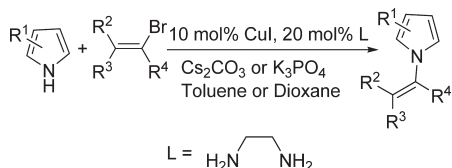# A General Copper-Catalyzed Coupling of Azoles with Vinyl Bromides

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Received May 29, 2009

A copper-catalyzed methodology for the coupling of vinyl bromides with azoles has been developed. This protocol uses a combination of 10 mol % of copper iodide and 20 mol % of ethylenediamine as catalyst. The reaction proceeds with various azoles and vinyl bromides, and the double bond geometry of vinyl bromides is retained under the reaction conditions.

N-Vinylazoles are important classes of building blocks in organic synthesis and are also key structural motifs in many medicaments. For instance, *N*-vinylazoles have been shown to serve as monomers for the synthesis of poly(*N*-vinylazoles),[1] which could be used as semiconductors and photosensitive materials. *N*-Vinylazoles have also been found to display antifungal activity.[2] Conventionally, protocols for their preparation included direct addition of azoles to alkynes,[3] alkylation of azoles with 1,2-dibromoethane, followed by dehydrohalogenation of the corresponding 2-haloethylazole.[4] Another way to prepare *N*-vinylazoles involved creation of the carbon−carbon double bond by Wittig−Horner,[5] Horner−Wadsworth−Emmons,[6] and Peterson[7] olefination reaction. Although these protocols provided access to *N*-vinylazoles, they suffered limitation in scope, selectivity, and generality. Furthermore, some procedures required harsh reaction conditions. A straightforward transition-metal-catalyzed N-vinylation of azoles by vinyl halides is an attractive alternative for the known methods. Palladium-catalyzed efficient vinylation of azoles with vinyl bromides has been reported.[8] Nevertheless, the use of expensive palladium limited the attractiveness of these methods for industrial applications. As far as copper-mediated methods were concerned, which had been widely used in many C−N bond formation,[9] N-vinylation with vinyl boronic acids displayed the major advantage of proceeding at room temperature but suffered from requirements for stoichiometric amount of cupric acetate.[10] More recently, copper-catalyzed methods involving *N,N*-bis(pyridin-2-ylmethylene)cyclohexane-1,2-diamine or L-proline as ligands enabled the coupling of vinyl bromides with azoles.[11] These protocols only worked for (*E*)-β-bromostyrene.

The development of general, cheap, stereospecific synthetic methodologies to create *N*-alkenylazoles is still challenging. Herein we would like to report copper-catalyzed N-vinylation of azoles with various vinyl bromides involving commercially available ethane-1,2-diamine as ligand.

Initial attempts to prepare **1a** by CuI-catalyzed cross-coupling between indole **2a** and α-bromostyrene **3a** failed. For example, the use of toluene as solvent, in combination

(1) Brustolin, F.; Castelvetro, V.; Ciardelli, F.; Rugger, G.; Colligiani, A. *J. Polym. Sci., A: Polym. Chem.* **2000**, *39*, 253–262.

(2) (a) Ogata, M.; Matsumoto, H.; Shimizu, S.; Kida, S.; Shiro, M.; Tawara, K. *J. Med. Chem.* **1987**, *30*, 1348–1354. (b) Hormi, O. E. O.; Hirvelä, L. *Tetrahedron Lett.* **1993**, *34*, 6463–6466. (c) Gopal, D.; Rajagopalan, K. *Tetrahedron Lett.* **1987**, *28*, 5327–5330.

(3) (a) Trofimov, B. A.; Tarasova, O. A.; Shemetova, M. A.; Afonin, A. V.; Klyba, L. V.; Baikalova, L. V.; Mikhaleva, A. I. *Russ. J. Org. Chem.* **2003**, *39*, 408–414. (b) Trofimov, B. A.; Tarasova, O. A.; Mikhaleva, A. I.; Kalinina, N. A.; Sinegovskaya, L. M.; Henkelmann, J. *Synthesis* **2000**, 1585–1590. (c) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193–6195. (d) Bourgeois, P.; Lucrece, J.; Dunogues, J. *J. Heterocycl. Chem.* **1978**, *15*, 1543–1545.

(4) Iddon, B.; Hartley, D. J. *Tetrahedron Lett.* **1997**, *38*, 4647–4650.

(5) Maier, L.; Rist, G. *Phosphorus Sulfur Relat. Elem.* **1987**, *32*, 65–72.

(6) Qian, H.; Huang, X. *Synth. Commun.* **2000**, *30*, 1413–1417.

(7) Surprenant, S.; Chan, W. Y.; Berthelette, C. *Org. Lett.* **2003**, *5*, 4851–4854.

