

Design of an electron-withdrawing benzonitrile ligand for Ni-catalyzed cross-coupling involving tertiary nucleophiles

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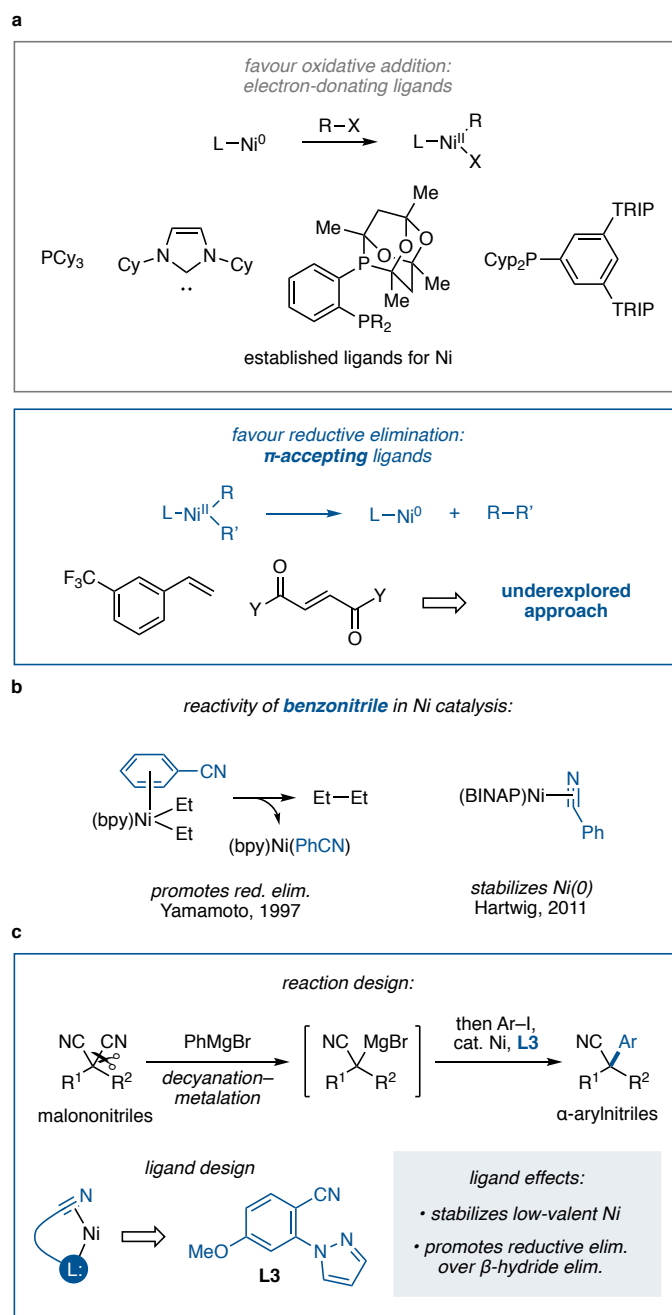
ABSTRACT: The design of new ligands for cross-coupling is essential for developing new catalytic reactions that access valuable products such as pharmaceuticals. In this report, we exploit the reactivity of nitrile-containing additives in Ni catalysis to design a benzonitrile-containing ligand for cross-coupling involving tertiary nucleophiles. Kinetic and Hammett studies are used to elucidate the role of the optimized ligand, which demonstrate that the benzonitrile moiety acts as an electron-acceptor to promote reductive elimination over β -hydride elimination, and stabilize low-valent Ni. With these conditions, a protocol for decyanation–metalation and Ni-catalyzed arylation is conducted, enabling access to quaternary α -arylnitriles from disubstituted malononitriles.

