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Silyl Radical Activation of Alkyl Halides in Metallaphotoredox Catalysis: A Unique Pathway for Cross-Electrophile Coupling

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Abstract

A strategy for cross-electrophile coupling has been developed via the merger of photoredox and transition metal catalysis. In this report, we demonstrate the use of commercially available tris(trimethylsilyl)silane with metallaphotoredox catalysis to efficiently couple alkyl bromides with aryl or heteroaryl bromides in excellent yields. We hypothesize that a photocatalytically generated silyl radical species can perform halogen-atom abstraction to activate alkyl halides as nucleophilic cross-coupling partners. This protocol allows the use of mild yet robust conditions to construct $C_{sp^3}-C_{sp^2}$ bonds generically via a unique cross-coupling pathway.

In recent years, the field of synthetic chemistry has witnessed the adoption of nickel as a complementary catalyst to palladium for traditional cross-coupling reactions (i.e., Suzuki–Miyaura, Kumada, Negishi, Stille, and Hiyama couplings).¹ In particular, the capacity of nickel to undergo rapid oxidative insertion yet be resistant to β -hydride elimination pathways has been exploited in the development of a variety of $C_{sp^3}-C_{sp^2}$ bond-forming technologies.² Traditionally, the C_{sp^3} fragment employed in these protocols consists of a boronic acid derivative, Grignard reagent, or organozinc reagent. Recently, however, an increasingly popular approach has emerged that involves cross-electrophile coupling, a strategy wherein the union of two bench-stable electrophiles (e.g., a combination of an alkyl and aryl halide) can be accomplished using transition metal catalysis and an external reductant.³ The application of reductive coupling to C–C bond formation first became synthetically viable with the initial reports of Périchon, Gosmini, Jacobi von Wangelin, and Lipshutz.⁴ Thereafter, seminal papers from Weix, Gong, Molander, and Buchwald demonstrated that use of a metal reductant (i.e., Zn, Mn, or Mg) with either a nickel or palladium catalyst can indeed produce a variety of $C_{sp^3}-C_{sp^2}$ bonds from the corresponding halides.⁵

A better understanding of the innate properties of nickel catalysis has enabled the discovery of new fragment-coupling mechanisms.⁶ One notable example is the merger of photoredox catalysis with nickel catalysis, termed metallaphotoredox catalysis.⁷ Since its conception,

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ASSOCIATED CONTENT

Supporting Information

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Experimental procedures and spectral data (PDF)

this platform has enabled the development of a variety of new cross-coupling processes on the basis that photoredox catalysts can (i) readily modulate the oxidation states of nickel and (ii) generate a wide variety of reactive radical species under mild conditions that can suitably interface with nickel catalytic cycles.⁸ On this basis, we recently questioned whether a cross-electrophile coupling could be possible via the use of a metallaphotoredox mechanism and attendant activation of alkyl and aryl halides toward $C_{sp^3}-C_{sp^2}$ bond formation. As a critical design element, we focused on the use of silyl radical intermediates—which are classically generated from heat-induced radical initiators (i.e., AIBN, peroxides, etc.)—and their established capacity to abstract halogen atoms from alkyl C_{sp^3} -halide bonds at near-diffusion-controlled rates (Figure 1).⁹ This abstraction step is effectively irreversible given the difference in bond dissociation energies (BDEs) of the Si-Br bond (96 kcal/mol for Me_3Si-Br) and the $C_{sp^3}-Br$ bond (69 kcal/mol for bromoethane).¹⁰ Thus, we hypothesized that a large variety of commercially available alkyl bromides could be converted to open-shell coupling partners for Ni catalysis via the use of transient silyl radicals that are generated at room temperature using photoredox activation (eq 2). Herein we disclose the successful execution of these ideals and present a unique mechanism for cross-electrophile coupling to generate $C_{sp^3}-C_{sp^2}$ bonds via the use of silyl halide abstraction in concert with photoredox and nickel catalysis.

