ORGANOMETALLICS

Organocalcium-mediated nucleophilic alkylation of benzene

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The electrophilic aromatic substitution of a C–H bond of benzene is one of the archetypal transformations of organic chemistry. In contrast, the electron-rich π-system of benzene is highly resistant to reactions with electron-rich and negatively charged organic nucleophiles. Here, we report that this previously insurmountable electronic repulsion may be overcome through the use of sufficiently potent organocalcium nucleophiles. Calcium *n*-alkyl derivatives—synthesized by reaction of ethene, but-1-ene, and hex-1-ene with a dimeric calcium hydride—react with protio and deutero benzene at 60°C through nucleophilic substitution of an aromatic C–D/H bond. These reactions produce the *n*-alkyl benzenes with regeneration of the calcium hydride. Density functional theory calculations implicate an unstabilized Meisenheimer complex in the C–H activation transition state.

The Friedel–Crafts (F-C) reaction has been one of the cornerstones of organic and industrial synthetic chemistry for 140 years (*1*, *2*). In its most fundamental manifestation, one of the hydrogen atoms of benzene is replaced by the alkyl component of an alkyl halide, R–Hal (Hal = Cl, Br, or I) (Fig. 1A). Typically, a Lewis acid catalyst such as $FeCl_3$ or $AlCl_3$ binds the halide to transform the alkyl carbon into a positively charged carbenium ion, which is a sufficiently electron-poor (electrophilic) target for the comparatively electron-rich (nucleophilic) aromatic π-system of benzene to attack (*3*). This process generates a new C–C bond via a Wheland intermediate in which the resultant positive charge is stabilized through its delocalization around the remaining five carbon atoms (*4*). Substitution is then effected through loss of a proton and the generation of the relevant hydrogen halide.

Despite its importance, F-C alkylation suffers from some serious limitations. Alkylbenzenes are generally more reactive to electrophilic substitution than benzene itself, and F-C conditions commonly result in over-alkylation (*5*). Primary carbenium ions are also prone to rearrangement to more stable secondary or tertiary carbenium ions so that, for example, F-C alkylation of benzene with *n*-propyl electrophiles provides primarily isopropylbenzene (cumene) (*5*, *6*).

These issues may be potentially circumvented through the alternative pathway of nucleophilic aromatic substitution. The substitution of a C–H bond in unsubstituted benzene by an organic nucleophile, however, is very much more disfavored. The electron-rich π-system, which renders benzene so susceptible to attack by electrophiles, tends to repel approaching nucleophiles, whereas the 6π-electron system is substantially destabilized through the formal addition of two extra electrons. Although these factors may be overcome through the installation of sufficiently powerful electron-withdrawing substituents (such as nitro, NO_2^-), whereupon nucleophilic attack provides Meisenheimer or σ^H-adduct intermediates (Fig. 1B) (*7*), the departure of the hydride anion invariably requires the addition of a potent external oxidant (*8*, *9*). The direct nucleophilic alkylation of benzene (Fig. 1C) has not been achieved, therefore, primarily for the lack of a sufficiently potent alkyl nucleophile.

