Martin Silicates as Partners in Photoredox/Ni Dual Catalysis for the Installation of CH3, CH2D, CD2H, CD3 and 13 CH3 Groups onto (Hetero)Arenes

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Abstract: The introduction of a methyl group and its ^{13}C and ^{2}H labeled analogs on Csp^2-centers remains a challenging issue in synthetic chemistry. While the photoredox/Ni dual catalysis has proven to constitute a valuable methodology for the forging of Csp^2-Csp^3 bonds, the high difficulty to generate the methyl radical and to control its reactivity has severely limited the development of reliable processes. Herein, we introduce the easily prepared and bench-stable Martin methylsilicates bearing two *C*,*O*-bidentate hexafluorocumyl alcohol ligands as a class of radical precursors for dual catalysis enabling the chemoselective methylation of (hetero)aryl halides and acyl chlorides as well as the access to the corresponding CD_3, CD_2H, CHD_2 and $^{13}CH_3$ analogs in good yields.

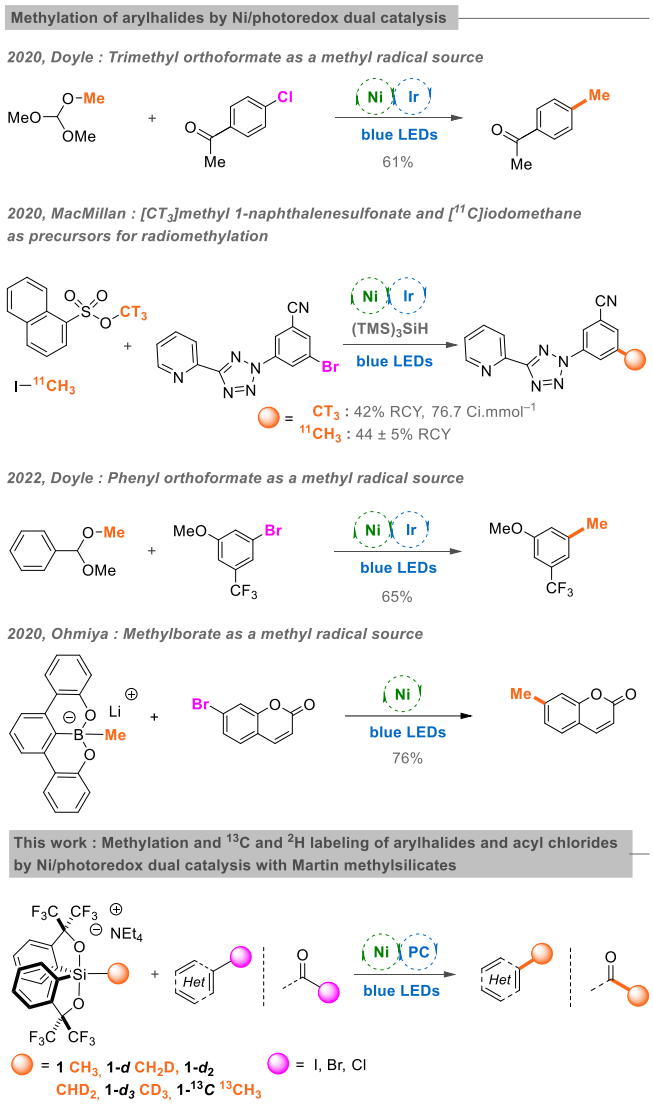
Despite its obvious interest, if only in medicinal chemistry,[1] commonly referred as the "magic methyl effect",[2] the installation of a methyl group, as well as of its isotopic analogues, on aromatic and heterocyclic backbones has remained synthetically challenging. Metal-catalyzed Csp^2-Csp^3 cross-coupling reactions such as Kumada-Corriu or Negishi coupling reactions represent obvious options.[3] However, in order to enable the introduction of the methyl group based on a $CH_3^{\ominus}$ synthon, these coupling processes rely on the use of stoichiometric nucleophilic organometallic reagents that potentially promote adverse reactivities. The recent use of trimethylboroxine as methylation reagent in Pd-catalyzed reactions partly alleviates some of these issues but high temperature conditions are still required.[4] Alternatively, reactions that rely on the intervention of the $CH_3^{\oplus}$ synthon (CH_3I and related reagents), such as electrophile cross-coupling[5] or some C-H activation reactions[6] are also limited by the use of substrates that must not exhibit strongly nucleophilic functions. Notwithstanding these potential polarity mismatches, a series of reagents have been recently developed for the introduction of a CH_3/CD_3 group,[7-9] but their use cannot be extended to other more costly isotopic analogs, as they are generally used in large excess or even as solvents. It is therefore not surprising that pathways involving the neutral $CH_3^{\bullet}$ synthon corresponding to the methyl radical have recently appeared as alternatives and witnessed intense developments.[10]

