REPORT

ORGANIC CHEMISTRY

Arylation of hydrocarbons enabled by organosilicon reagents and weakly coordinating anions

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Over the past 80 years, phenyl cation intermediates have been implicated in a variety of C–H arylation reactions. Although these examples have inspired several theoretical and mechanistic studies, aryl cation equivalents have received limited attention in organic methodology. Their high-energy, promiscuous reactivity profiles have hampered applications in selective intermolecular processes. We report a reaction design that overcomes these challenges. Specifically, we found that β-silicon–stabilized aryl cation equivalents, generated via silylium-mediated fluoride activation, undergo insertion into sp^3 and sp^2 C–H bonds. This reaction manifold provides a framework for the catalytic arylation of hydrocarbons, including simple alkanes such as methane. This process uses low loadings of Earth-abundant initiators (1 to 5 mole percent) and occurs under mild conditions (30° to 100°C).

Since 1891, when Merling unknowingly prepared an aromatic tropylium ion (*1*), carbocations have played a substantial role in the development of organic chemistry as a field of scientific and practical endeavor (*2*). Conceptually, carbenium ions serve as retrons, guiding the design of retrosynthetic analyses and elucidating the selection of synthetic equivalents (*3*). Practically, carbocations are equally important, as stabilized variants are routinely generated and used in standard synthetic transformations (*4*). On the other hand, carbocations that are divalent, and/or are not stabilized by resonance donating groups or hyperconjugation, are not easily manipulated or used in routine transformations (*5*). Although exquisite fundamental studies of these more reactive species have revealed remarkable reactivity profiles (*6*), studies aimed at methodological advances in this area are rare (*7*, *8*). This is particularly true for phenyl cations. Their reactive nature has thwarted characterization in the condensed phase, and even their existence as reactive intermediates remains a matter of debate (*9*–*11*).

We sought to discover a phenyl cation equivalent that could be used in catalytic, intermolecular C–H arylation reactions. We were inspired by seminal reports of analogous reactivity over the past 80 years. In the 1930s, Mascarelli reported that the thermolysis of aryl diazonium salt **1** led to the formation of fluorene **2**, presumably via C–H insertion of a phenyl cation intermediate (Fig. 1A) (*12*). More recently, reports from Albini's group (*13*, *14*) suggested that photogenerated phenyl cations participate in intramolecular C–H insertion reactions; Siegel and co-workers (*15*, *16*) proposed the intermediacy of phenyl cations in the silylium-mediated intramolecular Friedel-Crafts reaction of aryl fluorides (Fig. 1B); and Reed and co-workers (*17*) presented evidence for incipient aryl cations, where the structure of a phenyl halonium salt of undecachlorinated monocarba-*closo*-dodecaborate anion (**3**; Fig. 1C) was elucidated by x-ray crystallography (*17*). Despite these fundamental breakthroughs, catalytic intermolecular reactions of phenyl cation equivalents have been elusive. Considering these seminal efforts, as well as the frontier molecular orbital analogy that can be made with singlet carbene species (*18*, *19*), we pursued the application of phenyl cation equivalents in catalytic, intermolecular C–H functionalization reactions such as those depicted in Fig. 1C.

We envisioned that β-silylated aryl fluorides (**4a**; Fig. 2A) would be particularly well suited as phenyl cation precursors for several reasons: (i) We anticipated that β-silicon stabilization would lower the barrier for fluoride abstraction and temper the σ-electrophilicity of the

