



Cite this: *Chem. Commun.*, 2019, 55, 3544

Received 16th December 2018,
Accepted 25th February 2019

DOI: 10.1039/c8cc09949a

rsc.li/chemcomm

Unified enantioselective total syntheses of (–)-scholarisine G, (+)-melodinine E, (–)-leuconoxine and (–)-mersicarpine†

Yao Liu and Honggen Wang *

A unified strategy enabled the enantioselective syntheses of (–)-scholarisine G, (+)-melodinine E, (–)-leuconoxine and (–)-mersicarpine from a common 2-alkylated indole intermediate bearing an all-carbon quaternary stereogenic center. The Smith-modified Madelung indole synthesis was used to couple simple *o*-toluidine with chiral lactone (+)-**8**, incorporating the key elements for further cyclizations. Lactone (+)-**8** was prepared *via* a palladium-catalyzed intermolecular asymmetric allylic alkylation. The unified and protecting-group-free reaction sequences allowed the synthesis of these alkaloids in a maximum of 10 steps and with high efficiency.

The leuconolam–leuconoxine–mersicarpine triads are structurally complex and biologically interesting Aspidosperma-derived monoterpene indole alkaloids (Fig. 1).¹ Biosynthetically, these natural products share the same biogenetic origin from vincadifformine,² but feature intriguingly different ring connectivities. (–)-Scholarisine G (**1**),^{3a,e} (+)-melodinine E (**2**)^{3b} and (–)-leuconoxine (**3**)^{3c–e} are pentacyclic alkaloids comprising an interesting [5.5.6.6]diazafenestrane core⁴ with two or three contiguous quaternary stereogenic centers. (–)-Mersicarpine (**4**),^{3f} however, has a fused tetracyclic 6/5/6/7 ring system characterized by an unusual tetrahydro-2*H*-azepine ring and a hemiaminal motif. The structural complexity, along with the intriguing bioactivities has rendered these alkaloids popular targets in total synthesis.^{5–8} Specifically, the biosynthetic interrelationship of these compounds has inspired several unified synthetic strategies towards their synthesis.^{6i,7f,8} Nevertheless, only a handful of enantioselective total syntheses have been reported.^{7,8}

The intrinsic challenge to fulfil an enantioselective total synthesis lies in the construction of the all-carbon quaternary stereogenic carbon center.^{6,9} In 2010, Fukuyama and co-workers reported the first total synthesis of (–)-mersicarpine (**4**) (Scheme 1).^{7a} The key chiral intermediate ketoester (**B**) was

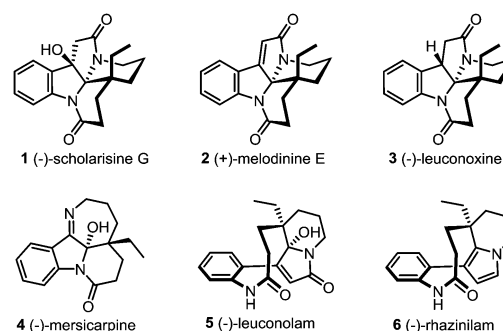


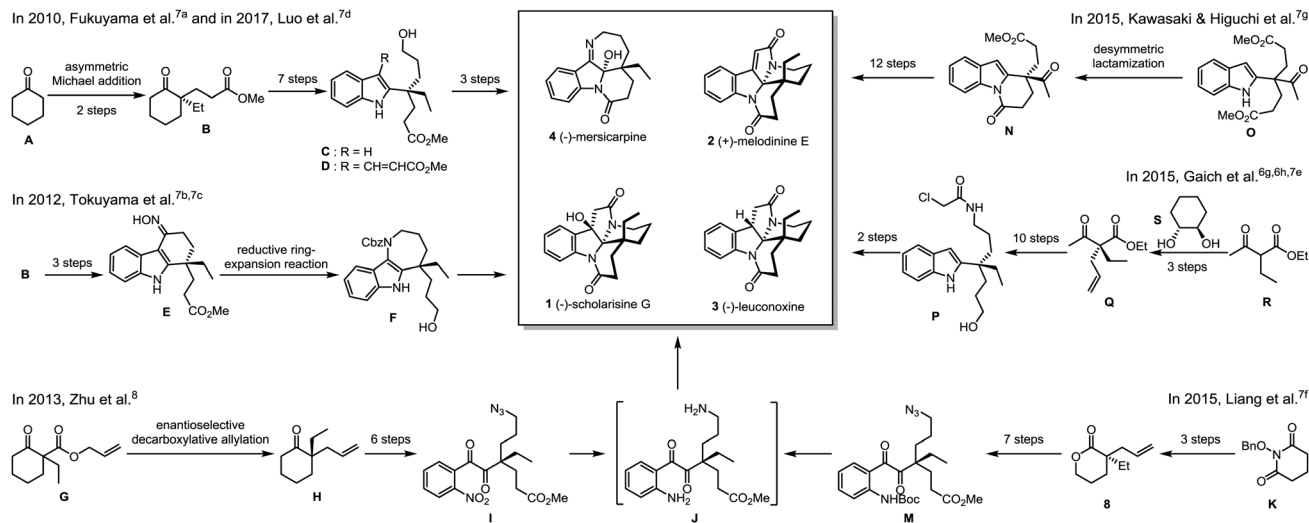
Fig. 1 The leuconolam–leuconoxine–mersicarpine group of alkaloids.

