

# Dual Copper- and Photoredox-Catalysed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) Coupling

Euan B. McLean,<sup>a</sup> Vincent Gauchot,<sup>a</sup> Sebastian Brunen,<sup>a</sup> David J. Burns<sup>b</sup> and Ai-Lan Lee<sup>\*a</sup>

Received 00th January 20xx,  
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

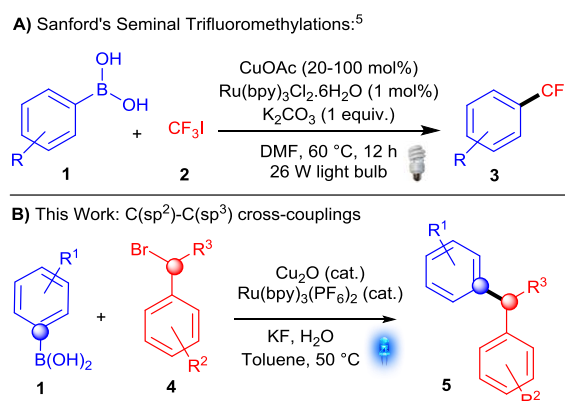
www.rsc.org/

**The use of copper catalysis with visible light photoredox catalysis in a cooperative fashion has recently emerged as a versatile means of developing new C-C bond forming reactions. In this work, dual copper- and photoredox catalysis is exploited to effect C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-couplings between aryl boronic acids and benzyl bromides.**

The synergistic combination of transition metal catalysis with photoredox catalysis has in recent years proven itself to be a versatile way to effect C-C cross-couplings.<sup>1</sup> Since its conception, the field has mainly been dominated by methodologies which utilise nickel in synergy with photoredox catalysts, including seminal contributions from Molander and MacMillan, which elegantly demonstrate the synthetic utility of this approach.<sup>2</sup> Nevertheless, commonly used nickel catalysts in dual-catalysis reactions are toxic and carcinogenic,<sup>3</sup> so alternatives with lower toxicity would be beneficial. An emerging, though much less-explored alternative is the use of relatively non-toxic copper salts.<sup>4</sup> These have an added benefit in that cheap inorganic copper salts can be used, without the need for ligands. For example, Sanford's seminal work in the area uses CuOAc in conjunction with a photoredox catalyst to effect mild trifluoromethylation of aryl boronic acids (Scheme 1A).<sup>5,6</sup> Nevertheless, a dual-copper and photoredox-catalysed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-coupling which involves standard, non-fluorinated C(sp<sup>3</sup>) centres such as alkyls or benzyls was, surprisingly, yet to be developed.<sup>7</sup> We therefore set out to explore and develop the first dual copper- and photoredox-catalysed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-couplings of aryls with benzylic sp<sup>3</sup> centres (Scheme 1B), and its successful development is described herein.<sup>8</sup>

Firstly, a mechanistic design was constructed for the dual copper- and photoredox-catalysed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-coupling (Scheme 2). As discussed above, Sanford has shown that

arylboronic acids **1** can undergo transmetallation in dual copper- and photoredox-catalysed systems, providing literature precedence for steps **6**→**I**→**II**.<sup>5</sup> Additionally, oxidation and reduction potentials from literature support the oxidation of Cu(I) to Cu(II) ( $E_{1/2}^{I/II} = -0.161$  V)<sup>9</sup> by Ru(bpy)<sub>3</sub><sup>2+</sup> ( $E_{1/2}^{*II/I} = 0.77$  V).<sup>1b</sup> For the sp<sup>3</sup> cross-partner, we opted for benzyl bromides **4**, since it has been shown that benzylic radicals **IV** can be generated from electron-deficient benzyl bromides **4** ( $E_{red} = -0.95$  V)<sup>10</sup> under photoredox catalysis ( $E_{1/2}^{I/II} = -1.33$  V for Ru(bpy)<sub>3</sub><sup>2+</sup>).<sup>1b,11</sup> Thus, we surmised that **IV** could plausibly react with **II** to form the intermediate **III** and subsequently the desired cross-coupled product **5**, following reductive elimination. At this stage, we envisaged that competing homocoupling of the benzylic radical (from **4**) may be a potential major challenge to successful cross-coupling.



