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Rhodium Catalyzed Allene Amination: Diastereoselective Synthesis of Aminocyclopropanes via a 2-Amidoallylcation Intermediate

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Our recent investigations into metallonitrene initiated cascade reaction processes lead us to postulate that an electrophilic metallonitrene could interact with an allene to generate an intermediate with a reactivity resembling that of a 2-amidoallylcation (Figure 1).

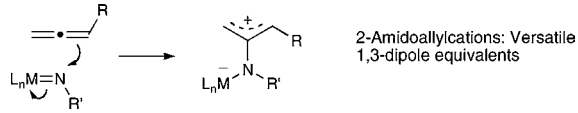


Figure 1. Allene amidation with electrophilic metallonitrenes: a general approach to 2-amidoallylcations.

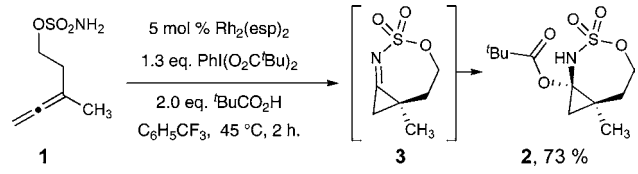
Historically, related trimethylenemethane and 2-oxyallylcation species have proven particularly useful for the construction of complex carbo- and heterocyclic molecules.[1] New methods to generate and control these powerful synthons remain the focus of many contemporary research groups.[2] Additionally allene epoxidation has been developed into a useful tool for complex molecule synthesis,[3] and these studies provide insight into possible reaction pathways. However, despite the prevalence of nitrogen functionality in pharmaceutically important molecules, conceptually related 2-amidoallylcations have received considerably less attention. Although these systems can be generated by halide abstraction from α-chloroimines and α-chloroenamines with stoichiometric silver(I) salts, starting material instability and generally low reaction efficiencies have hampered further development.[4] In an important advance, the Shipman group has recently demonstrated that strained methyleneaziridines can be activated with Lewis acids (typically 150 mol % $BF_3{\cdot}OEt_2$) to participate in efficient intramolecular [4+3] cycloadditions with tethered dienes.[5] Despite this important discovery, a general method for 2-amidoallylcation synthesis and subsequent exploration of 2-amidoallylcation reactivity have yet to be disclosed.

In this communication we report the successful implementation of an allene amination strategy and outline the utility of this approach for the synthesis of highly substituted aminocyclopropanes.[6] Additionally, we provide examples of the metallonitrene/allene cascade reactions terminated by either [3+2] or [3+3] cycloaddition processes, highlighting the versatility of this new methodology.

Sulfamate esters have been established as convenient and versatile precursors to reactive metallonitrenes.[7] Their propensity to form seven-membered rings in intramolecular reactions with alkynes led us to adopt homoallenylsulfamate ester **1** for our exploratory work (Scheme 1).[8] A brief optimization study surveying dirhodium(II) tetracarboxylate catalysts, hypervalent iodine oxidants, and various solvents identified Du Bois' $Rh_2(esp)_2$,[9] $PhI(O_2C^tBu)_2$, and trifluorotoluene as particularly effective for this reaction.

Under these conditions the reaction of sulfamate ester **1** gave *N*-sulfamoyl-*O*-pivaloylcyclopropylaminol **2** in 73% yield (93:7 d.r.).[10] Although no direct evidence of an intermediate *N*-sulfamoylmethyleneaziridine was observed, we cannot rule out the possibility that such a species is present on the reaction pathway. Oxidative rearrangement of the allene leads to the formation of strained cyclopropylimine **3** that is subsequently trapped by the pivalic acid present in the reaction mixture.

Scheme 1. Intramolecular Allene Amidation Results in Rearrangement Generating *N*-Sulfamoyl-*O*-pivaloylcyclopropylaminol **2**



