Spirocycles

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Silver(I)- or Copper(II)-Mediated Dearomatization of Aromatic Ynones: Direct Access to Spirocyclic Scaffolds**

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Abstract: *A high-yielding silver(I)- or copper(II)-catalyzed dearomatizing spirocyclization strategy allows the conversion of simple aromatic compounds that contain ynone substituents, including indole, anisole, pyrrole, and benzofuran derivatives, into functionalized spirocyclic scaffolds. A high-yielding asymmetric variant furnishes spirocyclic indolenines in up to 89:11 e.r.*

Dearomatizing spirocyclization reactions[1] are an effective means to generate functionalized three-dimensional scaffolds from simple aromatic precursors, which is important in research programs driven by the formation of molecular complexity and the exploration of chemical space.[2] The dearomatization strategy described herein is based on the conversion of aromatic ynone derivatives into spirocycles through alkyne activation with a simple Lewis or π-acidic catalyst, illustrated by the conversion of indole derivative **1** into 3,3-substituted spirocyclic indolenine **2** (Figure 1 a).[3,4] A significant problem with this type of transformation is the proclivity of the spirocyclic products to undergo a facile 1,2 migration under acidic conditions, which is driven by the restoration of aromaticity. This issue is particularly prevalent with indolenines. An illustrative example was recently reported by Van der Eycken (Figure 1 b):[5] spirocyclic indolenine **4a** was formed in low yield when alkyne **3** was treated with $AuPPh_3Cl/AgOTf$, the other major product being the rearomatized indole **4b**. Indeed, while processes involving the electrophilic activation of alkynes have been well studied in recent years,[6] Van der Eycken's example is, to the best of our knowledge, the highest-yielding acid-catalyzed spirocyclization of its type reported in the literature;[7] in related processes, rearomatized products such as compound **4b** are reported far more often (not only with indoles, but across a range of heteroaromatics).[7,8]

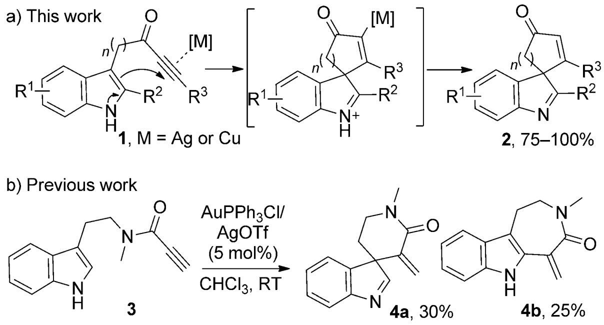

Figure 1. Dearomatizing spirocyclization through electrophilic alkyne activation.

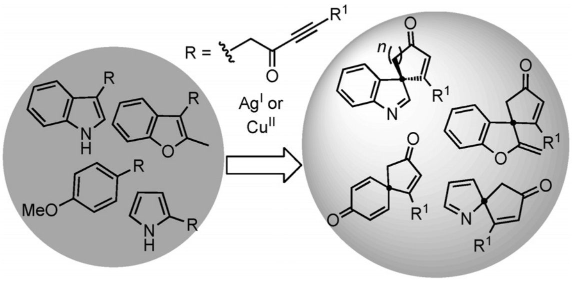

Figure 2. Dearomatizing spirocyclization.

The new methods described herein provide a general, high-yielding strategy for the conversion of a range of achiral heteroaromatics (left in Figure 2) into complex, spirocyclic enones (right in Figure 2) using low loadings of simple silver(I) or copper(II) salts. The ynone subunit was chosen on the basis of its synthetic accessibility and the utility of the enone products, but is also a key design feature, as the carbonyl group reduces the migratory aptitude of the adjacent alkene, thus stabilizing the spirocyclic products with respect to 1,2 migration. Studies demonstrating that asymmetric dearomatizing spirocyclization reactions can be achieved in high yield and good e.r. are also reported.