The methyl radical is a very high energy species and can be generated in harsh thermal or photochemical conditions, for instance by scission of peroxides and more recently by using di-*tert*-butylhyponitrite.[11] A seminal redox alternative was proposed by the Minisci group and consisted in the Ag(II)-mediated decarboxylation of acetic acid to provide a methyl radical that readily adds to heterocycles.[12]

Very recently, photoredox catalysis has tremendously changed the venues for the formation of radical species, notably the methyl radical from various precursors including methane.[13] A second benefit from this approach is that it can be merged with transition metal-catalysis, notably nickel catalysis (photoredox/Ni dual catalysis), which allows cross-coupling reactions of an electrophile with a tamed radical species.[14] This principle of single-electron transmetalation[15] initially devised with alkyl-carboxylates[16] and trifluoroborates[17] as oxidizable radical precursors has undergone significant development and has also found applications for the methylation of Csp^2 centers. Doyle and co-workers have developed elegant methylation pathways employing trimethyl orthoformate[18] or benzaldehyde di(alkyl) acetals[19] as methyl radical precursors through photo-induced β-scission of the acetal moiety (Scheme 1). Employing the Chatchilialoglu reagent for halide abstraction, MacMillan developed a photocatalyzed cross-electrophile coupling[20] for the introduction of CT_3, CD_3, $^{13}CD_3$, $^{14}CH_3$ and $^{11}CH_3$ groups on various pharmaceutical platforms.[21] MacMillan[22] and Li[23] have also designed radical methylations of pyridine derivatives in C_2 and C_4 positions, employing methanol as alkylating agent.

All these photocatalyzed protocols have their own virtues but also limitations in terms of ease of use, functions compatibility and/or stoichiometry and are not convenient for versatile isotope labeling. We therefore surmised it would be useful to devise a library of bench-stable radical methylation reagents based on a photooxidative process. Such an approach has already been devised with the use of self-excitable borates that can liberate a methyl radical under blue LEDs irradiation,[24] however relative stability[24a] and the unsuitability of isotope labeling appear as limitations.[24b] Our group[25] and the one of Molander[26] developed the use of alkyl *bis*-catecholatosilicates as versatile

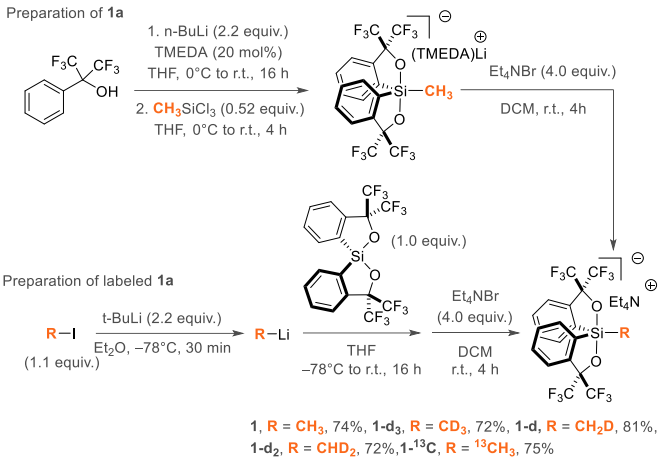
alkyl radical precursors,[27] also competent for photoredox/nickel dual catalysis with good yields of cross-coupling products as well as a great function tolerance.



