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Introduction

α -Arylated carboxylic acids and amides are ubiquitous substructures and indispensable building blocks in chemical synthesis.¹ The wide existence of such structural motifs in biologically active molecules² (Scheme 1A) has inspired much effort to develop efficient methods towards the synthesis of α -arylated carboxylate derivatives.³ Pioneered by Buchwald and Hartwig, methods relying on the use of transition-metal catalyzed α -arylation of enolates with aryl halides have been extensively developed.⁴ Later, metal-catalyzed cross-coupling of α -halo carbonyl electrophiles with aryl nucleophiles has also been described.⁵ However, these methods are typically not applicable to direct arylation of aliphatic carboxylic acids and amides with acidic N–H bonds.⁶ To address this issue, Hartwig reported an elegant Pd-catalyzed α -arylation of carboxylic acids and secondary amides through the *in situ* formation of the corresponding disilyl intermediates in the presence of a base and TMSCl (Scheme 1B).⁷ In 2020, Engle's group described the synthesis of α -arylated amides enabled by Pd-catalyzed α -selective hydroarylation of acrylamides (Scheme 1B).⁸ These methods suffer from the use of transition metals, multi-step synthesis of advanced starting materials, and/or harsh

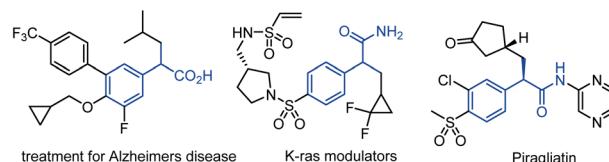
Modular synthesis of α -arylated carboxylic acids, esters and amides via photocatalyzed triple C–F bond cleavage of methyltrifluorides†

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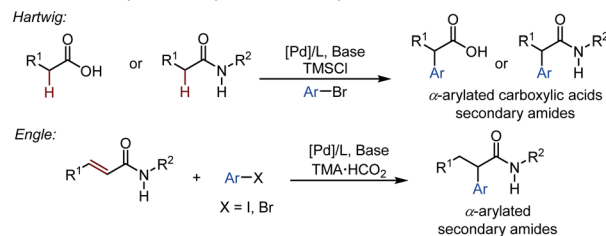
α -Arylated carboxylic acids, esters and amides are widespread motifs in bioactive molecules and important building blocks in chemical synthesis. Thus, straightforward and rapid access to such structures is highly desirable. Here we report an organophotocatalytic multicomponent synthesis of α -arylated carboxylic acids, esters and amides from exhaustive defluorination of α -trifluoromethyl alkenes in the presence of alkyltrifluoroborates, water and nitrogen/oxygen nucleophiles. This operationally simple strategy features a unified access to functionally diverse α -arylated carboxylic acids, esters, and primary, secondary, and tertiary amides through backbone assembly from simple starting materials enabled by consecutive C–F bond functionalization at room temperature. Preliminary mechanistic investigations reveal that the reaction operates through a radical-triggered three-step cascade process, which involves distinct mechanisms for each defluorinative functionalization of the C–F bond.

conditions. Different approaches for the non-transition metal catalyzed synthesis of α -arylated amides have also been reported. Nevado, Greaney, Clayden and Studer have independently reported aryl migration strategies,⁹ while Miyata and Maulide have each shown the umpolung α -arylation of

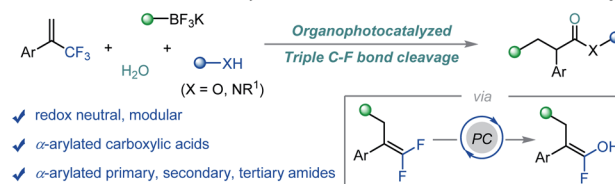
A. Examples of pharmaceutical agents displaying α -arylated carboxylic acid/amide motifs



