Silvi, M., Sandford, C., & Aggarwal, V. K. (2017). Merging Photoredox with 1,2-Metallate Rearrangements: The Photochemical Alkylation of Vinyl Boronate Complexes. *Journal of the American Chemical Society*, *139*(16), 5736-5739. https://doi.org/10.1021/jacs.7b02569

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Merging Photoredox with 1,2-Metallate Rearrangements: The Photochemical Alkylation of Vinyl Boronate Complexes

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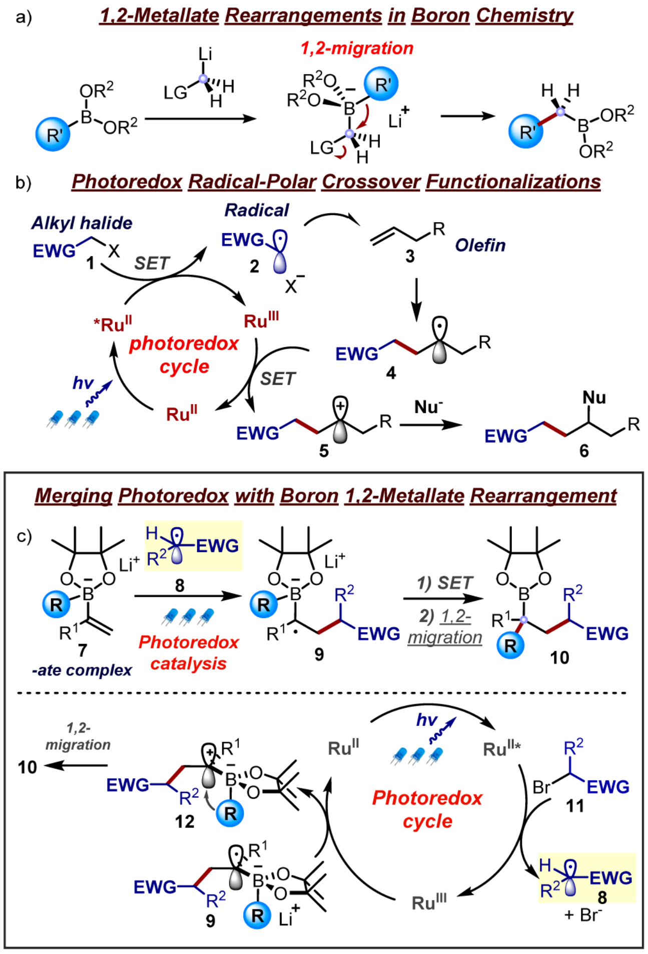
Supporting Information

ABSTRACT: Vinyl boronates react with electron-deficient alkyl iodides in the presence of visible light to give boronic esters in which two new C−C bonds have been created. The reaction occurs by radical addition of an electron-deficient alkyl radical to the vinyl boronate followed by electron transfer with another molecule of alkyl iodide, continuing the chain, and triggering a 1,2-metalate rearrangement. In a number of cases, the use of a photoredox catalyst enhances yields significantly. The scope of the radical precursor includes α-iodo ketones, esters, nitriles, primary amides, α-fluorinated halo-acetates and perfluoroalkyl iodides.

