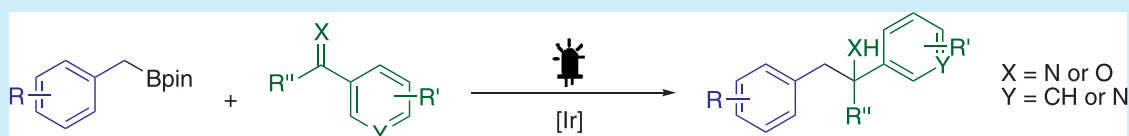# A Photoredox Coupling Reaction of Benzylboronic Esters and Carbonyl Compounds in Batch and Flow

Yiding Chen,[†] Oliver May,[†] David C. Blakemore,[‡] and Steven V. Ley*,[†]

[†]Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge CB2 1EW, United Kingdom
[‡]Medicine Design, Pfizer, Inc., Eastern Point Road, Groton, Connecticut 06340, United States

S Supporting Information

ABSTRACT: Mild cross-coupling reaction between benzylboronic esters with carbonyl compounds and some imines was achieved under visible-light-induced iridium-catalyzed photoredox conditions. Functional group tolerance was demonstrated by 51 examples, including 13 heterocyclic compounds. Gram-scale reaction was realized through the use of computer-controlled continuous flow photoreactors.

Carbonyl compounds serve as fundamentally important electrophilic building blocks during carbon−carbon bond-forming reactions commonly using transition-metal catalysis[1] or organometallic coupling processes.[2] While wide functional group tolerance can be achieved in these reactions,[3] there is interest in moving away from using strongly basic conditions or highly reactive substrates.[4] In this content, the current trend in the use of visible light photoredox methods has led to impressive discoveries, especially to bring about carbon−carbon bond formation with single electron-transfer processes.[5]

Previously we have noted the addition of Lewis bases to activate photoredox-mediated coupling reactions between normally unreactive benzylic boronic esters and olefinic acceptors.[6] Others have also reported useful processes whereby selective reductive addition to carbonyl compounds can be achieved.[7] More specifically, Rueping described the dimerization of aldehydes and ketones via intermediate photoredox-generated ketyl radicals.[8] Several other reports[9] concerning reactions with alkenes,[10] intramolecular cyclization,[11] or photocatalytic Barbier-type reactions[12] via putative radical−radical coupling pathways are known as well. In view of the opportunities that arise through these photoredox coupling processes, we commenced the study below employing benzylic boron esters as precursors during this potential direct coupling with carbonyl compounds and imines, thus avoiding strongly nucleophilic organometallic reagents.

From a test reaction based on the conditions we had explored previously,[6] we were pleased to observe an optimal yield of 84% for the specific cross-coupling event of the *p*-methoxybenzylboronic acid pinacol ester **1a** with *p*-chlorobenzaldehyde **2a**. This was achieved by employing iridium photoredox catalyst **i** with 3-quinuclidinol in a 0.05 M 1:1 methanol and acetone solvent system under a blue LED light for 8 h to give the addition product **3a** (Table 1, entry 1). For

Table 1. Reaction Optimization

entry[a]	variation from above conditions	yield (%)[b]
1	no variation	86 (84)[c]
2	2 mol % Mes-Acr-BF₄ (**ii**) instead of Ir	24
3	2 mol % [Ru(bpy)₃]Cl₂ (**iii**) instead of Ir	0
4	50 mol % DMAP as base	44
5	additional 20 mol % Sc(OTf)₂	70
6	acetonitrile (0.1 M) as solvent	19
7	0.1 M concentration instead of 0.05 M	54
8	without base	43
9	without photocatalyst	0
10	without light	0
11	green LEDs (540 nm, 14 W)	16

[a]Reaction conditions: 0.1 mmol boronic acid pinacol ester, 0.15 mmol aldehyde, 1 mL acetone, and 1 mL methanol. [b]NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c]Isolated yield.

full details of the optimization and screening, see the Supporting Information. Although these conditions bear a similarity to recent procedures,[6] the reaction progressed rather differently over the optimization process. Commonly used

