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Allene Functionalization via Bicyclic Methylene Aziridines

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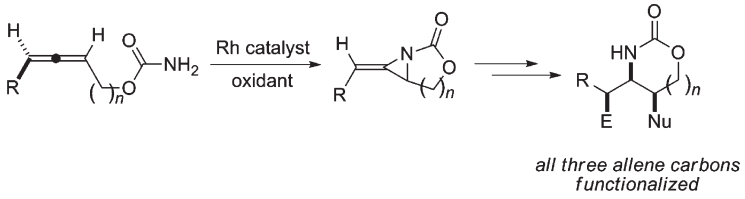
ABSTRACT

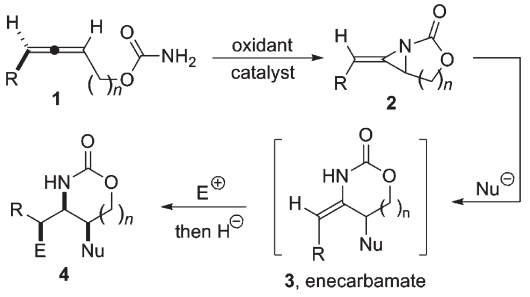


The oxidative functionalization of olefins is a common method for the formation of vicinal carbon−heteroatom bonds. However, oxidative methods to transform allenes into synthetic motifs containing three contiguous carbon−heteroatom bonds are much less developed. This paper describes the use of bicyclic methylene aziridines (MAs), prepared via intramolecular allene aziridination, as scaffolds for functionalization of all three allene carbons.

Olefins are popular substrates for a host of oxidative transformations designed to introduce new C−N bonds into molecules.[1] However, considerably less effort has been devoted to oxidations of allenes, despite the potential to efficiently generate three new contiguous heteroatom-bearing chiral centers.[2,3] Herein, we describe our preliminary efforts to utilize intramolecular allene amination as a key step for the stereoselective and flexible functionalization of allenes.[3]

One proposed approach toward this goal is illustrated in Scheme 1. Reaction of an intermediate bicyclic methylene aziridine (MA) **2** with a nucleophile would generate enecarbamate **3**. Sequential addition of an electrophile and a hydride source to reduce the resultant iminium could flexibly generate motifs such as **4**.[3a,4]

Scheme 1. Proposed Allene Functionalization



Despite the great potential of bicyclic MAs to serve as scaffolds for allene oxidation, a significantly more detailed understanding of their preparation and reactivity is needed.[4] A recent report on allene aziridination utilizing *N*-tosyloxycarbamates as nitrene precursors reported low yields of MAs and limited substrate scope.[3a] Thus, our first challenge was to examine factors including substrate,

(1) For selected reviews on the aziridination of olefins, see:(a) Pellissier, H. *Tetrahedron* **2010**, *66*, 1509. (b) Sweeney, J. B. *Chem. Soc. Rev.* **2002**, *31*, 247. (c) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, 2004. (d) Muller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905.

(2) For selected references on C−O bond-forming reactions with allenes, see: (a) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. (b) Ghosh, P.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2007**, *129*, 2438. (c) Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108. (d) Ghosh, P.; Cusick, J. R.; Inghrim, J.; Williams, L. J. *Org. Lett.* **2009**, *11*, 4672.

