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Heterogeneous Copper-in-Charcoal-Catalyzed Click Chemistry**

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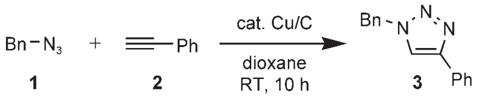
Quick inspection of the 2006 literature already turns up nearly 200 papers related to “click” cycloadditions. Click chemistry is clearly on the rise, and for good reason. It offers an almost unlimited array of inert triazole-containing architectures resulting from Huisgen [3+2] cycloadditions,[1] in particular between high-energy organic azides and terminal alkynes, for example, as shown in Equation (1) (Bn = benzyl). This process is significantly accelerated by Cu^I catalysis, independently discovered and published by the groups of both Sharpless[2] and Meldal[3] in 2002. Recently reviewed,[4] copper(II) sulfate (ca. 1%) in an aqueous medium (e.g. H_2O/*t*BuOH) is typically preferred, where the presence of sodium ascorbate (ca. 10%) serves to generate catalytically active Cu^I in situ. Alternative conditions, such as in situ oxidation of Cu^0 or direct introduction of Cu^I salts (usually CuI), have also been used quite successfully.[5] While both



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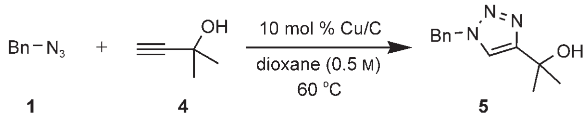
reaction partners have been individually coupled under solid-phase conditions, (e.g. on polystyrene),[3,6] examples of click chemistry mediated by a source of heterogeneous copper(I) are rare. One report relies on chelation to potentially labile copper by a polystyryl-based benzylic amine.[7a] Only unhindered, low-molecular-weight, and non-basic nitrogen-containing examples were studied therein, without data quantifying losses of copper from the solid support. Other studies are also limited, based on suspensions of unsupported copper clusters.[7b] Herein, we describe the virtues of copper-in-charcoal (Cu/C) as a simple, inexpensive, and especially general and efficient heterogeneous catalyst for use in this emerging area.

Impregnation of activated wood charcoal (Aldrich, 100 mesh, \$53.90/kilo)[8] with $Cu(NO_3)_2$ in water using an ultrasonic bath leads, after distillation of water and drying, to nanoparticle-sized Cu/C.[9] As both CuO and Cu_2O have been proposed as the species present within a charcoal matrix,[10] the presence of Cu^I suggested that a reducing agent might not be needed. Indeed, upon mixing benzyl azide (**1**) with phenylacetylene **2** (1:1) in dioxane at room temperature in the presence of 10 mol% Cu/C, cycloaddition was complete within 10 hours. Filtration and solvent evaporation afforded pure triazole **3** regiospecifically and near-quantitatively.

Aromatic alkynes are usually among the more reactive partners, while aliphatic alkynes oftentimes result in significantly slower cycloadditions. Steric hindrance in either substrate can also reduce rates, but with mild heating (60 °C) reactions are driven to completion (Scheme 1).



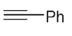
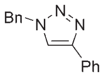
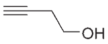
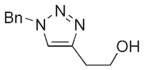
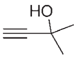
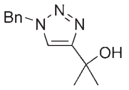
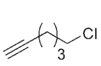
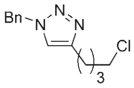
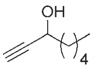
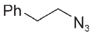
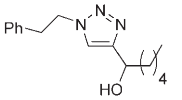
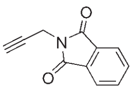
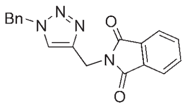
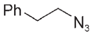
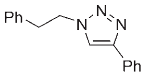
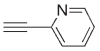
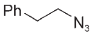
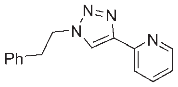
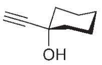
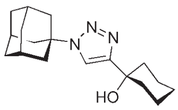
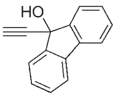
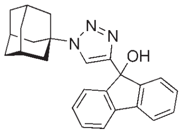
4 h : 99%
with Et_3N, 4 min : 99%

Scheme 1. A representative click reaction under mild heating.

