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Cu-Catalyzed N-Alkynylation of Imidazoles, Benzimidazoles, Indazoles, and Pyrazoles Using PEG as Solvent Medium

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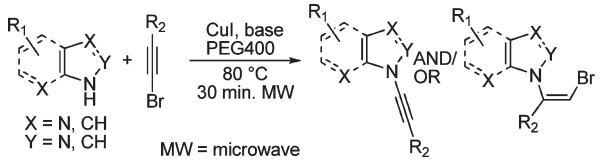

A facile and efficient Cu(I)-catalyzed cross-coupling method is reported for the preparation of *N*-alkynyl or *N*-bromoalkenyl heteroarenes from bromoalkynes. Generally superior yields and functional group tolerance were obtained with microwave (MW) irradiation using imidazole, benzimidazole, pyrazole, and indazole substrates and poly(ethylene glycol) 400 (PEG400) as an additive. We speculate that PEG400 acts as both a Cu(I)-stabilizing ligand as well as a phase transfer solvent.

Aromatic ynamines or *N*-alkynylheteroarenes are functional groups where the aromatic nitrogen atom is directly linked to an alkyne.[1] As a consequence of this, *N*-alkynylheteroarenes are useful yet under-utilized intermediates in organic synthesis[2−4] and medicinal chemistry; [5] the underlying reason is the dearth of mild and general preparative methods of their formation. In addition, understanding the structure−reactivity relationship of these functional groups is also limited, as highlighted by the small number (less than 20) of crystal structures present in the literature. Therefore mild and efficient routes toward their formation could provide access to new chemical reactivity particularly toward the synthesis of valuable heterocycles. In addition further structural studies may give insight into the effect of substituents on reactivity.

Previous preparative methods of *N*-alkynylheteroarenes have included the coupling of alkynyl iodonium species,[1,2] elimination of haloenamines,[1] nucleophilic substitution of metal amides, and isomerization of propargyl amines; however, these methods suffer from step and atom inefficiency and have limited functional group tolerance. We have recently become interested in utilizing *N*-alkynylheteroarenes as useful synthons in the combinatorial preparation of novel heterocyclic scaffolds. We envisaged that the recent developments in copper-catalyzed cross-couplings pioneered by groups such as Evano,[6] Buchwald,[7] Hsung,[8] Kerwin,[9] and others[10] could provide an efficient means to prepare such scaffolds from bromoalkynes and the appropriate *N*-containing heterocycle. In this communication, we report a simple and facile method for the synthesis of *N*-alkynylheteroarenes incorporating the imidazole, benzimidazole, pyrazole, and indazole heterocyclic cores.

Initial attempts to couple benzimidazole (**1**) with the bromoalkyne (**2**) provided moderate yields of *N*-alkynylheteroarene when Hsung's copper(II) (entry 1, Table 1)[8] or Buchwald's copper(I) protocols were applied (entry 2, Table 1).[7a,b,11] Direct cross-coupling of triisopropylsilylacetylene with benzimidazole using Stahl's conditions also proved unsuccessful (results not shown).[12] Buchwald and others have reported increases in yields and reproducibility of palladium- and copper-catalyzed cross-couplings when poly(ethylene glycol) (PEG) additives were used.[7d,13] PEG can act as a highly efficient phase transfer solvent by providing a compatible reaction bridge between the hydrophobic organic components (**1** and **2**) and the hydrophilic base (Cs_2CO_3). When poly(ethylene glycol) 400 (molecular weight 400, PEG400) was added to the reaction mixture and heated by conventional means (entry 5, Table 1), we observed similar yields of **3**; however, microwave irradiation resulted in a marked increase in isolated yield of **3** (entry 6, Table 1). These reactions were particularly facile with reaction times reduced from 24 h to 30 min (entry 7, Table 1) when microwave heating was applied. Interestingly we discovered that the presence of Cu(I)-stabilizing ligands such as

