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Communication

Lewis Basic Salt-Promoted Organosilane Coupling Reactions with Aromatic Electrophiles

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ABSTRACT: Lewis basic salts promote benzyltrimethylsilane coupling with (hetero)aryl nitriles, sulfones, and chlorides as a new route to 1,1-diarylalkanes. This method combines the substrate modularity and selectivity characteristic of cross-coupling with the practicality of a base-promoted protocol. In addition, a Lewis base strategy enables a complementary scope to existing methods, employs stable and easily prepared organosilanes, and achieves selective arylation in the presence of acidic functional groups. The utility of this method is demonstrated by the synthesis of pharmaceutical analogues and its use in multicomponent reactions.

1,1-Diarylalkanes are valuable compounds often prepared by coupling functionalized benzylic reagents with aromatic electrophiles.[1] In practice, the benzylic coupling partner and mechanism for achieving C−C bond formation define the scope and suitability of a given method. A widely used strategy is transition metal-catalyzed coupling of aryl (pseudo)halides with benzyl magnesium, zinc, and boron compounds.[2,3] This approach enables robust and predictable reactivity often at the expense of using reactive benzylic reagents prepared *in situ*. Significant effort has therefore been focused on alternative coupling partners and strategies to increase the efficiency and scope of 1,1-diarylalkane synthesis.[1,4−6]

Benzylic deprotonation represents one such attractive strategy that generates carbanion intermediates for metal-catalyzed[7] and catalyst-free[8] reactions with aryl electrophiles (Figure 1, left). Direct deprotonative arylation is perhaps ideal, as no catalyst is needed and only inexpensive reagents are used. However, this approach often leads to multiarylation side products and typically requires acidic pronucleophiles such as diarylmethanes.[8] Deprotonative activation also limits the coupling scope to relatively simple substrates in which the most acidic proton is at the desired benzylic position.

We sought a new benzylic arylation method that blends the modularity and selectivity of cross-coupling with the practicality of a base-promoted protocol. This drew our attention toward Lewis base activation of Lewis acidic benzyl compounds, an underdeveloped approach for aryl Csp^2−Csp^3 coupling.[9] In this regard, benzyltrimethylsilanes could be ideal coupling partners as they are air stable, nonhygroscopic, and easily accessed in great diversity.[10] Furthermore, distinct synthetic routes are available to complex benzyltrimethylsilanes that cannot be used to access analogous organometallic reagents.[11] To date, the high stability of benzyltrimethylsilanes has rendered them unreactive in metal-catalyzed cross-coupling,[12] and thus their use in arylation reactions is limited.[13] More specialized silanes are required to overcome this challenge in conjunction with Pd- and metallaphotoredox-catalyzed methodology (Figure 1, right).[14]

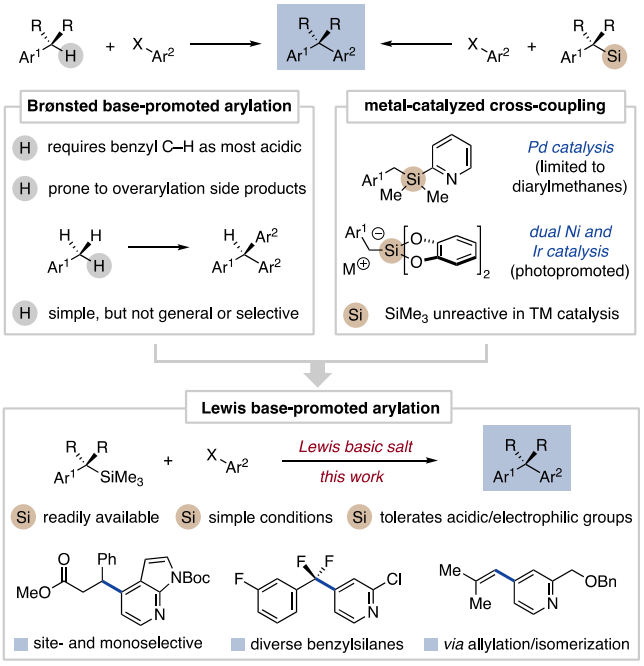

Figure 1. Background and motivation for Lewis base-promoted aryl coupling reactions of organotrimethylsilanes.

