ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2019, 55, 14299

Received 30th September 2019,
Accepted 22nd October 2019

DOI: 10.1039/c9cc07655g

rsc.li/chemcomm

Visible-light-promoted oxidative halogenation of alkynes†

Yiming Li,‡[a] Tao Mou,‡[a] Lingling Lu[a] and Xuefeng Jiang *[abc]

In nature, halogenation promotes the biological activity of secondary metabolites, especially geminal dihalogenation. Related natural molecules have been studied for decades. In recent years, their diversified vital activities have been explored for treating various diseases, which call for efficient and divergent synthetic strategies to facilitate drug discovery. Here we report a catalyst-free oxidative halogenation achieved under ambient conditions (halide ion, air, water, visible light, room temperature, and normal pressure). Constitutionally, electron transfer between the oxygen and halide ion is shuttled *via* simple conjugated molecules, in which phenylacetylene works as both reactant and catalyst. Synthetically, it provides a highly compatible late-stage transformation strategy to build up dihaloacetophenones (DHAPs).

Halogenase plays a significant role in metabolic processes, and produces a mass of important halide-containing secondary metabolites with unique bioactivities, including several effective drugs.[1,2] Among biogenic halogenated molecules (>5000),[3] there are more than 180 geminal dichloro- and 70 geminal dibromo-molecules. In particular, the ones with pharmaceutical data account for up to 57%.[4] In addition, more and more artificial geminal dihalo-compounds have been developed against serious diseases.[5] It is noteworthy to highlight that, recently, the simple dichloroacetophenone was exploited to inhibit the activity of pyruvate dehydrogenase kinase 1, an important target in cancer studies[6] (Fig. 1). In principle, the key functions of halogens upon bioactivity and bioavailability are attributed not only to the modulation of lipophilicity and nonspecific hydrophobic interaction with protein targets, but also to the formation of directional intermolecular interaction with proteins.[2] Urgent demand from pharmaceutical studies necessitates fast and highly tolerated synthetic strategies.

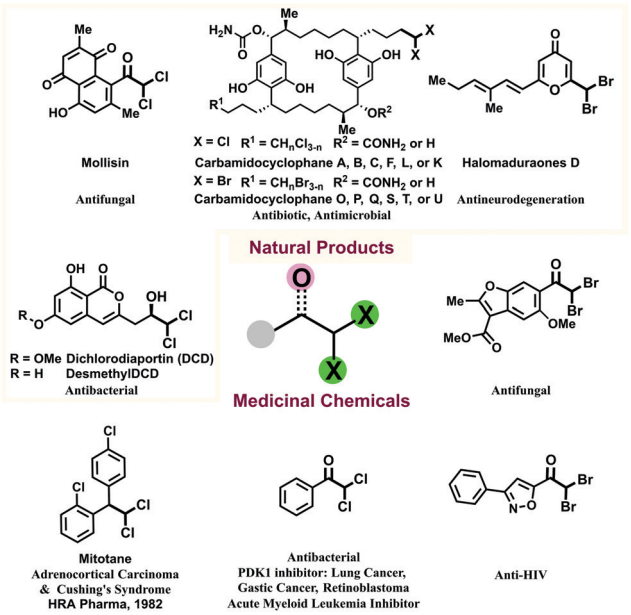

Fig. 1 Significant geminal dihalo-compounds.

Naturally, haloperoxidases and halogenases produce dihaloacetophenones (DHAPs) with inorganic halogen salts (Fig. 2a). Conventionally, DHAPs were constructed *via* halogenation of acetophenones and phenylacetylenes *via* corrosive and low-compatible molecular halogens.[7] Then, various electrophilic halogen sources mostly with polyamide backbones were utilized,[8] such as NBS,[9] NCS,[10] *etc.*[11] but with tedious workup and lower atom-efficiency. Recently, halide ions have been employed instead of electrophilic halogen sources. Paradoxically, halide ions are commonly inactive unless with strong oxidants, which makes sensitive functional groups incompatible (Fig. 2b).[12]

