Borylation Hot Paper

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Enhancing Metalating Efficiency of the Sodium Amide NaTMP in Arene Borylation Applications

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Abstract: Though LiTMP (TMP = 2,2′,6,6′-tetramethylpiperidide) is a commonly used amide, surprisingly the heavier NaTMP has hardly been utilised. Here, by mixing NaTMP with tridentate donor PMDETA (*N*,*N*,*N*′,*N*″,*N*″-pentamethyldiethylenetriamine), we provide structural, and mechanistic insights into the sodiation of non-activated arenes (e.g. anisole and benzene). While these reactions are low yielding, adding $B(OiPr)_3$ has a profound effect, not only by intercepting the C_{Ar}-Na bond, but also by driving the metalation reaction towards quantitative formation of more stabilized sodium aryl boronates. Demonstrating its metalating power, regioselective C2-metalation/borylation of naphthalene has been accomplished contrasting with single-metal based protocols which are unselective and low yielding. Extension to other arenes allows for in situ generation of aryl boronates which can then directly engage in Suzuki–Miyaura couplings, furnishing a range of biaryls in a selective and efficient manner.

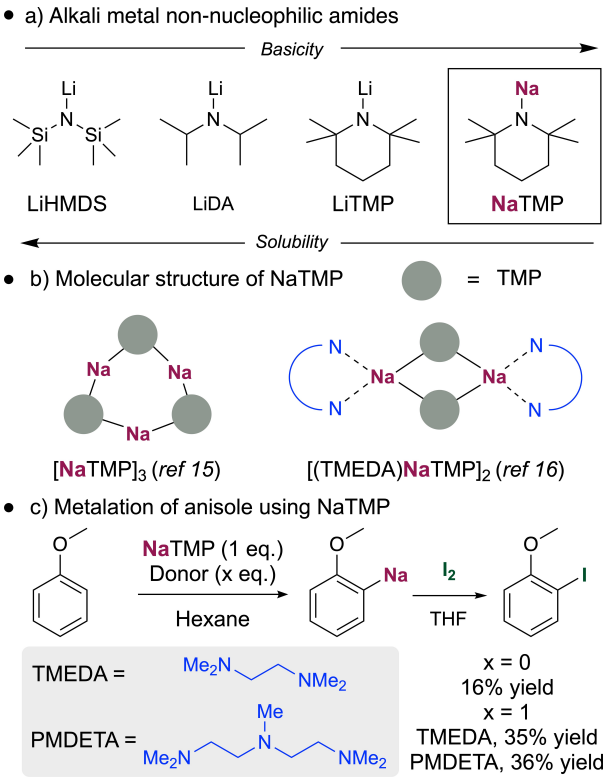

Figure 1. a) Alkali-metal non-nucleophilic basic amides, b) selected X-ray characterised structures of NaTMP, and c) reactivity of NaTMP towards anisole.

High Brønsted basicity coupled with low nucleophilicity are the properties of alkali-metal amides that have propelled these reagents to the forefront of organometallic synthesis.[1] The lithium amides LiHMDS, LiDA and LiTMP (HMDS = 1,1,1,3,3,3-hexamethyldisilazide, DA = diisopropylamide, TMP = 2,2′,6,6′-tetramethylpiperidide) find the most utility, in part due to their substantial stability and solubility in hydrocarbon solvents.[2] Often lacking these desirable traits, organosodium reagents, including sodium amides, have by comparison received much less study (Figure 1a). With increasing focus on sustainability, that picture is beginning to change with chemists turning attention to earth abundant sodium and organosodium compounds which are more reactive than lithium congeners.[3] Elemental sodium has been prominent in this work. Wagner and Mioskowski used sodium dispersions for in situ generation of an alkyl sodium for directed *ortho* metalation (D*o*M) of a small selection of activated arenes.[4] More recently, using sodium in the form of dispersion or packed-bed reactors, Takai[5] and Knochel[6] have separately reported efficient protocols for halogen/sodium exchange, for efficient preparation of organosodium compounds and their application in deprotonative metalation or transition-metal catalysed cross-coupling reactions. Despite these advances, knowledge on the organosodium intermediates involved in these reactions, which could help control their high reactivity and overcome poor solubility has been scarce.

A well-known strategy used to increase the solubility of poorly lipophilic organometallic reagents has been to introduce Lewis donor solvents and additives, facilitating deaggregation to permit access to more kinetically activated entities.[7] Collum has assessed the reactivity of Et_2O and THF solutions of both NaHMDS and NaDA in metalation

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and dehydrohalogenation reactions.[8] Combining insightful theoretical and kinetic studies, this work probes the solvation states of both NaHMDS[9] and NaDA[10] in various aromatic and Lewis donor solvent media, finding the trimeric forms of both amides breakdown to smaller, more reactive dimers and monomers. In contrast, except for a few recent reports,[11] the Brønsted basic properties of NaTMP are less understood and less utilised. This is surprising given the eminence that LiTMP holds as a strong base spanning applications within directed *ortho* metalation,[12] turbo-Hauser chemistry,[13] and, in more recent years, Trans-Metal Trapping (TMT).[14] Filling this gap in the knowledge, here we use NaTMP for arene metalation focusing especially on identifying the organometallic intermediates in these transformations. We also assess the role that additives play in boosting the reactivity of NaTMP, uncovering the regioselective metalation of non-substituted arenes such as benzene and naphthalene and add a new sodium-mediated method for arene borylation.

