

Synthetic Methods

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

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

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

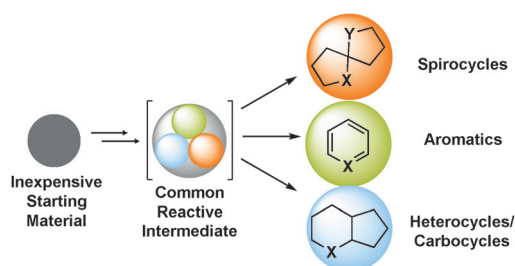


Figure 1. Catalyst-driven scaffold diversity.

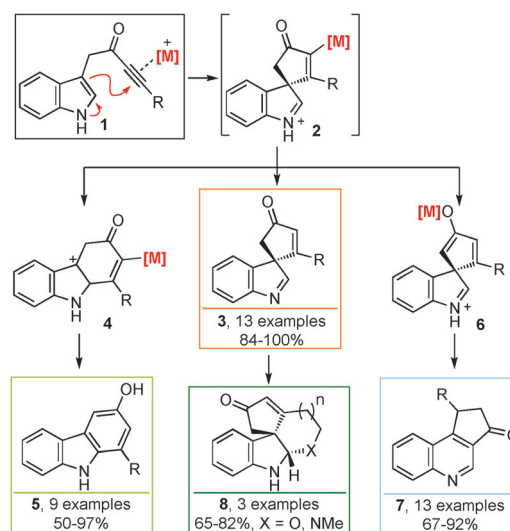
[a] Dr. J. T. R. Liddon, M. J. James, A. K. Clarke, Prof. P. O'Brien, Prof. R. J. K. Taylor, Dr. W. P. Unsworth
University of York, York, YO24 4PP (UK)
E-mail: richard.taylor@york.ac.uk
william.unsworth@york.ac.uk

Supporting information of this article can be found under
<http://dx.doi.org/10.1002/chem.201601836>.

© 2016 The Authors. Published by Wiley-VCH Verlag GmbH & Co. KGaA. This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

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

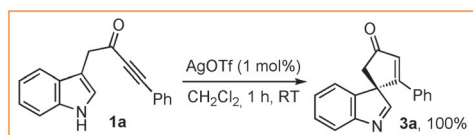


Scheme 1. Divergent synthesis of spirocycles **3**, carbazoles **5**, quinolines **7** and tetracyclic scaffolds **8** from indolyl ynone **1**.

demonstrated that the dearomatising spirocyclisation^[4] of ynone **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^I, carbazoles **5** using Au^I and quinolines **7** using Ag^I/Al^{III} in high yield, each by

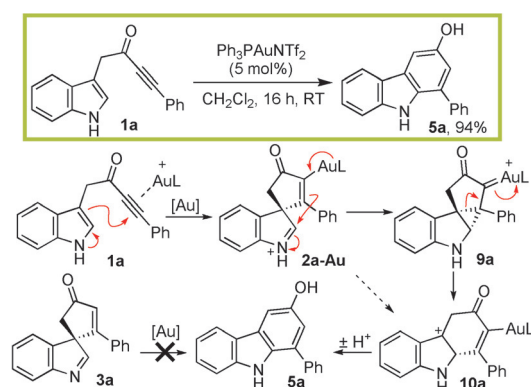
a simple, catalytic and atom-economical process. Furthermore, in suitable cases, tetracyclic scaffolds **8** can be formed with complete diastereoselectivity, by a telescoped spirocyclisation/nucleophilic addition sequence, which was performed using a chiral Ag^I salt to furnish an enantiopure product.

