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Copper-Catalyzed Desymmetric Intramolecular Ullmann C–N Coupling: An Enantioselective Preparation of Indolines

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Supporting Information

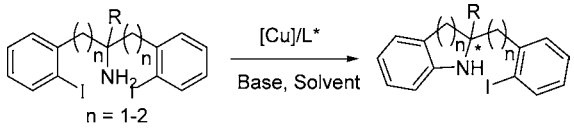
ABSTRACT: The first highly enantioselective copper-catalyzed intramolecular Ullmann C–N coupling reaction has been developed. The asymmetric desymmetrization of 1,3-bis(2-iodoaryl)propan-2-amines catalyzed by CuI/(R)-BINOL-derived ligands led to the enantioselective formation of indolines in high yields and excellent enantiomeric excesses. This method was also applied to the formation of 1,2,3,4-tetrahydroquinolines in high yields and excellent enantioselectivity.

Copper-catalyzed Ullmann-type coupling reactions have been extensively applied in both academia and industry, especially in recent years when great progress in the development of mild reaction conditions has been made.[1] However, achieving enantioselectivity in copper-catalyzed Ullmann-type coupling reactions remains a significant challenge.[2,3] So far, only one example for catalytic asymmetric Ullmann-type coupling reaction was reported by Ma et al.[3] in 2006. In their reaction, a quaternary stereochemical center was directly formed by coupling 2-halotrifluoroacetanilides with 2-methylacetoacetates. Satisfactory yields and good enantioselectivity were achieved at −45 °C. However, since other Ullmann-type couplings such as C–N, C–O, and C–S couplings did not involve direct formation of new stereochemical centers, little attention was focused on the asymmetric pattern of these copper-catalyzed coupling reactions.

Asymmetric desymmetrization has offered a general and powerful method for the enantioselective synthesis of chiral molecules.[4] This strategy has been successfully implemented through organocatalytic asymmetric reactions[5] such as the Stetter reactions and Michael additions as well as transition-metal-catalyzed asymmetric reactions,[6−8] including Pd-catalyzed coupling reactions,[6] copper-catalyzed reactions,[7] and so forth. Recently, Pd-catalyzed asymmetric desymmetric Buchwald–Hartwig reactions for enantioselective *N*-arylation[9,10] have been reported, which, however, afforded the desired products in only moderate enantiomeric excess (ee) values.[9d,e] To the best of our knowledge, no example of asymmetric desymmetrization was reported in copper-catalyzed Ullmann-type coupling reactions. In this paper, we would like to report the first example of copper-catalyzed asymmetric Ullmann C–N coupling reaction, which afforded chiral indolines in both high yields and excellent enantioselectivity, through a desymmetrization strategy.

We envisioned that, with the assistance of a chiral ligand, the copper-catalyzed desymmetric intramolecular Ullmann C–N coupling reaction of **1** would lead to the enantioselective formation of product **2** bearing a chiral quaternary carbon center (Scheme 1).

Scheme 1. Asymmetric Ullmann C–N Coupling Reaction via the Desymmetrization Strategy



The investigation was started with the desymmetric reaction of ethyl 2-(2-iodobenzyl)-2-amino-3-(2-iodophenyl)propanoate **1a**. In a brief screening of the chiral ligands and reaction conditions, we found that the reaction proceeded smoothly under the catalysis of 10 mol% CuI and 20 mol% (*R*)-BINOL (L1) in 1,4-dioxane at room temperature, with 150 mol% K_3PO_4 as the base.[11,12] The desired product **2a** was afforded in 54% yield and 40% ee (Table 1, entry 1). This result prompted us to further test several (*R*)-BINOL-derived ligands. The reactions were repeated under the same conditions by utilizing ligands L2–L4 with bulky aryl substituents in the 3,3′-positions of the BINOL backbone, and quenched after 10 h, disregarding the conversion ratio. As shown in Table 1, a remarkable improvement in the enantioselectivity was observed, albeit in lower yields. In all these new tests, the ee values of the products reached about 70% (Table 1, entries 2–4). It was also observed that ligand L4, which bears electron-withdrawing trifluoromethyl groups in the aryl rings, accelerated the reaction and afforded the desired product in relatively higher yield. This was perhaps caused by the enhancement of the acidity of the ligand which made it easier to be deprotonated and coordinate with CuI. Based on these observations, we then tested two other ligands, L5 and L6, which bear even more bulky substituents in the 3,3′-positions than L2–L4. As expected, the CuI-L5-catalyzed reaction proceeded very smoothly and afforded the desired product in both high yield and very good