[a] *Shanghai Key Laboratory of Green Chemistry and Chemical Process, East China Normal University, 3663 North Zhongshan Road, Shanghai 200062, P. R. China. E-mail: xfjiang@chem.ecnu.edu.cn*
[b] *State Key Laboratory of Organometallic Chemistry Shanghai Institute of Organic Chemistry Chinese Academy of Sciences, Shanghai, 200032, P. R. China*
[c] *State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin, 300071, P. R. China*

† Electronic supplementary information (ESI) available. CCDC 1915404. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc07655g

‡ These authors contributed equally.

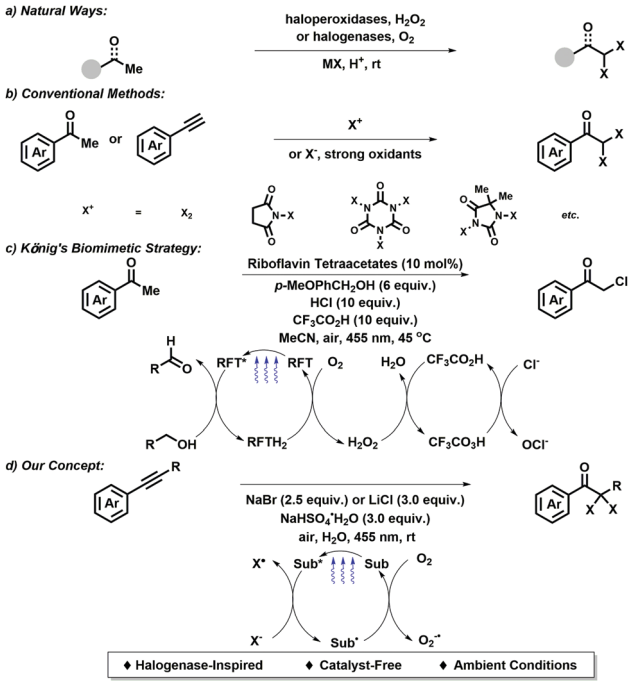

Fig. 2 The synthesis of dihaloacetophenones.

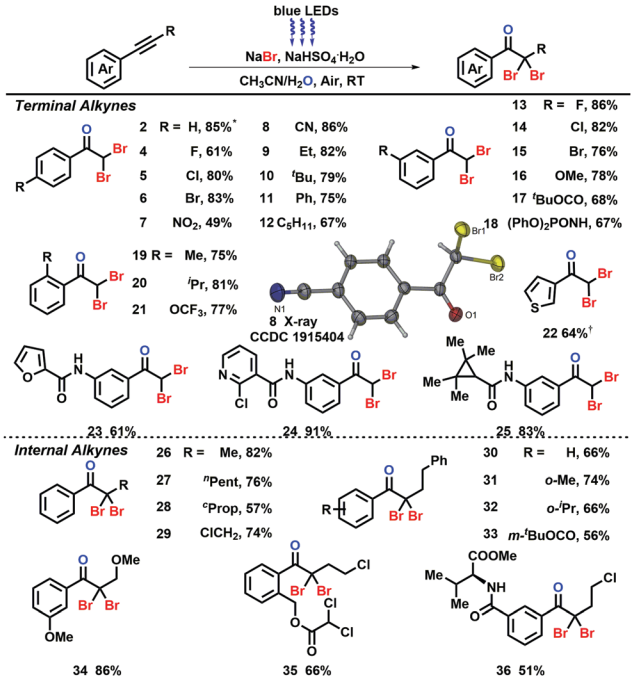

Fig. 3 Compatibility of oxybromination. * 10 mmol scale, 56%, 1.54 g. † 2 h.

