Stoichiometric and Catalytic Insights into the Lithium Nickelate Mediated C–F Bond Alkynylation of Fluoroarenes

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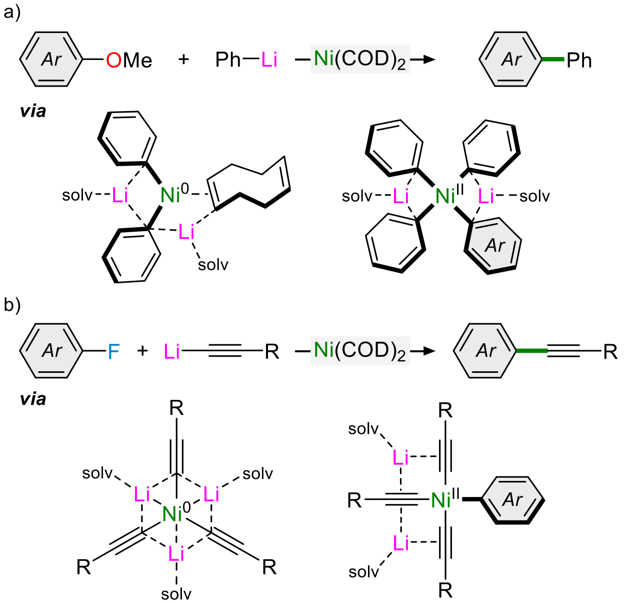
Supporting Information Placeholder

ABSTRACT: Low-valent nickelates have recently been shown to be key intermediates that facilitate challenging cross-coupling reactions under mild conditions. Expanding the synthetic potential of these heterobimetallic complexes, herein we report the ability of tri-lithium nickelate $Li_3(TMEDA)_3Ni(C{\equiv}C{-}Ph)_3$ to promote the stoichiometric C–F activation of aryl fluorides furnishing novel mixed Li/Ni(0) or Li/Ni(II) species depending on the substrate and conditions employed. These stoichiometric insights can be upgraded to catalytic regimes to enable the atom-efficient alkynylation of aryl fluorides and polyfluoroarenes with lithium acetylides and $Ni(COD)_2$ as pre-catalyst, and operates without the need for external ligands, Cu co-catalysts or additives.

The co-complexation of Ni(0)-olefin complexes with polar organometallics can give rise to heterobimetallic nickelates which were the subject of intense research efforts in the 1970s and 80s succeeding the pioneering work of Wilke into low-valent organonickel chemistry.[1–3] These species remained dormant in the literature for many decades, and it is only in recent years that they have reemerged and attracted broader interest.[4] Since numerous reactions employ polar organometallic nucleophiles in tandem with Ni(0)-olefin (pre)catalysts, it has been proposed based on theoretical and experimental studies that low-valent nickelates may be overlooked intermediates that facilitate cross-coupling reactions *via* non-classical mechanisms.[5–10] Supporting this interpretation, our group has recently shown that lithium nickelates are responsible for the $Ni(COD)_2$ catalyzed cross-coupling of PhLi with aryl ethers (**Scheme 1a**).[11–13] The recognition that heterobimetallic nickelates can functionalize challenging substrates under mild conditions, and often without the need for external ligands, holds promise for the development of sustainable and atom-efficient catalytic transformations.

Several new classes of heterobimetallic nickelates have been reported by our group and others in recent years, and these have been shown to be competent catalysts for the [2+2+2] cyclotrimerization of alkynes,[14] the aerobic oxidative homo-coupling of acetylides,[15] and in low-temperature Kumada-Corriu cross-coupling reactions.[8,9] The tri-lithium nickelate, $Li_3(TMEDA)_3Ni(C{\equiv}C{-}Ph)_3$,[16] which is readily accessed from $Ni(COD)_2$ and Ph–C≡C–Li in the presence of TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine), undergoes stoichiometric *sp*–*sp*^{2} cross-coupling with iodobenzene to give diphenylacetylene. Motivated by the ability for nickel to functionalize challenging electrophiles,[17–20] herein, we explore the reactivity of low-valent nickelate $Li_3(TMEDA)_3Ni(C{\equiv}C{-}Ph)_3$ towards aryl fluorides and polyfluoroarenes. Stoichiometric reactivity is upgraded to catalytic regimes, whilst the isolation of novel lithium nickelates provides mechanistic insights into this transformation (**Scheme 1b**).