**Scheme 1** Dual Copper- and Photoredox-catalysed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) Cross-couplings

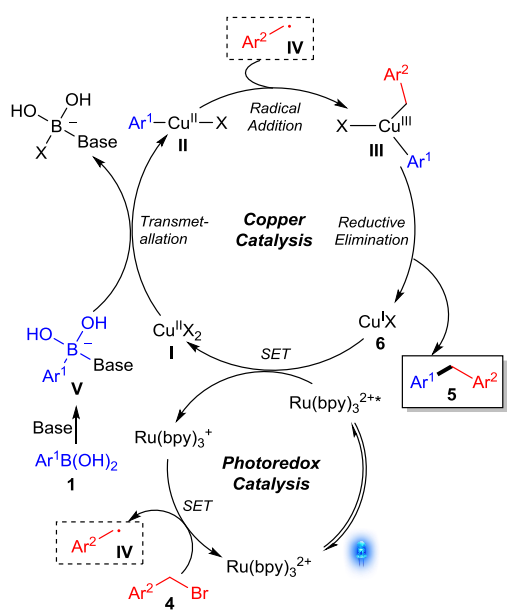
With this proposal in hand, we screened a variety of conditions on model substrates **1a** and **4a** (Table 1, see ESI for full optimisation studies). Initial screens using CuI, Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> and K<sub>2</sub>CO<sub>3</sub>, provided our first promising result (10% **5aa**, Entry 1). Subsequent solvent screen (see ESI) identified toluene as the most promising solvent (Entry 2). The yield of desired product **5aa** could be increased from 23% to

<sup>a</sup> Institute of Chemical Sciences, School of Engineering and Physical Sciences, Heriot-Watt University, Edinburgh EH14 4AS, UK. Email: [A.Lee@hw.ac.uk](mailto:A.Lee@hw.ac.uk)

<sup>b</sup> Syngenta, Jealott's Hill International Research Centre, Bracknell, Berkshire RG42 6EY, UK.

Electronic Supplementary Information (ESI) available: Experimental procedures, full optimisation and control studies, mechanistic studies, characterisation data and copies of NMR spectra of new compounds. See DOI: 10.1039/x0xx00000x

29% by reversing the stoichiometry (**4a** as limiting reagent, Entry 3). Next, a base screen (see ESI) identified KF as the optimum base (Entry 5), while increasing the equivalents of base improves the yield of **5aa** (Entry 6). The counterion of the base appears to have an effect: for example, the use of LiF or NaF resulted in no reaction while NH<sub>4</sub>F produced only homocoupled side product **7a** (Entry 4). Further investigations showed that the photocatalyst loading could be lowered to 1 mol% (40% **5aa**, Entry 7). Finally, a screen of copper catalysts (see ESI) identified Cu<sub>2</sub>O to be optimal (55% **5aa**, Entry 8). Initial results in Table 1 show that while the yield of the competing homocoupling product (**7a**) appears to remain fairly constant throughout, the yield of desired cross-coupling product **5aa** can nevertheless be successfully optimised to be the major product. Control reactions confirmed that the cross-coupling does not occur in the absence of light, photocatalyst or base respectively and also shows poor reactivity in the absence of Cu<sub>2</sub>O (see ESI).



**Scheme 2** Mechanistic Design

Up until this point, all optimisation had been carried out using model arylboronic acid **1a**. Much to our surprise and dismay, when any other arylboronic acids **1** were utilised under this set of initial optimised conditions (Entry 8, Table 1), the reaction failed to produce appreciable amounts of cross-coupled **5** and/or suffered from reproducibility issues. Therefore, a second series of optimisation studies had to be carried out in order to develop a set of more general and reproducible conditions (Table 2, see ESI for full studies).

We hypothesised that this unexpected and stark difference in reactivity between different arylboronic acids was due to the corresponding difference in positions of equilibrium between the arylboronic acid and its dehydrated arylboroxine.<sup>12</sup> Since the position of equilibrium is influenced by the presence of water,<sup>12,13</sup> the addition of controlled quantities of water was screened against phenylboronic acid **1b** (see ESI). From these experiments, we discovered that the addition of 30 equivalents

of water was optimal, improving the yields as well as the reproducibility of the reaction (Entry 3, Table 2).