A

photocatalysts mesityl acridinium salt **ii** and the ruthenium catalyst **iii** failed to deliver coupled products (entries 2 and 3). On the other hand, using 4-dimethylaminopyridine (DMAP) as additive, a moderate 44% of product **3a** was realized (entry 4), while addition of the Lewis acid Sc(OTf)$_3$ together with 20 mol % equivalent of the quinuclidine base did not significantly enhance the overall reactivity (entry 5). Solvent changes were usually detrimental; for example, acetonitrile leads to a yield of only 19% of the coupled product (entry 6). However, it is worth noting that the concentration of the reaction mixture does have a noticeable impact, in that a 0.1 M reaction mixture caused a drop in yield to 54% (entry 7). More difficult to understand in this specific coupling example was the 43% yield of product **3a** when no base was added to the mixture (entry 8), which is discussed later. Without either photocatalyst or a light source, the reaction was completely shut down (entries 9 and 10). Switching to a green light led to a decreased yield of 16% (entry 11). The reaction was accompanied by minor byproducts which were removed on workup by normal silica gel chromatography.

With the conditions from entry 1 in hand, we directed our attention to examine a series of benzyl boronic esters **1** and coupling partners **2** (Figure 1). Generally, electron-donating
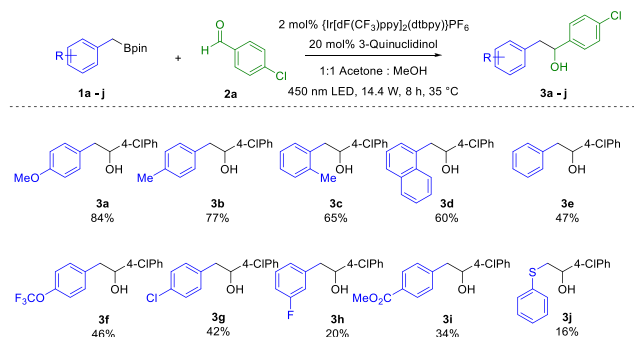

Figure 1. Scope of boronic acid pinacol esters.

group (EDG) substituents on the boronic ester component worked well, as exemplified by high yields from the optimized 4-methoxyphenyl substrate (**1a**) as well as *p*-methylbenzyl (**1b**), *o*-methylbenzyl (**1c**), and 1-nathphylmethyl (**1d**) boronic esters. The parent benzyl boronic ester (**1e**) also provided a moderate yield of coupled product (**3e**), although electron-withdrawing groups (EWGs) such as the *p*-trifluoromethoxybenzyl derivative (**1f**), *p*-chlorobenzyl (**1g**), *m*-fluorobenzyl (**1h**), and *p*-methylbenzoate (**1i**) all showed lower efficiencies. Likewise, for the phenylsulfanylmethyl boronic ester (**1j**), only 16% of the corresponding coupled product (**3j**) was obtained. Similarly, with other long-chain aliphatic boronic esters and aryl boronic esters, no useful products were observed.

