Synthetic Methods

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An Indoxyl-Based Strategy for the Synthesis of Indolines and Indolenines

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Abstract: *An indoxyl-based strategy for the synthesis of indolines and indolenines via unprecedented aza-pinacol and aza-semipinacol rearrangements was developed. This method provides direct access to the core structures of several classes of indole alkaloids. The synthetic utility was demonstrated by the divergent synthesis of an array of functionalized polycyclic structures from a common intermediate and the formal total synthesis of the indoline natural product minfiensine. The reversed reactivity of indoxyl as a building block compared to that of indole offers a conceptually distinct disconnection strategy for indoline- and indolenine-containing heterocycles and natural products.*

Indolines and indolenines based on a hydrocarbazole framework (Figure 1) are key structural features of akuammiline alkaloids and the *Strychnos* alkaloid minfiensine.[1,2] The intricate polycyclic structures and interesting biological activities of these complex natural products have attracted significant attention from synthetic chemists in recent years, leading to innovations in synthetic strategies[3] and stunning achievements in total synthesis.[4] Representative synthetic methods that have tremendously facilitated the chemical synthesis of related natural products include palladium-catalyzed asymmetric Heck reactions by the Overman group,[4a,b] carbene-mediated cyclopropanations by the Qin group,[2b,4c,k] interrupted Fischer indolization by the Garg group,[3d,4g,h] organocatalytic Diels–Alder reactions by the MacMillan group,[4d,m] and intramolecular oxidative coupling by the Ma group.[4j,l]

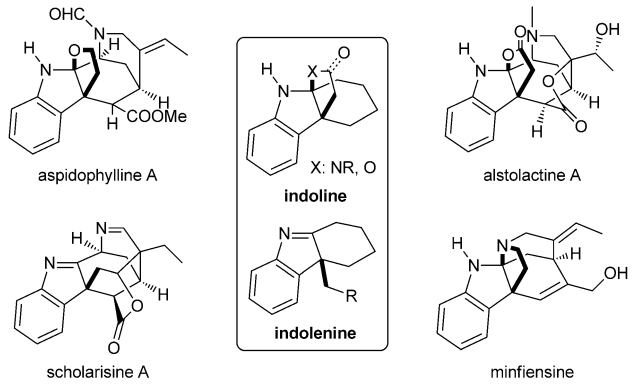
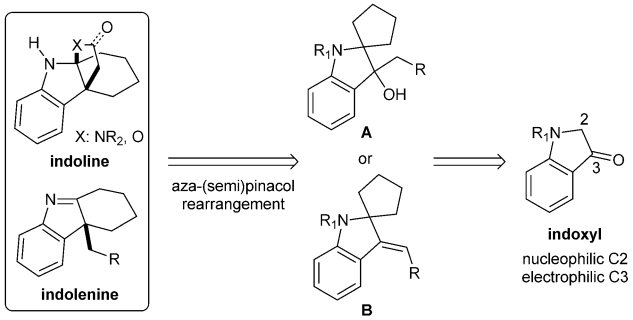


Figure 1. Representative natural products containing indolines/indolenines.

The majority of developed approaches toward the shown indolines and indolenines center on the transformation of the related indole derivatives or the construction the indole-type nucleus as the key strategy. New approaches employing different building blocks could offer alternative and distinct disconnection strategies to indolines and indolenines and thus facilitate the chemical synthesis of related natural products. Compared to indoles, indoxyls are heterocycles that have been far less investigated. Unlike indoles, in which C3 is most nucleophilic and C2 becomes electrophilic after C3 is activated, indoxyls are nucleophilic at C2 and electrophilic at C3.[5] The reversed reactivity of indoxyl compared to that of indole lays the basis for the development of unique disconnection strategies. Herein, we report an indoxyl-based strategy that proceeds via unprecedented aza-pinacol and aza-semipinacol rearrangements for the preparation of indolines and indolenines based on the hydrocarbazole framework.

