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Silver(I)-Catalyzed Dearomatization of Alkyne-Tethered Indoles: Divergent Synthesis of Spirocyclic Indolenines and Carbazoles

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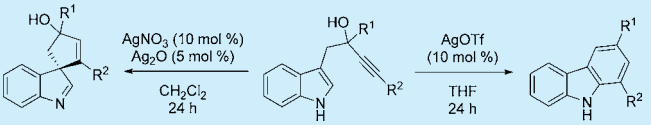
Supporting Information

ABSTRACT: A high-yielding, divergent approach to generate either spirocyclic indolenines or carbazoles from a common indole-tethered propargyl alcohol precursor is described, with mechanistic insight provided. Either product can be obtained upon treatment with different Ag(I) catalysts at rt. An unexpected hydration reaction to afford (±)-actinopolymorphol B is also reported.



The indole subunit can be found in numerous biologically active natural products and pharmaceutical compounds.[1] For example, benzo-fused indoles (carbazoles) have well established, broad therapeutic potential, with prominent examples exhibiting anticancer, anti-HIV, and antimalarial properties (**1**−**3**, Figure 1).[2] Spirocyclic indolenines have also

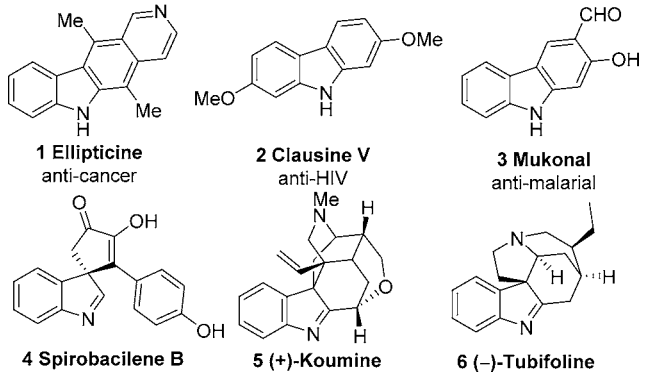
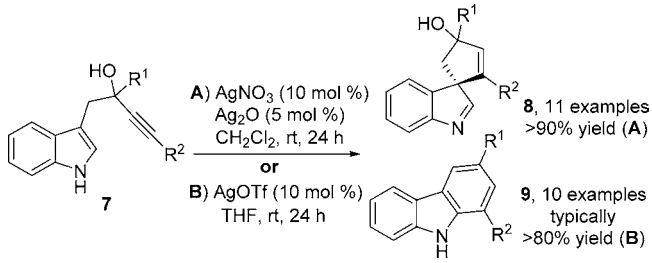


Figure 1. Carbazole and indolenine natural products.

attracted attention in recent years, in view of their presence in various natural products (**4**−**6**, Figure 1)[3] and their ability to act as precursors for other privileged heterocycles such as indolines and oxindoles[4] and as scaffolds to evaluate under-explored regions of chemical space in a range of bioassays.[5] New methods that expedite the synthesis of each of these scaffolds are therefore of significant interest.

Herein, a high yielding, divergent strategy for the selective synthesis of either spirocyclic indolenines (**8**) or carbazoles (**9**) from a common indole precursor (**7**) is described (Scheme 1). During a previous study in our research group,[6] we reported a single example of a novel carbazole-forming reaction, based on the activation of an indole-derived propargyl alcohol[7] with AgOTf. This transformation was proposed to proceed via an initial Ag(I)-catalyzed spirocyclisation (*cf.* **7** → **8**), before undergoing 1,2-migration[8] and subsequent elimination *in situ*,

Scheme 1. Divergent Synthesis of Spirocyclic Indolenines and Carbazoles



furnishing a carbazole product (*cf.* **9**). In this study, it was planned to identify reaction conditions that would deliver either spirocyclic indolenine **8** or carbazole **9** selectively. The known propensity for related spirocyclic alkenes to undergo the aforementioned 1,2-migration[9] makes the isolation of the spirocyclic products a challenge, but by careful choice of the Ag(I) catalyst and solvent, we have established that either product can be formed in high yield. Optimized procedures for the synthesis of either product class are reported, as well as mechanistic speculation to account for their formation.