To further investigate the scope with respect to aldehydes **2** (Figure 2), we examined a wide range of aromatic aldehydes with various ring substituents (**2k–z**). Among these, a number contain challenging features, such as bromo- (**2l**), boc-protected amino- (**2m**), photosensitive nitrile (**2n**), boron pinacol ester (**2o**), hydroxyl (**2p**), and pentafluoro (**2y**) groups. Also interestingly, given a choice between a ketone and aldehyde as coupling partners, we saw complete aldehyde specificity (**3s**). In three examples, addition to imines occurs readily to afford coupled products (**3v–x**). Particularly worth noting is that the method is compatible with many heterocyclic
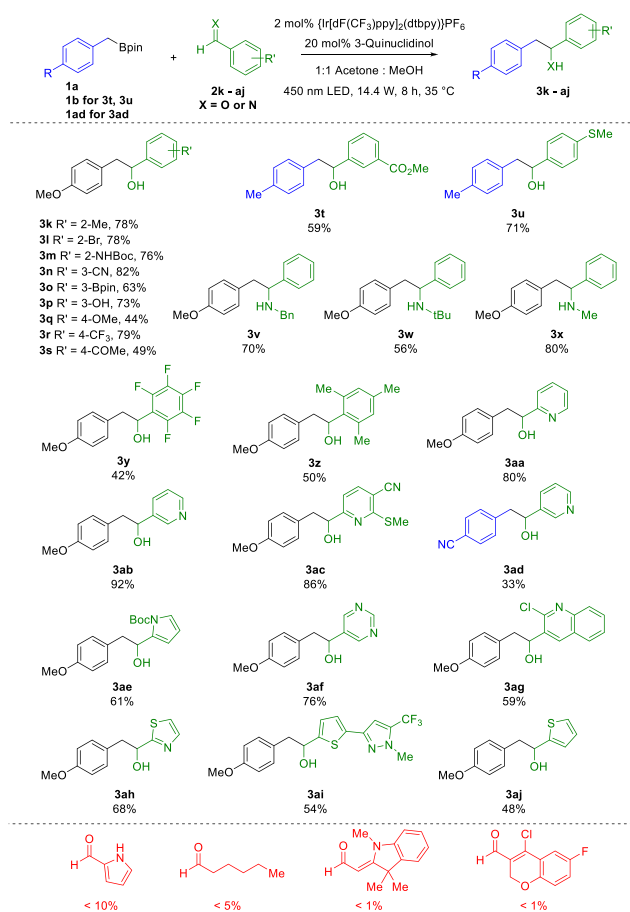

Figure 2. Scope of aryl and heteroaryl aldehydes and imines.

substrates. Moderate yields were obtained from pyridyl substrates (**3aa–3ad**). The nitrogen-containing heterocycles pyrrole, pyrimidine, and quinoline (**3ae–3ag**) as well as sulfur-containing heterocyclic compounds such as thiazole (**3ah**) and thiophene (**3ai** and **3aj**), all reacted satisfactorily. For completeness, listed in red are a few aldehyde coupling partners that failed to yield useful products.

We further expanded the scope of the reactions to include ketone derivatives (Figure 3). Acetophenone derivatives (**4a–4g**) were tolerated, while better yields were observed with benzophenone substrates (**5h–5j**). Photochemically active reagents such as xanthenone (**5k**), thioxanthenone (**5l**), and fluorenone (**5m**) were particularly reactive, which supports our later mechanistic proposals. Acetohexamide (**4n**)[13] successfully delivered the coupled product in 59% yield (**5n**). In this example, a reversed ratio of 1.5:1 boronic ester and ketone was employed to aid with the isolation of the benzylated product from acetohexamide starting material. In cases where there is significant enolization in the coupling partner (shown in red), very poor product yields are realized.

The use of continuous methods (Scheme 1)[14] has been shown to offer immediate improvements over equivalent batch photoredox procedures[15] when scaling reactions, particularly when new reactor designs lead to improved photon flux densities[16] and material throughput.[17]

