ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2018, **54**, 1125

Received 21st November 2017,
Accepted 6th January 2018

DOI: 10.1039/c7cc08938d

rsc.li/chemcomm

Nine-step total synthesis of (−)-strychnofoline†

Qingzhen Yu,‡[ab] Pan Guo,‡[ab] Jie Jian,‡[ab] Yuye Chen[abc] and Jing Xu *[ab]

Strychnofoline is a *Strychnos* alkaloid that has unique spirooxindole architecture and possesses important anticancer activity. Here, we have, for the first time, reported the enantioselective synthesis of strychnofoline proceeding in only nine steps from commercially available 6-methoxytryptamine. The efficiency of the synthesis derives from the use of two sequential transformation steps in the catalytic asymmetric construction of the spiro[pyrrolidine-3,3′-oxindole] motif in a facile manner. Our route is amenable to the synthesis of other natural and synthetic analogs of bioactive spirooxindole alkaloids to access their therapeutic potential.

Spirooxindole alkaloids are intriguing and challenging synthetic targets, which have highly complicated architecture combined with promising activity in various therapeutic areas.[1] Representative spirooxindole alkaloids include strychnofoline (**1**), palmirine,[2] spirotryprostatins,[3] gelsemine,[4] citrinadins[5] and cyclopiamines[6] (Fig. 1). Intensive synthetic studies toward these alkaloids, including many impressive and successful approaches, have been previously reported.[7–10]

Amongst these fascinating molecules, **1** appears to be an attractive target for chemical synthesis and biological studies. It was isolated from the leaves of *Strychnos usambarensis* by Angenot *et al.* in 1978, and has demonstrated very promising antimitotic activity against cultures of mouse melanoma and Ehrlich tumor cells.[11] An impressive synthesis of (±)-**1** was reported by the Carreira group, in 2002, who used an elegant, highly diastereoselective cyclopropane ring expansion strategy.[12] Given the significant physiological functions and complicated chemical skeleton of **1**, a simple, asymmetric synthesis is evidently required for accessing its therapeutic potential. The five stereocentres and the unique spiro[pyrrolidine-3,3′-oxindole] motif present a substantial challenge for its synthesis. Here, we describe a concise, catalytic asymmetric synthesis of (−)-strychnofoline in only nine steps from a commercially available starting material.

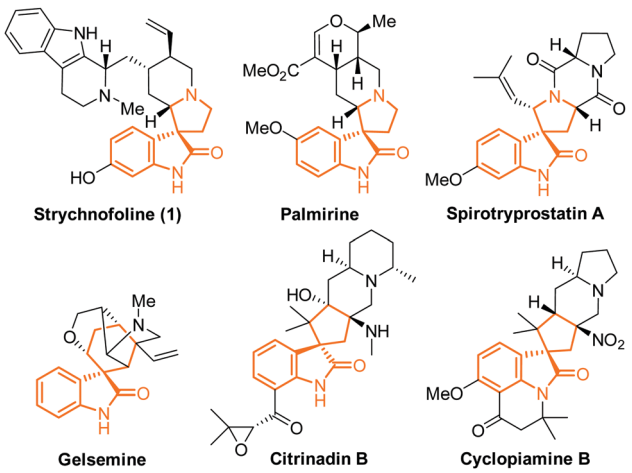

Fig. 1 Representative spirooxindole alkaloids.

Various innovative approaches have been developed to efficiently and asymmetrically construct the spirooxindole skeleton.[13–15] Inspired by these studies, we devised a synthesis of **1**, whose highlights are shown in Fig. 2. We envisioned that the β-carboline skeleton could be constructed *via* a late stage Pictet–Spengler reaction. A subsequent selective amide reduction and Shapiro tosylhydrazone decomposition would allow access to **10** from intermediate **6**, which could arise from the 6-methoxytryptamine **2** *via* sequential acylation/asymmetric Michael addition/Pictet–Spengler reaction/oxidative rearrangement.

