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Photoredox/Nickel Dual Catalysis for the Csp^3 - Csp^3 Cross-Coupling of Alkylsilicates with Alkyl Halides

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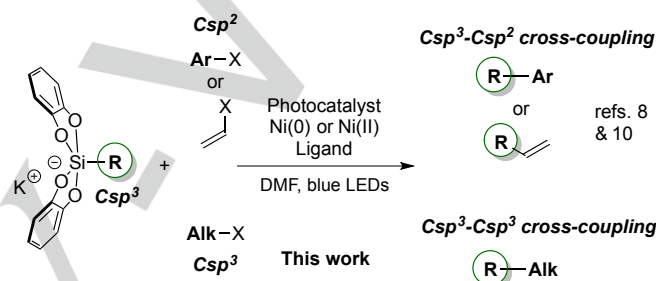
To Mich  le Bertrand

Abstract: Alkylsilicates have been engaged under photoredox/nickel dual catalysis conditions with alkyl halides for the first time. Csp^3 - Csp^3 cross coupling products have been obtained in moderate yields, accompanied by homocoupling products of the alkyl halide derivatives. These promising findings are strongly suggestive of the high synthetic potential of the dual catalytic approach for the forging of alkyl carbon-carbon bonds.

Introduction

The formation of carbon-carbon bonds has been at the heart of the preoccupations of the organic synthetic chemists since the origin of organic chemistry. In fact, most name reactions belong to the category of carbon-carbon bond forming reactions.^[1] Besides cycloadditions, a good part of these transformations have involved organometallic reagents or radical species, which have progressively matured into catalytic processes like for instance transition metal catalyzed cross coupling processes.^[2] The latter generally involves a nucleophilic organometallic component (R-M) and an electrophilic partner (R-X). More recently, the alternative coupling between two electrophiles (R-X) and (R'-X) in the presence of reducing agents has been worked out.^[3] However, both approaches suffer from severe weaknesses. In the first case, a tamed nucleophile, compatible with functionality, is needed; in the second one, electrophiles with different reactivity profiles are combined and an over stoichiometric amount of reducing agent is required. The very recent third strategy,^[4] involving a radical precursors and a R-X electrophilic partner also referred as single electron transmetalation,^[5] consists in merging the photocatalytic formation of radical entities with a nickel catalyzed cross-coupling event. This approach alleviates all the previous issues and therefore constitutes a versatile alternative.^[6] Among the different parameters at work in this type of reactions, the choice of the precursors of C-centered radical is certainly a key factor. Initially reported with carboxylates,^[4a] dimethylaniline^[4a] and trifluoroborates,^{[4b],[7]} we^{[8],[9]} and the group of Molander^[10] introduced silicates as very versatile sources of radicals. They notably display lower oxidation potentials than trifluoroborates. All examples of dual catalysis involving silicates have so far

concerned Csp^3 - Csp^2 (aryl or vinyl) cross couplings. While we were developing Csp^3 - Csp^3 coupling reactions,^[11] a recent report by MacMillan and coworkers of such transformations using carboxylates,^[12] prompted us to disclose now our own findings.

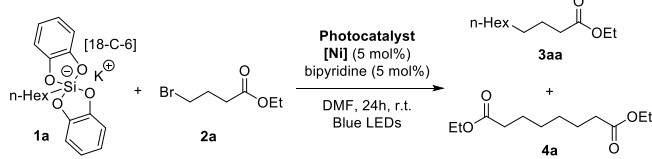


Scheme 1. Photoredox/nickel dual catalysis with alkylsilicates for cross-coupling reactions.

