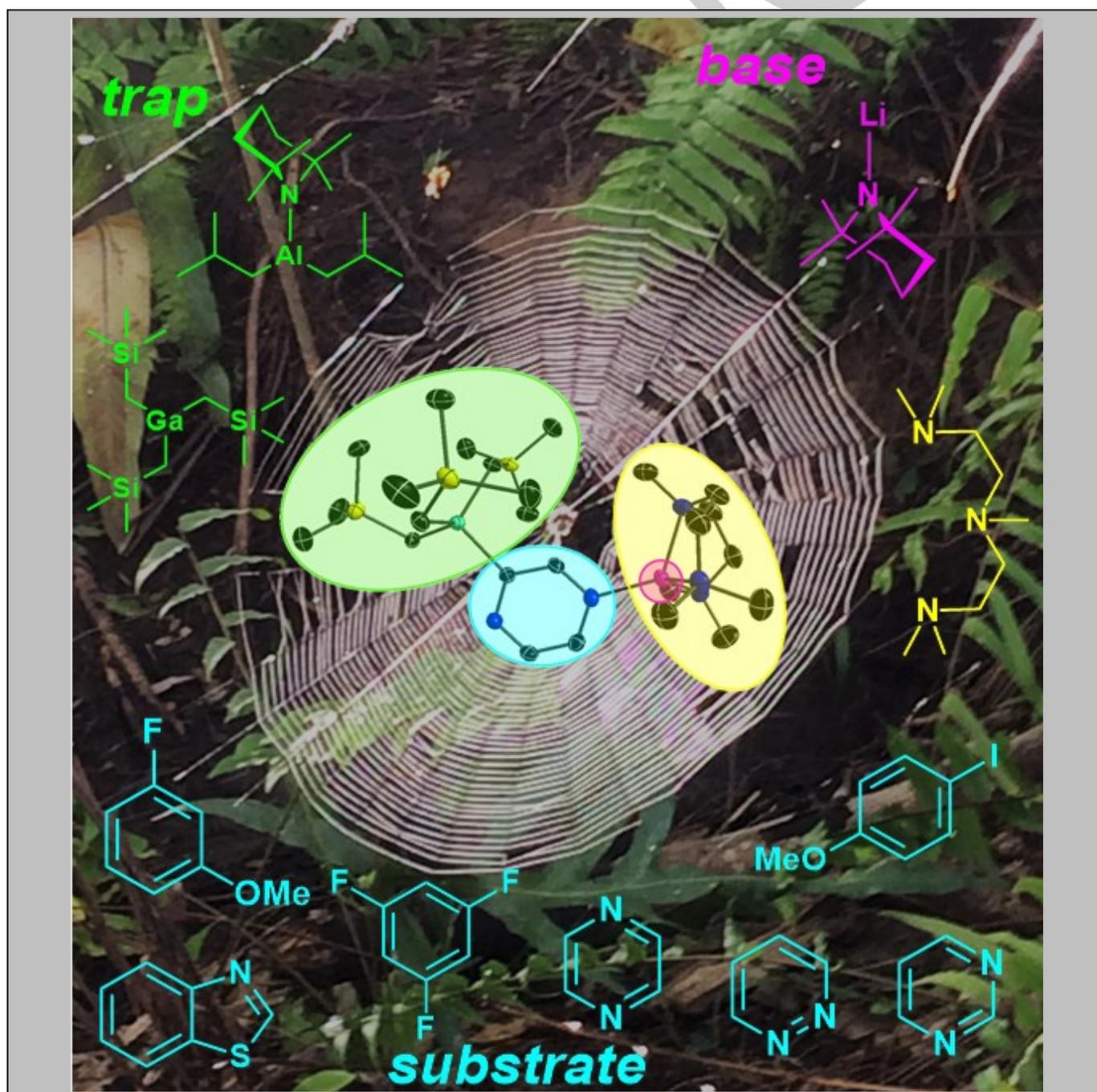


Trans-Metal-Trapping: Concealed Crossover Complexes En Route to Transmetalation?

