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Palladium-catalyzed diastereoselective cross-coupling of two aryl halides *via* C–H activation: synthesis of chiral eight-membered nitrogen heterocycles†

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A method for the synthesis of enantiopure eight-membered nitrogen heterocycles has been developed through diastereoselective cross-coupling of 2-iodobiphenyls with 2-bromobenzylamines. The products represent a novel type of chiral scaffold, which feature easy modification and high configurative stability and have the potential to be applied in asymmetric synthesis. Palladacycles that were formed *via* the C–H activation of 2-iodobiphenyls should act as the intermediates. The reaction provides a new strategy for the synthesis of medium-sized ring compounds.

Chirality is a fundamental property of molecules, and it is of prime significance in chemistry, medicine, and biology. Chirality can be factorized into three elements, namely stereogenic centers, axes of chirality, and planes of chirality.¹ Central chirality has been the topic of extensive research in asymmetric synthesis, and axial chirality has gained considerable interest and made noticeable progress recently.² As a comparison, planar chirality is underexploited and its studies are primarily limited to ferrocenes.³

Tetraphenylene (tetrabenzo[*a,c,e,g*]cyclooctatetraene) possesses a very intriguing saddle-shaped structure. Owing to their unique geometry, tetraphenylene and its derivatives are not only of great theoretical interest, but also can find numerous applications in materials science and supramolecular chemistry.⁴ More importantly, although tetraphenylene is achiral, the introduction of substituents may create chirality. The privileged planar chiral skeleton of substituted tetraphenylenes provides great opportunities for designing novel ligands for asymmetric synthesis.⁵ However, the construction of the chiral tetraphenylene core is very challenging, and very rare reactions are available, which restricts

the applications of tetraphenylenes in asymmetric synthesis.⁶ All the chiral tetraphenylene derivatives for use in asymmetric catalysis and materials science were obtained by resolution. Furthermore, the current research on the application of chiral tetraphenylenes is limited to the derivatization of the benzene rings of tetraphenylenes. We envisioned that replacing one of the phenyl groups of tetraphenylene with an N-containing functional group would give a new chiral scaffold (Fig. 1a). The nitrogen atom could act as a coordinating site. Moreover, the functional group would allow for the ready modification of the scaffold, which is essential to search for optimal chiral ligands in asymmetric synthesis.

To obtain the nitrogen-incorporated analogues of tetraphenylene, we first needed to develop a protocol for the construction of eight-membered nitrogen heterocycles. Medium-ring structures (8–11-membered rings), in particular N-heterocycles, exist in a variety of bioactive natural products,⁷ and are desirable scaffolds in drug discovery.⁸ However, the construction of medium-sized rings remains a challenging goal in organic synthesis due to the

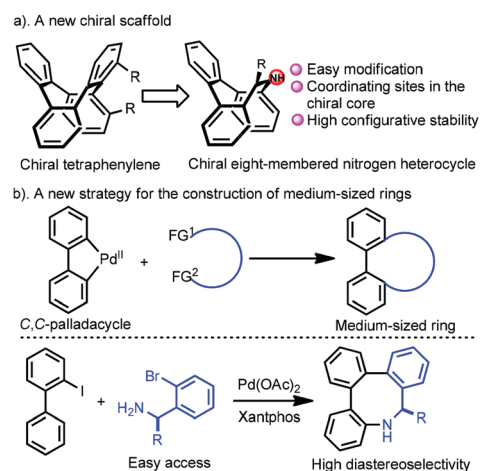


Fig. 1 Synthesis of chiral eight-membered nitrogen heterocycles through diastereoselective cross-coupling of palladacycles.

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unfavorable entropy effect and transannular interactions.⁹ Although diverse methods have been developed, including intramolecular cyclization, ring-expansion, and cycloaddition,¹⁰ it is still highly desirable to develop facile and efficient strategies to gain access to these intriguing structures.

