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Intermolecular sp^3-C−H Amination for the Synthesis of Saturated Azacycles

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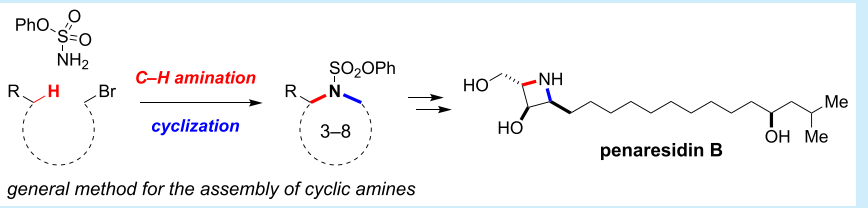
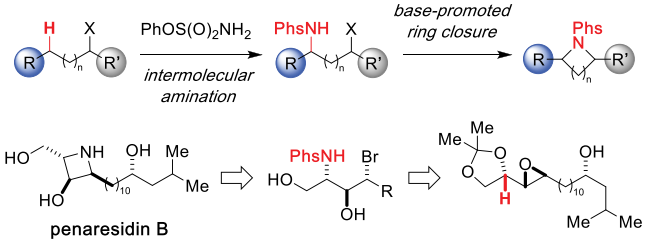
Supporting Information



ABSTRACT: The preparation of substituted azetidines and larger ring, nitrogen-containing saturated heterocycles is enabled through efficient and selective intermolecular sp^3-C−H amination of alkyl bromide derivatives. A range of substrates are demonstrated to undergo C−H amination and subsequent sulfamate alkylation in good to excellent yield. *N*-Phenoxysulfonyl-protected products can be unmasked under neutral or mild basic conditions to yield the corresponding cyclic secondary amines. The preparative convenience of this protocol is demonstrated through gram-scale and telescoped multistep procedures. Application of this technology is highlighted in a nine-step total synthesis of an unusual azetidine-containing natural product, penaresidin B.

Saturated azacycles are ubiquitous structural elements in natural products.[1] Cyclic amines also appear in designed molecules because of the unique and disparate physicochemical and topological properties of such heterocycles.[2,3] Accordingly, numerous methods, which rely on both conventional and modern C−N bond-forming tactics including C−H oxidation, enable access to pyrrolidine and piperidine derivatives.[4−6] We have been interested in developing a general protocol for assembling substituted azacycles of differing ring size, with a specific focus on azetidine structures. The value of such amines is considerable in synthesis, pharmacology, and medicine.[7−10] Herein, we present a method for the preparation of small (n = 3−5) and medium (n = 6−8) ring-sized azacycles that capitalizes on selective, intermolecular sp^3-C−H amination of brominated hydrocarbon substrates (Scheme 1). The efficient functionalization of substrates in which the desired site of C−H oxidation is proximal to an electron-withdrawing halogen group is unprecedented and underscores recent advances in Rh-catalyzed amination.[11−18]

Scheme 1. Selective Intermolecular C−H Amination for the Preparation of Cyclic Amines, Including Polyfunctionalized Azetidines



Typical methods for de novo azetidine synthesis include S_N2 displacement reactions of mono- and dihalopropanes with alkyl amines,[6,7,19] aziridine ring expansions,[6,7,20,21] thermal and photochemical [2+2] cycloadditions,[6,7,22,23] and Pd-catalyzed C−N cross-couplings (see Table S2 for relevant comparisons).[6,7,24,25] Our approach for constructing azetidine derivatives involves selective, intermolecular C−H amination of bromoalkanes to introduce the requisite nitrogen center followed by ring closure. Accordingly, the potential scope of this method is quite broad and extends beyond four-membered ring synthesis.

Exploratory studies to develop a process for azetidine synthesis were conducted with 1-bromo-3-phenylpropane **1a** (Table 1). The proximity of the electronegative Br group in **1a** to the benzylic site deactivates this position toward oxidation. Consequently, a number of reported C−H amination protocols fail to engage this substrate; others furnish small amounts of the desired product in combination with unidentifiable species (see Table S3 for relevant comparisons). Using a recently disclosed amination protocol developed in our lab,[26] intermolecular C−H amination of **1a** with phenyl sulfamate ($PhSNH_2$) proceeds in 64% yield to furnish **2a** (23% RSM). The intermediate bromoalkyl sulfamate ester efficiently cyclizes upon treatment with a base to provide the corresponding azetidine **3a** (see Table S1 for optimization). Through the application of this two-step sequence, **3a** is