Lappert and Mulvey uncovered the classic trimeric ring structure of unsolvated NaTMP in the solid state (Figure 1b),[15] which breaks down to more soluble and potentially more reactive dimers on adding TMEDA (*N*,*N*,*N*′,*N*′-tetramethylethylenediamine) or THF.[16]

Using anisole as a model substrate for directed *ortho* metalation, we started assessing its reactivity towards NaTMP in hexane in the absence of any donor.[17] This reaction delivered metalation in a modest 16% yield after iodolysis (Figure 1c). Repeating the reaction adding TMEDA increased the yield of 2-iodoanisole to 35%, in evidence of an increased reactivity of NaTMP upon its deaggregation induced by the Lewis donor. Addition of tridentate PMDETA, which has been cited as a superior donor for NaDA due to its hemilability,[10c] led to almost identical conversions to those for TMEDA (36%, Figure 1c).

Next, the reactions of NaTMP, PMDETA and anisole were monitored by ^{1}H NMR spectroscopy (C_6D_{12}, 298 K). Formation of mixed-aggregate [(PMDETA)$_2$Na$_2$(TMP)-(C_6H_4-OMe)] (**1·PMDETA**) was observed almost instantaneously (Figure 2, see Supporting Information for full details) in a 43% yield, based on anisole metalation. **1·PMDETA** contains an unreacted TMP anion which, even in the presence of excess anisole, does not react further, providing a rationale to explain the <50% yields of 2-iodoanisole (Figure 1c, $x=1$). ^{1}H DOSY NMR experiments of the reaction mixture confirm the mixed aryl/amide constitution of **1·PMDETA** whose signals diffuse together with those of PMDETA. The same solution behaviour occurred using TMEDA, giving [(TMEDA)$_2$Na$_2$(TMP)-(C_6H_4-OMe)] (**1·TMEDA**) (see Supporting Information for details, including ^{1}H DOSY NMR studies).

Complexes **1·PMDETA** and **1·TMEDA** were isolated as crystalline solids. Determined by X-ray crystallography, the structure of **1·TMEDA** (Figure 2b) is dinuclear, with each Na chelated by TMEDA and bridged by a TMP and *ortho*-sodiated anisyl fragment in a mixed "dimer". While the TMP group interacts almost equally with Na1 and Na2 [Na1-N3, 2.4195(9); Na2-N3 2.4322(9) Å], the aryl fragment binds strongly to Na2 [Na2-C13, 2.5323(10) Å]; while Na1 interacts with the OMe O atom and forms a long distance interaction with the metalated C [Na1-C13, 2.7330(14) Å]. As far as we know, this compound represents a rare example

