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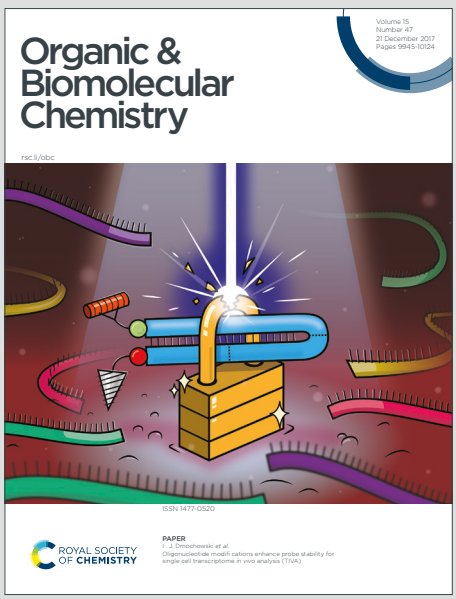

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Adapting Bower's Intramolecular Aziridination Reaction Allows for a Metal-Free Synthesis of N–H Aziridines

Raju Silver,[a] Steven P. Kelley,[b] and Shyam Sathyamoorthi[a,*]

[a] Department of Medicinal Chemistry, University of Kansas, Lawrence, KS 66047, USA

[b] Department of Chemistry, University of Missouri—Columbia, Columbia, MO 65211, USA

Abstract: Inspired by Bower's intramolecular aziridination reaction, we have developed an intermolecular protocol for the preparation of N–H aziridines from olefins. Our reaction is operationally simple and involves stirring substrate with commercial *N*-Boc-*O*-tosylhydroxylamine and trifluoroacetic acid in 2,2,2-trifluoroethanol. The reaction is stereospecific, scalable, and does not utilize expensive transition metals. The substrate scope is broad, and the functional group tolerance is impressive.

New methods for the syntheses of aziridines continue to be desired and developed.[1-16] As part of a campaign to extend our work with the ring-opening of aziridines,[17-21] we attempted to synthesize N–H aziridine **2** using some existing metal-free protocols[22, 23] (**Figure 1**), hoping to avoid the high cost of rhodium catalysts.[24-26] Unfortunately, stirring **1** with *N*-Boc-*O*-tosylhydroxylamine (BocNHOTs) in 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) gave oxazoline **3** as the major product,[25] among several minor ones. No reaction was observed using 2.4 equivalents of hydroxylamine-*O*-sulfonic acid and 2.4 equivalents of pyridine in HFIP at room temperature.[23] We were intrigued by a series of papers from the Bower group demonstrating successful intramolecular *aza*-Prilezhaev reactions under very mild and metal-free conditions.[27-29] Except in a few instances, the N–H aziridine intermediates were not isolated in these reports but were directly transformed into other important compounds. We thus wondered whether a modification of the Bower protocol would be generally useful for an intermolecular synthesis of isolable N–H aziridines and their derivatives. Here, we detail our efforts towards this goal.

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	N-Source[a]	Solvent	Yield of 2[b]	% of 1[b]
1	**BocNHOTs (1.5)**	**CF_3CH_2OH [0.2 M]**	**66%**	**0%**
2	BocNHOTs (1.5)	HFIP [0.2 M]	0%[c]	0%[c]
3	BocNHOTs (1.5)	CH_2Cl_2 [0.2 M]	40%	60%
4	BocNHOTs (1.5)	CH_3CN [0.2 M]	0%	65%
5	BocNHOTs (1.5)	CF_3Ph [0.2 M]	50%	50%
6	BocNHOTs (1.5)	MeOH [0.2 M]	0%	80%
7	BocNHOMs (1.5)	CF_3CH_2OH [0.2 M]	65%	15%
8	BocNHOPNBz (1.5)[d]	CF_3CH_2OH [0.2 M]	0%	60%
9	BocNHOTs (1.5)	CF_3CH_2OH [0.5 M]	66%	0%

Figure 1. Adapting Bower's intramolecular protocol solves a difficult intermolecular aziridination.

