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Palladium-Catalyzed Regiospecific Aminocarbonylation of Alkynes in the Ionic Liquid [bmim][Tf$_2$N]

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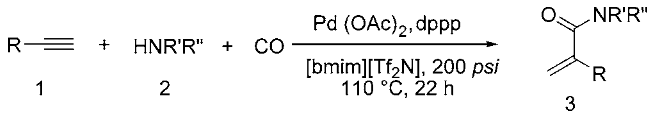
ABSTRACT



Regiospecific construction of 2-substituted acrylamides was achieved by palladium-catalyzed aminocarbonylation of alkynes in the ionic liquid [bmim][Tf$_2$N] without any acid additive under relatively mild conditions. The ionic liquid was used as the reaction medium and also acted as a promoter. Acrylamides were obtained in moderate to excellent yields, and an important feature is that the catalyst system can be recycled five times without loss of catalytic activity.

In recent years, ionic liquids have emerged as green solvents with unique properties such as high polarity, good thermal stability, and the capacity to dissolve various organic, inorganic, and organometallic compounds, as well as negligible vapor pressure and recyclability. Their high polarity and the ability to solubilize both inorganic and organic compounds can result in enhanced rates of chemical processes and provide higher selectivities compared to conventional solvents.[1] Accordingly, ionic liquids are emerging as novel replacements for volatile organic solvents in organic synthesis. Moreover, ionic liquids are easily prepared and recycled, and their properties can be fine-tuned by changing the anion or the alkyl group attached to the cation.[2]

Acrylamides and derivatives are employed in a wide range of organic reactions, which include nucleophilic additions and cycloaddition reactions, to name just a few.[3] They are also extensively used in the synthesis of polymeric materials.[4] Although currently the most widely utilized process for synthesis of acrylamides is hydration of acrylonitriles, synthesis of N-substituted acrylamides usually requires stepwise methods starting from acrylic acid or its esters.[5] Using a different approach, N-substituted acrylamides were formed in 35−52% yields from reaction of alkylidenecarbenes with isonitriles.[6] An alternative method for direct and clean synthesis of substituted acrylamides is carbonylation of alkynes in the presence of amines, i.e., aminocarbonylation, Scheme 1).[7] 2-Substituted acrylamides were synthesized via palladium-catalyzed aminocarbonylation of terminal

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(1) Recent reviews: (a) Welton, T. *Chem. Rev.* **1999**, *99*, 2071. (b) Wasserscheid, P.; Keim, W. *Angew. Chem., Int. Ed.* **2000**, *39*, 3772. (c) Sheldon, R. *Chem. Commun.* **2001**, 2399. (d) Wilkes, J. S. *Green Chem.* **2002**, *4*, 73. (e) Welton, T. *Coord. Chem. Rev.* **2004**, *248*, 2459.

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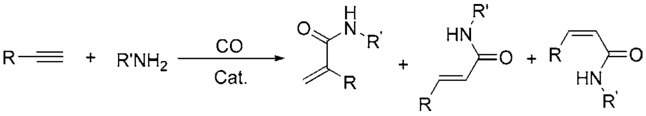
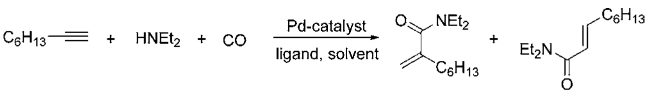
10.1021/ol061675v CCC: $33.50

Scheme 1. Carbonylation of Terminal Alkynes in the Presence of Amines



alkynes in a strong acidic medium[8] or in the presence of organic iodides,[9] p-TsOH or H_2.[10] Unfortunately, so far very limited work has been done toward carbonylative coupling of primary and secondary alkylamines with terminal alkyl alkynes, and regioselectivities and yields for the aimed products are rather unsatisfactory.[9] The acid component of the aminocarbonylation catalyst makes the process corrosive. It would be desirable to develop new aminocarbonylation catalysts that do not require an acid stabilizer or an activity booster.[11] Recently, Ryu and co-workers have reported tin-radical-catalyzed aminocarbonylation of alkynes.[12] A selective reaction for carbon monoxide insertion into the carbon nitrogen bond of propargylamines to give 2,3-dienamides or α-vinyl acrylamides was reported by Alper et al.[13] Recently, we investigated the palladium-catalyzed carbonylative coupling of a variety of alkylamines with alkyl alkynes in the ionic liquid [bmim][Tf_2N] and found that the ionic liquid efficiently promoted the reactions to proceed without any acid additive and that the catalyst system can be recycled for five runs without any significant loss of its catalytic activity. Herein, we report these results.