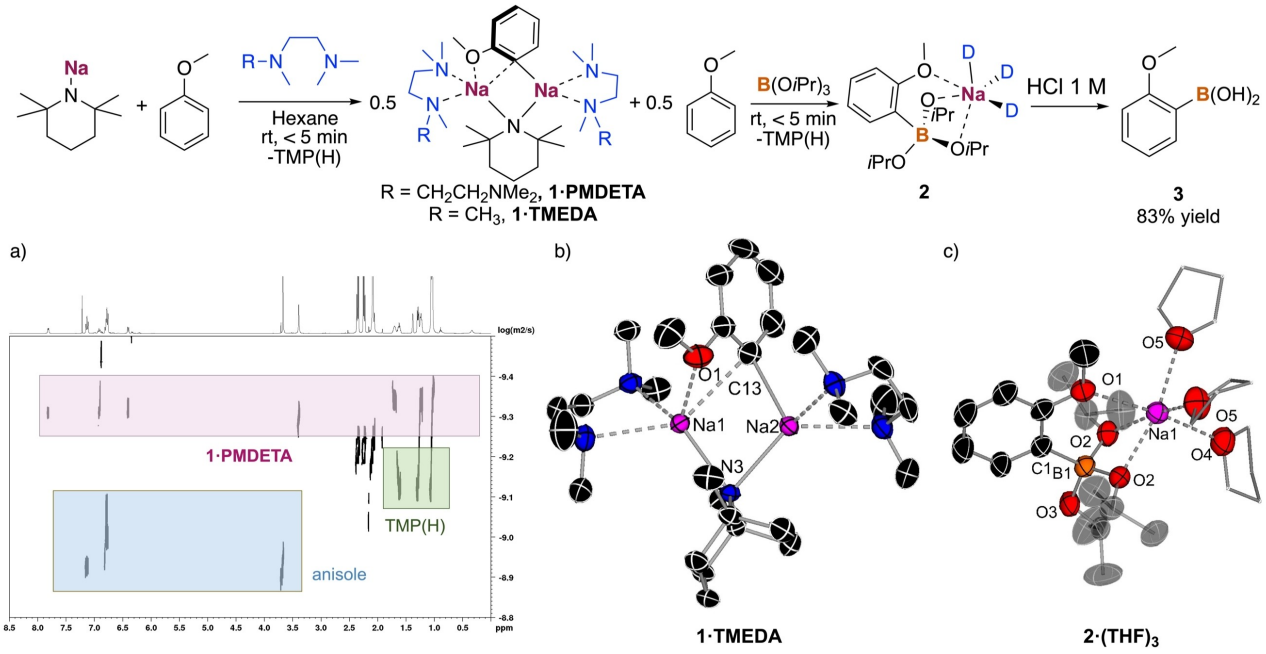


Figure 2. Metalation of anisole with NaTMP with TMEDA or PMDETA, followed by quenching with B(O*i*Pr)$_3$. a) ^{1}H DOSY NMR studies of the reaction with PMDETA, b) Molecular structure of **1·TMEDA** and c) Molecular structure of **2·(THF)$_3$** with 30% probability displacement ellipsoids. All H atoms have been omitted, for **1·TMEDA** cell unit contains two identical structures, but just one is shown and for **2·(THF)$_3$**, C atoms in THF are shown as wires for clarity.

of a structurally-defined mixed sodium-aryl/sodium-amido complex, particularly given it formed from attempted synthesis of the Na–Ar. Co-complexes of this nature have been proposed before by Collum and labelled as "*fleeting intermediates*" en route to the Na–Ar,[8a] with **1·TMEDA** allowing for structural proof of this proposal.

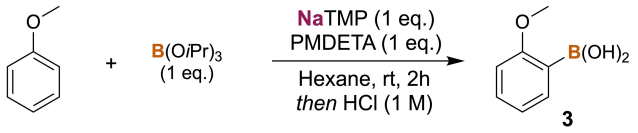
Monitoring these in situ reaction mixtures of equimolar amounts of NaTMP, anisole and PMDETA (or TMEDA) revealed that over extended periods of time, the TMP group present in **1** is not able to metalate the remaining anisole in solution (see Supporting Information), and that after 4 h at room temperature decomposition of **1** is observed.

Our previous work in TMT has used a Lewis acidic trapping agent such as iBu$_3$Al or Ga(CH$_2$SiMe$_3$)$_3$ to shift the equilibrium of deprotonation using LiTMP, leading to more stabilised ate intermediates in near quantitative yields, but with limited applications in onward functionalisation.[18] Furthermore, attempts to extend this approach to NaTMP revealed its preference to undergo co-complexation with Ga(CH$_2$SiMe$_3$)$_3$, forming an unreactive gallate complex.[11a] We pondered if switching the Lewis acid component to a boron-based species could overcome these limitations and offer further synthetic opportunities post-transmetalation stage. From the literature trialkylborates seemed good candidates to quench organometallic intermediates.[19] However, the nature of this trialkylborate seems to be influential in the speciation of the borates obtained with organometallic reagents[20] and more importantly, it should not react with NaTMP prior to arene deprotonation. Pleasingly, when one equivalent of B(OiPr)$_3$ was added to a mixture of NaTMP, anisole and PMDETA in hexane, complete consumption of anisole occurred with almost quantitative formation of 2-anisylboronate **2** (Figure 2). Crystals suitable for X-ray crystallography could be grown from the reaction mixture, confirming the selective formation of the C–B bond; whereas Na is hexacoordinated, bonded to six O atoms, two from OiPr groups on B, one from the anisole OMe and three from THF, which was added to aid crystallisation (**2·(THF)**$_3$, Figure 2c). Addition of 1.0 M HCl$_{(aq.)}$ produced boronic acid **3** in an 83 % yield, confirming the synergistic TMT effect of NaTMP, PMDETA and B(OiPr)$_3$ to promote the efficient *ortho*-functionalisation of anisole. These findings have uncovered the compatibility of NaTMP and B(OiPr)$_3$ in the reaction conditions, and the fact that upon addition of the Lewis acidic boron, the residual TMP fragment of **1·PMDETA** can be activated to react with the remaining substrate in solution, driving the deprotonation to a near quantitative yield. Thus, unlike previous studies where trialkylborates have been used for electrophilic interception,[19] here the role of B(OiPr)$_3$ goes beyond a simple quenching agent for the aryl sodium intermediate, pushing the Na–H exchange process to completion.

To shed light on how the different components of this synergistic mixture operate we carried out a systematic study changing the alkali-metal amide, Lewis donor, and boron reagent (Table 1).