Transition metal–catalyzed cross-coupling has revolutionized the synthesis of biologically relevant compounds such as pharmaceuticals and agrochemicals.^{1,2} The ability of chemists to access these compounds in new and efficient ways is dictated by the development of new catalysts,³ which largely depends on the design of ligands to modulate catalytic activity.⁴ For instance, in the area of Pd-catalyzed cross-coupling, ligand design has been impactful,^{5,6,7} and access to large and diverse arrays of ligand combinations has proven successful for the discovery of new catalytic reactions in the synthesis of pharmaceuticals.^{8,9,10}

As an underdeveloped cross-coupling catalyst in comparison to Pd, Ni has received attention because it is Earth-abundant, and because its unique reactivity renders it adept for certain transformations.¹¹ For instance, versus Pd, Ni has a smaller atomic radius and more electropositive character, which renders oxidative addition to Ni facile for various electrophiles.¹¹ The design and/or use of electron-donating ligands for Ni catalysis, such as phosphines^{12,13} and *N*-heterocyclic carbenes,^{14,15} has complemented this reactivity (Fig. 1a, top box).^{16,17}

The ligand design strategy for favouring reductive elimination is orthogonal to that for favouring oxidative addition, since the electronic requirements for reductive elimination are opposite to those for oxidative addition. Here, the design of electron-deficient π -acceptor ligands for Ni could favour reductive elimination, which is especially important for reactions involving C(sp³) coupling partners in which β -hydride elimination is a competing

pathway (Fig. 1a, bottom box). In this space, common derivatives are electron-deficient alkenes,^{18,19,20,21} such as styrenes and fumarates.^{22,23,24,25,26,27} However, besides these examples, the chemical space surrounding electron-deficient π -accepting ligands for Ni-catalysis is limited.



(1-column) **Fig. 1. Ligand design for challenging Ni-catalyzed reductive elimination.** **a**, Electron-donating and electron-withdrawing ligands in Ni catalysis. **b**, Benzonitrile effects in Ni catalysis. **c**, This work: Use of an electron-accepting bidentate benzonitrile ligand (**L3**) for Ni-catalyzed α -arylation.

We were intrigued by the known reactivities of a different π -accepting functional group, namely benzonitrile (Fig. 1b). In the context of Ni chemistry, Yamamoto and coworkers have reported that benzonitriles can promote

reductive elimination of Ni(II) intermediates (Fig. 1b).^{28,29} Hartwig and coworkers have also disclosed that benzonitrile can act as a side-bound ligand to stabilize Ni(0) (Fig 1b).^{30,31,32} Nitrile additives^{33,34} and ligands^{35,36} have been associated with Ni catalysis, however the focused design and study of a bidentate nitrile ligand that favours Ni-catalyzed reductive elimination has not been reported.