(1) Katritzky, A. R.; Jiang, R.; Singh, S. K. *Heterocycles* **2004**, *63*, 1455.
(2) Ishihara, T.; Mantani, T.; Konno, T.; Yamanaka, H. *Tetrahedron* **2006**, *62*, 3783.
(3) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett*. **2003**, 1379.
(4) Xu, Z. Q.; Joshi, R. V.; Zemlicka, J. *Tetrahedron* **1995**, *51*, 67.
(5) (a) Xu, Z. Q.; Joshi, R. V.; Zemlicka, J. *Tetrahedron* **1995**, *51*, 67. (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.
(6) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381.
(7) (a) Altman, R. A.; Anderson, K. W.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5167. (b) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190. (c) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2007**, *9*, 643. (d) Altman, R. A.; Buchwald, S. L. *Org. Lett.* **2006**, *8*, 2779.
(8) (a) Yao, P. Y.; Zhang, Y.; Hsung, R. P.; Zhao, K. *Org. Lett.* **2008**, *10*, 4275. (b) Zhang, X. J.; Zhang, Y. S.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L. C.; Tracey, M. R. *J. Org. Chem.* **2006**, *71*, 4170. (c) Zhang, Y.; Hsung, R. P.; Tracey, M. R.; Kurtz, K. C. M.; Vera, E. L. *Org. Lett.* **2004**, *6* (7), 1151–1154.
(9) Laroche, C.; Li, J.; Freyer, M. W.; Kerwin, S. M. *J. Org. Chem.* **2008**, *73*, 6462.
(10) (a) Gao, Y. X.; Wang, G.; Chen, L.; Xu, P. X.; Zhao, Y. F.; Zhou, Y. B.; Han, L. B. *J. Am. Chem. Soc.* **2009**, *131*, 7956. (b) Evano, G.; Toumi, M.; Coste, A. *Chem. Commun.* **2009**, 4166. (c) de Parrodi, C. A.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 4679.
(11) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78.
(12) Hamada, T.; Ye, X.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 833.
(13) (a) She, J.; Jiang, Z.; Wang, Y. *Tetrahedron Lett.* **2009**, *50*, 593. (b) Mao, J. C.; Guo, J.; Fang, F. B.; Ji, S. J. *Tetrahedron* **2008**, *64*, 3905. (c) Wang, L. A.; Zhang, Y. H.; Liu, L. F.; Wang, Y. G. *J. Org. Chem.* **2006**, *71*, 1284.

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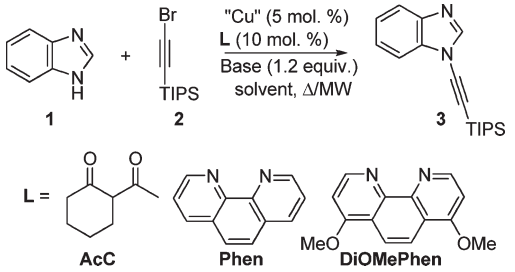
TABLE 1. Screening of Solvent, Ligand and Heating Conditions for the *N*-Alkynylation of Benzimidazole with the Bromoalkyne (2)



entry	solvent (1.0 M)	L (10 mol %)	base	yield of **3** (%)[a]
1	toluene	Phen	K_3PO_4	22[a]
2	DMF	Phen	Cs_2CO_3	43[b]
3	DMSO	AcC	Cs_2CO_3	12[b]
4	dioxane	AcC	Cs_2CO_3	51[b]
5	dioxane		Cs_2CO_3	53[c]
6	dioxane		Cs_2CO_3	72[d]
7	dioxane	AcC	Cs_2CO_3	74[d]
8	dioxane	DiOMePhen	Cs_2CO_3	72[d]
9	dioxane		K_3PO_4	64[d]
10	dioxane		K_2CO_3	57[d]

[a]All reactions conducted with **1** (1.0 equiv), **2** (1.2 equiv), 36 h, 90 °C unless stated otherwise. [b]$CuSO_4 \cdot 5H_2O$ (5 mol %). [c]CuI (5 mol %), PEG400 (200 mg). [d]CuI (5 mol %), PEG400, 90 °C, 30 min, MW (125 W).

