



Cite this: *RSC Adv.*, 2022, 12, 32097

Received 29th July 2022
Accepted 27th October 2022

DOI: 10.1039/d2ra04730f

rsc.li/rsc-advances

Lewis acid-catalyzed [4 + 2] cycloaddition of donor–acceptor cyclobutanes with iminooxindoles: access to spiro[piperidine-3,2'-oxindoles]†

Zuliang Chen,^{ID}*^{ab} Keyi Yan,^{‡a} Hui Luo,^{‡a} Jun Yan^a and Yang Zeng^a

A new approach is described for the synthesis of spiro[piperidine-3,2'-oxindoles] in 35–82 yields with excellent stereoselectivity via the [4 + 2] cycloaddition reaction of donor–acceptor cyclobutanes with iminooxindoles in the presence of 10–30 mol% Sc(OTf)₃ at room temperature. This methodology provides great potential for building spiro-heterocycle compounds from simple building blocks.

Spirocyclic oxindole skeletons are present in numerous naturally occurring alkaloids and medicinal active molecules.¹ Among them, spiro[piperidine-3,2'-oxindoles] molecular frameworks are attractive scaffolds because of their usefulness in potential biological activities. For instance, the drug KAE609 (formerly known as NITD609 or cipargamin), which has been identified as a potential treatment for malaria,² and quinoline spirooxindoles, which is a potential antitumour molecular.³ Furthermore, some spiro[piperidine-3,2'-oxindoles] are being investigated as peptide isosteres that can mimetic type II β -turn in the search for new enzyme inhibitors (Fig. 1).⁴ Given the importance of this structural class, the great advances that have occurred,^{1d,g-j} the continuous development of catalytic and versatile synthetic strategies that allow the direct formation of these frameworks is still needed. Herein, we report a general and efficient method for the synthesis of highly substituted spiro[piperidine-3,2'-oxindoles] from donor–acceptor (D–A) cyclobutanes and iminooxindoles catalyzed by Lewis acid under mild conditions.

Cycloaddition reactions of strained cycloalkanes represent one of the most efficient ways for the synthesis of carbo- and heterocycles in organic chemistry.⁵ Cyclobutanes are found in a large number of biologically active natural products.⁶ Moreover, as an important type of four-membered all-carbon building block, donor–acceptor (D–A) cyclobutanes have been used in the ring-opening reaction⁷ and applied in the construction of various cyclic molecular frameworks by [4 + *n*]

cycloaddition⁸ under the catalysis of Lewis acids.⁹ For example, in 2010, Pagenkopf group reported a Yb(OTf)₃ catalyzed [4 + 2] cycloaddition reaction of D–A cyclobutanes and imines, giving highly substituted piperidines (Scheme 1a). However, to the best of our knowledge, examples of cycloaddition of D–A cyclobutanes with iminooxindoles for constructing spiro[piperidine-3,2'-oxindoles] under Lewis acid have not been reported. Thus, the development of new synthetic protocols to access such spiro-heterocycle skeleton is still desirable (Scheme 1b).

Recently, we reported a Lu(OTf)₃-catalyzed [4 + 4] cycloaddition reaction of D–A cyclobutanes with anthranils to deliver oxa-bridged eight-membered heterocycles.¹⁰ Owing to our continuous interest in Lewis acid catalyzed reactions,¹¹ particularly in D–A cyclobutanes involved transformations, we envisioned that, upon suitable activation by acid, the reaction of D–A cyclobutanes and iminooxindoles would provide a new approach to deliver diverse spiro[piperidine-3,2'-oxindoles] (Scheme 1b).

We tested our hypothesis using iminooxindole **1a** and dimethyl 2-(4-methoxyphenyl)cyclobutane-1,1-dicarboxylate **2a** as model substrates. Initially, the use of 10 mol% Yb(OTf)₃ as a catalyst did not yield good results (Table 1, entries 1 and 2). To our delight, spiro[piperidine-3,2'-oxindoles] **3aa** was isolated in 82% yield as a single isomer and a trace amount of unidentified

^aCollege of Chemistry and Bio-engineering, Yichun University, Yichun 336000, P. R. China. E-mail: zai81789@163.com

^bKey Laboratory of Jiangxi University for Applied Chemistry and Chemical Biology, Yichun University, 336000, P. R. China

† Electronic supplementary information (ESI) available. CCDC 2143778. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d2ra04730f>

‡ These authors contributed equally to this work.

