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

Marina Uzelac[a] and Robert E. Mulvey*[a]

Dedication (optional)
CO
NCEPT

Abstract: Defined as the transfer of ligands from one metal to another, transmetallation 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 transmetallations. 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 transmetallation 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 tert-butyllithium (Figure 1d-e),[7] alkyllithium 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) "BuLi; and e) BuLi.

Trans-metal-trapping (TMT) could be interpreted as a partial transmetallation 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 transmetallation is not reached (Scheme 1).

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

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-
known transmetallation reaction is briefly touched on.

**Transmetallation**

A process that involves the transfer of for example σ-bonded alkyl, aryl, alkynyl or σ-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. The transfer of organic ligands between d-orbital 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. His protégé Wanklyn (1834–1906) then pioneered ate complexes by pairing diethylzinc with potassium. Not long afterwards, Schlenk (1879–1943) employed the same methodology to prepare the first organolithium compounds (Scheme 2), 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.

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 ground-breaking report on direct coupling of organolithium compounds with aryl halides (Scheme 4).

---

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

**Scheme 3.** A typical reaction cycle involving transmetallation.

**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. Knochel has led the way in this area reporting several multicomponent bases. 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.

Such multicomponent bases can be considered cocomplexes. Supporting evidence for this categorisation comes in the crystal structure of [(THF)_2Li(μ-Cl)]_2Mg(THF)TMP, 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).
An early example of such cocomplexes, zincate \([\text{THF}]\text{Li(}\mu-\text{TMP})\text{[t-Bu}Zn\text{[t-Bu]}\)](Figure 2)\(^{19}\) a 1:1:1 composite of LiTMP, ZnBu\(_2\) and THF is an effective and functional group tolerant zin cate (C-H to C-Zn) agent for aromatic substrates including ones containing cyano, ester or halide substituents sensitive to organolithium reagents.\(^{19}\)

![Figure 2. Molecular structure of TMP-zincate \([\text{THF}]\text{Li(}\mu-\text{TMP})\text{[t-Bu}Zn\text{[t-Bu]}\)]\]  

**Synchronistic Action: Template Metallation**

Spectacular examples of multicomponent synchronistically operate metallating agents can be found in inverse crown chemistry.\(^{20}\) Here, two distinct metal atoms are locked together in azametallo ring templates of various sizes. For example, six potassium, six magnesium and twelve nitrogen atoms are found in an alternating K-N-Mg-N arrangement within the 24-atom ring structure of \([\text{K}_6\text{Mg}_6\text{N}_{12}\text{TMP}]_2\text{[t-Bu]}\), while the butyls bound to magnesium project towards the ring centre.\(^{21}\) As this is the base structure pre-metallation, it is referred to as a pre-inverse-crown. Remarkably, the 24-membered \([\text{K}_6\text{Mg}_6\text{N}_{12}\text{]}\) ring is retained post-metallation as illustrated by deprotonation of naphthalene which occurs regioselectively at the 2-position to produce inverse-crown \([\text{K}_6\text{Mg}_6\text{N}_{12}\text{TMP}]_2\text{[2-C_6H_4]}\)](Figure 3).\(^{22}\) Although these are solid state structures it is important to caution that in solution there can be present multiple species with different constitutions. Therefore it is imperative that in order to get the full picture on structural arrangements, X-ray crystallographic data are supported with solution state studies such as DOSY NMR studies.\(^{23}\)

![Figure 3. Molecular structure of inverse crown \([\text{K}_6\text{Mg}_6\text{N}_{12}\text{TMP}]_2\text{[2-C_6H_4]}\)]