Scheme 1. Photoredox/Ni catalyzed methylations

A notable exception to this reactivity is the methyl biscatecholatosilicate derivative, which has provided only recently a single imine addition adduct in fairly moderate yield,[28] but has still not given any radical methylation adduct under dual catalysis conditions.[27,29] Nevertheless, a second class of alkylsilicates based on the 2,2,2,2',2',2'-hexafluorocumylalcohol dianion *C,O*-bidendate ligand, Martin type silicates,[30] has attracted our attention in recent years.[31] During the course of our investigations on their radical reactivity, the group of Morofuji and Kano evidenced that those derivatives, although having higher oxidation potentials (≈ 1.50 V vs SCE) than *bis*-catecholatosilicates (< 1.0 V vs SCE), are also good precursors of alkyl radicals[32] readily engaged in Giese reactions.[32b] Reasonable yields of photocatalytic generation of the methyl radical from **1** of Scheme 1 using *tert*-butyl-10-phenylacridinium tetrafluoroborate ([Mes-Acr$^+$], Nicewicz's catalyst)[33] and its trapping with a series of Michael acceptors were also reported.[32b]

This complementarity of reactivity between the *bis*-catecholato- and the Martin silicates led us to consider the latter as potential partners of photoredox/Ni dual catalysis for the installation of methyl fragments on aromatic platforms (Scheme 1).
Additional interesting features of Martin silicates consist in their easy preparation on gram scale as well as their very high air and moisture stability.[31c] In this context, we prepared tetraethylammonium methyl silicate **1** and the isotopic analogs **1-*d***, **1-*d*$_2$**, **1-*d*$_3$** and **1-^{13}*C*** through two routes.

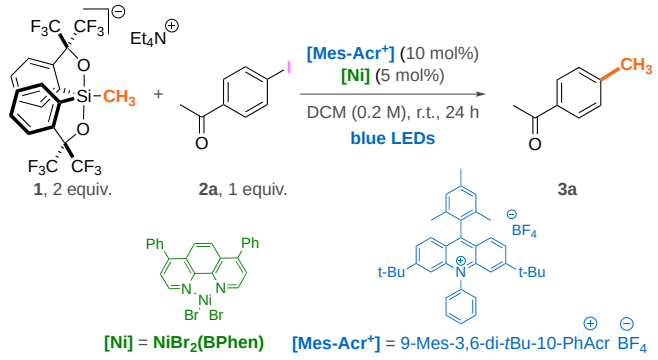


Scheme 2. Preparation of methyl radical precursors

Cyclic voltammetry of **1** showed an oxidation peak at 1.50 V vs SCE and confirmed the necessity to use highly oxidizing photocatalysts such as acridiniums.[34] Nevertheless, it remained unclear how to set reaction conditions that would optimize the concurrent operation of the two catalytic cycles and in particular to find nickel complexes compatible with these highly oxidative photocatalysts. A literature survey confirmed the paucity of cases and to the best of our knowledge, only two reports have highlighted the compatibility of both catalytic systems, the first one by Rueping dealing with the cross-coupling of cyclic alcohol precursors,[35] the second one by Xiao using alkyl germanes.[36]

Thus, the reaction conditions were optimized by varying the key parameters of the process (see Table 1 *&* SI). Using **2a** as electrophile, we found the best combination of catalysts consisted in a mixture of 10 mol% of Nicewicz's catalyst and of 5 mol% of $NiBr_2$(BPhen). The use of DCM as solvent proved to be very beneficial compared to the widely used DMF under typical Ni/photoredox cross-coupling conditions (entry 1 *vs* 3) and running the reaction at 0.2 M was better than at 0.1 M (entries 1 *vs* 4). Except 9-mesityl-10-methylacridinium perchlorate (Fukuzumi photocatalyst, entry 8, 51% of **3a**), all the other photocatalysts including $Ir(dF(CF_3)ppy)_2(dtbbpy)$ (PF_6) and 4CzIPN proved to be inefficient compared to Nicewicz's photocatalyst (entries 6 – 8). The ligand on the nickel catalyst was also of importance. Indeed, an extended π-system proved to be mandatory since no reaction was observed with a bipyridyl ligand while phenantroline showed some efficiency (entry 10 *vs* 9). This influence of the π-system was highlighted by the difference observed between phenantroline and bathophenantroline (entries 1 & 9). Lower amounts of silicate **1**

(entries 11 & 12), as well as a lower photocatalyst loading (entry 5) were also found to be detrimental to the reaction yield, which could be rationalized by the fact that a significant amount of methyl radical is necessary to promote the reaction. In this case, having an excess of 1 did not neither result in an improvement (82% of **3a**, entry 13).