**Table 1** Selected Initial Optimisation Reactions

Entry <sup>a</sup>	Sol.	Base	Ru (mol%)	Cu cat.	<b>4a</b> (%) <sup>a</sup>	<b>5aa</b> (%) <sup>a</sup>	<b>7a</b> (%) <sup>a,b</sup>
1 <sup>c,d,e</sup>	MeCN	K <sub>2</sub> CO <sub>3</sub> (1 equiv.)	2.5	CuI	N/A <sup>f</sup>	10	24
2 <sup>d,e</sup>	PhMe	K <sub>2</sub> CO <sub>3</sub> (1 equiv.)	2.5	CuI	N/A <sup>f</sup>	23	17
3	PhMe	K <sub>2</sub> CO <sub>3</sub> (3 equiv.)	2.5	CuI	28	29	20
4	PhMe	NH <sub>4</sub> F (3 equiv.)	2.5	CuI	45	0	26
5	PhMe	KF (3 equiv.)	2.5	CuI	13	37	22
6	PhMe	KF (6 equiv.)	2.5	CuI	0	45	28
7	PhMe	KF (3 equiv.)	1	CuI	7	40	26
8	PhMe	KF (4 equiv.)	1	Cu <sub>2</sub> O	0	55	20

<sup>a</sup>Determined by <sup>1</sup>H NMR analysis using mesitylene as internal standard, 0.1 mmol scale. <sup>b</sup>Yields with respect to theoretical maximum formation of **7a**. <sup>c</sup>Reaction carried out at R.T. <sup>d</sup>CuI (20 mol%). <sup>e</sup>Stoichiometry of **1a/4a** reversed. <sup>f</sup>Not applicable as **4a** is in excess.

**Table 2** Selected Further Optimisation Studies

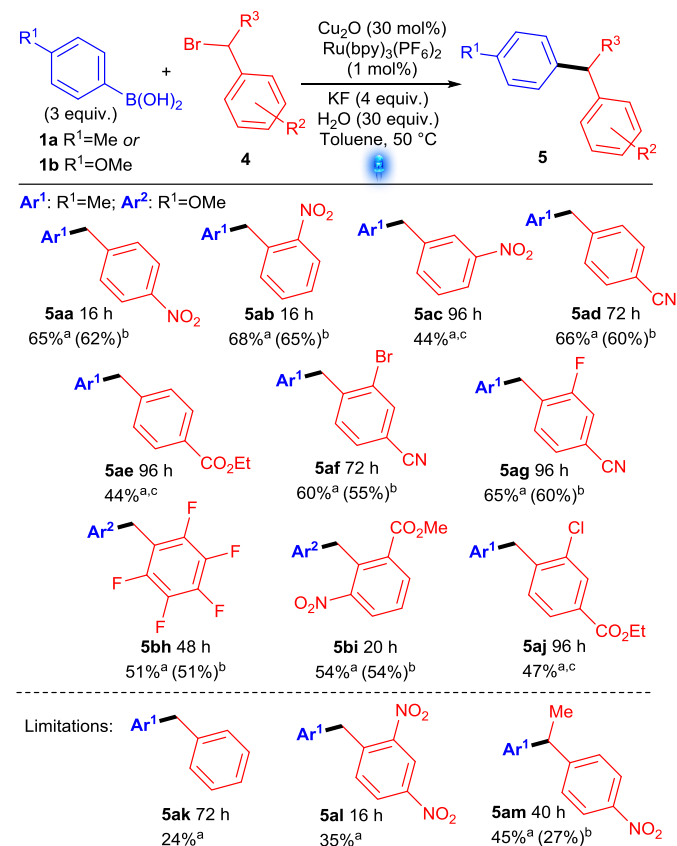
Entry	R <sup>1</sup>	R <sup>2</sup>	H <sub>2</sub> O equiv.	<b>4</b> (%) <sup>a</sup>	<b>5</b> (%) <sup>a</sup>	<b>7</b> (%) <sup>a,b</sup>
1	NO <sub>2</sub>	H	0	89	8	4
2	NO <sub>2</sub>	H	20	33	38	16
3	NO <sub>2</sub>	H	30	3	53	28
4	NO <sub>2</sub>	H	40	9	45	22
5	NO <sub>2</sub>	Me	30	3	59	24
6 <sup>c</sup>	NO <sub>2</sub>	Me	30	8	14	22
7 <sup>d,e</sup>	NO <sub>2</sub>	Me	30	62	20	10
8	CN	Me	30	41	42	28
9 <sup>f</sup>	CN	Me	30	6	60	30
10 <sup>e,f</sup>	CN	Me	30	0	66	34
11 <sup>e</sup>	NO <sub>2</sub>	Me	30	0	65	28