Since its discovery over 50 years ago, the 1,2-metalate rearrangement of boronate complexes possessing α-leaving groups (Scheme 1a, Matteson reaction) has been developed and refined into a powerful and versatile, substrate-controlled, asymmetric methodology, which has been widely used in synthesis.[1] In the past decade, we have established a suite of related reagent-controlled homologations of boronic esters.[2] This methodology allowed us to develop iterative processes that enable the conversion of simple starting materials into complex molecules without intermediate purification, a strategy that was applied to the synthesis of natural[3] and non-natural products.[4] Over the same period, photoredox catalysis has emerged as a tremendously versatile platform for organic synthesis, enabling reactive radical centers to be generated at specific positions in organic molecules under exceptionally mild conditions.[5,6] One of the key features of photoredox catalysis is the potential to crossover from a radical to a polar pathway[7] during the overall catalytic process. For example, in photoredox olefin functionalizations with electrophilic radicals,[8] single-electron transfer (SET) from radical **4** generates cation **5**, which can be trapped by nucleophiles to afford adducts **6** (Scheme 1b).[9] We considered the possibility of merging the features of photoredox reactions with 1,2-metalate rearrangements, two contemporary synthetic strategies that are currently unconnected. Specifically, we reasoned that related reactions of vinyl boronates **7** with electrophilic radicals **8** would lead to a new radical anion **9** that might undergo single-electron oxidation and trigger a 1,2-metalate rearrangement, generating diversely functionalized boronic esters **10** (Scheme 1c).[10] This strategy, which was ultimately successful, provides a novel three-component coupling reaction where two new C−C bonds are formed in one step, rapidly building up molecular complexity while retaining the highly versatile boronic ester moiety. During the preparation of this manuscript, Studer and co-workers reported a related radical three-component coupling reaction of alkyl iodides and vinyl boronate complexes, utilizing triethylborane/air for radical generation.[11]

Scheme 1. (a) 1,2-Metallate Rearrangements, (b) Photoredox Radical-Polar Crossover Reactions, (c) This Work: Merging Photoredox with 1,2-Metallate Rearrangements

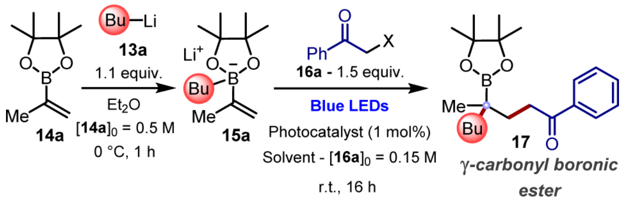


We began our studies by exploring the reaction between vinyl boronates and phenacyl halides and tested various solvents and metal catalysts under visible-light irradiation (Table 1). Phenacyl halides were selected as radical precursors owing to their well-

Received: March 14, 2017
Published: April 12, 2017

DOI: 10.1021/jacs.7b02569
J. Am. Chem. Soc. 2017, 139, 5736−5739

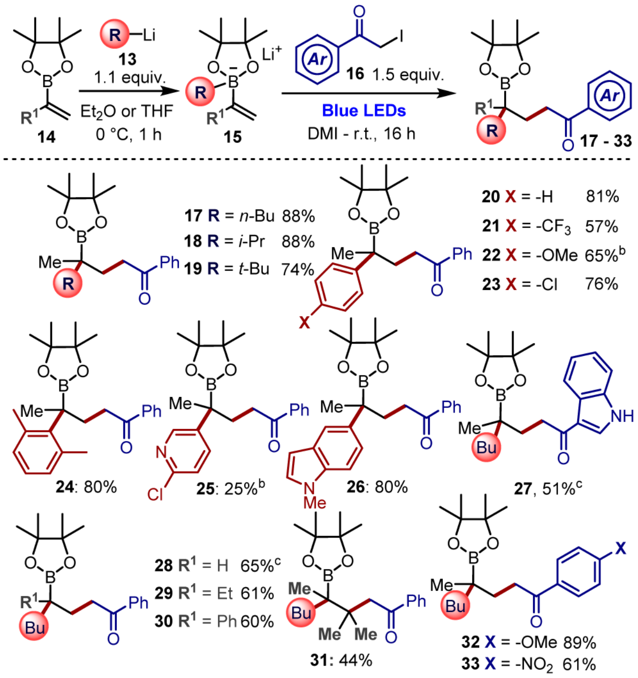
Table 1. Optimization Studies



entry[a]	solvent	X	photocatalyst	17 (%)[b]
1	DMSO	Cl	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	traces
2	DMSO	Br	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	57
3	DMSO	Br	$Ir(ppy)_3$	57
4	DMSO	I	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	80
5	THF	I	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	38
6	DMI	I	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	85
7[c]	DMI	I	$Ru(bpy)_3Cl_2{\cdot}6H_2O$	86 (85)
8[c]	DMI	I	none	87 (88)
9[c,d]	DMI	I	none	15

[a] Unless otherwise noted, all the reactions were carried out under a nitrogen atmosphere, using Schlenk techniques, on a 0.15 mmol scale. After boronate complex formation, solvent exchange to the selected solvent was performed. [b] ^1H NMR yield using 1,3,5-trimethoxybenzene as an internal standard; yield of isolated product based on a 0.3 mmol scale reaction is given in parentheses. [c] Reaction carried out by adding a DMI solution of iodoacetophenone to the ethereal suspension of boronate complex. [d] Reaction carried out in the dark.