To begin our study, we examined the conversion of indole **5a** into spirocycle **6a** using a range of Brønsted, Lewis, and π acids to activate the alkyne. Full details of this screen can be found in the Supporting Information, with the key results given in Table 1.

The most effective catalysts that were screened were $Cu(OTf)_2$, $AgNO_3$, and AgOTf (Table 1), while surprisingly, standard gold π -acids[9] were ineffective,[10] as was triflic acid (Table 1, entry 2).[11] The dearomatizing spirocyclization reaction of indole **5a** can be performed efficiently under a range of conditions (Table 1, entries 3–7),[12] with the use of 0.01 equivalents of AgOTf in dichloromethane at room

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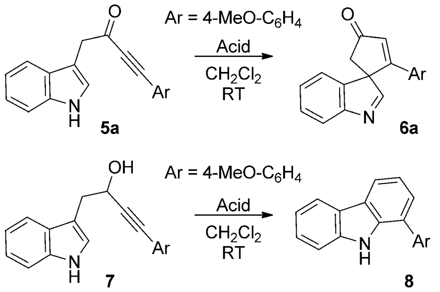
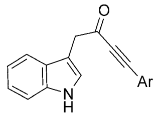
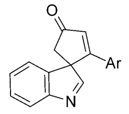
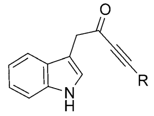
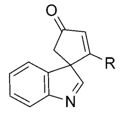
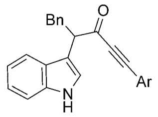
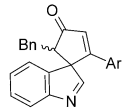
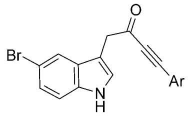
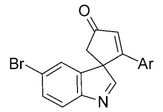
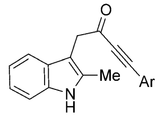
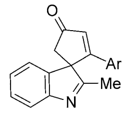
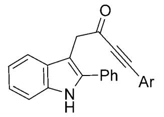
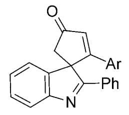
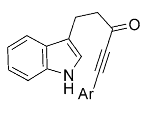
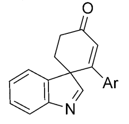
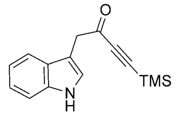
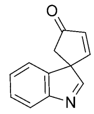
Table 1: Optimization of acid-catalyzed indole/alkyne spirocyclization.



Entry	Starting material	Acid (equiv)	*t* [h]	Product	Yield [%][a]
1	**5a**	–	20		–
2	**5a**	TfOH (0.01)	1	**6a**	trace
3	**5a**	Cu(OTf)$_2$ (1)	20	**6a**	80
4	**5a**	Cu(OTf)$_2$ (0.01)	8.5	**6a**	89
5	**5a**	$AgNO_3$ (0.01)	2.5	**6a**	97
6	**5a**	AgOTf (0.1)	1	**6a**	95
7	**5a**	AgOTf (0.01)	0.5	**6a**	100
8	**7**	AgOTf (0.1)	1	**8**	80

[a] All reactions performed in CH_2Cl_2 (0.1 M) at RT.

Table 2: Substrate scope of indole/ynone spirocyclization.[a]

Entry	Starting material	*t* [h]	Isolated product	Yield [%]
				
1	**5a** Ar = 4-MeO-C_6H_4	0.5	**6a** Ar = 4-MeO-C_6H_4	100[b]
2	**5b** Ar = Ph	0.5	**6b** Ar = Ph	100[b]
3	**5c** Ar = 4-Me_2N-C_6H_4	0.3	**6c** Ar = 4-Me_2N-C_6H_4	97[b]
4	**5d** Ar = 4-Br-C_6H_4	1.5	**6d** Ar = 4-Br-C_6H_4	100
				
5	**5e** R = Me	2	**6e** R = Me	95[b]
6	**5f** R = *n*Bu	3.5	**6f** R = *n*Bu	100[b]
				
7	**5g** Ar = 4-MeO-C_6H_4	0.5	**6g** Ar = 4-MeO-C_6H_4	95[c]
				
