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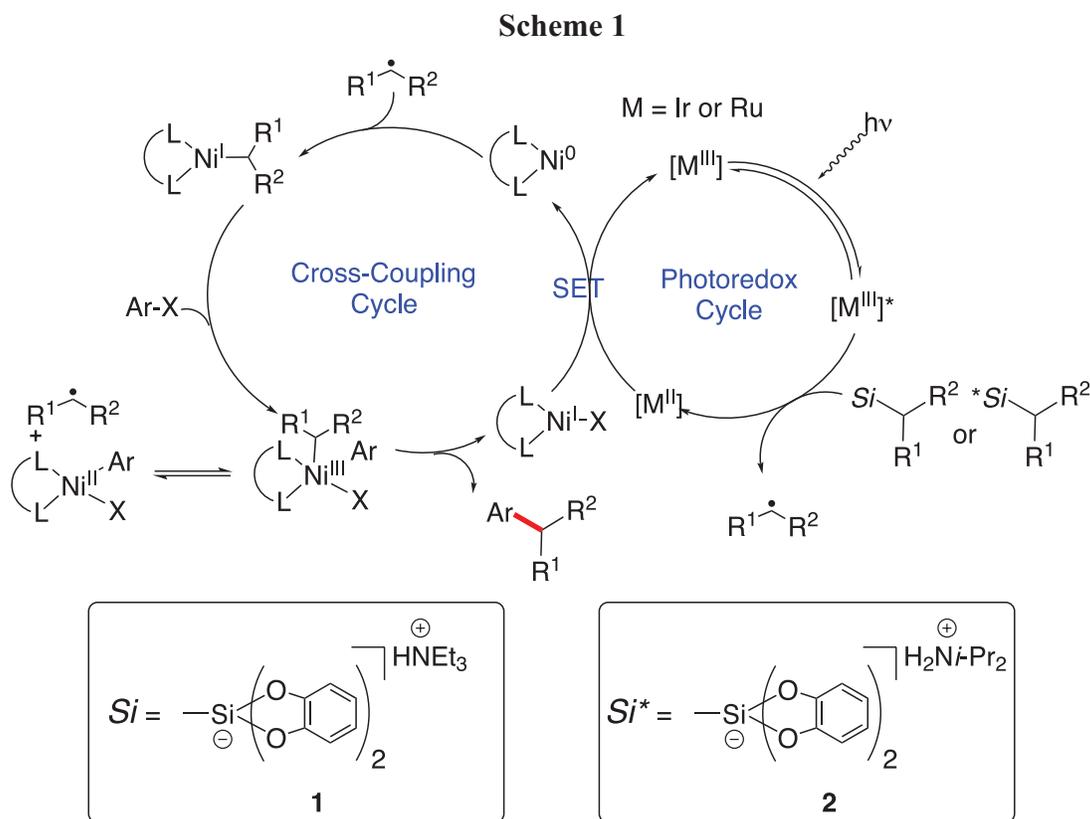
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Cross-Coupling Reactions with Alkylsilicates

Gerald L. Larson and Richard J. Liberatore

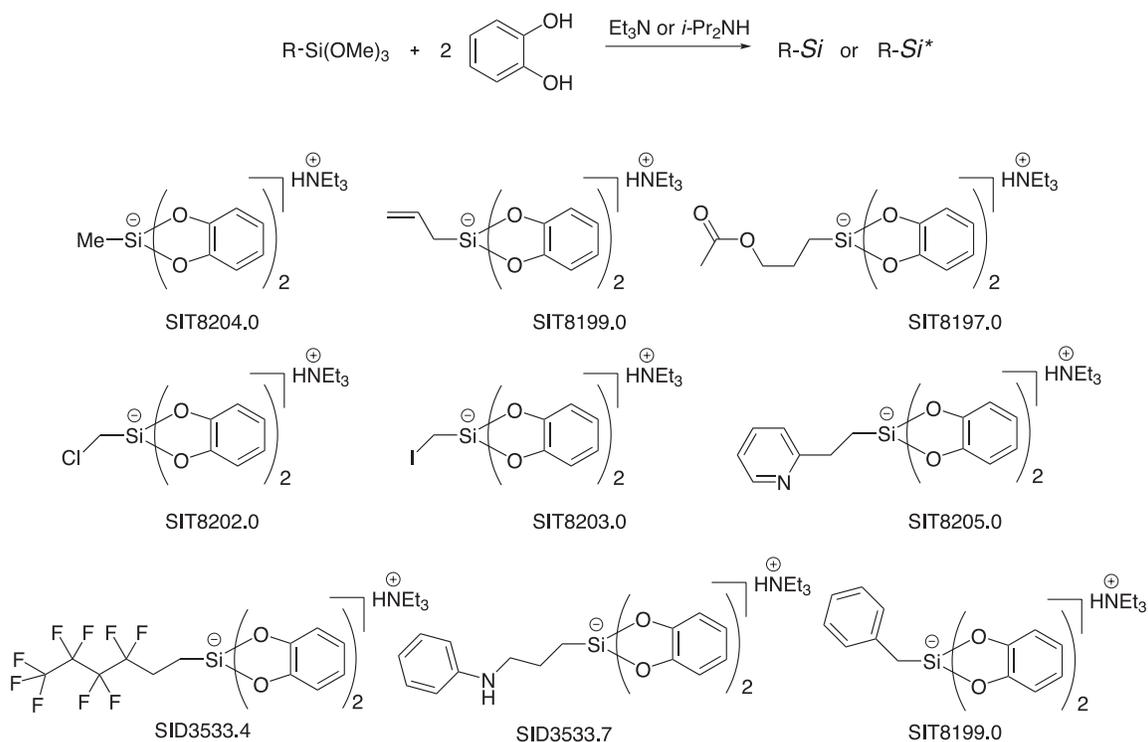
The now well-known cross-coupling of sp - sp^2 and sp^2 - sp^2 carbon centers has proved to be highly useful in synthetic organic chemistry. Lacking in the various C-C cross-coupling arsenal is the ability to couple sp^3 - sp^2 and sp^3 - sp^3 carbon centers. The Molander group at the University of Pennsylvania was the first to employ a photoredox/Ni dual catalysis approach to the resolution of this omission (Scheme 1). A general method for the coupling of sp^3 - sp^2 carbon centers is particularly important for drug discovery as it has been reported that compounds with lower sp^3 fractions have higher rates of attrition in drug development.¹ Their first attempts were to use a metal photoredox catalyst and an alkyltrifluoroborate as the radical provider. The second catalyst was a Ni^0 complex, which reacts with the radical generating a Ni^I intermediate. This then undergoes an oxidative addition of the aryl or vinyl halide to form a Ni^{III} intermediate, followed by a reductive elimination to Ni^I and the cross-coupled product. This work was followed by both Fensterbank and Molander utilizing alkylbis(catecholato)silicates as the alkyl radical source. A summary of that chemistry is the topic of this review. The photoredox-catalyzed, nickel-based cross-coupling of alkylsilicates and alkyltrifluoroborates has been reviewed.²

In the interest of space and repetition the two commonly used silicates are generalized in structures **1** for the triethylammonium silicate moiety and **2** for the diisopropylammonium silicate moiety. Thus the abbreviations Si and Si^* are used for the triethylammonium and diisopropylammonium silicate, respectively, throughout this review.