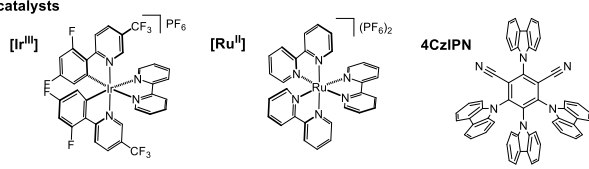
Results and Discussion

We initially focused on the coupling of the n-hexylsilicate **1a** with bromoester **2a** which involve two fragments of distinct polarities and facilitates the isolation of the various (cross coupling and homocoupling) adducts. A rapid screening of the previously used photocatalysts^{[8],[10]} (Table 1, entries 1-3) gave a mixture of expected product **3aa** accompanied however by homocoupling product **4a** which was in the three cases the major product. Since the iridium photocatalyst proved superior to the two other ones, we kept it in the following coupling reactions. We then varied the reaction conditions in order to invert the cross coupling – homocoupling ratio. Decreasing the loading of iridium(III) to 2 mol% proved quite detrimental (entry 4) however slightly increasing the number of equivalents of silicates from 1.2 to 1.5 equiv allowed the major generation of the cross coupling derivative, in yields above 40% (entry 5). Restoring the photocatalyst loading to 5 mol% turned out to give the best conditions (entry 6) while changing to 2 equiv of silicate (entry 7) or using a nickel(II) precatalyst proved to be less effective. It can be mentioned that no reaction was observed in acetonitrile or 1,3-dimethyl-2-imidazolidinone (DMI)^[13] even at higher concentration (1 M). A 0.01 M concentration results in lower yields in **3aa** (25%) and **4a** (26%).

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Table 1. Optimisation of reaction conditions.^[a]


Photocatalysts

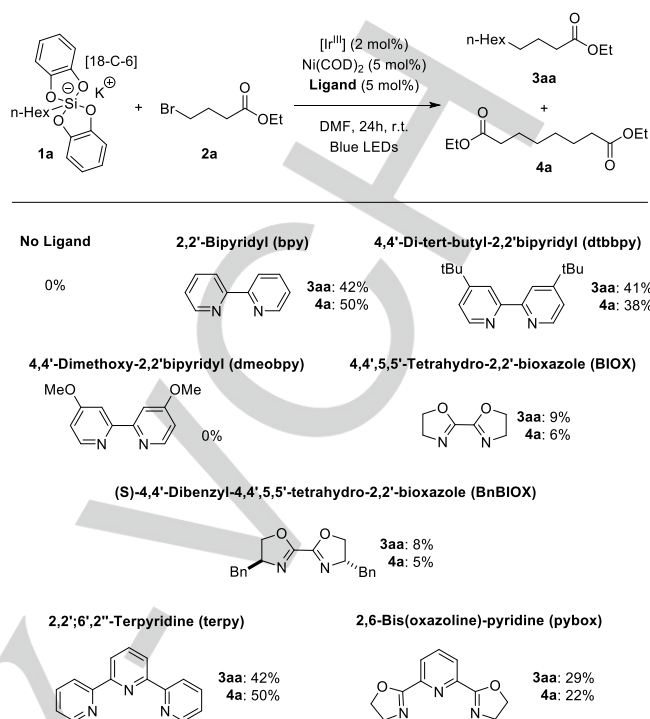
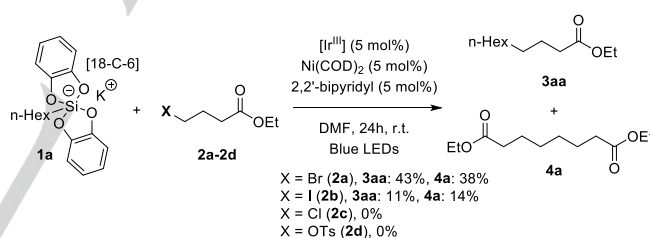


Entry	Equivalents of Silicate	Photocatalyst (mol%)	Ni complex	Yield ^[b] [%] (3aa%/4a%)
1	1.2	[Ir ^{III}] (5)	Ni(COD) ₂	3aa: 34% 4a: 38%
2	1.2	[Ru ^{II}] (5)	Ni(COD) ₂	3aa: 22% 4a: 36%
3	1.2	4CzIPN (5)	Ni(COD) ₂	3aa: 22% 4a: 25%
4	1.2	[Ir ^{III}] (2)	Ni(COD) ₂	3aa: 29% 4a: 52%
5	1.5	[Ir ^{III}] (2)	Ni(COD) ₂	3aa: 42% 4a: 50%
6	1.5	[Ir ^{III}] (5)	Ni(COD) ₂	3aa: 43% 4a: 38%
7	2	[Ir ^{III}] (5)	Ni(COD) ₂	3aa: 44% 4a: 42%
8	1.5	[Ir ^{III}] (5)	NiCl ₂ ·dme	3aa: 26% 4a: 30%

[a] Reaction conditions: **1a** (0.36, 0.45 or 0.6 mmol), **2a** (0.3 mmol), Ni complex (5 mol%), bipyridine (5 mol%), photocatalyst (2 or 5 mol%), DMF (0.1 M), 24h at room temperature, under blue LEDs irradiation. [b] Isolated yields.