<sup>a</sup>Determined by <sup>1</sup>H NMR analysis with 1,3,5-trimethoxybenzene as internal standard; 0.1 mmol scale. <sup>b</sup>Yields with respect to theoretical maximum formation of **7**. <sup>c</sup>Ir(ppy)<sub>3</sub> as photocatalyst. <sup>d</sup>Fluorescein as photocatalyst. <sup>e</sup>Cu<sub>2</sub>O (30 mol%). <sup>f</sup>72 h

A number of other photocatalysts were investigated in the reaction (see ESI), including organic dyes, but none were found to be as efficient as Ru(bpy)<sub>3</sub>(PF<sub>6</sub>)<sub>2</sub> (e.g. Entry 3 vs. Entries 6-7). In order to quickly assess the generality of these conditions, preliminary investigations into the benzyl bromide scope was carried out. In general, it was found that when the benzyl bromide substituent R<sup>1</sup> is less electron-withdrawing (CN vs. NO<sub>2</sub>), longer reaction times were required for the reaction to reach completion (Entries 8-9). Finally, increasing the copper catalyst loading to 30 mol% increased the yield of reaction to

66% and 65% for the -NO<sub>2</sub> and -CN substrates respectively and also improved reproducibility (Entries 10 and 11).

**Table 3** Benzyl Bromide Scope



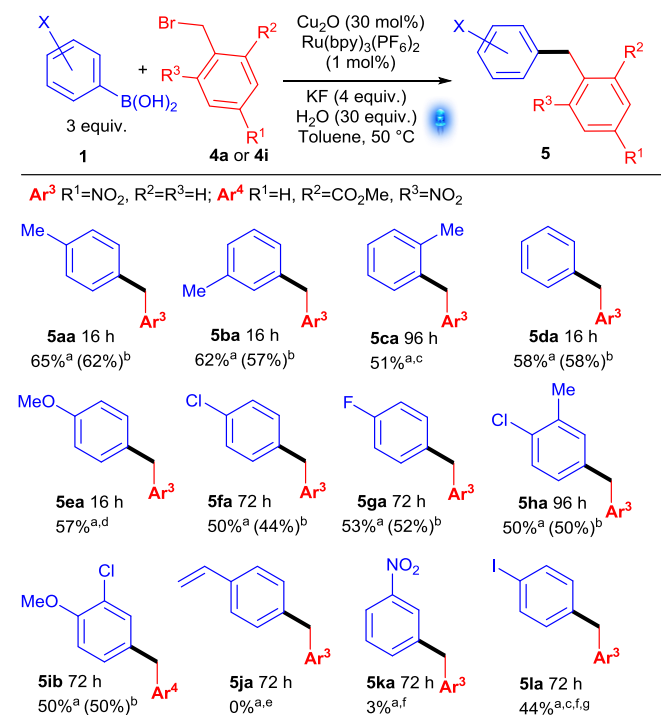
<sup>a</sup>Determined by <sup>1</sup>H NMR analysis of the crude product using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>Isolated yield. <sup>c</sup>Isolated yields not available due to co-elution with unreacted 4.