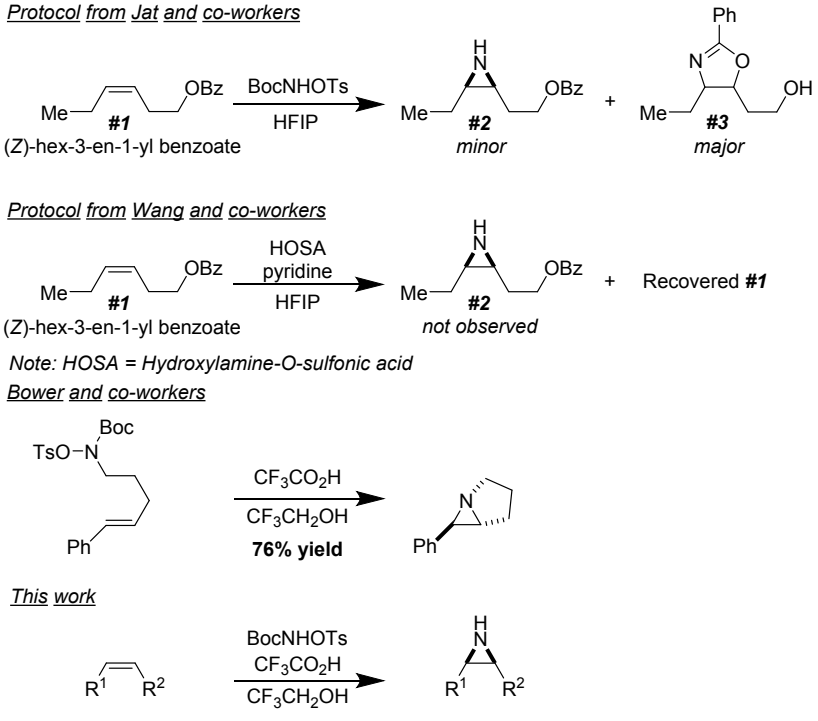
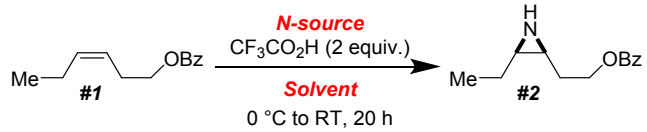


Table 1. Optimization experiments.



[a] Equivalents are given in parentheses.

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[b] Estimated by ^{1}H NMR integration against an internal standard.
[c] Oxazoline 3 (Scheme 1) was the exclusive product (~70% yield).
[d] BocNHOPNBz = tert-Butyl (4-nitrobenzoyl)oxycarbamate [35657-41-1]

Stirring commercial *cis*-3-hexen-1-yl benzoate (**1**) with 1.5 equivalents of BocNHOTs and 2 equivalents of trifluoroacetic acid in 2,2,2-trifluoroethanol (TFE) proceeded with full consumption of the starting material and gave N–H aziridine **2** in a good yield of 66% (**Table 1**, **Entry 1**). When the solvent was switched from TFE to HFIP, aziridine **2** disappeared, and only oxazoline **3** (**Scheme 1**) was formed (**Table 1**, **Entry 2**). Switching solvents from TFE to dichloromethane, acetonitrile, α,α,α-trifluorotoluene, and methanol was variably deleterious for the formation of aziridine **2** (**Table 1**, **Entries 3 – 6**). Switching the *N*-source from BocNHOTs to BocNHOMs or to *tert*-butyl (4-nitrobenzoyl)oxycarbamate did not help the reaction (**Table 1**, **Entries 7 – 8**). Finally, increasing the reaction concentration from 0.2 M to 0.5 M did not improve the yield of aziridine **2** (**Table 1**, **Entry 9**). With the related substrate *cis*-3-hexen-1-ol (*vide infra*), we found that greater reaction concentrations were deleterious for the product yield.