Design plan

A detailed mechanism for the proposed photoredox-mediated silyl abstraction Ni coupling is shown in Figure 2. It has been established that the commercially available heteroleptic photoredox catalyst $[Ir[dF(CF_3)ppy]_2(dtbbpy)]-PF_6$ (**1**)¹¹ readily absorbs photons for excitation to the strongly oxidizing complex $*Ir[dF(CF_3)ppy]_2(dtbbpy)^+$ (**3**)

($E_{1/2}^{red}[*Ir^{III}/Ir^{II}]=+1.21$ V vs saturated calomel electrode (SCE) in CH_3CN).¹² On this

basis, we hypothesized that single-electron oxidation of bromide ($E_{1/2}^{red}=+0.80$ V vs SCE in dimethoxyethane (DME)),¹³ a dissociable ligand on nickel,¹⁴ by photoexcited catalyst **3** to generate bromine radical (**5**) and the reduced photocatalyst (**6**) should be thermodynamically feasible.

It is well-precedented that, once generated, electrophilic bromine radicals can rapidly abstract hydrogen atoms from Si-H bonds.⁹ Thus, we postulated that hydrogen-atom abstraction from commercially available tris(trimethylsilyl)silane (TTMSS) to generate stabilized silyl radical intermediate **7** should occur. Subsequent halogen-atom abstraction from alkyl bromide **8** would then provide the corresponding nucleophilic radical species **9** and the silyl bromide byproduct. At the same time, Ni^0 complex **10** can readily undergo oxidative addition into aryl bromide **11** to furnish intermediate **12**. Facile oxidative capture of alkyl radical **9** by the nickel catalyst would then furnish the corresponding alkyl- Ni^{III} species **13**. Reductive elimination from the latter would afford the requisite $C_{sp^3}-C_{sp^2}$ bond and deliver the corresponding Ni^I catalyst **15**. Lastly, single-electron transfer from the available Ir^{II} species **6** ($E_{1/2}^{red}[Ir^{III}/Ir^{II}]=-1.37$ V vs SCE in CH_3CN) to complex **15** can reduce the metal catalyst back to the starting Ni^0 catalyst while simultaneously regenerating the ground-state photocatalyst **1**, effectively closing both catalytic cycles. As a key design

element, silyl radicals selectively abstract from the weaker alkyl halide bond in the presence of the stronger aryl halide bond. This complements the ability of the nickel catalyst to insert into aryl halides over alkyl halides.¹⁵

Initial investigations revealed the feasibility of the bromide oxidation step (**4** to **5**) via Stern–Volmer experiments.¹⁶ With these results in hand, we examined the proposed silyl-mediated photoredox cross-coupling of 4-bromotetrahydropyran and methyl 4-bromobenzoate using 1 mol % photocatalyst **1**, 1 equiv of TTMSS, 0.5 mol % Ni catalyst **2**, and blue light-emitting diodes (Table 1). We were delighted to find that the desired transformation was possible in a series of solvents (40–67% yield; entries 1–3). Ultimately, the use of sodium carbonate or lithium hydroxide in DME provided superior yields (80% isolated yield; entries 4 and 5). Furthermore, control experiments demonstrated the reaction requires photocatalyst, visible light, nickel catalyst, silane, and base (0–3% yield; entries 6–10). Notably, entry 6 indicates that the silyl radical is likely not generated via a silane-aryl halide energy-transfer complex as previously proposed.¹⁷

Results

We are glad to report that the optimal catalyst combination developed in Table 1 can be employed for a variety of alkyl and aryl halide substrates (Table 2). Investigations of the aryl bromide scope demonstrated that electron-neutral and electron-rich arenes containing alkyl and methoxy functionality may be employed in excellent yields (77–83% yield; entries 1–6). Moreover, electron-deficient adducts containing nitrile, fluoride, and trifluoromethyl groups were also readily produced (73–78% yield; entries 7–9). Notably, the efficiency of the reaction was not impeded by ortho substituents on the aryl ring (63–94% yield; entries 10–12). Additionally, unprotected aniline substrates can be employed directly (65% yield; entry 10).