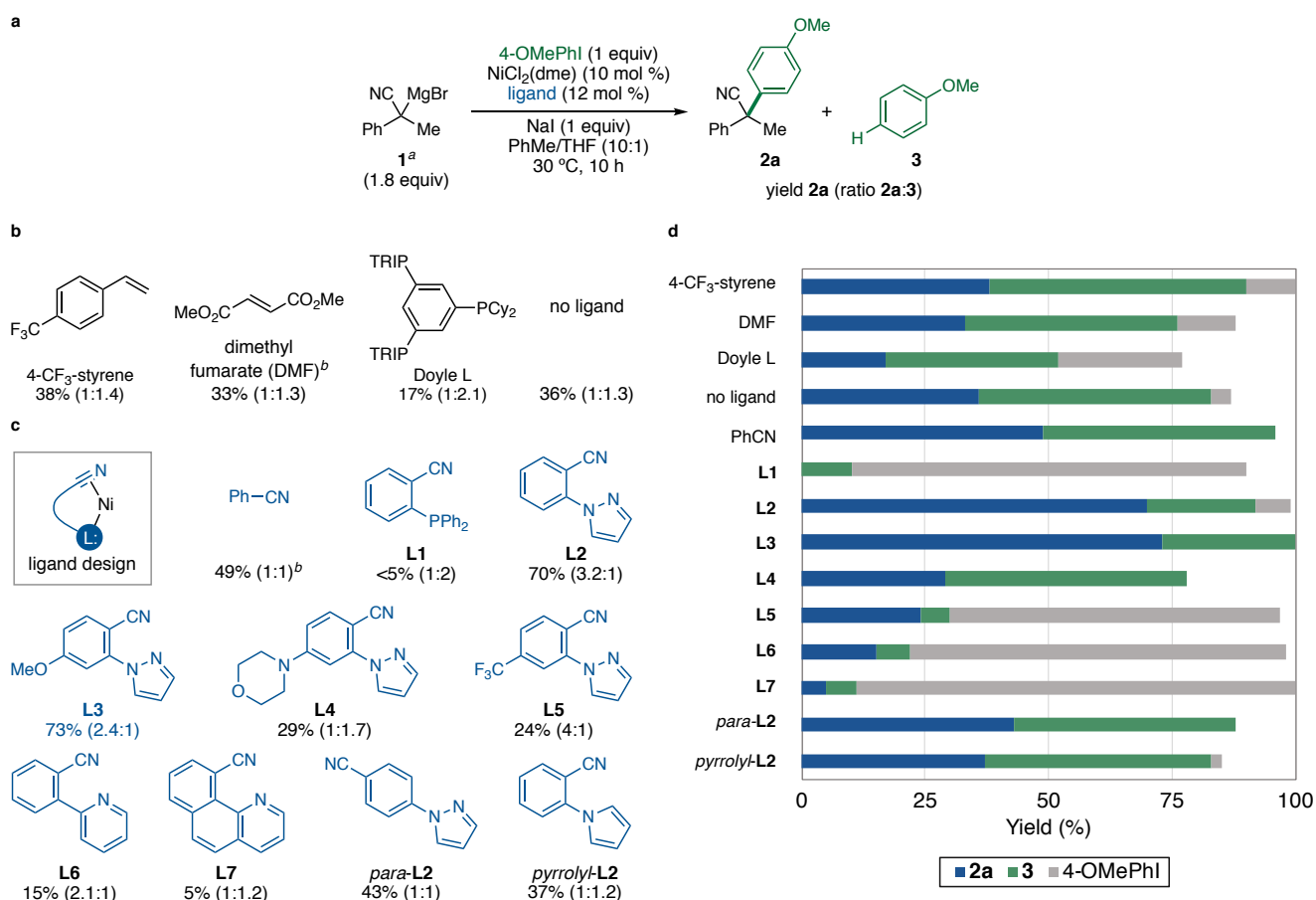
Herein, we disclose that a bidentate, benzonitrile-containing ligand promotes Ni-catalyzed C(sp²)-C(sp³) bond formation (Fig. 1c). In this transformation, disubstituted malononitriles undergo decyanation–metalation,^{37,38,39} followed by Ni-catalyzed arylation. As substrates, disubstituted malononitriles are convenient since they can be synthesized in one or two steps from commodity chemical malononitrile.^{40,41,42,43} The arylation step is enabled by an *ortho*-pyrazole benzonitrile-containing ligand (**L3**). Hammett studies reveal that **L3** acts as an electron-acceptor, which attenuates and stabilizes low-valent Ni, favouring reductive elimination. As a bidentate ligand, **L3** promotes formation of nitrile-bound Ni, which also disfavours β-hydride elimination. Together, this procedure accesses valuable quaternary α-arylnitriles,^{44,45} enabled by **L3** as a novel benzonitrile-containing ligand.

Results and discussion

Design and use of the benzonitrile ligand (L3). We began by exploring conditions for Ni-catalyzed arylation of α-magnesiated nitriles (**1a**) with 4-iodoanisole (Fig. 2). The reaction was evaluated for yields of α-arylnitrile (**2a**) and reduced arene (**3**), a side-product resulting from β-hydride elimination. The alkenyl nitrile resulting from β-hydride was also indirectly observed.⁴⁶ Electron-poor ligands gave appreciable yield of **2a**, including 4-trifluoromethylstyrene^{47,48} and dimethyl fumarate⁴⁹ (Fig. 2b). A sterically hindered Doyle ligand (Doyle L) gave low yield of **2a**.^{43,47} As a control, the reaction was performed in the absence of ligand (“no ligand”), which gave good conversion with some formation of **2a** (36% yield). A thorough screen of electron-donating ligands was also performed, however these ligands either inhibited catalysis or had no apparent effect in comparison to the control (see SI).

