Intramolecular C–H insertion vs. Friedel–Crafts coupling induced by silyl cation-promoted C–F activation†

Oliver Allemann,a,b Kim K. Baldridge*a,b and Jay S. Siegel*a,b

Silyl cation-promoted aryl C–F activation can lead to formal C–H activation and the formation of new C(ar)–C(alkyl) bonds. Deuterium-labeling experiments suggest an insertion of a phenyl cation into the C–H bond. From competition experiments, a relation between reaction rate and C–H bond strength could be established. Mechanistic parallels are drawn to the Mascarelli reaction.

Introduction

Silyl cations activate even highly stable C–F bonds.1,2 Prominent cases include hydrodefluorinations of fluoroalkanes, by simple3–5 as well as bridging6,7 cationic silanes, and catalytic intramolecular coupling of a fluoroarene with a non-functionalized arene.8,9 Specifically, trisopropylsilylium hexachlorocarba-closo-dodecaborate (1), induces the cleavage of an aryl carbon–fluorine bond allowing a proximal aryl moiety to attack the incipient phenyl cation. If attack by the adjacent arene generates too much strain, as in the formation of a 4-membered ring, the reaction is either very slow or not observed; however, in such cases the presence of an alternative nucleophile, such as the C–H sigma bond of a proximal methyl group, can create a competitive reaction path to capture the phenyl cation (Scheme 1). Exactly this C–F/C–H activation couple forms the basis of this report.

Reaction of 2-fluoro-2′-methylbiphenyl (2) with 5 mol% of [Pr3Si][CHB11H5Cl6] (1) and stoichiometric dimethyl- dimesitylsilane (DMDMS) illustrates the fundamental C–F/C–H activation couple (Scheme 2); wherein 1 serves as catalytic initiator and DMDMS serves as Brønsted base and pro-Lewis acid catalyst. Notably, C–F activation of 2 does not lead to the highly strained biphenylene, but rather to fluorene (3).

Analogous diazoniumbiphenyls exhibit similar reactivity under either thermal or acidic conditions, as observed by Mascarelli in 1932.10,11 Recently, studies on Brønsted acid-mediated intramolecular cyclization of biaryl triazenes for the synthesis of fluorenes showed similar results.12 Decomposition of these diazonium salts to form arene carbenium ions has precedence.13

Speculations on the mechanism of the Mascarelli and analogous reactions are plentiful with one of the most persistent theories being the shift of a hydride from the methyl group to the phenyl cation, resulting in a benzyl cation, followed by intramolecular electrophilic aromatic substitution (Scheme 3). Alternative mechanisms for the Mascarelli reaction include intermediates such as a pentacoordinated carbocation14 or a Zwitterion,15 postulated to be formed by abstraction of a benzylic proton; however no credible experimental evidence has been provided.

Scheme 1 Friedel–Crafts type arylation (right) and C–H insertion, involving an alkyl group (left).

Scheme 2 Transformation of 2-fluoro-2′-methylbiphenyl to give fluorene using silyl cation 1 as initiator.
Results and discussion

Evidence for a hydride shift was observed in the denitrogenation of 2-diazonium-\(N,N\)-dibenzylbenzamides;\(^{16}\) the resulting iminium ion does not undergo ring closure, but leads to products of hydrolysis. The phthalimidine originating from intramolecular cyclization, was proposed to be generated from the initial phenyl cation by an insertion mechanism.\(^{17}\) A hydride shift-derived mechanism was further inferred from the observation of a 2-phenylbenzyl alcohol, generated likely from the 2-phenylbenzyl cation for intermolecular coupling (Scheme 6). Only no fluorene, further demonstrating the preference of the IM1 partitions with preference for intramolecular migration over abstraction of D\(^{1}\). IM2 is fleeting and further hydride migration occurs to IM3 without appreciable elimination. A Hammond Postulate analysis allows this to be modeled by basic principles of physical organic chemistry (Scheme 5).