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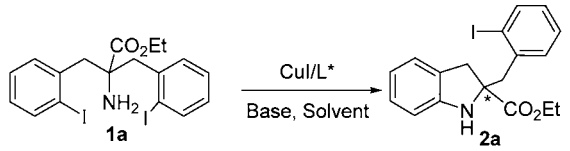
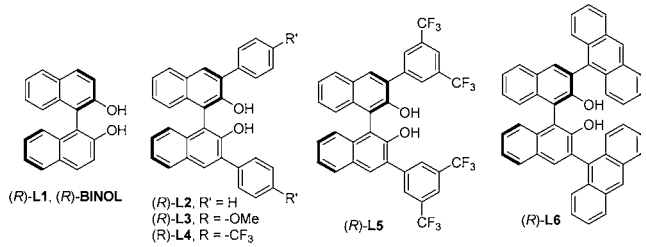
Table 1. Screening Reaction Conditions[a]

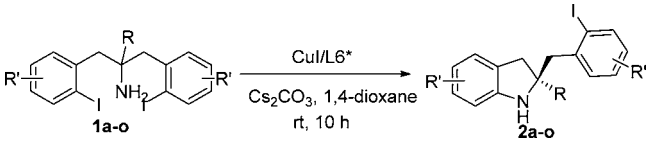


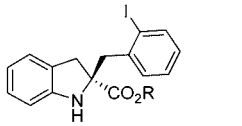


entry	ligand	base or additive	solvent	yield[b] (%)	ee[c] (%)
1	L1	K_3PO_4	1,4-dioxane	51	40
2	L2	K_3PO_4	1,4-dioxane	20	68
3	L3	K_3PO_4	1,4-dioxane	16	70
4	L4	K_3PO_4	1,4-dioxane	34	71
5	L5	K_3PO_4	1,4-dioxane	78	89
6	L6	K_3PO_4	1,4-dioxane	12	98
7	L5	K_3PO_4	MeCN	92	77
8	L5	K_3PO_4	toluene	90	73
9	L5	K_3PO_4	THF	61	85
10	L5	K_2CO_3	1,4-dioxane	53	87
11	L5	Cs_2CO_3	1,4-dioxane	95	87
12	**L6**	**Cs_2CO_3**	**1,4-dioxane**	**91**	**96**

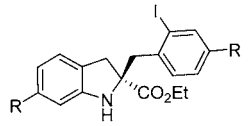
[a]Reagents and reaction conditions: **1a** (0.25 mmol, 1.0 equiv), CuI (0.025 mmol, 10 mol%), ligand (0.05 mmol, 20 mol%), base, (0.375 mmol, 1.5 equiv), solvent (1 mL), 10 h. [b]Isolated yields. [c]Determined by HPLC analysis (Chirapak AD-H column).

Table 2. Scope of the Substrates[a]

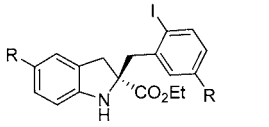




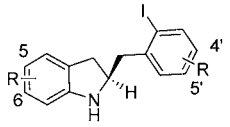
2a: R = -Et, 91% yield, 96% *ee*
2b: R = -*i*-Pr, 93% yield, 98% *ee*
2c: R = -*t*-Bu, 71% yield, 97% *ee*



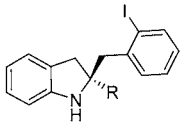
2d: R = -F, 81% yield, 97% *ee*
2e: R = -NO_2, 90% yield, > 99% *ee*
2f: R = -CO_2Me, 86% yield, 98% *ee*



