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Article

Two-Step Constitutional Isomerization of Saturated Cyclic Amines Using Borane Catalysis

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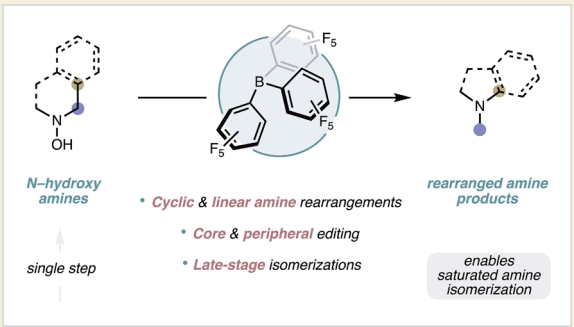
ABSTRACT: The prevalence of saturated azacycles within pharmaceuticals, natural products, and agrochemicals has prompted the development of many methods that modify their periphery. In contrast, technologies that interconvert distinct saturated azacyclic frameworks, which would uniquely facilitate access to underexplored chemical space, are highly limited. Existing approaches for modifying the core of azacycles usually require either the installation of reactive functionality, which must later be removed in subsequent steps, or the use of tailored substrates, limiting applicability to drug discovery. Herein, we report a borane-catalyzed contraction of saturated *N*-hydroxy azacycles. This transformation is uniquely enabling, allowing reorganization of the connectivity of the substrate without altering the molecular formula and generating products without vestigial functionality derived from auxiliary groups. The outcome of the reductive Stieglitz-type contraction can be attributed to a key stereoelectronic interaction enforced by geometric constraints, the mechanism of which we investigate using density functional theory. The method developed here enables the rapid late-stage reorganization of bioactive molecules featuring cyclic and linear amines. Overall, a general platform for saturated amine constitutional isomerization has been achieved.



KEYWORDS: *Azacycles, Isomerization, Borane Catalysis, Contraction, Editing*

The ability to precisely alter the core framework of an organic molecule at a late stage should expedite the exploration of novel chemical space by allowing access to diverse topologies and bond connections beyond those that can be achieved through peripheral modification. Although highly enabling in the correlation of structure and function, technologies for the interconversion of one core framework to another are limited. Often, a completely new synthesis is required to effect a small core structural change.[1] Ideally, direct interconversion of core structures without the incorporation of new functionality would be possible, thus controlling pharmacologically important variables such as molecular weight[2] or hydrogen bonding vectors,[3] while maintaining substituents on the periphery of a desired compound (Scheme 1A). Over the last half decade, a range of powerful methodologies have been reported for the "scaffold hopping" of saturated cyclic amines, which are among the most privileged heterocycles in pharmaceuticals and agrochemicals.[4] Despite major strides in saturated azacycle diversification, a survey of state-of-the-art methods highlights a common limitation of the field: while it is now possible to reasonably convert, for example, piperidines to pyrrolidines[5] or aminocyclopentanes,[6] such methods require the incorporation of functionality that facilitate the key transformation; groups which must later be removed in subsequent, sometimes difficult, steps. Ideally, this auxiliary functionality would be removed as part of the core modification, thus constituting a traceless reactive handle. In this way, it would be possible to effect constitutional isomerization of amines at a late stage, wherein only the connectivity of the molecule is changed and not the molecular formula (Scheme 1A). Although Murai and co-workers[7] disclosed a two-step oxidative rearrangement/borohydride reduction protocol to achieve this type of transformation, this method had strict substrate requirements, namely strongly electron-donating α-substituents, limiting its general applicability.

We recently disclosed a method for the borane-mediated reductive amination of carbonyl C−C σ-bonds that leveraged in situ generated *N*,*N*-disubstituted hydroxylamine nitrenoids to facilitate the cascade process via a reductive Stieglitz rearrangement.[8] On the basis of mechanistic insights garnered through these previous studies, we envisioned the core (and peripheral) modification of cyclic amines could be achieved via