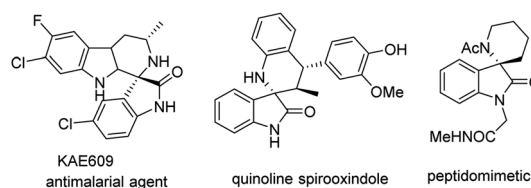
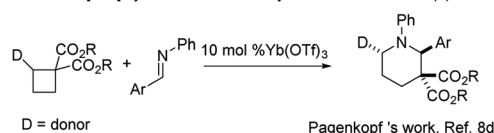


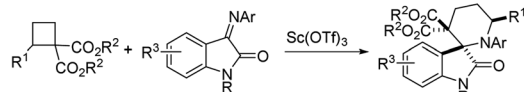
Fig. 1 Some examples of bioactive spiro[piperidine-3,2'-oxindoles].



Piperidines via [3+2] cycloaddition of D-A cyclobutanes to imines (a)



This work: D-A cyclobutanes in spiro[piperidine-3,2'-oxindoles] synthesis (b)



Scheme 1 Previous work and our strategy for this study.

Table 1 Screening the reaction conditions^a

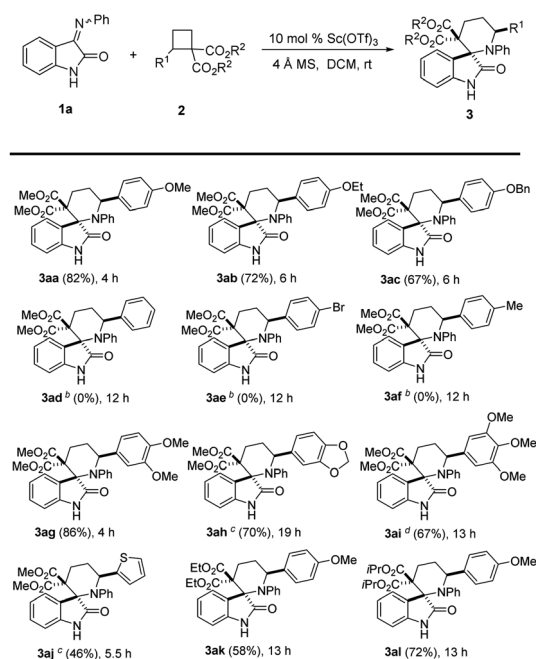
Entry	Catalyst	Solvent	Isolated yield (%)
1	Yb(OTf) ₃	DCM	Trace
2 ^b	Yb(OTf) ₃	DCM	n.r.
3	Sc(OTf) ₃	DCM	82
4	Y(OTf) ₃	DCM	Trace
5	Hf(OTf) ₄	DCM	Trace
6	In(OTf) ₃	DCM	Trace
7	Cu(OTf) ₂	DCM	Trace
8	Lu(OTf) ₃	DCM	Trace
9	Nd(OTf) ₃	DCM	Trace
10	Fe(OTf) ₃	DCM	n.r.
11	FeCl ₃	DCM	30
12	SnCl ₂	DCM	n.r.
13	SnCl ₄	DCM	Complex
14	Bi(OTf) ₃	DCM	n.r.
15	Tm(OTf) ₃	DCM	Trace
16	Gd(OTf) ₃	DCM	Trace
17	Er(OTf) ₃	DCM	Trace
18	Ho(OTf) ₃	DCM	Trace
19	MgI ₂	DCM	Trace
20	Sc(OTf) ₃	DCE	72
21	Sc(OTf) ₃	Toluene	40
22	Sc(OTf) ₃	CHCl ₃	28
23	Sc(OTf) ₃	CH ₃ CN	Trace
24	Sc(OTf) ₃	Acetone	Trace
25 ^c	Sc(OTf) ₃	DCM	32

^a Reaction conditions: **1a** (0.22 mmol), **2a** (0.2 mmol), 10 mol% catalyst, and 60 mg of activated 4 Å MS in 2.0 mL of solvent at room temperature, DCM = CH₂Cl₂, DCE = ClCH₂CH₂Cl, n.r. = no reaction. ^b The reaction was performed according to the ref. ^{8d}, at -50 °C for 1 h, then at 0 °C overnight. ^c Without 4 Å MS.

