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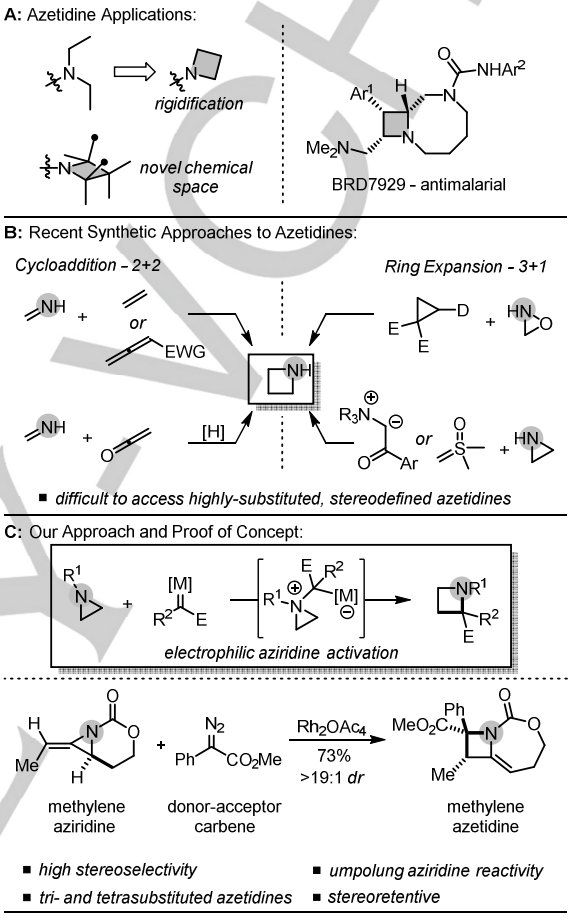
A Stereoselective [3+1] Ring Expansion for the Synthesis of Highly-Substituted Methylene Azetidines

Steven C. Schmid, Ilia A. Guzei, and Jennifer M. Schomaker*

Abstract: The reaction of rhodium-bound carbenes with strained bicyclic methylene aziridines results in a formal [3+1] ring expansion to yield highly-substituted methylene azetidines with excellent regio- and stereoselectivity. The reaction appears to proceed through an ylide-type mechanism, where the unique strain and structure of the methylene aziridine promotes a ring-opening/ring-closing cascade that efficiently transfers chirality from substrate to product. The resultant products can be elaborated into new azetidine scaffolds containing vicinal tertiary-quaternary and even quaternary-quaternary stereocenters.

Azetidines are four-membered saturated nitrogen heterocycles underexplored in comparison to their aziridine, pyrrolidine and piperidine counterparts.[1] However, azetidines have found great utility in medicinal chemistry to rigidify alkyl-substituted amines, to explore new chemical space, and as synthetic building blocks (Scheme 1A).[1-4] While azetidines occur infrequently in natural products, Kato et. al. recently disclosed the synthetic bicyclic azetidine BRD7929, a promising and potent antimalarial believed to have a novel mechanism of action.[5]

The increased interest in azetidines requires new synthetic approaches to access desired scaffolds with varied substitution and stereochemistry. Traditional methods employ cyclization of a linear precursor *via* a 4-*exo-tet* substitution, but are limited in scope.[4] Other strategies accomplish ring and stereocenter construction simultaneously by uniting two fragments; however, this often leads to difficulty in establishing the correct regio- and stereochemistry (Scheme 1B). The [2+2] reactions have been well-explored[6] while the corresponding [3+1] reactions are less common, although N-atom transfer from an oxaziridine to a donor-acceptor cyclopropane was recently disclosed, as well as two examples of nucleophilic aziridine opening with sulfoxonium or nitrogen ylides.[7,8] Despite these advances, stereoselective access to highly substituted, densely functionalized azetidines remains difficult. We hypothesized that an umpolung [3+1] approach could address these challenges by engaging strained aziridines with electrophilic one-carbon sources to trigger a ring-opening, ring-closing cascade to yield the azetidines (Scheme 1C).[9-12] While concerted [1,2]-Stevens rearrangements of aziridines are thermally forbidden, a step-wise reaction could, in principal, achieve a one-carbon ring expansion.[9c,d] Reports of analogous reactivity with epoxides and oxetanes are rare,[10] and display regioselectivity issues and inefficient ring-closure, presumably due to the promiscuity of the ring-opened ylide intermediate. We proposed bicyclic methylene aziridines, easily