With this in mind, we developed a one-pot, catalytic asymmetric synthesis of the quinolizidine skeleton,[14] which, with a subsequent rearrangement, allowed facile access to the spiro[pyrrolidine-3,3′-oxindole] motif in only two steps (Fig. 3). Our synthesis started with commercially available 6-methoxytryptamine (**2**).

[a] *Department of Chemistry, Southern University of Science and Technology, Shenzhen, Guangdong Province, China. E-mail: xuj@sustc.edu.cn*
[b] *SUSTech, Grubbs Institute, Shenzhen, Guangdong Province, China*
[c] *State Key Laboratory of Quality Research in Chinese Medicine, Institute of Chinese Medical Sciences, University of Macau, Macau, China*

† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and crystallographic data of **6**. CCDC 1571159. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7cc08938d

‡ These authors contributed equally to this work.

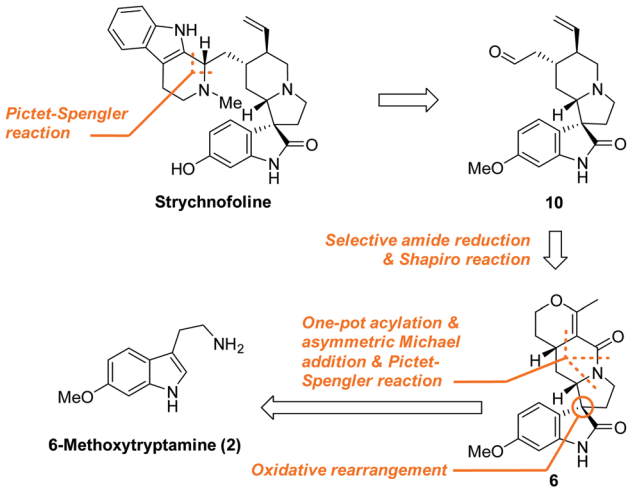

Fig. 2 Retrosynthetic analysis of strychnofoline (**1**).

By sequentially adding **2**; diketene, acrolein derivative **3**; organocatalyst **4** (Hayashi–Jørgensen catalyst); and acyl chloride to the reaction mixture, we were able to achieve the quinolizidine derivative **5** in good yield with excellent enantioselectivity (67% yield, ee > 99%).

Subsequently, the seemingly simple transformation from **5** to **7** turned out to be remarkably challenging. Although a reduction using $LiAlH_4$ conditions could easily afford the corresponding tertiary amine in good yield, the various rearrangement conditions[7a,b,10,16] tested were unsuccessful, most likely because of the presence of the sensitive tertiary amine. Trials using a Brønsted acid protonated substrate[17] also resulted in failure. Therefore, we had to perform the skeleton rearrangement first, hoping that subsequent selective amide reduction would provide access to the pivotal intermediate **7**. To this end, a *tert*-butyl hypochlorite induced rearrangement successfully furnished **6**.[16a–c,e,h,j] The plausible chloroindolenine intermediate was not isolated, but directly transformed into the spiro[pyrrolidine-3,3′-oxindole] intermediate **6** in a one-pot rearrangement using acidic methanol conditions. To our great pleasure, single-crystal X-ray diffraction unambiguously confirmed all the desired stereochemistry.[18] The undesired epimer due to the rearrangement was not observed, presumably because of the different thermodynamic stabilities of the two possible epimers. Then, various reductive conditions were intensively screened to selectively reduce the C-21 (based on the carbon numbering of **1**) amide functionality over the C-2 amide functionality. Although similar transformations are known from the literature using alane[16c,19] or Lawesson's reagent[15t,20] followed by certain reducing conditions, the extra unsaturated C–C bond, which is adjacent to the C-21 amide, created a significant challenge for the desired selective reduction. Most tested conditions resulted in either global reduction or disfavoured selectivity. Fortunately, we found that using six equivalents of DIBAL-H successfully differentiated between the