Table 1. Optimization of Reaction Conditions for the Palladium-Catalyzed Aminocarbonylation of Alkynes[a]



1 **2** **3** **4**

entry	catalyst /ligand	CO (psi)	solvent	yield (%)[b]	products[c] **3**:**4**
1	$Pd(OAc)_2$/dppp	400	[bmim]PF_6	27	98:2
2	$Pd(OAc)_2$/dppp	300	[bmim]PF_6	33	99:1
3	$Pd(OAc)_2$/dppp	200	[bmim]PF_6	56	98:2
4	$Pd(OAc)_2$/dppp	50	[bmim]PF_6	47	97:3
5[d]	$Pd(OAc)_2$/dppp	50	[bmim]PF_6	43	99:1
6	$Pd(PhCN)_2Cl_2$	200	[bmim]PF_6	trace	
7	$Pd(OAc)_2/PPh_3$	200	[bmim]PF_6	trace	
8	$Pd(OAc)_2$/dppp	200	[bmim][Tf_2N]	66	>99[e]:<1
9[f]	$Pd(OAc)_2$/dppp	200	[bmim][Tf_2N]	64	99:1
10	$Pd(OAc)_2$/dppp	400	[bmim][Tf_2N]	50	99:1
11	$Pd(OAc)_2$/dppp	200	[bmim]BF_4	trace	
12	$Pd(OAc)_2$/dppp	200	THF	0	
13	$Pd(OAc)_2$/dppp	200	DMF	0	

[a] Reaction conditions: alkyne **1** (1 mmol), amine **2** (5 mmol), catalyst (0.03 mmol), ligand (0.06 mmol), solvent (2 g), 110 °C, 22 h. [b] Yields after isolation by flash column chromatography on SiO_2. [c] Molar ratio is determined by ^1H NMR spectroscopy. [d] 90 °C. [e] Compound **4** was not detected. [f] 120 °C.

An initial study was carried out using 1-octyne and diethylamine as the substrates to optimize the reaction conditions, and the results are summarized in Table 1. It was found that the CO pressure affected the carbonylation, and the reaction proceeded faster at a relatively low pressure, i.e., 200 psi, (Table 1, entries 1−3). A similar behavior has previously been noticed when the same catalytic system is used in the alkoxycarbonylation of alkynes.[14] It is likely that CO competes with either the alkyne or amine for coordination to the active metal center in the catalytic cycle. The reaction is sensitive to the solvent, as shown in Table 1. The best result was achieved using $Pd(OAc)_2$/dppp as the catalyst in the ionic liquid [bmim][Tf_2N][15] (Table 1, entry 8). It should be noted that only a trace amount of the desired carbonylation product was detected when THF, DMF, or [bmim]BF_4 was used as the reaction medium (Table 1, entries 11−13). Both $Pd(CH_3CN)_2Cl_2$ and $Pd(OAc)_2/PPh_3$ instead of $Pd(OAc)_2$/dppp demonstrated very poor catalytic activity under the same conditions (Table 1, entries 6 and 7). Eventually, $Pd(OAc)_2$/dppp was chosen to be the catalyst precursor in [bmim][Tf_2N] at 200 psi of carbon monoxide.

A variety of primary and secondary amines were employed in the reaction, and very good results were obtained (Table 2). Terminal alkynes with substituents such as acetoxy, nitrile, diethoxy, phenylsulfide, and tetrahydro-pyran-2-yloxy were efficiently carbonylated, giving the corresponding α-methylene amides in moderate to excellent yields with excellent regioselectivities. It is assumed that the high regioselectivity is due to the hydropalladation of the alkyne occurring so as to place the palladium at the internal position of the alkyne. However, carbonylation of the internal alkyne **1i** afforded the desired product in low yield (Table 2, entry 16).

