White Rose Research Online

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk
Universities of Leeds, Sheffield and York

Deposited via The University of York.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/99300/

Version: Accepted Version

Article:
Liddon, John T R, James, Michael J., Clarke, Aimee K. et al. (2016) Catalyst-driven scaffold diversity: selective synthesis of spirocycles, carbazoles and quinolines from indolyl ynones. Chemistry : A European Journal. 8777–8780. ISSN: 0947-6539

https://doi.org/10.1002/chem.201601836

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

UNIVERSITY OF LEEDS
University of Sheffield
UNIVERSITY of York

CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Catalyst-driven scaffold diversity: selective synthesis of spirocycles, carbazoles and quinolines from indolyl ynones

Authors: John T R Liddon; Michael J James; Aimee K Clarke; Peter O'Brien; Richard J K Taylor; William Paul Unsworth

This manuscript has been accepted after peer review and the authors have elected to post their Accepted Article online prior to editing, proofing, and formal publication of the final Version of Record (VoR). This work is currently citable by using the Digital Object Identifier (DOI) given below. The VoR will be published online in Early View as soon as possible and may be different to this Accepted Article as a result of editing. Readers should obtain the VoR from the journal website shown below when it is published to ensure accuracy of information. The authors are responsible for the content of this Accepted Article.

To be cited as: Chem. Eur. J. 10.1002/chem.201601836

Link to VoR: http://dx.doi.org/10.1002/chem.201601836

Supported by
ACES

WILEY-VCH

10.1002/chem.201601836

WILEY-VCH

Catalyst-driven scaffold diversity: selective synthesis of spirocycles, carbazoles and quinolines from indolyl ynones

John T. R. Liddon, Michael J. James, Aimee K. Clarke, Peter O'Brien, Richard J. K. Taylor* and William P. Unsworth*

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 via 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.

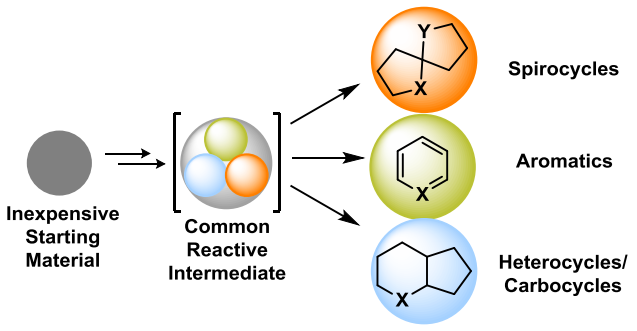
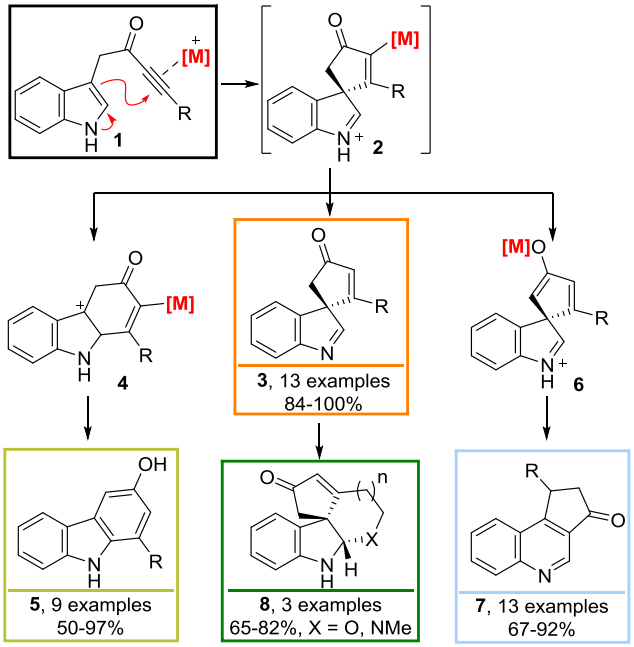


Figure 1. Catalyst-driven scaffold diversity.

