ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, 57, 6764

Received 16th May 2021,
Accepted 3rd June 2021

DOI: 10.1039/d1cc02570h

rsc.li/chemcomm

Asymmetric construction of six vicinal stereogenic centers on hexahydroxanthones *via* organocatalytic one-pot reactions†

Min Zhang,‡ Xue-Wen He,‡ Ya Xiong, Xiong Zuo, Wei Zhou and Xiong-Li Liu *

Inspired by the chemistry and biology of hexahydroxanthones, herein we report an organocatalytic Michael–Michael–Aldol-decarboxylation reaction that provides efficient access to biologically interesting fully substituted hexahydroxanthones bearing six contiguous stereogenic centers from readily accessible materials in acceptable yields (up to 63%) and excellent stereoselectivities (up to 10 : 1 dr and >99% ee). In other words, the reaction efficiently produces three chemical bonds and up to six vicinal stereogenic centers in a one-pot operation. In particular, to our knowledge, this is an asymmetric organocatalytic strategy enabling the first construction of six vicinal stereogenic centers on non-spirocyclic hexahydroxanthone frameworks.

Small molecules based on privileged natural product frameworks and rich in three-dimensional complexity are in high demand in the discovery of new drug molecules.[1] The synthesis of chiral heterocycles bearing multiple stereogenic centers, especially *via* asymmetric oragnocatalysis is an important issue.[1f–j] However, efficient and elegant syntheses of such complex heterocycles in an asymmetric fashion from readily available starting materials remain a primary challenge.[1] In this context, hexahydroxanthone scaffolds bearing multiple stereocenters make up a widespread and representative class of natural products that display various potent biological activities (Fig. 1).[2] Thus, they have been recognized as a "privileged structure", and have attracted an immense amount of attention.[2–4]

Generally, the reported literature methods for the synthesis of hexahydroxanthones need multiple steps.[3] Catalytic asymmetric reactions resulting in optically active hexahydroxanthones are, especially, still rare. Very recently, our group accomplished the first enantioselective construction of six vicinal stereogenic centers on spirohexahydroxanthones.[4f] However, the asymmetric synthesis of simple chiral hexahydroxanthones (non-spirohexahydroxanthones) bearing six contiguous stereogenic centers has not been reported, yet (Scheme 1a). Thus, the limited approaches[2–4] for the synthesis of hexahydroxanthones mean that innovative and efficient methodology is needed to expand their structural and stereochemical diversity.

We envisaged that the generated *in situ* γ-nitroaldehydes **3**[5] might serve as donor/acceptor synthons in asymmetric Michael–Aldol annulation reactions with chromone-3-carboxylic acid **4** in a one-pot operation. If successful, this would afford fully substituted hexahydroxanthones **5** bearing six contiguous stereogenic centers (Scheme 1b). In particular, to our knowledge, this is the first asymmetric strategy enabling construction of six vicinal stereogenic centers on simple hexahydroxanthones, which is an important continuation of our previous work on the stereocontrolled construction of fully substituted spirohexahydroxanthones.[4f]

Nevertheless, several challenging issues need to be addressed for this unprecedented one-pot reaction:[6] (1) this steric congestion makes construction of six vicinal stereogenic centers on simple hexahydroxanthones challenging; (2) the addition, aromatization, and facile opening of the chromone ring are also challenging and

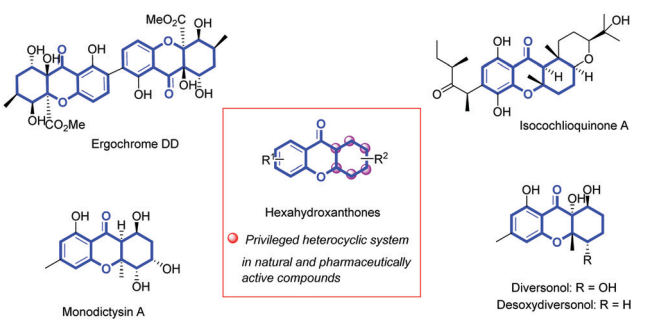
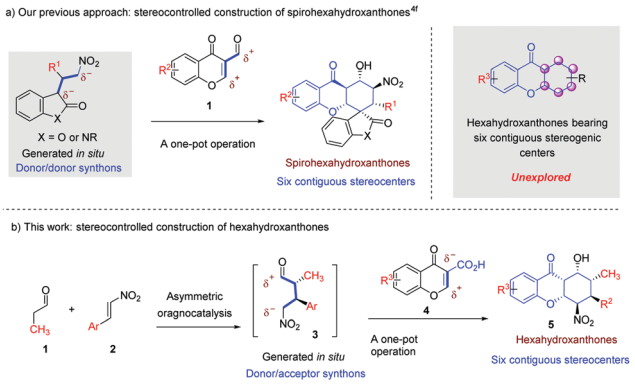