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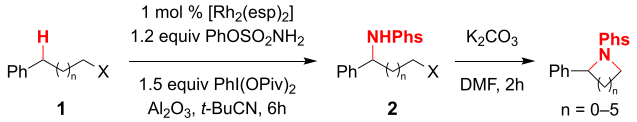
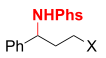
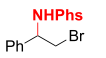
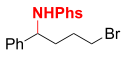
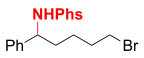
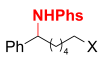
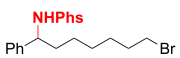
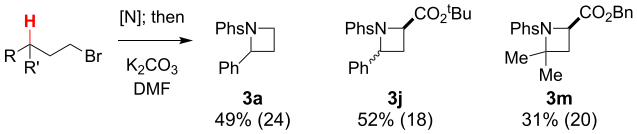
Table 1. Cyclic Amine Synthesis through C−H Amination



entry	C–H aminated product[a]				cyclized product[b]		
1		X = Br = OMs	**2a-1** **2a-2**	64% (23) 38% (56)		**3a**	97% 96%
2			**2b**	40% (15)		**3b**	–[c]
3			**2c**	42% (45)		**3c**	97%
4			**2d**	52% (40)		**3d**	98%
5		X = Br = OMs	**2e-1** **2e-2**	65% (22) 42% (47)		**3e**	98% 68%
6			**2f**	74% (17)		**3f**	22%[d]

[a]Reactions performed with 0.3 mmol of starting material and 0.3 mL of *t*-BuCN for 6 h; values in parentheses represent percent recovered starting material. [b]Cyclization performed with 0.1 mmol of C−H aminated product in 1 mL of DMF for 2 h. [c]The product aziridine is unstable to the reaction conditions; complete conversion of starting material is observed by ^{1}H NMR. [d]Reaction conducted for 10 h at ambient temperature. Piv = *t*-BuCO_2−; Phs = PhOS(O)$_2$−; DMF = *N*,*N*−dimethylformamide.

Scheme 2. Single-Flask Procedure for Azetidine Construction[a]

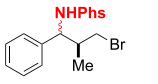
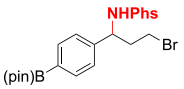
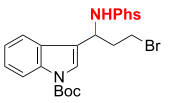
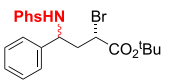
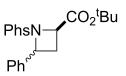
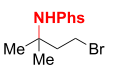
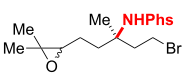
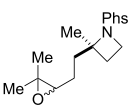
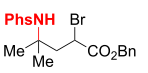
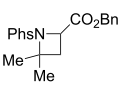
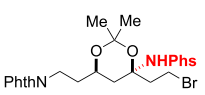
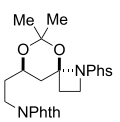
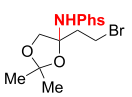
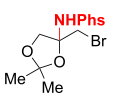
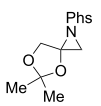
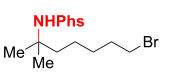


[a]Values in parentheses represent percent recovered starting material.

obtained in 62% overall yield (Table 1, entry 1). The effectiveness of the amination reaction, which affords largely product and recovered starting material, allows the cyclization reaction to be telescoped in a single-flask procedure. Following this protocol, pure azetidine **3a** can be isolated in 49% yield (Table S1; see Scheme 2 for more details).

To examine the generality of the amination method for assembling cyclic amines of varying ring size, a systematic analysis of reaction performance with phenyl-substituted bromoalkanes was conducted. Azacycles 3−8 units in size can be fashioned through our two-step sequence. For the most part, C−H amination yields improve as the distance between the Br-substituent and the benzylic center is increased; nonetheless, even phenethyl bromide **1b** can be oxidized in 40% yield to generate sulfamate **2b** (Table 1, entry 2). The cyclization event is consistently high yielding with the one exception involving azocane **3f** (Table 1, entry 6). As a final note, reactions performed with alkyl mesylate substrates show diminished product yields stemming from the inefficiency of

Table 2. Optimized Protocol for Cyclic Amine Assembly

entry	C–H aminated product[a]			cyclized product[b]		
1		**2g**[c]	60% (28)		**3g**	92%
2		**2h**	43% (37)		**3h**	78%
3		**2i**	71% (15)		**3i**	95%
4		**2j**[d]	69% (21)		**3j**	98%
5		**2k**[e]	61%		**3k**	83%
6		**2l**[f]	37% (57)		**3l**[f]	95%
7		**2m**[g]	53% (31)		**3m**[g]	93%
8		**2n**[h]	42% (38)		**3n**	91%
9		**2o**[g]	47% (10)		**3o**[g]	62%
10		**2p**[e]	63%		**3p**	78%
11		**2q**	64% (22)		**3q**	86%