Showcasing a strong alkali-metal effect, using LiTMP instead of NaTMP gave **3** in a poor 13 % yield (Table 1, entry 2). This is surprising as LiTMP has shown promise in metalation of arenes (including anisole) using TMT approaches.[18] The choice of sodium amide also seems to be crucial as NaHMDS fails to form **3**, which can be attributed to the lower basicity of HMDS (entry 3). Using an alkyl sodium reagent, NaCH$_2$SiMe$_3$, instead of NaTMP did not increase the product yield (entry 4). In this case, monitoring the reaction prior to the hydrolysis step suggests that that the alkyl sodium reacts preferentially with the boron, forming a sodium borate which is inert towards anisole metalation. Benefitting this case, the bulky amide NaTMP and B(OiPr)$_3$ do not form a co-complex in solution, as judged by ^{11}B NMR spectroscopy in C$_6$D$_{12}$ evidenced by a resonance at $\delta \approx 17.5$ ppm, indicative of free B(OiPr)$_3$.[21] Replacing PMDETA by TMEDA, did not have any significant affect (entry 5). This is consistent with our ^{1}H DOSY NMR studies which indicate that in C$_6$D$_{12}$ solutions and in the presence of one molar equivalent of these Lewis donors, NaTMP exists as a dimer. However, with no donor the yield of borylation decreases to 31 % (entry 6), probably due to the higher aggregation (and lower kinetic basicity) of unsolvated NaTMP, which does not dissolve in hexane (or C$_6$D$_{12}$) even in a large excess of anisole, suggesting that its trimeric structure in the solid state is retained. Contrastingly, using THF as a solvent inhibits the formation of **3**, possibly due to the fast degradation of NaTMP at room temperature in this ethereal solvent (entry 7). The choice of the electrophilic boron-containing partner also seems to be important. Thus, using B(OMe)$_3$ which has been previously used as a quenching agent in organolithium chemistry gives **3** in a poor 10 % yield; whereas BCl$_3$ affords only 4 % of **3** (entries 8 and 9). NMR studies indicate that NaTMP reacts with the B reagents prior to metalation, though not forming basic TMP-species. These findings suggest that the high yielding borylation of anisole is the result of the close interplay between the sodium amide with the donor PMDETA (or TMEDA) and B(OiPr)$_3$ (Scheme 1). Thus, kinetic activation of the sodium amide by the formation of smaller [Na(TMP)(N-donor)]$_2$[16] aggregates seems to be key as well as the fact that B(OiPr)$_3$ reacts preferentially with

Table 1: Deprotonation/borylation of anisole with alkali-metal amides.



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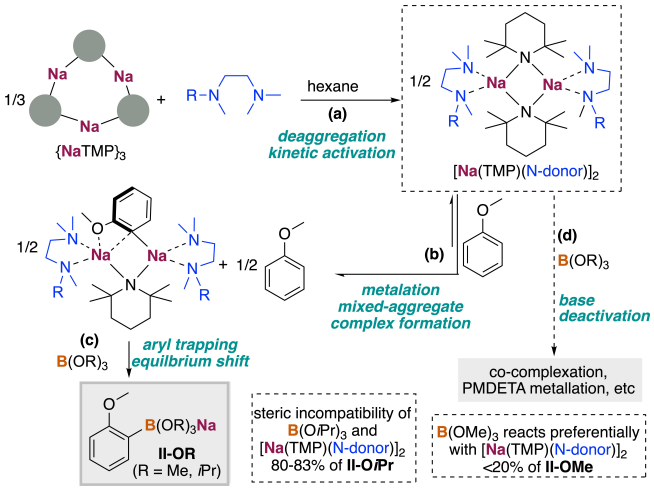
Entry	Deviation from the standard conditions	Yield **3** [%]
1	**None**	**83**
2	LiTMP instead of NaTMP	13
3	NaHMDS instead of NaTMP	0
4	NaCH$_2$SiMe$_3$ instead of NaTMP	1
5	TMEDA instead of PMDETA	82
6	Reaction in the absence of PMDETA	31
7	THF instead of Hexane	1
8	B(OMe)$_3$ instead of B(OiPr)$_3$	10
9	BCl$_3$ instead of B(OiPr)$_3$	4

Yields calculated by ^{1}H NMR spectroscopy using C$_6$Me$_6$ (10 mol %) as an internal standard.



Scheme 1. Proposed reaction pathway for sodium-mediated borylation of anisole.