prepared *via* asymmetric Michael addition. Upon 7-step synthetic manipulations including Eschenmoser–Tanabe fragmentation, Sonogashira cross-coupling reaction and gold-catalyzed cyclization, a 2-substituted indole (**C**) with a chiral quaternary carbon center was assembled, which was further elaborated to the final product. Intriguingly, in an effort to synthesize (–)-rhazinal, Luo observed an unexpected aziridination/rearrangement/oxidation tandem reaction leading to the total synthesis of (–)-mersicarpine (**4**) based on a similar alkenylated indole intermediate (**D**).^{7d} Starting from the same chiral intermediate (**B**), Tokuyama and co-workers accomplished a concise total synthesis of (–)-mersicarpine *via* the key Fischer indole synthesis and DIBAL-H-mediated reductive ring-expansion reaction.^{7b,c} In 2013, Zhu and co-workers disclosed an enantioselective total synthesis of leuconolam–leuconoxine–mersicarpine group monoterpene indole alkaloids⁸ based on an elegantly integrated oxidation/reduction/cyclization (iORC) process.¹⁰ The palladium-catalyzed enantioselective decarboxylative allylation was utilized to construct the chiral center. The same strategy was utilized by Liang and Stoltz by employing an optically active allylated lactone (**8**),^{7f} prepared from intramolecular palladium-catalyzed asymmetric decarboxylative allylic alkylation of *N*-benzyloxy cyclic imide (**K**),¹¹ as a key intermediate.

In another vein from Kawasaki and Higuchi, the phosphoric acid-catalyzed desymmetric lactamization of a prochiral indole-substituted diester (**O**) provided the key enantiomerically

School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou 510006, China. E-mail: wanghg3@mail.sysu.edu.cn

† Electronic supplementary information (ESI) available. See DOI: 10.1039/c8cc09949a



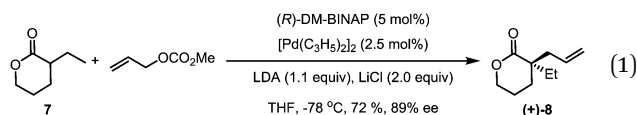
Scheme 1 Reported enantioselective total syntheses of the leuconolam–leuconoxine–mersicarpine group alkaloids.

enriched Kerr's intermediate with moderate ee of 74%.^{7g} In 2015, Gaich realized enantioselective total synthesis of (-)-leuconoxine (3) by employing photoinduced domino macrocyclization/transannular cyclization involving Witkop cyclization.^{6g,h,7e} The optically active precursor (P) was obtained *via* the diastereoselective alkylation of ethyl 2-ethylacetoacetate (R) using chiral 1,2-diol (S) as an acetal chiral auxiliary.

The notable feature of Smith-modified Madelung indole synthesis¹² in the construction of 2-quaternary carbon substituted indole inspired us to explore novel enantioselective synthesis of leuconolam–leuconoxine–mersicarpine alkaloids starting from simple *o*-toluidine (9) and chiral lactone (8) (Scheme 2). The latter is commercially available and could be prepared *via* palladium-catalyzed intermolecular asymmetric allylation developed by Hou.¹³ The Smith-modified Madelung indole synthesis would provide a pivotal indole derivative with the chiral center being installed. The hydroxyl and vinyl