Phen, AcC, or DiOMePhen was not essential for high yields of **3**, which is indicative of the PEG-400 additive not only acting as a phase transfer solvent but also participating as a Cu-stabilizing ligand. When applied to the *N*-alkynylation of imidazole, the isolated yield (88%) was superior using these conditions compared to previous conditions that yielded 53% of *N*-alkynylheteroarene product.[9]

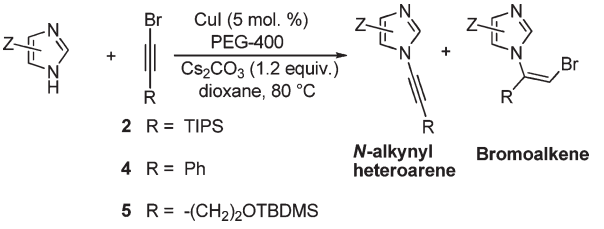
With a set of reaction conditions in hand, we screened a series of imidazole and benzimidazoles against bromoalkynes **2**, **4**, and **5**, which resulted in the formation of either *N*-alkynylheteroarene or *N*-alkenylbromoheteroarene products (Table 2). Bulky bromoalkynes such as **2** exclusively formed *N*-alkynylheteroarenes, whereas bromoalkyne **4** formed predominantly *N*-alkynylheteroarene products with nonhindered imidazole and benzimidazole substrates. Under microwave irradiation conditions, cross-couplings using **2** as the coupling partner generally afforded superior yields over reactions using the less sterically hindered bromoalkynes **4** and **5**. In these cases the lower yields are also associated with the formation of the corresponding debrominated alkyne in addition to small quantities of homocoupled bisalkyne products.

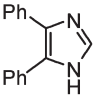
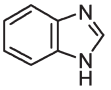
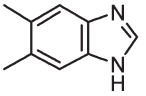
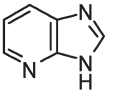
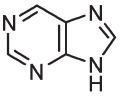
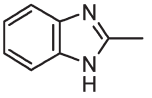
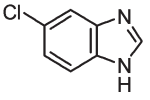
For imidazole substrates (entries 1−9, Table 2) we generally observed good yields, although the imidazole substrates (entries 1−3, Table 2) were found to be a little unstable, resulting in decomposition upon standing in the reaction mixture after 72 h. Sterically hindered imidazole substrates and alkyne **2** give good or moderate yields of *N*-alkynylheteroarene (entries 4 and 7, Table 2). However, with less bulky alkynes **4** and **5** no reaction occurs with 2-methylimidazole (entries 5 and 6, Table 2) as the substrate. For 4,5-diphenylimidazole the bromoalkene is formed exclusively (entries 8 and 9, Table 2) in moderate yields.

When 2-methylbenzimidazole was used, a moderate yield of the *N*-alkynylheteroarene derived from the coupling of the bulky bromoalkyne **2** was observed (entry 22, Table 2), similar to the 2-methylimidazole substrate (entry 7, Table 2), whereas **4** and **5** both afford exclusively the bromoalkene products in good yields (entries 23 and 24, Table 2).

NOE studies of the resultant bromoalkene products determined the alkene stereochemistry to be *Z*. This was

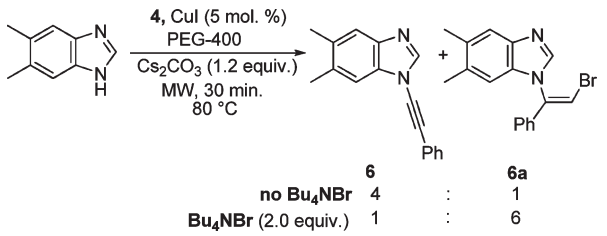
TABLE 2. Microwave-Promoted Copper-Catalyzed Cross-Coupling of Bromoalkynes (2, 4 and 5) with Imidazoles and Benzimidazoles



Entry	Starting material	Bromo-alkyne	Yield (%)[a] *N*-alkynyl-heteroarene	Yield (%)[a] Bromo-alkene
1		**2**	88[b]	-
2		**4**	65	6[d]
3		**5**	Product decomposition	
4		**2**	62	-
5		**4**	31	
6		**5**	NR	
7		**2**	43	-
8		**4**	-	55
9		**5**	-	47
10		**2**	72	-
11		**4**	74	
12		**5**	67	13
13		**2**	81	-
14		**4**	70	18[d]
15		**5**	9	45
16		**2**	75 (2.9 : 1)	-
17		**4**	NR	
18		**5**	-	22[c]
19		**2**	trace	-
20		**4**	trace	-
21		**5**	trace	
22		**2**	33	
23		**4**	-	60
24		**5**	-	63
25		**2**	82 (1.5 : 1)	-
26		**4**	62 (1.5 : 1)	12[b]
27		**5**	[d]	

[a]Hetereocycle (1.0 equiv), bromoalkyne (1.2 equiv), CuI (5 mol %), PEG400 (200 mg), Cs_2CO_3 (1.2 equiv), MW (125 W), 80 °C, 90 min. [b]GC−MS yield. [c]Afforded a regioisomeric mixture (3:1 ratio) of two bromoalkenes. [d]Afforded a complex mixture of homocoupled bisalkyne as well as a regioisomeric mixture of both *N*-alkynylheteroarene and bromoalkenes. NR = no reaction.