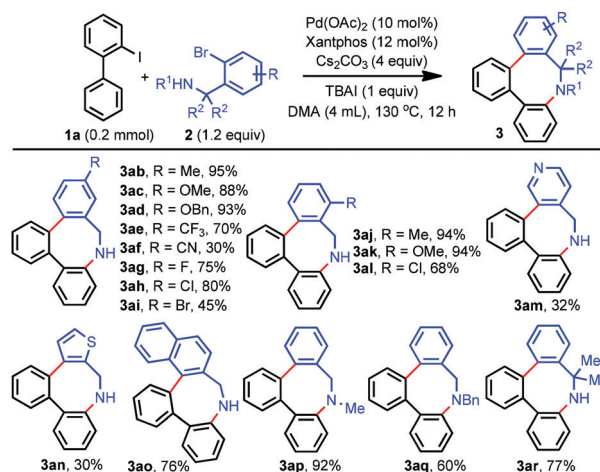
C,C-Palladacycles have a cyclic structure containing two C–Pd bonds (Fig. 1b). These two C–Pd bonds can be functionalized to develop organic reactions, in particular, those for the synthesis of cyclic molecules.¹¹ We envisioned that the unique complex could be utilized to develop new strategies for the construction of medium-ring structures. It should be mentioned that C,C-palladacycles can be obtained by the intramolecular C–H activation of aryl halides, and therefore the reactions have advantages such as high atom- and step-economy.¹²

Herein, we report a facile method for the construction of eight-membered N-heterocycles *via* the coupling of C,C-palladacycles with 2-bromobenzylamines. The reaction proceeded diastereoselectively to afford enantiopure products, which represent a novel type of chiral scaffold.

We commenced the studies by investigating the Pd-catalyzed coupling reaction of model substrates 2-iodobiphenyl **1a** and 2-bromobenzylamine **2a**. The major challenge to form the desired eight-membered ring is to overcome the potential double N-arylation of the benzylamine, which would form a carbazole product.¹³ The carbazole-forming reaction involves a five-membered ring closing process, so it is much more favorable than the formation of the eight-membered heterocycle. Gratefully, after an extensive survey of the reaction conditions, product **3aa** was obtained in 91% yield under the conditions as shown in eqn (1) (for the detailed condition survey, see the ESI†).



Having developed an efficient protocol for the construction of eight-membered rings, we then investigated its substrate scope. The performance of substituted 2-bromobenzylamines was first probed. As shown in Scheme 1, a range of 2-bromobenzylamines bearing a substituent at the 5-positions underwent the coupling reaction to afford the corresponding nitrogen heterocycles (**3ab–3af**). While electron-donating groups gave high yields, the presence of electron-withdrawing groups resulted in lower yields. In the low-yielding reactions, carbazoles were formed as the major side products by double N-arylation of the benzylamine. Halo groups, including F, Cl and Br, were well tolerated (**3ag–3ai**). An *ortho*-substituent had little influence on the yields (**3aj–3al**). Notably, the reaction was also compatible with heteroarenes, including pyridine and thiophene, albeit in a low yield, and the analogue derived from naphthalene was also suitable (**3am–3ao**). The reactions of secondary amines were also investigated. Methyl- and benzyl-substituted benzylamines coupled with **1a** effectively (**3ap** and **3aq**). Moreover, the reaction was also

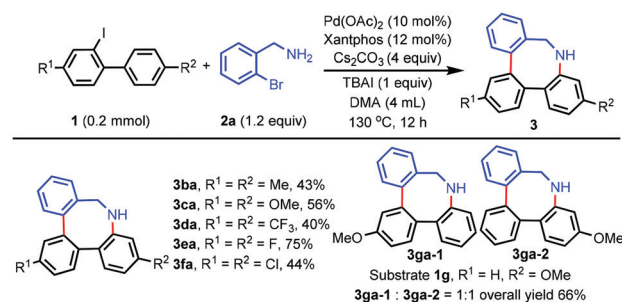


Scheme 1 Substrate scope with respect to 2-bromobenzylamines.

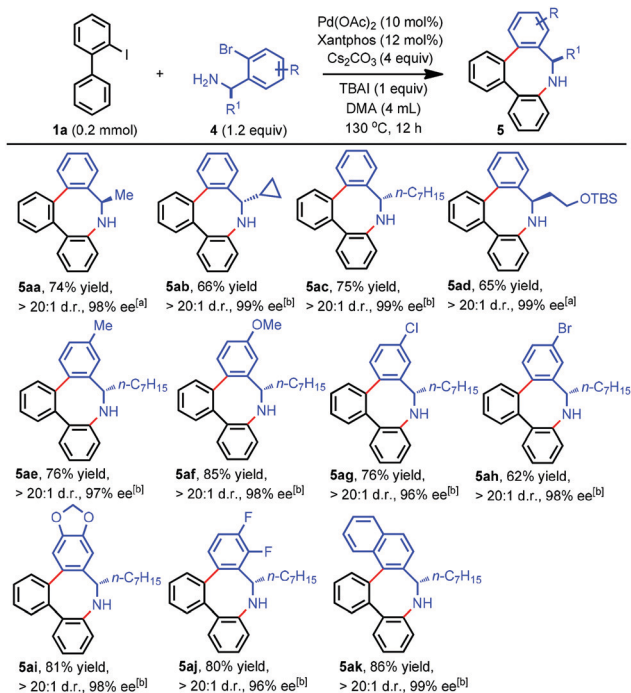
compatible with the benzylamine bearing two benzylic methyl groups (**3ar**).