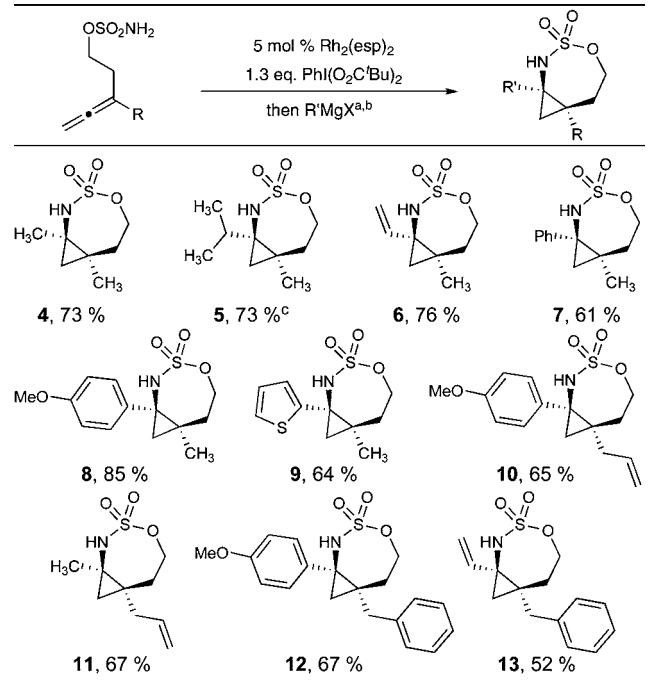


Figure 2. Metallonitrene initiated oxidative rearrangement of allenes provides highly substituted aminocyclopropanes. [a]Grignard reagents were either commercially available or prepared by insertion using Knochel's method (see Supporting Information).[11] [b]Products were obtained as single isomers unless otherwise noted. [c]93:7 d.r.

Further investigation revealed that this oxidative rearrangement is general for a variety of 1,1-disubstituted allenes and that the respective intermediate cyclopropylimines can be intercepted with a range of Grignard reagents to provide highly substituted aminocyclopropanes with excellent diastereoselectivity (Figure 2).

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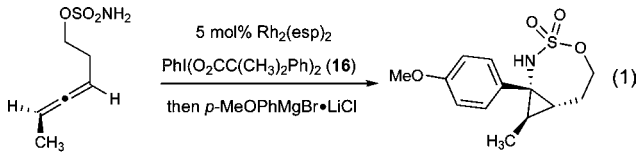
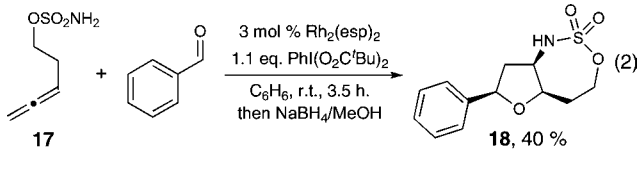
In all cases the nucleophile is observed to approach the cyclopropylimine predictably from the convex face of the bicyclic system. Alkyl, vinyl, aryl, and heteroaryl substituents were all introduced efficiently (**4**−**9**). With respect to allene substitution, moderately sized substituents (Me, allyl, and benzyl) were all tolerated (**8**−**13**). However, increases in steric bulk (e.g., ^{i}Pr, phenyl) suppressed the amination reaction.

Having established the basic reactivity of a sulfamate ester derived metallonitrene with a tethered allene, we investigated the possibility of chirality transfer from an enantioenriched allene to generate an enantioenriched aminocyclopropane. Thus, 1,3-disubstituted allene **14** (96% e.e.) was subjected to the standard reaction conditions, and upon quenching with *para*-methoxyphenylmagnesium bromide the enantioenriched tetrasubstituted aminocyclopropane **15** was isolated (56%, 74% e.e.). By employing alternative oxidant **16**, the racemization could be somewhat suppressed and the product was obtained in 53% yield and 82% e.e. as a single diastereomer (eq 1).[10,12]

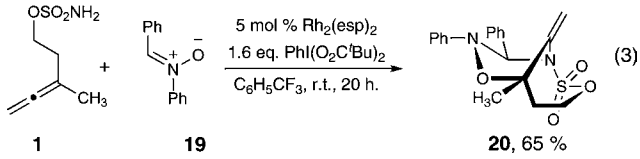


14, 96 % e.e. **15**, 53 %, 82 % e.e.

To probe the versatility of the 2-amidoallylcation intermediate with respect to alternative transformations, sulfamate ester **17** was subjected to standard oxidative conditions in the presence of catalytic $Rh_2(esp)_2$ and benzaldehyde as a dipolarophile. After reductive workup with sodium borohydride, trisubstituted tetrahydrofuran **18** was isolated in 40% yield as a single regio- and diastereoisomer (eq 2).[10] The 2,5-*cis*-stereochemistry observed in tetrahydrofuran **18** is consistent with an *endo* approach of the aldehyde to the 2-amidoallylcation.



17 **18**, 40 %



1 **19** **20**, 65 %

Additionally, we investigated the [3+3] cycloaddition of the postulated 2-amidoallylcation with nitrone **19** (eq 3). To our surprise, the cycloaddition proceeded with complementary regioselectivity to the [3+2] benzaldehyde cycloaddition. The nitrone was observed to add across the nitrogen and the most substituted carbon of the intermediate 2-amidoallylcation to give the bicyclic aminal **20**.[10] In this case, the observed stereochemistry suggests that steric interactions dominate the transition state, with the carbon substituent of the nitrone oriented away from the bulky sulfamate ester of the 2-amidoallylcation. Studies to elucidate the origin of the regiochemical dichotomy in these two reactions are ongoing in our laboratory.