B. Prior art of α -arylated carboxylic acids/amides synthesis



C. This work: Modular access to α -arylated acids/amides via exhaustive defluorination of CF_3



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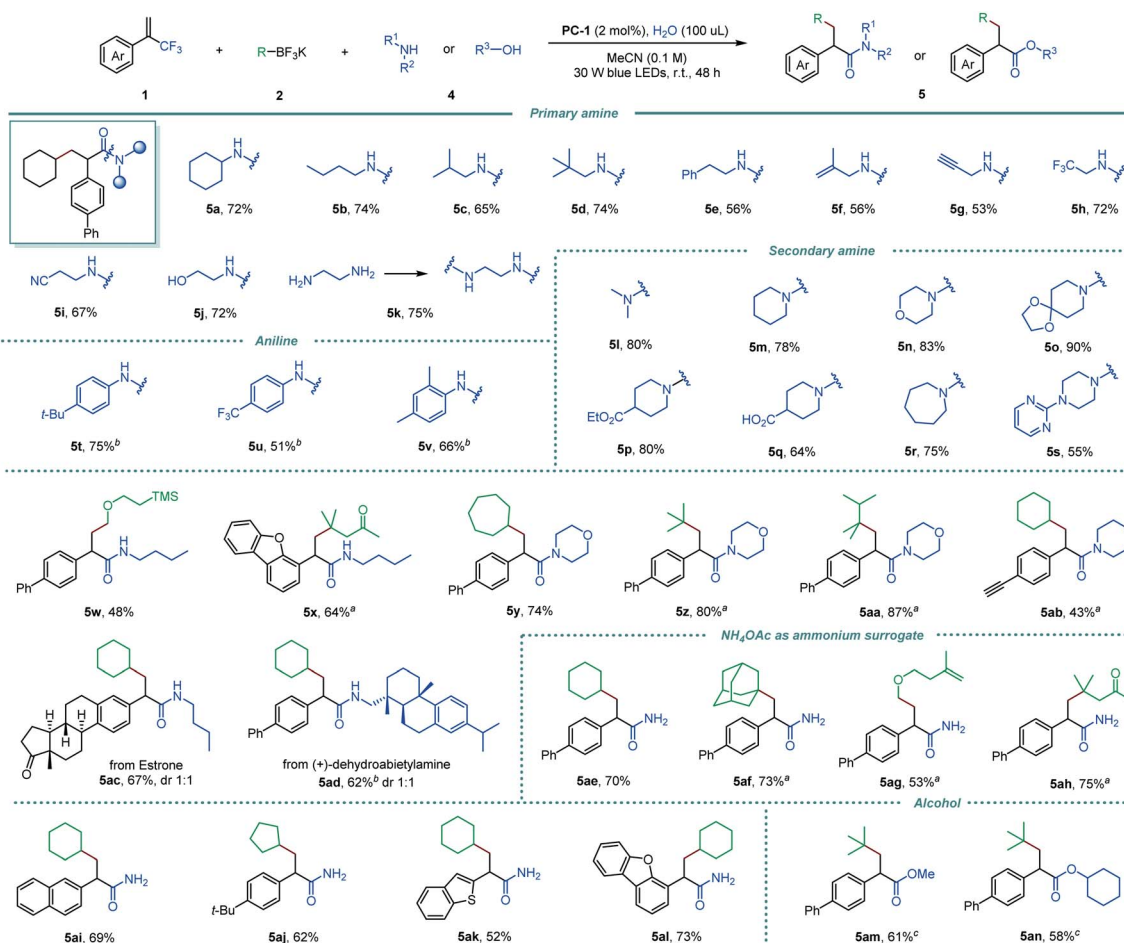
Scheme 1 Significance and synthetic design for α -arylated carboxylic acids and amides.



