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Cu-Catalyzed Tandem C–N Bond Formation for the Synthesis of Pyrroles and Heteroarylpyrroles

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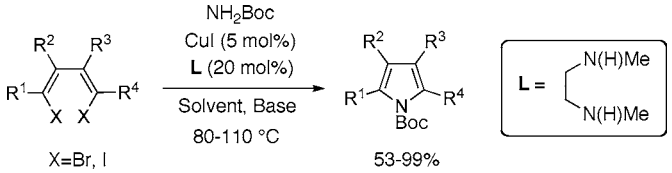
ABSTRACT



A highly efficient Cu-catalyzed tandem C–N bond-forming reaction of 1,4-dihalo-1,3-dienes has been developed. The transformation allows the synthesis of pyrroles and heteroarylpyrroles with a wide variety of functional groups and substitution patterns from readily available precursors.

Pyrroles are an important class of heterocyclic compounds and are structural units found in a vast array of natural products, synthetic materials, and bioactive molecules, such as heme, vitamin B12, and cytochromes.[1] Pyrroles also play crucial roles in nonlinear optical materials as well as in supramolecular chemistry.[2] Classical methods for their preparation include the Knorr,[3] Hantzsch,[4] and Paal−Knorr condensation reactions.[5] However, these methods have some limitations with respect to the regioselectivity and substitution patterns that can be introduced.[6] Despite recent advances, particularly in transition metal-catalyzed multicomponent processes and domino reactions,[7] a more flexible and general approach with a wide functional group tolerance is still of critical importance.[8]

We report herein the development of a Cu-catalyzed process[9] in which both C−N bonds of the pyrrole ring are formed in a tandem process,[10,11] thereby allowing for the

(1) (a) Bellina, F.; Rossi, R. *Tetrahedron* **2006**, *62*, 7213. (b) Butler, M. S. *J. Nat. Prod.* **2004**, *67*, 2141. (c) Fürstner, A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (d) Hoffmann, H.; Lindel, T. *Synthesis* **2003**, 1753. (e) Joule, J. A.; Mills, K. In *Heterocyclic Chemistry*, 4th ed.; Blackwell Science: Oxford, UK, 2000; Chapter 13. (f) Higgins, S. *Chem. Soc. Rev.* **1997**, *26*, 247.

(2) Lehn, J. M. *Supramolecular Chemistry*: *Concepts and Perspectives*; VCH; Weinheim, Germany, 1995.

(3) For recent examples: (a) Shiner, C. M.; Lash, T. D. *Tetrahedron* **2005**, *61*, 11628. (b) Bellingham, R. K.; Carey, J. S.; Hussain, N.; Morgan, D. O.; Oxley, P.; Powling, L. C. *Org. Process Res. Dev.* **2004**, *8*, 279.

(4) For recent examples: (a) Matiychuk, V. S.; Martyak, R. L.; Obushak, N. D.; Ostapiuk, Y. V.; Pidlypnyi, N. I. *Chem. Heterocycl. Compd.* **2004**, *40*, 1218. (b) Calvo, L.; González-Ortega, A.; Sañudo, M. C. *Synthesis* **2002**, 2450.

(5) For recent examples: (a) Chen, J.; Wu, H.; Zheng, Z.; Jin, C.; Zhang, X.; Su, W. *Tetrahedron Lett.* **2006**, *47*, 5383. (b) Minetto, G.; Raveglia, L. F.; Sega, A.; Taddei, M. *Eur. J. Org. Chem.* **2005**, 5277.

(6) For some reviews on the synthesis of pyrroles: (a) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238. (b) Ferreira, V. F.; de Souza, M. C. B. V.; Cunha, A. C.; Pereira, L. O. R.; Ferreira, M. L. G. *Org. Prep. Proced. Int.* **2001**, *33*, 411.

(7) For recent reviews: (a) de Meijere, A.; von Zezschwitz, P.; Braese, S. *Acc. Chem. Res.* **2005**, *38*, 413. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115.