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Dedication ((optional))



Abstract: Defined as the transfer of ligands from one metal to another, transmetalation is a common reaction in organometallic chemistry. Its chemical celebrity stems from its role in important catalytic cycles of cross-coupling reactions such as those of Negishi, Sonogashira, Stille, or Suzuki. This article focuses on trans-metal-trapping (TMT), which could be construed as partially complete transmetalations. On mixing two distinct organometallic compounds, of for example lithium with aluminium or gallium, the two metals meet in a crossover co-complex, but the reaction ceases at that point and full transmetalation is not reached. Though in its infancy, trans-metal-trapping shows promise in transforming failed lithiations into successful lithiations and in stabilising sensitive carbanions through cooperative bimetallic effects making them more amenable to onward reactivity.

Introduction

Transforming a relatively inert carbon-hydrogen bond to a reactive carbon-metal bond, metallation has been a core tool in synthetic chemistry for nearly a century. To this day chemists generally turn first to organolithium reagents when requiring a generic Brønsted base. Wilhelm Schlenk and his assistant Johanna Holtz pioneered organolithium compounds in 1917.^[1,2] Ten years later Schlenk and Bergmann employed ethyllithium to lithiate fluorene to generate fluorenyl lithium.^[3] Organolithium-mediated metallation chemistry was born. With their utility proliferating in subsequent years, such lithiating (C-H to C-Li) agents grew indispensable to synthetic laboratories, whether in academic or industrial settings. Since organolithium reagents are routinely used in manufacturing fine chemicals (e.g., agrochemicals and pharmaceuticals), Schlenk's pioneering work has undoubtedly touched the lives of a large proportion of the world's population. Reference 2 gives an enlightening essay on the life and work of this great chemist.

Sterically voluminous lithium amides of general formula $(R_2NLi)_n$ are also common lithiating agents.^[4] These include the "utility amides" so named because of their extensive employment in synthesis.^[5] In order of increasing reactivity these are LiHMDS (lithium 1,1,1,3,3,3-hexamethyldisilazide), LDA (lithium diisopropylamide) and LiTMP (lithium 2,2,6,6-tetramethylpiperidide) (Figure 1a-c).^[6] The rule of thumb is that a utility lithium amide is the base of choice in applications where nucleophilic addition across an unsaturated bond (e.g., C=O or C=N) could be a competing reaction to lithiation. Typified by *n*- or *t*-butyllithium (Figure 1d-e),^[7] alkyl lithium reagents are stronger bases than Li-N bonded compounds so in applications where nucleophilic addition is not an issue, these Li-C reagents would generally be employed. Utilisation of the bulkiest amide, the cyclic TMP anion has increased significantly, being a key component of the multicomponent metallating agents that have

emerged recently.

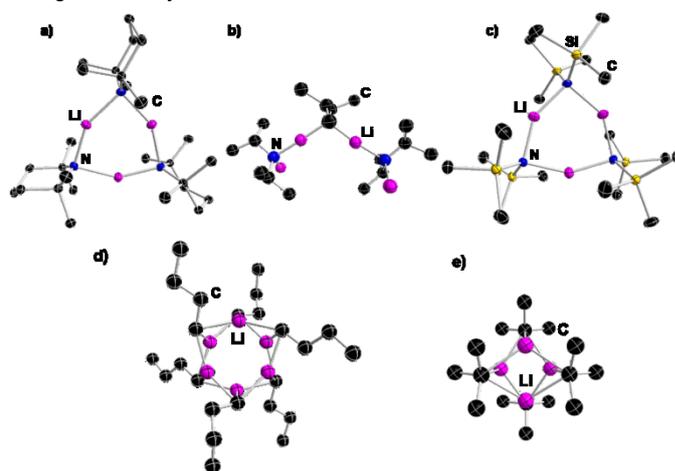
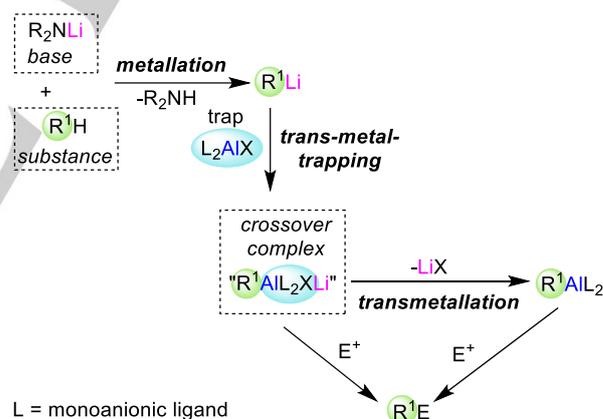


Figure 1. Common lithiating agents a) LiTMP; b) LDA; c) LiHMDS; d) *n*BuLi; and e) *t*BuLi.

