

Amino acid-promoted Ullmann-type coupling reactions and their applications in organic synthesis*

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Abstract: Ullmann-type coupling reactions between aryl halides and N-containing reagents, phenols, and other related nucleophilic agents are very valuable transformations for organic synthesis. Their conventional reaction conditions require high reaction temperatures. We describe here that some amino acids, either as substrates or ligands, can lead Cu-catalyzed C–N, C–O, C–S, and C–C bond formations work at relatively low temperatures. An *ortho*-substitution effect caused by NHCOR groups is discussed. Applications of these newly developed reactions to heterocycle preparation and asymmetric synthesis are also presented.

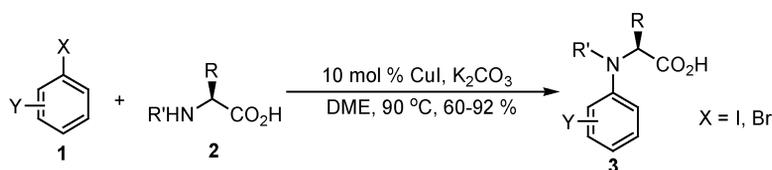
Keywords: amino acids; catalysis; copper; coupling; synthesis.

Since their discovery in the early 1990s, Ullmann-type coupling reactions have become a typical method for preparing aryl amines, biaryl ethers, and *N*-aryl heterocycles that are important in the pharmaceutical and materials world. However, a significant drawback of these reactions is the requirement of a high reaction temperature, which greatly limits its scope of application. This problem has been solved in recent years, mainly by using some *N,N*- or *N,O*-bidentate compounds as the reaction promoters [1]. These achievements not only provide mild conditions for known transformations, but also open a new avenue to heterocycle preparation and asymmetric synthesis. Herein, we wish to summarize our results on using amino acids as the promoters.

In 1998, we first revealed that there exists an accelerating effect induced by the structure of α -amino acid in Cu-catalyzed Ullmann reaction, leading to completion of the coupling reactions of aryl halides **1** and α -amino acids **2** at 80–90 °C (Scheme 1) [2]. This discovery offers a facile method for assembly of enantiopure *N*-aryl amino acids that are potential building blocks for assembling bioactive molecules [2]. Soon after that, several groups reported that some bidentate compounds like 1,10-phenanthroline, 1,2-diamines, and 1,2-diols could serve as ligands to facilitate Ullmann-type aryl amination at relatively low temperatures [3]. These results prompted us to explore if amino acids have the similar function. We were pleased to find that when L-proline was used as a ligand, coupling of aryl

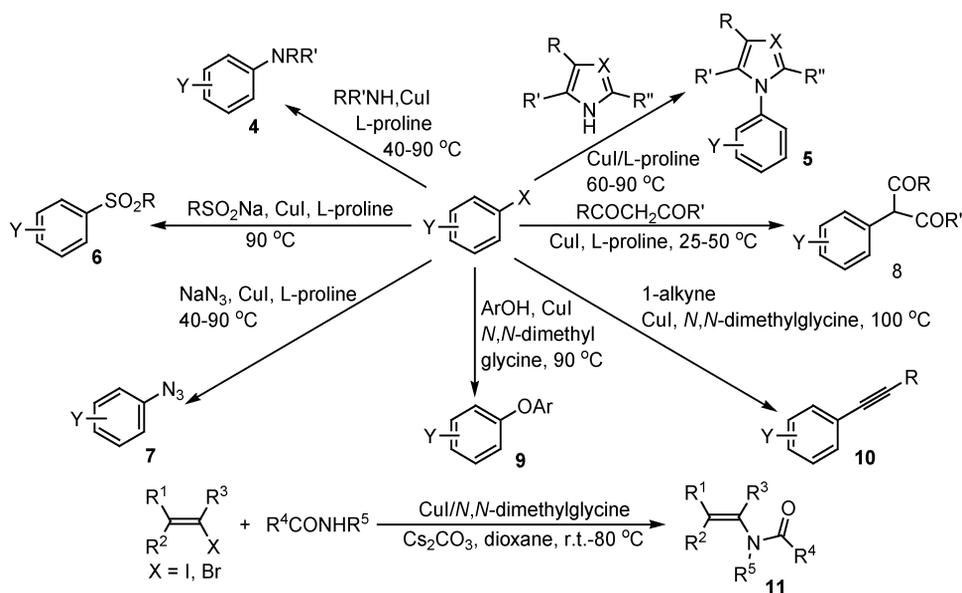
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Scheme 1 CuI-catalyzed coupling of aryl halides with α -amino acids.

