



Cite this: *RSC Adv.*, 2019, 9, 24212

Organocatalytic enantioselective conjugate addition of 2-naphthols to *ortho*-hydroxyphenyl substituted *para*-quinone methides: access to unsymmetrical triarylmethanes†

Yuyu Cheng,^a Zhiqiang Fang,^a Yanwen Jia,^a Zhongyue Lu,^a Wenjun Li^{ID}*^b and Pengfei Li^{ID}*^a

Received 25th June 2019
Accepted 30th July 2019

DOI: 10.1039/c9ra04768a

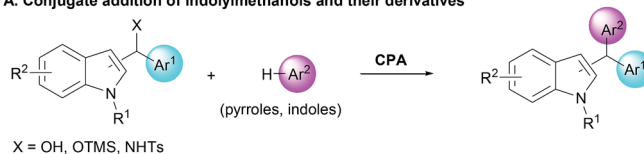
rsc.li/rsc-advances

The enantioselective conjugate addition of 2-naphthols to *ortho*-hydroxyphenyl substituted *para*-quinone methides has been achieved with the aid of a chiral phosphoric acid. Importantly, the reaction took place with excellent chemo- and regioselectivities. In addition, the protocol features a low catalyst loading, mild reaction conditions, and enables the formation of unsymmetrical triarylmethanes in good to high yields with generally high enantioselectivities.

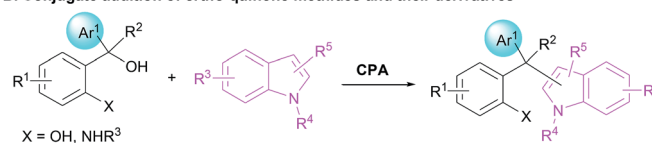
Unsymmetrical triarylmethanes, especially enantiomerically enriched triarylmethanes have been regarded as unique structural frameworks due to their remarkable significance in materials science, natural products, and medicinal chemistry.¹ Accordingly, much effort has been devoted to developing catalytic synthetic methodologies for accessing these motifs,² especially in an enantioselective fashion.³ However, besides limited examples of transition metal-mediated construction of chiral triarylmethanes,⁴ there are only a few organocatalytic enantioselective synthetic strategies,^{5–9} of which most processes focused on transformations of indolymethanols (Scheme 1A),¹⁰ *in situ* generated *ortho*-quinone methides (*o*-QMs, Scheme 1B),¹¹ and *para*-quinone methides (*p*-QMs, Scheme 1C).¹² On the other hand, triarylmethanes containing the 2-naphthol moiety is a family of biologically active compounds,¹³ but reports on catalytic enantioselective construction of triarylmethanes bearing the 2-naphthol motif are very limited.¹⁴ In 2015, Schneider *et al.* realized the enantioselective construction of chiral triarylmethanes *via* a chiral phosphoric acid (CPA) catalyzed 1,4-addition of 2-naphthol to *o*-QMs generated from *ortho*-hydroxy benzhydrols (Scheme 2A).¹⁵ Similarly, in the presence of squaramide combined with excess base as acid scavenger, Xu *et al.* established an enantioselective 1,4-addition of 2-naphthols to *in situ*

generated *o*-QMs from 2-[phenyl(tosyl)methyl]phenols (Scheme 2B).¹⁶ Independently, Sun *et al.* developed a CPA catalyzed 1,6-addition between 2-naphthols and *p*-QMs *in situ* generated from *para*-hydroxy benzhydrols to construct the optically active triarylmethanes bearing 2-naphthol motif (Scheme 2C).¹⁷ In spite of these elegant approaches, the organocatalytic enantioselective construction of chiral

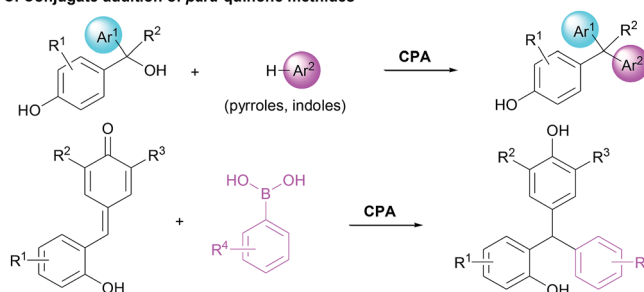
A. Conjugate addition of indolymethanols and their derivatives



B. Conjugate addition of *ortho*-quinone methides and their derivatives



C. Conjugate addition of *para*-quinone methides



Scheme 1 Organocatalytic enantioselective construction of chiral triarylmethanes.