(8) For recent synthesis of pyrroles: (a) Martín, R.; Rodríguez-Rivero, M.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079. (b) Hiroya, K.; Matsumoto, S.; Ashikawa, M.; Ogiwara, K.; Sakamoto, T. *Org. Lett.* **2006**, *8*, 5349. (c) Dong, C.; Deng, G.; Wang, J. *J. Org. Chem.* **2006**, *71*, 5560. (d) Harrison, T. J.; Kozak, J. A.; Corbella-Pane, M.; Dake, G. R. *J. Org. Chem.* **2006**, *71*, 4525. (e) Binder, J. T.; Kirsch, S. F. *Org. Lett.* **2006**, *8*, 2151. (f) Lu, L.; Chen, G.; Ma, S. *Org. Lett.* **2006**, *8*, 835. (g) Wan, X.; Xing, D.; Fang, Z.; Li, B.; Zhao, F.; Zhang, K.; Yang, L.; Shi, Z. *J. Am. Chem. Soc.* **2006**, *128*, 12046.

(9) For recent reviews on Cu-catalyzed C−N bond-forming reactions: (a) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (b) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (c) Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* **2003**, 2428.

(10) A related Pd-catalyzed protocol for the synthesis of indoles has been recently described: Willis, M. C.; Brace, G. N.; Findlay, T. J. K.; Holmes, I. P. *Adv. Synth. Catal.* **2006**, *348*, 851.

(11) A double N-arylation of amines has been reported: Nozaki, K.; Takahashi, K.; Nakano, K.; Hiyama, T.; Tang, H.-Z.; Fujiki, M.; Yamaguchi, S.; Tamao, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2051.

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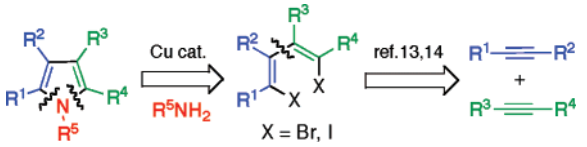
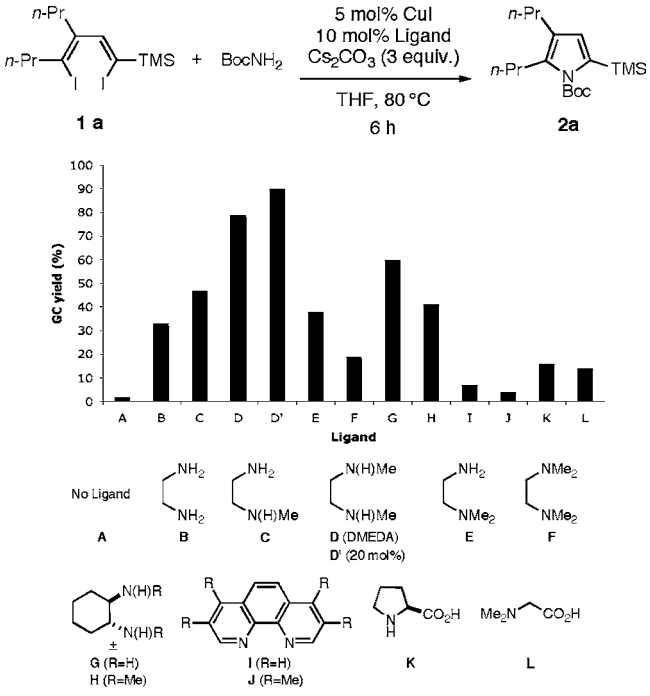
synthesis of a wide range of structurally diverse substrates, including alkyl-substituted electron-rich pyrroles and heteroarylpyrroles (Scheme 1).[12]

Scheme 1. Retrosynthetic Analysis of the Pyrrole Core



Several years ago, our research group developed a highly efficient one-pot procedure for the synthesis of 1,4-dihalo-1,3-dienes from a regioselective intermolecular coupling of two alkynes.[13] Subsequently, Sato reported a more practical process using titanium complexes, which allowed the synthesis of more functionalized 1,3-diene backbones.[14] In both protocols, the regioselectivity can be controlled by the use of terminal or silyl-substituted alkynes. Using this approach, a number of 1,4-dihalo-1,3-dienes were conveniently prepared.[15]

