ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Li, Y. Liu, X. Liu, K. Wang and W. Guo, *Chem. Commun.*, 2019, DOI: 10.1039/C8CC09382B.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

ROYAL SOCIETY OF CHEMISTRY
View Article Online
DOI: 10.1039/C8CC09382B

Journal Name

COMMUNICATION

Organic-base Catalyzed Asymmetric 1,4-Addition of Tritylthiol to *in Situ* Generated Aza-*o*-Quinone Methides at H_2O/DCM Interface

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

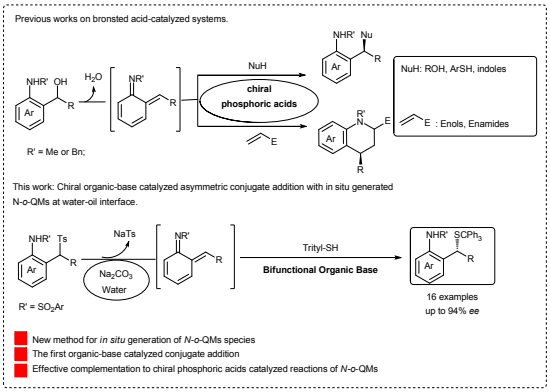
www.rsc.org/

Xianghui Liu,[ab] Kai Wang, [ab] Wengang Guo, [a] Yan Liu[a*] and Can Li [a*]

Based on an efficient method for *in situ* generation of N-*o*-QMs species in the presence of base, enantioselective catalytic conjugated additions of tritylthiol to *in situ* generated N-*o*-QMs are reported. Acid-base bifunctional organocatalyst 4c (10 mol%) enables these transformations with high stereoselectivities (up to 94% *ee*) using H_2O/DCM as solvent under mild conditions.

Aza-*o*-Quinone Methides (N-*o*-QMs), the nitrogen-based analogues of *o*-Quinone Methides (*o*-QMs)[1], have attracted much attention as versatile and highly reactive intermediates for the synthesis of useful nitrogenous compounds.[2] N-*o*-QMs are typically generated from precursors due to their unstable nature.[3] In the asymmetric reactions, diaryl methanols are most common precursors for the generation of N-*o*-QMs by dehydration in the presence of acid. Thus, chiral phosphoric acids have been identified as highly efficient catalysts for several conjugate additions and formal [4+2] cycloadditions with *in situ* generated N-*o*-QMs (Scheme 1a).[4] In addition, 2-aminobenzyl chlorides have also been employed to be precursors of unsubstituted N-*o*-QMs in N-heterocyclic carbenes-catalyzed [4+2] and [4+3] cycloaddition reactions.[5] Nevertheless, the development of asymmetric reactions with N-*o*-QMs are still restricted by the scanty precursors. Compared with the well-developed asymmetric reactions with *o*-QMs[6], the reported nucleophilic partners of N-*o*-QMs were confined to alcohols, thiophenols, indoles, enols and enamides (Scheme 1a). Accordingly, the development of mild and efficient approaches for N-*o*-QMs generation and subsequent new asymmetric catalytic reaction systems would be very desirable in organic synthesis and drug discovery.

Herein, we report an efficient method for *in situ* generation



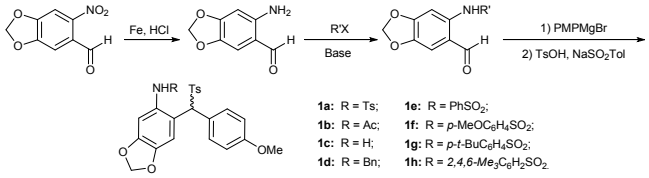
Scheme 1. Asymmetric catalytic reactions with *in situ* generated N-*o*-QMs.

species in the presence of inorganic bases from 2-(Tosylmethyl)anilines. Based on this approach, we developed the first organic-base catalyzed 1,4-conjugate addition of tritylthiol to *in situ* generated N-*o*-QMs with good to excellent enantioselectivities (up to 94% *ee*) using H_2O/DCM as the solvent (Scheme 1b). Moreover, experimental results indicate that water is crucial for achieving the high reactivity and stereoselectivity. This methodology can be complementary in scope to existing chiral phosphoric acids-catalyzed reactions of N-*o*-QMs, affording uniquely valuable methods for the synthesis of chiral *ortho*-amino substituted benzyl mercaptans.