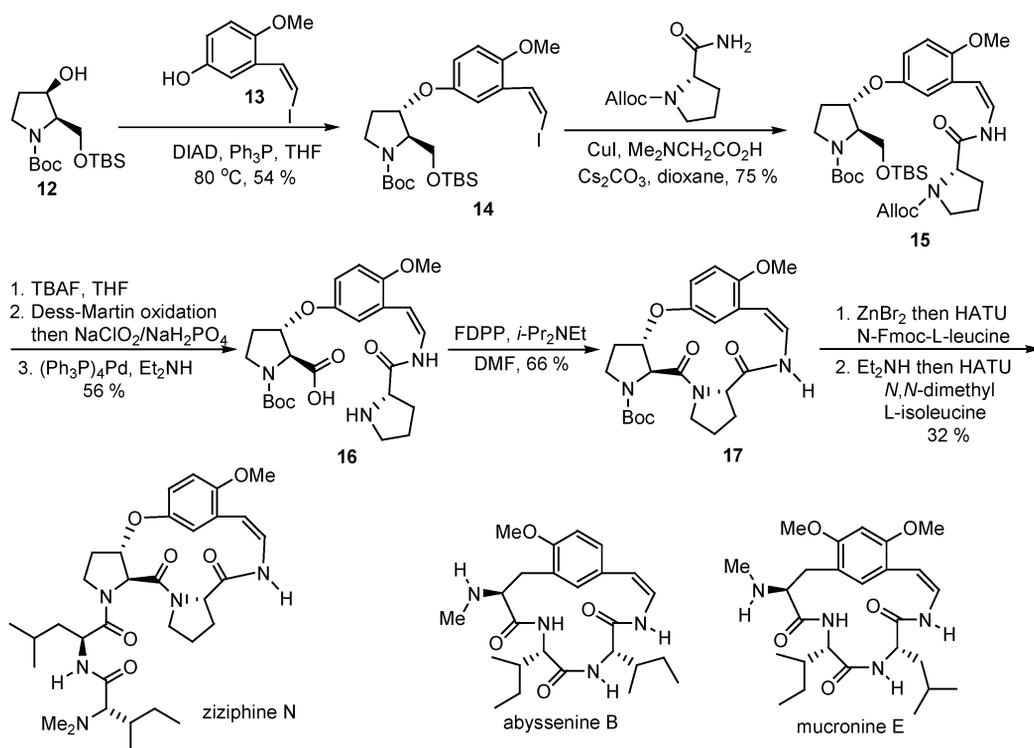
halides with primary amines, cyclic secondary amines, and N-containing heterocycles proceeded at 40–90 °C to give the corresponding anilines **4** and *N*-aryl heterocycles **5** in good yields (Scheme 2) [4]. Further investigations revealed that *L*-proline also worked to facilitate the following transformations: (1) elaboration aryl sulfones **6** via coupling of aryl halides with sulfinic acid salts [5]; (2) formation of aryl azides **7** and vinyl azides via azidation of aryl halides and vinyl halides with sodium azide at 40–95 °C [6]; and (3) coupling of aryl halides with β -keto esters and malonates at 25–50 °C to give β -aryl carbonyl compounds **8** [7]. At the same time, we discovered that *N,N*-dimethylglycine could promote Cu-catalyzed formation of biaryl ethers **9** to make reaction complete at 90 °C [8]. This ligand also led to Sonogashira reaction work in the absence of palladium and phosphine ligands [9], and facilitated production of enamides **11** from vinyl halides and amides at temperatures ranging from ambient temperature up to 80 °C [10].



Scheme 2 CuI/amino acid-catalyzed C–N, C–O, C–S, and C–C formation reactions from aryl halides and vinyl halides.

