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Selective radical cascade (4+2) annulation with olefins towards the synthesis of chroman derivatives *via* organo-photoredox catalysis†

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Due to the importance of chroman frameworks in medicinal chemistry, the development of novel synthetic methods for these structures is gaining increasing interest of chemists. Reported here is a new (4 + 2) radical annulation approach for the construction of these functional six-membered frameworks *via* photocatalysis. Featuring mild reaction conditions, the protocol allows readily available *N*-hydroxyphthalimide esters and electron-deficient olefins to be converted into a wide range of valuable chromans in a highly selective manner. Moreover, the present strategy can be used in the late-stage functionalization of natural product derivatives and biologically active compounds, which demonstrated the potential application. This method is complementary to the traditional Diels–Alder [4 + 2] cycloaddition reaction of *ortho*-quinone methides and electron-rich dienophiles, since electron-deficient dienophiles were smoothly transformed into the desired chromans.

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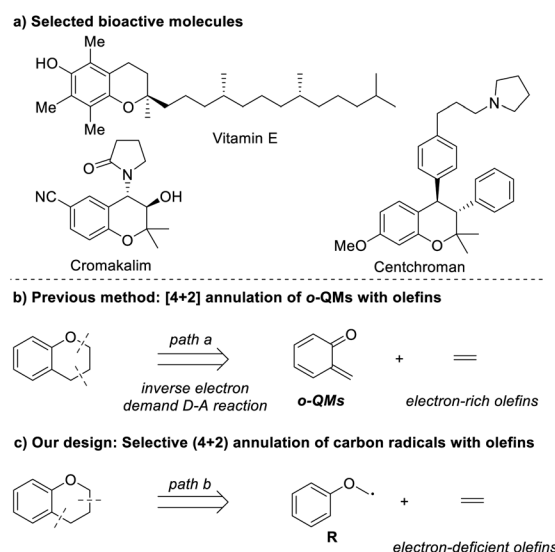
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Chroman moieties frequently exist as the key subunit in a wide array of natural products, pharmaceuticals, and bioactive molecules.¹ For example, vitamin E,² centchroman,² cromakalim³ and rubioncolin B⁴ are well-known active pharmaceutical ingredients in various therapeutic areas (Scheme 1a). Due to their significant importance in medicinal chemistry, developing new methods towards the synthesis of chromans and the installation of a variety of the functional groups in chroman frameworks are gaining increasing attention of the chemical community.⁵

In the past few decades, a great deal of methods have been developed for the assembly of substituted chromans, and among them, the Diels–Alder [4 + 2] cycloaddition reaction provides a highly efficient synthetic platform in the construction of these functional six-membered frameworks.⁶ Extensive work has been done with this strategy, resulting in a lot of significant progress. The *ortho*-quinone methides (*o*-QMs) are generally essential dienes for the Diels–Alder reaction towards the synthesis of chromans, as they are highly reactive for rapid rearomatization *via* Michael addition of nucleophiles, cycloaddition with a dienophile of 2 π partners or 6 π -electrocyclization (Scheme 1b).⁷ Herein, although various valuable chromans have

been successfully synthesized with the Diels–Alder [4 + 2] cycloaddition reaction, the use of *o*-QMs may lead to several potential limitations in some cases. One of the potential limitations is that *o*-QMs are used mainly as Michael acceptor and electron-deficient dienes to react only with nucleophiles and electron-rich dienophiles. In these considerations, the evolution of synthetic methods for chromans is very important and highly desirable. In particular, novel (4 + 2) cycloaddition