We herein report that Lewis basic salts promote the direct coupling of benzyltrimethylsilanes to a range of aromatic electrophiles (Figure 1, bottom). Benzylic arylation outcompetes potential anionic side reactions to enable monoselective coupling in the presence of acidic and electrophilic

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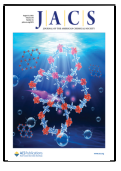

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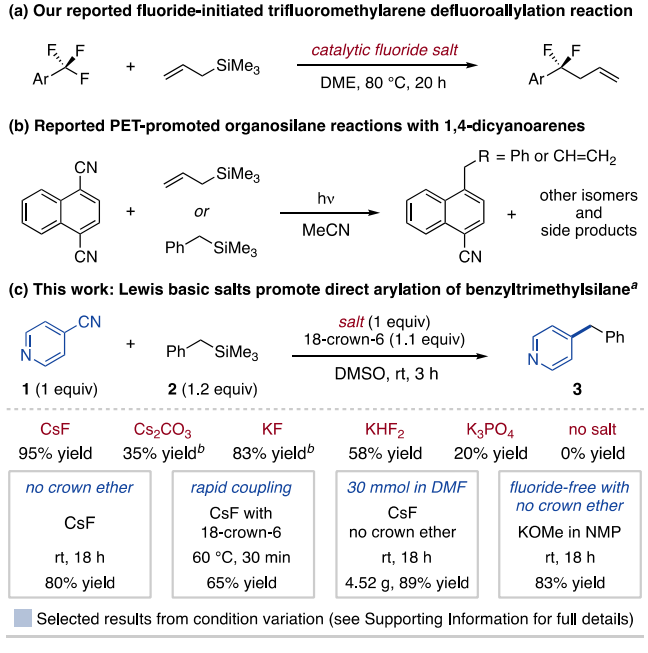
functional groups. This strategy can be extended to other organosilanes and reaction sequences, including the tandem arylation/isomerization of allylsilanes as a new route to alkenyl arenes. Thus, Lewis base-promoted arylation provides a practical coupling protocol with a reaction scope that complements established methods.

We recently reported the monoselective defluoroallylation of trifluoromethylarenes enabled by fluoride activation of allyltrimethylsilanes (Scheme 1a).[15] This reaction is proposed to operate through an anionic allyl intermediate that undergoes single electron transfer (SET) to the trifluoromethylarene, leading to C−F bond cleavage and allylation of the resulting difluorobenzylic radical. This sequence has similarities to photoinduced electron transfer (PET) allylation of 1,4-dicyanoarenes using allyltrimethylsilane, namely SET prior to C−C bond formation.[16] Benzyltrimethylsilane has also been examined in PET studies, although these reactions suffer from low regioselectivity and side product formation while requiring use of ultraviolet light (Scheme 1b).[16a,17] On the basis of these precedents, we hypothesized Lewis base activation of organotrimethylsilanes could promote their direct coupling with aromatic electrophiles beyond trifluoromethylarenes.