The sulfamate ester tether, which is important both for the positioning of the rhodium nitrene with respect to the allene and for imparting appropriate electrophilicity on the reactive nitrene, is a versatile functional handle, easily displaced by a variety of nucleophiles upon activation by *N*-acylation.[7,13]

In conclusion, we have demonstrated that the intramolecular interaction of a sulfamate ester derived metallonitrene with an allene generates a versatile intermediate with 2-amidoallylcation-like reactivity, capable of rearranging to give highly substituted iminocyclopropanes or acting as a novel dipolar species engaging external dipolarophiles. Studies to understand and exploit the reactivity of this intermediate remain a focus of our laboratory.

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

References

(1) (a) Trost, B. M. *Angew. Chem.* **1986**, *98*, 1. (b) Harmata, M. *Adv. Cycloaddit.* **1997**, *4*, 41. (c) Harmata, M. *Tetrahedron* **1997**, *53*, 6235. (d) Nakamura, E.; Yamago, S. *Acc. Chem. Res.* **2002**, *35*, 867. (e) Yamago, S.; Nakamura, E. *Org. React.* **2002**, *61*, 1. (f) Hoffmann, H. M. R. *Angew. Chem.* **1984**, *96*, 29.

(2) (a) Xiong, H.; Hsung, R. P.; Berry, C. R.; Rameshkumar, C. *J. Am. Chem. Soc.* **2001**, *123*, 7174. (b) Xiong, H.; Huang, J.; Ghosh, S. K.; Hsung, R. P. *J. Am. Chem. Soc.* **2003**, *125*, 12694. (c) Huang, J.; Hsung, R. P. *J. Am. Chem. Soc.* **2005**, *127*, 50. (d) Wei, L.-L.; Xiong, H.; Hsung, R. P. *Acc. Chem. Res.* **2003**, *36*, 773. (e) Harmata, M. *Adv. Synth. Catal.* **2006**, *348*, 2297. (f) Harmata, M.; Huang, C.; Rooshenas, P.; Schreiner, P. R. *Angew. Chem., Int. Ed.* **2008**, *47*, 8696. (g) Chung, W. K.; Lam, S. K.; Lo, B.; Liu, L. L.; Wong, W.-T.; Chiu, P. *J. Am. Chem. Soc.* **2009**, *131*, 4556. (h) Lee, J. C.; Cha, J. K. *J. Am. Chem. Soc.* **2001**, *123*, 3243. (i) Cho, S. Y.; Lee, H. I.; Cha, J. K. *Org. Lett.* **2001**, *3*, 2891.

(3) (a) Crandall, J. K.; Batal, D. J.; Lin, F.; Reix, T.; Nadol, G. S.; Ng, R. A. *Tetrahedron* **1992**, *48*, 1427. (b) Crandall, J. K.; Rambo, E. *Tetrahedron Lett.* **1994**, *35*, 1489. (c) Crandall, J. K.; Reix, T. *Tetrahedron Lett.* **1994**, *35*, 2513. (d) Crandall, J. K.; Rambo, E. *Tetrahedron* **2002**, *58*, 7027. (e) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. (f) Lotesta, S. D.; Kiren, S.; Sauers, R. R.; Williams, L. J. *Angew. Chem., Int. Ed.* **2007**, *46*, 7108.

(4) (a) Kende, A. S.; Huang, H. *Tetrahedron Lett.* **1997**, *38*, 3353. (b) Jin, S.-J.; Choi, J.-R.; Oh, J.; Lee, D.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 10914. (c) Oh, J.; Lee, J.; Jin, S.-J.; Cha, J. K. *Tetrahedron Lett.* **1994**, *35*, 3449.

(5) Prie, G.; Prevost, N.; Twin, H.; Fernandes, S. A.; Hayes, J. F.; Shipman, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 6517.

(6) For lead references on the importance of aminocyclopropanes in biologically active natural products and drugs, see: (a) Gnad, F.; Reiser, O. *Chem. Rev.* **2003**, *103*, 1603. (b) Burgess, K.-H.; Ho, K.-K; Moye-Sherman, D. *Synlett* **1994**, 575. (c) Salaün, J. *Top. Curr. Chem.* **2000**, *207*, 1. (d) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014.

(7) Espino, C. G.; Wehn, P. M.; Chow, J.; Du Bois, J. *J. Am. Chem. Soc.* **2001**, *123*, 6935.

(8) (a) Thornton, A. R.; Blakey, S. B. *J. Am. Chem. Soc.* **2008**, *130*, 5020. (b) Thornton, A. R.; Martin, V. I.; Blakey, S. B. *J. Am. Chem. Soc.* **2009**, *131*, 2434.

(9) Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378.

(10) Stereochemistry determined by X-ray crystallography. See Supporting Information for details.

(11) Piller, F. M.; Appukkuttan, P.; Gavryushin, A.; Helm, M.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 6802.

(12) Complete details of the solvents and oxidants investigated are included in the Supporting Information.

(13) (a) Du Bois, J. *Chemtracts-Org. Chem.* **2005**, *18*, 1. (b) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 4909.

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