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 a vinyl silver intermediate (**2**, [M] = Ag) a likely intermediate.[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 via 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(I), carbazoles **5** using Au(I), and quinolines **7** using Ag(I)/Al(III), in high yield, each via a simple, catalytic and atom-economical process. Furthermore, in suitable cases, tetracyclic scaffolds **8** can be formed with complete diastereoselectivity, via a telescoped spirocyclisation/ nucleophilic addition sequence, which was also performed using a chiral Ag(I) salt to furnish an enantiopure product.



Scheme 1. Divergent synthesis of spirocycles **3**, carbazoles **5**, quinolines **7** and tetracyclic scaffolds **8** from indolyl ynones **1**.

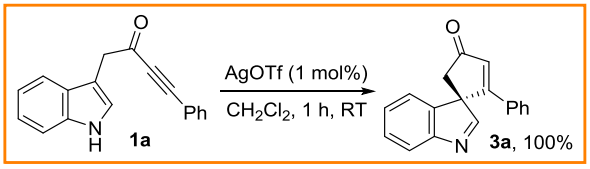
The spirocyclisation of **1a** using AgOTf formed indolenine **3a** in quantitative yield (Scheme 2);[5] the mild reaction conditions are believed to play a key role in this process, stabilising the spirocycle with respect to further reactions. However, in the proposed scaffold diversity approach, in which the synthesis of carbazole **5a** was an initial goal, the challenge was to deliberately promote 1,2-migration[7] in a controlled manner.[8] A

[a] Dr J. T. R. Liddon, M. J. James, A. K. Clarke, Prof. P. O'Brien, Prof. R. J. K. Taylor, Dr. W. P. Unsworth
University of York
York, YO24 4PP (UK)
E-mail: richard.taylor@york.ac.uk; william.unsworth@york.ac.uk

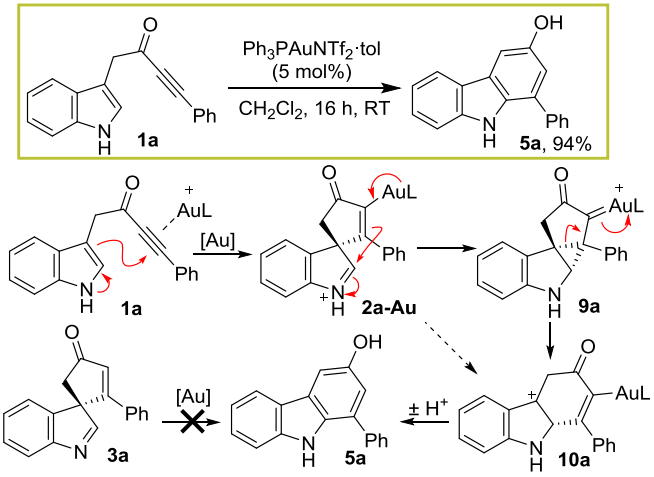
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Accepted Manuscript

$Ph_3PAuNTf_2$·tol 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 a via a direct 1,2-migration reaction (**2a**-**Au** → **10a**) based on related precedent.[7,9] The importance of the 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 $Ph_3PAuNTf_2$·tol under the same conditions.