a fluoride substituent (**3d**) are compatible under the reaction conditions. Terminal ethynyl-substituted α -arylated carboxylic acid **3g** was obtained in 68% yield when an α -trifluoromethyl alkene with a 4-(trimethylsilyl)ethynylphenyl group was used. Cleavage of the silyl group is likely due to the release of fluoride anions during the reaction. 3-Methoxy, 3-allyloxy and 3,5-dimethyl groups were well-tolerated (**3h–3j**). The use of fused aryl and heteroaryl vinylmethyltrifluorides allowed the incorporation of naphthyl (**3k**), benzothiophenyl (**3l**) and dibenzofuranyl (**3m**) substituted carboxylic acids in good yields (61–90%). Notably, α -pyridinyl carboxylic acid (**3n**) was effectively obtained in this reaction. A cyclic alkene was also transformed into α,β -cyclic- α -arylated carboxylic acid **3o** in 57% yield. However, α -trifluoromethyl alkenes with electron-withdrawing arenes failed to deliver the corresponding α -arylated carboxylic acids, with the reaction stalling at the corresponding *gem*-difluoroalkenes.¹⁶ A wide range of alkyltrifluoroborates (**2**) were found to be suitable for this reaction. Five-, six- and seven-membered cyclic secondary alkyl groups (**3p**, **3q**, and **3r**) with diverse substitution patterns can be readily incorporated by this route. Piperidine (**3s**) and tetrahydropyran (**3t**) motifs can also

be introduced in this exhaustive defluorination reaction (43% and 83% yield, respectively). Acyclic secondary (**3u**) and tertiary alkyl radical precursors (**3v–3x**) participated in this reaction with good efficiencies (68–82%). The formation of a 1,6-keto acid **3y** showcased a new approach to this desirable functional motif. Primary α -alkoxymethyltrifluoroborates can also be used, providing access to γ -alkoxy acids (**3z–3ab**).

We then questioned whether amines could be compatible in the reaction, thus allowing the direct formation of amides from vinylmethyltrifluorides *via* triple C–F bond functionalizations. Pleasingly, the desired α -arylated amides were obtained efficiently *via* exhaustive defluorinative C–N coupling (Scheme 3), despite the competing potential for single-electron oxidation of amines by the excited-state photocatalyst.¹⁷ Primary amines with a wide range of functional groups and structural elements worked well (**5a–5j**). Alongside linear and branched substituents (**5a–5e**), allylic (**5f**) and propargyl (**5g**) amines were good substrates. Moreover, trifluoromethyl and nitrile containing primary amines delivered the corresponding α -arylated amides **5h** and **5i** in 72% and 67% yields, respectively. Notably, free amino alcohol was compatible in the reaction, furnishing the



Scheme 3 Reaction scope for the triple defluorinative formation of α -arylated amides and esters. Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), **4** (0.15 mmol, 0.20 mmol for NH_4OAc , and 0.50 mmol for alcohol), PC-1 (0.002 mmol), and H_2O (100 μL) in MeCN (0.1 M) under 30 W blue LEDs irradiation at room temperature. Isolated yields are reported. ^a 5 mol% of PC-1 was used. ^b MeCN : CH_2Cl_2 = 3 : 1. ^c 10 μL of H_2O was used.

