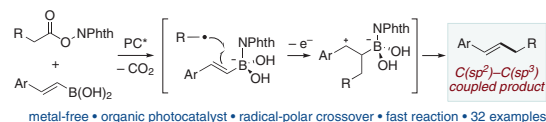# Organophotocatalytic Radical–Polar Cross-Coupling of Styrylboronic Acids and Redox-Active Esters

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metal-free • organic photocatalyst • radical-polar crossover • fast reaction • 32 examples

Abstract   We report the development of a radical–polar cross-coupling reaction using styrylboronic acids and redox-active esters under organophotoredox catalysis. The reaction proceeds through a formal polarity-mismatched radical addition. The use of an organic photocatalyst permitted very low loadings of the electron-shuttle additive and accelerated reaction times compared with established processes. The scope of the reaction was explored, and the utility of the products is demonstrated.

Key words   esters, styrylboronic acids, photocatalysis, radical–polar cross-coupling

Radical–polar cross-coupling reactions are broadly useful methods for synthesis.[1] The addition of a radical species to an alkene forges an initial C–C or C–X bond and produces an intermediate radical that can, in turn, be used to access several different products, depending on the reaction conditions (Scheme 1a). For example, oxidation of the intermediate radical delivers a carbocation that can be intercepted by a nucleophile or can lose a proton to forge an alkene. Alternatively, reduction of the intermediate radical generates an anion that can undergo reaction with an electrophile. Extensions to this chemistry where the intermediate radical reacts with another substrate (e.g., a second alkene or hydrogen donor) or a transition metal to promote further bond formations have also been developed.[2] The functionalization of the alkene starting material can be critical to the downstream reactivity of the intermediate radical.
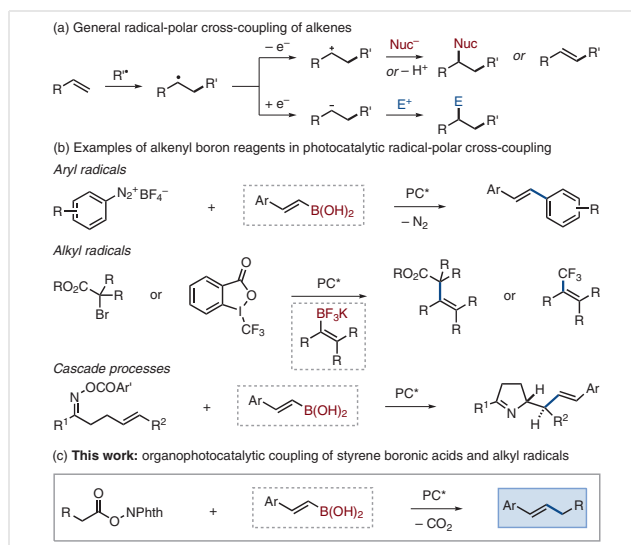
Scheme 1   Radical–polar cross-coupling and selected examples of radical–polar cross-couplings using styrylboronic acid derivatives

Borylated alkenes have been used in radical–polar cross-coupling in three main approaches: (i) as π-nucleophiles to intercept an intermediate carbocation,[3] (ii) to generate α-boryl radicals for addition to alkenes or as SOMO-philes,[4,5] and (iii) as SOMOphiles where the boryl unit acts as a leaving group to facilitate formation of alkene products.[5]

The third approach has seen several applications, selected examples of which are shown in Scheme 1b. For example, Wu and co-workers developed a method for photocatalytic coupling of aryl radicals, generated from diazonium salts, with styrylboronic acids.[5a] The groups of Leonori and Akita have developed photocatalytic couplings of potassi-

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um alkenyl(trifluoro)borates with radicals generated from α-halocarbonyls or the Togni reagent, respectively.[5b,c] Yu and co-workers have shown how styrylboronic acids can react with C-centered radicals generated from cascade processes.[5d,e]

We recently reported a method for coupling styrylboronic acids with redox-active N-hydroxyphthalimide (NHPI) esters using Ru photocatalysis.[5f] Here, we report an improved process based on organophotoredox catalysis that is metal-free and permits a faster reaction using lower loadings of the electron-shuttle additive (Scheme 1c).