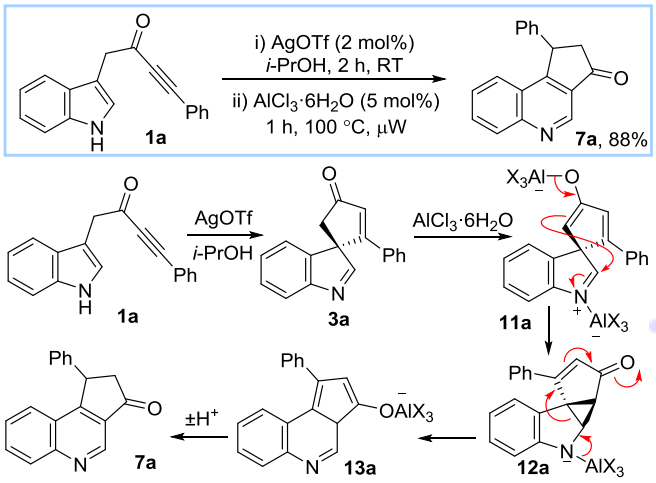


Scheme 2. Formation of spirocyclic indolenine **3a**



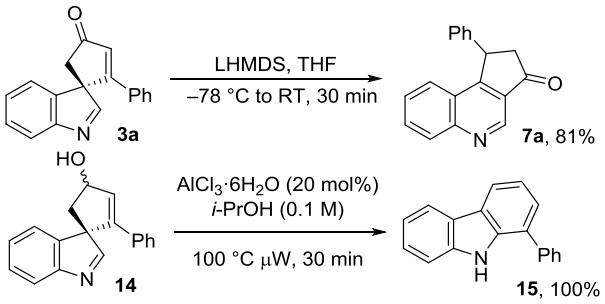
Scheme 3. Formation of carbazole **5a**; [Au] = $Ph_3PAuNTf_2$·tol, L = ligand

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 *iso*-propanol, followed by the addition of 5 mol% of $AlCl_3.6H_2O$ and subsequent heating in a microwave gave quinoline **7a** in high yield (Scheme 4).[10] Following Ag(I)-mediated spirocyclisation, it is thought that the Al(III) 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 via a series of 1,5-sigmatropic H-transfer reactions).



Scheme 4. Formation of quinoline **7a**; X = Cl or *i*-PrO

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**[11] with $AlCl_3.6H_2O$ 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 5. Base-mediated formation of quinoline **7a** and the contrasting reactivity of spirocyclic cyclopentenol **14**.

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 electron-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).

Accepted Manuscript

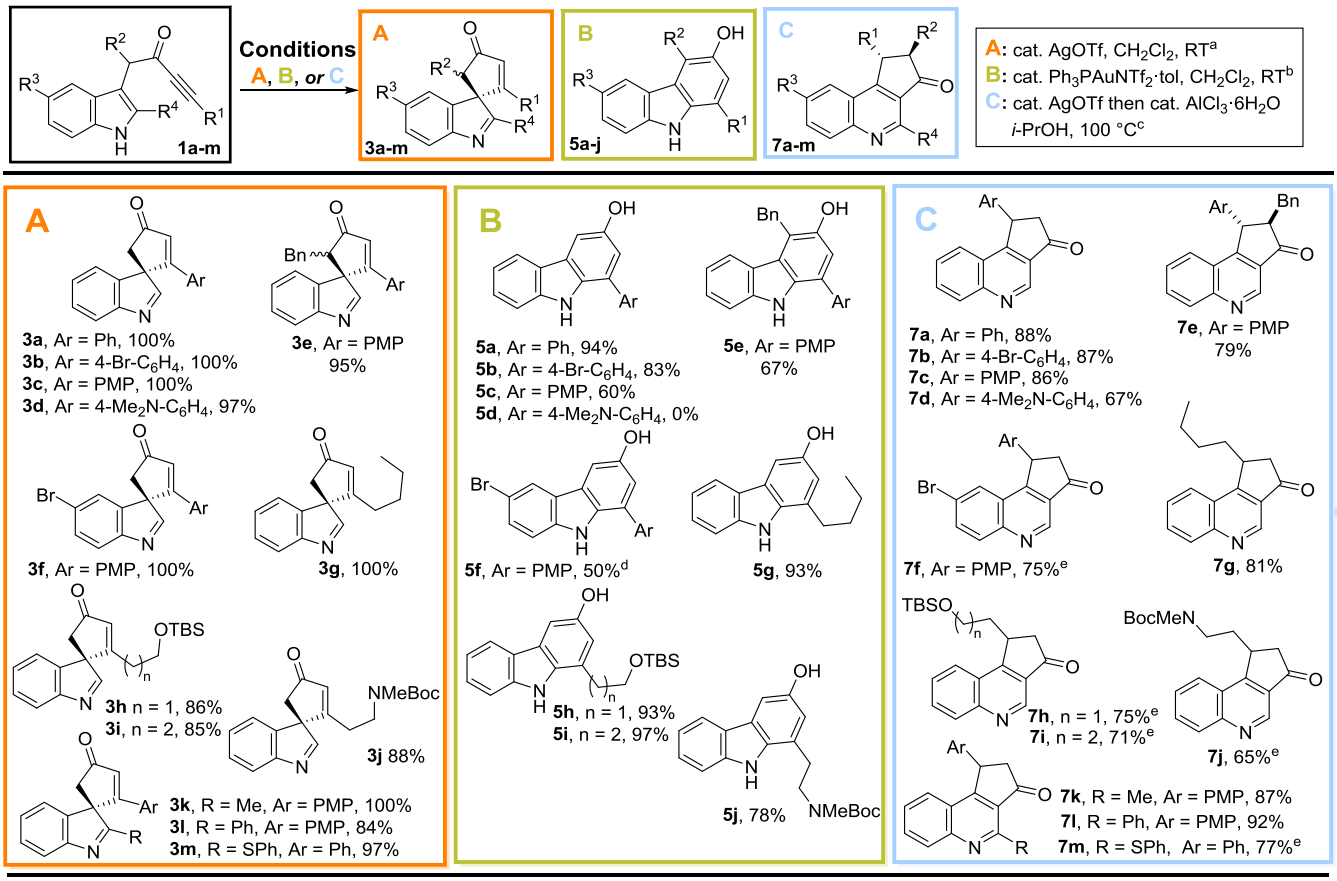
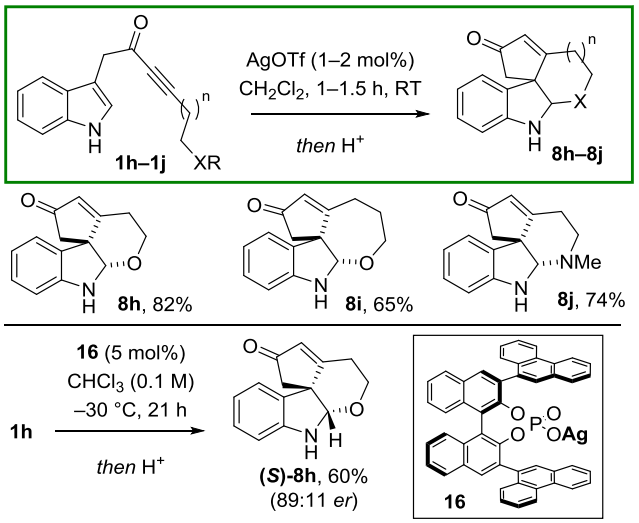


