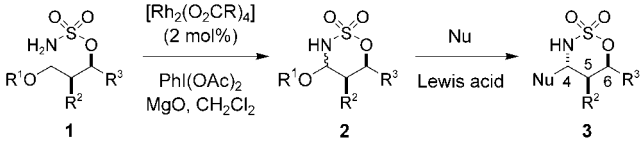
N,O-Acetals

Rh-Catalyzed Amination of Ethereal C^{α}–H Bonds: A Versatile Strategy for the Synthesis of Complex Amines**

*Kristin Williams Fiori, James J. Fleming, and Justin Du Bois**

The recent advancement of highly selective catalytic methods for the amination of C–H bonds has inspired novel approaches to complex natural products.[1] Our efforts to expand this chemistry further have led to the identification of a distinct class of 1,2,3-oxathiazinane-2,2-dioxide heterocycles **2**, made accessible through sulfamate ester **1** insertion into ethereal C^{α}–H centers (Scheme 1).[2,3] Herein, we demonstrate a simple and effective method, which capitalizes on catalyst-controlled regioselective C–H oxidation, for assembling these unique N,O-acetals **2**. Such compounds display exceptional versatility as iminium ion equivalents, coupling smoothly and with high diasteroinduction to allyl silanes, enol ethers, silyl ketene acetals, and, as reported previously, alkynyl zinc reagents.[2] From these studies has evolved a broadly predictive stereochemical model for nucleophilic addition reactions with **2**. In all, the stereoselective assembly of functionalized oxathiazinanes through this efficient two-step sequence opens untapped possibilities for C–H amination in synthesis.[4]



Scheme 1. Oxathiazinane N,O-acetals as iminium ion equivalents.

Metal–carbene and metal–nitrene oxidants display a high proclivity for insertion into ethereal C^{α}–H bonds.[5] In principle, this bias can be exploited to direct site selectivity in amination reactions of substrates that possess multiple reactive C–H centers. Such conjecture is readily tested with sulfamates **4**–**7** (Scheme 2). Each of these compounds can

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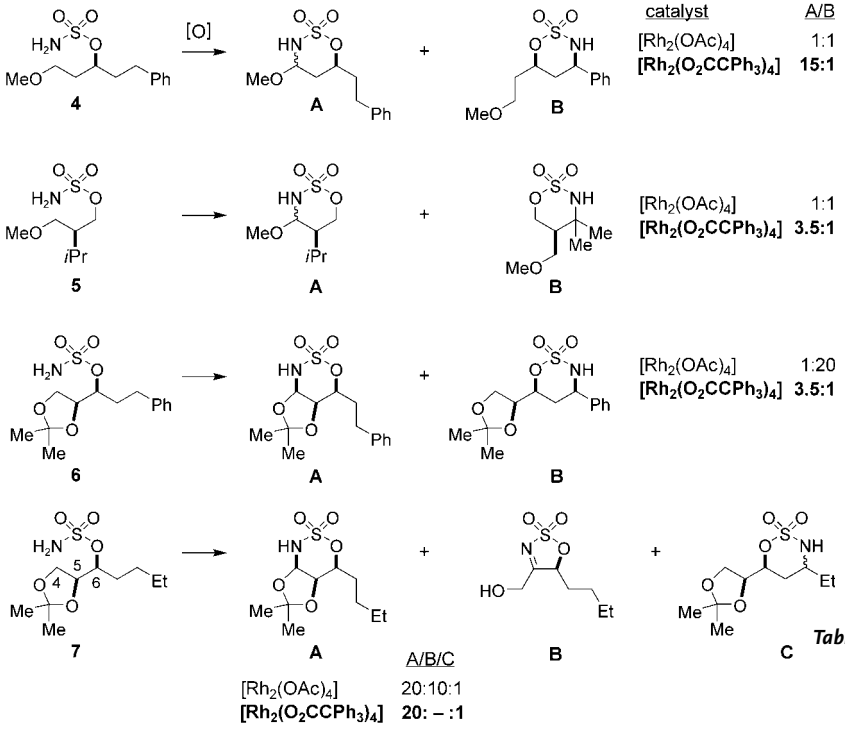


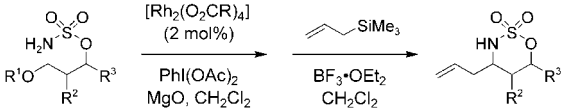
Scheme 2. Catalyst-controlled regioselectivity in C–H amination reactions.