To mimic mild natural synthesis, a revealing photocatalytic strategy was developed by König *et al.*,[13] utilizing riboflavin tetraacetate instead of flavin adenine dinucleotide as the catalyst and *p*-methoxy benzyl alcohol instead of nicotinamide adenine dinucleotide II ($NADH_2$) as a reductant. For enhancing the reactivity, hydrochloric acid (HCl) and trifluoroacetic acid were employed as chloride source and promoter (Fig. 2c). Essentially, the core of enzyme-catalyzed and biomimic halogenation is the electron transfer from the halide anion to oxygen, which generates active halogen and oxygen species followed by introduction of halogen atoms. However, to the best of our knowledge, no direct way has been reported, particularly under ambient conditions, especially with halide ions,[14] air, water, room temperature, normal pressure, and visible light. Here, photoredox[15] oxyhalogenation with phenylacetylene without extra catalyst[16] was introduced (Fig. 2d).

The spectrum of UV-visible light absorption showed that phenylacetylene possesses weak absorption even in 0.1 M concentration (ESI,† Section III-1). However, detailed mechanistic analyses and experimental screening found that a Brønsted acid played an important role in enhancing the activity of oxybromonation, especially when the light energy was confined into a small space (ESI,† Section IV), in which $NaHSO_4{\cdot}H_2O$ was the most efficient one (Table S1, entries 1–4, ESI†). Other bromide sources, such as KBr, LiBr, NH_4Br, and $MgBr_2$, did not perform better (Table S1, entries 5–8, ESI†). With similar conditions and LiCl as a chloro-source, the corresponding geminal dichloronation was realized as well (Table S2, ESI†).

Under optimized conditions, the generality of this strategy was comprehensively examined. For oxybromination (Fig. 3), functional groups with electron-withdrawing and electron-donating groups on different positions of the aromatic rings were tested, which obtained good to excellent yields (**4–36**). The transformable halogens (**4–6**, **13–15**), nitro- (**7**), cyano (**8**), ester (**17**), and even phosphamide (**18**) groups were tolerated. In addition, the oxidatively sensitive heteroaromatic and strained rings, such as thiophenyl (**22**), furanyl (**23**), pyridinyl (**24**), and cyclopropanyl (**25**), were investigated and found to be well tolerated. Moreover, the internal alkynes were also successfully tranformed under these mild conditions (**26–36**). The gram-scale reaction was realized in moderate yield (**2**). Meanwhile, oxychloro-molecules construction is also shown in Fig. 4 (**3**, **37–55**). Generally, electronic properties and steric hindrance of substituents did not affect its efficencies. Halogens (F, Cl, Br) (**39–41**, **43**, **47**, **48**, **55**), cyano (**50**), sensitive thiophenyl (**51**) and cyclopropanyl (**53**) groups are tolerated. Notably, the internal alkynes were also well converted. Aliphatic acetylenes with photon absorption groups worked as well but with low efficiency.

Last-stage oxyhalogenations were carried out on molecules with high complexity (Fig. 5). Natural motifs such as menthol (**56**), camphor (**57**), amino ester (**58**), and saccharides (**59** and **60**) were found to be tolerated. Moreover, multisubstituted pyridine (**61**) was also well preserved. An important geminal dichloro-drug Mitotan, treating adrenocortical carcinoma and Cushing's syndrome, was easily achieved with its analogous library, relying on the abundance of alkynes and excellent compatibility of this strategy (**62–64**).

Further mechanistic studies were carried out to disclose the essences of this strategy. First, possible active halogen species were explored. Phenylacetylene was confirmed as a photosensor according to UV-visible absorption spectra, which supplied energy for the subsequent electron transfer (ESI,† Section III-1). Fluorescent quenching experiments were conducted, showing

