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Copper-Catalyzed *N*-Allenylation of Allylic Sulfonamides

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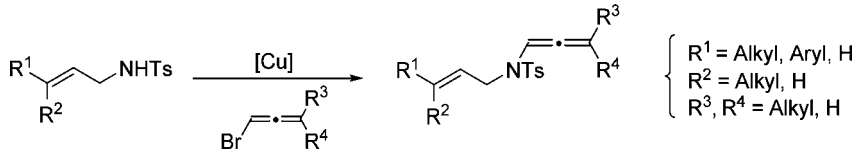
ABSTRACT



Allylic allenic amides have been synthesized via a copper-catalyzed cross-coupling between allylic sulfonamides and bromoallenes in moderate to good yields. Copper(I) thiophene-2-carboxylate (CuTC) was used a source of copper with DMEDA as the ligand. The allenylated products obtained are potential substrates for palladium-catalyzed carbocyclizations.

In recent years, transition-metal-catalyzed cross-coupling has become one of the reaction types most frequently used in organic synthesis.[1,2] Early methods were focused on C−C bond formation,[2] but more recently, selective cross-couplings between carbon and heteroatoms have been developed, e.g., formation of C−N and C−O bonds.[1] One of the major achievements in this area was the development of the Buchwald−Hartwig reaction, which employs Pd(0) as catalyst.[3,4] Another important contribution to this area has been the Ullmann protocol, which instead utilizes Cu(I) as the catalyst.[5,6] Although copper and palladium dominate this area of research, other metals such as nickel,[7] iridium,[8] and iron[9] can also be used.

We have for some time been interested in transition-metal-catalyzed reactions of ene− and diene−allenes.[10] Recently, we extended our interest in *C*-allenyls to also include *N*-allenyls. So far, the latter compounds have received limited attention, mainly due to the lack of good procedures for their preparation.[11] In most cases, preparation of allenamides proceeds via base-catalyzed isomerization of propragylic amides.[12] One major drawback with the isomerization protocol is that only terminal and monosubstituted allenamides can be easily prepared. Recently, the groups of Trost[13]

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(7) Chen, C.; Yang, L.-M. *J. Org. Chem.* **2007**, *72*, 6324.

(8) For the use of Rh, Ru, and Ir, see: (a) Ru: Bertelsen, S.; Nielsen, M.; Bachmann, S.; Jorgensen, K. A. *Synthesis.* **2005**, 2234. (b) Ir: Pouy, M. J.; Leitner, A.; Weix, D. J.; Ueno, S.; Hartwig, J. F. *Org. Lett.* **2007**, *9*, 3949. (c) Ru: Goossen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042.

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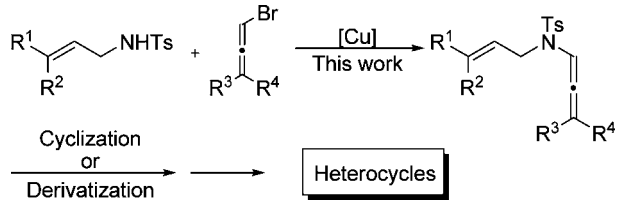
and Hsung[14] reported on copper(I)-catalyzed coupling of amides, carbamates, and ureas with iodo- and bromoallenes, which afforded *N*-allenylated products in good yields.[15]

In connection with a project on the carbocyclization of *N*-allyl-*N*-allenylamides, we required access to these compounds. Copper-catalyzed coupling seemed to be a viable method for their preparation, and herein we report on the copper-catalyzed coupling between allylic sulfonamides and bromoallenes, resulting in *N*-allenylated allylic amides (Scheme 1).

Scheme 1



In order to investigate the coupling, *N*-allyl-4-methylbenzenesulfonamide[16] (**1**) and 1-bromo-3-methylbuta-1,2-diene (**2a**) were chosen as model substrates for the initial optimization of the reaction conditions. First, the influence of the copper source was investigated for the model reaction using toluene as solvent. This showed that copper(I) thiophene-2-carboxylate (CuTC) was superior to other copper catalysts such as CuI, CuBr, and CuCN. Replacing CuTC with CuI consistently resulted in around 15% lower yield, which is in agreement with previously reported results.[13] Next we focused on the choice of ligand. It was found that *N*,*N*′-dimethylethane-1,2-diamine (DMEDA) was the best ligand of those investigated and with this ligand a 92% conversion was obtained after 16 h in toluene at 90 °C (Figure 1).