The synthesis of substituted heterocyclic arenes—common scaffolds in medicinally relevant targets—also proved successful. Precursors 2-,3-, and 4-bromopyridine are also suitable substrates (50–81% yield; entries 13–16). Multinitedrogen containing heterocycles such as pyrazine, pyrimidine, and pyridazine were also tolerated, albeit in slightly diminished yields (50–64% yield, entries 17–19). Extended aromatic systems also readily undergo the photoredox-mediated silyl-abstraction coupling, including quinolone, isoquinoline, and pyrazole-substituted pyrazine (75–86% yield; entries 20–22). Lastly, we were delighted to find that five-membered heteroaryl bromides (*N*-methylimidazole and *N*-methylpyrazole), which are notoriously problematic for many cross-coupling technologies, performed well under these conditions (60% and 66% yield, respectively; entries 23 and 24).¹⁸

We next examined the generality of the photoredox silyl-abstraction coupling with respect to the alkyl halide fragment. In addition to the model substrate, seven- and five-membered cyclic systems were also tolerated, along with an acyclic secondary alkyl halide (66–80% yield; entries 25–28). Moreover, smaller strained ring systems such as cyclobutane, cyclopropane, azetidine, and oxetane bromides work in good measure (32–92% yield; entries 29–32). Primary alkyl bromide precursors were highly successful reaction partners (82% and 92% yield; entries 33 and 34), and notably, methoxymethyl chloride was viable to

deliver an α -oxy adduct in 58% yield (entry 35). Sterically-encumbered neopentyl bromide was also shown to be a competent substrate (77% yield; entry 36). Interestingly, methylation of aryl bromides was successfully achieved with easy-to-handle reagents, methyl tosylate and LiBr (62% yield; entry 37), a result that we believe will have ramifications for isotopic labeling protocols.¹⁹ Lastly, tertiary alkyl bromides were found to readily couple with aryl halides in synthetically useful yields (52% and 62% yields; entries 38 and 39, respectively). Given the generality demonstrated in these studies, we expect this light-mediated cross-electrophile protocol to be useful for fragment couplings leading toward a large range of medicinal agents and complex targets.

Preliminary experiments were carried out to gain a deeper understanding of the role of TTMSS. As shown in Table 3, replacement of the silane with Hantzsch ester gave no desired product, and only formation of the biaryl product was observed (entry 1).²⁰ In addition, other commonly used silanes for reduction of Ni intermediates to Ni⁰ resulted in no observable efficiency (entry 2).²¹ Moreover, the use of photocatalysts with diminished oxidizing capacity also failed to give the desired coupled adduct (entries 3–5). Together, these observations suggest that our coupling strategy does not operate via a direct reduction of either the photocatalyst or the nickel catalyst. While further studies are currently being carried out to confirm the presence of a silyl radical, we were encouraged to observe a correlation between the reaction efficiency and the Si–H BDE (entries 6 and 7).⁹ We believe that the dependence on the Si–H BDE is in line with a hydrogen-atom abstraction mechanism. Complete results of our mechanistic studies will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) de Meijere, A.; Diederich, F., editors. *Metal-Catalyzed Cross-Coupling Reactions*. 2. Wiley-VCH; Weinheim, Germany: 2004. (b) Jana R, Pathak TP, Sigman MS. *Chem Rev*. 2011; 111:1417. [PubMed: 21319862]
2. For some reviews of the use of nickel in cross-coupling methods, see: Tasker SZ, Standley EA, Jamison TF. *Nature*. 2014; 509:299. [PubMed: 24828188] Netherton MR, Fu GC. *Adv Synth Catal*. 2004; 346:1525. Rudolph A, Lautens M. *Angew Chem, Int Ed*. 2009; 48:2656.
3. Knappke CEI, Grupe S, Gärtner D, Corpet M, Gosmini C, Jacobi von Wangelin A. *Chem - Eur J*. 2014; 20:6828. [PubMed: 24825799]
4. (a) Czaplak WM, Mayer M, Jacobi von Wangelin A. *Synlett*. 2009; 2009:2931. (b) Krasovskiy A, Duplais C, Lipshutz BH. *J Am Chem Soc*. 2009; 131:15592. [PubMed: 19827762] (c) Amatore M, Gosmini C. *Chem - Eur J*. 2010; 16:5848. [PubMed: 20379979] (d) Durandetti M, Gosmini C, Périchon J. *Tetrahedron*. 2007; 63:1146.
5. (a) Everson DA, Jones BA, Weix DJ. *J Am Chem Soc*. 2012; 134:6146. [PubMed: 22463689] (b) Wang S, Qian Q, Gong H. *Org Lett*. 2012; 14:3352. [PubMed: 22697415] (c) Molander GA, Traister KM, O'Neill BT. *J Org Chem*. 2014; 79:5771. [PubMed: 24892751] (d) Bhonde VR, O'Neill BT, Buchwald SL. *Angew Chem, Int Ed*. 2016; 55:1849.

