Development and Challenges in Copper-Catalyzed Asymmetric Ullmann-Type Coupling Reactions

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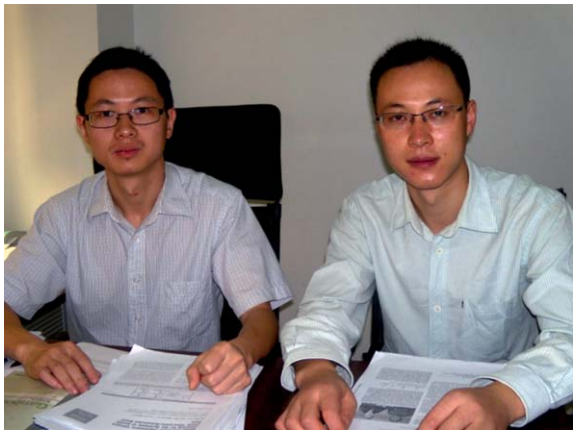
Abstract: Ullmann-type coupling is one of the most powerful methods for the formation of aryl C–C, C–N, and C–O bonds. Yet asymmetric Ullmann coupling has received little attention because of the great challenges in both ligand and reaction designs. The success of the first catalytic enantioselective intramolecular Ullmann C–N coupling reaction through an asymmetric desymmetrization strategy offers a new way to develop enantioselective variants of such reactions. This paper addresses the importance of the desymmetrization strategy in Ullmann-type couplings and outlines some future directions in this field.

Key words: copper catalysis, asymmetric desymmetrization, Ullmann coupling, enantioselectivity, indolines



Qian Cai (left) is a principal investigator at the Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences (GIBH). He received his B.S. degree in chemistry from Nankai University in 2001 and PhD in organic chemistry from Shanghai Institute of Organic Chemistry in 2006 under the supervision of Prof. Dawei Ma. After conducting postdoctoral research with Prof. Shaomeng Wang at the University of Michigan, Ann Arbor, he joined the faculty at GIBH in 2009 and has worked as a principal investigator since 2010.
Fengtao Zhou (right) received his B.S. degree from Sichuan University in 2008 and is now pursuing his doctoral degree under the supervision of Prof. Ke Ding and Prof. Qian Cai.

The copper-catalyzed Ullmann-type coupling reactions, including Ullmann, Ullmann–Goldberg, and Ullmann–Hurtley condensation and Ullmann diaryl ether formation, have been known for more than a century as one of the most efficient and powerful methods for the formation of aryl C–C, C–N and C–O bonds.[1] Traditional Ullmann-type coupling reactions suffered from the harsh reaction conditions such as high temperature, stoichiometric amounts of copper reagents, and limited substrate scope. However, with soluble copper salts or ligand coordinated Cu complexes as the catalysts, research on Ullmann-type coupling has been resurrected and many mild conditions have been developed since the 1990s. Now such reactions have been applied extensively in both academia and industry.[1c–f]

Despite the great progress that has been made in recent years, achieving high enantioselectivity in Ullmann-type coupling reactions remains a significant challenge. Until 2006, only some chiral substrate-induced asymmetric Ullmann reactions[2] have been developed for the synthesis of biaryl compounds, and, to the best of our knowledge, no catalytic asymmetric Ullmann-type coupling reactions have been reported.

In 2006, an important breakthrough was achieved by Ma and co-workers.[3] They reported the CuI and *trans*-4-hydroxy-L-proline catalyzed enantioselective arylation of 2-methylacetoacetate, affording 2,2-arylmethylacetates bearing chiral quaternary carbon centers in good yields and high ee values (Scheme 1). This reaction has some significant features: it runs at the lowest reaction temperature in the history of Ullmann-type coupling reactions (–45 to –20 °C), and it is also the first catalytic asymmetric Ullmann C–C coupling reaction. However, the scope of both reactants was greatly limited; only 2-iodotrifluoroacetanilides and 2-methylacetoacetates were suitable substrates for the reaction. The *ortho*-substituted -$NHCOCF_3$ group of the aryl halides is necessary for achieving high reactivity and good enantioselectivity. Furthermore, only 2-methylacetoacetates were suitable carbon nucleophiles for the formation of the enantioenriched products bearing quaternary carbon centers. Other carbon nucleophiles, such as ethyl acetoacetates, afforded the products bearing tertiary carbon centers accompanied by rapid racemization.