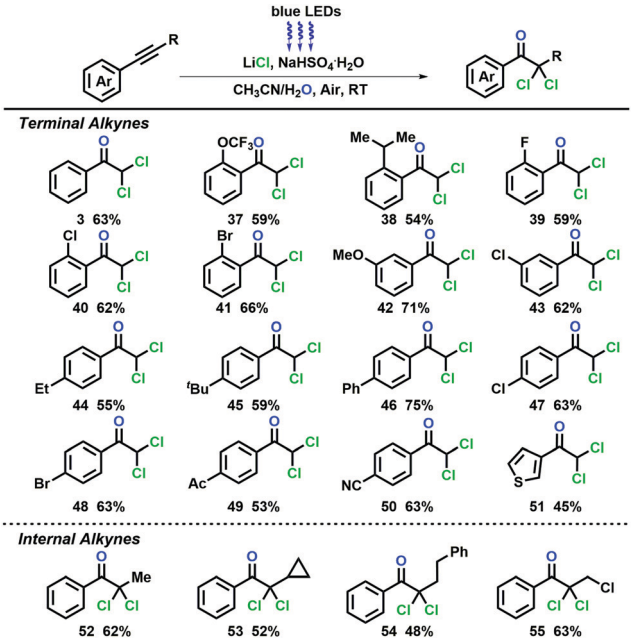

Fig. 4 Compatibility of oxychlorination.

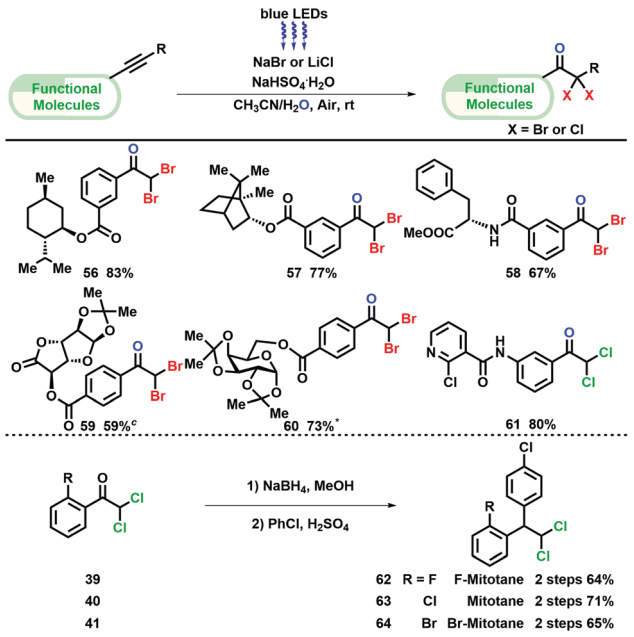

Fig. 5 Late-stage geminal dihalogenation. * 2 h.

that NaBr instead of $NaHSO_4$ functions with phenylacetylene. In addition, the corresponding quenching effort based on HBr, possibly generated *in situ* from NaBr and $NaHSO_4$, was more efficient (ESI,† Section III-2). Radical trapping experiments with TEMPO suggested the possible existence of bromide radicals *via* the detection of TEMPO-Br *via* LCMS (ESI,† Section III-3).[17] Considering the reductive potential of oxygen under acidic conditions (E^0 = 1.47 V *vs.* SCE),[18] which is lower than that of phenylacetylene ($E_{p/2}$ = 2.27 V *vs.* SCE in CH_3CN), the reaction was proposed to be initiated *via* an electron transfer between active phenylacetylene and bromide anions instead of oxygen. Furthermore, radical trapping experiments of compound **69** only afforded acyclic product **70** instead of cyclic products, implying that the active halogenation species reacted with phenylacetylene may not be a bromo-radical but a bromine cation (ESI,† Section III-4), which is an important species in enzyme-involved halogenations.[1–3] In short, it is suggested that the bromide anion was oxidized to radicals by acitive phenylacetylene, and then to a bromine cation with the assistance of *in situ* generated oxidants.