Scheme 1. Background and reaction design.

available from propargyl alcohols (Table 1), would be good substrates for [3+1] reactions to generate substituted azetidines.[13] The bicyclic structure forces the nitrogen lone pair orthogonal to the carbonyl, rendering it moderately nucleophilic. Additionally, ring strain should provide a driving force for ring-opening, with the carbamate tether ensuring regioselective ring-closure. Gratifyingly, initial experiments with a donor/acceptor diazoacetate (Scheme 1C) under dirhodium catalysis delivered endocyclic, bicyclic methylene azetidine in high yield and stereoselectivity. Notably, this result: a) validates our proposal that electrophilic one-carbon sources can be engaged in ring-expansion of strained, small heterocycles, b) delivers densely functionalized azetidines with substitution patterns not accessible by other methods and c) expands the reactivity profile of bicyclic methylene aziridines.

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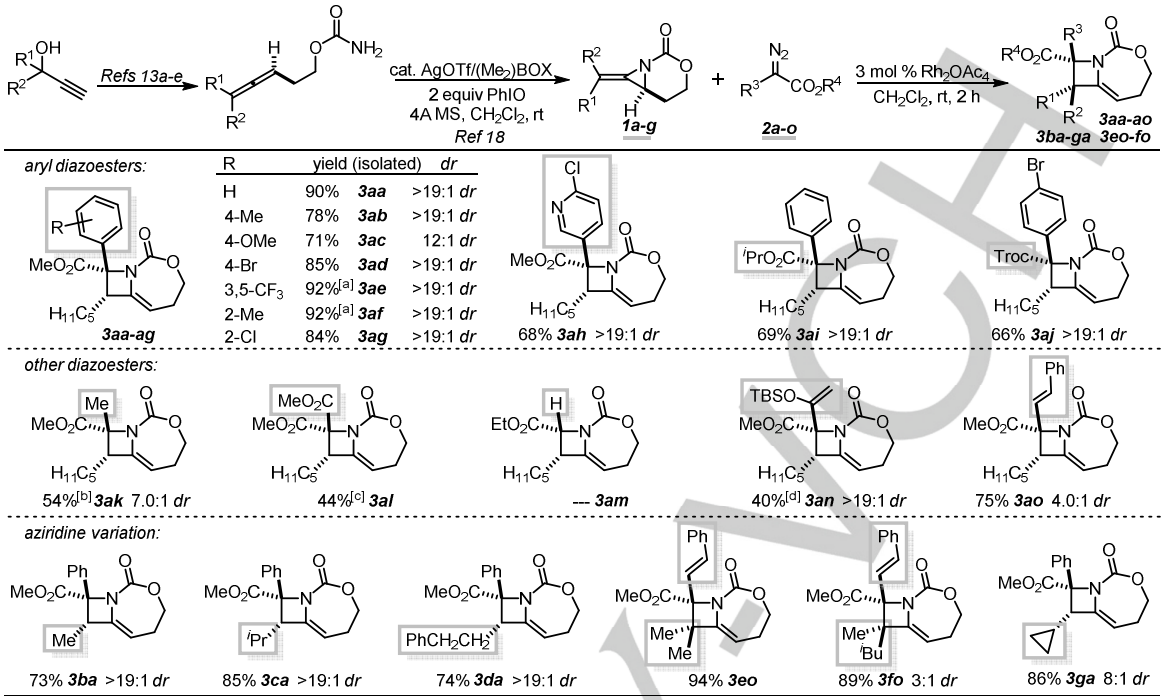


Standard conditions: Slow addition of the diazoester (1.3 equiv) to aziridine (1.0 equiv) over 2 h. Numbers refer to isolated yields. [a] 2.0 equiv of the diazoesters were used. [b] 4 equiv of the diazoesters were used. [c] 4.0 equiv of the iodonium ylide were added as two portions over 15 min. [d] 2.5 equiv of the diazoester were used at 40 °C.

Table 1. Scope of [3+1] ring expansion.