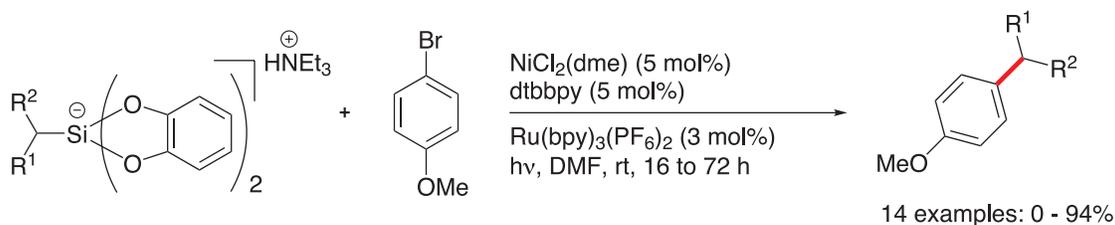
The introduction of the use of alkylbis(catecholato)silanes was brought about by the observation that the oxidation potential (E^0 for these species is +0.34 V vs SCE for R = primary alkyl) is well below the E^0 for photoexcited Ir or Ru catalyst ($E^0 = +1.32$ V vs SCE) as well as those for certain organic dyes. The Ir-based photocatalyst is very expensive, and Molander was able to replace it with a less costly Ru compound. The alkylbis(catecholato)silanes are readily prepared from the appropriate alkyltrimethoxysilane via reaction with a substoichiometric amount of catechol and either triethylamine or diisopropylamine (Scheme 2). Isolated yields of the alkylsilicates from this readily scaled procedure are in the high 80 to mid 90% range. The alkylbis(catecholato)silanes are air stable solids that can be stored for long periods of time.³ Gelest offers a wide range of alkylsilicates and can also make custom versions upon request.

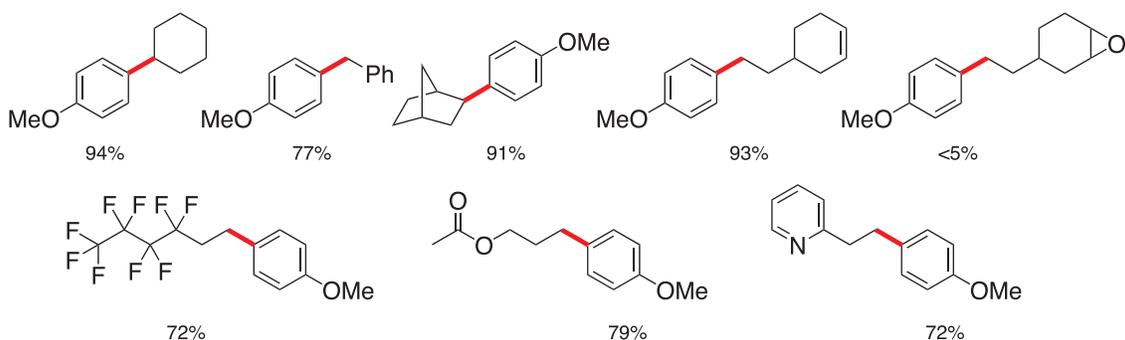
Scheme 2



The reaction of the alkylsilicates with aryl bromides under the influence of a Ni^{II} catalyst and the photoredox agent $\text{Ru}(\text{bpy})_3(\text{PF}_6)_2$ gave the alkylated aryl in 0 to 94% yields with methyl, chloromethyl and an epoxy functional system (when reacted with 4-phenyl-1-bromobenzene) all giving low or no yield (Scheme 3).³

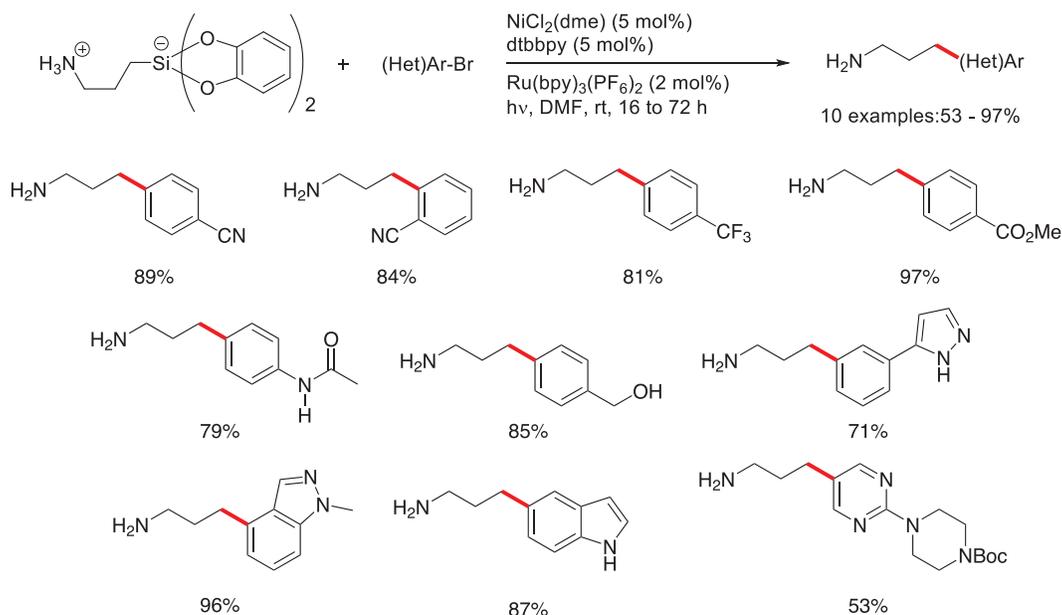
Scheme 3



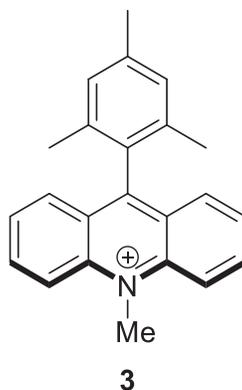


As an example of the ability to tolerate the amine functionality the 3-aminopropylsilicate (as the ammonium salt) was reacted with a variety of (het)aryl bromides under the conditions above to provide the aminopropyl-derivatized (het)aryl systems in good yield (Scheme 4). The reaction demonstrated tolerance for CN, CO₂Me, HNCOME, OH, and CF₃ groups.³

Scheme 4

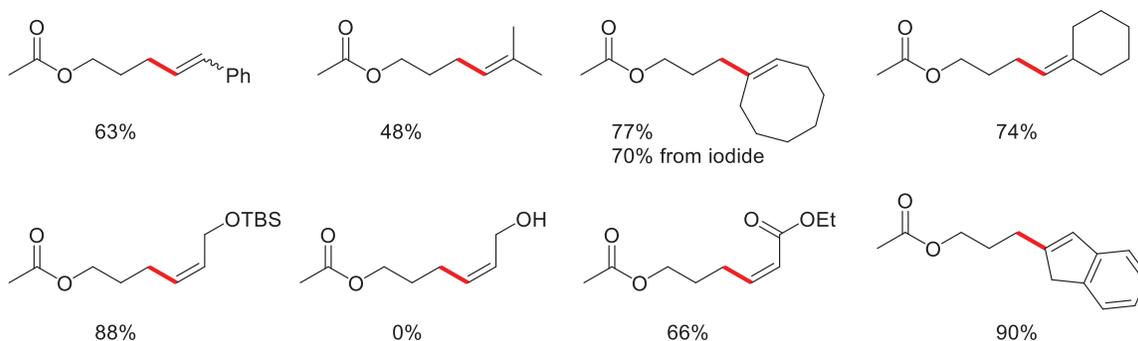
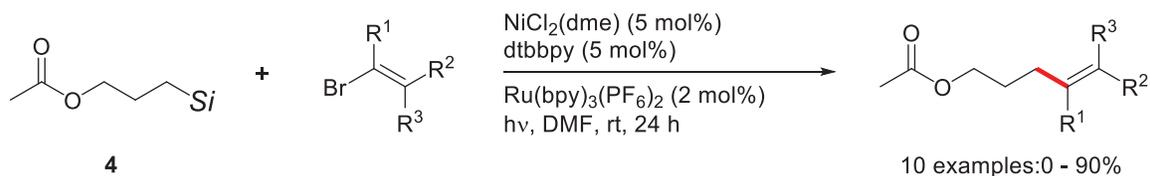


A comparison study of the single-electron-transfer oxidation of trifluoroborates and silicates has been reported. In general both species are able to generate C-centered radicals, although the trifluoroborates were slightly better with Fukuzumi catalyst **3**.⁴