We and other groups recently reported bifunctional organic-bases catalyzed highly enantioselective conjugate additions and cycloadditions of different nucleophilic partners with *o*-QMs which were generated *in situ* from the corresponding 2-(Tosylmethyl)phenols by removing HTs in the presence of inorganic bases.[7] In our reaction systems, bifunctional organic-base catalysts and oil–water biphasic system are crucial for achieving high reactivity and stereoselectivity. On the basis of our previous work, we envisioned the synthesis of 2-substituted anilines bearing a good leaving group at benzyl position which can be transformed *in situ* to N-*o*-QMs under mild basic conditions. A bifunctional organic-base catalyst enables the activation of both the nucleophile by

[a] State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China.
E-mail: yanliu503@dicp.ac.cn; canli@dicp.ac.cn
[b] Graduate University of Chinese Academy of Sciences, Beijing 100049, China
Electronic Supplementary Information (ESI) available: CCDC 1894977. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

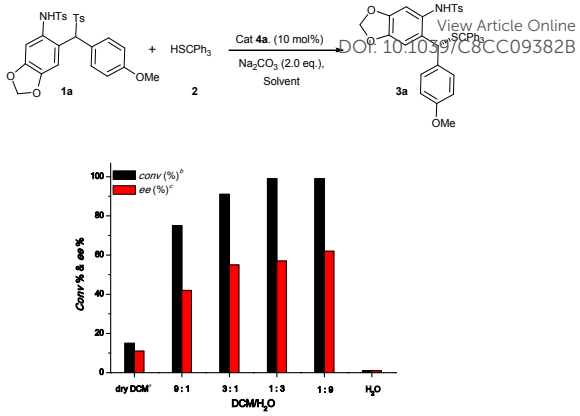
deprotonation with base and N-*o*-QMs by hydrogen-bonding interactions, resulting in a well-organized transition state. Moreover, oil–water biphasic system can effectively realize the spatial separation of the inorganic base from the organic phase to suppress the racemic background reaction. As shown in Scheme 2, to screen out effective precursors of N-*o*-QMs for the corresponding asymmetric reactions, we prepared a series of 2-(Tosylmethyl)anilines with different N-substituted groups from the commercially available 6-Aminopiperonal, Benzenesulfonyl chloride, Grignard reagents and the *p*-toluenesulfinic acid sodium salt via a four-step reaction sequence (see Supporting Information).



Scheme 2. The synthesis of 2-(Tosylmethyl)anilines.

With these precursors in hand, we started our investigation of the asymmetric conjugated addition to N-*o*-QMs *in situ* generated from **1a**. Tritylthiol (**2**) was chosen as its nucleophilic partner. Although Rueping's group has developed a chiral phosphoric acid-catalyzed thiolation of thiophenols to N-*o*-QMs for the synthesis of thioethers, it is still necessary to establish the methodology of asymmetric conjugated addition of tritylthiol to N-*o*-QMs, because the trityl group in products **3** could be readily cleaved under mild conditions to unmask the thiol functionality. As shown in Figure 1, using dry DCM as solvent, the reaction proceeded with very low reactivity and poor enantioselectivity. Remarkably, when we chose mixture of H_2O/DCM (solvent v/v = 1/9) as the solvent, the reaction was dramatically accelerated to 73% conversion in 4 hours, delivering product **3a** with 42% *ee*. Moreover, as increasing the proportion of water, the reactivity and stereoselectivity are enhanced gradually. We believe the combination of hydrogen-bonding network induced by water and the spatial separation between the chiral organic components and the inorganic base by oil-water biphasic system is crucial for enhanced reactivities and enantioselectivities, and our theoretical investigations are ongoing to elucidate the origin of observed stereoselectivities. When the reaction was performed in H_2O/DCM (solvent v/v = 9/1), almost complete conversion and 62% *ee* was obtained.