The study began by examining the reaction of novel indole **7a** with either AgOTf or $AgNO_3$ as catalyst (Table 1). First, compound **7a** was treated with 10 mol % AgOTf in CH_2Cl_2 at rt for 24 h (entry 1) and the major component of the unpurified reaction mixture was carbazole **9a** (90%), although a small amount of spirocyclic indolenine **8a** (10%) was also formed. Pleasingly, full conversion into carbazole **9a** could be achieved simply by changing the reaction solvent to either THF or toluene (entries 2 and 3). Interestingly, by switching the catalyst to $AgNO_3$, the selectivity was reversed under otherwise identical conditions; in each of the three solvents tested, the only product formed was the spirocyclic indolenine **8a**, as a

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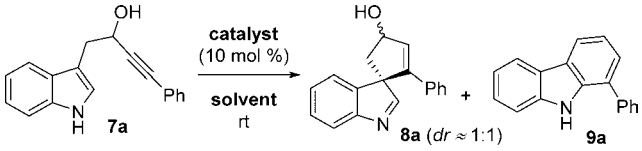
Table 1. Ag(I)-Mediated Reactions of Alkyne 7a



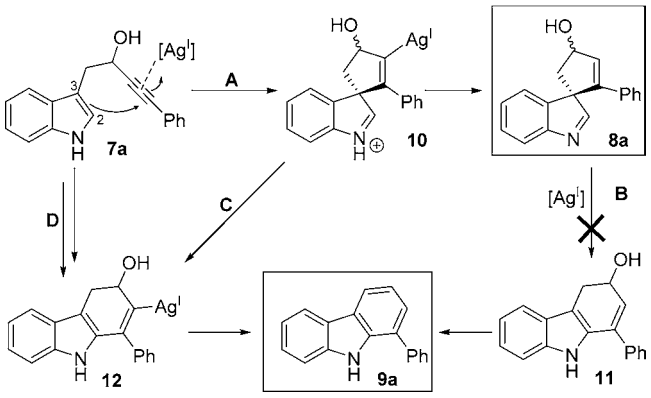
				proportion, %[d]		
entry	catalyst[a]	solvent	additive	7a	8a	9a
1	AgOTf	CH_2Cl_2	–	–	10	90
2	**AgOTf**	**THF**	–	–	–	**100**
3	AgOTf	PhMe	–	–	–	100
4	$AgNO_3$	CH_2Cl_2	–	trace	>95	–
5	$AgNO_3$	THF	–	10	90	–
6	$AgNO_3$	PhMe	–	90	10	–
7	AgOTf	THF	Et_3N[b]	55	45	–
8	$AgNO_3$	CH_2Cl_2	*p*-TSA[c]	20	40	40
9	**$AgNO_3$**	**CH_2Cl_2**	**Ag_2O[b]**	–	**100**	–

[a]Reactions performed with 0.1−0.2 mmol of **7a** and 10 mol % catalyst in the stated solvent (0.1 M) at rt. [b]5 mol %. [c]2 mol %. [d]Calculated using the ^{1}H NMR spectrum of the unpurified reaction mixture, rounded to the nearest 5%.

roughly 1:1 mixture of diastereoisomers (entries 4−6). One theory to account for this complementary reactivity is the presence of adventitious Brønsted acid (either present in the AgOTf reagent or formed *in situ*) in the carbazole forming reactions.[10] In order to probe this, triethylamine was included in a reaction with AgOTf in THF (entry 7); the expectation was that the basic additive would quench any Brønsted acid present and promote spirocyclic indolenine formation rather than carbazole formation. Pleasingly, this switch was indeed observed, albeit with an accompanying decrease in overall conversion. Furthermore, when *p*-TSA was included in a reaction with $AgNO_3$ in CH_2Cl_2 (which had selectively furnished spirocycle **8a** in the absence of acid), an appreciable amount of carbazole **9a** was formed, further corroborating the idea that a Brønsted acid has an important influence on the reaction outcome. Having learned that basic additives facilitate the formation of spirocycle **8a** over **9a**, other additives were tested, this time in combination with $AgNO_3$ in order to establish a reliable synthetic procedure for spirocycle formation; several additives were trialled, and the addition of 5 mol % of Ag_2O was found to be the most effective (entry 9). The optimal conditions for the formation of either product (entries 2 and 9) were taken on to further scoping studies (see later).

A number of mechanistic possibilities were considered to account for the formation of the two products (Scheme 2). The formation of spirocycle **8a** is the more straightforward of the two pathways; activation of the alkyne with the π-acidic Ag(I) catalyst[11] presumably promotes spirocyclization via nucleophilic attack of the indole 3-position (route **A**; **7a** → **10**) before protodemetalation reveals the indolenine product (**10** → **8a**). The formation of carbazole **9a** is more complicated. One possibility is that indolenine **8a** is an intermediate en route to **9a** and that it undergoes 1,2-migration (route **B**; **8a** → **11**) followed by elimination (**11** → **9a**). However, this pathway is unlikely, given that subjecting a purified sample of indolenine **8a** to the optimal carbazole-forming reaction conditions (10 mol % AgOTf in THF for 24 h) resulted in no reaction, while its treatment with various Brønsted acids under the same conditions resulted in the formation of complex product mixtures. A more likely pathway is therefore one in which the