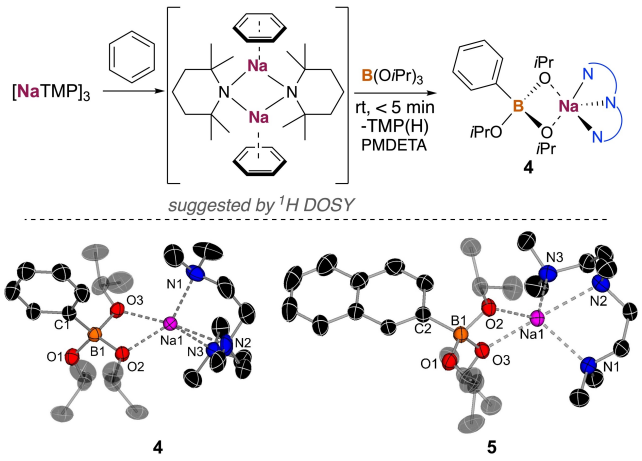


Figure 3. Deprotonative borylation of benzene. Molecular structures of [PhB(O*i*Pr)$_3$Na(PMDETA)] (**4**) and [($C_{10}H_7$)B(O*i*Pr)$_3$Na(PMDETA)] (**5**) with 30% probability displacement ellipsoids. All H atoms have been omitted for clarity.

the Na(anisyl) fragment rather than Na(TMP), regenerating more base that can then react with the anisole present, pushing the metalation to completion by forming a more stabilized sodium boronate **II-O*i*Pr** (Scheme 1). The steric incompatibility of NaTMP and B(O*i*Pr) is also key, as shown when monitoring the reaction using B(OMe)$_3$, which showed almost instantaneous decomposition of the sodium amide, furnishing **II-OMe** in low yield (see Supporting Information for details).

To examine the scope of the optimised conditions, we shifted our attention into more unreactive and challenging non-substituted arenes. Under the same conditions, we observed that benzene and naphthalene could be deprotonated at room temperature and rapidly trapped with B(O*i*Pr)$_3$ to form the tetracoordinated boronates [PhB(O*i*Pr)$_3$Na(PMDETA)] (**4**) and [($C_{10}H_7$)B(O*i*Pr)$_3$Na(PMDETA)] (**5**) in isolated crystalline yields of 26% and 44%, respectively. The solid state structures of **4** and **5** were elucidated by X-ray crystallography, confirming the selective formation of a C–B bond with the Na atoms in a pentacoordinated environment, comprising chelating PMDETA and two O atoms from O*i*Pr substituents (Figure 3). Interestingly, with naphthalene the deprotonation occurred exclusively in the 2-position, in contrast to the unselective mono- and double- deprotonation that is seen when *n*PentNa or the Lochmann-Schlosser superbase (*n*BuLi/KO*t*Bu) are used;[22] whereas *n*BuLi/TMEDA fails to deprotonate this arene. Remarkably, by monitoring these reactions by ^{1}H NMR we also found that borylation of benzene could also be carried out in the absence of PMDETA, provided that benzene was used as the reaction medium with the tridentate Lewis donor being added only at the end stage to aid in the crystallization of **4**. In this regard, previous theoretical[9] and structural studies[23] have outlined the deaggregation capabilities of simple aromatic solvents like benzene and toluene towards alkali-metal amides, where smaller, more reactive entities are consistently achieved and energetically favourable. In our case ^{1}H DOSY NMR studies[24] on solutions of NaTMP in C_6D_6 suggest the transformation of [NaTMP]$_3$ into a solvated dimer of the form [(C_6D_6)$_2$Na$_2$TMP$_2$] with a calculated molecular weight of 489 g mol^{-1} (±10%) referenced against $SiMe_4$ (Figure 3). An analogously-solvated dimer of NaHMDS has been cited computationally by Collum and proposed to be more stable than the parent trimer.[9] Taking a more atom economical approach, the synthesis of **4** was optimised using just 5 equivalents of C_6H_6 in the presence of PMDETA. The low equivalence employed here underlines the power of this sodiation/borylation protocol, given that deprotonative metalation of benzene frequently requires the arene to be used in bulk excess as the reaction medium.[25] Moreover, these reaction conditions also outperform typical conditions for C–H borylation of benzene, which often needs an Ir catalyst, long reaction times and high temperatures.[26]

Since tetracoordinated aryl boronates have been proposed as transmetalating agents in Suzuki–Miyaura cross-couplings,[27] we explored the possibility of carrying out a tandem deprotonation-borylation/Suzuki–Miyaura cross coupling, using one equivalent of NaTMP as the only base used for both steps. Similar transmetalation of reactive aryl sodium species to zinc and boron have been reported by Takai to work in Negishi/Suzuki–Miyaura cross-coupling reactions using sodium dispersions and arylbromides.[5b] The crude mixtures (Int 1, Figure 4) after the deprotonative-borylation were reacted with an aryl bromide in the presence of catalytic amounts of $PdCl_2$(dppf) in THF/H_2O solvent to synthesize the biaryls. Good to excellent yields of cross-coupled products were obtained, proving the applicability of our protocol to prepare biaryl motifs (Figure 4). Simple, unactivated arenes such as benzene (**6a**), naphthalene (**6b**) and anthracene (**6c**) could be successfully employed, albeit a lower yield was obtained with anthracene due to its low hexane solubility. Arenes containing methoxy groups could be used in directed *ortho* metalation, giving biaryls after cross-coupling in good yields (**6d–6i**). Note that