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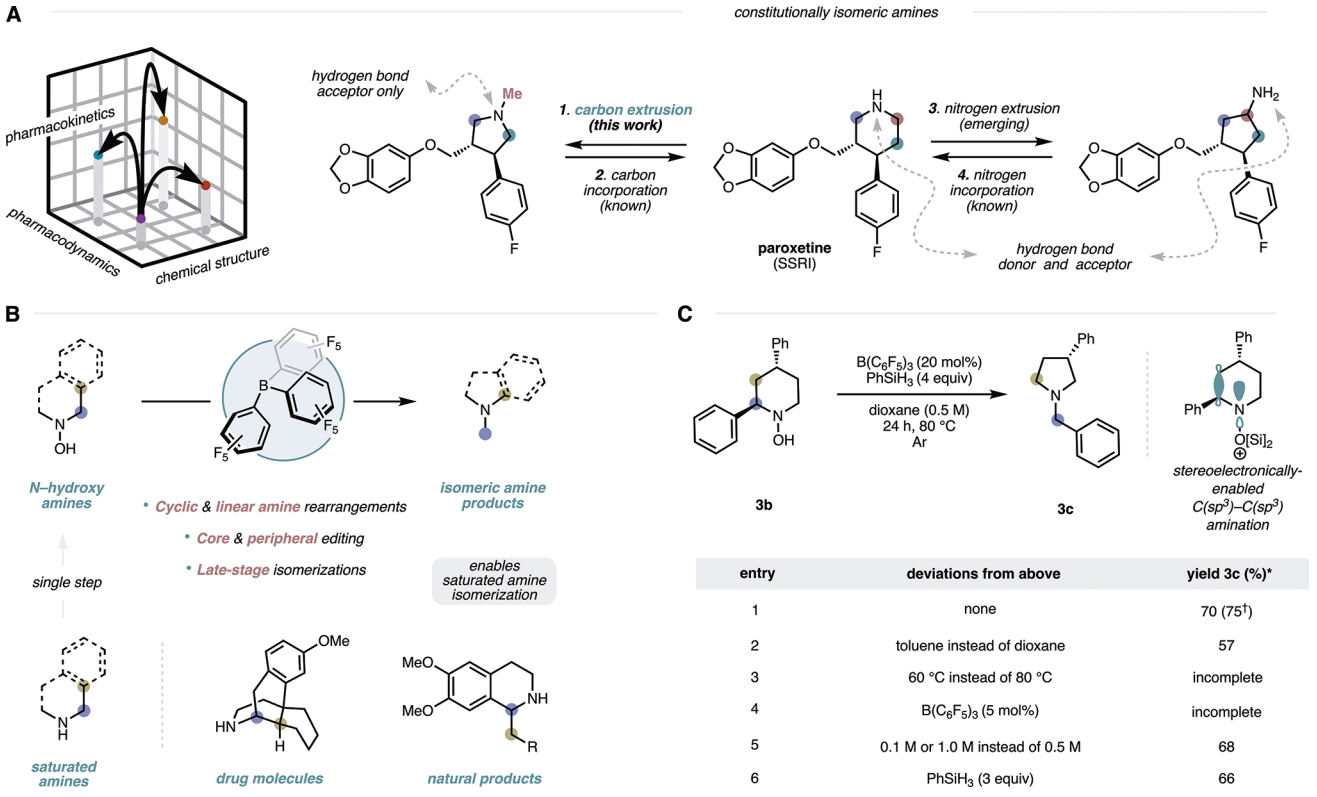
Scheme 1. (A) Value of Late-Stage Isomerization of Cyclic Amines within Drug Discovery; (B) Hydroxylamines As Traceless Reactive Handles for the Reorganization of Cyclic Amines; (C) and Optimization of the Borane-Mediated Contraction of Cyclic Hydroxylamines



entry	deviations from above	yield 3c (%)*
1	none	70 (75†)
2	toluene instead of dioxane	57
3	60 °C instead of 80 °C	incomplete
4	$B(C_6F_5)_3$ (5 mol%)	incomplete
5	0.1 M or 1.0 M instead of 0.5 M	68
6	$PhSiH_3$ (3 equiv)	66

[a]^{1}H NMR yield determined using 1,3,5-trimethoxybenzene as internal standard. [b]Isolated yield.