Entry	Deviations from optimal conditions	**3a**, yield %[a]
1	none	86 (77%[b])
2	Dark or no PC[c]	0
3	DMF as solvent	0
4	concentration in **2a** at 0.1 M	38
5	[Mes-Acr+] (5 mol%)	53
6	PC: Ir(dF(CF$_3$)ppy)$_2$(dtbbpy)(PF$_6$) (10 mol%)	0
7	PC: 4CzIPN (10 mol%)	0
8	PC: Fukuzumi (10 mol%)	51
9	NiBr$_2$(phen) as nickel catalyst	45
10	NiBr$_2$(dtbbpy) as nickel catalyst	0
11	1 equiv. of **1**	20
12	1.5 equiv. of **1**	65
13	4 equiv. of **1**	82

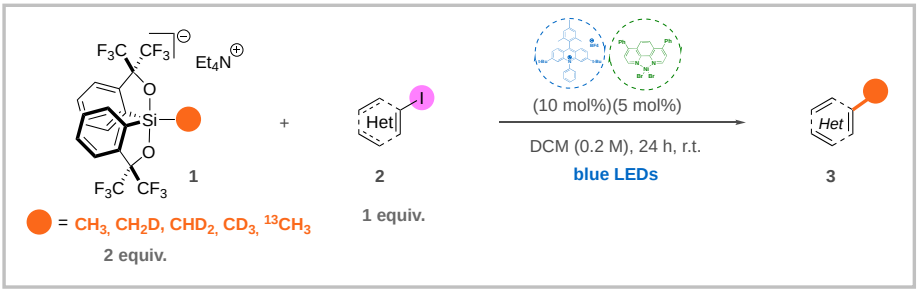
[a] NMR yield. [b] Isolated yield. [c] PC: photocatalyst

Table 1. Optimization of the cross-coupling reaction reaction of **1** with **2a**

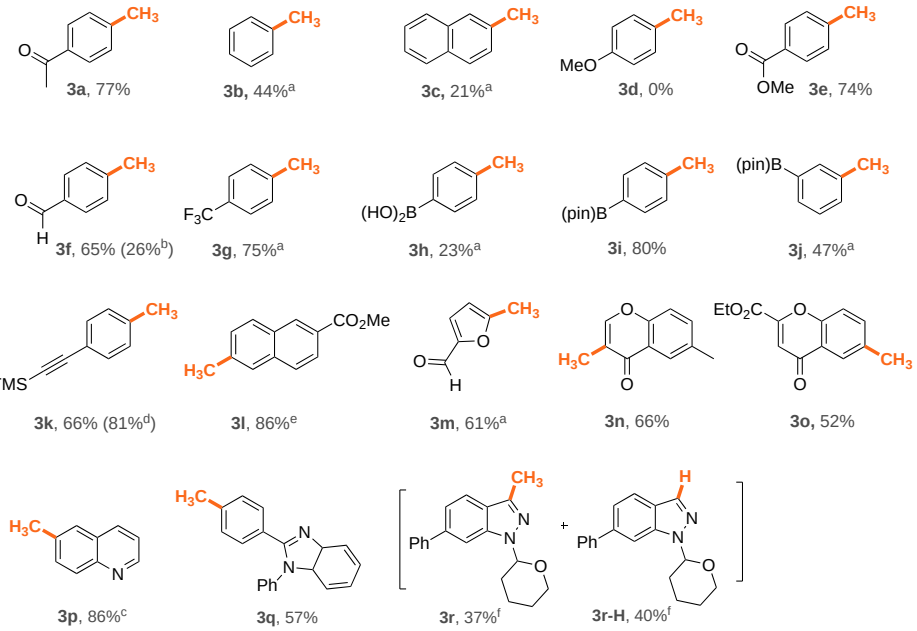
After having optimized the reaction conditions, we turned toward the scope of the process (Scheme 3). Electronically less depleted substrates (iodobenzene, 44% of **3b** and 2-iodonaphthalene, 21% of **3c**) or enriched one (4-iodoanisole, 0% of **3d**) showed significantly lower yields. Conversely, this methylation process is compatible with various electrophilic functions such as a CF_3 group (**3g**) and enables the chemoselective alkylation of aryl moieties bearing an ester (**3e**, 74% and **3l**, 86%) and even a formyl group (**3f**, 65%). In the latter case, no adverse nucleophilic reactivity from silicate **1** was observed. Another interesting example is the higher-yielding methylation of the 4-iodophenylboronic (Bpin)ester (**3i**, 80%) compared to the corresponding boronic acid (**3h**, 23%). This reaction was also performed on a larger scale (0.76 mmol of the aryl iodide partner) and provided **3i** in 62% yield.