In order to demonstrate the usages of these newly developed coupling reactions, we decided to apply them in the synthesis of two types of cyclopeptides. Cyclopeptide alkaloids are a growing family that contains over 200 members discovered from a wide range of plant species [11]. Structurally, they contain a 13-, 14-, or 15-membered macrocycle bearing a peptide unit, which is connected to a benzene ring with either a 1,4- or 1,3-orientation. The previous protocols to these molecules all chose elaboration of their enamide moiety via different elimination methods after macrocyclization [11b]. Such tedious and low-yielding manipulation remarkably decreased the synthetic efficiency. By using

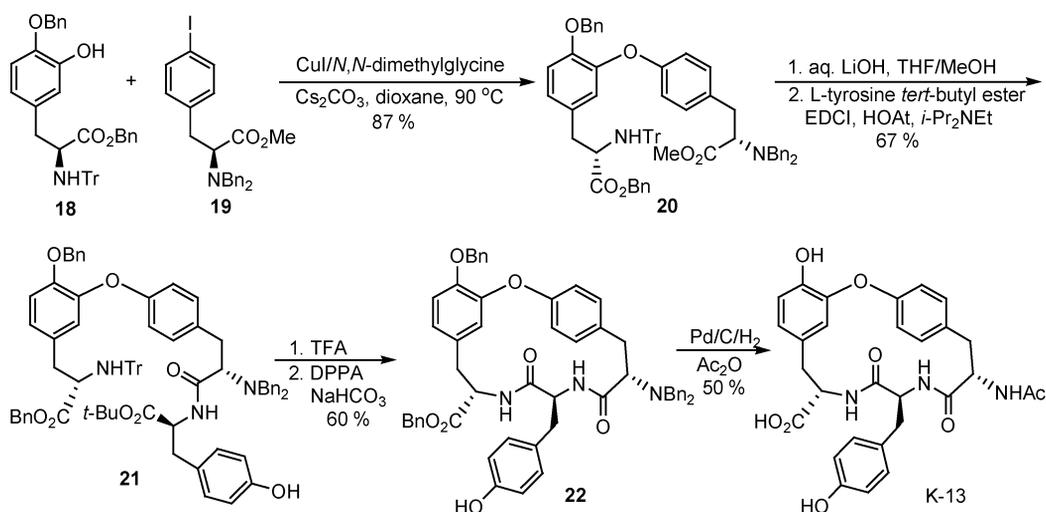
CuI/*N,N*-dimethylglycine-catalyzed coupling reaction of vinyl iodides with amides as the key step, we developed a new protocol to these compounds. As outlined in Scheme 3 [12], Mitsunobu reaction of alcohol **12** and phenol **13** was carried out at 80 °C to afford vinyl iodide **14** in 54 % yield. CuI/*N,N*-dimethylglycine-catalyzed coupling of **14** with an *L*-proline-derived amide delivered enamide **15** in 75 % yield [10a]. After cleavage of the silyl ether with tetrabutylammonium fluoride (TBAF), the liberated alcohol was converted into the corresponding acid via stepwise oxidation, which was exposed on Pd(0) and diethylamine to provide amino acid **16**. FDPP-mediated macrocyclization of **16** gave rise to lactam **17**, which was subjected to deprotection and subsequent introduction of two amino acid residues to furnish 13-membered cyclopeptide alkaloid ziziphine N [12]. Using the similar strategy, two 15-membered cyclopeptide alkaloids, abyssenine B and mucronine E, were assembled the first time [13]. It is noteworthy that Evano and coworkers developed a more efficient strategy to these cyclopeptide alkaloids [14], which highly relied on using an intramolecular CuI-catalyzed coupling reaction of vinyl iodides with amides for macrocyclization.



Scheme 3 Assembly of cyclopeptide alkaloids via CuI/*N,N*-dimethylglycine-catalyzed coupling of vinyl iodides with amides.