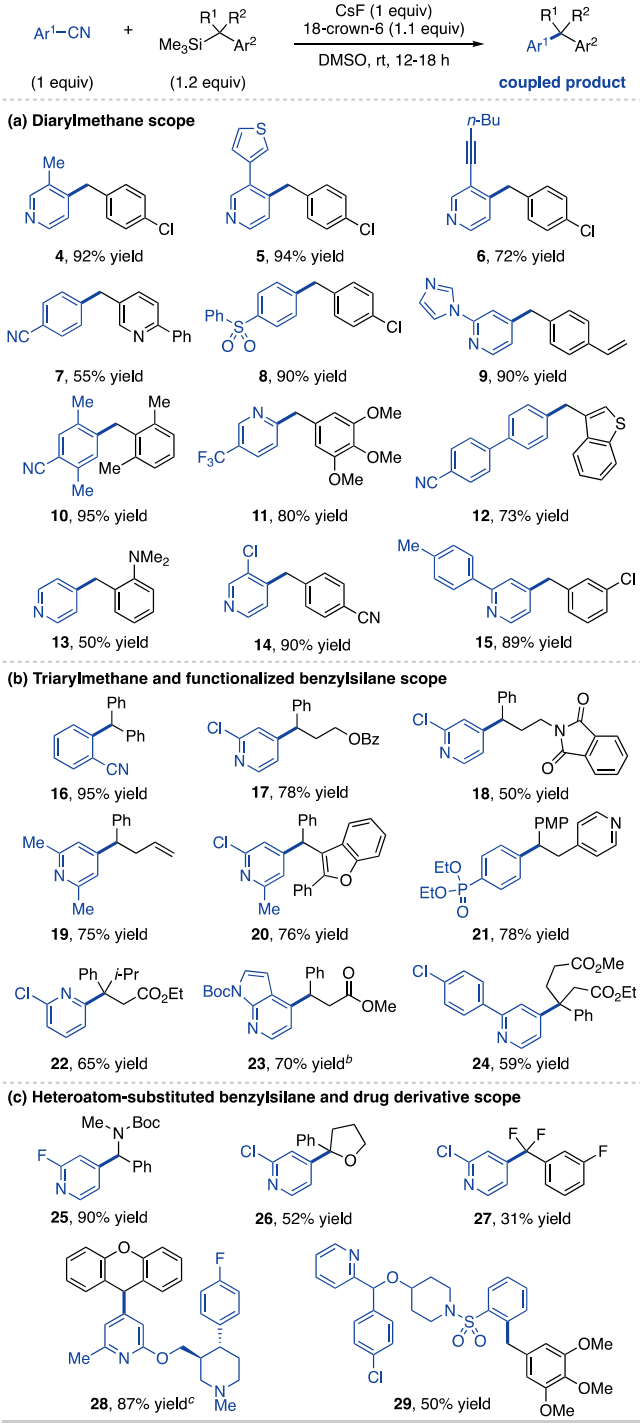
Scheme 1. Organosilane Reactions with Aryl Electrophiles and Development of Base-Promoted Arylation[a]



[a]Yields determined by ^{1}H NMR spectroscopy; 18-crown-6 added as a 1 M solution in THF. 18 h time for salts other than CsF. [b]Yields improve to 57% and 84% at 100 °C without 18-crown-6 for Cs_2CO_3 and KF, respectively.

To test this hypothesis, we examined the reaction of 4-cyanopyridine (**1**) with benzyltrimethylsilane (**2**) and found 18-crown-6-ligated cesium fluoride promotes monoselective coupling in 3 h at room temperature (rt) in DMSO (95% yield, Scheme 1c). Less basic anions, including carbonate, bifluoride, and phosphate salts, promote arylation in moderate yields. Conditions in the boxes of Scheme 1c show the ability to adjust reaction parameters depending on priority, ranging from the use of fluoride-free salts without 18-crown-6 to short reaction times or large reaction scale.

Table 1. Product Scope Using Cyanoarene Electrophiles[a]



[a]Isolated yields from reactions using 1.0 mmol of cyanoarene; 18-crown-6 added as a 1 M solution in THF. [b]1.5 equiv of silane. [c]2.0 equiv of silane.

Table 1 contains a product scope for benzyltrimethylsilane coupling with cyanoarenes using CsF and 18-crown-6 in DMSO. Primary, secondary, and tertiary benzylsilanes react with 2- and 4-cyanopyridines and electron-deficient cyanobenzenes (Table 1a,b). The products feature redox-active and electrophilic aryl substituents such as alkynes (**6**), styrenes (**9**), nitriles (**7**, **10**, **12**, **16**), sulfones (**8**), trifluoromethyl groups (**11**), and activated halides (**17**, **18**, **20**, **22**, and **25**–**27**).