A series of oxygen and nitrogen heterocyclic derivatives such as furfuryl (**3m**) and quinoline (**3p**) could be successfully engaged in the reaction, including also chromones (**3n** and **3o**), valuable scaffolds for drug-design[37,38] and indazoles (**3q, 3r**) also known for they biological properties.[39] In the case of the indazole precursor, the hydrogenated product **3r-H** was also isolated in 40% yield and could originate from the homolysis of the photosensitive oxidative addition Ni(II) complex (Scheme 4).[40]
Based on the high reactivity of 4-iodoacetophenone (Table 1), isotopic analogs of **1** were used and provided comparable yields of **3a-*d*$_3$**, **3a-*d*$_2$**, **3a-*d***, **3a-^{13}*C*** with a complete labeling control. Indeed, no erosion of isotopic incorporation at the labeled benzylic position, neither a side isotopic incorporation on the organic backbone have been observed. Similarly, the corresponding isotope labeled products **3l-*d*$_3$**, **3l-^{13}*C*** **3o-*d*$_3$** and **3n-*d*** could be synthesized chemoselectively. Finally, acyl chlorides could be used as electrophiles[41] and also appeared compatible with the isotopic labeling as **3s** and **3s-*d*$_3$** were formed in 58% and 62 %.

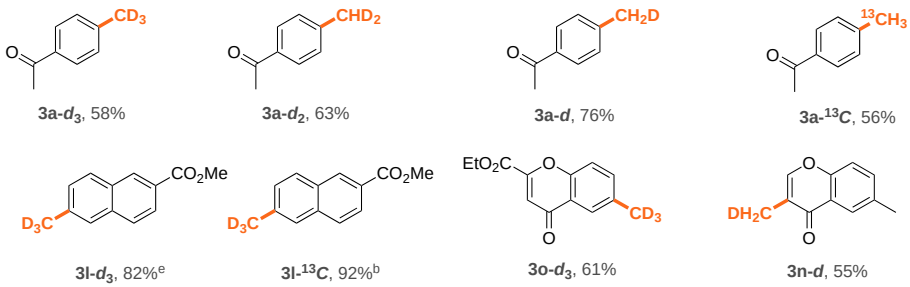
The scope of this reactivity pointed out different key parameters that can modulate the reaction efficiency. An electron poor π-system will be favorable to this reactivity, which explains the high yields obtained for heteroaryls such as quinoline or furfuryl groups (**3g** and **3k**). The case of the naphtyl scaffold epitomizes this point. Indeed, the substitution by an ester group, even remote from the halide position exerts a positive effect on the yield even from a bromide precursor (86% for **3l** *vs* 21% for the non-substituted naphthalene product **3c**). This is also consistent with the absence of reactivity observed for electron-richer aromatic systems such 4-iodo-anisole. The latter could even be used to poison the reactivity of 4-iodobenzaldehyde as the yield in **3f** dropped to 26% in the presence of 4-iodoanisole. Consistent with these findings, Nicewicz's catalyst was reported to oxidize anisole derivatives and a non-productive redox pathway may intervene.[42]
This scope suggests a high function tolerance for various electron-withdrawing and fragile functions, setting the stage for late-stage functionalization. This was demonstrated by the synthesis of the previously undescribed monodeuterated analog of the nonsteroidal anti-inflammatory celecoxib (**3u-*d***) from the iodinated precursor **2u** in good yield (Scheme 5). There is indeed a continuing interest in the synthesis of isotopic analogues of drugs containing a *p*-tolyl group prone to metabolic oxidation on the methyl group.[21,43-46] Overall, this example also offers a valuable alternative to the more general problem of the incorporation of a single deuterium in benzylic position, which remains challenging.[47-50]



