Reactions of Fluoroalkanes with Mg–Mg Bonds: Scope, sp³C–F / sp²C–F Coupling and Mechanism

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Abstract: sp³C–F bonds of fluoroalkanes (7 examples; 1°, 2° and 3°) undergo addition to a low-valent Mg–Mg species generating reactive organomagnesium reagents. Further reactions with a series of electrophiles result in a net C–F to C–B, C–Si, C–Sn or C–C bond transformation (11 examples, diversity). The new reactivity has been exploited in an unprecedented one-pot magnesium-mediated coupling of sp³C–F and sp²C–F bonds. Calculations suggest that the sp³C–F bond activation step occurs by frontside nucleophilic attack of the Mg–Mg reagent on the fluoroalkane.

The activation and functionalization of sp³C–F bonds of fluoroalkanes represents an important and largely unsolved challenge. Transformations that use sp³C–F bonds as reactive functional groups could potentially open up new avenues in synthesis, including upgrading refrigerants and the late-stage functionalisation of agrochemicals and pharmaceuticals. Slow progress in this area of research can, in part, be traced to the difficulties associated with the oxidative addition of sp³C–F bonds to transition metals. The high sp³C–F bond dissociation energy along with the lack of charge stabilisation in the transition state for bond breaking means that defined oxidative addition reactions are incredibly scarce. In cases where oxidative addition can occur, the resulting metal alkyl complexes are liable to undergo fast 1-methyldemethylation. Main group reagents and catalysts offer a complementary approach to transition metal systems. Electrophilic silylum ions and related species have proven remarkably adept catalysts for fluoride abstraction from fluoroalkanes, while a nucleophilic boryl anion has just emerged as a reagent capable of C–F cleavage of CF₃H (HFC-23). Although we, and others, demonstrated that sp³C–F bonds of fluoroalkanes undergo oxidative addition to single-site Al(I) complexes, no further reactivity of the resultant group 13 reagents has been reported. In related studies we have shown that the reaction of fluoroalkanes with 1a occurs by a concerted SuaR-type addition of the sp³C–F bond across the Mg–Mg bond (Scheme 1).

Fluorocarbons are often considered inert toward Grignard formation. There are however a series of somewhat contradictory reports that metallic magnesium can be used to generate Grignard reagents from fluoroalkanes: provided a suitable initiator (e.g I₂, Br₂, EtBr) is present. Captivated by these studies, we became interested in the reactivity of 1a towards fluoroalkanes. Here we show that these reagents activate a variety of sp³C–F bonds under mild conditions. The resultant organomagnesium reagents can be used to transfer the alkyl group to boron-, silicon-, tin- and carbon-based electrophiles. The latter carbon–carbon bond forming reaction is an unprecedented example of a transition metal free cross-coupling reaction of two C–F bonds.

Addition of 1.1 equiv. of 1-fluorohepane to a 0.02 M solution of 1a in CdX at 80 °C led to the consumption of the Mg–Mg reagent over 1 h and formation of the magnesium alkyl 2a in 92 % yield. 2a was characterized by a high-field triplet resonance in the ¹H NMR spectrum (δ = 0.22 ppm, J_Mg-H = 7.9 Hz) assigned to the methylene group adjacent to magnesium and formed alongside the previously characterised magnesium fluoride 3a.

![Scheme 1. The addition of sp³C–F bonds to Mg-Mg bonds. Yields measured by ¹H NMR spectroscopy by comparison against an internal standard.](image)

The scope of the reaction was considered. A series of substrates were investigated and the organomagnesium complexes 2b-e were formed in good yield (Scheme 1). The reaction tolerates 1°, 2° and 3° fluoroalkanes along with chain-branching both adjacent to and remote from the active site. There is precedent for the reaction products. Related organomagnesium complexes crystallise as bridged dimers (1° alkyl) or 3-coordinate monomers (2°/3° alkyl). In the solid-state 2a forms a dimer, bridged by 3-centre, 2-electron bonds (Figure 1a). DFT calculations show that the solid-state structures likely persist in solution and dimerization of these organomagnesiums only becomes unfavourable with branching of the chain (Figure 1b).

Although 1a did not react cleanly with 3° alkyl fluorides, the analogue 1b mediates the C–F bond activation of 1-fluoroadamantane. In this case, the resulting β-diketiminate stabilised organomagnesium is unstable with respect to Schlenk-like ligand redistribution preventing its characterisation in solution. Trapping of the organomagnesium with HBpin resulted in direct formation of 1-adamantylBpin in 69% yield from 1b (Bpin = pinacolatoborane, Figure 1c).

