ABSTRACT: Single-electron transmetalation is recognized as an enabling technology for the mild transfer of alkyl groups to transition metal catalysts in cross-coupling reactions. Hypercoordinate silicates represent a new and improved class of radical precursors because of their low oxidation potentials and the innocuous byproducts generated upon oxidation. Herein, we report the cross-coupling of secondary and primary ammonium alkylsilicates with (hetero)aryl bromides in good to excellent yields. The base-free conditions have exceptional protic group tolerance on both partners, permitting the cross-coupling of unprotected primary and secondary amines.

Metal-catalyzed cross-coupling reactions, utilized to forge \( \text{C}^1\text{C}^1 \) bonds, have become indispensable in small-molecule organic synthesis. Surprisingly, there are currently no reagents available that bear unprotected primary \((1^o)\) alkylamines\(^1\) and vanishingly few in the presence of organometallic coupling reagents bearing unprotected secondary \((2^o)\) alkylamines.\(^2\) To address this issue and other limitations of organometallic cross-couplings, a practical and broadly applicable photoredox Ru/Ni dual-catalysis protocol of ammonium alkylsilicates has been developed.

The naissance of this approach derived from the recently reported paradigm for transmetalation using organotrifluoroborates. In that protocol, the standard, energetically challenging, and thus rate-limiting 2-e\(^-\) transmetalation was replaced by two sequential, single-electron-transfer (SET) events.\(^3,4\) Under that manifold, the organometallic nucleophile was first oxidized by a photoexcited Ir catalyst to generate an alkyl radical, which rapidly combined with a Ni\(^0\) metal center. Subsequent oxidative addition and reductive elimination afforded a Ni\(^1\)--X species that was then reduced by the photocatalyst, closing both interwoven catalytic cycles (Figure 1).\(^5\) Recognizing the virtually instantaneous and barrierless nature of alkyl group transfer under this odd-electron model,\(^6\) we anticipated that selective \( \text{C}^1\text{C}^1 \) bond constructions might be possible in the presence of unprotected 1\(^o\) and 2\(^o\) amines, as well as other protic functional groups, without competitive side reactions.

Although alkyltriﬂuoroborate salts have been demonstrated to be viable coupling partners under both single-electron\(^7\) and conventional cross-coupling protocols,\(^8\) they also possess several drawbacks. For example, in the SET cross-coupling reaction, they require an expensive Ir-based photocatalyst owing to their high oxidation potential; in fact, 1\(^o\) alkyl radicals cannot be generated because the triﬂuoroborate precursors \((E^0 > +1.50 \text{ V vs SCE})\)\(^9\) are not readily oxidized by photoexcited Ir catalysts \((E^0 = +1.32 \text{ V vs SCE})\).\(^10\) Additionally, the initial oxidation of the alkyltriﬂuoroborates releases BF\(_3\), which not only is corrosive but also inhibits the reaction, requiring addition of excess base. Furthermore, the alkyltriﬂuoroborates are minimally soluble in many solvents, obstructing the transmission of light in photoredox reactions. In our quest to find new coupling partners able to address these issues, we noted the seminal studies of Nishigaichi et al. on the allylation of nitrile-containing arenes using photoexcited, hypercoordinate tetramethylammonium allylbis(catecholato)silicate. Those investigations highlighted the use of these complexes, known since the early 1960s,\(^11\) as a source of allyl radicals.\(^12\) Most notably, the bis(catecholato)silicates appeared amenable to photoredox/Ni dual catalysis and were intriguing because the benign byproducts generated from their fragmentation (bis-catecholsilane and tetramethylammonium bromide) would obviate the need for basic additives that might contribute to competitive metal-catalyzed amination.

During the course of our investigations into these hypercoordinate reagents, the groups of Fensterbank and Goddard described the use of related potassium organobis(catecholato)-silicates as alkyl radical precursors.\(^13\) They showed that, as expected, both 1\(^o\) and 2\(^o\) alkyl radicals could be generated from the corresponding pentacoordinate silicon species and employed in a number of transformations. Six such silicates were used in dual photoredox/Ni-catalyzed cross-coupling with a single aryl halide. Unfortunately, that brief study did not fully outline the advantages or potential of such synths. In those protocols, an expensive Ir catalyst was utilized, whereas the oxidation potentials of the silicates \((E^0 = +0.75 \text{ V vs SCE} \text{ for } 1^o \text{ alkylsilicate})\)\(^5\) Table 1\(^14\) lie in

Figure 1. Proposed catalytic cycle for photoredox/Ni dual-catalysis cross-coupling with organometallic nucleophiles.

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the range of the less expensive, photoexcited \([\text{Ru(bpy)}_3]^{2+}\)(PF_6)^− catalyst (\(E^\circ = +0.77 \text{ V vs SCE}\)) \((\text{bpy} = 2,2^\prime\text{-bipyridine})\). Also, using K⁺ as a counterion forced the authors to employ the cost-
prohibitive 18-crown-6 as both stabilizer and solubilizer, 16 making the corresponding silicates unusable for practical large-
scale/industrial purposes.