We have a longstanding interest in the development and use of highly polar organometallic derivatives of the heavier alkaline earth (AE = Ca, Sr, or Ba) elements as reagents and catalysts (*10*, *11*). The electropositive character of these elements and the resultant polarization of the [AE]-X bonding (X = for example, H, CR_3, or NR_2) provide systems which display a high degree of charge separation ($[AE]^+$ X^-) and which, as a result, are extremely nucleophilic sources of X. A relevant case in point is provided by the reactivity of 1-alkenes with molecular calcium hydrides, a variety of which have now been described (*12*–*19*). $[(BDI)Ca(THF)H]_2$ {**1**; BDI = CH[C(CH_3)N-Dipp]$_2$, Dipp = 2,6-diisopropylphenyl} (*12*, *13*) and $[Ca_2H_2(Me_4TACD)_2][BAr_4]_2$ [Me_4TACD = 1,4,7,10-tetramethyl-1,4,7,10-tetraazacyclododecane; Ar = C_6H_4-4-*t*-Bu (**2**) or C_6H_3-3,5-Me_2 (**3**)] (*16*) are active catalysts for the hydrogenation of alkenes. The catalysis by **1**, however, was restricted to substrates with more activated terminal C=C multiple bonds, whereas its stoichiometric reactivity with alkenes was limited to 1,1-diphenylethene. The resultant 1,1-diphenylethyl derivative, $[(BDI)CaC(CH_3)Ph_2(THF)]$ (**4**), was indefinitely stable in arene solvents (*14*). By contrast, the cationic hydridocalcium derivatives, **2** and **3**, catalyzed the hydrogenation of even hex-1-ene and oct-1-ene (*16*). In neither case, however, could the implied *n*-alkylcalcium intermediates be observed. These latter compounds were thus deduced to be unstable toward β-hydride elimination and the regeneration of the cationic hydrides. In this contribution, we show that use of a tetrahydrofuran (THF)–free version of compound **1** also facilitates reactions with nonactivated (*n*-aliphatic) terminal alkenes. The resultant calcium primary *n*-alkyls are stable and are able to effect the direct nucleophilic substitution of benzene at moderately elevated temperatures.

The reaction of $[(BDI)CaN(SiMe_3)_2]$ (**5**) (*20*) with phenylsilane has very recently been reported to result in inevitable dismutation of $[(BDI)CaH]_2$ (**6**) to $[(BDI)_2Ca]$ and a fine insoluble white powder that was presumed to be CaH_2 (*15*). In our hands, room-temperature reaction of a threefold excess of $PhSiH_3$ with compound **5** performed in hexane provides good yields (>70%) of compound **6**, which crystallizes readily from a saturated

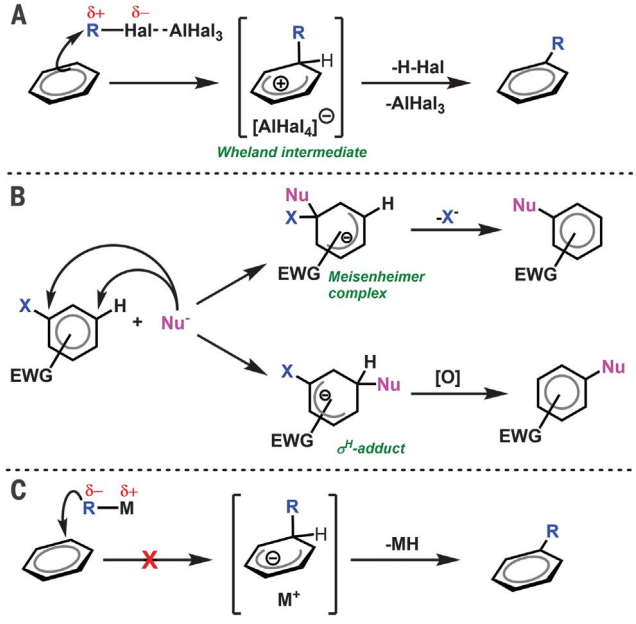

Fig. 1. Distinct aromatic alkylation mechanisms. (**A**) Electrophilic aromatic substitution: F-C alkylation of benzene via Wheland intermediate. (**B**) Nucleophilic aromatic substitution of electron-poor arenes via Meisenheimer or σ^H-adduct intermediates. (**C**) Direct nucleophilic aromatic substitution of benzene.

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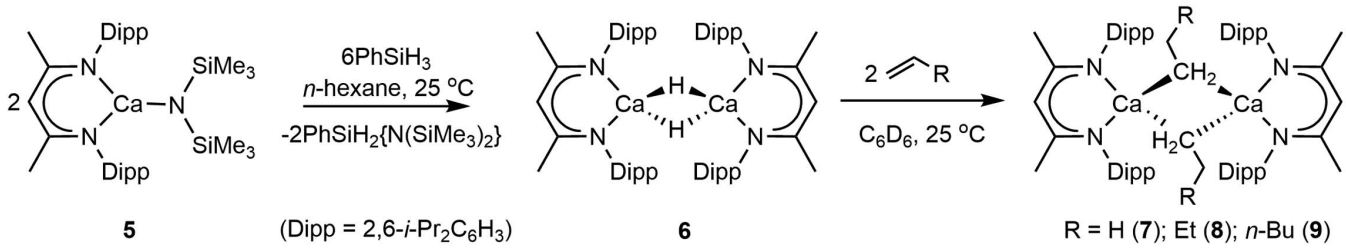

