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Oxidative [1,2]-Brook Rearrangements Exploiting Single-Electron Transfer: Photoredox-Catalyzed Alkylations and Arylations

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Abstract

Oxidative [1,2]-Brook rearrangements via hypervalent silicon intermediates induced by photoredox-catalyzed single-electron transfer have been achieved, permitting the formation of reactive radical species that can engage in alkylations and arylations.

Brook rearrangements comprise the transfer of a silyl group from a carbon to an oxygen atom with concomitant migration of charge resulting in a carbanion from the initiating alkoxide species.¹ This rearrangement, initially introduced by Brook et al.,² has been well studied^{1b,3} and is now known to proceed reversibly via a hypervalent silicon (Scheme 1a).⁴

Brook rearrangements have been employed extensively in our and other Laboratories in conjunction with a multicomponent coupling tactic we now term Anion Relay Chemistry (ARC).⁵ Although negative charge interchange via migration of a silyl group is now well-known, Brook rearrangements via single-electron transfer (SET) have not been extensively explored (Scheme 1b). Moreover, such rearrangements have not been employed synthetically,⁶ presumably due to the difficulty associated with the formation of an alkoxy radical. Organosilicon compounds, especially alkylsilanes, are generally known to be quite resistant to oxidants given their high oxidation potential (for example, $E_{ox} = +1.68$ V vs SCE⁷ for **I** in Scheme 2). Recently however a mild catalytic photoredox system has been introduced to employ hypervalent organosilicates as alkyl radical precursors.⁸ In these reports, pentacoordinate silicates⁹ are prepared and demonstrated to have relatively low oxidation potentials (for example, $E_{ox} = +0.61$ V^{8b} vs SCE for **II** in Scheme 2). As illustrated in Scheme 1a, the Brook rearrangement builds a direct linkage between alkylsilanes and hypervalent silicates. We therefore hypothesized that it might be possible to access a pentacoordinate alkylsilicate *in situ* via a Brook rearrangement, followed by achieving the oxidative cleavage of a strong C–Si bond via single-electron transfer

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Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b05165. Experimental procedures, NMR spectra for obtained compounds, and mechanistic studies (PDF)

Notes

The authors declare no competing financial interest.

employing photoredox catalysts.¹⁰ This chemistry might provide an alternative to the direct generation of an α -hydroxy radical. To the best of our knowledge, such a reaction sequence is unprecedented.

To achieve an oxidative [1,2]-Brook rearrangement, two criteria would be required: (i) the reduction potential of the excited-state photoredox catalysts must be sufficiently high to cleave a strong Si–C bond; and (ii) selective cleavage of the C–Si bond to form the alkyl radical must be achieved when the silicon is tetraalkyl-substituted (i.e., TMS, TBS, or TIPS). Thus, we report here the first visible-light-induced SET tactic to achieve an oxidative [1,2]-Brook rearrangement. Both photoredox-catalyzed alkylations and arylations have been achieved.

Based on the above hypothesis, we propose the reaction sequence in Scheme 3. First, deprotonation of an aryl-(trialkylsilyl)methanol to set up an equilibrium between the alcohol and the hypervalent silicon (i.e., **A**) in analogy to the well-known anionic Brook rearrangement. Intermediate **A** could then serve either as a radical precursor of the α -benzyl silyl ether radical (i.e., **B**), capable of alkylation with an electron-deficient olefin (catalytic cycle in Scheme 3a), or arylation with an electron-deficient aromatic compound (catalytic cycle in Scheme 3b).¹¹ For alkylation (Scheme 3a), oxidation of intermediate **A** by the excited state of an Ir photocatalyst must occur. The resulting open-shell intermediate **B** could then engage in a conjugate addition with an electron-deficient olefin to form an α -carbonyl radical **C**. Electron transfer from the reduced photocatalyst would then generate an enolate anion, which in turn would undergo protonation to provide the alkylation product **D**, with the photocatalyst returning to the ground state. For arylation (Scheme 3b), a photoactivated Ir photocatalyst would first undergo SET with an electron-deficient arene to furnish the corresponding arene radical anion **E**, with generation of the Ir(IV) photocatalyst. We hypothesize that the Ir(IV) species would then be able to oxidize the hypervalent silicon intermediate **A** to form radical **B**. A bond-forming step could then occur via radical union between intermediates **B** and **E**, followed by elimination of cyanide to yield the arylated product (i.e., **F**).