The substrate scope of this newly developed aziridination reaction was quite broad (**Figure 2**). Several olefin substitution patterns were compatible, including di-substituted, tri-substituted, tetra-substituted, and terminal alkenes. The functional group tolerance was also impressive. Substrates bearing alcohols, esters,

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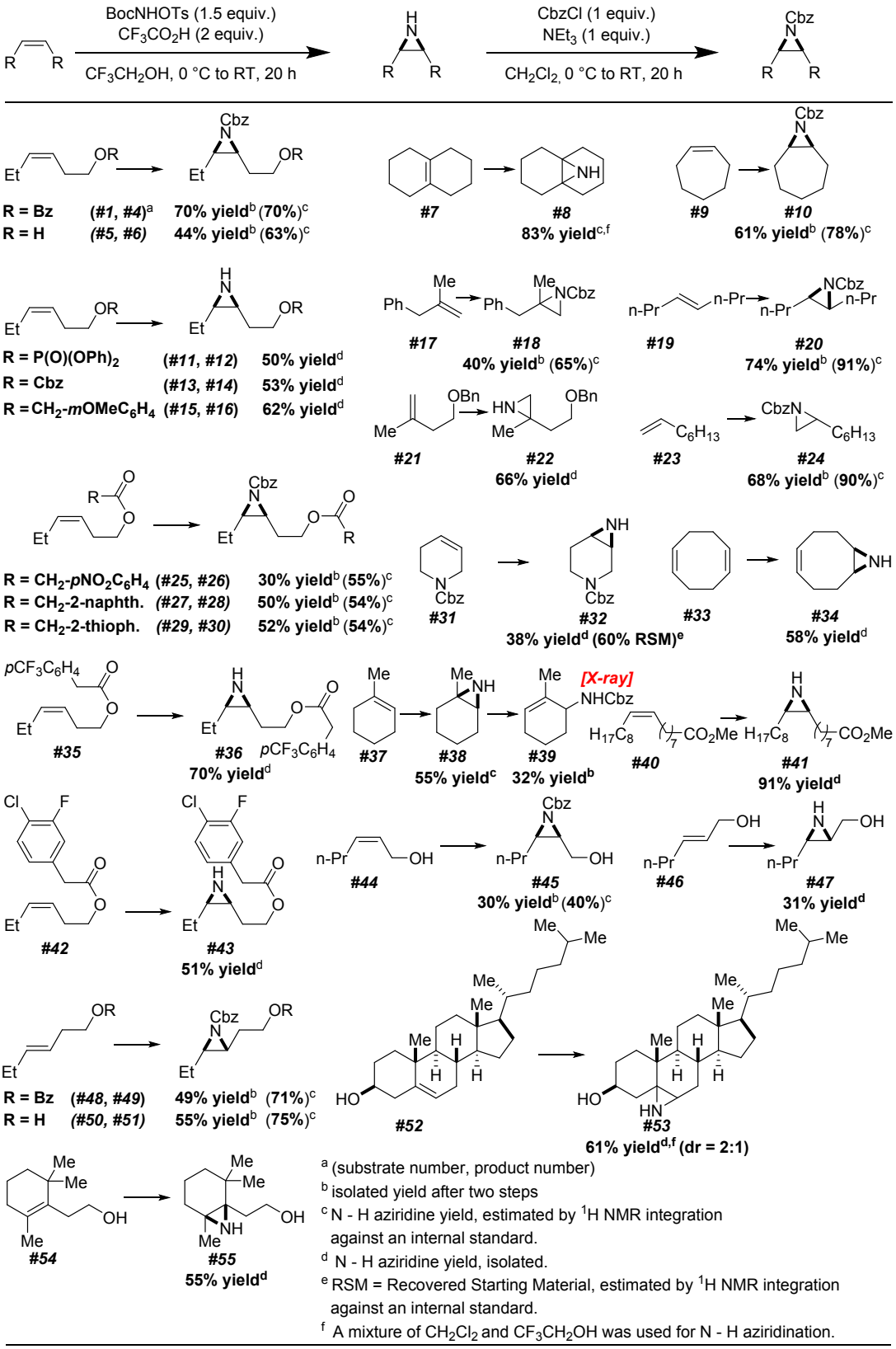
Figure 2. Substrate scope.



[a] (substrate number, product number)
[b] isolated yield after two steps
[c] N - H aziridine yield, estimated by ^{1}H NMR integration against an internal standard.
[d] N - H aziridine yield, isolated.
[e] RSM = Recovered Starting Material, estimated by ^{1}H NMR integration against an internal standard.
[f] A mixture of CH_2Cl_2 and CF_3CH_2OH was used for N - H aziridination.