The substrate scope with respect to 2-iodobiphenyls was also probed (Scheme 2). The reactions of symmetrically substituted 2-iodobiphenyls were first examined. A variety of substrates bearing two electron-donating, electron-withdrawing, or halo groups, could react with **2a** to afford the corresponding eight-membered products (**3ba–3fa**). However, the yields were lower than those obtained in the reactions of 2-iodobiphenyl. Lower yields were also caused by the side carbazole-forming reactions. For a substrate bearing one substituent, the reaction produced two isomeric products in a ratio of 1 to 1 (**3ga–1** and **3ga–2**).

It is noted that the eight-membered cyclic products are chiral. For example, **3aa** was separable by chiral HPLC. The eight-membered ring represents a novel chiral skeleton, which has great application potential in asymmetric synthesis. Therefore, we set out to study the synthesis of the enantiopure products. Notably, enantiopure 2-bromobenzylamine derivatives bearing a benzylic substituent are commercially available or can be readily synthesized *via* diastereoselective Grignard addition reaction of chiral *N*-sulfinyl imines.¹⁴ We envisioned that the enantiopure products could be obtained by using chiral 2-bromobenzylamine derivatives if the reactions were diastereoselective. We first investigated the reaction of methyl-substituted 2-bromobenzylamine (Scheme 3). Gratefully, the chirality of the benzylamine was completely transferred to the



Scheme 2 Substrate scope with respect to 2-iodobiphenyls.

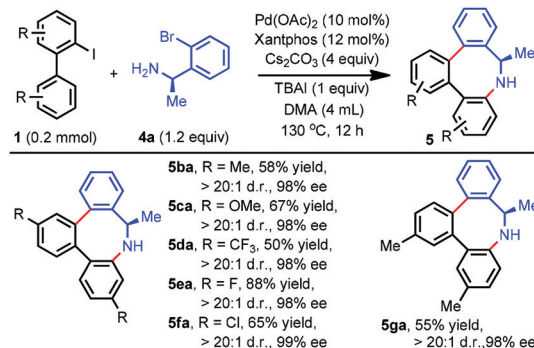


Scheme 3 Substrate scope with respect to 2-bromobenzylamines in the synthesis of enantiopure eight-membered cyclic products. [a] (*R*)-2-bromoaniline derivatives were used. [b] (*S*)-2-bromoaniline derivatives were used.

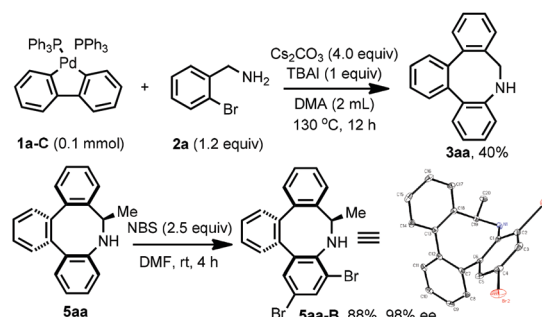
eight-membered ring. No diastereomers were observed and almost a single enantiomer was obtained (**5aa**). Encouraged by this result, we examined the reactions of other chiral 2-bromobenzylamines. The benzylamines bearing a cyclopropyl or *n*-heptyl underwent the coupling reaction with **1a** in excellent diastereoselectivity (**5ab** and **5ac**). A TBS-protected γ -aminoalcohol was also suitable (**5ad**). This outcome is significant because the TBS protecting group can be removed readily and the resulting γ -aminoalcohol allows easy access to bidentate ligands. The reactions of chiral 2-bromobenzylamines derivatives bearing substituents on the benzene rings were then studied. A range of substituents were compatible, and the corresponding products were obtained with very high enantiopurity and in moderate to good yields (**5ae**–**5ak**). Remarkably, although the reactions proceeded at 130 °C for 12 hours, excellent enantiomeric excesses were still obtained, which indicated that racemization did not occur even under harsh conditions and the chiral products are highly stable.

