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A Stereoselective Hydroamination Transform To Access Polysubstituted Indolizidines

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Supporting Information

ABSTRACT: Stereoselective, intramolecular, formal hydroamination of dienamines via directed hydroboration is reported. Four stereocenters are set in the process. Natural and unnatural indolizidine alkaloids can be synthesized from simple unsaturated amines using the title process.

The [*m.n.*0]-bicyclo-1-azaalkane ("izidine") structural motif is embedded within an estimated 25% of all known alkaloids.[1] Indolizidines ([4.3.0]-1-azabicycles) constitute a significant subset of izidines (Figure 1a), and those that bear

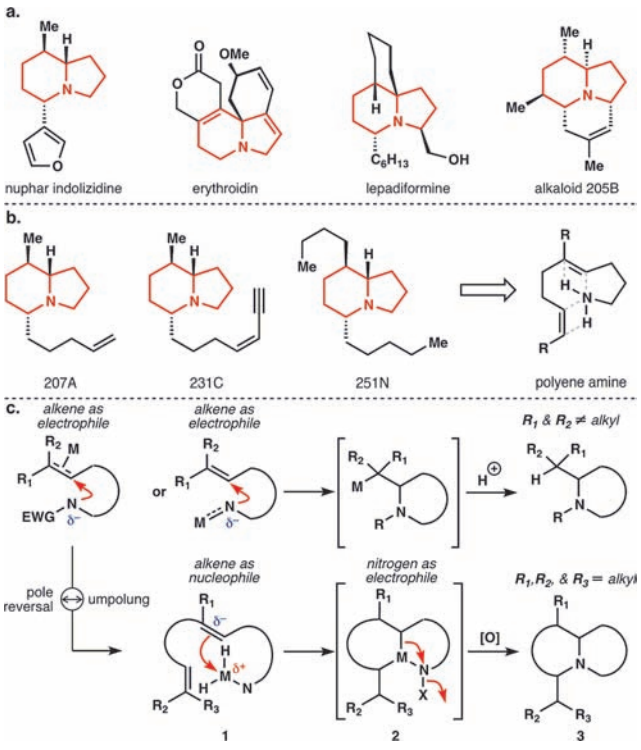

Figure 1. Indolizidines and the hydroamination transform.

a 5,8-disubstitution pattern are the prevailing alkaloid class in the pharmacologically important dart frog poisons.[2] Many of these 5,8-disubstituted indolizidines function as potent and subtype-selective noncompetitive blockers of nicotinic acetylcholine receptors (nAChRs),[3] which have been implicated in central nervous system disorders such as schizophrenia, epilepsy, Alzheimer's disease, Parkinson's disease, and major depressive disorder (MDD).[4] Retrosynthetic dissection of 5,8-disubstituted indolizidines via an intramolecular polyhydroamination transform (Figure 1b) is logical, obvious, and highly simplifying since it removes four covalent bonds and all three stereocenters in one step. However, existing hydroamination chemistry does not allow for this transform.[5]

As shown in Figure 1c (top), most hydroamination reactions proceed through the formation of a carbon−metal bond, and therefore, intramolecular hydroamination of a trisubstituted alkene in an anti-Markovnikov manner is particularly disfavored.[6,7] Furthermore, there are few examples of intramolecular *poly*hydroaminations that create more than two stereocenters.[8] We considered that an electron-deficient metal or metalloid hydride bound to nitrogen (**1**, Figure 1c, bottom) might allow for the necessary reaction to take place, as the alkene would instead participate as a nucleophile. Similarly, if the nitrogen could then be oxidized to accept nucleophiles, carbon-bond migration (**2** → **3**) might occur. Here we demonstrate that amine-directed hydroboration followed by in situ oxidation allows for a highly efficient hydroamination of tri- and tetrasubstituted alkenes and provides access to indolizidines bearing up to four stereocenters with high diastereoselectivity.

In 2003, Vedejs and co-workers pioneered a remarkable method for heteroatom-directed hydroboration that relies on iodine or triflic acid to open a valence on otherwise unreactive borane complexes.[9] However, dihydroboration[10] of polyunsaturated hydrocarbon chains was not reported, and indeed, when we explored this possibility on the borane complex derived from 2-(geranyl)ethylamine (**4a**) using the reported conditions (Scheme 1), very little borinic amide **6** was produced.