the corresponding *N*-hydroxy azacycles, readily accessed through known mild methods for nitrogen oxidation[9,10] (Scheme 1B). In this way, the installed hydroxylamine moiety could serve as a traceless reactive handle for the generation of products isomeric to the starting amine. Such a strategy would constitute a reorganization of the cyclic amine framework, wherein only the connectivity of core atoms of the molecule is altered (Scheme 1A). Herein, we report the successful development of such a method, which leverages hydroxylamines as traceless reactive handles for the extrusion of a single carbon atom from cyclic amine cores, achieving the contraction of various azacycles without the incorporation of vestigial functionality or protective groups. During the finalization of this manuscript, Oestreich and co-workers published a similar method for the borane-mediated contraction of cyclic hydroxylamines,[11] which focused primarily on the rearrangement of feedstock amine-derived hydroxylamines using $PhMeSiH_2$ as the reductant. Our work is complementary, as it provides insight into the functional group compatibility and electronic influence of α-substituents in piperidine and tetrahydroisoquinoline systems, although these substituents are not a requirement (vide infra).

We began our investigation by establishing optimized conditions for the contraction of azacycles using *N*-hydroxy-2,4-diphenylpiperidine (**3b**) as the model substrate (readily accessed in a single step from the corresponding amine in 79% yield on 200 mg scale; see the Supporting Information) (Scheme 1C). After an extensive screening of conditions, subjection of **3b** to tris(pentafluorophenyl)borane (BCF) (20 mol %) and phenylsilane (4 equiv) as reductant in dioxane at 80 °C, we observed a 75% isolated yield of the corresponding *N*-Bn pyrrolidine (**3c**), where the benzylic methine of the starting material had been extruded from the ring, generating a compound that is isomeric to the starting amine (prior to oxidation), containing no additional atoms (Scheme 1C, entry 1). On the basis of our previous work, which delineated the migratory preference in *N*,*N*-disubtituted hydroxylamine nitrenoids,[8] a 1,2-aryl migration to give the corresponding *N*-aryl amine might have been expected. Instead, in this case, we hypothesize that geometrical constraints (stereoelectronic effects) result in an interaction between the migrating endocyclic $C(sp^3)-C(sp^3)$ σ-bond and the N−O σ^*-antibonding orbital (Scheme 1C). Related stereoelectronically driven migration outcomes have been proposed by Aubé and Barton.[12,13] Changing the solvent (entry 2), decreasing the temperature (entry 3), or lowering the catalyst loading (entry 4) resulted in diminished yields, although the reaction efficiency seemed insensitive to variations in concentration (entry 5) or silane loading (entry 6).

With the optimized conditions in hand, we set out to test the scope of this ring contraction of *N*-hydroxy azacycles. As shown in Scheme 2, the chemistry proved general across a variety of electronically and sterically distinct substrates, providing good yields (41−85%) of the corresponding carbon-extrusion products (**1c**−**6c**). Importantly, amines with electron-neutral or -poor substituents (**3c**, **4c**, and **5c**) were well tolerated, a key limitation of the recent method by Murai and co-workers.[7] Notably, the benzylic stereogenic center α to the nitrogen in **6c** is formed stereospecifically, with complete retention of configuration. The products generated