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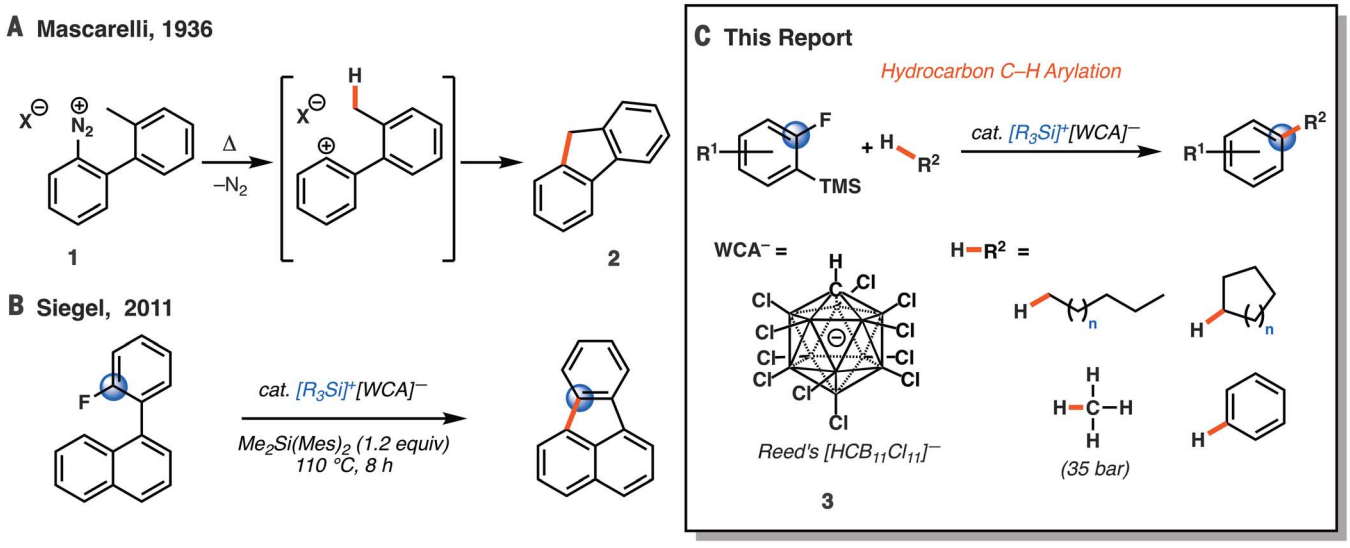


Fig. 1. Reactions involving putative phenyl cations. (**A**) Mascarelli's reaction (*12*). (**B**) Siegel's intramolecular Friedel-Crafts reaction of aryl fluorides (*15*). (**C**) Our dual C–F/C–H functionalization strategy. R = ethyl or triisopropyl; R^1 = aryl, alkyl, halide, or silyl ether; WCA, weakly coordinating anion; TMS, trimethylsilyl; Mes, mesityl; Me, methyl; cat., catalytic.

resulting phenyl cation equivalent **5** (*20*–*24*); (ii) we envisioned that silicon substitution would enhance the nucleophilicity of the arene π-system, perhaps improving the insertion reactivity of phenyl cation equivalent **5** (*25*); and (iii) we hypothesized that elimination of the β-silicon group from a reactive intermediate such as arenium **6** could regenerate the key reactive silicon species.

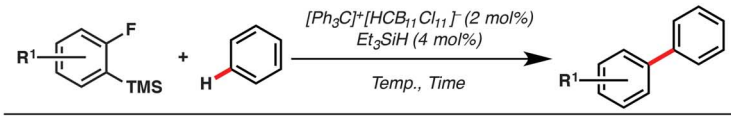
Taking into account these reaction design concepts, we envisioned the cationic chain process depicted in Fig. 2A. Here, a substoichiometric silylium-carborane initiator (*26*), generated via Bartlett-Condon-Schneider hydride transfer (*27*), could abstract a fluoride from fluoroarene **4a** to generate aryl cation equivalent **5** (Fig. 2A). Subsequent insertion into the hydrocarbon C–H bond would then yield β-silicon–stabilized Wheland intermediate **6**. Elimination of trimethylsilylium would then afford C–H arylation product **7**. This elementary step would generate the active trimethylsilylium-carborane salt that proceeds through the catalytic cycle (*28*).