The spirocyclisation of **1a** using AgOTf formed indolenine **3a** in quantitative yield (Scheme 2),^[5] the mild reaction condi-



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

tions 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 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 en-

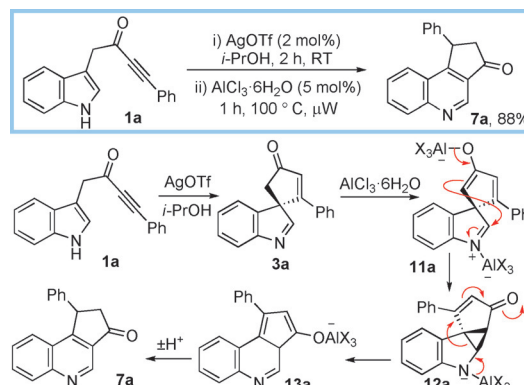


Scheme 3. Formation of carbazole **5a**; [Au] = Ph₃PAuNTf₂, L = ligand.

largement is believed to proceed either via cyclopropane intermediate **9a**, or by a direct 1,2-migration reaction (**2a-Au** → **10a**) based on related precedent.^[7,9] 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

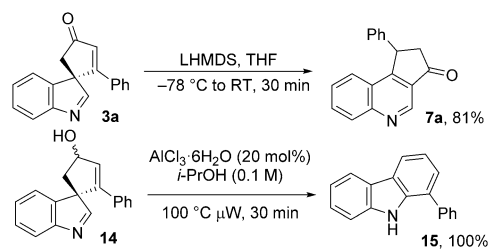
unable to uncover a catalyst that could successfully initiate spirocyclisation and subsequent rearrangement on its own. However, first performing the spirocyclisation using 2 mol% of AgOTf as catalyst in isopropanol, followed by the addition of 5 mol% of AlCl₃·6H₂O and subsequent heating in a microwave gave quinoline **7a** in high yield (Scheme 4).^[10] Following Ag^I-



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

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 by a series of 1,5-sigmatropic H-transfer reactions).

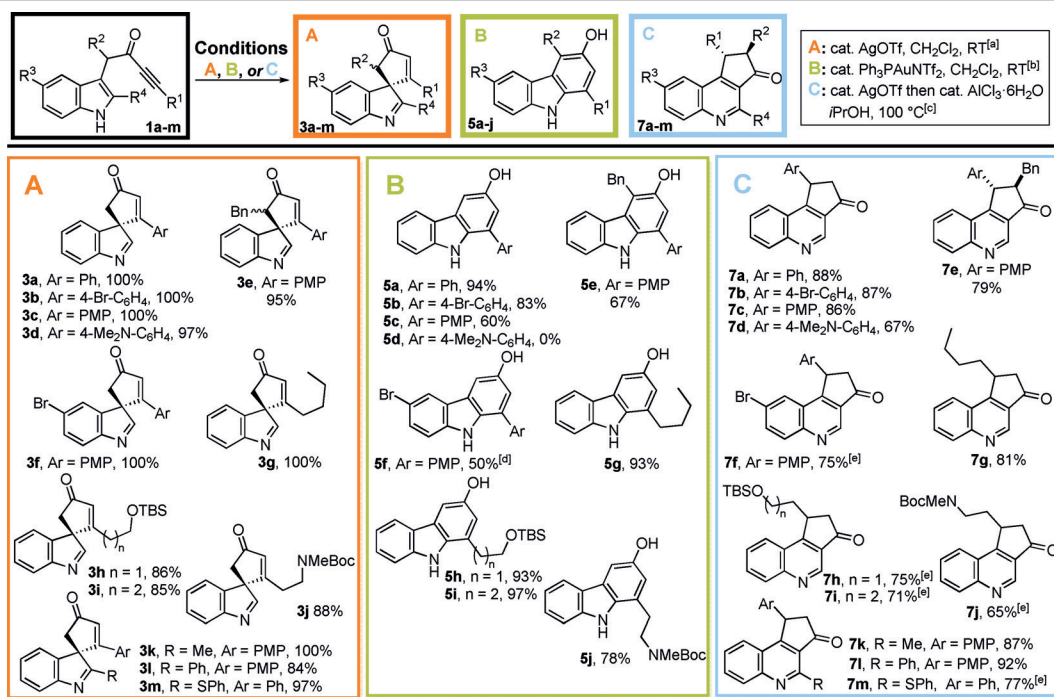
Supporting evidence for this unprecedented rearrangement was obtained: treatment of spirocycle **3a** with LHMDS in THF (i.e. conditions which almost certainly would result in enolate formation) also led to the formation of quinoline **7a**, in 81% yield. Furthermore, the importance of the carbonyl group was shown by the fact that treatment of known cyclopentenol **14**^[11] 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 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 yrones **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

