ORGANIC LETTERS

2012
Vol. 14, No. 1
280–283

Synthesis of Propargylic and Allenic Carbamates *via* the C–H Amination of Alkynes

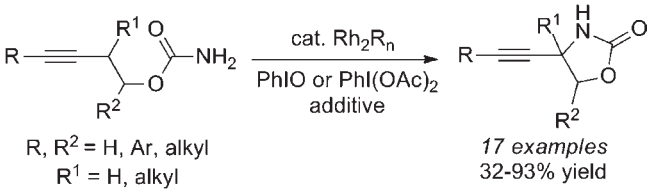
R. David Grigg,[†] Jared W. Rigoli,[†] Simon D. Pearce, and Jennifer M. Schomaker*

Department of Chemistry, University of Wisconsin—Madison, Madison, Wisconsin 53706, United States

**schomakerj@chem.wisc.edu*

Received November 12, 2011

ABSTRACT



Propargylic amines are important intermediates for the synthesis of nitrogen-containing heterocycles. The insertion of a nitrene into a propargylic C–H bond has not been explored, despite the attention directed toward the Rh-catalyzed amination of other types of C–H bonds. In this communication, the conversion of a series of homopropargylic carbamates to propargylic carbamates and aminated allenes is described.

Propargyl amines are versatile synthetic building blocks for the construction of diverse heterocycles, including oxazoles, indolizines, pyrroles, quinolines, and pyrrolidines.[1] The most common approaches to synthesize propargyl amines involve either the addition of an acetylide to an imine or ketimine or the transition-metal-catalyzed coupling of an aldehyde, amine, and alkyne. In many of these cases, the use of an aromatic aldehyde or a secondary amine is required, limiting the scope of the reaction.[2,3] In the context of other studies ongoing in our group, we were interested in the synthesis of allenic amines of the form **2b** (Scheme 1), where the nitrogen could be either readily deprotected or further functionalized.

Since the preparation of vicinal and 1,3-aminoalcohols *via* the Rh-catalyzed insertion of carbamate and sulfamate-derived nitrenes into benzylic, allylic, allenic, and methylene C–H bonds is so well-established, we attempted to prepare **2b** by employing allenic carbamate **1** as the substrate (Scheme 1).[4] However, allene aziridination to the bicyclic methylene aziridine **2a** was always a major competing reaction (Scheme 1, top) and, in fact, was the exclusive product obtained when sulfamate nitrene precursors were employed.[5] The desired C–H amination product **2b** could be obtained selectively only through substrate control; thus, we sought to gain exclusive access to allenic amines by an alternative approach.[5b]

A Mitsunobu-type reaction using NBSH (2-nitrobenzenesulfonylhydrazide), PPh_3, and DIAD (diisopropylazodicarboxylate)

[†] These authors contributed equally.

(1) (a) Lee, E.-S.; Yeom, H.-S.; Hwang, J.-H.; Shin, S. *Eur. J. Org. Chem.* **2007**, 3503. (b) Yan, B.; Liu, Y. *Org. Lett.* **2007**, *9*, 4323. (c) Yamamoto, Y.; Hayashi, H.; Saigoku, T.; Nishiyama, H. *J. Am. Chem. Soc.* **2005**, *127*, 10804. (d) Xiao, F.; Chen, Y.; Liu, Y.; Wang, J. *Tetrahedron* **2008**, *64*, 2755. (e) Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268.

(2) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407. (b) Jung, M. E.; Huang, A. *Org. Lett.* **2000**, *2*, 2659. (c) Murai, T.; Mutoh, Y.; Ohta, Y.; Murakami, M. *J. Am. Chem. Soc.* **2004**, *126*, 5968.