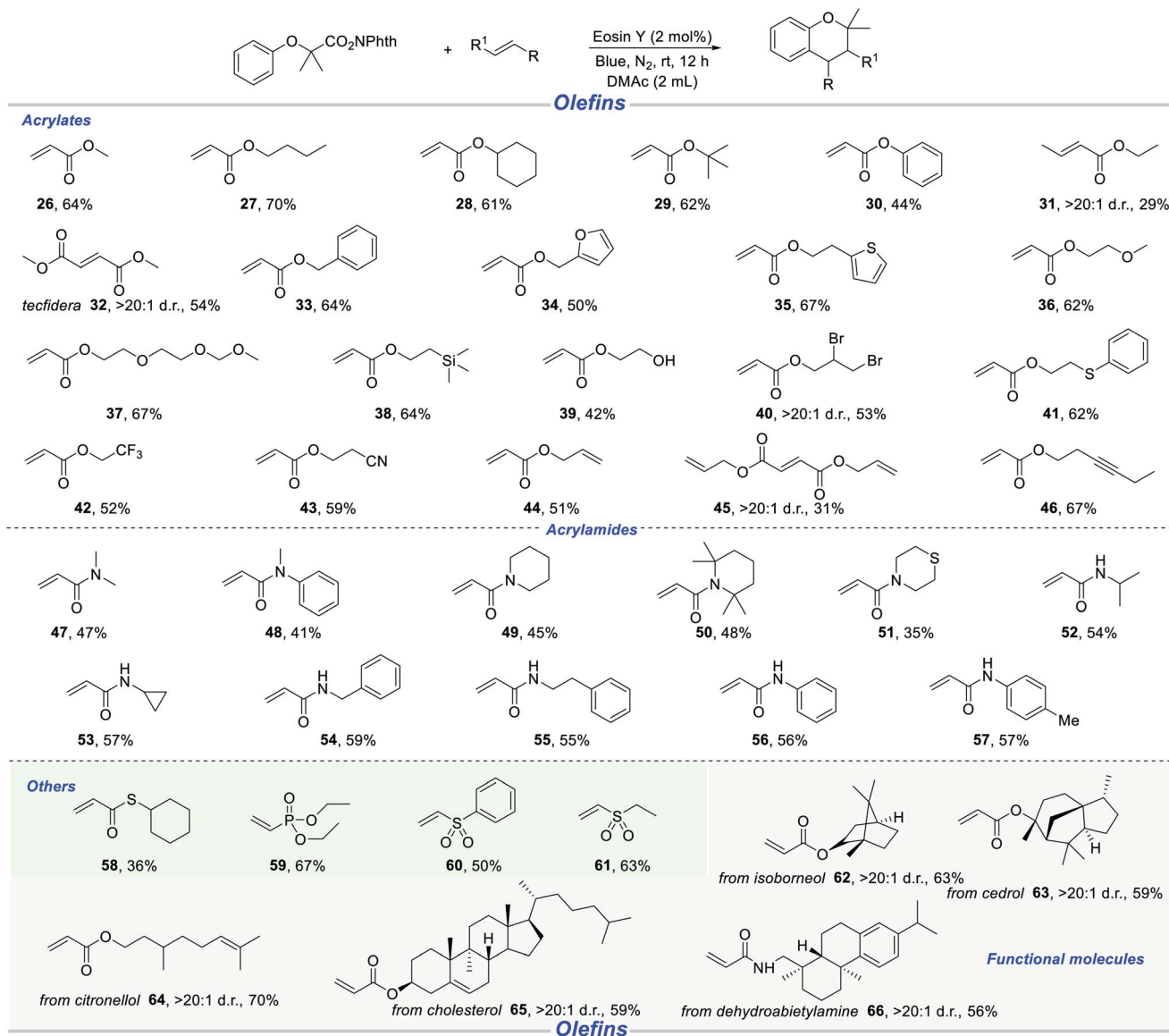
Scheme 1 Selected bioactive molecules and the synthetic methods of chromans.