SCHEME 1. Influence of Bromide on Product Distribution



confirmed by an absence of an NOE between the methyl and the alkenyl methine protons. However, strong NOEs were observed between the alkenyl proton and several of the protons derived from the bromoalkyne precursor (see Supporting Information).

Although Kerwin et al. observed bromoalkene formation with the same reported stereochemistry,[9] uniquely under these conditions the *N*-alkynylheteroarene was found to be the major product with the bromoalkene formed as a minor product. The formation of the bromoalkene is quite sensitive to the steric bulk of the heteroarene. With the more sterically bulky alkyne substituents (TIPS and Ph, entries 10 and 11, Table 2), no bromoalkene was formed, whereas with TBDMS-protected 2-hydroxyethyl (entry 12, Table 2) a 5:1 ratio of alkynylheteroarene/bromoalkene was observed. However, we observed a trend of increasing bromoalkene formation as the steric bulk of the heteroarene increases (compare entry 14 and 11), and this can even become the major product (entry 15, Table 2). This suggests that attack of the nitrogen nucleophile is slower and bromoalkene formation can then compete with *N*-alkynylation. We have checked that bromoalkene formation does not occur from the *N*-alkynylheteroarene product, but more detailed studies are necessary to elucidate the mechanism of formation of the bromoalkene.[14] However, the addition of a bromide source [$(Bu)_4NBr$] with the other reagents results in increased bromoalkene formation (for example, Scheme 1). Omission of a copper source affords no change in product distribution, which suggests that this process is indeed copper-mediated. It is likely that bromoalkene formation proceeds via π-activation of the alkyne species rather than an oxidative addition process as we assume is occurring in the case of *N*-alkynylhetereoarene formation.[15]

The regioselectivity of the reaction was found to be low for nonliganded reactions when nonsymmetrical benzimidazoles 5-chloro-1*H*-benzo[*d*]imidazole (entries 25−27, Table 2) and azabenzimidazoles (entries 16−18, Table 2) were used. *N*-Alkynylated purines, however, were formed in only trace quantities (entries 19−21, Table 2).

We determined the structures of two benzimidazole derivatives, **7** and **8** (Figure 1).[16]

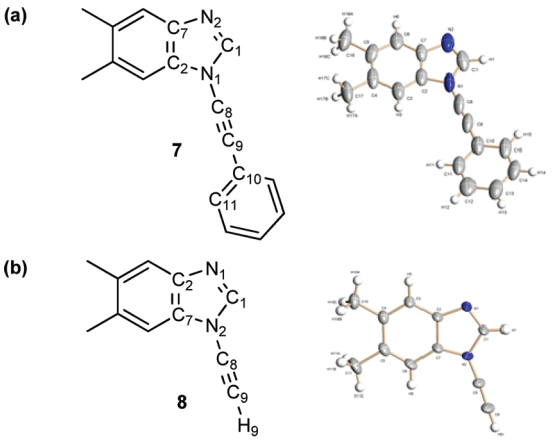


FIGURE 1. X-ray structures of (a) **7** and (b) **8**.

In **7** there is evidence of delocalization in the benzimidazole ring with N(1)—C(1) distance of 1.362(8) Å being intermediate between N(1)—C(2) 1.410(8) Å and N(2)—C(1) 1.306(8) Å as expected. The N(1)—C(8) bond is also shorter than a conventional single bond at 1.342(10) Å. The alkyne triple bond length though is relatively unaffected at 1.199(11)Å, which may be indicative of the limited interaction of the lone pair of nitrogen (N1) with the alkyne π-system because the former is tied into the aromatic system. The phenyl ring and benzimidazole ring are almost coplanar; the torsion angles C(11)−C(10)−N(1)−C(2) and C(15)−C(10)−N(1)−C(1) are 5.4° and 5.6°, respectively. This is consistent with a crystal structure of an imidazole-derived *N*-alkynylheteroarene recently published by Kerwin.[17] This is in contrast to a phenyl-substituted amidoalkyne where the phenyl and amido substituents are at an angle of 79.9°.[18] There is no evidence of π-stacking, but H(3) of one molecule is hydrogen-bonded to N(2) of another. Compound **8** forms dimers through H-bonding between N(1) and H(1). In addition N(1) is H-bonded to the alkyne hydrogen H(9) of another molecule, forming a two-dimensional layer of dimers.

