Applying Na/Co(II) bimetallic partnerships to promote multiple Co–H exchanges in polyfluoroarenes†

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Heterobimetallic base NaCo(HMDS)$_3$ [HMDS = N(SiMe$_3$)$_2$] enables regioselective di-cobaltation of activated polyfluoroarenes under mild reaction conditions. For 1,3,5-C$_6$H$_2X_3$ (X = Cl, F), NaCo(HMDS)$_3$ in excess at 80 °C impressively induces the collective cleavage of five bonds (two C–H and three C–X) of the substrates via a cascade activation process that cannot be replicated by LiCo(HMDS)$_3$ or KCo(HMDS)$_3$.

Deprotonative metalation where an inert C–H bond is converted into a more polar, and therefore more reactive, C–metal bond is a fundamentally important transformation in synthesis as a prerequisite for onward functionalisation of aromatic molecules. While organolithium reagents have traditionally been the reagents of choice to perform these reactions, often they lack good selectivity and exhibit limited functional tolerance even when working under cryogenic conditions so research towards development of improved bases remains a high priority. Main group heterobimetallic systems incorporating both an alkali-metal and a less electropositive metal such as Mg, Zn or Al have emerged as excellent alternatives. Promoting low polarity metalations, specifically alkali metal mediation (AMM), these systems are compatible with a large variety of functional groups and importantly provide greater stability to the metalated aryl fragments. Furthermore, in some cases by controlling the stoichiometry of the reaction selective dimetalations can be obtained, as demonstrated by Mulvey for the special ortho–meta’ dimagnesiation of substrates such as anisole or trifluorotoluene. Recent studies have shown that synergic reactivities can also be switched on when pairing an alkali-metal with a divalent earth abundant transition metal (M = Mn, Fe, Co) allowing direct metalation of arenes via M–H or M-halogen exchange. Interestingly, contrasting with other established C–H bond activation processes, these reactions operate without a change in the oxidation state of the 3d-transition metal.

Within fluoroarene studies sodium cobaltate NaCo(HMDS)$_3$ [HMDS = N(SiMe$_3$)$_2$] (I), in combination with homometallic NaHMDS, has shown particular promise in the regioselective cobaltation of a range of fluoroarenes at room temperature including pentafluorobenzene with excellent atom efficiency to give disodium tetra(aryl) Co(II) as the THF complex [(THF)$_4$Na$_2$Co(C$_6$F$_5$)$_4$] (I). In this molecule Co exhibits an unusual square planar geometry (Scheme 1). Mechanistic studies revealed that the reaction occurs with initial formation of [NaCo(HMDS)$_2$(C$_6$F$_5$)] (II) which undergoes ligand redistribution to form I (Scheme 1). This work concluded that while formally these reactions are cobaltations, sodium plays a key role not only on mediating the metalation but also on the stabilisation of I via formation of Na–F interactions. The mild reaction conditions employed and the thermal stability of I contrasts with previous reports on the metalation of fluoroarenes using organolithium reagents which inevitably require use of cryogenic temperatures in order to avoid unwanted side reactions (autometalation, benzene formation, multimetallation, etc.).

Scheme 1  Previous work on metalation of fluoroarenes using the heterobimetallic base NaCo(HMDS)$_3$ [HMDS = N(SiMe$_3$)$_2$] (I).
Recently our group has also reported that by using a two molar excess of a potassium salt supported by a large sterically demanding silyl(amide)silyl group it is possible to induce dianionization of 1,2,3,4-tetrafluorobenzene. In this case the bulky ligand was proposed to be key, providing steric protection for the trapping of the C6F4 dianion, although forcing reaction conditions were required (16 h, 70 °C). Sodium ferrate ([dioxane]NaFe(HMDS)3] can also promote the di-ferration of activated fluoroarenes, although the scope of this reactivity has not been fully investigated. Opening new ground in this area, building on the mechanistic understanding acquired in sodium-mediated cobaltations here we evaluate the potential of Na to promote dimetalations of fluoro- and chloro-arenes.

We commenced our studies by investigating the reactivity of heterobimetallic NaCo(HMDS)3 (1) towards the di-cobaltation of 1,4-difluorobenzene. With a pKα of 40.1 Sodium ferrate NaCo(HMDS)3 and refluxing conditions (80 °C for 1 h). Disappointingly, despite the excess of base and forcing conditions, NaCo(C6F2H)(HMDS)3 (2) was obtained as the only metallated product in a 56% isolated yield. 1H NMR monitoring of the reaction showed a conversion of 77% (Fig. 1a). The bimetallic constitution of 2 was established by X-ray crystallographic studies that also confirm the selective ortho-cobaltation of the substrate (see ESI†). Remarkably, activation of the remaining HMDS groups to form a tetra(aryl)cobaltate as 1 was not observed even in the presence of an excess of NaHMDS, which we attribute to the lack of F atoms in the appropriate disposition to stabilise the Na atoms via Na – F interactions as a core feature of 1.