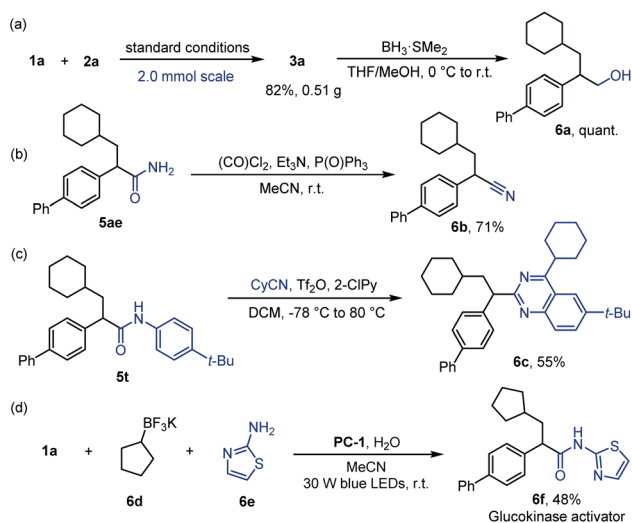


corresponding hydroxyl amide **5j** in 72% yield. Interestingly, a diamide product **5k** was formed in 75% yield when 1,2-diaminoethane was used. Acyclic and cyclic secondary amines were also shown to be suitable coupling partners in this reaction (**5l–5s**, 55–90% yields), including piperidines bearing ketal (**5o**), ester (**5p**), free carboxylic acid (**5q**), morpholine (**5n**) and a piperazine derivative (**5s**). Electron-rich and electron-deficient anilines participated smoothly in the reaction, affording **5t–5v** in 51–75% yields. Various alkyltrifluoroborates including primary, secondary, and tertiary alkyl groups, and silyl and ketone groups were also good precursors for the triple defluorinative amide formation (**5w–5aa**, 48–87% yields). The desilylated amide **5ab** was obtained in 43% yield when α -trifluoromethyl alkene with a 4-(trimethylsilyl)ethynylphenyl group was used. In addition, structurally complex substrates derived from natural products, such as estrone and (+)-dehydroabietylamine, were readily incorporated in this reaction, affording **5ac** and **5ad** in 67% and 62% yields, respectively.

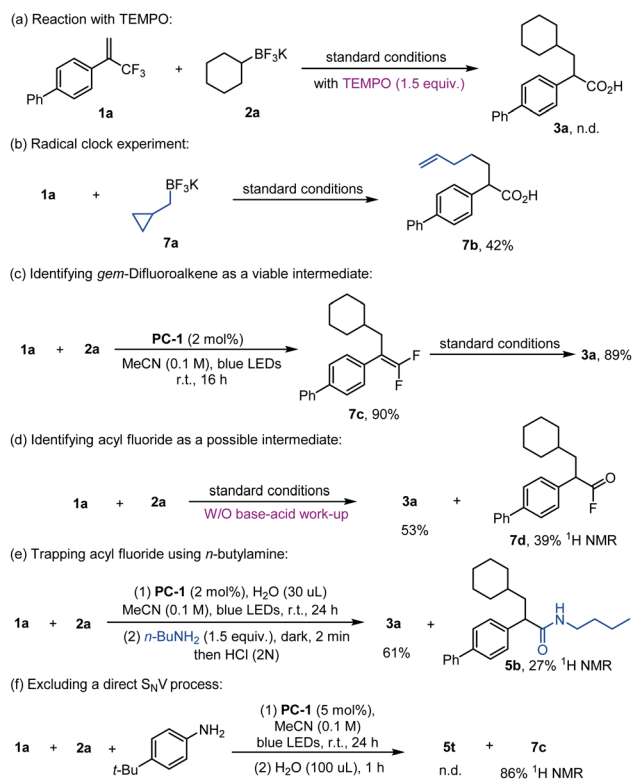
Next, the feasibility of transforming α -trifluoromethyl alkenes into primary amides by cleaving three C–F bonds was also tested. Ammonium acetate was identified as a readily available and cost-effective ammonia surrogate, allowing efficient access to a series of primary amides (**5ae–5al**, 52–75% yields). This protocol is also suitable for the synthesis of α -arylated esters by using alcohols as nucleophiles, affording **5am** and **5an** in good yields (61% and 58% yield, respectively).

To further demonstrate the utility of this protocol, product **3a** was prepared on a 2.0 mmol scale in 82% yield (Scheme 4a). This new transformation allows for ready access into other useful motifs, such as β -arylated alcohol **6a** in quantitative yield (Scheme 4a), α -arylated nitrile **6b** in 71% yield (Scheme 4b) and quinazoline **6c** in 55% yield (Scheme 4c). In addition, one-step synthesis of glucokinase activator **6f** from simple precursors was achieved, illustrating the great potential of this protocol to facilitate rapid analogue evaluation in medicinal chemistry (Scheme 4d).¹⁸

Control experiments were conducted to probe the reaction mechanism (Scheme 5). Addition of (2,2,6,6-tetramethylpiperidin-



Scheme 4 Synthetic applications.