Fig. 1 Representative hexahydroxanthones bearing multiple stereocenters.

National & Local Joint Engineering Research Center for the Exploition of Homology Resources of Medicine and Food, Guizhou University, Guiyang, Guizhou 550025, P. R. China. E-mail: xlliu1@gzu.edu.cn

† Electronic supplementary information (ESI) available: Details of reaction conditions screening, experimental procedures, spectral data of new products, and single crystal data of products **5m**, **6a** and **6b**. CCDC 2002620, 2084000 and 2084001. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1cc02570h

‡ These two authors contributed equally to this work.



Scheme 1 Stereocontrolled construction of hexahydroxanthones.

aromatization can remove the stereoinformation induced by key annulation reactions.[7]

Under optimized reaction conditions (for detailed optimization of reaction conditions see the ESI†), we evaluated the tolerance of the reaction to functional groups at position R^2 on β-aryl-substituted nitroalkenes **2** (Table 1). The reaction proceeded well for substituents with different electronic properties at different positions; the expected domino adducts **5b–p** were obtained efficiently (46–63% yields, 93–>99% ee and 4/1–10/1 dr). Furthermore, both heteroaromatic and alkyl nitroalkenes **2** were subjected to the conditions. However, the heteroaromatic product **5q** was obtained in less than 10%, while no expected product **5r** was observed for ethyl nitroalkene substrate **2**.

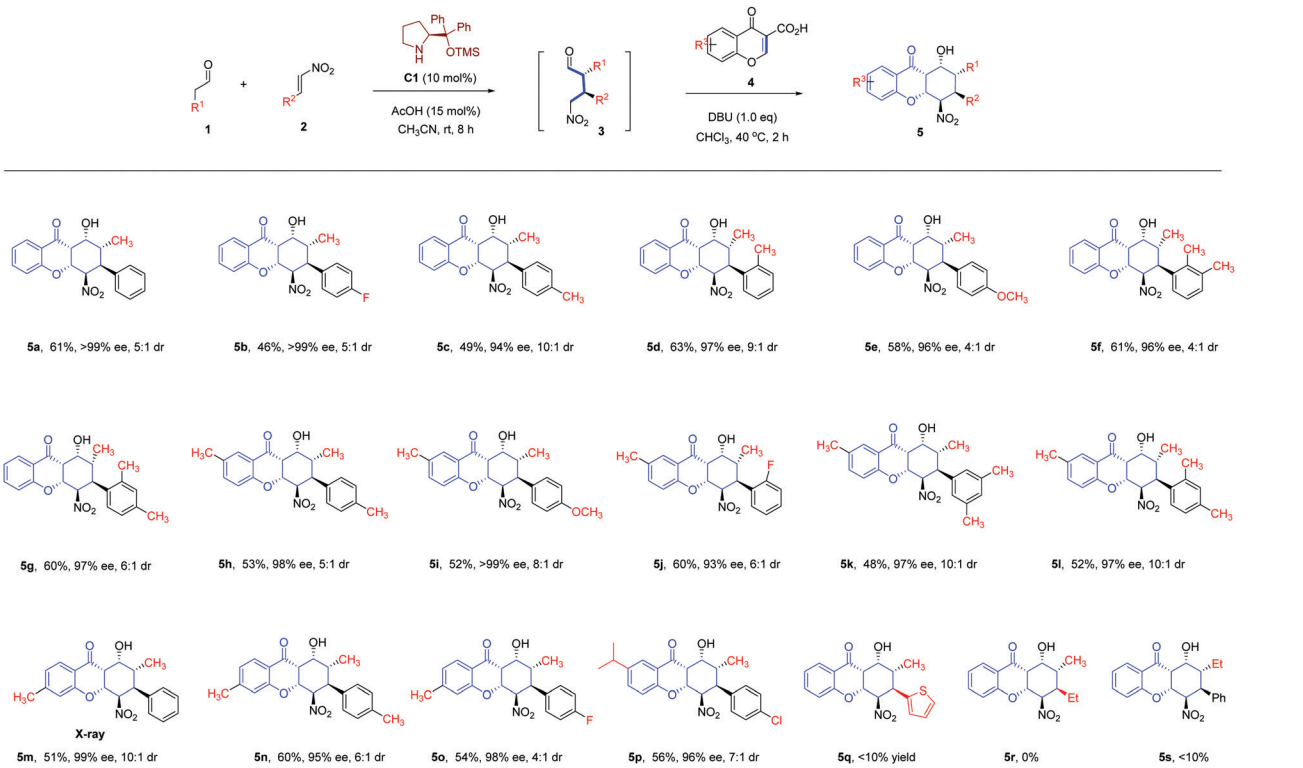
Screening of chromones **4** showed that electron rich substituted chromones also worked well under this one-pot procedure to afford fully functionalized hexahydroxanthones **5h–p** in 48–63% yield and high stereoselectivities (93–>99% ee and 4/1–10/1 dr). However, Screening of substrate **1** showed that butyraldehyde was not tolerated, and trace expected product **5s** was observed.