To begin, we selected (*tert*-butyldimethylsilyl)phenylmethanol (**1b**) as a model substrate and methyl vinyl ketone (**2a**) as the radical acceptor. After extensive screening, we found that employing KO₂Piv as the base in dichloroethane (DCE) led to alkylation product **3b** in 38% yield employing 3 mol % of Ir[dF(CF₃)ppy]₂(dtbpy)PF₆ as the photocatalyst (entry 1 in Table 1). Other photocatalysts led to poor results (entries 2–3).

The specific choice of base and solvent significantly influenced the yield. For example, polar solvents such as acetone and CH₃CN led to no product (entries 4–5). Stronger bases such as NaOH (entry 6) led to the formation of (benzyloxy)trimethylsilane, which is the byproduct of a base-mediated Brook rearrangement. A weaker base such as K₂CO₃ (entry 7) led to low conversion. The best combination of bases proved to be 1:1 equiv of KO₂Piv and CsOAc and 1:2 equiv of **1b** and **2a**; the isolated yield was then 78% (entry 9). To our delight, the loading of radical acceptor **2a** could be further decreased to 1 equiv with a 72% isolated yield when the reaction was run in high concentration (2.5 M) on 0.5 mmol scale (entry 10).

We next evaluated the scope of the alkylation protocol (Scheme 4). Initially, aryl(trialkylsilyl)-methanols were explored (**1a–1e**). Groups such as TMS, TES, TBS, and TIPS delivered over 70% of **3a–3e**, indicating that steric hindrance on the silicon atom does not influence the reaction. Generally, TES and TBS substrates proceeded in higher yield than the corresponding TMS congeners. This result is attributed to the higher stability of the TES- and TBS-carbon bonds. However, changing the silyl group to the dimethylphenylsilyl (DMPS) witnessed a modest decrease in yield (**3d**, 56% yield). The electron-withdrawing effect of the phenyl group on the Si atom appears to play a negative role in this photoredox reaction. Next, different functional groups on the aromatic ring attached to the carbinol were explored. Electron-donating groups were well tolerated leading in high yield to products **3f–3k**. Halogenated substrates were also well tolerated leading to **3l–3n**. However, in contrast with fluoro, the stronger electron-withdrawing group CF₃ in **3o** led to diminished reactivity. Sterically hindered systems such as *ortho*-methyl substituted aryl(trimethylsilyl)methanol also reacted well to provide a 67% yield of **3j**. Equally pleasingly, substrates possessing heterocyclic substituents proved to be viable substrates leading to **3p–3q** in moderate yields. We reason that the decrease in yield of **3q** is mainly due to facile decomposition of the corresponding substrate **1q**. Finally, the alkylation could be scaled up for gram-scale synthesis employing a high concentration (1.0 M) of **1f** using 2 mol % of Ir photocatalyst (Scheme 4b).

We next explored diverse radical acceptors testing both alkyl and aryl enones (Scheme 5, **2b–2k**). The presence of bulky alkyl groups did not influence the reactivity; good to high yields were obtained (**4b–4c**). An alkyl enone with a remote OTBS group (**2d**) was also well tolerated, thus providing a scaffold amenable to synthetic applications. Aryl enones normally gave better results than alkyl enones. Different functional groups on the aromatic ring were also explored (**2e–2i**). Neither electronic nor steric effects reduced the reactivity. However, a 1- and 2-substituted enone (**2k** and **2j**) revealed that steric and electronic effects on the enone can strongly influence the yield. For example, with a methyl group as in **2j**, the yield was significantly reduced, but with an electron-withdrawing phenyl group as in **2k**, an excellent yield was obtained. However, simple acrylates provided only a trace amount of the alkylation product. We reasoned that this outcome is likely due to the difficulty associated with reducing α -carbonyl radicals in simple acrylates.¹² However, when a phenyl group was introduced at the α -position, alkylation product **4l** was produced in 86% yield.

With the alkylation protocol established, we next explored whether a SET pathway could be employed to achieve arylation (catalytic cycle in Scheme 3b). We reasoned that radical **B** could enter the catalytic cycle of a photoredox-catalyzed radical–radical union protocol.¹¹ Thus, a formal arylation would be achieved, which in turn would increase the synthetic utility of this chemistry.