These Cu-catalyzed cross-coupling conditions were also suitable for the novel preparation of *N*-alkynylated pyrazole and indazole substrates (Table 3). *N*-Alkynylated pyrazoles have only been transiently observed by the rearrangement of alkynamides to the corresponding pyrazolo *N*-alkynylheteroarene using flash vacuum photolysis,[19] which provided us with the motivation to develop more convenient methods of their formation. The preparation of *N*-alkynylated pyrazole or indazole products was observed to be superior with microwave-assisted heating, albeit in the presence of 2.0 equiv of bromoalkyne. Previous reports of copper-catalyzed *N*-arylations using indazoles typically produced minor amounts of the N2 isomer; however, in our hands we observed N1-coupled products almost exclusively using either microwave-assisted or conventional heating protocols.[7b] NOE experiments confirmed the stereochemistry of the bromoalkene to be *Z*, again consistent with the imidazole/benzimidazole series. Of particular

(14) To a microwave tube were added solid CuI (0.05 mmol, 9.00 mg), compound **6** (34 mg, 0.14 mmol), Bu_4NBr (90 mg, 0.28 mmol), and Cs_2CO_3 (54 mg, 0.17 mmol). A solution of PEG400 (50 mg) in dioxane (0.5 mL) was added, and the reaction mixture evacuated and back filled with argon. The reaction mixture was then heated under microwave irradiation (125 W) at 85 °C for 60 min. GC−MS analysis observed only starting material present in the crude mixture.

(15) For a recent example of π-activation of an alkyne by copper, see: Laroche, C.; Kerwin, S. M. *J. Org. Chem.* **2009**, *74*, 9229–9232.

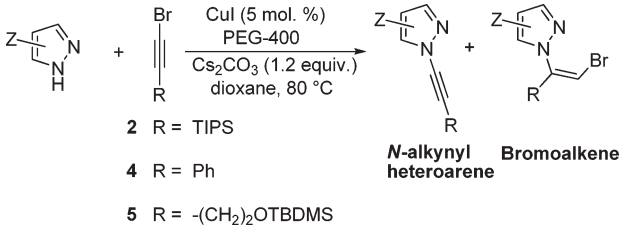
(16) The United Kingdom Chemical Database Service; Fletcher, D. A.; McMeeking, R. F.; Parkin, D. *J. Chem. Inf. Comp. Sci.* **1996**, *36*, 746.

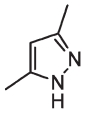
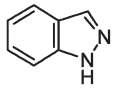
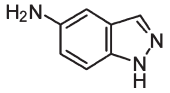
(17) Li, J.; Kaoud, T. S.; Laroche, C.; Dalby, K. N.; Kerwin, S. M. *Bioorg. Med. Chem. Lett.* **2009**, *19* (22), 6293–6297.

(18) Tracey, M. R.; Zhang, Y. S.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P. *Org. Lett.* **2004**, *6*, 2209.

(19) Brown, R. F. C.; Eastwood, F. W.; Fallon, G. D.; Lee, S. C.; McGeary, R. P. *Aust. J. Chem.* **1994**, *47*, 991.

TABLE 3. Copper-Catalyzed Cross-Coupling of Bromoalkynes (2, 4, 5) with Pyrazoles and Indazoles



Entry	Starting material	Bromo alkyne	Yield (%) [a] N-alkynyl heteroarene	Yield (%) [a] Bromo-alkene
1		**2**	73	-
2		**4**	58	-
3		**5**	17	46
4		**2**	15	-
5		**4**	16	-
6		**5**	trace	-
7		**2**	64	-
8		**4**	72	-
9		**5**	33 [c]	49 [c]
10		**2**	85	-
11		**4**	NR	
12		**5**	NR	