Scheme 2. Mechanistic Possibilities



same vinyl silver intermediate (**10**) is formed and that 1,2-migration occurs at this stage (route **C**; **10** → **12**) before subsequent protodemetalation and elimination (**12** → **9a**). A third possibility, in which intermediate **12** is formed directly via nucleophilic attack through the indole 2-position (route **D**; **7a** → **12**) cannot be ruled out, although it is less likely based on typical indole reactivity and on related precedent.[8,9,12] No reaction occurs when compound **7a** is treated with Brønsted acids in the absence of a Ag(I) catalyst, confirming the importance of Ag(I), presumably in promoting the initial spirocyclization reaction. It is less clear what species is responsible for the 1,2-migration step, but the initial screening results and additive studies clearly demonstrate the importance of a Brønsted acid in these reactions, indicating that this step may by mediated by a Brønsted acid, rather than the Ag(I) catalyst itself.[9] Further studies are clearly needed to fully elucidate the precise mechanism, but the observation that it is likely to be vinyl silver intermediate **10**, rather than spirocycle **8a**, that undergoes the key 1,2-migration is intriguing and is expected to be instructive during future endeavors in the field of Ag-catalysis.

The scope of each of the two reaction modes was examined using the optimized conditions, beginning with the spirocyclization procedure (Figure 2).[12,13] Good reactivity was observed for electron-neutral (**8a**), electron-rich (**8c**), and electron-poor (**8d**) aromatic examples, and silyl protection on the alcohol is also well tolerated (**8b**). Similarly, simple alkyl (**8e**) and cyclopropyl (**8f**) spirocycles were furnished in excellent yield. It was also shown that the protocol is not limited to secondary alcohols, with tertiary alcohol containing spirocycles (**8g** and **8h**) both formed in excellent yield. The inclusion of a thiophene group in product **8i** indicates that other heterocycles can be used in this method. Finally, indoles substituted on their 2-position are also suitable substrates, with indolenine **8j** being formed in quantitative yield under the standard conditions. There was no diastereocontrol in any of the reactions (all products were isolated as aproximately 1:1 mixtures of diastereoisomers; see Supporting Information), but the consistently high yields are pleasing nonetheless, especially in view of the fact that related spirocyclic alkenes have been shown to be unstable with respect to 1,2-migration.[9] Previously, it was suggested that an electron-withdrawing carbonyl group is needed to reduce the migratory aptitude of the alkene product,[6] but this study shows that this is not a strict requirement, provided suitably mild conditions are used; in particular, the absence of a Brønsted acid appears to be crucial. This knowledge is likely to be of importance during the development

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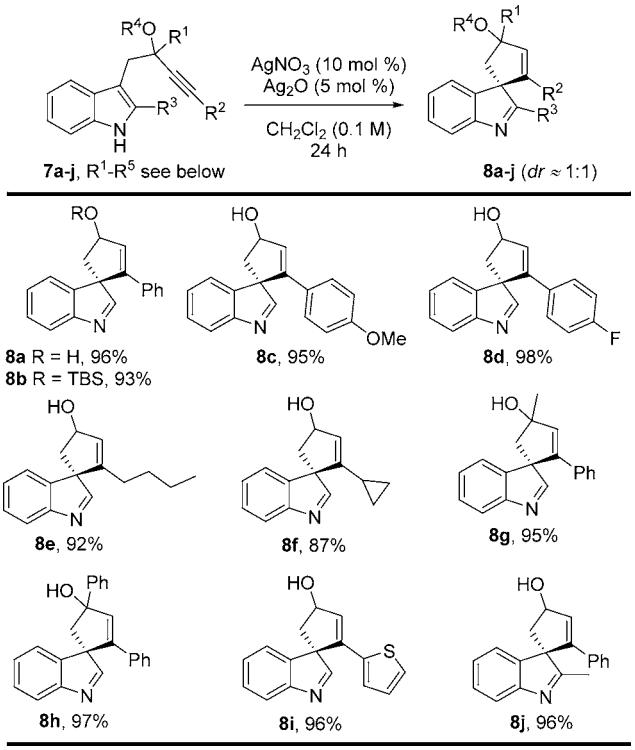
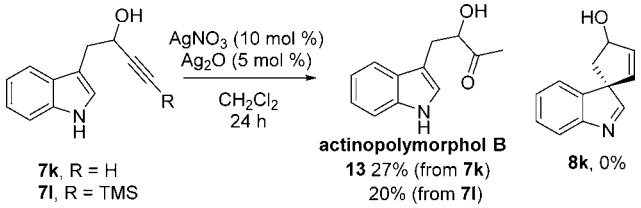


Figure 2. Ag(I) mediated dearomatizing spirocyclization to form spirocyclic indolenines.

of other dearomatization reactions involving electrophilic alkyne activation.