The reactivity in the absence of ligand suggested that some reaction components could be acting as ligands to (i) stabilize the Ni catalyst, especially low-valent Ni; and (ii) promote the formation of **2a**. We have previously observed that, in the presence of nitrile-containing intermediates, C–Br reductive elimination from Ni(II) oxidative addition intermediates can proceed.⁴⁸ The groups of Hartwig^{30,31,32} and Schoenebeck³³ have also demonstrated that

nitriles can coordinate Ni(0) intermediates. To probe if nitriles were facilitating cross-coupling, benzonitrile (20 mol %) was added to the reaction, and a modest but reproducible boost in the yield was observed (49% yield). This beneficial effect was concentration-dependent and could be improved with up to 10 equiv PhCN; *vide infra*.



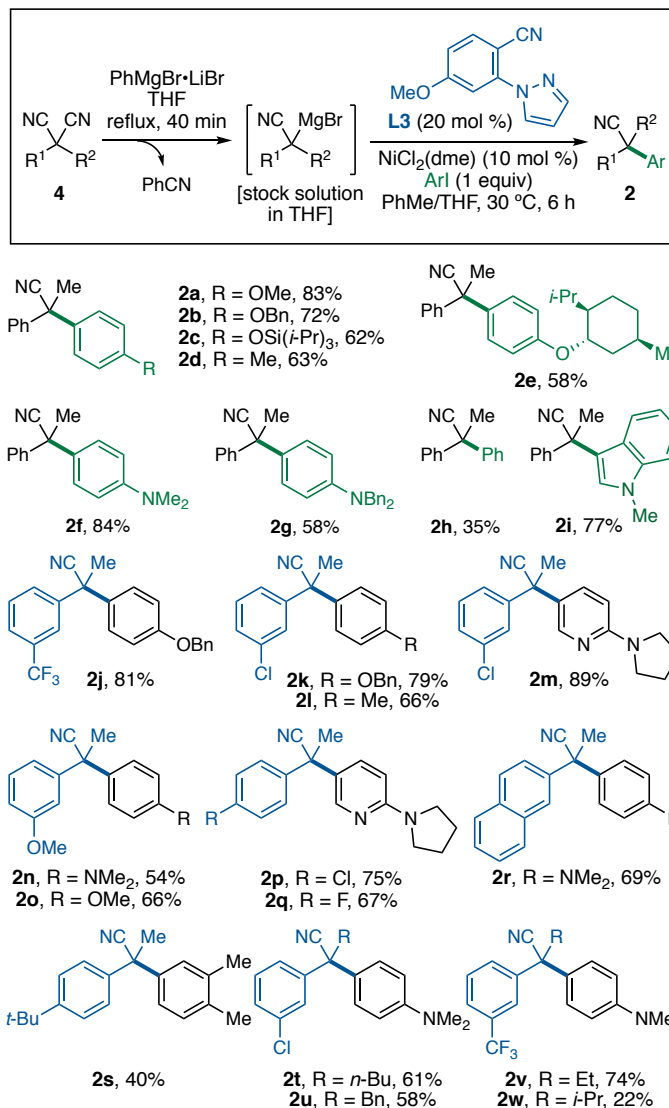
(2-column) **Fig. 2. Ligand Optimization.** **a**, Optimization conditions; reactions performed on 0.10-mmol scale; yields determined by GC-MS using *n*-dodecane as an internal standard. **b**, Initial ligand screen. **c**, Evaluation of benzonitrile-containing ligands. **d**, Graphical representation for yields of **2a** (blue), **3** (green), and remaining 4-OMePhI (grey). ^aPrepared from α -methylbenzyl cyanide (1.8 equiv) and PhMgBr•LiBr (1.8 equiv); ^bUsing 20 mol % ligand. For a complete list of ligands explored, see SI. TRIP = 2,4,6-triisopropylphenyl.