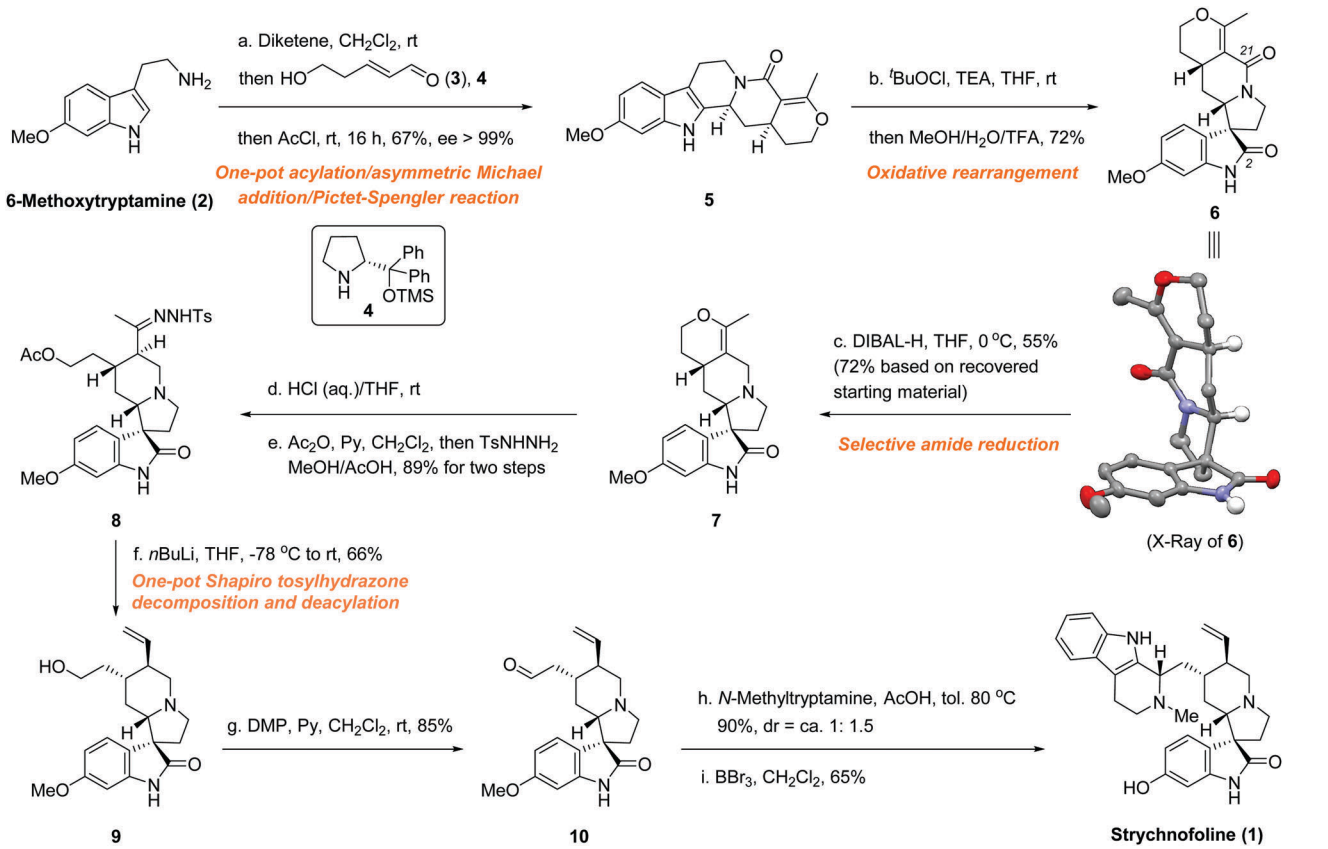

Fig. 3 Nine-step total synthesis of (–)-strychnofoline. DMP, Dess–Martin periodinane.

two amide functionalities to achieve the desired mono-reduced product **7** (55% yield, 72% brsm).

