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Access to Polycyclic Indol(en)ines via Base-Catalyzed Intramolecular Dearomatizing 3-Alkenylation of Alkynyl Indoles

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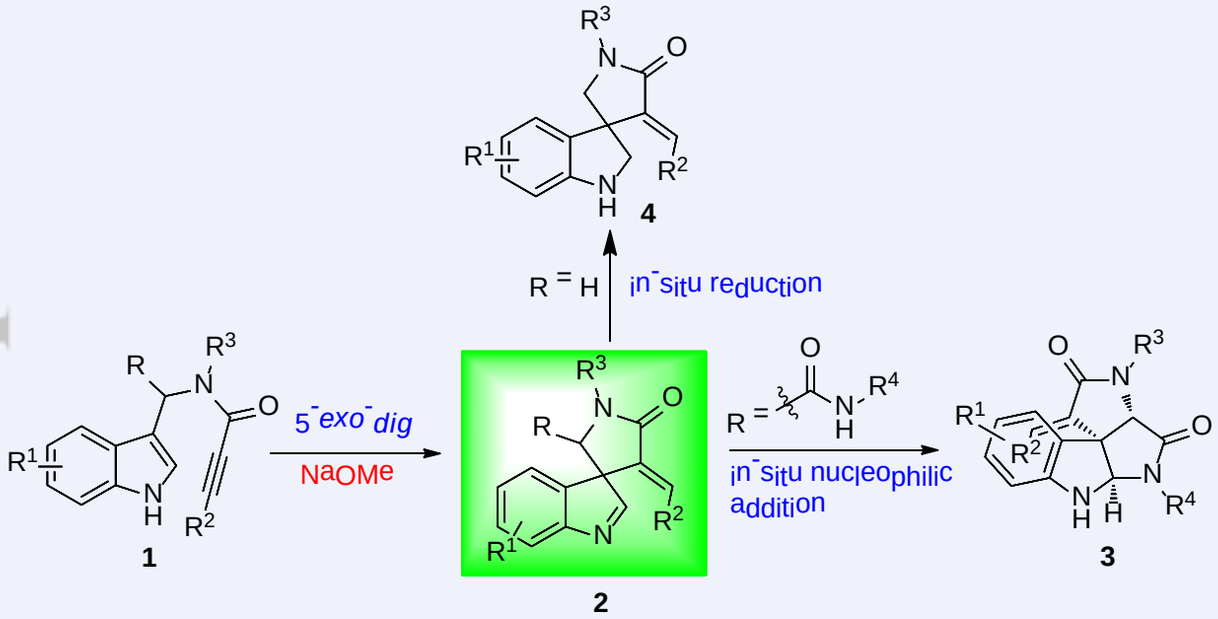
Keywords

Indoline| Dearomatization | Alkenylation | Alkynyl indole| Cascade cyclization

Main observation and conclusion

Polycyclic indolines and indolenines were synthesized via base-catalyzed intramolecular dearomatizing 3-alkenylation reactions of alkynyl indoles **1** at room temperature. The base enhanced the nucleophilicity of the carbon at the 3-position of the indole moiety, facilitating an exclusive 5-exo-dig cyclization reaction with the alkyne to form spiroindolenines **2**. The imine functionality of **2** could undergo in situ nucleophilic addition to form spiroindolines **3** when R was a carbamoyl group or reduction to form spiroindolines **4** when R was H.

Comprehensive Graphic Content



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Background and Originality Content

Polycyclic indolines and indolenines, particularly those with tertiary or quaternary C2 and C3 centers, are common in alkaloid natural products and biologically active molecules (Figure 1). In addition, polycyclic indol(en)ines are synthetically valuable as universal intermediates and building blocks for various molecular architectures.[1] The most step-economical methods for rapid access to these rigid compounds involve dearomatization reactions of readily available indoles, including dearomatizing allylation, arylation, and cycloaddition reactions.[2] Therefore, the development of novel dearomatizing methods to synthesize indol(en)ines is a subject of ongoing interest to both synthetic and medicinal chemists.

