **3m**: 86% ee (R^3 = CF_3), **3n**: 80% ee (R^3 = i-Pr), **3o**: 60% ee (R^3 = OBn), **3p**: 56% ee (R^3 = Me)].

Table 3 Substrate scope and limitation[a]



[a] Conditions: **1** (0.2 mmol), **2** (2 equiv.), Cu cat (25 mol%), ligand **4j** (50 mol%), MnO_2 (10 equiv.) in MeOH for 22 h at 25 °C. [b] Isolated yield. [c] MnO_2 (100 equiv.) [d] Determined by GC-MS.



Scheme 2 Transformation of coupling product.

Interestingly, 2,6-disubstituted phenylboronic acid **2l** (R^3 = OMe, R^4 = CH_3) was also a good substrate for this coupling reaction, giving **3q** in quantitative yield with 71% ee. The 2-substituted imidazoles [R^1 = Cl (**1f**), Br (**1g**), I (**1h**), CF_3 (**1i**)] were also applied under the optimal conditions. The coupling reactions of **1f–i** and **2a** afforded **3r–u** in 91–>99% yield and 62–76% ee.

After the recrystallization of the coupling product **3b** (85% ee, Table 1), several transformations of **3b** (>99% ee after recrystallization) were achieved without racemization (Scheme 2). The bromine atom on **3b** was replaced with phenyl and alkynyl groups by palladium-catalyzed cross-couplings, with hydrogen atom by reductive dehalogenation with Pd/C, and with methyl group by halogen-metal exchange and subsequent electrophilic trapping to furnish the products in good to excellent yields (67%–>99%). It is noteworthy that the ee of **3b** was maintained in all transformations even at high reaction temperatures such as 130 °C (97%–>99% ee). These transformations are extremely valuable because only moderate enantioselectivities of the Chan–Lam couplings using 2-substituted benzimidazole **1c** (R = Me) and **1d** (R = Ph) were moderate (48% and 52% ee; Table 1). Moreover, the reaction of benzimidazole **1j** with **2a** gave the corresponding biaryl **3w** with only 4% ee (ESI†).

A plausible reaction mechanism of the asymmetric Chan–Lam coupling is shown in Fig. 2, based on well-studied literature examples.[18] Coordination of imidazole **1** and ligand **4** to $Cu(NO_3)_2$ (**A**) gave complex **B**. Transmetallation *via* pretransmetallation of the boronic acid ester produced complex **E**. Complex **E** disproportionated with other copper species to form complex **F**. The reductive elimination of complex **F** and the aerobic reoxidation of complex **G** completed the catalytic cycle. The Chan–Lam couplings of sterically hindered benzimidazoles **1** were accelerated using MnO_2 (Table 1). These results suggest that the addition of MnO_2 probably affected the rate-determining disproportionation step. MnO_2 could facilitate the disproportionation of **E** or directly oxidize intermediate **E**. The enantioselectivities of our Chan–Lam couplings were determined at the reductive elimination step. The optically active bisoxazoline ligand **4j**, with excellent chelating ability, may control the formation of complex **F** and affect the energies of transition state structures of reductive elimination.

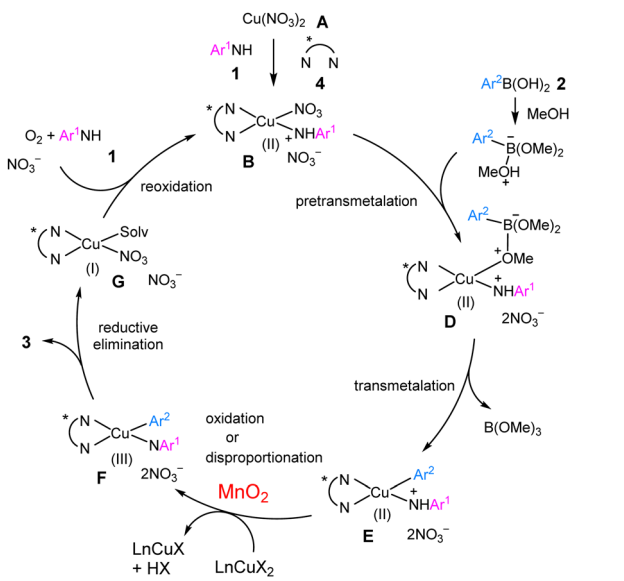


Fig. 2 Plausible reaction mechanism.

In conclusion, this is the first publication on the asymmetric Chan–Lam coupling for synthesizing C–N axially chiral biaryls. Diverse biaryls could be obtained in good yields and enantioselectivity at room temperature under copper-catalyzed conditions. This method will allow the easy synthesis of enantiomerically pure atropisomers for many industries, and in particular, the pharmaceutical industry where there is no existing methodology for this synthesis. Mechanistic studies using DFT calculations and kinetic studies are currently underway in our laboratory. Other diverse N–H substrates and boronic acid derivatives are also being explored.

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Conflicts of interest

There are no conflicts to declare.

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