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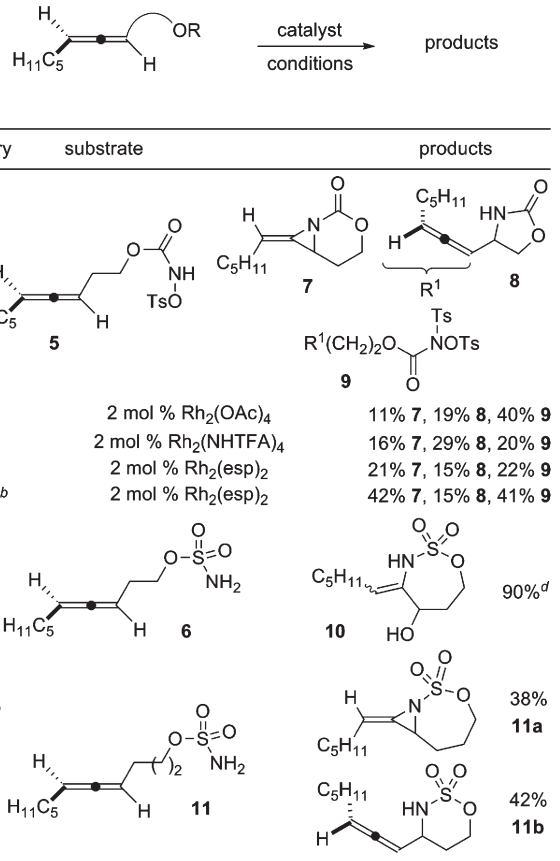
nitrene precursor, catalyst and oxidant identity to improve the efficiency of allene aziridination to synthetically useful levels and reasonable stereoselectivities.

Attempts to utilize *N*-tosyloxycarbamates as nitrene precursors were met with limited success for the synthesis of **7** (Table 1, entries 1−4), similar to previously reported results.[3a] The competitive formation of C−H amination product **8** was a recurring issue, as well as unproductive

Table 1. *N*-Tosyloxycarbamate and Sulfamate Precursors



[a] K_2CO_3, 0.1 M in acetone. [b] Substrate was added over 2 h, and the acetone was dried over 4 A MS. [c] 2.0 equiv of PhIO, 4 A MS, CH_2Cl_2, rt. [d] Products of hydrolysis of **10** were also observed. [e] 2.0 equiv of PhI(OAc)$_2$, MgO, CH_2Cl_2, 40 °C.

tosylation of **5** with another molecule of itself to yield **9**.[5] The use of sulfamate **6** was successful and gave no competing C−H amination, but ring-opening of the labile MA to **10** (entry 5) was problematic. Increasing the tether length between the allene and the sulfamate to three carbons (**11**, entry 6) completely suppressed ring-opening of the desired **11a** but also gave significant amounts of the C−H amination product **11b**.

For the purposes of isolating the target MAs, we found that carbamates provided the best balance between the reactivity of the nitrene precursor and the subsequent stability and reactivity of the product.[6] A series of allenic carbamates were subjected to various reaction conditions as illustrated in Table 2. We found that the $Rh_2(OAc)_4$ and $Rh_2(oct)_4$ (oct = $O_2CC_7H_{15}$) catalysts previously used in this type of chemistry did not perform well in our hands.[3a,b] Rh_2esp_2 (esp = α,α,α′,α′-tetramethyl-1,3-benzenedipropionate) and $Rh_2(TPA)_4$ (TPA = triphenyl acetate) proved to be more effective catalysts, giving complete conversion of the carbamate in most cases. The choice of oxidant was also crucial, as the leaving group released from the PhI(OAc)$_2$ or PhI(OPiv)$_2$ oxidants can ring-open sensitive MAs to yield the corresponding enecarbamates. For example (Table 2, entry 1), the *Z* isomer of MA **12a** was susceptible to ring-opening by pivalate to give **12b** in addition to the desired **12a**. Placing a methyl group at the carbon α to the allene (entry 2) suppressed ring-opening to give an 87% yield of MA **13a** as a 2.4:1 mixture of *E*/*Z* isomers at the olefin, with the methyl group and the aziridine proton maintaining a *trans* relationship in both alkene stereoisomers as observed by ^{1}H NMR. The use of PhIO in the presence of 4 Å molecular sieves minimized the MA ring-opening and was the oxidant of choice for most of the reactions in Table 2.