^aDepartment of Chemistry and Shenzhen Key Laboratory of Marine Archaea Geo-Omics, Southern University of Science and Technology, Shenzhen, Guangdong, 518055, China. E-mail: lipf@sustech.edu.cn; flyli1980@gmail.com

^bDepartment of Medicinal Chemistry, School of Pharmacy, Qingdao University, Qingdao, Shandong, 266021, China. E-mail: liwj@qdu.edu.cn

† Electronic supplementary information (ESI) available. CCDC 1908826. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ra04768a





Scheme 2 Limited examples and our work for chiral triarylmethanes bearing naphthol motif.

triarylmethanes still represents a challenging task. Therefore, a direct and facile synthetic strategy for this important structural motif would be highly valuable. On the basis of asymmetric additions to *ortho*-hydroxyphenyl substituted *para*-quinone methides^{18,19} and as a continuation of our efforts in asymmetric reactions of *p*-QMs,²⁰ we report herein a direct and efficient CPA-mediated asymmetric conjugate addition of 2-naphthols to *p*-QMs (Scheme 2D).

Initial investigations were carried out using a series of CPAs for the model reaction of 4-(2-hydroxybenzylidene)-2,6-di-*tert*-butylcyclohexa-2,5-dienone **1a** with 2-naphthol **2a** in dichloromethane at room temperature for 24 h. As shown in Table 1, with a catalyst loading of 10 mol%, CPA-1 mediated reaction proceeded smoothly to afford the triarylmethane **3aa** in 81% yield with 5% ee (entry 1). An essential enhancement was achieved when the reaction was catalyzed by CPA-3, furnishing **3aa** in 90% yield with 91% ee (entry 3). To our delight, further modification of catalyst structure led to the formation of **3aa** in 95% yield with 94% ee (entry 5). With CPA-5 as the suitable catalyst, reaction media was screened (entries 7–11). Solvent was found to have a great influence on the reaction efficiency and stereoselectivity, and dichloromethane was identified as the best reaction media. Notably, decreasing the catalyst loading from 10 mol% to 1 mol%, the desired triarylmethane **3aa** was still obtained in 95% yield with 94% ee when the reaction was carried out in CH₂Cl₂ of 1.0 mL at room temperature for 24 h (entry 12). Shorting reaction time

from 24 h to 12 h, the yield of triarylmethane **3aa** decreased from 95% to 83% without compromising the enantioselectivity (entry 13).

Having optimized the catalyst structure and reaction conditions, we then explored the substrate scope of this organocatalytic enantioselective transformation. Firstly, the generality of 2-naphthols component was evaluated (Table 2). Pleasingly, a wide range of 2-naphthols **2a–h** reacted smoothly with *p*-QM **1a** to afford the corresponding enantioenriched triarylmethanes **3aa–ah** in high yields (70–95%) with excellent enantioselectivities (93–96%). Various different substituents, including electron-withdrawing (Br, CN, CO₂Me, CO₂Et) and electron-donating groups (MeO, EtO) at different positions of the aromatic ring of the 2-naphthols component were tolerated with only slight effects on the reaction efficiency and asymmetric induction. No significant electronic effects were observed for the substituents on the aromatic moiety. Confirmed by the impressive results, the organocatalytic enantioselective conjugate addition of *p*-QMs has been successfully extended to a variety of 2-naphthols and provided an efficient and facile access to optically active triarylmethanes.