To this end, we selected (*tert*-butyldimethylsilyl)phenyl-methanol (**1b**) as a model substrate and terephthalonitrile (**5a**) as the radical acceptor. Octanal was used as an additive to sequester the cyanide anion formed in the reaction process.¹¹ Initially, dichloroethane was employed as solvent with 1 equiv of CsOAc as the base. We were pleased to find that a small amount of desired product could be detected (entry 1, Table 2). Again, solvent selection had a significant effect on reaction performance. Polar solvents such as DMF and DMA led to

the best results (entries 2–3). Based on the persistent radical effect, transient radical precursor **1b** self-terminates to cause a buildup of excess persistent radicals, thus accelerating the cross-reaction.¹³ Therefore, increasing the loading of the transient radical precursor **1b** provided an effective way to enhance conversion (entry 4).^{11,14} When we adjusted the amount of the base, we were surprised to find that a substoichiometric amount of base furnished a similar yield (entry 5). Finally, 83% isolated yield of **6a** was achieved with 3 equiv of **1b** (entry 6).

With these conditions in hand, we examined the structural diversity of both coupling partners. As shown in Scheme 6, both electron-donating and -withdrawing groups were well tolerated on the transient radical precursor leading to high yields (**6a–6e**, 66–85% yield). Furan and thiophene aromatic systems also proceeded in moderate to high yield (**6f–6g**). Changing the TBS group to a TES group also led to similar reactions, although a lower yield was observed for **6h** due to the desilylation. Turning to arene coupling partners, substituted terephthalonitriles, and cyanopyridines readily react with the benzylic radicals to yield similar products (**7a–7c**). Also of interest, benzonitriles substituted with sulfones and esters undergo this reaction, although lower yields were observed (**7d–7e**).

To gain mechanistic insights of the photochemical/oxidation Brook rearrangement, we conducted several control experiments. We first carried out a TEMPO radical quenching experiment with the (*tert*-butyldimethylsilyl)phenylmethanol as the substrate; a 42% yield of the TEMPO adduct **9** was isolated, with the yield of **3b** decreasing significantly to 16% (Scheme 7, eq 1). Also, control experiments revealed the requirement for base, light, and photocatalyst (eq 2). Without light or a photocatalyst, almost all starting material remained. Also, if a base is not added to the reaction, only a trace amount of **3b** could be detected with the conversion of **1b** at 55% due to over-oxidation to form benzaldehyde.

Notwithstanding the above results, consistent with the proposed photoredox-catalyzed mechanism in Scheme 3, there is the possibility of proton-coupled electron transfer (PCET)¹⁵ activation of the initial stronger O–H bond¹⁶ of the silyl alcohol, followed by a radical Brook rearrangement to generate the benzylic radical. Kinetic studies however revealed that although the reaction rate decreases as the basicity of the anion decreases, employing a higher oxidizing photocatalyst does not compensate for the lower rate of the weaker base. Moreover, cyclic voltammetry revealed no oxidation potential for **1b** within the tested range (0–2.00 V vs SCE in MeCN). Yet, in the presence of CsOAc, an oxidation potential was observed ($E_{1/2}^0=0.78$ V vs SCE in MeCN), indicating the necessity of the base. Finally, when employing weaker bases such as CsOBz, the oxidation potential remained the same (see Supporting Information). These results indicate the PCET model is less likely.

In summary, we have designed and validated an oxidative [1,2]-Brook rearrangement involving visible-light-induced SET exploiting the oxidation of a hypervalent silicon species. The resulting alkyl radical was found to engage both in conjugate additions to achieve formal alkylation and in radical coupling reactions to achieve arylation. Studies to extend Brook rearrangements involving visible-light-induced SET continue in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

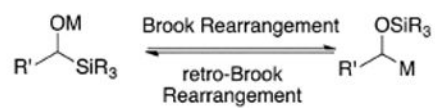
Acknowledgments

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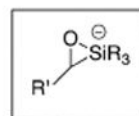
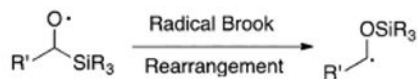
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(a) Brook Rearrangement