(8) (a) Lebedev, A. Y.; Izmer, V. V.; Kazyul'kin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett.* **2002**, *4*, 623–626. (b) Dejli, J. R.; Legros, J.; Bolm, C. *Chem. Commun.* **2005**, 973–968. (c) Dehli, J. R.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 8518–8520. (d) Dehli, J. R.; Bolm, C. *Adv. Synth. Catal.* **2005**, *347*, 239–242.

(9) For the latest examples of copper-catalyzed C−N bond formation, see: (a) Jiang, B.; Tian, H.; Huang, Z.-G.; Xu, M. *Org. Lett.* **2008**, *10*, 2737–2740. (b) Fukudome, Y.; Naito, H.; Hata, T.; Urabe, H. *J. Am. Chem. Soc.* **2008**, *130*, 1820–1821. (c) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109–2112. (d) Mao, J.; Hua, Q.; Guo, J.; Shi, D.; Ji, S. *Synlett* **2008**, 2011–2016. (e) Ma, D.; Cai, Q. *Acc. Chem. Res.* **2008**, *41*, 1450–1460. (f) Lu, H.; Yuan, X.; Zhu, S.; Sun, C.; Li, C. *J. Org. Chem.* **2008**, *73*, 8665–8668. (g) Martin, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521–5524. (h) Cesati, R. R. I.; Dwyer, G.; Jones, R. C.; Hayes, M. P.; Yalamanchili, P.; Casebier, D. S. *Org. Lett.* **2007**, *9*, 5617–5620. (i) Martin, R.; Larsen, C. H.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 3379–3382. (j) He, G.; Wang, J.; Ma, D. *Org. Lett.* **2007**, *9*, 1367–1369. (k) Yang, L.; Deng, G.; Wang, D.-X.; Huang, Z.-T.; Zhu, J.-P.; Wang, M.-X. *Org. Lett.* **2007**, *9*, 1387–1390. (l) Rivero, M. R.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 973–976. (m) Toumi, M.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572–575. (n) Yuan, X.; Xu, X.; Zhou, X.; Yuan, J.; Mai, L.; Li, Y. *J. Org. Chem.* **2007**, *72*, 1510–1513. (o) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400–5449. (p) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337–2364. (q) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054–3131. (r) Coste, A.; Karthikeyan, G.; François, C.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381–4385. (s) Xia, N.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 337–339. (t) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3096–3099. (u) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667–3669. (v) Jiang, D.; Fu, H.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2007**, *72*, 672–674.

(10) (a) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927–4931. (b) Bolshan, Y.; Batey, R. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 2109–2112.

(11) (a) Dehli, J. R.; Bolm, C. *J. Org. Chem.* **2004**, *69*, 8518–8520. (b) Wang, Z.; Bao, W.; Jiang, Y. *Chem. Commun.* **2005**, 2849–2851. (c) Ouali, A.; Laurent, R.; Caminade, A.-M.; Majoral, J.-P.; Taillefer, M. *J. Am. Chem. Soc.* **2006**, *128*, 15990–15991. (d) Taillefer, M.; Ouali, A.; Renard, B.; Spindler, J.-F. *Chem.—Eur. J.* **2006**, *12*, 5301–5313. (e) Bao, W.; Liu, Y.; Lv, X. *Synthesis* **2008**, 1911–1917.
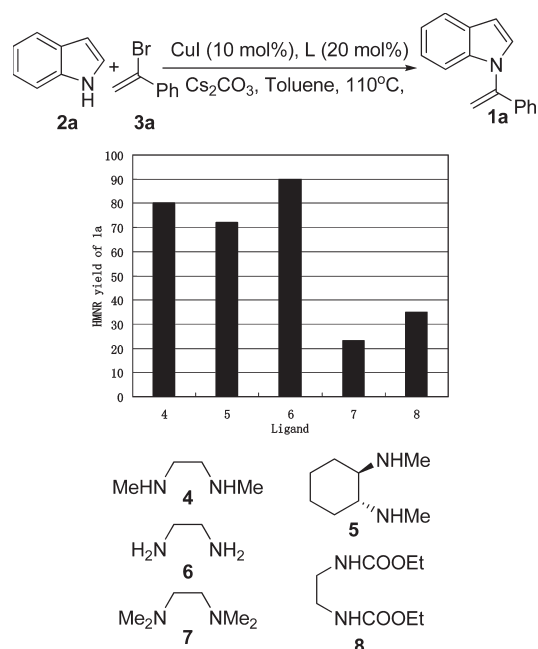
FIGURE 1. Comparison of ligands in CuI-catalyzed coupling of indole with α-bromostyrene.