Scheme 2. Scope of Boronates and Phenacyl Iodides[a]



[a] Reactions were carried out under a nitrogen atmosphere, using Schlenk techniques on a 0.3 mmol scale; yields after chromatographic purification. [b] Yield of the corresponding alcohol following H_2O_2/NaOH oxidation. [c] 1 mol % of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ was used.

established tendency to readily undergo one-electron reduction generating stabilized, electrophilic α-carbonyl radicals,[12] and because they have been used in photoredox-mediated reactions.[5a] For our optimization studies, boronate complex **15a** was generated in situ by treating the boronic ester **14a** with *n*-butyllithium in Et_2O. After solvent removal, a solution of phenacyl halide and the photocatalyst were added to the vessel and the mixture irradiated with blue light.

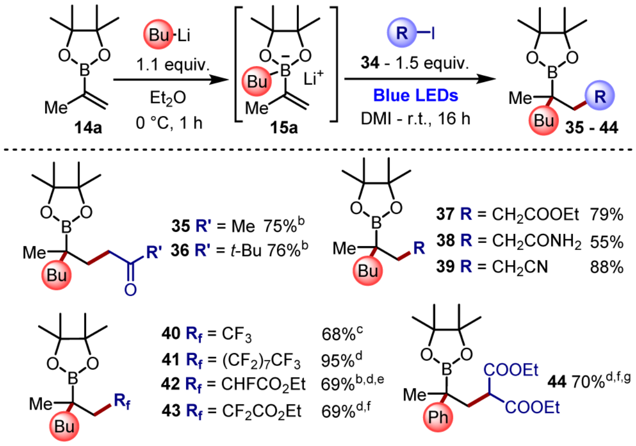
Although phenacyl chloride was not a good substrate for our reaction (entry 1), we were pleased to find that subjecting the corresponding bromide to our reaction conditions in the presence of $Ru(bpy)_3Cl_2{\cdot}6H_2O$ afforded boronic ester **17** in 57% yield (entry 2). The use of the more reducing photocatalyst $Ir(ppy)_3$ gave similar results (entry 3). Gratifyingly, simply by replacing phenacyl bromide with the corresponding iodide, the yield improved to 80% (entry 4). The improvement of yield going from Cl to Br to I follows the increasing ease of one-electron reduction along the series.[12,13] Solvent effects were also explored and further improvements were observed by switching from DMSO to 1,3-dimethyl-2-imidazolidinone (DMI, entry 6). We also found that Et_2O−DMI mixtures could be used (entry 7), simplifying the reaction set up: after formation of the boronate complex in ether, a DMI solution of the radical precursor was added to the boronate complex, avoiding solvent exchange. However, and much to our surprise, a control experiment without the photocatalyst and just irradiation with blue LEDs afforded the product in a similar yield (88%, entry 8).[14] A further control experiment (entry 9) showed that light was essential as little product was obtained in the dark.

With optimum reaction conditions established, we tested a range of different boronate complexes (Scheme 2). Boronate complexes obtained by treating boronic ester **14a** with *n*-butyllithium, *iso*-propyllithium or *tert*-butyllithium all reacted efficiently (Scheme 2, **17**−**19**), demonstrating that the level of steric hindrance around the boron center does not significantly impact on the radical addition, subsequent oxidation or 1,2-migration steps. A range of aryllithiums of different steric and electronic properties worked well (**20**−**24**). Organolithiums generated from heteroaromatics could also be used: the 5-indolyl-substituted compound **26** was obtained with high yield, although the 3-pyridyl compound **25** was obtained in lower yield. Variation of the α-substituent (R^1) of the vinyl boronate (products **28**−**30**) and a fully substituted vinyl moiety (product **31**) were tolerated, although the unsubstituted vinyl boronate (R^1=H, product **28**) required the use of a photocatalyst to achieve high yields (37% yield in the absence of $Ru(bpy)_3Cl_2{\cdot}6H_2O$). The scope of the phenacyl iodide radical precursors was also explored: electron-rich and electron-deficient aromatic groups (products **32**−**33**), as well as an *N*-H indole moiety (product **27**), were successfully introduced.

