

Uncovering the Untapped Potential of the Use of Sodium Amides for Regioselective Arene Functionalisation

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Abstract: Alkali-metal amides have become key reagents in synthetic chemistry, with special focus in deprotonation reactions. Despite the higher reactivity found in the heavier sodium and potassium amides, their insolubility and low stability has favoured the use of the more soluble lithium analogues, converting them into the most used non-nucleophilic bases. Studying the coordination effects of Lewis donor molecules such as tridentate amine PMDETA (*N,N,N',N'',N'''*-pentamethyldiethylenetriamine) in combination with the sodium amide NaTMP (TMP = 2,2',6,6'-tetramethylpiperidide), we have been able to unlock the use of these reagents for the functionalisation of arenes, *i.e.* deuterium incorporation by hydrogen isotope exchange and the deprotonative borylation of unactivated arenes. These findings show how sodium amides are not just a simple, more sustainable, replacement of their lithium counterparts, but also that they can display significantly enhanced reactivities allowing for the development of new transformations.

Keywords: Alkali metal · Amide · Borylation · Deuteration · Sodium



Andreu Tortajada was born in Benaguasil (Valencia, Spain) and moved to Tarragona, where he obtained his master's degree and PhD at the Catalan Institute of Chemical Research in 2020, under the supervision of Prof. Ruben Martin. During his doctoral studies he focused on the use of nickel catalysis for the incorporation of CO₂ and isocyanates into organic matter. He then moved as a postdoctoral researcher to the

group of Prof. Eva Hevia at the University of Bern, where he is currently investigating s-block and transition metal organometallic compounds for the selective metalation and functionalisation of arenes.

1. Alkali-metal Amides in Synthesis

From the first studies regarding the use of lithium amides for the α -deprotonation of esters in 1950 by Hamell and Levine,^[1] alkali-metal amides have become one of the most utilised reagents in synthetic chemistry today.^[2] The main reason for their success is based on their considerable complementary Brønsted basicity and poor nucleophilicity,^[3] promoting the abstraction of a proton from the substrate and disfavoured the nucleophilic attack into relatively reactive moieties present in the molecule (Fig. 1a). Combined with their generally high solubility in organic solvents and their simple handling, they have displaced the use of alkali-metal hydrides and alkyl organometallics to become the reagents of choice for deprotonative applications, *e.g.* the formation of enolates from the corresponding carbonyl compounds.

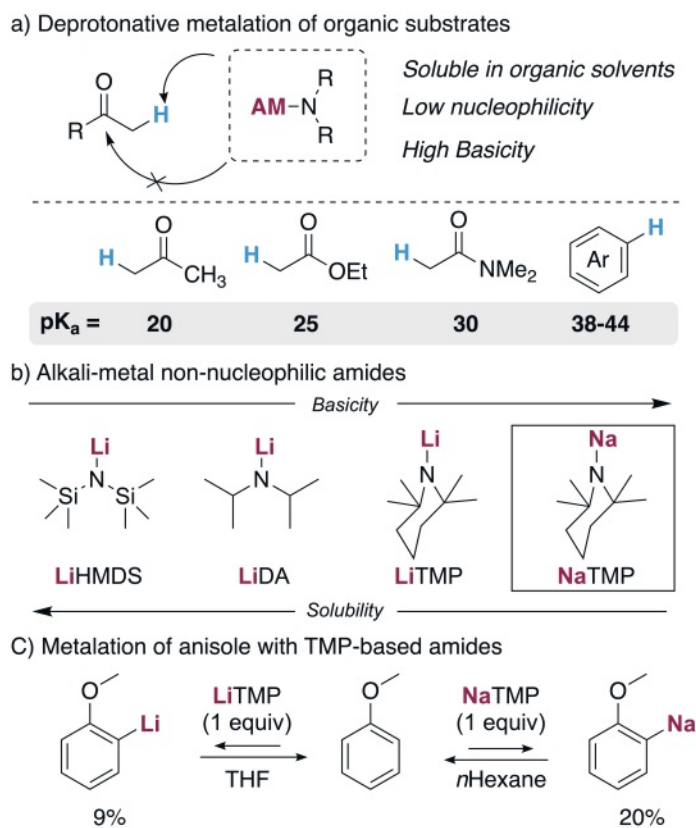


Fig. 1. Deprotonative metalation with alkali-metal amides. AM = alkali metal.

