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Organocatalyzed aerobic oxidative Robinson-type annulation of 2-isocyanochalcones: expedient synthesis of phenanthridines†

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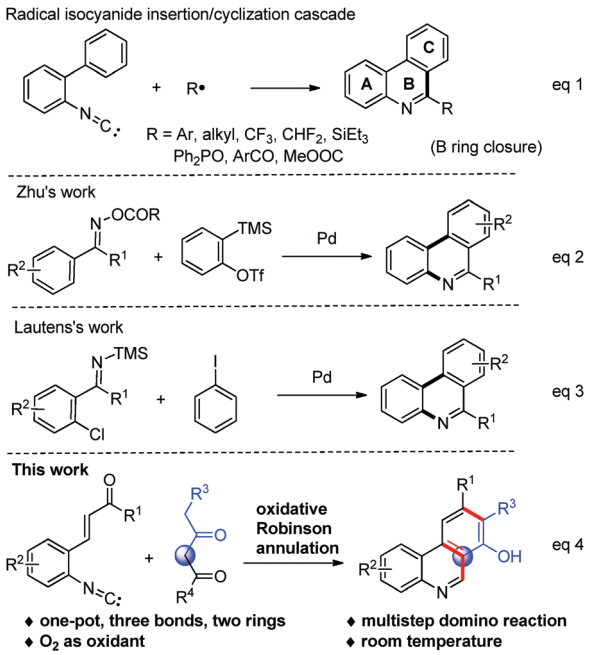
A DBU-catalyzed aerobic oxidative Robinson annulation of 2-isocyanochalcones with active methylene ketones was developed for the expedient synthesis of phenanthridines in high to excellent yields. This unprecedented multistep domino reaction represents a new strategy for the construction of this tricyclic scaffold by the sequential formation of two rings and three C–C bonds in a single operation at room temperature.

Phenanthridines are important frameworks of natural products and pharmacologically active compounds and other functional molecules. As a consequence, considerable effort has been devoted to developing new methods for the synthesis of these tricyclic heterocycles.[1a,b,2–6] However, most of the existing synthetic approaches rely on the closure of the central pyridine ring (B ring) from the substituted biaryl substrates by the formation of a C–C and/or C–N bond.[1–6] For example, (1) the recent powerful tandem radical isocyanide insertion/cyclization reactions of *ortho*-isocyanobiphenyls with various radicals for the synthesis of 6-position functionalized phenanthridines by the formation of a C–C bond (Scheme 1, eqn (1));[1a,3] (2) Zhu's palladium-catalyzed annulation of acyloximes with arynes (Scheme 1, eqn (2))[4] and Lautens' palladium-catalyzed domino direct arylation/*N*-arylation (Scheme 1, eqn (3))[5] for the elegant synthesis of phenanthridines by the sequential formation of C–C and C–N bonds. Despite these achievements,[1–6] the development of conceptually new and environmentally benign methodologies is still of great interest.

The Robinson annulation is one of the well-known organic reactions used to convert a ketone and an α,β-unsaturated ketone to a cyclohexenone moiety.[7] Since reported in 1935,[8] this domino process has been widely used in the synthesis of many mono- and polycyclic aliphatic frameworks,[7] especially those which are key intermediates in the total synthesis of natural products of the terpenoid and steroid series,[9] natural antibiotics,[10] and alkaloids.[11] Recently, the synthesis of phenol derivatives through oxidative aromatization of cyclohexenones has made extensive progress.[12,13] Furthermore, carbazoles and benzo[*c*]chromen-6-ones were efficiently prepared by the domino generation and transformation of Robinson's annulation products.[14] As a continuation of our studies on isocyanide-based annulations,[15] herein, we disclose the first example of organocatalyzed oxidative Robinson annulation for the efficient and practical synthesis of phenanthridines from the readily available 2-isocyanochalcones and active methylene compounds under mild metal-free conditions (Scheme 1, eqn (4)). In this new domino process, two rings of this tricyclic scaffold were



Scheme 1 Strategies for the synthesis of phenanthridine derivatives.