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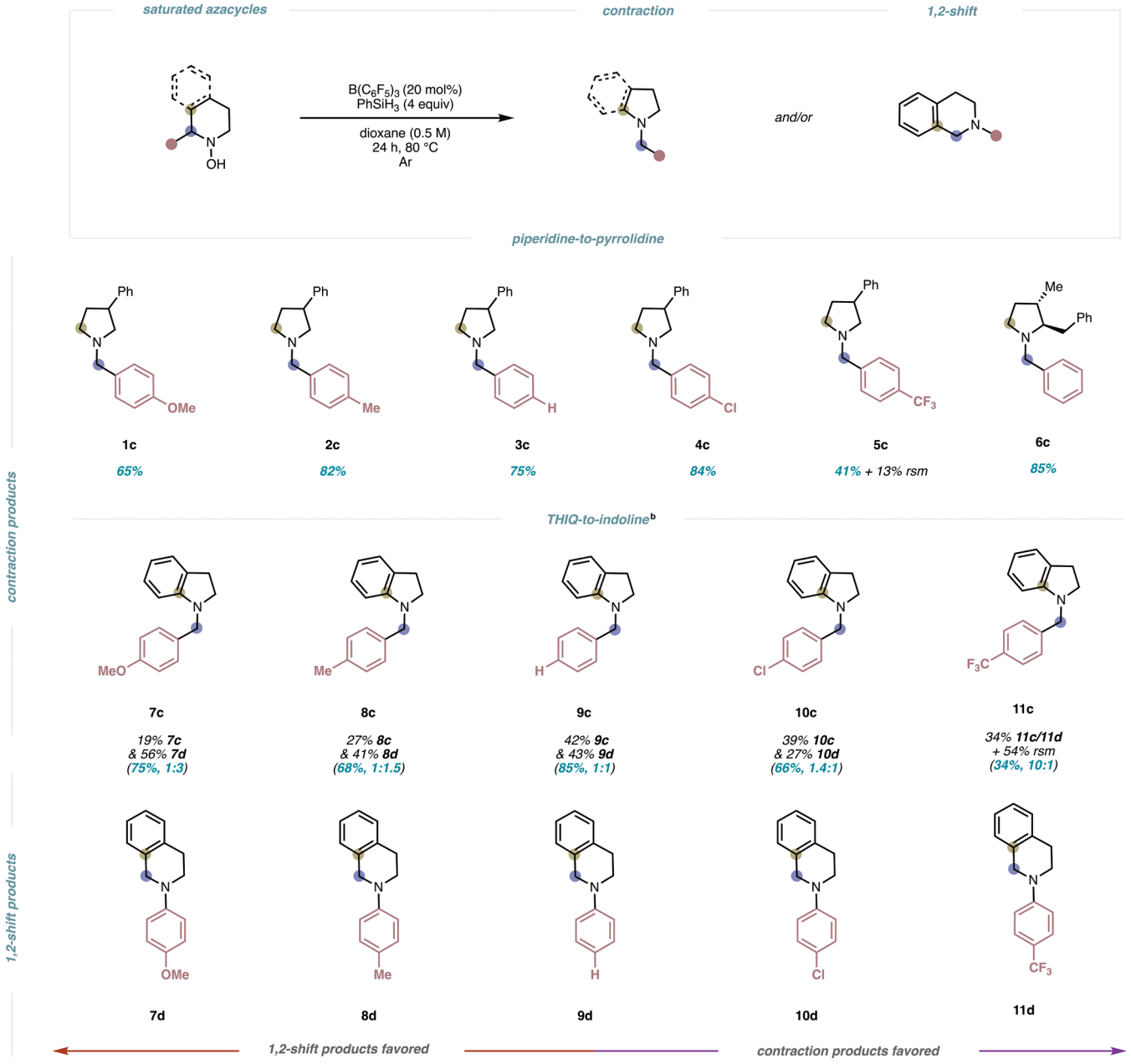
Scheme 2. Scope of the Borane-Mediated Ring Contraction of Saturated Azacycles[a]



[a]Reaction conditions: starting material (0.1 mmol), tris(pentafluorophenyl)borane (20 mol %), phenylsilane (4 equiv), dioxane (0.5 M), 80 °C, 24 h. Isolated yields and relative stereochemistry are shown. [b]Reactions conducted at 60 °C. Recovered starting material (rsm).

here are isomeric to the initial amine substrates (i.e., those which are oxidized to the corresponding hydroxylamine for the reductive rearrangement). Over the two-step process, we have reorganized the constituent core atoms, leaving the molecular periphery and molecular weight unaltered. Direct interconversion of azacyclic cores in such a rapid fashion obviates lengthy de novo synthesis and could therefore rapidly expedite drug discovery. In addition, a secondary amine has been exchanged for a tertiary amine, losing a hydrogen bond donor but keeping the H-bond acceptor properties. In this way, the angle and type of intermolecular interactions that are established by the amine nitrogen (i.e., vectors)[14] can be varied in a direct fashion.

