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A Single Cu(II) Catalyst for the Three-Component Coupling of Diverse Nitrogen Sources with Aldehydes and Alkynes

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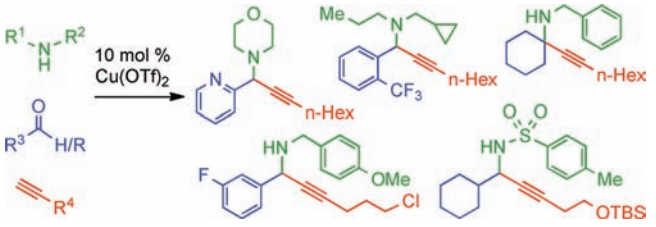
ABSTRACT



A single Cu(II) catalyst without the addition of ligand or base couples a diverse range of nitrogen sources with alkynes and aldehydes bearing alkyl, halogenated, silyl, aryl, and heteroaryl groups. The first example of a copper-catalyzed alkynylation involving *p*-toluenesulfonamide provides high yields of *N*-Ts-protected propargylamines. The superior activity of copper(II) triflate also allows this three-component alkynylation to incorporate a ketone.

From chiral HIV reverse transcriptase inhibitors to achiral antihypertensives, propargylamines display a wide range of therapeutic activity.[1,2] Methods for the catalytic alkynylation of imines (as opposed to stoichiometric metal acetylides[3]) are limited, as most reports use only anilines[4] or piperidines[5] as the nitrogen source. The scope is further restricted by the predominance of benzaldehyde-derived imines attacked by phenylacetylenes.[2−5] Knochel and co-workers utilized the broadest scope of alkynes with alkyl aldehydes, but only secondary amines are tolerated (e.g., *N*,*N*-dibenzyl).[6] A recent report for the alkynylation of *p*-toluenesulfonyl (Ts) imines required 6 equiv of Me_2Zn and 20 mol % of binol ligand, but the *N*-sulfonylated propargylamines were deprotected in high yield leaving the alkyne intact.[7]

To our knowledge, no catalyst has alkynylated imines from these readily deprotected sulfonamides.[2−7] As the reported procedures allowed for neither (1) the catalytic production of the electron-poor *N*-Ts-propargylamines required for our synthetic studies[8] nor (2) a single

(1) (a) Boulton, A. A. *J. Med. Chem.* **1992**, *35*, 3705. (b) Yu, P. H.; Davis, B. A.; Huffman, M. A.; Yasuda, N.; DeCamp, A. E.; Grabowski, E. J. J. *J. Org. Chem.* **1995**, *60*, 1590. (c) Jiang, B.; Si, Y.-G. *Angew. Chem., Int. Ed.* **2004**, *43*, 216. (d) Kihara, K.; Aoki, T.; Moriguchi, A.; Yamamoto, H.; Maeda, M.; Tojo, N.; Yamanaka, T.; Ohkubo, M.; Matsuoka, N.; Seki, J.; Mutoh, S. *Drug Dev. Res* **2004**, *61*, 233.

(2) (a) Yamada, K.; Tomoika, K. *Chem. Rev.* **2008**, *108*, 2874. (b) Trost, B. M.; Weiss, A. H. *Adv. Synth. Catal.* **2009**, *351*, 963. (c) Blay, G.; Monleón, A.; Pedro, J. R. *Curr. Org. Chem.* **2009**, *13*, 1498.

(3) (a) Zani, L.; Bolm, C. *Chem. Commun.* **2006**, 4263. (b) Zani, L.; Alesi, S.; Cozzi, P. G.; Bolm, C. *J. Org. Chem.* **2006**, *71*, 1558. (c) Zani, L.; Eichhorn, T.; Bolm, C. *Chem.—Eur. J.* **2007**, *13*, 2587.