All of the optimizations were conducted using cesium carbonate as our base of choice. Other bases such as K_3PO_4, K_2CO_3, and Na_2CO_3 were briefly tested, but they never gave as good results as the more soluble cesium carbonate.[17] After some further experiments, we found that optimal conversions were achieved by using the conditions described in Scheme 2, which afforded the desired product (**3**) in 89% isolated yield. It is worth noting that the current protocol proceeds well in both toluene and 1,4-dioxane but performs poorly in DMF.

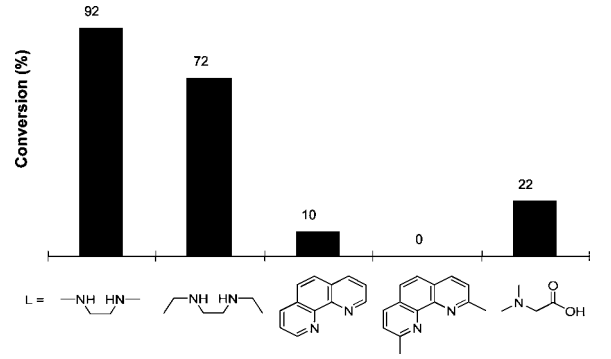
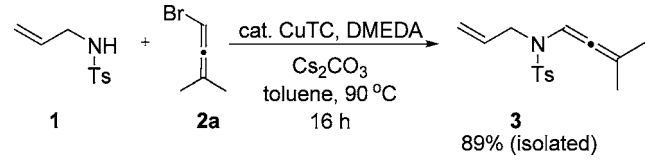


Figure 1. Evaluation of some ligands (L) in the coupling of sulfonamides and allenes. Reactions run for 16 h at 90 °C.

Scheme 2



As shown by the optimized reaction conditions, we were forced to use relatively high catalytic loadings of CuTC (0.15 equiv). All efforts to decrease the amount of catalyst resulted in poor yields. Decreasing the amount of CuTC to 0.1 equiv resulted in a 64% yield of **3**, and lowering the amount even further to 0.05 equiv gave only 25% of the desired product. Despite the high loadings of catalyst, we were intrigued to see that the coupling worked well under the conditions employed. During our investigation, 2.5 equiv of bromoallene was employed; however, we discovered at a late stage that 1.5 equiv is sufficient to promote the coupling without any substantial loss in yield.[18]

In the coupling protocol reported by Trost[13] it was mentioned that some substrates undergo coupling, followed by isomerization from allene to 1,3-diene, a phenomenon we have not observed with our substrates. We noticed, however, that the products obtained were very sensitive to acid, giving 1,3-dienes under acidic conditions. As a consequence, all column chromatograhy purifications were carried out with basic alumina.[19]

(11) For some recent reactions involving allenylamides, see: (a) Navarro-Vázquez, A.; Rodríguez, D.; Martínez-Esperón, M. F.; García, A.; Saá, C.; Domínguez, D. *Tetrahedron Lett.* **2007**, *48*, 2741. (b) Fuwa, H.; Tako, T.; Ebine, M.; Sasaki, M. *Chem. Lett.* **2008**, *37*, 904. (c) Bacci, J. P.; Greenman, K. L.; Van Vranken, D. L. *J. Org. Chem.* **2003**, *68*, 4955. (d) Shen, L.; Hsung, R. P. *Org. Lett.* **2009**, *7*, 775. (e) Fuwa, H.; Sasaki, M. *Org. Biomol. Chem.* **2007**, *5*, 2214. (f) Rameshkumar, C.; Hsung, R. P. *Angew. Chem., Int. Ed.* **2004**, *43*, 615.

(12) For preparation of allenamides, see: (a) Armstrong, A.; Emmerson, D. P. G. *Org. Lett.* **2009**, *11*, 1547. (b) Wei, L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (c) Xiong, H.; Tracey, M. R.; Grebe, T.; Mulder, J. A.; Hsung, R. P. *Org. Synth.* **2005**, *81*, 147. (d) Huang, J.; Xiong, H.; Hsung, R. P.; Rameshkumar, C.; Mulder, J. A.; Grebe, T. P. *Org. Lett.* **2002**, *4*, 2417. (e) Wei, L.; Mulder, J. A.; Xiong, H.; Zircsak, C. A.; Douglas, C. J.; Hsung, R. P. *Tetrahedron* **2001**, *57*, 459.