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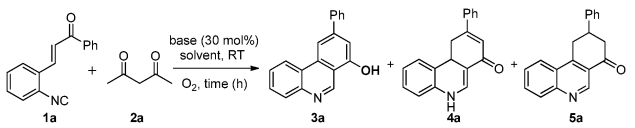
simultaneously constructed, followed by aerobic oxidative aromatization of the Robinson annulation products to deliver various phenanthridines at room temperature.

Initially, the readily available 2-isocyanochalcone **1a** and acetylacetone **2a** were used as model substrates to screen the reaction conditions (Table 1). When the reaction of **1a** with **2a** was treated with DBU (1,8-diazabicyclo-[5.4.0]undec-7-ene) in acetonitrile at room temperature for 0.3 h in open air, dihydrophenanthridin-7(5*H*)-one **4a** was obtained in 98% yield (Table 1, entry 1). It was found that **4a** could be readily transformed to phenanthridine **3a** by prolonging the reaction time to 72 h (Table 1, entry 2). To our delight, the reaction time could be shortened to 30 h and **3a** was produced in 97% yield, when the reaction was carried out under an oxygen atmosphere (Table 1, entry 3). When the temperature was increased to 60 °C, 46 h were needed to complete this reaction (Table 1, entry 4). Under these conditions, dihydrophenanthridinone **5a** was produced (detected by TLC) and it was found that the conversion of **5a** to **3a** was slow. After screening different solvents (Table 1, entries 5–8) and bases (Table 1, entries 9–12), the optimal conditions for the formation of **3a** were finally determined (Table 1, entry 3) according to the product yields and the reaction time required. In addition, it was observed that dihydrophenanthridinone **5a** could be prepared in 92% yield under the optimal conditions (Table 1, entry 3) but in a nitrogen atmosphere at 80 °C (Table 1, entry 13).

With the optimal conditions for the preparation of **3a** in hand (Table 1, entry 3), the scope of the domino protocol for the synthesis of fully aromatic phenanthridines **3** was explored first. An array of 2-isocyanochalcone and analogues **1** were tested by the reaction with acetylacetone **2a**. As the outcome of this reaction, all the desired products, phenanthridines **3a–u**, were obtained in high to excellent yields (Table 2).[16] This reaction can tolerate various R^1 groups on 2-isocyanochalcones **1**, including

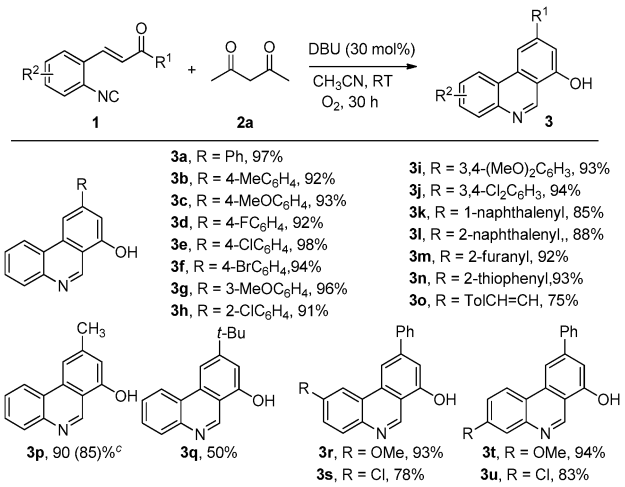
Table 1 Optimization of reaction conditions[a]



				Yield[b] (%)		
Entry	Base	Solvent	Time (h)	**3a**	**4a**	**5a**
1	DBU	CH_3CN	0.3		98	
2[c]	DBU	CH_3CN	72	88		
3	DBU	**CH_3CN**	**30**	**97**		
4[d]	DBU	CH_3CN	46	92		
5	DBU	DMF	48	91		
6	DBU	EtOH	75	74		
7	DBU	DCM	60	89		
8	DBU	THF	96	73		
9	TMG	CH_3CN	30	92		
10	K_2CO_3	CH_3CN	68	83		
11	KOH	CH_3CN	85	23		
12	*t*-BuOK	CH_3CN	57	80		
13[e]	DBU	CH_3CN	4			92

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), base (0.09 mmol), O_2 balloon and solvent (2 mL). [b] Yield of isolated products. [c] In open air. [d] At 60 °C. [e] At 80 °C, N_2 atmosphere.