We next decided to try more activated 1,3,5-trifluorobenzene (pKα = 31.5). Remarkably, at room temperature after 1 h selective 1,3 dicobaltation can be observed furnishing [Na2Co2(C6F3H)(HMDS)3] (3) in a 33% isolated yield (Fig. 1b). Similarly the reaction with 1,2,4,5-tetrafluorobenzene (pKα = 23.1) under the same reaction conditions yielded [Na2Co2(C6F4)(HMDS)3] (4) in a 62% isolated yield after just 5 minutes at room temperature (Fig. 1c). NMR reaction monitoring in C6D6 showed that formation of 3 and 4 is quantitative (see ESI†). Note that both dicobalated products are stable at room temperature for a long time in C6D6 solutions without observing any degradation. Demonstrating the importance on the choice of base to promote these metalations, while 3 and 4 are formed when using 2 molar excess of 1, if 1,3,5-trifluorobenzene or 1,2,4,5-tetrafluorobenzene are treated with one equivalent of 1 in combination with another equivalent of NaHMDS, which potentially could also promote dimetalation, selective monocobaltation is preferred yielding [Na2CoAr4] species like 1 (Scheme 1). Furthermore, treating these tetra(aryl) cobaltates with another four equivalents of 1 failed to promote a second Co–H exchange even under forcing conditions.

The solid-state structures of 3 and 4 are reminiscent to that of 2, with the Co(n) centres occupying the positions previously filled by a H atom (Co–C average distance of 2.05 Å for both 3 and 4). In both compounds Na atoms are stabilised by formation of dative bonds with the F substituents. For 3 each Na interacts with a F atom ortho to the metallated C (2.44 Å and 2.30 Å). In addition, one Na also interacts with the F of a neighbouring unit giving rise to a complex 3D structure (see Fig. S25, ESI†). For 4, a discrete pentameric motif is observed

![Diagram](image.png)

**Fig. 1.** (i) Monometalation of 1,4-difluorobenzene with 2 eq. of 1 to form product 2; (ii) reaction of 1,3,5-trifluorobenzene with 2 eq. of 1 to form the 1,4-dimetallation product 3; (iii) reaction of 1,2,4,5-tetrafluorobenzene with 2 eq. of 1 to form the 1,4-Dimetallation product 4. Conversions determined by 1H NMR using hexamethylbenzene as internal standard. Isolated yields shown in brackets. Molecular structures of 3 (b) and 4 (a) with H atoms omitted for clarity and ellipsoids set at 50% probability.
with two Na atoms coordinating to a molecule of benzene (see Fig. S26, ESI†). Both compounds contain medium-long electrostatic interactions between the Na atoms and one or two methyl units belonging to SiMe$_3$ groups (ranging from 2.835(5) to of 2.959(7) Å). As far as we can ascertain 3 and 4 constitute the first examples of aren di-co-baltation to be structurally defined. Examples of di-metalated fluoroarenes containing other transition metals are scarce and they are typically obtained via C–H or C–F bond activation processes. 11

To further understanding of these two-fold cobaltations we next assessed the sequential metalation of 1,2,4,5-tetrafluorobenzene (Scheme 2). 1H NMR monitoring of the reaction of equimolar amounts of 1 with this fluoroarene in d$_8$-Tol solution showed evidence of metalation at 0 °C with the immediate formation of the mono-arene [NaCo(HMDS)$_2$(C$_6$F$_4$H)] (5), which exhibits two distinct resonances at −15.59 ppm and 42.47 ppm (for the HMDS groups and $H_{\text{ortho}}$ respectively). If the reaction mixture is allowed to reach room temperature, 5 undergoes ligand redistribution to afford the tetra-arene [Na$_2$CoAr$_4$] (6) (Ar = C$_6$F$_4$H) with the same structure as 1 (Scheme 2). 7 However, when low temperature was maintained and a second equivalent of base 1 was added, an immediate colour change from light turquoise to dark green was observed together with the disappearance of a new broad signal at −4.17 ppm characteristic of the HMDS groups of the dimetalated product 4 (Scheme 2 and Fig. S26, ESI†). These initial findings prove the ability of heterobimetallic 1 to react with exceptional stoichiometric control via a consecutive dimetalation process, where both the mono- and twofold metalated product can be obtained quantitatively under mild reaction conditions.