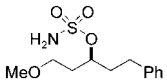
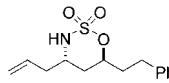
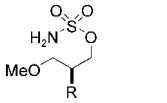
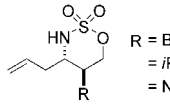
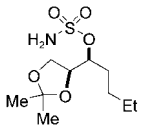
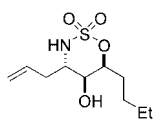
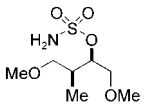
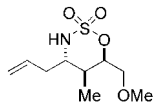
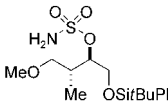
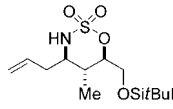
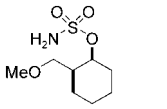
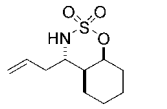
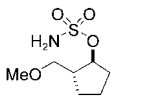
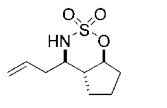
furnish two isomeric oxathiazinane products, as well as the smaller 5-membered ring sulfamidates. Under $[Rh_2(OAc)_4]$ catalysis, sulfamates **4** and **5** show only a slight preference for insertion into a C^{α}–H bond of the ether. These data indicate that the relative rates of ethereal, benzylic, and tertiary C–H amination are in fact comparable. Nonetheless, the regioselectivity is improved substantially when $[Rh_2(O_2CCPh_3)_4]$ is used in place of the tetraacetate complex.[6,7] As a general rule, we have found that the bulky Rh–triphenylacetate catalyst disfavors insertion into sterically crowded C–H bonds and is particularly disinclined towards reaction at benzylic sites. This latter conclusion is nicely illustrated with sulfamates **4** and **6**.[8] When more complex substrates, such as **7**, are employed, the choice of $[Rh_2(O_2CCPh_3)_4]$ also proves optimal, and formation of the undesired C5–H-insertion product is avoided. In contrast, the reaction of **7** with $[Rh_2(OAc)_4]$ is complicated by sulfamidate production. Collectively, these findings offer compelling support for a Rh-bound nitrene-type oxidant and provide an attractive strategy for the regioselective assembly of oxathiazinane N,O-acetals.

Access to structurally complex N,O-acetals has furthered our efforts to develop these compounds as iminium ion precursors.[9] Initially, this work was hampered by the instability of certain N,O-acetal derivatives towards silica gel, which often complicated their purification. The efficiency and high regioselectivity observed in the amination reaction have made it possible, however, to employ N,O-acetal products without recourse to chromatography. Following this new protocol, the reaction mixture is filtered after the oxidation to remove MgO, and the unpurified material is treated with $BF_3{\cdot}OEt_2$ and allyltrimethylsilane. The coupling of $Me_3SiCH_2CH{=}CH_2$ to a range of substituted heterocycles proceeds in high yield and in almost all cases with excellent diastereocontrol (Table 1).[10] These data constitute the first report of allyl additions to such starting materials.

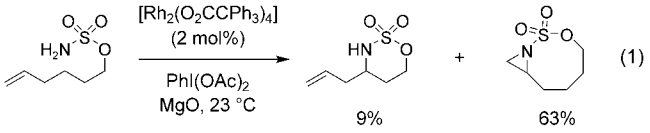
The uniqueness and utility of the allylated oxathiazinane products (Table 1) merits discussion. Preparation of these compounds through the direct insertion of an appropriately substituted sulfamate is limited by aziridine formation and poor product yields [Eq. (1)]. As such, our two-step protocol involving ethereal C^{α}–H amination makes available functionalized oxathiazinanes that are otherwise difficult to access. Further manipulation of these structures is facilitated through nucleophilic ring opening of the oxathiazinane core and/or alkene functionalization.[11,12] Such compounds should thus find service for the assembly of stereochemically complex amines.

Table 1: Coupling of an allyl silane with heterocyclic N,O-acetals.[a]

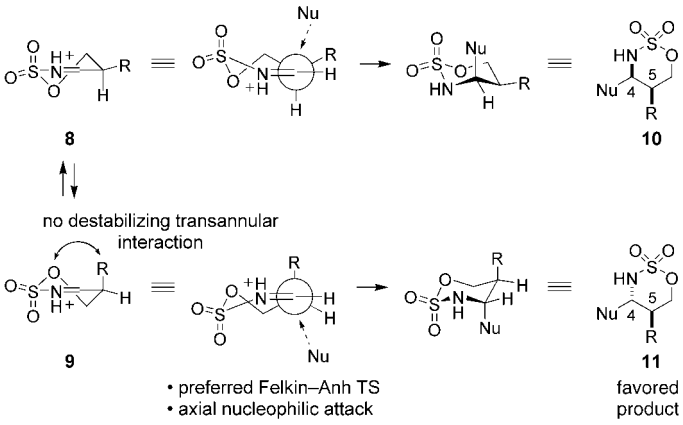


Entry	Substrate	Major product	d.r.[b]	Yield [%][c]
1			20:1	71[d]
2		 R = Bn = *i*Pr = NHP	20:1 10:1 20:1	75[d,e] 60 60[d,f]
3			20:1	78[d]
4			20:1	72
5			1.5:1	81
6			20:1	89
7			2.5:1	82