Intramolecular hydride transfer to form a benzyl cation followed by ring closure would place substantial deuteration at position 4, which is not observed. Additionally, abstraction of fluoride from 2-fluoromethylbiphenyl (4) yielded primarily 5 and 6 (coupling with mesitylene from DMDMS\(^{33}\)) and traces of 7 but no fluorene, further demonstrating the preference of the benzyl cation for intermolecular coupling (Scheme 6). Only trace amounts of two intermolecular coupling isomers with DMDMS could be observed for the reaction of 2. Thus, intramolecular hydride transfer seems mechanistically insignificant in the formation of fluorene from 2.

C–F activation of 2 led exclusively to 3 by benzyl C–H insertion. In contrast, for substrates 8a–8c where benzyl C–H insertion and Friedel–Crafts reaction pathways are probable, a competitive distribution of products can be observed (Scheme 7). Whereas the substrate possessing the stronger benzylic C–H bond (8a, toluene-like: 375 kJ mol\(^{-1}\)) prefers for-
Computational studies predict an activation energy for C–F activation of ~100 kJ mol⁻¹, which is consistent with the reaction proceeding at 90 °C over 2 h. Calculated transition states leading to products 9a and 10a are very close in energy (ΔE = -1.2 kJ mol⁻¹ [ε = 5.7 chlorobenzene]). Experimental product ratios also suggest that the transition states are very close in energy (ΔE = +1.5 kJ mol⁻¹). The difference between theory and experiment (2.7 kJ mol⁻¹ in chlorobenzene) is well within the limits of reliability – emphasizing the importance of small energy differences for product ratios in the range of 1:2 to 2:1 (ca. 4 kJ mol⁻¹). Computations suggest that changes in dielectric constant can influence the product selectivity (ΔE = +1.5 kJ mol⁻¹ [ε = 1 vacuum]) but, they do not change the general course and nature of the reaction.

Noteworthy is that only a small fraction of the difference in C–H bond strength shows up in the difference in transition state energy (ca. 5–10%). Invoking the Hammond postulate again here, one would conclude that the reaction product selectivity step has an early transition state, further supporting a direct C–H insertion mechanism. An early C–H insertion mechanism would predict the reaction to be relative promiscuous with regard to C–H insertion chemistry. Indeed, the reactivity is not restricted to weak benzylic CH groups. Applying the reaction conditions on 2-fluoro-2-butylbiphenyl (11) also yields ring-closed product (12) (Scheme 8). Despite the large difference in C–H bond strength for a primary aliphatic CH₃ group compared to a benzylic CH₃ group (ΔE ~40–50 kJ mol⁻¹), the formation of the six-membered ring, aliphatic insertion product, is only slightly slower than that of the model compound. This result further supports the early transition state, direct insertion model for this reaction.

Conclusions and outlook

Parallel to the Mascarelli reaction for diazonium salts, phenyl cations generated from arylfluorides by C–F bond activation with cationic Lewis acids can undergo intramolecular arene-coupling and C–H insertion. Deuterium labeling studies suggest a direct C–H insertion mechanism. Competition experiments showed only a slight dependence of aryl–aryl coupling vs. C–H insertion based on the C–H bond strength, consistent with an early-transition-state to a direct-insertion mechanism. The tandem activation of two generally stable functional groups (Ar–F, alkyl–H) provides a new reactivity pattern in cationic silyl Lewis acids.

formation of the fluoranthene derivative 9a over 10a, with a ratio of 1.6 : 1.0, the substrates featuring the weaker benzylic C–H bond (8b & 8c, cumene-like: 348 kJ mol⁻¹) rather form products of the insertion 10b and 10c (1.0 : 1.9 and 1.0 : 2.1, respectively).
Experimental and computational details

Synthesis and characterization data, together with computational details, are available in the ESI.†

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Notes and references

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22 The deuterium distribution was determined by using both 1H and 2H NMR spectroscopic data.
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