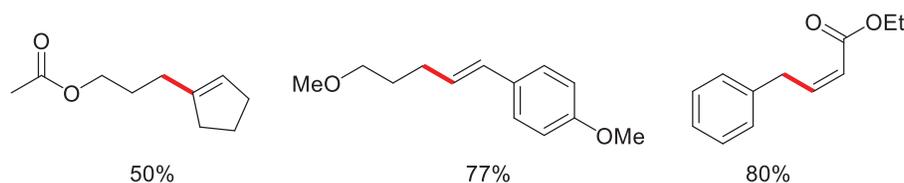


The photoredox dual catalysis was applied to the alkylation of vinyl bromides and iodides. Even the typically less reactive vinyl chlorides were found to react. For example, when the 3-acetoxypropylsilicate **4** was reacted with a series of vinyl bromides excellent results in the sp^3 - sp^2 cross-coupling took place (Scheme 5). The yields were good to excellent with the lone exception of a hydroxyl derivative that gave 0% coupling product, although the corresponding TBS ether reacted very well. A variety of alkylsilicates were reacted with vinyl bromides (15 examples: 0 – 94%) and vinyl iodides as well (12 examples: 27 – 86%).⁵

Scheme 5

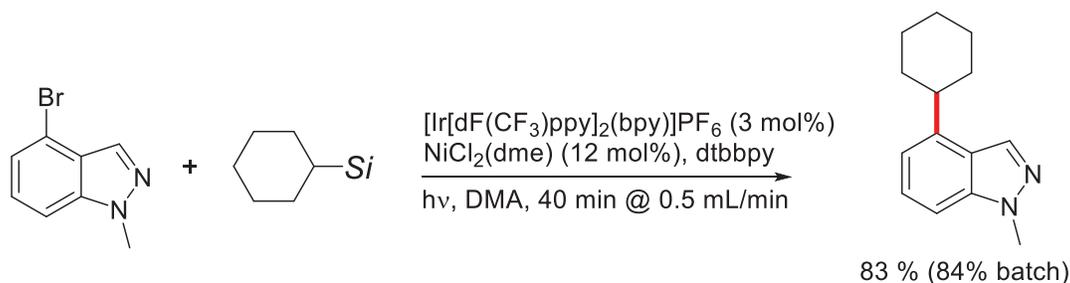


Examples from alkenyl chlorides:



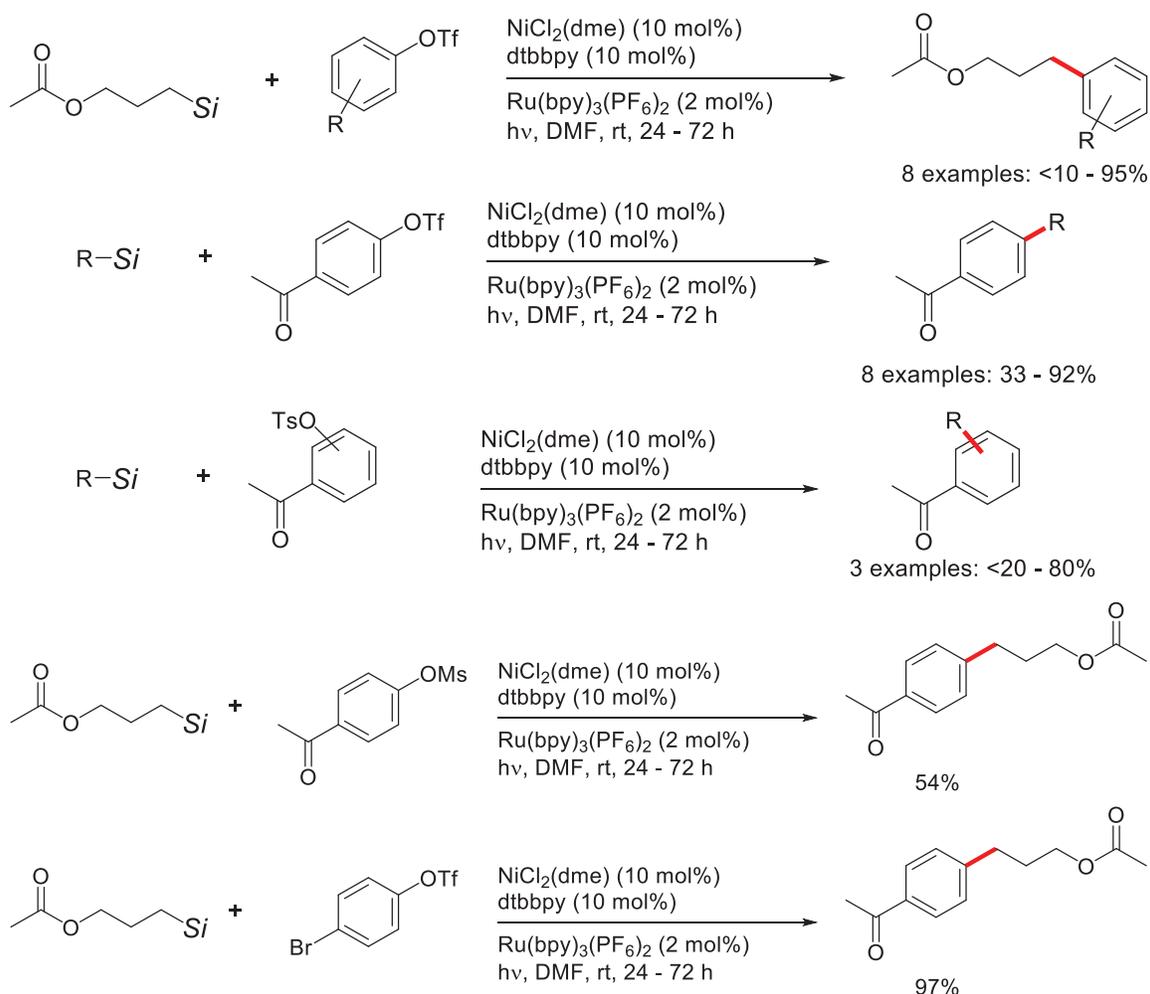
A Vertex group reported on a continuous flow approach to the photoredox coupling of alkyltrifluoroborates and alkylsilicates. With a flow rate of 0.5 ml/min sp^3 - sp^2 cross coupling with (het)aryl bromides was accomplished in a reaction time of 40 minutes versus 18 hours in a batch approach. The yields were excellent and the process scalable to larger levels (Scheme 6). The approach enables rapid parallel syntheses for library and diversification generation.⁶

Scheme 6



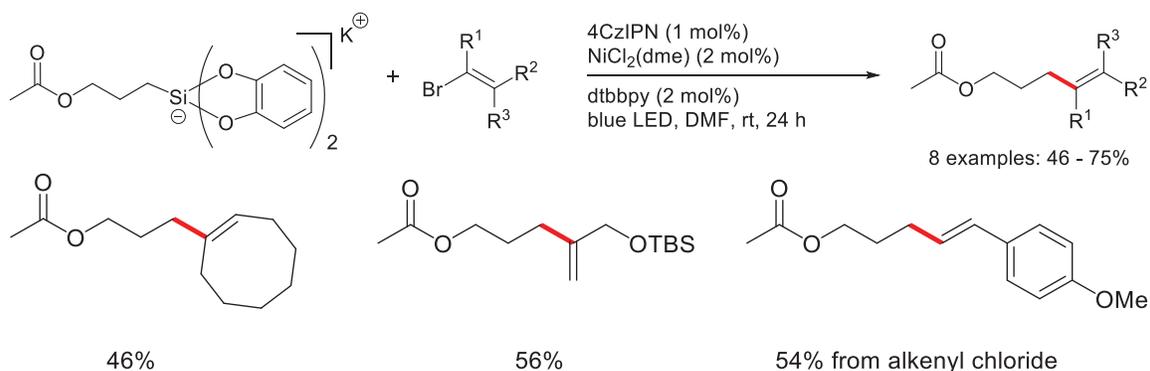
The Molander group also contributed to the alkylsilicate cross-coupling arena showing that derivatized phenols could be cross-coupled with the silicates (Scheme 7). Thus, triflates, mesylates and tosylates were all successfully cross-coupled. Amine functional alkylsilicates failed to react. In comparison, an aryl bromide proved to be more reactive than the corresponding aryl triflate.⁷