The motivation for this work was to move away from noble-metal-based photocatalysts to improve the sustainability of coupling processes.[6] Accordingly, we focused on the use of organic photocatalysts. The benchmark reaction between styrylboronic acid (**1**) and cyclohexyl (c-Hex) NHPI ester (**2**) to give the desired C(sp²)–C(sp³) coupled product is shown in Table 1. The optimized reaction conditions required 1 mol% of 1,2,3,5-tetrakis(carbazol-9-yl)-4,6-dicyanobenzene (4CzIPN)[7] as a photocatalyst and 2 mol% of Ph₃N as an electron shuttle (see below), with the reaction complete in one hour (Table 1, entry 1). This represented an improvement on previous conditions, which used 1 mol% of an Ru-based photocatalyst, 10 mol% of an electron-shuttle additive (PhNMe₂), and required three hours for a similar yield.[8] Selected optimization data are provided. First, the re-

action did not proceed with eosin Y[9] and PhNMe₂ under irradiation from blue LEDs (entry 2), but required green LEDs and an extended reaction time to give a low yield (entry 3). Using 4CzIPN with PhNMe₂ for an extended reaction time gave a good yield, but resulted in erosion of stereochemical integrity (entry 4). This extended reaction time resulted in photocatalytic alkene isomerization.[10] Solvent variation was not tolerated (entries 6 and 7). Control reactions confirmed the requirement for blue LEDs (entries 8 and 9). Other additives were assessed, such as catechol (entry 10), but none offered an improvement on Ph₃N. An increased loading of Ph₃N offered no advantage compared with 1 mol% (entry 11). Finally, the reaction was more effective with the boronic acid: the equivalent Bpin, Bcat (cat = 1,2-O₂C₆H₄), and BF₃K compounds were less effective or were unreactive (entries 12–14).

The generality of the benchmark reaction conditions was assessed by application to a range of NHPI esters and styrylboronic acids (Scheme 2). Variation of the NHPI component was generally well tolerated, with some fluctuations in the isolated yield (Scheme 2a). Cycloalkyl NHPI es-

Table 1 Reaction Development.

Entry	Deviation from standard conditions	Yield[a] (%) (E/Z)[a,b]
1	–	93, 85[c]
2	eosin Y (10 mol%), PhNMe₂ (10 mol%), 3 h	–
3	eosin Y (10 mol%), PhNMe₂ (10 mol%), green LEDs, 24 h	33
4	PhNMe₂ (10 mol%), 18 h	91 (3.3:1)
5	**1** (1.0 equiv), PhNMe₂ (10 mol%)	50
6	MeCN as solvent	47
7	acetone as solvent	46
8	darkness, 20 h	–
9	ambient light, 20 h	–
10	catechol (10 mol%)	82
11	Ph₃N (10 mol%)	90
12	**1** Bpin ester	37
13	**1** Bcat ester	51
14	**1** BF₃K salt	14

[a] Determined by ¹H NMR analysis using an internal standard.
[b] E/Z > 20:1 unless noted.
[c] Isolated yield.
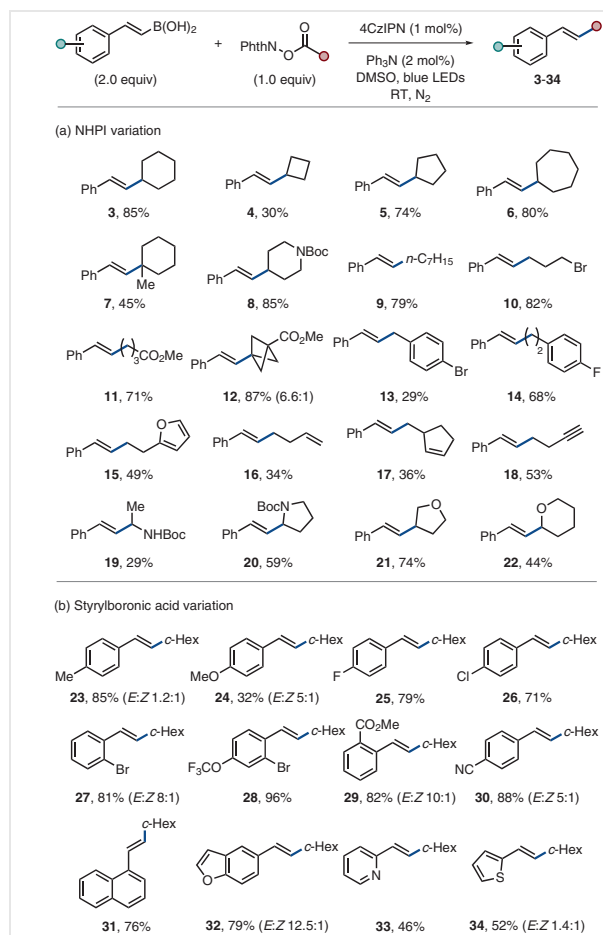
Scheme 2 Example scope. Isolated yields are reported. E/Z > 20:1 unless noted (determined by ¹H NMR).

