LiTMP Trans-Metal-Trapping of Fluorinated Aromatic Molecules: A Comparative Study of Aluminum and Gallium Carbanion Traps

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Dedicated to Professor Snieckus on the occasion of his 80th birthday

Abstract: Fluoroaromatic scaffolds pose a challenge to lithiation due to low stability of lithiated intermediates. Here we apply trans-metal-trapping (TMT) to a series of key fluorinated aromatics. In TMT, LiTMP performs the metalation, while an organometallic trap intercepts the emergent carbanion. This study contrasts the trapping abilities of iBu₂AlTMP and Ga(CH₃SiMe₃)₃, structurally mapping their TMT reactions and probing relative stabilities of metalated fluoroaromatic intermediates by NMR studies. Results show the installed Al–C(aryl) bonds are more prone to decomposition by benzyl formation and Li–F liberation, than the Ga–C(aryl) species. The latter are thus better for onward reactivity as demonstrated in cross-coupling reactions with benzoyl chloride that produce ketones.

In 2017, we witness the centenary of the advent of organolithium chemistry by Schlenk and Holtz.[1] Since then organolithium reagents have played leading roles in the synthesis of organic compounds especially through metalation (C–H to C–metal) applications.[2] Fluorinated aromatic compounds represent a special challenge to organolithium reagents on account of the instability of metalated intermediates.[3] This point and the profound complexity involved (e.g., benzyl formation, metalation, cascade processes) are exemplified in Schlosser’s classic report of multiple hydrogen/lithium interconversions induced by lithiation of 1,3,5-trifluorobenzene.[4] Significantly, fluoroaromatic compounds are rarely found in nature,[5] meaning that nearly all aryl fluorides utilized in pharmaceutical manufacture (as synthetic building blocks) must be generated synthetically. Incentivized by the growing importance of fluorinated aromatic compounds in active pharmaceutical ingredients (where it is estimated that 20–25% of forthcoming drugs contain at least one F atom),[6,7] we pondered whether emerging metalation methodologies could improve on the performances of the classical organolithium reagents. Notable advances to this end have been made with respect to either reaction rate or regioselectivity. Collum and co-workers demonstrated a rate enhancement on lithiating various fluorinated aromatics using lithium disopropylamide in THF at −78°C by adding catalytic quantities of LiCl.[8] Knochel and co-workers disclosed that specific aryllithium species can be selectively trapped from a mixture of isomers by transmetalation with a substoichiometric quantity of dichlorozirconocene.[9] Here we approach these challenging metalations through trans-metal-trapping (TMT), where two non-interacting organometallic reagents work in tandem (Scheme 1).[10] The first stage of TMT harnesses the bulky amide base, LiTMP (TMP = 2,2,6,6-tetramethylpiperidide) to deprotonate a substrate (these metalations can exist in equilibria lying towards starting materials). The second stage utilizes a bulky, soluble Lewis acidic organometallic trap to rapidly intercept and stabilise emergent carbanions, thereby driving equilibria toward metalated products. Still in its infancy, TMT has only been reported with a handful of organic/organometallic substrates using iBu₂AlTMP as the trap[11a,b] and with a series of diazines using a Ga(CH₃SiMe₃)₃ trap.[11c] We also note that Knochel’s Group used a similar Al reagent, iBu₂AlCl, to trap aromatic carbanions after lithium halogen exchange, though this proceeded with LiX elimination and thus gave neutral Al species as opposed to the ate species discussed here.[11d] Here, in applying TMT to challenging fluorinated aromatic substrates we present the first comparative study between Al and Ga traps, structurally mapping TMT reactions both crystallographically and spectroscopically, elucidating the complex reaction pathways that diminish the effectiveness of the Al trap, and establishing that the greater carbophilicity and, or the reduced fluorophilicity of the Ga trap makes its products

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Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under:
https://doi.org/10.1002/anie.201706064.

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Angew. Chem. Int. Ed. 2017, 56, 9566–9570
the preferred candidates for performing follow on reactions with electrophiles.

Initial TMT studies focused on the LiTMP/iBu₄AlTMP system with a range of fluorinated aromatic substrates. Reaction of 3-F-anisole with LiTMP and iBu₄AlTMP in hexane at −78°C gave a solid that ¹H NMR analysis confirms contains metalated substrate (in the 2-position) as indicated by three new resonances between 6.94 and 6.19 ppm. ¹³C and ³Li NMR spectra support formation of one product, displaying one resonance in each case. X-ray crystallography revealed this product to be the contacted ion pair 1 [2-{[(iBu)₄Al-µ-TMP]Li·THF}-3-fluoroanisyl] (Figure 1A), confirming regioselective ortho-metalation of 3-F-anisole. Al bonds to the 2-position of the substrate (C1-Al 2.087(17) Å).