Table 1 Optimization of the reaction conditions^a

CPA-1 R¹ = SiPh₃, R² = OH
 CPA-2 R¹ = 3,5-(CF₃)₂C₆H₃, R² = OH
 CPA-3 R¹ = 2,4,6-*i*-Pr₃C₆H₂, R² = OH
 CPA-4 R¹ = 2,4,6-*i*-Pr₃C₆H₂, R² = NH₂
 CPA-5
 CPA-6

Entry	Catalyst	Solvent	Yield ^b (%)	ee ^c (%)
1	CPA-1	CH ₂ Cl ₂	3aa , 81	5
2	CPA-2	CH ₂ Cl ₂	3aa , 77	28
3	CPA-3	CH ₂ Cl ₂	3aa , 90	91
4	CPA-4	CH ₂ Cl ₂	3aa , 56	3
5	CPA-5	CH ₂ Cl ₂	3aa , 95	94
6	CPA-6	CH ₂ Cl ₂	3aa , 91	35
7	CPA-5	CHCl ₃	3aa , 90	88
8	CPA-5	EtOAc	3aa , 70	69
9	CPA-5	Toluene	3aa , 84	88
10	CPA-5	THF	3aa , 59	10
11	CPA-5	MeCN	3aa , 83	94
12 ^d	CPA-5	CH ₂ Cl ₂	3aa , 95	94
13 ^e	CPA-5	CH ₂ Cl ₂	3aa , 83	93

^a Unless noted, **1a** (0.20 mmol), **2a** (0.24 mmol), catalyst (10 mol%) in the solvent (2.0 mL) at room temperature for 24 h. ^b Isolated yield. ^c Determined by HPLC analysis using a chiral stationary phase. ^d CPA-5 (1 mol%), CH₂Cl₂ (1.0 mL). ^e CPA-5 (1 mol%), CH₂Cl₂ (1.0 mL), 12 h.

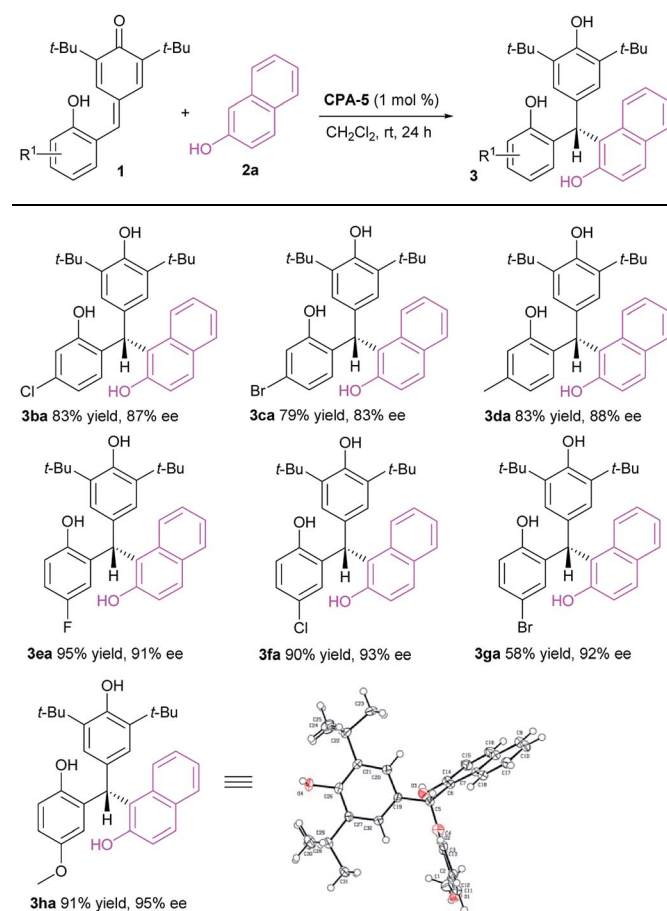


Table 2 Scope of 2-naphthols^a

^a Unless noted, **1a** (0.20 mmol), **2** (0.24 mmol), **CPA-5** (1 mol%) in CH_2Cl_2 (1.0 mL) at room temperature for 24 h. Products **3aa–ah** were obtained in isolated yield and ee values were determined by chiral HPLC analysis.