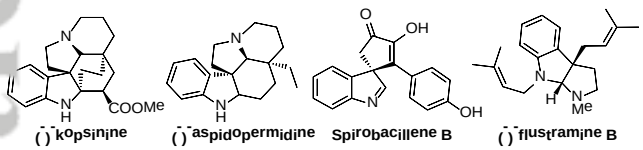


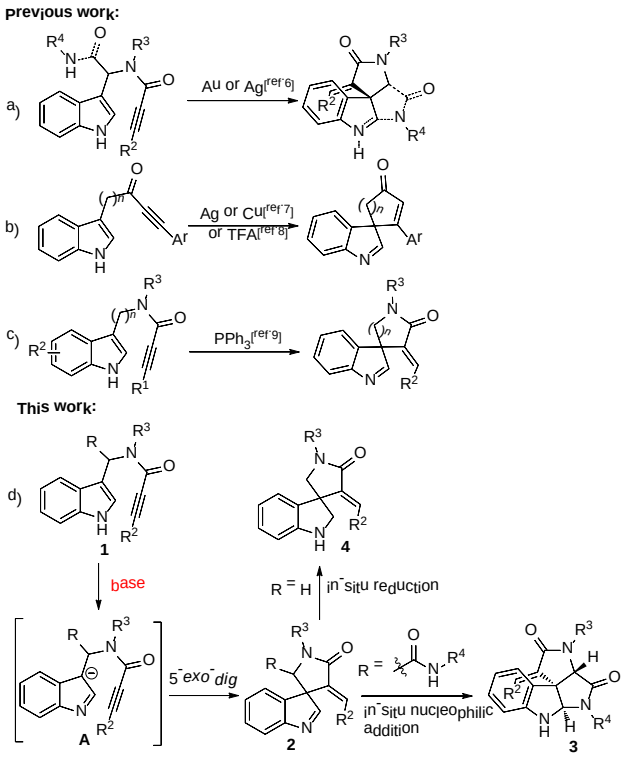
Figure 1 Indolenine and Indoline-containing Biologically Active Molecules

Because C3 of the indole moiety is nucleophilic[3] and alkynes are of versatile reactivities,[4] indoles bearing tethered alkyne side chains have frequently been employed as substrates for the construction of indol(en)ines via dearomatizing alkenylation reactions.[5] For example, Van der Eycken et al. used diastereoselective intramolecular Au- or Ag-catalyzed dearomatizing domino cyclization reactions of indolyl propiolamides to construct tetracyclic spiroindolines (Scheme 1a),[6] and Unsworth and co-workers reported an attractive protocol for Ag or Cu-catalyzed dearomatization of indole ynones to generate spiroindolenines (Scheme 1b).[7]

In addition to these transition-metal-catalyzed reactions, metal-free methods for dearomatizing alkenylation of alkynyl indoles have recently been reported. For example, Van der Eycken and co-workers reported a procedure involving intramolecular dearomatizing alkenylation of highly active indole ynones promoted by trifluoroacetic acid (Scheme 1b).[8] These investigators subsequently developed PPh_3-catalyzed intramolecular "umpolung Michael addition" reactions of active terminal indolyl propiolamides to form spiroindol(en)ines (Scheme 1c).[9a] More recently, visible-light-induced relaing radical methods for alkenylative spirocyclisation of indole-tethered ynone have also been documented.[9b-9d] Despite these dearomatizing alkenylation involving the activation of alkyne moiety, the development of new methods without requirement of precious metals，high temperature is still rare. Accordingly, it is highly desirable to develop new strategies involving enhancement of the nucleophilicity of C3 of the indole moiety by N-H deprotonation to undergo dearomatizing addition with the alkyne，which may avoid using of precious metals, allow the reaction to occur at low temperature. Moreover, the development of base-catalyzed cascade reactions of the obtained highly unsaturated spiroindolenines to produce polycyclic indolines are of special step-economy significance.

As part of our ongoing work on the synthesis of polyheterocycles via dearomatization of heteroaromatic rings,[10] we herein reported a base-mediated regioselective alkenylative dearomatization of N-((1H-indol-3-yl)methyl)propiolamides **1** to form indolenine **2** and its in situ addition reaction with a nucleophile or reduction to afford polycyclic indolines **3** and **4**, respectively (Scheme 1d). To the best of our knowledge, the anti-Michael addition of propiolamides with C-nucleophile under transition-metal-free conditions has seldom been reported yet. [11]

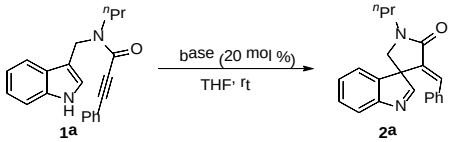
Scheme 1 Intramolecular Dearomatizing Alkenylation Reactions of Alkynyl Indoles



