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 Primary Alkyl Bis-Catecholato Silicates in Dual Photoredox/Nickel Catalysis: Aryl- and Heteroaryl-Alkyl Cross Coupling Reactions

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Primary alkyl bis-catecholato silicates have been successfully engaged with aryl and heteroaryl bromide substrates in photoredox/nickel dual catalysis to provide aryl- and heteroaryl-alkyl cross coupling products. The scope of the transformation is wide and the process appears to be tolerant of various functional groups present. Of note, most examples rely on the challenging use of highly reactive primary radicals which constitutes a significant advance in these cross coupling reactions.

Dedicated to John Murphy

Photoredox/nickel dual catalysis^{1,2} has recently emerged as a novel opportunity to form C-C bonds and rapidly couple functionalized fragments for the elaboration of more complex molecules.^{3} A key advantage of this strategy is to merge the mildness of visible light photoredox catalysis for the generation of hot radical entities^{4} with the robustness of nickel catalyzed cross coupling reactions.^{5} While the electrophilic partner involved in the oxidative addition to nickel has so far consisted of aryl halides and related substrates,^{6} more functional variation has been brought on the radical source. To the best of our knowledge, all works have involved \( \alpha \)-amino,^{2b,6,7} \( \alpha \)-O,^{7b,6} \( \alpha \)-phenyl,^{7b,8} \( \alpha \)-oxo,^{6} and secondary\(^6\) carboxylic acids, mixed anhydrides,^{10} dimethylaniline,^{2b} benzyl,^{2a,11} secondary^{2a,9,12} and activated (\( \alpha \)-\( \delta \)) primary trifluoroborates.^{13} More recently, potassium and ammonium bis-catecholato silicates have been reported by us^{14} as a valuable source of C-centered radicals upon visible light photooxidation using Ir(\( \text{dF(CF}_3\text{)}\text{ppy})_2(\text{bpy}))\( \text{PF}_3\) as catalyst. The silicate substrates offer neat advantages over the related trifluoroborates in terms of solubility, of byproducts (no gas release, no fluoride, no boron) and of the scope of the possibly generated radicals (from stabilized alkyl ones to highly reactive primary ones). As a perspective, it was also found that they could be engaged in photoredox/nickel dual catalysis for \( \text{C}_{\text{sp2}}\text{-C}_{\text{sp3}}\) cross-coupling reactions, notably involving unsta\( \text{blized}\) primary radicals.^{14a,15}

The limited sampling of these preliminary findings drove us to gain more insight into this transformation and define its scope by varying both partners (silicates and arylobromides, see Scheme 1). Subsequent to the first report of these cross coupling reactions by us,^{14b} the group of Molander described similar transformations of related ammonium bis-catecholato secondary and primary alkyl silicates with aryl- and heteroaryl-bromides.^{16} Herein, we focus on primary radical intermediates and bring a complementary picture to these highly powerful reactions.

![Scheme 1. Photoredox/nickel dual catalysis involving primary radicals from silicates](image)

We first prepared a series of potassium silicates 1. As found before,^{14} the latter are rendered rock stable by admixing the 18-C-6 crown ether additive. Nevertheless, we could show that...
this additive is not necessary to promote homolytic reactivity (see below). A preliminary screening of conditions with a given arylbromide, namely 4-bromoacetophenone 2a led us to the following protocol. To a DMF solution of silicate 1 (1.5 equiv, 0.1 M) in the presence of of Ir[(dF(CF3)2ppy)2(bpy)](PF6)2 (2 mol%), Ni(COD)2 (3 mol%) and dtbbpy (3 mol%) as ligand was added 4-bromoacetophenone 2a (1 equiv). After stirring for 24 h at rt, excellent yields of coupling products 3aa-3ca were obtained from benzyl, allyl and α-amino silicates (1a-c). Gratifyingly, less stabilized radicals could also be involved furnishing the corresponding coupling products 3 in 40−85% yields bearing various functional groups such as an ester (3ia, 3ja), a nitrile (3fa, 3ga) an oxirane (3ka, 3la) or a chloride (3ma). Interestingly, a comparison was made with the corresponding benzylfluororuborate precursor and showed in our conditions a more productive reaction (adduct 3aa) from the silicate 1a (88% vs. 58% yield). Also, potassium silicate 1i' with no 18-C-6 also provided a good yield (86%) of coupling product 3ia.