With these encouraging data in hand, we then investigated the substrate scope of *p*-QMs **1** in the **CPA-5** catalyzed conjugate addition of 2-naphthol **2a** (Table 3). It was found that this strategy was applicable to various *p*-QMs **1b–h** bearing different types of substituents to furnish the corresponding optically active triarylmethanes **3ba–ha** in generally high yields with enantioselectivities. Both electron-withdrawing (F, Cl, Br) and electron-donating groups (Me, MeO) could be introduced into different positions of the aromatic ring of *p*-QMs with a little effect on the reaction efficiency and stereoselectivity. The absolute configuration of **3ha** was unambiguously confirmed by X-ray crystallography.²¹ In all, a broad scope of *p*-QMs has been successfully involved in the organocatalytic conjugate addition of 2-naphthols for the chemo-, regio- and enantioselective construction of chiral triarylmethanes.

To demonstrate the robustness and utility of this synthetic strategy, the scale up of the reaction were carried out (Scheme 3A). The **CPA-5** mediated conjugate reaction of *p*-QM **1a** at 1.0 mmol proceeded well under the standard conditions to generate **3aa** in 82% yield with 93% ee. When

Table 3 Scope of *para*-quinone methides.^a

^a Unless noted, **1** (0.20 mmol), **2a** (0.24 mmol), **CPA-5** (1 mol%) in CH_2Cl_2 (1.0 mL) at room temperature for 24 h. Products **3ba–ha** were obtained in isolated yield and ee values were determined by chiral HPLC analysis.

the reaction was scaled up to 4.5 mmol, the product **3aa** was obtained in 84% yield with 95% ee, which indicated this protocol has the potential for a large-scale production. The reaction of 1-naphthol furnished racemic products in 76% yield under standard conditions (Scheme 3B). The transformation of **3aa** was also investigated. Treated with $\text{PhI}(\text{OAc})_2$, product **4aa** was isolated in 31% yield with 96% ee (Scheme 3C). Then employing **3aa** as ligand in catalytic asymmetric aldol reaction was surveyed. The initial result indicated that the $\text{Ti}(\text{Oi-Pr})_4/\mathbf{3aa}$ system mediated the asymmetric aldol reaction of ZnEt_2 to 2-naphthaldehyde effectively to generate adduct in 59% yield, although the enantioselectivity was low (Scheme 3D).

To light some insight into the reaction mechanism, control experiments were carried out (Scheme 4A). When the hydroxyl group of *p*-QM **1a** was shielded by *t*-butyldimethylsilyl (TBS) group (*p*-QM **5a**), the reaction was found to proceed quite slowly and the corresponding product **6aa** was





Scheme 3 Further investigations.

obtained in 11% yield after 72 h. The yield of **6aa** could be improved to 86% when the catalyst loading was increased to 10 mol%, however, the enantioselectivity remained poor (16% ee). When the hydroxyl group was removed, *p*-QM **5b** could also react smoothly with **2a** to generate the adduct **6ba** in 70% yield with 29% ee under the standard conditions. Consequently, it is not too hard to make the case that the free hydroxyl group of *p*-QM **1a** played a key role in terms of the reaction efficiency and stereoselectivity. Based on these results and considering reported plausible transition state,²² a possible reaction mechanism was suggested. As shown in Scheme 4B, *p*-QM **1a** was protonated and activated in the presence of CPA-5. Then, both *p*-QM **1a** and 2-naphthol **2a** were arranged by CPA-5 via hydrogen bond to generate the desired product **3aa** in high yield with high enantioselectivity. Particularly, Li *et al.* reported that the isomerization energy of **1a** and **1'a** was 6.7 kcal mol⁻¹, indicating that the transformation of *p*-QM **1a** to *o*-QM **1'a** was not difficult.^{19g} As a result, we could not exclude the possibility that 2-hydroxyphenyl *p*-QM **1a** isomerized initially to 6-(3,5-di-*tert*-butyl-4-hydroxybenzylidene) cyclohexa-2,4-dienone **1'a** and then the CPA-5 activated and oriented both *o*-QM **1'a** and 2-naphthol **2a** to afford the desired adduct **3aa** with high efficiency and enantioselectivity (Scheme 4C).