Reaction mixtures were prepared in a normal fashion and pumped through a photoreactor (Vapourtec UV-150) fitted with a blue LED module (17 W at λ = 420 nm) and a 10 mL coil (FEP, 1/16 in.). With a residence time of 100 min, 100%
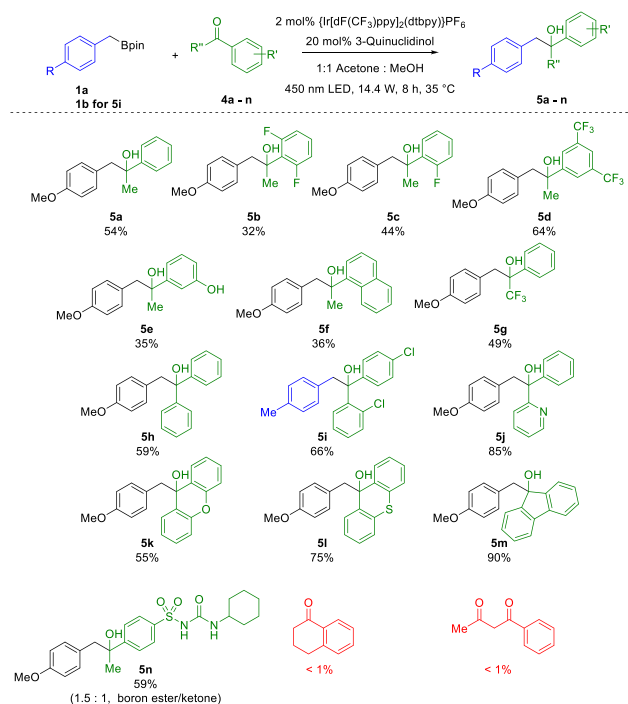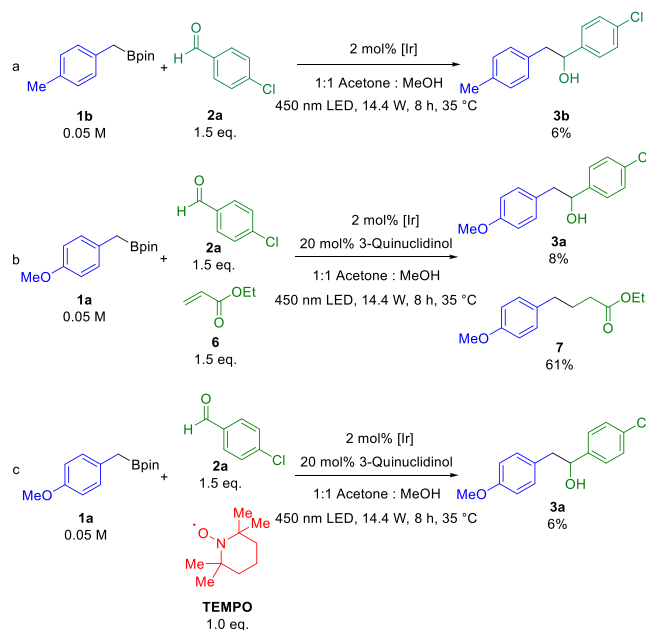
Figure 3. Scope of ketones.

conversion was obtained giving a 70% **3a** isolated yield (Scheme 1a). Encouraged by this early success, a larger scale experiment was carried out on the recently commercialized Uniqsis Photosyn reactor, which was equipped with a more powerful (420 W at λ = 450 nm) lamp and a bigger 20 mL (PFA, 1/16 in.) flow coil, which could further reduce the residence time to 60 min. The reaction was controlled with the LabVIEW program and was monitored with Uniqsis Flow-UV. A 10 h run was carried out to produce 1.69 g of product (**3ak**). (See Supporting Information for detailed reaction setup; no attempt at this stage was made to scale up the reaction any further.)

As mentioned above, this reaction was performed under similar catalytic conditions to our previous work.[6] However, two main differences in reactivity were noticed. First, while aromatic boronic acid pinacol esters and aliphatic boronic acids were viable precursors in our earlier study,[14] only benzylic Bpin esters were successful in the current work. Additionally, previous studies clearly demonstrated that other Lewis bases (e.g., DMAP) could be as efficient as quinuclidine,

whereas in this new work, DMAP did not promote the reaction to any equivalent level (Table 1, entry 4). These distinctive differences, though not direct evidence, suggested a mechanism that differed from a Lewis base-catalyzed photoredox activation of the boron species.[6]

In other control experiments (Table 1, entries 9 and 10, see more in Supporting Information) suggested the iridium complex **i** was the only functional photoredox catalyst, while no conclusion can be drawn about the absolute necessity of quinuclidinol additive (Table 1, entry 8). This observation contrasts with previous mechanistic proposals,[18] since the reduction potential of most carbonyl compounds presented are beyond the range of this particular photocatalyst.[19] For example, the reductive potential of benzophenone is ($E_{1/2}^{red}$ = −1.87 V vs SCE), whereas the reductive potential of the catalyst **i** is ($E_{1/2}^{red}$ = −1.37 V vs SCE).[20] Hence a further control experiment was performed (Scheme 2a). Using 4-methylbenzyl

Scheme 2. Additional Control Experiments[a]

[a](a) Coupling of *p*-methylbenzylboronic ester with *p*-chlorobenzaldehyde in the absence of quinuclidine. (b) Competition reaction between benzaldehyde and ethyl acrylate with benzylboronic ester. (c) Radical trap experiment.