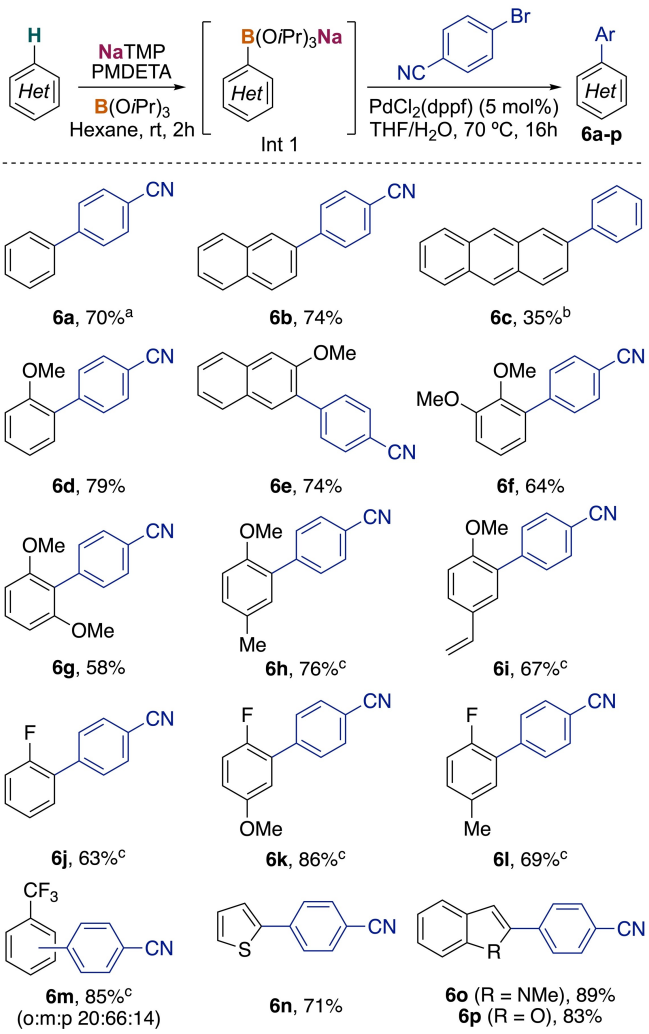


Figure 4. Tandem deprotonation/borylation and cross-coupling of arenes. Conditions: Arene (1 mmol), NaTMP (1 mmol), PMDETA (1 mmol), $B(OiPr)_3$ (1 mmol), hexane (10 mL), rt. After 2 h, ArBr (1 mmol), $PdCl_2(dppf)$ (0.05 mmol), THF (5 mL) and H_2O (0.3 mL) were added, 70 °C, 16 h. a) 5 mmol of PhH were used, b) PhBr was used as ArBr, c) Metalation done at −78 °C and warmed to rt.

selective functionalization was obtained for 2-methoxynaphthalene in the C3-position (**6e**), 1,3-dimethoxybenzene in the C2-position (**6g**) and 4-methylanisole in the C2-position (**6h**) leaving its methyl group intact.

Different fluoroarenes were also amenable to this method, though the deprotonation step had to be done at −78° C to avoid decomposition of the highly reactive sodiated intermediates (**6j**, **6k** and **6l**). When a OMe group and a F atom were present in the same molecule, functionalization was seen exclusively *ortho* to the fluorine (**6k**), mimicking the regioselectivity previously reported for the Lochman-Schlosser base, consistent with the metalation driven by the enhanced acidity of the H *ortho* to the F rather than by complex-induced proximity effects (CIPE). α,α,α-Trifluorotoluene was functionalised in good yields, but in this case a mixture of isomers was obtained, with the meta isomer the major product. This result contrasts with previously reported metalation with *n*BuNa, where it occurs mainly in the *ortho* site.[28] Finally, thiazole (**6n**), *N*-methylindole (**6o**) and benzoxazole (**6p**) were deprotonated and cross-coupled successfully in good yields. Limitations to this method were found when trying the metalation of diazines or substituted pyridines, where significant decomposition occurred as the reaction mixtures reached room temperature.

Expanding the synthetic utility of NaTMP, a method for regioselective arene borylation is reported. Borylation of non-activated arenes can be accomplished at room temperature, without need of a large excess of the aromatic substrate. In some cases, there are complementary selectivities to those typically seen in transition metal catalysed borylations. Moreover, the aryl boronates obtained could be used in Suzuki–Miyaura cross couplings without further manipulation, allowing the synthesis of biaryls in a selective and efficient way.

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the Supporting Information of this article.