Thus, we sought to design a bidentate benzonitrile ligand to promote formation of nitrile-bound Ni (Fig. 2c). With an *ortho*-diphenylphosphine-substituted benzonitrile (**L1**), poor yield was achieved, with the remaining mass balance being unreacted aryl iodide. As alternate Lewis base, an *ortho*-pyrazole-substituted benzonitrile was used (**L2**), which gave excellent conversion of aryl iodide (93% conv.), and good selectivity for the desired α -arylated product (70% and 22% yield of **2a** and **3**, respectively). Adding a methoxy substituent *para* to the nitrile (**L3**) resulted in improved conversion (100% conv.), while still maintaining good product selectivity (73% and 30%

yield of **2a** and **3**, respectively). A stronger *para*-electron-donating group (dialkylamino, **L4**) resulted in poorer yield (29%), and a *para*-electron-withdrawing group (trifluoromethyl, **L5**) resulted in worse conversion of aryl iodide (33% conv.). Other Lewis bases gave worse conversion or selectivity for **2a** versus **3** (**L6–L7**).

Controls demonstrated the importance of Lewis base proximity to the benzonitrile. In cases where the pyrazole was *para* to the nitrile (*para*-**L2**), or where the Lewis basic nitrogen was removed (*pyrrolyl*-**L2**), the selectivity for formation of **2a** over **3** was eroded in comparison to that observed with **L2**, suggesting that the role of the Lewis base is to coordinate Ni and localize it to the nitrile.

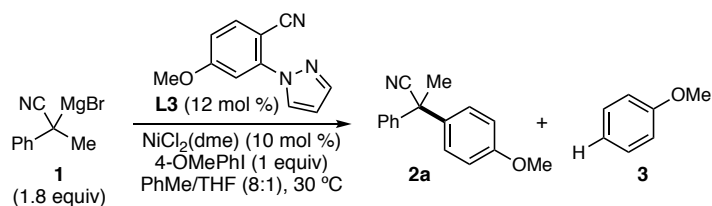
We next evaluated the catalytic activity of optimal ligand **L3** in the context of decyanation–arylation of disubstituted malononitriles, which are convenient materials that can be easily synthesized from commodity chemical malononitrile (Fig. 3). Here, exposure of malononitriles (**4**) to PhMgBr•LiBr⁴⁹ yields PhCN and an α -metalated nitrile *in situ*.^{50,51,52,53,54,55} Then, treatment with an aryl iodide (1 equiv), NiCl₂(dme) (10 mol %), and **L3** (20 mol %) in PhMe/THF at 30 °C yields the α -arylnitrile (**2**). A number of electrophiles were viable, including electron-rich (**2a–2c**, **2e–2g**) aryl iodides and (hetero)aryl iodides (**2i**, **2m**, **2p–2q**). Electron-neutral (**2h**) and electron-deficient (see SI) aryl iodides gave lower yields of α -arylnitrile (**2**), with the majority of the mass balance going towards reduced arene. With respect to malononitriles, the procedure works well with substrates bearing electron-deficient (**2k–2p**) and electron-neutral (**2s–2t**) aryl substituents. Halide-containing substrates like chloride (**2p**) and fluoride (**2q**) were viable. Substrates with weakly electron-donating aryl substituents (**2s**) could also be employed. While electron-rich malononitriles (not shown) underwent decyanation–metalation efficiently, these α -anions resulted in poor conversion of the aryl iodide in step two (*vide infra*). Finally, the arylation was compatible with some larger alkyl substituents on the nitrile, like *n*-butyl (**2t**), benzyl (**2u**), and ethyl (**2v**). Substrates with larger, branched alkyl substituents like isopropyl (**2w**) gave poor conversion of aryl iodide and more significant amounts of reduced arene.



