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Synthesis and Reactivity of Unique Heterocyclic Structures en Route to Substituted Diamines

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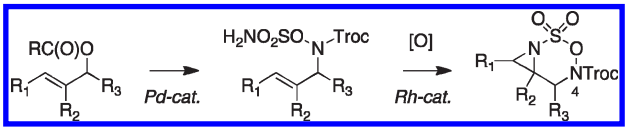
ABSTRACT



Rhodium-catalyzed oxidative cyclization of allylic hydroxylamine-derived sulfamate esters furnishes a novel family of bicyclic aziridines that serve as functional precursors to substituted diamines. Investigations with the N4-Troc form of these heterocycles have led to manifold improvements in reaction performance and scope and have revealed unique differences in the stability and reactivity of such compounds dictated by the choice of N4-protecting group.

The rapid assembly of aza-heterocycles from sulfamate derivatives is made possible through selective C−H and π-bond amination methods.[1] Our laboratories have recently reported that two catalytic processes, Pd π-allyl coupling and Rh-catalyzed alkene aziridination, may be used in sequence to generate a previously unknown class of strained heterobicyclic products.[2] While the potential to synthesize differentially substituted 1,2- and 1,3-diamines[3−6] from these unique oxathiadiazinane derivatives was evident, little was known about the factors that govern their stability and reactivity. Herein, we detail new protocols to prepare highly substituted forms of these heterocycles, and highlight for the first time the unusual stability and utility of Troc-protected oxathiadiazinanes for 1,2-diamine synthesis (Figure 1).

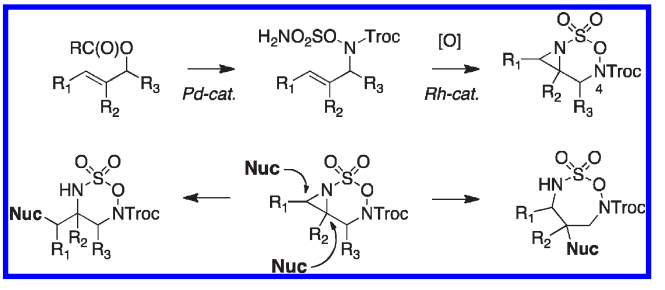


Figure 1. Novel heterocyclic substrates as precursors to substituted diamines.

(1) For general discussions on C−H and π-bond amination, see: (a) Zalatan, D. N.; Du Bois, J. *Top. Curr. Chem.* **2010**, *292*, 347–378. (b) Li, Z.; Capretto, D. A.; He, C. *Silver in Organic Chemistry*; John Wiley & Sons: New York, 2010; pp 167−182. (c) Collet, F.; Dodd, R. H.; Dauban, P. *Chem. Commun.* **2009**, 5061–5074. (d) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417–424.

(2) Trost, B. M.; Malhotra, S.; Olson, D. E.; Maruniak, A.; Du Bois, J. *J. Am. Chem. Soc.* **2009**, *131*, 4190–4191.

(3) For general applications of diamines, see: (a) Kizirian, J.-C. *Chem. Rev.* **2008**, *108*, 140–205. (b) Kotti, S. R. S. S.; Timmons, C.; Li, G. *Chem. Biol. Drug Des.* **2006**, *67*, 101–114. (c) de Parrodi, C. A.; Juaristi, E. *Synlett* **2006**, *17*, 2699–2715.

(4) For reviews on the synthesis of 1,2-diamines, see: (a) Cardona, F.; Goti, A. *Nature Chem.* **2009**, *1*, 269–275. (d) de Figueiredo, R. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 1190–1193. (b) Mortensen, M. S.; O'Doherty, G. A. *Chemtracts: Org. Chem.* **2005**, *18*, 555–561. (c) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627and references therein.

(5) For examples of polyamine-derived natural products, see: Busscher, G. F.; Rutjes, F. P. J. T.; van Delft, F. L. *Chem. Rev.* **2005**, *105*, 775–791.

(6) Differential diamine protection is possible using the diamination method of Shi; see: Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762–763. For the synthesis of differentially protected 1,2-diamines through Rh-catalyzed C−H amination, see: Olson, D. E.; Du Bois, J. *J. Am. Chem. Soc.* **2008**, *130*, 11248–11249.