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The most commonly used secondary alkali-metal amides are LiHMDS, LiDA and LiTMP (HMDS = 1,1,1,3,3,3-hexamethyl-disilazide, DA = diisopropylamide, TMP = 2,2',6,6'-tetramethylpiperidine, Fig. 1b).^[4] These amides are commercially available and are routinely used in organic and inorganic synthetic laboratories. When looking into the heavier alkali-metal analogues, we can observe that sodium and potassium secondary amides have generally higher basicity and reactivity.^[5] However, their much lower solubility in hydrocarbon solvents and low stability have precluded their widespread use, with the exception of the more soluble NaHMDS and KHMDS, which are commercially available. With an increased focus on sustainability in organometallic chemistry and the superior reactivity expected for these reagents, the interest on the preparation and the properties of more abundant sodium (and potassium) organometallic compounds have significantly increased in recent years.^[6] Several studies have proved the enormous potential of these reagents in deprotonative metalation reactions, both as a single component^[7] or in combination with another divalent metal such as Zn,^[8] Mg^[9] or Fe.^[10] Despite their enhanced reactivity, heavier alkali-metal amides still struggle to efficiently metalate less reactive substrates, such as non-activated arenes. For example, we can observe that the metalation of anisole with LiTMP or NaTMP without any additive is 9% and 20% respectively after iodolysis (Fig. 1c),^[11,12] very low values to be synthetically useful. With the aim of developing new methodologies using sodium amide bases and understanding the limitations of these transformations, in our lab we have focused on the identification and isolation of the organometallic intermediates involved in the deprotonation and functionalisation of arenes using the sodium amide NaTMP. With the use of X-ray crystallography and NMR spectroscopy, we have been able to identify superbasic sodium amide donor species soluble in hydrocarbon solvents, which have allowed us to develop a deuterium incorporation procedure by hydrogen isotope exchange (HIE)^[13] and the deprotonative borylation of unactivated arenes.^[14] Moreover, a safe and practical laboratory gram-scale synthesis of NaTMP has also been reported,^[15] which allows the easy access to this compound for research purposes.

2. Deuteration *via* Hydrogen Isotope Exchange

Despite the first organosodium compounds being reported 50 years earlier than their lithium analogues,^[16] their use has lagged behind due to their notorious insolubility in alkanes and their in-

compatibility with ethereal solvents. To increase the solubility of poorly lipophilic organometallic reagents, a well-known strategy has been the introduction of Lewis base donors,^[17] which facilitate deaggregation and permit access to more kinetically activated entities. For instance, the Collum group has assessed the effect of different donor molecules and solvents to NaHMDS and NaDa,^[18,19] finding that the trimeric forms of these amides formed in solution can be broken down to smaller and more reactive dimeric and monomeric species. Per contra, the basic properties of NaTMP and the effect of using Lewis donor molecules have been less understood and exploited. Lappert and Mulvey reported the classic trimeric ring motif for the structure of unsolvated NaTMP in the solid state (Fig. 2).^[20] Upon addition of the donor molecule TMEDA (*N,N,N',N'*-tetramethylethylenediamine), the structure breaks into a more reactive and soluble disolvated dimer.^[21]

With this structural information in mind, we decided to study the effect of polyamine Lewis donors into the metalation of different arenes. We started by monitoring the reaction by ¹H NMR spectroscopy of NaTMP, PMDETA (*N,N,N',N'',N'''*-pentamethyldiethylenetriamine) and anisole as a model aromatic substrate. The formation of mixed aggregate [(PMDETA)₂Na₂(TMP)-(C₆H₄-OMe)] **1** was observed, with a 43% yield based on anisole metalation. Crystallisation experiments with both TMEDA and PMDETA allowed the determination of its molecular structure in the solid state, confirming the presence of a metalated anisole fragment and an unreacted NaTMP unit. Despite the addition of an excess of anisole or the increase of the reaction time, the metalated TMP unit did not further proceed to deprotonate the arene molecule, showing a nearly 1:1 ratio between sodiated anisole and unreacted NaTMP in solution.