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Supporting information including experimental procedures, details of the DFT studies, X-ray data and multinuclear NMR spectra (PDF). X-ray crystallographic data for 2a, 2a-THF, 2d-THF and S1 ( cif) for this article is given via a link at the end of the document.
Initial experiments suggest that, in a case that forms two energetically dissimilar diastereomers, the reaction is stereoeconvergent. Hence, cis and trans 4-tert-butylcyclohexyl fluoride both react with 1a to give a single diastereomer assigned as trans-2e based on the $^{3}$J$_{H-H}$ values of the NMR resonance of the protons adjacent to Mg (Scheme 1). By DFT the trans isomer is calculated to be 5.4 kcal mol$^{-1}$ more stable than the cis isomer and they likely interconvert by epimerisation of the stereocentre adjacent to magnesium.

Insight into the functional group compatibility of the new transformation was gained by running the reaction of 1a with 1-fluorohexane in the presence of external reagents containing alkenes, alkenes, ethers, 3° amine and pyridine moieties. These additives had little or no impact on the yield of 2a (supporting information, Scheme S3). In the case of THF and DMAP this experiment led to the formation of the solvates 2a+THF and 2a+DMAP respectively. Substrates including an additional halogen atom on the hydrocarbon chain, such as 1-iodo-3-fluoropropane or 1-bromo-5-fluoropentane, underwent cyclisation to form 3- or 5-membered hydrocarbon rings (supporting information, Scheme S4).\(^{[39]}\)

The utility of the new organomagnesium complexes was investigated and specifically the polar Mg$^{+–}$C$^{–}$ bond derived from $sp^3$C–F activation was used as a nucleophilic source of the carbanion. Reaction of mixtures containing 2a, formed from C–F activation of 1-fluorohexane, with HBpin, B$_2$pin$_2$, B$_2$nep$_2$, 9-BBN, H$_2$SiPh, H$_2$SnBu, or C$_3$SnBu, or C$_3$SnBu leads to transfer of the alkyl group from magnesium to the electrophile and results in sp$^3$C–B, sp$^3$C–Si, and sp$^3$C–Sn bond formation respectively (Bnep = 5,5-dimethyl-1,3,2-dioxaborolane, 9-BBN = 9-borabicyclo[3.3.1]nonane). These reactions are highly efficient, with most proceeding in >80% yield over the two steps as measured by $^1$H NMR spectroscopy. An exception is the reaction of 2a with B$_2$nep$_2$ which forms n-HexBnep in only 50% yield (Scheme 2).\(^{[30]}\)

Buoyed by the ease of nucleophilic addition to main group electrophiles, we turned our attention to intermolecular carbon–carbon bond formation by the heterocoupling of two C–F bonds. 2a, generated directly from 1-fluorohexane, adds to perfluoroarenes under forcing conditions (Scheme 3). The reaction of in situ generated 2a with hexafluorobenzene forms 4a as evidenced by the emergence of a new triplet resonance in the $^1$H NMR spectrum ($\delta = 2.29$ ppm, $^{3}$J$_{H-H} = 7.7$ Hz) assigned to the methylene protons adjacent to the aromatic ring. The scope of this reaction was expanded and the overall yields of cross-coupled products 4a–e while modest, 34–72 %, represent a combination of two steps and an average 60–85% yield for each C–F bond cleavage reaction. Although related reactions of organomagnesium reagents with perfluoroarenes are known,\(^{[31–33]}\) this represents the first transition metal free procedure for C–C bond formation by the coupling of two C–F bonds.

**Figure 1.** (a) The crystal structure of 2a. Selected bond length (Å): 2a Mg–C 2.257(3). (b) Calculated Gibbs free energies (kcal mol$^{-1}$) of dimerization of magnesium alkyl complexes. (c) The reaction of 1b with 1-fluoroadamantane and trapping with HBpin.

**Scheme 2.** Stepwise sp$^3$C–F bond functionalisation resulting in the formation of sp$^3$C–B, sp$^3$C–Si and sp$^3$C–Sn bonds. For full details of these experiments see the supporting information.

**Scheme 3.** Carbon–Carbon bond formation by double carbon–fluorine bond activation. Yields measured by $^1$H NMR by comparison against an internal standard.
To gain a deeper understanding of the C–F bond cleavage steps involved in the carbon–carbon bond forming sequence, a series of calculations were undertaken on the reaction of 1-fluoropropane with hexafluorobenzene using the B3PW91 functional and a hybrid basis set (Figure 2a). We have previously benchmarked the computational methods used herein against experimentally determined activation parameters.