Tetrahydroisoquinoline (THIQ) is a common structural motif found in myriad drugs and natural products.[15] Upon subjecting the corresponding *N*-hydroxy THIQ to the optimized conditions, a 1:1 mixture of contraction (Scheme 2, **9c**) and 1,2-aryl shift (Scheme 2, **9d**) products arose in an 85% combined yield at 60 °C. Presumably, this outcome arises from competing migration of each of the aryl substituents. We therefore hypothesized that under substrate control, we might be able to dictate the product ratio of ring contraction vs peripheral substituent shift by altering the electronics of the exocyclic α-aryl substituent. We found that, indeed, more electron-donating substituents on the aryl groups (see **7** and **8**) led to more of the 1,2-aryl shift products, whereas more electron-withdrawing substituents (see **10** and **11**) largely favored the ring contraction. These results not only provide a qualitative entry to predicting the outcomes of these transformations but also support the use of substrate control

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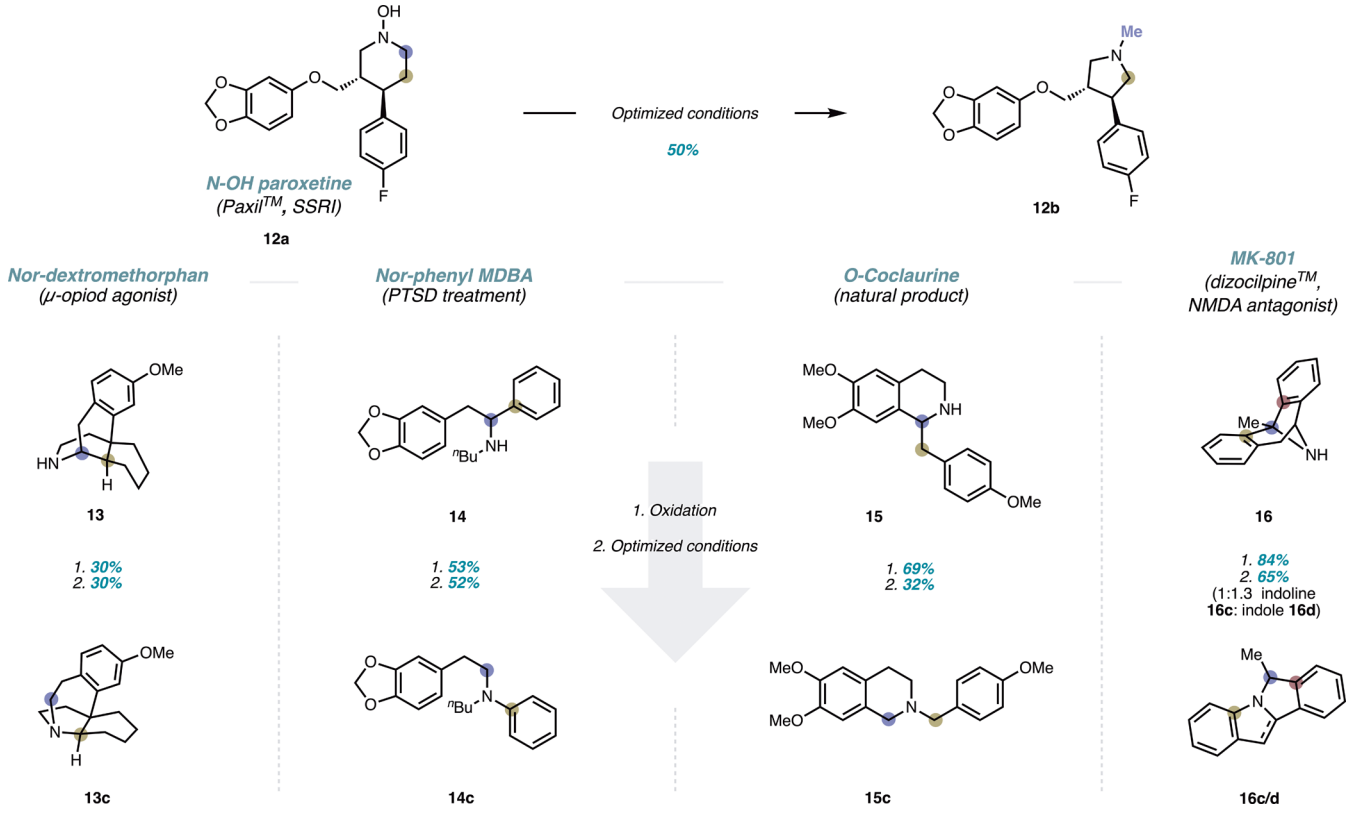
Scheme 3. Rapid Isomerization of Biologically Active Molecules Including FDA-Approved Drug Paxil[a]



[a]See the Supporting Information for experimental conditions.

to dictate the pathway for isomerization of the cyclic amine substrates (i.e., peripheral vs core modification).