TABLE 1. Base, Solvent, Copper Salts, and Temperature Optimization for Coupling of 2a and 3a

entry	base	solvent	CuX	T (°C)	1a yield (%)
1	Cs_2CO_3	toluene	CuI	110	90
2	K_2CO_3	toluene	CuI	110	66
3	K_3PO_4	toluene	CuI	110	91
4	KOH	toluene	CuI	110	33
5	^tBuOK	toluene	CuI	110	< 1
6	K_3PO_4	THF	CuI	80	8
7	K_3PO_4	DMF	CuI	110	6
8	K_3PO_4	dioxane	CuI	110	99
9	K_3PO_4	dioxane	CuI	80	71
10	K_3PO_4	dioxane	CuI	25	NR
11	K_3PO_4	dioxane	CuBr	110	56
12	K_3PO_4	dioxane	CuCl	110	49

^{a} ^{1}H NMR yields were obtained in proportion to the integral area of the CH_2Cl_2 signal; CH_2Cl_2 was used as internal standard.

with CuI and Cs_2CO_3, did not lead to the expected product at all. Stimulated by Buchwald's observation that 1,2-diamines were suitable ligands in copper-promoted C−N couplings,[12] the effect of such chelates on the indole/vinyl cross-coupling reaction was next evaluated. To our delight, the presence of such ligands affected the transformation significantly. Thus addition of *N,N'*-dimethylethane-1,2-diamine **4** or

(12) For representative examples, see: (a) Martín, R.; Rivero, M. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 7079–7082. (b) Martín, R.; Cuenca, A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 5521–5524. (c) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78–88. (d) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421–7428. (e) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727–7729.

TABLE 2. Expanding the Substrate Scope of the Coupling of Azoles with Vinyl Bromides

Entry	Azole	Vinylbromide	Time (h)	Temp.(°C)	Product	Yield (%)^a
1	2a	3a	24	110	1a	99 (85)
2	2a	3b	24 / 36	110 / 80	1b	80 (70) / 65
3	2a	3c	24	110	1c	- (80)
4	2a	3d	24	110	1d	93 (76)
5	2a	3e E/Z=3.9/3	24	110	1e	87 (63) E/Z=3.8/3
6	2a	3f	24	110	1f	84 (78)
7	2a	3g	24 / 36	110 / 50	1g	99 (88) / 35
8	2b	3a	24	110	1h	62 (52)
9	2c	3a	30	110	1i	80 (78)
10	2c	3d	36 / 36	110 / 80	1j	99 (90) / 78
11	2c	3b	24	110	1k	96 (78)
12	2d	3a	48	110	1l	88 (57)^b
13	2d	3d	48	110	1m	- (72)^c
14	2e	3a	48	110	1n	- (25)^d
15	2f	3b	48 / 48	110 / 50	1o	63 (58) / trace
16	2f	3a	48	110	1p	50 (41)^d
17	2g	3a	48 / 48	110 / 50	1q	21 (21)^d / trace

^{a} ^{1}H NMR yield, using CH_2Cl_2 or mesitylene as internal standard; yields referring to isolated products are given in parentheses. ^{b}2-(1-Phenylvinyl)indazole was also observed (10%). ^{c}(Z)-2-Styrylindazole was also observed (8%). ^{d}CuI (20 mol %), L (40 mol %).

trans-N,N'-dimethylcyclohexane-1,2-diamine **5** resulted in the formation of **1a** in 80 and 72% yields, respectively. Gratifyingly, the use of the simplest ethylenediamine gave the expected product in 90% yield. The use of tertiary diamine (TMEDA) **7** and diethylethane-1,2-diyldicarbamate **8** gave the expected product in 23 and 35% yields, respectively (Figure 1).

Next, the applicability of other bases and solvents was also evaluated (Table 1). Clearly, Cs_2CO_3 and K_3PO_4 proved to be superior to K_2CO_3 and KOH (entries 1−4). The stronger base KOBu^t yielded only a trace of the product (entry 5).[12c,12d] The reaction also showed a strong solvent dependence. Besides toluene, dioxane was the most applicable (entry 8), whereas the use of THF and DMF proved to be inappropriate (entries 6 and 7).

The effect of other copper salts was also examined in the test reaction. Using K_3PO_4 as base, dioxane as solvent, ethylenediamine as ligand, CuBr and CuCl as precatalyst gave product in 56 and 49% yield, respectively (entries 11 and 12).

The reaction also showed a strong dependence for temperature. When the reaction was treated at room temperature, the reaction did not proceed (entry 10). When the reaction mixture was warmed to 80 °C, the desired product was formed in 71% yield (entry 9).

On the basis of these results, the optimal conditions involved the following parameters: CuI as precatalyst, K_3PO_4 as base, ethylenediamine as ligand, and dioxane as solvent. Under these optimized conditions, a study on the substrate scope was carried out, and the results are summarized in Table 2.

