

# CuI/*N,N*-Dimethylglycine-Catalyzed Coupling of Vinyl Halides with Amides or Carbamates

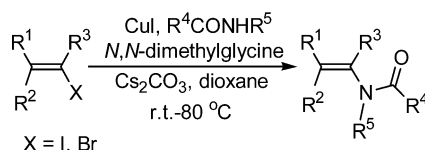
Xianhua Pan,<sup>†</sup> Qian Cai,<sup>‡</sup> and Dawei Ma<sup>\*‡</sup>

Department of Chemistry, Fudan University, Shanghai 200433, China,  
and State Key Laboratory of Bioorganic and Natural Products Chemistry,  
Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences,  
354 Fenglin Lu, Shanghai 200032, China

madw@pub.sioc.ac.cn

Received March 22, 2004

## ABSTRACT



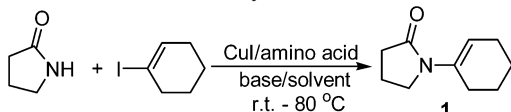
The CuI-catalyzed coupling reaction of vinyl halides with amides or carbamates proceeds well at room temperature to 80 °C in dioxane to give enamides using *N,N*-dimethylglycine as the promoter and Cs<sub>2</sub>CO<sub>3</sub> as the base. The geometry of the C–C double bond is retained during the reaction course.

Enamides are unique functional groups present in many natural products discovered during the past decades, which include protease inhibitors TMC-95-A-D,<sup>1</sup> sedative and antiinflammatory peptide franguloline,<sup>2</sup> cytotoxic agents aspergillamides,<sup>3</sup> chondriamides,<sup>4</sup> as well as salicylhalamide A and related compounds.<sup>5</sup> In addition, enamides have found a great deal of usage in the preparation of heterocycles<sup>6</sup> and in asymmetric synthesis of amides and amino acids.<sup>7</sup> It is not surprising then that synthetic interest in this target has been considerable.<sup>6,8–11</sup> Among the emerging methods, copper-catalyzed coupling reaction of amides with vinyl halides has received increasing attention and found applica-

tions in the total synthesis of natural products.<sup>9–11</sup> Very recently, two groups have independently observed that this

<sup>†</sup> Fudan University.<sup>‡</sup> Shanghai Institute of Organic Chemistry.(1) Kohno, J.; Koguchi, Y.; Nisshio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990.(2) (a) Tschesche, R.; Last, H. *Tetrahedron Lett.* **1968**, 2993. (b) Tschesche, R.; Wilhelm, H.; Fehlhaber, H.-W. *Tetrahedron Lett.* **1972**, 2609. (c) Han, Y. N.; Kim, G.-Y.; Han, H. K.; Han, B. H. *Arch. Pharm. Res.* **1993**, *16*, 289.(3) Toske, S. G.; Jensen, P. R.; Kauffman, C. A.; Fenical, W. *Tetrahedron* **1998**, *54*, 13459.(4) (a) Palermo, J. A.; Flower, P. B.; Seldes, A. M. *Tetrahedron Lett.* **1992**, *33*, 3097. (b) Davyt, D.; Entz, W.; Fernandez, R.; Mariezcurrena, R.; Momburu, A. W.; Saldana, J.; Dominguez, L.; Coll, J.; Manta, E. *J. Nat. Prod.* **1998**, *61*, 1560.(5) (a) Yet, L. *Chem. Rev.* **2003**, *103*, 4283. (b) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188. (c) Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II; Boyd, M. P. *J. Org. Chem.* **1997**, *62*, 8968. (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. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **2001**, *66*, 1532. (f) Dekker, K. A.; Aiello, R. J.; Hirai, H.; Inagaki, T.; Sakakibara, T.; Suzuki, Y.; Thompson, J. F.; Yamaguchi, Y.; Kojima, N. *J. Antibiot.* **1998**, *51*, 14. (g) Kunze, B.; Jansen, R.; Sasse, F.; Hofle, G.; Reichenbach, H. *J. Antibiot.* **1998**, *51*, 1075.(6) (a) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286. (b) Schultz, A. G.; Guzzo, P. R.; Nowak, D. M. *J. Org. Chem.* **1995**, *60*, 8044. (c) Brodney, M. A.; Padwa, A. J. *J. Org. Chem.* **1999**, *64*, 556. (d) Davies, D. T.; Kapur, N.; Parsons, A. F. *Tetrahedron* **2000**, *56*, 3941.(7) For recent reviews, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029. (b) Ma, J.-A. *Angew. Chem., Int. Ed.* **2003**, *42*, 4290.(8) (a) Wang X.; Porco, J. A., Jr. *J. Org. Chem.* **2001**, *66*, 8215 and references therein. (b) Snider, B. B.; Song, F. *Org. Lett.* **2000**, *2*, 407. (c) Fürstner, A.; Brehm, C.; Cancho-Grande, Y. *Org. Lett.* **2001**, *3*, 3955. (d) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67. (e) Kuramochi, K.; Osada, Y.; Kitahara, T. *Chem. Lett.* **2002**, 128. (f) Kuramochi, K.; Osada, Y.; Kitahara, T. *Tetrahedron* **2003**, *59*, 9447. (g) Lam, P. Y. S.; Vincent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927. (h) Wallace, D. J.; Klauber, D. J.; Chen, C.-Y.; Volante, R. P. *Org. Lett.* **2003**, *5*, 4749.(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.