Instead, the reaction unexpectedly stalled after monohydroboration, presumably at intermediate **5**. This was partly due to the insufficiency of 0.1 equiv of I_2 to catalyze the reaction, but stoichiometric activation (0.5 equiv of I_2) also failed when the iodine was added in a single portion. When 0.5 equiv of I_2 in CH_2Cl_2 was added dropwise, production of **6** was observed, but the product distributions were erratic. Since **5** also contains a potentially photolabile B−I bond, we explored the exclusion of ambient light. Indeed, in the absence of light, efficient and reproducible conversion of **4a** to **6** was observed by LC−MS.

After extensive screening of oxidants, we also discovered that additional I_2 and 3 equiv of sodium methoxide are competent to convert borinic amine **6** into pyrrolidine boronic amine **8** in essentially quantitative yield via an alkyl shift of iodoamine **7**

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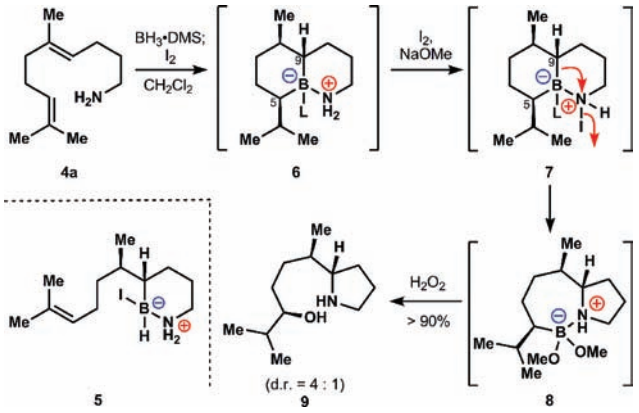
Scheme 1. Directed Double Hydroboration and Alkyl Shift



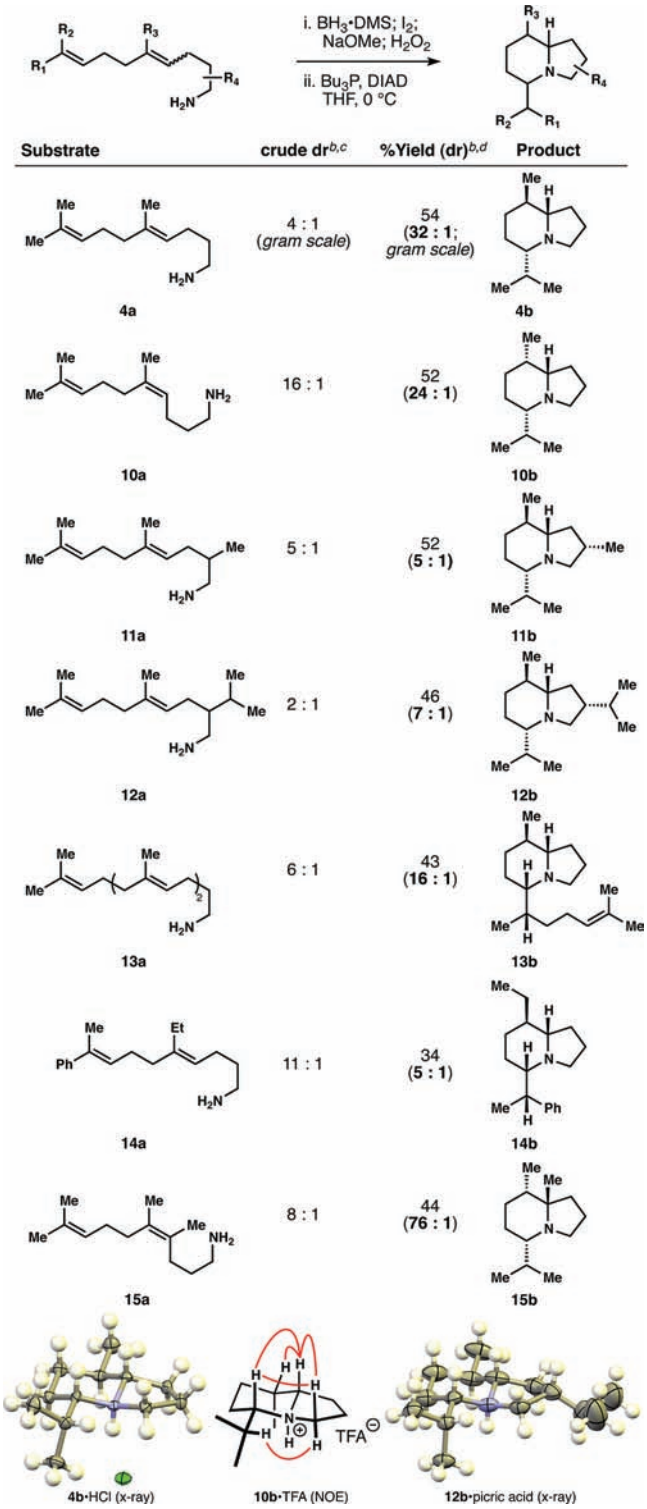
(Scheme 1; see below). X-ray crystallographic analysis of structures containing this pyrrolidine (e.g., **4b**; Table 12) showed that the alkyl migration occurs with retention of stereochemistry at C9. To our surprise, this oxidation is completely regioselective for C9 over C5 regardless of the steric environment (see entries **16a** and **17a** in Scheme 2). Oxidative workup of **8** with H_2O_2 cleanly produces amino alcohol **9** (>90% pure by HPLC, 4:1 d.r. by ^{1}H NMR analysis).[11]