Our strategy, which utilizes the unique reactivity of indoxyls for the synthesis of indolines and indolenines, is depicted in Scheme 1. We conceived that the shown indolines/indolenines could be furnished through aza-pinacol or aza-semipinacol rearrangements of the corresponding tertiary alcohol **A** or trisubstituted alkene **B**, which in turn could be readily generated through the synthetic elaboration of indoxyls. Although the pinacol and semipinacol rearrangements are powerful tools for constructing quaternary carbons,[6] their analogues the aza-pinacol and aza-semipinacol



Scheme 1. Indoxyl-based strategy towards indolines and indolenines.

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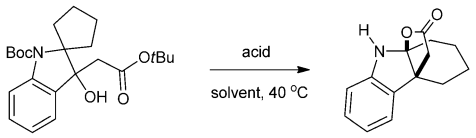
rearrangements enjoy much less success owing to the instability of the resultant imine, the weak driving force, and unpredictable side reactions.[7] While the scattered known examples mainly focus on extremely strained substrates, aza-pinacol and aza-semipinacol rearrangements involving ring expansion from a 5-membered ring to a 6-membered ring, as shown in Scheme 1, have been challenging. Mechanistically related to our design is the inventive work of the Driver group, which utilizes transition-metal-catalyzed ester migration for the synthesis of indolenines.[8]

A model reaction of **1a** was carried out first (Table 1) to produce an indoline with a fused lactone (**2a**), which represents the core structure of alstolactine A and lancifer-

Table 1: Optimized reaction conditions.[a]



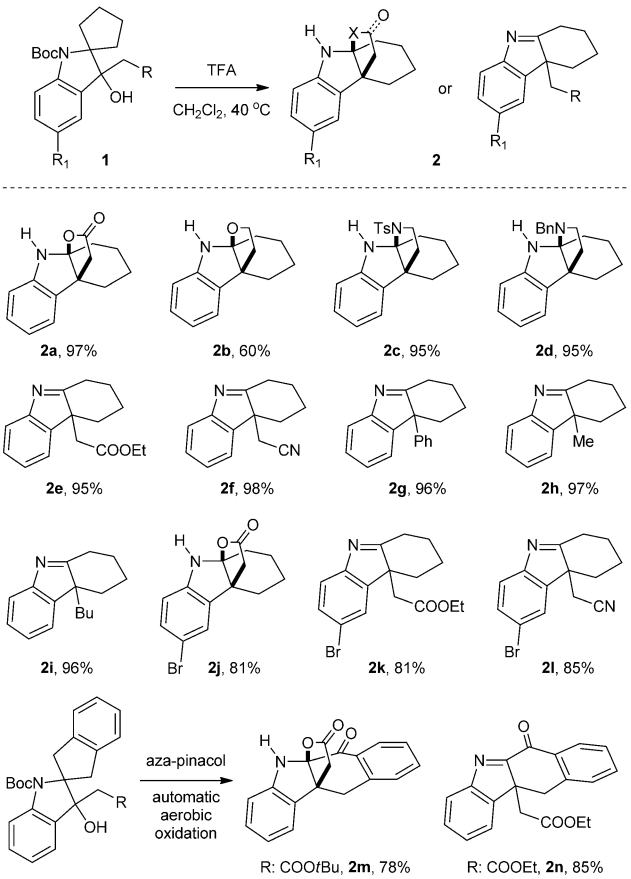
1a **2a**

Entry	Acid	Solvent	Yield [%][b]
1	TFA	DMF	0
2	TFA	1,4-dioxane	0
3	TFA	THF	0
4	TFA	CH_3CN	70
5	TFA	CH_2Cl_2	97[c]
6	4.0 M HCl in dioxane	CH_2Cl_2	88
7	TFA	CH_2Cl_2	90[d]

[a] Reaction conditions: The specified acid (0.4 mL) was added to a solution of **1a** (0.15 mmol) in 3.0 mL solvent. The resulting mixture was stirred at RT for 5 min and then heated to 40 °C for 5 h. [b] The yields were calculated by ^{1}H NMR using 1,3,5-trimethoxyl-benzene as the internal standard. [c] Yield of isolated product after silica-gel chromatography. [d] Yield of isolated product for the gram-scale synthesis (1.43 g, **2a**). TFA = trifluoroacetic acid, Boc = *tert*-butoxycarbonyl.