While the yields are only moderate in many cases (Table 1), this method allows for rapid access to structurally intriguing fully substituted hexahydroxanthones.

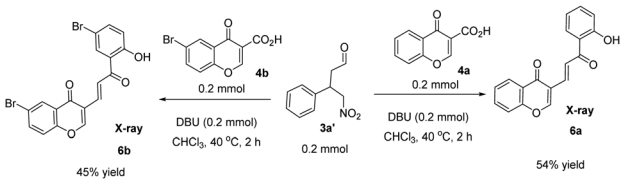
However, subjection of γ-nitroaldehyde **3a′**, as the donor–acceptor C4 synthon, with **4** to the DBU-promoted conditions did not provide the desired product **5**. Instead, the unexpected 2-hydroxybenzophenones **6** were obtained in moderate yields (Scheme 2). The structure of product **6** was determined by single crystal X-ray analysis (for details, see the ESI†). Without **3a′**, the reactions did not provide products **6**. We suspected that the substrate **4** led to ring opening of the chromone core and then a benzannulation sequence[7] to access unexpected **6** under **3a′** and DBU-promoted conditions. The detailed mechanistic study is currently underway.

The absolute configuration of the products **5** was assigned as 1′*R*,2′*R*,3′*R*,4′*R*,5′*S* and 6′*R* on the basis of the X-ray crystallographic analysis of **5m** (for details, see the ESI†).

Table 1 Substrate scope to hexahydroxanthones **5**[a]



[a] Reactions were performed with **1** (0.5 mmol), **2** (0.3 mmol), **C1** (10 mol%) and AcOH (0.03 mmol) in the CH_3CN (3 mL) at rt for 8 h. After the removal of solvent, **4** (0.2 mmol) and DBU (0.2 mmol) in the $CHCl_3$ (2 mL) were added and stirred at 40 °C for 2 h.



Scheme 2 γ-Nitroaldehyde **3a′** in this transformation.

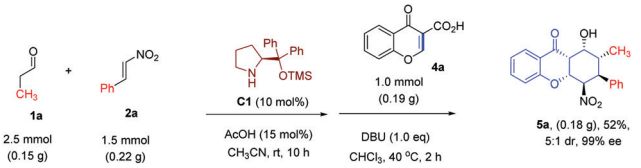
In order to further demonstrate the practical utility of this one-pot protocol, we have performed a 1.0 mmol scale Michael–Michael–Aldol-decarboxylation reaction between **1a**, **2a**, and **4a** under optimized reaction conditions (for details, see the ESI†). Delightedly, the desired hexahydroxanthone **5a** was obtained in 52% yield without deteriorating the stereochemical outcome of the reaction (Scheme 3).

