



Cite this: *Chem. Sci.*, 2020, **11**, 4204

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

Received 25th February 2020

Accepted 31st March 2020

DOI: 10.1039/d0sc01138j

rs.c.li/chemical-science

meta-Selective olefination of fluoroarenes with alkynes using CO₂ as a traceless directing group†

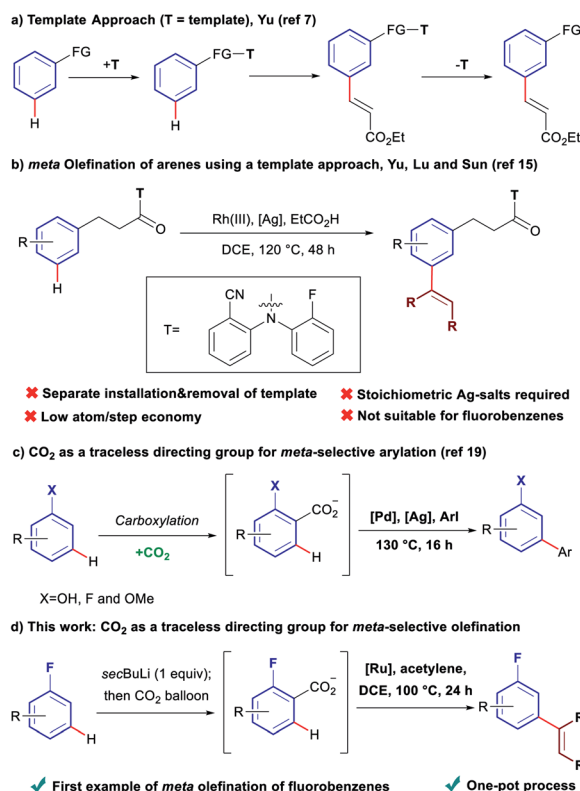
Andrew R. A. Spencer, Rishi Korde, Marc Font and Igor Larrosa *

Over the last few decades C–H olefination has received significant interest, due to the importance and usefulness of aryl olefins both as synthetic targets and intermediates. While a wide range of *ortho*-olefination protocols have been developed, only a small number of *meta*-olefinations are currently available. Importantly, the most common approach to *meta*-olefination, using a large *meta*-directing template, is not suitable for substrates such as fluorobenzenes, which cannot be derivatised. We report that the *meta*-selective olefination of fluoroarenes can be achieved *via* the use of CO₂ as a traceless directing group, which can be easily installed and removed in a one-pot process. Furthermore, this approach avoids the use of stoichiometric Ag(I)-salts, commonly used in C–H olefinations, and affords complete *meta*- over *ortho/para*-regioselectivity.

Introduction

Over the last decades, direct C–H bond activation has emerged as a powerful tool providing a wide variety of novel disconnections simplifying access to, and accelerating the synthesis of complex molecules.¹ Aryl olefins are synthetically important motifs, as useful intermediates in synthesis,² and also due to their widespread presence in bioactive molecules and pharmaceuticals.³ Consequently, large efforts have been devoted to the development of C–H olefination methodologies.⁴ While a large number of strategies have been developed for the olefination of C–H bonds *ortho* to a directing group,⁵ comparatively few exist for those in *meta* positions.⁶ To date, the only available 'direct' strategy for *meta*-olefination, involves the use of the U-shaped directing groups pioneered by the group of Yu (Scheme 1a).⁷ This approach has been used to perform *meta*-olefinations on derivatives of benzyl alcohols,⁸ *N*-methyl anilines,⁹ phenyl acetic acids,¹⁰ benzyl sulfonyl esters,¹¹ benzoic acids,¹² aromatic carbonyls¹³ and aryl boronic acids,¹⁴ using alkenes as coupling partners. The major drawback of this approach arises from the need to install the large U-shaped directing group, covalently bound, and its subsequent removal after the C–H olefination, as separate synthetic steps. In addition, stoichiometric toxic Ag(I)-salts are required as terminal oxidants in these oxidative couplings. A recent report has expanded the applicability of this strategy to the Rh(III)-catalysed *meta*-olefination of hydrocinnamic acid derivatives using alkynes as coupling partners (Scheme 1b).¹⁵ However, despite it being a redox neutral process, it still requires over

three equivalents of Ag(I)-salts as an additive. Furthermore, in addition to the main *meta*-olefination product, 5–10% of the sometimes difficult to separate *ortho* and *para* olefination products are typically obtained. Additionally, the U-shaped directing group strategy is only applicable to aromatics containing a group that can be easily derivatised.