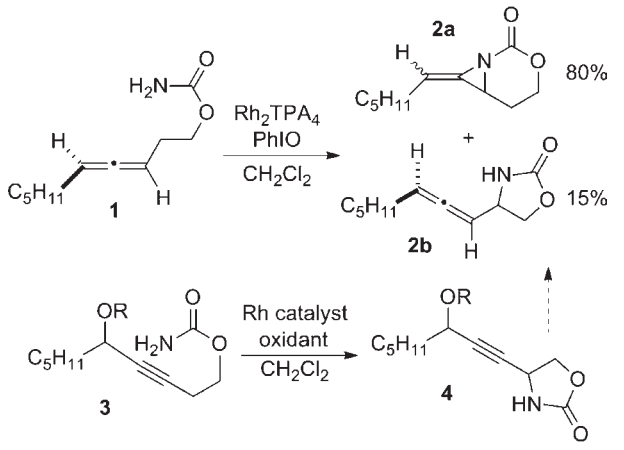
(3) For selected references, see: (a) Bisai, A.; Singh, V. K. *Org. Lett.* **2006**, *8*, 2405. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5363. (c) Lu, T.; Johnstone, C.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2009**, *131*, 11284. (d) Lo, V. K.; Liu, Y.; Wong, M. K.; Che, C. M. *Org. Lett.* **2006**, *8*, 1529. (e) Okamura, T.; Asano, K.; Matsubara, S. *Synlett* **2010**, 3053. (f) Wei, C.; Li, C. J. *J. Am. Chem. Soc.* **2002**, *124*, 5638. (g) Aschwanden, P.; Stephenson, C. R.; Carreira, E. M. *Org. Lett.* **2006**, *8*, 2437. (h) Yoshida, A.; Hattori, G.; Miyake, Y.; Nishibayashi, Y. *Org. Lett.* **2011**, *13*, 2460. (i) Hattori, G.; Sakata, K.; Matsuzawa, H.; Tanabe, Y.; Miyake, Y.; Nishibayashi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 10592.

(4) For selected references, see: (a) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061. (b) Collet, F.; Lescot, C.; Dauban, P. *Chem. Soc. Rev.* **2011**, *40*, 1926. (c) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377. (d) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (e) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378. (f) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562.

(5) (a) Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924. (b) Grigg, R. D.; Schomaker, J. M.; Timokhin, V. *Tetrahedron* **2011**, *67*, 4318.

10.1021/ol203055v
Published on Web 12/19/2011

Scheme 1. Two Approaches to Allenic Carbamates

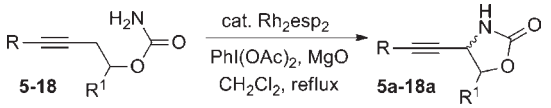


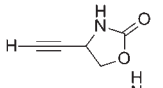
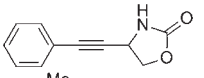
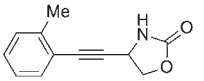
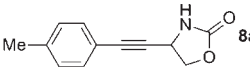
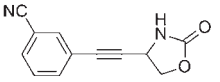
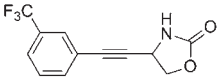
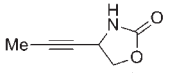
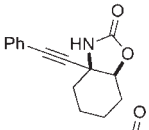
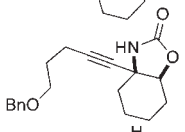
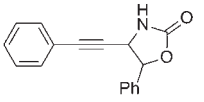
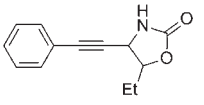
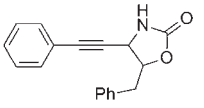
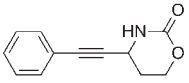
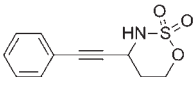
has been employed to generate allenes from propargyl alcohols. We thought application of this method to substrates similar to **4** would allow us to obtain **2b** exclusively without competing methylene aziridine formation.[6] The formation of the key intermediate **4** could arise from a simple Rh-catalyzed amination of the alkyne **3**.

To our surprise, the Rh-catalyzed amination of a propargylic C−H bond has not been explored. Blakey and co-workers have reported the Rh-catalyzed transformation of homopropargylic sulfamates to aminocyclopropanes and aminostyrenes using an intriguing metallonitrene/alkyne metathesis reaction, but the propargyl amine was not observed.[7] We quickly found that switching the nitrene precursor to a carbamate (Table 1, **5**−**17**) generated the desired propargyl carbamates in moderate to excellent yields using Rh_2esp_2 as the catalyst and $PhI(OAc)_2$ as the oxidant. In the case of alkyne **5**, the yield was lowered due to the volatility of the product (Table 1, entry 1). Substitution of the H with a Ph group (entry 2) gave a 93% yield of the desired product, with no products from competing alkyne oxidation observed.