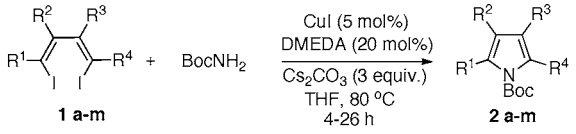
Scheme 2. Ligand Screen

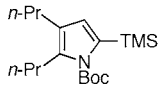
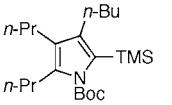
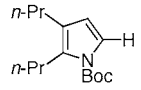
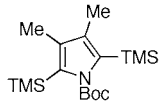
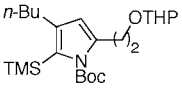
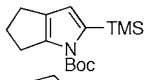
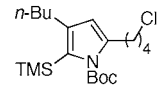
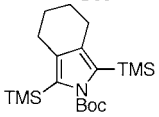
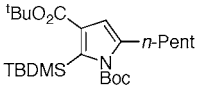
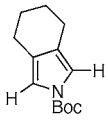
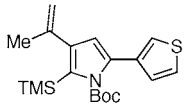
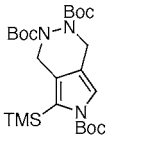
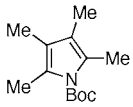


A variety of ligands, bases and solvents were examined for the Cu-catalyzed reaction of substrate **1a** with *tert*-butyl carbamate, using CuI as the precatalyst. In line with our previous findings on the Cu-catalyzed amidation of vinyl halides,[16] 1,2-diamine-based ligands provided higher yields than amino acids or phenanthroline-type ligands (Scheme 2). In particular, *N*,*N*′-dimethylethylenediamine (DMEDA, **D**) was superior among the ligands examined at 80 °C, providing the desired product **2a** in 86% yield. The choice of the base also plays a crucial role; the use of 3 equiv of Cs_2CO_3 was found to be optimal while reactions with K_2CO_3 or K_3PO_4 were much slower.

The transformation described herein allows the synthesis of di-, tri-, and tetrasubstituted pyrroles. A number of functional groups were tolerated, including esters, ethers, alkyl halides, *Boc*-protected hydrazines, alkenes, heterocycles, and silyl groups (Table 1). Moreover, the presence of either electron-withdrawing or electron-donating groups on the diene backbone does not hinder the reaction. Access to electron-rich pyrroles is particularly noteworthy as synthetic routes to such compounds are rare.[17]

Table 1. Scope of the Cu-Catalyzed Tandem C−N Bond-Forming Reactions of 1,4-Dihalo-1,3-dienes[a]



entry	product	yield(%)[b]	entry	product	yield(%)[b]
1		86 (**2a**)	8		80 (**2h**)
2		75 (**2b**)	9		98 (**2i**)
3		89 (**2c**)	10		96 (**2j**)[c]
4		92 (**2d**)	11		99 (**2k**)
5		97 (**2e**)	12		99 (**2l**)
6		98 (**2f**)	13		82 (**2m**)[d]
7		96 (**2g**)			

[a] Reaction conditions: 1,4-diiodo-1,3-diene (1.0 equiv), *tert*-butyl carbamate (1.2 equiv), CuI (5 mol %), DMEDA (20 mol %), Cs_2CO_3 (3 equiv), THF (0.5 M) at 80 °C. [b] Yields of the isolated products are the average of two runs. [c] From 1-bromo-4-iodo-1,3-diene. [d] R_4 = TMS.

(12) During the preparation of this manuscript, a related procedure for the synthesis of *N*-acylpyrroles was published: Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510.

(13) Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870.

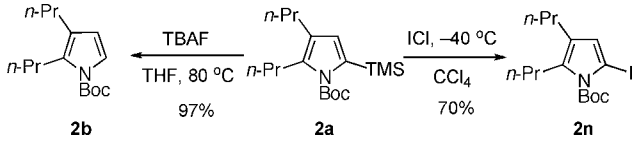
(14) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342.

(15) For experimental details, see the Supporting Information.

(16) (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (b) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (b) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333.

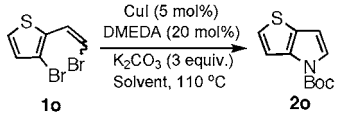
In addition to acting as a directing group in the metal-mediated cross-coupling of alkynes, the silyl group also provides a convenient functional handle for further manipulation (Scheme 3). Protodesilylation of **2a** was near quantitative with TBAF, thus allowing access to other substitution patterns on the pyrrole core. More importantly, the reaction of **2a** with ICl at −40 °C cleanly delivered the synthetic precursor 2-iodopyrrole **2n** in 70% yield.

