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Synthesis of Allenamides by Copper-Catalyzed Coupling of Allenyl Halides with Amides, Carbamates, and Ureas

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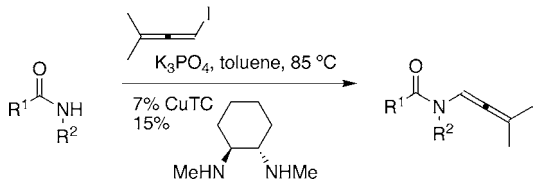
ABSTRACT



A variety of N-substituted allenes have been synthesized by the copper-catalyzed coupling reaction between allenyl halides and amides, carbamates, and ureas. The reactions proceed in good to excellent yield using 7 mol % copper thiophenecarboxylate and 15 mol % of a diamine catalyst.

Allenes are a versatile class of organic compounds that feature numerous patterns of reactivity.[1] Allenamides are a subclass of allenes that have recently received much attention in the synthetic community.[2,3] They are viable precursors for numerous subsequent elaborations such as metal-catalyzed cyclizations,[4] [4 + 2] cycloadditions,[5] [4 + 3] cycloadditions,[3a,f] and radical cyclizations.[6] To date, there have been a limited number of ways to prepare allenamides. Allenamides are most commonly constructed by the base-catalyzed isomerization of propargylic amides.[7] Aside from the need to use strong bases such as potassium *t*-butoxide, products of such isomerizations are limited to simple terminal or monosubstituted allenes. Other methods to prepare allenamides, like the sigmatropic rearrangement of propargylic imidates,[8] also suffer from a limited substrate scope.

We became interested in a 3,3-dimethyl-substituted allenamide for use in a metal-catalyzed allylic alkylation directed toward the synthesis of a natural alkaloid. As 3,3-dialkyl-substituted allenamides are not accessible by current methodology, we turned toward a metal-catalyzed cross-coupling procedure. Only a limited number of cross-coupling reactions

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(6) Schen, L.; Hsung, R. P. *Org. Lett.* **2005**, *7*, 775.

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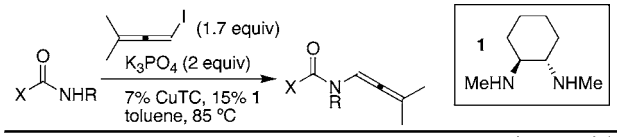
Table 1. Coupling with Carbamates, Hydantoins, and Ureas[a]



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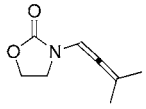
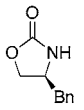
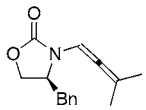
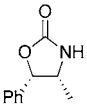
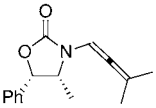
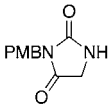
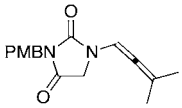
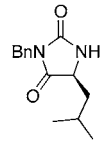
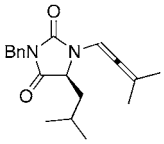
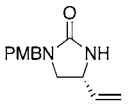
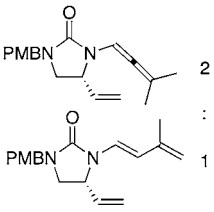
1			7	97
2			6	95
3			5	99
4			6	99
5			7	100
6			7	79 (2 : 1)

[a] Bn = benzyl; PMB = *p*-methoxybenzyl.