Surprisingly, no bases, ligands,[11] or other additives are required for Cu/C to effectively catalyze these cycloadditions. However, given the likely intermediacy of copper acetylides,[4,5,12] the impact of an amine base was examined. This additive is assumed to aid in both anion formation as well as Cu^I stabilization, thereby significantly increasing rates of triazole formation.[13] Cycloaddition catalyzed by Cu/C in the presence of several different bases led to the unexpected finding, contrary to literature precedent (which encourages use of excess Hünig's base),[14] that one equivalent of Et_3N was particularly effective. Stronger (e.g. 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU)) and weaker (e.g. pyridine) amine bases had marginal impact (< 10% conversion under otherwise identical conditions), while lithium *tert*-butoxide showed no catalytic effect whatsoever. The dramatic role of Et_3N was noted in the case of partners **1** and **4**, for example, where the reaction time leading to product **5** was reduced from 4 h to 4 min (Scheme 1).

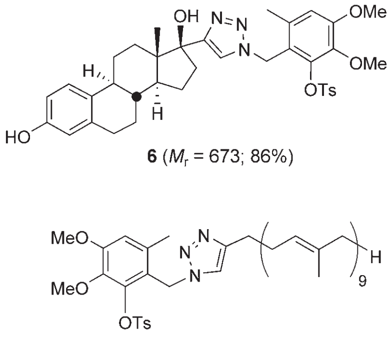
Several additional examples were carried out using the same conditions: Cu/C (cat.), Et_3N (1 equiv), dioxane, 60 °C (Table 1). Noteworthy features of this process include a) the regiochemistry (1,4-triazole) of addition follows that anticipated for such Cu-catalyzed reactions;[2] b) outstanding functional group tolerance is observed under these heterogeneous conditions; c) yields are uniformly high; d) generally, reactions are complete within minutes; e) sterically demanding precursors are not precluded from participation; f) heteroaromatics couple smoothly; and g) high-molecular-weight adducts, such as the triazole-containing steroidal derivative **6** ($M_r = 673$), and the precursor to an analogue of coenzyme Q_{10}, **7** ($M_r = 1029$), were both readily formed and isolated in good yields (Figure 1).

Table 1: Click reactions catalyzed by Cu/C.[a]

Entry	Alkyne	Azide	*t* [min]	Triazole	Yield [%]
1		Bn-N_3	10		99
2		Bn-N_3	20		97
3		Bn-N_3	20		99
4		Bn-N_3	20		94
5			45		99
6[b]		BnN_3	20		96
7			30		92
8			30		98
9			120		99
10[c]			120		97

[a] Run at 0.5 M in dioxane at 60 °C with 5 mol% Cu/C and 1 equivalent Et_3N. [b] Direct comparison to Sharpless' method (88% yield).[2] [c] Product was further purified by silica gel chromatography.

Numerous control experiments indicated not only that the Cu^I dispersed within charcoal is essential for catalysis but that Cu/C is also quite robust. Treatment of **1** and **4** with activated charcoal alone, from the same source used to make Cu/C,[8] gave no trace of product **5** (Table 2, entry A). Meticulous drying of these substrates, solvent, and catalyst (including the use of 4-Å molecular sieves) did not noticeably alter the rate



6 (M_r = 673; 86%)

7 (M_r = 1029; 87%)

Figure 1. Examples of higher-molecular-weight adducts. Ts = *para*-toluenesulfonyl.

Table 2: Assessment of catalyst (Cu/C).

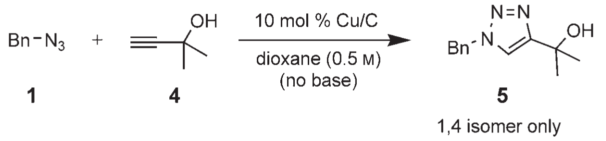
$$\mathbf{1} + \mathbf{4} \xrightarrow[\text{Et}_3\text{N, solvent}]{\text{cat. Cu/C}} \mathbf{5}$$

Entry	Conditions	Yield [%]
A	charcoal, (no Cu), 60 °C, 1 h	0
B	dry dioxane with 4-Å mol. sieves	99
C	wet, 2:1 dioxane/H_2O	99
D	recycled catalyst in air	99
E	repeat (D), third use in air	99
F	dioxane, room temperature, 6 h	99
G	toluene, room temperature, 2 h	98
H	95 % EtOH, 60 °C, 10 min	98
I	H_2O, 60 °C, 10 min	97

or yield of reaction (Table 2, entry B). At the other extreme, using water as co-solvent, likewise, had no impact (Table 2, entry C). Upon formation of triazole **5**, generated without exclusion of moisture or air, the Cu/C was filtered (in air) and reused in at least two additional cycles without loss of activity (Table 2, entries D and E). In addition to unprocessed dioxane as the medium, other solvents appear to be of equal or even greater potential in these reactions. Toluene led to triazole **5** at room temperature at three times the rate seen in dioxane (entry F vs G, Table 2). Both 95 % EtOH (Table 2, entry H) and even pure water (entry I) are perfectly amenable to heterogeneous Cu/C-catalyzed click reactions, with these cycloadditions reaching completion at 60 °C in less than 10 min.