Scheme 3. Silyl-Substituted Pyrroles as Versatile Intermediates



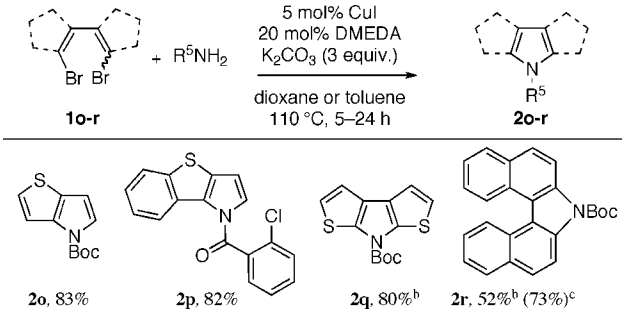
Our success described above prompted us to expand this method to other compounds, such as sterically encumbered heterocycles and heteroarylpyrroles, which have important optical and electronic properties.[18,19] In particular, the preparation of heteroarylpyrroles is challenging. They are less stable than their simple pyrrole counterparts and, in general, classical methods are not applicable for their synthesis.[20] We began this segment of our work by examining the conversion of dibromide **1o** to thienopyrrole **2o** (Scheme 4). Although the conditions we originally developed for the Cu-catalyzed amidation of vinyl bromides[16a] did yield the desired thienopyrrole, the reaction required 40 h to proceed to completion (Scheme 4).[21,22] After a systematic examination of the reaction conditions, it was found that performing the reaction in dioxane gave a faster rate, reducing the reaction time to 5 h. Interestingly, both *E*- and *Z*-**1o** isomers provided the final compound **2o** in excellent yield, suggesting an isomerization of the initially formed *E*-enamido intermediates to undergo ring closure.[10,23] In this manner, the ability to use readily available mixtures of isomers further increases the synthetic applicability of the process.[24]

Scheme 4. Synthesis of Thienopyrroles



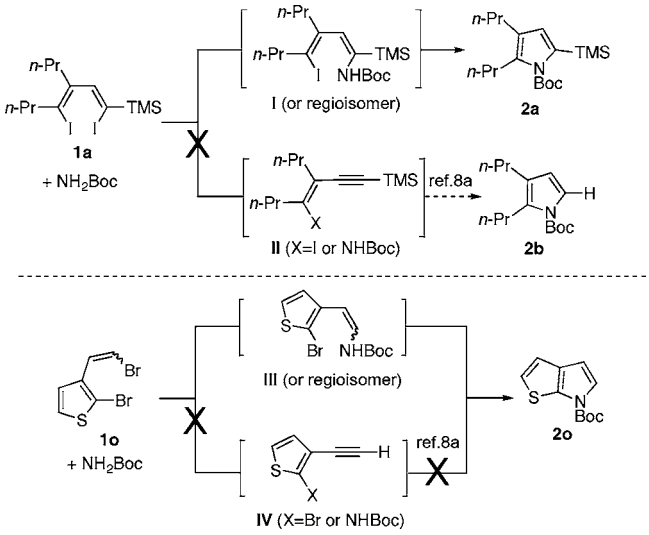
1o (*Z*:*E*)	Solvent	t(h)	yield(%)
99:1	Toluene	40	82
3:1	Toluene	40	83
3:1	Dioxane	5	83

Scheme 5. Synthesis of Heteroarylpyrroles and Sterically-Encumbered Heterocycles[a]



[a] Reaction conditions: dihalodiene (1.0 equiv), amine nucleophile (1.2 equiv), CuI (5 mol %), **L** (20 mol %), K_2CO_3 (3 equiv), dioxane (0.5 M); isolated yields (average of two runs). [b] K_2CO_3 (3 equiv) in toluene (0.5 M) at 110 °C for 14 h. [c] From the diiodide, using Cs_2CO_3 (3 equiv) in THF (0.5 M) at 80 °C for 24 h.

Scheme 6. Possible Mechanistic Pathways



The transformation allowed the synthesis of thieno- (**2o**) and benzothiophenopyrroles (**2p**) bearing different nitrogen

(17) For a recent example, see: Rodríguez-Rivero, M.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973.

(18) (a) Krayushkin, M. M.; Yarovenko, V. N.; Semenov, S. L.; Zavarzin, I. V.; Ignatenko, A. V.; Martynkin, A. Y.; Uzhinov, B. M. *Org. Lett.* **2002**, *4*, 3879. (b) Roncali, J. *Chem. Rev.* **1997**, *97*, 173. (c) Pagani, G. A. *Heterocycles* **1994**, *37*, 2069. (d) Lazzaroni, R.; Riga, J.; Verbist, J. J.; Christiaens, L.; Renson, M. *J. Chem. Soc., Chem. Commun.* **1985**, 999.