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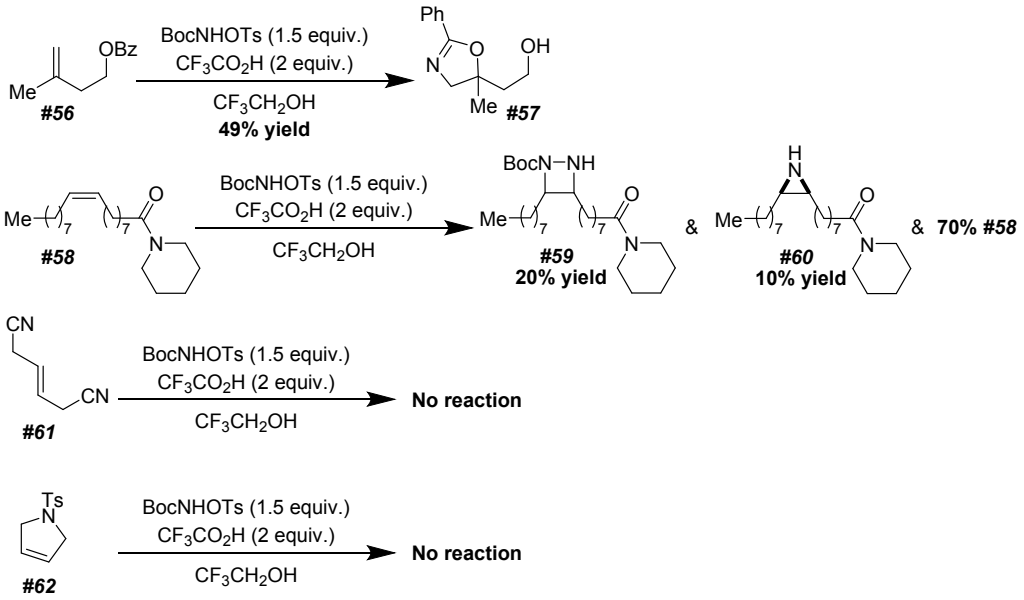
aromatic halides, phosphates, carbonates, and benzyl ethers all gave products in synthetically useful yields. Where relevant, the aziridination was stereospecific, at least by the limits of ^{1}H NMR detection. We were pleased to see productive reactions with cholesterol, methyl oleate, and an alcohol derivative of β-homocyclocitral, suggesting that this aziridination protocol may be useful for derivatizing other natural products of interest. In some cases, we have converted the *N*-H aziridine products to their corresponding *N*-Cbz derivatives for ease of isolation.

Figure 3. Unexpected results and poor performers.



As with any new technology, there were some substrates that gave unexpected results or were uncooperative (**Figure 3**). With benzoate **56**, oxazoline **57** was the major product, reminiscent of compound **3** in **Figure 1**. We were most interested to observe an unusual product when the piperidine amide of oleic acid was subjected to our reaction conditions. We have tentatively assigned its identity as diazetidine **59**. While we can only speculate regarding the mechanism of formation, we hypothesize that an *N*-Boc aziridine intermediate reacted with an additional equivalent of *N*-Boc-*O*-tosylhydroxylamine. Based on available data, a regioisomer of **59**, in which the Boc group is attached to the other nitrogen, is also possible. Our mechanistic hypothesis for the formation of compound **59** can be found in the **Supporting Information**, **Associated data for Manuscript Figure 3** section). No reaction was observed with *trans*-3-hexenedinitrile