Scheme 1 Comparison of the template approach and the traceless directing group relay strategy for the *meta* olefination of arenes.

School of Chemistry, University of Manchester, Oxford Road, Manchester, M13 9PL, UK. E-mail: igor.larrosa@manchester.ac.uk

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d0sc01138j

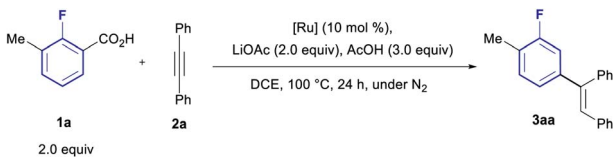


Fluoroarenes are recurring structural motifs in pharmaceuticals, agrochemicals, organic materials and other biologically relevant compounds.¹⁶ Approximately 30% of pharmaceuticals and 40% of agrochemicals currently contain at least one fluorine atom, usually at the aromatic ring.¹⁶ Thus, the direct C–H functionalisation of monofluorobenzenes can provide straightforward access to valuable materials (Fig. 1).^{3b–d} While monofluoroarenes generally present low reactivity towards direct C–H olefination, a number of examples have been reported that use the arene as cosolvent to achieve *ortho*, *para*-selective olefination.¹⁷ Some pioneering methods for direct olefination using the fluoroarene as the limiting reagent have been reported by Yu *et al.*, but mixtures of *ortho*, *meta* and *para* substitution are obtained.¹⁸ However, *meta*-selective olefination has never been achieved. Importantly, the U-shaped directing group strategy cannot be applied to this class of substrates. We have previously shown that CO₂ can be used as a traceless directing group for the *meta*-selective arylation of phenols, fluorobenzenes and anisoles (Scheme 1c).¹⁹ The process relies on the easy carboxylation of these aromatic substrates, to install a temporary carboxylate directing group. The carboxylate can then direct the arylation before it is cleaved, in a tandem process, thus allowing a one-pot *meta*-arylation to proceed. However, the CO₂ traceless directing group approach has never been demonstrated on any other type of functionalisation. Herein we report the first example of a *meta*-olefination of fluorobenzenes (Scheme 1d). This ruthenium-catalysed process involves the *in situ* installation and removal of a carboxylate, from CO₂, uses alkynes as coupling partners and avoids the need for stoichiometric use of Ag(I)-salts.

Results and discussion

We have previously developed an optimised protocol for the lithiation/carboxylation of fluoroarenes suitable for combination in a one-pot process with a Pd-catalysed tandem arylation/protodecarboxylation, leading to the *meta*-arylation of fluoroarenes.^{19c} In 2016, three methods for the Ru-catalysed tandem *ortho*-olefination/protodecarboxylation of benzoic acids by hydroarylation of alkynes were reported by Hartwig and Zhao,²⁰ Ackermann²¹ and Gooßen.²² Miura and co-workers have also

Table 1 Optimisation of catalyst. Yields were determined by ¹⁹F NMR analysis using 1-bromo-4-fluorobenzene as an internal standard



| Entry | [Ru] | 3aa (yield%) |
|----------------|---|--------------|
| 1 ^a | Ru(<i>p</i> -cymene)(CO ₂ Me) ₂ | 81 |
| 2 ^b | Ru(<i>p</i> -cymene)(CO ₂ Me) ₂ | 60 |
| 3 | Ru(<i>p</i> -cymene)(CO ₂ Me) ₂ | 86 |
| 4 | [Ru(<i>t</i> BuCN) ₆][BF ₄] ₂ | 0 |
| 5 | [Ru(C ₆ H ₆)(OPiv) ₂] | 25 |
| 6 | [Ru(C ₆ Me ₆)(OAc) ₂] | 93 |

^a Without LiOAc and AcOH. ^b Without AcOH.

reported numerous methods for the *ortho*-olefination/protodecarboxylation of benzoic acids using acrylates and styrenes as coupling partners.²³ We envisaged these methods could be ideally adapted to operate in combination with the directed *ortho*-metalation/carboxylation approach to furnish the desired *meta*-olefination of fluorarenes.