Keywords: Amide · Borylation · Metalation · Sodium · Structural Elucidation

[1] E. Carl, D. Stalke in *Lithium Compounds in Organic Synthesis—From Fundamentals to Applications* (Eds.: R. Luisi, V. Capriati), Wiley-VCH, Weinheim, **2014**, pp. 1–31.
[2] R. E. Mulvey, S. D. Robertson, *Angew. Chem. Int. Ed.* **2013**, *52*, 11470–11487; *Angew. Chem.* **2013**, *125*, 11682–11700.
[3] P. B. De, S. Asako, L. Ilies, *Synthesis* **2021**, *53*, 3180–3192.
[4] a) A. Gissot, J.-M. Becht, J. R. Desmurs, V. Pévère, A. Wagner, C. Mioskowski, *Angew. Chem. Int. Ed.* **2002**, *41*, 340–343; *Angew. Chem.* **2002**, *114*, 350–353. For an overview of the DoM field with organolithium reagents see: b) V. Snieckus, *Chem. Rev.* **1990**, *90*, 879–933; c) G. Queguiner, F. Marsais, V. Snieckus, J. Epsztajn in *Advances in Heterocyclic Chemistry* (Ed.: A. R. Katritzky), Academic Press, New York, **1991**,

pp. 187–304; d) P. Knochel, K. P. Cole, *Org. Process Res. Dev.* **2021**, *25*, 2188–2191.
[5] a) S. Asako, M. Kodera, H. Nakajima, K. Takai, *Adv. Synth. Catal.* **2019**, *361*, 3120–3123; b) S. Asako, H. Nakajima, K. Takai, *Nat. Catal.* **2019**, *2*, 297–303; c) S. Asako, I. Takahashi, H. Nakajima, L. Ilies, K. Takai, *Commun. Chem.* **2021**, *4*, 76.
[6] J. H. Harenberg, N. Weidmann, A. J. Wiegand, C. A. Hoefer, R. R. Annapureddy, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 14296–14301; *Angew. Chem.* **2021**, *133*, 14416–14421.
[7] H. J. Reich, *Chem. Rev.* **2013**, *113*, 7130–7178.
[8] a) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 15197–15204; b) A. Woltornist, Y. Ma, R. F. Algera, Y. Zhou, Z. Zhang, D. B. Collum, *Synthesis* **2020**, *52*, 1478–1497; c) R. A. Woltornist, D. B. Collum, *J. Am. Chem. Soc.* **2021**, *143*, 17452–17464.
[9] a) R. A. Woltornist, D. B. Collum, *J. Org. Chem.* **2021**, *86*, 2406–2422; b) R. Neufeld, R. Michel, R. Herbst-Irmer, R. Schöne, D. Stalke, *Chem. Eur. J.* **2016**, *22*, 12340–12346.
[10] a) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 7921–7930; b) R. F. Algera, Y. Ma, D. B. Collum, *J. Am. Chem. Soc.* **2017**, *139*, 11544–11549; c) Y. Ma, R. A. Woltornist, R. F. Algera, D. B. Collum, *J. Am. Chem. Soc.* **2021**, *143*, 13370–13381.
[11] a) R. McLellan, M. Uzelac, L. J. Bole, J. M. Gil-Negrete, D. R. Armstrong, A. R. Kennedy, R. E. Mulvey, E. Hevia, *Synthesis* **2019**, *51*, 1207–1215; b) T. Inoue, S. Yamamoto, Y. Sakagami, M. Horie, K. Okano, A. Mori, *Organometallics* **2021**, *40*, 3506–3510; c) see 5a.
[12] Selected references: a) J. Kristensen, M. Lysén, P. Vedsø, M. Begtrup, *Org. Lett.* **2001**, *3*, 1435–1437; b) M. Campbell, V. Snieckus, E. W. Baxter, *Encyclopedia of Reagents for Organic Synthesis*, Wiley, Hoboken, **2008**.
[13] Selected references: a) A. Krasovskiy, V. Krasovskaya, P. Knochel, *Angew. Chem. Int. Ed.* **2006**, *45*, 2958–2961; *Angew. Chem.* **2006**, *118*, 3024–3027; b) G. C. Clososki, C. J. Rohbogner, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7681–7684; *Angew. Chem.* **2007**, *119*, 7825–7828; c) S. H. Wunderlich, P. Knochel, *Angew. Chem. Int. Ed.* **2007**, *46*, 7685–7688; *Angew. Chem.* **2007**, *119*, 7829–7832; d) C. Schnegelsberg, S. Bachmann, M. Kolter, T. Auth, M. John, D. Stalke, K. Koszinowski, *Chem. Eur. J.* **2016**, *22*, 7752–7762; e) R. Neufeld, T. L. Teuteberg, R. Herbst-Irmer, R. A. Mata, D. Stalke, *J. Am. Chem. Soc.* **2016**, *138*, 4796–4806; f) S. Bachmann, R. Neufeld, M. Dzemski, D. Stalke, *Chem. Eur. J.* **2016**, *22*, 8462–8465.