Table 2. Coupling with Lactams and Arylamines[a]

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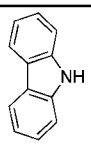
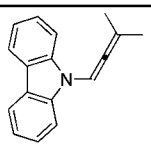
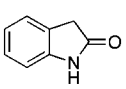
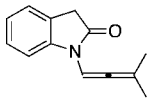
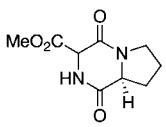
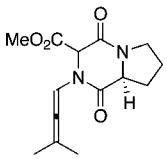
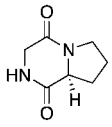
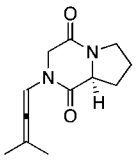
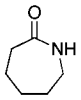
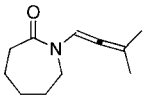
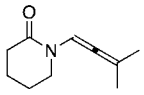
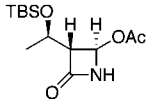
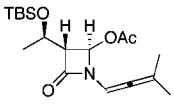
1[b]			16	94
2			6	86
3[c]			12	63
4[c,d]			12	58
5			6	46
6			9	28
7[e]			5	36

[a] TBS = *tert*-butyldimethylsilyl. Reaction conditions: 1.7 equiv of allenyl iodide, 2.0 equiv of K_3PO_4, 7% CuTC, 15% ligand **1**, toluene, 85 °C. [b] Added 2.0 equiv of BaO, workup by filtration. [c] The diminished optical rotation of this product indicates some amount of racemization may have occurred. [d] Run using CuI and Cs_2CO_3 in DMF at 75 °C. [e] Isolated as one diastereomer.

involving allenes have been reported,[9] invoking allenylstannanes in Stille-type couplings with aryl halides. Drawing from recent work by Porco and Buchwald in the field of copper-catalyzed coupling between amides and vinyl halides,[10] we asked whether such a reaction could be extended to utilize allenyl halides. To our delight, we found that allenyl halides function well in this context.

Copper thiophenecarboxylate (CuTC)[11] was selected as a source of copper(I) because of its shelf-stability. The combination of potassium phosphate as a base and the commercially available *trans-N,N′*-dimethylcyclohexyl-diamine ligand was found to be highly effective in promoting the reaction.[12] The reaction proceeds well in toluene, though dioxane could also be used.

Amide derivatives such as oxazolidinones and hydantoins underwent coupling with 1-iodo-3-methylbuta-1,2-diene[13] most efficiently (Table 1). Reactions were generally complete within 6 h, and the yields were usually >90%. Lactams were more sluggish to react (Table 2), with incomplete conversion even after extended heating. In these cases, the majority of

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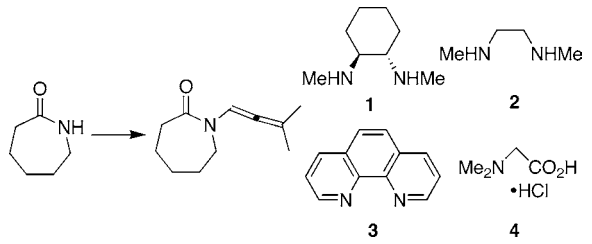
(12) **Typical Procedure** (Table 1, entry 1): An oven-dried 10 mL round-bottom flask was charged with 2-oxazolidinone (30 mg, 0.345 mmol), CuTC (4.6 mg, 24 μmol), and K_3PO_4 (146 mg, 0.689 mmol). After the flask was flushed with nitrogen three times, 1.5 mL of toluene was added, followed by ligand **1** (8.1 μL, 7.4 mg, 52 μmol) and then 1-iodo-3-methylbuta-1,2-diene (70 μL, 114 mg, 0.587 mmol). The flask was covered with aluminum foil and heated to 85 °C for 7 h. The reaction was cooled and added to 10 mL of water and then extracted with ethyl acetate (3 × 5 mL), washed with brine, dried over magnesium sulfate, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (eluted with 95% ether, 5% triethylamine) to afford the allenamide (51 mg, 97%) as an oil.

(13) This allene was prepared by a modification of the procedure of Landor et al.: Greaves, P. M.; Kalli, M.; Landor, P. D.; Landor, S. R. *J. Chem. Soc. C* **1971**, 667.