Using the same conditions, a series of arylbromides 2a-2q with varied substitution pattern could be used in conjunction with acetate silicate 1i or 1i' (Table 2). First, reaction scope proved to be quite wide. Second, a closer examination of these results revealed interesting features. For instance, the difference of reactivity between a C9(2)-Br and a C9(2)-I bond was investigated with 1-bromo-4-iodobenzene 2g. Not surprisingly, a preferred oxidative addition took place at the carbon-iodide bond giving a 10:1 ratio of products 3ig (X = Br) and 3ig' (X = I). This appeared quite opportune for electron enriched aryl substrates. While meta-bromo anisoles (2p and 2q) could be effectively used (adducts 3ip and 3iq), only starting material was recovered with ortho-bromoanisole and para-bromoanisole. The reluctant behavior of para-bromoanisole could be partly fixed by using the corresponding iodo derivative since cross coupling product 3io was obtained albeit in modest yield (46%). These findings contrast with Molander’s report in which electron rich substrates proved to be competent. Their catalytic mixture (5 mol% NiCl2(dme), 5 mol% dtbbpy, 2 mol% Ru(bpy)3(PF6)2) differs from ours (3 mol% Ni(COD)2, 3 mol% dtbbpy and 2 mol% Ir[(dF(CF3)2ppy)2(bpy)](PF6)2) implying interesting metal and ligand effects that we are now investigating.

<table>
<thead>
<tr>
<th>Name</th>
<th>Substituent</th>
<th>Yield %</th>
</tr>
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<tbody>
<tr>
<td>3ia</td>
<td>AcO</td>
<td>85%</td>
</tr>
<tr>
<td>3ib</td>
<td>AcO</td>
<td>80%</td>
</tr>
<tr>
<td>3ic</td>
<td>AcO</td>
<td>72%</td>
</tr>
<tr>
<td>3id</td>
<td>TMS</td>
<td>72%</td>
</tr>
<tr>
<td>3ie</td>
<td>AcO</td>
<td>79%</td>
</tr>
<tr>
<td>3if</td>
<td>AcO</td>
<td>80%</td>
</tr>
<tr>
<td>3ig</td>
<td>Br</td>
<td>66%</td>
</tr>
<tr>
<td>3ig'</td>
<td>AcO</td>
<td>94%</td>
</tr>
<tr>
<td>3ih</td>
<td>AcO</td>
<td>73%</td>
</tr>
<tr>
<td>3ii</td>
<td>AcO</td>
<td>76%</td>
</tr>
<tr>
<td>3ij</td>
<td>AcO</td>
<td>94%</td>
</tr>
<tr>
<td>3ik</td>
<td>AcO</td>
<td>69%</td>
</tr>
<tr>
<td>3il</td>
<td>AcO</td>
<td>53%</td>
</tr>
<tr>
<td>3im</td>
<td>AcO</td>
<td>69%</td>
</tr>
<tr>
<td>3in</td>
<td>AcO</td>
<td>54%</td>
</tr>
<tr>
<td>3io</td>
<td>OMe</td>
<td>0%</td>
</tr>
<tr>
<td>3ip</td>
<td>OMe</td>
<td>58%</td>
</tr>
<tr>
<td>3iq</td>
<td>OMe</td>
<td>69%</td>
</tr>
</tbody>
</table>

* Starting from the corresponding potassium silicate with no 18-C-6 1i' and 2a.

Gratifyingly, less stabilized radicals could also be involved furnishing the corresponding coupling products 3 in 40−85% yields bearing various functional groups such as an ester (3ia, 3ja), a nitrile (3fa, 3ga) an oxirane (3ka, 3la) or a chloride (3ma). Interestingly, a comparison was made with the corresponding benzylfluororuborate precursor and showed in our conditions a more productive reaction (adduct 3aa) from the silicate 1a (88% vs. 58% yield). Also, potassium silicate 1i' with no 18-C-6 also provided a good yield (86%) of coupling product 3ia.
Remarkably, a pinacol boronate function could also be tolerated in these conditions as illustrated by the formation of 3i that could be utilized for further coupling reactions. Nevertheless, direct isolation of this product after column chromatography was detrimental to the yield. Instead, when the crude reaction mixture was oxidized (NaOH, H₂O₂), a higher yield (69% vs 53% for 3ii) of phenol product 3im was recorded. Similar protocol was applied to give phenol product 3in.