Trans-metal-trapping (TMT) could be interpreted as a partial transmetalation process. Starting off in two separate compounds, the two metals meet in a crossover co-complex but the reaction stops at that point and complete transmetalation is not reached (Scheme 1).



Scheme 1. Trans-metal-trapping and its connection with transmetalation.

In perusing established cases of TMT, this article shows that metallations achieved by it can have profound advantages over conventional single-metal mediated metallations. While still at an early stage in development, TMT has the potential to transform failed lithiations into successful ones. Before discussing TMT, the fundamental importance of the related but distinct well-

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known transmetallation reaction is briefly touched on.

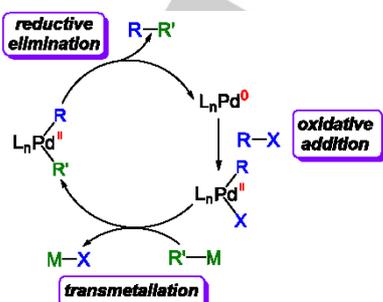
Transmetallation

A process that involves the transfer of for example σ -bonded alkyl, aryl, alkynyl or π -bonded allyl ligands from one metal to another, transmetallation is one of the most common and useful methods to prepare organometallic compounds of different metals or metalloids.^[8] The transfer of organic ligands between d^{10} metal complexes can be traced back to the seminal work of Sir Edward Frankland (1825-1899) who employed it to prepare the first organozinc compounds from zinc metal and organomercurials.^[9] His protégé Wanklyn (1834–1906) then pioneered ate compounds by pairing diethylzinc with potassium.^[9] Not long afterwards, Schlenk (1879-1943) employed the same methodology to prepare the first organolithium compounds (Scheme 2),^[11] which today, together with Grignard reagents, are popular commercial starting materials that readily undergo transmetallation with halogeno or pseudohalogeno complexes of transition metals, Group 13 and 14 elements. Along with its significance as a preparative method, organic ligand transfer between two metal complexes is present in numerous metal-mediated organic transformations including polymerization of alkenes, carbometallation and cross-coupling reactions.^[8]



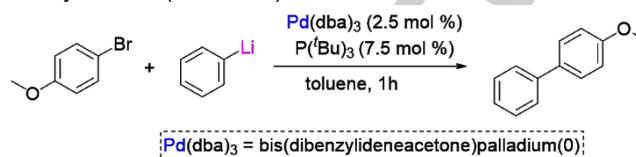
Scheme 2. An early example of transmetallation involving an organolithium.

Palladium-catalysed cross-coupling reactions (Scheme 3) have become near ubiquitous in both academia and industry for construction of carbon-carbon and carbon-heteroatom bonds, to prepare complex organic molecules such as pharmaceuticals, materials and dyes.^[10] Kharasch's original report on the homo- and cross-coupling of Grignard reagents in the presence of catalytic amounts of transition-metal salts (e.g., CoCl_2 , MnCl_2 , FeCl_3 or NiCl_2) seeded^[11] the development of transition-metal catalysed cross-coupling which has grown with the possibilities to use a wide variety of organometallic reagents and organic halides, yielding fundamental coupling methodologies such as Kumada, Sonogashira, Negishi or Suzuki, to name a few.



Scheme 3. A typical reaction cycle involving transmetallation.

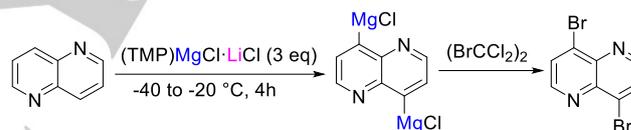
With sustained interest from the scientific community, new challenges are constantly being set, whilst old hurdles are conquered. One notable recent example was Feringa's groundbreaking report on direct coupling of organolithium compounds with aryl halides (Scheme 4).^[12]



Scheme 4. Representative example of Pd-catalysed cross coupling using organolithium and aryl halide partners.