With such limitations, no further research was reported in asymmetric Ullmann C–C coupling reactions since Ma's work in the last few years and direct asymmetric Ullmann C–C coupling still remains a great challenge. Other Ullmann-type coupling, such as Ullmann C–N or C–O coupling, did not involve the direct formation of a chiral

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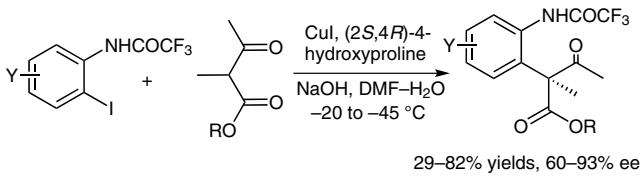


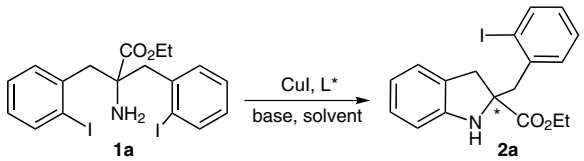
Scheme 1 Copper-catalyzed enantioselective arylation of 2-methylacetoacetates

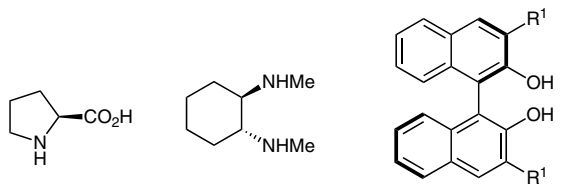
center, thus, little attention was focused on their asymmetric variation.

Normally, for reactions in which the chiral center does not participate directly at the reactive site of bond formation, there are two ways to achieve enantioselectivity: kinetic resolution of racemic substrates[4] and asymmetric desymmetrization reactions.[5] Based on the desymmetrization strategy, we have recently reported the 'indirect' formation of chiral centers through the copper-catalyzed asymmetric desymmetric intramolecular Ullmann C–N coupling,[6] which offered a new way to achieve enantioselective Ullmann-type coupling reactions.

In our research, we anticipated that the desymmetric intramolecular coupling reaction of compound **1a** would lead to the enantioselective formation of product **2a** bearing a chiral quaternary carbon center (Table 1). The success of such enantioselective coupling relied on the appropriate selection of chiral ligands and reaction conditions. In recent years, many ligands have been developed for copper-catalyzed Ullmann-type coupling reactions. By exploiting those well-developed ligands, we found that low enantioselectivity was obtained in the model reaction with the assistance of three types of chiral ligands (Table 1): L-proline (**L1**), (1*R*,2*R*)-N^1,N^2-dimethylcyclohexane-1,2-diamine (**L2**) and (*R*)-BINOL (**L3**). Further optimization of BINOL-derived ligands and reaction conditions led to the development of a highly enantioselective intramolecular Ullmann C–N coupling reaction (Table 1, entry 4).

Table 1 Screening of Ligands and Reaction Conditions





L1: L-proline **L2**: (1*R*,2*R*)-N^1,N^2-dimethyl cyclohexane-1,2-diamine **L3**: R^1 = H, *(R)*-BINOL **L4**: R^1 = 9-anthracenyl **L5**: R^1 = 3,5-bis(trifluoromethyl)-phenyl