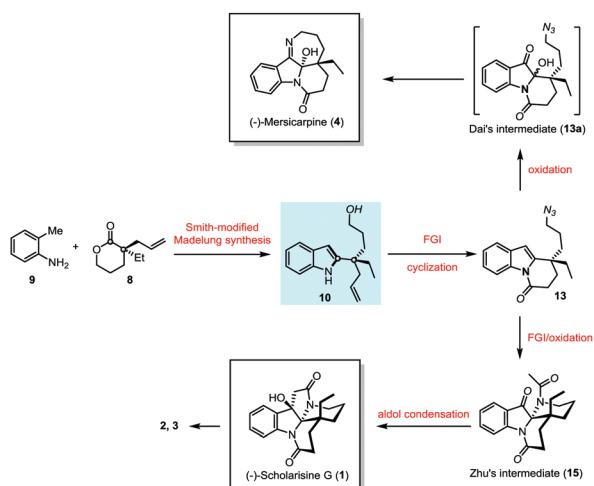
functionality in 10 serve as valuable handles for further transformation. Therefore, upon proper functional group manipulation, lactam (13) is expected to be obtained. This species could be further elaborated to Zhu⁸ and Dai's^{6f} intermediates *via* oxidation of the indole motif,^{6a,14} paving the way for (-)-scholarisine G (1) and (-)-mersicarpine (4) synthesis, respectively.

Our synthesis commenced with the preparation of the allylated lactone (+)-8 starting from 3-ethyltetrahydro-2H-pyran-2-one and allyl methyl carbonate (7). In the presence of the palladium catalyst and (*R*)-DM-BINAP ligand as developed by Hou,¹³ (+)-8 was obtained in 72% yield and 89% ee (eqn (1)).

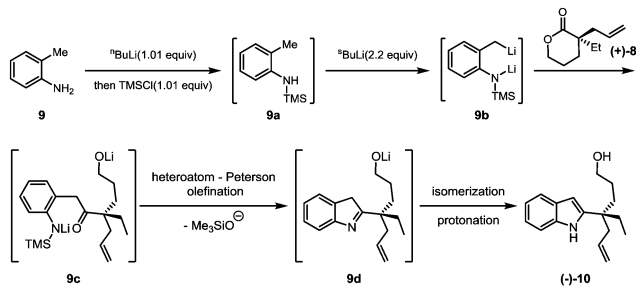


The key Smith-modified Madelung indole synthesis was started with the preparation of *N*-silylated *o*-toluidine (9a) *via* the reaction of *o*-toluidine (9) with a stoichiometric amount of *n*-butyllithium and followed by quenching with chlorotriethylsilane (Scheme 3). Without isolation, this intermediate was exposed to 2.2 equivalents of *sec*-butyllithium solution at low temperature to form a reactive lithium dianion (9b). Upon slow addition of lactone (+)-8, cascade acylation/heteroatom Peterson olefination/isomerization proceeded smoothly to produce 2-quaternary carbon substituted indole (-)-10 in an overall 85% yield.

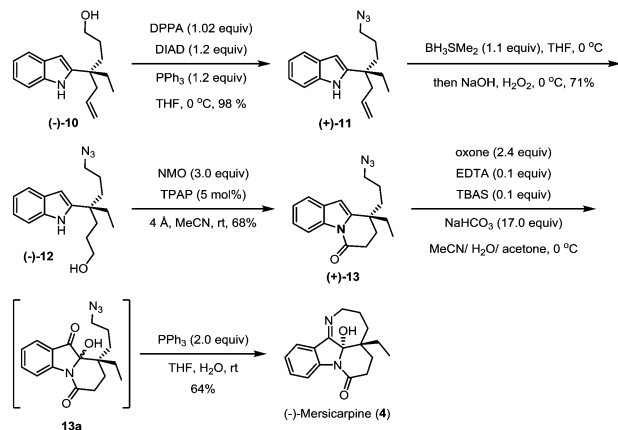
The hydroxyl group in indole (-)-10 was then replaced by azido in a good yield *via* a Mitsunobu reaction in the presence of diisopropyl azodiformate (DIAD), triphenylphosphine and diphenylphosphonic azide (DPPA) (Scheme 4). The maintenance of low temperature (0 °C) is crucial for this step as a higher temperature (room temperature) led to a significant amount of the intramolecular nitrogen alkylation product. Following hydroboration/oxidation of the C=C bond, azidoindole (+)-11 was converted to (-)-12 in good efficiency (a 71% yield). Exposure of



Scheme 2 Proposed synthetic strategy.