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(15) For preparation of bromo allenes, see: Black, D. K.; Landor, S. R.; Patel, A. N.; Whiter, P. F *Tetrahedron Lett.* **1963**, *4*, 483.

(16) For preparation of *N*-allylsulfonamides, see the following. Aryl substituted: Busacca, C. A.; Dong, Y. *Tetrahedron Lett.* **1996**, *37*, 3947. (b) Alkyl substituted: Lei, A.; Lu, X *Org. Lett.* **2000**, *2*, 2357.

(17) Cella, A.; Bacon, S. W. *J. Org. Chem.* **1984**, *49*, 1122.

(18) Using 1.5 equiv of bromoallene gave product **5** in 76% yield.

(19) All attempts to purify the obtained products by column chromatography on silica or deactivated silica (SiO_2/Et_3N) resulted in isomerized product. Chromatography on basic alumina (pH = 9.5) was therefore chosen.

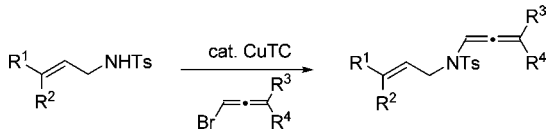
After the initial screening and overcoming some purification issues, we moved on to investigating the versatility of the present method. The results are shown in Table 1. A selection of bromoallenes is readily available,[15] and variations of the allene moiety in the reaction with allylic sulfonamides was studied. It was found that 3,3-disubstituted allenamides generally give good to high yields in the coupling with allylic sulfonamides (Table 1).

Coupling of a monosubstituted allene gave a lower yield (Table 1, entry 4). Allylic sulfonamides containing both alkyl and aryl substituents on the allylic moiety were investigated in the coupling reaction.[16]

Increased bulk around the olefin of the allylic amide results in slightly lower yields of coupled product (Table 1, entries 2 and 3). Introduction of a methyl group on the internal carbon of the olefin results in a very inefficient reaction, and only small amounts of product could be isolated (not shown). In addition, when the olefin is replaced by a simple ethyl group only 10% of the coupled product can be detected with the present protocol. To our surprise, the introduction of an aromatic ring on the olefin (Table 1, entry 8) produced no desired product at 80 °C (decomposition); however, lowering the temperature to 40 °C gave coupled products in moderate yields (entries 8−10). As a consequence, the copper-catalyzed coupling can in these cases proceed at temperatures close to room temperature. This is a phenomenon we have not yet fully rationalized.[20]

Apart from substrates bearing the allylic side chain some other useful sulfonamides were subjected to the coupling protocol (Table 2). Protected aryl amines undergo coupling in moderate yields even with an acyl group introduced in the *ortho*-position (Table 2, entries 1 and 2). Surprisingly, ditoslylated-1,2-diamines (Table 2, entry 3) yielded a cyclic product in 63% yield. We believe that this product arises from a monoallenylated intermediate, which undergoes a cyclization under the conditions employed.

Table 1. Copper-Catalyzed Cross-Coupling of Allylic Sulfonyl Amides and Bromoallenes[a]



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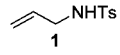
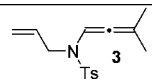
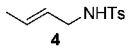
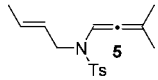
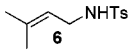
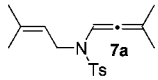
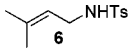
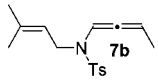
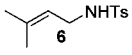
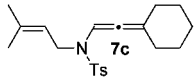
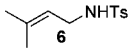
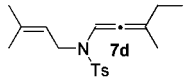
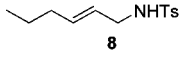
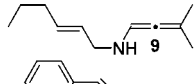
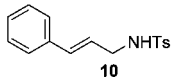
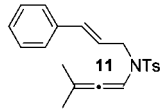
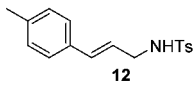
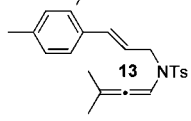
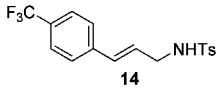
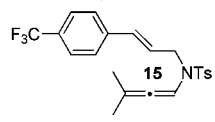
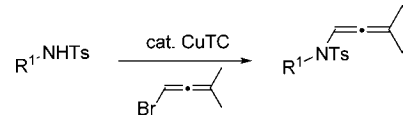
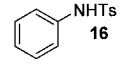
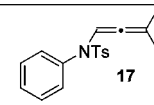
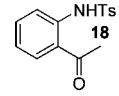
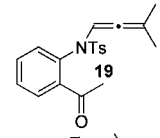
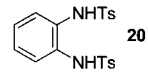
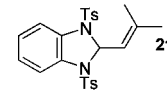
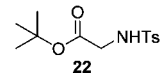
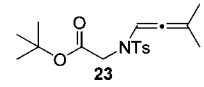
1			89
2			82
3			74
4			35
5			65
6			67
7			72
8			53[c]
9			20[c]
10			52[c]