product when the reaction was carried out under the catalysis of 10 mol% Sc(OTf)₃ at room temperature (Table 1, entry 3). Catalysts such as Y(OTf)₃, Hf(OTf)₄, In(OTf)₃, Cu(OTf)₂, Lu(OTf)₃ and Nd(OTf)₃ result in low efficiency (Table 1, entries 4–9). To improve the yield, Lewis acids, including iron salts, tin salts and

other kinds of Lewis acids, were also tested, and the results are unsatisfactory (Table 1, entries 10–19). The yield decreased when the reaction was carried out in DCE, toluene and CHCl₃ (Table 1, entries 20–22). Polar solvents were unsuitable for this cycloaddition reaction (Table 1, entries 23 and 24). Only a 32% isolated yield was obtained when the reaction was performed without 4 Å molecular sieves (MS), indicating that a trace amount of water might result in a side product (Table 1, entry 25).

With the optimized reaction conditions in hand, the scope of this Lewis-acid catalyzed [4 + 2] cycloaddition reaction was explored with iminooxindole **1a** and various D-A cyclobutanes **2**, and the results are summarized in Table 2. 4-Phenyl D-A cyclobutane with an ethoxyl or benzyloxyl on the phenyl ring afforded the corresponding products in 67–72% yield (Table 2, **3ab–3ac**). However, cyclobutane **2d** without a substituent on the phenyl ring (**R**¹ position) and **2e** with a weak electron-withdrawing group (Br) on the phenyl ring (**R**¹ position) could not undergo the cycloaddition reaction with **1a**, and no desired cycloadducts were detected (Table 2, **3ad–3ae**). The reaction of iminooxindole **1a** and cyclobutanes **2f** (**R**¹ being 4-methyl-phenyl) also failed (Table 2, **3f**). Di- and trisubstituted cyclobutanes **2g–2i** with electron-donating groups on the phenyl ring (**R**¹ position) also worked in this reaction, furnishing [4 + 2] cycloaddition products in 41–80% isolated yields albeit higher catalyst loading and longer reaction time were needed in some cases (Table 2, **3ag–3ai**). For thienyl-substituted cyclobutane **3i**, the desired [4 + 2] cycloaddition product **3aj** was obtained in

Table 2 Substrate scope^a

^a Reaction conditions: **1a** (0.22 mmol), **2** (0.2 mmol), 10 mol% Sc(OTf)₃, and 60 mg of activated 4 Å MS in 2.0 mL of DCM at rt, isolated yield. ^b 100 mol% Sc(OTf)₃ was used at 90 °C, and no desired product was detected. ^c 20 mol% Sc(OTf)₃ was used. ^d 30 mol% Sc(OTf)₃ was used.

46% yield (Table 2, **3aj**). The aforementioned results indicate that the nature and position of the substituents on the aromatic rings significantly affect the reaction activity. Surprisingly, the dicarboxylates can be switched to other esters to give the desired spiro[piperidine-3,2'-oxindoles] **3ak–3al** in 58–72% yields (Table 2, **3ak–3al**). The structure and the relative stereochemistry of the products were established by X-ray crystallography analysis of **3aa** (Fig. 2).

We studied the scope of this reaction due to the variation of the iminoxindole component (Table 3). The data in Table 3 showed that various functional groups were introduced into the oxindole fragment of iminoxindole **1b–1g** (R^3 position), such as halides (F, Cl, Br), methyl, methoxyl and nitro group, were