**Table 1.** Coupling Reaction of 1-Iodocyclohexene with 2-Pyrrolidinone under the Catalysis of CuI and Amino Acids<sup>a</sup>



entry	amino acid	base	solvent	yield (%) <sup>b</sup>
1	Me <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H·HCl	Cs <sub>2</sub> CO <sub>3</sub>	toluene	35
2	Me <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H·HCl	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	85
3	Me <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H·HCl	Cs <sub>2</sub> CO <sub>3</sub>	DMSO	50
4	Me <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H·HCl	K <sub>2</sub> CO <sub>3</sub>	dioxane	61
5	Me <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H·HCl	KOH	dioxane	<10
6	L-proline	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	20
7	MeHNCH <sub>2</sub> CO <sub>2</sub> H	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	21
8	BnHNCH <sub>2</sub> CO <sub>2</sub> H	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	25
9	Bn <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	50
10	Me <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H·HCl	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	85 <sup>c</sup>
11	Me <sub>2</sub> NCH <sub>2</sub> CO <sub>2</sub> H·HCl	Cs <sub>2</sub> CO <sub>3</sub>	dioxane	78 <sup>d</sup>

<sup>a</sup> Reaction conditions: CuI (0.1 mmol), amino acid (0.2 mmol), 1-iodocyclohexene (1 mmol), 2-pyrrolidinone (1.2 mmol), base (2 mmol), solvent (1 mL), 80 °C, 12 h. <sup>b</sup> Isolated yield. <sup>c</sup> Reaction was carried out at 60 °C. <sup>d</sup> Reaction was carried at rt for 30 h, and CuI (1 mmol) and *N,N*-dimethylglycine hydrochloride salt (1 mmol) were used.

reaction could be carried out under relatively mild conditions with the assistance of either *N,N'*-dimethyl ethylenediamine or substituted 1,10-phenanthrolines.<sup>10</sup> A similar strategy was used by Coleman and Liu to develop a facile route to the enamide side chains of salicylhalamide A and related compounds.<sup>11</sup> Herein we wish to describe a new catalytic system for this transformation, which showed advantage in some aspects over the existing two systems.

Our previous studies have demonstrated that some amino acids are excellent promoters for copper-catalyzed Ullmann-type coupling reactions.<sup>12</sup> In Buchwald's report,<sup>10b</sup> *N,N*-dimethylglycine was reported to be much less active than *N,N'*-dimethyl ethylenediamine as an additive for CuI-catalyzed coupling of 2-pyrrolidinone and 2-methyl-1-bromopropene. We reasoned that this problem might result from the solvent they used, and therefore controlled experiments were undertaken. As shown in Table 1, heating a mixture of 1-iodocyclohexene, 2-pyrrolidinone, Cs<sub>2</sub>CO<sub>3</sub>, CuI, and *N,N*-dimethylglycine hydrochloride salt in toluene at 80 °C for 12 h gave coupling product **1** in only 35% yield (entry 1). However, it was observed that the yield jumped to 85% if the solvent was switched to dioxane (entry 2). Changing the solvent to DMSO or base to K<sub>2</sub>CO<sub>3</sub> and KOH all gave considerably lower yields (entries 3–5). We next tested other amino acid additives and found that *N,N*-dimethyl glycine

was the first choice for this transformation because *N*-monosubstituted amino acids showed a poor ability to promote this reaction (entries 6–8) and only moderate yield was observed in case of *N,N*-dibenzylglycine as the additive (entry 9). Thus, we concluded that the optimized combination for this reaction was to use dioxane as the solvent, Cs<sub>2</sub>CO<sub>3</sub> as the base, and *N,N*-dimethylglycine as the additive. Further exploration indicated that, employing this combination, the reaction still worked well at 60 °C or even at room temperature by using stoichiometric amounts of CuI and additive (entries 10 and 11).