We then tested a more diverse range of alkyl halide radical precursors (Scheme 3). We were delighted to find that subjecting aliphatic α-iodo ketones (preformed in the reaction medium by treatment of the corresponding bromides or chlorides with stoichiometric NaI, see SI and vide infra) to our reaction conditions afforded the desired compounds in high yield (compounds **35**−**36**). Other functionalities such as esters, nitriles and, remarkably, primary amides could also be employed affording the desired products in good to excellent yields (products **37**−**39**). α-Fluorinated halo-acetates and perfluoroalkyl iodides,[8,15,16] including CF_3I,[17] were also successfully employed, affording the corresponding fluorinated tertiary boronic esters in good to excellent yields (products **40**−**43**), although the use of a photocatalyst was found to be necessary in most cases in order to achieve good reaction efficiency. Diethyl bromomalonate, an efficient reagent for atom-transfer radical additions (ATRA) to olefins,[8] was also a competent radical

DOI: 10.1021/jacs.7b02569
J. Am. Chem. Soc. 2017, 139, 5736−5739

Scheme 3. Scope of Radical Precursors[a]



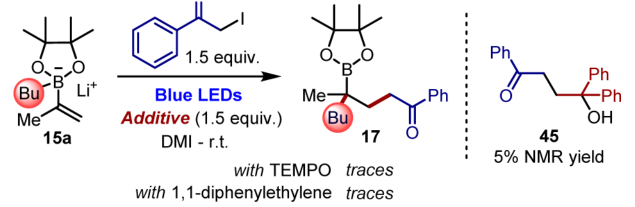
[a]Reactions were carried out under a nitrogen atmosphere, using Schlenk techniques, on a 0.3 mmol scale; yields after chromatographic purification. [b]Reaction carried out starting from the corresponding bromide or chloride, premixed with NaI prior to addition (see SI). [c]5 equiv of CF$_3$I·2DMSO were used. [d]1 mol % of Ru(bpy)$_3$Cl$_2$·6H$_2$O was added. [e]2:1 d.r. [f]Reaction carried out starting from the corresponding bromide. [g]Boronate complex derived from phenyllithium.

precursor furnishing, in the presence of a ruthenium photocatalyst, boronic ester **44** in high yield.

The products from these reactions are noteworthy. For example, although ample methods are available for the synthesis of β-carbonyl boronic esters (e.g., by conjugate addition to Michael acceptors),[18] there are few examples for the synthesis of γ-carbonyl boronic esters[19] that are now easily accessible using the current methodology. Furthermore, it is not possible to create compounds like **40** by existing metalate rearrangements since intermediate boronate complexes with β-leaving groups undergo elimination instead of 1,2-migration.[20]

Next, we conducted further experiments to probe the reaction mechanism. Carrying out the reaction in the presence of a nitroxyl radical (TEMPO) completely shut down the reaction, suggesting that a radical mechanism is operative (Scheme 4).