The final steps of our synthesis began with the acidic hydrolysis of the cyclic enol ether functionality of **7**, which easily furnished the corresponding ketone (Fig. 3). Gratifyingly, we found that the acylation of the primary hydroxyl group and the transformation from ketone to tosylhydrazone could be performed in one-pot, thus further improving the overall efficiency, to yield hydrazone **8** (89% overall yield from **7**). Shapiro tosylhydrazone decomposition and concomitant deacylation using an excess amount of *n*-BuLi smoothly produced alkene **9** in 66% yield.[14c] Subsequently, the Dess–Martin oxidation of the primary hydroxyl group afforded aldehyde **10** in 85% yield. Condensation of aldehyde **10** with *N*-methyltryptamine produced the corresponding *O*-methyl strychnofoline in 90% yield. We observed the same diastereoselectivity issue that was encountered by Carreira *et al.* (dr = ~1 : 1.5).[12] Efforts to improve the diastereoselectivity of this Pictet–Spengler reaction were unsuccessful, although a few examples have been reported.[21] Nonetheless, this minor botheration was well compensated for by the high overall efficiency of our strategy. Eventually, demethylation of the *O*-methyl strychnofoline using boron tribromide successfully furnished **1** in 65% yield. To our great pleasure, the synthetic material, thus obtained, exhibited identical spectroscopic and analytical properties to those reported for the natural product.[11,12]

In summary, we have successfully conducted the rapid, enantioselective synthesis of the anti-tumor alkaloid strychnofoline (**1**) in only nine steps. Our strategy is highlighted by (a) a one-pot, catalytic asymmetric construction of quinolizidine intermediate **5**; (b) an efficient, diastereoselective skeleton rearrangement that formed the spiro[pyrrolidine-3,3′-oxindole] motif of **1**; and (c) a selective amide reduction that successfully differentiated two similar amide motifs. A convenient preparation of **1** will be of great assistance in addressing its therapeutic promise. Moreover, our work provides an efficient strategy toward the synthesis of various bioactive spirooxindole alkaloids. Encouraged by this promising result, further efforts to synthesize natural and unnatural spirooxindoles and related biological investigations are currently underway in our laboratory and will be reported in due course.

Financial support from the National Natural Science Foundation of China (No. 21402082, No. 21772082 and No. 21702094), SZSTI (Pu20150267, Ji20170314 and Peacock Tech-Innovation 2018), and SZDRC (K16205905) is greatly appreciated. We also thank Professor Bin Tan (SUSTech) for useful comments.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) H. Lin and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2003, **42**, 36–51; (*b*) C. Marti and E. M. Carreira, *Eur. J. Org. Chem.*, 2003, 2209–2219; (*c*) M. M. C. Lo, C. S. Neumann, S. Nagayama, E. O. Perlstein and S. L. Schreiber, *J. Am. Chem. Soc.*, 2004, **126**, 16077–16086; (*d*) C. Chen, X. D. Li, C. S. Neumann, M. M. C. Lo and S. L. Schreiber, *Angew. Chem., Int. Ed.*, 2005, **44**, 2249–2252; (*e*) K. Ding, Y. Lu, Z. Nikolovska-Coleska, S. Qiu, Y. Ding, W. Gao, J. Stuckey, K. Krajewski, P. P. Roller, Y. Tomita, D. A. Parrish, J. R. Deschamps and S. Wang, *J. Am. Chem. Soc.*, 2005, **127**, 10130–10131; (*f*) A. K. Franz, P. D. Dreyfuss and S. L. Schreiber, *J. Am. Chem. Soc.*, 2007, **129**, 1020–1021; (*g*) C. V. Galliford and K. A. Scheidt, *Angew. Chem., Int. Ed.*, 2007, **46**, 8748–8758; (*h*) S. Shangary, D. Qin, D. McEachern, M. Liu, R. S. Miller, S. Qiu, Z. Nikolovska-Coleska, K. Ding, G. Wang, J. Chen, D. Bernard, J. Zhang, Y. Lu, Q. Gu, R. B. Shah, K. J. Pienta, X. Ling, S. Kang, M. Guo, Y. Sun, D. Yang and S. Wang, *Proc. Natl. Acad. Sci. U. S. A.*, 2008, **105**, 3933–3938; (*i*) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. Gonzalez-Paéz, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175–1180; (*j*) B. K. S. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E. K. Schmitt, P. Krastel, E. Francotte, K. Kuhen, D. Plouffe, K. Henson, T. Wagner, E. A. Winzeler, F. Petersen, R. Brun, V. Dartois, T. T. Diagana and T. H. Keller, *J. Med. Chem.*, 2010, **53**, 5155–5164; (*k*) M. M. M. Santos, *Tetrahedron*, 2014, **70**, 9735–9757; (*l*) T. L. Pavlovska, R. Gr. Redkin, V. V. Lipson and D. V. Atamanuk, *Mol. Diversity*, 2016, **20**, 299–344.