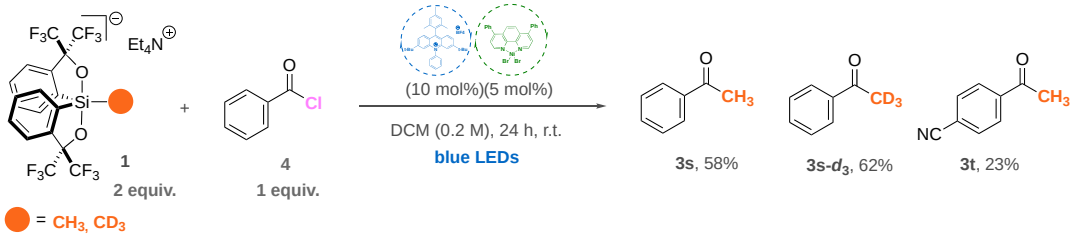
Methylation scope



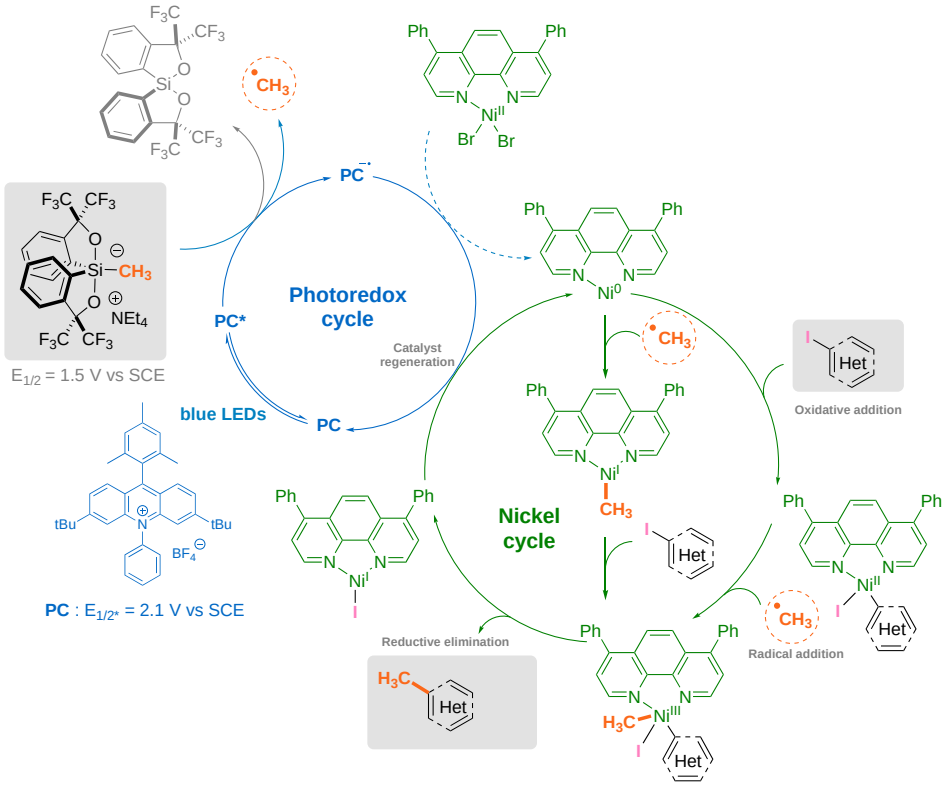
Labeling scope



[a]NMR yield, [b]In the presence of 1 equiv. of 4-iodoanisole, [c]Isolated as a mixture with the starting halide (see SI),[d]4 equiv. in silicate have been used instead of 2,[e]Starting from the corresponding bromide, [f]Isolated as a mixture.