With the optimized condition in hand, we then explored the scope of this reaction by varying vinyl halides, amides, and carbamates. As displayed in Table 2, using the coupling with 1-iodocyclohexene as a model reaction, both cyclic and acyclic amides were found suitable substrates (entries 1–3). Carbamates also worked to give the corresponding vinylation products **5** and **14** (entries 4 and 17). When *cis*-type acyclic vinyl iodides were used, only *cis*-vinylation products were isolated (entries 5 and 6), which indicated that the geometry of the C–C double bond was retained during the reaction course. Interestingly, coupling of 3-iodo-2-cyclohexenone with benzamide furnished enamide **8** in 82% yield (entry 7), which implied that this process could be used for synthesizing a class of potential anticonvulsants.<sup>13</sup>

To develop an efficient protocol to prepare *N*-acyl vinyllogous carbamic acids and derivatives, Porco and co-workers have investigated systematically copper-mediated coupling reaction of amides with  $\beta$ -iodoacrylates.<sup>10c</sup> They found that the reaction yields could be improved by using some substituted 1,10-phenanthrolines as the additives, while the diamine ligands were less effective for this reaction. On the basis of these studies, a mild condition was discovered to obtain the desired coupling products in moderate to good yields; however, a drawback is that 3 equiv of amides should be used to ensure satisfactory yields. Thus, this transformation became an ideal model to test our catalytic system. To our delight, heating a mixture of (*E*)-allyl 3-iodoacrylate (1 mmol) and sorbic amide (1 mmol), CuI (0.1 mmol), *N,N*-dimethylglycine hydrochloride salt (0.2 mmol), and Cs<sub>2</sub>CO<sub>3</sub> (2 mmol) in dioxane at 45 °C for 12 h produced the cross-coupling product **9** in 56% yield (entry 8). By using stoichiometric amounts of CuI and *N,N*-dimethylglycine hydrochloride salt this reaction even worked at room temperature to give **9** in 43% yield (entry 9). Similarly, a coupling reaction using equal molar amounts of (*E*)-allyl 3-iodoacrylate and 2-pyrrolidinone at the above two conditions afforded enamide **10** in good yields (entries 10 and 11). These yields are almost identical with those obtained by using a 3-fold excess of amides.<sup>10c</sup> Furthermore, our catalytic system was found compatible with the coupling of methyl *cis*-3-iodoacrylate with several amides or carbamides to give the corresponding enamides **11–14** in good yields at either 60 °C or room temperature (entries 11–17). Thus, the combination of CuI as the catalyst, *N,N*-


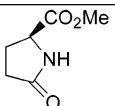
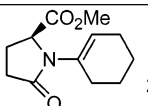

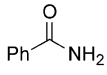
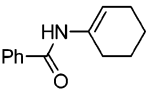

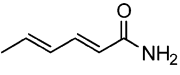
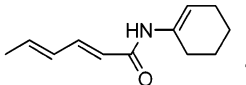


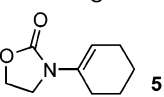
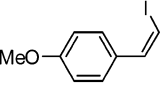

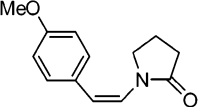
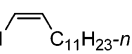

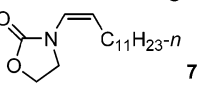
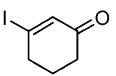
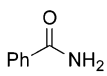
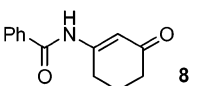
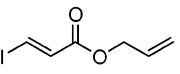
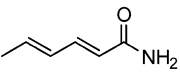
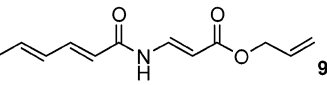
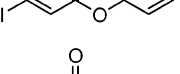

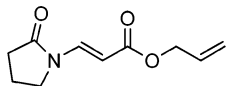
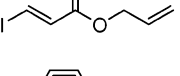

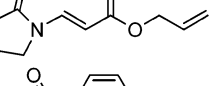
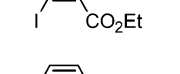

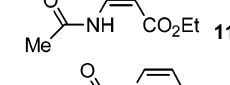
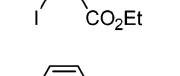
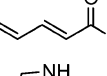
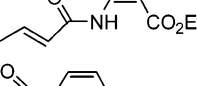
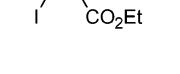
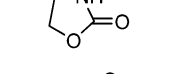
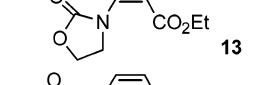
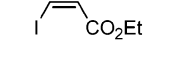

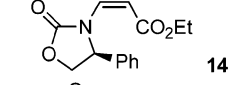
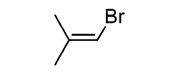

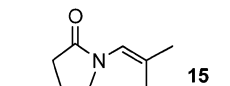
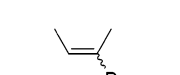

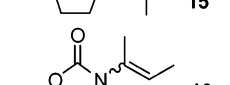
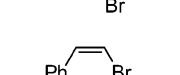
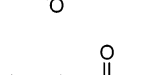
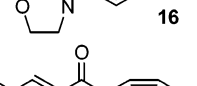


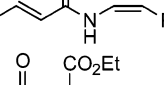


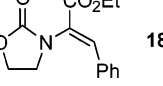
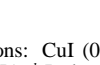
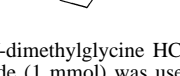
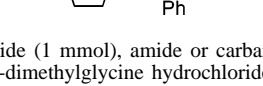
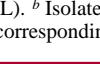

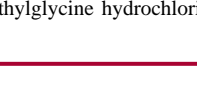
(10) (a) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (c) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27.