6. (a) Terrett JA, Cuthbertson JD, Shurtleff VW, MacMillan DWC. *Nature*. 2015; 524:330. [PubMed: 26266976] (b) Tellis JC, Primer DN, Molander GA. *Science*. 2014; 345:433. [PubMed: 24903560] (c) Zuo Z, Ahneman DT, Chu L, Terrett JA, Doyle AG, MacMillan DWC. *Science*. 2014; 345:437. [PubMed: 24903563]
7. Chu L, Lipshultz JM, MacMillan DWC. *Angew Chem, Int Ed*. 2015; 54:7929.
8. (a) Noble A, McCarver SJ, MacMillan DWC. *J Am Chem Soc*. 2015; 137:624. [PubMed: 25521443] (b) Gutierrez O, Tellis JC, Primer DN, Molander GA, Kozlowski MC. *J Am Chem Soc*. 2015; 137:4896. [PubMed: 25836634]
9. (a) Chatgililoglu C. *Acc Chem Res*. 1992; 25:188. (b) Chatgililoglu C, Lalevée J. *Molecules*. 2012; 17:527. [PubMed: 22269866] (c) Chatgililoglu, C. *Organosilanes in Radical Chemistry*. Wiley; Chichester, U.K.: 2004. (d) Ballestri M, Chatgililoglu C, Clark KB, Griller D, Giese B, Kopping B. *J Org Chem*. 1991; 56:678.
10. For Si–Br BDE, see: Walsh R. *Acc Chem Res*. 1981; 14:246. For C–Br BDE, see: Gordon AJ, Ford RA. *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*. Wiley New York 1972
11. dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine; dtbbpy = 4,4'-di-*t*-Bu-2,2'-bipyridine.
12. Lowry MS, Goldsmith JI, Slinker JD, Rohl R, Pascal RA Jr, Malliaras GG, Bernhard S. *Chem Mater*. 2005; 17:5712.
13. See Supporting Information for cyclic voltammogram. For other potential mechanisms to generate the halogen radical, see: Hwang SJ, Powers DC, Maher AG, Anderson BL, Hadt RG, Zheng S-L, Chen Y-S, Nocera DG. *J Am Chem Soc*. 2015; 137:6472. Galicia M, Gonzalez FJ. *J Electrochem Soc*. 2002; 149:D46. See the Supporting Information for the cyclic voltammogram. For other potential mechanisms to generate the halogen radical, see: Hwang SJ, Powers DC, Maher AG, Anderson BL, Hadt RG, Zheng S-L, Chen Y-S, Nocera DG. *J Am Chem Soc*. 2015; 137:6472. [PubMed: 25950146]
14. For the lability of halides on nickel salts, see: Klein A, Kaiser A, Sarkar B, Wanner M, Fiedler J. *Eur J Inorg Chem*. 2007; 2007:965.
15. Biswas S, Weix DJ. *J Am Chem Soc*. 2013; 135:16192. [PubMed: 23952217]
16. For Stern–Volmer data on the bromide, see the Supporting Information.
17. Piva da Silva G, Ali A, da Silva RC, Jiang H, Paixão MW. *Chem Commun*. 2015; 51:15110.
18. Su M, Buchwald SL. *Angew Chem, Int Ed*. 2012; 51:4710.
19. Miller PW, Long NJ, Vilar R, Gee AD. *Angew Chem, Int Ed*. 2008; 47:8998.
20. Elimination of the silicon component, while maintaining the reducing ability of the system, demonstrates the noninnocent role of the silane.
21. Jackson EP, Montgomery J. *J Am Chem Soc*. 2015; 137:958. [PubMed: 25531576]