We started our investigation by probing the decarboxylative olefination of the fluorotoluic acid **1a** with diphenyl acetylene (**2a**), using Ackermann's protocol (Table 1, entry 1).²¹ To evaluate the effect of the installation of the carboxylic acid using *ortho*-lithiation during the desired one-pot process we tested the addition of 2 equiv. of LiOAc (entry 2), revealing a significant negative effect in reactivity. Gratifyingly, addition of 3 equiv. of AcOH efficiently reversed the effect of the presence of the Li-salt (entry 3), providing a method to ensure compatibility of the protocol with the carboxylation step. In previous work on Ru-catalysed *ortho*-arylation of polyfluorobenzenes we observed an inhibitory effect of coordinated *p*-cymene, leading to the development of the arene-free Ru-precatalyst [Ru(*t*BuCN)₆][BF₄]₂.²⁴ However, the use of this catalyst in the olefination reaction led to no product formation (entry 4), suggesting the η⁶-coordinated arene is essential for reactivity towards olefination. Accordingly, the weaker coordinating benzene-complex led to poor reactivity (entry 5), whereas the highly coordinating C₆Me₆-bearing Ru complex gave an improved yield, an effect which has previously been observed by Gooßen.²⁵

We then moved to optimize the full one-pot protocol, starting from *ortho*-fluorotoluene (**4a**, Table 2). Carboxylation of the fluoroarene was observed to occur in nearly quantitative conversion using *sec*BuLi at –78 °C for 30 min, followed by quenching with CO₂. Subsequent addition to the same flask of AcOH (3 equiv.), alkyne **2a** and 5 mol% Ru(C₆Me₆)(OAc)₂ in DCE led to the formation of the *meta*-olefinated product **3aa** in an excellent 85% yield (entry 1). The use of 4 equiv. or 5 equiv. of AcOH led to reduced yields (entries 2 and 3). Examination of other organic acids also led to lower yields (entries 4–6),

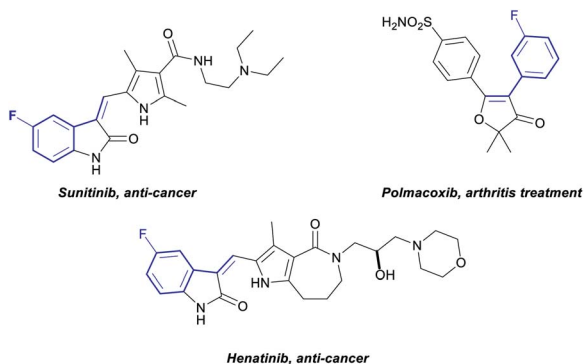
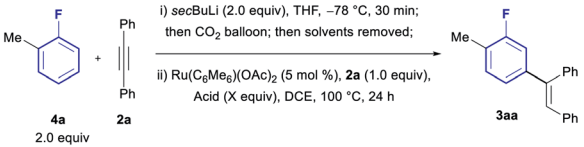


Fig. 1 Commercially available pharmaceuticals containing a *meta* alkenyl fluoroarene.



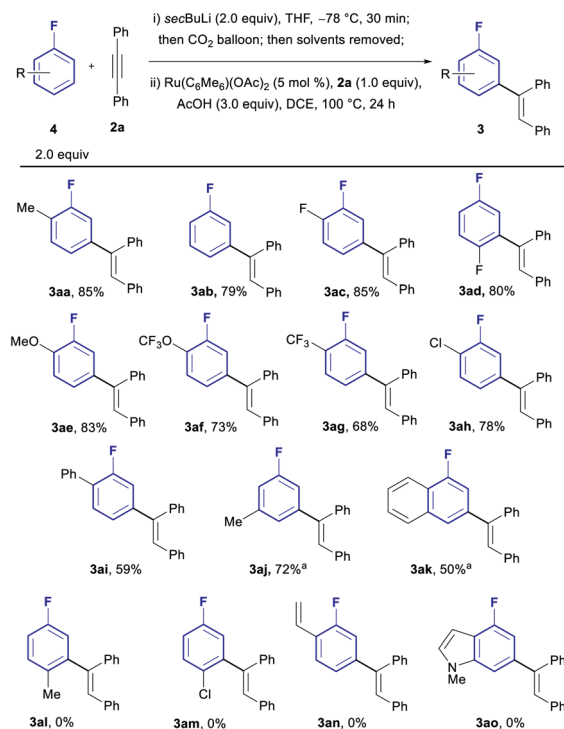
Table 2 Optimisation of one-pot protocol. Yields were determined by ^{19}F NMR analysis using 1-bromo-4-fluorobenzene as an internal standard



| Entry | Acid (equiv.) | 4aa (yield%) |
|-------|---------------------|--------------|
| 1 | AcOH (3) | 85 |
| 2 | AcOH (4) | 75 |
| 3 | AcOH (5) | 72 |
| 4 | PivOH (3) | 1 |
| 5 | <i>i</i> BuCOOH (3) | 71 |
| 6 | TFA (3) | 5 |

revealing AcOH as the optimal acid to facilitate this one-pot process.