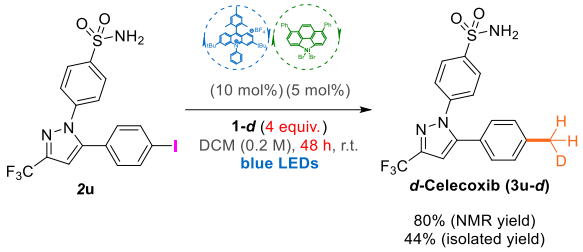
Scheme 3. Scope of the reaction



Scheme 4. Possible mechanism for the dual catalyzed methylation

A mechanism proposal was drawn based on several elements. First, the quenching constant of the acridinium's excited state by silicate **1** was determined to be $1.3x10^{11}$ $L.mol^{-1}.s^{-1}$ (see SI). This is consistent with a SET event controlled by the solvent diffusion. In the low viscosity DCM solvent, the short-lived excited acridinium (t = 13.8 ns)[51] can react with silicates **1** to promote the key electron-transfer, which is also thermodynamically favored (2.10 V *vs* SCE for [Mes-Acr$^+$]*/ [Mes-Acr$^\cdot$] *vs* 1.50 V for **1a**). This oxidative quenching of the methylsilicate **1** by the photoexcited acridinium liberates a methyl radical, presumably trapped by the nickel(II) complex originating from the oxidative addition of the arylhalide. The generated Ni(III) complex then undergoes reductive elimination to liberate the methylated cross-coupling product **3** as well as Ni(I) that would be further reduced by the acridinium radical. Alternatively, the methyl radical could also be trapped by Ni(0) followed by oxidative addition to give the same Ni(III) intermediate.[52]

In this study, we have devised a versatile methylation method enabling the smooth methylation of (hetero)aryl halide and acyl chloride substrates in good to very good yields with a high function tolerance. Despite the limitation observed for electron-rich aromatic substrates, this methodology is broadly compatible with the isotopic labeling and allows access to mono- di- or tri-deuterated and ^{13}C-labeled derivatives. In addition, this process uses non-sensitive silicate methylating agents, diminishing drastically the experiment cautions, the preparation time and thus the transformation cost. All these elements as well as the bioactive molecules targeted in scope suggest that this reaction is compatible with late-stage functionalization, alleviating tedious protection steps. This was demonstrated by the synthesis of d-celecoxib. Moreover, one of the key advantages of this methodology is the complete control of the number of deuterium incorporated on the newly created benzylic position and so, without side over-labeling or scrambling during the reaction, which can be valuable for drug design.



Scheme 5. Synthesis of the *d*-celecoxib via last-stage methylation of **2u**

Experimental Section

***General procedure 1 for the synthesis of d-labeled starting materials* 1 *applied to* 1a-d_3:**

In a flame-dried Schlenk flask was added the d_3-iodomethane CD_3-I (0.22 mL, 3.49 mmol, 1.1 equiv.) and Et_2O (5 mL). The resulting solution was cooled down to -78°C and *tert*-BuLi 1.7 M in pentane (4 mL, 6.86 mmol, 2.2 equiv.) was added dropwise and the reaction mixture was stirred at -78°C for 30 minutes. A solution of Martin spirosilane (1.60 g, 3.12 mmol, 1.0 equiv.) in Et_2O (20 mL) was added to the white solution, and the reaction was warmed up to room temperature and stirred overnight. The reaction was quenched with abs. EtOH and solvents were

removed *in vacuo*. The oily residue was dissolved in DCM (25 mL), tetraethylammonium bromide (2.62 g, 12.48 mmol, 4.0 equiv.) was added and the reaction mixture was stirred at room temperature for 4h. HCl 1M was added and the organic layer was washed with water (x 3), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting yellowish crude residue was dissolved in minimal volume of DCM and precipitation was triggered by addition of pentane. Filtration afforded **1a-*d*$_3$** as a white solid (1.48 g, 72 %).

General procedure 2 for the cross-coupling reaction to give the products 3 applied to 3a

In a flame-dried sealed microwave tube purged with three argon/vacuum cycles, the silicate **1a** (263 mg, 0.40 mmol, 2.0 equiv.), the nickel catalyst $NiBr_2$(BPhen) (5.5 mg, 0.01 mmol, 5 mol%), the photocatalyst [Mes-Acr$^+$] (11.5 mg, 0.02 mmol, 10 mol%) are introduced under argon with the 2 with 4-iodoacetophenone **2a** (49 mg, 0.20 mmol, 1.0 equiv.). Distilled DCM is then added (1 mL) under argon and the mixture is degassed through three freeze pump thaw cycles. The resulting solution is then irradiated by a blue LED for 24h at room temperature. The reaction mixture is then quenched by a saturated aqueous solution of K_2CO_3 (5 mL) and extracted with Et_2O/Water (3x10 mL of each). The combined organic layers are then concentrated under vacuum and the crude was purified by flash chromatography to provide **3a** as a white solid (20.7 mg, 77%).

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Keywords: methyl radical, isotope labeling, Martin silicates, photoredox catalysis, nickel catalysis

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