In addition, the potential synthetic usefulness of our methodology was also demonstrated by the transformation. For example, the reduction of **5** with $NaBH_4$ led to the corresponding hydroxylation product **7** in good yield by selectively reducing the carbonyl group without erosion of the enantiomeric excess (Scheme 4).

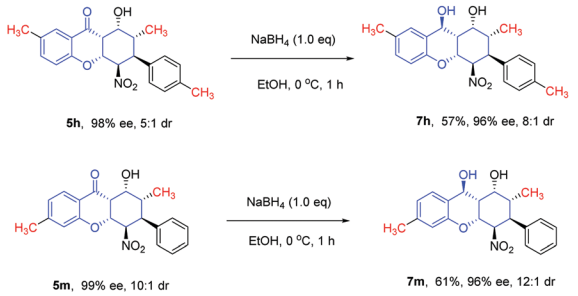
On the basis of our results, a plausible Michael–Michael–Aldol-decarboxylation reaction mechanism is tentatively proposed (Scheme 5). First, the chiral γ-nitroaldehyde intermediates **4** are easily prepared in a single Michael addition step and nearly enantiopure form from aldehydes and nitroalkenes by means of well-established Hayashi–Jørgensen secondary amine catalyzed methods.[5] Subsequently, as donor/acceptor bifunctional synthons, the intermediates **4** trapped the vinylogous ester function of chromone-3-carboxylic acid **4** *via* a Michael–Aldol procedure. Finally, the expected products **5** were readily afforded *via* a decarboxylation[8] reaction.

With the successful generation of optically pure hexahydroxanthones (Table 1), we finally attempted to identify the potential bioactivity of these compounds. Some selected compounds were subjected to *in vitro* cytotoxicity tests against different human cancer cells, including K562 leukemia cells and A549 lung cancer cells, by the MTT-based assays[9] using the commercially available broad-spectrum anticancer drug, cisplatin as a positive control (K562 IC_{50} 21.32 μM and A549 IC_{50} 20.14 μM). The preliminary results revealed that all of the tested 5 compounds exhibited cytotoxicity against the cell lines of K562. Compounds **5c**, **5k**, and **5l** also showed impressive cytotoxicity to the A549 lung cancer cells (Scheme 6).

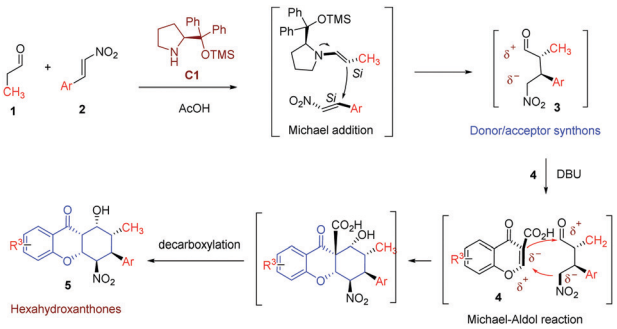
In conclusion, we have developed an organocatalytic Michael–Michael–Aldol-decarboxylation reaction in a one-pot operation, which provides efficient access to biologically interesting fully substituted hexahydroxanthones in acceptable yields (up to 63%) and excellent stereoselectivities (up to 10 : 1 dr and >99% ee), by employing the generated *in situ* γ-nitroaldehydes **3** as donor/acceptor bifunctional building blocks. In particular, to our knowledge, this is an asymmetric organocatalytic strategy enabling the first construction of non-spirocyclic hexahydroxanthone frameworks that possess up to six vicinal stereogenic centers. Furthermore, the convenient and general method is also an important continuation of our previous work on the stereocontrolled construction of fully substituted spirohexahydroxanthones, further expanding the diversity of hexahydroxanthones. Further studies on the bioactivity of the resulting enantioenriched hexahydroxanthones are currently in progress in our laboratories.



