ORGANIC LETTERS

2004
Vol. 6, No. 7
1151−1154

Copper Sulfate-Pentahydrate-1,10-Phenanthroline Catalyzed Amidations of Alkynyl Bromides. Synthesis of Heteroaromatic Amine Substituted Ynamides

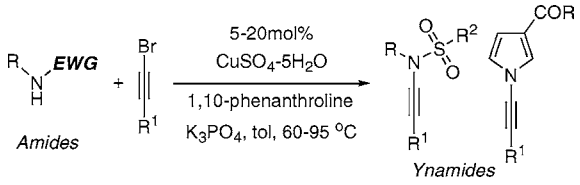
Yanshi Zhang, Richard P. Hsung,* Michael R. Tracey, Kimberly C. M. Kurtz, and Eymi L. Vera

Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

hsung@chem.umn.edu

Received January 29, 2004

ABSTRACT



EWG = electron withdrawing carbonyl groups

A practical cross-coupling of amides with alkynyl bromides using catalytic $CuSO_4 \cdot 5H_2O$ and 1,10-phenanthroline is described here. This catalytic protocol is more environmentally friendly than the use of CuCN or copper halides and provides a general entry for syntheses of ynamides including various new sulfonyl and heteroaromatic amine substituted ynamides. Given the interest in ynamides, this *N*-alkynylation of amides should be significant for the future of ynamides in organic synthesis.

Ynamides have been attracting wide attention from the synthetic community in the past 10 years.[1−3] Inspired by Buchwald's copper-catalyzed N-arylations of amides,[4] we communicated syntheses of ynamides **3** via a Cu(I)-catalyzed cross-coupling[5−9] of alkynyl bromides **1** with amides **2** (Scheme 1).[10a] This study illustrates the concept of transition-metal-catalyzed N-alkynylations of amides[10b,c] and provides a practical and improved synthetic access to ynamides over

(1) For reviews on ynamides, see: (a) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (b) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. For the first preparations of ynamides, see: (c) Janousek, Z.; Collard, J.; Viehe, H. G. *Angew. Chem., Int. Ed.* **1972**, *11*, 917.

(2) For recent efforts in synthesis and applications of ynamides, see: (a) Rodriguez, D.; Castedo, L.; Saá, C. *Synlett* **2004**, ASAP. (b) Klein, M.; König, B. *Tetrahedron* **2004**, *60*, 1087. (c) Marion, F.; Courillon, C.; Malacria, M. *Org. Lett.* **2003**, *5*, 5095. (d) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem., Int. Ed.* **2003**, *42*, 4257. (e) Witulski, B.; Lumtscher, J.; Bergsträsser, U. *Synlett* **2003**, 708. (f) Witulski, B.; Alayrac, C. *Angew. Chem. Int. Ed.* **2002**, *41*, 3281. (g) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67. (h) Gravestock, D.; Dovey, M. C. *Synthesis* **2003**, 523. (i) Naud, S.; Cintrat, J.-C. *Synthesis* **2003**, 1391. (j) Saito, N.; Sato, Y.; Mori, M. *Org. Lett.* **2002**, *4*, 803. (k) Timbart, J.-C.; Cintrat. J.-C. *Chem. Eur. J.* **2002**, *8*, 1637. (l) Minière, S.; Cintrat. J.-C. *Synthesis* **2001**, 705. (m) Minière, S.; Cintrat. J.-C. *J. Org. Chem.* **2001**, *66*, 7385. (n) Hoffmann, R. W.; Brückner, D. *New. J. Chem.* **2001**, *25*, 369. (o) For papers before 2000, please refer to ref 1a and b.

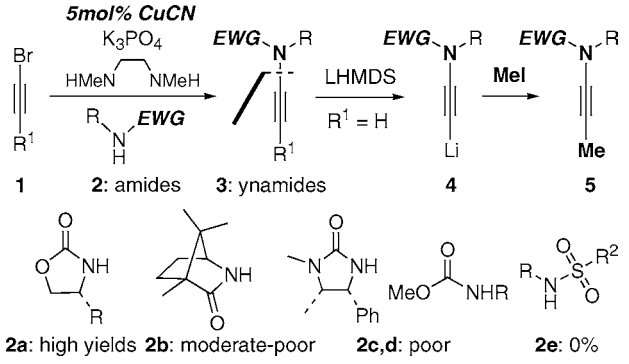
(3) For our recent applications of ynamides, see: (a) Shen, L.; Hsung, R. P. *Tetrahedron Lett.* **2003**, *44*, 9353. (b) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A. Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663. (c) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P.; Coverdale, H. A.; Frederick, M. O.; Shen, L.; Zificsak, C. A. *Org. Lett.* **2003**, *5*, 1547. (d) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar. C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (e) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383.