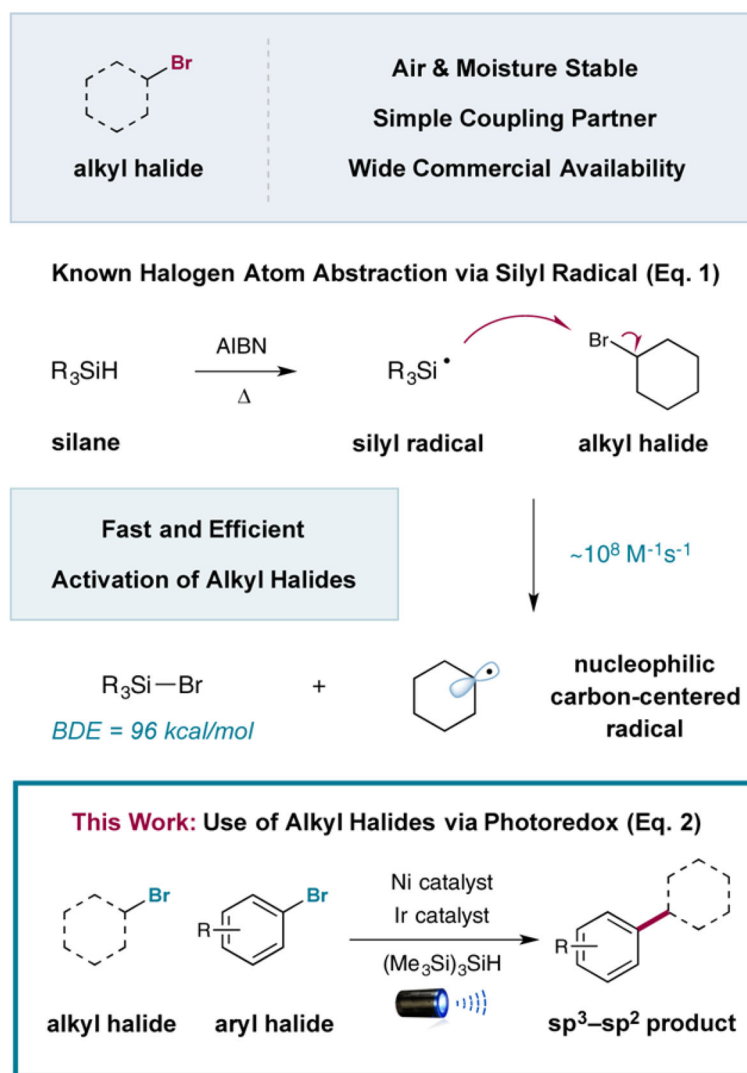


Figure 1. Alkyl bromide–aryl bromide coupling via photoredox.