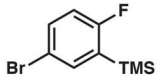
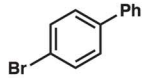
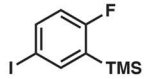
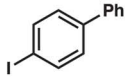
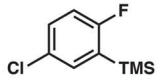
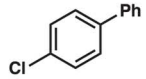
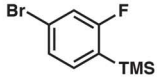
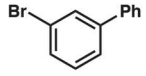
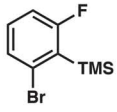
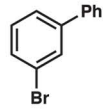
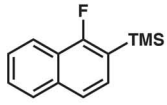
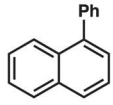
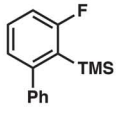
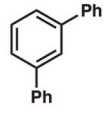
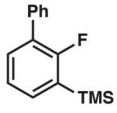
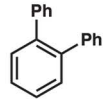
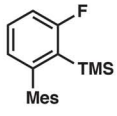
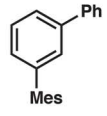
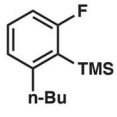
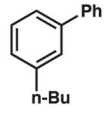
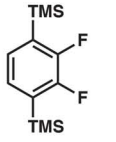
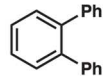
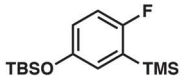
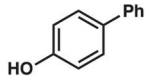
We report the successful execution of this methodological hypothesis, wherein a broad scope of β-silylated aryl fluorides are shown to be competent reagents for the arylation of unactivated sp^3 and sp^2 C–H bonds, including the characteristically inert bonds in methane (Fig. 1C). After a short examination of reaction conditions (table S1) (*29*), we found that exposure of fluoride **4a** to 1 mol % of $[Ph_3C]^+$ $[HCB_{11}Cl_{11}]^-$ and 2 mol % of triethylsilane in benzene solvent resulted in the facile formation of biphenyl (**7a**; Fig. 2B) in 55% yield at 30°C in 1 hour. Application of Siegel's intramolecular reaction conditions to fluorobenzene (**4b**; Fig. 2B) resulted only in trace product **7a**, and use of *meta*- and *para*-silylated aryl fluorides **4c** and **4d** did not result in product formation.

With this initial finding in hand, we investigated the scope of this arylation reaction. We were pleased to observe selective C–F functionalization in the presence of weaker carbon-halogen (C–X) bonds, similar to previous reports from Ozerov and co-workers (*30*). Specifically, entries 1 to 4 in Table 1 highlight the fluorophilicity of the silylium-carborane catalyst. In these cases, weaker C–X bonds that have less steric encumbrance than the C–F bond do not undergo ionization. This selectivity stands in stark contrast to many traditional reactions of aryl halides, where reactivity is often inversely proportional to bond dissociation energy (*31*, *32*). To further investigate this unusual selectivity and to separate β-silicon effects from fluorophilicity, we exposed (2-bromo-6-fluorophenyl)trimethylsilane (Table 1, entry 5) to our reaction conditions. Remarkably, *m*-bromobiphenyl was formed in good yield, supporting our claim of halide selectivity. In general, halide substitution was well tolerated.

Polycyclic aromatic fluorides (Table 1, entry 6) also were competent under the reaction conditions, as demonstrated by the formation of 1-phenylnaphthalene in 49% yield. Additionally, aryl and alkyl substitution (Table 1, entries 7 to 10) were tolerated under the reaction conditions,

Table 1. Scope of arylation reaction. Reactions were performed at 0.1 M fluoroarene in benzene solvent. *Yield determined by gas chromatography–flame ionization detector (GC-FID) using nonane as an internal standard. †Yield determined by NMR using an internal standard. ‡Isolated yield. TBS, *tert*-butyldimethylsilyl; *n*-Bu, butyl; Et, ethyl.