In conclusion, we have established the enantioselective construction of optically active triarylmethanes bearing naphthol motif via a chiral phosphoric acid mediated conjugate addition of 2-naphthols to 2-hydroxyphenyl *p*-QMs. A series of enantioenriched (83–96%) triarylmethanes were obtained in 58–95% yields. Moreover, transformation



Scheme 4 Control experiments and the proposed reaction mechanism.

and application of triarylmethanes were investigated. Further modification of substrates to generate practical chiral triarylmethanes are undergoing in our lab.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We acknowledge the financial support from National Natural Science Foundation of China (21871128), Shenzhen Innovation of Science and Technology Commission (JCYJ20170817110526264, ZDSYS201802081843490).



Notes and references

- 1 For reviews, see: (a) D. F. A. Duxbury, *Chem. Rev.*, 1993, **93**, 381; (b) M. S. Shchepinov and V. A. Korshun, *Chem. Soc. Rev.*, 2003, **32**, 170; (c) V. Nair, S. Thomas, S. C. Mathew and K. G. Abhilash, *Tetrahedron*, 2006, **62**, 6731; (d) H. N. Kim, M. H. Lee, H. J. Kim, J. S. Kim and J. Yoon, *Chem. Soc. Rev.*, 2008, **37**, 1465; (e) M. Beija, C. A. M. Afonso and J. M. G. Martinho, *Chem. Soc. Rev.*, 2009, **38**, 2410; (f) M. Shiri, M. A. Zolfigol, H. G. Kruger and Z. Tanbakouchian, *Chem. Rev.*, 2010, **110**, 2250.
- 2 For reviews, see: (a) S. Mondal and G. Panda, *RSC Adv.*, 2014, **4**, 28317; (b) M. Nambo and C. M. Crudden, *ACS Catal.*, 2015, **5**, 4734.
- 3 For a comprehensive review, see: S. Mondal, D. Roy and G. Panda, *ChemCatChem*, 2018, **10**, 1941.
- 4 (a) B.-F. Shi, N. Maugel, Y.-H. Zhang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2008, **47**, 4882; (b) L.-L. Cao, Z.-S. Ye, G.-F. Jiang and Y.-G. Zhou, *Adv. Synth. Catal.*, 2011, **353**, 3352; (c) Y. Lou, P. Cao, T. Jia, Y. Zhang, M. Wang and J. Liao, *Angew. Chem., Int. Ed.*, 2015, **54**, 12134; (d) Y. Huang and T. Hayashi, *J. Am. Chem. Soc.*, 2015, **137**, 7556; (e) J. Zheng, L. Lin, L. Dai, X. Yuan, X. Liu and X. Feng, *Chem.–Eur. J.*, 2016, **22**, 18254; (f) J. H. Kim, S. Grešies, M. Bouladakis-Arapinis, C. Daniliuc and F. Glorius, *ACS Catal.*, 2016, **6**, 7652.
- 5 F.-L. Sun, M. Zeng, Q. Gu and S.-L. You, *Chem.–Eur. J.*, 2009, **15**, 8709.
- 6 S. Shirakawa, K. Koga, T. Tokuda, K. Yamamoto and K. Maruoka, *Angew. Chem., Int. Ed.*, 2014, **53**, 6220.
- 7 S. Lu, X. Song, S. B. Poh, H. Yang, M. W. Wong and Y. Zhao, *Chem.–Eur. J.*, 2017, **23**, 2275.
- 8 Y. Zhang, S.-X. Zhang, L.-N. Fu and Q.-X. Guo, *ChemCatChem*, 2017, **9**, 3107.