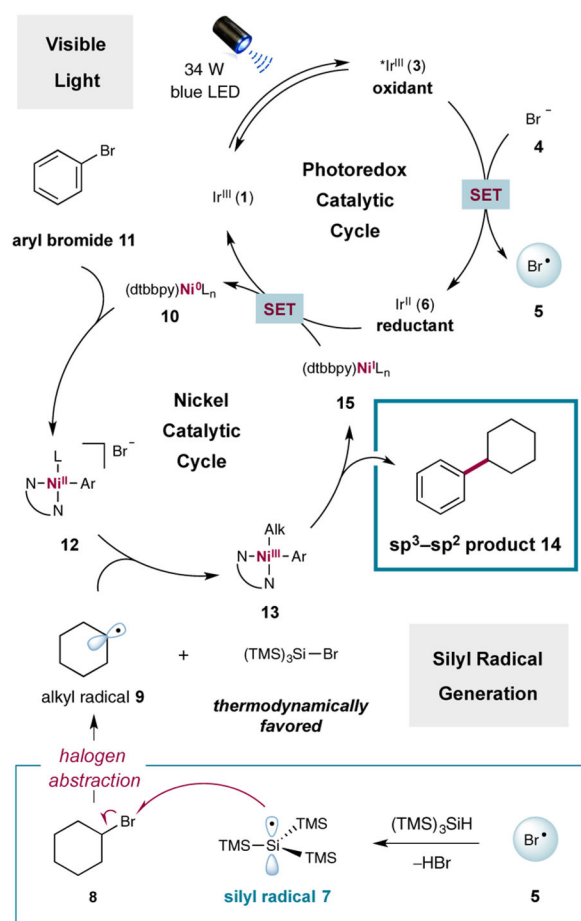
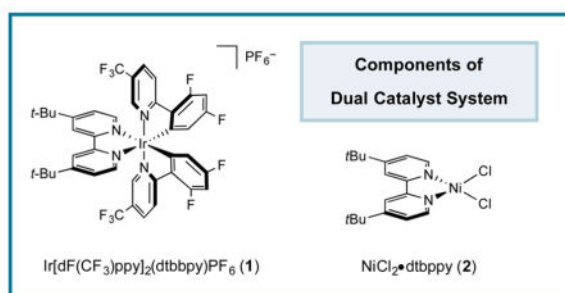


Figure 2.
Mechanistic cycle for silyl-mediated cross-coupling.