Competing C−H amination can occur when the tether between the allene and the carbamate is two or more carbons. As illustrated in entry 3, the nature of the catalyst and oxidant influenced the aziridination vs C−H amination ratio and the overall yield of the reaction. A Rh_2esp_2 catalyst with PhI(OAc)$_2$ (condition A) gave good conversion to a mixture of **14a** and **14b**, but with no selectivity for azirdination over C−H amination. Changing the oxidant to PhI(OPiv)$_2$ (condition B) improved the *E*/*Z* ratio of the MA product from 1.5:1 to 4.1:1 but did not increase the ratio of **14a**:**14b**. Switching the oxidant to PhIO (condition C) increased the ratio of **14a**:**14b** to 4:1, with a 66% yield of the MA. Finally, changing the catalyst to $Rh_2(TPA)_4$ resulted in a 5.3:1 ratio of **14a**:**14b**, with an 80% yield of the desired MA **14a** (condition D). Changing the side chain on the allene in combination with the use of $Rh_2(TPA)_4$ as the catalyst gave only the isolated *E* isomer (entries 4 and 6), but C−H amination was competitive. Placement of alkyl groups at positions α or β to the allene resulted in increased amounts of C−H amination products (entries 7−9), although the use of $Rh_2(TPA)_4$ did improve the aziridination/C−H amination ratio to some extent. Finally, shutting down the possibility of C−H amination (entry 10) gave an excellent 94% yield of the desired MA **21a**.

The *E*/*Z* ratios of the MAs in Table 2 also deserve comment. NOESY 1D studies suggest that the *E* olefin geometry is present in the major product (see the Supporting Information for further details). Indirect evidence that interactions between the nitrenoid intermediate and the alkyl chain play a role in determining the *E*/*Z* ratio is suggested by entry 3 in Table 2. The more sterically demanding $Rh_2(TPA)_4$ complex increased the *E*/*Z* ratio from 1.5:1 to around 4:1. Further studies are underway to increase the

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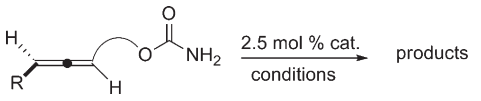
(6) (a) Padwa, A.; Flick, A. C.; Leverett, C. A.; Stengel, T. *J. Org. Chem.* **2004**, *69*, 6377. (b) Lebel, H.; Huard, K.; Lectard, S *J. Am. Chem. Soc.* **2005**, *127*, 14198. (c) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (d) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (e) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

Table 2. Carbamate Precursors for Allene Aziridination



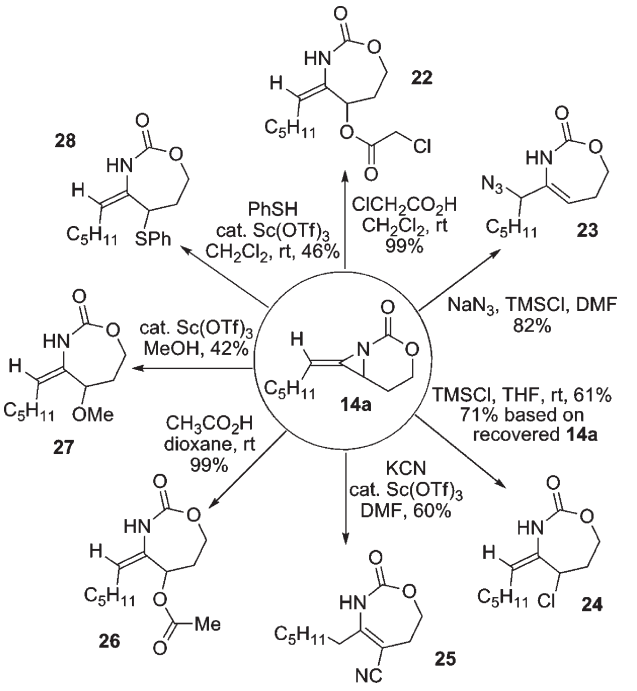
entry	conditions[a]	products
1	B: 67%[b] (39%) **12a** *E*:*Z* > 9:1 29%[b] (17%) **12b** *Z*:*E* > 9:1	**12a**, **12b**
2	B: 87% **13a** *E*:*Z* 2.4:1	**13a**
3	**14a** / **14b** A: 46% *E*:*Z* 1.5:1 / 44% B: 42% *E*:*Z* 4.1:1 / 45% C: 66% *E*:*Z* 3:1 / 16% D: 80% *E*:*Z* 4:1 / 15%	**14a**, **14b**
4	D: 46%[c] **15a** *E* only 21% **15b**	**15a**, **15b**
5	C: 49% **16a** *E*:*Z* 1:1 17% **16b**	**16a**, **16b**
6	D: 45%[c] **17a** *E* only 23% **17b**	**17a**, **17b**
7	D: 48% **18a** (*E*:*Z* 1.5:1) 31% **18b** (*dr* 2:1)	**18a**, **18b**
8	B: 10% **19a** *E*:*Z* 2.8:1 72% **19b** D: 5% **19a** *E*:*Z* 1.9:1 84% **19b**	**19a**, **19b**
9	B: 21% **20a** *E*:*Z* 3:1 57% **20b** D: 44% **20a** *E*:*Z* 2.6:1 48% **20b**	**20a** (*dr* > 95:5), **20b**
10	B: 94% **21a** *E*:*Z* 3:1	**21a**