The different N-substituted 2-(Tosylmethyl) anilines **1a**–**1d** were then evaluated with regard to reactivity and enantioselectivity with bifunctional catalyst **4a** (10 mol%) in H_2O/DCM (solvent v/v = 9/1) (Table 1, entries 1–4). **1a, 1c**–**1d** exhibited high reactivity and the reactions were completed in 12 hours. However, the enantioselectivities showed that N-sulfonyl substituted **1a** is the precursor of choice. By lowering the reaction temperature to 4°C, the **4a**-catalyzed reaction of **2** to **1a** generated the corresponding product **3a** in 72% *ee* (entry



Reaction conditions: **1a** (0.05 mmol), tritylthiol (**2**, 2.0 equiv, 0.10 mmol), and **4a** (10 mol%) with Na_2CO_3 (2.0 equiv) in solvent (different DCM/H_2O ratio) were stirred (1500 r/min) at room temperature for 4 hours. [a] Reaction time: 23 hours ; [b] Conversion was determined by crude ^{1}HNMR; [c] *ee* was determined by chiral HPLC (column AD-H).

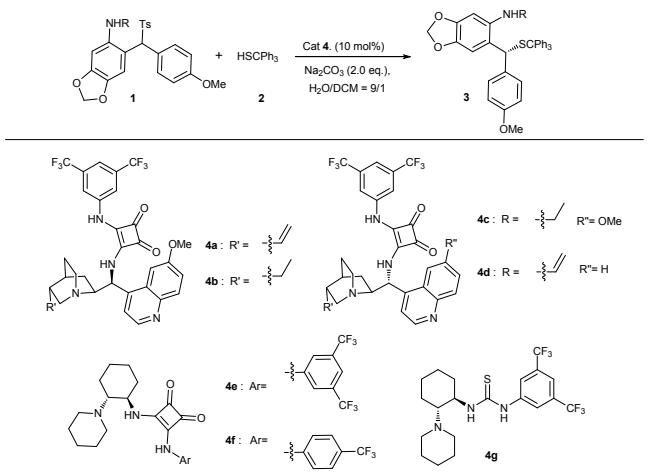
Fig. 1 Water effect in the asymmetric conjugated addition of **2** to **1a**.

5). We continued to examine the catalytic potential of some well-established bifunctional organocatalysts, including Cinchona alkaloid derived squaramide catalysts (**4a–4d**) and chiral (R,R)-Cyclohexane-1,2-diamine-derived squaramide or thiourea catalysts (**4e–4g**). Hydroquinidine-derived squaramides **4b** exhibited high catalytic activity, completing the reaction in 12 hours, the desired product **3a** was obtained with 78% *ee* (Table 1, entry 6). To our delight, hydroquinidine-derived squaramides **4c** significantly improved the enantioselectivity to 86% without loss of activities (Table 1, entry 7). (R,R)-Cyclohexane-1,2-diamine-derived thiourea or squaramide catalysts **4e–4g** were also evaluated, providing access to **3a** in unsatisfactory enantioselectivies (Table 1, entries 9-11). To improve the enantioselectivity of this reaction, substrates **1** are under refined regulation with changing different benzenesulfonyl groups at N-position. Surprisingly, the products were obtained in higher *ee* values when the N-substituent became more electron-donating. For example, with catalyst **4c**, N-*p*-methoxy benzenesulfonyl substituted substrate **1f** and N-*p*-tert-butyl benzenesulfonyl substituted substrate **1g** led to the corresponding products in 87% and 88% *ee*, respectively (Table 1, entries 13 and 14). The enantioselectivity of the product was further increased to 93% *ee* by the use of **1h** as the precursor of N-*o*-QM (Table 1, entry 15)