(1-column) **Fig. 3. Scope of the decyanation/arylation procedure.** Reactions performed on 0.20–0.30 mmol scale. Yields are isolated. For full details and incompatible substrates, see SI.

Rate law and catalytic cycle. Kinetic studies were performed using a model system (Fig. 4). Concentration-dependent initial rates were obtained (see SI), revealing a rate law that showed first-order dependence on both aryl iodide and catalyst, inverse first-order dependence on the α -metallated nitrile (**1**), and no product inhibition (Eq. 1). These data show that aryl iodide and catalyst alone are involved in the turnover-limiting step, which is most consistent with a catalytic cycle where oxidative addition is rate-determining. This was corroborated by a positive Hammett correlation with respect to aryl iodide ($\rho = 0.40$, see SI).^{36,37} Inverse first-order dependence on α -anion (**1**) implies that one equivalent of α -anion can bind to the catalyst to inhibit the rate-determining step. Consistent with this, malononitriles with electron-

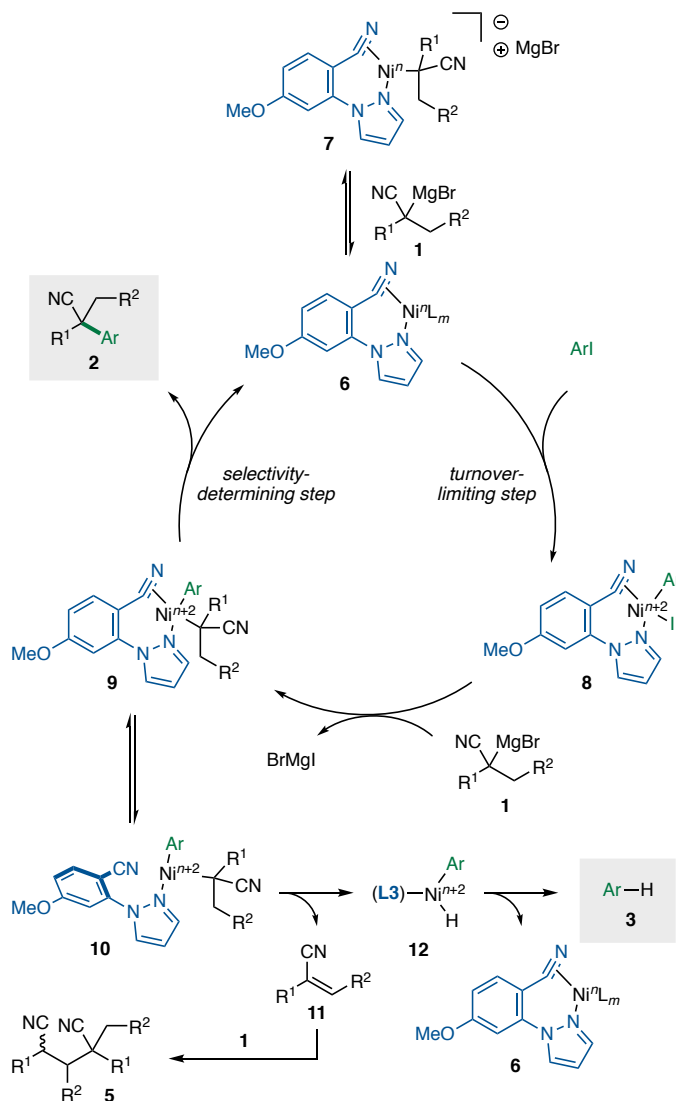
donating substituents were found to be ineffective in the decyanation–arylation procedure, as a result of longer reaction times and inefficient conversion (see SI).