Next, we investigated the diastereoselective reactions of 2-iodobiphenyl derivatives. As outlined in Scheme 4, a variety of symmetrically substituted 2-iodobiphenyls reacted with **4a** diastereoselectively, affording the desired enantiopure products.

To gain insight into the mechanism of the coupling reaction, we prepared palladacycle **1a-C** (Scheme 5). **1a-C** was allowed to react with **2a** under the analogous conditions. Product **3aa** was obtained in a 40% yield. Furthermore, two isomers were formed in a ratio of 1 to 1 in the reaction of **1g**. These outcomes indicate that the reactions should involve palladacycles as the intermediates (for the detailed mechanism, see the ESI[†]). To determine the absolute configuration of the



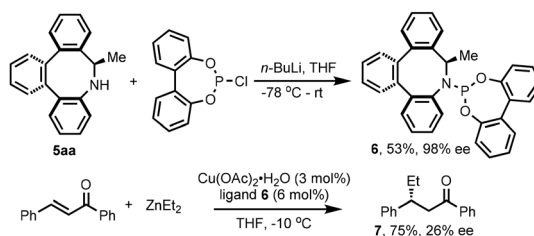
Scheme 4 Substrate scope with respect to 2-iodobiphenyls in the synthesis of enantiopure eight-membered cyclic products.



Scheme 5 Preliminary mechanistic studies and determination of the absolute configuration.

chiral products, **5aa** was brominated to give compound **5aa-B**. The structure of **5aa-B** was identified by single-crystal X-ray crystallography. Remarkably, the molecule still has a saddle-shaped structure. The two opposite benzene rings are oriented above the average plane of the molecule, and the other benzene ring is below the plane.

The products have a unique chiral structure and provide opportunities for designing chiral ligands. In particular, the amino group in the products can be readily derivatized and allows easy access to various ligands. On the other hand, chiral phosphoramidite ligands are a class of robust ligands for asymmetric catalysis and have found wide applications in diverse catalytic asymmetric reactions.¹⁵ Therefore, we transformed product **5aa** to phosphoramidite ligand **6** (Scheme 6). It should be mentioned that the ee value of **6** remains unchanged.



Scheme 6 Synthesis of chiral phosphoramidite ligands and application in the asymmetric reactions.

Next, ligand **6** was applied to copper-catalyzed conjugate addition of diethylzinc to chalcone.¹⁶ The desired product **7** was obtained with 26% ee. Although the enantioselectivity was low, it indicates that the eight-membered skeleton has application potential in asymmetric catalysis.