2 J. Borges, M. T. Manresa, J. L. Martín Ramón, C. Pascual and A. Rumbero, *Tetrahedron Lett.*, 1979, **20**, 3197–3200.

3 (*a*) C. B. Cui, H. Kakeya and H. Osada, *J. Antibiot.*, 1996, **49**, 832–835; (*b*) C. B. Cui, H. Kakeya and H. Osada, *Tetrahedron*, 1996, **51**, 12651–12666.

4 (*a*) F. L. Sonnenschein, *Ber. Dtsch. Chem. Ges.*, 1876, **9**, 1182–1186; (*b*) H. Conroy and J. K. Chakrabarti, *Tetrahedron Lett.*, 1959, **1**, 6–13; (*c*) Y. Schun and G. A. Cordell, *J. Nat. Prod.*, 1985, **48**, 969–971; (*d*) F. M. Lovell, R. Pepinsky and A. J. C. Wilson, *Tetrahedron Lett.*, 1959, **1**, 1–5.

5 (*a*) M. Tsuda, Y. Kasai, K. Komatsu, T. Sone, M. Tanaka, Y. Mikami and J. Kobayashi, *Org. Lett.*, 2004, **6**, 3087–3089; (*b*) T. Mugishima, M. Tsuda, Y. Kasai, H. Ishiyama, E. Fukushi, J. Kawabata, M. Watanabe, K. Akao and J. Kobayashi, *J. Org. Chem.*, 2005, **70**, 9430–9435.

6 R. F. Bond, J. C. A. Boeyens, C. W. Holzapfel and P. S. Steyn, *J. Chem. Soc., Perkin Trans. 1*, 1979, 1751–1761.

7 For total syntheses of spirotryprostatins: (*a*) S. D. Edmonson and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 1998, **37**, 1138–1140; (*b*) S. D. Edmonson and S. J. Danishefsky, *J. Am. Chem. Soc.*, 1999, **121**, 2147–2155; (*c*) F. von Nussbaum and S. J. Danishefsky, *Angew. Chem., Int. Ed.*, 2000, **39**, 2175–2178; (*d*) L. E. Overman and M. D. Rosen, *Angew. Chem., Int. Ed.*, 2000, **39**, 4596–4599; (*e*) H. Wang and A. Ganesan, *J. Org. Chem.*, 2000, **65**, 4685–4693; (*f*) P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666–5667; (*g*) P. R. Sebahar, H. Osada, T. Usui and R. M. Williams, *Tetrahedron*, 2002, **58**, 6311–6322; (*h*) T. D. Bagul, G. Lakshmaiah, T. Kawabata and K. Fuji, *Org. Lett.*, 2002, **4**, 249–251; (*i*) C. Meyers and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2003, **42**, 694–696; (*j*) T. Onishi, P. R. Sebahar and R. M. Williams, *Org. Lett.*, 2003, **5**, 3135–3137; (*k*) T. Onishi, P. R. Sebahar and R. M. Williams, *Tetrahedron*, 2004, **60**, 9503–9515; (*l*) F. Y. Miyake, K. Yakushijin and D. A. Horne, *Angew. Chem., Int. Ed.*, 2004, **43**, 5357–5360; (*m*) F. Y. Miyake, K. Yakushijin and D. A. Horne, *Org. Lett.*, 2004, **6**, 4249–4251; (*n*) C. Marti and E. M. Carreira, *J. Am. Chem. Soc.*, 2005, **127**, 11505–11515; (*o*) B. M. Trost and D. T. Stiles, *Org. Lett.*, 2007, **9**, 2763–2766; (*p*) K. Kitahara, J. Shimokawa and T. Fukuyama, *Chem. Sci.*, 2014, **5**, 904–907.