Table 2 Scope of **1** for the synthesis of phenanthridines **3**[a,b]



[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), base (0.09 mmol), O_2 balloon and solvent (2 mL). [b] Yield of isolated products. [c] Yield in parentheses for a 10 mmol scale reaction, and 1.8 g of **3p** was obtained.

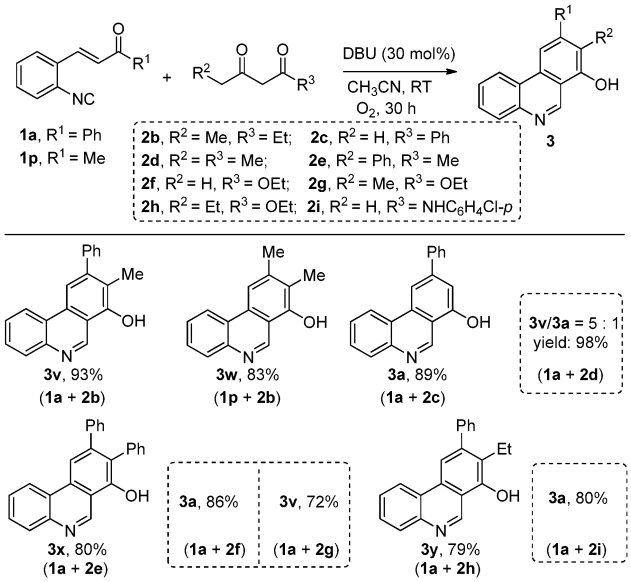
phenyl (Table 2, **1a**), aryl groups having *para*- (Table 2, **1b–f**), *meta*- (Table 2, **1g**), *ortho*- (Table 2, **1h**), or two (Table 2, **1i** and **1j**) substituents on the phenyl ring, and α- or β-naphthyl (Table 2, **1k** and **1l**), heteroaryl (Table 2, **1m** and **1n**), alkenyl (Table 2, **1o**), and alkyl (Table 2, **1p** and **1q**) groups. On the other hand, R^2 on the aryl ring of **1** can be either an electron-donating or an electron-withdrawing group (Table 2, **1r–u**). In addition, this domino reaction is practical according to the gram scale synthesis of **3p** under very mild reaction conditions.

Next, the scope of this domino reaction with respect to β-dicarbonyl compounds **2** was also investigated under identical conditions as in Table 2 and the results are tabulated in Table 3.

Similar to acetylacetone **2a**, the reaction of heptane-3,5-dione **2b** as a symmetrical β-diketone with 2-isocyanochalcone **1a** gave the desired product, 8-methylphenanthridine **3v**, in excellent yield. When 4-(2-isocyanophenyl)but-3-en-2-one **1p** was treated with **2b**, the desired 8,9-dimethylphenanthridine **3w** was obtained exclusively in high yield. In the case of unsymmetrical 1-benzoylacetone **2c** as the trinucleophile, the benzoyl group was eliminated to afford **3a** in 89% yield. Unsymmetrical hexane-2,4-dione **2d** with methyl and ethyl groups gives a mixture of phenanthridines **3v** and **3a** in a ratio of 5 : 1, while 1-phenylpentane-2,4-dione **2e** exclusively gives phenanthridines **3x** in 80% yields by selective elimination of the acetyl group. In addition, β-ketoesters (such as ethyl acetoacetate **2f**, ethyl propionylacetate **2g**, and methyl butyrylacetate **2h**) and *N*-(4-chlorophenyl)-3-oxobutanamide **2i** were also proven to be suitable trinucleophiles to enable the construction of the corresponding phenanthridines **3a**, **3v** and **3y** in high yields along with the elimination of alkoxycarbonyl and aminocarbonyl groups, respectively.