In conclusion, we have developed a facile method for the synthesis of eight-membered nitrogen heterocycles through Pd-catalyzed cross-coupling of 2-iodobiphenyls with 2-bromobenzylamines. C,C-Palladacycles that are formed *via* the C–H activation of 2-iodobiphenyls should act as the intermediates. This reaction provides a new strategy for the construction of medium-sized rings. The coupling reaction proceeded with high diastereoselectivity to form enantiopure products. The resulting eight-membered nitrogen heterocycles represent a novel type of chiral scaffold, which has great potential to be applied in asymmetric synthesis. Studies towards the synthesis of other medium-sized rings and applications of the chiral products are underway in our lab.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 B. Testa, *Helv. Chim. Acta*, 2013, **96**, 351–374.
- 2 (a) Y. B. Wang and B. Tan, *Acc. Chem. Res.*, 2018, **51**, 534–547; (b) C. G. Newton, E. Braconi, J. Kuziola, M. D. Wodrich and N. Cramer, *Angew. Chem., Int. Ed.*, 2018, **57**, 11040–11044; (c) M. Tian, D. Bai, G. Zheng, J. Chang and X. Li, *J. Am. Chem. Soc.*, 2019, **141**(24), 9527–9532; (d) G. Liao, T. Zhou, Q. J. Yao and B. F. Shi, *Chem. Commun.*, 2019, **55**, 8514–8523; (e) X. Wang, Q. J. An, S. H. Xiang, S. Li, Y. B. Wang and B. Tan, *Angew. Chem., Int. Ed.*, 2020, **59**, 6775–6779; (f) Q. J. Yao, P. P. Xie, Y. J. Wu, Y. L. Feng, M. Y. Teng, X. Hong and B. F. Shi, *J. Am. Chem. Soc.*, 2020, **142**, 18266–18276; (g) Q. H. Nguyen, S. M. Guo, T. Royal, O. Baudoin and N. Cramer, *J. Am. Chem. Soc.*, 2020, **142**, 2161–2167.
- 3 (a) B. Ferbera and H. B. Kagana, *Adv. Synth. Catal.*, 2007, **349**, 493–507; (b) D. W. Gao, Q. Yin, Q. Gu and S. L. You, *J. Am. Chem. Soc.*, 2014, **136**, 4841–4844; (c) R. Deng, Y. Huang, X. Ma, G. Li, R. Zhu, B. Wang, Y. B. Kang and Z. Gu, *J. Am. Chem. Soc.*, 2014, **136**, 4472–4475; (d) T. Shibata and T. Shizuno, *Angew. Chem., Int. Ed.*, 2014, **53**, 5410–5413; (e) Q. W. Zhang, K. An, L. C. Liu, Y. Yue and W. He, *Angew. Chem., Int. Ed.*, 2015, **54**, 6918–6921; (f) D. W. Gao, Q. Gu, C. Zheng and S. L. You, *Acc. Chem. Res.*, 2017, **50**, 351–365.
- 4 (a) T. C. W. Mak and H. N. C. Wong, *Tetraphenylene and Related Hosts*, in *Comprehensive Supramolecular Chemistry*, ed. D. D. MacNicol, F. Toda and P. Bishop, Pergamon Press, Oxford, 1996, Vol. 6, pp. 351–369; (b) T. C. W. Mak and H. N. C. Wong, *Top. Curr. Chem.*, 1987, **140**, 141–164; (c) J. W. Han, X. S. Peng and H. N. C. Wong, *Natl. Sci. Rev.*, 2017, **4**, 892–916.
- 5 (a) H. Huang, C. K. Hau, C. C. M. Law and H. N. C. Wong, *Org. Biomol. Chem.*, 2009, **7**, 1249–1257; (b) J.-W. Han, J.-X. Chen, X. Li, X.-S. Peng and H. N. C. Wong, *Synlett*, 2013, 2188–2198.
- 6 (a) H.-Y. Peng, C.-K. Lam, T. C. W. Mak, Z. Cai, W.-T. Ma, Y.-X. Li and H. N. C. Wong, *J. Am. Chem. Soc.*, 2005, **127**, 9603–9611; (b) A.-H. Wu, C.-K. Hau and H. N. C. Wong, *Adv. Synth. Catal.*, 2007, **349**, 601–608; (c) T. Shibata, T. Chiba, H. Hirashima, Y. Ueno and K. Endo, *Angew. Chem., Int. Ed.*, 2009, **48**, 8066–8069; (d) C.-K. Hau, S. S.-Y. Chui, W. Lu, C.-M. Che, P.-S. Cheng, T. C. W. Mak, Q. Miao and H. N. C. Wong, *Chem. Sci.*, 2011, **2**, 1068–1075.
- 7 A. Hussain, S. K. Yousuf and D. Mukherjee, *RSC Adv.*, 2014, **4**, 43241–43257.