8	**5h** Ar = 4-MeO-C_6H_4	1	**6h** Ar = 4-MeO-C_6H_4	100
				
9	**5i** Ar = 4-MeO-C_6H_4	0.2	**6i** Ar = 4-MeO-C_6H_4	100
				
10	**5j** Ar = 4-MeO-C_6H_4	0.1	**6j** Ar = 4-MeO-C_6H_4	84
				
11[d]	**5k** Ar = 4-MeO-C_6H_4	16	**6k** Ar = 4-MeO-C_6H_4	75
				
12[e]	**9**	16	**10**	93

[a] All reactions performed using 0.01 equiv AgOTf as catalyst in CH_2Cl_2 (0.1 M) at RT, unless otherwise stated. [b] Compounds **6a–c** and **6e–f** can also be formed using 0.01 equiv Cu(OTf)$_2$ (see the Supporting Information). [c] d.r. = 55:45. [d] Reaction performed using 0.1 equiv AgOTf as catalyst at 35 °C. [e] Reaction performed in acetone using $AgNO_3$ (0.2 equiv) as catalyst.

temperature being optimal, furnishing spirocyclic indolenine **6a** in quantitative yield (entry 7, for X-ray crystallographic data see the Supporting Information).[13] The importance of the ynone carbonyl group is noteworthy, as demonstrated by the contrasting reactivity of propargyl alcohol **7** (Table 1, compare entries 6 and 8); treatment of compound **7** with 0.1 equivalents of AgOTf for 1 h at room temperature resulted in its complete conversion into known carbazole **8**,[14] presumably through an initial spirocyclization, followed by 1,2 migration (compare **4a** to **4b**, Figure 1b) and dehydration.[8] The relative ease of the migration in the conversion of **7** into **8** is presumably driven by the higher migratory aptitude of the more electron-rich alkene.

In addition to ynone **5a**, three electronically diverse aryl substrates **5b**–**5d** were treated with 0.01 equivalents of AgOTf in dichloromethane and furnished indolenines **6a**–**6d** in very good yields with short reaction times at room temperature (Table 2, entries 1–4). Alkyl-substituted ynones **5e** and **5f** were similarly good substrates, furnishing indolenines **6e** and **6f**, respectively, in excellent yields under the same conditions (Table 2, entries 5 and 6).[15] Additional substitution around the indole system is also well tolerated: for example, benzyl- and bromo-substituted spirocycles **6g** and **6h** were each formed in high yields (Table 2, entries 7 and 8). Indolenines **6i** and **6j** were also formed rapidly in excellent yields under the standard conditions (Table 2, entries 9 and 10). These results are particularly pleasing as the proximity of the substituents on the 2 -position of the indole to the reaction site could have impeded the reaction. The six-membered-ring product **6k** was also formed using ynone homologue **5k**. In this case, the reaction was slower and required moderate heating (35 °C) in order to reach completion within 16 h, but nonetheless, the desired product was still obtained in good yield (Table 2, entry 11). Indolenine **10**[15] was also synthesized, through a desilylation/spirocyclization sequence, by stirring ynone **9** with 0.2 equivalents of $AgNO_3$[16] in acetone at room temperature for 16 h, affording spirocyclic cyclopentenone **10**, which is unsubstituted at C3 (Table 2, entry 12). This high-yielding one-pot process is important, given that the terminally unsubstituted alkyne (i.e. **9** with

TMS = H) required to access spirocycle **10** in the standard way is unstable and could not be isolated.

Promising preliminary studies have also been performed using Ag^I salts of chiral phosphoric acids (CPAs) as catalysts for the indole/ynone spirocyclization (Figure 3). Six catalysts were screened, all of which are simple Ag^I salts of commercially available BINOL-based CPAs.[17] First, ynone **5a** was treated with 0.1 equivalents of catalyst **A** in dichloromethane at room temperature, which led to the rapid formation of spirocycle **6a**, with a small amount of asymmetric induction (54:46 e.r.). Bulkier CPA catalysts (**B**–**F**) were next examined and additional modifications were also made; chloroform replaced dichloromethane as the solvent, the catalyst loading was reduced to 0.01 equivalents, the temperature was lowered to −10 °C, and the reaction time was increased to 16 h. These modifications significantly improved the enantioselectivity, with the highest e.r. observed using 9-phenanthryl derivative **F**, which furnished spirocycle **6a** in quantitative yield, in 89:11 e.r.