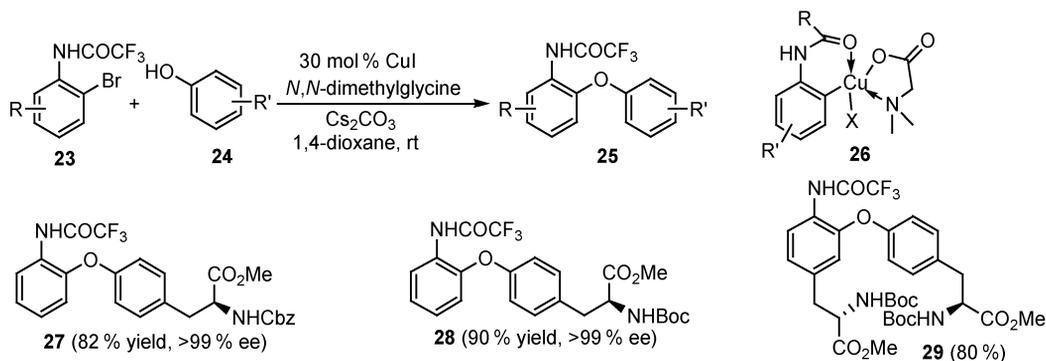
Biaryl ether-embodied cyclopeptides are another class of cyclopeptides we studied, which include antibiotics vancomycin and teicoplanin, antitumor agents K-13 and bouvardin, and neurotensin antagonist RP-664536 [15]. Ullmann-type diaryl ether formation is an ideal method for elaboration of their biaryl ether amino acid parts owing to convenient availability of the chiral building blocks. During the past decades, several groups have tried this strategy by developing milder coupling conditions, but limited progress has been made [15a]. By using *N*-trityl or *N,N*-dibenzyl protected amino esters as substrates and *N,N*-dimethylglycine as a reaction promoter, we could achieve the coupling of *L*-phenylalanine-derived aryl bromides with *L*-tyrosine-derived phenols in good yields and excellent

enantiopurities [16]. The synthetic application was illustrated by elaboration of K-13 as outlined in Scheme 4. CuI/*N,N*-dimethylglycine-catalyzed coupling of phenol **18** and bromide **19** provided biaryl ether **20** in 87 % yield, which was connected with another L-tyrosine derivative, after deprotection, to afford amide **21**. Treatment of **21** with trifluoroacetic acid (TFA) followed by diphenyl phosphoryl azide (DPPA)-mediated macrocyclization of the resultant amino acid produced lactam **22**, which was subjected to hydrogenolysis and acylation to give K-13. This route represents the simplest one for assembling K-13 up to date.



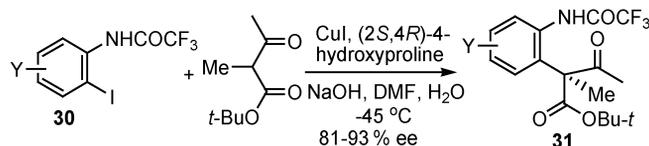
Scheme 4 CuI/*N,N*-dimethylglycine-catalyzed coupling route to K-13.

When 2-bromotrifluoroacetanilides **23** were used as a substrate for CuI/*N,N*-dimethylglycine-catalyzed biaryl ether synthesis (Scheme 5), we observed that the reaction turned out to be very fast even at room temperature. This phenomena revealed that there is an accelerating effect caused by an *ortho*-amide group in Ullmann-type coupling reactions [17]. This effect could be rationalized by formation of a complex **26** in which the carbonyl group of the amide moiety may coordinate with Cu to lead to the oxidative addition intermediate more stable. By combination of *ortho*-substituent and ligand effects, we could synthesize amino acid comprising biaryl ethers **27–29** at room temperature. No racemization occurred even when N-Boc and N-Cbz protecting groups were employed (Scheme 5) [17].



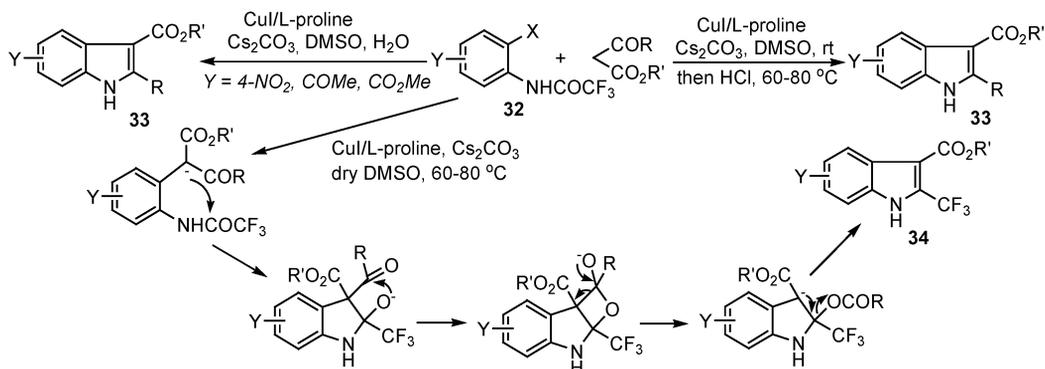
Scheme 5 Biaryl ether formation at room temperature caused by *ortho*-substituent and ligand effects.