Scheme 1. a) Ni-catalyzed cross-coupling of aryl ethers with PhLi; b) This work - Ni-catalyzed cross-coupling of aryl fluorides with lithium acetylides.

Whilst $Li_3(TMEDA)_3Ni(C{\equiv}C{-}Ph)_3$ (**1a**) reacts rapidly with iodobenzene to give dinickelate complex **2a**,[16] no reaction is observed with one equivalent of fluorobenzene at room temperature, reflecting the increased bond dissociation energy (BDE) of C–F bonds.[21] Heating to 80 °C for 1 hour however results in a color change from deep blue to red and formation of **2a** and Ph–C≡C–Ph (**Figure 1a**). Compound **2a** can be isolated as a crystalline THF solvate (see Figure S20) in 61% yield and exhibits comparable structural parameters to the previously documented Et_2O solvate obtained from iodobenzene.[16] This motif can be viewed as two trigonal planar $\{Li_2(solv)_nNi(C{\equiv}C{-}Ph)_2\}$ units that coordinate orthogonally to a single Ph–C≡C–Ph core which is built through C–C bond formation. Remarkably, dissolution of **1a** in neat fluorobenzene and storage at -30 °C afforded crystals suitable for single-crystal X-ray diffraction identified as a fluorobenzene adduct **1a.PhF** alongside trace quantities (<5% by ^{1}H NMR) of **2a** (see Figure S21), both as TMEDA solvates. In the solid-state structure of **1a.PhF**, two molecules of fluorobenzene approach the

Ni(0) center and are weakly interacting *via* C–H···Ni contacts [range = 2.842–3.161 Å] (**Figure 1b**). This motif contrasts to that observed for aryl ethers in which the arene binds in a η^2-fashion to Ni(0) with additional coordination of the OMe substituent to the Lewis acidic lithium cation.[13] This latter interaction is key for substrate docking and activation whilst for **1a** and aryl fluorides appears to be less crucial. When moving to more activated aryl fluoride substrates such as 1-fluoronaphthalene, complete conversion of **1a** was observed within 15 minutes at room temperature to give **2b** in 86% crystalline yield. The solid-state structure of a mixed THF/TMEDA solvate displays μ-η^2:η^2 coordination of the unsymmetric alkyne product 1-Naph–C≡C–Ph across two Ni centers with significant bending away from linearity [C1–C2–C3 = 129.6(1) °; C2–C1–C13 = 130.7(1) °] consistent with significant back-donation from the electron-rich Ni-centers (**Figure 1c**). Even for tri-lithium nickelates which cannot be isolated, such as "$Li_3(solv)_nNi(C{\equiv}C{-}SiMe_3)_3$" (**1b**), the combination of $Ni(COD)_2$, $Me_3Si{-}C{\equiv}C{-}Li$ and 1-fluoronaphthalene in a 1:3:1 ratio afforded single crystals of **2c** (see Figure S23), which bears similar structural features to **2a-b** and other dinickelate μ-η^2:η^2alkyne complexes reported.[14,16,22]

