

Cite this: *Chem. Sci.*, 2018, **9**, 8711

All publication charges for this article have been paid for by the Royal Society of Chemistry

Received 5th August 2018
 Accepted 17th September 2018

DOI: 10.1039/c8sc03480j
rsc.li/chemical-science

Introduction

Diarylmethyl units are widely present in functional molecules and natural products. Examples of such molecules include the antidepressant drug Sertraline,¹ Bz-IB conjugates with anti-inflammatory activities² and the natural product voacamine³ with cannabinoid CB1 receptor antagonistic activity (Fig. 1a). Notably, the diaryl methyl sp^3 carbon in these bioactive molecules is often present as a chiral center.⁴ To date, the most well-studied approach for the incorporation of diaryl methane unit relies on reactions between diarylmethyl carbocations and nucleophilic substrates⁵ (Fig. 1b). Diarylmethyl carbocation intermediates are typically generated *in situ* from their precursors such as diarylmethanols.⁶ In contrast, as a potentially more straightforward approach, direct modification of diarylmethanes is much less studied (Fig. 1c). This is in part due to the weak acidity of the methyl C–H and the difficult enantiofacial discrimination of two sterically similar aryl substituents. Deprotonation of such a benzylic C–H bond typically requires the use of a strong base such as $^7\text{BuLi}$ or Na^+ .⁷ As an alternative choice, oxidative transformations of diarylmethanes via benzylic organometallic species⁸ or benzylic radicals⁹ can be realized under milder conditions. However, in all these approaches, direct enantioselective modification of

diarylmethane remains challenging. Limited examples in this direction include oxidative or photoredox transformations *via* *o*-quinone methides (*o*-QM)¹⁰ or *o*-quinonodimethanes (*o*-QDM)¹¹ as the key intermediates, and recent Rh-mediated asymmetric C–H arylation of diarylmethane.¹²

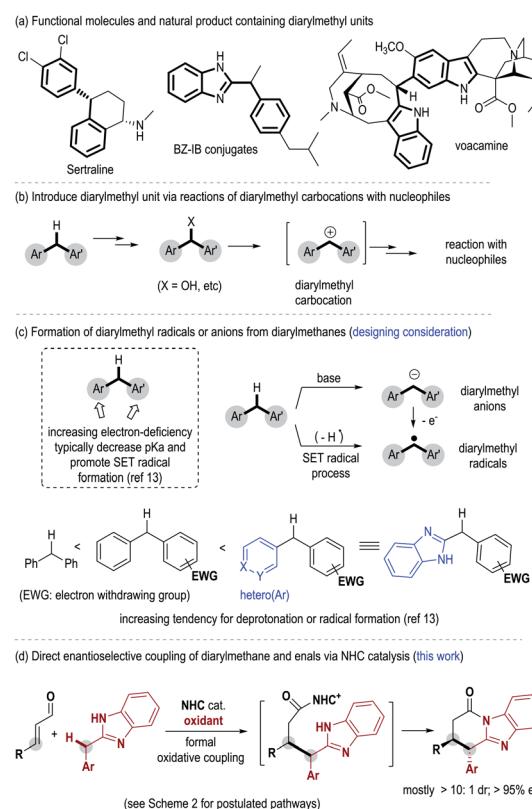


Fig. 1 Diarylmethyl compounds and their enantioselective synthesis.

^a Guiyang College of Traditional Chinese Medicine, Guizhou, P. R. China^b Division of Chemistry & Biological Chemistry, School of Physical & Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore. E-mail: robinchi@ntu.edu.sg[†] Electronic supplementary information (ESI) available. CCDC 1843274 and 1843275. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc03480j[‡] Qiao Chen and Tingshun Zhu contributed equally.[§] Present address: School of Chemistry, Sun Yat-Sen University, Guangzhou, 510275, P. R. China.