Table 3. Attempted Optimization of Reactions with Caprolactam



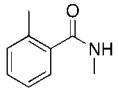
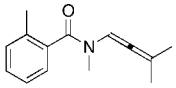
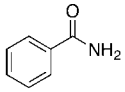
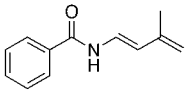
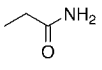
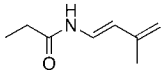
base	solvent	Cu(I), mol %	ligand	temp (°C)/ time (h)	yield (%)
K_3PO_4	toluene	7% CuTC	**1**	85/6	46
Cs_2CO_3	*t*-BuOH	7% CuTC	**1**	70/9.5	39
K_3PO_4	dioxane	15% CuTC	**1**	80/13	38
Cs_2CO_3	toluene	10% $Cu(MeCN)_4PF_6$	**1**	80/10	33
Cs_2CO_3	NMP	100% CuTC	**none**	80/14	31
NaHMDS	toluene	10% CuTC	**1**	75/5	22
Cs_2CO_3	DMF	7% CuI	**1**	80/14	20
Cs_2CO_3	DMA	7% CuTC	**1**	100/10	6
Cs_2CO_3	toluene	10% $Cu(MeCN)_4PF_6$	**2**	80/10	trace
Cs_2CO_3	dioxane	10% CuI	**4**	80/12	trace
Cs_2CO_3	NMP	10% CuTC	**3**	80/14	trace

the mass balance is made up of unreacted starting material. Clearly, the electron-withdrawing nature of the carbonyl moiety, and thus the pK_a of the amide proton, plays a large role in the overall efficiency of the transformation. Particularly noteworthy is the β-lactam (Table 2, entry 7). While the yield is modest, the chemoselectivity is startling. In the case of the malonate-type substrate (Table 2, entry 3), no C-allenylation was observed.

In an effort to increase the yields of the reactions with lactams, a variety of ligands, bases, copper sources, and solvents were screened with caprolactam as a test substrate (Table 3). Combinations that are frequently used in the coupling of vinyl halides with amides[10a−f] could not improve the yield beyond 46%.

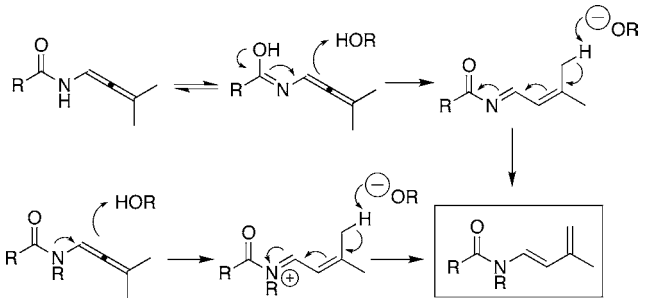
Acyclic amides also reacted slowly to give lower yields of allenamide products (Table 4). In the cases of primary acyclic amides, the products obtained were 1,3-dienes.

Table 4. Coupling with Acyclic Amides[a]

entry	reactant	product	time (h)	yield (%)
1			22	20[b]
2			11	47
3			4.5	24

[a] Reaction conditions: 1.7 equiv of allenyl iodide, 2.0 equiv of K_3PO_4, 7% CuTC, 15% ligand **1**, toluene, 85 °C. [b] Obtained as a 2:1 mixture of amide rotomers.

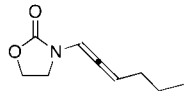
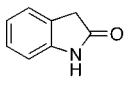
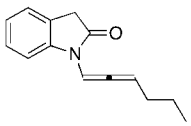
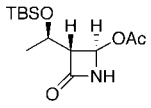
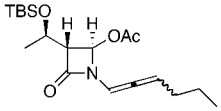
Scheme 1. Isomerization Mechanism of Allenamides



Presumably, this isomerization occurs through a sequence of tautomerizations and proton shifts (Scheme 1). These dienamides, although not the intended product, are useful in their own right as Diels−Alder substrates.[14] Such 1,3-dienamides were also observed as products from coupling with an imidazolidinone (Table 1, entry 6) and carbazole (Table 2, entry 1). In these cases, the isomerization probably occurs through a similar series of prototropic shifts involving adventitious water in the reaction medium or perhaps during the aqueous workup[15] (Scheme 1). For carbazole, the isomerization could be completely suppressed by the addition of 2 equiv of the proton scavenger barium oxide and by performing an anhydrous workup. This protocol did not improve the allenyl purity of the imidazolidinone.