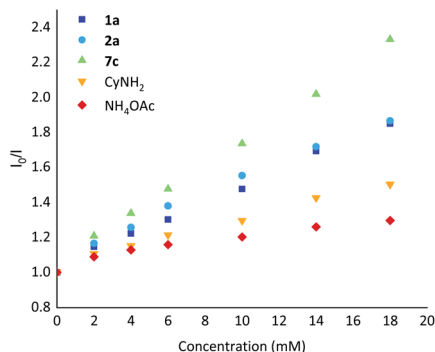


Scheme 5 Control experiments.

1-yl)oxyl (TEMPO) into the reaction completely inhibited the formation of **3a**, whilst the use of the radical precursor **7a** led to the ring-opening product **7b** in 42% yield (Scheme 5a and b). Conducting the reaction in the absence of H₂O did not yield the product **3a**, and *gem*-difluoroalkene **7c** was obtained in 90% yield instead. Moreover, **7c** was productive under the standard reaction conditions to afford **3a** in good yield (Scheme 5c), suggesting that *gem*-difluoroalkene might be the intermediate of this reaction. When **1a** and **2a** were subjected to the standard conditions without a NaOH/HCl work-up procedure, acid **3a** was formed in 53% yield alongside acyl fluoride **7d** in 39% yield as detected by NMR spectroscopy and HRMS (Scheme 5d). Further evidence for the formation of an electrophilic acyl fluoride intermediate was obtained by replacing NaOH in the reaction work-up protocol with *n*-butylamine which led to the formation of **3a** in 61% yield and amide **5b** in 27% yield (Scheme 5e). *gem*-Difluoroalkene **7c** was formed rather than amide **5t** when H₂O was excluded from the standard reaction conditions for the amide formation, indicating that water was required for the second defluorination step (Scheme 5f). These results support the involvement of alkyl radical species during the reaction, indicating that *gem*-difluoroalkene is an intermediate in this transformation that is converted into acyl fluoride species and not subject to a direct S_NV process.¹⁹

Stern–Volmer luminescence quenching studies were also performed using representative substrates **1a** and **2a**, cyclohexylamine (CyNH₂), ammonium acetate and the intermediate *gem*-difluoroalkene **7c** (Scheme 6). The results showed that *gem*-difluoroalkene **7c** quenched the excited photocatalyst

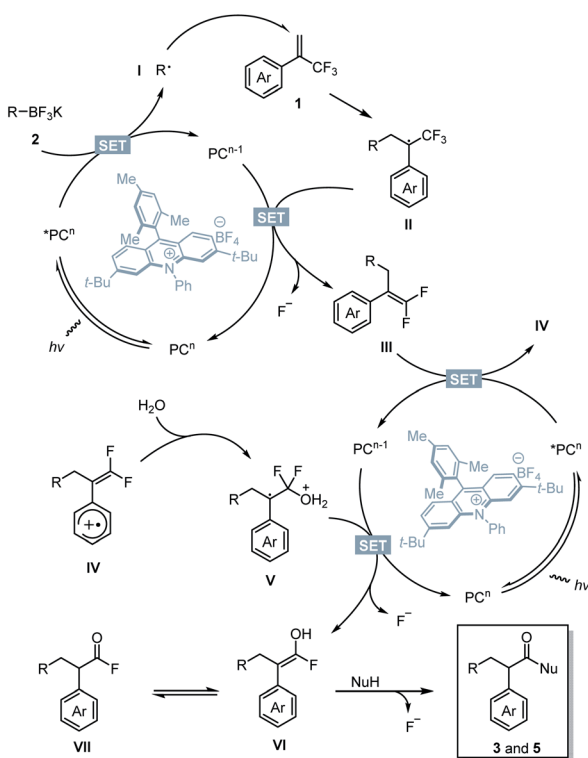




Scheme 6 Stern–Volmer luminescence quenching studies with PC-1.

significantly, and that **2a** and **1a** were also suitable quenchers for the excited photocatalyst.