(1-column) **Fig. 4.** Model system for kinetic studies

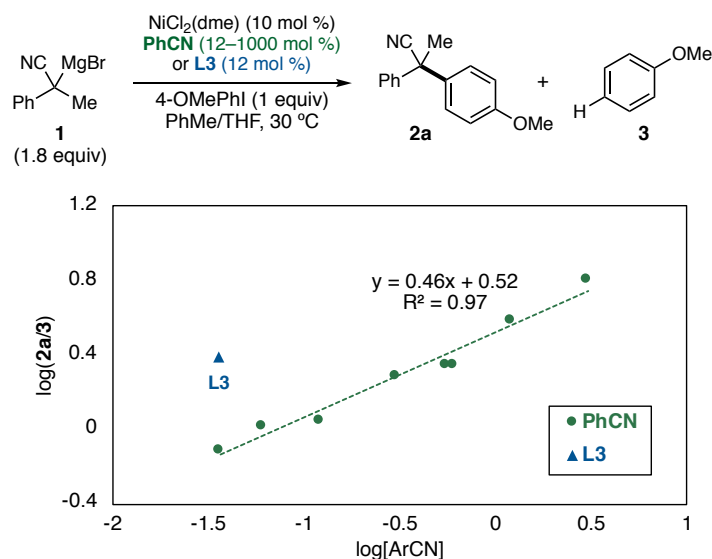
$$\text{rate} = \frac{k[\text{ArI}][\text{Ni}][\mathbf{2}]^0}{[\mathbf{1}]} \quad (1)$$

A proposed catalytic cycle for arylation is shown in Fig. 5. Starting with a low-valent Ni intermediate (**6**), rate-determining oxidative addition to the aryl iodide yields the oxidative addition intermediate (**8**). The low-valent Ni intermediate (**6**) may also react with one equivalent of α -anion (**1**), yielding an off-cycle intermediate (**7**). After oxidative addition (**8**), transmetalation with **1** yields the pre-reductive elimination intermediate (**9**). Reductive elimination releases the α -arylnitrile, regenerating the low-valent Ni intermediate (**6**). Alternatively, from the pre-reductive elimination intermediate (**9**), the nitrile may become unbound to Ni (**10**), which would render a vacant coordination site to allow β -hydride elimination to occur. β -Hydride elimination releases an alkenyl nitrile (**11**), which reacts with another equivalent of **1** to yield the Michael adduct (**5**) (see SI for characterization). The corresponding pre-reductive elimination Ni-hydride (**12**) can yield the reduced arene (**3**) and regenerate the low-valent nickel species (**6**).



(1-column) **Fig. 5. Proposed catalytic cycle**

Role of the benzonitrile. In the absence of ligand, benzonitrile was added to the arylation reaction in varying amounts (Fig. 6). When the selectivity for α -arylnitrile (**2a**) versus reduced arene (**3**) was evaluated (green series), a positive trend was observed, demonstrating that increased concentration of benzonitrile improves the efficiency of α -arylnitrile formation, potentially by occupying open coordination sites necessary for Ni-catalyzed β -hydride elimination. When catalytic **L3** (12 mol %) was used (blue datum), positive selectivity for desired α -arylnitrile (**2a**) was observed, akin to the selectivity obtained with high concentrations of benzonitrile (ca. 200 mol %). This suggests that **L3** coordinates Ni to place it in close proximity to the benzonitrile, increasing the effective concentration of nitrile-bound Ni.