Results and Discussion

At the outset, we treated N-((1H-indol-3-yl)methyl)-3-phenyl-N-propylpropiolamide (**1a**) with a series of bases in THF at room temperature (Table 1). The outcome of the reaction depended markedly on basicity of the base. Weak bases (DABCO, DBU, Et_3N, Na_2CO_3, K_2CO_3, and Cs_2CO_3; entries 1-6) did not give the desired product, whereas strong bases (NaOMe, LiO^{t}Bu, NaO^{t}Bu, and KO^{t}Bu; entries 7 – 10) afforded the 5-exo-dig-type product spiroindolenine **2a**. Surprisingly, the 6-endo-dig-type product (convention Michael addition product) was not detected. The regioselectivity agrees well with the outcomes reported by Manoharan,[12] demonstrating that anionic endo-dig cyclizations are intrinsically less favorable than the competing exo-dig closures. The optimal base proved to be NaOMe, which gave **2a** in 84% yield (Table 1, entry 7).

Table 1 Optimization of the reaction conditions.[a]



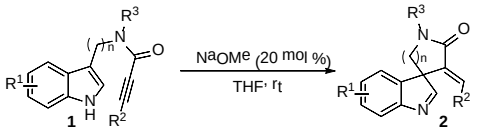
Entry	Base	Yield (%)[b]
1	DABCO	ND
2	DBU	ND
3	Et_3N	ND
4	Na_2CO_3	ND
5	K_2CO_3	ND
6	Cs_2CO_3	ND

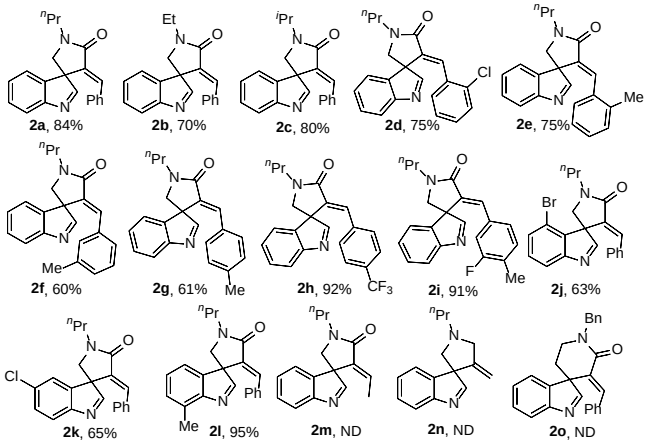
7	NaOMe	84
8	LiO^{t}Bu	70
9	NaO^{t}Bu	63
10	KO^{t}Bu	77

[a]Reaction conditions: **1a** (0.2 mmol), base (20 mol %), THF (1 mL), room temperature, N_2 atmosphere. [b]Isolated yields are provided. ND = not detection.

With the optimized reaction conditions in hand (Table 1, entry 7), we investigated the scope of the reaction by evaluating substrates **1** with various R^1, R^2 and R^3 groups (Scheme 2). When R^1 was H and R^2 was Ph, R^3 could be *n*-Pr, Et, or *i*-Pr, the corresponding products (**2a–2c**) were obtained in 70–84% yields. When R^1 was H, R^3 was *n*-Pr, and R^2 was a phenyl ring bearing a Me group or a Cl atom, the corresponding products (**2d–2g**) were obtained in moderate yields (60–75%). We were pleased to find that substrates in which the Ph group of R^2 had a 4-CF_3 group or a 3-F-4-Me substitution pattern gave excellent yields of the products **2h** and **2i** (92% and 91%), respectively. In addition, reactions of substrates bearing a Br or Cl atom or a Me group on the indole moiety proceeded well, giving corresponding products **2j–2l** in moderate to excellent yields (63–95%). Unfortunately, when R^2 was non-arylated group of Me, the desired **2m** did not formed. The failure may be owe to the instability of the corresponding alkenyl carbanion. This protocol complements with the method catalyzed by silver-nanoparticle, which are suitable for those substrates with non-arylated alkynes.[5d] Simple alkyne **1n** led to a complex reaction mixture without the formation of **2n**. Substrate **1o**, which has one-carbon extended, did not given the six-membered ring product **2o**. The exact reason for the failure of **1o** is not clear presently. We inferred that a higher energy barrier might be needed for it.