The only substrates tested which failed to deliver the desired spirocyclic indolenines are shown in Scheme 3. The terminal

Scheme 3. Synthesis of Actinopolymorphol B 13



alkyne starting material **7k** and its trimethylsilyl-substituted analogue **7l**[14] were each treated under the standard conditions for indolenine formation in the expectation of forming spirocycle **8k**. However, none of the desired product was isolated in either example; in both cases the bulk of the reaction mixture was unreacted starting material, along with a small amount of the natural product (±)-actinopolymorphol B **13**.[15] Alkyne hydration reactions of this type have traditionally been performed under acidic conditions using a Hg(II) catalyst,[16] although, more recently, Ag(I) and Au(I) variants have also been reported;[17] these variants are typically performed at much higher temperatures than used in this study; hence, it was somewhat surprising to isolate natural product **13** under such mild conditions.

The scope of the carbazole formation protocol was also explored.[18] Generally good functional group compatibility was observed, with carbazoles **9a**,**c**−**g** all being formed in good to excellent yield upon treatment with AgOTf in THF (Figure 3). However, there are some differences between the scope of each

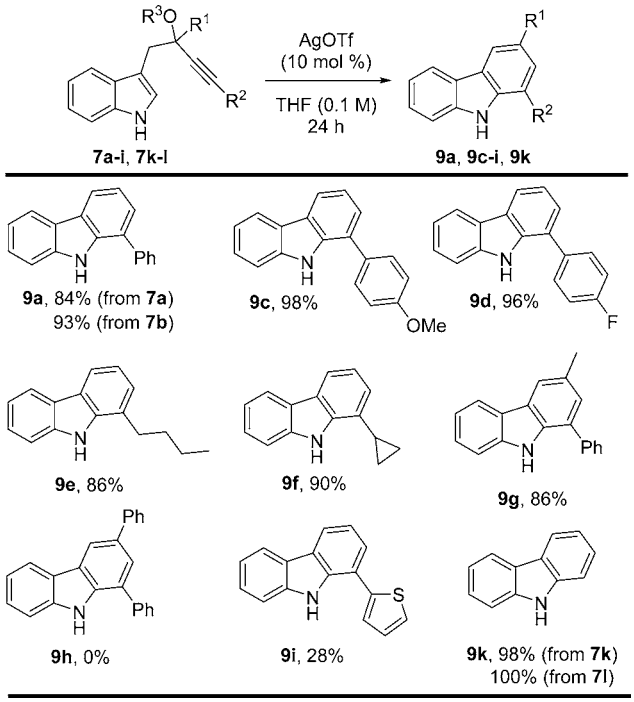


Figure 3. Ag(I) mediated carbazole synthesis.

protocol. Carbazole **9h** was not formed under the standard reaction conditions, which instead furnished a complex mixture of products.[19] Also, carbazole **9i** was isolated in much lower yield in this series, with the majority of the material recovered being spirocycle **8i**, indicating that there is a higher energy barrier to the 1,2-migration pathway in this system. However, in contrast to the indolenine series, terminal alkyne starting material **7l** and its trimethylsilyl-substituted analogue **7m** were both very well tolerated, furnishing parent carbazole **9k** in excellent or quantitative yield, respectively.[20] Note that the carbazole product was formed as a single regioisomer in all cases, with the regiochemical outcome being consistent with the 1,2-migration of the alkenyl group (see **10** → **12**, Scheme 2). This outcome is to be expected, based on a consideration of the relative migratory aptitudes of the two substituents in the presumed intermediate spirocycle and is supported by comparing the spectroscopic data of carbazoles **9a** and **9c** to those previously reported,[21] and also by X-ray crystallographic data for carbazole **9d** (see Supporting Information).[22]

In summary, we have identified mild and operationally simple conditions to selectively generate spirocyclic indolenines and carbazoles from the same readily available starting material. Both procedures typically proceed in high yield and have been shown to work on a range of functionalized alkyne tethered indoles. The results accrued shed light on the mechanism of each process, indicating that the spirocyclization step is Ag(I)-catalyzed, whereas the 1,2-migration step, which appears to proceed via a vinyl silver intermediate, could be promoted by an adventitious Brønsted acid. Finally, the natural product (±)-actinopolymorphol B was synthesized unexpectedly when the standard indolenine-forming conditions were applied to terminal alkyne substrate **7k**, or its TMS-substituted analogue **7l**. Although the yields of the two hydration reactions are low at present, these preliminary results offer hope that with additional optimization other silver-mediated hydration con-

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ditions may be uncovered, for use in the improved synthesis of hydroxyl ketone **13** and related natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02216.

Experimental procedures, spectroscopic data, and X-ray data (PDF)

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Notes

The authors declare no competing financial interest.

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(20) The contrasting reactivity of substrates **7k**/**7l** under the two sets of reaction conditions is surprising; further studies are planned to probe this effect.

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(22) CCDC 1404713 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/.

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