ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2021, **57**, 1762

Received 26th November 2020,
Accepted 7th January 2021

DOI: 10.1039/d0cc07761e

rsc.li/chemcomm

Asymmetric organocatalytic vinylogous Michael addition triggered triple-cascade reactions of 2-hydroxycinnamaldehydes and vinylogous nucleophiles: construction of benzofused oxabicyclo[3.3.1]nonane scaffolds†

Hui-Chun Wu,[a] Chen Wang,[a] Ying-Han Chen[a] and Yan-Kai Liu *[ab]

An organocatalytic vinylogous Michael addition triggered triple-cascade reaction has been developed. 2-Hydroxycinnamaldehydes worked under iminium activation with either acyclic or cyclic ketone-derived α,α-dicyanoalkenes, yielding the benzofused oxabicyclo[3.3.1]nonanes bearing one quaternary stereocenter with excellent stereoselectivities.

Benzofused oxabicyclo[3.3.1]nonane scaffolds bearing a chromane moiety are found in many biologically interesting natural products and synthetic compounds (Fig. 1).[1] However, despite their wide occurrence, there is a lack of asymmetric catalytic methodologies available for the enantioselective preparation of this methylene-bridged ring system,[2] which was possibly attributed to the formation of two bridgehead carbon stereocenters, especially one of which is an oxa-quaternary stereocenter. Therefore, the development of a direct asymmetric synthetic protocol to access enantiopure benzofused oxabicyclo[3.3.1]nonane scaffolds from readily available starting materials is highly desirable.

The principle of vinylogy,[3] by its nature, is particularly suitable for the design of a cascade process, and has thus attracted great interest. In the last few decades, the employment of this principle in asymmetric organocatalytic reactions,[4] especially the vinylogous Michael reaction,[5] has provided an efficient synthetic protocol for the preparation of highly functionalized chiral compounds. Undoubtedly, it would be desirable to develop a strategy to further extend the synthetic power and versatility of vinylogous nucleophiles in the field of asymmetric synthesis.

On the basis of reactivity analysis, the readily available simple ketone-derived α,α-dicyanoalkenes have at least four potential reactive sites (Scheme 1; E = electrophile, Nu = nucleophile, FG = functional group). However, despite considerable efforts having been devoted to the application of these kinds of vinylogous nucleophiles in the aforementioned Michael reactions,[6] the reported examples were mainly furnished as single addition with various electrophiles,[7] and only a few methods dealt with vinylogous Michael reaction triggered double cascade reactions,[8] yet leading to a simple ring structure. To the best of our knowledge, there is no enantioselective procedure for the triple cascade reactions of such vinylogous nucleophiles, which may result in more complex ring skeletons. Obviously, the key to the success of this proposed triple cascade process is to identify a functional Michael acceptor with diverse reactivity.

We recently found that the 2-hydroxycinnamaldehydes could be efficiently activated by iminium catalysis to undergo Michael addition triggered cascade reactions, which are particularly useful for the creation of methylene-bridged acetals[9] or aminals[10] bearing a chromane moiety. According to our previous results, we reasoned that the 2-hydroxycinnamaldehydes

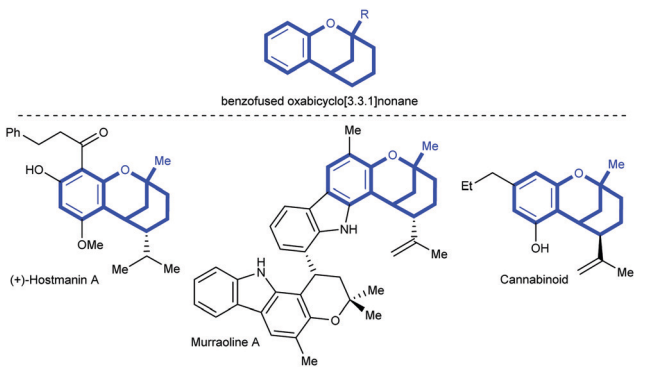
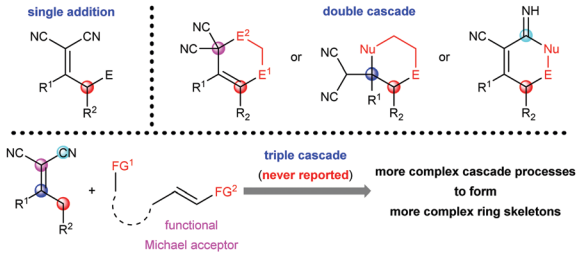