8 For total syntheses of gelsemine: (*a*) Z. Sheikh, R. Steel, A. S. Tasker and A. P. Johnson, *J. Chem. Soc., Chem. Commun.*, 1994, 763–764; (*b*) J. K. Dutton, R. W. Steel, A. S. Tasker, V. Popsavin and A. P. Johnson, *J. Chem. Soc., Chem. Commun.*, 1994, 765–766; (*c*) N. J. Newcombe, F. Ya, R. J. Vijn, H. Hiemstra and W. N. Speckamp, *J. Chem. Soc., Chem. Commun.*, 1994, 767–768; (*d*) T. Fukuyama and G. Liu, *J. Am. Chem. Soc.*, 1996, **118**, 7426–7427; (*e*) S. Atarashi, J.-K. Choi, D.-C. Ha, D. J. Hart, D. Kuzmich, C.-S. Lee, S. Ramesh and S. C. Wu, *J. Am. Chem. Soc.*, 1997, **119**, 6226–6241; (*f*) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *Angew. Chem., Int. Ed.*, 1999, **38**, 2934–2936; (*g*) S. Yokoshima, H. Tokuyama and T. Fukuyama, *Angew. Chem., Int. Ed.*, 2000, **39**, 4073–4075; (*h*) F. W. Ng, H. Lin and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2002, **124**, 9812–9824; (*i*) H. Lin, F. W. Ng and S. J. Danishefsky, *Tetrahedron Lett.*, 2002, **43**, 549–551; (*j*) W. G. Earley, J. E. Jacobsen, A. Madin, G. P. Meier, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *J. Am. Chem. Soc.*, 2005,

127, 18046–18053; (*k*) A. Madin, C. J. O'Donnell, T. Oh, D. W. Old, L. E. Overman and M. J. Sharp, *J. Am. Chem. Soc.*, 2005, **127**, 18054–18065; (*l*) X. Zhou, T. Xiao, Y. Iwama and Y. Qin, *Angew. Chem., Int. Ed.*, 2012, **51**, 4909–4912; (*m*) X. Chen, S. Duan, C. Tao, H. Zhai and F. G. Qiu, *Nat. Commun.*, 2015, **6**, 7204–7210.

9 For total syntheses of citrinadins: (*a*) Z. Bian, C. C. Marvin and S. F. Martin, *J. Am. Chem. Soc.*, 2013, **135**, 10886–10889; (*b*) K. Kong, J. A. Enquist Jr., M. E. McCallum, G. M. Smith, T. Matsumaru, E. Menhaji-Klotz and J. L. Wood, *J. Am. Chem. Soc.*, 2013, **135**, 10890–10893; (*c*) Z. Bian, C. C. Marvin, M. Pettersson and S. F. Martin, *J. Am. Chem. Soc.*, 2014, **136**, 14184–14192.

10 For total syntheses of cyclopiamine B: E. V. Mercado-Marin, P. Garcia-Reynaga, S. Romminger, E. F. Pimenta, D. K. Romney, M. W. Lodewyk, D. E. Williams, R. J. Andersen, S. J. Miller, D. J. Tantillo, R. G. S. Berlinck and R. Sarpong, *Nature*, 2014, **509**, 318–324.

11 (*a*) L. Angenot, *Plant. Med. Phytother.*, 1978, **12**, 123–129; (*b*) R. Bassleer, M. C. Depauw-Gillet, B. Massart, J.-M. Marnette, P. Wiliquet, M. Caprasse and L. Angenot, *Planta Med.*, 1982, **45**, 123–126.

12 (*a*) A. Lerchner and E. M. Carreira, *J. Am. Chem. Soc.*, 2002, **124**, 14826–14827; (*b*) A. Lerchner and E. M. Carreira, *Chem. – Eur. J.*, 2006, **12**, 8208–8219.