Moderate to good yields were obtained with a variety of substituents on the aromatic ring (entries 3−6). Alkyl substitution on the alkyne was also tolerated (entries 7 and 9). When cyclic homopropargylic carbamates were employed as substrates (entries 8 and 9), the propargylic amines were obtained in high yield as the *syn* products with both terminal aryl and alkyl substitution on the alkyne. Unfortunately, the use of substrates bearing acyclic chiral centers (entries 10−12) gave poor diastereoselectivities and attempts to use less bulky Rh catalysts were not successful. The reaction favored insertion into the propargylic C−H over the benzylic C−H by a ratio of

Table 1. Propargylic Carbamates *via* C−H Insertion



entry	product		yield	*dr* (*syn*:*anti*)
1		**5a**	66%	---
2		**6a**	93%	---
3		**7a**	84%	---
4		**8a**	81%	---
5		**9a**	77%	---
6		**10a**	57%	---
7		**11a**	80%	---
8		**12a**	90%	> 20:1
9		**13a**	75%	> 20:1
10		**14a**	74%	2:1
11		**15a**	67%	1:1
12		**16a**	6.6:6.2:2.5:1 98% conversion	
13		**17a**	no reaction	---
14		**18a**	47%	---

about 4:1 (entry 12), as determined by ^1H NMR spectroscopy. When the tether between the alkyne and the carbamate was extended to three carbons (entry 13), no reaction was observed. However, with this tether length, an alkyne bearing a sulfamate nitrene precursor did give a moderate amount of the desired propargylic amine (entry 14).

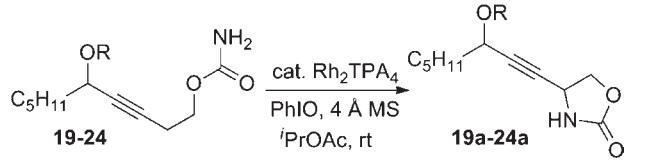
With these results in hand, more functionalized carbamates were explored as substrates to allow access to the desired allenic amines (Table 2). In contrast to the entries

(6) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492.

(7) (a) Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434. (b) Thornton, A. R.; Blakey, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 5020. (c) Stoll, A. H.; Blakey, S. B. *J. Am. Chem. Soc.* **2010**, *132*, 2108.

in Table 1, these substrates performed better using Rh_2TPA_4 as the catalyst and PhIO as the oxidant. The success of the amination was strongly affected by the nature of the propargylic alcohol protecting group. No protecting group (entry 1) gave a complex mixture of products, while an acetate group (entry 2) did yield some of the desired **20a**. However, the reaction was sluggish and 35% **20** was recovered from the reaction mixture. Increasing the temperature or prolonging the reaction time did not lead to an improvement in the yield. A TBS

Table 2. Propargylic Amines from C−H Amination



entry	R	yield		entry	R	yield	
1	H	complex mixture	**19a**	4	TBDPS	0%	**22a**
2	Ac	45%	**20a**	5	TES	32%	**23a**
3	TBS	57%	**21a**	6	TIPS	43%	**24a**

protecting group (entry 3) gave the highest yield of the desired **21a**, while a TBDPS group (entry 4) proved too bulky and no reaction was observed. Both TES and TIPS protecting groups did yield product, but the majority of the mass balance was starting material. Despite the moderate yield of **21a**, this route is still preferable to allene amination (Scheme 1, **1** to **2b**).

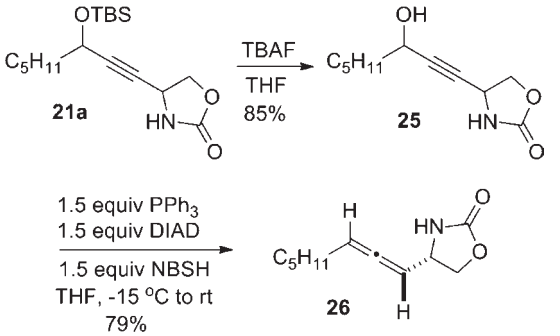
The propargylic amine **21a** was deprotected using TBAF and subjected to Myers' conditions (Scheme 2).[9] The desired allenic amine **26** was isolated in 79% yield, showing that, for problematic allenic carbamate substrates, the sequence of reactions involving an amination at a propargylic C−H bond could be used as an alternative approach.