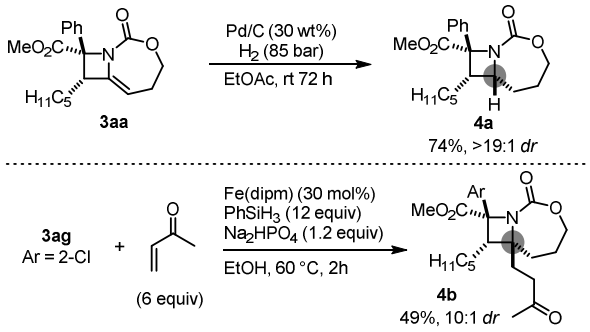
The [3+1] reaction scope was explored, first using model substrate **1a** (R^1 = C_5H_{11}; R^2 = H) with an array of aryl/ester diazo compounds **2a-g** (Table 1) and catalytic $Rh_2(OAc)_4$. Reaction of phenyl diazoacetate **2a** with **1a** furnished azetidine **3aa** in 90% yield with >20:1 *dr*. Electron-rich and electron-poor aryl diazoacetates were successful, providing azetidines **3ab-3ae** in high yields and selectivity. Ortho substitution on the aryl rings of **2f** and **2g** was tolerated, although increased loading of the diazoacetate was necessary. Pyridinyl diazo **2h** delivered azetidine **3ah** in moderate yield. Changing the ester group of the carbene precursor was also well-tolerated. Increasing the steric bulk of the ester in **2i** resulted in a noticeably cleaner reaction with an equally impressive *dr*. Use of a Troc ester in **2j** required no slow addition, giving excellent *dr* in **3aj**.[14] The [3+1] reaction was also successful when the aryl of the diazo compound was replaced with a Me in **2ak**. Dimerization of the diazoacetate was solved using multiple equivalents of **2k** to provide **3ak** in good *dr*. Diester azetidine **3al** was formed efficiently using an iodonium ylide, as the corresponding diazo gave product mixtures. Acceptor carbene precursors, including ethyl diazoacetate, have been unsuccessful thus far.

Diazoacetates with vinyl substitution surprisingly gave no higher-order [3+n] ring expansions.[15] While higher temperatures were required, treatment of **1a** with silyl enol ether **2n** resulted in exclusive [3+1] addition, delivering azetidine **3an** in 40% yield as a single diastereomer, despite the propensity of silyl enol ether Rh-bound carbenes to act as three-carbon synthons.[16] Styrenyl derivative **2o** also cleanly gave azetidine **3ao**; the lower *dr* was attributed to lesser steric differentiation between a styrene and methyl ester, compared to the phenyl variant **2a**.

The methylene aziridine scope was explored next. *E* isomers (>10:1 *E:Z*) containing Me, *i*Pr, cyclopropyl and remote phenyl substituents were well-tolerated. The relative configuration of **3ba** was confirmed *via* a single-crystal X-ray structure (details in the Supporting Information), showing the major diastereomer maintains a *syn* relationship between the ester and the methyl group. Despite numerous attempts, reaction of phenyl diazo **2a** with **1e** was unsuccessful, likely due to slow reaction of substrates containing *Z*-substituents with bulky carbenes; indeed, switching to less-hindered styrenyl diazo **2o** delivered the fully-substituted methylene azetidine **3eo** in an impressive 94% yield. We then sought to explore diastereocontrol in the synthesis of **3fo** to set adjacent quaternary carbons, a challenging feat.[17] Silver-catalyzed nitrene transfer enabled access to aziridine **1f** as a 4:1 mixture of inseparable *E/Z* isomers.[18] Subjecting this mixture to **2o** and $Rh_2(OAc)_4$ delivered **3fo** in a moderate 3:1 *dr* and good yield. The diastereomers were separable, yielding the *syn*-Me/CO_2Me isomer of **3fo** in 54% yield and 15:1 *dr*.

The alkene of the methylene azetidine represents a valuable handle for divergent elaborations of the product. Hydrogenation of **3aa** gave azetidine **4a** in high stereoselectivity (Scheme 2). Baran's iron-catalyzed C-C coupling[19] successfully yielded **4b** in good *dr*, an impressive radical coupling due to forging a second quaternary carbon on the azetidine ring.

To explore the mechanism, enantioenriched **1a** was treated with **2a** (Scheme 3A); the reaction showed excellent chirality transfer from the aziridine stereocenter prior to its ablation. A