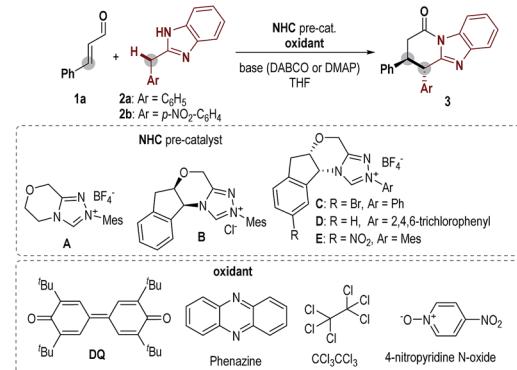
Herein we disclose an N-heterocyclic carbene (abbreviated as NHC or carbene) organic catalyst-mediated formal oxidative coupling of enal β -carbon and diarylmethanes (Fig. 1d). Our initial designing consideration is to generate a diarylmethyl radical from a diarylmethane substrate as a key intermediate under oxidative conditions (Fig. 1c). It is known that the tendency for deprotonation and radical formation of benzylic carbons can be well-tuned by altering the electronic properties of the aryl substituents¹³ (Fig. 1c). We therefore eventually introduce heterocyclic benzimidazole as one of the aryl units of the diarylmethane substrate in order to achieve suitable reactivity. The selection of benzimidazole units also provides two additional benefits: benzimidazole is a structural analogue of purine and a potential pharmacophore;¹⁴ the NH group in benzimidazole can facilitate the turnover of the NHC catalyst *via* the formation of a lactam product at the end of the catalytic cycle.¹⁵ Mechanistic studies suggest that some of our carbene-catalyzed reactions likely go through single-electron-transfer (SET) processes and radical intermediates in the key steps, although an electron pair pathway cannot be completely ruled out.

Results and discussion

Key results in searching for suitable conditions by using cinnamaldehyde (**1a**) and diarylmethane **2** as model substrates are summarized in Table 1. We firstly used achiral triazolium salt **A**¹⁶ as the NHC pre-catalyst, DABCO as the base, and 3,3',5,5'-tetra-*tert*-butyl-4,4'-diphenoxquinone (DQ) as the oxidant.¹⁷ With 2-benzyl benzimidazole **2a** as the substrate, the proposed lactam product was not observed in an appreciable amount under various conditions. We then introduced an electron-withdrawing nitro group into the phenyl ring of diarylmethane (using **2b** as the substrate), and obtained the corresponding lactam product in 22% yield (entry 2). The use of amino indanol-derived triazolium carbene pre-catalyst **B**¹⁸ led to the lactam product in 36% yield with excellent ee (95% ee, entry 3). Several chiral NHC catalysts evaluated here did not provide better results in terms of both yields and ee values (entries 4–6). We then decided to use pre-catalyst **B** for further condition optimization (entries 7–12). The switch of the base from DABCO to DMAP significantly improved the yield from 36% (entry 3) to 60% (entry 7) with a slight increase of ee (from 95% to 98% ee) as well. Further optimization by using 1.5 equivalents of **1a** and DQ and performing the reaction at 40 °C gave a better result of 84% yield and 98% ee (entry 8). Several oxidants (phenazine,¹⁹ hexachloroethane²⁰ and 4-nitro pyridine *N*-oxide²¹) previously used in oxidation and single-electron-transfer (SET) radical reactions could also mediate the reaction with low to moderate yields and excellent ee values (entries 9–11). Finally, the reaction outcome with **B** as the catalyst could be further improved by lowering the reaction concentration (entry 12).

With an acceptable condition in hand (Table 1, entry 12), we evaluated the scope of enals by using **2b** as a model diarylmethane substrate (Table 2). Placing halogens, carboxylic esters, nitro groups, methyl, and methoxyl units as substituents at the *para*-position of the enal β -phenyl ring was well tolerated