Conversion of **8** or **9** to an indolizidine was not straightforward, but eventually we found that a modified intramolecular Mitsunobu reaction of **9** could be used to produce **4b** (Table 1) in acceptable yield. Purification initially proved challenging, but a useful procedure was developed in which the crude reaction mixture was adsorbed onto Amberlyst resin, washed with methanol to remove byproducts, and then treated with 2 N methanolic HCl to elute the indolizidine as the hydrochloride salt. Overall, the process displays good conversion (54% yield, amine **4a** → indolizidine **4b**), is simple to conduct on large scale (1.8 g of **4b**·TFA, 7.11 mmol), and provides a high level of stereoselectivity for the production of, in this case, three stereocenters (see the X-ray structure of **4b**•HCl, shown in Table 1).

This formal hydroamination process is applicable to a range of substrates, some of which are illustrated in Table 1. For clarity, only the ratio of the major diastereomer to the largest minor diastereomer is shown in the table (d.r. before and after chromatography). Since other isomers were observed by GC–MS, we included the total isomer content ratios in footnotes *c* and *d* of Table 1 (crude and purified, respectively). In most cases, the diastereomer ratios can be enriched by chromatography. The ratios of indolizidine diastereomers after chromatographic purification on silica are displayed with the yield.

Substrate **10a** demonstrates that the process is stereospecific, since the stereochemical outcome [see the nuclear Overhauser effect (NOE) signals of **10b**·TFA, shown in Table 1] can be specified by the alkene geometry. Substrates **11a** and **12a** illustrate stereochemical direction by existing chiral centers, the stereochemical outcome of which was established by X-ray crystallographic analysis of **12b**·picric acid.[12] Although the methyl and isopropyl groups both provide stereodirection, the stereochemical outcome is significantly worse for **12b** than for **11b**, for reasons discussed below. Alkenes distal to the intermediate borane are tolerated, as seen in farnesol-derived amine **13a**. Diverse substitution patterns such as the phenyl-, methyl-, and ethyl-substituted aminodiene **14a** can also be present, although the Mitsunobu reaction gives competitive

Table 1. Reaction Scope and Features[a]



[a]Conditions: (i) BH_3·DMS (1.0 equiv), CH_2Cl_2 (0.04 M), −78 to 22 °C; then I_2 (0.5 equiv), no light, 22 °C; then I_2 (1.0 equiv), NaOMe (4 equiv) in MeOH; then H_2O_2 (2 equiv). (ii) PBu_3 (3.0 equiv), DIAD (3.0 equiv), THF, 0 °C. [b]Determined by GC–MS. [c]Total crude isomer content for each entry: **4b**, 81:19; **10b**, 93:6:0.7:0.4; **11b**, 65:17:14:2:1:1; **12b**, 59:30:5:4:2:0.4; **13b**, 58:11:9:7:7:4:2:1; **14b**, 83:8:5:4:0.3; **15b**, 88:12. [d]Total isomer content for each purified indolizidine: **4a**, 97:3; **10b**, 96:4; **11b**, 84:16; **12b**, 88:12; **13b**, 93:6:1; **14b**, 79:17:3:1.5:0.2; **15b**, 98.7:1.3.