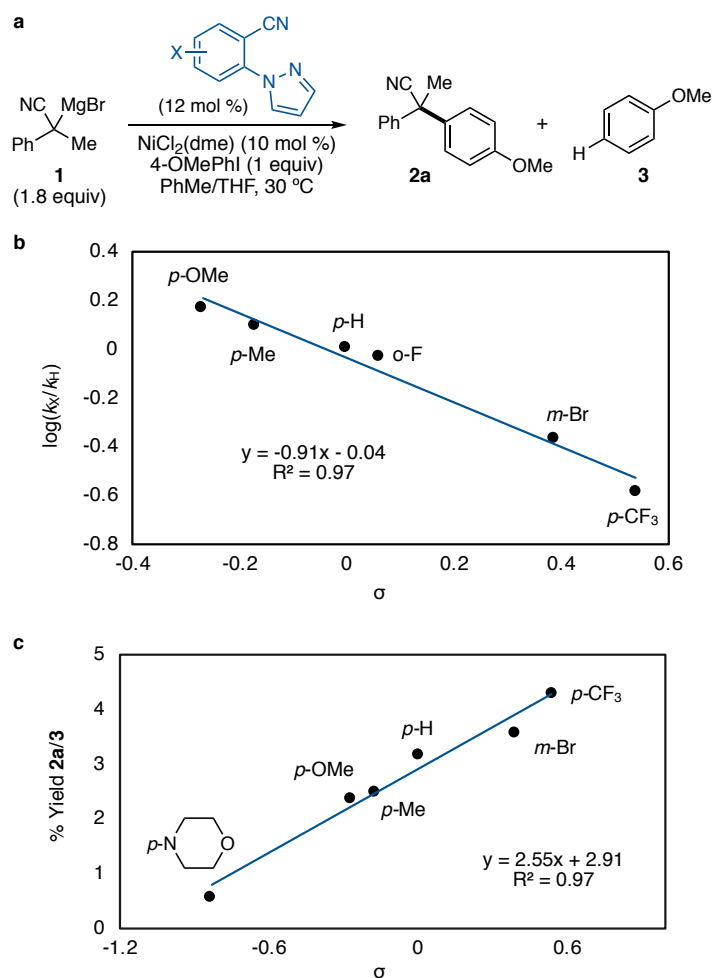


(1-column) **Fig. 6.** Product selectivity in the presence of PhCN (green series) or **L3** (blue series)

Finally, we evaluated how the electronic properties of **L3** affected oxidative addition, as well as selective formation of α -arylnitrile (**2a**) (Fig. 7). First, initial reaction rates were evaluated according to ligand electronic properties (Fig. 7a–b). After Hammett analysis, a negative slope was obtained ($\rho = -0.91$), indicating that during the rate-limiting step (oxidative addition), there is a buildup of positive charge on the ligand, corresponding to a loss of electron-density on the catalyst.

Next, the selectivity for α -arylnitrile (**2a**) versus reduced arene (**3**) was evaluated according to ligand electronic properties (Fig. 7c). Plotting the ratio of desired product (**2a**) to undesired product (**3**) after 6 h (% Yield **2a/3**) gave a significant positive slope ($\rho = 2.55$), with electron-deficient ligands favouring **2a**. These data indicate a buildup of negative charge in the selectivity-determining step. By stabilizing a buildup of electron-density, the ligand may either (a) favour reductive elimination or (b) disfavour β -hydride elimination. In general, electron-withdrawing ligands favour reductive elimination; and since electron-donating ligands are known to increase the rate of β -hydride elimination,^{58,59} these data (Fig. 7c) indicate that both scenarios are possible. The positive slope also shows that the benzonitrile functional group acts primarily as an electron-acceptor rather than an electron-donor. For the design of

L3 in this system, there is a catch-22, since the electronic requirements for selective product formation are opposite those for efficient reaction turnover.



(1-column) **Fig. 7. Ligand electronic effects.** **a**, Reaction conditions. **b**, Initial rates according to ligand electronics (substituent positions with respect to nitrile). **c**, Product selectivity ratios after 6 h (**2a** vs. **3**) according to ligand electronics (substituent positions with respect to nitrile).

Conclusion

We have disclosed a procedure for decyanation–metalation of malononitriles, followed by Ni-catalyzed α -arylation using a novel bidentate benzonitrile-containing ligand (**L3**) to access quaternary α -arylnitriles. Key roles of **L3** include the promotion of reductive elimination over β -hydride elimination, leading to efficient product formation. While some effects of nitrile additives in Ni catalysis have been reported, this report clearly demonstrates the utility of nitriles as ligands, and the potential noninnocence of nitriles in

catalysis, especially in terms of stabilizing low-valent metal centers. We anticipate this work may lead to new chemistry and ligand design for Ni-catalyzed reactions involving C(sp³) coupling partners.

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