Fig. 1 Representative examples bearing a benzofused oxabicyclo[3.3.1]-nonane scaffold.

[a] *Molecular Synthesis Center & Key Laboratory of Marine Drugs, Ministry of Education, School of Medicine and Pharmacy, Ocean University of China, 5 Yushan Road, Qingdao 266003, China. E-mail: liuyankai@ouc.edu.cn*

[b] *Laboratory for Marine Drugs and Bioproducts of Qingdao National Laboratory for Marine Science and Technology, Qingdao 266003, China*

† Electronic supplementary information (ESI) available: Detailed optimization, experimental procedures, and spectroscopic data for all new compounds. CCDC 2014883. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0cc07761e



Scheme 1 Reactivity analysis and our design.

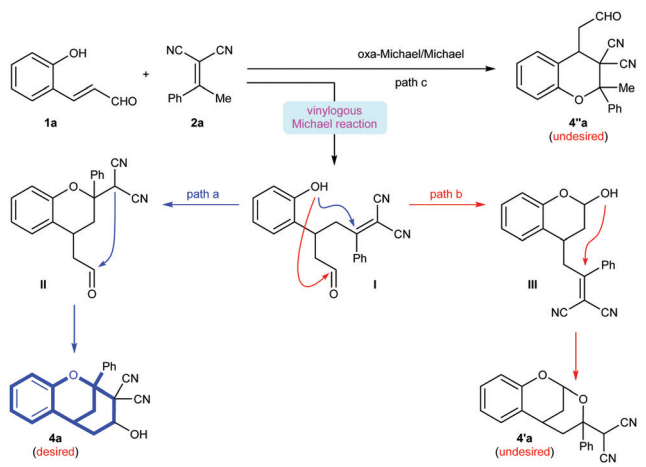
may perfectly match the structure and reactivity requirements of the aforementioned functional Michael acceptors, which could be used in the designed asymmetric vinylogous Michael addition triggered triple cascade reactions.

Indeed, because both 2-hydroxycinnamaldehydes **1** and α,α-dicyanoalkenes **2** are substrates bearing multiple reactive sites, the identification of an efficient enantioselective catalytic system that did not promote competitive background reactions during the triple cascade process is the future challenge. Herein we report an asymmetric vinylogous Michael reaction triggered cascade process for the preparation of a benzofused oxabicyclo [3.3.1]nonane scaffold containing two bridgehead chiral centers, one of which is an oxa-quaternary stereocenter. It is noteworthy that the designed cascade reaction proceeds with both 2-hydroxycinnamaldehydes and α,α-dicyanoalkenes as three reactive site substrates under mild reaction conditions at low catalyst loading, affording methylene-bridged benzofused bicyclic products in good yields with excellent enantioselectivities as a single diastereoisomer.