Scheme 7



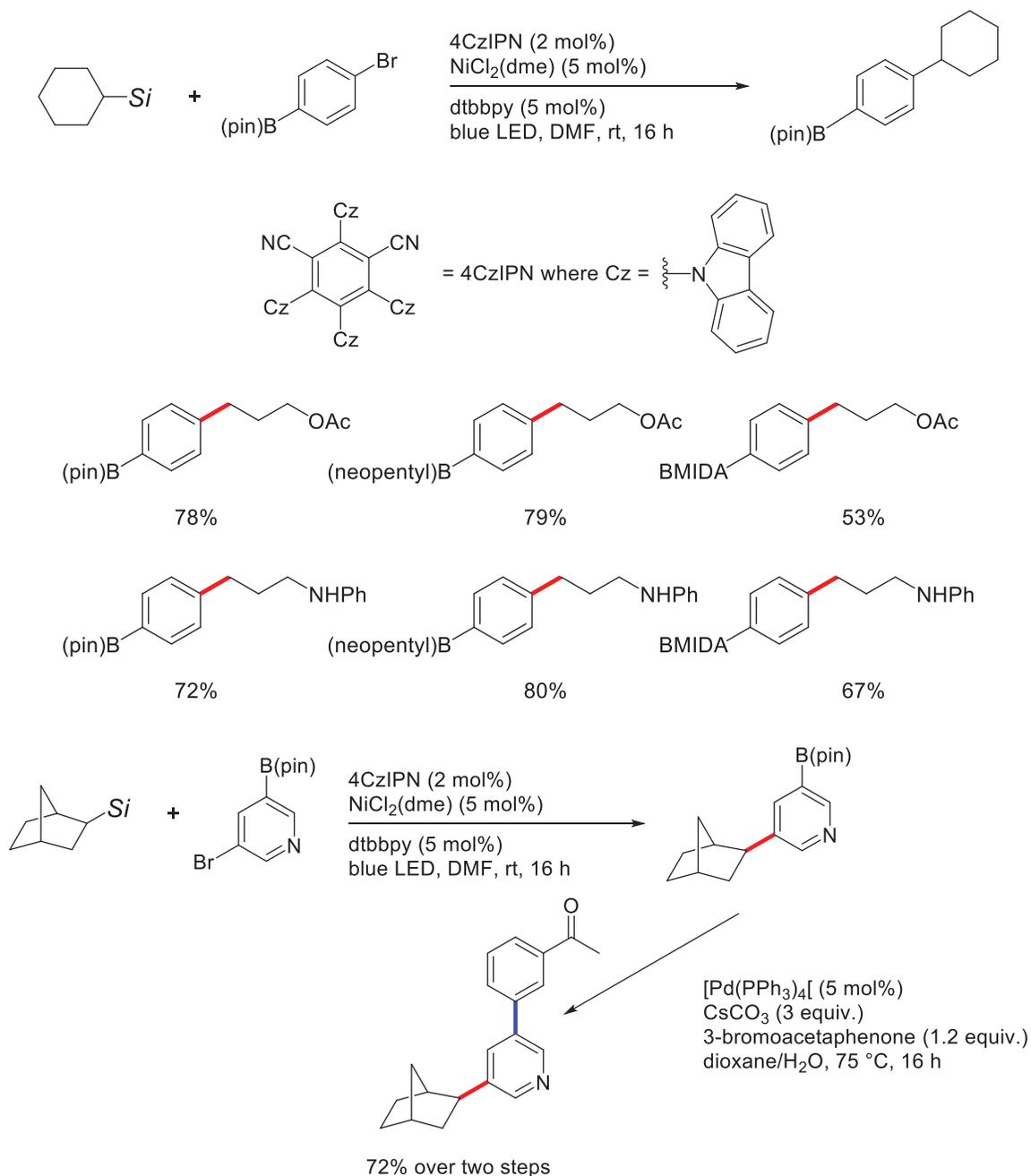
The Fensterbank group reported on the metal-free photooxidation of alkylsilicates to generate alkyl radicals, which could then be used in the metal-catalyzed cross-coupling with suitable acceptors. This protocol makes use of the organic dye 1,2,3,5-tetrakis(carbozol-9-yl)4,6-dicyano-benzene (4CzIPN), which allows for the facile generation of alkyl radicals from the alkylsilicate. In this work the potassium silicate was used (Scheme 8).⁸

Scheme 8



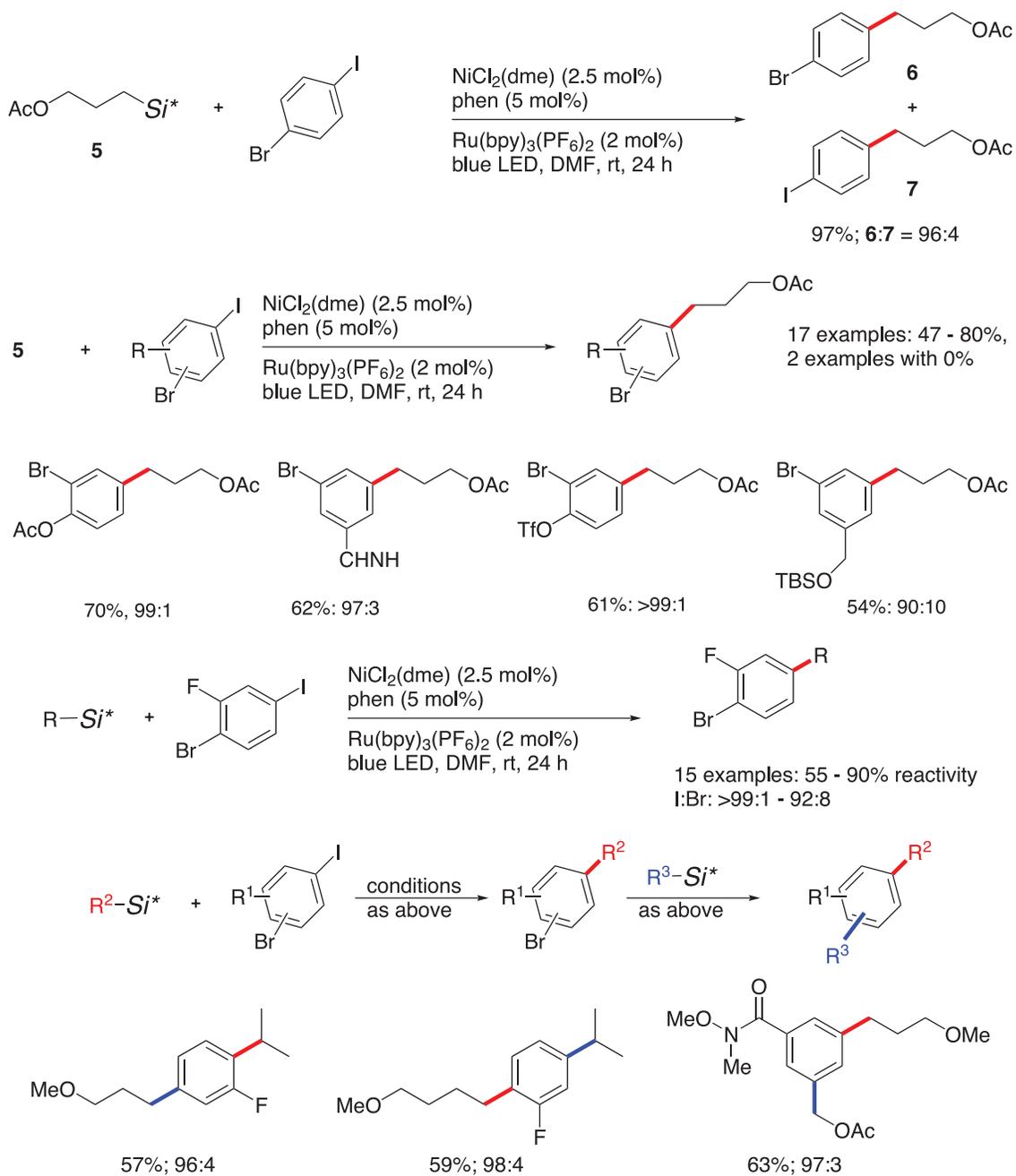
The Molander group with their interest in both organoboron and organosilicon chemistry have worked on the Csp^3-Csp^2 cross-coupling of alkylsilicates with various borylated aryl bromides. The alkylsilicate cross-coupling occurs without affecting the arylboronate, which is then available for Suzuki-Miyaura cross-coupling. Whereas the pinacol, neopentyl and the N-methyliminodiacetoxy boronates reacted well the 1,8-diaminonaphthalene derivatives did not. A total of 25 examples were reported (Scheme 9).⁹