Hydrophenanthridine derivatives show valuable biological activities,[17] and they are also used as a key intermediate for the synthesis of natural product[18] and pharmaceutical molecules.[19] Therefore, the synthetic potential of this domino oxidative Robinson annulation was further explored by the facile construction of

Table 3 Scope of active methylene compounds **2**[a,b]



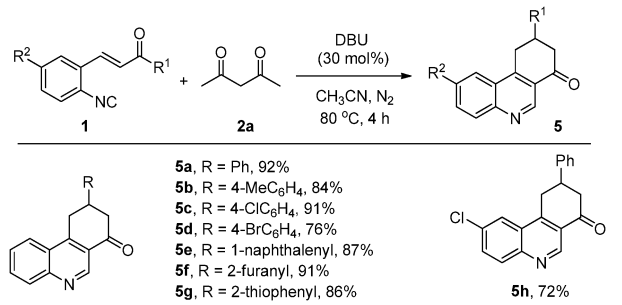
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), base (0.09 mmol), O_2 balloon and solvent (2 mL). [b] Yield of isolated products.

hydrophenanthridinone derivatives **5**. Under the aforementioned conditions (Table 1, entry 13), selected hydrophenanthridinone **5a–h** were prepared in good to excellent yields and the results are listed in Table 4.

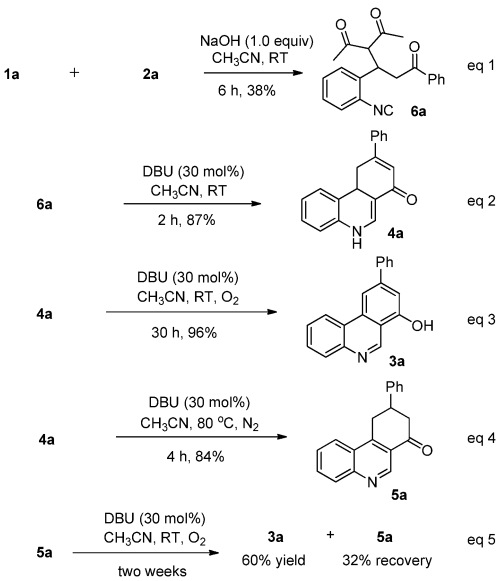
To shed light on the mechanism of this oxidative Robinson annulation, control experiments were performed. When isocyanochalcones **1a** and acetylacetone **2a** were treated with NaOH in CH_3CN at room temperature for 6 h, the Michael addition product **6a** was obtained in 38% yield (Scheme 2, eqn (1)).

Upon treatment of **6a** with DBU (30 mol%) in CH_3CN at room temperature for 2 h, tetrahydrophenanthridinone **4a** was obtained in 87% yield (Scheme 2, eqn (2)). In the presence of DBU (30 mol%), **4a** was converted to phenanthridine **3a** and dihydrophenanthridinone **5a**, respectively, under an oxygen atmosphere at room temperature (Scheme 2, eqn (3)) or under a nitrogen atmosphere at 80 °C (Scheme 2, eqn (4)). These results indicate that **6a** and **4a** are intermediates for the synthesis of phenanthridine **3a** and dihydrophenanthridinone **5a** in the oxidative

Table 4 Synthesis of dihydrophenanthridinones **5**[a,b]



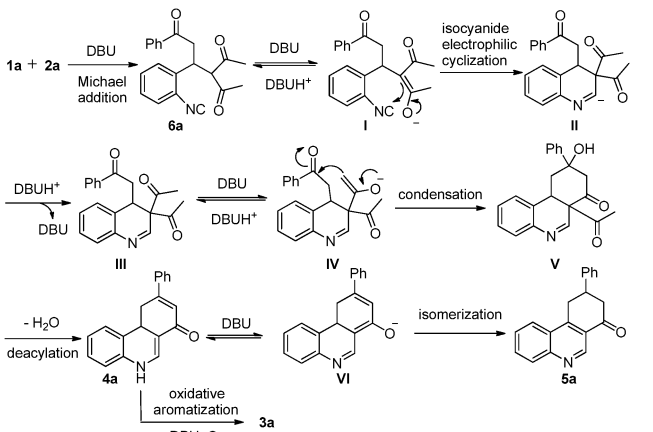
[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.36 mmol), base (0.09 mmol), N_2 balloon and solvent (2 mL). [b] Yield of isolated products.