(4) Selected references with aniline as nitrogen source (dozens more in ref 2c): (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (b) Wei, C. M.; Mague, J. T.; Li, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5749. (c) Ji, J.-X.; Wu, J.; Chan, A. S. C. *Proc. Natl. Acad. Sci. U.S. A.* **2005**, *102*, 11196. (d) Rueping, M.; Antonchick, A. P.; Brinkmann, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 6903. (e) Lu, Y.; Johnstone, T. C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284. (f) de Armas, P.; Tejedor, D.; Garcia-Tellado, F. *Angew. Chem., Int. Ed.* **2010**, *49*, 1013.

(5) Piperidine examples after ref 2c: (a) Zhou, L.; Bohle, D. S.; Jiang, H.-F.; Li, C.-J. *Synlett* **2009**, 937. (b) Li, P.; Zhang, Y.; Wang, L. *Chem.—Eur. J.* **2009**, *15*, 2045. (c) Chen, W.-W.; Nguyen, R. V.; Li, C.-J. *Tetrahedron Lett.* **2009**, *50*, 2895. (d) Zeng, T.; Chen, W.-W.; Cirtiu, C. M.; Moores, A.; Song, G.; Li, C.-J. *Green Chem.* **2010**, *12*, 570.

(6) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535. (b) Three-component coupling: Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763. (c) Koradin, C.; Gommerman, N.; Polborn, K.; Knochel, P. *Chem.—Eur. J.* **2003**, *9*, 2797. (d) As an application of pinap ligand: Knöpfel, T. F.; Aschwanden, P.; Ichikawa, T.; Watanabe, T.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 5971. (e) Reviewed in: Gommerman, N.; Knochel, P. *Chem.—Eur. J.* **2006**, *12*, 4380.

(7) *N*-Ts-propargylamine formed with 6 equiv of Me_2Zn and deprotected with SmI_2 leaving alkyne intact: Blay, G.; Cardona, L.; Climent, E.; Pedro, J. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 5593.

(8) Cu-catalyzed *N*-vinylation needs sulfonamide/amide: (a) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333. (b) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667. (c) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809. (d) Lu, H.; Li, C. *Org. Lett.* **2006**, *8*, 5365. (e) Lu, H.; Yuan, X.; Sun, C.; Li, C. *J. Org. Chem.* **2008**, *73*, 8665.

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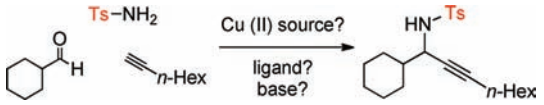
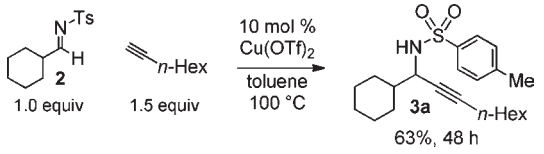
protocol that could tolerate a wide variety of functional groups on amine, aldehyde, and alkyne, we began by exploring the copper-catalyzed alkynylation of alkyl-*N*-Ts-imines with alkylalkynes (Scheme 1). Ideally, this catalyst should also prove operable for anilines, alkylamines, *N*-heterocycles, amides, and benzylamines. Herein we report that copper(II) trifluoromethanesulfonate, $Cu(OTf)_2$, is unique in its ability to catalyze the three-component coupling of the aforementioned nitrogen sources with alkyl, aryl, and heteroaryl aldehydes and even ketones.

Scheme 1. Could Cu(II) Catalyze the Direct Synthesis of Propargylamines with Electron-Poor Protecting Groups Like Ts?



To identify a catalyst capable of generating a range of propargylamines, we postulated that the increased Lewis acidity of Cu(II) catalysts could activate Ts-imine **2** toward the addition of 1-octyne via its copper acetylide (Scheme 2).[9] The sole catalyst found to produce **3a** was $Cu(OTf)_2$. The key to the *first catalytic alkynylation to form sulfonylated propargylamines*[3,7] was the specific combination of Cu(II) with the triflate counteranion.