With a better understanding of the factors that control product outcomes, we set out to apply this chemistry to the late-stage isomerization of biologically active compounds without the incorporation of vestigial functionality or protective groups. By leveraging mild, pre-existing technologies for amine oxidation,[10,16] the hydroxylamine derivatives of various biologically relevant molecules were accessed and subjected to the optimized conditions. As shown in Scheme 3, Paxil™ (**12**), a widely used FDA-approved selective-serotonin-reuptake-inhibitor[17] (SSRI), could be converted to the corresponding *N*-methyl pyrrolidine in short order in a remarkable 50% yield, though this transformation required elevated temperatures (120 °C). Often, in drug discovery campaigns, high yields are sacrificed in favor of direct routes to a given target. The isomerization method described here allows for rapid access to underexplored areas of chemical space that would otherwise be inaccessible in such a short fashion.

The antitussive NMDA-receptor antagonist dextromethorphan[18] derivative **13** was isomerized to the corresponding tertiary amine. In this case, and in agreement with our recent work,[8] the corresponding nitrone intermediate could be used in place of the hydroxylamine, which was difficult to isolate. This highlights that overoxidation is a nonissue and either the hydroxylamine or nitrone can be competent starting materials for the reductive rearrangement. A contraction of the aza-decalin was favored (30% yield for the contraction at 120 °C), going from a 6/6/6 bridged system to a highly caged 5/7/6 fused system, which could find potential use in asymmetric catalysis.[19] The phenethylamine *nor*-phenyl-MDBA **14** was converted to the corresponding aniline (**14c**, 52% yield for the 1,2-shift) and under mild conditions (40 °C), highlighting the utility of this chemistry in both cyclic and linear amines. Similar phenethylamines are currently in Phase III trials for the treatment of post-traumatic stress disorder.[20] The antimicrobial natural product *O*-methyl coclaurine[21] (**15**) was isomerized to the corresponding *N*-paramethoxybenzyl THIQ (**15c**) via 1,2-shift of the benzyl group (32% yield), again requiring elevated temperatures (120 °C). Lastly, the *N*-methyl-D-aspartate (NMDA)-receptor antagonist[22] Dizocilpine™ (**16**) was isomerized with the established protocol, enabling the conversion of a [3.2.1] bridged polycyclic amine to the corresponding fused 6/5/5/6 indoline system (**16c**) (28% yield, along with 38% of the indole **16d**) as a single diastereomer (see the SI). Interestingly, attempts to favor the indoline product via borane-mediated reduction with excess silane (6 equiv) and higher temperature (100 °C) resulted in a 60% isolated yield of the indole product, suggesting a dehydrogenative pathway is thermodynamically preferred in this case.

We have used density functional theory (DFT) calculations to better understand the observed selectivity for the ring contraction (vs the 1,2-shift of the peripheral substituent) of α-aryl piperidines. Geometry optimization and frequency calculations were conducted at the B3LYP-D3/6-311G(d,p) level of theory[23] using the asymmetric SMD implicit solvation model in 1,4-dioxane, and single point energy calculations were conducted at the M06-2X-D3/6-311G(d/p) level[24] using the same solvation model. DFT calculations were conducted using Gaussian 16 with the assistance of Spartan 20 and Orca5 for minima and saddle point starting structures, respectively (see