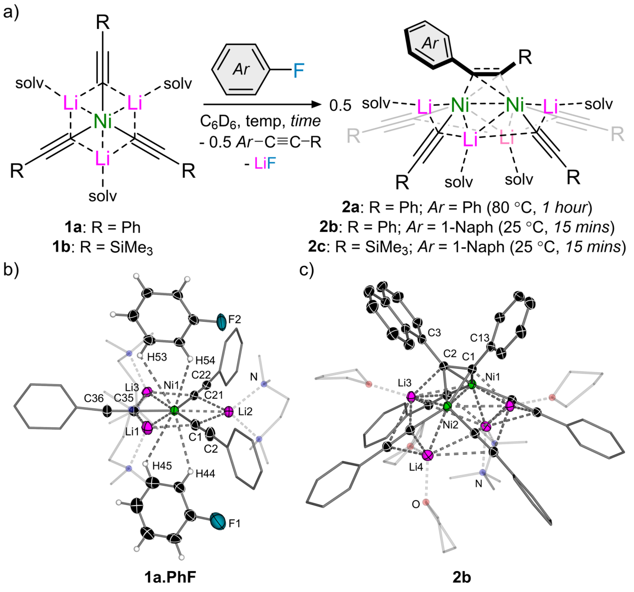
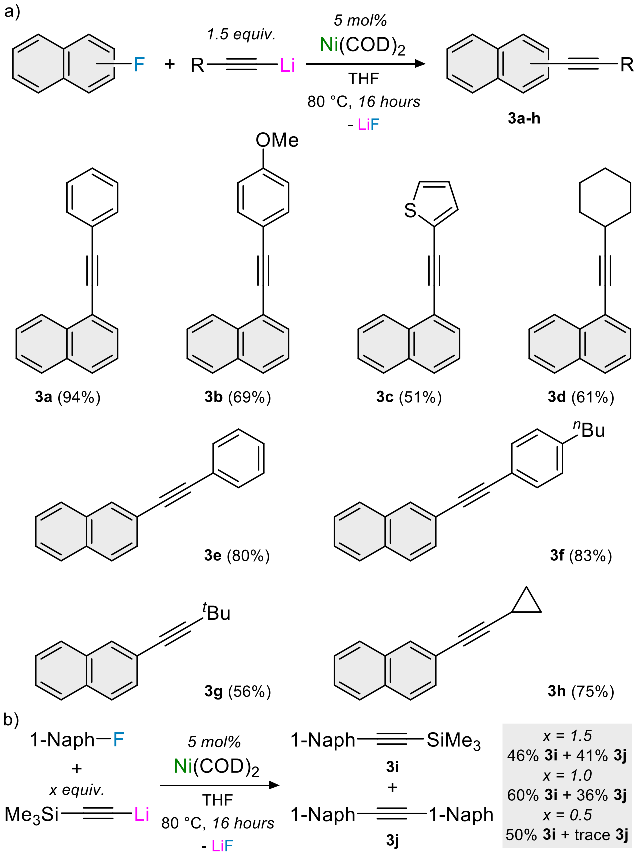


Figure 1. a) Reactivity of tri-lithium nickelates **1a-b** with aryl fluorides to give dinickelate complexes **2a**–**c**. b) Solid-state structure of **1a.PhF**. Thermal ellipsoids shown at 30% probability. Coordinated TMEDA and Ph substituents shown as wireframes for clarity. c) Solid-state structure of **2b**. Thermal ellipsoids shown at 30% probability. Coordinated TMEDA/THF and peripheral Ph substituents shown as wireframes for clarity.

The stoichiometric alkynylation of aryl fluorides can be upgraded to catalytic regimes by simply using $Ni(COD)_2$ as a precatalyst and lithium acetylides as nucleophilic coupling partner (**Scheme 2a**). As far as we can ascertain, this represents the first example of a Ni-catalyzed alkynylation of aryl fluorides and proceeds under simple operating conditions without the need for any external ligands or Cu co-catalysts, which are typically required for (Pd-catalyzed) Sonogashira cross-coupling reactions.[23,24] This methodology bears similarities to a recent report by Zhao who employed $Pd_2(dba)_3$ (dba = dibenzylideneacetone) and LiHMDS (HMDS = hexamethyldisilazane) for the catalytic cross-coupling of aryl fluorides with terminal alkynes, and without external ligands.[25] In this case however, no organometallic intermediates were isolated and the involvement of lithium palladates was not considered. The scope of the reaction was first explored with 1-fluoronaphthalene and various lithium acetylides to give **3a–d** in good to excellent yields (51–94%). Similarly, 2-fluoronaphthalene gave **3e-h** with aromatic or aliphatic lithium acetylides in good yields. Deactivated aryl fluorides such as 4-fluoroanisole do show evidence of catalytic alkynylation (*ca.* 20% isolated yield), however higher catalysts loadings (10 mol%) and elevated temperatures (120 °C) are required which ultimately lead to undesirable oligomerization of the formed alkyne products.[14,26–28] Isolated lithium nickelates **1a** and **2b** are also catalytically competent and deliver **3a** in comparable yields to $Ni(COD)_2$ (see Figures S1–3), suggesting that they may be involved in the transformation (*vide infra*).