5 (Dipp = 2,6-*i*-$Pr_2C_6H_3$) 6

Fig. 2. Synthesis of compounds 6 through 9.

toluene solution at −35°C (Fig. 2). Analysis of compound **6** by means of nuclear magnetic resonance (NMR) spectroscopy provided data indicative of a single β-diketiminate (BDI) ligand environment and a singlet resonance observed in the ^{1}H NMR spectrum at δ 4.27 parts per million (ppm), which was assigned to the hydridic Ca–H proton (fig. S1). This latter chemical shift resembles the analogous hydride resonances arising from compound **1** (δ 4.45 ppm) (*12*) and other previously reported bridged calcium hydrides (*15*–*19*). These data suggest that **6** adopts a comparable bridged dimeric structure in solution, a supposition which was subsequently confirmed in the solid state with a single-crystal x-ray diffraction analysis (Fig. 3A).

Although there have been recent notable advances in the synthesis of calcium σ-aryl derivatives (*21*–*23*), the successful isolation of well-defined calcium σ-alkyls has been historically dependent on the use of highly sterically demanding and kinetically stabilizing organic anions (*24*–*32*). The synthesis of compound **6** prompted us to study its reactivity with less bulky terminal alkenes in an attempt to synthesize the corresponding calcium *n*-alkyl derivatives. Compound **6** was thus treated with 1 atm of the gaseous alkenes ethene and but-1-ene and with three molar equivalents of hex-1-ene at room temperature in d_6-benzene to provide the respective ethyl (**7**), *n*-butyl (**8**), and *n*-hexyl (**9**) calcium compounds (Fig. 2). Monitoring with ^{1}H NMR spectroscopy indicated that the reaction to generate the ethyl derivative (**6**) appeared to be less discriminating than those of its longer chain homologs and resulted in the production of additional reaction products. Although this onward reactivity precluded the isolation of a pure bulk sample of compound **7**, all three reactions resulted in the disappearance of the ^{1}H NMR hydride resonance of compound **6** over a period of 48 hours at room temperature. In each case, the simultaneous generation of β-diketiminato calcium ethyl (**7**), *n*-butyl (**8**), and *n*-hexyl (**9**) derivatives was clearly evidenced through the appearance of upfield (δ −0.7 to −0.8 ppm) α-methylene ^{1}H NMR resonances as quartet (**7**) and triplet (**8** and **9**) signals, respectively. In each case, a similar resonance was also observed to persist at ~0.3 ppm higher field throughout the course of the reactions but to disappear on complete consumption of the hydride starting material. The solid-state constitutions of compounds **7** through **9** were confirmed with x-ray diffraction analysis [Fig. 3B (**7**) and figs. S20 (**8**) and S29 (**9**)], which demonstrated that each compound crystallizes as a centrosymmetric dimer. Although initial attempts to synthesize calcium analogs of magnesium Grignard reagents were described more than 100 years ago (*33*, *34*), and the structures of a number of σ-bonded aryl (*21*–*23*), benzyl (*35*–*39*), and trimethylsilylmethyl (*21*–*32*) derivatives have been described, aliphatic *n*-alkylcalcium compounds have not been previously crystallographically characterized. All three compounds display asymmetric calcium-to-α-methylene bond lengths (~ 2.49 and 2.58 Å), allowing discrimination between the formal intra- and intermolecular Ca–C bonds. Despite the bridging nature of these interactions, the shorter distance is, in each case, closely comparable with the terminal Ca–C interactions observed in several trimethylsilyl-substituted calcium methyl derivatives—for example, [Ca{CH($SiMe_3$)$_2$}$_2$(THF)$_2$] (2.4930(18) Å) (*26*)—and are significantly shorter than the Ca–C bonds typically observed in the various benzylcalcium compounds that have been reported (~2.58 Å) (*35*–*39*). The structures of **7** to **9** also display close contacts (~2.8 Å) between the calcium centers and the carbons of the methyl (**7**) or β-methylene (**8** and **9**) units of each *n*-alkyl chain.