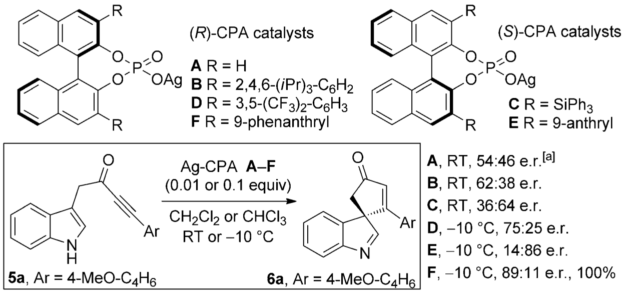


Figure 3. Asymmetric spirocyclization of **5a**. All reactions were performed using 0.09–0.30 mmol of **5a** in chloroform (0.1 M) and 0.01 equiv of the specified CPA catalyst. The reaction mixtures were stirred at either RT or −10 °C for 16 h, unless otherwise stated. Enantiomeric ratios were measured by HPLC using a Chiralpak IB column, eluting with 10% IPA in hexane, and the major enantiomer formed using the (*R*)-CPA catalysts **A**, **B**, **D**, and **F** is shown. [a] Reaction was performed in CH_2Cl_2 using 0.1 equiv of catalyst **A** for 5 min. IPA = isopropanol.

These conditions were then applied to other ynone substrates. Pleasingly, in all cases the spirocyclic products were isolated in high yields (**6b**, **6d**,**e**, **6h**,**i**, 62–100 %) and with consistently good enantioselectivity (e.r. 70:30–89:11), thus indicating that the reaction is likely to be applicable to a broad range of substrates (Figure 4). Notably, the e.r. of compounds **6a** and **6d** could be easily increased (98:2 e.r.) following recrystallization from ethyl acetate/hexane. The fact that good enantiomeric ratios were achieved by testing a relatively small number of commercially available CPAs augurs well that further optimization will lead to greater improvements.[18] The major enantiomer formed in reactions using (*R*)-CPA catalysts is the (*S*)-spirocycle (as shown in Figures 3 and 4) based on X-ray crystallographic data of spirocycle **6d**.[13,19] A tentative mechanism consistent with this outcome is included in the Supporting Information.

Finally, preliminary studies demonstrate that a wider range of aromatic ynones undergo dearomatizing spirocyclization, expanding the potential scope of the method (Table 3). Anisole-substituted ynone **11** furnished spirocyclic dienone **12**[20,21] upon treatment with 0.1 equivalents of Cu(OTf)$_2$, while ynone **13** reacted very efficiently when treated with 0.1 equivalents of AgNO$_3$, affording spirocycle **14**, with both reactions proceeding in excellent yields (Table 3, entries 1 and 2). Benzofuran **15** also reacted well, in this case furnishing the unusual spirocyclic enol ether **16** in good yield (Table 3, entry 3).

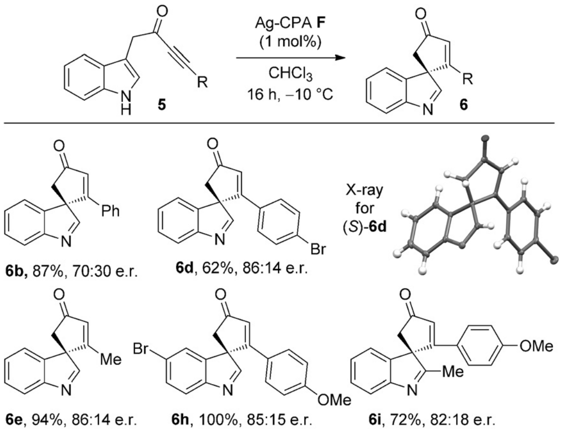
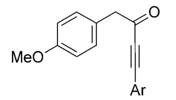
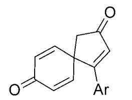
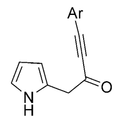
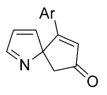
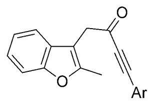
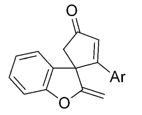