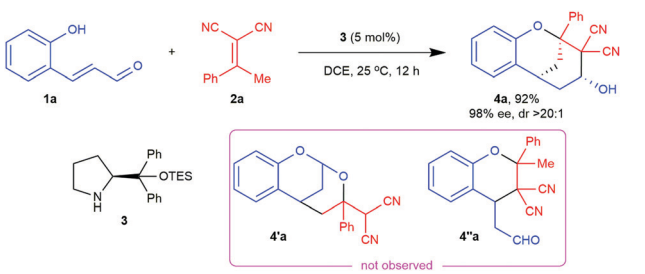
We proposed that the asymmetric vinylogous Michael reaction of 2-hydroxycinnamaldehyde **1a** and α,α-dicyanoalkene **2a** could enable the efficient construction of the key intermediate **I** (Scheme 2), which may introduce two competitive reaction pathways to give two different benzofused bridged ring systems. In path a, the nucleophilic attack of the phenolic hydroxyl group onto the electron-deficient olefin moiety will afford intermediate **II**, followed by an intramolecular aldol-type reaction to give the desired benzofused oxabicyclo[3.3.1]nonane scaffold **4a** bearing an oxa-quaternary stereocenter. While in path b, the nucleophilic attack of the phenolic hydroxyl group onto the aldehyde group enables the formation of intermediate **III**, and the subsequent intramolecular oxa-Michael addition will produce the undesired bridged acetal product **4′a**. By comparison, considering the strong electron-withdrawing effect of the two cyano groups, it might be expected that nucleophilic attack of the electron-deficient olefin moiety by the phenolic hydroxyl group should take precedence over the aldehyde group, despite the former giving a more sterically encumbered oxa-quaternary stereocenter. Of course, the known cascade process of 2-hydroxycinnamaldehydes with electron-deficient Michael acceptors would also be likely involved in this transformation to yield another undesired cyclic product **4″a** (path c; oxa-Michael/Michael).[11] Clearly, the control of chemo- and regioselectivity is still a stringent issue in this vinylogous Michael reaction triggered cascade transformation.

After an extensive optimization study,[12] we found that the designed vinylogous triple-cascade process was obtained in a fast, clean and highly stereoselective process by using 5 mol% chiral aminocatalyst **3**, affording the desired product **4a** in 92% yield with excellent enantioselectivity as a single diastereoisomer (Scheme 3, 98% ee, dr $>20:1$; TES = triethylsilyl, DCE = 1,2-dichloroethane). It is noteworthy that **4a** was obtained as the only product, and no products **4′a**/**4″a** were observed, which indicated that this transformation was a completely chemo- and regioselective cascade process.

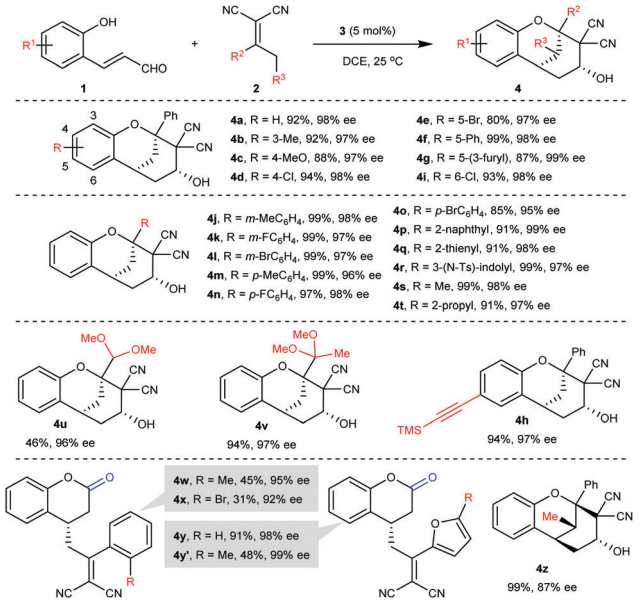
The scope of the vinylogous Michael reaction triggered cascade reaction was then investigated (Scheme 4). A series of substituted 2-hydroxycinnamaldehydes **1** bearing various electronically different substituents, including 3-furyl, alkynyl and phenyl functional groups, with different substitution patterns were well-tolerated, leading to the desired benzofused bridged bicyclic products **4b–i** in high to excellent yields with excellent enantioselectivities. Next, the scope of the reaction was explored with respect to α,α-dicyanoalkene substrates **2**. It could be seen that **2** with different *meta*- and *para*-substituted phenyl groups including 2-naphthyl were smoothly employed in the cascade reaction (**4j–p**). Moreover, heteroaromatic substituents, such as 2-thienyl and 3-indolyl, as well as alkyl groups could also be used to give the target products **4q–t** with good results. Noteworthily, α,α-dicyanoalkenes with functionalities such as ketal or acetal groups were compatible with the reaction conditions (**4u** and **4v**). However, substituents with