To further examine the possibility of Cu/C catalysis in the absence of additives (e.g. Et_3N), reactions were exposed to controlled microwave irradiation (Table 3). As expected, the time needed for cycloaddition resulting in triazole **5** was reduced from 4 h to less than 10 min with the reaction temperature being increased from 60 °C to 120 °C. More remarkably, Cu/C quantitatively catalyzed formation of **5** in less than 3 min at 150 °C with no loss of regioselectivity. This flawless 1,4-selectivity suggests that the process is discriminatory towards catalysis by copper (and not driven thermally), which is made all the more apparent when the same reaction in the absence of catalyst afforded no trace of triazole.

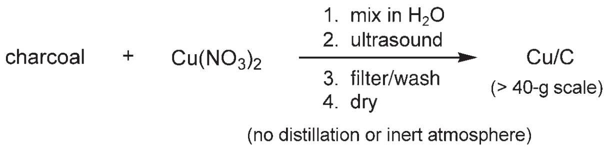
Table 3: Microwave irradiation in the absence of base.



T [°C]	*t*	Yield [%]
conventional heating		
23	48 h	65
60	4 h	99
microwave irradiation		
120	10 min	99
150	3 min	99
150 (no catalyst)	3 min	0

In addition to the simplicity and efficiency of cycloadditions carried out in the presence of Cu/C, product contamination by copper is minimized if not completely averted. Quantitative ICP-AES[15] analyses of triazole products from multiple reactions revealed insignificant copper; indeed, copper concentrations observed were too low for accurate measurement of these millimole-scale reactions. Thus, these data further suggest that Cu/C-catalyzed click cycloadditions take place heterogeneously with negligible leaching of copper into solution, a characteristic that could simplify both preparation and isolation of triazoles for many applications.

Most recently, we have further streamlined the preparation of Cu/C (see Experimental Section) by bypassing the distillation step. To demonstrate utility, a batch of catalyst (> 40 gram) was quickly prepared (Scheme 2) and tested successfully in the conversion of **1** and **4** into **5**. No noticeable difference in reaction rate or extent of leaching (by ICP-AES) was observed, notwithstanding impregnation of copper(II) nitrate.[16] Assuming catalysis by Cu^I, partial reduction by charcoal could account for the observed activity.



Scheme 2. Simplified, scaled-up preparation of Cu/C.

In conclusion, highly efficient click chemistry between organic azides and terminal alkynes can be heterogeneously catalyzed by copper nanoparticles mounted within the pores of activated charcoal.[9] Reactions can be accelerated with stoichiometric Et_3N or by simply increasing the reaction temperature. Under microwave irradiation, triazoles can be formed in minutes at 150 °C. Cycloadditions can be carried out in a purely organic medium, in aqueous solvent mixtures, or in pure water. Solubility issues, copper contamination, and modest yields usually associated with the choice of copper salt are completely averted. External ligands known to accelerate click reactions are not needed. The catalyst appears to be unaffected by exposure to air, suggesting a substantial shelf-life. Steric congestion in one or both partners is well-tolerated, and product isolation is notably facile.[17] Further studies that take advantage of Cu/C in several contexts (e.g. kinetic resolutions, mechanistic questions, formation of new triazole-containing ligands, etc.) are ongoing, the results from which will be reported in due course.

Experimental Section

Simplified preparation of Cu/C:[18] Darco KB activated carbon (50.0 g, 100 mesh, 25% H_2O content) was added to a 500-mL round-bottomed flask containing a stir bar. A solution of $Cu(NO_3)_2·3H_2O$ (Acros Organics, 11.114 g, 46.0 mmol) in deionized water (100 mL) was added to the flask, and further deionized H_2O (100 mL) was added to wash down the sides of the flask. The flask was loosely capped and stirred under air for 30 min and then submerged in an ultrasonic bath for 7 h. Subsequent washing (toluene) and air drying (3 h) by vacuum filtration yielded about 85 grams of "wet" Cu/C. The catalyst could be used at this stage or further dried in vacuo at 120 °C overnight (41 g yield of "dry" Cu/C).