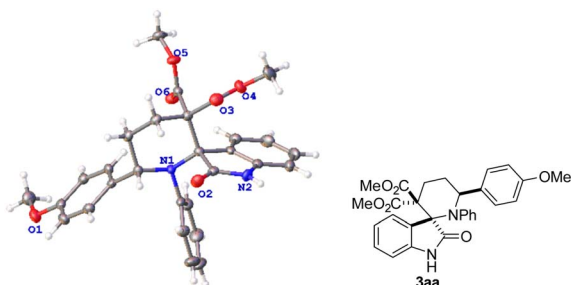
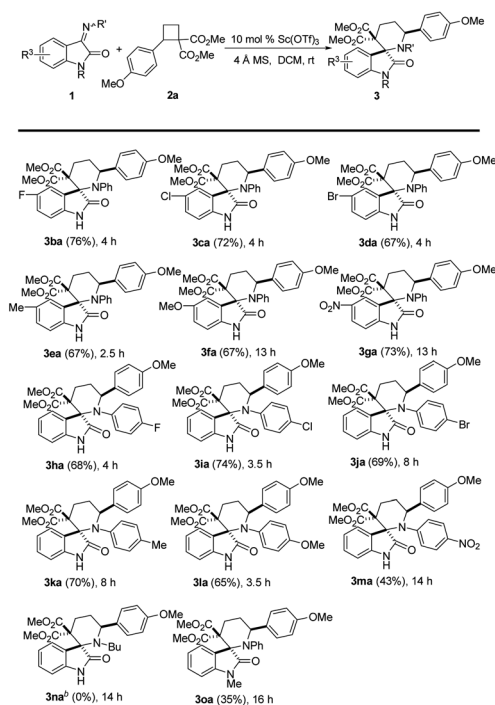


Fig. 2 X-ray crystal structure of compound **3aa** (CCDC 2143778†).

Table 3 Substrate scope^a

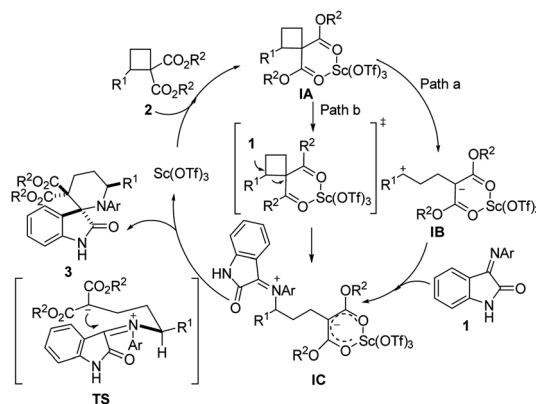


^a Reaction conditions: **1a** (0.22 mmol), **2** (0.2 mmol), 10 mol% Sc(OTf)₃, and 60 mg of activated 4 Å MS in 2.0 mL of DCM at rt, isolated yield.
^b 100 mol% Sc(OTf)₃ was used at 90 °C, and no desired product was detected.

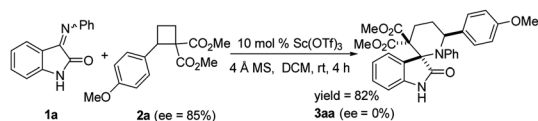
compatible, affording the desired [4 + 2] cycloaddition products **3ba–3ga** in 67–76% isolated yields (Table 3, **3ba–3ga**). Similarly, iminoxindole **1h–1m**, bearing both electron-withdrawing and electron-donating groups in the aromatic substituent at the imine N atom (R' group), also reacted with D–A cyclobutane **2a** and yielded corresponding products **3ha–3ma** (Table 3, **3ha–3ma**). Unfortunately, when we used iminoxindole **1** with alkyl groups (e.g., Bu, **1n**) at the imine N atom, no desired cycloadduct **3na** was detected. The reaction of *N*-protected iminoxindole **1o** (R = Me) with cyclobutane **2a**, affording the desired product in 35% yield (Table 3, **3oa**). It is noteworthy to mention that no other stereoisomer was detectable in all the reactions we carried out.

Based on these experimental results, a plausible mechanism that accounts for these results is proposed in Scheme 2. Initially, the Lewis acid Sc(OTf)₃ binds to the ester moiety to produce intermediate **IA**. The direct C–C heterolysis of **IA** would yield intermediate **IB** (path a), which would readily react with iminoxindole to yield a zwitterionic intermediate **IC**. Subsequent cyclization *via* the favored conformation **TS** would afford cycloadducts **3** and regenerate the catalyst. The alternative reaction pathway (path b) to generate **IC** from **IA** is *via* an S_N2-like nucleophilic attack of iminoxindole to the activated D–A cyclobutane, thereby causing the inversion of the stereochemistry at the activated R^1 substituted carbon center of cyclobutane, which has been explored by Johnson group in donor–acceptor cyclopropanes.¹² Thus, the reaction of enantioenriched cyclobutane would give an enantioenriched cycloadduct. To know which reaction pathway is the real one, enantioenriched **2a** was prepared based on the method developed by Tang *et al.*¹³ After running for 4 h under standard reaction conditions, the reaction affords a racemic cycloadduct **3aa** (Scheme 3), indicating that reaction path a may be a more possible reaction pathway.