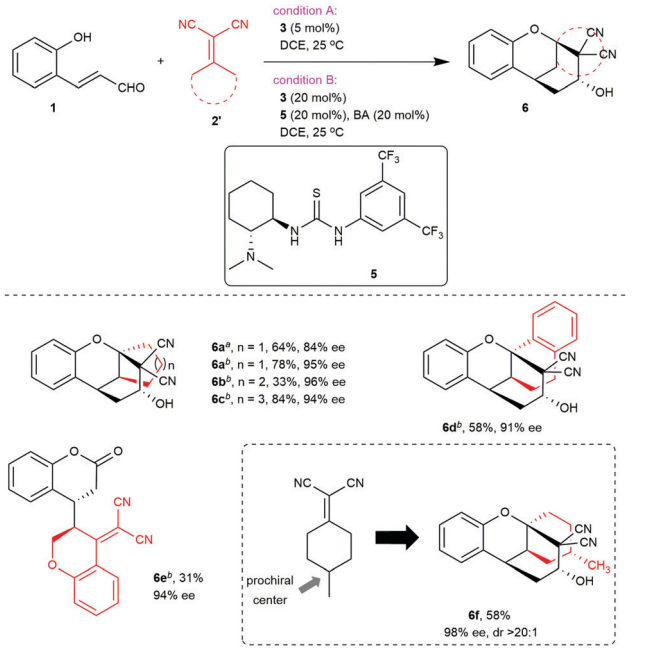
Scheme 2 Proposed competitive reaction pathways.



Scheme 3 Highly chemo-, regio- and stereoselective formation of **4a**.



Scheme 4 Substrate scope with respect to acyclic **2**.



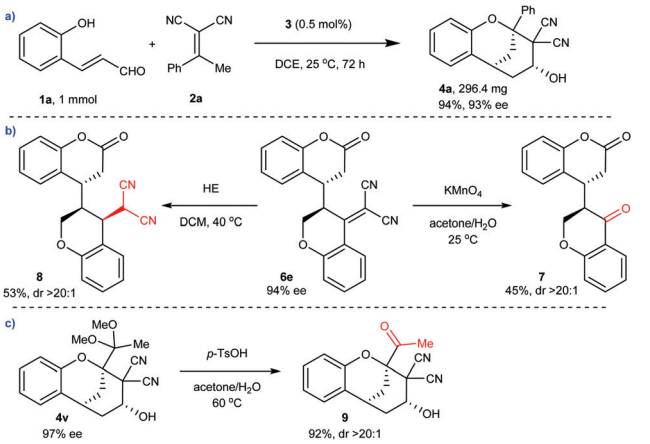
Scheme 5 Substrate scope with respect to cyclic **2′**. [a]Condition A; [b]condition B.

different electronic properties, such as methyl and bromo groups, at the *ortho*-position of the aromatic moiety of **2** as well as 2-furyl and 5-methylfuran-2-yl groups did not yield the desired bicyclic products. Indeed, a vinylogous Michael reaction followed by intramolecular hemiacetal formation reaction sequence was observed (see Scheme 2, path b, intermediate **III**), delivering 4-substituted chroman-2-one derivatives **4w–y′** after an additional oxidation reaction with pyridinium chlorochromate (PCC) as the oxidant (see the ESI,† for details). Furthermore, propiophenone-derived α,α-dicyanoalkene was employed, resulting in the formation of **4z** with one more chiral center as a single diastereoisomer.