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Our initial studies described the synthesis and reactivity of aziridine-fused *N*-Mbs-[1,2,3,6]oxathiadiazinane-2, 2-dioxide heterocycles, which were found, in select cases, to undergo nucleophilic ring-opening with modest efficiency (Figure 2a).[7−9] Studies to further optimize these addition reactions and to determine the origin of material loss led us to conclude that aziridine displacement occurred with little regiocontrol. The intermediate generated from nucleophilic attack at C7 was, however, unstable to the reaction conditions and decomposed to liberate $MbsNH_2$. A series of control experiments using oxathiadiazinane **2**[10] demonstrated that base additives (e.g., $KN(SiMe_3)_2$, pyridine, or NaH) would promote rapid ring fragmentation (Figure 2b). The unusual and unprecedented reactivity of the *N*-Mbs oxathiadiazinane heterocycle has no obvious explanation. We speculated that replacing the N4-Mbs group with an acyl substituent might mitigate the decomposition of these heterocycles by influencing the ring conformation. Such an alteration would present new challenges for substrate synthesis and would likely affect the oxidative cyclization reaction; however, the ease of removing the N4-acyl group as compared to the Mbs- would be advantageous for the overall utility of the method. Accordingly, N-Boc and N-Troc substrates were targeted with these considerations in mind.

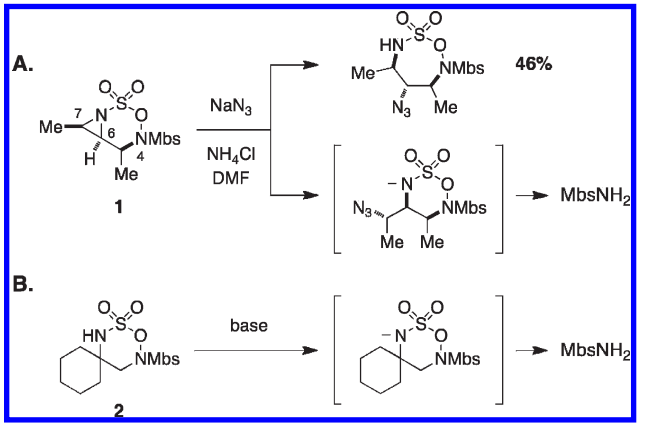


Figure 2. Unusual base-promoted decomposition of Mbs-substituted oxathiadiazinanes. Mbs = *p*-methoxybenzenesulfonyl.

Synthesis of $TrocNHOSO_2NH_2$ **3** and $BocNHOSO_2NH_2$ **4** is easily accomplished in two steps from hydroxylamine. Both reagents are crystalline and can be prepared on > 10 g scale without recourse to chromatography. These sulfamate derivatives engage in either Mitsunobu or asymmetric π-allyl Pd-coupling reactions with alcohol or carbonate starting materials, respectively. The Troc-reagent **3**, in particular, operates with superior performance in both types of displacement reactions when compared to either **4** or the Mbs-variant. As shown in Figure 3, Pd-catalyzed π-allylation of **3** using carbonate **7** gives the α, α-disubstituted sulfamate in high yield and with excellent regiocontrol (> 20:1 branched/linear product). The analogous reaction utilizing **4** proceeds in modest yield while the same reaction, when performed with $MbsNHOSO_2NH_2$, fails to give any allylated product. In light of these findings, most of our subsequent investigations have been conducted with the *N*-Troc sulfamate reagent **4**. The identification of this sulfamate derivative should markedly facilitate access to a range of substituted oxathiadiazinane heterocycles and thus 1,2- and 1,3-diamine products.

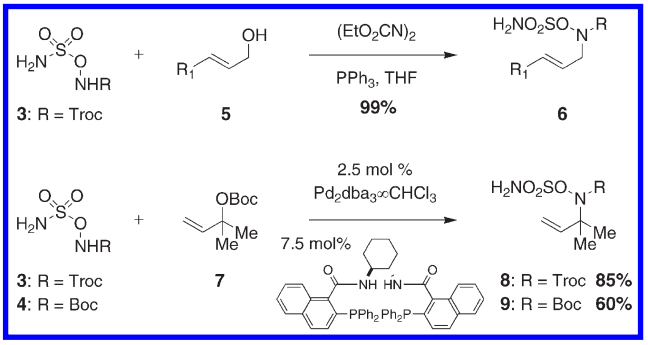


Figure 3. *N*-Carbamoyl sulfamate reagents perform optimally in allylation reactions.

