

Copper-Catalyzed Coupling of Amides
and Carbamates with Vinyl Halides

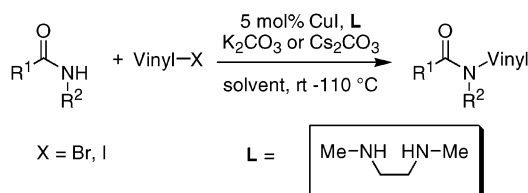
Lei Jiang, Gabriel E. Job, Artis Klapars, and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology,
Cambridge, Massachusetts 02139

sbuchwal@mit.edu

Received July 21, 2003

ABSTRACT



A general and efficient copper-catalyzed method for the amidation of vinyl bromides and iodides has been developed. This protocol uses a combination of 5 mol % copper iodide and 20 mol % *N,N*-dimethyl ethylenediamine. Substrates bearing ester, silyl ether, and amino groups were successfully coupled under the reaction conditions. The double bond geometry of the vinyl halides was retained under the reaction conditions.

Enamides are important synthetic intermediates,¹ as well as a structural component of many natural products.² Conventionally, protocols for their preparation include direct addition of amides to alkynes,³ acylation of imines,⁴ the Curtius rearrangement of α,β -unsaturated acyl azides,⁵ and the olefination of amides.⁶ Although these protocols provide access to enamides, they suffer from either low yield or lack of stereocontrol on the double bond geometry. Transition-

metal-catalyzed C–N bond formation has been an area of intensive research during the past 10 years.⁷ Most of the work has concentrated on the formation of aromatic C–N bonds, with only two examples of the palladium-catalyzed intramolecular vinylation of an amide reported.⁸ In contrast, the intermolecular vinylation of amides has been demonstrated using copper as the catalyst or promoter.⁹ For example,

(1) (a) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*; Wiley-VCH: New York, 1999. (b) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286.

(2) (a) Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968. (b) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laasko, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805. (c) Suzumura, K.-i.; Takahashi, I.; Matsumoto, H.; Nagai, K.; Setiawan, B.; Rantiamodjo, R. M.; Suzuki, K.-i.; Nagano, N. *Tetrahedron Lett.* **1997**, *38*, 7573. (d) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153. (e) Erickson, K. L.; Beutler, J.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. (f) Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamauchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14. (g) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.

(3) (a) Mohre, H.; Kilian, R. *Tetrahedron* **1969**, *25*, 5745. (b) Kondo, T.; Tanaka, A.; Kotachi, S.; Watanabe, Y. *J. Chem. Soc., Chem. Commun.* **1995**, 413.

(4) (a) Boeckmann, R. K., Jr.; Goldstein, S. W.; Walters, M. A. *J. Am. Chem. Soc.* **1988**, *110*, 8250.

(5) (a) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407. (b) Brettle, R.; Mosedale, A. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, *2*, 185.

(6) For palladium-catalyzed C–N bond formation, see: (a) Hartwig, J. F. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; p 1051. (b) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. For leading references on the copper-catalyzed C–N bond formation, see: (a) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (b) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (d) Gujadhur, R. K.; Bates, C. G.; Venkataraman, D. *Org. Lett.* **2001**, *3*, 4315. (e) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (f) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233.

(7) (a) Palomo, C.; Aizpurua, J. M.; Legido, M.; Picard, J. P.; Dunogues, J.; Constantieux, T. *Tetrahedron Lett.* **1992**, *33*, 3903. (b) Cuevas, J.-c.; Patil, P.; Snieckus, V. *Tetrahedron Lett.* **1989**, *30*, 5841.

(8) (a) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 111. For palladium-catalyzed vinylation of azoles, see: (b) Lebedev, A. Y.; Izmer, V. V.; Kazyl'kin, D. N.; Beletskaya, I. P.; Voskoboinikov, A. Z. *Org. Lett.* **2002**, *4*, 623. For palladium-catalyzed vinylation of amines, see: (c) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *Chem. Commun.* **2002**, 2362. (d) Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085.

(9) (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443. (b) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (c) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650.

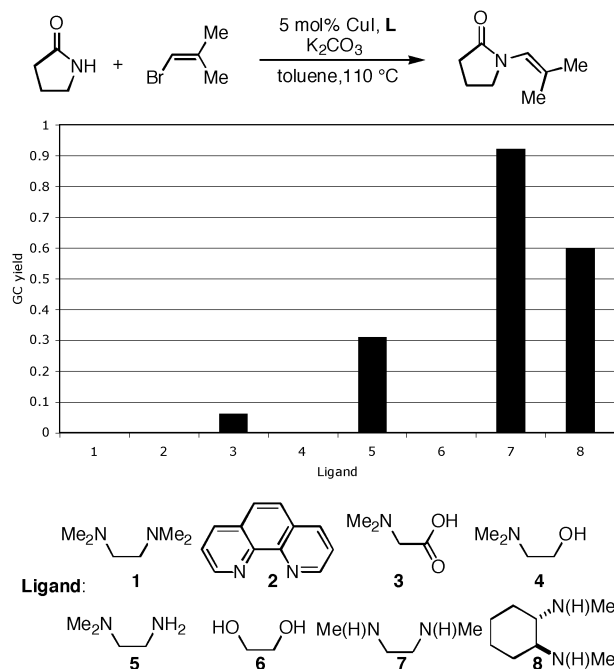


Figure 1.

Ogawa reported^{9a} the cross-coupling reaction between potassium amides and vinyl bromides mediated by a stoichiometric quantity of CuI.¹⁰ More recently, using CuTc (Tc = thiophene-2-carboxylate) as a catalyst, Porco described^{9b} a copper-catalyzed amidation of vinyl iodides to give enamides in moderate yield. Both protocols only worked for terminal vinyl halides. Moreover, they required the use of either HMPA or NMP as solvent.