Prior to the publication of the Fensterbank/Goddard study, we had begun our own investigation with the synthesis of alkylbis(catecholate)silicate derivatives having an alkyl-ammo-
nium cation, using modified literature reaction conditions.\(^{11a}\) Reaction of a substoichiometric amount of catechol with benzyltrimethoxysilane in re-
fluxing THF using triethylamine as base led to the isolation of the latter salts as
compact hygroscopic, colorless, bench-stable powders that can be stored at
room temperature under air without noticeable decomposition even after 5 months (see Supporting Information (SI)).

With a suitable library of substrates in hand, we turned our attention to the development of a practical photoredox/Ni dual-
catalyzed cross-coupling using ary1 bromide electrophiles. Screening the reaction conditions using 4-bromobenzonitrile and triethylammonium cyclohexylbis(catecholate)silicate 2 indicated that the catalyst system previously established for the cross-coupling of 2° alkylarylboronates\(^{10}\) (5.0 mol% of \([\text{NiCl}_2]^{-}\)(dme)), 5.0 mol% of 4,4′-di-tert-butyl-2,2′-bipyridine (dibppy), and 2.0 mol% of \([\text{Ir(dFCCF}_3\text{ppy})_2](\text{ppy})\)PF_6, using a 26-W compact fluorescent lightbulb; dFCCF_3ppy = 2-(2,4-difluorophenyl)-5-(trifluoromethyl)pyridine) could be applied almost directly to alkylbis(catecholate)silicates. Using DMF as solvent at higher concentration (0.1 M instead of 0.05 M) led to significantly improved conversions (see SI). Whereas additives were crucial in
previously reported photoredox/Ni and conventional cross-
couplings with organotrifluoroborates, their use here proved detrimental. Various photocatalysts were assessed to replace the expensive Ir photocatalysts, and, as anticipated from the low oxidation potential of organobis(catecholate)silicate,\(^{14}\) \([\text{Ru(bpy)}_3]^{2+}\)(PF_6)^− could be substituted without any loss in yield (see SI).

Using these reaction conditions with the electron-rich 4-
bro-moanisole and 1, coupled product 15 was obtained in 77% isolated yield (Table 2)\(^{18}\). The study was extended to all other silicates synthesized, affording coupled products in good to excellent yields with both 2° and 1° alkylsilicates. These reactions, which involve highly reactive 1° and 2° alkyl radicals, proved to be applicable in sterically demanding systems (17) and tolerant of reactive functional groups such as esters (27) and lactams/ureas (23). Remarkably, substrates containing coordinating groups such as pyridine (25) and 1° alkylamines (28) coupled in good yields. Furthermore, to the best of our knowledge, substrate 14 represents the first successful example of an alkylmetallic cross-coupling partner bearing a free 1° amine functional group.\(^{19}\) As introducing 1° alkylammonium is a common method to increase solubility and/or biocompatibility of lead candidates in medicinal chemistry, this tolerance is highly relevant for diversification efforts in drug discovery.\(^{20}\) Also notably, very few examples of the cross-coupling of free 2° alkylamine-containing nucleophiles have been reported.\(^{21,23}\) Of further importance, using the less highly oxidizing Ru photocatalyst allows the incorporation of oxidizable amines such as that found in aniline derivative 24 (\(E^\circ = +0.76 \text{ V vs SCE}\)).\(^{22}\) Unfortunately, silicates 4, 6, and 8 failed to give any cross-
coupling product.\(^{23}\)

To assess the limitations of the 1° amine coupling reaction, silicate 14 was reacted with various aryl and heteroaryl electrophiles using unmodified reaction conditions (Table 3). Electron-rich (33, 34), electron-poor (29–32), and ortho-
substituted (30) cross-coupled products were accessed in good to excellent yield. In particular, the presence of further protic functional groups such as those found in acetanilide 33, benzyl alcohol 34, and unprotected pyrazole 35 and indole 37 did not affect the reaction, which is surprising because these substrates have proven to be recalcitrant coupling partners under previous cross-coupling protocols.\(^{11}\) N-Containing heterocycles (35–38), which represent important substructures in pharmaceutical libraries,\(^{24}\) were well tolerated and afforded the corresponding

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**Table 1.** Preparation of Primary and Secondary Ammonium Alkylbis(catecholate) Silicates

| Reaction | Product | Yield |
|----------|---------|-------|
| THF, NEt₃ | 1-2 | 92% |
| THF, (i-Pr)₂NH | 3-4 | 81% |
| THF, (i-Pr)₂NH | 5-6 | 89% |

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**Table 2.** Photoredox Cross-Coupling of Ammonium Alkylbis(catecholate)silicates with Bromoanisole

| Reaction | Product | Yield |
|----------|---------|-------|
| THF, NEt₃ | 15 | 77% |
| THF, (i-Pr)₂NH | 16 | 94% |
| THF, (i-Pr)₂NH | 17 | 91% |
| THF, (i-Pr)₂NH | 18 | 83% |
| THF, (i-Pr)₂NH | 19 | 80% |
| THF, (i-Pr)₂NH | 20 | 0% |