Scheme 9



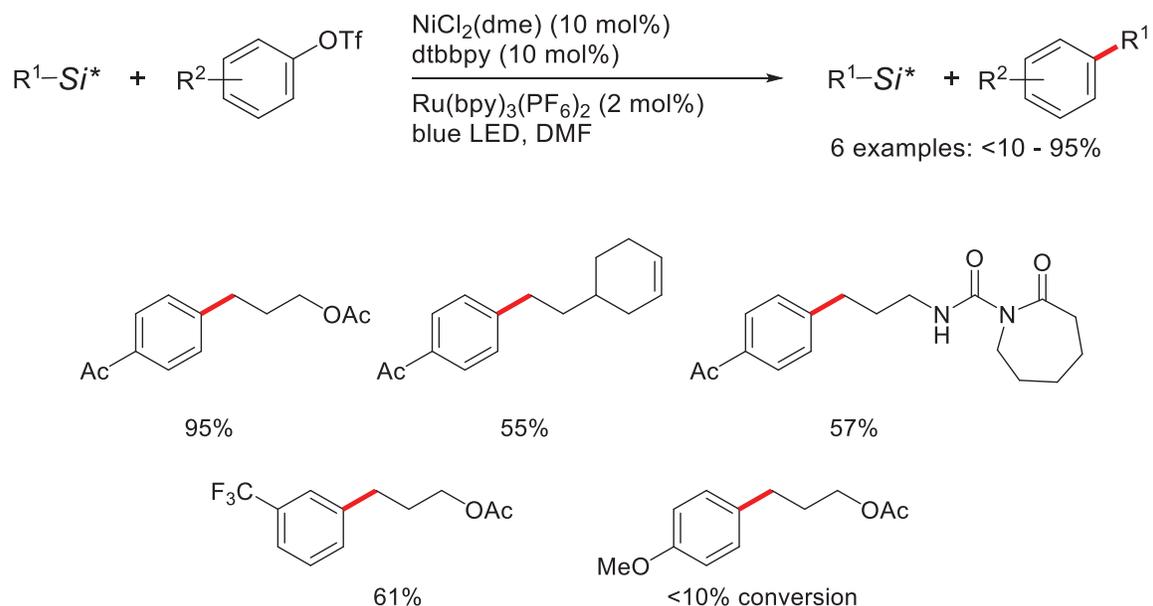
The chemoselective Ni/photoredox dual catalyzed sp^3 - sp^2 cross coupling as a function of the aryl halide showed a definite enhanced reactivity of the iodide substrates over the bromides. This represents the first investigation of the chemoselective sp^3 - sp^2 cross-coupling. An extensive investigation of a variety of bromo(iodo)arenes and alkylsilicates revealed excellent functional group tolerance although a benzylic alcohol gave no yield (Scheme 10).¹⁰

Scheme 10



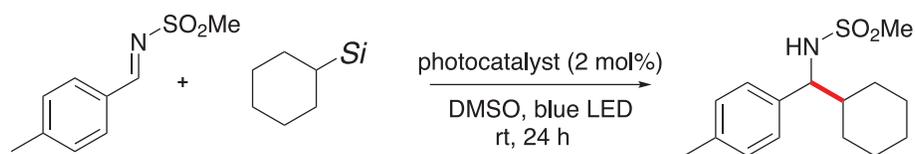
The alkylsilicate Csp³-Csp² cross-coupling with aryl triflates gave good yields of the alkylated arene with the exception of the reaction with a strong electron-donating group substituted aryl triflate. The chemoselectivity of the cross-coupling alkylation favored the reaction with an aryl bromide over that with an aryl triflate (Scheme 11).¹¹