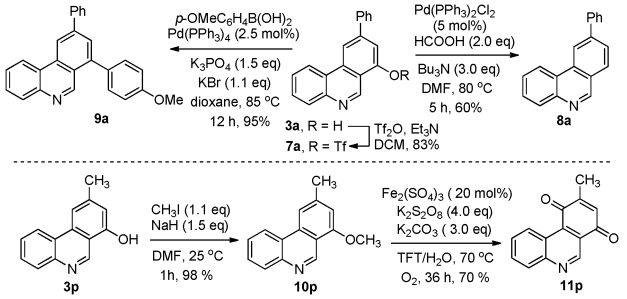
Scheme 2 Control experiments.

Robinson annulation of isocyanochalcones **1a** and acetylacetone **2a**. The aromatization of **5a** to **3a** is sluggish under aerobic oxidative conditions. Even though dihydrophenanthridinone **5a** was treated with DBU (30 mol%) and oxygen at room temperature for two weeks, **3a** was obtained in 60% yield, along with recovery of 32% of **5a** (Scheme 2, eqn (5)).

From the aforementioned results described in Tables 1–3, Scheme 2, and the results of control experiments, a plausible mechanism for the formation of phenanthridines **3** is proposed in Scheme 3 (for example **3a**). Phenanthridine **3a** would be produced by a tandem oxidative Robinson annulation process involving (1) DBU-catalyzed Michael addition of **2a** to **1a** providing the Michael adduct **6a**,[15d,20] (2) followed by a double annulation to give the tricyclic intermediate **V** *via* isocyanide electrophilic cyclization and aldol condensation, respectively, (3) then, a consecutive base-catalyzed dehydration–deacetylation process resulting in tetrahydrophenanthridinone **4a**; (4) and finally, oxidative aromatization of **4a** producing phenanthridines



Scheme 3 Proposed mechanism for the formation of **3** and **5**.



Scheme 4 Potential synthetic applications of hydroxy-substituted **3**.

3a by molecular oxygen (Scheme 3).[21] Alternatively, dihydrophenanthridin-7(5*H*)-ones **4a** can be converted to dihydrophenanthridin-7(8*H*)-ones **5a** through base-catalyzed isomerization.

Finally, in order to highlight the synthetic potential of this new strategy, selected transformations of the generated hydroxyl-substituted phenanthridines were conducted (Scheme 4). Phenanthridine **3a** was readily converted to the triflate **7a** by triflation with Tf_2O in high yield. Reductive cleavage of the *O*-triflate group with $Pd(PPh_3)_2Cl_2$ and HCOOH provided the 9-phenylphenanthridine **8a** in good yield. The Suzuki coupling reaction of triflate **7a** with 4-methoxylphenylboronic acid afforded the 7-(4-methoxyphenyl)-9-phenylphenanthridine **9a** in excellent yield. Furthermore, the 9-methylphenanthridine **3p** could be readily converted to the tricyclic 9-methylphenanthridine-7,10-dione **11p**, which is the structural motif existing in natural products calothrixin A and B.[22]

In conclusion, the first example of organocatalyzed aerobic oxidative Robinson annulation was successfully developed for the expedient one-pot synthesis of phenanthridine derivatives from easily available starting materials under mild metal-free conditions. This unprecedented domino transformation, featuring successive construction of two rings and three C–C bonds in a single operation, represents a new strategy for the general construction of these tricyclic scaffolds. On the basis of control experiments, a multistep reaction mechanism is proposed involving Michael addition, intramolecular isocyanide electrophilic cyclization, intramolecular aldol condensation, dehydration, deacylation and aerobic oxidative aromatization. Furthermore, this domino reaction is amenable to gram scale syntheses, and the 7-hydroxyl group on the phenanthridines can be used as a handle for further diversity.