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\(\text{Ar} = 4\text{-biphenyl} \text{ for 18, 20, and 26.}\)
Table 3. Aryl and Heteroaryl Bromide Scope with 1° Amine-Containing Silicate 14

![Diagram of silicate structure](image1)

| R      | NMR (ppm) | Mass (g) | Yield (%) |
|--------|-----------|----------|-----------|
|        |           |          |           |

*Reaction with 32 run on gram scale using white LEDs.

coupling products in reasonable (38) to excellent (36) yields. Although poorer reactivity was observed in accessing 38, the remaining mass balance could be accounted for as unreacted aryl halide after 16 h. To confirm the scalability of this 1° alkylamine cross-coupling, a gram-scale reaction was performed, affording coupled product 32 in 97% isolated yield after only 4 h. This increase in reaction rate compared to those of organotrifluoroborates was achieved through using high-intensity, broadband white LEDs, accompanied by a slight increase in reaction temperature (36 °C, see SI).

The scope of the reaction was next extended to sterically encumbered 2° (3) as well as 1° alkylsilicates bearing acetoxyl (13) or 2° alkylamine (10) functional groups (Table 4). The use of 2° alkylic silicons in cross-coupling is perhaps unremarkable in light of our previous success with 2° alkylboron reagents, but it still represents the first time that unactivated 2° Hiyama-type reagents have been widely employed in cross-coupling. Furthermore, the far lower oxidation potentials and/or higher solubility of these reagents in organic media leads in many cases to reactions that are complete in dramatically shorter time frames (as short as 2 h for pyridyl derivative 41) than their trifluoroborate or carboxylic acid counterparts, and even those previously developed by Fensterbank/Goddard (24 h).

A wide variety of aryl and heteroaryl bromides were assessed to highlight the broad compatibility of these extremely mild cross-coupling conditions. Coupled products bearing electron-withdrawing (49, 51, 52) or electron-donating groups (44, 46) were easily accessed, as well as more sterically encumbered systems (44) or those bearing a potential competitive site for oxidative addition (51). Nitrogen heterocycles (39, 41, 43, 48, 53) could be acquired in the process in good to excellent yield (even for the challenging α-aminopyridine 43). O- (47) and S-containing (42) heteroaryls could be procured as well. Furthermore, target structures bearing protic groups (43, 45, 46, 48, 50) were readily synthesized. Overall, the success of ammonium organobis(catechol)silicates makes them partners of choice for metal-catalyzed C−C bond-forming reactions, as both their functional group tolerance and reactivity outperform previously reported photoredox/Ni dual-catalysis methods and conventional Hiyama/Suzuki cross-couplings.

As a final showcase of these hypercoordinate silicates, two successive, photoredox/Ni dual-cross-couplings were carried out with dibrominated arenes 54 and 56 (Scheme 1). In both cases, an initial cross-coupling with a 2° alkyltrifluoroborate was first performed under conditions previously optimized in our laboratory using the Ir photoredox catalyst. After filtration of the resulting salts in air, concentration, solvent switch, and addition of a 1° silicate 13 for aryl 56), a second cross-coupling was then completed to provide functionalized arenes 55 and 57. Most notably, these transformations require no intermediate isolation and can be performed without the further addition of either the photoredox or cross-coupling catalyst, underlining the robustness of both dual-catalysis systems. This chemistry has the potential to be applied to successive one-pot cross-coupling operations in either batch or photo-flow systems. Furthermore, given the report by Burke et al. on successive MIDA boronate cross-couplings and our own on mechanistically orthogonal boron couplings, innumerable opportunities exist for rapid complexity-building operations without isolation of intermediates.

In summary, we have developed a synthetic procedure for ammonium organobis(catechol)silicates that is operationally simple and does not require the use of expensive crown ether additives. These silicates represent ideal radical precursors because of their low oxidation potentials, excellent physical properties, and the innocuous byproducts formed upon oxidation. Further, these silicates have been demonstrated for the first time as 1° and 2° alkyl radical precursors in the dual-catalytic Ru/Ni cross-coupling. The conditions developed herein are general, functional group tolerant, and, when dealing with protic functional groups, unmatched by competing alkyltrifluoroborate and carboxylate protocols. Most remarkably, using these reagents allows the selective coupling of an alkylmetallic reagent in the presence of primary amines for the first time, representing an expansion into new reactivity space. Whereas traditional 2−e− cross-couplings of alkylmetallics feature strongly basic reagents and/or additives that...
favor amine deprotonation and coordination, using a base-free, odd-electron transmetalation manifold inhibits competitive metal-catalyzed amination. Considering the absence of a single-step method for the introduction of primary alkylamines onto (hetero)aryl halide cores, aminalkylsilicates have the potential to improve the late-stage introduction of primary amines into bioactive compounds. Taken together, these findings introduce alkylsilicates as key players in the photoredox/Ni dual-catalytic cross-coupling regime.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10963.

Experimental details and spectral data (PDF)

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**Notes**

The authors declare no competing financial interest.

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