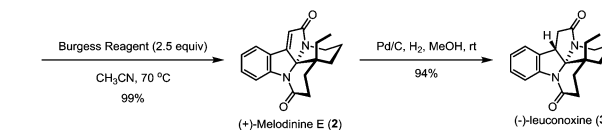
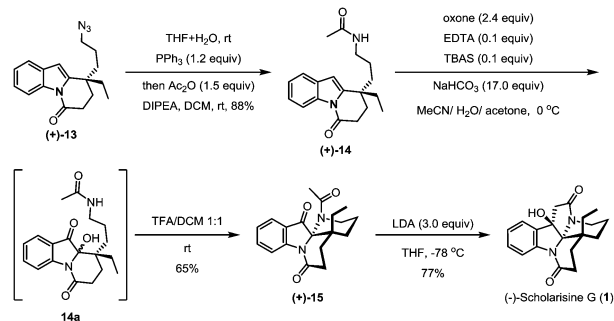
Scheme 3 Smith-modified Madelung synthesis.



Scheme 4 Syntheses of (-)-mescarpine.

(-)-12 to Ley oxidation¹⁵ (TPAP and NMO, at rt) resulted in an intramolecular *N*-acylation reaction to afford *N*-acyl indole (+)-13 in 68% yield. With (+)-13 in hand, we next explored the synthesis of (-)-mescarpine (4). Previous studies indicated that 2-substituted indole could easily be oxidized with various oxidants to form a keto hemiaminal structure.¹⁴ Indeed, subjection of (+)-13 to Kerr's conditions^{6a} (oxone, acetone) afforded the desired keto hemiaminal (13a). Upon *in situ* treatment with PPh₃, 13a underwent Staudinger-aza-Wittig cyclization to give (-)-mescarpine (4) in 64% yield over two steps. It should be noted that the same intermediate 13a has been obtained in Dai's (\pm)-mescarpine synthesis *via* a Witkop-Winterfeldt oxidative cleavage of an advanced indole structure.

The azide intermediate (+)-13 could also be converted to leuconoxine family alkaloids (Scheme 5). Thus, (+)-13 was first reduced using triphenylphosphine and then acetylated by a follow-up treatment with acetic anhydride to give acetamide (+)-14. Under similar indole oxidation conditions with oxone as described above, keto hemiaminal 14a was produced. Without isolation, 14a was converted under acidic conditions to Zhu's intermediate (+)-15 for their leuconolam-leuconoxine indole alkaloid syntheses in 65% yields over two steps. LDA-promoted intramolecular aldol cyclization provided leuconoxine in a good yield of 77%. Previously, mesylation of the tertiary hydroxyl group in (-)-scholarisine G (1) followed by base-promoted elimination was used to prepare (+)-melodinine E (2). We found that higher efficiency could be obtained when treating



Scheme 5 Synthesis of (-)-scholarisine G, (+)-melodinine E and (-)-leuconoxine.

(-)-scholarisine G (1) with a Burgess reagent (2.5 equiv.) in acetonitrile at 70 °C. Finally, hydrogenation of (+)-melodinine E (2) delivered another member (-)-leuconoxine (3) in 94% yield. The spectroscopic data of (+)-melodinine E (2) and (-)-leuconoxine (3) (¹H and ¹³C NMR) matched well with those reported in the literature. Interestingly, the NMR spectra of our synthetic (-)-scholarisine G (1) match with that of Zhu,^{8a} but show discrepancies with the isolated samples^{3a,e} and some other synthetic samples.^{6e,j,7f} We assume that the differences are a result of different quality, and therefore different acidity, of CDCl₃ used for the NMR studies.¹⁶

In conclusion, we have accomplished divergent enantioselective syntheses of four monoterpene indole alkaloids: (-)-scholarisine G (1), (+)-melodinine E (2), (-)-leuconoxine (3) and (-)-mescarpine (4). The syntheses feature a palladium-catalyzed intermolecular asymmetric allylation to construct an optically active lactone, Smith-modified Madelung indole synthesis to quickly forge a quaternary carbon-substituted indole, and an oxone-mediated indole oxidation to form Dai' and Zhu's intermediates, respectively. Efforts were also attempted to improve the synthetic efficiency of transforming Zhu's intermediates (15) to the leuconoxine group alkaloid. No protecting group is needed for the whole process, allowing concise syntheses of the title natural products in a maximum of 10 steps with high efficiency.

