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Cu(I)-catalyzed intramolecular cyclization of ene-carbamates: synthesis of indoles and pyrrolo[2,3-*c*]pyridines

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Abstract—Over the past few years, the use of palladium-catalyzed aromatic carbon–nitrogen bond forming reactions by the cross-coupling of aryl halides or triflates and amines has become a useful synthetic tool. Herein, we describe a copper(I) catalyst system that allows efficient synthesis of functionalized indoles and pyrrolo[2,3-*c*]pyridines. This method takes advantage of amino acid promoted copper coupling of amines with aryl halides, in particular, the use of the CuI/L-proline catalyst system.

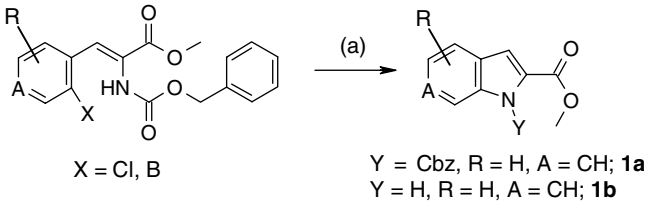
Nitrogen heterocycles are among the most important classes of pharmacologically active compounds. The biological significance of indole derivatives in particular has made this heterocyclic system one of the most frequent subunits encountered in pharmacologically active compounds. Examples of pharmaceutically relevant indole containing drugs include vincristine, indomethican, sumatriptan and pindolol.[1]

A significant number of methods to synthesize nitrogen containing heterocyclic targets such as indoles have been developed using intramolecular or intermolecular approaches.[2] Over the past few years, these efforts have been aided by progress in the transition metal-catalyzed formation of carbon–nitrogen bonds. Mainly, the use of palladium- and copper-catalyzed aromatic carbon–nitrogen bond forming reactions by the cross-coupling of aryl halides or triflates with amines or amides have become increasingly useful synthetic tools.[3] The use of palladium and copper catalysis has also overcome some of the hurdles encountered in the synthesis of indoles such as substitution pattern tolerance.[4]

The copper-mediated N-arylation reaction is an important transformation and has been developed to include a wide range of substrates.[5] Recently, it has been observed that amino acids not only accelerate Cu-mediated self-coupling with aryl halides[6] but also promote the coupling reaction of amines and phenols with aryl halides.[7]

Herein, we describe the use of a CuI/L-proline catalyst system in the intramolecular cyclization of ene-carbamates leading to either indoles[8] or pyrrolo[2,3-*c*]pyridines (Scheme 1).

An initial probe into the reaction conditions (Table 1) led us away from nucleophilic bases such as *t*-BuONa in order to reduce exchange of the ester group and cleavage of the Cbz protecting group. Though acceptable for Horner–Wadsworth–Emmons condensation, DBU did not appear to be optimal for cyclization. In fact, only 30% of deprotected cyclized product was observed (Table 1, entry 1) along with multiple by-products.



X = Cl, B

Y = Cbz, R = H, A = CH; **1a**
Y = H, R = H, A = CH; **1b**

Scheme 1. Reagents and conditions: (a) CuI (10 mol %), (L)-proline (20 mol %), K_2CO_3 (3 equiv), 1,4-dioxane, 100 °C, 24 h.

Keywords: Copper catalysis; Indole; Pyrrolo[2,3-*c*]pyridine; L-Proline.
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Table 1. Investigation of copper salt and base via Scheme 1

Entry	Base (3.0 equiv)	Cu(I) salt[a] (0.1 equiv)	Yield (%)[b] **1a**	Yield (%)[b] **1b**
1	DBU	CuI	0	30
2	K_2CO_3	CuI	95	0
3	Cs_2CO_3	CuI	8	74
4	*t*-BuONa	CuI	0	0
5	K_2CO_3	CuBr	95	3
6	K_2CO_3	CuCl	95	3

[a] All reactions were run under an inert atmosphere of nitrogen utilizing L-proline (0.2 equiv) in 1,4-dioxane at 100 °C, 24 h.
[b] Based on HPLC conversion.

The carbonate bases, K_2CO_3 and Cs_2CO_3, were essentially equivalent in their ability to accomplish cyclization to indole. However, the use of Cs_2CO_3 resulted in nearly complete loss of the Cbz protecting group (Table 1, entry 3). For this reason, we chose to proceed with K_2CO_3 as base.