Table 1 Screening of reaction conditions^a

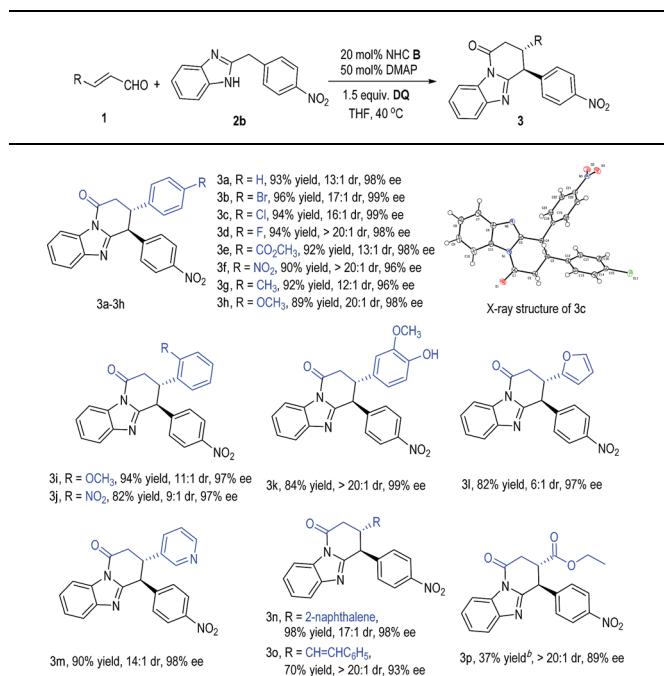


Entry	2	NHC, base	Oxidant	Yield ^b /%	ee ^c /%
1	2a	A , DABCO	DQ	Trace	—
2	2b	A , DABCO	DQ	22	—
3	2b	B , DABCO	DQ	36	95
4	2b	C , DABCO	DQ	27	–73
5	2b	D , DABCO	DQ	18	–77
6	2b	E , DABCO	DQ	25	–95
7	2b	B , DMAP	DQ	60	98
8 ^d	2b	B , DMAP	DQ	84	98
9 ^d	2b	B , DMAP	Phenazine	46	96
10 ^d	2b	B , DMAP	CCl ₃ CCl ₃	7	nd
11 ^d	2b	B , DMAP	4-Nitropyridine <i>N</i> -oxide	40	98
12 ^{d,e}	2b	B , DMAP	DQ	92	98

^a Reaction conditions: **1a** (0.06 mmol, 1.2 equiv.), **2** (0.05 mmol, 1.0 equiv.), NHC (20 mol%), base (0.5 equiv.) and oxidant (1.2 equiv.) in 0.5 mL THF at rt. ^b Determined by ¹H NMR, with 1,3,5-trimethoxybenzene as an internal standard. ^c Determined by chiral-phase HPLC analysis. ^d 1.5 equiv. of **1a** and oxidant were used; reaction temperature was 40 °C. ^e In 1 mL THF. DABCO = 1,4-diazabicyclo[2.2.2]octane; DMAP = 4-dimethylaminopyridine.

(**3a–3h**). The absolute configuration of **3c** was unambiguously confirmed by single-crystal X-ray diffraction analysis (for details, see the ESI†). The use of enals with different substitution patterns on the phenyl ring all gave products with excellent yield, dr, and ee values (**3i–3k**). Heterocyclic, naphthalene, and alkene substituents were all tolerated in β -substitution of enals (**3l–3o**). Enal with a β -carboxylate substituent gave product **3p** in moderate yield with excellent dr and good ee. The use of enals with a β -alkyl substituent led to products with low yields (around 10% yields as estimated *via* NMR).

We next studied the scope of diarylmethanes by using cinnamaldehyde **1a** as the model enal substrate (Table 3). The nitro substituent in **2b** can be replaced with other electron-withdrawing units such as CN, CO₂CH₃, SO₂CH₃, CF₃, and Br (**4b–4f**). Placing nitro groups at the *ortho*- or *meta*-position of the benzyl group of substrate **2** led to some decrease in reaction yields without affecting enantioselectivities (**4g–4h**). We also investigated the effect of substituents on the benzimidazole framework, and found that various substituents and substitution patterns were well tolerated (**4i–4o**). When unsymmetrical benzimidazoles were used, the corresponding lactam products were obtained as a mixture of two regio-isomers (**4k–4o**, see the