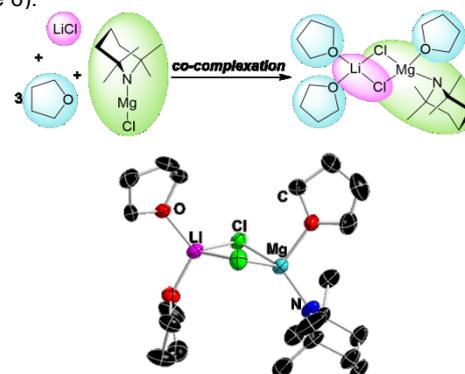
Second Generation Metallating Agents

If we regard organolithium and lithium amide compounds as first generation metallating agents, then multicomponent spin-offs can be thought of as second generation types.^[13] Knochel has led the way in this area reporting several multicomponent bases.^[14,15] Scheme 5 shows a typical application of his most utilised base, the turbo-Grignard reagent (TMP)MgCl·LiCl, whereby it selectively doubly deprotonates the heterocycle 1,5-naphthyridine to form a di-Grignard compound in situ, which following trapping with 1,2-dibromotetrachloroethane generates a dibromo derivative that is a precursor to OLED materials.^[16]



Scheme 5. Representative recent example of magnesiation of a heterocycle using a turbo-Grignard reagent and a subsequent electrophilic interception.

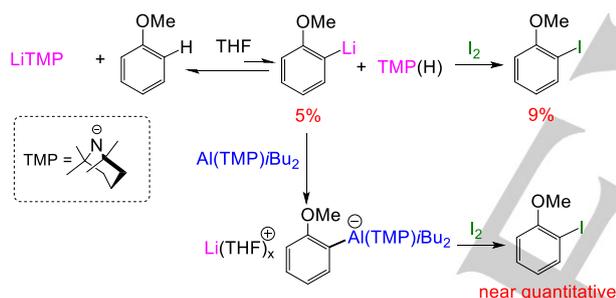
Such multicomponent bases can be considered cocomplexes. Supporting evidence for this categorisation comes in the crystal structure of $[(\text{THF})_2\text{Li}(\mu\text{-Cl})_2\text{Mg}(\text{THF})\text{TMP}]$,^[17] which formally can be interpreted as a 3-component cocomplex, namely of (TMP)MgCl, LiCl and THF (the solvent used in such reactions) (Scheme 6).



Scheme 6. Molecular structure of a turbo-Grignard cocomplex.

Stepwise Action: Trans-Metal-Trapping

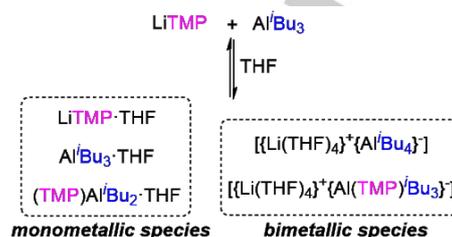
Template metallation is an unequivocal example of bimetallic cooperative behaviour where distinct metals work in unison within the same structure to effect novel C-H to C-metal transformations. In contrast, the cooperativity inherent to TMT occurs sequentially.^[26,27] First, the substrate is deprotonated by LiTMP, the strongest Brønsted base within the mixture. The second step involves organometallic compounds, for example, triisobutylaluminium (^tBu₃Al) or the mono-TMP derivative [^tBu₂Al(TMP)], that are weak Brønsted bases due to significantly less polar metal-ligand bonding versus Li-N bonding. These organoaluminium complexes act as carbanion traps, inserting into the initially formed Li-C bonds of the deprotonated substrate in a crossover complex containing both metals. Transforming Li-C bonds into Al-C bonds boosts the stability of the complexes, but there are more benefits to TMT. Reaction of anisole with the LiTMP/[^tBu₂Al(TMP)], base-trap partnership (Scheme 9) exemplifies the major benefit. Without a trap, deprotonation is inefficient since an equilibrium exists between LiTMP and its conjugate acid TMP(H), hence less than 10% of *ortho*-lithiated anisole is accessible. Adding the trap drives the equilibrium forward to the product side to afford the desired *ortho*-aluminated anisole in near quantitative yield, which in turn can be intercepted with iodine.



Scheme 9. Concept of trans-metal-trapping illustrated in the conversion of anisole to 2-iodoanisole.