[a]A: $Rh_2(esp)_2$, 2.0 equiv $PhI(OAc)_2$, 2.6 equiv MgO, CH_2Cl_2, 35 °C
B: $Rh_2(esp)_2$, 2.0 equiv $PhI(OPiv)_2$, 2.6 equiv MgO, CH_2Cl_2, 35 °C
C: $Rh_2(esp)_2$, 2.0 equiv PhIO, 4 A MS, CH_2Cl_2, rt
D: $Rh_2(TPA)_4$, 2.0 equiv PhIO, 4 A MS, CH_2Cl_2, rt
[b]Based on recovered starting material. [c]None of the *Z* was isolated.

bulk of the Rh ligands to improve the stereoselectivity of the aziridination.

The reactions in Table 2 represent the first reliable methods to access bicyclic MAs bearing electron-withdrawing groups on the aziridine nitrogen. The next step was to determine what types of nucleophiles would yield the necessary enecarbamate (Scheme 1, **3**) intermediate via aziridine ring-opening. We expected the additional ring strain present in **14a** might allow for milder conditions than would typically be expected for aziridine ring-opening (Scheme 2).[7] Indeed, carboxylic acid nucleophiles gave the

Scheme 2. Nucleophilic Ring-Opening of Bicyclic MAs

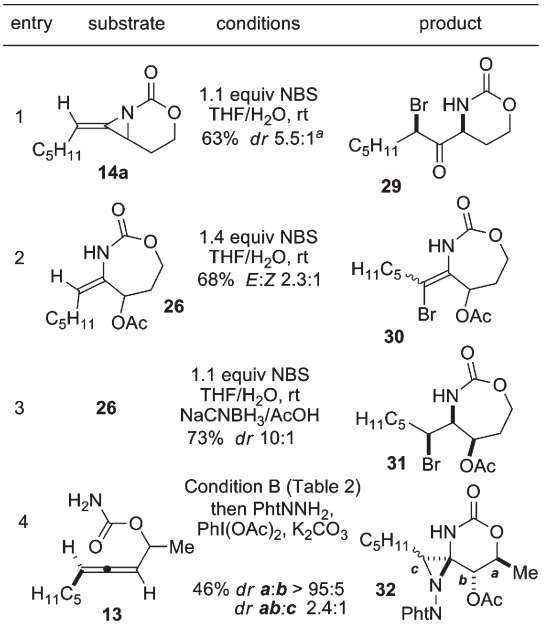


enecarbamates **22** and **26** in excellent yields, while the use of TMSCl at rt gave **24** in good yield. We hypothesized that since MA ring-opening using carboxylic acids as nucleophiles was so facile, Lewis acids might also activate the aziridine toward ring-opening with neutral nucleophiles. Indeed, the use of $Sc(OTf)_3$ as a mild Lewis acid in the presence of methanol and thiophenol promoted the ring-opening of **14a** to give **27** and **28** in modest yields. No reaction occurred in the absence of the Lewis acid. Reaction with a cyanide nucleophile was also improved in the presence of a Lewis acid, although the double bond migrated to give an isomeric enecarbamate **25**. Finally, treatment of **14a** with NaN_3/TMSCl generated **23** in 82% yield, likely via initial ring-opening of the MA, followed by a [3,3]-sigmatropic rearrangement.[8]

Based on the results in Scheme 2, we felt that carboxylic acids were the most promising nucleophiles to pursue for further studies. As illustrated in entry 1 of Scheme 3, eliminating the ring-opening step and simply treating the MA **14a** with NBS in a mixture of THF/H_2O gave **29** with an initial dr of 5.5:1. Not surprisingly, the α-bromo ketone epimerized slowly over time to give a 1.1:1 mixture of

(7) Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.
(8) (a) Feldman, A. K.; Colasson, B.; Sharpless, K. B.; Fokin, V. V. *J. Am. Chem. Soc.* **2005**, *127*, 13444. (b) VanderWerf, C. A.; Heasley, V. L. *J. Org. Chem.* **1966**, *31*, 3534.

Table 3. Formation of Three Contiguous Carbon–Heteroatom Bonds from Allenes via Bicyclic Methyleneaziridines



[a] Compound epimerized to a 1.1:1 mixture upon standing.