Based on these results, a possible mechanism is depicted (Scheme 7). Upon blue LED irradiation, the excited acridinium photocatalyst $^*PC^n$ ($E_{red}^* = +2.15$ V) would undergo single electron transfer (SET) with **2** to generate alkyl radical species **I** and reduced photocatalyst PC^{n-1} .^{14,20} Radical species **I** underwent radical addition with **1** to generate a benzylic radical **II**. Single-electron reduction of **II** by PC^{n-1} followed by β -fluoride elimination yielded *gem*-difluoroalkenes **III** and the photocatalyst PC^n to complete the first catalytic cycle. After this stage, single-electron oxidation of intermediate **III** by the excited photocatalyst $^*PC^n$ afforded a radical cationic species **IV** and reduced photocatalyst PC^{n-1} .²¹ **IV** would be trapped by H_2O to generate intermediate **V**.^{22,23} The presence of strongly electron-



Scheme 7 Proposed mechanism.

withdrawing aryl substituents renders this step inefficient. The SET process between PC^{n-1} and **V** followed by second β -fluoride elimination affords the enol intermediate **VI** or its tautomer acyl fluoride species **VII**, and the photocatalyst PC^n . The desired products were then obtained through acyl substitution with oxygen or nitrogen nucleophiles to cleave the third C–F bond.

Conclusions

In summary, a photocatalyzed multicomponent triple defluorinative functionalization of α -trifluoromethyl alkenes was achieved to afford a variety of α -arylated carboxylic acids, esters, and primary, secondary, and tertiary amides at room temperature. The reaction operates through three consecutive and distinct C–F bond cleavages opening an avenue for converting methyltrifluorides into synthetically valuable functional groups. α -Trifluoromethyl alkenes, themselves readily prepared in one step from boronic acids,²⁴ can be combined with alkyltrifluoroborates, water, and alcohols/amines to prepare α -arylated carboxylic acids, esters and amides by the simple alternation of nucleophiles. As a result, these important motifs can now be assembled bearing significant structural and functional group variations in a modular way from simple and readily accessible molecular building blocks.

Data availability

Experimental data has been provided as ESI.†

Author contributions

S. L. discovered the reaction. W. S. and P. W. D. conceived and directed the project. S. L. performed the experiments and analysed the data. S. L., W. S. and P. W. D. prepared the manuscript. All authors discussed the experimental results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