[a]Hetereocycle (1.0 equiv), bromoalkyne (2.0 equiv), CuI (5 mol %), PEG400 (200 mg), 90 min, MW (125 W), 80 °C. [b]GC yield as compound degrades after purification. [c]Present as an inseparable 1:1.5 [*N*-alkynyl-heteroarene/bromoalkene] mixture by column chromatography. Analytically pure sample obtained by HPLC. NR = no reaction.

note is the regioselective *N*-alkynylation of 6-aminoindazole (entry 10, Table 3). Bromoalkyne **2** exclusively afforded the *N*-alkynylated product at N1 with very little N2 and N6 coupled products observed according to GC−MS. Additionally this reaction only proceeded with the sterically hindered bromoalkyne **2** with no product obtained with the bromoalkyne substrates **4** and **5**.

In summary, we have described here a simple and cost-effective method of *N*-alkynylation of *N*-containing heterocycles. The reaction utilizes inexpensive starting materials and affords either *N*-alkynylated or *N*-bromoalkenylated products in generally good yield. The use of the PEG additive and microwave-based heating is key to the good yields and short reaction times. Future studies will endeavor to investigate broadening the scope and regioselectivity of *N*-alkynylation to other heterocycles and investigating their reactivity.

Experimental Section

General Procedure for the Copper-Catalyzed *N*-Alkynylation of Bromoalkynes with Aromatic Nitrogen Nucleophiles under Microwave Irradiation (1.0 mmol scale). To a microwave tube were added solid CuI (0.05 mmol, 9.00 mg), the aromatic *N*-heterocycle (1.0 mmol), and Cs_2CO_3 (1.2 mmol, 392 mg). The reaction flask was capped, evacuated, and backfilled with nitrogen three times. In a separate flask, a solution of dry dioxane (1 mL) containing poly(ethylene glycol) 400 (PEG400, 200 mg) and the bromoalkyne (1.10 mmol) was evacuated and backfilled with nitrogen gas three times. The solution was then added to the reaction vessel and irradiated (125 W) at 70 °C for 30−90 min. The reaction mixture was then diluted with diethyl ether (100 mL), filtered through a pad of Celite, and concentrated *in vacuo*. Flash column chromatography (SiO_2) eluting with a gradient of ethyl acetate/hexane (1:20→1:10) provided the *N*-alkynylated hetereocycle.

Procedure for the Formation of 1-Ethynyl-5,6-dimethyl-1*H*-benzo[*d*]imidazole (8). To a solution of 5,6-dimethyl-1-((triisopropylsilyl)ethynyl)-1*H*-benzo[*d*]imidazole (640 mg, 1.96 mmol) in THF was added tetrabutylammonium fluoride (2.40 mL, 1.0 M, 2.36 mol) under a nitrogen atmosphere. The reaction mixture was stirred at rt under a nitrogen atmosphere for 30 min, followed by concentration *in vacuo*. Flash column chromatography (SiO_2) eluting with a gradient of ethyl acetate/hexane (1:10 → 1:5) provided **8** as a pale yellow crystalline solid (208 mg, 62%). Analytically pure crystals suitable for X-ray analysis were obtained by crystallization from a diethyl ether/hexane mixture (5:95) to form colorless plates. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.33 (s, 3H, Ar-CH_3), 2.34 (s, 3H, Ar-CH_3), 3.27 (s, 1H, CC*H*), 7.27 (s, 1H, Ar-*H*), 7.53 (s, 1H, Ar-*H*), 7.94 (s, 1H, Ar-*H*). ^{13}C NMR ($CDCl_3$, 125.76 MHz): δ 20.2 (1C, Ar-*C*H$_3$), 20.4 (1C, Ar-*C*H$_3$), 61.7 (1C, C*C*H), 70.7 (1C, Ar-*C*CH), 110.9 (1C, Ar*C*), 120.7 (1C, Ar*C*), 132.7 (1C, Ar*C*), 133.0 (1C, Ar*C*), 134.2 (1C, Ar*C*), 140.2 (1C, Ar*C*), 142.8 (1C, Ar*C*). HRMS (EI, +ve) calcd for $C_{11}H_{10}N_2$ 170.08440 $[M]^+$, found 170.08407.

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Supporting Information Available: Procedures for the preparation of bromoalkynes (**2**, **4**, **5**) and their use in the preparation of *N*-alkynes and *N*-bromoalkenes; characterization data and ^{1}H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.