Some reports have evidenced an important effect of the ancillary ligand of nickel^{[7a,e],[12]} on the efficiency of the process. Therefore, we tested a series of them (Scheme 2). Di-tert-butyl bipyridine or terpyridine ligands gave the same yield (42%) of product **3aa**. However, no reaction was observed with dimethoxy bipyridine. BIOX and pybox ligands proved to be less productive (Scheme 2). For the rest of the study, we therefore kept the simplest bipyridine ligand.

Scheme 3 also shows that the best electrophile is the bromide **2a**. No coupling was observed with the corresponding chloride or tosylate while the iodo ester gave a poor yield of **3aa** (11%) with a major formation of **4a** (14%).

**Scheme 2.** Ancillary ligand screening**Scheme 3.** Electrophile screening

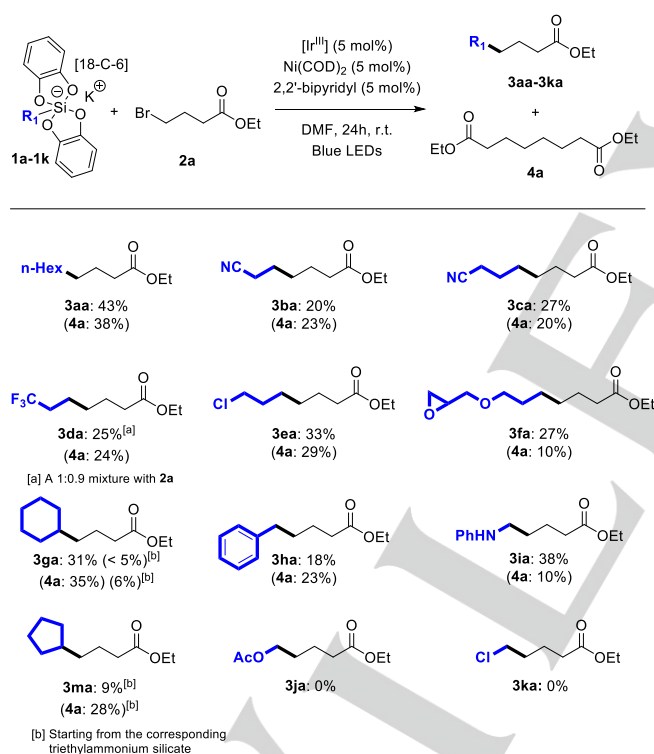
Variation on the silicate partner (Scheme 4) provided consistent results and delivered coupling adducts **3ba-3ma** bearing different types of useful functionalities from low to moderate yields (from 9 to 38%). An α -amino substituted radical could be successfully engaged (product **3ia**, 38% yield) while the corresponding α -oxygenated and α -chloro radicals did not react properly. Of note, cross-coupling reactions are less efficient with ammonium cyclohexyl- and cyclopentylsilicates (**1g'** and **1m**) for the formation of adducts **3ga** and **3ma**.

Finally, we also engaged different bromides (Scheme 5). Primary and secondary bromides reacted more or less efficiently (27-37% and 16-35% respectively). No reaction was observed with cyclopropyl bromide. Hexenyl bromide **2g** provided a mixture of direct $\text{Csp}^3\text{-Csp}^3$ cross coupling products **3lg/3lg'** and 5-*exo-trig* – cross coupling tandem **3lg''**. The later presumably indicates the generation of the 5-hexenyl radical from **2g** and its further interception by nickel to enter the cross coupling catalytic

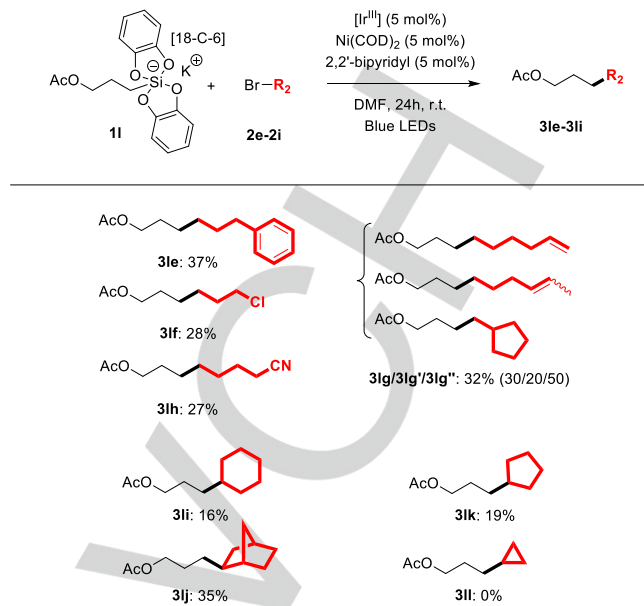
cycle. This radical generation from the alkyl bromide partner might also be at the origin of the homocoupling product.^[14] A better understanding of the mechanism of this dual catalysis is highly desirable and further studies are still ongoing in our laboratory.