Trap efficiency is a prime consideration in these reactions. Comparing [^tBu₂Al(TMP)] and (^tBu₃Al) illustrates the main points. The best traps should: (i) have sufficient steric bulk to ensure they cannot cocomplex with LiTMP; and (ii) their molecular constitutions should be stable to dimerization. Both points are satisfied by the alkyl-amido complex [^tBu₂Al(TMP)] as it does not engage in cocomplexation with LiTMP and in THF it forms a secure tetrahedral complex [^tBu₂Al(TMP)·THF].^[28] In contrast, (^tBu₃Al) exists as a dimer-monomer equilibrium in solution and its reduced steric profile enables it to engage with LiTMP. This engagement takes the form of complicated equilibria comprising five species in THF solution (Scheme 10). Significantly, the only species capable of aromatic C-H deprotonation to any significant extent is LiTMP. The inertness of the ate species, [THF·Li(TMP)Al(^tBu)₃] and its charge-separated variant [[Li(THF)₄]⁺{Al(TMP)(^tBu)₃}⁻], provides a contrast with the aforementioned magnesiate and zincate bases which have

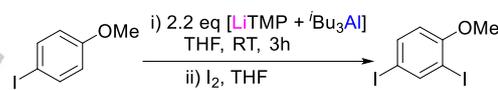
broad scope in aromatic deprotonation applications. Moreover, the Al ate species are not viable traps either.



Scheme 10. Species formed on mixing LiTMP and (^tBu₃Al) in THF solution.

The lack of such equilibria makes [^tBu₂Al(TMP)] the more efficient trap since all of the LiTMP is in its native state to perform lithiation; whereas with (^tBu₃Al) some LiTMP is tied up and unavailable in these non-basic ate forms.

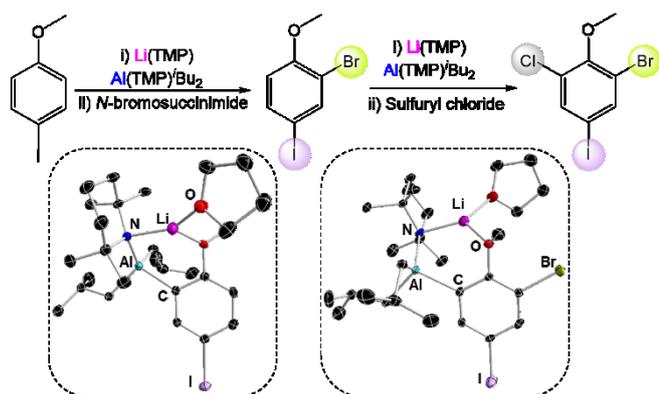
Uchiyama demonstrated that using excess (^tBu₃Al), regioselective aluminations in impressive yields could still be realised.^[29] Most significantly, while first generation alkyllithium or Grignard bases generally perform poorly with aromatic iodides due to competition from metal-iodine exchange, this Al-based TMT exhibits a high degree of iodine tolerance, though reaction with trifluoromethylbenzene proved poor yielding and unselective. Electron-withdrawing substituents (e.g., C≡N), electron-donating substituents (e.g., OMe), and substrates containing two substituent groups could also be tolerated. This third asset proved convenient for the synthesis of 1,2,3-trisubstituted aromatic products (Scheme 11).



Scheme 11. Trans-metal-trapping method to trisubstituted aromatic species.

Onward reactivity of the functionalised arylaluminum intermediates from these TMT reactions was accomplished with an assortment of electrophiles (e.g., D₂O, iodine) or through copper- and palladium-catalyzed C-C bond-forming reactions (e.g., allylation, benzoylation, phenylation), in good yields and high chemo- and regioselectivities.

The halogen tolerance of the LiTMP/[^tBu₂Al(TMP)] base/trap combination has been exploited to synthesise multi-heterohalogenated anisoles starting from 4-halo-anisoles.^[30] This provides entry to anisole derivatives containing three different halogen substituents as in 2-bromo-4-iodo-6-chloroanisole, whereby initial almination produced intermediate [(THF)Li(μ-TMP)-(μ-{1-OMe-2-Br-4-I-6-Al(^tBu)₂-C₆H₂})] which, following reaction with sulfonyl chloride, affords 2-bromo-4-iodo-6-chloroanisole in 90% yield (Scheme 12). Insight into the bimetallic cooperativity within these reactions came from characterisation of the intermediate Li-Al crossover complexes formed along the route.