- 1 (a) T. Y. Shen, *Angew. Chem., Int. Ed.*, 1972, **11**, 460–472; (b) W. B. Wright Jr, J. B. Press, P. S. Chan, J. W. Marsico, M. F. Haug, J. Lucas, J. Tauber and A. S. Tomcufcik, *J. Med. Chem.*, 1986, **29**, 523–530.
- 2 (a) G. Koenig and J.-F. Blain, *US Pat.*, 2013106328A1, 2013; (b) A. Pandey, S. K. Samanta, A. J. Duraiswamy, A. E. Maciag, D. Turner, M. A. J. Duncton, V. Kumari, A. R. Renslo, E. Low, C. Brassard, H. V. Adcock, D. Hamza and S. T. Onions, *US Pat.*, 2019204505A2, 2019; (c) R. Sarabu, F. T. Bizzaro, W. L. Corbett, M. T. Dvorozniak, W. Geng, J. F. Grippo, N.-E. Haynes, S. Hutchings, L. Garofalo, K. R. Guertin, D. W. Hilliard, M. Kabat, R. F. Kester, W. Ka, Z. Liang, P. E. Mahaney, L. Marcus, F. M. Matschinsky, D. Moore, J. Racha, R. Radinov, Y. Ren, L. Qi, M. Pignatello, C. L. Spence, T. Steele, J. Teng and J. Grimsby, *J. Med. Chem.*, 2012, **55**, 7021–7036.
- 3 For selected reviews, see: (a) G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2002, **41**, 953–956; (b) D. A. Culkun and J. F. Hartwig, *Acc. Chem. Res.*, 2003, **36**, 234–245; (c) C. C. C. Johansson and T. J. Colacot, *Angew. Chem., Int. Ed.*, 2010, **49**, 676–707; (d) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082–1146; (e) Y.-J. Hao, X.-S. Hu, Y. Zhou, J. Zhou and J.-S. Yu, *ACS Catal.*, 2020, **10**, 955–993.
- 4 For selected examples, see: (a) K. H. Shaughnessy, B. C. Hamann and J. F. Hartwig, *J. Org. Chem.*, 1998, **63**, 6546–6553; (b) M. Kawatsura and J. F. Hartwig, *J. Am. Chem. Soc.*, 1999, **121**, 1473–1478; (c) J. M. Fox, X. Huang, A. Chieffi and S. L. Buchwald, *J. Am. Chem. Soc.*, 2000, **122**, 1360–1370; (d) S. Lee, N. A. Beare and J. F. Hartwig, *J. Am. Chem. Soc.*, 2001, **123**, 8410–8411; (e) W. A. Moradi and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7996–8002; (f) J. Cossy, A. de Filippis and D. G. Pardo, *Org. Lett.*, 2003, **5**, 3037–3039; (g) T. Hama, X. Liu, D. A. Culkun and J. F. Hartwig, *J. Am. Chem. Soc.*, 2003, **125**, 11176–11177; (h) X. Liu and J. F. Hartwig, *J. Am. Chem. Soc.*, 2004, **126**, 5182–5191.
- 5 E. Barde, A. Guérinot and J. Cossy, *Synthesis*, 2019, **51**, 178–184.
- 6 (a) H. A. Chiong, Q.-N. Pham and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 9879–9884; (b) S.-C. Sha, J. Zhang and P. J. Walsh, *Org. Lett.*, 2015, **17**, 410–413; (c) R. A. Altman, A. M. Hyde, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2008, **130**, 9613–9620; (d) Z.-K. Xiao, H.-Y. Yin and L.-X. Shao, *Org. Lett.*, 2013, **15**, 1254–1257.
- 7 Z.-T. He and J. F. Hartwig, *J. Am. Chem. Soc.*, 2019, **141**, 11749–11753.
- 8 A. M. Vasquez, J. A. Gurak Jr, C. L. Joe, E. C. Cherney and K. M. Engle, *J. Am. Chem. Soc.*, 2020, **142**, 10477–10484.
- 9 (a) C. Hervieu, M. S. Kirillova, T. Suárez, M. Müller, E. Merino and C. Nevado, *Nat. Chem.*, 2021, **13**, 327–334; (b) H. L. Barlow, P. T. G. Rabet, A. Durie, T. Evans and M. F. Greaney, *Org. Lett.*, 2019, **21**, 9033–9035; (c) D. J. Leonard, J. W. Ward and J. Clayden, *Nature*, 2018, **562**, 105–109; (d) N. Radhoff and A. Studer, *Angew. Chem., Int. Ed.*, 2021, **60**, 3561–3565.