To explore the possibility of deprotonating less reactive arenes, we tested the reaction of benzene with the NaTMP/TMEDA combination in hexane solution. Crystallisation of the crude mixtures at low temperature allowed the isolation of mixed aggregate [(TMEDA)₂Na₃(TMP)₂(Ph)] (**2**), showing the ability of these superbasic sodium amide donor species to metalate benzene. This novel trimeric motif can be seen as the cocomplexation of NaPh with the dimer formed by NaTMP/TMEDA. In a similar way to anisole, the metalation of benzene is not complete and both the sodium base and the metalated arene are present at the same time in solution.

Having isolated and characterised these mixed-aggregates and taking advantage of the incomplete metalation observed in

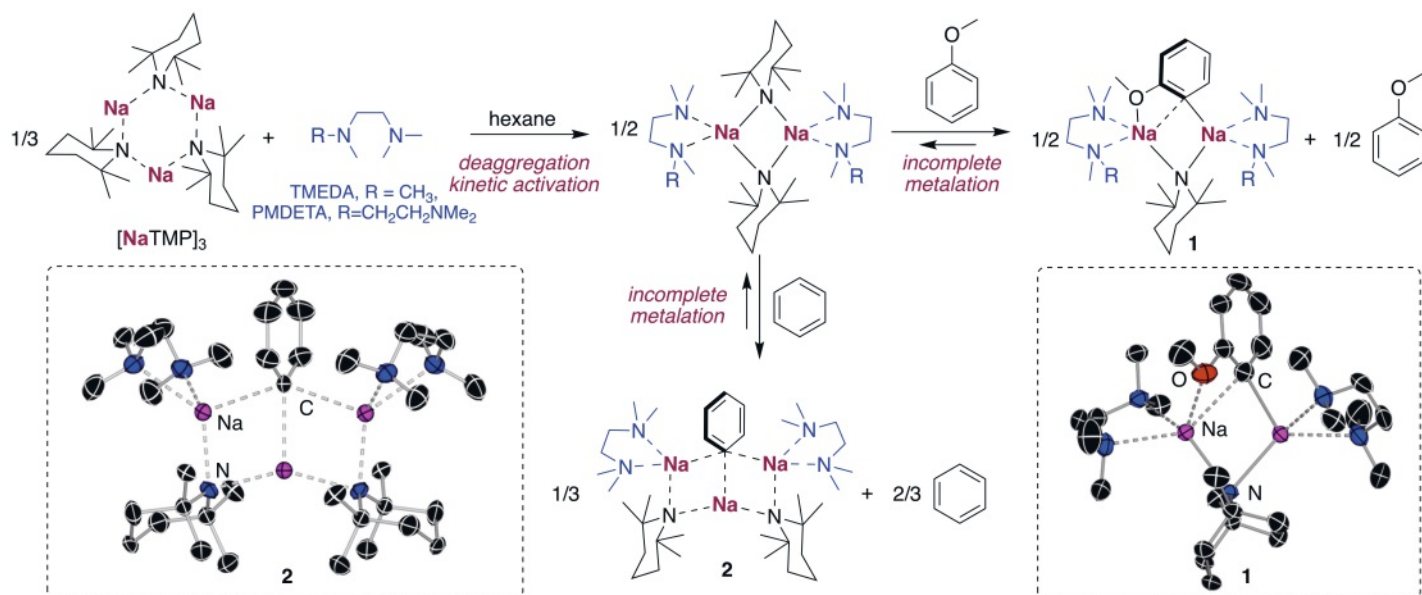


Fig. 2. Deaggregation of NaTMP and metalation of anisole and benzene by NaTMP in the presence of Lewis donors TMEDA and PMDETA.