(4) For recent key papers on copper-catalyzed N-arylations of amides from the Buchwald group, see: (a) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (b) Klapars, A.; Huang, X.; Buchwald S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. (c) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (d) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581.

(5) For recent contributions on copper-catalyzed N-arylations of amides from the Porco group, see: (a) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27. (b) Shen, R.; Lin, C. T.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. Jr. *J. Am. Chem. Soc.* **2003**, *125*, 7889. (c) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333.

10.1021/ol049827e CCC: $27.50
Published on Web 03/02/2004

Scheme 1

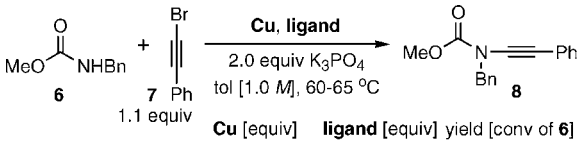


existing protocols.[1b,2h−i,11,12] It also allows subsequent access to ynamides such as **5** via deprotonation of parent ynamides **3** ($R^1 = H$) and methylation of lithium acetylides **4**. However, despite such development, there remain severe limitations. Although oxazolidinones **2a** were useful in the coupling with **1**, amides **2b**−**d** were mostly poor and sulfonamides **2e** were not suitable at all. This latter limitation is the least desirable since sulfonyl ynamides are the substrates employed most in an array of elegant methodologies that has been developed.[2,13,14]

In addressing this limitation, Danheiser[15] recently reported a useful solution using a stoichiometric amount of copper along with a strong base, KHMDS. Danhesier's protocol should capture much interest, for it allows reactions to proceed at room temperature, which is much lower than ours at 110 °C, thereby rendering potential preparations of thermally sensitive ynamides feasible. We elected to re-examine this coupling reaction and overcome this limitation by developing a catalytic protocol[16] based on Buchwald's[4,17] and Porco's[5] meticulous studies on copper-catalyzed N-arylations of amides and enamides. We report here copper sulfate-pentahydrate-1,10-phenanthroline catalyzed amidations of alkynyl bromides using sulfonamides and heteroaromatic amines in addition to lactams and urethanes.

To successfully develop a general catalytic protocol for preparation of ynamides, variables such as Cu(I) or Cu(II) salts,[18a] ligands, solvents,[18b] concentrations,[18c] bases,[18d] and temperatures[18e] were carefully screened using acyclic carbamate **6** and alkynyl bromide **7** as model substrates as summarized in Scheme 2. The best Cu(I) salt, CuCN, could give **8**[19] in an optimal 36% isolated yield at 0.2 equiv, similar to what we had reported.[10] A stoichiometric amount of CuCN led to **8** in only 7% yield with the major product being the homocoupled product from **7** when K_3PO_4 was the base of

Scheme 2



Cu [equiv]	**ligand** [equiv]	yield [conv of **6**]
CuCN [0.2]	DMED [0.4]	36%
CuCN [1.0]	DMED [2.0]	7
$CuSO_4$ [0.2]	DMED [0.4]	20 [45]
$CuSO_4$ [0.2]	DMDC [0.4]	41 [90]
$CuSO_4$ [0.2]	DAC [0.4]	<5 [90]
$CuSO_4$ [0.2]	**1,10-Phen [0.4]**	**73 [80]**

$CuSO_4$ = $CuSO_4$-$5H_2O$. DMED: *N,N*-dimethylethylenediamine; DMDC: *N,N*-dimethyl-*trans*-1,2-diaminocyclohexane; DAC: *trans*-1,2-diamino-cyclohexane; 1,10-Phen:1,10-phenanthroline.