Scheme 2. a) Ni-catalyzed cross-coupling of fluoronaphthalenes and lithium acetylides. Yields refer to isolated products after purification by column chromatography. b) Ni-catalyzed cross-coupling of 1-fluoronaphthalene with $Me_3Si{-}C{\equiv}C{-}Li$ to give a **3i** and **3j**. Yields refer to separated products after purification by column chromatography.

When attempting to prepare 1-Naph–C≡C–$SiMe_3$ (**3i**) *via* the cross-coupling of 1-fluoronaphthalene with $Me_3Si{-}C{\equiv}C{-}Li$, 1-Naph–C≡C–1-Naph (**3j**) was observed as a significant product of the reaction in 41% yield alongside **3i** in 46% yield (**Scheme 2b**). The ratio of **3i** to **3j** could be manipulated by lowering the equivalents of $Me_3Si{-}C{\equiv}C{-}Li$ from 1.5 equivalents down to 0.5 equivalents, which selectively afforded **3i**. Control experiments and multinuclear NMR spectroscopy monitoring ruled out the involvement of LiF and instead revealed that **3i** reacts with $Me_3Si{-}C{\equiv}C{-}Li$ to give $Me_3Si{-}C{\equiv}C{-}SiMe_3$ and 1-Naph–C≡C–Li, where the latter reacts further with 1-fluoronaphthalene under nickel-catalysis to give **3j** (see Figures S4–5). Buter and Feringa has successfully employed $Me_3Si{-}C{\equiv}C{-}Li$ as a coupling partner in the Pd-catalyzed alkynylation of aryl bromides, but since these reactions operate in short reaction times and in non-donor solvents at room temperature, competing C–SiMe$_3$ bond cleavage is likely not observed.[25]

Encouraged by these stoichiometric and catalytic transformations, we next explored the reactivity of **1a** with polyfluorinated arenes. Addition of a toluene solution of **1a** to hexafluorobenzene at -30 °C results in an immediate color change from deep blue to pale brown, and the appearance of three new signals in the ^{19}F NMR spectrum at δ -118, -168.9 and -169.8, consistent with selective mono-C–F activation (**Figure 2a**). The formation of **4a** was confirmed by single crystal X-ray diffraction which shows a square-planar heteroleptic Ni(II) complex in which the two lithium cations coordinate in a *cis*-configuration with η^2-coordination to two acetylide π-systems (**Figure 2b**). We propose that the highly electron-withdrawing nature of the C$_6$F$_5$ substituent prevents reductive elimination and formation of Li/Ni(0) species. The isolation of this species is reminiscent of observations made for the cross-coupling of aryl ethers with PhLi which also proceeds *via* heteroleptic Ni(II) intermediates (see **Scheme 1a**).[13] Other polyfluorinated arenes such as C$_6$F$_5$–C≡C–Ph also reacted smoothly with **1a** to give compound **4b** in which C–F activation is regioselective for the *para*-position (see Figure S25 for solid-state structure). The oxidative addition of (poly)fluoroarenes to Ni(0) typically requires electron-rich phosphine or *N*-heterocyclic carbene (NHC) ligands and delivers the corresponding Ar–Ni(II)–F species.[29–32] In contrast, oxidative addition to lithium nickelate **1a** is facilitated by both its electron-rich character alongside LiF precipitation.