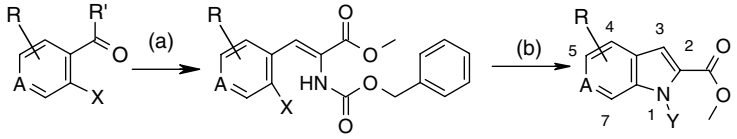
Review of various copper halide sources demonstrated that Cu(I) salts were essentially equivalent when used in combination with L-proline. For further studies, we chose the inexpensive CuI (99.999% purity, Aldrich) as the preferred copper source among copper halides evaluated. Catalyst loading could be varied from 5–20% and 10 mol for reactions herein.

To investigate the scope of our synthetic strategy, we synthesized a number of ene-carbamates by Horner–Wadsworth–Emmons condensation[9] with a corresponding phenyl or pyridyl carboxaldehyde (Scheme 2). The ene-carbamates could be isolated in moderate to high yield. Once isolated, the carbamates were subjected to cyclization conditions as described in Scheme 2.

The results indicate a preference for electron rich over electron-poor systems. For electron rich systems, yields of cyclized products were found to be in the 66–99% range with the exception of ene-carbamate **7** (Table 2). This analog is unique, however, in that it is the only *ortho*-substituted analog. Electron-poor systems such as those substituted with fluorine or nitro were somewhat less reactive overall with total yields of cyclized products in the 64–88% range (Table 2). Combination of an electron deficient ring with the less reactive chlorine as in the case of substrates **6** resulted in a 10% yield of the Cbz protected indole and only a 44% yield of cyclized products. In many of the electron deficient analogs, a significant amount of *N*-1 deprotected product was isolated. It should be noted, however, that examples of both electron-poor systems and electron-rich systems are shown to produce *N*-1 protected indole products in moderate to high yield (Table 2, entries 3 and 8).

As electron-poor analogs can be considered activated for simple intramolecular aromatic nucleophilic substitution, there was a concern that the cyclization could proceed via a S_NAr-type mechanism. However, results in our hands indicate the reaction does not proceed uncatalyzed.[10]

An extension of this process toward pyrrolo[2,3-*c*]pyridines is shown in Table 2 (entry 11). The yield is lower presumably due to the more electron-deficient heterocyclic ring, and is consistent with observations in the case of electron-poor indoles. Similar to electron-deficient indole examples, a significant amount of deprotected product was observed during cyclization of the electron-deficient pyridine **11** to give pyrrolo[2,3-*c*]pyridine system **11b**.

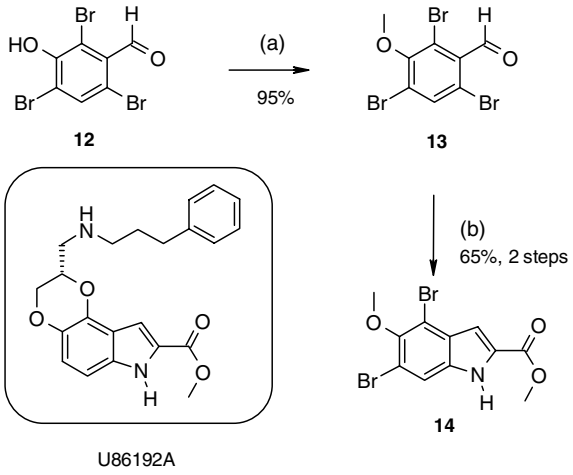


Scheme 2. Reagents and conditions: (a) DBU (1.5 equiv), *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester (1.3 equiv) and aldehyde (1 equiv) in DCM at rt for 2 h. (b) 1,4-Dioxane, K_2CO_3 (3 equiv), L-proline (0.2 equiv) and CuI (99.999%, 0.1 equiv), 100 °C, 24 h.

Table 2. Investigation of reaction scope: effect of aryl substitution via Scheme 2

Entry	A	R	R′	X	Yield %[a] (ene-carbamate)	Yield %[a] (**a**)	Yield %[a] (**b**)
1	CH	H	H	Br	87 (**1**)	91 (**1a**)	0 (**1b**)
2	CH	3,4 (C═C─C═C)	H	Br	91 (**2**)	73 (**2a**)	0 (**2b**)
3	CH	5-F	H	Br	54 (**3**)	62 (**3a**)	26 (**3b**)
4	CH	6-F	H	Br	91 (**4**)	61 (**4a**)	16 (**4b**)
5	CH	H	Me	Br	0[b] (**5**)	0 (**5a**)	0 (**5b**)
6	CH	5-NO_2	H	Cl	97 (**6**)	10 (**6a**)	34 (**6b**)
7	CH	6,7-(dimethoxy)	H	Cl	68 (**7**)	0 (**7a**)	0 (**7b**)
8	CH	5,6-(dimethoxy)	H	Br	92 (**8**)	95 (**8a**)	0 (**8b**)
9	CH	5,6-(O–CH_2–O)	H	Br	88 (**9**)	66 (**9a**)	0 (**9b**)
10	CH	5-OMe	H	Br	79 (**10**)	99 (**10a**)	0 (**10b**)
11	N	4-Br	H	Br	77 (**11**)	0 (**11a**)	85 (**11b**)