Generous financial support from the Key Project of Chinese National Programs for Fundamental Research and Development (2016YFA0602900), the National Natural Science Foundation of China (21472250), and the "1000-Youth Talents Plan" is gratefully acknowledged.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- (a) M. Ishikura, T. Abe, T. Choshi and S. Hibino, *Nat. Prod. Rep.*, 2013, **30**, 694; (b) Y.-Y. Low, F.-J. Hong, K.-H. Lim, N. F. Thomas and

- T.-S. J. Kam, *Nat. Prod.*, 2014, **77**, 327; (c) F. Abe and T. Yamauchi, *Phytochemistry*, 1993, **35**, 169; (d) J. Hájíček, *Collect. Czech. Chem. Commun.*, 2011, **76**, 2023–2083.
- 2 (a) G. Hugel, J. Lévy and J. L. Men, *Tetrahedron Lett.*, 1974, **15**, 3109; (b) G. Croquelois, N. Kunesch and J. Poisson, *Tetrahedron Lett.*, 1974, **15**, 4427; (c) S. H. Goh and A. R. M. Ali, *Tetrahedron Lett.*, 1986, **27**, 2501; (d) S. H. Goh, A. R. M. Ali and W. H. Wong, *Tetrahedron*, 1989, **45**, 7899.
- 3 (a) T. Feng, X.-H. Cai, P.-J. Zhao, Z.-Z. Du, W.-Q. Li and X.-D. Luo, *Planta Med.*, 2009, **75**, 1537; (b) T. Feng, X.-H. Cai, Y.-P. Liu, Y. Li, Y.-Y. Wang and X.-D. Luo, *J. Nat. Prod.*, 2010, **73**, 22; (c) S.-H. Lim, K.-M. Sim, Z. Abdulla, O. Hiraku, H. Masahiko, K. Komiyama and T.-S. J. Kam, *Nat. Prod.*, 2007, **70**, 1380; (d) K.-H. Lim and T.-S. Kam, *Hev. Chim. Acta*, 2007, **90**, 31; (e) C.-Y. Gan, Y.-Y. Low, N. F. Thomas and T.-S. Kam, *J. Nat. Prod.*, 2013, **76**, 957; (f) T.-S. Kam, G. Subra-maniam, K.-H. Lim and Y.-M. Choo, *Tetrahedron Lett.*, 2004, **45**, 5995.
- 4 For reviews, see: (a) R. Keese, *Chem. Rev.*, 2006, **106**, 4787; (b) A. Boudhar, M. Charpenay, G. Blond and J. Suffert, *Angew. Chem., Int. Ed.*, 2013, **52**, 12786; (c) B. Bredenkötter, B. Neumann and H.-G. Stammer, *Eur. J. Org. Chem.*, 2014, 53.
- 5 For reviews, see: (a) H. J. Tokuyama, *J. Synth. Org. Chem., Jpn.*, 2015, **73**, 1120; (b) M. Pfaffenbach and T. Gaich, *Chem. – Eur. J.*, 2016, **22**, 3600; (c) Q. Geng, Z. Li, Z. Lv and G. Liang, *Chin. J. Org. Chem.*, 2016, **36**, 1447.
- 6 (a) J. Magolan, C. A. Carson and M. A. Kerr, *Org. Lett.*, 2008, **10**, 1437; (b) A. Biechy and S. Z. Zard, *Org. Lett.*, 2009, **11**, 2800; (c) X. Zhong, Y. Li and F.-S. Han, *Chem. – Eur. J.*, 2012, **18**, 9784; (d) Z. Li and G. Liang, *Tetrahedron Lett.*, 2013, **54**, 242; (e) Z. Lv, Z. Li and G. Liang, *Org. Lett.*, 2014, **16**, 1653; (f) A. Umehara, H. Ueda and H. Tokuyama, *Org. Lett.*, 2014, **16**, 2526; (g) X. Zhong, S. Qi, Y. Li, J. Zhang and F.-S. Han, *Tetrahedron*, 2015, **71**, 3734; (h) M. Pfaffenbach and T. Gaich, *Eur. J. Org. Chem.*, 2015, 3427; (i) M. Pfaffenbach, A. Roller and T. Gaich, *Chem. – Eur. J.*, 2016, **22**, 8444; (j) Y. Yang, Y. Bai, S. Sun and M. Dai, *Org. Lett.*, 2014, **16**, 6216.