With a more general optimised protocol in hand, our attention turned to investigating the benzyl bromide substrate scope (Table 3). It should be noted that electron-deficient benzyl bromides, which have lower reduction potentials than their electron-rich counterparts,<sup>14</sup> have previously been required for efficient benzyl radical IV formation under photoredox catalysis.<sup>11</sup> Consequently, strongly electron-withdrawing substituents (e.g. NO<sub>2</sub>) are tolerated well in the *para* and *ortho* positions, furnishing the corresponding products 5aa and 5ab in good yields (62% and 65%). However, when the NO<sub>2</sub> substituent is moved to the *meta* position (5ac), the reaction becomes sluggish and the yield is modest even at prolonged reaction times (44%, 96 h). The sluggish reaction with 4c is consistent with the higher reduction potential<sup>14</sup> of benzyl bromide 4c (vs. 4a-b) as NO<sub>2</sub> exerts a smaller withdrawing effect in the *meta* position. Increasing the reaction time allows for the use of benzyl bromides bearing more moderately electron withdrawing substituents (e.g. CN and ester groups), furnishing the desired products 5ad and 5ae in good and moderate yields respectively (60% and 44%). Halogenated benzyl bromides are also good substrates providing products 5af and 5ag in yields of 55% and 60% respectively. The selectivity in activating the C(sp<sup>3</sup>)-Br bond preferentially over the C(sp<sup>2</sup>)-Br bond (5af) is significant as it renders this protocol orthogonal in reactivity to traditional palladium cross-couplings and provides a platform for

further functionalisation. This protocol also tolerates highly fluorinated moieties, giving the product 5bh in 51% yield. Substrates bearing a mixture of various electron-withdrawing groups are also tolerated, furnishing the desired products 5bi and 5aj in moderate yields. In particular, the formation of 5bi highlights that the reaction is tolerant of steric hindrance on the benzyl bromide substrate.

As expected, attempts to expand the scope beyond electron-poor benzyl bromides proved challenging due to the higher reduction potentials, with benzyl bromide 4k providing only 24% yield of desired product (5ak) despite extended reaction times (72 h).<sup>15</sup> Surprisingly, reducing the reduction potential even further (e.g. by having two electron-withdrawing nitro groups) does not necessarily improve the cross-coupling (35% 5al), due to competing protodebromination of starting material 4l (31%). Secondary benzyl bromide 4m successfully cross-couples, albeit less efficiently than its primary counterpart under these conditions (5am vs. 5aa). Having ascertained the substrate scope and limitations, we proceeded to demonstrate that the reaction can be successfully scaled up to 1 mmol, albeit with a slightly reduced yield and increased reaction time (51% 5aa after 96 h, see ESI).

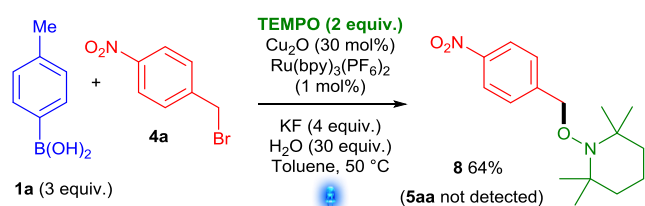
**Table 4** Arylboronic Acid Scope



<sup>a</sup>Yield determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>Isolated yield. <sup>c</sup>Isolated yields not available due to co-elution with unreacted 4. <sup>d</sup>Isolated yields not available due to co-elution with homocoupling product. <sup>e</sup>1j consumed to form insoluble polymers. <sup>f</sup>Poor solubility of arylboronic acid. <sup>g</sup>Using boroxine instead of boronic acid, portionwise addition.

The arylboronic acid scope was investigated next (Table 4). Electron-rich tolylboronic acids perform well as substrates, furnishing the desired products 5aa-5ca with a slight and gradual reduction in yield when moving from *para* (62%) to *meta* (57%) to (51%) *ortho*, presumably reflecting the gradual increase in sterics. Unsubstituted phenylboronic acid 1d and electron rich *p*-anisylboronic acid 1e also proved to be good coupling partners, yielding products 5da and 5ea in 58% and 57% respectively. Electron-