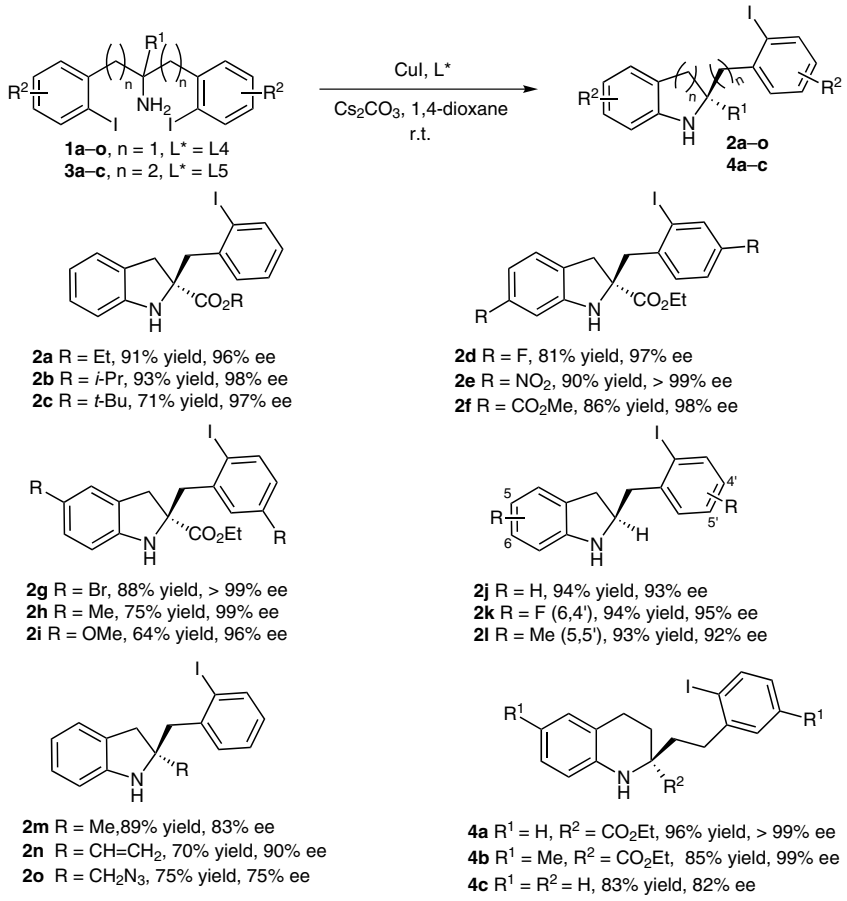
Entry	L*	Base	Solvent	Time (h)	Yield (%)	ee (%)
1	**L1**	K_3PO_4	DMSO	3	95	41 (*R*)
2	**L2**	K_3PO_4	DMSO	20	35	25 (*S*)
3	**L3**	K_3PO_4	1,4-dioxane	10	51	40 (*S*)
4	**L4**	Cs_2CO_3	1,4-dioxane	10	91	96 (*S*)
5	**L5**	Cs_2CO_3	1,4-dioxane	10	95	87 (*S*)

This CuI-catalyzed asymmetric desymmetric intramolecular Ullmann C–N coupling reaction[7] is effective for preparing a wide range of indolines bearing quaternary or tertiary chiral carbon centers. As shown in Scheme 2, different substitutes on the aryl rings were well-tolerated and the desired products were obtained in high yields (typically 64–94%) and good to excellent enantioselectivity (typically 75–99% ee). Furthermore, despite the fact that formation of a six-membered ring is more difficult than a five-membered ring, extending the reaction to enantioselective preparation of 1,2,3,4-tetrahydroquinolines **4a–c** was also successful with the assistance of higher dosing of CuI and ligand **L5**.

Based on the literature reports[8] and on our experimental observations, we proposed a preliminary model for chirality induction. As shown in Scheme 3, the CuI may coordinate with the substrate and the chiral ligand to form a tetrahedral Cu^I-complex in two different ways. Clearly, TS-1 suffers less problematic steric interactions between the aryl group of the binol moiety and the phenyl ring of the residual 2-iodobenzyl than TS-2. Thus, one would expect the reaction through TS-1 leading to the formation of enantiomer I to be more favorable than TS-2, which would produce enantiomer II.