Scheme 11

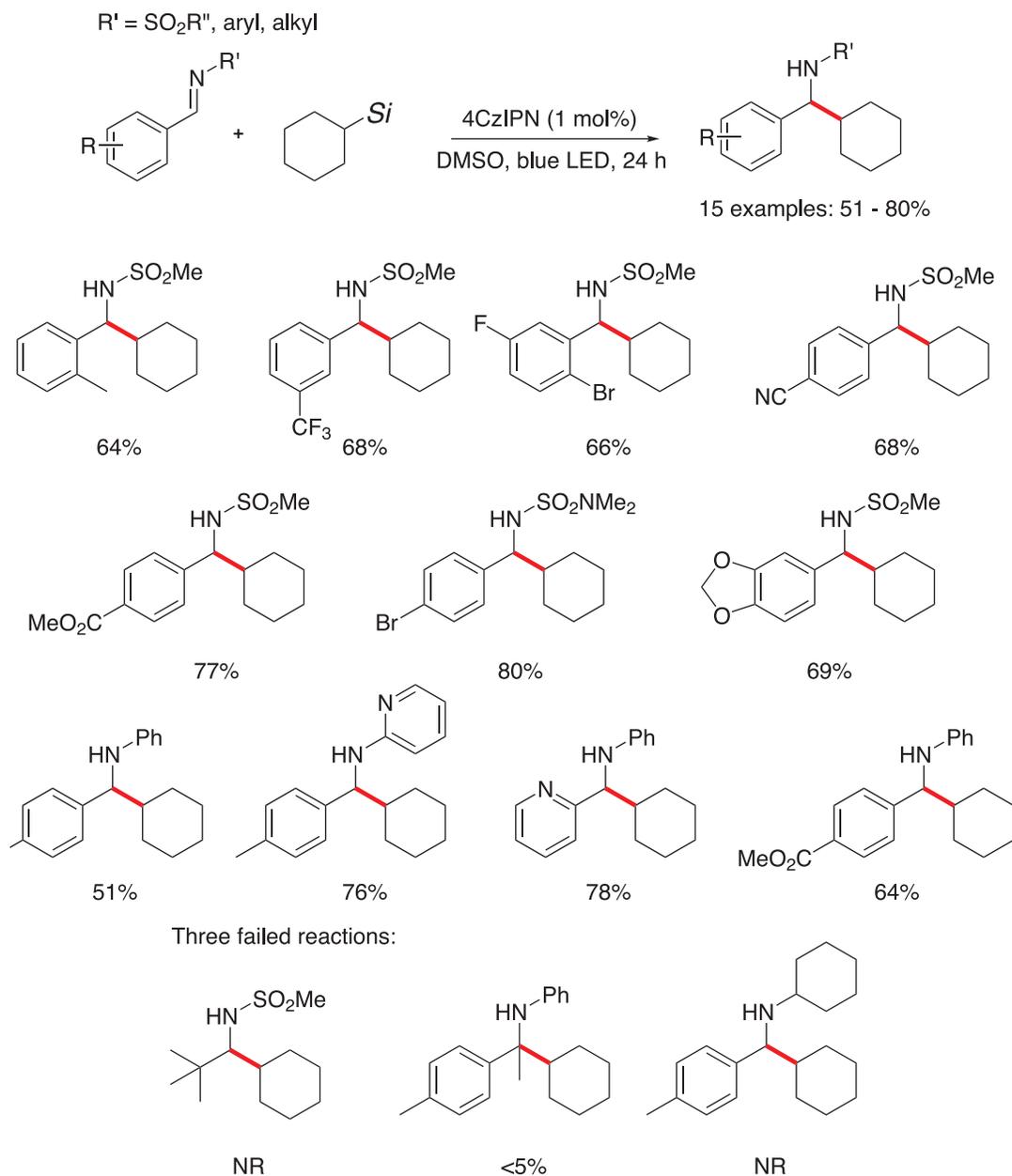


A mild, redox-neutral direct alkylation of imines with alkylsilicates was accomplished with the organic photocatalyst 4CzIPN rather than the more common Ru or Ir-based photocatalysts. The conditions for the alkylation are mild and provide the product in high yield. The method nicely avoids the potential chain-terminating dimerization of the generated radicals by virtue of their being generated in low concentration. Interestingly, lacking the presence of a Ni catalyst, aryl bromides were tolerated under the reaction conditions. Although the majority of examples used cyclohexylsilicates, other primary and secondary alkylsilicates gave excellent results with a variety of N-protected imines (Scheme 12) 15 examples: 43 – 73%).¹²

Scheme 12

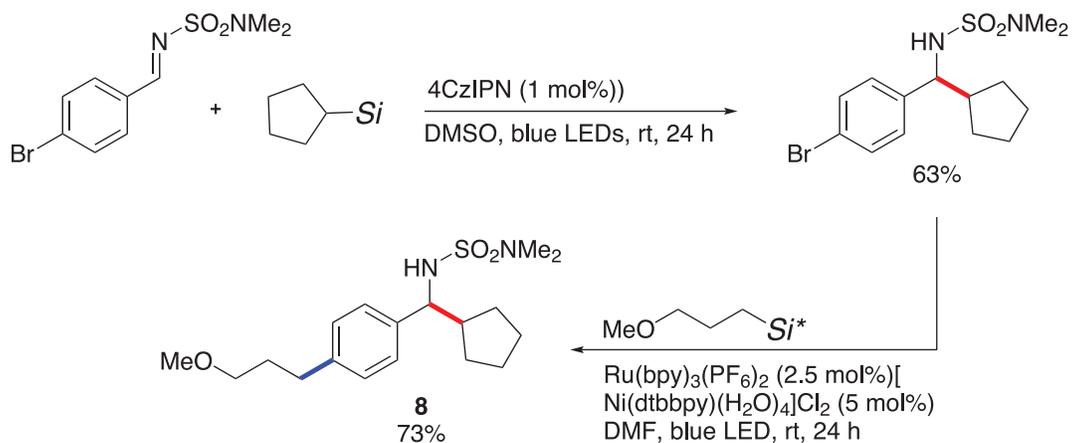


Photocatalyst	Conversion (%)
4CzIPN	>99
Ru(bpy) ₃ (PF ₆) ₂	94
[Ir(dFCF ₃ ppy) ₂ (bpy)]PF ₆	97
Ir(ppy) ₃	98
(MesAcr)ClO ₄	8
Eosin Y	74



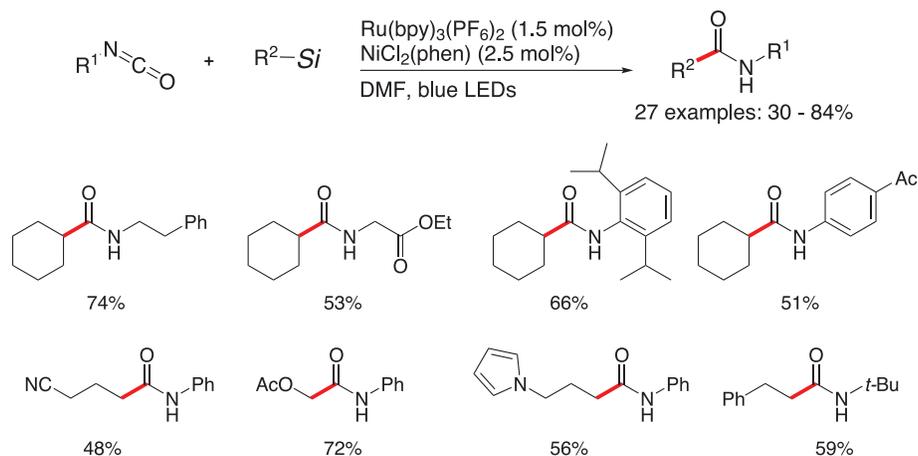
Taking advantage of the tolerance for an aryl bromide a two-step sequence of alkylation of an imine functionality followed by an alkylsilicate cross-coupling led to a 46% overall yield of **8** (Scheme 13).¹²

Scheme 13



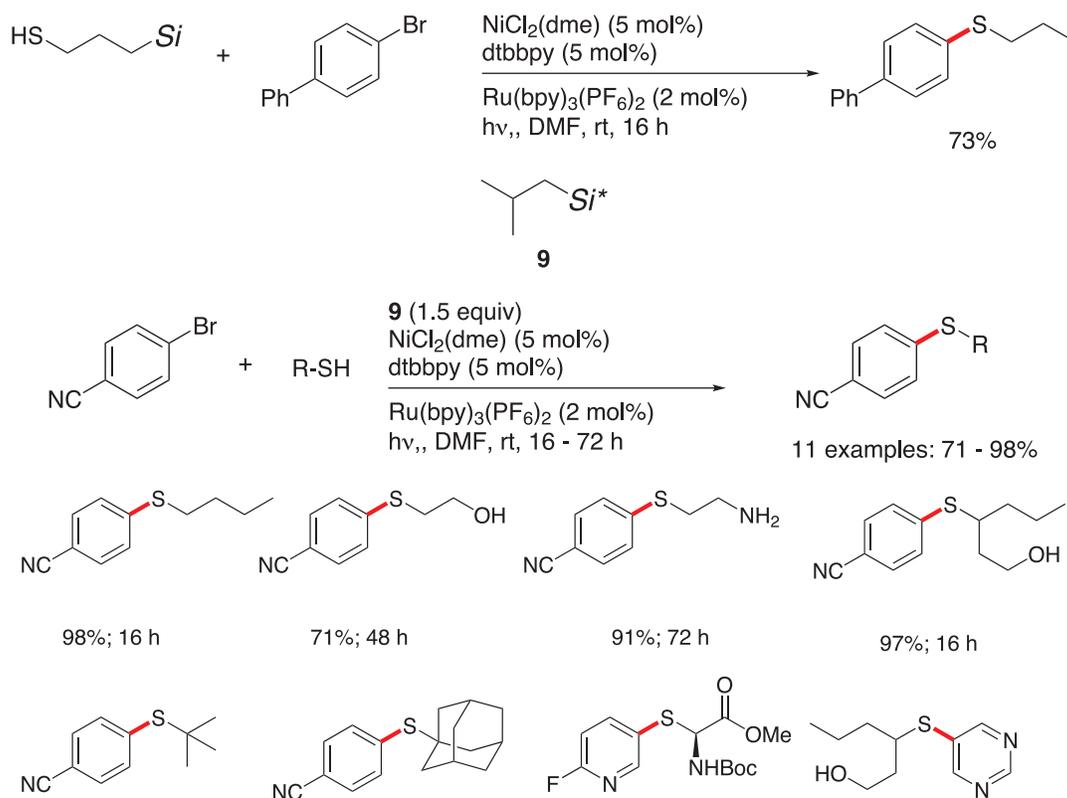
Alkylsilicates reacted with isocyanates under Ni/photoredox-catalyzed conditions to give excellent yields of the amidated alkyl group. The authors propose a Ni-isocyanate adduct as an intermediate in the reaction (Scheme 14).¹³