withdrawing substituents are also tolerated in the reaction, with **5fa** and **5ga** formed in 44 and 52% respectively. Arylboronic acids bearing a combination of electron-withdrawing and electron-donating groups are also amenable to the coupling conditions: **5ha** and **5ib** are formed in 50% yields. Unsurprisingly, alkene moieties, which are liable to react with intermediate radicals, are not tolerated (e.g. **5ja**). Although the reaction is tolerant of both electron-rich and electron-poor arylboronic acids, some arylboronic acids, especially ones containing highly polar substituents (e.g. NO<sub>2</sub>) suffer from poor solubility in the reaction mixture, which detrimentally affects their ability as coupling partners (**5ka**). Any polar groups such as NO<sub>2</sub> are thus best introduced *via* the benzyl bromide coupling partner instead. In some cases, such as with **5la**, the solubility problem can be partially overcome by utilising the arylboroxine (44% **5la**).



**Scheme 3** Radical Trap Experiment

Having investigated the scope of both coupling partners, preliminary mechanistic investigations were conducted next. Carrying out the reaction under our optimised conditions in the presence of known radical trap TEMPO results in complete inhibition of the reaction, with no observed formation of desired product **5aa** (Scheme 3). In addition, the TEMPO trapped benzylic radical adduct **8** can be isolated in 64% yield. This result supports our hypothesis that the mechanism is radical based and most likely involves benzylic radicals **IV** as intermediates. Experiments to determine the quantum yield of the reaction were also carried out (see ESI). The quantum yield of the reaction was calculated to be  $\phi = 0.012$ , which rules out the presence of any radical chain mechanisms in the reaction.<sup>16</sup>

In conclusion, we have successfully developed the first dual copper- and photoredox-catalysed C(sp<sup>2</sup>)-C(sp<sup>3</sup>) cross-couplings of aryls with benzylic sp<sup>3</sup> centres. Surprisingly, addition of water was found to be necessary for the generality and reproducibility of the reaction, thereby allowing the successful cross-coupling of a variety of arylboronic acids with electron-deficient benzyl bromides.

We would like to thank the Engineering and Physical Sciences Research Council, Heriot-Watt University and CRITICAT Centre for Doctoral Training and Syngenta [Ph.D. studentship to EM; Grant code: EP/L016419/1] and Leverhulme Trust (RPG-2014-345) for financial support. Mass spectrometry data were acquired at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

## References

- For selected reviews, see: (a) X. Lang, J. Zhao and X. Chen, *Chem. Soc. Rev.*, 2016, **45**, 3026; (b) C. K. Prier, D. A. Rankic and D. W. C. MacMillan, *Chem. Rev.*, 2013, **113**, 5322; (c) J. C. Tellis, C. B. Kelly, D. N. Primer, M. Jouffroy, N. R. Patel and G. A. Molander, *Acc. Chem. Res.*, 2016, **49**, 1429; (d) K. L. Skubi, T. R. Blum and T. P. Yoon, *Chem. Rev.*, 2016, **116**, 10035; (e)