Iodination of this molecule produces 2-iodo-naphthalene. In conventional monometallic chemistry organopotassium compounds are orders of magnitude more reactive than organomagnesium compounds, yet in these bimetallic modifications the aromatic substrate is deprotonated by the less reactive magnesium centre. As well as reversing relative organometallic reactivities, this structural control can deliver new reaction selectivities. Benzene ring substituents generally direct lithiation ortho to themselves depending on their Lewis basic prowess (to attract Lewis acidic Li) and their electron withdrawing capacity (inductive effect). Illustrating that the base structure can overcome DoM, a selective meta, meta dimagnesiation takes place with substrates such as \(N, N\)-dimethylaminiine and \(t\)-butylbenzene, when reacted with \([\text{Na}_4\text{Mg}_6\text{N}_{12}\text{TMP}]_2\text{[t-Bu]}\).\(^{24}\) Remarkably, the polyaryl substrate para-terphenyl could be deprotonated twice on one terminal Ph ring to generate mono-inverse-crown, \([\text{Na}_4\text{Mg}_6\text{N}_{12}\text{TMP}]_2\text{[3,5-para-terphenyl-di-ide]}\), or four times (twice on each terminal Ph ring) to afford bis-inverse-crown \([\text{Na}_4\text{Mg}_6\text{N}_{12}\text{TMP}]_2\text{[3,3″,5,5″-para-terphenyl-tetra-ide]}\) (Scheme 7).\(^{25}\)

![Scheme 7. Polymagnesiation of para-terphenyl via a pre-inverse-crown base.]

Template metallation offers applicability in synthetic campaigns where twofold metallation is required for onward functionalisation. This was nicely illustrated through conversion of biphenyl to \([\text{Na}_4\text{Mg}_6\text{N}_{12}\text{TMP}]_2\text{[3,5-biphenyl-di-ide]}\), which following iodolysis and Cu-catalyzed Ullmann-type coupling of carbazole generates 3,5-bis(N-carbazolyl)-1,1″-biphenyl (Scheme 8), of interest in organic light-emitting diode technology.

![Scheme 8. Regioselective conversion of biphenyl to a bis-carbazolyl derivative.]

---

\(^{19}\) S. H. \& T. \(\cdot\) \(\cdot\) \(\cdot\) 2021, \(\cdot\) \(\cdot\) \(\cdot\)

\(^{20}\) S. H. \& T. \(\cdot\) \(\cdot\) \(\cdot\) 2021, \(\cdot\) \(\cdot\) \(\cdot\)

\(^{21}\) S. H. \& T. \(\cdot\) \(\cdot\) \(\cdot\) 2021, \(\cdot\) \(\cdot\) \(\cdot\)

\(^{22}\) S. H. \& T. \(\cdot\) \(\cdot\) \(\cdot\) 2021, \(\cdot\) \(\cdot\) \(\cdot\)

\(^{23}\) S. H. \& T. \(\cdot\) \(\cdot\) \(\cdot\) 2021, \(\cdot\) \(\cdot\) \(\cdot\)

\(^{24}\) S. H. \& T. \(\cdot\) \(\cdot\) \(\cdot\) 2021, \(\cdot\) \(\cdot\) \(\cdot\)

\(^{25}\) S. H. \& T. \(\cdot\) \(\cdot\) \(\cdot\) 2021, \(\cdot\) \(\cdot\) \(\cdot\)
**Stepwise Action: Trans-Metal-Trapping**

Template metallation is an unequivocal example of bimetallic cooperative behaviour where distinct metals work in unison within the same environment to effect novel C-H to C-metal transformations. In contrast, the cooperativity inherent to TMT occurs sequentially. First, the substrate is deprotonated by LiTMP, the strongest Brønsted base within the mixture. The second step involves organometallic compounds, for example, triisobutylaluminium (Bu₃Al) or the mono-TMP derivative [Bu₂Al(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/[Bu₂Al(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-aluminiated anisole in near quantitative yield, which in turn can be intercepted with iodine.

\[
\text{OMe} + \text{LiTMP} \rightarrow \text{OMe}^{-} + \text{Li}^{+} \quad \text{THF}
\]

\[
\text{OMe}_{2} + \text{Al(TMP)Bu}_{2} \rightarrow \text{OMe}_{2}^{-} + \text{Al}^{+} \quad \text{THF}
\]