Entry	Substrate	Temp. (°C)	Time (hours)	Product	Yield (%)
1		60	1		56*
2		70	1		71†
3		70	9		47*
4		60	1		52*
5		60	1		77*
6		30	1		49‡
7		30	1		63*
8		70	36		45*
9		30	1		47‡
10		30	0.2		99†
11		60	36		36*
12		60	48		29‡

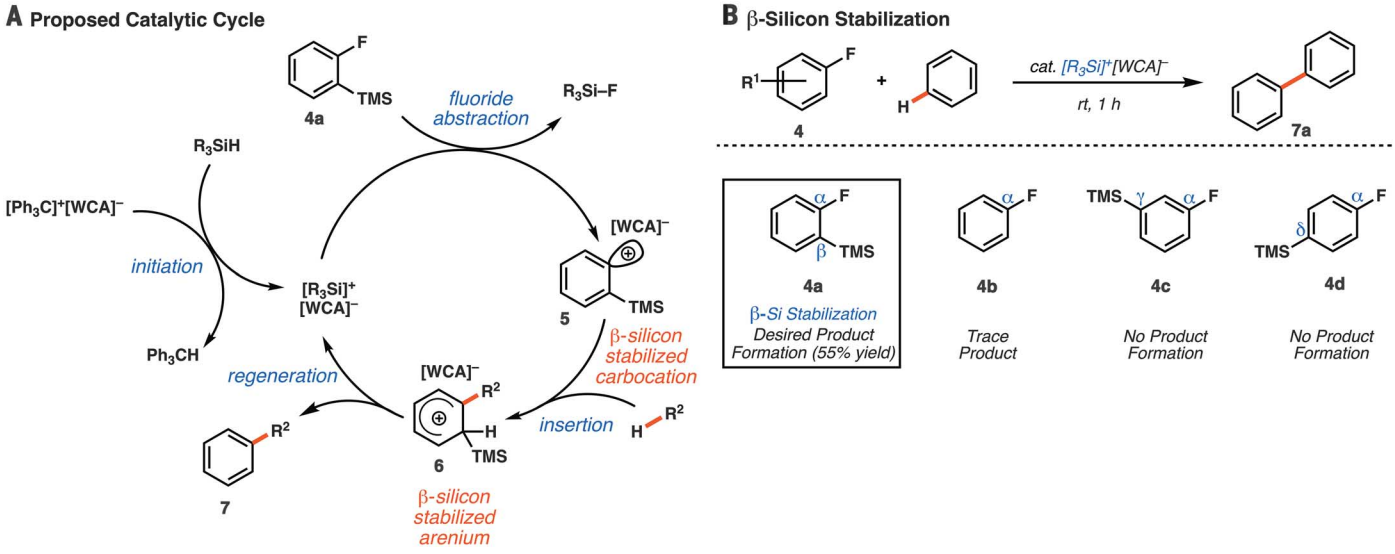
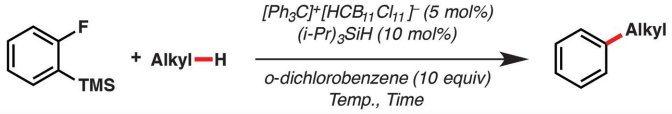
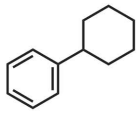
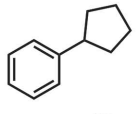
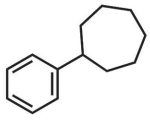
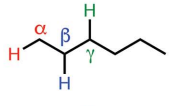
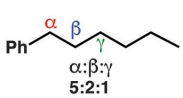
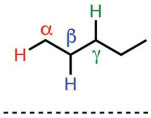
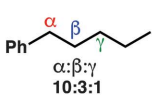


Fig. 2. Catalytic design. (**A**) Proposed catalytic cycle. (**B**) Initial investigation of aryl fluorides. Ph, phenyl; rt, room temperature.