Intramolecular aziridination reactions with both Boc- and Troc-derived sulfamates are highlighted in Table 1. In general, cyclizations performed optimally using a dinuclear tetracarboxylate rhodium catalyst (2 mol %), PhI(OAc)$_2$, and MgO.[11] Oxidations occur smoothly in isopropyl acetate, which proves more effective as a solvent than others typically employed for Rh-catalyzed amination (e.g., CH_2Cl_2, benzene).[12] Olefinic substitution does not have a large influence on the reaction as terminal (entries 1 and 2), disubstituted (entries 3 and 4), and trisubstituted (entry 5) alkenes are all converted in high yields to the corresponding bicyclic aziridines. While product yields of *N*-Boc substrates were slightly depressed, those of *N*-Troc substrates were excellent and comparable to the performance of analogous *N*-Mbs substrates.[2,6]

(7) We refer to these heterocycles as oxathiadiazinanes for simplicity.

(8) Prior to our work, we are only aware of one report of these heterocycles; see: Arfaei, A.; Smith, S. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1791–1794.

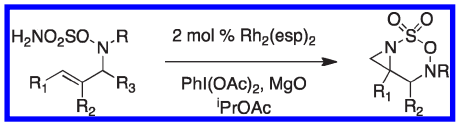
(9) For the synthesis and reactivity of related aziridine-fused oxathiazinanes, see: (a) Wehn, P. M.; Du Bois, J. *Angew. Chem.* **2009**, *121*, 3860–3863. (b) Guthikonda, K.; Wehn, P. M.; Caliando, B. J.; Du Bois, J. *Tetrahedron* **2006**, *62*, 11331–11342. (c) Wehn, P. M.; Lee, J.; Du Bois, J. *Org. Lett.* **2003**, *5*, 4823–4826. (d) Duran, F.; Leman, L.; Ghini, A.; Burton, G.; Dauban, P.; Dodd, R. H. *Org. Lett.* **2002**, *4*, 2481–2483.

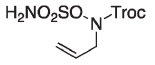
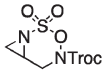
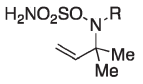
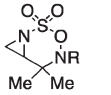
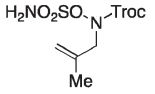
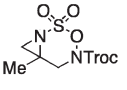
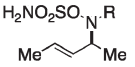
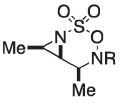
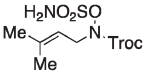
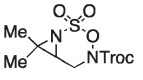
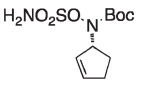
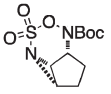
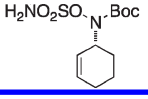
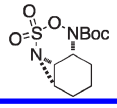
(10) Compound **2** was prepared using Rh-catalyzed C−H amination; see ref 6.

(11) $Rh_2(esp)_2$ is sold by Aldrich Chemical Co. as $Rh_2(\alpha,\alpha,\alpha',\alpha'$-tetramethyl-1,3-benzenedipropionate$)_2$. For the initial report of this catalyst, see: Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. *J. Am. Chem. Soc.* **2004**, *126*, 15378–15379.

(12) The use of *i*-PrOAc was prompted by a previous report describing aldehyde C−H sulfamidation; see: Chan, J.; Baucom, K. D.; Murry, J. A. *J. Am. Chem. Soc.* **2007**, *129*, 14106–14107.