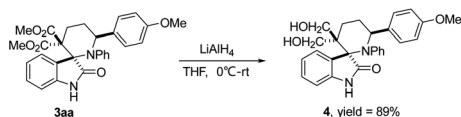
Finally, the derivatization of spiro[piperidine-3,2'-oxindoles] **3** was investigated by the selective transformations of the representative compound **3aa**. The diester group of **3aa** can be reduced by LiAlH₄ in THF, yielding the desired product **4** in an 89% isolated yield (Scheme 4).



Scheme 2 Plausible mechanism.



Scheme 3 Stereospecificity of the [4 + 2] cycloaddition reaction of enantioenriched cyclobutane **2a**.



Scheme 4 Transformations of product **3aa**.

In conclusion, we have developed an $\text{Sc}(\text{OTf})_3$ -catalyzed [4 + 2] cycloaddition reaction from D-A cyclobutanes and *N*-unprotected iminooxindoles under mild reaction conditions, providing the corresponding spiro[piperidine-3,2'-oxindoles] with good yields and excellent diastereoselectivity. Further studies on Lewis acid-catalyzed cycloaddition reactions are ongoing in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This research was supported by National Natural Science Foundation of China (Grant No. 21861041) and Research Start-up Funding in University, China.

Notes and references

- (a) A. A. Akaev, S. I. Bezzubov, V. G. Desyatkin, N. S. Vorobyeva, A. G. Majouga, M. Y. Melnikov and E. M. Budynina, *J. Org. Chem.*, 2019, **84**, 3340–3356; (b) A. J. Boddy and J. A. Bull, *Org. Chem. Front.*, 2021, **8**, 1026–1084; (c) B. Yu, D.-Q. Yu and H.-M. Liu, *Eur. J. Med. Chem.*, 2015, **97**, 673–698; (d) G. S. Singh and Z. Y. Desta, *Chem. Rev.*, 2012, **112**, 6104–6155; (e) M. M. M. Santos, *Tetrahedron*, 2014, **70**, 9735–9757; (f) T. L. Pavlovskaya, R. G. Redkin, V. V. Lipson and D. V. Atamanuk, *Mol. Diversity*, 2016, **20**, 299–344; (g) G.-J. Mei and F. Shi, *Chem. Commun.*, 2018, **54**, 6607–6621; (h) L. Hong and R. Wang, *Adv. Synth. Catal.*, 2013, **355**, 1023–1052; (i) Z.-Y. Cao, F. Zhou and J. Zhou, *Acc. Chem. Res.*, 2018, **51**, 1443–1454; (j) N. R. Ball-Jones, J. J. Badillo and A. K. Franz, *Org. Biomol. Chem.*, 2012, **10**, 5165–5181.
- (a) H. Takada, N. Kumagai and M. Shibasaki, *Org. Lett.*, 2015, **17**, 4762–4765; (b) M. Rottmann, C. McNamara, B. K. S. Yeung, M. C. S. Lee, B. Zou, B. Russell, P. Seitz, D. M. Plouffe, N. V. Dharia, J. Tan, S. B. Cohen, K. R. Spencer, G. E. González-Páez, S. B. Lakshminarayana, A. Goh, R. Suwanarusk, T. Jegla, E. K. Schmitt, H.-P. Beck, R. Brun, F. Nosten, L. Renia, V. Dartois, T. H. Keller, D. A. Fidock, E. A. Winzeler and T. T. Diagana, *Science*, 2010, **329**, 1175–1180; (c) B. K. S. Yeung, B. Zou, M. Rottmann, S. B. Lakshminarayana, S. H. Ang, S. Y. Leong, J. Tan, J. Wong, S. Keller-Maerki, C. Fischli, A. Goh, E. K. Schmitt, P. Krastel, E. Francotte, K. Kuhen, D. Plouffe, K. Henson, T. Wagner, E. A. Winzeler, F. Petersen, R. Brun, V. Dartois, T. T. Diagana and T. H. Keller, *J. Med. Chem.*, 2010, **53**, 5155–5164.