General procedure for Cu/C-catalyzed "click" reaction: Cu/C (50 mg, 1.01 $mmol\,g^{-1}$, ca. 0.05 mmol) is added to a clean 10-mL flask fitted with a stir bar and septum. Dioxane (1–2 mL) is added slowly to the sidewalls of the flask to rinse the catalyst down. While the heterogeneous solution is stirred, triethylamine (1.1 mmol), alkyne (1.1 mmol), and azide (1.0 mmol) are added. The flask is stirred at room temperature (or warmed to 60 °C), and the reaction progress is monitored by TLC until complete consumption of azide has occurred. The mixture is filtered through a pad of celite to remove the catalyst, and the filter cake is further washed with EtOAc to ensure complete transfer. The volatiles are removed in vacuo to give pure triazole.

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Keywords: click chemistry · copper · cycloaddition · heterogeneous catalysis · microwave irradiation

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[1] R. Huisgen, *1,3-Dipolar Cycloaddition Chemistry* (Ed.: A. Padwa), Wiley, New York, **1984**.

[2] K. B. Sharpless, V. V. Fokin, L. G. Green, V. V. Rostovtsev, *Angew. Chem.* **2002**, *114*, 2708; *Angew. Chem. Int. Ed.* **2002**, *41*, 2596.

[3] M. Meldal, C. Christensen, C. W. Tornoe, *J. Org. Chem.* **2002**, *67*, 3057.

[4] J. H. Maarseveen, H. Hiemstra, V. D. Bock, *Eur. J. Org. Chem.* **2006**, 51.

[5] a) K. B. Sharpless, V. V. Fokin, V. V. Rostovtsev, L. Noodleman, R. Hilgraf, T. Lovell, F. Himo, *J. Am. Chem. Soc.* **2005**, *127*, 210; b) C. J. Hawker, T. P. Russell, P. Wu, V. V. Fokin, E. Drockenmuller, K. Schleicher, M. Malkoch, *Macromolecules* **2005**, *38*, 3663.

[6] a) P. Gmeiner, H. Hubner, S. Lober, P.-R. Loaiza, *J. Comb. Chem.* **2006**, *8*, 252; b) M. G. Finn, Q. Wang, J. Kuzelka, S. Punna, *Angew. Chem.* **2005**, *117*, 2255; *Angew. Chem. Int. Ed.* **2005**, *44*, 2215.

[7] a) C. Girard, E. Onen, M. Aufort, S. Beauviere, E. Samson, J. Herscovici, *Org. Lett.* **2006**, *8*, 1689; b) G. Rothenberg, J.-V. Maarseveen, L. D. Pachon, *Adv. Synth. Catal.* **2005**, *347*, 811; see also: A. Ponti, N. Santo, G. Marinoni, C. L. Bianchi, G. Molteni, *New J. Chem.* **2006**, *30*, 1137.

[8] Aldrich Catalogue, #278092. Darko KB, Wet Powder, 100 mesh, contains less than 30% water.

[9] B. H. Lipshutz, B. A. Frieman, A. E. Tomaso, *Angew. Chem.* **2006**, *118*, 1281; *Angew. Chem. Int. Ed.* **2006**, *45*, 1259.

[10] T. Tsoncheva, S. Vankova, D. Mehandjiev, *Fuel* **2003**, *82*, 755.

[11] V. V. Fokin, K. B. Sharpless, R. Hilgraf, T. R. Chan, *Org. Lett.* **2004**, *6*, 2853.

[12] M. G. Finn, V. V. Fokin, V. O. Rodionov, *Angew. Chem.* **2005**, *117*, 2250; *Angew. Chem. Int. Ed.* **2005**, *44*, 2210.

[13] M. R. Ghadiri, C. D. Stout, W. S. Horne, *J. Am. Chem. Soc.* **2003**, *125*, 9372.

[14] C-H. Wong, J. C. Paulson, O. Blixt, M. C. Bryan, F. Fazio, *J. Am. Chem. Soc.* **2002**, *124*, 14397.

[15] ICP-AES: inductively coupled plasma–atomic emission spectroscopy. A. W. Varnes, *Handbook of Instrumental Techniques for Analytical Chemistry* (Ed.: F. Settle), Prentice Hall, Upper Saddle River, NJ, **1997**, p. 395.

[16] For a recent article that describes use of copper(II) salts to catalyze click cycloadditions in water, see: M. L. Kantam, K. Rajgopal, K. R. Reddy, *Synlett* **2006**, 957–959.

[17] Removal of catalyst by filtration followed by evaporation of volatiles gives pure triazole products with little to no copper contamination. See Experimental Section.

[18] Some $Cu(NO_3)_2·3H_2O$ remained in the filtrate and was recovered by evaporation of the water. Further optimization of this preparation is ongoing.