[a] All reported yields are based on isolated products. Yield is given for individual isolated yields of Y = Cbz (a) and Y = H (b).
[b] Failed to form ene-carbamate under standard conditions, further optimization was not attempted.



Scheme 3. Reagents and conditions: (a) K_2CO_3, MeI. (b) DBU, *N*-benzyloxycarbonyl-α-phosphonoglycine trimethyl ester, DCM; CuI, L-proline, Cs_2CO_3, 1,4-dioxane, 100 °C, 24 h.

The general utility of this technique was evaluated by preparing a key indole described in the synthesis of the antihypertensive agent, U86192A (Scheme 3). Starting from the commercially available symmetric tribromophenol **12**, the target indole **14** was prepared in overall yield comparable to published results in one less step.[11] Our initial approach via a one-pot conversion of aldehyde precursor **13** directly to indole **14** was unsuccessful. Though complete consumption of starting aldehyde was noted, considerable by-product was observed during cyclization consistent with model studies employing DBU (Table 1). Isolation of the ene-carbamate followed by cyclization proved superior. When K_2CO_3 was used as base, a 75% conversion was observed for the cyclization. However, isolation of products confirmed the presence of both *N*-1-Cbz protected (40%) and *N*-1-deprotected (35%) indoles. As noted above, the use of Cs_2CO_3 (Table 1, entry 3), results in primarily deprotected indole. By taking advantage of this fact, complete conversion to deprotected indole **14** with an isolated yield of 71% was achieved. This rapid entry into highly substituted indoles such as **14** demonstrates the utility of this method.

A comparison of the Cu/L-proline system with palladium catalysis confirms that both reactions proceed in comparable yields (Scheme 4). Starting from the commercially available bromo or chloro substituted benzaldehyde, yields are in line with both solution phase[8a] and solid supported[8b,c] Pd methods. It is noteworthy in the copper catalyzed reactions described herein that both bromo and chloro substituted aromatic systems are effective precursors allowing the use of a broader range of commercially available starting materials. The cost, ease of synthesis and the simple purification make the CuI/L-proline catalyst system an attractive entry into these and other nitrogen-containing heterocycles.

In summary, we have shown a new mild and efficient method to produce 2-substituted indole and pyrrolo[2,3-*c*]pyridines via a key C–N bond forming reaction. This method utilizes commercially available aldehydes as starting materials and is complementary to existing methods.

Acknowledgements

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Supplementary data

Synthetic procedures including analytical data are included. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.077.

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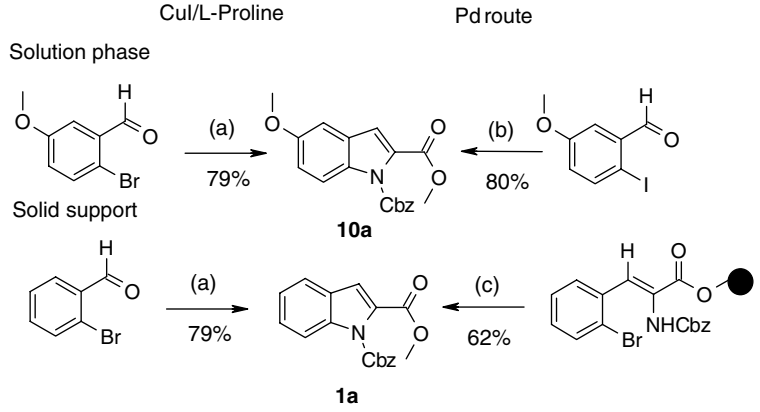

Scheme 4. Reagents and conditions: (a) 1. DBU, glycine phosphonate ester, DCM; 2. CuI, L-proline, K_2CO_3, 1,4-dioxane, 100 °C, 24 h. (b) 1. DBU, glycine phosphonate ester, DCM; 2. $PdCl_2(dppf)$, KOAc, DMF, 90 °C (c) 1. $Pd_2(dba)_3$, Cy_2NMe, *t*-Bu_3P, toluene, 80 °C; 2. MeONa, THF/MeOH, rt, 12 h.

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