2g: R = -Br, 88% yield, > 99% *ee*
2h: R = -Me, 75% yield, 99% *ee*
2i: R = -OMe, 64% yield, 96% *ee*



2j: R = -H, 94% yield, 93% *ee*
2k: R = -F (6, 4'), 94% yield, 95% *ee*
2l: R = -Me (5, 5'), 93% yield, 92% *ee*



2m: R = -Me,89% yield, 83% *ee*
2n: R = --CH=CH_2, 70% yield, 90% *ee*
2o: R = -CH_2N_3, 75% yield, 75% ee

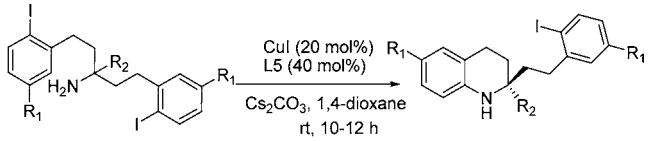
[a]Reagents and reaction conditions: **1** (0.25 mmol, 1.0 equiv), CuI (0.025 mmol, 10 mol%), L6 (0.05 mmol, 20 mol%), Cs_2CO_3, (0.375 mmol, 1.5 equiv), 1,4-dioxane (1 mL), 10 h. Yields given are isolated yields. Enantiomeric excesses were determined by HPLC analysis (Chirapak AD-H or OD-H column).

enantioselectivity (78% yield and 89% ee, Table 1, entry 5), while the CuI-L6-catalyzed reaction proceeded very slowly and afforded the desired product in only 12% yield, but in excellent enantioselectivity (98% ee, Table 1, entry 6). With L5 as the ligand, further screening of the solvents were performed and the results revealed that the reaction also worked well under several tested solvents such as MeCN, THF, and toluene (Table 1, entries 7–9), while 1,4-dioxane turned out to be the best solvent for the high enantioselectivity. It seemed that the base played an important role in affecting the rate of the reaction. Cs_2CO_3 was found to accelerate the reaction most significantly and the product was obtained in higher yield and with only a slightly loss of enantioselectivity as compared with that of K_3PO_4 (Table 1, entries 11 and 5). Similar result was observed with L6 as the ligand and the desired product was afforded in both excellent yield and excellent enantioselectivity (91% yield, 96% ee) in 1,4-dioxane at room temperature with Cs_2CO_3 as the base (Table 1, entry 12).

With the optimized conditions in hand, we then explored the reaction scope with a series of substrates and the results are shown in Table 2. First, the substrates bearing different ester groups at the quaternary prochiral center were tested and all delivered the corresponding products in high yields and excellent enantioselectivity (Table 2, **2a–c**). Both electron-withdrawing and electron-donating substituents in the aryl rings of the substrates were well tolerated (Table 2, **2d–i**). In some cases, the ee values of the desired products even reached more than 99% (Table 2, **2e** and **2g**). Furthermore, the absolute configurations of these products were assigned to be *S* in analogy to that of **2g**, whose absolute configuration was ambiguously determined through the X-ray crystal diffraction analysis.[13] Further exploration of substrate scope revealed that the reactions of **1j–l**, which bear a hydrogen atom at the tertiary prochiral center, also proceeded well and afforded the corresponding products **2j–l** in high yields and excellent enantioselectivity, while other substrates like **1m–o** furnished the desired products **2m–o** in high yields but slightly lower enantioselectivity.[14]

Encouraged by the success of enantioselective preparation of the chiral indoline products, we then explored a similar intramolecular desymmetric Ullmann C–N coupling reaction for the enantioselective synthesis of 1,2,3,4-tetrahydroquinoline derivatives. As shown in Scheme 2, although they were less reactive than their one-carbon-shorter counterparts, **3a** and **3b** could undergo desymmetrization smoothly under the catalysis of 20 mol% CuI and 40 mol% L5, to afford the corresponding

Scheme 2. Enantioselective Formation of 1,2,3,4-Tetrahydroquinoline Derivatives via Intramolecular Desymmetric Ullmann C–N Coupling Reaction