- V. V. Kouznetsov, J. S. Bello Forero and D. F. Amado Torres, *Tetrahedron Lett.*, 2008, **49**, 5855–5857.
- G. Lesma, N. Landoni, A. Sacchetti and A. Silvani, *Tetrahedron*, 2010, **66**, 4474–4478.
- (a) H. K. Grover, M. R. Emmett and M. A. Kerr, *Org. Biomol. Chem.*, 2015, **13**, 655–671; (b) N. Vemula and B. L. Pagenkopf, *Org. Chem. Front.*, 2016, **3**, 1205–1212; (c) T. F. Schneider, J. Kaschel and D. B. Werz, *Angew. Chem., Int. Ed.*, 2014, **53**, 5504–5523; (d) V. A. Rassadin and Y. Six, *Tetrahedron*, 2016, **72**, 4701–4757; (e) B. L. Pagenkopf and N. Vemula, *Eur. J. Org. Chem.*, 2017, **2017**, 2561–2567; (f) F. de Nanteuil, F. De Simone, R. Frei, F. Benfatti, E. Serrano and J. Waser, *Chem. Commun.*, 2014, **50**, 10912–10928; (g) N. De and E. J. Yoo, *ACS Catal.*, 2018, **8**, 48–58; (h) D. B. Werz and A. T. Biju, *Angew. Chem., Int. Ed.*, 2020, **59**, 3385–3398; (i) V. Pirenne, B. Muriel and J. Waser, *Chem. Rev.*, 2021, **121**, 227–263; (j) J. C. Namyslo and D. E. Kaufmann, *Chem. Rev.*, 2003, **103**, 1485–1538; (k) H.-U. Reissig and R. Zimmer, *Angew. Chem., Int. Ed.*, 2015, **54**, 5009–5011.
- (a) M. Wang and P. Lu, *Org. Chem. Front.*, 2018, **5**, 254–259; (b) Y.-Y. Fan, X.-H. Gao and J.-M. Yue, *Sci. China: Chem.*, 2016, **59**, 1126–1141; (c) J. Li, K. Gao, M. Bian and H. Ding, *Org. Chem. Front.*, 2020, **7**, 136–154.
- (a) S. Kolb, M. Petzold, F. Brandt, P. G. Jones, C. R. Jacob and D. B. Werz, *Angew. Chem., Int. Ed.*, 2021, **60**, 15928–15934; (b) A. Kreft, S. Ehlers, P. G. Jones and D. B. Werz, *Org. Lett.*, 2019, **21**, 6315–6319; (c) N. L. Ahlburg, T. Freese, S. Kolb, S. Mummel, A. Schmidt and D. B. Werz, *Eur. J. Org. Chem.*, 2021, **2021**, 1603–1606; (d) S. Kolb, N. L. Ahlburg and D. B. Werz, *Org. Lett.*, 2021, **23**, 5549–5553; (e) B. Mondal, D. Das and J. Saha, *Org. Lett.*, 2020, **22**, 5115–5120.
- (a) S. Shigeru, S. Kazuhiko, N. Hideyuki and H. Masaki, *Chem. Lett.*, 1991, **20**, 1149–1152; (b) E. A. Allart, S. D. R. Christie, G. J. Pritchard and M. R. J. Elsegood, *Chem. Commun.*, 2009, 7339–7341; (c) A. T. Parsons and J. S. Johnson, *J. Am. Chem. Soc.*, 2009, **131**, 14202–14203; (d) M. M. A. R. Moustafa and B. L. Pagenkopf, *Org. Lett.*, 2010, **12**, 4732–4735; (e) M. M. A. R. Moustafa, A. C. Stevens, B. P. Machin and B. L. Pagenkopf, *Org. Lett.*, 2010, **12**, 4736–4738; (f) A. C. Stevens, C. Palmer and B. L. Pagenkopf, *Org. Lett.*, 2011, **13**, 1528–1531; (g) F. de Nanteuil and J. Waser, *Angew. Chem., Int. Ed.*, 2013, **52**, 9009–9013; (h) M. Kawano, T. Kiuchi, S. Negishi, H. Tanaka, T. Hoshikawa, J.-i. Matsuo and H. Ishibashi, *Angew. Chem., Int. Ed.*, 2013, **52**, 906–910; (i) N. Vemula, A. C. Stevens, T. B. Schon and B. L. Pagenkopf, *Chem. Commun.*, 2014, **50**, 1668–1670; (j) J.-L. Hu, L. Wang, H. Xu,