13 For reviews: (*a*) F. Zhou, Y.-L. Liu and J. Zhou, *Adv. Synth. Catal.*, 2010, **352**, 1381–1407; (*b*) R. Dalpozzo, G. Bartoli and G. Bencivenni, *Chem. Soc. Rev.*, 2012, **41**, 7247–7290; (*c*) N. R. Ball-Jones, J. J. Badille and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165–5181; (*d*) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023–1052; (*e*) D. Cheng, Y. Ishihara, B. Tan. and C. F. Barbas, III, *ACS Catal.*, 2014, **4**, 743–762; (*f*) Z.-Y. Cao and J. Zhou, *Org. Chem. Front.*, 2015, **2**, 849–858; (*g*) R. Dalpozzo, *Adv. Synth. Catal.*, 2017, **359**, 1772–1810.

14 (*a*) J. Franzén and A. Fisher, *Angew. Chem., Int. Ed.*, 2009, **48**, 787–791; (*b*) W. Zhang and J. Franzén, *Adv. Synth. Catal.*, 2010, **352**, 499–518; (*c*) W. Zhang, J. Bah, A. Wohlfarth and J. Franzén, *Chem. – Eur. J.*, 2011, **17**, 13814–13824.

15 For related studies, see: (*a*) X. Y. Wu, X. Y. Dai, L. L. Nie, H. H. Fang, J. Chen, Z. J. Ren, W. G. Cao and G. Zhao, *Chem. Commun.*, 2010, **46**, 2733–2735; (*b*) H. H. Fang, X. Y. Wu, L. L. Nie, X. Y. Dai, J. Chen, W. G. Cao and G. Zhao, *Org. Lett.*, 2010, **12**, 5366–5369; (*c*) Z. C. Jin, X. Wang, H. C. Huang, X. M. Liang and J. X. Ye, *Org. Lett.*, 2011, **13**, 564–567; (*d*) S. L. Zhou, J. L. Li, L. Dong and Y. C. Chen, *Org. Lett.*, 2011, **13**, 5874–5877; (*e*) X. Y. Wu, X. Y. Dai, H. H. Fang, L. L. Nie, J. Chen, W. G. Cao and G. Zhao, *Chem. – Eur. J.*, 2011, **17**, 10510–10514; (*f*) X. Sun and D. Ma, *Chem. – Asian J.*, 2011, **6**, 2158–2165; (*g*) Z. C. Jin, H. C. Huang, W. J. Li, X. Y. Luo, X. M. Liang and J. X. Ye, *Adv. Synth. Catal.*, 2011, **353**, 343–348; (*h*) M. Rueping, C. M. R. Volla, M. Bolte and G. Raabe, *Adv. Synth. Catal.*, 2011, **353**, 2853–2859; (*i*) Z. Jin, F. Yu, X. Wang, H. Huang, X. Luo, X. Liang and J. Ye, *Org. Biomol. Chem.*, 2011, **9**, 1809–1816; (*j*) M. Rueping and C. M. R. Volla, *RSC Adv.*, 2011, **1**, 79–82; (*k*) X. Y. Dai, X. Y. Wu, H. H. Fang, L. L. Nie, J. Chen, H. M. Deng, W. G. Cao and G. Zhao, *Tetrahedron*, 2011, **67**, 3034–3040; (*l*) X. Y. Wu, H. H. Fang, Q. Liu, L. L. Nie, J. Chen, W. G. Cao and G. Zhao, *Tetrahedron*, 2011, **67**, 7251–7257; (*m*) X. Wu, Y. Zhang, X. Dai, H. Fang, J. Chen, W. Cao and G. Zhao, *Synthesis*, 2011, 3675–3679; (*n*) X. Wu, Q. Liu, H. Fang, J. Chen, W. Cao and G. Zhao, *Chem. – Eur. J.*, 2012, **18**, 12196–12201; (*o*) M. E. Muratore, L. Shi, A. W. Pilling, R. I. Storer and D. J. Dixon, *Chem. Commun.*, 2012, **48**, 6351–6353; (*p*) S. Z. Lin, L. Deiana, A. Tseggai and A. Córdova, *Eur. J. Org. Chem.*, 2012, 398–408; (*q*) B.-C. Hong, W.-K. Liao, N. S. Dange and J.-H. Liao, *Org. Lett.*, 2013, **15**, 468–471; (*r*) I. Aillaud, D. M. Barber, A. L. Thompson and D. J. Dixon, *Org. Lett.*, 2013, **15**, 2946–2949; (*s*) P. A. Suryavanshi, V. Sridharan and J. C. Menéndez, *Chem. – Eur. J.*, 2013, **19**, 13207–13215; (*t*) H. Zhang, X. Ma, H. Kang, L. Hong and R. Wang, *Chem. – Asian J.*, 2013, **8**, 542–545; (*u*) Y. Tan, H.-L. Luan, H. Lin, X.-W. Sun, X.-D. Yang, H.-Q. Dong and G.-Q. Lin, *Chem. Commun.*, 2014, **50**, 10027–10030; (*v*) H. Du, J. Rodriguez, X. Bugaut and T. Constantieux, *Adv. Synth. Catal.*, 2014, **356**, 851–856; (*w*) L. Li, P. Aibibula, Q. Jia and Y. Jia, *Org. Lett.*, 2017, **19**, 2642–2645.