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Scheme 3 Reactions of A with various olefins. Standard conditions: A (0.2 mmol), olefin (0.5 mmol), Eosin Y (2 mol%), DMAc (2.0 mL), blue light, N₂, rt, 12 h, isolated yield.

suitable to produce the corresponding chromans in satisfactory yields, which enable potential application in further functionalization (9–12). Surprisingly, electron-withdrawing substituents, such as MeCO, OCF₃, and CF₃, were also tolerated under standard conditions (13–15). This reaction could proceed effectively with *N*-hydroxyphthalimide esters containing one group or multiple groups in different positions, which delivered a variety of chroman compounds in moderate to good yields (16–19, 21–23). The annulation reaction is not limited to the construction of benzene compounds, as ethyl-3,3-dimethyl-2,3-dihydro-1*H*-benzo[*f*]chromene-1-carboxylate was also obtained in 68% yield (20). After the simple esterification, drug molecules, such as clofibrac acid, fenofibrac acid and ciprofibrate, could be transformed into the corresponding *N*-hydroxyphthalimide esters, further engaging with ethyl acrylate (10 and

24–25), which highlighted the synthetic applicability of this protocol.

Next, we shifted attention to the scope with respect to a wide range of acrylates, as shown in Scheme 3. Methyl acrylate and butyl acrylate were well amenable with *N*-hydroxyphthalimide esters (26–27). Other acrylates, such as cyclohexyl, *tert*-butyl and phenyl, were also competent reaction partners with a satisfactory efficiency (28–30). Ethyl (*E*)-but-2-enoate was tolerant to afford the desired chroman product, albeit in 29% yield (31). It is particularly noteworthy that dimethyl maleate was demonstrated to be a suitable substrate, leading to the formation of sterically hindered product (32). The sensitive benzylic C–H bond and the fragile furan and thiophene moieties could be retained in the radical cascade reaction, providing a series of functionalized chromans (33–35). Alkoxy and aligned alkoxy on



substances did not reduce the reaction efficacy (36–37). Chromans possessing various subtle trimethylsilyl, hydroxyl, primary/secondary bromoalkene, cyano and thiomethylene were accessed in reasonable yields, which provided the basis for late-stage derivatization of products (38–41, 43). Owing to the superiority of lipophilicity, permeability and metabolism, we tried to introduce trifluoromethyl into chroman skeletons. To our delight, 2,2,2-trifluoroethyl acrylate gave rise to the corresponding chromans with 52% yield (42). The unactivated alkynyl moiety and alkenyl moiety survived in the photoredox catalysis (44–46).

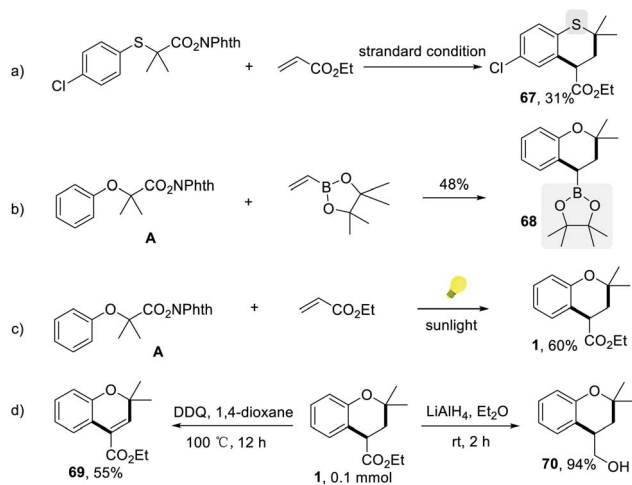
It is well-known notorious that compounds possessing nitrogen atoms are a very important class of biologically active and functional molecules. Thus, we turned our attention from acrylates to acrylamide derivatives. We were delighted to find that *N,N*-dimethylacrylamide was a suitable radical receptor to give the target molecule in moderate yield (47). Similarly, a series of chroman products were obtained with cyclic and acyclic acrylamides (48–51). Subsequently, we continued to investigate the reaction of different secondary acrylamides with *N*-hydroxyphthalimide ester **A**. These secondary acrylamides bearing *NH*-isopropyl, -cyclopropyl, -benzyl, -phenylethyl and -aryl functionalities, could smoothly be transformed into the desired (4 + 2) annulation products under standard conditions (52–57). Besides acrylates and acrylamides, this method was successfully applied to other Michael acceptors resulting in the synthesis of various functionalized chromans (58–61). In order to demonstrate the potential applicability of this methodology, a variety of natural products, their derivatives and functional molecules, such as isoborneol (62), cedrol (63), citronellol (64), cholesterol (65), and dehydroabietylamine (66), were examined, and all these structures could be embedded into target products in 56–70% yields.