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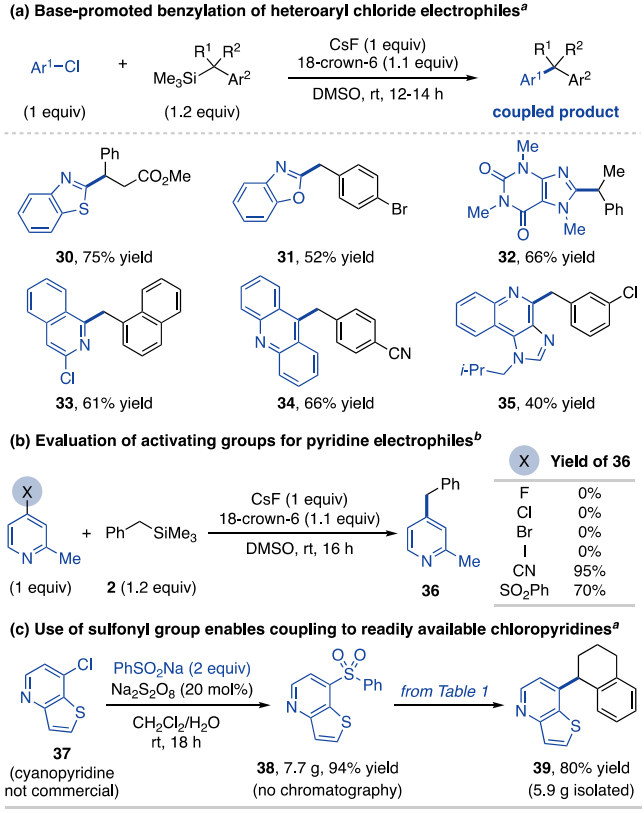
Acidic and electrophilic functional groups, including alkyl benzoates (**17**), phthalimides (**18**), alkenes (**19**), alkylpyridines (**19**–**21**, **28**), and esters (**22**–**24**) are also tolerated. Table 1c shows products of α-heteroatom benzylsilanes (**25**–**27**) and with paroxetine (**28**) and bepotastine (**29**) drug substructures. Product **27**, derived from an α,α-difluorobenzyltrimethylsilane prepared *via* trifluoromethylarene defluorosilylation, illustrates a benzylic coupling partner unique to this method.[11a,18] In sum, the scope features substitution patterns and functionalities that are difficult to access or not tolerated in alternative arylation strategies.

We next examined aryl electrophiles that do not generate cyanide byproducts (Scheme 2a). 2-Chloro-1,3-azoles are effective coupling partners (**30**–**32**), as are chlorides with extended π-systems, such as 1,3-dichloroisoquinoline (**33**), 9-chloroacridine (**34**), and the 2-chloroquinoline derivative of the antitumor drug imiquimod (**35**). Although 4-halopyridines do not react under these conditions, 4-sulfonylpyridines provide good yields (Scheme 2b).[19] To show the benefits of this finding, 4-chloropyridine **37**, for which the 4-cyano congener is not commercially available, was converted to sulfone **38** on a multigram scale without chromatography (Scheme 2c).[20] Benzylsilane coupling to **38** under the standard conditions without crown ether yielded 5.9 g of diarylalkane **39**. Thus, base-promoted benzylation is applicable to heteroaryl halides either directly or after sulfonyl group installation.

Scheme 2. Expansion of Aryl Electrophile Scope[a]



[a]Isolated product yields. [b]Yields determined by ^{1}H NMR spectroscopy of crude reaction mixtures. 18-Crown-6 added as a 1 M solution in THF.

This method can facilitate access to 1,1-diarylalkane compound libraries from abundantly available cyano- and chloroarenes. We selected the antihistamine chlorpheniramine to demonstrate this concept, for which the corresponding benzylsilane precursor **40** was readily prepared on 75 mmol scale (Figure 2).[21] Coupling of **40** with eight arene electrophiles generated diverse chlorpheniramine analogues, including trifluoromethyl- (**41**), methyl- (**42**), halo- (**43**, **44**) and aryl-substituted (**46**) variants. A 2-chloro-1,3-benzothiazole (**45**), a 4-cyanoquinazoline (**47**), and 4-chloroquinoline (**48**) also reacted to access greater structural variety.