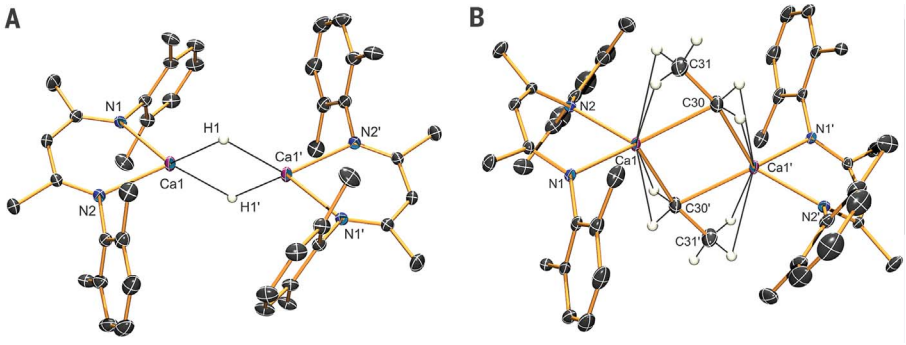

Fig. 3. Crystal structures of 6 and 7. (**A** and **B**) Oak Ridge thermal ellipsoid plot representations (25% probability ellipsoids) are shown for (A) compound **6** and (B) compound **7**. In each case, hydrogen atoms (except for H1 and H1′ in **6** and those attached to C30 and C31 in **7**), isopropyl methyl groups and cocrystallized solvent molecules have been omitted for clarity. Selected distances (angstroms) and angles (degrees) are (**6**) Ca1-N1 2.3097(12), Ca1-N2 2.3222(12), N1-Ca1-N2 79.24(4); (**7**) Ca1-Ca1′ 3.3401(6), Ca1-N1 2.3432(12), Ca1-N2 2.3336(13), Ca1-C30′ 2.4847(19), Ca1-C30 2.5733(19), Ca-C31 2.840(2); N1-Ca1-Ca1′ 136.97(3), N1-Ca1-C30 122.64(6), N1-Ca1-C30′ 115.09(6), N1-Ca1-C31′ 101.84(6). Symmetry operations to generate equivalent atoms are (**6**) ′ −*x*, 1−*y*, 1−*z*; (**7**) ′ 1 − *x*, 1 − *y*, −*z*.

The formation of compound **9** was studied by means of density functional theory (DFT; B3PW91) calculations. This analysis (fig. S55) indicated that the exothermic (ΔH = −18.4 kcal mol^{-1}) reaction takes place with the retention of the dimeric structure of compound **6**. The rate-determining step is a classical highly polarized Ca–H/C=C insertion, which, consistent with the necessary room-temperature conditions, occurs via an accessible barrier of 19.6 kcal mol^{-1}. The π component of the C=C bond is almost fully broken during the assembly of the highly polarized transition state (TS_{BC} in fig. S55), which induces partial charges of −0.6 and −0.2 on the C1 and C2 carbon atoms of the hexene molecule, respectively. Hex-1-ene insertion into the dimeric calcium hydride was also found to take place sequentially via the formation of a dicalcium alkyl-hydrido complex (fig. S55, **C**). On this basis, we suggest that the higher field methylene ^{1}H NMR resonances observed during the formation of compounds **7** through **9** arise from the intermediacy of the relevant ethyl-, *n*-butyl-, and *n*-hexylhydrido-dicalcium intermediates.

In an attempt to optimize the synthesis of compound **7**, the reaction of ethene with compound **6** was repeated in d_{12}-cyclohexane. Although this procedure resulted in a similar rate and level of consumption of the calcium hydride, monitoring of the solution with ^{1}H NMR spectroscopy revealed that compound **7** displayed substantially enhanced stability in the aliphatic solvent. Comparison with the corresponding spectrum of the