To test the scope of allenyl halides that can be used in the reaction, 1-iodo-1,2-hexadiene[16] was prepared. This monosubstituted allenyl iodide was found to undergo coupling in slightly higher yield than the disubstituted allenyl iodide (Table 5). As chiral allenyl iodides are readily prepared from chiral propargylic mesylates,[17] this method makes chiral allenamides available.

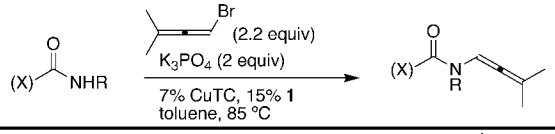
Table 5. Coupling with Monoalkyl Allenyl Iodide[a]

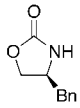
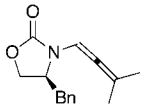
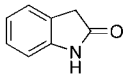
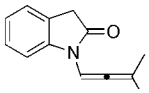
entry	reactant	product	time (h)	yield (%)
1			5	100
2			6	100
3			6.5	47

[a] Reaction conditions: 1.7 equiv of allenyl iodide, 2.0 equiv of K_3PO_4, 7% CuTC, 15% ligand **1**, toluene, 85 °C.

Finally, we prepared 1-bromo-3-methylbuta-1,2-diene[18] and were pleased to see that it too undergoes cross coupling in yields that are comparable to those with the analogous

Table 6. Cross Coupling with Allenyl Bromide



entry	reactant	product	time (h)	yield (%)
1			8	96[a]
2			5	71

[a] Obtained as a 6:1 mixture of allene/1,3-diene isomers.

iodide (Table 6). Although most of the reactions in this text were carried out with the iodide, the bromide may in fact be preferred for reasons of stability and ease of handling.

In conclusion, we have developed a simple procedure for the coupling of amides and amide derivatives with allenyl iodides and bromides. Our process allows access to a range of allenes that are unavailable by other synthetic routes. The utilization of such allenes in the context of total synthesis is presently being explored in our laboratories.

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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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(14) For reviews, see: (a) Petrzilka, M.; Grayson, J. I. *Synthesis* **1981**, 753. (b) Campbell, A. L.; Lenz, G. R. *Synthesis* **1987**, 421.

(15) To mitigate isomerization to 1,3-dienes, column chromatography on all products was performed with 5% triethylamine in the eluting phase.

(16) This allene was prepared from the mesylate of 1-hexyn-3-ol following the procedure of Tanaka et al.: Ohno, H.; Ando, K.; Hamaguchi, H.; Takeoka, Y.; Tanaka, T. *J. Am. Chem. Soc.* **2002**, *124*, 15255.

(17) (a) Marshall, J. A.; Grant, C. M. *J. Org. Chem.* **1999**, *64*, 8214. (b) Elsevier: C. J.; Vermeer, P.; Gedanken, A.; Runge, W. *J. Org. Chem.* **1985**, *50*, 364. (c) D'Aniello, F.; Mann, A.; Taddei, M.; Wermuth, C.-G. *Tetrahedron Lett.* **1994**, *35*, 7775. (d) Montury, M.; Gore, J. *Synth. Commun.* **1980**, *10*, 873.

(18) This allene was prepared by a modification of the procedure of Landor, et al.: Landor, S. R.; Patel, A. N.; Whiter, P. F.; Greaves, P. M. *J. Chem. Soc. C* **1966**, 1223.