Afterward, the active oxidant in this system was surveyed. The yields of reaction barely changed with active oxygen inhibitors, such as singlet oxygen ($^1O_2$) inhibitors (NaN_3, 1,3-diphenylisobenzofuran), superoxide radical ($O_2^{-\bullet}$) inhibitors (1,3-diphenylisobenzofuran), and hydroxy radical ($^\bullet$OH) inhibitor (^{t}BuOH) (ESI,† Section III-5). Moreover, electron paramagnetic resonance (EPR) reactions with DMPO (trapping reagents of $O_2^{-\bullet}$ and $^\bullet$OH) and TEMP (trapping reagents of $^1O_2$) showed no radical signals (ESI,† Section III-6). Afterward, quantitative iodometric experiments detected the presence of hydrogen peroxide (0.112 mmol) even after the completion of transformation (ESI,† Section III-7). Considering the highly oxidative potential of phenylacetylene, it is suggested that active phenylacetylene and H_2O_2 instead of $^1O_2$, $O_2^{-\bullet}$, and $^\bullet$OH might be the active oxidants that convert bromo radicals to bromine cations.

Subsequently, the origin of the oxygen atom in the products was analyzed. A control experiment without oxygen failed to afford **2**, implying the necessity of oxygen (ESI,† Section III-10, entry 1). The reaction with only $^{18}O_2$ afforded **2** with fully ^{18}O-labelled product, albeit with only 10% yield (ESI,† Section III-10, entry 2). Product **2** was partially labelled when H_2O^{18} was used instead of H_2O^{16} (ESI,† Section III-10, entry 3). When both H_2O^{18} and $^{18}O_2$ were introduced together, complete labelling occurred (ESI,† Section III-9, 10). The above results demonstrated that oxygen atoms in the products mainly originated from water which might come from oxygen partially.

Based on the above control experiments, the possible process of this oxyhalogenation is proposed as below (ESI,† Section III-11): initially, phenylacetylene is activated *via* visible light, and then accepts an electron from a halide anion generating phenylacetylene anion radical **A** and a halide radical. Oxidation of radical **A** by air was assisted by protons, generating hydrogen peroxide and water, and then regenerated ground-state phenylacetylene. Consequently, the halide radical was oxidized to a halide cation by active starting materials or hydrogen peroxide. Subsequent nuclephilic addition between the halide cation and **1** produced halonium **B**, which was attacked by water and produced the desired product after proton release. Mostly, no obvious monohaloketones were observed during transformation, and the prepared monohaloketones cannot produce desired dihaloketone. Hence, monohaloketones were not considered as intermediates.

Inspired by the halogenase enzyme, an oxyhalogenation strategy was accomplished under ambient conditions (inorganic halide sources, air, water, visible light, room temperature, and normal pressure). A novel halogenation mode, directly utilizing substrate as a catalyst for shuttling electrons between oxygen and

halide anions which controllably released active halogen and oxygen species, can be utilized in relevant areas. The transition-metal free photocatalytic strategy with a simple conjugated molecule (phenylacetylene) as both a catalyst and a reactant can help scientists to develop novel strategies, such as various biorthogonal reactions. Synthetically, in the light of the abundance of halide anions, oxygen, and phenylacetylenes, the simplicity of the reaction conditions and the efficiency of the reactive mode, this method will be useful for efficient synthesis and medicinal studies. Further corresponding drug discovery is underway in our lab.