ine[9] (structure not shown in Figure 1) and has been challenging to access by other approaches. We envisioned that in the presence of a suitable acid, the cascade sequence involving cleavage of both protecting groups, aza-pinacol rearrangement, and cyclization of the carboxylic acid onto the resulting imine could occur in a single operation, thereby generating **2a** with remarkable efficiency. To our delight, after several attempts, we observed the formation of the desired product **2a** in 70% yield when using TFA as the acid and acetonitrile as the solvent (entry 4). Further optimization in terms of solvents, acids, concentration, and temperature led to the identification of optimized reaction conditions: the reaction was carried out in dichloromethane at 40 °C in the presence of TFA, delivering **2a** in 97% yield (entry 5). The structure of **2a** was unambiguously confirmed by X-ray structure analysis.[10] It should be noted that the reaction can be carried out on a gram scale with excellent yield (entry 7).

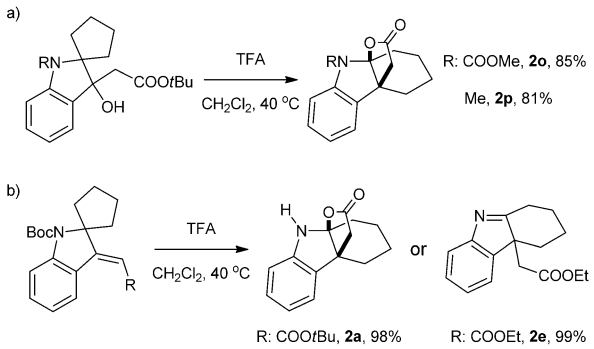
Under optimized reaction conditions, the substrate scope was investigated. A variety of tertiary alcohols **1** with different side chains (carboxylic ester, alcohol, protected amines,



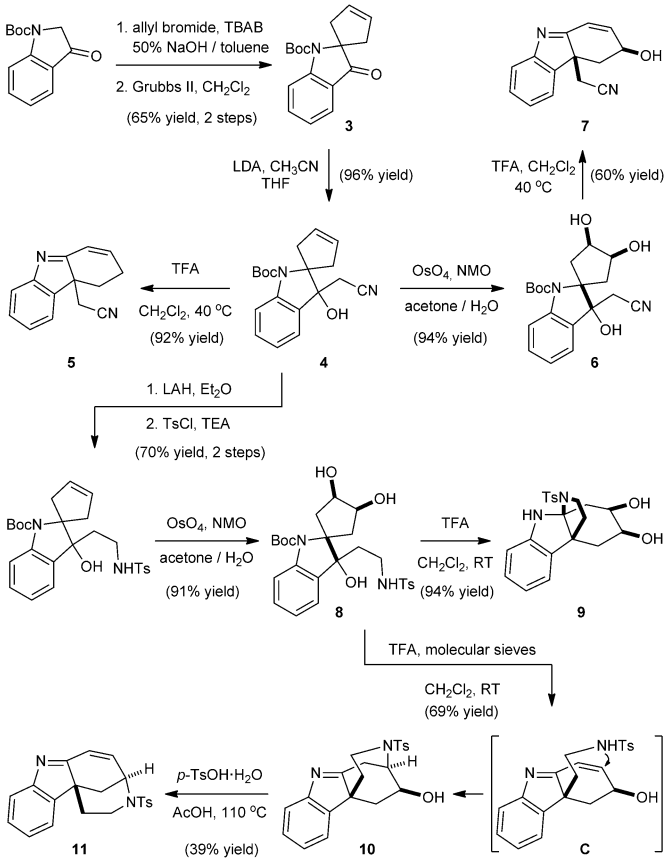
Scheme 2. Synthesis of indolines and indolenines based on the hydrocarbazole framework via aza-pinacol rearrangements.