With the optimized reaction conditions in hand, the generality of our catalytic protocol was evaluated through enantioselective conjugated additions of **2** to a range of *in situ* generated N-*o*-QMs, and these results are summarized in Scheme 3. Regardless of the electronic and steric nature of the substituents on the aromatic ring, the *in situ* generated N-*o*-QMs were smoothly transformed to the corresponding 1,4-adducts **3i**–**3p** with high yields and excellent enantioselectivities (*ee* = up to 93%). Substrates **1q**-**1t**, which possess disubstituted groups on the benzene ring, worked well

View Article Online
DOI: 10.1039/C8CC09782B

Table 1. Optimization of catalytic reaction conditions [a]

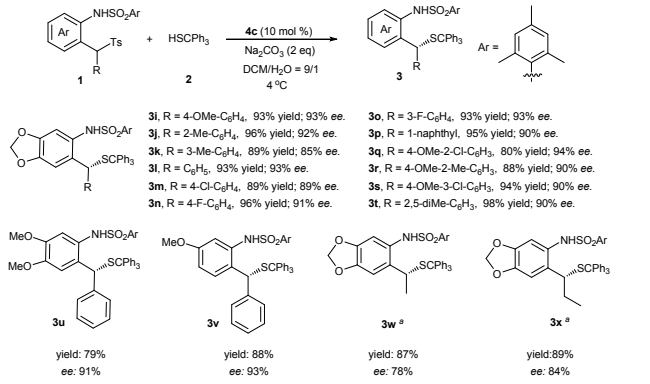


Entry	Substrate	Cat.	Conv.(%) [b]	ee (%) [c]
1	**1a**	**4a**	>99	62
2	**1b**	**4a**	--	--
3	**1c**	**4a**	> 99	0
4	**1d**	**4a**	> 99	0
5[d]	**1a**	**4a**	> 99	72
6[d]	**1a**	**4b**	> 99	78
7[d]	**1a**	**4c**	> 99	86
8[d]	**1a**	**4d**	> 99	68
9[d]	**1a**	**4e**	> 99	30
10[d]	**1a**	**4f**	> 99	0
11[d]	**1a**	**4g**	> 99	10
12[d]	**1e**	**4c**	> 99	84
13[d]	**1f**	**4c**	> 99	87
14[d]	**1g**	**4c**	> 99	88
15[d]	**1h**	**4c**	> 99	93

[a] Reaction conditions: **1** (0.1 mmol), tritylthiol (**2**, 2.0 equiv, 0.2 mmol), and catalyst **4** (10 mol%) with Na_2CO_3 (2.0 equiv) in DCM : H_2O = 0.4 mL : 3.6 mL) were stirred (1500 r/min) at room temperature for 4 hours. [b] Conversion was determined by crude ^{1}HNMR; [c] *ee* was determined by chiral HPLC (column AD-H); [d] Reaction temperature: 4 °C, reaction time: 8-12 hours.

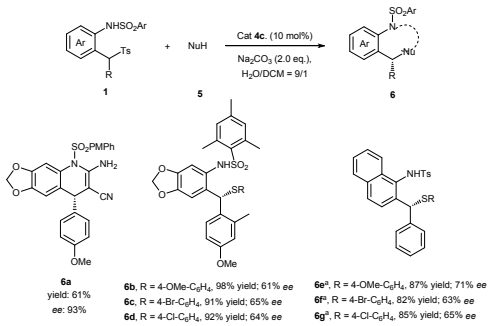
to afford the **3q**–**3t** in excellent yields and high enantioselectivities. Although the reactions were comparatively slower, alkyl-substituted 2-(tosylmethyl)anilines **1w**–**1x** also underwent the 1,4-conjugated additions, producing the corresponding chiral thiols with good yields and enantioselectivities (*ee* = 78–84%). To our delight, different electron-donating substituents on the quinone methide fragment were tolerated as well, and products **3u**–**3v** were obtained with 91–93% *ee*. However, the conjugated additions to substrates which possess ether unsubstituted or electron-withdrawing groups on the phenyl moiety of quinone methide fragment did not occur. Perhaps, it is not easy for these substrates to generate the corresponding N-*o*-QM under the reaction conditions. The absolute configuration of the product **3v** was unambiguously determined to be *R* by X-ray crystallographic analysis(see Supporting Information).