The (4 + 2) annulation protocol is not limited to the synthesis of chromans. Under standard conditions, the thiochromane derivative could be formed, although less efficiently

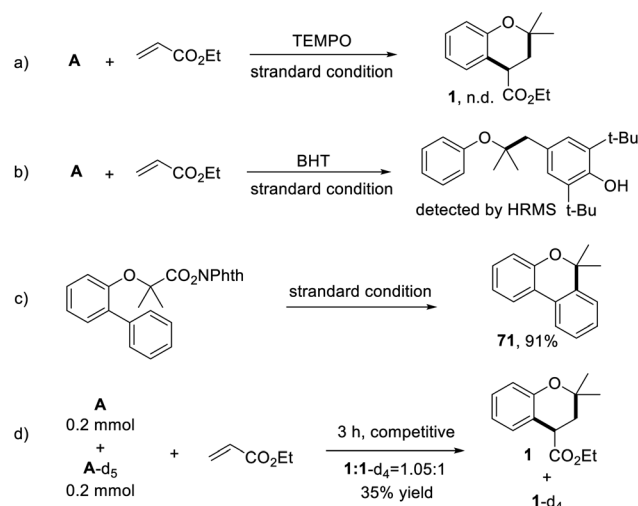
(Scheme 4a). With curiosity, we tried to use the commercially available pinacol vinylboronate instead of acrylates for this transformation because of the widespread use of organoboron compounds in organic synthesis. The target compound 2-(2,2-dimethylchroman-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane, which is a versatile building block in functionalization of chromans, was obtained in 48% yield under the slightly revised conditions (Scheme 4b). It is noting that the reaction could be conducted smoothly to afford 60% yield under sunlight irradiation, showing the potential of industrial application (Scheme 4c). Furthermore, the versatility of chroman **1** was also explored. The oxidative dehydrogenation process of **1** led to the formation of value-added ethyl 2,2-dimethyl-2*H*-chromene-4-carboxylate **69** by using DDQ as the oxidant (Scheme 4d). **1** could also be reduced to (2,2-dimethylchroman-4-yl)methanol **70** with lithium aluminum hydride in ethyl ether (Scheme 4d).

To further gain mechanistic insights into this process, a series of experiments were conducted. When the model reaction was performed under standard conditions but in the presence of 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) as a radical scavenger, the target product was not detected (Scheme 5a). Notably, when butylated hydroxytoluene (BHT) was added to this reaction system, the annulation reaction was significantly suppressed, meanwhile, a coupling product was detected by GC-MS and HRMS (Scheme 5b). These results indicated a radical-involved pathway for this transformation. Subsequently, the carbon radical was captured by an intramolecular aromatic ring, giving the cyclization product **69** in excellent yield (Scheme 5c). Moreover, the intermolecular kinetic isotope effect (KIE) experiment was carried out by using **A** and **A-d5** as competitive substrates. Under standard conditions, a KIE value of 1.05 was observed, indicating that the cleavage of the aromatic C–H bond might not be the rate-determining step in the transformation (Scheme 5d).

On the basis of the above experimental results, we proposed a possible mechanism cycle for the reaction, as shown in

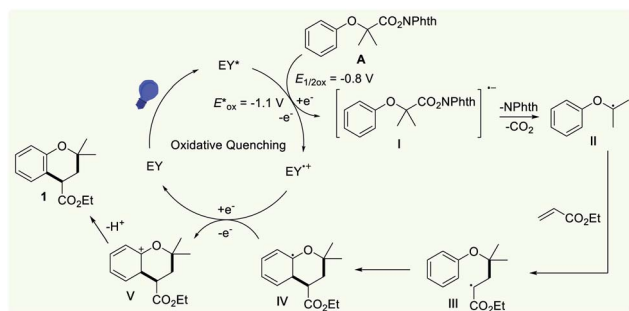


Scheme 4 The synthetic applications. (a) The synthesis of thiochromane. (b) Pinacol vinylboronate as a substrate. (c) Sunlight condition. (d) The derivatization of products.