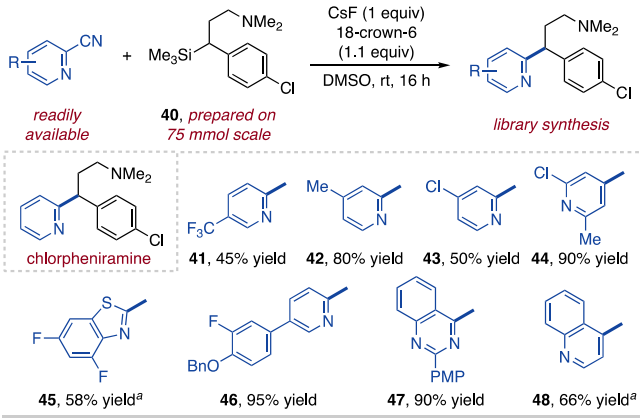


Figure 2. Synthesis of chlorpheniramine analogues. Yields shown are of purified products. 18-Crown-6 added as a 1 M solution in THF. [a]Chloroarene substrate used.

We next performed studies on the reaction selectivity for arylation over other anionic processes. When the aryl electrophile is removed from the standard conditions, toluene forms in 80% yield after 2 h (Scheme 3a).[22] This suggests benzylic protonation is a competing pathway with arylation; however, it is interesting to note that benzylation of 4-cyanopyridine occurs in solvents significantly more acidic than toluene (Scheme 3b).[23,24] Furthermore, separate reactions of two benzylsilane isomers (**50** and **52**) led to regiospecific arylation for the original position of the $-SiMe_3$ group (Scheme 3c). These results demonstrate arylation occurs preferentially over potential proton transfer events.[25] An important implication is that deprotonation of acidic diarylalkane products is minimized, thus preventing multiarylation side reactions. These findings also illustrate critical advantages of a Lewis base-promoted arylation method, as a Brønsted base approach would not generate benzylic carbanions in the presence of more acidic protons, and would likely lead to multiarylation and poor selectivities in substrates with multiple benzylic positions.[26]

To explain the high arylation selectivity, we propose an anionic benzylic intermediate[25] undergoes rapid aromatic substitution *via* a polar or SET-based mechanism (Figure 3).[27] The SET mechanism is the base-promoted analogous pathway to PET reactions of organosilanes with 1,4-dicyanoarenes.[17,28,29] A polar process is also plausible as cyano- and sulfonylarenes can participate in typical addition–elimination substitution reactions.[30] Distinguishing between these processes is known to be challenging for addition of anionic reagents to similar electrophiles,[31,32] and we have made observations explainable by both pathways.[33] The coupling mode may also be substrate dependent, although arylation

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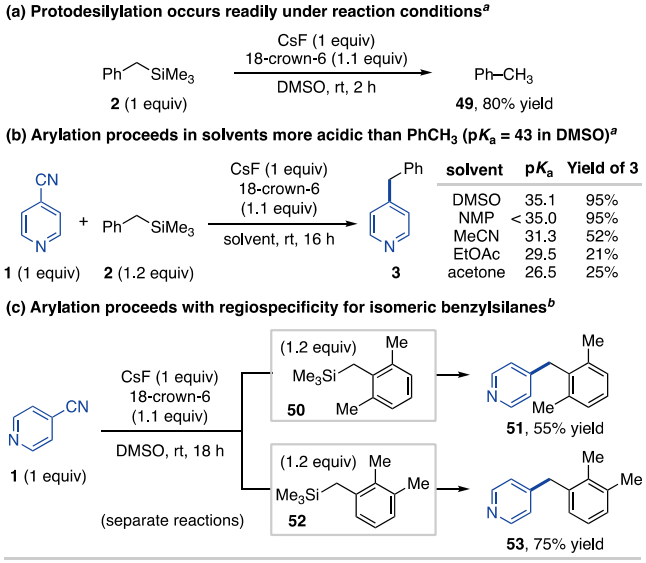
Scheme 3. Investigation of Benzylic Arylation Selectivity[a]



[a]Yields determined by ^{1}H NMR spectroscopy of crude reaction mixture. [b]Isolated product yields. 18-Crown-6 added as 1 M solution in THF.