We are grateful for financial support provided by the National Key Research and Development Program of China (2017YFD0200500), NSFC (21971065, 21722202, 21672069), the S&TCSM of Shanghai (Grant 18JC1415600), Professor of Special Appointment (Eastern Scholar) at Shanghai Institutions of Higher Learning, and the National Program for Support of Top-notch Young Professionals.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova and C. T. Walsh, *Chem. Rev.*, 2006, **106**, 3364–3378; (*b*) A. Butler and M. Sandy, *Nature*, 2009, **460**, 848–854.
2 J. Latham, E. Brandenburger, S. A. Shepherd, B. R. K. Menon and J. Micklefield, *Chem. Rev.*, 2018, **118**, 232–269.
3 M. L. Landry and N. Z. Burns, *Acc. Chem. Res.*, 2018, **51**, 1260–1271.
4 The data were collected *via* Reaxy up to 26th March 2019.
5 (*a*) A. M. Hutter and D. E. Kayhoe, *Am. J. Med.*, 1966, **41**, 581–592; (*b*) S. Srivastava, L. K. Bajpai, S. Batra, A. P. Bhaduri, J. P. Maikhuri, G. Gupta and J. D. Dhar, *Bioorg. Med. Chem.*, 1999, **7**, 2607–2613; (*c*) P. T. Wyche, M. Standiford, Y. Hou, D. Braun, A. D. Johnson, A. J. Johnson and S. T. Bugni, *Mar. Drugs*, 2013, **11**, 5089–5099.
6 (*a*) L. Qin, Y. Tian, Z. Yu, D. Shi, J. Wang, C. Zhang, R. Peng, X. Chen, C. Liu, Y. Chen, W. Huang and W. Deng, *Oncotarget*, 2016, **7**, 1395–1407; (*b*) S. Sradhanjali, D. Tripathy, S. Rath, R. Mittal and M. M. Reddy, *PLoS One*, 2017, **12**, e0177744; (*c*) B. Xu, Z. Yu, S. Xiang, Y. Li, S.-L. Zhang and Y. He, *Eur. J. Med. Chem.*, 2018, **155**, 275–284.
7 I. Saikia, A. J. Borah and P. Phukan, *Chem. Rev.*, 2016, **116**, 6837–7042.
8 A. Podgoršek, M. Zupan and J. Iskra, *Angew. Chem., Int. Ed.*, 2009, **48**, 8424–8450.
9 (*a*) D. Hellwinkel and S. Bohnet, *Chem. Ber.*, 1987, **120**, 1151–1173; (*b*) J. Liu, W. Li, C. Wang, Y. Li and Z. Li, *Tetrahedron Lett.*, 2011, **52**, 4320–4323; (*c*) L. Finck, J. Brals, B. Pavuluri, F. Gallou and S. Handa, *J. Org. Chem.*, 2018, **83**, 7366–7372.
10 (*a*) N. De Kimpe, R. Verhé, L. De Buyck, S. Tukiman and N. Schamp, *Tetrahedron*, 1979, **35**, 789–798; (*b*) Z. Chen, B. Zhou, H. Cai, W. Zhu and X. Zou, *Green Chem.*, 2009, **11**, 275–278.
11 (*a*) S. Kajigaeshi, T. Kakinami, H. Tokiyama, T. Hirakawa and T. Okamoto, *Bull. Chem. Soc. Jpn.*, 1987, **60**, 2667–2668; (*b*) G. A. Hiegel, C. D. Bayne and B. Ridley, *Synth. Commun.*, 2003, **33**, 1997–2002; (*c*) J. M. D'Oyley, A. E. Aliev and T. D. Sheppard, *Angew. Chem., Int. Ed.*, 2014, **53**, 10747–10750; (*d*) C. Wu, X. Xin, Z.-M. Fu, L.-Y. Xie, K.-J. Liu, Z. Wang, W. Li, Z.-H. Yuan and W.-M. He, *Green Chem.*, 2017, **19**, 1983–1989; (*e*) P. Wu, S. Xu, H. Xu, H. Hu and W. Zhang, *Tetrahedron Lett.*, 2017, **58**, 618–621; (*f*) E. Cho, A. Jayaraman, J. Lee, K. C. Ko and S. Lee, *Adv. Synth. Catal.