nitrile, aryl, and alkyl) proved to be efficient substrates (Scheme 2). The deprotection/aza-pinacol rearrangement cascade sequence proceeded smoothly, generating indolines with different fused rings (**2a–d**) and indolenines with rich functionality (**2e–2i**), which represent the core structures of alstolactine A, aspidophylline A, vincorine, minfiensine, and many other akuammiline natural products. In addition, substrates bearing a bromide substituent on the phenyl ring were also investigated, furnishing products with synthetic handles for further elaboration (**2j–2l**). Moreover, the related aza-pinacol rearrangements with substrates containing an additional fused phenyl ring at the 5-membered ring were accompanied by automatic aerobic oxidation,[11] thereby affording the ketones **2m** and **2n** with good yields. Further decoration of the 5-membered ring and related transformations are reported in Scheme 4.

Besides using Boc as the protecting group, which was cleaved during the reaction, an alkyl substituent or other protecting groups, such as a methyl carbamate, on the nitrogen atom were also well tolerated (Scheme 3a), and the corresponding reactions furnished protected indolines (**2o, 2p**) in high yields. Besides tertiary alcohols, trisubstituted alkenes also turned out to be suitable substrates, and the related aza-semipinacol rearrangements (upon protonation) proceeded very well, generating **2a** and **2e** in comparable yields to those obtained by aza-pinacol rearrangement.



Scheme 3. Different protecting groups and substrates for the aza-semipinacol rearrangements.

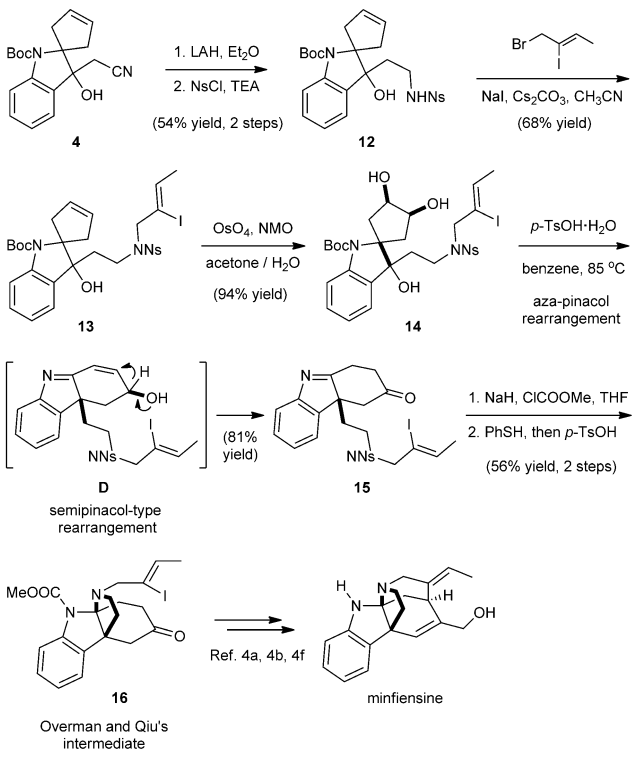


Scheme 4. Divergent synthesis of functionalized indolines/indolenines from a common intermediate. TBAB = tetrabutylammonium bromide, LDA = lithium diisopropylamide, LAH = lithium aluminum hydride, TEA = triethylamine, Ts = 4-toluenesulfonyl, NMO = 4-methylmorpholine N-oxide.

(Scheme 3b). These complementary results further demonstrated the generality of the reaction and provide more options for retrosynthetic design.