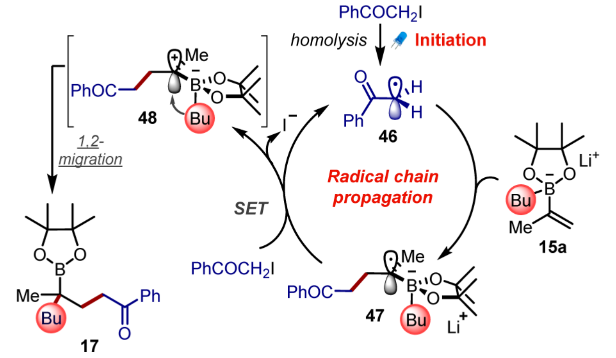
Scheme 4. Control Experiments



Furthermore, when the reaction was carried out in the presence of a styryl radical trap (1,1-diphenylethylene),[21] addition to the boronate was suppressed and adduct **45** was observed in the crude reaction mixture.[22] This product could arise from addition of the phenacyl radical to the radical trap[23] followed by either oxidation of the stabilized benzylic radical generated, or hydrolysis of the benzyl iodide atom-transfer product upon workup.

To gain insight into the mechanism of the photoinitiation event, we conducted UV/vis absorption analysis of both the boronate complex and iodoacetophenone separately and then combined; however, no new bands in the visible region were observed, indicating that a ground-state charge-transfer complex was not formed in solution.[14a,b] We did observe very low residual visible-light absorption of the iodoacetophenone (see SI for further details), which we postulate is the photoinitiation event. Thus, the mechanism proposed involves homolytic cleavage of the alkyl iodide by visible light, generating the electrophilic alkyl radical **46**,[23,24] which reacts with the electron-rich vinyl boronate complex **15a** to form boronate radical **47** (Scheme 5). This electron-rich radical anion then undergoes facile single-electron oxidation (or iodine atom transfer, not shown)[25] with another molecule of alkyl iodide,[11,26] thus triggering rapid (or concerted)[27] 1,2-metalate rearrangement to afford the product **17**. The process also releases a new α-carbonyl radical **46**, thereby feeding a radical chain propagation pathway. We have found that for the reactions affording compounds **27**, **28** and **41**−**44**, the addition of a Ru photocatalyst was necessary to achieve high yields. In these cases, in the absence of photocatalyst, the innate radical chain is likely to be inefficient, stemming from slow initiation or slow electron/atom transfer. However, in these particular cases, a ruthenium photocatalyst is able to mediate these steps, leading to high yields.

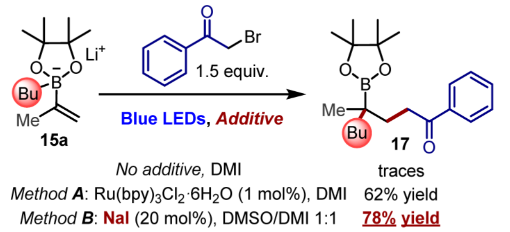
Scheme 5. Proposed Mechanism



Finally, because alkyl iodides are often not commercially available, are light- and air sensitive, and are severe lachrymators, we sought to generate them in situ from the corresponding bromides with NaI. Subjecting phenacyl bromide to our reaction conditions in the presence of sodium iodide (20 mol %), we were delighted to observe the formation of the desired compound in 78% yield, further improving the efficiency and sustainability of our approach (Scheme 6). Thus, two pathways are available from the bromoketone: use of 1 mol % of the Ru photosensitizer or 20 mol % of NaI.

In conclusion, after over 50 years of 1,2-metalate rearrangements involving α-leaving groups, we have discovered a novel trigger mechanism involving oxidation of an α-boronate radical. This radical species can be generated from a halide and a vinyl

Scheme 6. Using NaI for Bromoacetophenone Activation



boronate by photoredox, visible-light-induced activation or by Studer's Et_3B/air protocol.[11] The collective methods cover vast substrate scope providing a novel, efficient and atom-economic three-component coupling reaction. Furthermore, many of the products are simply not accessible through traditional 1,2-metalate rearrangements, thereby opening up new chemical space.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b02569.

Detailed experimental procedure and characterization data for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank the University of Bristol for financial support. M.S. thanks the EU for H-2020 Marie Skłodowska-Curie Fellowship (grant no. 744242). We thank Dr. Eddie Myers for useful discussions.

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(25) In this scenario, radical anion **47** abstracts an I atom from another molecule of iodoacetophenone, generating radical **46** and an α-iodo boronate complex, which is expected to undergo 1,2-migration rapidly to afford product **17**. See ref 11.

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