Scheme 14



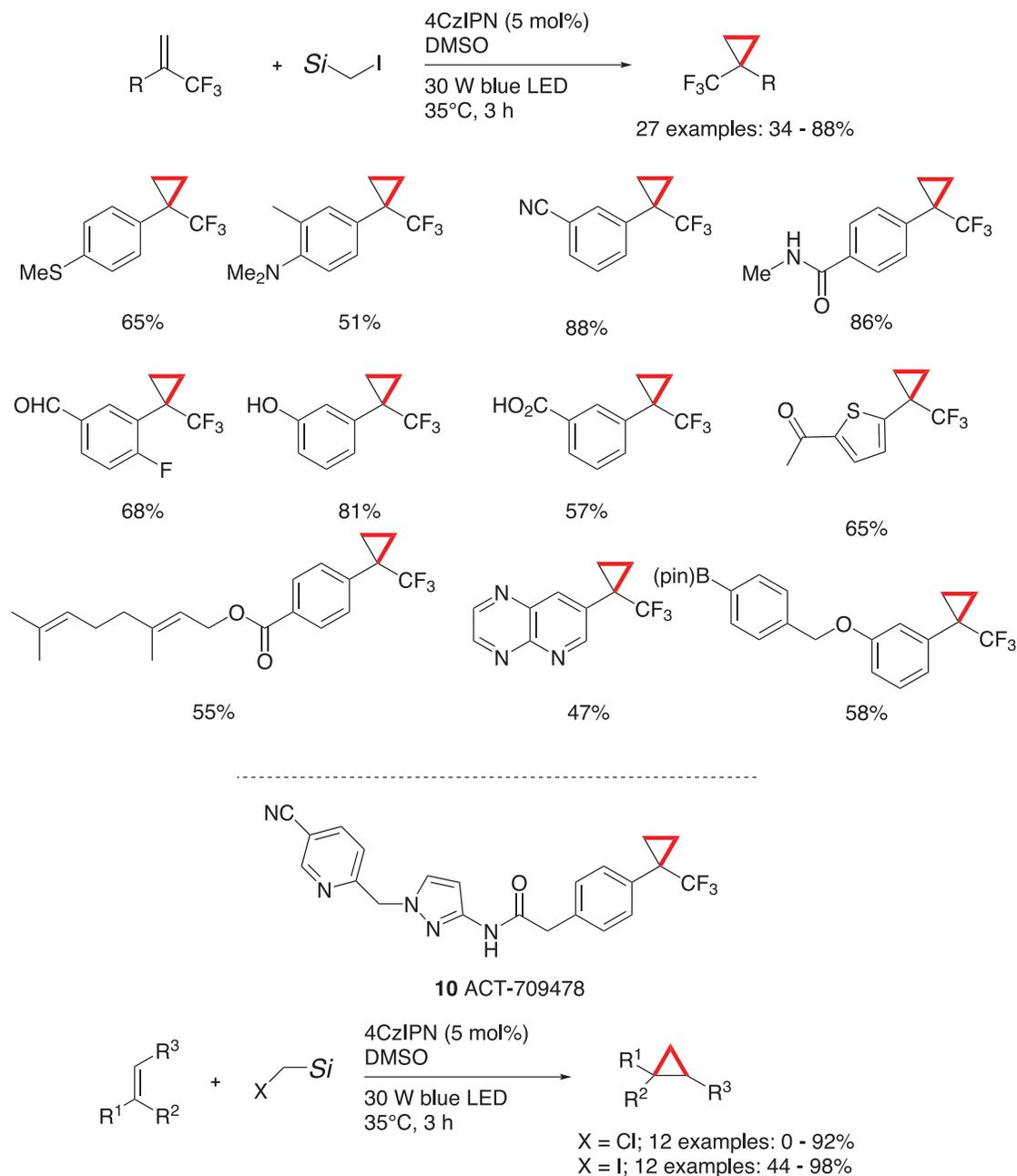
The nickel-catalyzed thioetherification of alkylsilicates wherein the initially generated alkyl radical converts a thiol to the thiyl radical, which then couples with a (het)aryl bromide was reported by the Molander group. Primary, secondary as well as tertiary thiols were all found to react well. This highly useful reaction was serendipitously discovered when the $\text{sp}^3\text{-sp}^2$ cross-coupling of 3-mercaptopropylsilicate with 4-phenyl-1-bromobenzene was attempted and 4-phenyl-1-propylthiobenzene was isolated rather than the expected 4-phenylphenylpropylthiol. Although this proved to be a useful entry into various propylthioaromatics and propylthioheteroaromatics (19 examples: 0 – 97%), it proved to be more general to employ the isobutylsilicate **9** in conjunction with different thiols to thioalkylate aryl and heteroaryl bromides (Scheme 15).¹⁴

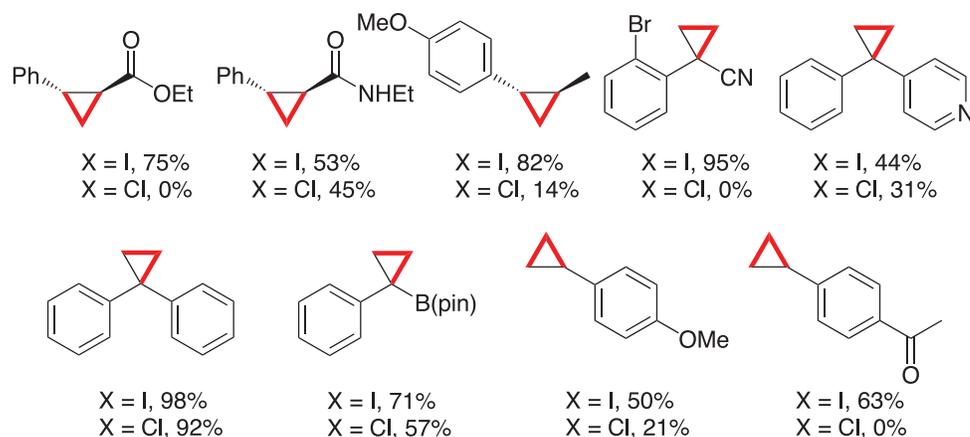
Scheme 15



Triethylammonium bis(catecholato)iodomethylsilicate, preparable on multigram scale, reacted under photoredox conditions with olefins to provide the corresponding cyclopropanes in high yields. The reaction conditions avoid many of the undesirable aspects of other cyclopropanation protocols. The method is safe, scalable, and lacks the need for strong bases and low temperatures, and has excellent functional group tolerance.¹⁵ An investigation of the role of the halogen in three halomethylsilicates revealed the advantages of the iodomethylsilicate. An initial emphasis was placed on the preparation of trifluoromethyl-substituted cyclopropanes due to the interest in trifluoromethyl pharmacophores such as the calcium channel blocker *ACT-709478* **10**.¹⁶ Under similar conditions the chloromethylsilicate reacted with various olefins to give the cyclopropane in yields ranging from 0 to 92% compared with the iodomethylsilicate with yields of 44 to 98% (Scheme 16).