- 9 A. B. Gade, P. N. Bagle, P. S. Shinde, V. Bhardwaj, S. Banerjee, A. Chande and N. T. Patil, *Angew. Chem., Int. Ed.*, 2018, **57**, 5735.
- 10 (a) F.-L. Sun, X.-J. Zheng, Q. Gu, Q.-L. He and S.-L. You, *Eur. J. Org. Chem.*, 2010, **47**; (b) M.-H. Zhuo, Y.-J. Jiang, Y.-S. Fan, Y. Gao, S. Liu and S. Zhang, *Org. Lett.*, 2014, **16**, 1096; (c) S. Qi, C.-Y. Liu, J.-Y. Ding and F.-S. Han, *Chem. Commun.*, 2014, **50**, 8605; (d) Y.-X. Gong, Q. Wu, H.-H. Zhang, Q.-N. Zhu and F. Shi, *Org. Biomol. Chem.*, 2015, **13**, 7993; (e) M. H. Zhuo, G.-F. Liu, S.-L. Song, D. An, J. Gao, L. Zheng and S. Zhang, *Adv. Synth. Catal.*, 2016, **358**, 808; (f) C. Yue, F. Na, X. Fang, Y. Cao and J. C. Antilla, *Angew. Chem., Int. Ed.*, 2018, **57**, 11004.
- 11 (a) W. Zhao, Z. Wang, B. Chu and J. Sun, *Angew. Chem., Int. Ed.*, 2015, **54**, 1910; (b) H.-H. Liao, A. Chatupheeraphat, C.-C. Hsiao, I. Atodiressei and M. Rueping, *Angew. Chem., Int. Ed.*, 2015, **54**, 15540; (c) 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.
- 12 (a) Z. Wang, Y. F. Wong and J. Sun, *Angew. Chem., Int. Ed.*, 2015, **54**, 13711; (b) G.-B. Huang, W.-H. Huang, J. Guo, D.-L. Xu, X.-C. Qu, P.-H. Zhai, X.-H. Zheng, J. Weng and G. Lu, *Adv. Synth. Catal.*, 2019, **361**, 1241; (c) J.-R. Wang, X.-L. Jiang, Q.-Q. Hang, S. Zhang, G.-J. Mei and F. Shi, *J. Org. Chem.*, 2019, **84**, 7829.
- 13 S. K. Das, G. Panda, V. Chaturvedi, Y. S. Manju, A. K. Gaikwad and S. Sinha, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 5586.
- 14 For catalytic non-enantioselective construction of triarylmethanes bearing 2-naphthol unit, see: (a) S. Yaragorla, P. L. Saini, P. V. Babu, A. I. Almansour and N. Arumugam, *Tetrahedron Lett.*, 2016, **57**, 2351; (b) R. Dada, G. Singh, A. Pareek, S. Kausar and S. Yaragorla, *Tetrahedron Lett.*, 2016, **57**, 3739; (c) P. Arde and R. V. Anand, *RSC Adv.*, 2016, **6**, 77111; (d) T. Zhou, S. Li, B. Huang, C. Li, Y. Zhao, J. Chen, A. Chen, Y. Xiao, L. Liu and J. Zhang, *Org. Biomol. Chem.*, 2017, **15**, 4941; (e) G.-P. Yang, D. Dilixiati, T. Yang, D. Liu, B. Yu and C.-W. Hu, *Appl. Organomet. Chem.*, 2018, **32**, e4450; (f) G. Singh, P. Goswami and R. V. Anand, *Org. Biomol. Chem.*, 2018, **16**, 384; (g) G.-J. Mei, S.-L. Xu, W.-Q. Zheng, C.-Y. Bian and F. Shi, *J. Org. Chem.*, 2018, **83**, 1414.
- 15 S. Saha, S. K. Alamsetti and C. Schneider, *Chem. Commun.*, 2015, **51**, 1461.
- 16 Y. Wang, C. Zhang, H. Wang, Y. Jiang, X. Du and D. Xu, *Adv. Synth. Catal.*, 2017, **359**, 791.
- 17 Y. F. Wong, Z. Wang and J. Sun, *Org. Biomol. Chem.*, 2016, **14**, 5751.