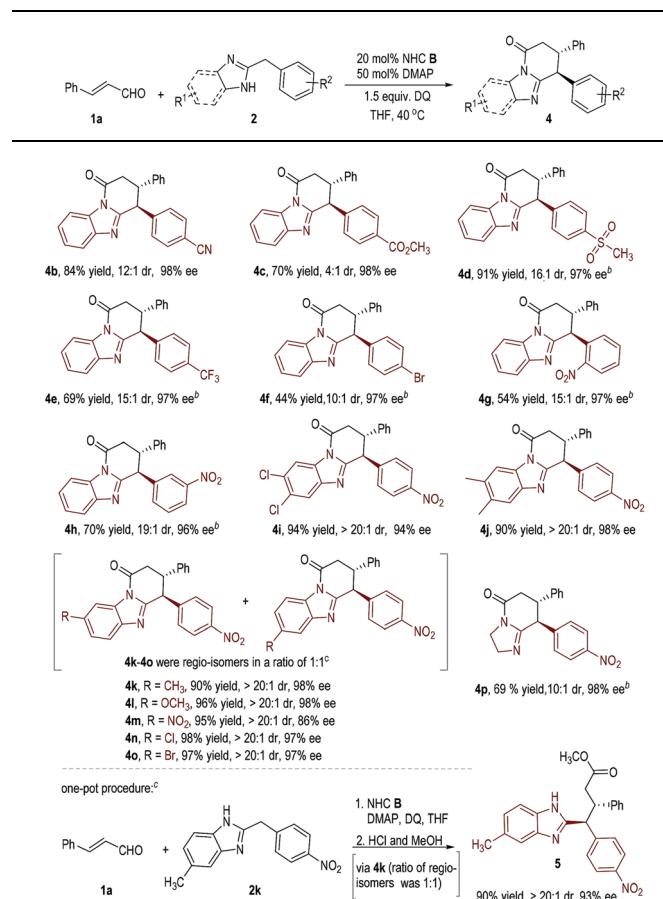
Table 2 Examples of enal substrates^a

^a Unless otherwise noted, all reactions were run on a 0.2 mmol scale under the standard conditions (Table 1, entry 12). Yield refers to isolated yield. ^b The reaction temperature was 80 °C.

ESI† for details). This regio-isomer issue can be circumvented *via* one additional step in a one-pot operation: the lactam ring opened in acid alcohol in quantitative yield with ee and dr retained (as exemplified in 2k to 5, Table 3, one-pot procedure). Substrate bearing simple imidazolidine can also be used, giving product 4p in 69% yield, 10 : 1 dr, and 98% ee.

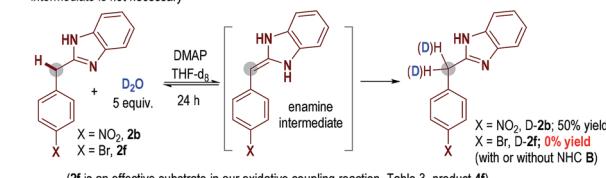
To understand the reaction pathways, we performed several control experiments. We performed H/D exchange experiments for diarylmethane substrates 2b and 2f (Scheme 1a). With 2b as the substrate, deuterated adduct D-2b was observed in 50% yield (NMR yield, see the ESI† for details). However, when 2f (an effective substrate in our oxidative coupling reaction, Table 3, product 4f) was used, no H/D exchange was observed. This result suggested that the formation of an enamine intermediate was not necessary in our catalytic coupling reaction. When 2b was mixed with the radical scavenger BHT (butylated hydroxytoluene) in the presence of a DQ oxidant, adduct 7 could be obtained in 47% yield (Scheme 2b), suggesting the existence of benzylic radical intermediates. It is also worth noting that ketones 6 derived from 2 *via* oxidation of the benzylic carbon were observed as the main side products in nearly all examples. 2q-dimer generated from homo-coupling of benzylic carbon was also observed when 2q was used as a substrate (Scheme 1c). This evidence suggested the presence of benzylic radical intermediates (see the ESI† for details of other mechanism study).

Two possible reaction pathways are illustrated in Scheme 2. In the 1st possible pathway (Scheme 2a), oxidation of 1a under

Table 3 Examples of di(hetero)arylmethane substrates^a

^a Unless otherwise noted, all reactions were run on a 0.2 mmol scale under the standard conditions. Yield refers to isolated yield. ^b The reaction temperature was 80 °C. ^c The regio-isomer issues can be circumvented *via* one additional step in a one-pot operation.