[a]Reactions performed with 0.3 mmol of starting material and 0.3 mL of *t*-BuCN for 6 h; values in parentheses represent percent recovered starting material. [b]Cyclization performed with 0.1 mmol of C−H aminated product in 1 mL of DMF for 2 h. [c]Product isolated as a 1:1.8 mix of diastereomers; cyclization was conducted on the pure *syn*-diastereomer. [d]Product isolated as a 1:1.1 mix of diastereomers. [e]Recovered starting material was not obtained due to the high volatility of this compound. [f]Product isolated as a 1:1 mix of diastereomers. [g]Product decomposition occurs on silica gel. [h]Amination gives a >10:1 mix of isomeric products; ring closure was conducted on a pure sample of the isomer shown.

the amination reaction (Table 1, entries 1 and 5). Somewhat surprisingly, this finding holds even for 6-phenylhexyl mesylate (Table 1, entry 5), thus leaving in question an explanation for the suboptimal performance of the amination reaction with mesylate-derived starting materials.

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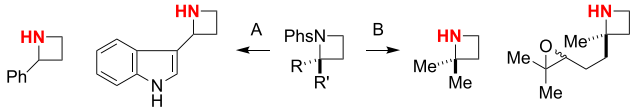
Scheme 3. Facile Phs Deprotection Affords N−H Azetidines[a]



[a]Method A: H_2O/CH_3CN, 90 °C; product isolated as the CF_3CO_2H salt following HPLC purification. Method B: H_2O/pyridine; oxalate salt of the product isolated by trituration.

To further explore the scope of our azacycle assembly method and to demonstrate its utility for fine chemical synthesis, substituted primary and secondary alkyl bromide derivatives were subjected to the optimized protocol (Table 2). C−H amination generally proceeds in yields ranging from 37 to 71%; subsequent ring closure is efficient and affords the desired azacycle products. In several cases, Phs-protected cyclic amines are obtained in high purity following aqueous workup without recourse to silica gel chromatography (Table 2, entries 1, 4, and 5).

Substrates bearing benzylic (Table 2, entries 1−4), tertiary (Table 2, entries 5−7 and 11), and protected carbinol C−H bonds (Table 2, entries 8−10) are successfully converted to the corresponding azacycles. The mild conditions for cyclization are tolerant of base-sensitive functional groups, including pinacolborane (Table 2, entry 2), *N*-Boc indole (Table 2, entry 3), and esters (Table 2, entries 4 and 7). Subjecting 1,3-dioxane and dioxolane-derived substrates (Table 2, entries 8−10) to the two-step sequence affords unusual *N,O*-acetal azetidines, which are amenable to further modification.[27,28] In addition, the stereospecificity of Rh-catalyzed C−H amination makes available optically active cyclic amines bearing tetrasubstituted centers (cf. entries 6 and 8).[26,29] As highlighted previously (see Table 1), cyclic amines of different ring sizes can be accessed using our amination/cyclization technology. Entry 10 is notable in this regard, as the glycerol-based substrate undergoes site-selective oxidation and ring closure with K_2CO_3 to furnish an isolable, spirocyclic aziridine *N,O*-acetal.

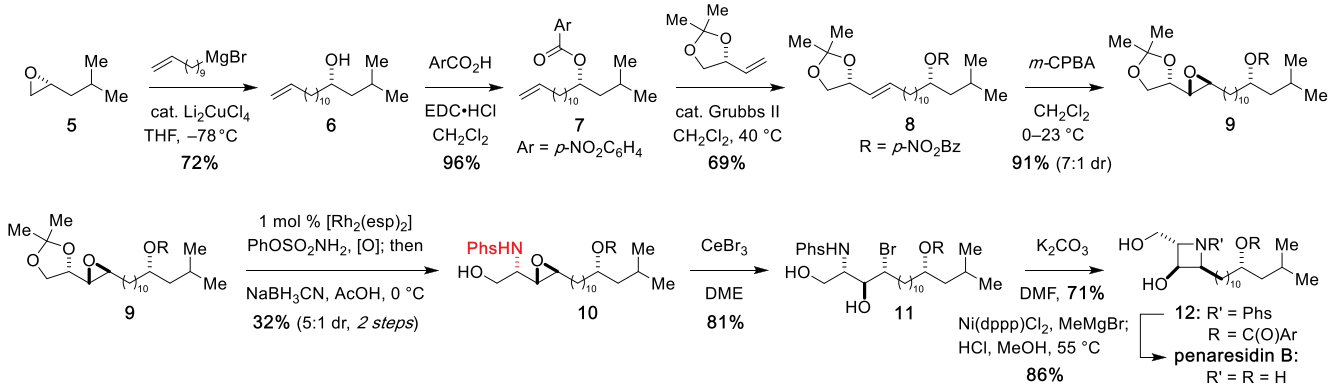
It is possible to conduct sequential C−H amination/cyclization in a single flask with only a small diminution in overall reaction performance (Scheme 2). This modified protocol is convenient when isolation of the C−H amination product is capricious, as is sometimes the case for *N,O*-acetal and other derivatives.