Heterocyclic bromides completed the reach of this transformation and established its high synthetic potential. 2-Fluoro-4-bromopyridine 2r was used as partner of the dual catalysis in the presence of silicates 1c-m and delivered a small library of new alkylpyridines 3cr-3mr in satisfactory yields (Table 3). Other pyridyl systems 2s-u proved to be competent for this cross-coupling transformation. The corresponding products 3is-3lu were obtained in a 40-75% yield range. Finally, various heterocyclic systems such as quinoline 2v, pyrimidine 2w, indole 2x, benzofuran 2y and thiophene 2z were engaged and yielded the corresponding cross coupling adducts 3 from mitigated to fair yields.

The proposed catalytic cycle is outlined in Scheme 2. It is well established that excitation of photoredox catalyst \( \text{I}r(\text{dF(CF}_3\text{ppy})_2(\text{bpy})) \) produces a long-lived photoexcited state \( \text{I}r(\text{dF(CF}_3\text{ppy})_2(\text{bpy}))^* \). The latter acts as a strong oxidant \( [\text{Ir}^*\text{I}r]/\text{I}r] = +1.32 \, \text{V vs SCE in MeCN}^9 \) and undergoes a single electron transfer (SET) with bis-catecholato silicates 1 (\( E_{\text{ox}} \) between +0.34 and +0.87 V vs SCE in DMF)\(^{10} \) generating a primary alkyl radical which interacts with a Ni species. However, the mechanism of this dual catalysis is still in debate.\(^{9,11} \) All proposals converge toward a Ni(III) intermediate which upon reductive elimination delivers the cross coupling product and a Ni(I) intermediate complex, the latter being further reduced \( E [\text{Ni}^{III}/\text{Ni}^{II}] = -1.2 \, \text{V vs SCE in DMF}^9 \) by SET from the iridium(III) \( [\text{I}r^{III}\text{I}r]/\text{I}r] = -1.37 \, \text{V vs SCE in MeCN} \) to generate a Ni(0) complex. From this zero-valent nickel entity, two possibilities have been advanced. Initial oxidative addition of the ArX gives a Ni(II) species that would trap the nucleophilic radical intermediate. Alternatively, an alkyl Ni(0) species would result from the trapping of the radical intermediate by Ni(0) followed by oxidative addition of the ArX to the Ni(III) intermediate (Scheme 2). Some of our results in Table 2 with the formation of 3ig and 3io highlight the importance of the oxidative addition step. However, this will necessitate more investigation to clarify that matter.

In conclusion, this study illustrates that bis-catecholato silicates are very reliable partners for photoredox/nickel dual catalysis. We have focused our efforts on the use of highly reactive primary radicals which so far has remained an uncharted territory. Our generally successful results in terms of yields and structure scope, since notably heteroatomic functions and heterocyclic platforms do not appear as limiting factors in these transformations, augur well for the application of this methodology in different settings.

### Acknowledgements

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postdoc grant to VC). COST Action CM1201 is gratefully acknowledged.

Notes and references


15. A primary carboxylic (5-phenylvaleric acid) has also been used as unstabilized radical precursor, providing the cross-coupling product but in 11% yield, see ref. 6.


18. Cross coupling of 11 with 2o using 3 mol% of NiCl2.dme and 3 mol% of dtbbpy, and 2 mol% of Ir[(dF(CF3)ppy)](PF6) provided 81% of 3io. For a recent discussion about the importance of the oxidation state of the nickel precatalyst, see: M. S. Oderinde, M. Frenette, D. W. Robbins, B. Aquila and J. W. Johannes J. Am. Chem. Soc., 2016, DOI: 10.1021/jacs.5b11244.

19. The poor yields observed on 3it, 3iw and 3ix remain unexplained, since the crude products looked clean for each reaction.