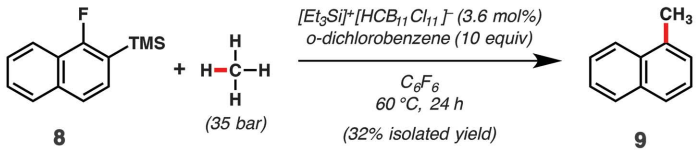
Table 2. sp³ C–H functionalization. Top: Arylation of cyclic and acyclic alkanes performed at 0.05 M fluoroarene in alkane solvent. Bottom: Arylation of methane performed at 0.1 M fluoroarene in C_6F_6 solvent. *Yield determined by GC-FID using nonane as an internal standard. †Yield determined by NMR using an internal standard. ‡Reaction was performed in the absence of *o*-dichlorobenzene. *i*-Pr, isopropyl.

Alkanes



Entry	Alkane	Temp. (°C)	Time (hours)	Product	Yield (%)
1		60	2		41*
2		70	1		54†
3		100	9		40†‡
4		60	8	 α:β:γ 5:2:1	40* α:β:γ 26:9:5
5		60	8	 α:β:γ 10:3:1	42* α:β:γ 30:10:2

Methane



providing phenylated aromatics in moderate to excellent yields (45 to 99%). Consecutive arylation of difluorides was also possible, as demonstrated by the formation of *o*-terphenyl (Table 1, entry 11), albeit in a diminished 36% yield. Finally, the presence of heteroatom donor substituents, typically incompatible with silylium catalysis (Table 1, entry 12), provided 29% yield of the desired phenol derivative. In cases where the yields were moderate, we observed several byproducts, including fluoroarenes resulting from protodesilylation of the starting materials (presumably resulting from highly acidic arenium intermediates) as well as products resulting from a second arylation event (*29*, *33*).

Throughout our scope studies, some general reactivity trends were apparent. Positional selectivity was preserved in all cases, including those with lower yields. Halide substituents required higher reaction temperatures, whereas alkyl and aryl substituents allowed faster, lower-temperature arylation. These observations are consistent with the intermediacy of a cationic aryl species.

Bolstered by these results, we began our investigation into the arylation of alkanes. After optimization of reaction conditions (table S2) (*29*), we found that cyclohexane could be phenylated by aryl fluoride **4a** in 41% yield (Table 2, entry 1). We were surprised to find that this alkane arylation reaction proceeded at 60°C in 2 hours. Likewise, cyclopentane underwent smooth arylation under similar conditions in 54% yield (Table 2, entry 2). Cycloheptane could also be arylated in 40% yield (Table 2, entry 3). With these results in hand, we set out to investigate reactivity with acyclic alkanes. We were pleased to find that *n*-hexane underwent arylation to yield all three phenylhexane isomers in 40% overall yield (Table 2, entry 4). This C–H arylation reaction displayed terminal selectivity, with an α:β:γ ratio of 5:2:1.

In a similar fashion, *n*-pentane also underwent terminal-selective arylation to yield phenylpentane isomers in 42% yield with a 10:3:1 ratio (Table 2, entry 5). In an earlier report, direct and terminal-selective arylation of saturated hydrocarbons required zeolite catalysts at >200°C and delivered <5% yield (*34*).

The terminal C–H bonds of alkanes, although kinetically more accessible, have higher bond dissociation energies (98 kcal/mol) than their internal counterparts (93 to 95 kcal/mol) (*35*). Given our ability to arylate the strongest of C–H bonds (Table 2, entries 4 and 5) and the long-standing interest in hydrocarbon gas functionalization (*36*, *37*), we became intrigued by the prospect of arylating methane gas (C–H bond dissociation energy ~105 kcal/mol) (*32*). Initial experiments were thwarted by deleterious arylation of solvent. After optimization (table S3) (*29*), we found that use of C_6F_6 solvent allowed for the arylation of methane in 32% yield at low temperatures (60°C) and synthetically relevant pressures (35 bar) (Table 2, lower panel). The conversion of naphthalene **8** to 1-methylnaphthalene **9** serves as a rare example of methane gas functionalization using main-group catalysis (*38*).