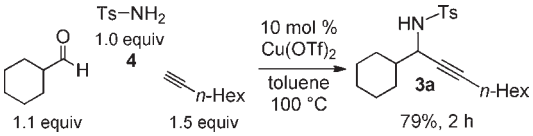
Scheme 2. Copper(II) Triflate Is Uniquely Capable As the Catalyst



As comparison to internal standard confirmed that **3a** did not decompose under reaction conditions, incomplete conversion after two days was attributed to the hydrolysis of *N*-Ts-imine **2** to sulfonamide observed by gas chromatography. Buffering with 10 mol % of base (Cs_2CO_3, K_2CO_3, KO-*t*-Bu) slowed the reaction rate, while 20 mol % of base halted the reaction completely.

To circumvent imine hydrolysis (and the two-step, three-day synthesis of *N*-Ts-imine),[10] the three-component coupling of cyclohexane carboxaldehyde, sulfonamide **4**, and 1-octyne was attempted (Scheme 3). Mixing the coupling partners with 10 mol % $Cu(OTf)_2$ in toluene at 100 °C was sufficient to provide 79% yield of desired product **3a** in 2 h, a rate 20 times faster than with preformed imine. The dramatic rate increase between the alkynylation of isolated imine (Scheme 2) versus in situ formed imine (Scheme 3) suggests that rate-determining alkynylation could occur on the protonated iminium of **2** rather than copper-bound imine **2**.[6c]

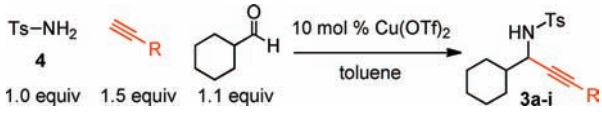
Scheme 3. Three-Component Coupling Proceeds More Rapidly and with a Higher Yield than from Preformed Imine



Cu(I) sources[11] were uniformly inactive with or without added base or ligand. Propargyl alcohols from direct alkynylation of aldehyde were not observed.[12] The sole byproduct of this one-pot process is 1 equiv of water; the addition of water (1−5 equiv) to the reaction has a negligible effect.

Table 1 shows the variety of functional groups available on the terminal alkyne. Both straight chain and branched alkyl alkynes reacted efficiently, and *tert*-butyl acetylene provided **3c** in 88% yield. Propargylsulfonamides **3d** and **3f** from sensitive alkynes bearing phenyl groups required an equivalent of sodium sulfate (Na_2SO_4) to proceed cleanly to 76% and 80% yield, respectively. Similarly, higher yields of acid-sensitive silyl alkynes **3e** and **3h** (78% and 80%) were produced with 10 mol % of Cs_2CO_3 added.

Table 1. Alkyne Variation in Forming *N*-Ts-propargylamines[a]



entry	R	product	time (h)	temp (°C)	yield (%)
1	*n*-Hex	**3a**	2	100	79
2	*n*-Bu	**3b**	42	60	70
3	*t*-Bu	**3c**	3	100	88
4	Ph	**3d**	72	60	76[a]
5	Si(*i*-Pr)$_3$	**3e**	18	80	78[ab]
6		**3f**	28	60	80[a]
7		**3g**	2	100	81
8		**3h**	18	80	80[ab]
9		**3i**	3	100	79

[a] Isolated yields with (a) 1.0 equiv of Na_2SO_4 and (b) 10 mol % of Cs_2CO_3.

While 10 mol % of $Cu(OTf)_2$ at elevated temperatures was routinely employed in this investigation, couplings with sulfonamides did proceed at room temperature, but

(9) Homocoupling of terminal alkynes via highly reactive Cu(II)-acetylides not observed under these optimized conditions: Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2633.

(10) Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis* **2000**, 75.

(11) CuI, CuBr, CuBr·Me_2S, CuCl, Cu(OAc), Cu(OTf), $[(PPh_3)_2Cu]NO_3$, $[(CH_3CN)_4Cu]PF_6$, and $[(CH_3CN)_4Cu]OTf$.