(6) For some earlier accounts, see: (a) Yamamoto, T.; Kurata, Y. *Can. J. Chem.* **1983**, *61*, 86 and references therein. (b) Yamamoto, T.; Ehara, Y.; Kubota, M.; Yamamoto, A. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1299. (c) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. For recent references of copper catalyzed N-arylations of amides and enamides, see: (d) Lam, P. Y. S.; Vinvent, G.; Bonne, D.; Clark, C. G. *Tetrahedron Lett.* **2003**, *44*, 4927. (e) Yamada, K.; Kubo, T.; Tokuyama, H.; Fukuyama, T. *Synlett* **2002**, 231. (f) Lam, P. Y. S.; Deudon, S.; Averill, K. M.; Li, R.; He, M. Y.; DeShong, P.; Clark, C. G. *J. Am. Chem. Soc.* **2000**, *122*, 7600. (g) Collman, J. P.; Zhong, M. *Org. Lett.* **2000**, *2*, 1233. (h) Mederski, W. W. K. R.; Lefort, M.; Germann, M.; Kux, D. *Tetrahedron* **1999**, *55*, 12757. (i) Murakami, Y.; Watanabe, T.; Hagiwara, T.; Akiyama, Y.; Ishii, H. *Chem. Pharm. Bull.* **1995**, *43*, 1281. (j) Kato, Y.; Conn, M. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1994**, *116*, 3279. (k) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.***1991**, 1443. For recent references of copper-catalyzed N-arylations of amides alcohols, see: (l) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org Lett.* **2002**, *4*, 973. (m) Fagan, P. J.; Hauptman, E.; Shapiro, R.; Casalnuovo, A. *J. Am. Chem. Soc.* **2000**, *122*, 5043.

(7) For a recent review on copper-mediated C−N and C−O bond formation, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. Also see: (b) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(8) For reviews on the related palladium-catalyzed N-arylations of amines and amides, see: (a) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046. (b) Wolfe, J. P.; Wagaw, S.; Marcoux, J.-F.; Buchwald, S. L. *Acc. Chem. Res.* **1998**, *31*, 805. For an earlier account, see: (c) Kosugi, M.; Kameyama, M, Migita, T. *Chem. Lett.* **1983**, 927.

(9) For recent examples on palladium-catalyzed N-arylations of amines and amides, see: (a) Yin, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 6043. (b) Hartwig, J. F.; Kawatsura, M.; Hauck, S. I.; Shaughnessy, K. H.; Alcazar- Roman, L. M. *J. Org. Chem.* **1999**, *64*, 5575. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Zappia, G. *Org. Lett.* **2001**, *3*, 2539. (d) Artamkina, G. A.; Sergeev, A. G.; Beletskaya, I. P. *Tetrahedron Lett.* **2001**, *42*, 4381. (e) Edmondson, S. D.; Mastracchio, A.; Parmee, E. R. *Org. Lett.* **2000**, *2*, 1109. (h) Bolm, C.; Hildebrand, J. *J. Org. Chem.* **2000**, *65*, 169.

(10) (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368. (b) For an earlier documentation of copper-promoted coupling of amide with alkyne, see: Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A. *Tetrahedron Lett.* **1985**, *26*, 4141. (c) For a much earlier account of such copper(II) acetate/O_2 catalyzed C_{sp}−N bond formation in synthesis of ynamines, see: Petersen, L. I. *Tetrahedron Lett.* **1968**, *9*, 5357.

(11) (a) Brückner, D. *Synlett* **2000**, 1402. (b) Fromont, C.; Masson, S. *Tetrahedron* **1999**, *55*, 5405. (c) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440. (d) Novikov, M. S.; Khlebnikov, A. F.; Kostikov, R. R. *J. Org. Chem. USSR* **1991**, *27*, 1576. (e) Tikhomirov, D. A.; Eremeev, A. V. *Chem. Heterocycl. Compd. (N. Y.)* **1987**, *23*, 1141.

(12) Wei, L.-L.; Mulder, J. A.; Xiong, H.; Zificsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

(13) For Witulski's earlier work, see: (a) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *37*, 489. (b) Witulski, B.; Stengel, T. *Angew. Chem., Int. Ed.* **1998**, *38*, 2426. (c) Witulski, B.; Gössmann, M. *Chem. Commun.* **1999**, 1879. (d) Witulski, B.; Gössmann, M. *Synlett* **2000**, 1793. (e) Witulski, B.; Stengel, T.; Fernàndez-Hernàndez, J. M. *Chem. Commun.* **2000**, 1965. (f) Witulski, B.; Buschmann, N.; Bergsträsser, U. *Tetrahedron* **2000**, *56*, 8473.

(14) (a) Rainier, J. D.; Imbriglio, J. E. *J. Org. Chem.* **2000**, *65*, 7272. (b) Rainier, J. D.; Imbriglio, J. E. *Org. Lett.* **1999**, *1*, 2037.

(15) Dunetz, J. R.; Danheiser, R. L. *Org. Lett.* **2003**, *5*, 4011.