With the optimised conditions in hand, we investigated the generality of the process with regards to the fluoroarene core (Scheme 2). Substitution patterns in *ortho*, *meta* or *para* positions were all tolerated, albeit only the relatively small F-atom was compatible in *para* (3ad). When larger groups were installed in the *para* position such as Me and Cl, no reactivity could be observed (3al and 3am). Furthermore, the reaction is in all cases completely selective towards mono-olefination and towards the *meta* position, with no traces of neither

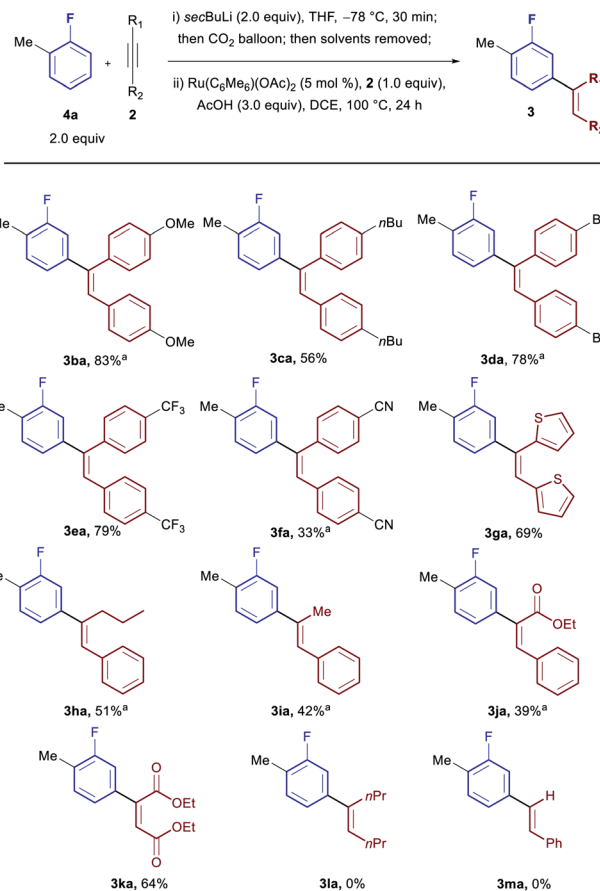


Scheme 2 Scope in fluoroarene core. ^a10 mol% catalyst used.

bisolefination nor other regioisomers observed by NMR and GCMS analysis of the reactions, even for simple fluorobenzene (3ab). Both electron withdrawing groups (3ac, 3ad, 3ag and 3ah) and donating groups (3aa, 3ae, 3af and 3aj) were compatible with the procedure. Chloroarenes (3ah) were also tolerated with no traces of de-halogenated products. Biaryl and naphthyl-based aromatic systems were also suitable substrates (3ai and 3ak).

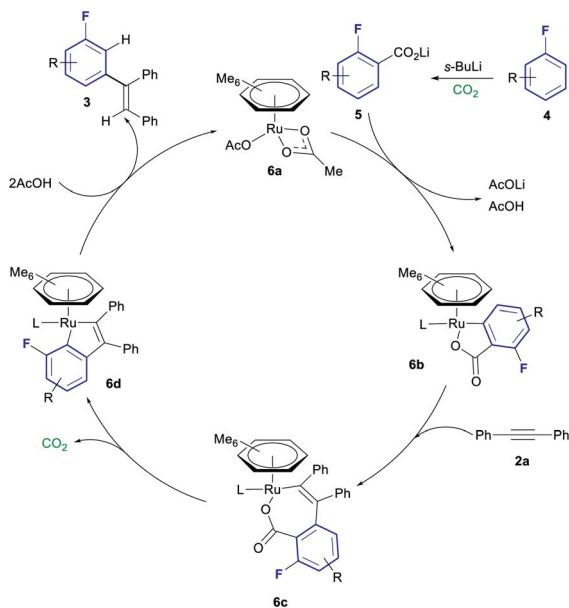
Subsequently we investigated the scope with respect to the alkyne coupling partner (Scheme 3). Both electron donating (3ba and 3ca) and electron withdrawing groups (3da, 3ea and 3fa) were reactive giving excellent yields. Heterocyclic moieties were also tolerated (3ga). While bisalkyl acetylenes were incompatible with the procedure (3la), unsymmetrical alkyl, aryl-acetylenes led to completely regioselective addition at the carbon adjacent to the alkyl group (3ha and 3ia). Diesters and unsymmetrical ester, aryl-acetylenes were also tolerated offering a handle for further functionalisation (3ja and 3ka) with ethyl phenyl propiolate preferentially forming the α -aryl ester (3ja). No product was observed when terminal acetylenes were used (3ma).