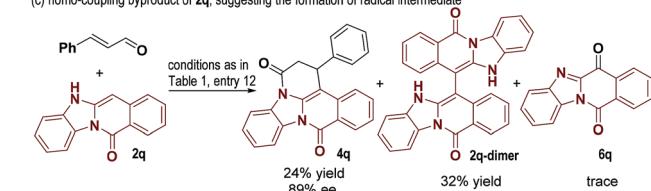
(a) H/D exchange (via direct deprotonation of diarylmethane) is not observed for 2f, suggesting the formation of enamine intermediate is not necessary



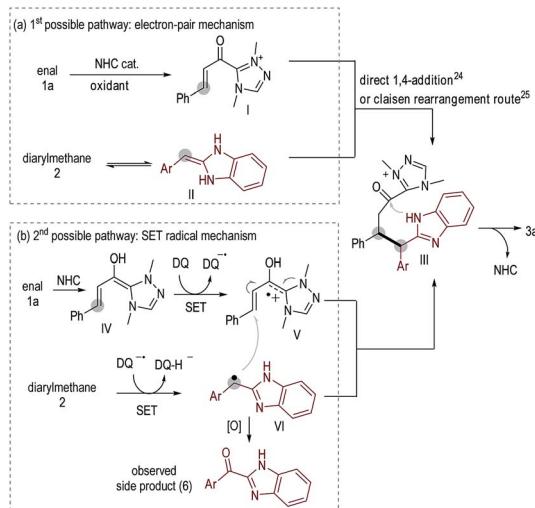
(b) coupling of diarylmethane 2b with radical scavenger BHT (butylated hydroxytoluene), suggesting the formation of radical intermediate



(c) homo-coupling byproduct of 2q, suggesting the formation of radical intermediate



Scheme 1 Control test.



Scheme 2 Possible reaction pathways.

NHC catalysis leads to α,β -unsaturated azolium ester intermediate **I**.²² Isomerization of **2** leads to an enamine intermediate **II**. Nucleophilic addition of **II** to **I** via an electron-pair pathway²³ (direct 1,4-addition²⁴ or Claisen rearrangement²⁵ route) leads to **III**. Cyclization of **III** leads to product **3a** with regeneration of the NHC catalyst. In the 2nd possible pathway (Scheme 2b), NHC-bound radical cation intermediate **V** is formed via a SET oxidative process^{21,26} starting from enal **1a**. Under oxidative conditions, diarylmethane **2** is converted to a benzylic radical intermediate **VI**.⁹ Coupling of radical intermediates **V** and **VI** via a SET process²⁷ leads to intermediate **III**, which is subsequently converted to product **3a**. Ketones **6** derived from **2** via oxidation of the benzylic carbon, as well as the homo-coupling generated 2-dimer (Scheme 1c), were observed as the main side products in nearly all examples, suggesting the presence of radical intermediate **VI**.⁹

The oxidative coupling products from our catalytic reactions can undergo further transformations under simple conditions (Scheme 3). For example, adduct **3a** was reduced by DIBAL-H to *N,N*-acetal **8** in 84% yield. Nitro group reduction with simultaneously ring opening of lactam can also transform **3a** to ester **9** in 86% yield. Reduction of adduct **4e** with LiAlH₄ efficiently gave alcohol **10** (89% yield), which was further cyclized under MsCl

to afford benzimidazole fused piperidine **11** in 98% yield. In all cases, the ee and dr of the molecules were completely retained during the transformations.

Conclusions

In summary, we have developed an NHC-catalyzed highly enantioselective oxidative coupling of di(hetero)arylmethanes and enals to give benzimidazole fused lactams. Ongoing studies include the development of effective methods for enantioselective oxidative coupling of more challenging inactivated carbon–hydrogen bonds, application of this method for assembly or modification of pesticides and active components of Chinese medicines, and bioactivity evaluations of relevant molecules.

Conflicts of interest

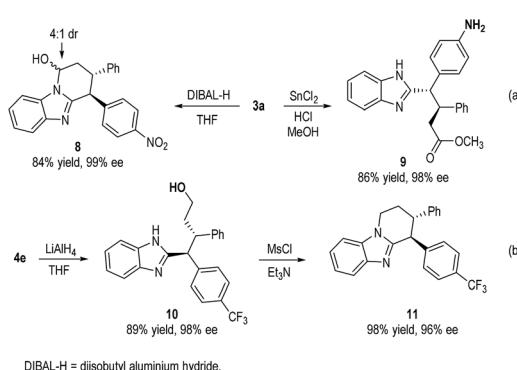
There are no conflicts of interest to declare

Acknowledgements

We acknowledge financial support by the Singapore National Research Foundation (NRF-NRFI2016-06), Ministry of Education of Singapore (MOE2013-T2-2-003; MOE2016-T2-1-032; RG108/16), A*STAR Individual Research Grant (A1783c0008), Nanyang Technological University, Singapore; Guizhou Province First-Class Disciplines Project (YiLiu Xueke Jianshe Xiangmu)-GNYL(2017)008, and Guiyang College of Traditional Chinese Medicine, China.

