

# Benzene submits to main group power

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As is common practice in organic chemistry, important chemical reactions are often called after scientists who discovered them. The Friedel-Crafts reaction (1), named after its respective French and American pioneers, is a typical example. Reflecting its importance in academic and industrial chemistry as well as its remarkable longevity in serving synthetic chemistry since 1877, this is such a classic reaction that all chemistry students will be introduced to it at an early stage in their course. Formally the reaction is known as electrophilic aromatic substitution. Electrophiles are defined as electron-poor species, whereas nucleophiles are electron-rich species. Electron-rich aromatic molecules such as benzene can utilise their surplus of electrons to react with electron-poor positively charged species enabling benzene to exchange one of its hydrogen atoms for the electrophilic group to make a new, substituted benzene. Simply put, an electron-rich species will react with an electron-poor species to fulfill the maxim “opposite species attract”. By the same logic, “like species repel” so an electron-rich species should not react with another electron-rich species. One pillar of foundation organic chemistry is therefore that benzene never undergoes direct nucleophilic alkylation only electrophilic alkylation. It may have withstood the test of time for 140 years but this pillar has finally collapsed as revealed on page X of this issue, as Hill *et al* report the facile nucleophilic alkylation of benzene accomplished through highly reactive alkylcalcium nucleophiles (2).

Benzene, C<sub>6</sub>H<sub>6</sub>, is one of the most fascinating molecules in science. The image of its aromatic six-membered ring structure could be viewed as aesthetically attractive artwork but in practice it is an indispensable feedstock for the chemical industry finding utilization in the manufacture of countless everyday items from pharmaceuticals to cosmetics through to automotive and aircraft components. The chemists' challenge is to transform the unsubstituted benzene ring into the substituted variations that are key components of these commodities. In Friedel-Crafts electrophilic alkylation, benzene is transformed to an alkylbenzene, by substituting one C-H bond by one C-alkyl bond. Though extremely useful, this reaction can be challenging to control as the alkyl group may isomerise to a different structure or more than one alkyl group can attach to the benzene ring. In exceptional cases nucleophilic alkylation of pre-substituted benzenes can be achieved where the pre-installed substituent is a powerful electron-withdrawing group such as a nitro (NO<sub>2</sub>) group as it renders the carbon atom to which it is attached electron poor and even then a strong oxidant is generally required to complete the reaction.

Appearing to defy logic, Hill *et al* have pioneered a nucleophilic alkylation approach to try and overcome such limitations. How can such an approach

possibly succeed when benzene and the nucleophile should repel each other since both are electron-rich? The answer lies in the special nature of the nucleophile. Languishing in relative obscurity for years since their highly polar metal–carbon bonds were thought to render them too reactive to be useful, organic compounds of the heavier alkaline earth metals (here calcium) have recently been making successful expeditions as reagents into the realm of synthesis and catalysis. Protagonists have been attracted to developing the chemistry of such earth abundant main group metals because of cost benefits, longer sustainability and lower toxicity they potentially offer compared to those of the precious transition metals that rule this realm at present (3). Hydride compounds of main group metals (4) have been particularly prevalent in catalytic applications due to them functioning as catalysts or precatalysts in hydrofunctionalisation reactions such as hydroboration or hydrosilylation (5). Hill *et al* have used their expertise in hydride chemistry to prepare a series of alkylcalcium complexes where unusually the alkyl groups are small, linear chains such as n-butyl or n-hexyl, as previous syntheses only appeared successful with much larger, more stable organic groups. These new alkylcalcium compounds were prepared by reaction of calcium hydride species with aliphatic alkenes that have C=C bonds (6). Their alkyl anions are well known with other metals, especially lithium, to be strongly reactive nucleophiles and pairing them with highly polarising calcium serves to increase this reactivity even more. The final key experiment was to react these new n-alkylcalcium compounds with benzene. To follow the course of these reactions in solution by NMR (nuclear magnetic resonance) spectroscopy, deuterated benzene (C<sub>6</sub>D<sub>6</sub>), a form of benzene in which the hydrogen atom is substituted by its deuterium isotope, was employed. This confirmed that nucleophilic alkylation of deuterated benzene occurred through formation of the alkylated-benzene product. As a bonus, the byproduct of the reaction is the calcium hydride compound used as the starting material for formation of the n-alkylcalcium compounds, suggesting that it may be possible to render such reactions catalytic though this remains to be investigated. Computational studies revealed that a key factor in the success of this reaction was that the negative charge introduced by the incoming nucleophile is dispersed amongst five carbons atoms of the benzene ring, while the breaking C-H bond is polarized such that the H is primed to leave as a nucleophile.

Time will tell whether this first direct nucleophilic alkylation of benzene will be the forerunner of a nucleophilic aromatic substitution methodology to rival or surpass that of electrophilic aromatic substitution. What is probably more certain at present is that an advance of this magnitude is likely to be the launching pad for more extensive future research that could reposition organic compounds of the heavier alkaline metals from esoteric curiosities to common chemical reagents of widespread utility.

## References and Notes

1. M. Rueping, B. J. Nachtsheim, *Beilstein J. Org. Chem.* **6**, doi:10.3762/bjoc6.6 (2010).
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3. S. Harder, *Chem. Rev.* **110**, 3852 (2010).
4. S. Harder, *Chem. Commun.* **48**, 11165 (2012).

5. M. S. Hill *et al*, *Chem. Soc. Rev.* **45**, 972 (2016).
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**Calcium overpowers benzene.** The most important aromatic raw material benzene can be functionalized by electrophiles but not with nucleophiles (top reactions). However, using a powerful calcium nucleophile Hill *et al* have successfully performed the first direct nucleophilic alkylation of benzene (bottom reaction). The transparent image shows the structure of the calcium nucleophile.