Solvated by the MeO oxygen atom and a THF molecule, Li further bonds to a µ-TMP ligand. Two iBu groups complete the distorted tetrahedral Al coordination. Demonstrating generality, substrate scope was extended to fluoroarenes containing 2–4 fluorine atoms (Scheme 2): 3,5-difluoroanisole, 1,3,5-trifluorobenzene (giving [2-{[(iBu)₄Al-µ-TMP]Li·THF}-1,3,5-F₃C₆H₃][Li(THF)]³⁻), 2, and 1,2,4,5-tetrafluorobenzene (giving [3-{[(iBu)₄Al-µ-TMP]Li·THF}-1,2,4,5-F₄C₆H₂][Li(THF)]⁴⁻). Due to the lack of a suitably positioned Lewis basic group on the substrate, all three adopt solvent-separated ion pair (SSIP) structures (Figure 1B shows the anion of 3) with a Li(THF)₂ counterion (see the Supporting Information for details). Note, the C(aryl)–Al distances reveal an increasing trend with additional F substituents from 1–4 (1 2.0872–2.0872 Å; 2 2.076(4) Å; 3 2.090(3) Å; 4 2.106(4) Å). Thus it is anticipated that as the F content increases the carbanionic charge decreases, and in theory the trapping step should become less facile. Unfortunately, full characterization of 2–4 was hampered by poor yields and propensity of crystals to decompose into oils.

The moderate yields of 1–4 prompted more investigation. Using 1 as a representative example, the ¹H NMR spectrum of its reaction filtrate revealed four aromatic resonances each integrating to one H, consistent with an asymmetric 1,3-disubstituted anisole. From this we suggest that a secondary competing process is occurring. After initial metalation with LiTMP, rapid loss of aluminate LiAlF(TMP)iBu occurs to generate a benzyne intermediate and TMPH, which can add across and trap the incipient benzyne affording 1-(3-methoxyphenyl)-2,2,6,6-tetramethylpiperidine (1; confirmed by aqueous work-up and ¹H and ¹³C NMR spectra of the resulting oil). Importantly, this process could not be arrested even at cryogenic temperatures. A control reaction between 1 and TMPH in C₆D₆ in a J. Young NMR tube established that 1 can be prepared via this pathway (see the Supporting Information). However, we cannot rule out the possibility that an autometallation process may also be contributing to the formation of the TMP-substituted product. LiTMP is more nucleophilic than neutral TMPH, thus any present in solution (due to variations in stoichiometry or rapid generation of the benzyne before the LiTMP has all reacted) could also react with the benzene, wherein the generated lithiated species could deprotonate a second substrate molecule.

The decomposition pathways were probed further. Reaction between 3-F-anisole, LiTMP, and iBu₄AlTMP-THF was monitored over time in a J. Young NMR tube in C₆D₆ at room temperature. Initially the ¹H NMR spectrum displayed signals corresponding to 1 and coproduct 1, albeit after forming the metalated compound slowly decomposes. Confirming that coproduct TMPH, or potentially some unreacted LiTMP, is necessary for formation of 1, the ¹H NMR of 1 was recorded over 48 h. During this time resonances of 1 are essentially lost, and crucially no resonances corresponding to 1 emerge. Decomposition of 1 was confirmed via formation of a benzene intermediate as demonstrated in an intentional trapping experiment by reacting either 1 or the in situ reaction mixture with 1,3-diphenylisobenzofuran in hexane (Scheme 3). After filtration a solid was collected and identi-
fied by NMR spectroscopy as the known Diels–Alder cyclo-
addition product 1-methoxy-9-10-diphenyl-9-10-epoxy-
thracene in 86% (from 1) or 49% (in situ mixture) yield. That 1, an ary1 aluminum decomposes via benzine formation is interesting albeit not entirely unknown. A related process was seen during the sodium mediated ortho-zincation of chlorobenzene using [TMEDA]-Na(μ-Tmp)(μ-iBu)Zn-
(iBu)].\(^{[23]}\) Metallation of fluoroarenes using the LiTMP/ iBu\(_2\)AlTMP TMT system is thus more complex than seen with other non-fluorobenzene-based systems. Specifically, trapping appears too sluggish to prevent benzine formation and autometalation side reactions even at low temperature. Further, even metalated products are unstable in relatively innocent hydrocarbon solvents suggesting that the propensity of the aluminated species to eliminate Li-F as part of an aluminate has a particularly deleterious effect on C-Al bond stability.