Scheme 2 Substrate Scope for Spiroindolenine Formation.[a]

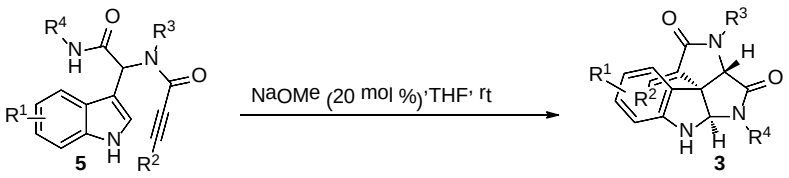


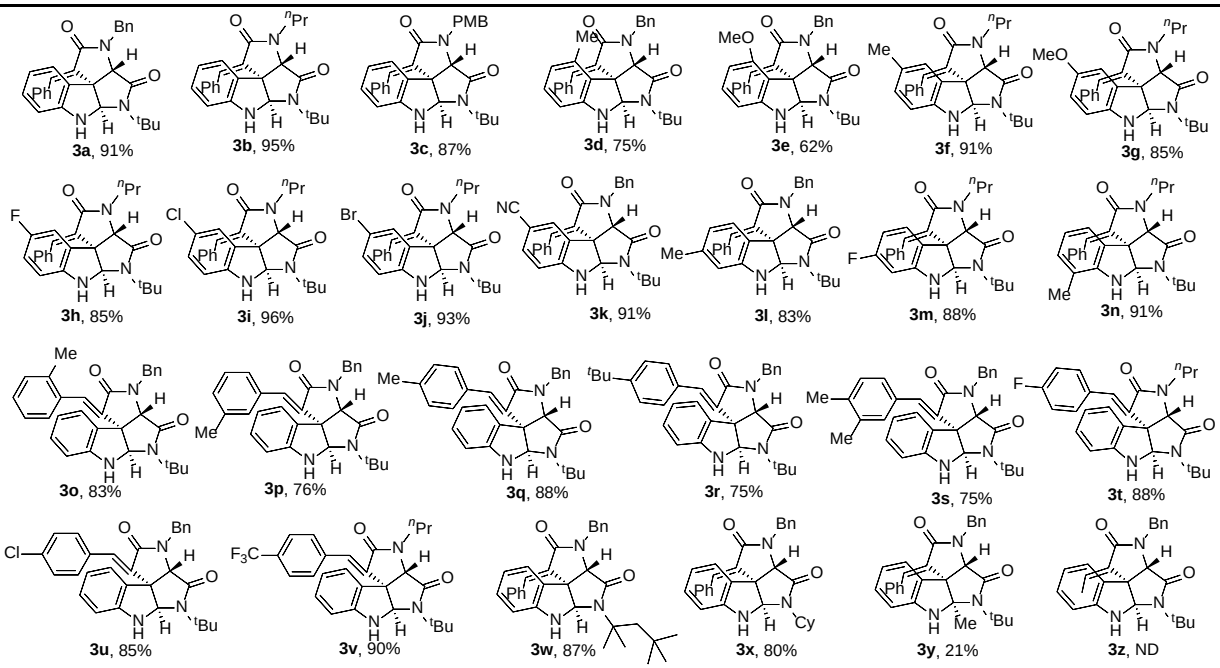


[a] Reaction conditions: **1** (0.2 mmol), NaOMe (20 mol %), THF (1 mL), room temperature, N_2 atmosphere. Isolated yields are provided. ND = not detection.

Next, a variety of Ugi condensation products **5** prepared by reactions of indole-3-carboxaldehydes, amines, and propiolic acids were subjected to the optimized conditions for the dearomatizing alkenylation (Scheme 3). To our delight, almost all these substrates were converted to tetracyclic spiroindolines **3** in good to excellent yields. These transformations involve tandem intramolecular 5-exo-dig cyclization to provide the corresponding spiroindolenine and subsequent in situ nucleophilic addition reaction toward the imine functionality with the amide acting as the nucleophile. Specifically, substrates with R^1 = H, R^2 = Ph, R^4 = ^{t}Bu, and R^3 = *n*-Pr, benzyl, or PMB (p-methoxyphenyl) were found to afford products **3a–3c** in excellent yields (87–95%). The structure of **3a** was verified by single-crystal X-ray analysis (see the SI). Furthermore, high yields were obtained when R^1 was either electron-donating (Me or OMe) or electron-withdrawing (F, Cl, Br, or CN) (**3d–3n**, 62–96%). The substituent at R^2 could also be electron-donating or electron-withdrawing: desired products **3o–3v** were obtained in 75–90% yields. In addition, substrates bearing a 2,4,4-trimethylpentyl or cyclohexyl group at R^4 also delivered excellent yields of corresponding products **3w** and **3x**, respectively. Notably, even when there was a Me group at C2 of the indole moiety, the in situ nucleophilic addition still occurred to give **3y**, albeit in low yield (21%). However, when R^2 was Me, corresponding product **3z** was not detected, and most of the substrate decomposed.