Table 1

Optimization of the Silyl-Mediated Coupling^a

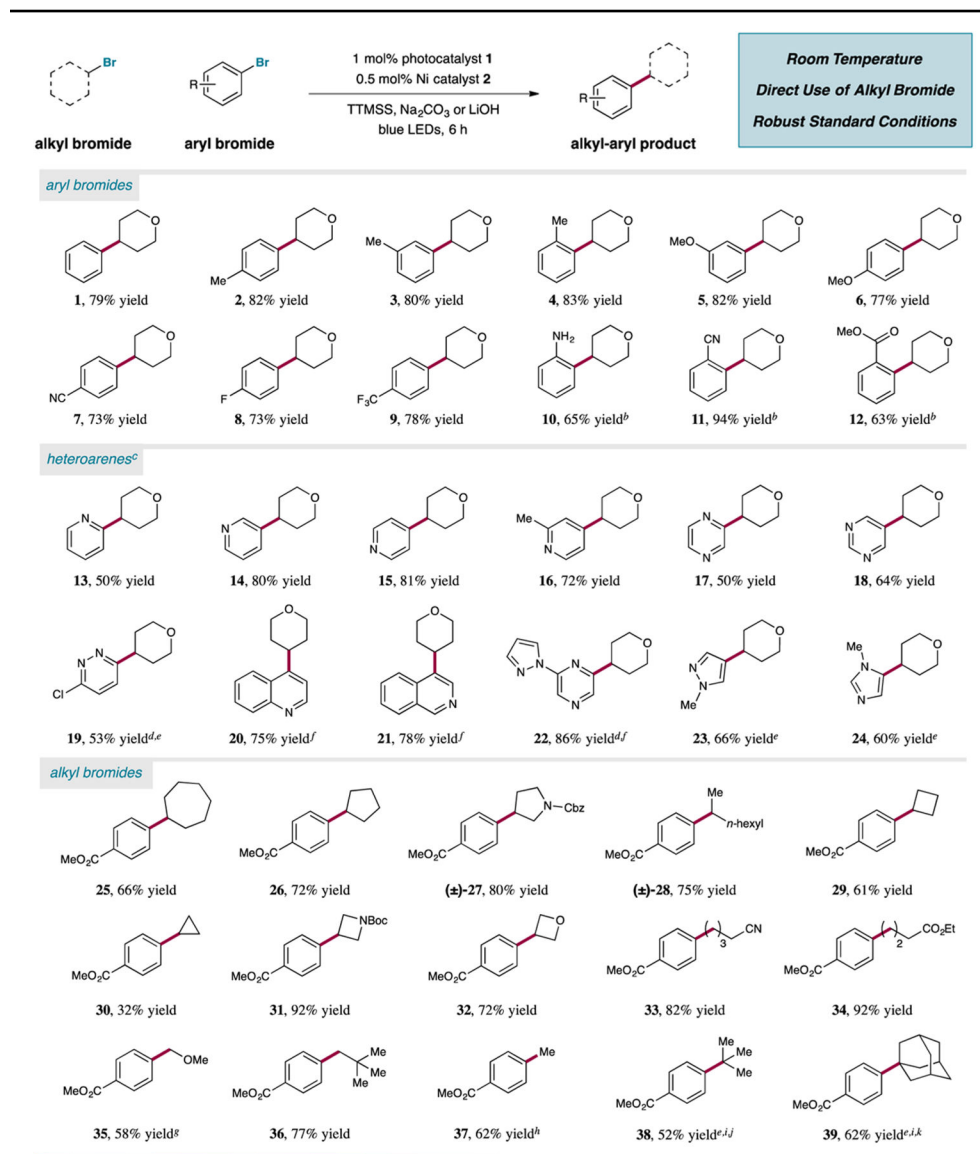
entry	conditions	base	yield ^b
1	DMA	K ₂ CO ₃	40%
2	CH ₃ CN	K ₂ CO ₃	54%
3	as shown	K ₂ CO ₃	67%
4	as shown	Na ₂ CO ₃	84% (80%)
5	as shown	LiOH	85% (80%)
6	no photocatalyst	Na ₂ CO ₃ or LiOH	0%
7	no light	Na ₂ CO ₃ or LiOH	0%
8	no Ni	Na ₂ CO ₃ or LiOH	0%
9	no silane	Na ₂ CO ₃ or LiOH	0%
10	no base	–	3%

^aPreliminary reactions were run with photocatalyst **1** (1 mol %), NiCl₂-dtbbpy (0.5 mol %), aryl halide (1 equiv), alkyl halide (1.5 equiv), TTMSS (1 equiv), and base (2 equiv).

^bYields were obtained by ¹H NMR analyses of the crude reaction mixtures with mesitylene as an internal standard. Yields in parentheses are isolated yields.

Table 2

Photoredox-Enabled Csp³-Csp² Coupling from Alkyl and Aryl Halide Precursors: Comprehensive Scope of Products^a



^a All yields are isolated yields using photocatalyst **1** (1 mol %), NiCl₂-dtbbpy (0.5 mol %), aryl halide (0.5 mmol), alkyl halide (0.75 mmol), TTMS

(0.5 mmol), and Na₂CO₃ (2 equiv).

^b 12 h

^c LiOH as base.

^d Aryl chloride.

e 10 mol % **2**.

f 5 mol % **2**.

g MOMCl.

h MeOTs and LiBr.

i Dioxane as solvent.

j 48 h.

k 24 h.

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Table 3Examination of Alternative Reductants^a

entry	reductant	photocatalyst	yield ^b
1	Hantzsch ethyl ester	1	0% ^c
2	(MeO) ₃ SiH or Et ₃ SiH	1	0%
3	TMSS	Ir(ppy) ₃	0%
4	TMSS	Ru(bpy) ₃ (PF ₆) ₂	0%
5	TMSS	Ru(phen) ₃ Cl ₂	0%
6	Ph ₃ SiH	1	50%
7	Me ₂ (TMS)SiH	1	18%

^aSee Supporting Information for conditions.^bYields were obtained by ¹H NMR analyses with mesitylene as an internal standard.^cGave an 80% yield of the biaryl product.