Table 1. [a] 1 mol% AgOTf in CH_2Cl_2 (0.1 M) at RT for 0.1–3.5 h; [b] 2–5 mol% $Ph_3PAuNTf_2$·tol in CH_2Cl_2 (0.1 M) at RT for 7–18 h. [c] 1 mol% AgOTf in *i*-PrOH (0.1 M) at RT for 1–3 h, then 5–10 mol% $AlCl_3·6H_2O$ at 100 °C μW for 1–2 h; [d] Reaction performed in toluene; [e] 1 mol% AgOTf in CH_2Cl_2 (0.1 M) at RT for 1–3 h, then solvent swap for *i*-PrOH (0.1 M) then 5–10 mol% $AlCl_3·6H_2O$ at 100 °C μW for 1–2 h. PMP = *para*-methoxyphenyl

The $Ph_3PAuNTf_2$·tol mediated carbazole forming reaction was similarly broad in scope (Table 1, 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.[13]

Finally, the quinoline forming reaction sequence was also found to be very general (Table 1, Conditions C). For ynones **1a–1e**,**1g**,**1k–1l**, the sequential AgOTf spirocyclisation and $AlCl_3.6H_2O$ mediated rearrangement steps could both be performed in *i*-PrOH 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 CH_2Cl_2 before concentration and addition of *i*-PrOH prior to the $AlCl_3.6H_2O$ step. The $AlCl_3.6H_2O$ reactions were typically performed under microwave irradiation at 100 °C, but it was also shown to proceed well, on gram scale, with conventional heating, albeit with a longer reaction time being required.[14] The structure of quinoline **7f** was confirmed by X-ray crystallography.[15]

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, see Supporting Information for details).[16] The tetracycles were formed as the single diastereoisomers shown, and in addition, **(*S*)-8h** was prepared in enantioenriched form (89:11 *er*) by utilising (*R*)-CPA silver(I) salt **16** in place of AgOTf.[17] The *er* of **(*S*)-8h** could be increased to ~100:0 by recrystallisation from ethanol and its structure was confirmed by X-ray crystallography (see Supporting Information).[15]



Scheme 6. One-pot spirocyclisation/trapping to form tetracycles **8h–8j**.