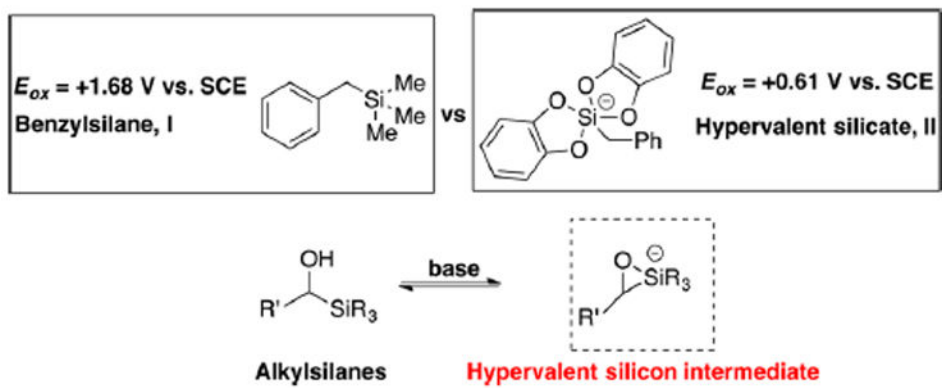


M= Li, Na, K

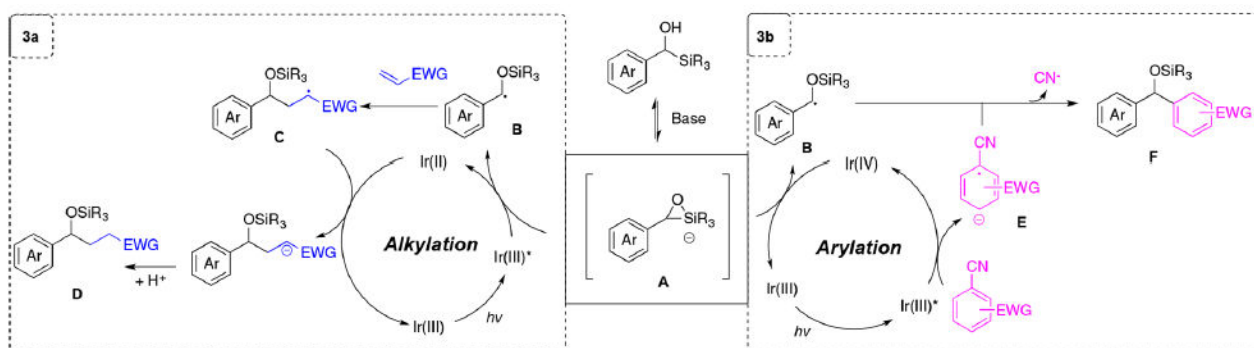
(b) Radical Brook Rearrangement

**Hypervalent silicon species**

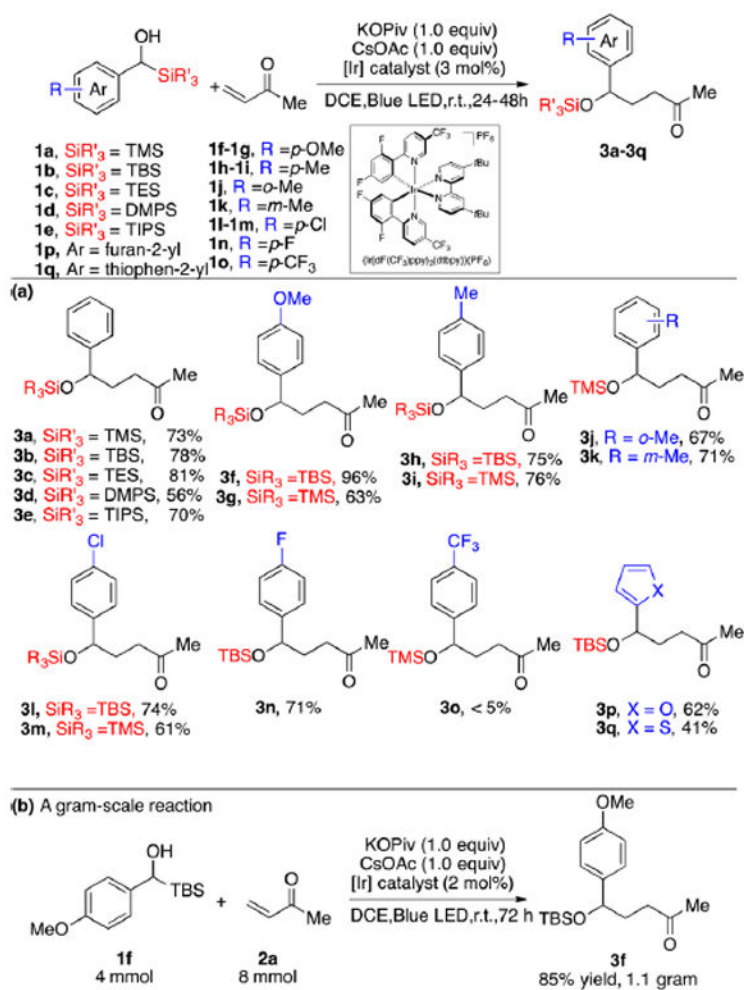
Scheme 1.
Brook and Radical Brook Rearrangement