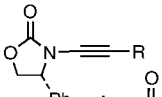
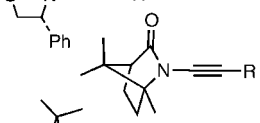
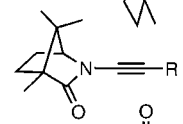
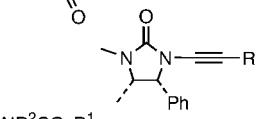
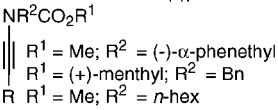
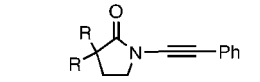
(16) During the submission of our work, we became aware of the success in the synthesis of sulfonyl-substituted ynamides using catalytic CuI, see: Hirano, S.; Tanaka, R.; Urabe, H.; Sato, F. *Org. Lett.* **2004**, *6*, ASAP.

(17) For key references in using 1,10-phenanthroline as a ligand in copper catalyzed N-arylations of amides from the Buchwald group, see: (a) Kiyomori, A.; Marcoux, J.-F.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 2657. (b) Kwong, F. Y.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 581. (c) Wolter, M.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2001**, *3*, 3803.

choice. The outcome improved incrementally when we switched to Cu(II) salts and, specifically, $CuSO_4 \cdot 5H_2O$. It was not until 1,10-phenanthroline[4,5,17,20,21] was used as the ligand that ynamide **8** was isolated in 73% yield with 80% conversion of **6** and complete suppression of homocouplings.

The use of $CuSO_4 \cdot 5H_2O$ represents a catalytic protocol that is much cheaper and more environmentally friendly than the CuCN method, and it compares quite favorably with the CuCN catalyst, as shown in entries 1 and 2 in Table 1. In addition, we found that formerly poor substrates such as azacamphor (entries 3−6), imidazolidinone (entries 7−10), and acyclic-urethanes (11−13) are now quite suitable for coupling with their respective alkynyl bromides using the new protocol. Even simple lactams underwent coupling to give ynamides **21** and **22** (entries 14 and 15). It is noteworthy that the loading is mostly in the range of 5−10 mol % of $CuSO_4 \cdot 5H_2O$ and that temperature is now at 60−65 °C instead of 110 °C,[10a] which is much lower than what had been used in the CuCN protocol.

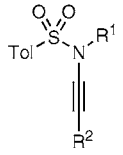
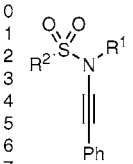
Table 1.

entry	ynamide product[a]	R = [*mol% CuSO4*]	yield[b]
1		**9** Ph [*10mol%*]	88%[69][c]
2		**10** TIPS [*10*]	85%[85]
3		**11** Ph [*10*]	98
4		**12** $(CH_2)_4$OTBS [*5*]	70
5		**13** Ph [*10*]	97
6		**13** Ph [*5*]	95
7		**14** Ph [*20*]	86
8		**15** TIPS [*10*]	81[d]
9		**16** 2-MeO-Np [*10*]	37
10		**17** *n*-hex [*10*]	61[e]
11	 R = $NR^2CO_2R^1$; R^1 = Me; R^2 = (-)-α-phenethyl	**18** Ph [*20*]	56
12	R^1 = (+)-menthyl; R^2 = Bn	**19** Ph [*20*]	63
13	R^1 = Me; R^2 = *n*-hex	**20** Ph [*20*]	59
14		**21** Me [*20*]	58[f]
15		**22** H [*20*]	38[g]

[a] Reactions were carried out using 5−20 mol % $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline (2 equiv to copper), 2.0 equiv of K_3PO_4 in toluene (0.5−1.0 M based on the amide) at 60−65 °C for 18−36 h. [b] Isolated yields. [c] Yields from using 5 mol % CuCN and DMED. [d] Run at 80−85 °C. [e] Run at 90−95 °C. [f] Base was Cs_2CO_3. [g] 2 equiv of 1,10-phenanthroline and 1.6 equiv of alkynyl bromide were used.