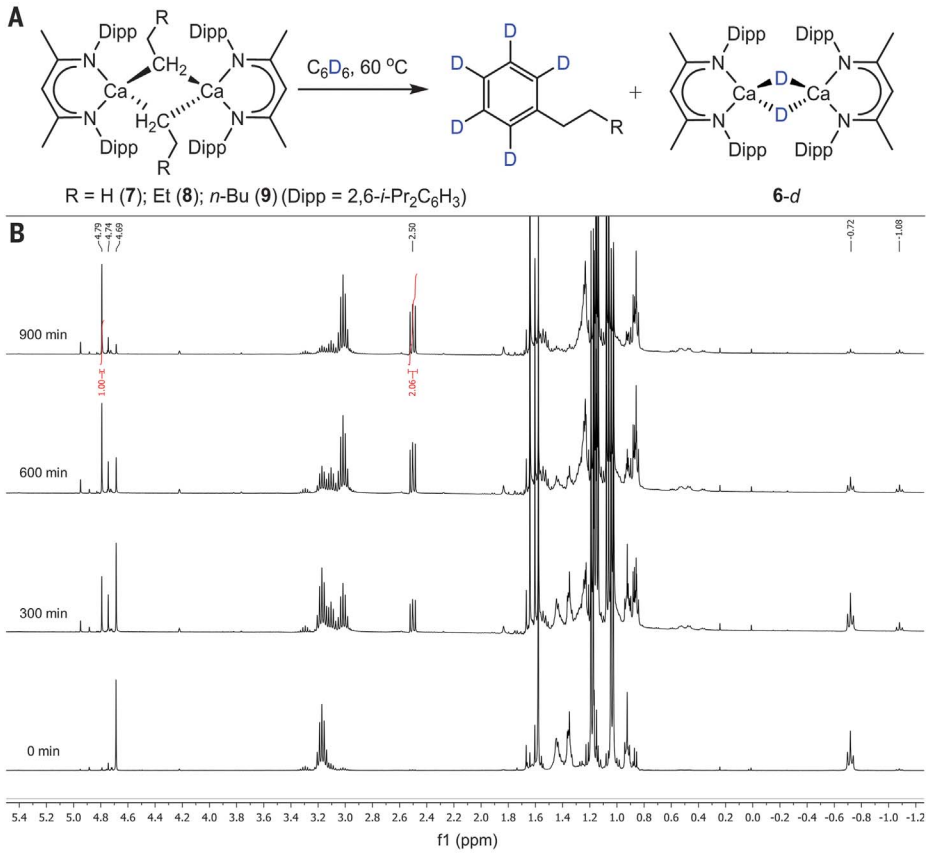

Fig. 4. Monitoring the reaction with benzene. (**A**) Nucleophilic C-D activation of C_6D_6 by **7** through **9** to provide the alkylated d_5-benzene products and **6**-*d*. (**B**) Stacked ^{1}H NMR spectra of a 30-mg sample of compound **9** in 0.55 mL of C_6D_6 heated to 60°C after 0, 300, 600, and 900 min. The signal at 4.79 ppm corresponds to the BDI methine of **6**-*d*. As the reaction proceeds, an intermediate proposed to be [{(BDI)Ca}$_2$(D)*n*-hexyl] displays resonances at δ 4.74 and −1.08 ppm. This compound appears and maintains a steady-state concentration until completion of the reaction. The methine resonance at δ 4.69 ppm and multiplet at δ −0.72 ppm correspond to compound **9**. Concurrent formation of d_5-*n*-hexylbenzene is indicated by the increase in intensity of the multiplet at 2.50 ppm arising from the α-CH_2 of *n*-hexylbenzene. This latter resonance displays a 2:1 ratio by relative integration with the methine signal at δ 4.69 ppm at the completion of the reaction.

reaction performed in d_6-benzene highlighted that the generation and subsequent disappearance of compound **7** was accompanied by the formation of a further predominant compound, which was characterized by the appearance of a quartet signal at δ 2.45 ppm. Subsequent trap-to-trap distillation and analysis of the volatiles by means of NMR spectroscopy identified this compound as d_5-ethylbenzene (figs. S30 to S33). This observation prompted us to study the stability of the isolable longer chain analogs, compounds **8** and **9**, in d_6-benzene, which revealed that these *n*-alkylcalcium complexes display a remarkable capacity to effect the nucleophilic alkylation of benzene (Fig. 4A).