solution, we envisioned that this system could be used for the deuteration of arenes *via* hydrogen isotope exchange (HIE). Using deuterated benzene in excess, as a solvent of the reaction, the ability of this superbasic species to deprotonate both the substrate and the solvent partially and reversibly could allow the incorporation of the deuterium atoms into different functionalised aromatic molecules. To test our hypothesis, we reacted anisole with catalytic amounts of NaTMP and different donor molecules in C_6D_6 . To our delight, the donor PMDETA gave the best result and allowed the incorporation of deuterium in very mild conditions not only in the *ortho* position, but in every single position of the anisole molecule, including its methyl group (Fig. 3). The reaction takes place with the formation of C_6D_5H , showing the exchange of the different hydrogen isotopes between the substrate and the solvent. Other reported base-mediated HIE processes of arenes require the use of more activated deuterium sources, such as deuterated DMSO or acetone, need harsher conditions and are limited to the deuteration of relatively acidic C–H bonds.^[22] This approach proved also to be successful with a different set of unactivated arenes, such as diphenylacetylene, naphthalene or toluene. Not only $C(sp^2)$ –H could be activated, but also $C(sp^3)$ –H in benzylic position or next to a Si or P atom could be efficiently deuterated, showing the versatility of this system to prepare deuterated molecules. Mechanistic studies have shown the key role of the free amine TMP(D) for an effective deuterium incorporation and a clear alkali-metal effect, since neither LiTMP nor KTMP can effectively promote this reaction.

3. Deprotonative Borylation of Unactivated Arenes

Having identified the increased solubility and reactivity exerted by the amine donors into NaTMP, we focused our attention into improving the extent of the metalation of different arenes. Previous work of our group has showed that the use of Lewis acidic trapping agents such as *i*Bu₂AlTMP and Ga(CH₂SiMe₃)₃ allows the shift of the equilibrium to allow the deprotonation of $C(sp^2)$ –H bonds with LiTMP.^[23] The main limitation of this approach was the low applicability of the obtained metalated compounds in subsequent functionalisation. We foresaw that a boron-based Lewis

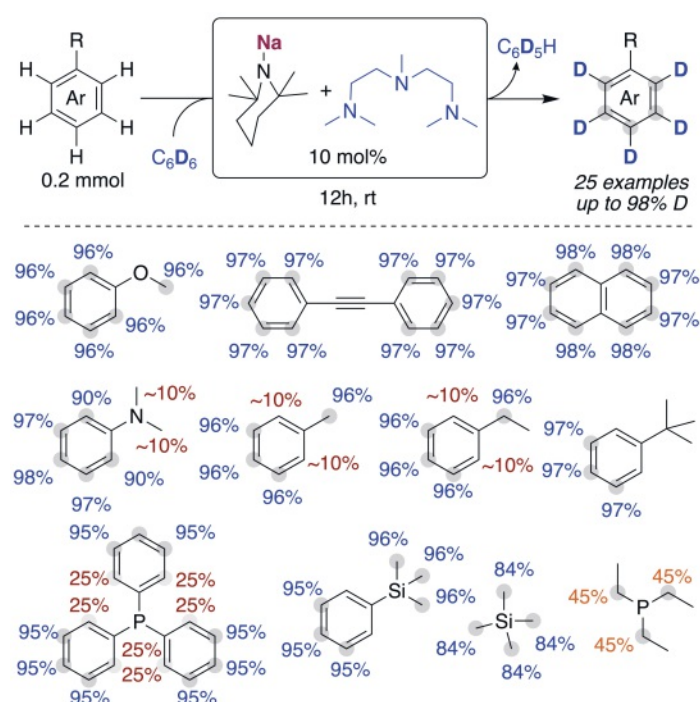


Fig. 3. Selected examples of deuterium incorporation into arenes by HIE employing catalytic amounts of NaTMP/PMDETA (10 mol%) in C_6D_6 at room temperature.