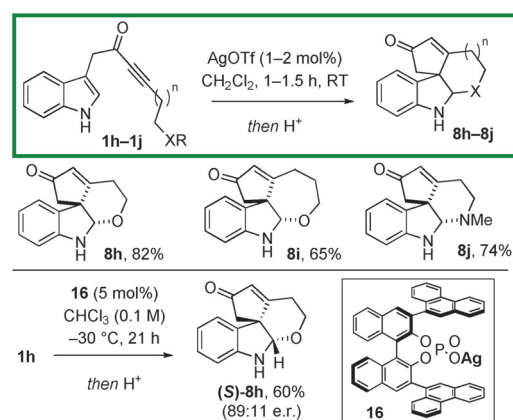
Table 1. Reaction scope for the formation of spirocyclic indolenines, carbazoles and quinolones.



[a] AgOTf (1 mol%) in CH₂Cl₂ (0.1 M) at RT for 0.1–3.5 h. [b] Ph₃PAuNTf₂ (2–5 mol%) in CH₂Cl₂ (0.1 M) at RT for 7–18 h. [c] AgOTf (1 mol%) in *i*PrOH (0.1 M) at RT for 1–3 h, then AlCl₃·6H₂O (5–10 mol%) at 100 °C μ W for 1–2 h. [d] Reaction performed in toluene. [e] AgOTf (1 mol%) in CH₂Cl₂ (0.1 M) at RT for 1–3 h, then solvent swap for *i*PrOH (0.1 M) then AlCl₃·6H₂O (5–10 mol%) at 100 °C μ W for 1–2 h. PMP = *para*-methoxyphenyl.

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.^[13] Finally, the quinoline-forming reaction sequence was also found to be very general (conditions C). For yrones **1a–1e**, **1g**, **1k–1l**, the sequential AgOTf spirocyclisation and AlCl₃·6H₂O mediated rearrangement steps could both be performed in *i*PrOH in one-pot as described, whereas for yrones 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 *i*PrOH prior to the 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.^[14] The structure of quinoline **7f** was confirmed by X-ray crystallography.^[15]

Another strand of scaffold diversity starting from more functionalised yrones **1h–1j** was briefly explored. Tetracyclic scaffolds **8h–j**, equipped with additional complexity, were easily obtained following reaction of yrones **1h–1j** with AgOTf and subsequent acid-mediated protecting group cleavage in one pot (Scheme 6, and see the Supporting Information for de-



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

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

In summary, readily available indolyl yrones have been shown to be versatile starting materials for the synthesis of spirocyclic indolenines **3a–m**, carbazoles **5a–j**, quinolones **7a–m** and tetracyclic compounds **8h–j** using a catalyst-driven scaffold

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 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: carbazoles · catalysis · diversity · quinolines · spirocycles

- [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. 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. USA* **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. Morgentín, 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. Dumas, 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, *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; *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 dearomatising spirocyclisation reactions, see: a) C.-X. Zhuo, W. Zhang, S.-L. You, *Angew. Chem. Int. Ed.* **2012**, *51*, 12662; *Angew. Chem.* **2012**, *124*, 12834; b) S. P. Roche, 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; *Angew. Chem.* **2015**, *127*, 7750–7753.
- [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; *Angew. Chem.* **2012**, *124*, 1712–1715; 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. Hennessey, 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; *Angew. Chem.* **2004**, *116*, 2456–2460; 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; *Angew. Chem.* **2011**, *123*, 9242–9246; 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) R. 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. Clubleby, 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: 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, and references [8a–c].
- [14] 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 8 h (see the Supporting Information for full details).
- [15] CCDC 1453490 (**7f**) and 1453491 (**(S)-8h**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- [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; *Angew. Chem.* **2012**, *124*, 9710–9713.
- [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; *Angew. Chem.* **2014**, *126*, 239–243.
- [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**, *112*, 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.

Received: April 19, 2016
Published online on May 19, 2016