Building on these findings, we next pondered whether all three aromatic protons of 1,3,5-trifluorobenzene could be activated towards Co–H exchange. Seminal work by Schlosser assessing lithiation of this substrate with a three-molar excess of tBuLi at −115 °C in the presence of Me$_3$SiCl concluded that only dillithiation species could be formed. In fact, attempts to access a trilithiated product by increasing the temperature to −75 °C led to the formation of 1,3,5-tri-tert-butylbenzene. 8c In our case a 3:1 stoichiometry of 1:1,3,5-trifluorobenzene was used and the solution was stirred at 80 °C for 16 hours. Re-crystallization from a hexane/THF solution led to the isolation of [1,3-bis(CoHMDS)-2,4,6-tris(HMDS)-C$_6$H] (7) in a 78% isolated yield (Fig. 2). X-ray crystallographic studies established the molecular structure of 7 that proved the fluoroarene has undergone a rare two-fold Co–H exchange, 3-fold C–F bond activation event, where three strong C–F bonds have been replaced by HMDS groups. This reactivity resembles that reported previously by our group for the reaction of the same substrate with the ferrate NaFe(HMDS)$_3$ under similar harsh reaction conditions. 5b Nevertheless, it should be noted that unlike other cobalt mediated C–F bond activations where cobalt changes its oxidation state, 7 7 retains two low coordinate Co(a) centres. This is also consistent with the measured magnetic moment of 7 (5.56 μB) showing the presence of two S = 3/2 centres, akin to what was seen for dimetalated compounds 3 and 4 (see ESI† for details). Each Co in 7 binds to one C of the aromatic ring [2.015(7) and 1.976(7) Å for Co1 and Co2 respectively] as well as engaging in an additional further medium-range contact with the N from a neighbouring HMDS group directly attached to the aryl ring [2.281(6) and 2.340(6) Å for Co1 and Co2 respectively] which induces a considerable distortion from linearity of the N–Co–C angles [156.5(3) and 156.6(3)° for Co1 and Co2 respectively].

Reactivity studies revealed that while dimetalated complex 3 is stable in solution at room temperature for long periods of time, addition of an extra equivalent of NaHMDS at 80 °C for 16 h affords 7 in quantitative yields. 1H NMR monitoring of this reaction showed that along with 7 only a white solid identified as NaF is obtained. Interestingly, no HMDS(H) is detected which suggests the extra equivalent of Na amide is required for the C–F bond activation process but is not involved in a metalation step. Remarkably this reactivity is not available for
di-cobaltation product 4 which under the same reaction conditions is completely inert towards the C–F bond activation step. Interestingly 7 could also be obtained when reacting three equivalents of 1 with 1,3,5-trichlorobenzene (93% isolated yield). $^1$H NMR analysis of the reaction crude showed that along with 7 and NaCl, in this case HMDS(H) and Co(HMDS)$_2$ are formed. This reactivity marks a significant departure from that of NaFe(HMDS)$_3$ which fails to metatalize chloroarenes. Based on these findings and the previous studies carried out by Schlosser for the polyolitisation of 1,3,5-trifluorobenzene we postulate that 7 is formed as the result of a cascade process (Scheme 3), which under forcing reaction conditions initiates a fast sequence of reactions alternating NaF eliminations with the addition of Co(HMDS)$_2$. The fact that other intermediates of this process cannot be trapped or even detected spectroscopically supports that each di-cobaltet intermediate is less stable than precursor 3. The third equivalent of 1 or NaHMDS is required to facilitate the activation of the last F centre. The presence of intramolecular Na···F contacts in 3 may also contribute to facilitate these cascade process as previously proposed by Mikami for the C–F bond activation of CF$_3$H by lithium enolates. $^{11}$ This was further supported by adding three equivalents of 15-crown-5 to 3, which resulted in the abstraction of the Na cation and formation of a solvent-separated ion pair complex, which is completely inert towards the C–F bond activation processes.

Finally, an important alkali-metal dependence was noted, with only Na found capable of promoting these transformations. This was discerned on reacting these three molar equivalents of MCo(HMDS)$_2$ (M = Li, K) with 1,3,5-trifluorobenzene: the Li/Co base only promoted mono-cobaltation of the substrate to form [LiCo(HMDS)$_2$(C$_6$F$_5$H$_2$)] [8], and even under forcing reaction conditions (16 h, 80 °C) no evidence of dimetallation was observed; whereas surprisingly the potassium cobaltate is completely inert towards 1,3,5-trifluorobenzene metatation (see ESI† for details). This Li < Na > K trend goes against that normally encountered in group one where reactivity increases in the order Li < Na < K.

To conclude, through isolating key reaction intermediates and NMR reaction monitoring experiments we have revealed the unique ability of sodium cobaltates to promote di-cobaltation of activated fluoroarenes. Under forcing reaction conditions some of these systems can undergo regioselective C–F bond activation via a consecutive NaF elimination/Co amide addition cascade process. Assessment of alkali-metal and coordination effects uncovers the key roles of sodium in mediating these Co–H exchanges and transforming C–F into C–N bonds.

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**Conflicts of interest**

There are no conflicts to declare.

**Notes and references**