The *ortho*-substituent effect also exists in the coupling reaction of aryl halides with activated methylene compounds, leading to the reaction taking place at $-45\text{ }^{\circ}\text{C}$. This result represents a new record low in reaction temperatures for Ullmann-type coupling reactions. Taking this advantage, we could create α -aryl all-carbon quaternary centers with high enantioselectivity (up to 93 % ee) through coupling reaction of **30** and 2-methyl acetoacetates. In this case, *trans*-4-hydroxy-L-proline was used as a ligand because it showed better asymmetric induction than L-proline (Scheme 6) [18].



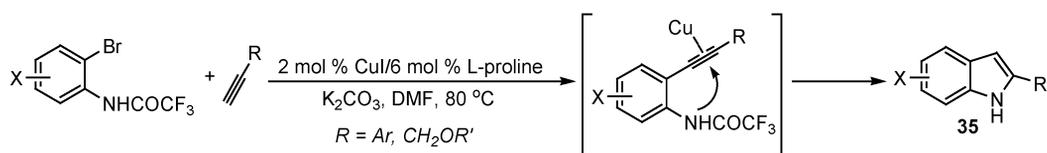
Scheme 6 CuI/*trans*-4-hydroxy-L-proline-catalyzed enantioselective coupling of 2-iodotrifluoroacetanilides with 2-methyl acetoacetates.

The *ortho*-substituent directed by amide groups also provides an opportunity for assembly of heterocycles via Cu-catalyzed coupling reactions. For example, following three procedures were developed for construction of 2,3-disubstituted indoles **33** or **34** based on coupling of 2-halotrifluoro-acetanilides **32** and β -keto esters (Scheme 7) [19]: (1) acid-induced hydrolysis of the crude coupling products and subsequent condensative cyclization; (2) base-induced hydrolysis of the coupling products and subsequent condensative cyclization, which limits substrates to those bearing an strong electronic withdrawing group at the 4-position of 2-halotrifluoro-acetanilides [19a]; and (3) heating the coupling mixture at $60\text{--}80\text{ }^{\circ}\text{C}$ under anhydrous conditions, which provided 2-trifluoromethyl indoles **34** through a novel coupling/condensation/deacylation process as indicated in Scheme 7 [19b].



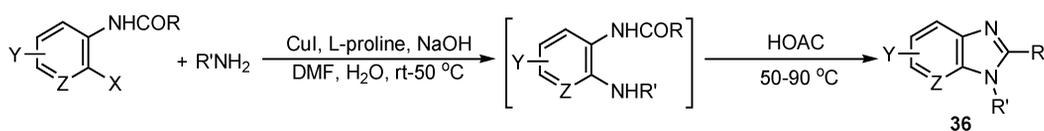
Scheme 7 Three cascade processes to 2,3-disubstituted indoles from 2-halotrifluoroacetanilides and β -keto esters via CuI/L-proline catalyzed coupling.

Scheme 8 outlined another method for assembly of indoles via our coupling methods. This conversion involves a CuI/L-proline-catalyzed coupling between aryl bromide and the 1-alkyne followed by a CuI-mediated cyclization process. An *ortho*-substituent effect directed by NHCOCF₃ may make this reaction proceed under these mild conditions ($80\text{ }^{\circ}\text{C}$) because higher reaction temperatures are required for CuI/*N,N*-dimethylglycine-catalyzed Sonogashira reaction with simple aryl bromides [9a]. It is noteworthy that good yields were obtained from both aryl acetylenes and O-protected propargyl alcohol, while simple aliphatic alkynes gave lower yields.



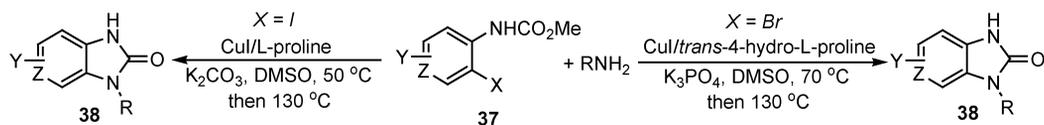
Scheme 8 Synthesis of 2-substituted indoles via CuI/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides and 1-alkynes.