On the basis of our previous work on the copper-catalyzed C–N bond formation of aryl halides,^{7a–c} we felt that the use of an appropriate ligand would allow us to realize a mild and general procedure for the synthesis of enamides. Using 2-pyrrolidinone and 2-methyl-1-bromopropene as the prototypical substrate combination, an initial ligand screen was carried out with CuI as a catalyst and K₂CO₃ as a base. To our delight, among the eight ligands examined, *N,N'*-dimethylethylenediamine (**7**) and *trans-N,N'*-dimethylcyclohexyldiamine (**8**) gave excellent results. Of the bases examined, K₂CO₃ turned out to give the best yield. The combination of CuI, **7**, and K₂CO₃ could be successfully employed in a variety of solvents including THF, dioxane, toluene, and DMF. Coupling reactions involving vinyl bromides were carried out at 110 °C, and the process generally went to completion in less than 16 h. To the best of our knowledge, this is the first example of the copper-catalyzed amidation of an unactivated vinyl bromide. A variety of enamides have been prepared employing these conditions, as shown in Table 1. Four-, five-, and six-membered lactams were all viable substrates; the reaction

(10) While this manuscript was being prepared, a paper utilizing a stoichiometric quantity of CuTc and *N,N'*-dimethylethylenediamine was reported: Wang, X.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 6040.

Table 1

entry	amide	vinyl halide	temp.(°C)	time(h)	yield(%) ^a
1			90	22	93
2			110	25	88
3			110	21	91
4			115	30	76
5			110	24	84
6 ^b			110	14	90
7 ^b			110	15	84
8 ^c			80	15	94
9 ^c			110	16	95
10 ^c			110	16	94
11 ^{c,d}			110	16	81

^a Isolated yield average of two runs. ^b Rotameric mixture was isolated. ^c 1.2 equiv of vinyl bromide was employed. ^d 10 mol % of CuI and 20 mol % of **7** were employed.

of five-membered lactams was generally faster than those of the others.¹¹ Both cyclic amides and acyclic amides could be combined with vinyl halides to give the desired enamides in excellent yields. Notably, an amide with a free anilino group was also successfully coupled using this catalytic system (Table 1, entry 11). We found, however, that acyclic secondary amides were not suitable substrates, most likely because of their increased level of steric hindrance. In contrast, this protocol was less sensitive to the size of the

(11) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035.

Table 2.

$\text{R}^1-\text{C}(=\text{O})\text{NH}-\text{R}^2 + \text{I}-\text{CH}=\text{CH}-\text{R}^3 \xrightarrow[\text{THF, temp.}]{5 \text{ mol\% CuI, } 7 \text{ Cs}_2\text{CO}_3} \text{R}^1-\text{C}(=\text{O})\text{N}(\text{R}^2)-\text{CH}=\text{CH}-\text{R}^3$					
entry	amide	vinyl halide	temp.(°C)	time(h)	yield(%) ^a
1 ^b			rt	15	82
2			50	12	84
3			70	5	67
4			70	6	62
5 ^{c,d}			70	14	86
6 ^c			70	14	92

^a Isolated yield (average of two runs). ^b Reaction was run in DMF. ^c K₂CO₃ was used as base. ^d The starting vinyl iodide contained ~5% *cis*-isomer.

vinyl halides used. For example, di- and trisubstituted vinyl bromides performed well under the reaction conditions and afforded the desired enamides in excellent yield. Particularly important was that we were able to, for the first time, accomplish the catalytic coupling of tetrasubstituted vinyl bromides with an amide using a copper catalyst (Table 1, entries 2–4). We note that the amidation of tetrasubstituted vinyl bromides required slightly longer reaction time than that of di- or tri-substituted substrates. Vinyl bromides bearing a silyl ether moiety were also compatible under the reaction conditions (Table 1, entries 6 and 7). It is also important to note that a small amount of double vinylation product was observed when an excess of vinyl halide was

employed. This general protocol could also be applied to the vinylation of carbamates (Table 1, entries 8–10).

The coupling of vinyl iodides was also examined with the same catalyst system. The amidation of vinyl iodides was found to proceed under mild conditions (<70 °C), and in one case the reaction proceeded at room temperature. For the amidation of vinyl iodides, the use of Cs₂CO₃ as a base generally gave better results than K₂CO₃. As shown in Table 2, α,β -unsaturated amides were also viable substrates. More importantly, the double bond geometry of the vinyl halides was retained in the product. We also found that α,β -unsaturated- β -iodoesters were successfully coupled with amides to provide the dehydro- β -amino ester, a precursor for β -amino acids.¹² In these cases, it is important to stop the reaction at the time indicated; extended heating results in decomposition of the products.

In conclusion, we have developed a mild and efficient protocol for the copper-catalyzed coupling of amides and carbamates with vinyl bromides and iodides. This procedure provides access to the structurally important enamide moiety. The mild reaction conditions and increased scope relative to previous methods, the operational simplicity, and the functional group compatibility of this process should render this protocol attractive to synthetic chemists.

Acknowledgment. We thank the NIH (GM 58160) for funding. Pfizer, Merck, and Bristol-Myers Squibb are acknowledged for additional unrestricted support. L.J. was supported as a postdoctoral trainee of the National Cancer Institute (NCI training grant CI T32CA09112).

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

OL035355C

(12) For a recent report on asymmetric hydrogenation of β -acylamido acrylates, see: Holz, J.; Monsees, A.; Jiao, H.; You, J.; Kormarov, I. V.; Fischer, C.; Drauz, K.; Borner, A. *J. Org. Chem.* **2003**, *68*, 1701.