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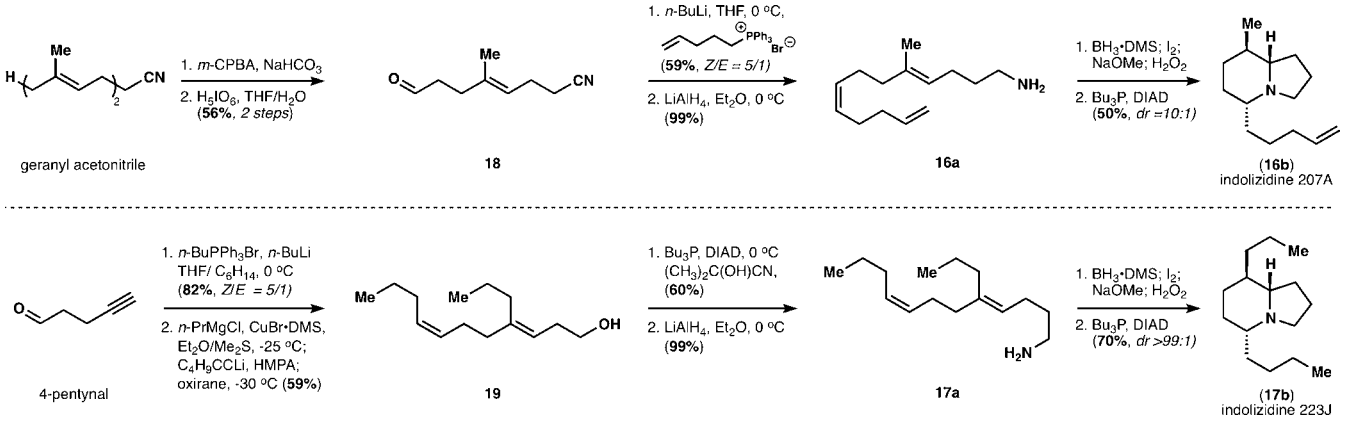
Scheme 2. Total Syntheses of Indolizidines 207A and 223J[a,b]



[a]Total crude isomer contents: **16b**, 88:8:4; **17b**, 99.8:0.2. [b]Total isomer content for each purified indolizidine: **16b**, 90.9:9.1; **17b**, 99.9:0.1.

elimination and decreased yield. It is worth emphasizing that eight diastereomers are possible in the formation of indolizidines **11b**−**14b**.

Syntheses of naturally occurring 5,8-disubstitited indolizidines are straightforward using this method (Scheme). Unsaturated amine **16a** is readily available in four steps from geranyl acetonitrile by oxidative cleavage of the terminal prenyl unit to provide **18**, followed by Wittig olefination and reduction. Cyclization of **16a** using our method produces the dart frog poison indolizidine 207A (**16b**) in 50% yield (10:1 d.r.). Indolizidine 207A has been synthesized seven times; the most efficient synthesis is enantioselective but requires 13 steps.[13] It is important to note that the directed double hydroboration is selective for the two internal trisubstituted alkenes over the terminal alkene, even though unhindered monosubstituted olefins hydroborate 4 times faster than 2-methyl-2-butene.[14] The subsequent oxidation step also does not affect the alkenes in **13a** or **16a**. Aminodiene **17a** is available in four steps by the following sequence. First, 4-pentynal is subjected to Wittig olefination and carbocupration/alkylation[15] to provide **19**. This alcohol can then be converted to **17a** by Mitsunobu cyanation and reduction. Amine **17a** is cyclized to the dart frog poison indolizidine 223J (**17b**) in good yield (70%) with exceptional diastereoselectivity (>99:1 d.r.). Racemic **17b** has previously been prepared in 19 steps.[16] Enantioselective syntheses of (−)-**17b** in 13 and 12 steps were reported by Enders[17] and Charette,[18] respectively.