To investigated the amenability of the reaction, we chose malononitrile and different substituted benzyl thiols as nucleophiles, and executed the reactions under the standard conditions (Scheme 4). To our delight, [4+2] cycloaddition product **6a** was obtained with excellent enantioselectivity (93% *ee*) by the use of malononitrile as nucleophile. Moderate enantioselectivities (61-71%) were obtained when using benzyl thiols as nucleophiles, albeit with almost quantitative yields(**6b**-**6h**).



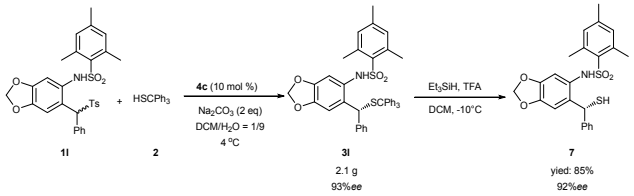
Reaction conditions: **1** (0.1 mmol), tritylthiol (**2**, 2 equiv, 0.2 mmol), and catalyst (10 mol%) with base (2 equiv) in solvent (DCM: water=0.4 mL: 3.6 mL) were stirred (1500 r/min) at 4 °C for 8-12 hours. Yields were for the isolated products after column chromatography. The *ee* values were determined by chiral HPLC (column AD-H). [a] Reaction condition: 50 °C in $CHCl_3/H_2O$ for 72 hours.

Scheme 3. Substrate scope for 1,4-conjugated addition.



Scheme 4. Substrate scope for other nucleophiles. [a] 50 °C in $CHCl_3/H_2O$ for 48 hours.

To evaluate the practical utility of the 1,4-conjugated addition to N-*o*-QMs, the enantiomerically enriched benzylic thiol **3l**, which could be prepared via gram-scale 1,4-conjugated addition of **2** and **1l** under the standard conditions, was transformed to chiral benzyl mercaptan **7** by the selective removal of the trityl group in good yield and without loss of enantiopurity (Scheme 5).



Scheme 5. Synthetic transformations of **3l.**

In conclusion, we developed the first bifunctional organic-base catalyzed 1,4-conjugate addition to *in situ* generated N-*o*-QMs with good to excellent enantioselectivities (up to 94% *ee*) at H_2O/DCM interface. Being complementary in scope to existing chiral phosphoric acids-catalyzed reactions of N-*o*-QMs, this reaction provides a uniquely valuable method for the enantioselective synthesis of *ortho*-amino substituted benzyl mercaptans. Experimental results indicate that water is crucial for achieving the high reactivity and stereoselectivity. This study paves a new route for the asymmetric reactions involving N-*o*-QMs. Future studies are underway to extend this strategy to other nucleophiles in our laboratory.

Acknowledgements

This work is financially supported by the National Natural Science Foundation of China (21871254, 21532006, 21472187) and DICP (DICP ZZBS201602).

Notes and references

1 For reviews, see: (a) T. P. Pathak and M. S. Sigman, *J. Org. Chem.*, 2011, **76**, 9210; (b) N. J. Willis and C. D. Bray, *Chem. Eur. J.*, 2012, **18**, 9160; (c) M. S. Singh, A. Nagaraju, N. Anand and S. Chowdhury, *RSC Adv.*, 2014, **4**, 55924; (d) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu and T. R. Pettus, *Acc. Chem. Res.*, 2014, **47**, 3655; (e) J.-W. Sun and Z.-B Wang, *Synthesis*, 2015, **47**, 3629; (f) L. Caruana, M. Fochi and L. Bernardi, *Molecules*, 2015, **20**, 11733; (g) A. A. Jaworski and K. A. Scheidt, *J. Org. Chem.*, 2016, **81**, 10145.