[a] Conditions: CuTC (0.15 equiv), DMEDA (0.30 equiv), Cs_2CO_3 (2.0 equiv), Br-allene (2.5 equiv), toluene, 80 °C, 24 h. [b] Isolated yields. [c] Performed at 40 °C.

Table 2. Cross-Coupling of Sulfonyl Amides and Bromoallenes[a]



entry	substrate	product	yield (%)[b]
1			56[c]
2			44[c]
3			63[d]
4			41[c]

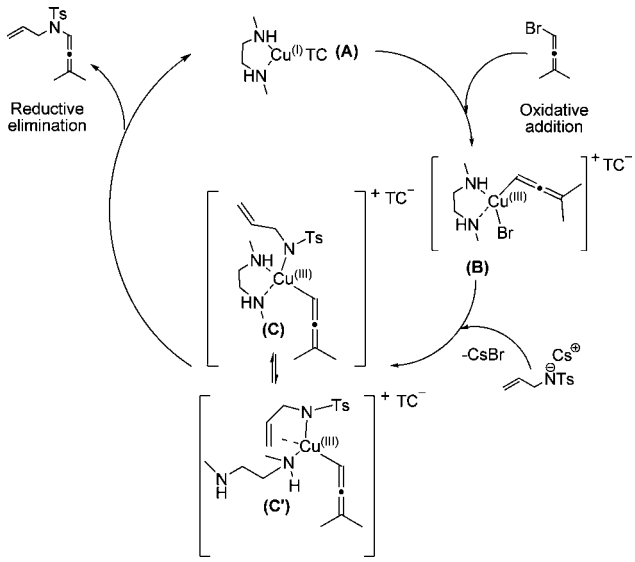
[a] Conditions: CuTC (0.15 equiv), DMEDA (0.30 equiv), Cs_2CO_3 (2.0 equiv), Br-allene (2.5 equiv), THF or 1,4-dioxane (65 or 80 °C), 24 h. [b] Isolated yields. [c] Refluxing 1,4-dioxane. [d] Refluxing THF.

A protected amino acid also furnished coupling product in moderate yield without any further optimization (Table 2, entry 4).

The present protocol developed has some limitations. All attempts to replace the sulfonyl group by other protective groups such as acetyl, Cbz, Boc, or trifluoroacetyl were unsuccessful and led only to recovered starting material. We

(20) No product formation was observed when the copper catalyst was removed from the system.

Scheme 3. Proposed Mechanism for the Copper-Catalyzed Cross-Coupling



speculate that this has to do with the pK_a of the amides, where the *p*-toluenesulfonamide has a pK_a of around 16, whereas the other amides have a pK_a above 20.[21] In addition, introducing a substituent in the α-position of the sulfonamide shuts down the reaction yielding only traces of coupled product.

A mechanism of the copper-catalyzed cross-coupling reaction is proposed in Scheme 3. Oxidative addition of the bromoallene to the copper(I) diamine (**A**) complex would produce a copper(III) intermediate (**B**).[22] Exchange of the bromide with the tosyl amide (**C**, **C′**) followed by reductive elimination would lead to coupling product. Our experimental data suggest that the presence of an allylic double bond on the amide might act as a ligand in the catalytic cycle. This would explain why increased bulk around the olefin or removal of this moiety results in lower yields and longer reaction times.

In conclusion, we have developed a method for copper-catalyzed coupling of bromoallenes and *N*-allylsulfonamides to give *N*-allyl-*N*-alleneylsulfonamides. These structures can serve as excellent substrates for further transition-metal-catalyzed transformations.[23]

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Supporting Information Available: Complete experimental procedures, characterization data, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(23) Carbocyclization of the aza-enallene product in table 1 (entry 3) in the presence of 5 mol % of $Pd(OAc)_2$ and 2 equiv of *p*-benzoquinone in THF at 55 °C afforded the the pyrroline product (1-tosyl-3-(2-isopropenyl-4-vinyl-2-pyrroline) in 89% yield: Persson, A. K. Å; Bäckvall, J. E. Unpublished results.