Several experiments were performed to probe the nature of the reactive intermediate. Arynes, as well as their transition metal complexes, have been shown to undergo C–H insertion reactions (*39*, *40*); however, intermolecular insertion into sp^3 C–H bonds has not been reported (*41*, *42*). The different products observed in Table 1, entries 1 versus 4 and 7 versus 8, which would presumably go through an identical aryne intermediate (**10**; Fig. 3A), suggest that an aryne intermediate is not active. Instead, these entries suggest that an electrophilic site is localized to the fluorine-bound carbon. As a further means of investigation, we prepared butyl derivative **11** (Fig. 3A). The intermediacy of aryne **10** (R = butyl) would lead to the formation of biaryl **14** from both fluorides **11** and **13**. However, unlike the arylation reactivity observed in Table 1, entry 10 (i.e., **13** → **14**), compound **14** was not observed in the reaction of butyl derivative **11** (Fig. 3A). Instead, we observed rapid intramolecular C–H insertion to form 1-methylindane (**12**) in 35% yield (43% after optimization) (*29*).

These observations do not rule out an unsymmetrical silylium-dicarbenoid species analogous to the silver complex proposed by Lee and co-workers (*40*). However, it is clear that the reactive intermediate is not an aryne, as C–C bond formation occurs at the C–F carbon exclusively. Furthermore, although we draw the reactive intermediate **5** (Fig. 2A) as a formal carbocation, it is possible that a free phenyl cation is not operative. As one of several mechanistic possibilities, the C–H insertion event may occur through reactive aryl cation-halide adducts that form reversibly under the reaction conditions. One could envision a species analogous to the unreactive