Scheme 12. Synthesis of 2-bromo-4-iodo-6-chloroanisole using trans-metal-trapping showing the structures of the bimetallic Li/Al intermediates.

A limit to this iodine-tolerance is seen when the initial metallation occurs adjacent (*ortho*) to the halogen position as with 3-iodoanisole.^[28] LiTMP lithiation between the two substituents coupled with Al trapping generates an unstable crossover intermediate. This falls apart in hexane solution even at -78°C to the homometallic species $[\text{LiI-TMP(H)}]$ and $\text{t-Bu}_2\text{Al(TMP)·THF}$ and a benzyne (proved *via* Diels–Alder cyclization), while in THF solution LiTMP adds across the benzyne functionality to yield the trisubstituted product after iodine interception. Reflecting the greater stability of C–Cl bonds versus C–I bonds, switching to 3-chloroanisole restores halogen tolerance producing 2-iodo-3-chloroanisole after iodolysis.

Knochel used the related compound $\text{t-Bu}_2\text{AlCl}$ to trap aromatic carbanions following lithium halogen exchange, which proceeds through LiCl elimination giving neutral Al species as opposed to the charged ate species discussed above.^[31] More relevant to TMT is Knochel's *in situ* trapping transmetallations, whereby a range of arenes metallated by LiTMP are trapped by metal salts (e.g., $\text{ZnCl}_2\cdot 2\text{LiCl}$, MgCl_2 , $\text{CuCN}\cdot 2\text{LiCl}$) under continuous-flow conditions (Table 1).^[32] The speed of the reactions, which are complete in THF in seconds at 0°C negate any mechanistic insight though it can be assumed that LiTMP reacts faster with the arene (lithiation) than with the metal salt (transmetallation). This speed allows the benzyne problem to be circumvented in *ortho*-lithiations of haloarenes.

Mongin has also used salt adduct $\text{ZnCl}_2\cdot\text{TMEDA}$ as a trap in reactions of LiTMP with diarylketones, which then undergo iodolysis.^[33] From NMR and IR spectroscopic studies, it was concluded that $\text{ZnCl}_2\cdot\text{TMEDA}$ only operates after lithiation and intercepts the generated aryllithium. The transmetallation product $\text{TMPZnCl}\cdot\text{LiCl}$ was ruled out as the base since it is incapable of deprotonation at low temperature.

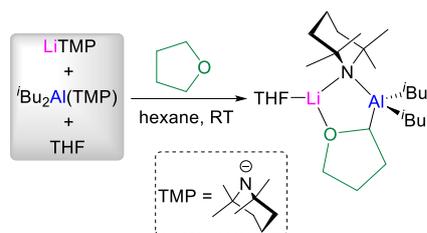
Table 1. Continuous-flow trapping metallation of aromatic substrates followed by electrophilic quench.

Entry	Substrate	Electrophile	Product
1 ^[a]			
2 ^[a]			
3 ^[b,c]			
4 ^[b,d]			
5 ^[a]			
6 ^[b,c]			

[a] Metallation conditions: LiTMP (1.5 equiv), MgCl_2 (0.5 equiv), THF, 0°C , 40 s. [b] Metallation conditions: LiTMP (1.5 equiv), $\text{ZnCl}_2\cdot 2\text{LiCl}$ (0.5 equiv), THF, 0°C , 40 s. [c] Obtained using 2 mol % $[\text{Pd}(\text{dba})_2]$ and 4 mol % $\text{P}(2\text{-furyl})_3$. [d] Obtained by Cu-catalyzed allylation.