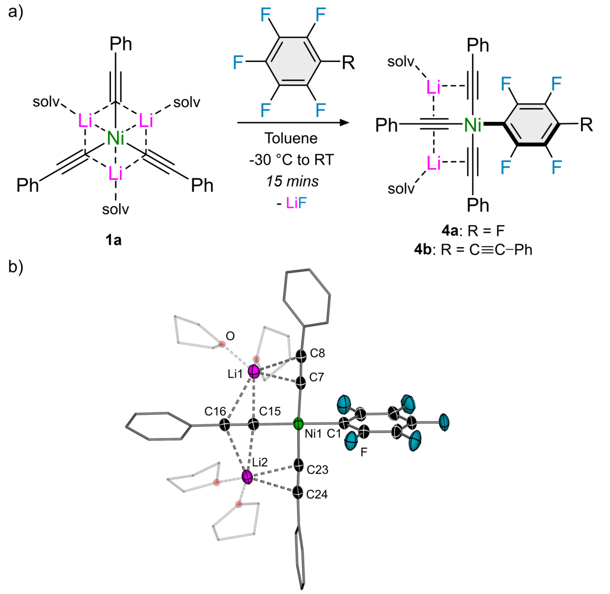
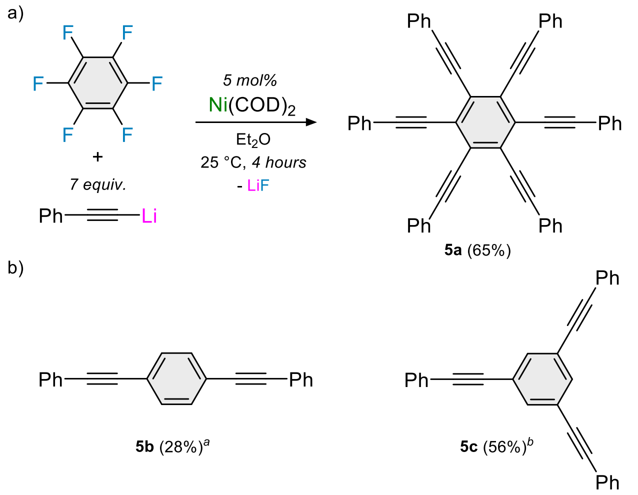


Figure 2. a) Reactivity of tri-lithium nickelate **1a** with polyfluoroarenes to give lithium nickelate complexes **4a-b**. b) Solid-state structure of **4a**. Thermal ellipsoids shown at 30% probability level. Coordinated THF and phenyl substituents shown as wireframes for clarity.