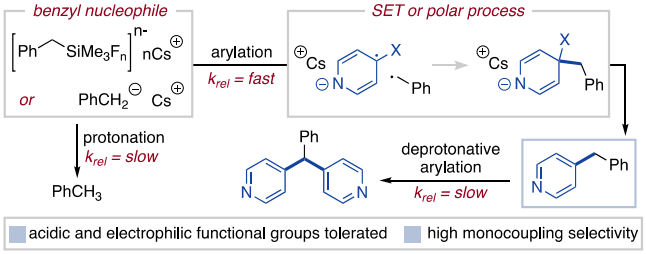


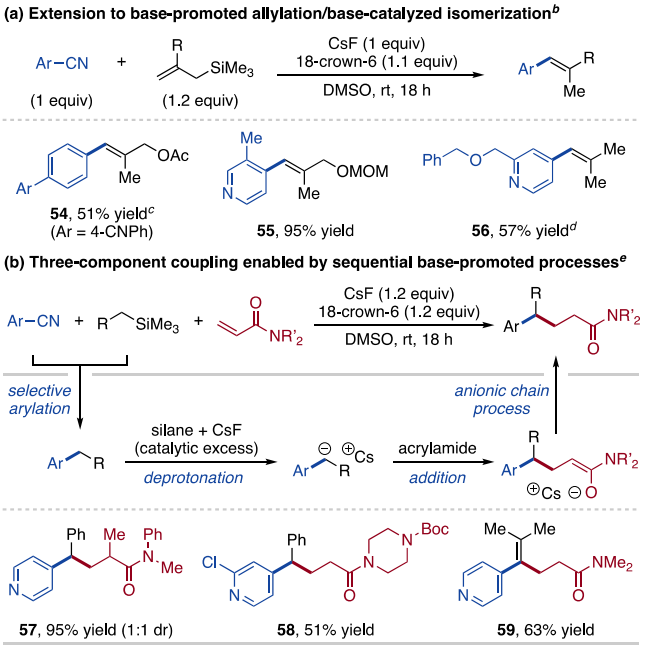
Figure 3. Potential pathways and rationale for selective arylation.

uniformly outcompetes other potential anionic side reactions.[34]

From these studies, we realized organosilane arylation could be incorporated into tandem base-promoted reaction sequences. First, we found allyltrimethylsilanes react to form allyl arene intermediates that undergo stereoselective isomerization to aryl alkenes **54**, **55**, and **56** (Scheme 4a).[35,36] Next, we targeted a three-component coupling process between organosilanes, aryl electrophiles, and Michael acceptors. We hypothesized selective benzylic arylation would occur and the remaining catalytic organosilane/fluoride combination could initiate a Michael addition reaction (Scheme 4b).[37] Thus, *γ*,*γ*-diaryl amides **57** and **58** can be prepared *via* this strategy. Using methallyltrimethylsilane, tetrasubstituted alkene **59** forms through three selective base-promoted processes (arylation, addition, and alkene isomerization).

In conclusion, Lewis basic salts provide a practical means of engaging benzyl- and allyltrimethylsilanes in aryl coupling reactions. This approach enables regio- and monoselective access to 1,1-diarylalkane and aryl alkene products with complementary scope to existing methods. The strategic application of multiple base-promoted processes also facilitates advanced coupling sequences, a prospect we continue to explore.

Scheme 4. Expanded Scope Using New Coupling Partners[a]



[a]Yields are of purified product; diastereoselectivities determined by ^{1}H NMR spectroscopy; 18-crown-6 added as 1 M solution in THF. [b]>10:1 alkene *E*:*Z* ratios observed. [c]Reaction performed at 60 °C. [d]Corresponding 4-phenylsulfonylpyridine used as substrate. [e]ArCN (1 equiv), organosilane (1.2 equiv) and acrylamide (1–2 equiv) used.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c05764.

Detailed experimental procedures, characterization data, and NMR spectra for all compounds (PDF)

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Notes

The authors declare no competing financial interest.

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