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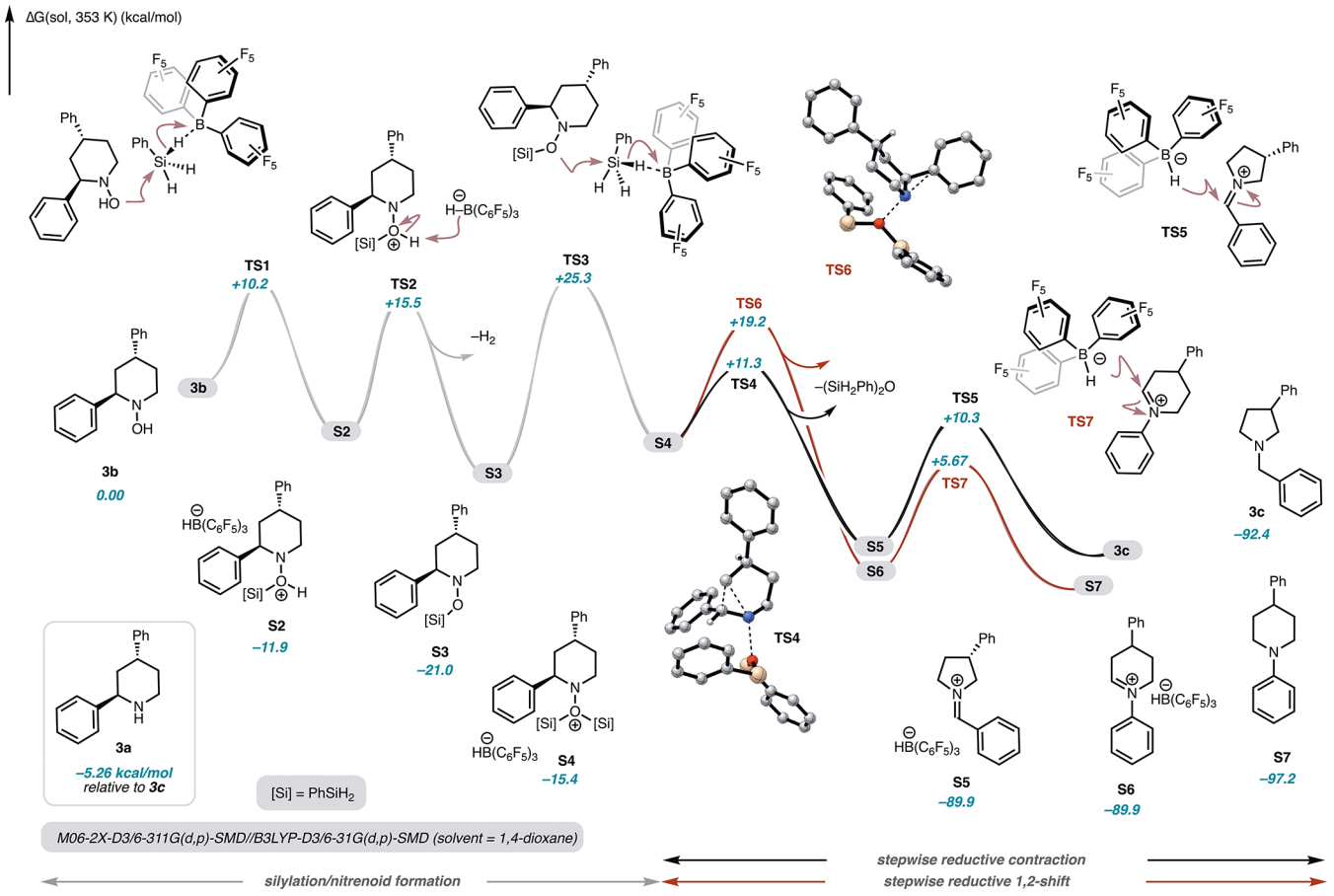
Scheme 4. Density Functional Theory Calculations: Reaction Path for the Borane-Mediated Contraction of Cyclic Hydroxylamines