Lastly, we wanted to quickly determine if typical cycloaddition reactions could be performed using these substrates to access polycyclic ring systems. The vicinal amino alcohol moiety would provide a convenient synthetic handle for further manipulations of the products.

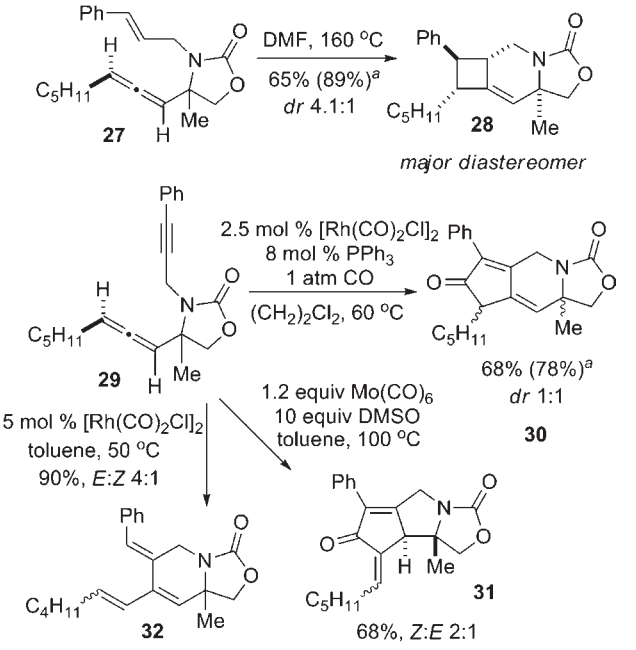
As illustrated in Scheme 3, the alkylated allenic amine **27** was heated in DMF to give the thermal-mediated [2 + 2] product in good isolated yield and excellent yield based on recovered **27**.[8] The product was obtained as a 4.1:1 mixture of diastereomers.

Treatment of the functionalized allene **29** (Scheme 3) under two different Pauson−Khand conditions gave the tricyclic products **30** and **31** in good yields.[9] A minor product was obtained in 8% yield in the reaction to **31**

Scheme 2. Synthesis of Allenic Amines



Scheme 3. Transformations of Functionalized Allenic Amines



(not shown), where the adjacent Me and H groups had a *syn* relationship. Finally, an allenic Alder-ene reaction of **29** gave the unsaturated piperidine **32** in excellent yield and a reasonable *E*/*Z* ratio of 4:1.[10]

In conclusion, the C−H amination of homopropargylic carbamates has been accomplished using a dinuclear Rh catalyst in the presence of a hypervalent iodine oxidant. In contrast to the reaction of the more popular sulfamate precursors under these reaction conditions, the alkyne did not undergo significant oxidation and the desired propargylic carbamates were obtained in good yields. These intermediates could be converted into allenic carbamates, which themselves were capable of a variety of

(8) (a) Brummond, K. M.; Chen, D. *Org. Lett.* **2005**, *7*, 3473. (b) Ohno, H.; Mizutani, T.; Kadoh, Y.; Aso, A.; Miyamura, K.; Fuji, N.; Tanaka, T. *J. Org. Chem.* **2007**, *72*, 4378.

(9) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245.

(10) (a) Brummond, K. M.; Chen, H.; Mitasev, B.; Casarez, A. D. *Org. Lett.* **2004**, *6*, 2161. (b) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186.

transition-metal-catalyzed carbocyclizations to yield diverse heterocycles.

Acknowledgment. Financial support was provided by start-up funds from the University of Wisconsin, Madison and the Wisconsin Alumni Research Foundation. The NMR facilities at UW—Madison are funded by the NSF (CHE-9208463, CHE-9629688) and NIH (RR08389-01). The authors also thank Dr. John Hershberger and Dr. Dan Wherrit of the University of Wisconsin—Madison for helpful discussions.

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