3a: R_1 = -H, R_2 = -CO_2Et
3b: R_1 = -Me, R_2 = -CO_2Et
3c: R_1 = R_2 = -H

4a: 96% yield, > 99% *ee*
4b: 85% yield, 99% *ee*
4c: 83% yield, 82% ee

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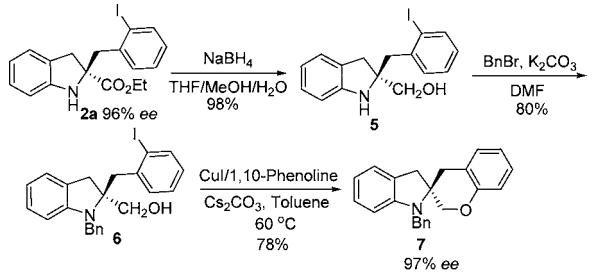
1,2,3,4-tetrahydroquinolines **4a** and **4b** with quaternary chiral centers in high yields and excellent enantioselectivity. Under the same condition, the reaction of 1,5-bis(2-iodophenyl)-pentan-3-amine **3c** also proceeded smoothly and provided the desired product **4c** with a tertiary chiral center in high yield and good enantioselectivity.

To further elucidate the application of such desymmetric reactions in organic synthesis, we chose the synthesis of the chiral spirocyclic compound **7** as an example. As shown in Scheme 3, compound **7** was synthesized through a simple three-step transformation from the desymmetric product **2a**.

Scheme 3. Example for the Synthesis of Chiral Spirocyclic Compounds



Based on the literature reports[8b,15] and our experimental observations, we propose a plausible mechanism to account for the chirality induction. As shown in Figure 1, the CuI may

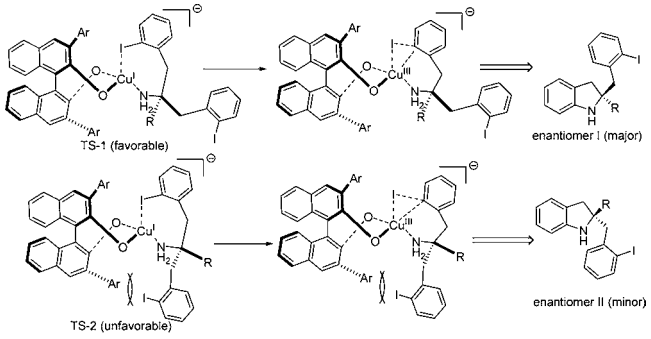


Figure 1. Plausible intermediates for the chirality induction.

coordinate with the substrate and the chiral ligand to form a tetrahedral Cu^{I} complex in two different ways. Obviously, TS-1 has suffered less steric interactions between the aryl group of the binol moiety and the phenyl ring of the residual 2-iodobenzyl than does TS-2. Thus, one would expect the reaction through TS-1 leading to the formation of enantiomer I to be more favorable than that through TS-2, which would produce enantiomer II. Furthermore, for the ester-embodied substrates, a hydrogen bond between the oxygen atom of the ester group and the amine group may be formed.[16] The formation of such hydrogen bond will increase the ability of the substrate to coordinate with Cu(I) and also reduce the steric interaction between the aryl group of the BINOL moiety and the ester group, which may also attribute to the excellent enantioselectivity of such ester-embodied substrates.

In summary, we have developed the first enantioselective intramolecular Ullmann C−N coupling reaction by asymmetric copper catalysis through desymmetrization of the 1,3-bis(2-iodoaryl)propan-2-amines, which led to the formation of the chiral indolines in good yields and high ee values in 1,4-dioxane with Cs_2CO_3 as the base. This method was also applied to the enantioselective synthesis of 1,2,3,4-tetrahydroquinoline derivatives. Further exploration and application of this reaction in organic synthesis is underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Full experimental and characterization data, including ^{1}H and ^{13}C NMR for all the new compounds, chiral HPLC spectra for the products, and crystal structure (CIF) of **2g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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