Scheme 3 Substrate Scope for Spiroindoline Formation.[a]

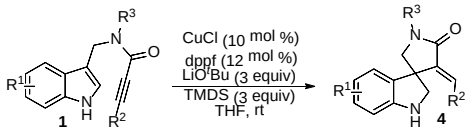


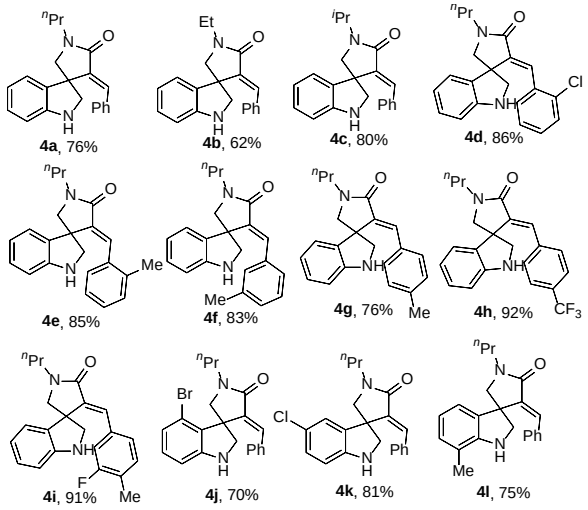


Reaction conditions, unless otherwise noted: **5** (0.2 mmol), NaOMe (20 mol %), THF (1 mL), room temperature, N_2 atmosphere. Isolated yields are provided. ND = not detection.

Encouraged by the above-described results, we carried out experiments aimed at converting alkynyl indoles **1** into spiroindolines **4** by means of a cascade involving 5-exo-dig cyclization to afford spiroindolenines and subsequent in situ reduction of the imine moiety. This transformation would avoid the necessity of isolating the intermediate spiroindolenines, which tend to decompose during silica gel chromatography.[13] For a reductant, we chose copper(I) hydride (CuH), which is frequently used in reduction reactions[14] and was generated by the reaction of a copper salt, an alkoxide, and a silane. We envisioned that the alkoxide might also simultaneously catalyze the dearomatizing alkenylation step. To our delight, upon treatment of **1** with CuCl, dppf (bis(diphenylphosphino)ferrocene), LiO^tBu, and TMDS (tetramethyldisilylsilyl)amine)) in THF containing trace amount of H_2O as a proton source at room temperature, corresponding spiroindolines **4a–4l,** were formed in one pot in moderate to excellent yields (62–92%, Scheme 4). It is notable that during such process, [Cu-H] can chemoselectively reduce the C=N bond in the presence of an electron-deficient C=C bond. The keeping of the C=C bond might result from its weaker electron-withdrawing ability and large steric hidrance of the tri-substitutents. For the detailed reaction optimization for the formation of **4a**, please see the Eletronic Supporting Information. Notably, other alkoxides, such as, NaOMe NaO^{t}Bu, KO^{t}Bu led to no formation of **4a** but a significant amount of **2a**. Conventionally, tert-butyl oxygen anion is used as a base to generate CuH species and lithium ion faciliates the reductive amination.[15] LiO^tBu possibly promoted the formation of Cu-H species and reduction steps simultaneously.

Scheme 4 Substrate Scope for One-Pot Spiroindoline Formation.[a]



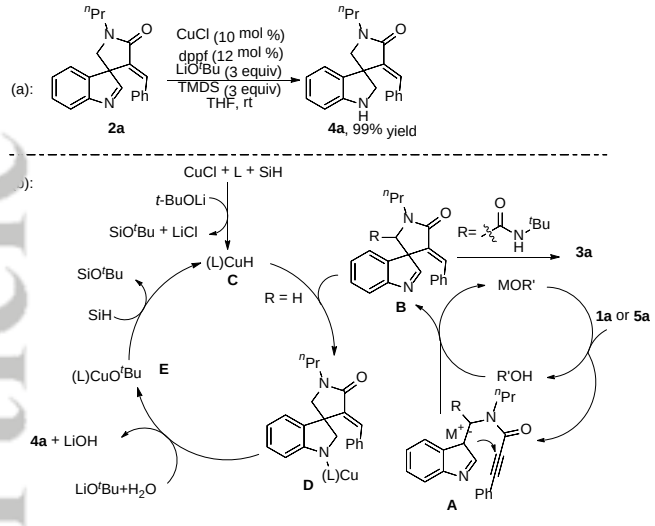


[a]Reaction conditions Reaction conditions, unless otherwise noted: **1** (0.2 mmol), CuCl (10 mol %), dppf (12 mol %), LiO^tBu (3.0 equiv), TMDS (3.0 equiv), THF (1000 ppm H_2O, 3 mL), room temperature, N_2 atmosphere, 12 h. Isolated yields are provided. TMDS = 1,1,3,3-tetramethyldisilazane.