[14] a) M. Uzelac, R. E. Mulvey, *Chem. Eur. J.* **2018**, *24*, 7786–7793; b) N. M. Brikci-Nigassa, G. Bentabed-Ababsa, W. Erb, F. Mongin, *Synthesis* **2018**, *50*, 3615–3633. For selected references of LiTMP in TMT see c) R. McLellan, M. Uzelac, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2017**, *56*, 9566–9570; *Angew. Chem.* **2017**, *129*, 9694–9698; d) M. Uzelac, A. R. Kennedy, E. Hevia, R. E. Mulvey, *Angew. Chem. Int. Ed.* **2016**, *55*, 13147–13150; *Angew. Chem.* **2016**, *128*, 13341–13344.
[15] B. Gehrhus, P. H. Hitchcock, A. R. Kennedy, M. F. Lappert, R. E. Mulvey, P. J. A. Rodger, *J. Organomet. Chem.* **1999**, *587*, 88–92.
[16] D. R. Armstrong, D. V. Graham, A. R. Kennedy, R. E. Mulvey, C. T. O'Hara, *Chem. Eur. J.* **2008**, *14*, 8025–8034.
[17] NaTMP was isolated as a pure solid from 1:1 reaction of *n*BuNa and TMP(H) in hexane, see the Supporting Information for the further details. This method differs from the work reported by Takai where NaTMP is prepared in situ using a Na dispersion, and then used for metalation of activated heteroarenes, see reference [5a].
[18] a) M. Uzelac, A. R. Kennedy, E. Hevia, *Inorg. Chem.* **2017**, *56*, 8615–8626; b) D. R. Armstrong, E. Crosbie, E. Hevia, R. E. Mulvey, D. L. Ramsay, S. D. Robertson, *Chem. Sci.* **2014**, *5*, 3031–3045; c) See references [11a] and [14].
[19] Selected references: a) M. Lysén, H. M. Hansen, M. Begtrup, J. L. Kristensen, *J. Org. Chem.* **2006**, *71*, 2518–2520; b) T. Leermann, F. R. Leroux, F. Colobert, *Org. Lett.* **2011**, *13*, 4479–4481; c) M. A. Oberli, S. L. Buchwald, *Org. Lett.* **2012**, *14*, 4606–4609; d) A. Hafner, M. Meisenbach, J. Sedelmeier, *Org. Lett.* **2016**, *18*, 3630–3633; e) see ref. [4] and [12a].
[20] a) H. C. Brown, M. Srebnik, T. E. Cole, *Organometallics* **1986**, *5*, 2300–2303.
[21] An equimolar mixture of NaTMP and $B(OiPr)_3$ in C_6D_{12} did not show the formation of any interaction, as judged by ^{11}B NMR spectroscopy. Upon addition of PMDETA, the formation of TMP(H) and the change in the signals of PMDETA in the ^1H NMR spectrum suggest its metalation. ^{11}B NMR shows a new signal at 4.45 ppm, consistent with a 4-coordinated B environment. Similar metalation of PMDETA has been seen in Trans Metal Trapping with LiTMP and $Ga(CH_2TMS)_3$: see ref. [11a].
[22] a) A. A. Morton, J. B. Davidson, T. R. P. Gibb, E. L. Little, E. F. Clarke, A. G. Green, *J. Am. Chem. Soc.* **1942**, *64*, 2250–2253; b) M. Schlosser, H. C. Jung, S. Takagishi, *Tetrahedron* **1990**, *46*, 5633–5648.
[23] A. I. Ojeda-Amador, A. J. Martínez-Martínez, G. M. Robertson, S. D. Robertson, A. R. Kennedy, C. T. O'Hara, *Dalton Trans.* **2017**, *46*, 6392–6403.
[24] R. Neufeld, D. Stalke, *Chem. Sci.* **2015**, *6*, 3354–3364.
[25] Selected examples: a) S. Liang, N.-W. Liu, G. Manolikakes, *Adv. Synth. Catal.* **2016**, *358*, 159–163; b) C. Unkelbach, D. F. O'Shea, C. Strohmann, *Angew. Chem. Int. Ed.* **2014**, *53*, 553–556; *Angew. Chem.* **2014**, *126*, 563–567; c) L. C. H. Maddock, M. Mu, A. R. Kennedy, M. García-Melchor, E. Hevia, *Angew. Chem. Int. Ed.* **2021**, *60*, 15296–15301; *Angew. Chem.* **2021**, *133*, 15424–15429.
[26] For a review see: I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.
[27] a) B. P. Carrow, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 2116–2119; b) A. A. Thomas, A. F. Zahrt, C. P. Delaney, S. E. Denmark, *J. Am. Chem. Soc.* **2018**, *140*, 4401–4416.
[28] J. A. Garden, D. R. Armstrong, W. Clegg, J. García-Alvarez, E. Hevia, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, L. Russo, *Organometallics* **2013**, *32*, 5481–5490.
[29] Deposition Numbers 2159450 (for **1·TMEDA**), 2159451 (for **2·(THF)$_3$**), 2159452 (for **4**), and 2159453 (for **5**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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