Next, we turned our attention to the cyclic α,α-dicyanoalkenes. However, as shown in Scheme 5, the aliphatic cyclic α,α-dicyanoalkene **2′** with a five-membered ring exhibited much lower reactivity under standard conditions, while much better enantioselectivity was observed for product **6a** when the reaction was performed under our previously developed multiple catalysis conditions (unoptimized) by using **3d** (20 mol%) together with bifunctional catalyst **5** (20 mol%) and benzoic acid (BA, 20 mol%).[9b,c] Other cyclic α,α-dicyanoalkenes with a six- or seven-membered ring were also compatible with the developed reaction sequence, and the desired products **6b** and **6c** were afforded in good yields and high enantioselectivities. With regard to the benzofused cyclic α,α-dicyanoalkenes, carbocyclic **2′d** delivered the desired product **6d** with good enantioselectivity, while oxacyclic **2′e** failed to give the cyclized product but afforded the 4-substituted chroman-2-one **6e** after the oxidation with PCC (see Scheme 3, path b, intermediate **III**; see also the ESI,† for details). Delightfully, the desymmetrisation of prochiral α,α-dicyanoalkene could also be involved in this triple cascade process, leading to product **6f** as a single diastereoisomer.

To highlight the synthetic utility of the formed products, we explored their conversion to other valuable chiral organic molecules. As outlined in Scheme 6, the reaction of **1a** and **2a** could be carried out on a 1 mmol scale. It is noteworthy that the low catalyst loading (0.5 mol%) can provide excellent levels of stereocontrol at a reasonable reaction rate (Scheme 6a).[12] The oxidative double bond cleavage of **6e** could be accomplished in the presence of $KMnO_4$, giving access to ketone **7** without decrease in the enantioselectivity (Scheme 6b). Reduction of the double bond in **6e** with diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate Hantzsch ester (HE) as the reducing agent provided product **8** along with the stereoselective formation of a new chiral center (Scheme 6b). Additionally, hydrolysis of the ketal moiety of **4v** under acidic conditions gave ketone **9** in good yield (Scheme 6c, *p*-TsOH = *p*-toluenesulfonic acid).

The absolute configuration of product **4o** (CCDC 2014883†) was determined by X-ray crystallography (see the ESI,† for details), while the absolute configuration of bridged cyclic



Scheme 6 Useful transformations.

product **6a** was assigned by means of TD-DFT calculations of the electronic circular dichroism (ECD) spectra (see the ESI,† for details). The stereochemistry of the remaining products **4** and **6** was assigned analogously.

In summary, we have developed an efficient asymmetric organocatalytic triple-cascade reaction, which was initiated by the vinylogous Michael reaction between 2-hydroxycinnamaldehydes and either acyclic or cyclic ketone-derived α,α-dicyanoalkenes under iminium ion activation, followed by oxa-Michael reaction and aldol-type reaction sequence, yielding the methylene-bridged benzofused oxabicyclo[3.3.1]nonane derivatives bearing one oxa-quaternary stereocenter in good yields with excellent stereoselectivities. It should be noted that, although both 2-hydroxycinnamaldehydes and α,α-dicyanoalkenes exhibited multisite reactivities in the reaction process, only one of the three possible reaction pathways worked, which could be smoothly scaled up even at low catalyst loading (as low as 0.5 mol%), affording similar good results. Further applications of this methodology with other vinylogous substrates are under investigation.

We acknowledge the National Science and Technology Major Project for Significant New Drugs Development (No. 2018ZX09735004), the Scientific and Technological Innovation Project financially supported by the Qingdao National Laboratory for Marine Science and Technology (No. 2015ASKJ02-06), and the NSFC-Shandong Joint Fund for Marine Science Research Centers (No. U1606403) for financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) A. T. McPhail, T.-S. Wu, T. Ohta and H. Furukawa, *Tetrahedron Lett.*, 1983, **24**, 5377; (*b*) T.-S. Wu, M.-L. Wang, P.-L. Wu and T.-T. Jong, *Phytochemistry*, 1995, **40**, 1817; (*c*) B. Portet, N. Fabre, V. Roumy, H. Gornitzka, G. Bourdy, S. Chevalley, M. Sauvain, A. Valentin and C. Moulis, *Phytochemistry*, 2007, **68**, 1312; (*d*) S. A. T. Fobofou, K. Franke, G. Sanna, A. Porzel, E. Bullita, P. L. Colla and L. A. Wessjohann, *Bioorg. Med. Chem.*, 2015, **23**, 6327.