(19) Recently, thienopyrroles have been shown to be potent human histamine H_4 antagonists: Venable, J. D.; Cai, H.; Chai, W.; Dvorak, C. A.; Grice, C. A.; Jablonowski, J. A.; Shah, C. R.; Kwok, A. K.; Ly, K. S.; Pio, B.; Wei, J.; Desai, P. J.; Jiang, W.; Nguyen, S.; Ling, P.; Wilson, S. J.; Dunford, P. J.; Thurmond, R. L.; Lovenberg, T. W.; Karlsson, L.; Carruthers, N. I.; Edwards, J. P. *J. Med. Chem.* **2005**, *48*, 8289.

(20) For selected classical methods for the synthesis of heteroarylpyrroles, see: (a) Zanirato, P.; Spagnolo, P.; Zanardi, G. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2551. (b) Binder, D.; Habison, G.; Noe, C. R. *Synthesis* **1977**, 255. (c) Wierzbicki, M.; Cagniant, P. *Bull. Chem. Soc. Chim. Fr.* **1975**, *7*, 1786. (d) Srinivasan, K.; Srinivasan, K. G.; Balasubramanian, K. K.; Swaminathan, S. *Synthesis* **1973**, 313. (e) Keener, R. L.; Skelton, H. R.; Snyder, H. R. *J. Org. Chem.* **1968**, *33*, 1355.

(21) For a review on the synthesis of thienopyrroles, see: Garcia, F.; Galvez, C. *Synthesis* **1985**, 143.

(22) For selected synthesis of thienopyrroles or benzothienylpyrroles, see: (a) Abreu, A.; Silva, N, O.; Ferreira, P. M. T.; Queiroz, M.-J. R. P.; Venanzi, M. *Eur. J. Org. Chem.* **2003**, 4792. (b) Ogawa, K.; Rasmussen, S. C. *J. Org. Chem.* **2003**, *68*, 2921. (c) Sommen, G.; Comel, A.; Kirsch, G. *Tetrahedron* **2003**, *59*, 1557.

(23) A similar isomerization has been reported in the preparation of enamides from vinyl triflates: Wallace, D. J.; Klauber, D. J.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749.

(24) Starting materials were prepared from commercially available aldehydes in a one-pot procedure: Matsumoto, M.; Kuroda, K. *Tetrahedron Lett.* **1980**, *21*, 4021.

sources or fully heterocyclic-fused compounds such as **2q** in good yields (Scheme 5). Additionally, sterically encumbered biaryl compounds could also be successfully prepared (**2r)**, although the corresponding diiodide was needed to achieve better yields.

In a recent disclosure,[8a] we have shown that compound **II** afforded a non-silylated pyrrole **2b** under reaction conditions that were essentially identical with those reported herein (Scheme 6). In our current study, however, neither **II** nor **2b** was observed by GC or NMR analysis.[25] On the other hand, the fact that either *E*- or *Z*-isomer of **1o** was equally effective might indicate the intermediacy of a terminal alkyne **IV** via trans-dehydrohalogenation. However, as reported, haloenynes bearing terminal alkynes led to decomposition under these reaction conditions.[8a] In line with these findings, we believe that a mechanism involving enyne intermediates **II** or **IV** is highly unlikely (bottom pathways, Scheme 6). Therefore, a mechanism consisting of rapid intramolecular C−N bond formation from preformed C−N coupling intermediates **I** or **III**[10] is proposed (top pathways, Scheme 6).

In summary, an efficient Cu-catalyzed method for the conversion of 1,3-dihalo-1,3-dienes into valuable heterocycles, such as N-*Boc*-substituted pyrroles and heteroarylpyrroles, has been developed. The transformation is distinguished by its mild conditons, allowing the tolerance of a wide variety of functional groups in a range of substitution patterns.

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Supporting Information Available: Experimental procedures and spectral data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) (a) After 30 min of reaction time, 20% conversion of **1a**, 16% yield **2a**. (b) After 2 h of reaction time, 44% conversion of **1a**, 35% yield **2a**.