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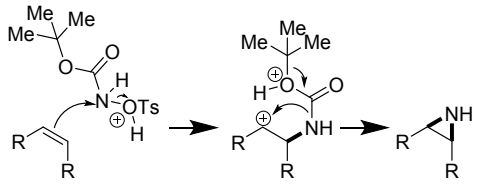
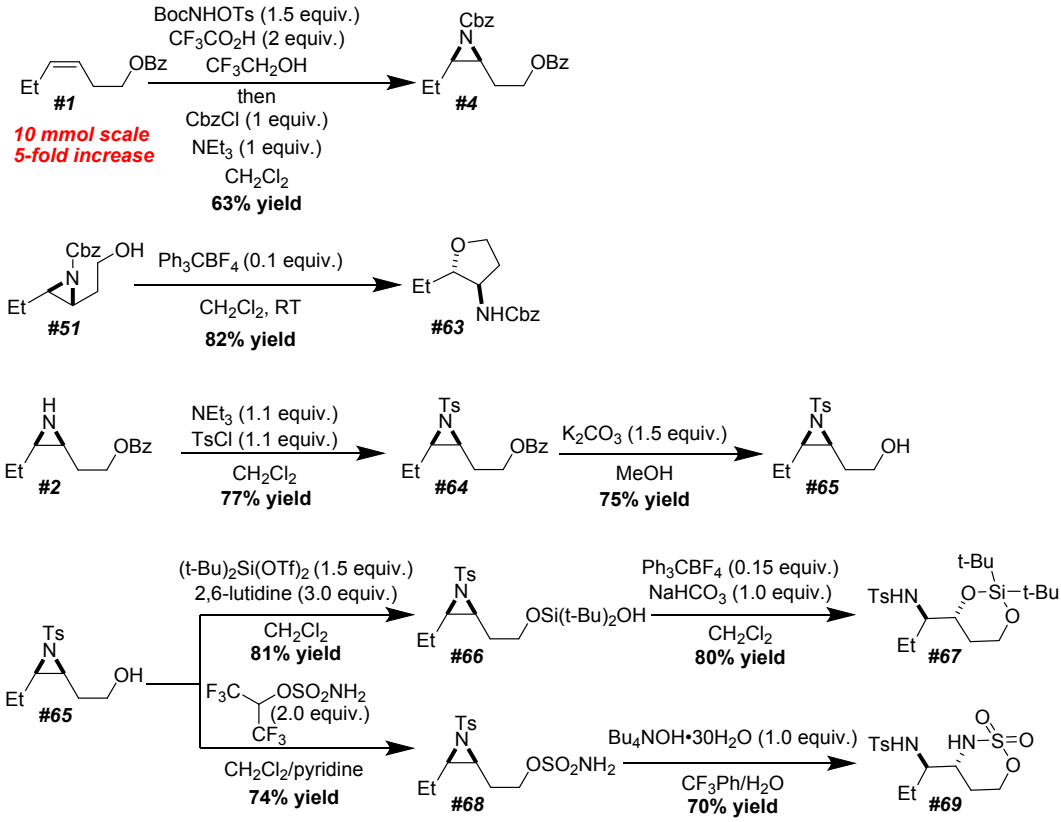
and with *N*-(*p*-toluenesulfonyl)-3-pyrroline. We have provided additional examples of substrates that failed to react cleanly in the **Supporting Information**.

Figure 4. Proposed mechanism.



While Bower and co-workers have proposed a concerted mechanism for their intramolecular aziridination reaction, we hypothesize that a stepwise mechanism as depicted in **Figure 4** is also plausible. The alkene may attack a protonated *N*-Boc-*O*-tosylhydroxylamine derivative. The carbocation will be trapped by the adjacent nitrogen, following Boc deprotection.

Figure 5. Scale up and Applications.



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The aziridination scale could be increased from 2 mmol to 10 mmol (~2 g of substrate) without much decrease in yield (**Figure 5**). While N-H aziridines must be forced to ring-open, attaching an electron withdrawing group to the nitrogen allows for a variety of interesting transformations under mild conditions. Activated aziridine alcohol **51** was cyclized into tetrahydrofuran **63** upon treatment with triphenylcarbenium tetrafluoroborate in dichloromethane. Starting with aziridine alcohol **65**, we used our laboratory's silanol[18] and sulfamate[19] tethered technology for the syntheses of polyfunctional heterocycles.

In summary, we have developed an intermolecular preparation of N–H aziridines from olefins. Our operationally simple protocol involved stirring substrate with commercial *N*-Boc-*O*-tosylhydroxylamine and trifluoroacetic acid in 2,2,2-trifluoroethanol. The reactions were stereospecific, scalable, and did not utilize expensive transition metals. The substrate scope was broad, and the functional group tolerance was impressive. Given that aziridines are ubiquitous in academic and industrial organic chemistry, we expect that this method will be widely utilized.

Associated Content

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Additional experimental details including reaction procedures and NMR spectra.

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Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.