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Notes and references

1 For recent reviews, see: (*a*) B. Zhang and A. Studer, *Chem. Soc. Rev.*, 2015, **44**, 3505; (*b*) L.-M. Tumir, M. R. Stojković and I. Piantanida, *Beilstein J. Org. Chem.*, 2014, **10**, 2930; (*c*) S. D. Phillips and R. N. Castle, *J. Heterocycl. Chem.*, 1981, **18**, 223; (*d*) Z. Luo, F. Wang, J. Zhang, X. Li, M. Zhang, X. Hao, Y. Xue, Y. Li, F. D. Horgen, G. Yao and Y. Zhang, *J. Nat. Prod.*, 2012, **75**, 2113.
2 For a review on the synthesis of phenanthridines (also see ref. 1*a* and *b*), see: (*a*) P. A. Keller, in *Science of Synthesis*, ed. D. StC. Black, Thieme, Stuttgart, 2004, vol. 15, p. 1065; (*b*) J. C. Walton, *Molecules*, 2016, **21**, 660; for selected recent examples, see: (*c*) Y. Wu, S. M. Wong, F. Mao, T. L. Chan and F. Y. Kwong, *Org. Lett.*, 2012, **14**, 5306; (*d*) D. Leifert, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2013, **15**, 6286; (*e*) W. Han, X. Zhou, S. Yang, G. Xiang, B. Cui and Y. Chen, *J. Org. Chem.*, 2015, **80**, 11580; (*f*) P. Natarajan, N. Kumara and M. Sharma, *Org. Chem. Front.*, 2016, **3**, 1265.
3 For some selected examples, see: (*a*) T.-H. Zhu, S.-Y. Wang, Y.-Q. Tao, T.-Q. Wei and S.-J. Ji, *Org. Lett.*, 2014, **16**, 1260; (*b*) T. Xiao, L. Li, G. Lin, Q. Wang, P. Zhang, Z.-W. Mao and L. Zhou, *Green Chem.*, 2014, **16**, 2418; (*c*) B. Zhang, C. G. Daniliuc and A. Studer, *Org. Lett.*, 2014, **16**, 250; (*d*) H. Jiang, Y. Cheng, R. Wang, M. Zheng, Y. Zhang and S. Yu, *Angew. Chem., Int. Ed.*, 2013, **52**, 13289; (*e*) L. Wang, H. Zhu, S. Gao, J. Cheng and J.-T. Yu, *Chem. Commun.*, 2014, **50**, 10864; (*f*) J.-J. Cao, X. Wang, S.-Y. Wang and S.-J. Ji, *Chem. Commun.*, 2014, **50**, 12892; (*g*) J. Rong, L. Deng, P. Tan, C. Ni, Y. Gu and J. Hu, *Angew. Chem., Int. Ed.*, 2016, **55**, 2743.
4 T. Gerfaud, L. Neuville and J. Zhu, *Angew. Chem., Int. Ed.*, 2009, **48**, 572.
5 D. A. Candito and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 6713.
6 Only two references on the synthesis of phenanthridines by closure the B and C rings through an Rh-catalyzed alkyne [2+2+2] cycloaddition were reported: (*a*) Y. Li, J. Zhu, L. Zhang, Y. Wu and Y. Gong, *Chem. – Eur. J.*, 2013, **19**, 8294; (*b*) L. Sripada, J. A. Teske and A. Deiters, *Org. Biomol. Chem.*, 2008, **6**, 263.
7 For reviews, see: (*a*) R. E. Gawley, *Synthesis*, 1976, 777; (*b*) M. E. Jung, *Tetrahedron*, 1976, **32**, 3; (*c*) M. A. Varner and R. B. Grossman, *Tetrahedron*, 1999, **55**, 13867; (*d*) E. R. Jarvo and S. J. Miller, *Tetrahedron*, 2002, **58**, 2481; (*e*) C. M. R. Volla, I. Atodiresei and M. Rueping, *Chem. Rev.*, 2014, **114**, 2390.
8 W. S. Rapson and R. Robinson, *J. Chem. Soc.*, 1935, 1285.