(12) (a) Yamamoto, K.; Hirusawa, Y.; Yoshimura, M. *Bull. Chem. Soc. Jpn.* **1954**, *27*, 386. (b) Reppe, W. *Liebigs Ann. Chem.* **1955**, *596*, 25. (c) Asano, Y.; Hara, K.; Ito, H.; Sawamura, M. *Org. Lett.* **2007**, *9*, 3901. (d) Asano, Y.; Ito, H.; Hara, K.; Sawamura, M. *Organometallics* **2008**, *27*, 5984.

reaction time increased from hours to a week. Catalyst loadings could be lowered to 2 mol % in some cases if the temperature was decreased to avoid decomposition while awaiting reaction of the remaining starting materials.

A limitation to the scope of the aldehyde appeared with sulfonamide **4**, which when treated with a benzaldehyde and $Cu(OTf)_2$ formed imines that subsequently did not react. As all other nitrogen sources that form imine under Cu(II) triflate catalysis underwent alkynylation, this could be attributed to the expanded conjugation extending from the aryl imine through the *p*-toluenesulfonyl group.

The reactions in Figure 1 were carried out with the amino source (**5**) as the limiting reagent and a slight excess of aldehyde (**6**, 1.1 equiv) and alkyne (1.5 equiv). For coupling partners whose label states "air sensitive" or recommends desiccator or cold storage, the addition of Na_2SO_4 improved conversion to product whereas $MgSO_4$ or pulverized 4 or 5 Å molecular sieves did not.

Benzylamine provided propargylamines with 2-fluorophenyl (**7a**) and isopropyl groups (**7b**)[13] in 88% and 94% yield (Figure 1). Dibenzyl propargylamine **7c** bears a furan. Not surprisingly, 3-fluorobenzaldehyde combines efficiently with piperidine[5] to afford **7d** in 90% yield. While one of the highlights of this protocol is that it applies to nonaniline nitrogen sources, even hindered *N*-methylaniline reacts efficiently (**7e**). Heterocycle–heteroaryl propargylamines **7f** and **7i** connect morpholine via one carbon to benzothiophene or pyridine. The nearly quantitative reaction of morpholine forms 4-CF_3-phenyl-substituted **7g** in 97% yield.

The last row depicts propargylamines bearing protecting groups: *p*-methoxybenzyl (PMB, **7m**), Ts (**7n**), and *tert*-butoxycarbonyl (Boc, **7o**). While phenylacetylene-derived **7o** is a rare example of alkynylation providing an α-substituted *N*-Boc-propargylamine,[14] **7o** is unstable to base-treated silica or alumina.[15] Therefore, it is not useful when compared to the ease of handling and deprotecting *N*-Ts-propargylamines.[3,7,16] Figure 1 showcases how this single catalyst can couple a variety of aldehyde-derived pharmacophores (R^3) with a wide range of amino sources: anilines, alkylamines, benzylamines, *N*-heterocycles (piperidine, morpholine, and pyrrolidine), *p*-methoxybenzylamine, and sulfonamide.

Commercially available starting materials can provide over 70% yield of *o*-, *m*-, or *p*-fluorobenzylpropargylamines **8a**, **8b**, or **8c** (Scheme 4). The molecular complexity developed in this single reaction is extensive and allows