*, 2019, **361**, 1846–1858; (*g*) R. Chawla, A. K. Singh and L. D. S. Yadav, *Synlett*, 2013, 1558–1562; (*h*) S. Rather, A. Kumar and Q. N. Ahmed, *Chem. Commun.*, 2019, **55**, 4511–4514; (*i*) G. I. Nikishin, N. I. Kapustina, L. L. Sokova, O. V. Bityukov and V. Terent'ev, *RSC Adv.*, 2018, **8**, 28632–28636; (*j*) X. Zhang, Y. Wu, Y. Zhang, H. Liu, Z. Xie, S. Fu and F. Liu, *Tetrahedron*, 2017, **73**, 4513–4518; (*k*) V. Kotek, P. Polák and T. Tobrman, *Monatsh. Chem.*, 2016, **147**, 405–412; (*l*) T. Nobuta, S.-i. Hirashima, N. Tada, T. Miura and A. Itoh, *Tetrahedron Lett.*, 2010, **51**, 4576–4578; (*m*) J.-Y. Wang, Q. Jiang and C.-C. Guo, *Synth. Commun.*, 2014, **44**, 3130–3138.
12 (*a*) C. Ye and J. n. M. Shreeve, *J. Org. Chem.*, 2004, **69**, 8561–8563; (*b*) P. Pandit, K. S. Gayen, S. Khamarui, N. Chatterjee and D. K. Maiti, *Chem. Commun.*, 2011, **47**, 6933–6935; (*c*) S. Madabhushi, R. Jillella, K. K. R. Mallu, K. R. Godala and V. S. Vangipuram, *Tetrahedron Lett.*, 2013, **54**, 3993–3996.
13 (*a*) T. Hering, B. Mühldorf, R. Wolf and B. König, *Angew. Chem., Int. Ed.*, 2016, **55**, 5342–5345; (*b*) T. Hering, A. U. Meyer and B. König, *J. Org. Chem.*, 2016, **81**, 6927–6936.
14 Y. Yuan, A. Yao, Y. Zheng, M. Gao, Z. Zhou, J. Qiao, J. Hu, B. Ye, J. Zhao, H. Wen and A. Lei, *iScience*, 2019, **12**, 293–303.
15 (*a*) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322–5363; (*b*) D. M. Schultz and T. P. Yoon, *Science*, 2014, **343**, 1239176; (*c*) N. A. Romero and D. A. Nicewicz, *Chem. Rev.*, 2016, **116**, 10075–10166; (*d*) L. Marzo, S. K. Pagire, O. Reiser and B. König, *Angew. Chem., Int. Ed.*, 2018, **57**, 10034–10072; (*e*) Y. Wang, Y. Li and X. Jiang, *Chem. – Asian J.*, 2018, **13**, 2208–2242; (*f*) M. Silvi and P. Melchiorre, *Nature*, 2018, **554**, 41; (*g*) Y. Li, S. A.-e.-A. Rizvi, D. Hu, D. Sun, A. Gao, Y. Zhou, J. Li and X. Jiang, *Angew. Chem., Int. Ed.*, 2019, **58**, 13499–13506; (*h*) Y. Li, M. Wang and X. Jiang, *ACS Catal.*, 2017, **7**, 7587–7592.
16 (*a*) Q. M. Kainz, C. D. Matier, A. Bartoszewicz, S. L. Zultanski, J. C. Peters and G. C. Fu, *Science*, 2016, **351**, 681–684; (*b*) B. Liu, C.-H. Lim and G. M. Miyake, *J. Am. Chem. Soc.*, 2017, **139**, 13616–13619; (*c*) G.-Z. Wang, R. Shang, W.-M. Cheng and Y. Fu, *J. Am. Chem. Soc.*, 2017, **139**, 18307–18312; (*d*) J.-H. Ye, M. Miao, H. Huang, S.-S. Yan, Z.-B. Yin, W.-J. Zhou and D.-G. Yu, *Angew. Chem., Int. Ed.*, 2017, **56**, 15416–15420; (*e*) B. Schweitzer-Chaput, M. A. Horwitz, E. de Pedro Beato and P. Melchiorre, *Nat. Chem.*, 2019, **11**, 129–135.
17 J. Tang, S. Zao, Y. Wei, Z. Quan and C. Huo, *Org. Biomol. Chem.*, 2017, **15**, 1589–1592.
18 M. L. Pegis, C. F. Wise, D. J. Martin and J. M. Mayer, *Chem. Rev.*, 2018, **118**, 2340–2391.

