Catalyst-Driven Scaffold Diversity: Selective Synthesis of Spirocycles, Carbazoles and Quinolines from Indolyl Ynones

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Abstract: Medicinally relevant spirocyclic indolenines, carbazoles and quinolines can each be directly synthesised selectively from common indolyl ynone starting materials by catalyst variation. The high yielding, divergent reactions all proceed by an initial dearomatising spirocyclisation reaction to generate an intermediate vinyl–metal species, which then rearranges selectively by careful choice of catalyst and reaction conditions.

The synthesis of structurally diverse compounds is central to the discovery of pharmaceutical lead compounds.\(^1\) However, the formation of distinct compound sets usually requires multiple synthetic routes, which is time-consuming and labour-intensive; therefore, strategies capable of selectively forming multiple products from common starting materials are of high value. The concept underpinning our approach is the formation of a common reactive intermediate (from a simple, inexpensive starting material), which depending on the catalyst used can rearrange into different scaffolds (e.g., spirocycles, aromatics and heterocycles/carbocycles; Figure 1). This approach has the potential to significantly streamline existing synthetic methods, and lead to a broader understanding of catalysis and reaction mechanisms. Although there have been numerous examples of catalyst variation leading to different products in recent years,\(^2,3\) such methods have mainly focused on the formation of products with similar frameworks (e.g., redox isomers, regioisomers or stereoisomers). In this work, our aim was to develop a series of divergent processes capable of selectively delivering multiple products with the level of scaffold diversity outlined in Figure 1.

To demonstrate the synthetic potential of our scaffold-diversity approach, we chose to explore the formation and subsequent reaction of spirocyclic vinyl–metal intermediates of the form 2 (Scheme 1). Previous work in our research group has demonstrated that the dearomatising spirocyclisation\(^4\) of ynones 1 into spirocyclic indolenines 3 can be catalysed by AgOTf, with vinyl–silver species 2 ([M] = Ag) as likely intermediates.\(^5\) A key design feature of our strategy was the idea that varying the catalyst would alter the nature and reactivity of the vinyl–metal intermediate 2 in a programmable way, such that alternative products could be formed by different rearrangement reactions. Herein, we report the successful realisation of this approach. Notably, by judicious choice of catalyst, simple, inexpensive ynone starting materials 1 can be converted into spirocyclic indolenines\(^6\) 3 using Ag\(^+\), carbazoles 5 using Au\(^+\) and quinolines 7 using Ag\(^+\)/Al\(^3\)+ in high yield, each by

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**Figure 1.** Catalyst-driven scaffold diversity.

**Scheme 1.** Divergent synthesis of spirocycles 3, carbazoles 5, quinolines 7 and tetracyclic scaffolds 8 from indolyl ynones 1.
a simple, catalytic and atom-economical process. Furthermore, in suitable cases, tetracyclic scaffolds 8 can be formed with complete diastereoselectivity, by a telescoped spirocyclisation/nucleophilic addition sequence, which was performed using a chiral Ag⁺ salt to furnish an enantiopure product.

The spirocyclisation of 1a using AgOTf formed indolenine 3a in quantitative yield (Scheme 2).[^2] The mild reaction conditions are believed to play a key role in this process, stabilising the spirocycle with respect to further reactions. However, in the proposed scaffold diversity approach, in which the synthesis of carbazole 5a was an initial goal, the challenge was to deliberately promote 1,2-migration[^7] in a controlled manner. A Ph₃PAuNTf₂ catalyst was chosen based on the prediction that the π-acidic gold(I) catalyst would effectively promote the initial spirocyclisation reaction and that the intermediate vinyl–gold species (2a–Au) would be prone to 1,2-migration, based on known reactivity of related vinyl–gold and gold–carbenoid species.[^9] This idea was validated (94% yield of 5a) with a likely reaction mechanism depicted in Scheme 3; the ring enlargement is believed to proceed either via cyclopropane intermediate 9a, or by a direct 1,2-migration reaction (2a–Au → 10a) based on related precedent.[^7] The importance of vinyl–gold intermediate 2a–Au in the 1,2-migration is evidenced by the fact that no reaction takes place when spirocycle 3a is treated with Ph₃PAuNTf₂ under the same conditions.

We next examined whether we could initiate an alternative rearrangement commencing from ynone 1a, by seeking to promote cyclopropanation of an enolate from the less substituted branch of the cyclopentenone; more oxophilic catalysts were chosen for this task, as it was thought that they would better promote the necessary enolate formation. We were unable to uncover a catalyst that could successfully initiate spirocyclisation and subsequent rearrangement on its own. However, first performing the spirocyclisation using 2 mol% of AgOTf as catalyst in isopropanol, followed by the addition of 5 mol% of AlCl₃·6H₂O and subsequent heating in a microwave gave quinoline 7a in high yield (Scheme 4).[^10] Following Ag⁺-mediated spirocyclisation, it is thought that the Al³ catalyst promotes enolate formation and subsequent cyclopropanation to form 12a, which can then fragment to form 13a and aromatise to give quinoline 7a (either by simple proton shuttling, or by a series of 1,5-sigmatropic H-transfer reactions).