- 10 (a) N. Takeda, E. Futaki, Y. Kobori, M. Ueda and O. Miyata, *Angew. Chem., Int. Ed.*, 2017, **56**, 16342–16346; (b) J. Li, M. Berger, W. Zawodny, M. Simaan and N. Maulide, *Chem*, 2019, **5**, 1883–1891.
- 11 For selected examples, see: (a) C. Saboureau, M. Troupel, S. Sibille and J. Périchon, *J. Chem. Soc., Chem. Commun.*, 1989, 1138–1139; (b) S. Yoshida, K. Shimomori, Y. Kim and T. Hosoya, *Angew. Chem., Int. Ed.*, 2016, **55**, 10406–10409; (c) K. Chen, N. Berg, R. Gschwind and B. König, *J. Am. Chem. Soc.*, 2017, **139**, 18444–18447; (d) H.-B. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2018, **140**, 163–166; (e) C. Luo and J. S. Bandar, *J. Am. Chem. Soc.*, 2019, **141**, 14120–14125; (f) Y.-J. Yu, F.-L. Zhang, T.-Y. Peng, C.-L. Wang, J. Cheng, C. Chen, K. N. Houk and Y.-F. Wang, *Science*, 2021, **371**, 1232–1240; (g) J. B. I. Sap, N. J. W. Straathof, T. Knauber, C. F. Meyer, M. Médebielle, L. Buglioni, C. Genicot, A. A. Trabanco, T. Noël, C. W. am Ende and V. Gouverneur, *J. Am. Chem. Soc.*, 2020, **142**, 9181–9187; (h) S.-S. Yan, S.-H. Liu, L. Chen, Z.-Y. Bo, K. Jing, T.-Y. Gao, B. Yu, Y. Lan, S.-P. Luo and D.-G. Yu, *Chem*, 2021, **7**, 3099–3113; (i) M. W. Campbell, V. C. Polites, S. Patel, J. E. Lipson, J. Majhi and G. A. Molander, *J. Am. Chem. Soc.*, 2021, **143**, 19648–19654; (j) J.-H. Ye, P. Bellotti, C. Heusel and F. Glorius, *Angew. Chem., Int. Ed.*, 2022, **61**, e202115456; (k) S. Li and W. Shu, *Chem. Commun.*, 2022, **58**, 1066–1077; (l) G. Yan, K. Qiu and M. Guo, *Org. Chem. Front.*, 2021, **8**, 3915–3942.
- 12 For selected examples, see: (a) T. Xiao, L. Li and L. Zhou, *J. Org. Chem.*, 2016, **81**, 7908–7916; (b) S. B. Lang, R. J. Wiles, C. B. Kelly and G. A. Molander, *Angew. Chem., Int. Ed.*, 2017, **56**, 15073–15077; (c) J. Qi, F.-L. Zhang, J.-K. Jin, Q. Zhao, B. Li, L.-X. Liu and Y.-F. Wang, *Angew. Chem., Int. Ed.*, 2020, **59**, 12876–12884; (d) W.-J. Yue, C. S. Day and R. Martin, *J. Am. Chem. Soc.*, 2021, **143**, 6395–6400.
- 13 (a) L. Li, T. Xiao, H. Chen and L. Zhou, *Chem.–Eur. J.*, 2017, **23**, 2249–2254; (b) H. Chen, Y. He and L. Zhou, *Org. Chem. Front.*, 2018, **5**, 3240–3244.
- 14 J. K. Matsui, D. N. Primer and G. A. Molander, *Chem. Sci.*, 2017, **8**, 3512–3522.
- 15 For more details on the condition evaluation, see ESI†
- 16 See ESI† for unsuccessful substrates.
- 17 (a) A. Adenier, M. M. Chehimi, I. Gallardo, J. Pinson and N. Vilà, *Langmuir*, 2004, **20**, 8243–8253; (b) H. G. Roth, N. A. Romero and D. A. Nicewicz, *Synlett*, 2016, **27**, 714–723.
- 18 W. L. Corbett, N.-E. Haynes and R. Sarabu, *US Pat.*, 2001085706A1, 2001.
- 19 B. Wang, X. Zhao, Q. Liu and S. Cao, *Org. Biomol. Chem.*, 2018, **16**, 8546–8552.
- 20 N. A. Romero, K. A. Margrey, N. E. Tay and D. A. Nicewicz, *Science*, 2015, **349**, 1326–1330.
- 21 H. Liu, L. Ge, D.-X. Wang, N. Chen and C. Feng, *Angew. Chem., Int. Ed.*, 2019, **58**, 3918–3922.
- 22 G. Zhang, X. Hu, C.-W. Chiang, H. Yi, P. Pei, A. K. Singh and A. Lei, *J. Am. Chem. Soc.*, 2016, **138**, 12037–12040.
- 23 J. B. McManus, J. D. Griffin, A. R. White and D. A. Nicewicz, *J. Am. Chem. Soc.*, 2020, **142**, 10325–10330.
- 24 J. Walkowiak, T. M. del Campo, B. Ameduri and V. Gouverneur, *Synthesis*, 2010, **11**, 1883–1890.