(11) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577.

(12) (a) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (b) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799. (c) Ma, D.; Cai, Q. *Synlett* **2004**, 128. (d) Zhu, W.; Ma, D. *Chem. Commun.* **2004**, 888. For a related work, see: (e) Deng, W.; Wang, Y.; Zou, W.; Liu, L.; Guo, Q. *Tetrahedron Lett.* **2004**, *45*, 2311.

(13) Foster, J. E.; Nicholson, J. M.; Butcher, R.; Stables, J. P.; Edafiogho, I. O.; Goodwin, A. M.; Henson, M. C.; Smith, C. A.; Scott, K. R. *Bioorg. Med. Chem.* **1999**, *7*, 2415.

**Table 2.** Coupling Reaction of Vinyl Halides with Amides or Carbamates under the Catalysis of CuI and *N,N*-Dimethylglycine<sup>a</sup>

entry	vinyl halide	amide	temp. (°C)/ time (h)	Product	Yield (%) <sup>b</sup>
1			60/12		78
2			60/12		81
3			60/12		74
4			60/12		70
5			60/12		78
6			60/12		78
7			60/12		82
8			45/12		56 <sup>c</sup>
9			r.t./30		43 <sup>c,d</sup>
10			45/12		87 <sup>c</sup>
11			r.t./30		70 <sup>c,d</sup>
12			60/12		75
13			r.t./30		65 <sup>d</sup>
14			60/12		73
15			60/12		82
16			r.t./30		71 <sup>d</sup>
17			60/12		76
18			80/24		62
19			80/24		63 <sup>e</sup>
20			80/24		65
21			80/24		63

<sup>a</sup> Reaction conditions: CuI (0.1 mmol), *N,N*-dimethylglycine HCl salt (0.2 mmol), vinyl halide (1 mmol), amide or carbamate (1 mmol), Cs<sub>2</sub>CO<sub>3</sub> (2 mmol), dioxane (1 mL). <sup>b</sup> Isolated yield. <sup>c</sup> Amide (1 mmol) was used. <sup>d</sup> CuI (1 mmol) and *N,N*-dimethylglycine hydrochloride salt (1 mmol) were used. <sup>e</sup> Product Z/E = 4/1 corresponding to the starting vinyl bromide Z/E = 4/1.

dimethylglycine as the additive, Cs<sub>2</sub>CO<sub>3</sub> as the base, and dioxane as the solvent provided a more practical condition

for preparation of *N*-acyl vinylogous carbamic acids and derivatives.

When substrates were switched from vinyl iodides to vinyl bromides, higher reaction temperature was needed to complete the coupling reaction (entries 18–21). When a mixture of 2-bromo-*cis*-2-butene and 2-bromo-*trans*-2-butene was used, both *cis*- and *trans*-products were detected by  $^1\text{H}$  NMR in the same ratio (4:1) as the starting material (entry 19). This result indicated that the geometry of the C–C double bond was retained in this condition, which was further proved since only *cis*-enamide was determined in the coupling of *cis*- $\beta$ -bromostyrene (entry 20). More importantly, we observed that *cis*- $\beta$ -bromocinnamic acid methyl ester reacted with a carbamide to deliver a stereochemically retained product **18** in 63% yield (entry 21), which may be a potential precursor for asymmetric synthesis of amino acids.<sup>7,8h</sup>

In summary, we have demonstrated that *N,N*-dimethylglycine is a powerful promoter for CuI-catalyzed coupling reactions of vinyl halides with amides or carbamides using dioxane as the solvent and  $\text{Cs}_2\text{CO}_3$  as the base. A wide range of functional groups such as ketone, ester, and dienoid amide

groups were found to tolerate to this condition, which would allow the preparation of a variety of enamides. In addition, the present catalytic system can be easily removed from the reaction system by simple washing, which makes separation more convenient. Thus, it should find applications in the synthesis of biologically and synthetically important enamides.

**Acknowledgment.** The authors are grateful to the Chinese Academy of Sciences, National Natural Science Foundation of China (grants 20321202 and 20132030), and Science and Technology Commission of Shanghai Municipality (grants 02JC14032 and 03XD14001) for their financial support.

**Supporting Information Available:** Experimental procedures and characterization for compounds **1–18**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL049464I