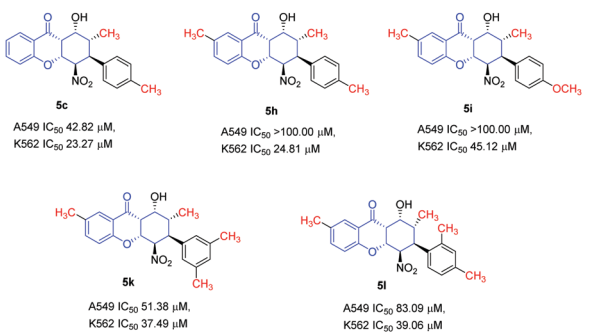
Scheme 3 Large-scale synthesis of product **5a**.



Scheme 4 Product elaboration.



Scheme 5 A proposed mechanism.



Scheme 6 The biological evaluation.

This work has received financial support from NSFC (81760625 and 22061006), and Project of Guizhou province ([2020]4Y205, [2020]1Z074, and [2018]5781).

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) K. C. Nicolaou, D. J. Edmonds and P. G. Bulger, *Angew. Chem., Int. Ed.*, 2006, **45**, 7134–7186; (*b*) Y. C. Zhang, F. Jiang and F. Shi, *Acc. Chem. Res.*, 2020, **53**, 425–446; (*c*) Z. Y. Cao, F. Zhou and J. Zhou, *Acc. Chem. Res.*, 2018, **51**, 1443–1454; (*d*) H. J. Miao, L. L. Wang, H. B. Han, Y. D. Zhao, Q. L. Wang and Z. W. Bu, *Chem. Sci.*, 2020, **11**, 1418–1424; (*e*) H. J. Miao, X. G. Bai, L. L. Wang, J. H. Yu, Z. W. Bu and Q. L. Wang, *Org. Chem. Front.*, 2021, **8**, 204–211; (*f*) F.-T. Sheng, J.-Y. Wang, W. Tan, Y.-C. Zhang and F. Shi, *Org. Chem. Front.*, 2020, **7**, 3967–3998; (*g*) T. Z. Li, S. J. Liu, W. Tan and F. Shi, *Chem. – Eur. J.*, 2020, **26**, 15779–15792; (*h*) M. Sun, C. Ma, S. J. Zhou, S. F. Lou, J. Xiao, Y. Jiao and F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 8703–8708; (*i*) C. S. Wang, T. Z. Li, S. J. Liu, Y. C. Zhang, S. Deng, Y. Jiao and F. Shi, *Chin. J. Chem.*, 2020, **38**, 543–552; (*j*) T. Z. Li, S. J. Liu, Y. W. Sun, S. Deng, W. Tan, Y. Jiao, Y. C. Zhang and F. Shi, *Angew. Chem., Int. Ed.*, 2021, **60**, 2355–2363.

2 (*a*) F. Zhang, L. Li, S. Niu, Y. Si, L. Guo, X. Jiang and Y. Che, *J. Nat. Prod.*, 2012, **75**, 230–237; (*b*) R. Goel, V. Sharma, A. Budhiraja and M. P. S. Ishar, *Bioorg. Med. Chem. Lett.*, 2012, **22**, 4665–4667; (*c*) K.-S. Masters and S. Bräse, *Chem. Rev.*, 2012, **112**, 3717–3776; (*d*) R. N. Kharwar, A. Mishra, S. K. Gond, A. Stierle and D. Stierle, *Nat. Prod. Rep.*, 2011, **28**, 1208–1228; (*e*) S. Sato, Y. Suga, T. Yoshimura, R. Nakagawa, T. Tsuji, K. Umemura and T. Andoh, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 2653–2656; (*f*) S. H. Shim, J. Baltrusaitis, J. B. Gloer and D. T. Wicklow, *J. Nat. Prod.*, 2011, **74**, 395–401.