2 (a) H. Steinhagen and E. J. Corey, *Angew. Chem. Int. Ed.*, 1999, **38**, 1928; (b) K. Wojciechowski, *Eur. J. Org. Chem.*, 2001, 3587; (c) S. L. Crawley and R. L. Funk, *Org. Lett.*, 2003, **5**, 3169; (d) F. Avemaria, S. Vanderheiden and S. Bräse, *Tetrahedron*, 2003, **59**, 6785; (e) P. S. Baran and R. A. Shenvi, *J. Am. Chem. Soc.*, 2006, **128**, 14028; (f) H.-X Wu, F. Xue, X. Xiao and Y. Qin, *J. Am. Chem. Soc.*, 2010, **132**, 14052.

3 (a) E. M. Burgess and L. McCullagh, *J. Am. Chem. Soc.*, 1966, **88**, 1580; (b) Y.-L. Mao and V. Boekelheide, *J. Org. Chem.*, 1980, **45**, 1547; (c) Y. Ito, S. Miyata, M. Nakatsuka and T. Saegusa, *J. Am. Chem. Soc.*, 1981, **103**, 5250; (d) C. W. G. Fishwick, R. C. Storr and P. W. J. Manley, *J. Chem. Soc., Chem. Commun.*, 1984, 1304; (e) I. Hodgetts, S. J. Noyce and R. C. Storr, *Tetrahedron Lett.*, 1984, **25**, 5435; (f) K. Wojciechowski, *Tetrahedron*, 1993, **49**, 7277.

4 (a) G.-X Li, H.-X Liu, G. Lv, Y.-W Wang, Q.-Q Fu and Z. Tang, *Org. Lett.*, 2015, **17**, 4125; (b) H.-H. Liao, A. Chatupheeraphat, C.-C. Hsiao, I. Atodiresei and M. Rueping, *Angew. Chem. Int. Ed.*, 2015, **54**, 15540; (c) A. Chatupheeraphat, H.-H. Liao, S. Mader, M. Sako, H. Sasai, I. Atodiresei and M. Rueping, *Angew. Chem. Int. Ed.*, 2016, **55**, 4803; (d) M. Kretzschmar, T. Hodik and C. Schneider, *Angew. Chem. Int. Ed.*, 2016, **55**, 9788; (e) T. Hodik and C. Schneider, *Chem. Eur. J.*, 2018, DOI: 10.1002/chem.201803886.

5 (a) A. Lee, A. Younai, C. K. Price, J. Izquierdo, R. K. Mishra and K. A. Scheidt, *J. Am. Chem. Soc.*, 2014, **136**, 10589; (b) L. Wang, S. Li, M. Blumel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen and D. Enders, *Angew. Chem. Int. Ed.*, 2016, **55**, 11110.