More significantly, the $CuSO_4 \cdot 5H_2O$/1,10-phenanthroline catalytic system was very useful in the preparation of sulfonyl ynamides (Table 2).[22] An array of sulfonyl ynamides were prepared to illustrate (1) the range of different alkynyl bromides employed (entries 1−8), (2) the ability to synthesize chiral sulfonyl ynamides (entries 9 and 12), (3) tolerance of various substituted sulfonamides (entries 10 and 17), including those containing functional groups such as shown in ynamides **38** and **39** (entries 16 and 17), and (4) permutations in substitution patterns one can achieve in these ynamides. In these reactions, K_2CO_3 appears to be a better base than K_3PO_4. Given the current synthetic interest, these new sulfonyl ynamides should find further utility in organic synthesis.

Table 2.

entry	ynamides[a]	R^1 =	R^2 = [*mol% Cu(II)*]	yield[b]
1		**23** Bn	Ph[*10mol%*]	96%
2		**24** $PhCH_2CH_2$	Ph[*5*]	97
3		**25** Bn	2-MeO-Ph[*10*]	93
4		**26** Bn	2-MeO-Naph[*10*]	88
5		**27** Bn	*n*-hex [*10*]	84
6		**28** Bn	$[CH_2]_4$OTBS[*10*]	75
7		**29** Bn	CH_2OTBDPS[*5*]	74
8		**30** Bn	TIPS[*10*]	97
9		**31** (-)-α-phenethyl	Ph[*10*]	92
10		**32** Bn	Ph[*10*]	97
11		**33** Ph	Ph[*10*]	91[c]
12		**34** (-)-α-phenethyl	Ph[*10*]	94
13		**35** Bn	4-MeO-Ph[*5*]	98
14		**36** Bn	4-NO_2-Ph[*5*]	97
15		**37** Bn	Me [*10*]	97
16		**38** $CH_2CH{=}CH_2$	tolyl [*10*]	69
17		**39** CH_2CH_2OTBS	tolyl [*10*]	92

[a] Reactions were carried out using 5−10 mol % $CuSO_4 \cdot 5H_2O$, 1,10-phenanthroline (2 equiv to copper), 2.0 equiv of K_2CO_3 in toluene (0.5−1.0 M based on the amide) at 60−65 °C for 18−36 h. [b] Isolated yields. [c] Run in DMF.

Finally, given the pharmaceutical significance of heteroaromatic amine substituted alkynes,[23] we applied this catalytic

(18) (a) Cu(I) salts screened: CuCl, CuI, Cu_2O, CuTc [Tc = thiophenecarboxylate], and CuCN. Cu(II) salts screened: $Cu(OAc)_2$ and CuO. Cu(0) metal was also examined. (b) Solvents screened: Dioxane, NMP, $CH_3CH_2OCH_2CH_2OH$, DMSO, and DMF. (c) Concentration points: 0.1, 0.2, 0.25, 0.4, 0.5, and 1.0 M. (d) Bases screened: KO*t*-Bu, K_2CO_3, and *n*-Bu_4NOH. (e) Temperature points: 110 versus 60 °C.

(19) All new compounds were characterized by ^1H NMR, ^{13}C NMR, FTIR, mass spectroscopy, and $[\alpha]^{23}_D$.

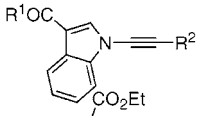
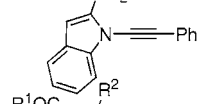
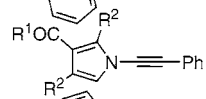
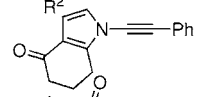
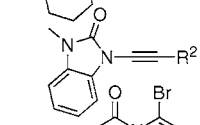
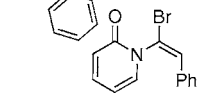
(20) For the usage of 1,10-phenanthroline in ligand accelerated couplings of N-arylations of diarylamines, see: Goodbrand, H. B.; Hu, N.-X. *J. Org. Chem.* **1999**, *64*, 670.

(21) For the usage of 1,10-phenanthroline as ligand in intramolecular N-arylations of guanidines, see: Evindar, G.; Batey, R. A. *Org. Lett.* **2003**, *5*, 133.