The initial endergonic coordination of 1-fluoropropane at 1a to form Int-1, is followed by C–F bond cleavage in TS-1 ultimately leading to the formation of Int-2/3. Schlenk-like redistribution of two equiv. of Int-2/3 forms the experimentally observed products Int-2a and Int-3. While the dissociation of Int-2/3 into the monomeric fragments Int-2 and Int-3 required for redistribution is endergonic $\Delta G^{\text{298K}} = 25.3$ kcal mol$^{-1}$, this energy barrier represents complete dissociation and, as such, is an upper limit of the activation energy. Overall this Schlenk-like redistribution is thermoneutral. The second C–F bond cleavage step forms the carbon–carbon bond and proceeds by nucleophilic addition of the newly formed magnesium alkyl complex to the electron-deficient arene. Dissociation of Int-2a is required to access the reactive three-coordinate magnesium alkyl species Int-2, and is on the way to the concerted S_{Ar}-like transition state TS-2. In combination these steps lead to a high activation barrier for carbon–carbon bond formation, $\Delta G^{\text{298K}} = 26.2$ kcal mol$^{-1}$.

The unusual geometry of TS-1 warrants further discussion. TS-1 contains a near planar arrangement of Mg, C, and F atoms in which the C–F bond is planar, perpendicular to the Mg–Mg bond with the fluorine atom approaching head-on. The C–F bond stretches to 1.84 Å from 1.39 Å in 1-fluoropropane, the Mg–F distances are short (2.1 Å) while both Mg–C distances are long (3.6 Å). A similar transition state was located for the reaction of 1a with 2-fluoropropane. TS-1 bears all the hallmarks of front-side nucleophilic attack in an S$_{n}2$ mechanism; the carbon substituent takes the role of the leaving group and the electron-pair between the magnesium atoms of 1a the role of the nucleophile. This geometry is starkly different to that observed in the side-on and S$_{Ar}$ like transition states calculated for the reaction of 1a with CO$_2$ and CF$_3$ respectively. While all these processes can be classified as oxidative additions from the perspective of the main group reagent there are significant deviations in the TS geometries (Figure 2c).

Frontside nucleophilic attack, taught as an unfavourable pathway to undergraduate students, has been modelled in dynamics calculations on nucleophilic substitution reactions of alkyl halides. These pathways have been shown, universally, to be prohibitively high in energy when compared to back-side nucleophilic attack. In the current case, it appears the unusual nature of 1aoverrides the standard selectivity. There is limited precedent for the geometry of 1a. Eisenstein and co-workers have postulated that a cerocene hydride attacks CF$_3$ through a transition state involving an end-on H--F--C interaction.

The Mg–Mg reagent 1a possesses a non-nuclear local maximum in electron density at the centre of the metal–metal bond that acts as a highly nucleophilic electron-pair[45,46]. Second-order perturbation calculations on TS-1 show donor–acceptor interactions from not only the Mg–Mg σ-bond to the low-lying $\sigma^*$ (F–C) orbital of the fluoroalkane (37 kcal mol$^{-1}$) but also from the filled F π-orbitals to the empty $\sigma^*$ (Mg–Mg) orbital (7 kcal mol$^{-1}$). This latter interaction contributes to the stabilisation of the frontside TS as the electrostatic interactions between fluorine and magnesium atoms anchor the C–F bond in place and polarise it. In TS-1, the hydrocarbon chain acts as a leaving group. This moiety adopts carbanion character and following breaking of the C–F bond migrates directly to magnesium (supporting information, movie). The carbanion character is evidenced by the NPA charges on the carbon atom in TS-1 which is more negative than that in Int-1 alongside the deviation of the carbon centre from sp$^3$ to sp$^2$ hybridised (degree of pyramidalization: Int-1 = 42%, TS-1 = 12.5%).

In summary, we report a new reaction that transforms sp$^3$C–F bonds into reactive sp$^3$C–Mg bonds. This methodology can be considered as an equivalent of Grignard formation that occurs in homogeneous solution and allows expansion of the substrate scope to include fluorocarbons. The organomagnesium products react with a series of electrophiles leading to the development of an unprecedented carbon–carbon bond forming reaction that couples two C–F bonds. A preliminary assessment of the mechanism hints that sp$^3$C–F bond activation occurs by a remarkable pathway involving frontside nucleophilic attack. We
are currently investigating the stereospecificity of the reaction of 1a (and related reagents) with fluorokanes alongside a more detailed study of the stereointegrity of the resulting organometallics.

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Keywords: C–F activation • cross-coupling • fluorocarbons • frontside Sn2 • organomagnesium reagents

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sp\(^3\)C–F bonds of fluoroalkanes undergo addition to a low-valent Mg–Mg reagent generating reactive organomagnesium reagents

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