Phenoxysulfonyl (Phs) is a convenient and chromatographically stable N-protecting group, which can be readily removed to liberate the amine product (Scheme 3). Heating a Phs-amine starting material in aqueous CH_3CN or aqueous pyridine cleaves the Phs group; both conditions afford the desired amine in high purity following reversed-phase chromatography (HPLC) or trituration of the oxalate salt.[30]

To demonstrate the synthetic utility of our method for complex chemical synthesis, an unusual, azetidine-derived lipid penaresidin B was identified as a natural product target (Scheme 4).[31] Penaresidin B consists of a densely functionalized azetidine core with three contiguous stereocenters and a distally hydroxylated alkane side chain. Several total syntheses of penaresidin B[32−34] and related congeners[35−41] have been described, all relying on early stage nitrogen incorporation using starting materials such as Garner's aldehyde[42] and/or multistep functional group interconversions to construct the azetidine core. The shortest of the reported syntheses of penaresidin B is 17 linear steps.[34] Application of our C−H amination/cyclization method streamlines access to this natural product. Our route to penaresidin B capitalizes on the performance of dioxolane substrates for C−H amination. Beginning from enantiopure oxirane **5**,[43] addition of organocuprate to the less hindered terminus yielded alcohol **6**. Protection of the alcohol group as the *p*-nitrobenzoyl ester was intended to deactivate the carbinol C−H bond and the proximal tertiary site toward C−H amination. Grubbs' cross-metathesis of **7** with commercially available (*R*)-2,2-dimethyl-4-vinyl-1,3-dioxolane afforded olefin **8**, which was subsequently epoxidized to give **9** as an ∼7:1 mixture of diastereomeric products.

Generation of the desired sulfamate ester **10** from **9** necessitated the development of a single-flask protocol for sequential amination/reduction owing to problems with isolation of the intermediate *N,O*-acetal. Subjecting **9** to standard amination conditions followed by $NaBH_3CN$ furnished aminoalcohol **10** as an ∼5:1 mixture favoring the desired stereoisomer. This result is striking given the large number of disparate C−H bonds in **9** and the adjacent functional groups flanking the desired site of oxidation. This includes the epoxide moiety, which, much like a neighboring bromide group, strongly deactivates the C−H bond undergoing reaction. We anticipate that this amination/reduction protocol will prove useful for the assembly of structurally related amino-polyol motifs.

Scheme 4. Asymmetric Synthesis of Penaresidin B



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To complete the synthesis of penaresidin B, epoxide **10** was converted to bromohydrin **11** under the action of $CeBr_3$. Bromide displacement of **10** occurred regioselectively at C4 (penaresidin B numbering) to give **11** as the only detectable product.[44,45] The ordering of steps through this sequence obviates the use of protecting groups and affords a single bromohydrin regioisomer.

Finally, ring closure of the azetidine followed by sulfamate and nitrobenzoate deprotection yielded the desired target. Removal of the Phs-protecting group in **12** proved to be more challenging than with less functionalized azetidines (see Scheme 3).[46] Successful deprotection, however, was ultimately achieved by adapting a procedure for cross-coupling of cyclic sulfamate esters.[47] Under nickel catalysis with MeMgBr, displacement of the phenyl ring afforded the sulfated azetidine; subsequent treatment with methanolic HCl furnished the natural product. All told, the enantioselective synthesis of penaresidin B proceeds in nine steps from commercial starting materials, a substantial decrease in the overall step count compared to previous efforts.

We have described reaction technology for the generation of structurally diverse small- and medium-sized cyclic secondary amines. This process capitalizes on site-selective, intermolecular C−H amination to first introduce the obligatory nitrogen center as a sulfamate ester. Efficient C−H oxidation is viable across a range of functionalized propyl and longer chain alkyl bromide starting materials, substrates that have not been previously documented for amination reactions. We expect this work to advance the utility of C−H amination for the preparation of complex chemicals.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04096.

Experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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