One appealing advantage of the current approach is that the unique reactivity of indoxyl could be utilized for the synthesis of more complicated substrates and thus offer a distinct disconnection strategy and complexity-generating approach for the synthesis of functionalized indolines and indolenines. As illustrated in Scheme 4, compound **3** was prepared in good yield through a two-step synthetic sequence[12] involving double allylation followed by Grubbs metathesis, utilizing the nucleophilic reactivity of C2 of the Boc-protected indoxyl. Next, electrophilic addition with acetonitrile occurred at the C3 carbonyl to produce tertiary alcohol **4**, which was subsequently transformed into **5** by aza-pinacol rearrangement accompanied by an alkene isomerization. Divergently, **6** was made by diastereoselective dihydroxylation[13] of **4** and converted into **7** in a similar manner upon dehydration. It should be noted that the synthetic transformation of **6** into **7** proceeded with excellent diastereoselectivity, thus highlighting the potential for the development of a highly efficient chirality-transfer process with a preinstalled chiral center. Nitrile **4** was further elaborated to tosyl amine **8** through a three-step manipulation: reduction of the nitrile, protection of the resultant amine, and dihydroxylation of the alkene. The cascade reaction of **8**, which involves deprotection/aza-pinacol rearrangement/cyclization, afforded **9** in 94% yield. Divergently, **10** was generated from **8** in good yield simply by adding molecular sieves to the reaction, presumably through a process involving intermediate **C**. Under forcing conditions, **10** was further transformed into **11**, which is a unique polycyclic structure that would be challenging to synthesize by other approaches. Thus, from a common intermediate **4**, which is readily prepared through the synthetic elaboration of indoxyl, several functionalized indoline/indolenines were successfully constructed in a chemically divergent manner.[14]

Next, we turned our attention to the chemical synthesis of minfiensine, a complex alkaloid that has received considerable attention from the synthetic community owing to its unique interconnected indoline ring system. Since its first isolation,[1f] the natural product has become a molecular benchmark to inspire the development of novel synthetic strategies and calibrate the utility of these methods in the synthesis of complex molecules. Several elegant approaches have been developed by the groups of Overman, Qin, MacMillan, Qiu/Zhang, and Padwa, and successfully applied to the total synthesis of this natural product.[4a–f] In this context, we chose minfiensine as a synthetic target to further demonstrate the utility of our indoxyl-based strategy and envisioned that conceptually distinct bond disconnections could be realized via aza-pinacol rearrangement (Scheme 5). From the common intermediate **4**, reduction of the nitrile and protection of the resultant amine afforded **12**, which was further transformed into **13** upon S_N2 alkylation. Diastereoselective dihydroxylation of **13** furnished **14** as a single isomer in excellent yield, which led to the formation of ketone **15** directly in a highly efficient manner. This remarkable single-step transformation highlights a cascade process involving deprotection/aza-pinacol rearrangement/elimination to furnish a transient intermediate **D**,[15] which is isomerized to **15** upon semipinacol-type rearrangement under acidic conditions. Finally, protection of the nitrogen atom followed by removal of the nosyl group and an intramolecular cyclization delivered **16**, which represents the key advanced intermediate employed in Overman and Qiu's total synthesis.



Scheme 5. Formal total synthesis of minfiensine. Ns = 2-nitrobenzenesulfonyl, THF = tetrahydrofuran.

In conclusion, an indoxyl-based strategy for the synthesis of indolines and indolenines via unprecedented aza-pinacol and aza-semipinacol rearrangements was developed. This strategy allows direct access to the core structures of several classes of indole alkaloids. From a common intermediate **4**, which is readily elaborated from indoxyl, the chemical synthesis of a diverse range of unique polycyclic structures and the formal total synthesis of the indoline natural product minfiensine were achieved, thus demonstrating the utility of this complexity-generating approach. We believe that the unique reactivity of indoxyl as a building block compared to that of indole could offer an alternative and distinct disconnection strategy for indoline/indolenine-containing natural products. Research along these lines, as well as the development of an asymmetric variant of the aza-pinacol rearrangement by using chiral acids, is currently underway within our group.

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[10] CCDC 1402825 (the structure of compound **2a** was determined by X-ray crystal analysis) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[11] Benzylic oxidation by molecular oxygen directed by the imine/enamine functionality.

[12] A single-step direct double allylation using the corresponding dibromide catalyzed by a simple phase-transfer catalyst (TBAB) produced **3** in 41 % yield.

[13] The excellent diastereoselectivity was presumably directed by the tertiary alcohol.

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[15] Intermediate **D** can be isolated and further converted into **15** (see the Supporting Information).

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