Scheme 5 The control experiments. (a) The addition of TEMPO. (b) The addition of BHT. (c) Intramolecular reaction. (d) KIE experiment.





Scheme 6 Proposed reaction mechanism.

Scheme 6. Initially, the photocatalyst Eosin Y (EY) was transformed into the excited species EY^* ($E_{1/2}[EY^+/EY^*] = -1.1$ V vs. SCE) under the irradiation with visible light. As a redox-active species, EY^* was able to reduce *N*-hydroxyphthalimide ester ($E_{1/2}[A/I] = -0.8$ V, see the CV in the ESI†) via a single-electron-transfer (SET) process, generating the $EY^{+\bullet}$ radical cation and the corresponding *N*-hydroxyphthalimide ester radical anion **I**. The intermediate **I** underwent rapid homolytic fragmentation to generate carbon-centered nucleophilic radical **II** by releasing the phthalimide anion and carbon dioxide. Subsequently, the carbon radical **II** was captured by ethyl acrylate to form the electrophilic radical **III**, which underwent rapid intramolecular radical cyclization to afford aryl radical **IV**. Then, the intermediate **IV** was converted into cation **V** via a SET oxidation. On the other hand, the $EY^{+\bullet}$ radical cation was transformed into Eosin Y to accomplish the photocatalytic cycle. The rapid deprotonation of **V** leads to the formation of the product **1**.

Conclusions

In summary, a novel (4 + 2) radical annulation approach has been established for the synthesis of diverse chromans from readily available redox-active esters and olefins. This method operates under mild conditions and provides reactivity with a broad range of *N*-hydroxyphthalimide esters and electron-deficient olefins. The demonstrated late-stage utility of this protocol makes it particularly promising as a versatile tool to generate diverse valuable chroman structures for drug discovery and chemical biology. Compared with the traditional Diels–Alder [4 + 2] cycloaddition reaction of *ortho*-quinone methides with electron-rich dienophiles, this protocol opens a new pathway for the synthesis of chromans that generally can't be accessed by the use of *ortho*-quinone methides. We anticipate that the (4 + 2) radical annulation reaction will continue to be developed and deployed for the synthesis of highly functionalized six-membered rings, ideally providing synthetic chemists access to diverse drug and natural product derivatives by the utilization of readily available starting materials.

Data availability

The datasets supporting this article have been uploaded as part of the ESI† material.

Author contributions

Z. G. and A. L. conceived the project. Z. G., X. Z., Y. Y., and X. L. conducted and analyzed the experiments. H. C. performed the crystallographic data. Z. G., A. L., Z. H., X. Z., H. Z. and H. Y. wrote the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