Scheme 1. Continuous Flow Synthesis with (a) Vapourtec UV-150 and (b) Uniqsis Photosyn controlled by LabVIEW
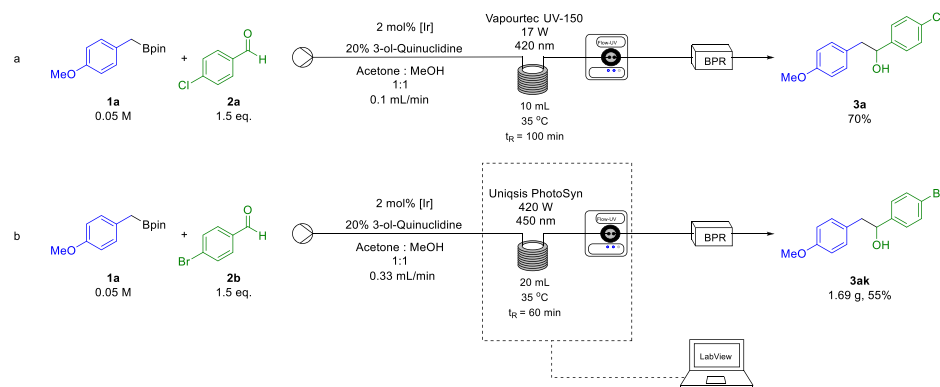
boronic pinacol ester **1b** as a precursor, only 6% of desired product **3b** was detected in the absence of a base additive. This contrasts with a 77% yield when a 20 mol % 3-quinuclidinol was added (Figure 1, **3b**), indicating that the quinuclidine base plays a crucial role. These results might suggest that the methoxyboronic ester could initiate reaction activation, where a similar observation was reported by König et al.[21] Competition reactions between chlorobenzaldehyde and ethyl acrylate as coupling partners were also briefly investigated (Scheme 2b). In the presence of quinuclidine base, 61% of the coupled boronic ester **7** was realized, and only 8% **3a** was isolated. Lastly, the product yield dropped dramatically with the addition of radical scavenger TEMPO (Scheme 2c), further proving the existence of a radical pathway. Stern−Volmer experiments showed 3-quinuclidinol was able to quench the photocatalyst under reaction conditions, while Bpin ester and aldehyde presented no such effect (see Supporting Information).[22]

The reaction analysis may suggest a ketyl radical pathway could also be operating. In most cases, a byproduct formed in the reaction which was thought to be a diol from aldehyde/ketone dimerization, as expected from a ketyl radical mechanism. To the best of our knowledge, although radical trapping with carbonyl compounds is known,[7e,23] the generation of a thermodynamically unfavorable alkoxy radical often lead to a reversible process[24] or homolytic C−C β-scission.[25]

We therefore propose the mechanism shown in Figure 4. Initially, the Ir(III) catalyst **i**, when exposed to blue light, is
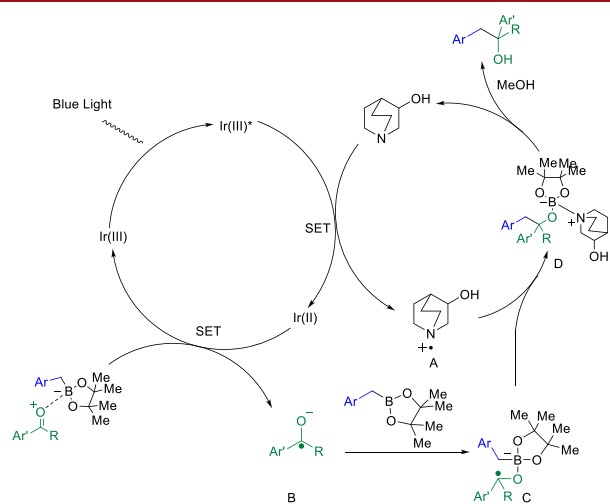

Figure 4. The proposed mechanism.