- 18 For reviews on asymmetric reactions of *p*-QMs, see: (a) A. Parra and M. Tortosa, *ChemCatChem*, 2015, **7**, 1524; (b) W. Li, X. Xu, P. Zhang and P. Li, *Chem.–Asian J.*, 2018, **13**, 2350.
- 19 For examples, see: (a) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 12104; (b) S. Liu, X.-C. Lan, K. Chen, W.-J. Hao, G. Li, S.-J. Tu and B. Jiang, *Org. Lett.*, 2017, **19**, 3831; (c) Z.-P. Zhang, K.-X. Xie, C. Yang, M. Li and X. Li, *J. Org. Chem.*, 2018, **83**, 364; (d) G.-J. Mei, S.-L. Xu, W.-Q. Zheng, C.-Y. Bian and F. Shi, *J. Org. Chem.*, 2018, **83**, 1414; (e) Y. Zhi, K. Zhao, C. von Essen, K. Rissanen and D. Enders, *Org. Chem. Front.*, 2018, **5**, 1348; (f) J. Yan, M. Chen, H. H.-Y. Sung, I. D. Williams and J. Sun, *Chem.–Asian J.*, 2018, **13**, 2440; (g) Z.-P. Zhang, K.-X. Xie, C. Yang, M. Li and X. Li, *J. Org. Chem.*, 2018, **83**, 364; (h) Z.-P. Zhang, L. Chen, X. Li and J.-P. Cheng, *J. Org. Chem.*, 2018, **83**, 2714; (i) L. Liu, Z. Yuan, R. Pan, Y. Zeng, A. Lin, H. Yao and Y. Huang, *Org. Chem. Front.*, 2018, **5**, 623; (j) F. Jiang, F.-R. Yuan, L.-W. Jin, G.-J. Mei and F. Shi, *ACS Catal.*, 2018, **8**, 10234; (k) G.-H. Yang, Q. Zhao, Z.-P. Zhang, H.-L. Zheng, L. Chen and X. Li, *J. Org. Chem.*, 2019, **84**, 7883; (l) Z. Li, W. Wang, H. Jian, W. Li, B. Dai and L. He, *Chin. Chem. Lett.*, 2019, **30**, 386; (m) M. Sun, C. Ma, S.-J. Zhou, S.-F. Lou, J. Xiao, Y. Jiao and F. Shi, *Angew. Chem., Int. Ed.*, 2019, **58**, 8703.
- 20 (a) L. Zhang, X. Zhou, P. Li, Z. Liu, Y. Liu, Y. Sun and W. Li, *RSC Adv.*, 2017, **7**, 39216; (b) L. Zhang, Y. Liu, K. Liu, Z. Liu, N. He and W. Li, *Org. Biomol. Chem.*, 2017, **15**, 8743; (c) W. Li, H. Yuan, Z. Liu, Z. Zhang, Y. Cheng and P. Li, *Adv. Synth. Catal.*, 2018, **360**, 2460; (d) W. Li, X. Xu, Y. Liu, H. Gao,



- Y. Cheng and P. Li, *Org. Lett.*, 2018, **20**, 1142; (e) L. Zhang, H. Yuan, W. Lin, Y. Cheng, P. Li and W. Li, *Org. Lett.*, 2018, **20**, 4970; (f) P. Zhang, Q. Huang, Y. Cheng, R. Li, P. Li and W. Li, *Org. Lett.*, 2019, **21**, 503.
- 21 CCDC 1908826 (**3ha**).
- 22 For reviews, see: (a) E. P. Ávila and G. W. Amarante, *ChemCatChem*, 2012, **4**, 1713; (b) M. Mahlau and B. List, *Angew. Chem., Int. Ed.*, 2013, **52**, 518; for recent reports, see: (c) H. G. O. Alvim, D. L. J. Pinheiro, V. H. Carvalho-Silva, M. Fioramonte, F. C. Gozzo, W. A. da Silva, G. W. Amarante and B. A. D. Neto, *J. Org. Chem.*, 2018, **83**, 12143; (d) J. Zhang, P. Yu, S.-Y. Li, H. Sun, S.-H. Xiang, J. Wang, K. N. Houk and B. Tan, *Science*, 2018, **361**, eaas8707.