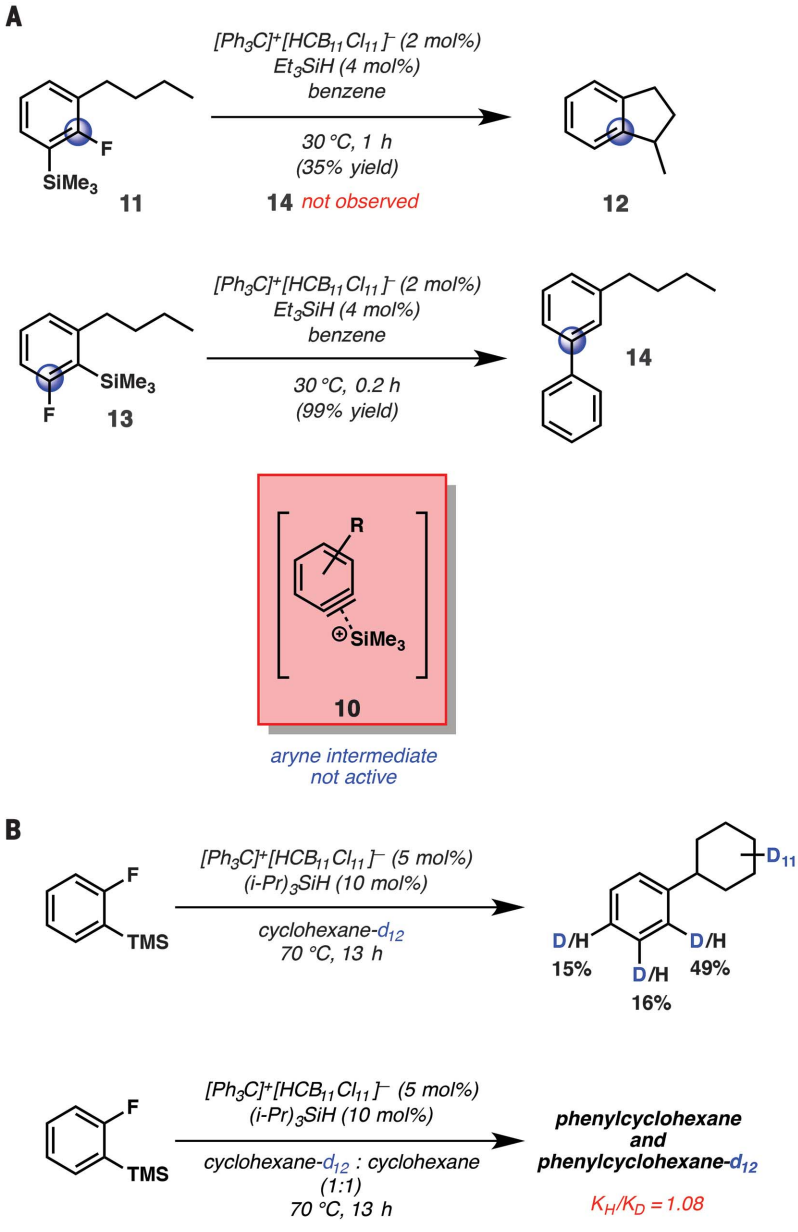


Fig. 3. Mechanistic studies. (**A**) Comparison of products obtained from exposure of isomers **11** and **13** to standard reaction conditions. (**B**) Isotopic labeling studies that support a concerted insertion mechanism and intermolecular competition experiment to determine the presence of a kinetic isotope effect, ruling out C–H insertion as rate-determining step.

phenyl chloronium salt described in (*17*), wherein the β-trimethylsilyl group enhances reactivity through steric buttressing or electronic perturbation. Additionally, a trialkylsilyl phenyl fluoronium salt, resulting from the interaction between the fluoroarene substrate and a cationic silicon species, could be operative (fig. S51).

To investigate the nature of the key C–H insertion event, we carried out isotopic labeling studies. Using cyclohexane-d_{12}, we observed formation of phenylcyclohexane-d_{12} with an overall deuterium incorporation of 80% (Fig. 3B). Although deuterium was incorporated primarily at the *ortho*-positions, enrichment of the *meta*- and *para*-positions was also observed. We attribute the mixture of D_{12} isomers to rapid hydride shifts of Wheland intermediate **6** (Fig. 2A) (*43*). However, the lack of apparent deuterium crossover (i.e., the presence of $D_{12\pm n}$ products) supports a concerted C–H insertion process. Furthermore, a competition experiment using a 1:1 mixture of C_6D_{12} and C_6H_{12} provided a kinetic isotope effect of 1.08 (Fig. 3B). This intermolecular competition experiment rules out C–H insertion as the rate-determining step (*44*).

Our work constitutes a methodology for generating aryl cation equivalents that engage in

the intermolecular C–H arylation of arenes and alkanes through main-group catalysis. Reagents were designed wherein β-silicon substitution facilitated C–F bond activation and catalyst turnover. Furthermore, we found that the hyperfluorophilicity of the silylium-carborane catalyst mediates selective functionalization of C–F bonds in the presence of weaker C–X bonds. This selectivity trend is complementary to transition metal–catalyzed cross-coupling reactions and traditional nucleophilic substitution reactions. More fundamentally, this work represents an exciting paradigm in catalysis, where strong bonds (C–F and C–H) are directly engaged in C–C bond-forming cross-coupling reactions.

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/355/6332/1403/suppl/DC1
Materials and Methods
Figs. S1 to S51
Tables S1 to S3
References (*45*–*69*)
Spectral Data

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Arylation of hydrocarbons enabled by organosilicon reagents and weakly coordinating anions

Brian Shao, Alex L. Bagdasarian, Stasik Popov and Hosea M. Nelson (March 30, 2017)

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Editor's Summary

Turning benzene into a C–H bond cleaver

Ask chemists for the best way to break a strong bond, and they will tell you to make an even stronger one. Shao *et al.* applied this principle by using silicon-fluorine bonds to break carbon-hydrogen bonds. They prepared benzene rings with adjacent fluorine and silicon substituents. Then they used a little extra activated silicon, paired with a carborane, to prime a cycle that draws away the fluorine to produce a cation-like aryl intermediate. This intermediate can then slice through the t ypically inert C–H bonds in alkanes, including methane. The alkylated rings go on to release their silicon, which keeps the process going.

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