Figure 4. Asymmetric spirocyclization reactions. All reactions were performed using 0.09–0.30 mmol of ynone in chloroform (0.1 M) and 0.01 equiv of catalyst **F**. The reaction mixtures were stirred at −10 °C for 16 h. Enantiomeric ratios were measured by HPLC using a Chiralpak IB column, eluting with 10% IPA in hexane.

In summary, a range of high-yielding dearomatizing spirocyclization reactions are described, including an asymmetric variant, for the generation of synthetically useful spirocyclic building blocks from simple heteroaromatic precursors containing ynone side chains. The reactions are easy to perform, proceed at room temperature or −10 °C and are insensitive to both air and moisture.

Table 3: Alternative spirocyclization reaction systems.[a]

Entry	Starting material	*t* [h]	Isolated product	Yield [%]
1[b]	 **11** Ar = 4-Me$_2$N-C$_6$H$_4$	1	 **12** Ar = 4-Me$_2$N-C$_6$H$_4$	95
2[c]	 **13** Ar = 4-MeO-C$_6$H$_4$	0.5	 **14** Ar = 4-MeO-C$_6$H$_4$	99
3[d]	 **15** Ar = 4-MeO-C$_6$H$_4$	18	 **16** Ar = 4-MeO-C$_6$H$_4$	68

[a] Reactions performed in CH_2Cl_2 (0.1 M) at RT. [b] 0.1 equiv Cu(OTf)$_2$ used as catalyst. [c] 0.1 equiv AgNO$_3$ used as catalyst. [d] 0.01 equiv AgOTf used as catalyst.

Keywords: asymmetric catalysis · dearomatization · indolenines · silver · spirocycles

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Angew. Chem. **2015**, *127*, 7750–7753

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[3] For recent syntheses of 3,3-disubstituted indolenines using iridium-, palladium-, or ruthenium-based catalysts, see: a) Q.-F. Wu, H. He, W.-B. Liu, S.-L. You, *J. Am. Chem. Soc.* **2010**, *132*, 11418; b) Q.-F. Wu, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 1680; *Angew. Chem.* **2012**, *124*, 1712; c) P. Dhankher, L. Benhamou, T. D. Sheppard, *Chem. Eur. J.* **2014**, *20*, 13375; d) T. Nemoto, Z. Zhao, T. Yokosaka, Y. Suzuki, R. Wu, Y. Hamada, *Angew. Chem. Int. Ed.* **2013**, *52*, 2217; *Angew. Chem.* **2013**, *125*, 2273; e) R.-D. Gao, C. Liu, L.-X. Dai, W. Zhang, S.-L. You, *Org. Lett.* **2014**, *16*, 3919; f) Y. Zhu, V. H. Rawal, *J. Am. Chem. Soc.* **2012**, *134*, 111; g) T. D. Montgomery, Y. Zhu, N. Kagawa, V. H. Rawal, *Org. Lett.* **2013**, *15*, 1140.

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[7] To the best of our knowledge, only two additional examples of acid-catalyzed dearomatizing spirocyclization reactions of alkynes leading to indolenine products have been reported. In each case, the spirocyclic product was formed as a minor side product during another transformation (8% and 25%, respectively): a) J. Badorrek, D. Enders, C. C. J. Loh, G. Raabe, *Chem. Eur. J.* **2011**, *17*, 13409; b) D. Benito, D. R. Carbery, S. J. Heffernan, M. F. Mahon, M. E. Queru, A. C. Silvanus, J. P. Tellam, B. I. Andrews, A. J. Hennessy, *Adv. Synth. Catal.* **2013**, *355*, 1149.