Supporting evidence for this unprecedented rearrangement was obtained: treatment of spirocycle 3a with LHMDS in THF (i.e., conditions which almost certainly would result in enolate formation) also led to the formation of quinoline 7a, in 81% yield. Furthermore, the importance of the carbonyl group was shown by the fact that treatment of known cyclopentenol 14 with AlCl₃·6H₂O did not result in quinoline formation. Instead, 1,2-migration of the alkenyl group took place, furnishing carbazole 15 following tautomerisation and dehydration (Scheme 5).

![Scheme 2. Formation of spirocyclic indolenine 3a.](image)

![Scheme 3. Formation of carbazole 5a; [Au] = Ph₃PAuNTf₂, L = ligand.](image)

![Scheme 4. Formation of quinoline 7a; X = Cl or iPrO.](image)

![Scheme 5. Base-mediated formation of quinoline 7a and the contrasting reactivity of spirocyclic cyclopentenol 14.](image)

To probe the scope of all three reaction manifolds, various functionalised indole-tethered ynones 1a–1m were prepared, substituted in several positions with electron-rich and -poor aromatics, alkyl substituents, O- and N-protected alkyl groups and PhS.[^12] First, using the AgOTf-mediated spirocyclisation...
methodology, substrates 1a–1m were cleanly converted into the corresponding spirocyclic indolenines 3a–3m, all in excellent yields (Table 1, conditions A). The Ph3PAuNTf2-mediated carbazole-forming reaction was similarly broad in scope (conditions B); some reactions were less efficient than the analogous spirocycle formations, and ynone 1d did not produce any of the desired product (instead stalling at the formation 3d), but the majority of the carbazole products 5a–j were isolated in very good yields.

Finally, the quinoline-forming reaction sequence was also found to be very general (conditions C). For ynones 1a–1e,1g,1k–1l, the sequential AgOTf spirocyclisation and AlCl3·6H2O mediated rearrangement steps could both be performed in iPrOH in one-pot as described, whereas for ynones with more sensitive functional groups (1f, 1h, 1i, 1j, 1m), the process benefited from a solvent swap, with the spirocyclisation first being performed in CH2Cl2 before concentration and addition of AlCl3·6H2O step. The AlCl3·6H2O reactions were typically performed under microwave irradiation at 100 °C, but they were also shown to proceed well on a gram scale with conventional heating, albeit with a longer reaction time being required. The structure of quinoline 7f was confirmed by X-ray crystallography.

Another strand of scaffold diversity starting from more functionalised ynones 1h–1j was briefly explored. Tetracyclic scaffolds 8h–j, equipped with additional complexity, were easily obtained following reaction of ynones 1h–1j with AgOTf and subsequent acid-mediated protecting group cleavage in one pot (Scheme 6, and see the Supporting Information for details). The tetracycles were formed as the single diastereoisomers shown, and in addition, (S)-8h was prepared in enantiomerically pure form (89:11 e.r.) by utilising (R)-CPA silver(I) salt 16 in place of AgOTf. The e.r. of (S)-8h could be increased to >25:0 by recrystallisation from ethanol, and its structure was confirmed by X-ray crystallography (see the Supporting Information).

In summary, readily available indolyl ynones have been shown to be versatile starting materials for the synthesis of spirocyclic indolenines 3a–m, carbazoles 5a–j, quinolines 7a–m and tetracyclic compounds 8h–j using a catalyst-driven scaf-
fold diversity approach. The reactions are typically high yielding, work on a wide range of indolyl ynone substrates, are operationally simple and can all be performed with no effort to exclude air or moisture. All of the procedures are thought to proceed by an initial deamortising spirocyclisation to form a key vinyl–metal intermediate before diverging at this point depending on the nature of the catalyst used. The synthetic methods are expected to be of value both in target synthesis projects and to enable the rapid generation of compound libraries for biological screening.

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[1] a) M. D. Burke, S. L. Schreiber. Angew. Chem. Int. Ed. 2004, 43, 46–58; Angew. Chem. 2004, 116, 48–60; b) F. Lovering, J. Bickle, C. Humblet. J. Med. Chem. 2009, 52, 6752–6756; c) A. W. Hung, A. Ramek, Y. Wang, T. Kaya, J. A. Wilson, P. A. Clemons, D. W. Young. Proc. Natl. Acad. Sci. USA 2011, 108, 7699–8004; d) M. Aldeghi, S. Malhotra, D. L. Selwood, A. W. E. Chan. Chem. Biol. Drug Des. 2014, 83, 450–461; e) A. Karawajczyk, F. Giordanetto, J. Benninghof, D. Hamza, T. Kallikokskis, K. Pouver, R. Morgentorn, A. Nelson, G. Muller, A. Pierchot, D. Tzalis. Drug Discovery Today 2015, 20, 1310–1316.

[2] For a review on ‘Catalytic Selective Synthesis’, see: J. Mahatthananchai, A. M. Durnas, J. W. Bode, Angew. Chem. Int. Ed. 2012, 51, 10954–10990; Angew. Chem. 2012, 124, 11114–11152.