- (a) E. E. Schweizer and O. Meeder-Nycz, *Chromenes, Chromanes, and Chromones*, Wiley-Interscience, New York, 1977; (b) G. P. Ellis, in *Chemistry of Heterocyclic Compounds*, 1977, pp. 1–10; (c) H. C. Shen, *Tetrahedron*, 2009, **65**, 3931–3952; (d) K. C. Nicolaou, J. A. Pfefferkorn, S. Barluenga, H. J. Mitchell, A. J. Roecker and G. Q. Cao, *J. Am. Chem. Soc.*, 2000, **122**, 9968–9976; (e) G. Zeni and R. C. Larock, *Chem. Rev.*, 2004, **104**, 2285–2310.
- (a) V. W. Bowry and R. Stocker, *J. Am. Chem. Soc.*, 1993, **115**, 6029–6044; (b) M. Uyanik, H. Hayashi and K. Ishihara, *Science*, 2014, **345**, 291–294.
- (a) J. De Crée, H. Geukens, J. Leempoels and H. Verhaegen, *Drug Dev. Res.*, 1986, **8**, 109–117; (b) A. Van de Water, W. Janssens, J. Van Neuten, R. Xhonneux, J. De Cree, H. Verhaegen, R. S. Reneman and P. A. J. Janssen, *J. Cardiovasc. Pharmacol.*, 1988, **11**, 552–563.
- J.-P. Lumb, K. C. Choong and D. Trauner, *J. Am. Chem. Soc.*, 2008, **130**, 9230–9231.
- (a) P.-S. Wang, P. Liu, Y.-J. Zhai, H.-C. Lin, Z.-Y. Han and L.-Z. Gong, *J. Am. Chem. Soc.*, 2015, **137**, 12732–12735; (b) B. J. Nachtsheim, *Science*, 2014, **345**, 270–271; (c) S. E. Ammann, G. T. Rice and M. C. White, *J. Am. Chem. Soc.*, 2014, **136**, 10834–10837; (d) J. Barluenga, M. Trincado, E. Rubio and J. M. González, *J. Am. Chem. Soc.*, 2004, **126**, 3416–3417; (e) A. F. Ward, Y. Xu and J. P. Wolfe, *Chem. Commun.*, 2012, **48**, 609–611; (f) S. W. Youn and J. I. Eom, *J. Org. Chem.*, 2006, **71**, 6705–6707; (g) R. T. Thornbury, V. Saini, T. d. A. Fernandes, C. B. Santiago, E. P. A. Talbot, M. S. Sigman, J. M. McKenna and F. D. Toste, *Chem. Sci.*, 2017, **8**, 2890–2897; (h) D. W. Manley, R. T. McBurney, P. Miller, R. F. Howe, S. Rhydderch and J. C. Walton, *J. Am. Chem. Soc.*, 2012, **134**, 13580–13583; (i) J. D. Hepworth and B. M. Heron, in *Progress in Heterocyclic Chemistry*, ed. G. W. Gribble and T. L. Gilchrist, Elsevier, 2002, vol. 14, pp. 332–