ters were typically well tolerated (**3–8**, **12**, **20–22**), except for the cyclobutyl example (**4**). Linear alkyl NHPI esters bearing a range of functionalities were similarly well accommodated (**9–11**, **13–19**), including those bearing alkyl bromide (**10**), ester (**11**), or (het)arene groups (**14**, **15**). Compounds with side chains containing alkene, alkyne (**16–18**), or benzyl units (**13**) underwent coupling but in lower yields in general. Finally, NHPI esters with α-heteroatoms, including nitrogen or oxygen, could be employed (**19**, **20**, **22**).

A range of styrylboronic acids with various electronic and steric parameters were generally effective reactants (Scheme 2b). There was no clear electronic trend, with some electron-rich (**24**) or electron-deficient (**33**) examples providing diminished yields.

Lastly, the majority of products were isolated with >20:1 *E/Z* ratios; however, several examples notably displayed an erosion of stereochemical integrity through uncontrolled photocatalytic isomerization (noted in Scheme 2).[10]

To showcase the synthetic utility of this photocatalytic coupling method, we used product **3** in a range of downstream derivatization processes (Scheme 3). Photocatalytic *E→Z* isomerization was achieved under the conditions reported by Gilmour and co-workers to give **35**.[10d] Ru-catalyzed aziridination delivered **36**.[11] Catalytic dihydroxylation smoothly delivered diol **37**,[12] whereas dibromination was also straightforward, giving **38**.[13] Hydrogenation using a Pt catalyst gave the linear alkane **39** in a good yield.[14] Finally, Prilezhaev epoxidation gave **40**.[15]
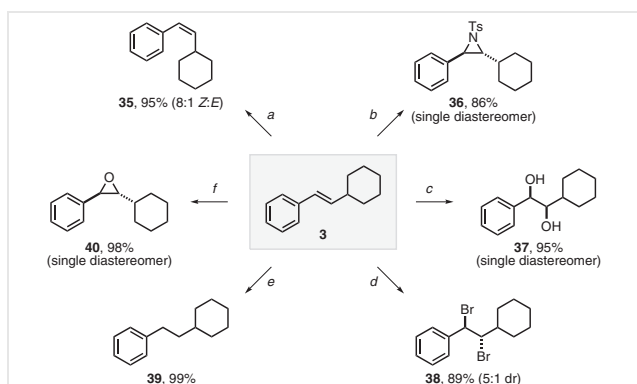
Scheme 3 Examples of diversification of products. *Reaction conditions*: (a) Ir(ppy)$_3$ (1 mol%), MeCN (0.1 M), blue LEDs, RT, 16 h. (b) TsNH$_2$ (2.0 equiv), PhIO (2.0 equiv), Ru(bpy)$_3$PF$_6$ (2 mol%), CH$_2$Cl$_2$ (0.1 M), 3 Å MS, blue LEDs, N$_2$, RT, 4 h. (c) OsO$_4$ (1.5 mol%), NMO (1.5 equiv), MeSO$_2$NH$_2$ (1.0 equiv), acetone–H$_2$O (0.1 M), RT, 1 h. (d) Br$_2$ (1.5 equiv), CHCl$_3$ (0.1 M), RT, 2 h. (e) PtO$_2$ (5 mol%), EtOH (0.1 M), H$_2$, RT, 2 h. (f) *m*CPBA (1.5 equiv), CH$_2$Cl$_2$ (0.1 M), N$_2$, RT, 16 h.