Scheme 2.
Comparison of Hypervalent Silicon Species

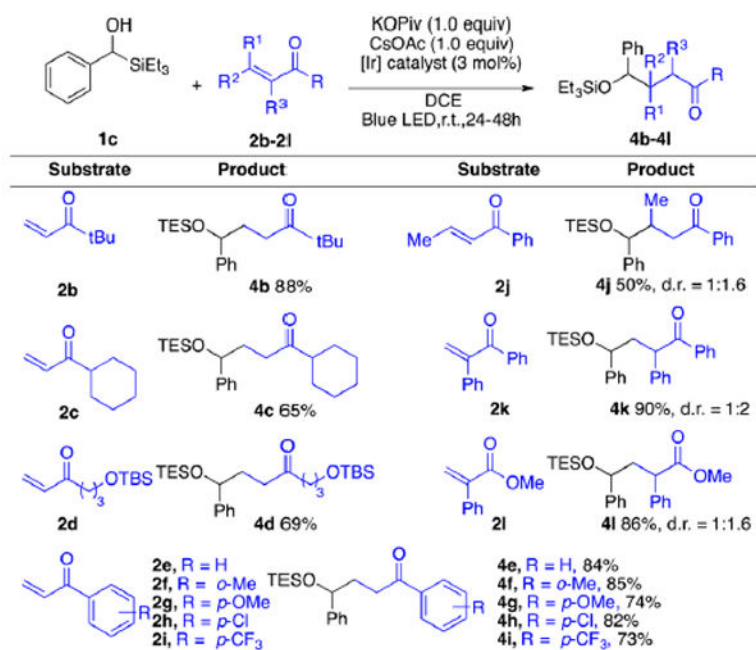


Scheme 3.
Proposed Reaction Route



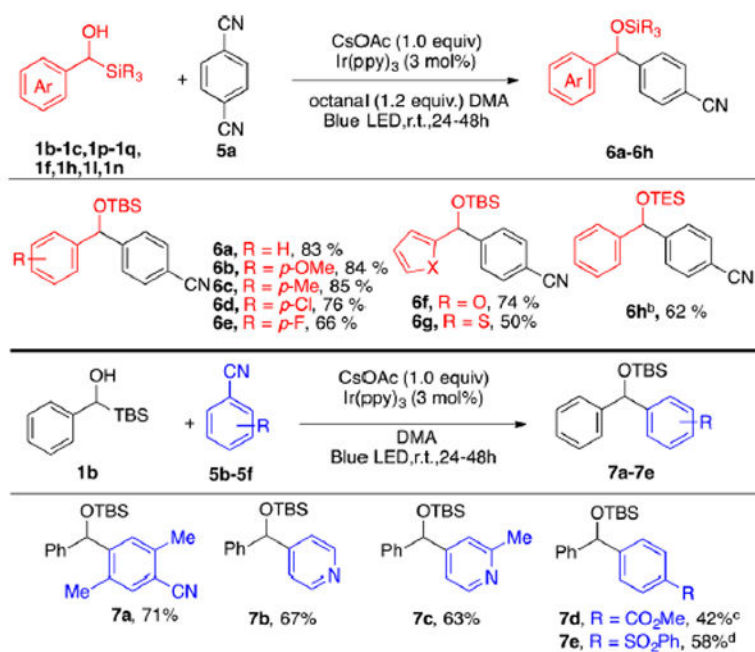
Scheme 4. Arylsilylmethanol Substrate Scope^a

^aReactions were run with **1a–q** (1.0 equiv), methylvinylketone (2.0 equiv), photocatalyst (3 mol %), KOPIv (1.0 equiv), CsOAc (1.0 equiv) in 2 mL of DCE on 0.2 mmol scale.