2 (*a*) D. F. Yu, Y. Wang and P. F. Xu, *Adv. Synth. Catal.*, 2011, **353**, 2960; (*b*) D. H. Dethe and B. D. Dherange, *J. Org. Chem.*, 2015, **80**, 4526; (*c*) K. Yoshida, Y. Fujino, Y. Takamatsu, K. Matsui, A. Ogura, Y. Fukami, S. Kitagaki and K.-I. Takao, *Org. Lett.*, 2018, **20**, 5044.

3 For selected reviews, see: (*a*) R. C. FusoN, *Chem. Rev.*, 1935, **16**, 1; (*b*) R. Chinchilla and C. Nájera, *Chem. Rev.*, 2000, **100**, 1891; (*c*) H. Li and L. Yin, *Tetrahedron Lett.*, 2018, **59**, 4121; (*d*) B.-X. Xiao, X.-Y. Gao, W. Du and Y.-C. Chen, *Chem. – Eur. J.*, 2019, **25**, 1607; (*e*) C. Curti, L. Battistini, A. Sartori and F. Zanardi, *Chem. Rev.*, 2020, **120**, 2448.

4 For selected reviews, see: (*a*) G. Casiraghi, F. Zanardi, G. Appendino and G. Rassu, *Chem. Rev.*, 2000, **100**, 1929; (*b*) S. E. Denmark, J. R. Heemstra Jr and G. L. Beutner, *Angew. Chem., Int. Ed.*, 2005, **44**, 4682; (*c*) G. Casiraghi, L. Battistini, C. Curti, G. Rassu and F. Zanardi, *Chem. Rev.*, 2011, **111**, 3076; (*d*) S. V. Pansare and E. K. Paul, *Chem. – Eur. J.*, 2011, **17**, 8770.

5 For selected reviews, see: (*a*) C. Schneider and F. Abels, *Org. Biomol. Chem.*, 2014, **12**, 3531; (*b*) Y. L. Yin and Z. Y. Jiang, *ChemCatChem*, 2017, **9**, 4306For selected examples, see: (*c*) B. Zhu, B. Lu, H. Zhang, X. Xu, Z. Jiang and J. Chang, *Org. Lett.*, 2019, **21**, 3271; (*d*) B.-X. Xiao, C.-H. Shi, S.-Y. Liang, B. Jiang, W. Du and Y.-C. Chen, *Org. Lett.*, 2019, **21**, 7554; (*e*) Z.-H. Wang, X.-Y. Zhang, C.-W. Lei, J.-Q. Zhao, Y. You and W.-C. Yuan, *Chem. Commun.*, 2019, **55**, 9327; (*f*) W. Lin, X. Lin, Y. Cheng, X. Chang, S. Zhou, P. Li and W. Li, *Org. Chem. Front.*, 2019, **6**, 2452.

6 For selected examples of vinylogous Michael reaction *via* asymmetric iminium activation, see: (*a*) W. Xie, L. Yue, D. Xue, X. L. Ma, Y. C. Chen, Y. Wu, J. Zhu and J. G. Deng, *Chem. Commun.*, 2006, 1563; (*b*) J. W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. C. Chen, Y. Wu, J. Zhu and J. G. Deng, *Angew. Chem., Int. Ed.*, 2007, **46**, 389; (*c*) J. Lu, F. Liu and T.-P. Loh, *Adv. Synth. Catal.*, 2008, **350**, 1781; (*d*) J. Lu, F. Liu, W. J. Zhou and T. P. Loh, *Tetrahedron Lett.*, 2008, **49**, 5389.