The recyclability of the palladium catalyst system for the aminocarbonylation of alkynes was investigated in [bmim][Tf_2N] (Table 3). As a result of the good solubility of $Pd(OAc)_2$ and dppp in the ionic liquid, reuse of the catalyst was performed without any significant loss of its catalytic activity after five runs with 4 mL of toluene per extraction. Because of the strong delocalization of the negative charge

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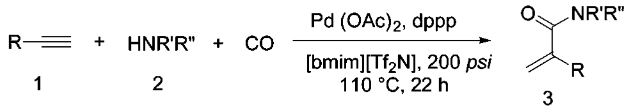
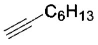
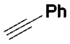
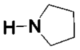
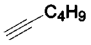
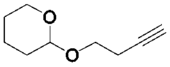
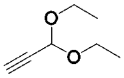
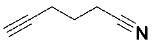
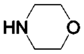
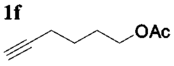
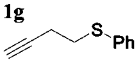
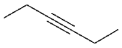
(14) Scrivanti, A.; Beghetto, V.; Campagna, E.; Zanato, M.; Matteoli, U. *Organometallics* **1998**, *17*, 630.

(15) The ionic liquid were synthesized according to published procedures: Huddleston, G. J.; Visser, A. E.; Reichert, W. M.; Willauer, H. D.; Broker, G. A.; Rogers, R. D. *Green Chem.* **2001**, *3*, 156. Subsequent washing of the ionic liquid with a biphasic mixture $H_2O-CH_2Cl_2$ eliminated sodium and chloride impurities. Water was removed by vacuum drying.

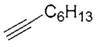
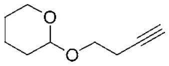
Table 2. Palladium-Catalyzed Aminocarbonylation of Alkynes in [bmim][Tf_2N][a]



Entry	Alkyne	Amine	Product	Yield (%)[b]
1	 **1a**	$HNEt_2$ **2a**	**3a**	66
2	**1a**	H_2NBu **2b**	**3b**	64
3	 **1b**	**2a**	**3c**	79
4	**1b**	 **2c**	**3d**	73[c]
5	 **1c**	**2a**	**3e**	61
6	 **1d**	**2a**	**3f**	80
7	**1d**	**2b**	**3g**	67
8	**1d**	H_2NBn **2d**	**3h**	70
9	 **1e**	**2a**	**3i**	66
10	 **1f**	 **2e**	**3j**	85
11	**1f**	**2d**	**3k**	64
12	 **1g**	**2a**	**3l**	84
13	**1g**	**2b**	**3m**	52
14	 **1h**	**2a**	**3n**	50
15	**1b**	H_2NPh **2f**	**3o**	81[d]
16	 **1i**	**2e**	**3p**	26

[a] Alkyne **1** (1 mmol), amine **2** (5 mmol), Pd (OAc) $_2$ (0.03 mmol), dppp (0.06 mmol), CO (200 psi), [bmim][Tf_2N] (2 g), 110 °C, 22 h. [b] Yields after isolation by flash column chromatography on SiO_2. [c,d] <6% linear aminde was detected.

Table 3. Recycling of the Catalytic System for the Palladium-Catalyzed Aminocarbonylation of Alkynes

Entry	Alkyne	Amine	Product	Run	Yield (%)
1	 **1a**	$HNEt_2$ **2a**	**3a**	1	66
2				2	64
3				3	70
4				4	70
5				5	68
6	 **1d**	H_2NBu **2b**	**3g**	1	67
7				2	71
8				3	71
9				4	68
10				5	68

over all atomic centers and the high flexibility of the C−S−N−S−C backbone, the Tf_2N^- is regarded as a weakly coordinating anion,[16] and the ionic liquid exhibits polarities similar to those of polar organic solvents, which makes this ionic liquid a promising solvent for the stabilization of charged metal centers and recycling of the catalytic system.

In conclusion, the palladium-catalyzed aminocarbonylation of alkynes with amines proceeds efficiently in [bmim][Tf_2N] under mild conditions, without any acid additive, regiospecifically affording α-methylene amides in good yields. As the reaction medium, the ionic liquid gave improved product yields and regioselectives compared with use of a conventional solvent. A competitive advantage is that the catalyst system can be recycled and reused five times without the loss of catalytic activity.

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Supporting Information Available: Experimental procedures, spectroscopic data, and copies of ^1H and ^{13}C NMR spectra for the acrylamide products. This material is available free of charge via the Internet at http://pubs.acs.org.

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