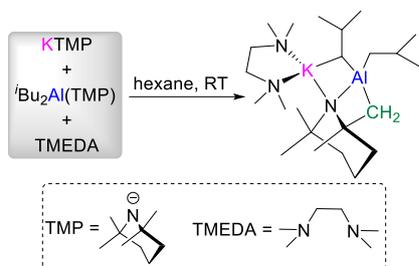
Stabilising Sensitive Metallated Substrates

A problem often encountered in organolithium chemistry is that the organic anions formed upon metallation may be unstable and susceptible to decomposition.^[4] TMT may offer a solution in certain cases to reduce or even prevent this decomposition. A notable example is with THF. Metallation of THF even at subambient temperatures can lead to ring opening and ethylene evolution.^[34] Performing TMT with LiTMP/ $\text{t-Bu}_2\text{Al(TMP)·THF}$ in bulk hexane with one additional THF equivalent yields the lithium tetrahydro-2-furanylaluminumate $[(\text{THF})\text{Li}(\mu\text{-TMP})(\mu\text{-OC}_4\text{H}_7)\text{Al}(\text{t-Bu})_2]$ (Scheme 13).^[35] Its salient feature is that the heterocyclic OC_4 ring of the α -deprotonated THF has not opened, but is stabilised cooperatively through Li and Al binding to its O and deprotonated C atoms, respectively. Sulfur heterocycle tetrahydrothiophene undergoes the same ring-retained conversion to form a trapped α -deprotonated SC_4H_7 anion.



Scheme 13. Trans-metal-trapping and stabilisation of the sensitive THF anion.

An eye-catching example of a special deprotonation is seen on mixing KTMP with $t\text{Bu}_2\text{Al}(\text{TMP})$ and TMEDA in hexane.^[36] No mechanistic details were revealed in this reaction but inspecting the product $[(\text{TMEDA})\text{K}(\mu\text{-TMP}^*)(\mu\text{-}t\text{Bu})\text{Al}(t\text{Bu})]$ (where TMP^* represents a unique CH_3 -deprotonated dianionic variant of the cyclic amine), it can be hypothesized that a TMEDA adduct of KTMP has deprotonated a Me arm on the TMP of $t\text{Bu}_2\text{Al}(\text{TMP})$ through an intramolecular steric clashing as the molecules come together to cocomplex.

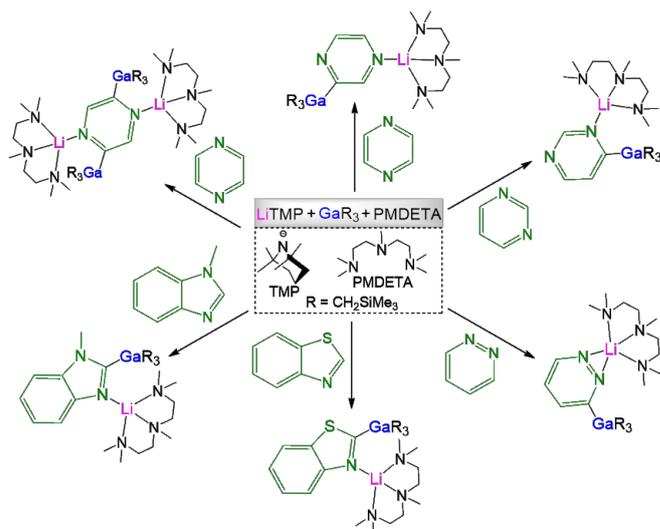


Scheme 14. Rare example of trans-metal-trapping involving a potassium base

Trans-Metal-Trapping Extended to Gallium

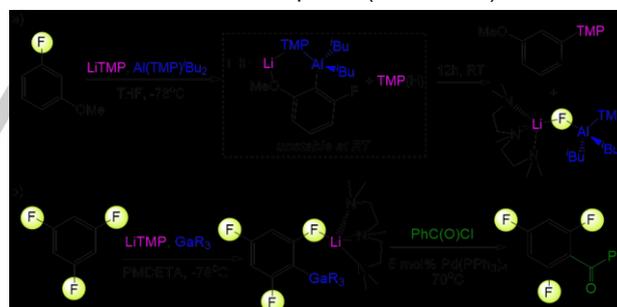
Establishing that TMT is not confined to Al-based traps, tris(trimethylsilylmethyl)gallium $[\text{Ga}(\text{CH}_2\text{SiMe}_3)_3, \text{GaR}_3]$ proved an effective trap combined with LiTMP in reactions with diazines.^[37] This important class of natural heterocycle finds application in commodities such as agrochemicals, foodstuffs, and pharmaceuticals. Substrates that common deprotonating bases find formidable due to factors such as poor selectivity or competition from nucleophilic addition, the diazines, pyrazine, pyridazine and pyrimidine, as well as the N,S heterocycle benzothiazole, were all cleanly deprotonated regioselectively by this $\text{LiTMP}/\text{GaR}_3$ protocol (Scheme 15).