excited to a long-lifetime excited-state Ir(III)*.[20] The quinuclidine base ($E_{1/2}^{ox}$ = +1.00 V vs SCE)[26] then undergoes a single electron oxidation by a photoexcited Ir(III)* catalyst ($E_{1/2}^{ox}$ = +1.21 V vs SCE),[20] leading to the initiation of radical cation **A** and the reduced Ir(II) complex.[27] The aldehyde/ketone activated by boronic ester[21] is then reduced by a Ir(II) complex ($E_{1/2}^{red}$ = −1.37 V vs SCE) via a single electron reduction, thus completing the photoredox cycle. The resulting ketyl radical anion **B** subsequently attacks the benzylboronic acid pinacol ester to assemble the borate radical anion **C**. Alternatively, the aldehyde/ketone could be activated by a boronic ester through a boron−oxygen interaction, thus the single electron reduction creates radical anion **C** directly. **C** is

then oxidized by radical cation **A**, which terminates the radical sequence and gives borate **D** and the quinuclidine catalyst. Finally, **D** is hydrolyzed to the targeted alcohol product.

In summary, we describe above a cross-coupling reaction of benzylic organoboron reagents with carbonyl compounds via photoredox catalysis, displaying a wide functional group tolerance. Preliminary results also show the reactions could be scaled using more powerful light sources coupled to computer-controlled flow chemistry devices.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02307.

Details of experimental procedure, compound characterization data and NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: svl1000@cam.ac.uk.

ORCID Ⓘ

Yiding Chen: 0000-0001-6932-9005
Steven V. Ley: 0000-0002-7816-0042

Notes

■ ACKNOWLEDGMENTS

■ REFERENCES

(1) (a) Kuriyama, M.; Shimazawa, R.; Shirai, R. *J. Org. Chem.* **2008**, 73, 1597−1600. (b) Gois, P. M. P.; Trindade, A. F.; Veiros, L. F.; André, V.; Duarte, M. T.; Afonso, C. A. M.; Caddick, S.; Cloke, F. G. N. *Angew. Chem., Int. Ed.* **2007**, 46, 5750−5753.

(2) Hollerbach, M. R.; Barker, T. J. *Organometallics* **2018**, 37, 1425−1427.

(3) Sakai, M.; Ueda, M.; Miyaura, N. *Angew. Chem., Int. Ed.* **1998**, 37, 3279−3281.

(4) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, 93, 2207−2293.

(5) (a) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. *Science* **2019**, 363, No. eaat0805. (b) Banerjee, A.; Lei, Z.; Ngai, M.-Y. *Synthesis* **2019**, 51, 303−333. (c) Shu, C.; Noble, A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2019**, 58, 3870−3874. (d) Shaw, M. H.; Shurtleff, V. W.; Terrett, J. A.; Cuthbertson, J. D.; MacMillan, D. W. C. *Science* **2016**, 352, 1304−1308. (e) Le, C.; Liang, Y.; Evans, R. W.; Li, X.; MacMillan, D. W. C. *Nature* **2017**, 547, 79.

(6) Lima, F.; Sharma, U. K.; Grunenberg, L.; Saha, D.; Johannsen, S.; Sedelmeier, J.; Van der Eycken, E. V.; Ley, S. V. *Angew. Chem., Int. Ed.* **2017**, 56, 15136−15140.

(7) (a) Schwarz, J. L.; Schäfers, F.; Tlahuext-Aca, A.; Lückemeier, L.; Glorius, F. *J. Am. Chem. Soc.* **2018**, 140, 12705−12709. (b) Capaldo, L.; Riccardi, R.; Ravelli, D.; Fagnoni, M. *ACS Catal.* **2018**, 8, 304−

309. (c) Vu, M. D.; Das, M.; Liu, X.-W. *Chem. - Eur. J.* **2017**, *23*, 15899−15902. (d) Matos, J. L. M.; Vásquez-Céspedes, S.; Gu, J.; Oguma, T.; Shenvi, R. A. *J. Am. Chem. Soc.* **2018**, *140*, 16976−16981. (e) Pitzer, L.; Sandfort, F.; Strieth-Kalthoff, F.; Glorius, F. *J. Am. Chem. Soc.* **2017**, *139*, 13652−13655.

(8) Nakajima, M.; Fava, E.; Loescher, S.; Jiang, Z.; Rueping, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 8828−8832.