This new *meta*-olefination methodology can be easily scaled up with, for example, 3aa being formed in 70% yield (1.10 g) without any changes to the protocol.



Scheme 3 Scope in acetylene. ^a10 mol% catalyst used.





Scheme 4 Plausible mechanism for the Ru catalysed *meta* olefination of fluoroarenes.

A plausible mechanism for this transformation is shown in Scheme 4, based on the mechanistic studies performed by Hartwig and Zhao.²⁰ *ortho*-Lithiation and carboxylation of fluoroarene **4** affords lithium benzoate **5**. *ortho*-C–H activation of lithium benzoate **5** with ruthenium complex **6a** affords cyclo-metallated complex **6b**. Insertion of alkyne **2a** into the Ru–C of **6b** forms complex **6c**, which can in turn decarboxylate to form the 5-membered metallocycle in complex **6d**. Protonation of this complex with 2 equiv. of AcOH liberates the final product **3** and reforms complex **6a**, thus closing the catalytic cycle.

Conclusions

In conclusion, we have developed the first example of a methodology for the *meta*-selective olefination of fluoroarenes. The natural *ortho*, *para*-reactivity of this class of substrates has been overcome by employing CO₂ as a traceless directing group, that can be installed, used to control reactivity and then seamlessly removed in a one-pot process. Good to excellent yields can be obtained with a variety of functional groups and substitution patterns in both fluoroarene and alkyne, and in all cases complete *meta*-regioselectivity is observed.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully acknowledge the Engineering and Physical Sciences Research Council (EPSRC, EP/L014017/2) and the Marie Skłodowska Curie actions (IF-656841 to MF) for funding.