- 355; (j) X.-F. Wang, Q.-L. Hua, Y. Cheng, X.-L. An, Q.-Q. Yang, J.-R. Chen and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2010, **49**, 8379–8383; (k) Y. K. Chung and G. C. Fu, *Angew. Chem., Int. Ed.*, 2009, **48**, 2225–2227; (l) B. M. Trost, H. C. Shen, L. Dong and J.-P. Surivet, *J. Am. Chem. Soc.*, 2003, **125**, 9276–9277; (m) M. Wollenburg, J. Bajohr, A. D. Marchese, A. Whyte, F. Glorius and M. Lautens, *Org. Lett.*, 2020, **22**, 3679–3683; (n) K. Fukamizu, Y. Miyake and Y. Nishibayashi, *J. Am. Chem. Soc.*, 2008, **130**, 10498–10499; (o) H. Ishibashi, K. Ishihara and H. Yamamoto, *J. Am. Chem. Soc.*, 2004, **126**, 11122–11123.
- 6 (a) W. Oppolzer, *Angew. Chem., Int. Ed.*, 1977, **16**, 10–23; (b) B.-s. Jeon, S.-A. Wang, M. W. Ruzsyczky and H.-w. Liu, *Chem. Rev.*, 2017, **117**, 5367–5388; (c) A. G. Fallis, *Acc. Chem. Res.*, 1999, **32**, 464–474; (d) W.-J. Bai, J. G. David, Z.-G. Feng, M. G. Weaver, K.-L. Wu and T. R. R. Pettus, *Acc. Chem. Res.*, 2014, **47**, 3655–3664; (e) B. Liu, S. Fu and C. Zhou, *Nat. Prod. Rep.*, 2020, **37**, 1627–1660.
- 7 (a) C.-C. Hsiao, S. Raja, H.-H. Liao, I. Atodiresei and M. Rueping, *Angew. Chem., Int. Ed.*, 2015, **54**, 5762–5765; (b) J.-J. Zhao, S.-B. Sun, S.-H. He, Q. Wu and F. Shi, *Angew. Chem., Int. Ed.*, 2015, **54**, 5460–5464; (c) S. K. Alamsetti, M. Spanka and C. Schneider, *Angew. Chem., Int. Ed.*, 2016, **55**, 2392–2396; (d) K. Zhao, Y. Zhi, T. Shu, A. Valkonen, K. Rissanen and D. Enders, *Angew. Chem., Int. Ed.*, 2016, **55**, 12104–12108; (e) M. Uyanik, K. Nishioka, R. Kondo and K. Ishihara, *Nat. Chem.*, 2020, **12**, 353–362; (f) X. Lin, X. Liu, K. Wang, Q. Li, Y. Liu and C. Li, *Nat. Commun.*, 2021, **12**, 4958; (g) M. Xiang, C.-Y. Li, X.-J. Song, Y. Zou, Z.-C. Huang, X. Li, F. Tian and L.-X. Wang, *Chem. Commun.*, 2020, **56**, 14825–14828; (h) G. Desimoni, G. Faita and P. Quadrelli, *Chem. Rev.*, 2018, **118**, 2080–2248; (i) B. Yang and S. Gao, *Chem. Soc. Rev.*, 2018, **47**, 7926–7953; (j) Y. Xie and B. List, *Angew. Chem., Int. Ed.*, 2017, **56**, 4936–4940; (k) F. Göricke and C. Schneider, *Angew. Chem., Int. Ed.*, 2018, **57**, 14736–14741; (l) J. Zhang, L. Lin, C. He, Q. Xiong, X. Liu and X. Feng, *Chem. Commun.*, 2018, **54**, 74–77; (m) T. J. Doyon, J. C. Perkins, S. A. Baker Dockrey, E. O. Romero, K. C. Skinner, P. M. Zimmerman and A. R. H. Narayan, *J. Am. Chem. Soc.*, 2019, **141**, 20269–20277.
- 8 (a) W. Zhao, R. P. Wurz, J. C. Peters and G. C. Fu, *J. Am. Chem. Soc.*, 2017, **139**, 12153–12156; (b) A. Fawcett, J. Pradeilles, Y. Wang, T. Mutsuga, E. L. Myers and V. K. Aggarwal, *Science*, 2017, **357**, 283; (c) L. Candish, M. Teders and F. Glorius, *J. Am. Chem. Soc.*, 2017, **139**, 7440–7443; (d) J. Xuan, Z.-G. Zhang and W.-J. Xiao, *Angew. Chem., Int. Ed.*, 2015, **54**, 15632–15641; (e) H.-M. Huang, M. Koy, E. Serrano, P. M. Pflüger, J. L. Schwarz and F. Glorius, *Nat. Catal.*, 2020, **3**, 393–400; (f) A. Tlahuext-Aca, R. A. Garza-Sanchez and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56**, 3708–3711; (g) R. Mao, A. Frey, J. Balon and X. Hu, *Nat. Catal.*, 2018, **1**, 120–126; (h) M.-C. Fu, R. Shang, B. Zhao, B. Wang and Y. Fu, *Science*, 2019, **363**, 1429; (i) X. Yi, R. Mao, L. Lavrencic and X. Hu, *Angew. Chem., Int. Ed.*, 2021, **60**, 23557–23563; (j) R. Mao, J. Balon and X. Hu, *Angew. Chem., Int. Ed.*, 2018, **57**, 9501–9504; (k) R. Mao, J. Balon and X. Hu, *Angew. Chem., Int. Ed.*, 2018, **57**, 13624–13628; (l) C. Zhu, H. Yue, L. Chu and M. Rueping, *Chem. Sci.*, 2020, **11**, 4051–4064.
- 9 D. P. Hari and B. Konig, *Chem. Commun.*, 2014, **50**, 6688–6699.