Accepted Manuscript

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 scaffold 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 via an initial dearomatising 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[18] and to enable the rapid generation of compound libraries for biological screening.

Acknowledgements

The authors wish to thank the EPSRC (J. T. R. L. EP/M018601/01) and the University of York (M. J. J., A. K. C. and W. P. U.) for funding and Dr A. C. Whitwood (University of York) for X-ray crystallography.

Keywords: Catalysis• Diversity • Spirocycles • Carbazoles• Quinolines

[1] (a) M. D. Burke, S. L. Schreiber, *Angew. Chem. Int. Ed.* **2004**, *43*, 46–58; (b) F. Lovering, J. Bikker, 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.* **2011**, *108*, 6799–6804; (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. Benningshof, D. Hamza, T. Kalliokoski, K. Pouwer, R. Morgentin, A. Nelson, G. Muller, A. Pierchot, D. Tzalis, *Drug Discov. Today* **2015**, *20*, 1310–1316.

[2] For a review on 'Catalytic Selective Synthesis', see: J. Mahatthananchai, A. M. Dumas, J. W. Bode, *Angew. Chem. Int. Ed.* **2012**, *51*, 10954–10990.

[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; (c) P. A. Donets, N. Cramer, *Angew. Chem. Int. Ed.* **2015**, *54*, 633–637; (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, *J. Am. Chem. Soc.* **2015**, *137*, 628–631; (g) A. Galván, J. Calleja, A. B. González-Pérez, R. Álvarez, A. R. de Lera, F. J. Fañanás, 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; (i) Q.-Q. Cheng, J. Yedoyan, H. Arman, M. P. Doyle, *J. Am. Chem. Soc.* **2016**, *138*, 44–47.

[4] For reviews on dearomatising spirocyclisation reactions, see: (a) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; (b) S. P. Roché, J.-J. Y. Tendoung, T. Tréguier, *Tetrahedron* **2015**, *71*, 3549.

[5] M. J. James, J. D. Cuthbertson, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Angew. Chem. Int. Ed.* **2015**, *54*, 7640–7643.

[6] For a review on spirocyclic indolenine synthesis, see: M. J. James, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Chem. Eur. J.* **2016**, *22*, 2856–2881.

[7] For examples of related 1,2-migration reactions, see: (a) Q. F. Wu, C. Zheng, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 1680–1683; (b) V. A. Peshkov, O. P. Pereshivko, 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. Hennessy, B. I. Andrews, D. R. Carbery, *Adv. Synth. Catal.* **2013**, *355,* 1149–1159.

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

[9] (a) C. Nieto-Oberhuber, M. P. Muñoz, E. Buñuel, C. Nevado, D. J. Cárdenas, A. M. Echavarren, *Angew. Chem. Int. Ed.* **2004**, *43*, 2402–2406; (b) C. Nieto-Oberhuber, S. López, M. P. Muñoz, E. Jiménez-Núñez, E. Buñuel, D. J. Cárdenas, A. M. Echavarren, *Chem. Eur. J.* **2006**, *12*, 1694–1702; (c) V. López-Carrillo, N. Huguet, Á. Mosquera, A. M. Echavarren, *Chem. Eur. J.* **2011**, *17*, 10972–10978; (d) K. Wittstein, K. Kumar, H. Waldmann, *Angew. Chem. Int. Ed.* **2011**, *50*, 9076–9080; (e) R. Meiss, K. Kumar, H. Waldmann, *Chem. Eur. J.* **2015**, *21*, 13526–13530; (f) A. Zhdanko, M. E. Maier, *ACS Catal.* **2015**, *5*, 5994–6004; (g) Dorel, A. M. Echavarren, *Chem. Rev.* **2015**, *115*, 9028–9072.

[10] These reaction conditions were originally developed for the cleavage of silyl protecting groups, see: D. González-Calderón, L. J. Benitez-Puebla, C. A. Gonzalez-Gonzalez, M. A. Garcia-Eleno, A. Fuentes-Benitez, E. Cuevas-Yañez , D. Corona-Becerril, C. González-Romero, *Synth. Commun.* **2014**, *44*, 1258–1265.