Notes and references

- (a) R. H. Crabtree, *Chem. Rev.*, 1985, **85**, 245–269; (b) A. E. Shilov and G. B. Shul'pin, *Chem. Rev.*, 1997, **97**, 2879–2932; (c) J. A. Labinger and J. E. Bercaw, *Nature*, 2002, **417**, 507–514; (d) R. G. Bergman, *Nature*, 2007, **446**, 391–393; (e) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (f) X. Chen, K. M. Engle, D.-H. Wang and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (g) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem., Int. Ed.*, 2009, **48**, 9792–9826; (h) C.-J. Li, *Acc. Chem. Res.*, 2009, **42**, 335–344; (i) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761; (j) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292; (k) M. Tobisu and N. Chatani, *Science*, 2014, **343**, 850–851; (l) M. Simonetti, D. M. Cannas and I. Larrosa, *Adv. Organomet. Chem.*, 2017, **67**, 299–399.
- Selected examples of aryl olefins as intermediates for the synthesis of bioactive molecules (a) T. Nishimata, Y. Sato and M. Mori, *J. Org. Chem.*, 2004, **69**, 1837–1843; (b) L. V. White, B. D. Schwartz, M. G. Banwell and A. C. Willis, *J. Org. Chem.*, 2011, **76**, 6250–6257; (c) C. Singh, M. Hassam, V. P. Verma, A. S. Singh, N. K. Naikade, S. K. Puri, P. R. Maulik and R. Kant, *J. Med. Chem.*, 2012, **55**, 10662–10673.
- Examples of aryl olefins in bioactive molecules (a) J. Joseph-Charles and M. Bertucat, *Anal. Chim. Acta*, 1993, **284**, 45–52; (b) D. B. Mendel, A. D. Laird, X. Xin, S. G. Louie, J. G. Christensen, G. Li, R. E. Schreck, T. J. Abrams, T. J. Ngai, L. B. Lee, L. J. Murray, J. Carver, E. Chan, K. G. Moss, J. Ö. Haznedar, J. Sukbuntherng, R. A. Blake, L. Sun, C. Tang, T. Miller, S. Shirazian, G. McMahon and J. M. Cherrington, *Clin. Cancer Res.*, 2003, **9**, 327–337; (c) S. Hirankarn, J. S. Barrett, N. Alamuddin, G. A. FitzGerald and C. Skarke, *Clin. Pharmacol. Drug Dev.*, 2013, **2**, 379–386; (d) J. Qian, Y. Wang, J. Cao and J. Li, *J. Pharm. Biomed. Anal.*, 2013, **80**, 173–179.
- Selected reviews on C–H olefination of arenes (a) C. Nevado and A. M. Echavarren, *Synthesis*, 2005, **2**, 167–182; (b) V. P. Boyarskiy, D. S. Ryabukhin, N. A. Bokach and A. V. Vasilyev, *Chem. Rev.*, 2016, **10**, 5894–5986; (c) W. Ma, P. Gandeepan, J. Li and L. Ackermann, *Org. Chem. Front.*, 2017, **4**, 1435–1467.
- Selected examples of *ortho* C–H olefination (a) G. Cai, Y. Fu, Y. Li, X. Wan and Z. Shi, *J. Am. Chem. Soc.*, 2007, **129**, 7666–7673; (b) L. Wang, S. Liu, Z. Li and Y. Yu, *Org. Lett.*, 2011, **13**, 6137–6139; (c) B. Liu, H.-Z. Jiang and B.-F. Shi, *J. Org. Chem.*, 2014, **79**, 1521–1526; (d) A. Deb, S. Bag, R. Kancharla and D. Maiti, *J. Am. Chem. Soc.*, 2014, **136**, 13602–13605; (e) G. Li, L. Wan, G. Zhang, D. Leow, J. Sprangler and J.-Q. Yu, *J. Am. Chem. Soc.*, 2015, **137**, 4391–4397.
- Selected reviews on *meta* selective C–H functionalisation (a) J. Yang, *Org. Biomol. Chem.*, 2015, **13**, 1930–1941; (b) J. Lie, S. De Sarkar and L. Ackermann, *Top. Organomet. Chem.*, 2015, **55**, 217–257; (c) A. Dey, S. Agasti and D. Maiti, *Org. Biomol. Chem.*, 2016, **14**, 5440–5453; (d) J. A. Leitch and C. G. Frost, *Chem. Soc. Rev.*, 2017, **46**, 7145–7153.