(9) Wang, R.; Ma, M.; Gong, X.; Fan, X.; Walsh, P. J. *Org. Lett.* **2019**, *21*, 27−31.

(10) (a) Fava, E.; Nakajima, M.; Nguyen, A. L. P.; Rueping, M. *J. Org. Chem.* **2016**, *81*, 6959−6964. (b) Lee, K. N.; Lei, Z.; Ngai, M.-Y. *J. Am. Chem. Soc.* **2017**, *139*, 5003−5006. (c) Qi, L.; Chen, Y. *Angew. Chem.* **2016**, *128*, 13506−13509.

(11) Li, W.; Duan, Y.; Zhang, M.; Cheng, J.; Zhu, C. *Chem. Commun.* **2016**, *52*, 7596−7599.

(12) Berger, A. L.; Donabauer, K.; König, B. *Chem. Sci.* **2018**, *9*, 7230−7235.

(13) Field, J. B.; Ohta, M.; Boyle, C.; Remer, A. *N. Engl. J. Med.* **1967**, *277*, 889−894.

(14) Lima, F.; Grunenberg, L.; Rahman, H. B. A.; Labes, R.; Sedelmeier, J.; Ley, S. V. *Chem. Commun.* **2018**, *54*, 5606−5609.

(15) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.* **2016**, *116*, 10276−10341.

(16) Roibu, A.; Fransen, S.; Leblebici, M. E.; Meir, G.; Van Gerven, T.; Kuhn, S. *Sci. Rep.* **2018**, *8*, 5421.

(17) (a) Loubière, K.; Oelgemöller, M.; Aillet, T.; Dechy-Cabaret, O.; Prat, L. *Chem. Eng. Process.* **2016**, *104*, 120−132. (b) Su, Y.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. - Eur. J.* **2014**, *20*, 10562−10589.

(18) Xia, Q.; Dong, J.; Song, H.; Wang, Q. *Chem. - Eur. J.* **2018**, *25*, 2949−2961.

(19) Wagner, P. J.; Truman, R. J.; Puchalski, A. E.; Wake, R. *J. Am. Chem. Soc.* **1986**, *108*, 7727−7738.

(20) Lowry, M. S.; Goldsmith, J. I.; Slinker, J. D.; Rohl, R.; Pascal, R. A.; Malliaras, G. G.; Bernhard, S. *Chem. Mater.* **2005**, *17*, 5712−5719.

(21) Wang, S.; Lokesh, N.; Hioe, J.; Gschwind, R. M.; König, B. *Chem. Sci.* **2019**, *10*, 4580−4587.

(22) (a) Proctor, R. S. J.; Davis, H. J.; Phipps, R. J. *Science* **2018**, *360*, 419−422. (b) Ashley, M. A.; Yamauchi, C.; Chu, J. C. K.; Otsuka, S.; Yorimitsu, H.; Rovis, T. *Angew. Chem., Int. Ed.* **2019**, *58*, 4002−4006. (c) Tian, H.; Xia, Q.; Wang, Q.; Dong, J.; Liu, Y.; Wang, Q. *Org. Lett.* **2019**, *21*, 4585−4589.

(23) (a) Dowd, P.; Zhang, W. *Chem. Rev.* **1993**, *93*, 2091−2115. (b) Saladrigas, M.; Bosch, C.; Saborit, G. V.; Bonjoch, J.; Bradshaw, B. *Angew. Chem., Int. Ed.* **2018**, *57*, 182−186. (c) Saladrigas, M.; Loren, G.; Bonjoch, J.; Bradshaw, B. *ACS Catal.* **2018**, *8*, 11699−11703.

(24) Wilsey, S.; Dowd, P.; Houk, K. N. *J. Org. Chem.* **1999**, *64*, 8801−8811.

(25) Salamone, M.; Bietti, M. *Synlett* **2014**, *25*, 1803−1816.

(26) Smith, J. R. L.; Masheder, D. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1732−1736.

(27) (a) Dimakos, V.; Su, H. Y.; Garrett, G. E.; Taylor, M. S. *J. Am. Chem. Soc.* **2019**, *141*, 5149−5153. (b) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T. *Nat. Chem.* **2018**, *10*, 1037−1041.