[11] M. J. James, R. E. Clubley, K. Y. Palate, T. J. Procter, A. C. Wyton, P. O'Brien, R. J. K. Taylor, W. P. Unsworth, *Org. Lett.* **2015**, *17*, 4372.

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

[13] For related carbazole syntheses, see: (a) L. Wang, G. Li, Y. Liu, *Org. Lett.* **2011**, *13*, 3786–3789; (b) A. S. K. Hashmi, W. Yang, F. Rominger, *Chem. Eur. J.* **2012**, *18*, 6576–6580; (c) Y. Qiu, C. Fu, X. Zhang, S. Ma, *Chem. Eur. J.* **2014**, *20*, 10314–10322; (d) J. Wang, H.-T. Zhu, Y.-F. Qiu, Y. Niu, S. Chen, Y.-X. Li, X.-Y. Liu, Y.-M. Liang, *Org. Lett.* **2015**, *17*, 3186–3189.

[14] Ynone **1a** (3.8 mmol) was converted into qunioline **7a** in 82% yield upon conventional heating with $AlCl_3.6H_2O$ at reflux under an air atmosphere for 8 h (see Supporting Information for full details) .

[15] CCDC 1453490 (**7f**) and 1453491 (**(*S*)-8h**) 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/

[16] For a related reaction involving *in situ* indolenine formation and intramolecular trapping, see: S. G. Modha, A. Kumar, D. D. Vachhani, J. Jacobs, S. K. Sharma, V. S. Parmar, L. Van Meervelt, E. V. Van der Eycken, *Angew. Chem. Int. Ed.* **2012**, *51*, 9572–9575.

[17] (a) G. L. Hamilton, E. J. Kang, M. Mba, F. D. Toste, *Science*, **2007**, *317*, 496–499; (b) Y. Wang, K. Zheng, R. Hong, *J. Am. Chem. Soc.* **2012**, *134*, 4096–4099; (c) M. Terada, F. Li, Y. Toda, *Angew. Chem. Int. Ed.* **2014**, *53*, 235–239.

[18] For details of potential natural product targets, see: (a) P. Magnus, B. Mugrage, M. R. Deluca, G. A. Cain, *J. Am. Chem. Soc.* **1990**, *122*, 5220–5230; (b) T. S. Kam, K. M. Sim, T. M. Lim, *Tetrahedron Lett.* **2001**, *42*, 4721–4723; (c) M. Mori, M. Nakanishi, D. Kajishima, Y. Sato, *J. Am. Chem. Soc.* **2003**, *125*, 9801–9807; (d) D. Crich, S. Rumthao, *Tetrahedron* **2004**, *60*, 1513–1516; (e) H.-J. Knölker, W. Fröhner, R. Heinrich, *Synlett* **2004**, 2705–2708; (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. Choshi, H. Fujioka, S. Hibino, *Eur. J. Org. Chem.* **2013**, 7391–7401.

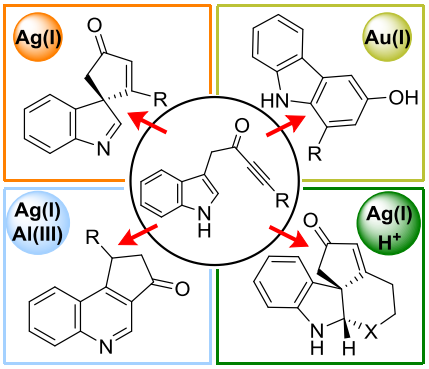
Accepted Manuscript

Entry for the Table of Contents (Please choose one layout)

Layout 1:

COMMUNICATION

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 via an initial dearomatising spirocyclisation reaction to generate an intermediate vinyl metal species which then rearranges selectively by careful choice of catalyst and reaction conditions.



John T. R. Liddon, Michael J. James, Aimee K. Clarke, Peter O'Brien, Richard J. K. Taylor and William P. Unsworth**

Page No. – Page No.

Catalyst-driven scaffold diversity: selective synthesis of spirocycles, carbazoles and quinolines from indolyl ynones

Layout 2:

COMMUNICATION

((Insert TOC Graphic here))

*Author(s), Corresponding Author(s)**

Page No. – Page No.

Title

Text for Table of Contents

Accepted Manuscript