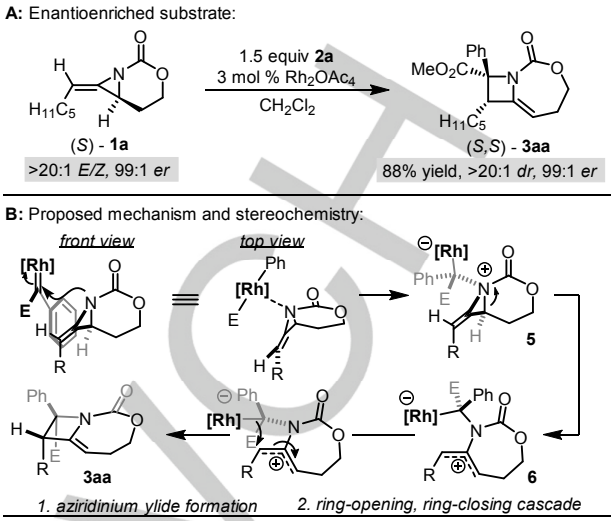
Scheme 2. Product derivatizations.

control reaction excluding the Rh catalyst gave no conversion, validating the role of the Rh-bound carbene. TEMPO addition gave no change in selectivity and the cyclopropane ring of **1g** did not ring-open in delivering azetidine **3ga** (Table 1), rendering radical intermediates unlikely.

Our proposed mechanism (Scheme 3B) occurs through aziridinium ylide formation *via* attack of the aziridine nitrogen on the Rh-bound carbene to form **5**. Ring-opening to **6**, followed by bond rotation and ring closure yields **3a** in an overall ring-opening/ring-closing cascade. Support for formation of ylide **5** over competing alkene cyclopropanation is provided by the known ability of the nitrogen to react with potent electrophiles or Lewis acids.[13a] Additionally, intermolecular cyclopropanation of unactivated, sterically hindered tri- or tetrasubstituted alkenes is difficult with donor/acceptor rhodium carbenes, typically yielding C-H activation instead. [20]

The assumption that the ylide **6** retains its stereochemistry by existing as a C-bound Rh enolate that does not racemize *via* isomerization through an O-bound Rh species,[21] coupled with our transfer of chirality experiments, suggests that aziridinium formation occurs with high *dr* using aryl diazoacetates. The crystal structure of **3ba** and the nOe data of **3aa**, **3ak**, **3an**, and **3ao** (SI for details) indicate the same major diastereomer for **3aa-eo**, where the ester is *syn* to the aziridine R group.[22] This configuration can be rationalized *via* a steric-based model wherein the approaching Rh-bound carbene orients its larger R group (aryl, styrenyl, etc. vs. the ester) in the back, convex pocket of the bowl-shaped methylene aziridine, avoiding steric interactions with the alkene.

Given the strain present in **5**, we propose that ring-opening to give the (*Z*)-2-amidoallyl cation zwitterion **6** is governed by $A^{1,3}$ strain. Diastereoselective ring-closure from the back face of **6** delivers **3a** with the observed stereochemistry. Sterics likely play a role, where the smaller ester substituent aligns *syn* to the aziridine R group. While we currently favor this ring-opening/ring-closing pathway, an alternative mechanism in which ylide **5** does not fully open to the 2-amido allyl cation, but begins to form the azetidine C-C bond formation prior to full planarization of the nitrogen in a concerted and asynchronous fashion, cannot be ruled out. A comprehensive mechanistic study is underway to address these nuances.



Scheme 3. Stereochemical probe and proposed mechanism.

In conclusion, we have outlined a new [3+1] ring expansion strategy that harnesses unique features of bicyclic methylene aziridines, in combination with Rh-supported carbenes, to deliver tri- and tetra-substituted methylene azetidines. This reaction demonstrates an impressive use of ring strain, as it forges new C-C and C-N bonds centered around a quaternary center in good selectivity and highlights the potential of methylene aziridines as a unique entry point to nitrogen heterocycles. We anticipate this work will spur design of new ring expansion reactions using small-ring heterocycles.

Acknowledgements

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Keywords: aziridine • carbene • azetidine • rearrangement • enantiospecific

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[22] nOe data on **3fo** indicates formation of the opposite diastereomer expected – work on understanding this selectivity is underway.

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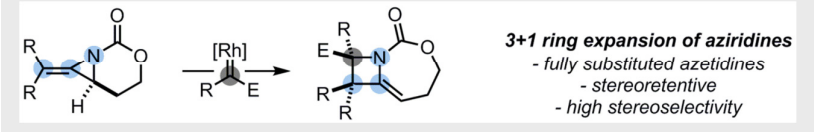

A tale of two rings: A one carbon ring expansion of methylene aziridines to methylene azetidines occurs upon reaction with a rhodium-bound carbene. This 3+1 ring expansion efficiently delivers substituted azetidines in high yields and stereoselectivities.

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Page No. – Page No.

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