(22) **Preparative Procedure Illustrating the Preparation of Ynamide 30.** (Entry 8 in Table 2) To a solution of 1-bromo-2-triisopropylsilylacetylene (575.0 mg, 2.20 mmol) in 2 mL of freshly anhydrous toluene in a reaction vial were added *N*-benzyltoluenesulfonamide (522.0 mg, 2.00 mmol), K_2CO_3 (560.0 mg, 4.00 mmol), $CuSO_4 \cdot 5H_2O$ (50.0 mg, 0.20 mmol), and 1,10-phenanthroline (74.0 mg, 0.40 mmol). The reaction mixture was capped under a blanket of nitrogen and heated in an oil bath at 60−65 °C for 32 h. The progress of the reaction was monitored using TLC analysis. Upon completion, the reaction mixture was cooled to room temperature and diluted with 12 mL of chloroform. The resulting mixture was filtered through a pipet-size Celite column, and the filtrate was concentrated in vacuo. The crude residue was purified using silica gel column flash chromatography (gradient eluent 0−10% EtOAc in hexane) to give ynamide **30** (852.0 mg, 97%) as clear oil. Note: This amidation procedure is also suitable for larger scale preparations. Specifically, we were able to prepare the relatively less stable ynamide **12** at a 6.69-mmol scale and obtained 2.52 g of **12** in 70% yield (entry 4 in Table 1).

(23) (a) Majumdar, K. C.; Ghosh, S. K. *Synth. Commun.* **1994**, *24*, 217. (b) Joshi, R. V.; Xu, Z.-Q.; Ksebati, M. B.; Kessel, D.; Corbett, T. H.; Drach, J. C.; Zemlicka, J. *J. Chem. Soc., Perkin Trans 1* **1994**, 1089. (c) Galy, J. P.; Elguero, J.; Vincent, E. J.; Galy, A. M.; Barbe, J. *Synthesis* **1979**, 944. (d) Mahamoud, A.; Galy, J. P.; Vincent, E. J.; Barbe, J. *Synthesis* **1981**, 917. (e) Radl, S.; Kovarova, L.; Holubeck, J. *Coll. Czech. Chem. Commun.* **1991**, *56*, 439. (f) Radl, S.; Kovarova, L. *Collect. Czech. Chem. Commun.* **1991**, *56*, 2413. (g) Katritzky, A. R.; Ramer, W. H. *J. Org. Chem.* **1985**, *50*, 852.

Table 3.

entry	ynamide product[a,b]		R^1	R^2	yield[c]
1		**40**	OMe	Ph	92%
2		**41**	OMe	TIPS	93
3		**42**	OMe	*n*-hex	85
4		**43**	Me	Ph	80
5		**44**	Ph	Ph	72
6		**45**			81[d]
7		**46**	Me	Me	50
8		**47**	Ph	H	71
9		**48**			77
10		**49**		Ph	67
11		**50**		TIPS	62
12		**51**			42

[a] Reactions were carried out in toluene (0.5−1.0 M based on the amide) using 10 mol % $CuSO_4 \cdot 5H_2O$, 20 mol % 1,10-phenanthroline, 2.0 equiv of K_3PO_4 at 70−80 °C for 18−36 h. For entries 2, 4, 5, and 10−12, 2.0 equiv of K_2CO_3 was used. [b] Except for entries 5 and 7−9, 1.1 equiv of alkynyl bromide was used; for entries 5 and 7−9, it was 1.3−1.4 equiv. [c] Isolated yields. [d] Run at 85 °C.

protocol to the synthesis of various novel vinylogous ynamides.[2h] As shown in Table 3, indoles (entries 1−6), pyrroles (entries 7−9), benzo-2-imidazolidinone (entries 10 and 11), and pyridones (entry 12) could all be successfully coupled to give respective vinylogous ynamides **40**−**51** that can be very attractive for further synthetic as well as medicinal applications. Temperatures for these reactions were higher at 70−80 °C, and both K_2CO_3 and K_3PO_4 appeared to be suitable bases.

Interestingly, α-bromoenamide **51** was isolated as a result of formal addition of "HBr" to the vinylogous ynamide product formed initially.[3c] The assignment of *E*-stereochemistry is based on our previous work on formation of α-haloenamides from treatment of ynamides with hydrated magnesium halides.[3c] However, we would note that in this reaction, the only metal halide species would likely be CuBr, but CuI was found not to be effective in giving α-iodoenamide in our earlier studies.[3c] In addition, this appears to be the sole case in all of the Cu-coupling reactions. We are looking into the possible cause of this unexpected hydrobromonation.

We have described here a useful copper(II) salt catalyzed amidation of acetylenic carbons. This route provides a general entry to a diverse array of ynamides including sulfonyl and heteroaromatic amine substituted ynamides. Given the surging interest in ynamides, this catalytic protocol should have a significant impact on the future utility of ynamides in organic synthesis.

Acknowledgment. This work is supported by the NSF [CHE-0094005].

Supporting Information Available: Experimental details and ^1H NMR spectral and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049827E