1,2-Disubstituted benzimidazoles are an important class of heterocyclic compounds that have a wide range of biological properties. An effective method for assembly of these molecules was developed via CuI/L-proline-catalyzed amination of 2-halotrifluoroacetanilides. Owing to strong *ortho*-substituent effect directed by amide groups, the coupling reaction occurred at room temperature to 50 °C to provide amination products, which delivered 1,2-disubstituted benzimidazoles **36** upon treatment with acetic acid at 50–90 °C (Scheme 9) [21]. This method allows the assembly of a wide range of poly-substituted benzimidazoles because variation at the 1- and 2-positions of the benzimidazole is possible by employing different primary amines and varying the amido groups of the 2-haloacetanilides, and introduction of substituents in different positions of the benzimidazole phenyl ring could be achieved by changing aryl halides.



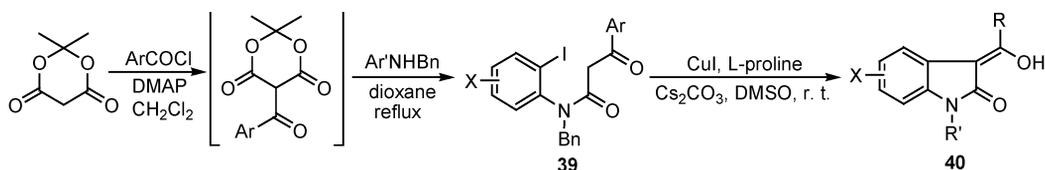
Scheme 9 Assembly of 1,2-disubstituted benzimidazoles via CuI/L-proline-catalyzed coupling of 2-halotrifluoroacetanilides and primary amines.

The *ortho*-substituent effect directed by carbamate groups is considerably weak, as evident from that the amination of methyl *o*-haloarylcarbamates **37** needed reaction temperatures above 50 °C (for iodides) and 70 °C (for bromides) to ensure good conversion (Scheme 10). The reaction products were further converted into biologically important N-substituted 1,3-dihydrobenzimidazol-2-ones **38**, upon heating at 130 °C [22]. It is noteworthy that for bromides *trans*-4-hydroxy-L-proline gave better results than L-proline. A number of functional groups are tolerated by these reaction conditions, including vinyl, nitro, carboxylate, amide, ester, ketone, and silyl ether groups.



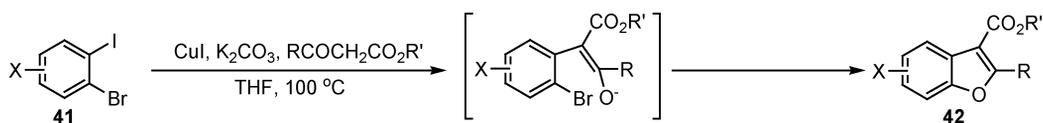
Scheme 10 Aryl amination route to N-substituted 1,3-dihydrobenzimidazol-2-ones.

Intramolecular cross-coupling is another promising approach to heterocycles [23–25]. To this end, a convenient synthesis of 3-acyl oxindoles **40** was developed (Scheme 11). The required amides **39** were prepared from Meldrum's acid, acyl chlorides, and 2-iodoanilines in a one-pot manner, which were effected with CuI/L-proline to give **40** at room temperature. Electronic effects on the aromatic ring have little influence on this reaction. Variations at the 1-, 3-, 4-, 5-, and 6-positions of the oxindoles were achieved by employing the corresponding amides [23].



Scheme 11 Elaboration of 3-acyl oxindoles via an intramolecular coupling reaction.

As depicted in Scheme 12, CuI-catalyzed coupling of 1-bromo-2-iodobenzenes **41** with β -keto esters in tetrahydrofuran (THF) at 100 °C leads to 2,3-disubstituted benzofurans **42**. This domino transformation involves an intermolecular C–C bond formation and a subsequent intramolecular C–O bond formation process. Benzofurans with different substituents at the 5- and 6-positions are accessible by employing the corresponding 1-bromo-2-iodobenzenes [24].



Scheme 12 Synthesis of 2,3-disubstituted benzofurans via CuI-catalyzed coupling of 1-bromo-2-iodobenzenes and β -keto esters

As a conclusion, we have demonstrated that some amino acids are powerful promoters for Ullmann-type coupling reactions and led to these reactions proceeding under relatively mild conditions. These newly developed conditions make these old transformations more useful, as illustrated by synthesis of two types of cyclopeptides and development of new methods for assembly of heterocycles.