Table 1. Rh-Catalyzed Intramolecular Aziridination



entry[a]	substrate[b]	product		yield	
1				64[c]	
2			R = Troc R = Boc	98 78	
3				94	
4[d]			R = Troc R = Boc R = Mbs	86 82 93	3:1 dr 3:1 dr 13:1 dr
5				82	
6				65	
7				51	

[a] Reactions conducted in ^{i}PrOAc using 2 mol % of $Rh_2(esp)_2$, 2.3 equiv of MgO, and 1.1 equiv of $PhI(OAc)_2$. [b] Substrates were prepared using either Mitsunobu or π-allyl Pd chemistry in yields ranging from 60–99%. See the Supporting Information for details. [c] Isolated yield of this aziridine was reduced due to difficulties associated with its purification. See the Supporting Information for details. [d] Product diastereomeric ratios determined by 1H NMR integration.

As noted in Table 1, modest to high levels of product diastereocontrol are observed for acyclic and cyclic alkene starting materials, respectively (entries 4, 6, and 7). For acyclic structures (entry 4), stereoselectivity is clearly influenced by the choice of the N4-substituent group. The sense of induction in these products may be rationalized through a chairlike transition state model (Figure 4). Introduction of a destabilizing $A^{1,3}$-type interaction in both the *N*-Boc and *N*-Troc sulfamate derivatives could account for the reduced degree of product stereocontrol in comparison to the *N*-sulfonyl compound.[13] With cyclic olefins, cis-fused tricyclic structures are formed exclusively regardless of the N-blocking group.[2]

Oxathiadiazinane-derived aziridines undergo facile ring-opening with a range of nucleophiles. In agreement with

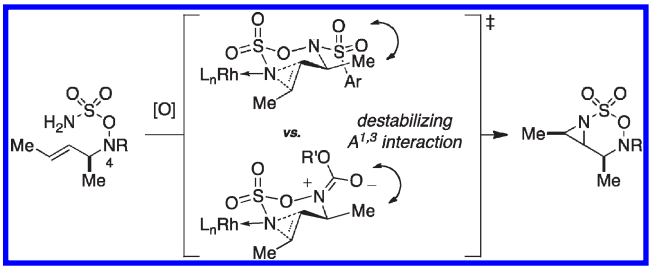


Figure 4. Diastereoselectivity in aziridination reactions influenced by nitrogen protecting group (R = Troc, Boc, or Mbs; R′ = CH_2CCl_3 or ^{t}Bu).

our earlier observation, tricyclic structures like the one depicted in entry 7 (Table 1) react to form bridged 7-membered ring products. One of these derivatives, **11**, has been crystallographically characterized (Figure 5).[14] Interestingly, the cyclohexane unit in **11** adopts an almost perfect chair-like configuration despite having all three substituent groups positioned axially. The preferential formation of **11** over the corresponding fused-bicyclic [4.4.0] isomer is likely the result of stereoelectronic factors, which favor a *trans*-diaxial transition structure for ring-opening. The predilection for the aziridine derived from **10** and related tricyclic aziridines to ring open in this manner appears to be invariant of the choice of N-substituent group (i.e., acyl or sulfonyl).

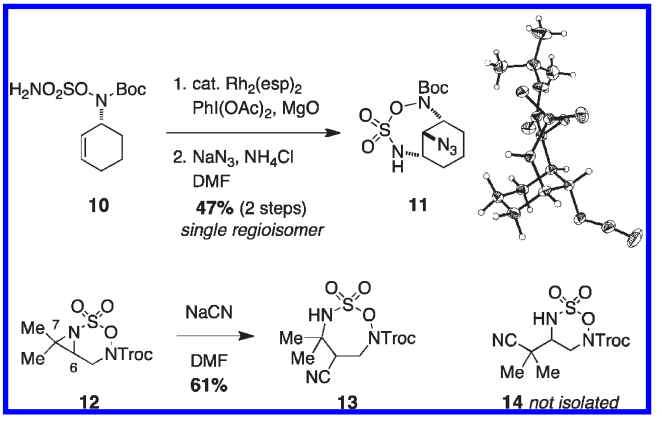


Figure 5. Regioselective aziridine ring-opening favors seven-membered ring projects.

We have found that bicyclic aziridines, like their tricyclic counterparts, share a similar tendency for nucleophilic ring-opening to afford 7-membered ring heterocycles; however, optimal selectivity is only achieved when steric factors reinforce this preference (Figure 5).[15] Furthermore, judicious placement of substitutent groups can in select cases bias attack toward C7. As shown in Figure 6,

(13) A similar rationale was put forth to explain diastereoselectivity in analogous reactions involving sulfamides; see: Kurokawa, T.; Kim, M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 2777–2779.