16 (*a*) N. Finch and W. I. Taylor, *J. Am. Chem. Soc.*, 1962, **84**, 1318–1320; (*b*) J. Shavel and H. Zinnes, *J. Am. Chem. Soc.*, 1962, **84**, 1320–1321; (*c*) S. F. Martin and M. Mortimore, *Tetrahedron Lett.*, 1990, **31**, 4557–4560; (*d*) X. Zhang and C. S. Foote, *J. Am. Chem. Soc.*, 1993, **115**, 8867–8868; (*e*) M. Ito, C. W. Clark, M. Mortimore, J. Betty Goh and S. F. Martin, *J. Am. Chem. Soc.*, 2001, **123**, 8003–8010; (*f*) X. Z. Wearing and J. M. Cook, *Org. Lett.*, 2002, **4**, 4237–4940; (*g*) H. Takayama, R. Fujiwara, Y. Kasai, M. Kitajima and N. Aimi, *Org. Lett.*, 2003, **5**, 2967–2970; (*h*) P. S. Baran and J. M. Richter, *J. Am. Chem. Soc.*, 2005, **127**, 15394–15396; (*i*) T. J. Greshock and R. M. Williams, *Org. Lett.*, 2007, **9**, 4255–4258; (*j*) C. Poriel, M. Lachia, C. Wilson, J. R. Davies and C. J. Moody, *J. Org. Chem.*, 2007, **72**, 2978–2987; (*k*) M. Pettersson, D. Knueppel and S. F. Martin, *Org. Lett.*, 2007, **9**, 4623–4626; (*l*) J. Yang, X. Z. Wearing, P. W. Le Quesne, J. R. Deschamps and J. M. Cook, *J. Nat. Prod.*, 2008, **71**, 1431–1440; (*m*) D. A. Mundal and R. Sarpong, *Org. Lett.*, 2013, **15**, 4952–4955.

17 C. A. Guerrero and E. J. Sorensen, *Org. Lett.*, 2011, **13**, 5164–5167.

18 CCDC 1571159.† Some hydrogen atoms of compound **6** were omitted for clarity.

19 M. Amat, C. Ramos, M. Pérez, E. Molins, P. Florindo, M. M. M. Santos and J. Bosch, *Chem. Commun.*, 2013, **49**, 1954–1956.

20 J.-Y. Laronzo, B. Guilleteau, D. Cartier, J. Laronze and J. Lévy, *Heterocycles*, 1989, **29**, 2051–2055.

21 R. S. Klausen, C. R. Kennedy, A. M. Hyde and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2017, **139**, 12299–12309 and references therein.