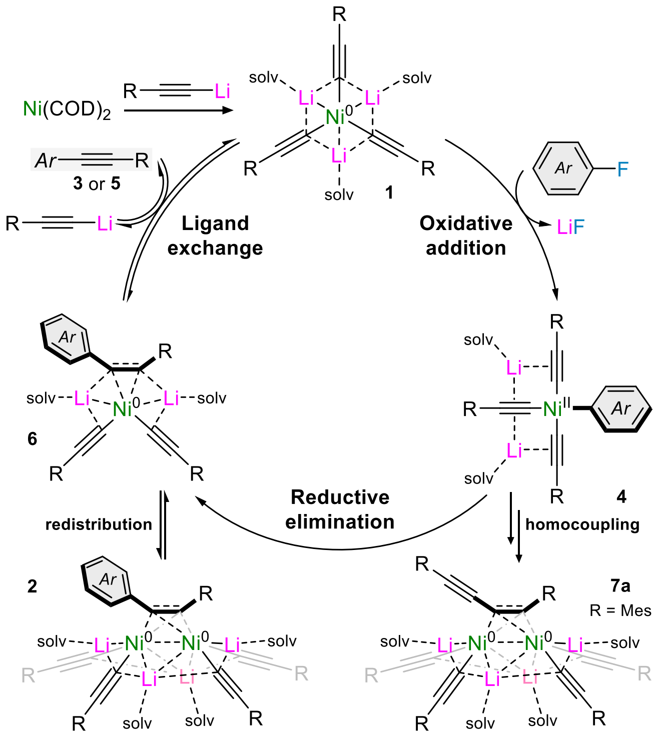
Under catalytic conditions with 5 mol% Ni(COD)$_2$, hexafluorobenzene reacts with 7 equivalents of Ph–C≡C–Li to give hexakis(phenylethynyl)benzene (**5a**) in 65% isolated yield after just 4 hours at room temperature (**Scheme 3a**). **5a** precipitates directly from the reaction mixture as a crystalline solid suitable for single-crystal X-ray diffraction (see Figure S26 for solid-state structure) and therefore can simply be filtered and washed, avoiding the need for time-consuming purifications. Previous synthetic methods to **5a** *via* Pd-catalyzed Sonogashira cross-coupling requires the use of hexaiodo- or hexabromobenzene,[33,34] whilst elevated reaction temperatures are needed to synthesize **5a** from more challenging polychlorinated aromatics.[35] Zhang has reported that hexafluorobenzene reacts directly with Ph–C≡C–Li *via* S$_N$Ar in the absence of transition-metal catalysts, however this yields the 1,4-disubstituted product Ph–C≡C–C$_6$F$_4$–C≡C–Ph in just 36% yield after 36 hours.[25] Initial reactivity studies suggest that **5a** is formed by a rapid Ni-mediated cascade process since attempts to isolate or observe mono- or di-substituted products by reducing reaction times and modifying the stoichiometry simply gave **5a** in variable yields, with recovery of unconsumed starting materials or homo-coupling products. Numerous other polyfluoroarenes were also tested with mixed success: 1,4-difluorobenzene reacts with 3 equivalents of Ph–C≡C–Li at 80 °C [16 hours, 10 mol% Ni(COD)$_2$] to give the di-functionalized product **5b** in 28% yield, whilst 1,3,5-trifluorobenzene reacts with 4 equivalents of Ph–C≡C–Li at 60 °C [16 hours, 10 mol% Ni(COD)$_2$] to give the tri-functionalized product **5c** in 56% yield (**Scheme 3b**). All other polyfluoroarenes tested gave intractable mixtures of products in which the homo-coupled diyne Ph–C≡C–C≡C–Ph was observed in large quantities.



Scheme 3. a) Ni-catalyzed cross-coupling of hexafluorobenzene and Ph–C≡C–Li to give hexakis(phenylethynyl)benzene (**5a**). b) Synthesis of polyfunctionalized **5b** and **5c** products from 1,4-difluorobenzene and 1,3,5-trifluorobenzene respectively. [a] 80 °C for 16 hours [10 mol% Ni(COD)$_2$]. [b] 60 °C for 16 hours [10 mol% Ni(COD)$_2$]. Yields refer to isolated products after purification by column chromatography.

Based on stoichiometric and catalytic reactions, together with prior mechanistic studies,[11,13] a tentative catalytic-cycle for the Ni-mediated alkynylation of aryl fluorides can be proposed in **Scheme 4**. The cycle begins with tri-lithium nickelate **1** which forms rapidly by treatment of Ni(COD)$_2$ with the corresponding lithium acetylide. The involvement of higher-order systems (i.e. complexes with higher Li:Ni ratios) cannot be fully discarded however, since we have also demonstrated that Ni(COD)$_2$ can co-complex with up to 10 equivalents of aliphatic lithium acetylides to give polynuclear lithium nickelate clusters which are active catalysts in acetylide homo-coupling.[15] Coordination of the aryl fluoride substrate to the tri-lithium nickelate **1** is followed by C–F activation and oxidative addition to give square-planar heteroleptic Ni(II) complex **4**, which are sufficiently stable to be isolated and characterized for electron-withdrawing systems (see **Figure 2**). Complex **4** then undergoes reductive elimination to give the cross-coupled alkyne product which remains coordinated to the Ni(0) center in an η^2-motif, giving the proposed mononickelate complex **6**. Finally, complex **6** undergoes ligand exchange with the lithium acetylide nucleophile to release the cross-coupled product (**3** or **5**) and regenerate tri-lithium nickelate **1**.