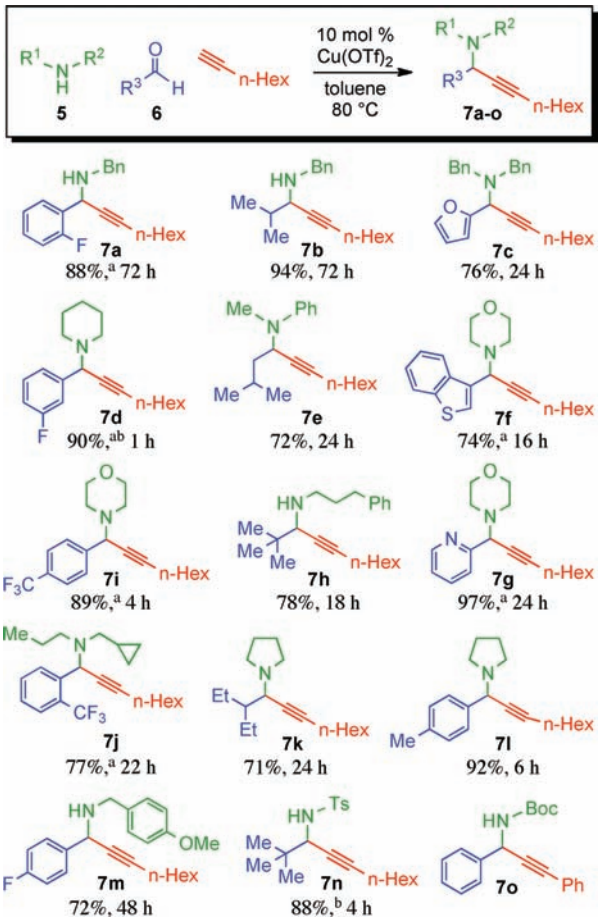
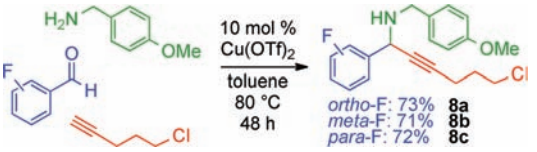


Figure 1. Diverse range of nitrogen sources with single $Cu(OTf)_2$ catalyst: amines, amides, anilines, and *N*-heterocycles. Isolated yields and times with (a) 1 or 2 equiv of Na_2SO_4 and/or (b) 100 °C.

for further derivatization at multiple positions: free position at nitrogen, electron-rich *p*-methoxybenzyl group, aryl fluoride, alkyne, and alkyl chloride.

Scheme 4. One Step to Products with Multiple Functional Groups



Formation of benzyl-protected propargylamine **9** in 80% yield from cyclohexanone represents a rare *catalytic three-component alkynylation involving a ketone* (Scheme 5).[2–7] Despite the lower general reactivity of ketones compared to aldehydes, no additional reagents are required besides catalytic Cu(II) triflate for conversion of cyclohexanone to product.[17]

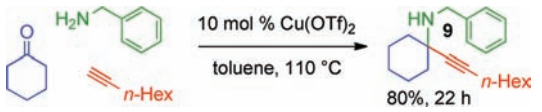
(13) Alkynylation of the benzylamine–isobutyraldehyde imine was one of the few cases where 10 mol % of $CuBr \cdot Me_2S$ was a more effective catalyst than 10 mol % of $Cu(OTf)_2$: 99% versus 90% conversion to **7b** in 2 days. In contrast, formation of **7a** from its benzylimine proceeded to 74% with $Cu(OTf)_2$ but only 42% with $CuBr \cdot Me_2S$ in the same period.

(14) Repeated trials with benzyl carbamate (Cbz-NH_2) under our conditions or then as in Dou, X.-Y.; Shuai, Q.; He, L.-N.; Li, C.-J. *Adv. Synth. Catal.* **2010**, *352*, 2437 never gave more than 20–30% conversion.

(15) Compare commercially available, stable unsubstituted *N*-Boc propargylamine versus a sole report of 16% yield of α-substituted compound: Hatano, M.; Asai, T.; Ishihara, K. *Tetrahedron Lett.* **2008**, *49*, 379.

(16) Utility of deprotected propargylamines: Klauber, E. G.; De, C. K.; Shah, T. K.; Seidel, D. *J. Am. Chem. Soc.* **2010**, *132*, 13624.