[3] For more recent examples, see: a) J. D. Dooley, S. Reddy Chidipudi, H. W. Lam, J. Am. Chem. Soc. 2013, 135, 10829–10836; b) D. S. B. Daniels, A. S. Jones, A. L. Thompson, R. S. Paton, E. A. Anderson. Angew. Chem. Int. Ed. 2014, 53, 1915–1920; Angew. Chem. 2014, 126, 1946–1951; c) P. A. Donets, N. Cramer. Angew. Chem. Int. Ed. 2015, 54, 633–637; Angew. Chem. 2015, 127, 643–647; d) Y.-S. Zhang, X.-Y. Tang, M. Shi, Org. Chem. Front. 2015, 2, 1516–1520; e) L. Xu, H. Li, Z. Liao, K. Lou, H. Xie, H. Li, W. Wang, Org. Lett. 2015, 17, 3434–3437; f) J.-Y. Liao, P.-L. Shao, Y. Zhao, Z. J. Am. Chem. Soc. 2015, 137, 628–631; g) A. Galván, J. Calleja, A. B. González-Pérez, R. Álvarez, A. R. de Lera, F. Rodríguez, Chem. Eur. J. 2015, 21, 16769–16774; h) D. Y. Li, H. J. Chen, P. N. Liu, Angew. Chem. Int. Ed. 2016, 55, 373–377; Angew. Chem. 2016, 128, 381–385; i) Q.-Q. Cheng, J. Yedoyan, H. Arman, M. P. Doyle, J. Am. Chem. Soc. 2016, 138, 44–47.

[4] For reviews on deamortising spirocyclisation reactions, see: a) C.-X. Zhuo, W. Zhang, S.-L. You, Angew. Chem. Int. Ed. 2012, 51, 12944–12945; b) C. Zeng, S.-L. You, Angew. Chem. Int. Ed. 2012, 51, 1680–1683; Angew. Chem. 2012, 124, 1712–1715; b) V. A. Peskov, O. P. Peregudov, E. V. Van der Eycken. Adv. Synth. Catal. 2012, 354, 2841–2848; c) C. Zheng, Q.-F. Wu, S.-L. You. J. Org. Chem. 2013, 78, 4357–4365; d) S. J. Heffernan, J. P. Tellam, M. E. Queru, A. C. Silvanus, D. Benito, M. F. Mahon, A. J. Hennessey, B. Andrews, D. R. Carbery. Adv. Synth. Catal. 2013, 355, 1149–1159.

[5] For other syntheses of carbazoles involving alkyne activation, see: a) L. Wang, G. Li, Y. Liu, Org. Lett. 2011, 13, 3786–3789; b) A. K. Hashmi, W. Yang, F. Rominger. Chem. Eur. J. 2012, 18, 6576–6580; c) Y. Qiu, C. Fu, Z. Xiang, S. Ma. Chem. Eur. J. 2014, 20, 10314–10322.

[6] For related carbazole syntheses, see: J. Wang, H.-T. Zhu, Y.-F. Qiu, Y. Niu, S. Chen, Y.-X. Liu, X.-Y. Liu, Y.-M. Liang, Org. Lett. 2015, 17, 3186–3189, and references [5a–c].

[7] Ynone 1a–g and 1k–l were prepared as described in reference [5], while ynoles 1h–j and 1m were synthesised for the first time in this work (see Supporting Information for preparative details).

[8] For related carbazole syntheses, see: J. Wang, H.-T. Zhu, Y.-F. Qiu, Y. Niu, S. Chen, Y.-X. Liu, X.-Y. Liu, Y.-M. Liang, Org. Lett. 2015, 17, 3186–3189, and references [5a–c].

[9] Ynone 1a (3.8 mmol) was converted into quinoline 7a in 82% yield upon conventional heating with AlCl3·6H2O at reflux under an air atmosphere for 8h (see the Supporting Information for full details).

[10] For details of potential natural product targets, see: a) P. Magnus, B. Mugrage, M. R. Deluca, G. A. Caim. J. Am. Chem. Soc. 1990, 112, 5220–5230; b) T. S. Kam, K. M. Sim, T. M. Lim. Tetrahedron Lett. 2001, 42, 4721–4723; c) O. M. Mori, M. Nakashishi, D. Kajishima, Y. Sato, J. Am. Chem. Soc. 2003, 125, 9801–9807; d) C. Chic, S. Runnsthao, Tetrahedron 2004, 60, 1513–1516; e) H.-J. Knölker, W. Fröhner, R. Heinrich, Synlett 2004, 2085–2087; f) H. Yang, J. Feng, Y. Tang. Chem. Commun. 2013, 49, 6442–6444; g) W. P. Unsworth, J. D. Cuthbertson, R. J. K. Taylor. Org. Lett. 2013, 15, 3306–3309; h) N. Ramkumar, R. Nagarajan. J. Org. Chem. 2013, 78, 2802–2807; i) Y. Hieda, T. Choshii, H. Fujikawa, S. Hribno, Eur. J. Org. Chem. 2013, 7391–7401.

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