acid molecule could have greater synthetic opportunities after transmetalation, due to their ample use as trans-metalating reagent in palladium-catalysed Suzuki-Miyaura couplings.^[24] To that end, a molecule that would not react with NaTMP prior to arene metalation should be first found (Fig. 4a). After screening different tricoordinated boron-based molecules, trialkylborates resulted in the ideal Lewis acidic trap, with the nature of the alkyl chain being crucial for the success of this interception. B(O*i*Pr)₃ gave the desired sodium tetracoordinated borate in 83% yield, whereas when B(OMe)₃ was used the corresponding product was detected in low yields with full conversion of the sodium amide base. This contrasting reactivity was attributed to the steric incompatibility between NaTMP and B(O*i*Pr)₃, which favours the reactivity of the latter with the metalated anisyl fragment rather than with the sodium amide. To assess the generality of the deprotonative borylation with B(O*i*Pr)₃ and NaTMP/PMDETA, we tested the metalation of different aromatic compounds. We combined the transformation with a palladium catalysed cross coupling, obtaining the corresponding biaryls in a straightforward manner (Fig. 4b). Simple arenes such as benzene or anisole could be reacted with excellent yields. Naphthalene was selectively functionalised in the C2 position, contrasting with previous reports using alkyl sodium reagents^[25] or the Lochman-Schlosser superbases^[26] where mixtures of monometalated and multimetalated products were observed. Remarkably, the combination *n*BuLi/TMEDA fails to deprotonate this substrate, showing the enhanced reactivity of organosodium compounds. For the deprotonation of molecules containing more sensitive functional groups, such as fluorine or double bonds, good yields were obtained when the metalation step was performed at -78 °C. Overall, this represents a new approach for the formation of C–B bonds in non-activated arenes, without the need of using a large excess of the aromatic substrates and with complementary selectivity to that observed with transition metal catalysed borylations.

4. Gram-scale Synthesis of Sodium Organometallics

Recent advances in the synthesis of sodium organometallic compounds have resulted in the direct use of elemental sodium in the form of packed reactors for flow synthesis^[27] or fine sodium dispersions.^[28] While synthetically very useful, these methods present some drawbacks, *i.e.* an excess of sodium metal is generally required and the sodiated species are difficult to isolate and characterise. The classical approach to the synthesis of said organosodium reagents in a laboratory scale has been the conversion of commercially available organolithium reagents to the sodium counterparts, by using a sodium alkoxide.^[29] In this route, the pure insoluble organosodium product can be simply separated by filtration from the soluble lithium alkoxide by-product. Even though the synthesis of NaTMP was previously described using this method, we recognised the need of reporting an illustrated procedure for the preparation of this compound in a gram scale, stressing on the experimental details to achieve it in a safe and reproducible manner. We described the preparation of *n*BuNa starting from *n*BuLi and NaO*t*Bu, which could then be used to prepare NaTMP by direct deprotonation of the parent amine (Fig. 5). Accessing this amide in pure form has enabled the study of the organosodium intermediates in solution and in the solid state, proving essential for the development of these new arene functionalisation protocols.

5. Conclusions and Outlook

Understanding the coordination effects of donor molecules and their implication into the solubility and kinetic activation of sodium amides have been key for discovering new synthetic uses of alkali-metal amides. The combination of the sodium amide NaTMP with amine donors TMEDA or PMDETA forms a soluble and reactive base in hydrocarbon solvents, which is able