[a] Sulfamate oxidation: $[Rh_2(OAc)_4]$ (2 mol%), $PhI(OAc)_2$ (1.1 equiv), MgO (2.3 equiv); coupling reaction: $Me_3SiCH_2CH{=}CH_2$ (4 equiv), $BF_3{\cdot}OEt_2$ (1.5 equiv); $BF_3{\cdot}OEt_2$ was added dropwise over 75 min to a solution of the allylsilane and the oxathiazinane; see Supporting Information for details. [b] Diastereomeric ratios were determined by ^1H NMR spectroscopy. [c] Combined yield of the two diastereomers over two steps. [d] $[Rh_2(O_2CCPh_3)_4]$ was employed in place of $[Rh_2(OAc)_4]$. [e] Bn = benzyl. [f] NHP = $NHCO_2CH_2CCl_3$.

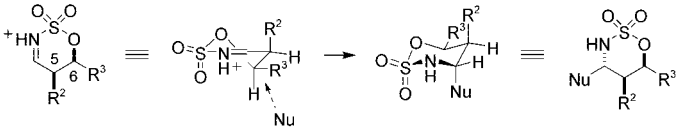


The addition of allylsilanes to oxathiazinane N,O-acetals **2** has proven highly diastereoselective and has enabled the refinement of a predictive transition-state model for this process. Our original investigations demonstrated that alkynyl zinc reagents couple to **2** with a strong bias for the formation of the 4,5-*syn* product **10** (Scheme 3).[2] To rationalize these data, the work of Stevens was considered.[13] In this context, the expected result of axial attack by the zinc reagent on the twist-chair form of iminium ion **8** was consistent with the observed stereochemical outcome. This proposal also accounts for the *anti* selectivity observed in allylsilane reactions with C6-branched N,O-acetals, as highlighted in entry 1 of Table 1. For C5-substituted oxathiazinanes (Table 1, entry 2), however, the analysis becomes more complex. Iminium intermediates generated from such starting materials can adopt either conformation **8** or **9** with minimal energetic cost, as 1,3-*trans* diaxial interactions are virtually absent in **9**. Observed formation of the 4,5-*anti* oxathiazinanes in entry 2 is consistent with allylsilane coupling along a pathway in which the substituent at C5 is aligned axially. Such a model parallels that of Felkin, Anh, and Eisenstein for nucleophilic additions to carbonyl groups.[14,15] Accordingly, the transition state (TS) leading from **9** minimizes steric and torsional strain in the developing product and, in certain cases (e.g. R = $NHCO_2CH_2CCl_3$, OH), profits from stereoelectronic stabilization.[16]

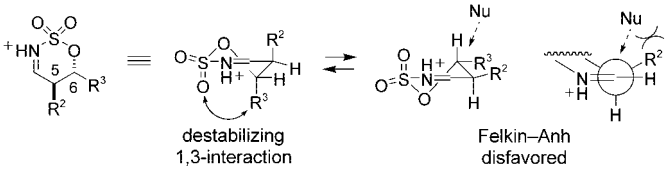


Scheme 3. Stereochemical models for iminium ion additions.

5,6-Disubstituted oxathiazinane acetals (Table 1, entries 3–7) were used to test further the proposed TS model. In these examples, the configuration of the vicinal C5,C6 centers can reinforce or oppose the Felkin–Anh preferred arrangement. Sulfamate esters with a 5,6-*syn* substitution pattern (Table 1, entries 3, 4, 6) are in consonance with both the Stevens and Felkin–Anh constructs, and thus the allylsilane adds with excellent selectivity (Scheme 4). Conversely, the *anti*-configured sulfamates (Table 1, entries 5, 7) can not adopt a conformation that satisfies both models simultaneously (Scheme 5). As a result, diastereoinduction is greatly diminished in the allylsilane coupling reaction. Although these TS designs are speculative, their predictive power should prove beneficial for synthesis development.



Scheme 4. Highly selective addition to 5,6-*syn*-substituted iminium ions.