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 [Bu₂Al(TMP)] and (Bu₃Al) 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 dismutation. Both points are satisfied by the alkyl-amido complex [Bu₂Al(TMP)] as it does not engage in cocomplexation with LiTMP and in THF it forms a secure tetrahedral complex [Bu₂Al(TMP)-THF]. In contrast, (Bu₃Al) 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(Bu₃)] and its charge-separated variant [Li(THF)₂⁺][Al(TMP)⁺(Bu₃)], 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.

\[
\text{LiTMP} + \text{AlBu₃} \quad \text{THF}
\]

\[
\text{LiTMP} + \text{THF} \rightarrow \text{Li}^{+} \quad \text{THF}
\]

Scheme 10. Species formed on mixing LiTMP and (Bu₃Al) in THF solution.

The lack of such equilibria makes [Bu₂Al(TMP)] the more efficient trap since all of the LiTMP is in its native state to perform lithiation; whereas with (Bu₃Al) some LiTMP is tied up and unavailable in these non-basic ate forms.

Uchihama demonstrated that using excess (Bu₃Al), regioselective aluminations in impressive yields could still be realised. Most significantly, while first generation alkylolithium 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 trifluoromethyl benzene 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).

\[
\text{OMe} + \text{LiTMP} + \text{Bu₂Al} \quad \text{THF, RT, 3h}
\]

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

Onward reactivity of the functionalised arylaluminate 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/[Bu₂Al(TMP)] base/trap combination has been exploited to synthesise multi-heterohalogenated anisoles starting from 4-halo-anisoles. This provides entry to anisole derivatives containing three different halogen substituents as in 2-bromo-4-ido-6-chloroanisole, whereby initial alumination produced intermediate ([THF-Li(μ-TMP)-(μ-1-OMe-2-Br-4-I-Al(Bu₃)₆-C₆H₃)]) which, following reaction with sulfuryl chloride, affords 2-bromo-4-ido-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.
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. 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. Performing TMT with LiTMP/BAu(THF)·THF in bulk hexane with one additional THF equivalent yields the lithium tetrahydro-2-furanylamalinate ([THF]Li(µ-THF)(µ-OC6H5)Au(Bu)2) (Scheme 13). Its salient feature is that the heterocyclic OC6H5 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 S2C2H7 anion.
An eye-catching example of a special deprotonation is seen on mixing KTMP with iBu₂Al(TMP) and TMEDA in hexane.\(^3\) No mechanistic details were revealed in this reaction but inspecting the product \(\text{[(TMEDA)}\text{K(µ-TMP*)µ-iBu)Al(iBu)}\) (where TMP* represents a unique CH₃-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 iBu₂Al(TMP) through an intramolecular steric clashing as the molecules come together to cocomplex.

**Trans-Metal-Trapping Extended to Gallium**

Establishing that TMT is not confined to Al-based traps, tris(trimethylsilylmethyl)gallium \([\text{Ga(CH₂SiMe₃)}₃] \) proved an effective trap combined with LiTMP in reactions with diazines.\(^4\) 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 LiTMP/GaR₂ protocol (Scheme 15).

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 iBu₂Al(TMP) and GaR₂ traps using LiTMP.\(^5\) 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 \([\text{LiAlF(TMP)}\text{iBu}²\text{Al]}\) 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 13.** Trans-metal-trapping and stabilisation of the sensitive THF anion.

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

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

**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.

GaR₂ proved a more effective carbanion trap and stabilizer of the sensitive fluorooaromatic 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 transmetalation occurs the same electrophilically quenched substrate R'E 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 transmetalation 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 • transmetalation

“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.

M. Uzelac, R. E. Mulvey
Page No. – Page No.
Trans-Metal-Trapping: Concealed Crossover Complexes En Route to Transmetallation?