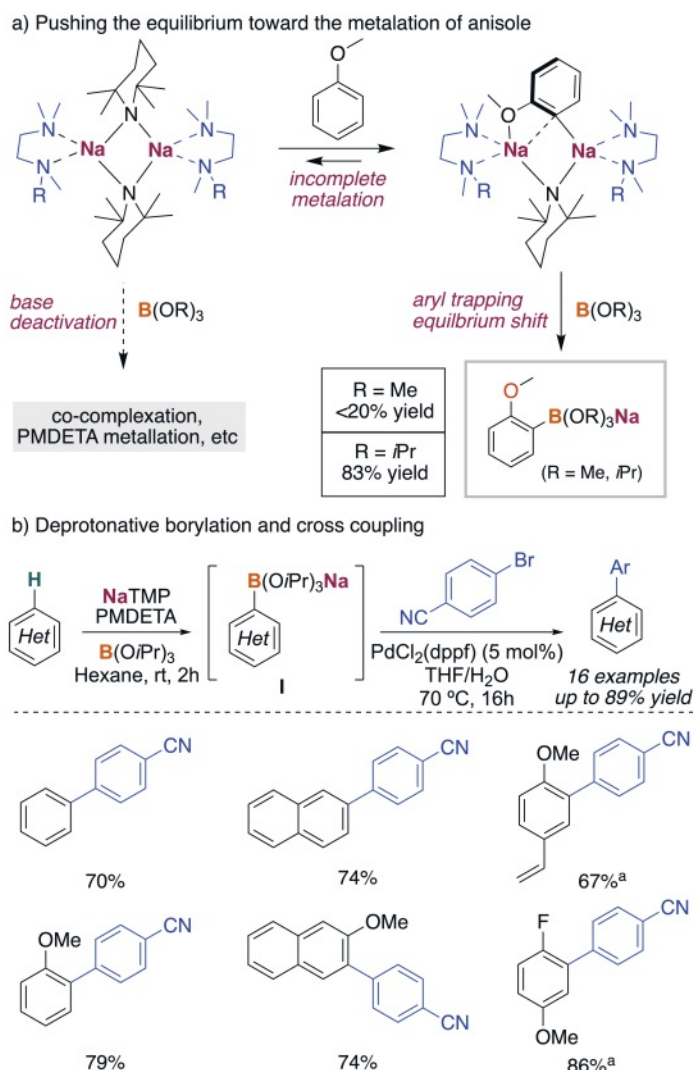


Fig. 4. Selected examples of sodium-mediated deprotonative borylation and cross coupling of arenes. ^aMetalation performed at $-78\text{ }^{\circ}\text{C}$.



Synthesised solids in glovebox:

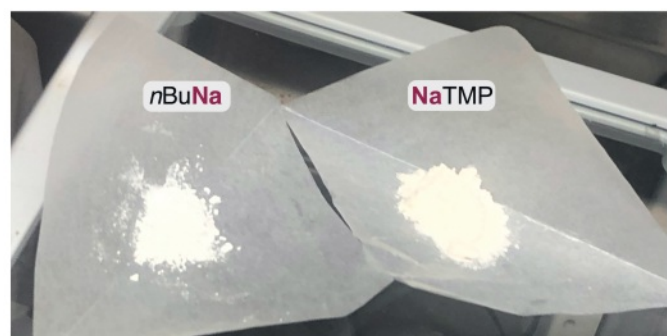


Fig. 5. Gram-Scale synthesis of salt free NaTMP.

to metalate unactivated arenes such as anisole or benzene. The preparation and isolation of these organometallic reagents in pure form has been crucial to investigate the different metalation reactions in solution and in the solid state. These studies revealed the formation of novel mixed-aggregates between the sodiated arenes and the sodium amide base, resulting in an equilibrium that

explains the low yields of metalation observed after electrophilic quenching. However, exploiting the reversible nature of the metalation reaction, a new method for the deuterium incorporation into arenes could be achieved. Moreover, the sodiated intermediates could also be trapped with a sterically demanding boron Lewis acid, pushing the equilibrium towards the formation of the metalated products.

The main limitation of these superbasic sodium amides resides in their high reactivity, which currently limits the tolerance of some more sensitive functional groups, such as ketones, nitriles or heterocycles. Future work will focus on studying the effect of the alkali-metal amide backbone to improve their selectivity and functional group compatibility, and the application of these powerful bases into the functionalisation of other synthetically relevant substrates, such as alkenes or H_2 .

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