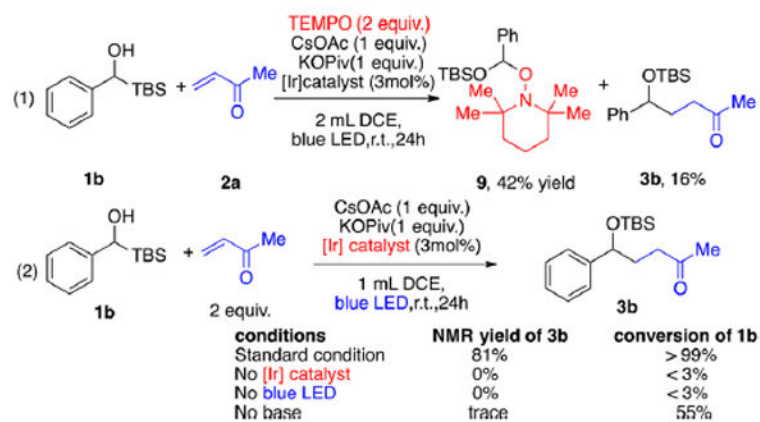
Scheme 5. Radical Acceptor Scope^a

^aReactions were run with **1c** (1.0 equiv), **2b–2l** (2.0 equiv), KOPIv (1.0 equiv), CsOAc (1.0 equiv), photocatalyst (3 mol %) in 2 mL of DCE on 0.2 mmol scale.



Scheme 6. Substrate Scope for the Arylation Reaction ^a

^aReactions were run with arylsilylmethanol (3.0 equiv), aryl cyanide (1.0 equiv), Ir(ppy)₃ (3 mol %), CsOAc (1.0 equiv), octanal (1.2 equiv) in 1 mL of DMA on 0.2 mmol scale. ^b2 equiv of 1c. ^cCsOAc (1.0 equiv) and KO^tPiv (1.0 equiv). ^dCsOAc (0.5 equiv)



Scheme 7.
Control Experiments

Table 1

Optimization of the Alkylation Reaction ^a

entry	photocatalyst	equiv. of 2a	base	solvent	yield ^b
1	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	2	KOPiv	DCE	38%
2	Ru(bpy) ₃ PF ₆	2	KOPiv	DCE	19%
3	Ru(bpz) ₃ PF ₆	2	KOPiv	DCE	trace
4	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	2	KOPiv	Acetone	trace
5	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	2	KOPiv	CH ₃ CN	< 10%
6	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	2	NaOH	DCE	trace
7	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	2	K ₂ CO ₃	DCE	31%
8	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	2	CsOAc	DCE	36%
9	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	2	KOPiv+CsOAc ^c	DCE	83% (78%)
10 ^d	Ir[dF(CF ₃)ppy] ₂ (dtbpy)PF ₆	1	KOPiv+CsOAc ^c	DCE	77% (72%)

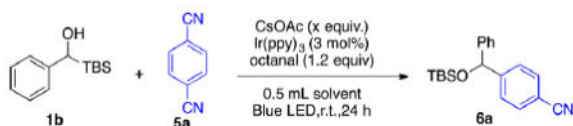
^aReactions were run with **1b** (0.1 mmol, 1 equiv), **2a**, photocatalyst (3 mol %), base (1.0 equiv), in 1 mL of solvent.

^b¹H NMR yields. Isolated yield is given in parentheses.

^c1.0 equiv of KOPiv and 1.0 equiv of CsOAc.

^d0.5 mmol scale of **1b** in 0.2 mL of DCE for 4 days.

Table 2

Optimization of the Arylation Reaction^a

entry	equivalent of 1b	solvent	equiv. of CsOAc	yield ^b
1	1	DCE	1	trace
2	1	DMF	1	58%
3	1	DMA	1	61%
4	2	DMA	1	68%
5	2	DMA	0.5	67%
6	3	DMA	1	87% (83%)

^aReactions were run with **1b**, terephthalonitrile (0.1 mmol, 1 equiv), photocatalyst (3 mol %), base in 0.5 mL of solvent.

^bYields were determined by ¹H NMR analysis, and isolated yield is given in parentheses.