diastereomers. Loss of stereochemical integrity was also noted when **26** was subjected to similar conditions, giving the tetrasubstituted bromoalkene **30** as a 2.3:1 mixture of *E*/*Z* isomers (entry 2). We postulated that isomerization of an intermediate imine was leading to the brominated olefin. This prompted us to add $NaCNBH_3$ as a reductant to the reaction mixture, whereupon **31** was obtained in 73% yield with a dr of 10:1 (see the Supporting Information for details and a proposed stereochemical model). It is possible that anchimeric assistance from the acetate group of the enecarbamate is playing a role in controlling the stereochemical outcome of the reaction. This result, coupled with the ease of ring-opening MAs with acids, is an exciting step toward flexible, stereoselective methods for allene functionalization. The power of allene aziridination to generate multiple carbon-heteroatom bonds in a single pot was further demonstrated by a tandem aziridination/ring-opening of the allene **13** to **32** (entry 4). The substrate was treated under condition B (Table 2) to form the intermediate MA. *N*-aminophthalimide and additional oxidant were then added to the same pot to yield the unusual spiroaminal **32** in 46% yield, where four new carbon–heteroatom bonds have been formed in a single pot. The stereochemistry between the Me and OAc groups at ***a*** and ***b*** was exclusively *trans* by ^{1}H NMR (see Supporting Information for further details). The 2.4:1 *E*/*Z* ratio of the MA olefin isomers (see **13a**, Table 2, entry 2) appears to have been translated from the intermediate MA into a 2.4:1 dr in the final product **32**. This result suggests that better control of the *E*/*Z* stereochemistry in the MA formation will translate into excellent dr in the spiroaminal products.

In conclusion, we have described a synthetically viable approach toward bicyclic MAs activated by electron-withdrawing groups. The potential of these MAs as scaffolds for the construction of motifs bearing three contiguous heteroatom-bearing carbons has been demonstrated. Future work is directed toward expansion of the substrate scope, particularly in the use of different nitrene precursors to minimize competing C–H amination. The asymmetric syntheses of MAs from enantioenriched allenes[9] and their subsequent reactivity will be further explored. The scope of nucleophiles and electrophiles for efficient and flexible multicomponent reactions that install multiple carbon–heteroatom bonds into a simple allene precursor will be expanded.

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

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