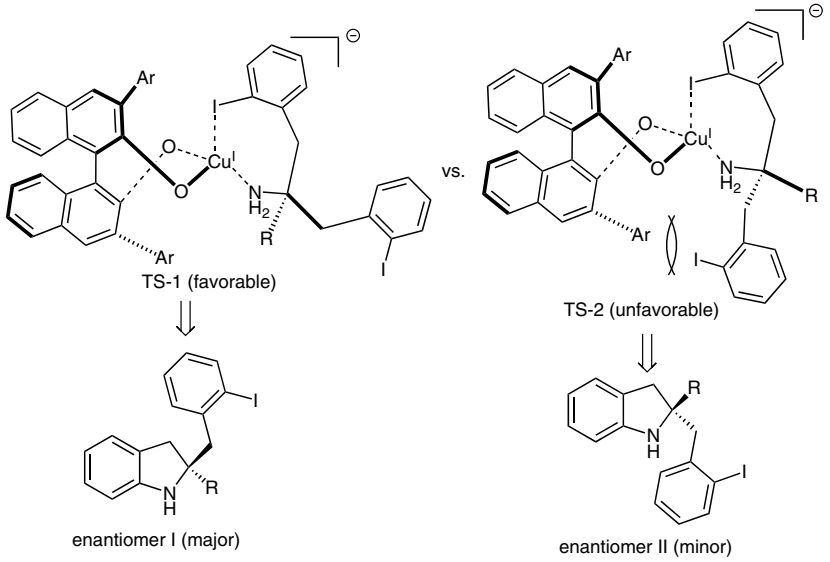
Although this model is in agreement with the observed stereochemistry, a contradiction existed in this explanation. Based on the data analysis of products **2j** and **2m–o**, it seemed that a bulky substitute reduced the enantioselectivity (recently, we further studied the reaction by putting a bulkier alkyl group at this position, which offered lower enantioselectivity in comparison with **2j** and **2m**). However, the enantioselectivity of **2a** is clearly higher than that of **2j** and **2m**, despite the fact that the ester group is much bulkier than a hydrogen atom or methyl group, which implied other factors may also be operative for the enantioselectivity. We proposed that a hydrogen bond between the oxygen atom of the ester group and the amine group may be formed to account for the higher enantioselectivity of ester-substituted substrates. However, such a model is still only a hypothesis based on current experimental observations. It is still a great challenge to fully understand the mechanism of such reactions.

With the successful development of the first copper-catalyzed asymmetric intramolecular Ullmann C–N coupling reaction, we envisioned that such an approach would offer opportunities for developing novel asymmetric Ullmann-type coupling and to further extend the applications of such reactions. In the future, in our view, at least four aspects are worth further endeavor: (1) The modification and optimization of the chiral ligands. Current binol-



Scheme 2 Substrate scope of the asymmetric desymmetric Ullmann C–N coupling reactions

derived ligands work well in some cases, however, as we pointed out earlier, the enantioselectivity for substrates bearing bulky alkyl groups on the prochiral center is still relatively low. This problem may be solved by further ligand optimization. (2) The exploration of substrates bearing special functional groups and further understanding of the reaction mechanism. As observed, the ester-substituted substrates showed higher enantioselectivity in our reactions, which may be explained by the formation of a hydrogen bond. However, more evidence is needed. Other substrates bearing special functional groups as directing groups should be explored to help better understand the



Scheme 3 Proposed transition state

reaction mechanism, which, in return, may help further ligand design and extension of substrate scope. (3) The development of asymmetric desymmetric intermolecular Ullmann C–N coupling and other Ullmann-type couplings. Similar to the intramolecular Ullmann C–N coupling reaction, other enantioselective Ullmann-type couplings may also be achieved through the same strategy. (4) The kinetic resolution of racemic reactants. The desymmetric reaction provided the optically active products bearing the same substituents on both of the aryl rings, which would cause some problems in further selective transformations. The kinetic resolution of racemic substrates may be a good way to solve this problem, which would also provide more attractive synthetic compounds.

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(7) **Typical Procedure:** A mixture of **1** or **3** (0.25 mmol), ligand (0.05 mmol), CuI (0.025 mmol) and Cs_2CO_3 (0.375 mmol) in 1,4-dioxane (1.0 mL) was stirred at r.t. for 10 h. H_2O (5.0 mL) and EtOAc (5.0 mL) were added and the organic phase was separated. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with H_2O and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was loaded on a silica column and purified by flash chromatography to afford the desired products.

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