Next, \(\text{N,N',N''-pentamethyldienetriamine (PMDETA)}\) was added to the reaction mixture containing LiTMP, iBu\(_2\)AlTMP, and a fluoroaromatic (3-F-anisole, fluorobenzene, or 1,3,5-trifluorobenzene). We reasoned that the donor would draw Li away from the carbanionic centre, hastening transmetalation with Al. With 3-F-anisole, [PMDETA-Li(F)Al(iBu)\(_2\)TMP], 5 was obtained (Scheme 3). X-ray crystallography revealed a CIP aluminate containing a μ-F ( expelled from the metalated anisole) between metal ions (Figure 2). Note that 5 can alternatively be made by adding PMDETA to 1 in hexane, whereas it cannot be accessed via co-complexation of LiF, PMDETA, and the Al trap.

Importantly, 5 establishes that TMT can be used not only to trap carbanions but also to trap novel monomeric modifications of high lattice energy salts, that is, species that usually exist as polymeric or network lattices. This study unequivocally maps out structurally and spectroscopically the varied reaction pathways available to metallo-fluoroarenes, by trapping both organic and inorganic components of decomposition alongside that of the target metalated product. Clearly the new TMT-installed Al–C bonds are sensitive enough to facilitate decomposition by benzine formation and concomitant ate elimination.

Next we turned to the gallium trapping reagent (Ga-
(CH\(_3\)SiMe\(_3\))\(_3\)). Reaction of LiTMP and Ga(CH\(_3\)SiMe\(_3\))\(_3\) with fluorobenzene in hexane at \(-78^\circ\)C for one hour, followed by PMDETA addition gave a precipitate, that was recrystallized in 67% yield. An X-ray diffraction study of these crystals revealed 2-Ga(CH\(_3\)SiMe\(_3\))\(_3\)-1-F-C\(_6\)H\(_5\)-Li(PMDETA), 6 (see the Supporting Information) proving that, as expected, fluorobenzene was selectively metallated ortho to the F substituent (Ga1–C1 2.051(3) Å). Interestingly, this distance is shorter than the Al–C\(_\text{Ga}\) distances in 1–4, signifying enhanced Ga carboxiphility. The F atom interacts with a Li-PMDETA unit (F1–Li 1.867(6) Å), resulting in a CIP structure. The \(^1\)H NMR spectrum of 6 in C\(_6\)D\(_6\) displayed four aromatic resonances consistent with the solid-state arrangement. The \(^{19}\)F NMR spectrum displays a singlet at \(-111.35\) ppm whereas the \(^7\)Li NMR spectrum has two singlets at 0.52 and \(-0.22\) ppm with a broad featureless hump in-between suggestive of a fluxional process.

Reaction scope was extended to 1,3-difluorobenzene (giving 2-Ga(CH\(_3\)SiMe\(_3\))\(_3\)-1,3-F\(_2\)-C\(_6\)H\(_5\)-Li(PMDETA), 7, 63%), 1,3,5-trifluorobenzene (giving (2-Ga(CH\(_3\)SiMe\(_3\))\(_3\)-1,3,5-F\(_3\)-C\(_6\)H\(_5\)-Li(PMDETA), 8, 58%), and 1,3,4,5-tetrafluorobenzene (giving (2-Ga(CH\(_3\)SiMe\(_3\))\(_3\)-1,3,4,5-F\(_4\)-C\(_6\)H\(_5\)-Li(PMDETA), 9, 70%). In each case NMR data share the fluxional characteristics of 6, and are in agreement with regioselective ortho-metalation of the fluorinated arenes. Complexes 6–9 all crystallize as mixtures of two conformers as evidenced by NMR data in C\(_6\)D\(_6\), though in [D\(_6\)]THF they all adopt a single SSIP arrangement (see the Supporting Information for spectroscopic characterization). Each “gallation” proceeds in good isolated yield and leads to stable crystalline solids, in contrast to that observed with Al. Crystal structures of 8 (Figure 3) and 9 (see the Supporting Information) enabled a comparison of C\(_\text{Ga}\)–Ga distances, which elongate with increased fluorination of the aromatic ring. 6 Ga–C1 2.051(3) Å, 8 Ga–C1 2.086(4) Å, and 9 Ga1–C1 (2.093(3) Å), in line with a reduced carboxiphonic character of the metallated carbon atom. Notably, 6–9 are the first structurally characterized examples prepared by metallation.