Samples of compounds **8** and **9** were heated in C_6D_6 at 60°C and monitored over a 16-hour period by means of ^{1}H NMR spectroscopy. These reactions resulted in the respective stoichiometric production of d_5-*n*-butylbenzene (fig. S41) and d_5-*n*-hexylbenzene (Fig. 4B), which were identified with two-dimensional NMR spectroscopy and mass spectrometry as the sole organic products of the reactions (figs. S34 to S42 and S43 to S50). During both reactions, the ^{1}H NMR resonances associated with compounds **8** and **9** were observed to decrease in intensity concurrently with the generation of the alkylated benzenes and to be replaced by a single BDI-containing calcium product. Although the BDI ligand resonances associated with this latter compound were identical to those of **6**, no Ca–H signal could be observed in the ^{1}H NMR spectra. Rather,

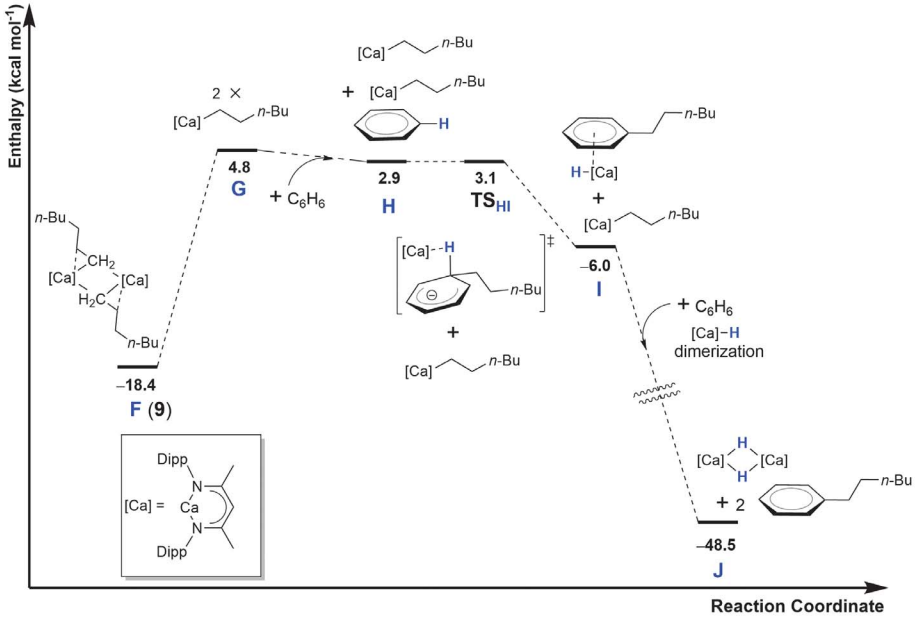

Fig. 5. Computed (DFT, B3PW91) energy profile for the reaction between compound 9 and benzene.

resonances at δ 4.30 ppm, which were detected in the corresponding ^{2}H NMR spectra, led to its identification as [(BDI)CaD]$_2$ (**6**-*d*), a supposition that was subsequently confirmed through a further x-ray diffraction analysis performed on single crystals (fig. S54) isolated from a typical reaction performed with compound **9**. Monitoring of the transformation of **9** at 60°C suggested that this reaction was half order in [**9**] (fig. S51). Further NMR scale reactions performed in protio-benzene

with a minimum amount of C_6D_6 as an internal locking source demonstrated that this reactivity could be extended to the synthesis of the non-deuterated alkylbenzenes, which were formed through the activation of a single C(sp^2)–H bond and the generation of compound **6** (figs. S52 and S53).