Spectroscopic monitoring of the reaction under various conditions identified the proposed mononickelate complex **6** but revealed complex ligand exchange and redistribution processes involving **1**, **2**, **6**, the lithium acetylide and the cross-coupled alkyne (see Figures S11–18 for full details and extended mechanism). Treatment of **1a** with 1-fluoronaphthalene initially gives signals characteristic for **2b**, whilst over time, this species evolves into the corresponding mononickelate complex **6b** (see Figures S6–8). The identification of this species as **6b** is supported by ^{13}C NMR spectroscopy which displays diagnostic signals for the coordinated alkyne at δ 144.2 and 133.8 ppm which is significantly downfield shifted compared to dinickelate **2b** (δ 92.0, 85.0 ppm).[14] Furthermore, estimated molecular weights determined by diffusion ordered spectroscopy (DOSY NMR) are consistent with a mononickelate complex (see Figures S9–10). All efforts to isolate **6b** were unsuccessful however, and regardless of the crystallization conditions employed, only dinickelate **2b** was recovered. Alternative strategies to isolate a mononickelate η^2-alkyne complex in the solid-state targeted the use of bulky substituents, however in this case, the combination of $Ni(COD)_2$, Mes–C≡C–Li and Mes-Br (where Mes = mesityl or 2,4,6-trimethylphenyl) gave a dinickelate μ-η^2:η^2-diyne complex **7a** (see Figure S27 for solid-state structure) which results from homocoupling of the acetylide substituents. The final stage of the catalytic cycle is proposed to be ligand exchange between **6** (or **2**) and the lithium acetylide to regenerate tri-lithium nickelate **1**, but all attempts to verify this experimentally were unsuccessful. Contrastingly, tri-lithium nickelate **1a** was observed to react rapidly with 1-Naph–C≡C–Ph (**3a**) to give **6b** and/or **2b** depending on the stoichiometry, with concomitant release of Ph–C≡C–Li (see Figures S15–16). This suggests that ligand exchange and product release is best described as an equilibrium that lies strongly towards **6** (or **2**), and points towards this step being the rate limiting step of the catalytic cycle given that the formation of **2**, **4** or **6** occurs under ambient conditions, whilst elevated reaction temperatures are required for catalytic turnover.



Scheme 4. Proposed catalytic cycle for the Ni-catalyzed cross-coupling of aryl fluorides and lithium acetylides (see Figure S18 for extended mechanism).

In conclusion, we have demonstrated that tri-lithium nickelates undergo C–F activation with aryl fluorides and polyfluoroarenes to give structurally diverse Li/Ni(0) or Li/Ni(II) complexes. These stoichiometric reactions can be upgraded to catalytic regimes to develop the first example of a Ni-catalyzed alkynylation of aryl fluorides, without the need for Pd, Cu co-catalysts or external ligands. This work expands the scope of catalytic transformations that are mediated by low-valent nickelate complexes as well providing important mechanistic understanding.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website:

Full synthetic, spectroscopic and crystallographic details (PDF)

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Notes

The authors declare no competing financial interests.

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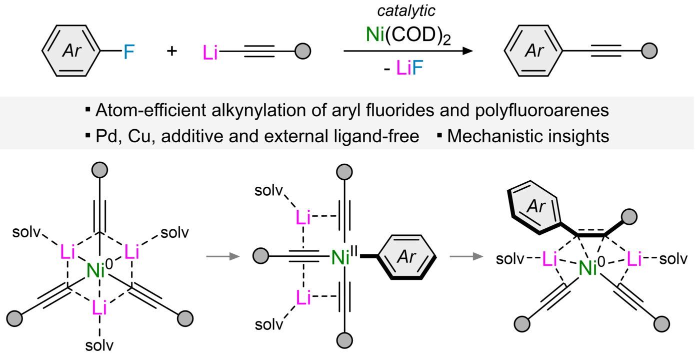

- Atom-efficient alkynylation of aryl fluorides and polyfluoroarenes
- Pd, Cu, additive and external ligand-free
- Mechanistic insights