The solution stability of gallated fluoroarene 6 was probed by monitoring its \(^1\)H NMR spectra in C\(_6\)D\(_6\) over time against
ferrocene as an internal standard. In contrast to the aluminated fluoroarenes, ca. 77% of 6 is intact after 48 h, and 65% after 160 h, highlighting the profound synthetic advantage of the Ga trap over Al for stabilization of sensitive fluoroaromatic anions. Furthermore a sample of 8 in [D₂]THF shows little sign of decomposition, even after 6 days, signifying that donor solvents enhance the stability of these systems, and evidence points to SSIP constitutions of these gallated structures. A related factor regarding the stability enhancement of the gallium complexes is the greater fluorophilicity of aluminum. Thus formation of Al–F bonds is promoted, hastening decomposition. A similar effect was reported by the group of Gessner in the stabilization of fluorene carbonoids with the heavier alkali metals.[14]

The final piece of this comparative study was to quantify how the distinct properties of these Al and Ga TMT systems would affect onward reactivity in an organic application. We chose a Pd(PPh₃)₄-catalyzed cross-coupling reaction between the metalated TMT products of 1,3,5-trifluorobenzene with benzyl chloride (Table 1). Note that LiTMP on its own proved ineffective in this reaction over a variety of conditions.

### Table 1: Metalation reactions (using Al and Ga traps), and subsequent cross-coupling with benzyl chloride and Pd(PPh₃)₄.

| M-trap                   | Yield [%] | T [°C] |
|-------------------------|-----------|--------|
| None                    | 0–20[8]   | 25[8]  |
| iBu₂Al(TMPT)            | < 10[9]   | 25     |
| Ga(CH₂SiMe₃)₂          | 79[10]    | 70     |

[a] Yield of product determined by ¹H NMR of the hydrolyzed mixture with ferrocene as an internal standard. [b] 5 mol% Pd(PPh₃)₄ does not improve the yield. [c] Reaction at room temperature results in complete decomposition of the substrate. Reaction at −78 °C afforded the product in 20%. [d] 5 mol% of Pd(PPh₃)₄.

The aluminated product 3 gave poor yields of ketone 10 (6–8%) with ²F NMR spectra of isolated solid from the quench reaction in [D₂]THF solution implying several F-containing side products. In contrast, the analogous gallated product 8 reacted with benzyl chloride more efficiently affording a best yield of 10 of 80% as quantified by NMR studies using ferrocene as internal standard. Hydrolysis at the onset of the reaction, presumably through moisture contamination, appears to be the only side reaction (see the Supporting Information for experimental details). Though Huang and co-workers have previously prepared ketones in good yield from benzyl chloride and assisted lithium tetraorganoaluminates without a catalyst, the transferred nucloephiles were much less sensitive than the fluorinated examples probed here.[15] In our case reactions were more efficient with the catalyst. Note, however, that examples of organogallium participation in organic synthesis is relatively uncommon,[16] and furthermore, in cross-coupling chemistry it is exceptionally rare.[15,17]

In conclusion, this study has (i) shown the ability of TMT to generate and stabilize sensitive fluoroaromatic carbanions, (ii) extended TMT for the trapping of molecular forms of inorganic salts, (iii) unravelled key complex decomposition pathways involved in metalation of fluoroarenes, and (iv) established the greater robustness of arylgallium intermediates versus arylaluminum species thus opening potential new synthetic uses for the heavier group 13 metal.

### Acknowledgements

We thank the European Research Council (ERC-StG, MixMetApps) and the EPSRC (EP/N011384/1) for their generous sponsorship of this research. Data supporting this research are openly available from https://doi.org/10.15129/cdd3e405-545a-494a-84ff-0a85986070a3.

### Conflict of interest

The authors declare no conflict of interest.

**Keywords:** aluminum · carbanions · fluoroaromatic compounds · gallium · metalation

How to cite: Angew. Chem. Int. Ed. 2017, 56, 9566–9570

**Angew. Chem. 2017, 129, 9694–9698**

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Manuscript received: June 14, 2017
Accepted manuscript online: June 29, 2017
Version of record online: July 17, 2017