To provide further insight into the nature of these processes, the reaction of compound **9** with benzene was assessed with DFT (B3PW91) calculations (Fig. 5). Consistent with the half-order dependence of the reaction on [**9**], the dimeric calcium alkyl must first dissociate to a monomeric form (**G**). As implied by the reaction temperature (60°C), this process is substantially endothermic (ΔH = +23.2 kcal mol^{-1}). The resultant coordinatively unsaturated calcium center interacts via an η^6 contact with the aromatic electron density of a molecule of benzene (**H**). The subsequent barrier toward the nucleophilic attack of the *n*-hexyl α-methylene carbon on a benzene C(sp^2)-H bond via $TS_{\mathbf{HI}}$ is negligible. At this transition state, the *n*-hexyl group acts as a charge-separated external nucleophile and attacks the benzene molecule at a C–H bond from the opposite face to that engaged with the calcium center. This process enforces an interaction between calcium and the hydrogen bonded to the now four-coordinate carbon, so that the negative charge (−0.9) is relocalized on the remaining five carbon atoms of the benzene ring, in a manner analogous to a nonstabilized Meisenheimer complex. Whereas the maximum negative charges are located at the *ortho*, *ortho*′, and *para* positions, a positive charge is found on the newly four-coordinate carbon (+1.2), and the reactive hydrogen accumulates a charge (−0.3) that is consistent with incipient hydridic character before the C–H bond–breaking process. The overall reaction, therefore, is not a classical σ-bond metathesis in which both Ca–C bond–breaking and Ca–H bond formation ensue simultaneously, but is best described as an effective nucleophilic (S_N2) displacement of hydride from the benzene C–H bond (*40*). The breaking of the benzene C–H bond results in the generation of a further π complex of the as-formed calcium hydride and *n*-hexylbenzene (**I**), while arene dissociation and dimerization of the monomeric hydride ensures the overall exothermicity of the reaction (ΔH = −30.1 kcal mol^{-1}). The reaction is thus heavily dependent on a sequence of monomer-dimer equilibria of both the initial calcium *n*-hexyl and ultimate calcium hydride species. In support of this latter hypothesis, further examination of the in situ ^{1}H NMR spectra recorded during the experimental monitoring of the reactions between compounds **8** and **9** and C_6D_6 revealed an additional upfield triplet resonance at ~δ −1.1 ppm, which persisted in low but steady-state concentrations until the complete consumption of the calcium *n*-alkyl derivatives and which we ascribe to the presence of dimeric hydrido(*n*-alkyl)dicalcium compounds analogous to species **C** shown in fig. S55.

The reactions of compounds **7** through **9** with benzene show that nucleophilic alkylation of benzene may be achieved through the use of sufficiently potent alkylcalcium nucleophiles. This reactivity also achieves the net hydroarylation of terminal alkenes. The simultaneous reformation of the calcium hydride (**6**) therefore indicates that this chemistry holds the potential for elaboration to catalysis.