Scheme 5. Three-Component Alkynylation with a Ketone



As imine alkynylation generally proceeds with Cu(I),[2−7] the possibility of disproportionation of Cu(II) as a source of an active Cu(I) species was addressed with a mixed catalyst study (Figure 2). Gas chromatography analysis of aliquots provided the concentration of propargylamine (product **3a**) formed by correcting to a known amount of dodedcane internal standard. Treating *N*-Ts-imine **2** with 10 mol % of $Cu(OTf)_2$ and 1-octyne in dichloroethane (a solvent that provides nearly identical results to toluene) at a lower temperature of 40 °C to slow the rate of reaction allowed tracking of the initial rate of formation of product **3a** (Figure 2, purple). An additional 10 mol % of $Cu(OTf)_2$ doubled the initial rate (blue, 20 mol % of catalyst). Adding an additional 10 mol % of either CuBr *or* CuI (red or green) resulted in a rate nearly identical to only 10 mol % of $Cu(OTf)_2$ rather than 20 mol % of catalyst.

In summary, we have found that $Cu(OTf)_2$ is uniquely capable of alkynylating sulfonamide-derived imines, and the three-component coupling of aldehydes, amines, and alkynes proceeds at a faster rate and higher yield than from preformed imine. Whether electron-rich or -poor, nitrogen sources that form imine/iminium are alkynylated with this catalyst, and the sole byproduct is water. While not tolerant of aerobic conditions, these reactions proceed in the presence of up to 5 equivalents of water.

The dense functionality of these propargylic products, all from commercially available starting materials, marks them as malleable synthetic building blocks. As alkyl, aryl, heteroaryl, and fluoroaryl aldehydes react efficiently, compounds for structure−activity studies can be delivered rapidly. With a three-component alkynylation incorporating ketones, fully substituted nitrogen-bearing carbon centers can be attained in one step. The factors underlying the need for the precise combination of triflate counterion with Cu(II) remain to be determined. Further studies to explore the complete range of operable coupling partners are underway.

(17) $[IrCl(COD)]_2$ and MgI_2 for alkynylation of *N*-benzylcyclohexylketimine: Fischer, C.; Carreira, E. M. *Synthesis* **2004**, 1497.

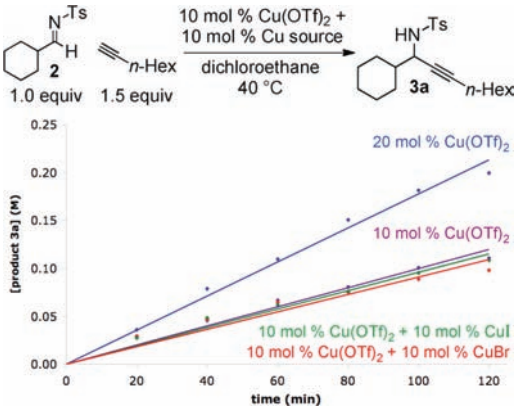


Figure 2. Rate dependent on $Cu(OTf)_2$, not CuBr or CuI.

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Note Added after ASAP Publication. In the version published ASAP on January 19, 2012, in the Abstract, line 3, and on p C, under Scheme 4, the claim "...first catalytic three-component alkynylation involving a ketone..." was incorrect. The following references discuss catalytic three-component alkynylations with a ketone and should have been included: (1) Aliaga, M. J.; Ramón, D. J.; Yus, M. *Org. Biomol. Chem.* **2010**, *8*, 43. (2) Pereshivko, O. P.; Peshkov, V. A.; Van der Eycken, E. V. *Org. Lett.* **2010**, *12*, 2638. (3) Cheng, M.; Zhang, Q.; Hu, X.-Y.; Li, B.-G.; Ji, J.-X.; Chan, A. S. C. *Adv. Synth. Catal.* **2011**, *353*, 1274. The corrected statement now asserts the rarity of these examples. We apologize to these authors. The corrected version was posted ASAP on February 7, 2012.

Supporting Information Available. Experimental procedures and spectroscopic data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.