- 7 (a) R. Nakajima, T. Ogino, S. Yokoshima and T. Fukuyama, *J. Am. Chem. Soc.*, 2010, **132**, 1236; (b) Y. Iwama, K. Okano, K. Sugimoto and H. Tokuyama, *Org. Lett.*, 2012, **14**, 2320; (c) Y. Iwama, K. Okano, K. Sugimoto and H. Tokuyama, *Chem. – Eur. J.*, 2013, **19**, 9325; (d) Y. Zhang, Y. Xue and T. Luo, *Tetrahedron*, 2017, **73**, 4201; (e) M. Pfaffenbach and T. Gaich, *Chem. – Eur. J.*, 2015, **21**, 6355; (f) Z. Li, Q. Geng, Z. Lv, B. P. Pritchett, K. Baba, Y. Numajiri, B. M. Stoltz and G. Liang, *Org. Chem. Front.*, 2015, **2**, 236; (g) K. Higuchi, S. Suzuki, R. Ueda, N. Oshima, E. Kobayashi, M. Tayu and T. Kawasaki, *Org. Lett.*, 2015, **17**, 154.
- 8 (a) Z. Xu, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2013, **135**, 19127; (b) Z. Xu, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2015, **137**, 6712.
- 9 (a) J. Magolan and M. A. Kerr, *Org. Lett.*, 2006, **8**, 4561; (b) X. Zhong, Y. Li, J. Zhang and F.-S. Han, *Org. Lett.*, 2015, **17**, 720; (c) H. Li, S. A. Bonderoff, B. Cheng and A. Padwa, *J. Org. Chem.*, 2014, **79**, 392; (d) H. Li, B. Cheng, N. Boonnak and A. Padwa, *Tetrahedron*, 2011, **67**, 9829; (e) V. J. Colandrea, S. Rajaraman and L. S. Jimenez, *Org. Lett.*, 2003, **5**, 785.
- 10 For iORC examples, see: (a) Z. Xu, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2013, **52**, 3272; (b) O. Wagnieres, Z. Xu, Q. Wang and J. Zhu, *J. Am. Chem. Soc.*, 2014, **136**, 15102; (c) C. Piemontesi, Q. Wang and J. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 6556 and references cited therein.
- 11 N. B. Bennett, D. C. Duquette, J. Kim, W.-B. Liu, D. C. Be-henna, S. C. Virgil and B. M. Stoltz, *Chem. – Eur. J.*, 2013, **19**, 4414.
- 12 (a) A. B. Smith and M. Visnick, *Tetrahedron Lett.*, 1985, **26**, 3757; (b) A. B. Smith, M. Visnick, J. N. Haseltine and P. A. Sprengeler, *Tetrahedron*, 1986, **42**, 2957; (c) A. B. Smith, E. G. Nolen, R. Shi-rai, F. R. Blase, M. Ohta, N. Chida, R. A. Hartz, D. M. Fitch, W. M. Clark and P. A. Sprengeler, *J. Org. Chem.*, 1995, **60**, 7837; (d) A. B. Smith, N. Kanoh, H. Ishiyama and R. A. Hartz, *J. Am. Chem. Soc.*, 2000, **122**, 11254; (e) A. B. Smith, N. Kanoh, H. Ishiyama, N. Minakawa, J. D. Rainier, R. A. Hartz, Y. S. Cho, H. Cui and W. H. Moser, *J. Am. Chem. Soc.*, 2003, **125**, 8228; (f) A. B. Smith, A. H. Davulcu and L. Kürti, *Org. Lett.*, 2006, **8**, 1665; (g) A. B. Smith, A. H. Davulcu, Y. S. Cho, K. Ohmoto, L. Kürti and H. Ishiyama, *J. Org. Chem.*, 2007, **72**, 4596.
- 13 X.-H. Li, S.-L. Wan, D. Chen, R. Q. Liu, C.-H. Ding, P. Fang and X.-L. Hou, *Synthesis*, 2016, 1568.
- 14 (a) L. Zhao, J. P. May, J. Huang and D. M. Perrin, *Org. Lett.*, 2012, **14**, 90; (b) V. J. Colandrea, S. Rajaraman and L. Jimenez, *Org. Lett.*, 2003, **5**, 785; (c) K. Higuchi, Y. Sato, M. Tsuchimochi, K. Sugiura, M. Hatori and T. Kawasaki, *Org. Lett.*, 2009, **11**, 197; (d) A. Karadeolian and M. A. Kerr, *J. Org. Chem.*, 2010, **75**, 6830; (e) C. I. A. Kiraz, T. J. Emge and L. S. Jimenez, *J. Org. Chem.*, 2004, **69**, 2200; (f) C. Zhu, Z. Liu, G. Chen, K. Zhang and H. Ding, *Angew. Chem., Int. Ed.*, 2015, **54**, 879.
- 15 B. E. Maki and K. A. Scheidt, *Org. Lett.*, 2009, **11**, 1651.
- 16 For detailed discussion, see ESI†.