3 (*a*) P. S. Wang, P. Liu, Y. J. Zhai, H. C. Lin, Z. Y. Han and L. Z. Gong, *J. Am. Chem. Soc.*, 2015, **137**, 12732–12735; (*b*) K. C. Nicolaou and A. Li, *Angew. Chem., Int. Ed.*, 2008, **47**, 6579–6582; (*c*) M. C. Brohmer, E. Bourcet, M. Nieger and S. Brase, *Chem. – Eur. J.*, 2011, **17**, 13706–13711; (*d*) Ł. Albrecht, F. CruzAcosta, A. Fraile, A. Albrecht, J. Christensen and K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2012, **51**, 9088–9092; (*e*) J. L. Li, S. L. Zhou, P. Q. Chen, L. Dong, T. Y. Liu and Y. C. Chen, *Chem. Sci.*, 2012, **3**, 1879–1882; (*f*) A. Albrecht and J. Bojanowski, *Adv. Synth. Catal.*, 2017, **359**, 2907–2911; (*g*) Z.-H. You, Y.-H. Chen, Y. Tang and Y.-K. Liu, *Org. Lett.*, 2019, **21**, 8358–8363.

4 (*a*) X. L. Liu, G. Zhou, Y. Gong, Z. Yao, X. Zuo, W. H. Zhang and Y. Zhou, *Org. Lett.*, 2019, **21**, 2528–2531; (*b*) X. L. Liu, Y. Gong, S. Chen, X. Zuo, Z. Yao and Y. Zhou, *Org. Chem. Front.*, 2019, **6**, 1603–1607; (*c*) X. L. Liu, X. Zuo, J. X. Wang, S. Chang, Q. D. Wei and Y. Zhou, *Org. Chem. Front.*, 2019, **6**, 1485–1490; (*d*) M. Zhang, J. X. Wang, S. Q. Chang, X. L. Liu, X. Zuo and Y. Zhou, *Chin. Chem. Lett.*, 2020, **31**, 381–385; (*e*) X. L. Liu, Q. D. Wei, X. Zuo, S. W. Xu, Z. Yao, J. X. Wang and Y. Zhou, *Adv. Synth. Catal.*, 2019, **18**, 2836–2843; (*f*) S. Q. Chang, X. Zou, Y. Gong, X. W. He, X. L. Liu and Y. Zhou, *Chem. Commun.*, 2019, **55**, 14003–14006; (*g*) W. H. Zhang, Y. Zhou, X. W. He, Y. Gong, X. L. Liu and Y. Zhou, *Org. Biomol. Chem.*, 2019, **17**, 8369–8373; (*h*) H. J. Zhou, W. Zhou, X. L. Liu, Y. P. Tian, J. X. Wang and Y. Zhou, *Synthesis*, 2020, 3047–3057; (*i*) M. Zhang, Y. Gong, W. Zhou, Y. Zhou and X. L. Liu, *Org. Chem. Front.*, 2021, DOI: 10.1039/D1QO00269D.

5 (*a*) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature*, 2006, **441**, 861–863; (*b*) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe and B. Wendt, *Angew. Chem., Int. Ed.*, 2007, **46**, 467–469; (*c*) Y. Wang, D. F. Yu, Y. Z. Liu, H. Wei, Y. C. Luo, D. J. Dixon and P. F. Xu, *Chem. – Eur. J.*, 2010, **16**, 3922–3925; (*d*) H. Ishikawa, S. Sawano, Y. Yasui, Y. Shibata and Y. Hayashi, *Angew. Chem., Int. Ed.*, 2011, **50**, 3774–3779; (*e*) P. Chauhan, G. Urbanietz, G. Raabe and D. Enders, *Chem. Commun.*, 2014, **50**, 6853–6855; (*f*) R. Hahn, G. Raabe and D. Enders, *Org. Lett.*, 2014, **16**, 3636–3639; (*g*) B. Han, W. Huang, W. Ren, G. He, J. Wang and C. Peng, *Adv. Synth. Catal.*, 2015, **357**, 561–568; (*h*) M. C. Yang, C. Peng, H. Huang, L. Yang, X. H. He, W. Huang, H. L. Cui, G. He and B. Han, *Org. Lett.*, 2017, **19**, 6752–6755; (*i*) Y. Hayashi, H. Gotoh, T. Hayashi and M. Shoji, *Angew. Chem., Int. Ed.*, 2005, **44**, 4212–4215; (*j*) T. Husch, D. Seebach, A. K. Beck and M. Reiher, *Helv. Chim. Acta*, 2017, **100**, e1700182.