7 (*a*) D. Xue, Y. C. Chen, Q. W. Wang, L. F. Cun, J. Zhu and J. G. Deng, *Org. Lett.*, 2005, **7**, 5293; (*b*) T. Y. Liu, H. L. Cui, J. Long, B. J. Li, Y. Wu, L. S. Ding and Y. C. Chen, *J. Am. Chem. Soc.*, 2007, **129**, 1878; (*c*) B. Niess and K. A. Jørgensen, *Chem. Commun.*, 2007, 1620; (*d*) J. Aleman, C. B. Jacobsen, K. Frisch, J. Overgaard and K. A. Jørgensen, *Chem. Commun.*, 2008, 632; (*e*) J. Lu, W. J. Zhou, F. Liu and T. P. Loh, *Adv. Synth. Catal.*, 2008, **350**, 1796; (*f*) X.-L. Zhu, W.-J. He, L.-L. Yu, C.-W. Cai, Z.-L. Zuo, D.-B. Qin, Q.-Z. Liu and L.-H. Jing, *Adv. Synth. Catal.*, 2012, **354**, 2965; (*g*) S. Rout, S. K. Ray, R. A. Unhale and V. K. Singh, *Org. Lett.*, 2014, **16**, 5568; (*h*) X. Li, X. Xu, W. Wei, A. Lin and H. Yao, *Org. Lett.*, 2016, **18**, 428.

8 (*a*) H. L. Cui, J. Peng, X. Feng, W. Du, K. Jiang and Y. C. Chen, *Chem. – Eur. J.*, 2009, **15**, 1574; (*b*) J. W. Xie, W. Chen, R. Li, M. Zeng, W. Du, L. Yue, Y. C. Chen, Y. Wu, J. Zhu and J. G. Deng, *Angew. Chem., Int. Ed.*, 2007, **46**, 389; (*c*) T. R. Kang, J. W. Xie, W. Du, X. Feng and Y. C. Chen, *Org. Biomol. Chem.*, 2008, **6**, 2673; (*d*) Z. W. Guo, X. S. Li, W. D. Zhu and J. W. Xie, *Eur. J. Org. Chem.*, 2012, 6924; (*e*) X. M. Shi, W. P. Dong, L. P. Zhu, X. X. Jiang and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 3119; (*f*) X. F. Huang, Y. F. Zhang, Z. H. Qi, N. K. Li, Z. C. Geng, K. Li and X. W. Wang, *Org. Biomol. Chem.*, 2014, **12**, 4372; (*g*) S. Meninno, A. Mazzanti and A. Lattanzi, *Adv. Synth. Catal.*, 2018, **361**, 79.

9 (*a*) X.-J. Lv, Y.-H. Chen and Y.-K. Liu, *Org. Lett.*, 2019, **21**, 190; (*b*) C. Wang, Y.-H. Chen, H.-C. Wu, C. Wang and Y.-K. Liu, *Org. Lett.*, 2019, **21**, 6750; (*c*) X.-Q. Zhang, X.-J. Lv, J.-P. Pei, R. Tan and Y.-K. Liu, *Org. Chem. Front.*, 2020, **7**, 292.

10 (*a*) Z.-H. You, Y.-H. Chen, Y. Tang and Y.-K. Liu, *Org. Lett.*, 2018, **20**, 6682; (*b*) Y.-H. Chen, X.-J. Lv, Z.-H. You and Y.-K. Liu, *Org. Chem. Front.*, 2019, **6**, 3725; (*c*) Y.-H. Chen, X.-J. Lv, Z.-H. You and Y.-K. Liu, *Org. Lett.*, 2019, **21**, 5556.

11 (*a*) L. Zu, S. Zhang, H. Xie and W. Wang, *Org. Lett.*, 2009, **11**, 1627; (*b*) D. B. Ramachary, M. S. Prasad, S. Vijaya Laxmi and R. Madhavachary, *Org. Biomol. Chem.*, 2014, **12**, 574.

12 See the ESI† for full optimization studies.