REFERENCES AND NOTES

1. C. Friedel, J.-M. Crafts, *Compt. Rend.* **84**, 1392 (1877).
2. A. A. Ashdown, *Ind. Eng. Chem.* **19**, 1063–1065 (1927).
3. M. B. Smith, J. March, *Advanced Organic Chemistry: Reactions, Mechanisms, and Structure* (Wiley-Interscience, 6 ed., 2007)
4. G. W. Wheland, *J. Am. Chem. Soc.* **64**, 900–908 (1942).
5. N. O. Calloway, *Chem. Rev.* **17**, 327–392 (1935).
6. D. V. Nightingale, *Chem. Rev.* **25**, 329–376 (1939).
7. M. Mąkosza, *Chem. Soc. Rev.* **39**, 2855–2868 (2010).
8. I. S. Kovalev *et al*., *Russ. Chem. Rev.* **84**, 1191–1225 (2015).
9. O. N. Chupakhin, V. N. Charushin, *Tetrahedron Lett.* **57**, 2665–2672 (2016).
10. M. S. Hill, D. J. Liptrot, C. Weetman, *Chem. Soc. Rev.* **45**, 972–988 (2016).
11. S. Harder, *Chem. Rev.* **110**, 3852–3876 (2010).
12. S. Harder, J. Brettar, *Angew. Chem. Int. Ed.* **45**, 3474–3478 (2006).
13. J. Spielmann, F. Buch, S. Harder, *Angew. Chem. Int. Ed.* **47**, 9434–9438 (2008).
14. J. Spielmann, S. Harder, *Chemistry* **13**, 8928–8938 (2007).
15. A. Causero *et al*., *Dalton Trans.* **46**, 1822–1831 (2017).
16. D. Schuhknecht, C. Lhotzky, T. P. Spaniol, L. Maron, J. Okuda, *Angew. Chem. Int. Ed.* **56**, 12367–12371 (2017).
17. P. Jochmann, J. P. Davin, T. P. Spaniol, L. Maron, J. Okuda, *Angew. Chem. Int. Ed.* **51**, 4452–4455 (2012).
18. V. Leich, T. P. Spaniol, J. Okuda, *Inorg. Chem.* **54**, 4927–4933 (2015).
19. A. Causero *et al*., *Organometallics* **35**, 3350–3360 (2016).
20. M. R. Crimmin, M. S. Hill, P. B. Hitchcock, M. F. Mahon, *New J. Chem.* **34**, 1572–1578 (2010).
21. M. Westerhausen *et al*., *Chemistry* **13**, 6292–6306 (2007).
22. M. Westerhausen, M. Gärtner, R. Fischer, J. Langer, *Angew. Chem. Int. Ed.* **46**, 1950–1956 (2007).
23. M. Westerhausen, A. Koch, H. Görls, S. Krieck, *Chemistry* **23**, 1456–1483 (2017).
24. F. G. N. Cloke, P. B. Hitchcock, M. F. Lappert, G. A. Lawless, B. Royo, *J. Chem. Soc. Chem. Commun.* **vol. 0**, 724–726 (1991).
25. C. Eaborn, P. B. Hitchcock, *Chem. Commun.* 1961–1962 (1997).
26. M. R. Crimmin *et al*., *Chemistry* **14**, 11292–11295 (2008).
27. M. S. Hill, M. F. Mahon, T. P. Robinson, *Chem. Commun.* **46**, 2498–2500 (2010).
28. M. Köhler, A. Koch, H. Görls, M. Westerhausen, *Organometallics* **35**, 242–248 (2016).
29. K. Yan, B. M. Upton, A. Ellern, A. D. Sadow, *J. Am. Chem. Soc.* **131**, 15110–15111 (2009).
30. M. P. Coles, S. E. Sözerli, J. D. Smith, P. B. Hitchcock, I. J. Day, *Organometallics* **28**, 1579–1581 (2009).
31. K. Izod *et al*., *Organometallics* **34**, 2406–2414 (2015).
32. A. R. Kennedy, R. E. Mulvey, R. B. Rowlings, *J. Organomet. Chem.* **648**, 288–292 (2002).
33. E. Beckmann, *Chem. Ber.* **38**, 904–906 (1905).
34. H. Gilman, F. Schulze, *J. Am. Chem. Soc.* **48**, 2463–2467 (1926).
35. F. Feil, S. Harder, *Organometallics* **19**, 5010–5015 (2000).
36. S. Harder, F. Feil, A. Weeber, *Organometallics* **20**, 1044–1046 (2001).
37. S. Harder, F. Feil, K. Knoll, *Angew. Chem. Int. Ed.* **40**, 4261–4264 (2001).
38. S. Harder, F. Feil, *Organometallics* **21**, 2268–2274 (2002).
39. D. F.-J. Piesik, K. Häbe, S. Harder, *Eur. J. Inorg. Chem.* **2007**, 5652–5661 (2007).
40. A similar interpretation has previously been implicated in the activation of C–F bonds of fluoromethane by a cerium benzyl derivative (*41*).
41. E. L. Werkema, R. A. Andersen, L. Maron, O. Eisenstein, *Dalton Trans.* **39**, 6648–6660 (2010).

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/358/6367/1168/suppl/DC1
Materials and Methods
Figs. S1 to S56
Table S1
References (*42*–*51*)
Data Files S1 and S2

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Calcium can breach benzene's defenses

Calcium plays a major, multifaceted role in biology and mineralogy. In organic chemistry, though, it is largely overlooked and overshadowed by the carbon compounds of its cousins lithium and magnesium. Wilson *et al.* now report that the element was just biding its time: Several organocalcium compounds that they prepared can alkylate benzene by displacing a hydride, with no need for a more conventionally reactive leaving group such as chloride (see the Perspective by Mulvey). This surprising, previously elusive reaction attests to the unusual nucleophilicity of the carbons bound to calcium.

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