- 7 D. Leow, G. Li, T.-S. Mei and J.-Q. Yu, *Nature*, 2012, **486**, 518–522.
- 8 (a) S. Lee, H. Lee and K. L. Tan, *J. Am. Chem. Soc.*, 2013, **135**, 18778–18781; (b) S. Fang, X. Wang, F. Yin, P. Cai, H. Yang and L. Kong, *Org. Lett.*, 2019, **21**, 1841–1844.
- 9 R.-Y. Tang, G. Li and J.-Q. Yu, *Nature*, 2014, **507**, 215–220.
- 10 (a) M. Bera, A. Modak, T. Patra, A. Maji and D. Maiti, *Org. Lett.*, 2014, **16**, 5760–5763; (b) Y. Deng and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2015, **54**, 888–891.
- 11 (a) M. Bera, A. Maji, S. K. Sahoo and D. Maiti, *Angew. Chem., Int. Ed.*, 2015, **54**, 8515–8519; (b) M. Brochetta, T. Borsari, S. Bag, S. Jana, S. Maiti, A. Porta, D. B. Werz, G. Zanoni and D. Maiti, *Chem.–Eur. J.*, 2019, **25**, 10323–10327.
- 12 S. Li, L. Cai, H. Ji, L. Yang and G. Li, *Nat. Commun.*, 2016, **7**, 10443.
- 13 S. Xie, S. Li, W. Ma, X. Xu and Z. Jin, *Chem. Commun.*, 2019, **55**, 12408–12411.
- 14 A. F. Williams, A. J. P. White, A. C. Spivey and C. J. Cordier, *Chem. Sci.*, 2020, **11**, 3301–3306.
- 15 H.-J. Xu, Y.-S. Kang, H. Shi, P. Zhang, Y.-K. Chen, B. Zhang, Z.-Q. Liu, J. Zhao, W.-Y. Sun, J.-Q. Yu and Y. Lu, *J. Am. Chem. Soc.*, 2019, **141**, 76–79.
- 16 (a) P. Kirsch and M. Bremer, *Angew. Chem., Int. Ed.*, 2000, **39**, 4216–4235; (b) W. R. Dolbier, *J. Fluorine Chem.*, 2005, **126**, 157–163; (c) C. Isanbor and D. O'Hagan, *J. Fluorine Chem.*, 2006, **127**, 303–319; (d) F. Babudri, G. M. Farinola, F. Naso and R. Ragni, *Chem. Commun.*, 2007, 1003–1022; (e) M. Hird, *Chem. Soc. Rev.*, 2007, **36**, 2070–2095; (f) D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308–319; (g) P. Jeschke, *Pest Manage. Sci.*, 2010, **66**, 10–27; (h) R. Berger, G. Resnati, P. Metrangolo, E. Weber and J. Hulliger, *Chem. Soc. Rev.*, 2011, **40**, 3496–3508; (i) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok and H. Liu, *Chem. Rev.*, 2014, **114**, 2432–2506; (j) E. A. Ilardi, E. Vitaku and J. T. Njardarson, *J. Med. Chem.*, 2014, **57**, 2832–2842; (k) T. Fujiwara and D. O'Hagan, *J. Fluorine Chem.*, 2014, **167**, 16–29; (l) Y. Zhou, J. Wang, Z. Gu, S. Wang, W. Zhu, J. L. Aceña, V. A. Soloshonok, K. Izawa and H. Liu, *Chem. Rev.*, 2016, **116**, 422–518.
- 17 (a) K. S. Kanyiva, N. Kashihara, Y. Nakao, T. Hiyama, M. Ohashi and S. Ogoshi, *Dalton Trans.*, 2010, **39**, 10483–10494; (b) C.-H. Ying, S.-B. Yan and W.-L. Duan, *Org. Lett.*, 2014, **16**, 500–503; (c) L. G. Y. Chung, N. A. B. Juwaini and J. Seayad, *ChemCatChem*, 2015, **7**, 1270–1274.
- 18 (a) H. U. Vora, A. P. Silvestri, C. J. Engelin and J.-Q. Yu, *Angew. Chem., Int. Ed.*, 2014, **53**, 2683–2686; (b) P. Wang, P. Verma, G. Xia, J. Shi, J. X. Qiao, S. Tao, P. T. W. Cheng, M. A. Poss, M. E. Farmer, K.-S. Yeung and J.-Q. Yu, *Nature*, 2017, **551**, 489–493.
- 19 (a) J. Luo, S. Preciado and I. Larrosa, *J. Am. Chem. Soc.*, 2014, **136**, 4109–4112; (b) J. Luo, S. Preciado, S. O. Araromi and I. Larrosa, *Chem.–Asian J.*, 2016, **11**, 347–350; (c) M. Font, A. R. A. Spencer and I. Larrosa, *Chem. Sci.*, 2018, **9**, 7133–7137.
- 20 J. Zhang, R. Shrestha, J. F. Hartwig and P. Zhao, *Nat. Chem.*, 2016, **8**, 1144–1151.
- 21 N. Y. P. Kumar, A. Bechtoldt, K. Raghuvanshi and L. Ackermann, *Angew. Chem., Int. Ed.*, 2016, **55**, 6929–6932.
- 22 L. Huang, A. Biafora, G. Zhang, V. Bragoni and L. J. Gooßen, *Angew. Chem., Int. Ed.*, 2016, **55**, 6933–6937.
- 23 (a) A. Maehara, H. Tsurugi, T. Satoh and M. Miura, *Org. Lett.*, 2008, **10**, 1159–1162; (b) S. Mochida, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2010, **12**, 5776–5779; (c) S. Mochida, K. Hirano, T. Satoh and M. Miura, *J. Org. Chem.*, 2011, **76**, 3024–3033.
- 24 M. Simonetti, G. J. P. Perry, X. C. Cambeiro, F. Juliá-Hernández, J. N. Arokianathar and I. Larrosa, *J. Am. Chem. Soc.*, 2016, **138**, 3596–3606.
- 25 A. Biafora, B. A. Khan, J. Bahri, J. M. Hewer and L. J. Gooßen, *Org. Lett.*, 2017, **19**, 1232–1235.