the SI for computational details and full citations). Thermodynamic values (ΔG) shown are with respect to hydroxylamine **3b**, while kinetic values ($\Delta G^{\ddagger}$) are relative to the lowest preceding minimum (Scheme 4). Overall, the formation of pyrrolidine **3c** from hydroxylamine **3b** is highly exergonic (−92.4 kcal/mol), with the thermodynamic driving force arising primarily from conversion of bissiloxonium nitrenoid **S4** to pyrrolidinium intermediate **S5** (−89.9 kcal/mol with respect to **3b**). Interestingly, when the energies of the starting piperidine (**3a**; i.e., prior to oxidation) and its isomeric pyrrolidine contraction product (**3c**) are compared, this two-step process constitutes an introduction of strain (**3c** is +5.26 kcal/mol higher in energy than **3a** at the M06-2*X*-D3/6-311G(d,p)-SMD // B3LYP-D3/6-31G(d,p)-SMD level), which is offset by scission of the weak N−O bond. Direct contrathermodynamic isomerization is often achieved using photoirradiation, wherein the energy input is decoupled from the overall thermodynamics by partitioning between ground and excited state surfaces.[25,26] In this case, the energy input (i.e., oxidation to hydroxylamine) is decoupled from the isomerization thermodynamics by partitioning between two synthetic steps.

While the initial silylation (**TS1**, $\Delta G^{\ddagger}$ = +10.2 kcal/mol with respect to **3b**) and deprotonation (**TS2**, $\Delta G^{\ddagger}$ = +15.5 kcal/mol with respect to **S2**) are fast, bissiloxonium nitrenoid formation (i.e., **S3** → **S4** via **TS3**) was found to be the rate determining process ($\Delta G^{\ddagger}$ = 25.3 kcal/mol with respect to **S3**). The product-determining path from bis(siloxonium) **S4** to contraction product **3c** (via **TS4**) was kinetically favored over the corresponding path toward aniline product **S7** through iminium **S6** (via **TS6**). Our computations indicate that piperidine contraction is kinetically favored ($\Delta\Delta G^{\ddagger}$ = 7.91 kcal/mol), in excellent agreement with our experimental observations (only a single product is formed). Hydrogen and BCF are omitted in **TS4** and **TS6** for clarity. We propose that for the formation of **3c**, the interaction between the endocyclic σ_{C-C} bonding and σ^{*}_{N-O} antibonding orbitals results in a preorganized, concerted rearrangement process (supported by the stereospecific formation of **6c**, Scheme 2). In contrast, in the formation of **S6**, no such stereoelectronic interaction is geometrically feasible (see **TS6**), thus requiring significant distortion from the lowest energy conformation, wherein the bis(siloxonium) and α-aryl moieties are forced into the higher energy pseudoaxial positions.

In conclusion, we have developed a general strategy for the isomerization of cyclic amines, enabling core reorganization without the need for the addition or modulation of peripheral functional groups. The contraction method is mild and general for cyclic amines possessing electron-rich and electron-poor α-substituents, occurs with retention of configuration at the migrating carbon, and is not dependent on the presence of α-substituents. In the case of THIQ substrates, substrate control can be leveraged to enable a switch between ring contraction and 1,2-aryl shift modes. This chemistry enables the late-stage isomerization of biologically active molecules, effecting contractions and 1,2-shifts in cyclic amines as well as a 1,2-

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shift in a linear amine. Overall, we anticipate that this method will find use in drug discovery to enable the rapid survey of diverse amine topologies, with increased control over crucially important biological variables such as molecular weight, peripheral decorations, and hydrogen bonding vectors.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01093.

Additional experimental details, materials, and methods, and spectroscopic data for complete reproducibility of all experimental findings (PDF)

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Author Contributions

C.A. discovered and developed the reaction, designed the experiments, and conducted the computations. C.A., T.M.P., G.S., R.T.S., B.S., and J.D. ran the experiments. C.A. and R.S. directed the project. C.A. and R.S. wrote the manuscript. D.W.S. provided guidance on the computations. CRediT: **Charis Amber** conceptualization, data curation, formal analysis, investigation, methodology, visualization, writing - original draft, writing - review & editing; **Timothée Marie Petitjean** formal analysis, investigation, methodology, writing - review & editing; **Giedre Sirvinskaite** formal analysis, investigation, methodology, writing - review & editing; **Ryan T Steele** formal analysis, investigation, methodology, writing - review & editing; **Breanna Sprague** investigation, methodology; **Julius Domack** methodology; **David W. Small** data curation, formal analysis, investigation, methodology, writing - review & editing; **Richmond Sarpong** conceptualization, funding acquisition, project administration, writing - review & editing.

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Notes

The authors declare no competing financial interest.

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