Scheme 16

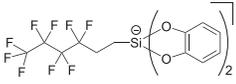
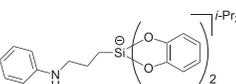
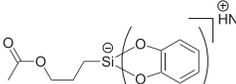
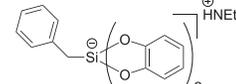
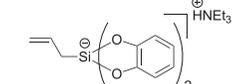
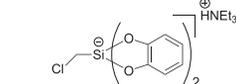
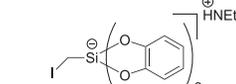
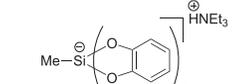
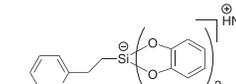




References:

- Lovering, F.; Bikker, J.; Humblet, C. Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem.* **2009**, *52* (21), 6752–6756. <https://doi.org/10.1021/jm901241e>.
- Tellis, J. C.; Kelly, C. B.; Primer, D. N.; Jouffroy, M.; Patel, N. R.; Molander, G. A. Single-Electron Transmetalation via Photoredox/Nickel Dual Catalysis: Unlocking a New Paradigm for Sp³–Sp² Cross-Coupling. *Acc. Chem. Res.* **2016**, *49* (7), 1429–1439. <https://doi.org/10.1021/acs.accounts.6b00214>.
- Jouffroy, M.; Primer, D. N.; Molander, G. A. Base-Free Photoredox/Nickel Dual-Catalytic Cross-Coupling of Ammonium Alkylsilicates. *J. Am. Chem. Soc.* **2016**, *138* (2), 475–478. <https://doi.org/10.1021/jacs.5b10963>.
- Chenneberg, L.; Lévêque, C.; Corcé, V.; Baralle, A.; Goddard, J.-P.; Ollivier, C.; Fensterbank, L. Single-Electron-Transfer Oxidation of Trifluoroborates and Silicates with Organic Reagents: A Comparative Study. *Synlett* **2016**, *27* (05), 731–735. <https://doi.org/10.1055/s-0035-1561337>.
- Patel, N. R.; Kelly, C. B.; Jouffroy, M.; Molander, G. A. Engaging Alkenyl Halides with Alkylsilicates via Photoredox Dual Catalysis. *Org. Lett.* **2016**, *18* (4), 764–767. <https://doi.org/10.1021/acs.orglett.6b00024>.
- Raynor, K. D.; May, G. D.; Bandarage, U. K.; Boyd, M. J. Generation of Diversity Sets with High Sp³ Fraction Using the Photoredox Coupling of Organotrifluoroborates and Organosilicates with Heteroaryl/Aryl Bromides in Continuous Flow. *J. Org. Chem.* **2018**, *83* (3), 1551–1557. <https://doi.org/10.1021/acs.joc.7b02680>.
- Patel, N. R.; Molander, G. A. Phenol Derivatives as Coupling Partners with Alkylsilicates in Photoredox/Nickel Dual Catalysis. *J. Org. Chem.* **2016**, *81* (16), 7271–7275. <https://doi.org/10.1021/acs.joc.6b00800>.
- Lévêque, C.; Chenneberg, L.; Corcé, V.; Ollivier, C.; Fensterbank, L. Organic Photoredox Catalysis for the Oxidation of Silicates: Applications in Radical Synthesis and Dual Catalysis. *Chem. Commun.* **2016**, *52* (64), 9877–9880. <https://doi.org/10.1039/C6CC04636C>.
- Vara, B. A.; Jouffroy, M.; Molander, G. A. C(Sp³)–C(Sp²) Cross-Coupling of Alkylsilicates with Borylated Aryl Bromides – an Iterative Platform to Alkylated Aryl- and Heteroaryl Boronates. *Chem. Sci.* **2017**, *8* (1), 530–535. <https://doi.org/10.1039/C6SC03236B>.
- Lin, K.; Wiles, R. J.; Kelly, C. B.; Davies, G. H. M.; Molander, G. A. Haloselective Cross-Coupling via Ni/Photoredox Dual Catalysis. *ACS Catal.* **2017**, *7* (8), 5129–5133. <https://doi.org/10.1021/acscatal.7b01773>.
- Matsui, J. K.; Lang, S. B.; Heitz, D. R.; Molander, G. A. Photoredox-Mediated Routes to Radicals: The Value of Catalytic Radical Generation in Synthetic Methods Development. *ACS Catal.* **2017**, *7* (4), 2563–2575. <https://doi.org/10.1021/acscatal.7b00094>.
- Patel, N. R.; Kelly, C. B.; Siegenfeld, A. P.; Molander, G. A. Mild, Redox-Neutral Alkylation of Imines Enabled by an Organic Photocatalyst. *ACS Catal.* **2017**, *7* (3), 1766–1770. <https://doi.org/10.1021/acscatal.6b03665>.
- Zheng, S.; Primer, D. N.; Molander, G. A. Nickel/Photoredox-Catalyzed Amidation via Alkylsilicates and Isocyanates. *ACS Catal.* **2017**, *7* (11), 7957–7961. <https://doi.org/10.1021/acscatal.7b02795>.
- Jouffroy, M.; Kelly, C. B.; Molander, G. A. Thioetherification via Photoredox/Nickel Dual Catalysis. *Org. Lett.* **2016**, *18* (4), 876–879. <https://doi.org/10.1021/acs.orglett.6b00208>.
- Phelan, J. P.; Lang, S. B.; Compton, J. S.; Kelly, C. B.; Dykstra, R.; Gutierrez, O.; Molander, G. A. Redox-Neutral Photocatalytic Cyclopropanation via Radical/Polar Crossover. *J. Am. Chem. Soc.* **2018**, *140* (25), 8037–8047. <https://doi.org/10.1021/jacs.8b05243>.
- Bezençon, O.; Heidmann, B.; Siegrist, R.; Stamm, S.; Richard, S.; Pozzi, D.; Corminboeuf, O.; Roch, C.; Kessler, M.; Ertel, E. A.; et al. Discovery of a Potent, Selective T-Type Calcium Channel Blocker as a Drug Candidate for the Treatment of Generalized Epilepsies. *J. Med. Chem.* **2017**, *60* (23), 9769–9789. <https://doi.org/10.1021/acs.jmedchem.7b01236>.

Alkylsilicates

Name	MW	bp °C/mm (mp)	
SID3533.4 DIISOPROPYLAMMONIUM NONAFLUOROHEXYLBIS(CATECHOLATO)SILICATE $C_{24}H_{28}NO_4F_9Si$	593.55	180 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate	HMIS: 2-1-1-X	Package sizes 10g 50g	
SID3533.7 DIISOPROPYLAMMONIUM 3-PHENYLAMINOPROPYL BIS(CATECHOLATO)SILICATE $C_{27}H_{38}N_2O_4Si$	480.67	137-142 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate 1844886-91-4 / 123-91-1	HMIS: 2-1-1-X	Package sizes 10g 50g	
SIT8197.0 TRIETHYLAMMONIUM 3-ACETOXYPROPYLBIS(CATECHOLATO)SILICATE $C_{32}H_{33}NO_5Si$	539.69	84-90 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate	HMIS: 2-1-1-X	Package sizes 10g 50g	
SIT8199.0 TRIETHYLAMMONIUM BENZYLBI(CATECHOLATO)SILICATE $C_{25}H_{31}NO_4Si$	437.60	112-120 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate	HMIS: 2-1-1-X	Package sizes 10g 50g	
SIT8201.0 TRIETHYLAMMONIUM BIS(CATECHOLATO)ALLYLSILICATE $C_{21}H_{25}NO_4Si$	383.51	130 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate	HMIS: 2-1-1-X	Package sizes 10g 50g	
SIT8202.0 TRIETHYLAMMONIUM CHLOROMETHYLBIS(CATECHOLATO)SILICATE $C_{19}H_{26}ClO_4NSi$	395.95	103-109 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate 1844886-87-8	HMIS: 2-1-1-X	Package sizes 10g 50g	
SIT8203.0 TRIETHYLAMMONIUM IODOMETHYL BIS(CATECHOLATO)SILICATE $C_{19}H_{26}NO_4Si$	487.40	125 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate	HMIS: 2-1-1-X	Package sizes 10g 50g	
SIT8204.0 TRIETHYLAMMONIUM METHYLBIS(CATECHOLATO)SILICATE $C_{19}H_{27}NO_4Si$	361.51	118 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate 1843232-66-5	HMIS: 2-1-1-X	Package sizes 10g 50g	
SIT8205.0 TRIETHYLAMMONIUM 2-(2-PYRIDYLETHYL)BIS(CATECHOLATO)SILICATE $C_{25}H_{32}N_2O_4Si$	438.61	160-164 °C (m.p.)	
 HYDROLYTIC SENSITIVITY: 6: forms irreversible hydrate	HMIS: 2-1-1-X	Package sizes 10g 50g	



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