A control experiment was conducted to gain insight into the reaction mechanism. Specifically, we subjected spiroindolenine **2a** to the standard conditions shown in Scheme 4 and obtained corresponding product **4a** in 99% yield (Scheme 5a). On the basis of this outcome，previously reported results on dearomatizing alkenylation reactions of indoles[5-8] and CuH-catalyzed reduction reactions,[14] we propose the mechanism shown in Scheme 5b. First, indolenine anion intermediate **A** is generated by reaction of **1a** or **5a** with the alkoxide. Then C3 of the indole undergoes 5-exo-dig-type intramolecular nucleophilic addition with the alkyne, which is followed by protonation to generate spiroindolenine intermediate **B** and regenerate the alkoxide. When R is an amide, the imine can be trapped and **3a** is formed. In contrast, when R is H, spiroindolenine **2a** reacts with (L)CuH to form the

intermediate **D**, which is then transformed into **4a** and (L)CuO*t*Bu (**E**). The reaction of **E** with silane regenerates (L)CuH.

Scheme 5 Control Experiment and Possible Reaction Mechanism



Conclusions

In summary, we have developed a protocol for accessing polycyclic indolines and indolenines via base-catalyzed intramolecular dearomatizing alkenylation reactions of alkynyl indoles at room temperature. This transformation involves the use of a simple base to enhance the nucleophilicity of C3 for dearomatizing alkenylation, which is an unusual strategy. This protocol provides an alternative route to dearomatizing alkenylation of indole ring with arylated alkynoic amide under simple and mild conditions in anti-michael addition fashion. The initially formed spiroindolenine products can undergo a cascade sequence involving in situ nucleophilic addition or in situ reduction to afford spiroindolines. These mild reactions use readily available starting materials and show high step- and atom-economy. We are currently investigating further applications of this protocol, including the use of other (hetero)aromatic rings, and we are exploring the bioactivities of the structurally novel products.

Experimental

General Procedure for the Synthesis of 2 and 3. To an oven-dried 25 mL Schlenk tube under N_2 atmosphere equipped with a magnetic bar were added substrate **1** or **5** (0.2 mmol, 1.0 equiv), NaOMe (2.0 mg, 20 mol %) and THF (1.0 mL). The mixture was stirred at room temperature for 12 h. The corresponding reaction mixture was filtered through a pad of celite, washed with EtOAc and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate = 5/1) to give corresponding products.

General Procedure for the Synthesis of 4. To an oven-dried 25 mL Schlenk tube under N_2 atmosphere equipped with a magnetic bar were added CuCl (10 mol %, 2.0 mg), dppf (12.3 mg, 12 mol %), *t*-BuOLi (48.0 mg, 3 equiv), TMDS (80.0 mg, 3 equiv) and THF (2 mL), the mixture was stirred at room temperature for 10 minutes. And then substrate **1** in THF (1.0 mL) was added. The mixture was stirred at room temperature for 12 h. After completion of the reaction, the corresponding reaction mixture was filtered through a pad of celite, washed with EtOAc and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (petroleum ether /ethyl acetate = 3/1) to give corresponding products.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2021xxxxx.

Acknowledgement

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Access to Polycyclic Indol(en)ines via Base-Catalyzed Intramo-lecular Dearomatizing 3-Alkenylation of Alkynyl Indoles

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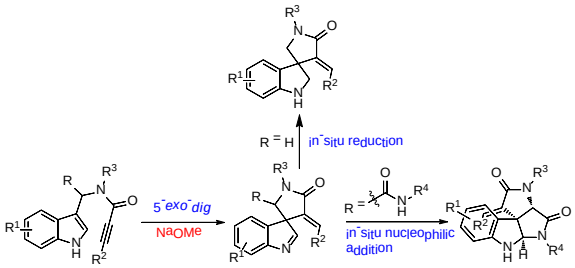

Polycyclic indolines and indolenines were synthesized via base-catalyzed intramolecular dearomatizing 3-alkenylation reactions of alkynyl indoles at room temperature.