6 For selected examples, see: (a) D. Wilcke, E. Herdtweck and T. Bach, *Synlett*, 2011, 1235; (b) J. T. Spence and J. H. George, *Org. Lett.*, 2013, **15**, 3891; (c) H. Lv, W.-Q. Jia, L.-H. Sun and S. Ye, *Angew. Chem. Int. Ed.*, 2013, **52**, 8607; (d) O. El-Sepelgy, S. Haseloff, S. K. Alamsetti and C. Schneider, *Angew. Chem. Int. Ed.*, 2014, **53**, 7923; (e) C.-C. Hsiao, H.-H. Liao and M. Rueping, *Angew. Chem. Int. Ed.*, 2014, **53**, 13258; (f) A. Adili, Z.-L. Tao, D.-F. Chen and Z.-Y. Han, *Org. Biomol. Chem.*, 2015, **13**, 2247; (g) L. Caruana, M. Mondatori, V. Corti, S. Morales, A. Mazzanti, M. Fochi and L. Bernardi, *Chem. Eur. J.*, 2015, **21**, 6037; (h) H.-P Hu, Y.-B Liu, J. Guo, L. Lin, Y. Xu, X.-H Liu and X.-M Feng, *Chem. Commun.*, 2015, **51**, 3835; (i) Y. Huang and T. Hayashi, *J. Am. Chem. Soc.*, 2015, **137**, 7556; (j) S. Saha and C. Schneider, *Chem. Eur. J.*, 2015, **21**, 2348; (k) Z.-B Wang, F. Ai, Z. Wang, W.-X Zhao, G.-Y Zhu, Z.-Y Lin and J.-W Sun, *J. Am. Chem. Soc.*, 2015, **137**, 383; (l) J.-J. Zhao, Y.-C. Zhang, M.-M. Xu, M. Tang and F. Shi, *J. Org. Chem.*, 2015, **80**, 10016; (m) S. K. Alamsetti, M. Spanka and C. Schneider, *Angew. Chem. Int. Ed.*, 2016, **55**, 2392; (n) Z.-W. Lai and J.-W. Sun, *Synlett*, 2016, **27**, 555; (o) Q. Wu, C. Ma, X.-H. Du, Y. Chen, T.-Z. Huang, X.-Q. Shi, S.-J. Tu and P.-J. Cai, *Tetrahedron Asymmetry*, 2016, **27**, 307; (p) X.-Y. Yu, J.-R. Chen, Q. Wei, H.-G. Cheng, Z.-C. Liu and W.-J. Xiao, *Chem. Eur. J.*, 2016, **22**, 6774; (q) Y.-C. Zhang, Q.-N. Zhu, X. Yang, L.-J. Zhou and F. Shi, *J. Org. Chem.*, 2016, **81**, 1681; (r) Z.-B Wang and J.-W Sun, *Org. Lett.*, 2017, **19**, 2334; (s) Z. Wang, T.-L Wang, W.-J Yao and Y.-X Lu, *Org. Lett.*, 2017, **19**, 4126; (t) C. Gharui, D. Behera and S. C. Pan, *Adv. Synth. Catal.*, 2018, DOI: 10.1002/adsc.201801015; (u) S.-Q Jia, Z.-L Chen, N. Zhang, Y. Tan, Y.-D Liu, J. Deng and H.-L Yan, *J. Am. Chem. Soc.*, 2018, **140**, 7056; (v) H. Lam, Z. Qureshi, M. Wegmann and M. Lautens, *Angew. Chem. Int. Ed.*, 2018, DOI: 10.1002/anie.201810760; (w) Y.-B. Shen, S.-S. Li, L. Wang, X.-D. An, Q. Liu, X. Liu and J. Xiao, *Org. Lett.*, 2018, **20**, 6069; (x) C.-S. Wang, Y.-C. Cheng, J. Zhou, G.-J. Mei, S.-L. Wang and F. Shi, *J. Org. Chem.,* 2018, DOI: 10.1021/acs.joc.8b02186; (y) D. Yadagiri, M. Chaitanya, A. C. S. Reddy and P. Anbarasan, *Org. Lett.*, 2018, **20**, 3762.

7 (a) W.-G. Guo, B. Wu, X. Zhou, P. Chen, X. Wang, Y.-G. Zhou, Y. Liu and C. Li, *Angew. Chem. Int. Ed.*, 2015, **54**, 4522; (b) B. Wu, X. Gao, Z. Yan, W.-X. Huang and Y.-G. Zhou, *Tetrahedron Lett.*, 2015, 56, 4334; (c) J. Zhou, M.-L. Wang, X. Gao, G.-F. Jiang and Y.-G. Zhou, *Chem. Commun.*, 2017, **53**, 3531; (d) P. Chen, K. Wang, W.-G. Guo, X.-H. Liu, Y. Liu and C. Li, *Angew. Chem. Int. Ed.*, 2017, **56**, 3689; (e) B. Wu, Z. Yu, X. Gao, Y. Lan and Y.-G. Zhou, *Angew. Chem. Int. Ed.*, 2017, **56**, 4006.