[8] a) J. G. Rodríguez, Y. Benito, F. Temprano, *J. Heterocycl. Chem.* **1985**, *22*, 1207; b) K. G. Liu, A. J. Robichaud, J. R. Lo, J. F. Mattes, Y. Cai, *Org. Lett.* **2006**, *8*, 5769; c) A. S. K. Hashmi, W. Yang, F. Rominger, *Chem. Eur. J.* **2012**, *18*, 6576.

[9] A. Fürstner, P. W. Davies, *Angew. Chem. Int. Ed.* **2007**, *46*, 3410; *Angew. Chem.* **2007**, *119*, 3478.

[10] A complex mixture of products was formed when the mixed $AuPPh_3Cl$/AgOTf catalyst system used in the work of Van der Eycken (see Figure 1b and reference [5]) was tested.

[11] The unpurified reaction mixture (Table 1, entry 2) contained approximately 90% unreacted **5a**, along with other unidentified impurities and only trace amounts of spirocycle **6a**. This appears to rule out the possibility that the successful reactions using AgOTf or $Cu(OTf)_2$ are catalyzed by adventitious triflic acid through "hidden Brønsted acid catalysis". See: T. T. Dang, F. Boeck, L. Hintermann, *J. Org. Chem.* **2011**, *76*, 9353.

[12] Dichloromethane was retained as the optimal solvent for further development, although the reaction can also be performed with comparable efficiency in chloroform, THF, toluene, or dichloroethane (see Supporting Information).

[13] CCDC 1023667 (**6a**) and 1049165 (**6d**) contain 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/cif.

[14] J.-H. Chu, C.-C. Wu, D.-H. Chang, Y.-M. Lee, M.-J. Wu, *Organometallics* **2013**, *32*, 272.

[15] Compounds **6f** and **10** exist as equilibrating mixtures of indolenine and imine trimers in $CDCl_3$. To simplify its NMR spectra, compound **10** was characterized as its salt with TFA. See: J. S. L. Ibaceta-Lizana, A. H. Jackson, N. Prasitpan, P. V. R. Shannon, *J. Chem. Soc. Perkin Trans. 2* **1987**, 1221.

[16] For $AgNO_3$-mediated desilylation of alkynes, see: Y. Yamamoto, *Chem. Rev.* **2008**, *108*, 3199, and references therein.

[17] a) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science* **2007**, *317*, 496; b) M. Terada, F. Li, Y. Toda, *Angew. Chem. Int. Ed.* **2014**, *53*, 235; *Angew. Chem.* **2014**, *126*, 239; c) Y. Wang, K. Zheng, R. Hong, *J. Am. Chem. Soc.* **2012**, *134*, 4096.

[18] SPINOL-based CPA catalysts have been shown to improve the e.r. of related processes. See: C.-H. Xing, Y.-X. Liao, J. Ng, Q.-S. Hu, *J. Org. Chem.* **2011**, *76*, 4125, and references therein.

[19] A sample of spirocycle **6d** was enriched to 98:2 e.r. by recrystallization from ethyl acetate/hexane, before a single crystal was then grown by slow crystallization from ethyl acetate/hexane, with the heavy Br atom allowing the absolute configuration to be determined. The specific crystal used to obtain the X-ray data was confirmed as being the major enantiomer using HPLC.

[20] The core structure of dienone **12** is present in spirobacillene A: W. P. Unsworth, J. D. Cuthbertson, R. J. K. Taylor, *Org. Lett.* **2013**, *15*, 3306.

[21] For the synthesis of aza analogues of this framework using $AgNO_3$, see: L.-J. Wang, A.-Q. Wang, Y. Xia, X.-X. Wu, X.-Y. Liu, Y.-M. Liang, *Chem. Commun.* **2014**, *50*, 13998.

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