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REFERENCES

1. For reviews, see: (a) S. V. Ley, A. W. Thomas. *Angew. Chem., Int. Ed.* **42**, 5400 (2003); (b) I. P. Beletskaya, A. V. Cheprakov. *Coord. Chem. Rev.* **248**, 2337 (2004).
2. D. Ma, Y. Zhang, J. Yao, S. Wu, F. Tao. *J. Am. Chem. Soc.* **120**, 12459 (1998).
3. (a) H. B. Goodbrand, N.-X. Hu. *J. Org. Chem.* **64**, 670 (1999); (b) A. Klapars, J. C. Antilla, X. Huang, S. L. Buchwald. *J. Am. Chem. Soc.* **123**, 7727 (2001); (c) R. K. Gujadhur, C. G. Bates, D. Venkataraman. *Org. Lett.* **3**, 4315 (2001); (d) F. Y. Kwong, A. Klapars, S. L. Buchwald. *Org. Lett.* **4**, 581 (2002).
4. (a) D. Ma, Q. Cai, H. Zhang. *Org. Lett.* **5**, 2453 (2003); (b) D. Ma, Q. Cai. *Synlett* 128 (2004); (c) H. Zhang, Q. Cai, D. Ma. *J. Org. Chem.* **70**, 5164 (2005).
5. W. Zhu, D. Ma. *J. Org. Chem.* **70**, 2696 (2005).
6. W. Zhu, D. Ma. *Chem. Commun.* 888 (2004).
7. X. Xie, G. Cai, D. Ma. *Org. Lett.* **7**, 4693 (2005).
8. D. Ma, Q. Cai. *Org. Lett.* **5**, 3799 (2003).
9. (a) D. Ma, F. Liu. *Chem. Commun.* 1934 (2004); (b) for a related work, see: H. Jiang, H. Fu, R. Qiao, Y. Jiang, Y. Zhao. *Synthesis* 2417 (2008).

10. (a) X. Pan, Q. Cai, D. Ma. *Org. Lett.* **6**, 1809 (2004); (b) for a review, see: J. R. Dehli, J. Legros, C. Bolm. *Chem. Commun.* 973 (2005).
11. (a) D. C. Gournelis, G. G. Laskaris, R. Verpoorte. *Nat. Prod. Rep.* 75 (1997); (b) M. M. Joullié, D. J. Richard. *Chem. Commun.* 2011 (2004).
12. G. He, J. Wang, D. Ma. *Org. Lett.* **9**, 1367 (2007).
13. J. Wang, L. Schaeffler, G. He, D. Ma. *Tetrahedron Lett.* **48**, 6717 (2007).
14. (a) M. Toumi, F. Couty, G. Evano. *Angew. Chem., Int. Ed.* **46**, 572 (2007); (b) M. Toumi, F. Couty, G. Evano. *J. Org. Chem.* **72**, 9003 (2007).
15. For reviews, see: (a) A. V. R. Rao, M. K. Gurjar, G. K. L. Reddy, A. S. Rao. *Chem. Rev.* **95**, 2135 (1995); (b) J. Zhu. *Synlett* 133 (1997); (c) K. C. Nicolaou, C. N. C. Boddy, S. Bräse, N. Winssinger. *Angew. Chem., Int. Ed.* **38**, 2096 (1999).
16. Q. Cai, G. He, D. Ma. *J. Org. Chem.* **71**, 5268 (2006).
17. Q. Cai, B. Zou, D. Ma. *Angew. Chem., Int. Ed.* **45**, 1276 (2006).
18. X. Xie, Y. Chen, D. Ma. *J. Am. Chem. Soc.* **128**, 16050 (2006).
19. (a) Y. Chen, X. Xie, D. Ma. *J. Org. Chem.* **72**, 9329 (2007); (b) Y. Chen, Y. Wang, Z. Sun, D. Ma. *Org. Lett.* **10**, 625 (2008).
20. F. Liu, D. Ma. *J. Org. Chem.* **72**, 4844 (2007).
21. B. Zou, Q. Yuan, D. Ma. *Angew. Chem., Int. Ed.* **46**, 2598 (2007).
22. B. Zou, Q. Yuan, D. Ma. *Org. Lett.* **9**, 4291 (2007).
23. B. Lu, D. Ma. *Org. Lett.* **8**, 6115 (2006).
24. B. Lu, B. Wang, Y. Zhang, D. Ma. *J. Org. Chem.* **72**, 5337 (2007).
25. S. Tanimori, Y. Ozaki, Y. Iesaki, M. Kirihata. *Synlett* 1973 (2008).