6 (*a*) P. Chauhan, S. Mahajan, C. C. J. Loh, G. Raabe and D. Enders, *Org. Lett.*, 2014, **16**, 2954–2957; (*b*) P. Chauhan, G. Urbanietz, G. Raabe and D. Enders, *Chem. Commun.*, 2014, **50**, 6853–6855; (*c*) D. Enders, C. Grondal and M. R. M. Hüttl, *Angew. Chem., Int. Ed.*, 2007, **46**, 1570–1581; (*d*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167–178; (*e*) Ł. Albrecht, H. Jiang and K. A. Jorgensen, *Angew. Chem., Int. Ed.*, 2011, **50**, 8492–8509; (*f*) A. Grossmann and D. Enders, *Angew. Chem., Int. Ed.*, 2012, **51**, 314–325; (*g*) H. Pellissier, *Adv. Synth. Catal.*, 2012, **354**, 237–294; (*h*) P. Chauhan and D. Enders, *Angew. Chem., Int. Ed.*, 2014, **53**, 1485–1487.

7 (*a*) B. Appel, N. N. R. Saleh and P. Langer, *Chem. – Eur. J.*, 2006, **12**, 1221–1236; (*b*) B. Appel, S. Rotzoll, R. Kranich, H. Reinke and P. Langer, *Eur. J. Org. Chem.*, 2006, 3638–3644; (*c*) A. Danda, N. Kesava-Reddy, C. Golz, C. Strohmann and K. Kumar, *Org. Lett.*, 2016, **18**, 2632–2635; (*d*) M. S. Akhtar, R. S. Thombal, R. J. I. Tamargo, W. G. Yang, S. H. Kim and Y. R. Lee, *Green Chem.*, 2020, **22**, 4523–4531; (*e*) J. Lei, J. Xu, D. Y. Tang, J. W. Shao, H. Y. Li, Z. Z. Chen and Z. G. Xu, *Org. Chem. Front.*, 2020, **7**, 2657–2663; (*f*) L. Chen, R. Huang, K. Li, X.-H. Yun, C.-L. Yang and S.-J. Yan, *Green Chem.*, 2020, **22**, 6943–6953; (*g*) M. Giardinetti, N. I. Jessen, M. L. Christensen and K. A. Jørgensen, *Chem. Commun.*, 2019, **55**, 202–205; (*h*) X.-W. He, W. Zhou, M. Zhang, M.-Y. Tian, H.-J. Wang, Y.-P. Tian and X.-L. Liu, *Org. Biomol. Chem.*, 2020, **18**, 9039–9043.

8 (*a*) A. G. Neo, J. Díaz, S. Marcaccini and C. F. Marcos, *Org. Biomol. Chem.*, 2012, **10**, 3406–3416; (*b*) Z. Shao, L. Wang, L. Xu, H. Zhao and J. Xiao, *RSC Adv.*, 2014, **4**, 53188–53191; (*c*) L. Xu, Z. Shao, L. Wang and J. Xiao, *Org. Lett.*, 2014, **16**, 796–799; (*d*) Z. Shao, L. Xu, L. Wang, H. Wie and J. Xiao, *Org. Biomol. Chem.*, 2014, **12**, 2185–2188; (*e*) O. Talhi, L. Brodziak-Jarosz, J. Panning, B. Orlikova, C. Zwergel, T. Tzanova, S. Philippot, D. C. G. A. Pinto, F. A. Almeida Paz and C. Gerhäuser, *Eur. J. Org. Chem.*, 2016, 965–975; (*f*) S. Peng, L. Wang, H. Guo, S. Sun and J. Wang, *Org. Biomol. Chem.*, 2012, **10**, 2537–2541; (*g*) A. Albrecht, *Eur. J. Org. Chem.*, 2018, 6482–6485.

9 Y. Zhang, S. Chen, C. Wei, G. O. Pankin, X. Ye and Y. C. Chen, *Eur. J. Med. Chem.*, 2018, **147**, 218–226.