- 8 (a) E. Vitaku, D. T. Smith and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 10257–10274; (b) T. Guney, T. A. Wenderski, M. W. Boudreau and D. S. Tan, *Chem. – Eur. J.*, 2018, **24**, 13150–13157.
- 9 *Modern Physical Organic Chemistry*, ed. E. V. Anslyn and D. A. Dougherty, Higher Education Press, Beijing, 2009.
- 10 (a) K. C. Majumdar and B. Chattopadhyay, *Curr. Org. Chem.*, 2009, **13**, 731–751; (b) Z.-X. Yu, Y. Wang and Y. Wang, *Chem. – Asian J.*, 2010, **5**, 1072–1088; (c) J. R. Donald and W. P. Unsworth, *Chem. – Eur. J.*, 2017, **23**, 8780–8799.
- 11 (a) M. Chaumontet, R. Piccardi, N. Audic, J. Hitce, J. L. Peglion, E. Clot and O. Baudoin, *J. Am. Chem. Soc.*, 2008, **130**, 15157–15166; (b) S. Rousseaux, M. Davi, J. Sofack-Kreutzer, C. Pierre, C. E. Kefalidis, E. Clot, K. Fagnou and O. Baudoin, *J. Am. Chem. Soc.*, 2010, **132**, 10706–10716; (c) J.-X. Yan, H. Li, X.-W. Liu, J.-L. Shi, X. Wang and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2014, **53**, 4945–4949; (d) D. García-Cuadrado, A. A. C. Braga, F. Maseras and A. M. Echavarren, *J. Am. Chem. Soc.*, 2006, **128**, 1066–1067; (e) H. Jiang, Y. Zhang, D. Chen, B. Zhou and Y. Zhang, *Org. Lett.*, 2016, **18**, 2032–2035; (f) S. Pan, H. Jiang, Y. Zhang, D. Chen and Y. Zhang, *Org. Lett.*, 2016, **18**, 5192–5195; (g) A. Gutiérrez-Bonet, F. Juliá-Hernández, B. de Luis and R. Martín, *J. Am. Chem. Soc.*, 2016, **138**, 6384–6387; (h) Z. Wu, D. Ma, B. Zhou, X. Ji, X. Ma, X. Wang and Y. Zhang, *Angew. Chem., Int. Ed.*, 2017, **56**, 12288–12291; (i) S. Xu, R. Chen, Z. Fu, Q. Zhou, Y. Zhang and J. Wang, *ACS Catal.*, 2017, **7**, 1993–1997; (j) A. Lu, X. Ji, B. Zhou, Z. Wu and Y. Zhang, *Angew. Chem., Int. Ed.*, 2018, **57**, 3233–3237; (k) Y.-B. Zhao, B. Mariampillai, D. A. Candito, B. Laleu, M. Li and M. Lautens, *Angew. Chem., Int. Ed.*, 2009, **48**, 1849–1852; (l) D. Nicola Ca', G. Maestri, M. Malacria, E. Derat and M. Catellani, *Angew. Chem., Int. Ed.*, 2011, **50**, 12257–12261; (m) V. Narbonne, P. Retailleau, G. Maestri and M. Malacria, *Org. Lett.*, 2014, **16**, 628–631; (n) Y. Yang, B. Zhou, X. Zhu, G. Deng, Y. Liang and Y. Yang, *Org. Lett.*, 2018, **20**, 5402–5405; (o) B. Tan, B. Lu, P. Ding, J. Liu, Y. Wang and X. Luan, *Angew. Chem., Int. Ed.*, 2019, **58**, 1474–1478; (p) S.-L. Cai, Y. Li, C. Yang, J. Sheng and X.-S. Wang, *ACS Catal.*, 2019, **9**, 10299–10304.
- 12 (a) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (b) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754–8786; (c) B. Olivier, *Acc. Chem. Res.*, 2017, **50**, 1114–1123; (d) G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1698–1712; (e) Y. Ping, Y. Li, J. Zhu and W. Kong, *Angew. Chem., Int. Ed.*, 2019, **58**, 1562–1573.
- 13 (a) F. Jafarpour, M. Ghasemi, F. Mohaghegh, S. Asgari and A. Habibi, *Org. Lett.*, 2019, **21**, 10143–10148; (b) X. Liu, H. Sheng, Y. Zhou and Q. Song, *Chem. Commun.*, 2020, **56**, 1665–1668.
- 14 D. M. Schultz and J. P. Wolfe, *Org. Lett.*, 2011, **13**, 2962–2965.
- 15 (a) J. F. Teichert and B. L. Feringa, *Angew. Chem., Int. Ed.*, 2010, **49**, 2486–2528; (b) W. Fu and W. Tang, *ACS Catal.*, 2016, **6**, 4814–4858.
- 16 (a) A. Alexakis, C. Benhaim, S. Rosset and M. Humam, *J. Am. Chem. Soc.*, 2002, **124**, 5262–5263; (b) H. Zhou, W.-H. Wang, Y. Fu, J.-H. Xie, W.-J. Shi, L.-X. Wang and Q.-L. Zhou, *J. Org. Chem.*, 2003, **68**, 1582–1584; (c) H. Yu, F. Xie, Z. Ma, Y. Liu and W. Zhang, *Org. Biomol. Chem.*, 2012, **10**, 5137–5142.