Based on our previous work,[5f] a proposed mechanism for the reaction is shown in Scheme 4. Irradiation of the 4CzIPN (PC; **41**) gives the excited photocatalyst **42** [$E_{1/2}$

(**42/43**) = 1.35 V vs SCE].[8b] This is capable of one-electron oxidation of Ph$_3$N ($E_{1/2}$ = 0.98 V vs SCE) to give the reduced photocatalyst **43** and the aminium radical **48**.[16] Radical anion **43** [$E_{1/2}$ (**41/43**) = −1.21 V vs SCE][8b] facilitates single-electron transfer to **45** ($E_{1/2}$ = −1.26 V vs SCE),[17] resulting in decarboxylation and loss of a phthalimide anion (NPhth$^-$) to give alkyl radical **46**. Concomitant boronate formation from **44** and NPhth$^-$ gives **47**. Radical **46** can then undergo addition to alkene **47** to give radical intermediate **49**. Oxidation of **49** [$E_{1/2}$ (**50/49**) = 0.37 V][18] by **48** ($E_{1/2}$ = −0.98 vs SCE)[16] gives carbocation **50**, which is primed for elimination of the boron unit to give the product **51**.
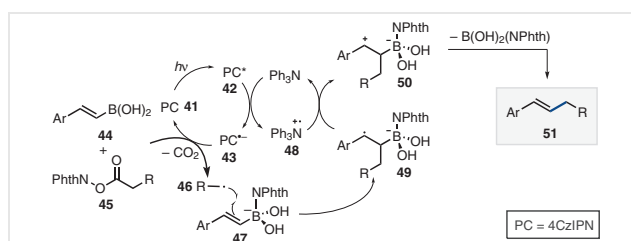
Scheme 4 Proposed mechanism

In summary, a metal-free approach to radical-polar cross-coupling of styrylboronic and NHPI esters has been developed. The reaction conditions offer several advantages over established methods, including the avoidance of noble metals, lower loadings of catalytic additives, and shorter reaction times. This C(sp^3)–C(sp^2) coupling is general and affords the desired products in typically good yields.[19]

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

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(19) **Alkenes 3–34; General Procedure**

An oven-dried photoreactor vial equipped with a Teflon-coated stirrer bar was charged with the appropriate NHPI ester (200 µmol, 1.0 equiv) and styrylboronic acid (400 µmol, 2.0 equiv), together with 4CzIPN (1.6 mg, 2.0 µmol, 1 mol%) and Ph$_3$N (1.0 mg, 4.0 µmol, 2 mol%). The vial was then sealed, purged by using N$_2$–vacuum cycles (×3), and backfilled with N$_2$. Degassed dry DMSO-d_6 (2.0 mL, 0.1 M) was then added from a syringe. The cap was wrapped with Parafilm, and the mixture was stirred under blue LEDs at RT (~20 °C) for 1 h. The mixture was then partitioned between Et$_2$O (5 mL) and brine (5 mL), and the organics were extracted with Et$_2$O (2 × 10 mL). The organic phases were combined, washed with brine (15 mL), dried (Na$_2$SO$_4$), filtered, and concentrated under vacuum. The crude residue was purified by flash chromatography (silica gel; hexane, hexane–EtOAc, or hexane–Et$_2$O).

[(*E*)-2-Cyclohexylvinyl]benzene (3)

Prepared according to the general procedure from 1,3-dioxoisoindolin-2-yl cyclohexanecarboxylate (**2**; 54.7 mg, 200 µmol, 1.0 equiv), [(*E*)-2-phenylvinyl]boronic acid (**1**; 59.2 mg, 400 µmol, 2.0 equiv), 4CzIPN (1.6 mg, 2.0 µmol, 1 mol%), and Ph$_2$N (1.0 mg, 4.0 µmol, 2 mol%) in DMSO-d_6 (2 mL, 0.1 M). The crude residue (95% ^{1}H NMR yield) was purified by flash chromatography (silica gel, hexane) to give a colorless oil; yield: 31.8 mg (85%, *E*/*Z* > 20:1).

^{1}H NMR (500 MHz, CDCl$_3$): δ = 7.37–7.33 (m, 2 H), 7.31–7.27 (m, 2 H), 7.21–7.16 (m, 1 H), 6.35 (d, *J* = 16.01 Hz, 1 H), 6.18 (dd, *J* = 15.98, 6.96 Hz, 1 H), 2.18–2.08 (m, 1 H), 1.86–1.74 (m, 4 H), 1.72–1.65 (m, 1 H), 1.39–1.25 (m, 2 H), 1.25–1.14 (m, 3 H). ^{13}C NMR (126 MHz, CDCl$_3$): δ = 138.2, 137.0, 128.6, 127.3, 126.9, 126.1, 41.3, 33.1, 26.3, 26.2.