- N. Hoffmann, *ChemCatChem*, 2015, **7**, 393; (f) J. Twilton, C. Le, P. Zhang, M. H. Shaw, R. W. Evans and D. W. C. MacMillan, *Nat. Rev. Chem.*, 2017, **1**, 0052; (g) M. N. Hopkinson, B. Sahoo, J.-L. Li and F. Glorius, *Chem. Eur. J.*, 2014, **20**, 3874.
- For selected reviews, see: (a) J. C. Tellis, D. N. Primer and G. A. Molander, *Science*, 2014, **345**, 433; (b) Z. Zuo, D. T. Ahneman, L. Chu, J. A. Terrett, A. G. Doyle and D. W. C. MacMillan, *Science*, 2014, **345**, 437.
- For example, nickel(II) chloride ethylene glycol dimethyl ether complex and bis(1,5-cyclooctadiene)nickel(0) are known carcinogens.
- For review on dual copper- and photoredox catalysis, see: E. B. McLean and A.-L. Lee, *Tetrahedron*, 2018, **74**, 4881.
- Y. Ye and M. S. Sanford, *J. Am. Chem. Soc.*, 2012, **134**, 9034.
- For selected recent dual copper-catalysed perfluoroalkylations, see also: (a) J. A. Kautzky, T. Wang, R. W. Evans and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2018, **140**, 6522; (b) C. Le, T. Q. Chen, T. Liang, P. Zhang and D. W. C. MacMillan, *Science*, 2018, **360**, 1010; (c) D. B. Bagal, G. Kachkovskiy, M. Knorn, T. Rawner, B. M. Bhanage and O. Reiser, *Angew. Chem. Int. Ed.*, 2015, **54**, 6999; (d) Q.-Y. Lin, Y. Ran, X.-H. Xu and F.-L. Qing, *Org. Lett.*, 2016, **18**, 2419; (e) H.-R. Zhang, D.-Q. Chen, Y.-P. Han, Y.-F. Qiu, D.-P. Jin and X.-Y. Liu, *Chem. Commun.*, 2016, **52**, 11827; (f) T. Rawner, E. Lutsker, C. A. Kaiser and O. Reiser, *ACS Catal.*, 2018, **8**, 3950.
- For examples of other dual copper- and photoredox C-C bond forming reactions, see: (a) M. Rueping, R. M. Koenigs, K. Poschary, D. C. Fabry, D. Leonori and C. Vila, *Chem. Eur. J.*, 2012, **18**, 5170; (b) I. Perepichka, S. Kundu, Z. Hearne and C.-J. Li, *Org. Biomol. Chem.*, 2015, **13**, 447; (c) F. Yang, J. Koeller and L. Ackermann, *Angew. Chem. Int. Ed.*, 2016, **55**, 4759; (d) H. Zhang, P. Zhang, M. Jiang, H. Yang and H. Fu, *Org. Lett.*, 2017, **19**, 1016; (e) X.-F. Xia, G.-W. Zhang, D. Wang and S.-L. Zhu, *J. Org. Chem.*, 2017, **82**, 8455; (f) D. Wang, N. Zhu, P. Chen, Z. Lin and G. Liu, *J. Am. Chem. Soc.*, 2017, **139**, 15632; (g) R. Jin, Y. Chen, W. Liu, D. Xu, Y. Li, A. Ding and H. Guo, *Chem. Commun.*, 2016, **52**, 9909; (h) S.-Y. Hsieh and J. W. Bode, *ACS Cent. Sci.*, 2017, **3**, 66; (i) W. Deng, W. Feng, Y. Li and H. Bao, *Org. Lett.*, 2018, **20**, 4245; (j) W. Sha, L. Deng, S. Ni, H. Mei, J. Han and Y. Pan, *ACS Catal.*, 2018, **8**, 7489.
- For examples of other dual metal- and photoredox-catalysed reactions developed in our group, see: (a) V. Gauchot and A.-L. Lee, *Chem. Commun.*, 2016, **52**, 10163; (b) V. Gauchot, D. R. Sutherland and A. L. Lee, *Chem. Sci.*, 2017, **8**, 2885.
- S. G. Bratsch, *J. Phys. Chem. Ref. Data*, 1989, **18**, 1.
- E. M. Kosower and M. Mohammad, *J. Am. Chem. Soc.*, 1971, **93**, 2713.
- For example, see: (a) H. Huo, X. Shen, C. Wang, L. Zhang, P. Röse, L.-A. Chen, K. Harms, M. Marsch, G. Hilt and E. Meggers, *Nature*, 2014, **515**, 100; (b) H.-W. Shih, M. N. Vander Wal, R. L. Grange and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2010, **132**, 13600.
- A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412.
- See also: ref.8a and G. Barker, S. Webster, D. G. Johnson, R. Curley, M. Andrews, P. C. Young, S. A. Macgregor and A.-L. Lee, *J. Org. Chem.*, 2015, **80**, 9807.
- (a) B. A. Sim, D. Griller and D. D. M. Wayner, *J. Am. Chem. Soc.*, 1989, **111**, 754; (b) D. A. Koch, B. J. Henne and D. E. Bartak, *J. Electrochem. Soc.*, 1987, **134**, 3062.
- The reaction was also attempted using the more reducing *fac*-Ir(ppy)<sub>3</sub> photocatalyst, but this resulted in only trace amounts of the desired product **5ak**, see ESI.
- M. A. Cismesia and T. P. Yoon, *Chem. Sci.*, 2015, **6**, 5426.