Notes and references

- 1 D. Murdoch and D. McTavish, *Drug*, 1992, **44**, 604.
- 2 Y. Bansal, M. Kaur and O. Silakari, *Eur. J. Med. Chem.*, 2015, **89**, 671.
- 3 M. Kitajima, M. Iwai, R. Kikura-Hanajiri, Y. Goda, M. Iida, H. Yabushita and H. Takayama, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 1962.
- 4 D. Ameen and T. J. Snape, *MedChemComm*, 2013, **4**, 893.
- 5 (a) Y. Li, F.-Q. Shi, Q.-L. He and S.-L. You, *Org. Lett.*, 2009, **11**, 3182; (b) F.-L. Sun, X.-J. Zheng, Q. Gu, Q.-L. He and S.-L. You, *Eur. J. Org. Chem.*, 2010, **2010**, 47; (c) M.-H. Zhuo, Y.-J. Jiang, Y.-S. Fan, Y. Gao, S. Liu and S. Zhang, *Org. Lett.*, 2014, **16**, 1096; (d) Y. Huang and T. Hayashi, *J. Am. Chem. Soc.*, 2015, **137**, 7556; (e) L. Caruana, M. Mondatori, V. Corti, S. Morales, A. Mazzanti, M. Fochi and L. Bernardi, *Chem.-Eur. J.*, 2015, **21**, 6037; (f) M. Nambo, Z. T. Ariki, D. Canseco-Gonzalez, D. D. Beattie and C. M. Crudden, *Org. Lett.*, 2016, **18**, 2339.
- 6 For selected examples, see: (a) G. Bergonzini, S. Vera and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2010, **49**, 9685; (b) C. Xing, H. Sun, J. Zhang, G. Li and Y. R. Chi, *Chem.-Eur. J.*, 2011, **17**, 12272; (c) Z. Wang, Y. F. Wong and J. Sun, *Angew. Chem., Int. Ed.*, 2015, **54**, 13711; (d) H.-H. Liao, A. Chatupheeraphat, C.-C. Hsiao, I. Atodiresei and



Scheme 3 Product Transformation.



M. Rueping, *Angew. Chem., Int. Ed.*, 2015, **54**, 15540; (e) M. Chen and J. Sun, *Angew. Chem., Int. Ed.*, 2017, **56**, 4583.

7 (a) W. G. Kofron and J. Mathew, *J. Org. Chem.*, 1976, **41**, 114; (b) M. S. Hill and P. B. Hitchcock, *Organometallics*, 2002, **21**, 220.

8 (a) H. Sterckx, J. D. Houwer, C. Mensch, I. Caretti, K. A. Tehrani, W. A. Herrebout, S. V. Doorslaer and B. U. W. Maes, *Chem. Sci.*, 2016, **7**, 346; (b) A. Vasilopoulos, S. L. Zultanski and S. S. Stahl, *J. Am. Chem. Soc.*, 2017, **139**, 7705.

9 (a) Y.-Z. Li, B.-J. Li, X.-Y. Lu, S. Lin and Z.-J. Shi, *Angew. Chem., Int. Ed.*, 2009, **48**, 3817; (b) S. Guo, Y. Li, Y. Wang, X. Guo, X. Meng and B. Chen, *Adv. Synth. Catal.*, 2015, **357**, 950; (c) L. Ren, L. Wang, Y. Lv, G. Li and S. Gao, *Org. Lett.*, 2015, **17**, 2078; (d) D. P. Hruszkewycz, K. C. Miles, O. R. Thiel and S. S. Stahl, *Chem. Sci.*, 2017, **8**, 1282; (e) E. Larionov, M. M. Mastandrea and M. A. Pericàs, *ACS Catal.*, 2017, **7**, 7008; (f) D. Uraguchi, M. Torii and T. Oii, *ACS Catal.*, 2017, **7**, 2765.

10 (a) K. Gebauer, F. Reuß, M. Spanka and C. Schneider, *Org. Lett.*, 2017, **19**, 4588; (b) B. Wu, X. Gao, Z. Yan, M.-W. Chen and Y.-G. Zhou, *Org. Lett.*, 2015, **17**, 6134.