9 For selected examples, see: (*a*) H. M. Lee, C. Nieto-Oberhuber and M. D. Shair, *J. Am. Chem. Soc.*, 2008, **130**, 16864; (*b*) S. P. Waters, Y. Tian, Y. M. Li and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2005, **127**, 13514; (*c*) P. Stahl, L. Kissau, R. Mazitschek, A. Huwe, P. Furet, A. Giannis and H. Waldmann, *J. Am. Chem. Soc.*, 2001, **123**, 11586; (*d*) S. J. Danishefsky, J. J. Masters, W. B. Young, J. T. Link, L. B. Snyder, T. V. Magee, D. K. Jung, R. C. A. Isaacs, W. G. Bornmann, C. A. Alaimo, C. A. Coburn and M. J. DiGrandi, *J. Am. Chem. Soc.*, 1996, **118**, 2843.
10 P. Li, J. N. Payette and H. Yamamoto, *J. Am. Chem. Soc.*, 2007, **129**, 9534.
11 X. Hu, J. J. Kennedy-Smith and F. D. Toste, *Angew. Chem., Int. Ed.*, 2007, **46**, 7671.
12 (*a*) Y. Izawa, D. Pun and S. S. Stahl, *Science*, 2011, **333**, 209; (*b*) Y. Izawa, C. Zheng and S. S. Stahl, *Angew. Chem., Int. Ed.*, 2013, **52**, 3672; (*c*) D. Pun, T. Diao and S. S. Stahl, *J. Am. Chem. Soc.*, 2013, **135**, 8213; (*d*) J. Zhang, Q. Jiang, D. Yang, X. Zhao, Y. Dong and R. Liu, *Chem. Sci.*, 2015, **6**, 4674; (*e*) Z. Zhang, T. Hashiguchi, T. Ishida, A. Hamasaki, T. Honma, H. Ohashi, T. Yokoyama and M. Tokunaga, *Org. Chem. Front.*, 2015, **2**, 654.
13 (*a*) X. Feng and E. D. Edstrom, *Tetrahedron: Asymmetry*, 1999, **10**, 99; (*b*) R. M. Harris, B. I. Andrews, S. Clark, J. W. B. Cooke, J. C. S. Gray and S. Q. Q. Ng, *Org. Process Res. Dev.*, 2013, **17**, 1239; (*c*) T. N. Poudel and Y. R. Lee, *Org. Lett.*, 2015, **17**, 2050.
14 (*a*) T. N. Poudel and Y. R. Lee, *Chem. Sci.*, 2015, **6**, 7028; (*b*) T. N. Poudel and Y. R. Lee, *Org. Biomol. Chem.*, 2014, **12**, 919.
15 (*a*) Z. Hu, H. Yuan, Y. Men, Q. Liu, J. Zhang and X. Xu, *Angew. Chem., Int. Ed.*, 2016, **55**, 7077; (*b*) X. Xu, L. Zhang, X. Liu, L. Pan and Q. Liu, *Angew. Chem., Int. Ed.*, 2013, **52**, 9271; (*c*) Y. Li, X. Xu, J. Tan, C. Y. Xia, D. Zhang and Q. Liu, *J. Am. Chem. Soc.*, 2011, **133**, 1775; (*d*) J. Tan, X. Xu, L. Zhang, Y. Li and Q. Liu, *Angew. Chem., Int. Ed.*, 2009, **48**, 2868.
16 CCDC 1524232 (**3h**).
17 (*a*) F. Castan and D. C. H. Bigg, *J. Heterocycl. Chem.*, 1993, **30**, 1125; (*b*) J. A. Valderrama, A. Ibacache, J. A. Rodriguez, C. Theoduloz and J. Benites, *Eur. J. Med. Chem.*, 2011, **46**, 3398.
18 (*a*) A. E. Bunnell, L. A. Flippin and Y. Liu, *J. Org. Chem.*, 1997, **62**, 9305; (*b*) T. Kumemura, T. Choshi and J. Yukawa, *Heterocycles*, 2005, **66**, 87.
19 M. P. Hay and W. A. Denny, *Synth. Commun.*, 1998, **28**, 463.
20 A. Chao, J. A. Lujan-Montelongo and F. F. Fleming, *Org. Lett.*, 2016, **18**, 3062.
21 (*a*) M. Wang, Z. Fu, H. Feng, Y. Dong, J. Liu and Q. Liu, *Chem. Commun.*, 2010, **46**, 9061; (*b*) C.-H. Lei, D.-X. Wang, L. Zhao, J. Zhu and M.-X. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 4708; (*c*) J. Liu, Z. Liu, P. Liao, L. Zhang, T. Tu and X. Bi, *Angew. Chem., Int. Ed.*, 2015, **54**, 10618.
22 R. W. Rickards, J. M. Rothschild, A. C. Willis, N. M. de Chazal, J. Kirk, K. Kirk, K. J. Saliba and G. D. Smith, *Tetrahedron*, 1999, **55**, 13513.