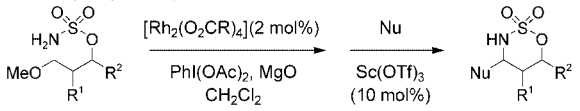


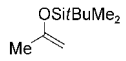
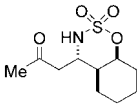
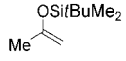
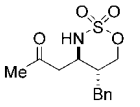
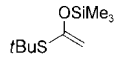
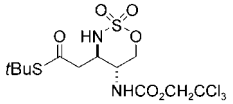
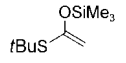
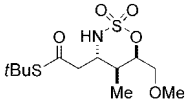
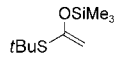
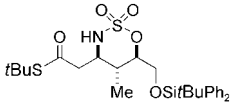
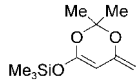
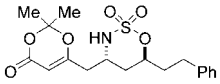
Scheme 5. Selectivity erodes with 5,6-*anti*-configured substrates.

An interest in examining further the validity of the iminium ion stereochemical model combined with the successful addition of allyltrimethylsilane to N,O-acetals **2** prompted investigations with alternative nucleophiles (Scheme 6, Table 2). Reactions of **2** with silyl enol ethers and ketene acetals would furnish Mannich-type products conveniently disposed for an assortment of subsequent transformations.[17] These reagents, however, were unstable to stoichiometric amounts of $BF_3{\cdot}OEt_2$ at ambient temperature, conditions utilized previously for the allylsilane additions. Not surprisingly, initial test reactions to condense **12** with **13** afforded oxathiazinane **14** in poor yields (Scheme 6). Guided by notable reports of Mannich additions catalyzed by metal triflates, we identified $Sc(OTf)_3$ as an exceptionally effective agent.[18,19] An optimized protocol thus employs $Sc(OTf)_3$ (10 mol %) in CH_3CN to promote efficient and diastereoselective coupling of silyl enol ethers and ketene acetals with structurally disparate N,O-acetals (Table 2).[10,20] The procedure is straightforward and does not require purification of the intermediate oxathiazinane. Importantly, the sense and degree of induction recorded for these addition reactions is

Scheme 6. Coupling with a silyl ketene O,S-acetal under catalytic conditions.

Table 2: $Sc(OTf)_3$-catalyzed Mannich reactions of N,O-acetals.[a]



Entry	Nucleophile	Major product	d.r.[b]	Yield [%][c]
1			20:1	80
2			20:1	68[d]
3			20:1	60[d]
4			20:1	65
5			2.5:1	76
6			20:1	72[d]

[a] Sulfamate oxidation: $[Rh_2(OAc)_4]$ (2 mol%), $PhI(OAc)_2$ (1.1 equiv), MgO (2.3 equiv); coupling reaction: nucleophile (4 equiv), $Sc(OTf)_3$ (0.1 equiv); see Supporting Information for details. [b] Diastereomeric ratios determined by ^1H NMR spectroscopy. [c] Combined yield of the two diastereomers over two steps. [d] $[Rh_2(O_2CCPh_3)_4]$ was employed in place of $[Rh_2(OAc)_4]$. Tf = trifluoromethanesulfonyl.

entirely consistent with the Stevens/Felkin–Anh TS analysis outlined above.

Methods for the oxidation of C–H bonds are finding ever-increasing application to problems in synthesis. The continued evolution of such work is contingent upon the ability to functionalize with high precision specific C–H centers in structurally intricate substrates. We have shown that the architecture of the Rh catalyst and the reactivity of ethereal C^{α}–H bonds can be used in combination to direct the regioselective amination of substituted sulfamate starting materials. These findings make available a novel class of heterocyclic N,O-acetals that function proficiently as iminium ion equivalents. High-yielding nucleophilic addition to these latent electrophiles is now possible with allylsilanes, silyl enol ethers, and ketene acetals, as well as alkynyl zinc reagents.[2] Predictable and, in most cases, marked levels of diastereoselectivity underscore the addition process. Thus, with the ability to assemble an impressive range of chiral oxathiazinane derivatives, catalytic C–H amination appears as a forefront strategy for accessing nitrogen-containing products.

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Keywords: amination · C–H insertion · N,O-acetals · rhodium · sulfamates

[1] a) P. M. Wehn, J. Du Bois, *J. Am. Chem. Soc.* **2002**, *124*, 12950; b) B. M. Trost, J. L. Gunzner, O. Dirat, Y. H. Rhee, *J. Am. Chem. Soc.* **2002**, *124*, 10396; c) H. Huang, J. S. Panek, *Org. Lett.* **2003**, *5*, 1991; d) K. A. Parker, W. Chang, *Org. Lett.* **2003**, *5*, 3891; e) A. Hinman, J. Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 11510.

[2] J. J. Fleming, K. Williams Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2003**, *125*, 2028.

[3] Compounds **2** and **3** are known generally as 1,2,3-oxathiazinane-2,2-dioxides or as 2,2-dioxotetrahydro-1,2,3-oxathiazines. We refer to such structures as oxathiazinanes or oxathiazinane N,O-acetals for convenience.

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