Tetrasubstituted alkenes such as **15a** (Table 1) can also be used in this process, as shown in the formation of *tert*-alkylamine **15b**. This result argues against an alternative scenario for oxidation involving stereoinvertive[19] C−B bond iodination[20] (**20** → **21**) followed by stereoinvertive S_N2 attack by the amine on the C−I bond (**21** → **22**) (Figure 2a). It is unlikely that this iodination would be exclusively regioselective for C9 over C5 (see **20**), and the subsequent S_N2 reaction on a tertiary halide is improbable. On the other hand, iodination of the nitrogen (**20** → **23**) followed by coordination to boron (**24**) would align the N−I bond antiperiplanar to the migrating C−B bond in the *cis*-azaboradecalin (see **24** → **22**). An axial N−I bond would lead to the alternative carbon migration, but this configuration may be disfavored on steric grounds. Similarly, the alternative *trans*-azaboradecalin would position the isopropyl substituent axially and should be disfavored.

On the basis of the stereochemical outcome of the reaction and mechanistic considerations, a stereochemical model for the

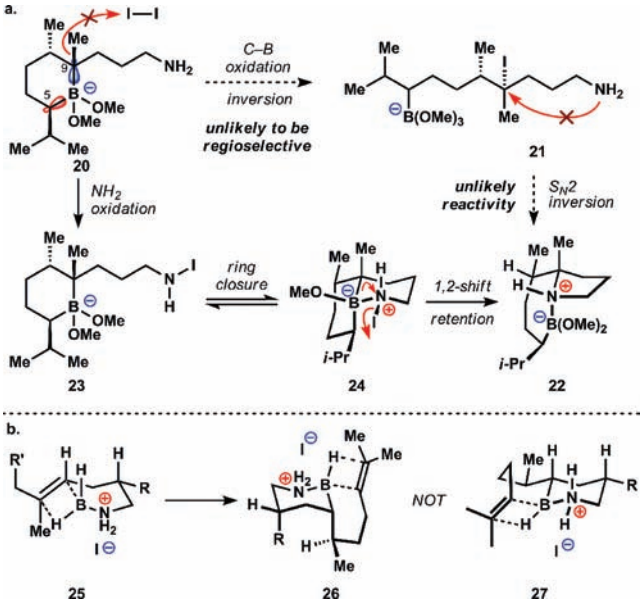


Figure 2. Possible Mechanistic Models.

double hydroboration is likely defined by two boat transition states (**25** and **26**; Figure 2b).[10] It is interesting that the major diastereomer appears to derive from conformation **26**, where the alkenyl side chain populates an axial position. No other trajectory for the observed stereochemical outcome appears feasible if we assume a four-centered transition state for C−B/C−H bond formation.[21] If the alkene side chain is positioned equatorially (e.g., **27**), the only reasonable geometries for hydroboration lead to the opposite (minor) diastereomer or a regioisomer (Markovnikov hydroboration). The above model is supported by entry **12a** in Table 1, where the isopropyl group leads to deteriorated diastereoselectivity, which is expected since this bulky group would suffer a 1,3 diaxial interaction with the unsaturated side chain in **26**. A possible explanation for the preference of conformation **26** over **27** is the additional requirement of axial attack by the alkene on boron to displace the iodide ligand prior to or in concert with hydroboration.[22]

In conclusion, we have demonstrated a diastereo-, regio-, and chemoselective hydroamination transform to access indolizidines from simple unsaturated amines that is based on a directed hydroboration/oxidative migration strategy. The hydroboration step can be highly stereoselective and works

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well on di-, tri-, and tetrasubstituted alkenes without the necessity of geminal disubstitution. The carbon−nitrogen bond-forming step appears to proceed through amine oxidation followed by alkyl transfer from the boron. The ease with which this reaction can be executed in the laboratory and the low cost of the reagents involved should expand the use of hydroamination transforms in retrosynthetic analysis. We are currently working to enable oxidative double alkyl transfer[23] and to render this process asymmetric. In view of the availability of polyolefinic feedstock chemicals coupled with recent advances in alkene synthesis, we expect this hydroamination transform to allow concise syntheses of diversely substituted izidine alkaloids in all stereochemical permutations.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reaction and products, including ^{1}H NMR and ^{13}C NMR spectra and CIF files. This material is available free of charge via the Internet at http://pubs.acs.org.

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