Participation of PMDETA facilitated crystallisation of these Li-Ga diazine derivatives, providing rare examples of crystallographically authenticated metallodiazine complexes. As with $t\text{Bu}_2\text{Al}(\text{TMP})$, a key factor in the success of GaR_3 is its inability to cocomplex with LiTMP . Onward reactivity of the gallated pyrazine and gallated benzothiazole products was achieved with trimethylsilyl chloride, though whether these gallated species are amenable to a wider range of electrophiles is still an open question.



Scheme 15. Representative examples of trans-metal-trapping using a Ga trap.

Fluoro-substituted aromatic molecules also present a formidable challenge to lithiation due to the instability of lithiated intermediates. For this reason, a series of key fluorinated aromatics were the subject of a study comparing $t\text{Bu}_2\text{Al}(\text{TMP})$ and GaR_3 traps using LiTMP .^[38] While the former could effect alumination adjacent to a F-substituent in all cases, yields were poor, with the problem presumed to be elimination of aluminate $[\text{LiAlF}(\text{TMP})t\text{Bu}_2]$ to generate a benzyne intermediate, which in turn reacts with TMPH from the initial deprotonation to produce a TMP substituted aromatic compound (Scheme 16).



Scheme 16. Examples of trans-metal-trapping of fluoroarenes with an a) Al or b) Ga trap, highlighting the greater stability of the gallated derivative.

GaR_3 proved a more effective carbanion trap and stabilizer of the sensitive fluoroaromatic ions generated by *ortho*-gallating 3-fluoroanisole, 3,5-difluoroanisole, 1,3,5-trifluorobenzene and 1,2,4,5-tetrafluorobenzene. The reduced fluorophilicity of Ga versus Al is likely a factor in the reduced tendency for decomposition to occur via metal-F elimination. Therefore, gallated fluoroaromatic species are thus better for onward reactivity as demonstrated in cross-coupling reactions with benzoyl chloride that produce ketones.

Current and Future Perspectives

Since in situ tandem metallation-electrophilic interception processes are widespread in synthetic chemistry, where such processes involve two distinct metals TMT could be missed because only the metal-free organic products would have been studied and identified. As Scheme 1 depicts, whether partial or complete transmetallation occurs the same electrophilically quenched substrate R¹E could be produced from either process. Hence, TMT could be more prevalent than those examples identified in the literature as others might simply have been considered routine transmetallation reactions. Deliberate development of TMT is still in its infancy as to date it has been limited to one base LiTMP and a few traps. Studies are now required where base and trap are systematically altered. The scope appears potentially huge given the large number of known bases (e.g., of Li, Na or K). The challenge will be to match a base with a trap that is easily removed from the nascent carbanion when treated with electrophiles. Since the trap offers stability to the carbanion this seems contradictory to its easy removal. However, such a challenge is there to be met by clever design of traps with appropriate steric and electronic features.

Acknowledgements

We thank Professor Eva Hevia for her insightful comments, Dr Samantha Orr for help with figures, and Dr Donna Ramsay for her excellent work that led to the TMT concept.

Keywords: main group elements • metallation • organometallic chemistry • stepwise synergy • trans-metal-trapping • transmetallation

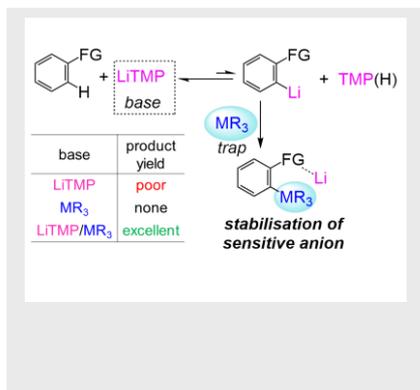
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Layout 1:

CONCEPT

“Double or nothing”: Arenes and heteroarenes metallated by the harsh lithium base, LiTMP, can often give rise to unstable lithiated intermediates in poor yields. However, doubling up the metals by intercepting with gentle organoaluminium or organogallium trapping agents stabilizes these metallated intermediates and increases their yields, making them more favourable towards onward functionalization.



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Trans-Metal-Trapping: Concealed Crossover Complexes En Route to Transmetalation?