Conclusions

Among all strategies to form C-C bonds, Csp^3-Csp^3 cross coupling reactions have more recently represented a very attractive option. For that purpose, the single electron transmetalation approach is still in its infancy. Our report introduces silicates as radical precursors in photoredox/nickel dual catalysis process. Although moderate yields of cross coupling products have been obtained, plagued notably by the formation of homocoupling products, feasibility of the approach is confirmed. Of note, these reactions are highly tolerant of functionality. Clearly, all this opens new synthetic perspectives in this very active field and poses intriguing mechanistical questions.



Scheme 4. Silicate screening.



Scheme 5. Bromide screening.

Experimental Section

To a Schlenk flask was added hexylsilicate **1a** (1.5 eq., 0.45 mmol, 284 mg), the iridium photocatalyst [Ir^{III}] (5 mol%, 15 μ mol, 15 mg) and 2,2'-bipyridine (5 mol%, 15 μ mol, 2.3 mg). Ni(COD)₂ (5 mol%, 15 μ mol, 4.1 mg) was then added in the glovebox. The Schlenk flask was sealed with a rubber septum, removed from the glovebox, and evacuated / purged with vacuum / argon three times. Degassed DMF (3 mL) was introduced followed by addition of ethyl 4-bromobutyrate **2a** (0.3 mmol, 43 μ l) and the reaction mixture was irradiated with blue LEDs (477 nm) at room temperature for 24h under an argon atmosphere. The reaction mixture was diluted with diethyl ether (50 mL), washed with aqueous saturated Na₂CO₃ solution (2 times), brine (2 times), dried over MgSO₄ and evaporated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel (pentane/diethyl ether, 98/2 to pentane/diethyl ether, 90/10) to afford the coupling adduct, ethyl decanoate **3aa** (26 mg, 43%) as a colorless oil and the homocoupling product diethyl, octanedioate **4a** as a colorless oil (26 mg, 38%). The spectroscopic data are in agreement with those reported in the literature. **3aa**.^[15] ¹H NMR (400 MHz, CDCl₃): δ 4.12 (q, J = 7.1 Hz, 2H), 2.30 – 2.26 (m, 2H), 1.65 – 1.58 (m, 2H), 1.35 – 1.25 (m, 12H), 1.25 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃): δ 174.1, 60.3, 34.6, 32.0, 29.6, 29.4, 29.4, 29.3, 25.2, 22.8, 14.4, 14.2. **4a**.^[16] ¹H NMR (400 MHz, CDCl₃): δ 4.12 (q, J = 7.1 Hz, 4H), 2.28 (t, J = 7.5 Hz, 4H), 1.66 – 1.58 (m, 4H), 1.35 – 1.31 (m, 4H), 1.25 (t, J = 7.1 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃): δ 173.9 (2 C), 60.3 (2 C), 34.4 (2 C), 28.9 (2 C), 24.9 (2 C), 14.4 (2 C).

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Keywords: photoredox catalysis • nickel • cross coupling • radical chemistry • dual catalysis

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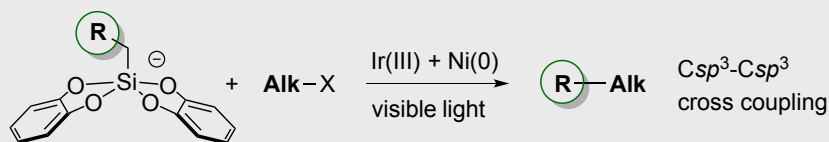
COMMUNICATION

Csp³-Csp³ cross coupling

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Louis Fensterbank*

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**Photoredox/Nickel Dual Catalysis for
the Csp³-Csp³ Cross-Coupling of
Alkylsilicates with Alkyl Halides**



We introduce bis-catecholato silicates as radical precursors in photoredox/nickel dual catalysis process. Moderate yields of Csp³-Csp³ cross-coupling products have been obtained thus confirming the feasibility of this approach.