11 (a) L. Dell'Amico, A. Vega-Peña, S. Cuadros and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2016, **55**, 3313; (b) L. Dell'Amico, V. M. Fernández-Alvarez, F. Maseras and P. Melchiorre, *Angew. Chem., Int. Ed.*, 2017, **56**, 3304; (c) X. Yuan, S. Dong, Z. Liu, G. Wu, C. Zou and J. Ye, *Org. Lett.*, 2017, **19**, 2322.

12 J. H. Kim, S. Fribes, M. Boultadakis-Arapinis, C. Daniliuc and F. Glorius, *ACS Catal.*, 2016, **6**, 7652.

13 F. G. Bordwell, J.-P. Cheng, M. J. Bausch and J. E. Bares, *J. Phys. Org. Chem.*, 1988, **1**, 209.

14 W. Akhtar, M. F. Khan, G. Verma, M. Shaquiquzzaman, M. A. Rizvi, S. H. Mehdi, M. Akhter and M. M. Alam, *Eur. J. Med. Chem.*, 2017, **126**, 705.

15 For selected examples, see: (a) D. E. A. Raup, B. Cardinal-David, D. Holte and K. A. Scheidt, *Nat. Chem.*, 2010, **2**, 766; (b) A. G. Kravina, J. Mahatthananchai and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 9433; (c) P. Wheeler, H. U. Vora and T. Rovis, *Chem. Sci.*, 2013, **4**, 1674; (d) C. Guo, B. Sahoo, C. G. Daniliuc and F. Glorius, *J. Am. Chem. Soc.*, 2014, **136**, 17402; (e) L. Wang, S. Li, M. Blümel, A. R. Philipps, A. Wang, R. Puttreddy, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 1110.

16 P.-C. Chiang, M. Rommel and J. W. Bode, *J. Am. Chem. Soc.*, 2009, **131**, 8714.

17 (a) S. D. Sarkar and A. Studer, *Angew. Chem., Int. Ed.*, 2010, **49**, 9266; (b) S. D. Sarkar, S. Grimme and A. Studer, *J. Am. Chem. Soc.*, 2010, **132**, 1190.

18 (a) M. He, J. R. Struble and J. W. Bode, *J. Am. Chem. Soc.*, 2006, **128**, 8418; (b) J. R. Struble and J. W. Bode, *Org. Synth.*, 2010, **87**, 362.

19 (a) C. Noonan, L. Baragwanath and S. J. Connolly, *Tetrahedron Lett.*, 2008, **49**, 4003; (b) X. Zhao, K. E. Ruhl and T. Rovis, *Angew. Chem., Int. Ed.*, 2012, **51**, 12330.

20 X. Wu, B. Liu, Y. Zhang, M. Jeret, H. Wang, P. Zheng, S. Yang, B.-A. Song and Y. R. Chi, *Angew. Chem., Int. Ed.*, 2016, **55**, 12280.

21 (a) N. A. White and T. Rovis, *J. Am. Chem. Soc.*, 2014, **136**, 14674; (b) N. A. White and T. Rovis, *J. Am. Chem. Soc.*, 2015, **137**, 10112.

22 For recent review, see: C. Zhang, J. F. Hooper and D. W. Lupton, *ACS Catal.*, 2017, **7**, 2583.

23 (a) M. D. Greenhalgh, S. Qu, A. M. Z. Slawin and A. D. Smith, *Chem. Sci.*, 2018, **9**, 4909; (b) S. Vera, Y. Liu, M. Marigo and E. C. Escudero-Adán, *Synlett*, 2011, **4**, 489.

24 R. C. Samantha, B. Maji, S. D. Sarkar, K. Bergander, R. Fröhlich, C. Mück-Lichtenfeld and H. Mayr, *Angew. Chem., Int. Ed.*, 2012, **51**, 5234.

25 J. Mahatthananchai, J. Kaeobamrung and J. W. Bode, *ACS Catal.*, 2012, **2**, 464.

26 Y. Zhang, Y. Du, Z. Huang, J. Xu, X. Wu, Y. Wang, M. Wang, S. Yang, R. D. Webster and Y. R. Chi, *J. Am. Chem. Soc.*, 2015, **137**, 2416.

27 H. Fischer, *Chem. Rev.*, 2001, **101**, 3581.