First, various azoles were coupled with α-bromostyrene **3a**. Indole **2a**, carbazole **2c**, and 1*H*-indazole **2d** proved suitable substrates, and the corresponding products were formed in excellent yields (entries 1, 9, and 12). 3-Methyl-1*H*-indole **2b** afforded moderate yield (entry 8). 1*H*-Imidazole **2f** also afforded moderate yield with high loading of CuI and ligand (entry 16). 4-Methyl-1*H*-imidazole **2e** and *H*-pyrrole **2g** gave low yields (entries 14 and 17). Although the α-bromostyrene **3a** was applicable, other vinyl bromides were also useful. 2-Bromoprop-1-ene **3b** and (*E*)-β-bromostyrene **3c** performed well under the reaction conditions and afforded the desired products in good yields (entries 2, 3, 11, and 15). The vinylation of indole **2a**, carbazole **2c**, and 1*H*-indazole **2d** with (*Z*)-β-bromostyrene **3c** gave (*Z*)-1-styryl-1*H*-indole **1d**, (*Z*)-9-styryl-9*H*-carbazole **1j**, and (*Z*)-1-styryl-1*H*-indazole **1m** in excellent yields, respectively (entries 4, 10, and 13), which are in contrast to the report on the vinylation of azoles catalyzed by CuI-*N,N*-bis(pyridin-2-ylmethylene)-cyclohexane-1,2-diamine catalyst system.[11d] 2-Bromobut-2-ene **3e**, a commercial vinyl source available as a mixture of both *E*- and *Z*-isomers in a *E* to *Z* ratio of 3.9:3, was accepted as substrate, and its coupling proceeded with complete retention of configuration (as confirmed by NMR spectroscopy); the vinylation products were formed in high yield with stereospecificity (entry 5). Furthermore, tetrasubstituted vinyl bromide **3f** performed well under the reaction conditions and afforded the corresponding product **1f** in high yield. Vinyl bromides bearing a NMePh moiety **3g** were also compatible, and the corresponding product **1g** was formed in excellent yield under the reaction conditions. When triazoles and tetrazoles, such as 1*H*-1,2,3-triazole, 1*H*-1,2,4-triazole, 1*H*-benzo[*d*]-[1,2,3]triazole, and 5-phenyl-1*H*-tetrazole were treated with vinyl bromides under the similar reaction conditions, the desired products were not observed.

In summary, a general copper-catalyzed methodology for the coupling of vinyl bromides with azoles has been described. This protocol has low reagent (CuI as precatalyst, ethylenediamine as ligand) cost and broader substrates with double bond geometry of vinyl bromides retained under the reaction conditions

Experimental Section

General procedure for N-vinylation: CuI (10 mg, 0.1 mmol), azole (1.2 mmol), and K_3PO_4 (425 mg, 2.0 mmol) were added to a screwcapped test tube with a Teflon-lined septum. The tube was then evacuated and backfilled with N_2 (3 cycles). Vinyl bromide (1 mmol), ethylenediamine (0.2 mmol), and 1,4-dioxane (1.0 mL) were added by syringe at room temperature. The tube was then sealed, and the reaction mixture was stirred at 110 °C for indicated time. The reaction was cooled to room temperature. Ethyl acetate (3 mL) was added and stirred for 10 min. The deposition was separated and washed with ethyl acetate (3 mL×3). The organic phase was combined. The solvent was removed under vacuum, and the residue was analyzed by ^{1}H NMR. For example, preparation of *N*-(2-(indolyl-1)-allyl)-*N*-methylaniline (**1g**), the crude product was purified by column chromatography on silica gel with petroleum ether/EtOAc = 15/1 to give the desired product as pale yellow oil: R_f = 0.6 (petroleum ether); ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.65−7.62 (d, *J* = 7.5 Hz, 1H), 7.56−7.53 (d, *J* = 8.2 Hz, 1H), 7.27−7.14 (m, 5H), 6.77−6.74 (m, 3H), 6.59−6.58 (d, *J* = 3.1 Hz, 1H), 5.37 (s, 1H), 5.31 (s, 1H), 4.27 (s, 2H), 2.99 (s, 3H); ^{13}C NMR (75.45 MHz, CDCl$_3$) δ 149.0, 140.7, 136.1, 129.3, 129.1, 126.4, 122.4, 121.1, 120.4, 117.2, 112.5, 111.2, 108.8, 103.3, 56.5, 38.4; GC-MS (EI, *m/z*) 262 (M$^+$), 144, 120; HRMS calcd for $C_{15}H_{12}N_2$ 220.1000, found 220.1003.

Supporting Information Available: Experimental procedures and full characterization including ^{1}H NMR and ^{13}C NMR data for compounds **1e**−**1h** and **1l**−**1n**. NMR spectra for **1a**−**1q**. This material is available free of charge via the Internet at http://pubs.acs.org.