- Z. Xie and Y. Tang, *Org. Lett.*, 2015, **17**, 2680–2683; (k) D. Perrotta, S. Racine, J. Vuilleumier, F. de Nanteuil and J. Waser, *Org. Lett.*, 2015, **17**, 1030–1033; (l) N. Vemula and B. L. Pagenkopf, *Eur. J. Org. Chem.*, 2015, **2015**, 4900–4906; (m) L.-W. Feng, H. Ren, H. Xiong, P. Wang, L. Wang and Y. Tang, *Angew. Chem., Int. Ed.*, 2017, **56**, 3055–3058; (n) L. K. B. Garve, A. Kreft, P. G. Jones and D. B. Werz, *J. Org. Chem.*, 2017, **82**, 9235–9242; (o) X.-K. Kuang, J. Zhu, L. Zhou, L. Wang, S. R. Wang and Y. Tang, *ACS Catal.*, 2018, **8**, 4991–4995; (p) E. Igarashi, K. Sakamoto, T. Yoshimura and J.-i. Matsuo, *Tetrahedron Lett.*, 2019, **60**, 13–15; (q) D. Tong, J. Wu, N. Bazinski, D. Koo, N. Vemula and B. L. Pagenkopf, *Chem.–Eur. J.*, 2019, **25**, 15244–15247; (r) S. Wei, L. Yin, S. R. Wang and Y. Tang, *Org. Lett.*, 2019, **21**, 1458–1462; (s) J. Wu, P. Winiarz, D. Patel, J. de Jong, D. Tong, T. Chidley, N. Vemula and B. L. Pagenkopf, *Org. Lett.*, 2020, **22**, 3140–3144; (t) A. Manel, J. Berreur, F. R. Leroux and A. Panossian, *Org. Chem. Front.*, 2021, **8**, 5289–5295.
- 9 (a) R. Dalpozzo, G. Bartoli, L. Sambri and P. Melchiorre, *Chem. Rev.*, 2010, **110**, 3501–3551; (b) S. Kobayashi, M. Sugiura, H. Kitagawa and W. W. L. Lam, *Chem. Rev.*, 2002, **102**, 2227–2302; (c) X.-M. Wang, P. Zhang, Q. Xu, C.-Q. Guo, D.-B. Zhang, C.-J. Lu and R.-R. Liu, *J. Am. Chem. Soc.*, 2021, **143**, 15005–15010; (d) Z. Chen, Z. Tian, J. Zhang, J. Ma and J. Zhang, *Chem.–Eur. J.*, 2012, **18**, 8591–8595; (e) D. B. Baudry, A. Dormond, F. Duris, J. M. Bernard and J. R. Desmurs, *J. Fluorine Chem.*, 2003, **121**, 233–238; (f) P. Zhang, X.-M. Wang, Q. Xu, C.-Q. Guo, P. Wang, C.-J. Lu and R.-R. Liu, *Angew. Chem., Int. Ed.*, 2021, **60**, 21718–21722; (g) S. Antonioti, V. Dalla and E. Duñach, *Angew. Chem., Int. Ed.*, 2010, **49**, 7860–7888.
- 10 M. Hou, J. Li, F. Rao, Z. Chen and Y. Wei, *Chem. Commun.*, 2022, **58**, 5865–5868.
- 11 (a) J. Yan, H. Luo, Z. Chen, Y. Wei, H. Zhan and Y. Mei, *Tetrahedron Lett.*, 2020, **61**, 151453; (b) H. Luo, J. Yan, Z. Chen, Y. Wei, B. Chen and Y. Liu, *ChemistrySelect*, 2020, **5**, 4074–4077; (c) H. Zhan, M. Hou, Y. Li, Z. Chen, Y. Wei and S. Liu, *ChemistrySelect*, 2021, **6**, 11537–11540.
- 12 P. D. Pohlhaus, S. D. Sanders, A. T. Parsons, W. Li and J. S. Johnson, *J. Am. Chem. Soc.*, 2008, **130**, 8642–8650.
- 13 J.-L. Hu, L.-W. Feng, L. Wang, Z. Xie, Y. Tang and X. Li, *J. Am. Chem. Soc.*, 2016, **138**, 13151–13154.