(14) Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre (CCDC 809399).

nucleophilic displacement reactions with **15** afford the corresponding six-membered oxathiadiazinanes as the exclusive products. These *N*-Troc-substituted oxathiadiazinanes are stable to chromatography and are isolable, a finding that stands in stark contrast to the marked instability of analogous *N*-Mbs oxathiadiazinane derivatives (see Figure 2). As shown in eq 1, the *N*-Troc heterocycles serve as precursors to highly functionalized, differentially protected 1,2-diamines. While the assembly of structures of this type using traditional methods for amine synthesis would generally require multiple transformations, such products are now easily prepared from commercial allylic alcohols using the protocols outlined in this report.

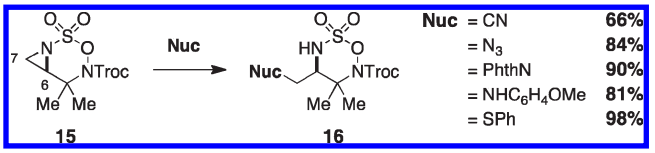
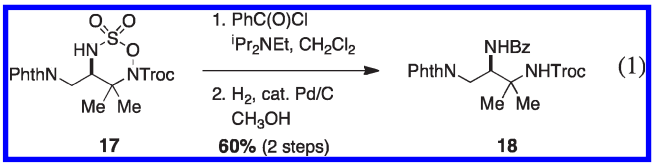


Figure 6. Isolable oxathiadiazinane derivatives through regioselective aziridine displacement.

We speculate that subtle conformational differences between the *N*-Troc **16** (see Figure 6) and *N*-Mbs **2** (see Figure 2) six-membered heterocycles are responsible for the striking difference in stability between these two structurally related species. Although the mechanism by which oxathiadiazinanes such as **2** undergo fragmentation to liberate $MbsNH_2$ is still opaque, the switch from Mbs to a carbamoyl blocking group has resulted in manifold improvements in the overall aziridination process and, perhaps more importantly, has made available a potentially important class of six-membered heterocyclic structures as 1,2-diamine surrogates. These findings have motivated us to examine the use of saturated *N*-Troc hydroxylamine sulfamate esters as substrates for C−H amination.[16]



Rhodium-catalyzed alkene aziridination has given rise to a collection of unprecedented heterocyclic structures that serve as useful precursors to functionalized diamine products. In the course of developing these chemistries, we have identified an unexpected and heretofore unknown fragmentation reaction of *N*-sulfonyl oxathiadiazinanes. This reaction is entirely suppressed by changing the nature of the N-protecting group, a modification that enables for the first time isolation and subsequent reactions of structures such as **16**. Importantly, the necessary *N*-Troc sulfamate starting materials can be synthesized in high yield through two different protocols and perform exceptionally well in intramolecular Rh-catalyzed olefin aziridination. All told, our discoveries should facilitate the use of and greatly expand the application potential of this unique family of oxathiadiazinane heterocycles.

Acknowledgment. This work has been supported by the National Institutes of Health and the National Science Foundation. Partial funding for this work was also provided to J.D.B. by the National Science Foundation Center for Stereoselective C−H Functionalization (CSCHF). D.E.O. and S.M. gratefully acknowledge Eli Lilly and Stanford University, respectively, for fellowship support. Palladium salts were generously supplied by Johnson-Matthey. X-ray crystallographic analysis was performed by Dr. Allen Oliver; diffraction data were recorded on an instrument supported by the National Science Foundation, Major Research Instrumentation (MRI) Program under Grant No. CHE-0521569.

Supporting Information Available. Experimental procedures, characterization data, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Ring opening reactions of bicyclic aziridines such as those featured in Figure 5 are currently limited to azide, cyanide, and thiolate nucleophiles. Reactions performed with oxygen-based nucleophiles (e.g., carboxylates, alkoxides, peroxide) fail to give the desired 7-membered ring product.

(16) Olson, D. E.; Roberts, D. A.; Du Bois, J. Manuscript in preparation.