LiCl-Accelerated Multimetallic Cross-Coupling of Aryl Chlorides with Aryl Triflates

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S *Supporting Information*

ABSTRACT: While the synthesis of biaryls has advanced rapidly in the past decades, cross-Ullman couplings of aryl chlorides, the most abundant aryl electrophiles, have remained elusive. Reported here is the first general cross-Ullman coupling of aryl chlorides with aryl triflates. The selectivity challenge associated with coupling an inert electrophile with a reactive one is overcome using a multimetallic strategy with the appropriate choice of additive. Studies demonstrate that LiCl is essential for effective cross-coupling by accelerating the reduction of Ni(II) to Ni(0) and counteracting autoinhibition of reduction at Zn(0) by Zn(II) salts. The modified conditions tolerate a variety of functional groups on either coupling partner (42 examples), and examples include a three-step synthesis of flurbiprofen.

The synthesis of biaryls has become one of the most commonly used reactions in pharmaceutical, agro-chemical, and materials science industries,[1] yet access to arylmetal reagents remains limiting. The low commercial availability of arylmetal reagents has inspired a number of active areas of research (Scheme 1A), including improved methods for arylmetal synthesis,[2] C−H arylation,[3] and decarboxylative cross-coupling.[4]

The relative abundance of aryl electrophiles (Scheme 1B[5]) would make the cross-Ullman reaction[6,7] an attractive approach, but our recently reported catalytic nickel and palladium method *was not broadly effective* with the most abundant and versatile aryl electrophiles, aryl chlorides.[8] In addition to opening up more chemical space, aryl chlorides are often lower in cost, and their lower reactivity would allow for sequential coupling in fragment-based drug discovery[9] or late-stage coupling on complex molecules.[10]

Although significant advances in the use of aryl chlorides in cross-coupling have been made recently,[7c,11−14] there are no general methods for the direct cross-coupling of electron-neutral or electron-rich aryl chlorides with other aryl electrophiles.[15,16] In our prior report, we established that in order to promote a successful cross-Ullman reaction, the electrophiles employed had to be orthogonally paired in reactivity: the Ni catalyst activated aryl bromides at a higher rate than aryl triflates; the Pd catalyst activated aryl triflates at a higher rate than aryl bromides. When sufficiently electron-deficient aryl chlorides were substituted for aryl bromides, they were still activated enough to maintain catalyst selectivity. However, when less

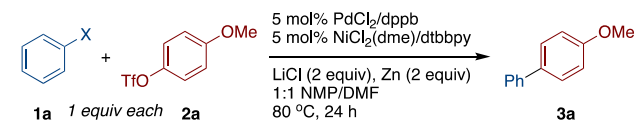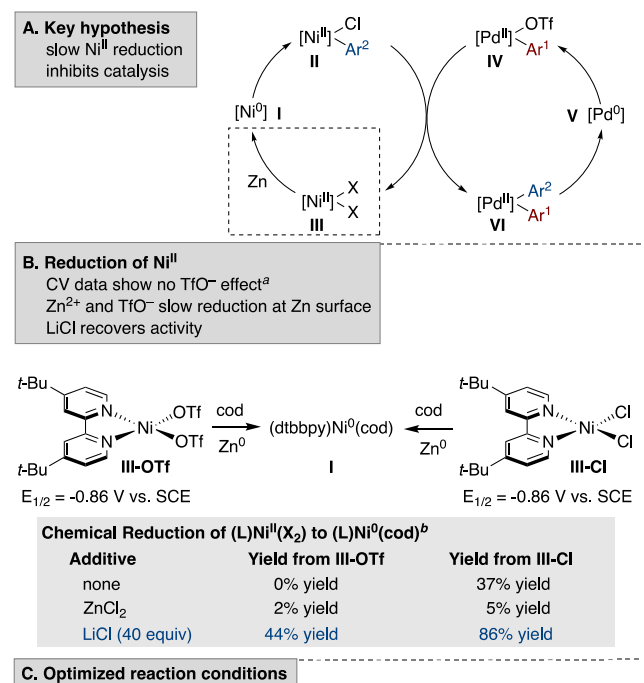## Scheme 1. Cross-Ullman Reaction in Biaryl Synthesis
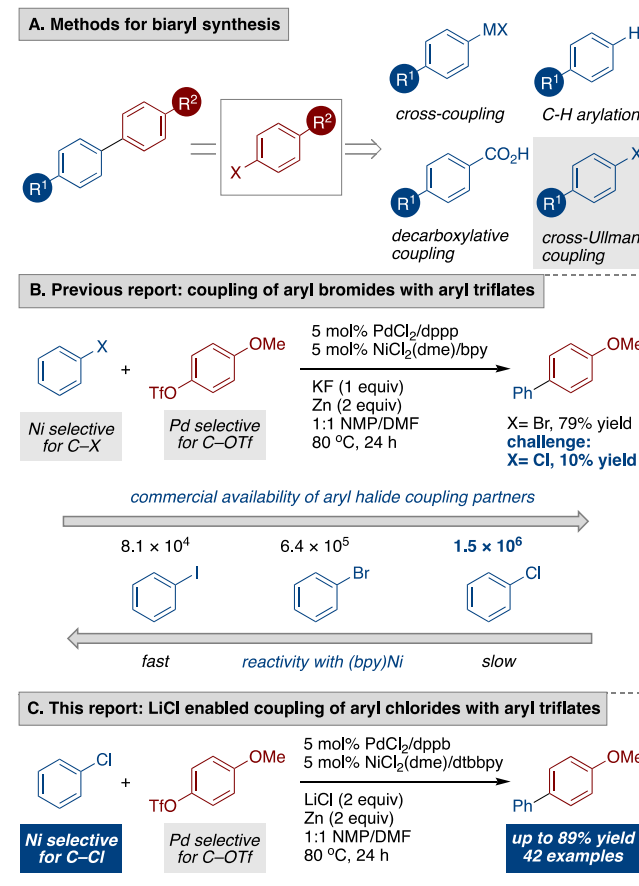
activated aryl chlorides were used, poor results were obtained. Preliminary studies attempting to couple more electron-rich chlorides with aryl triflates led to production of the triflate-derived dimer and incomplete conversion of both the aryl chloride and the aryl triflate. Herein we report a general multimetallic solution that achieves the selective coupling of a variety of aryl chlorides with aryl triflates (Scheme 1C).

On the basis of the mechanism proposed in our earlier studies with nickel and palladium multimetallic catalysis (Table 1A),[8] the slow consumption of the aryl chloride *and* aryl triflate suggested that arylnickel (**II**) formation was being

Table 1. Mechanistic Study and Optimization of the Ar–Cl Cross-Ullman Reaction

A. Key hypothesis
slow Ni[II] reduction
inhibits catalysis

B. Reduction of Ni[II]
CV data show no TfO− effect[a]
Zn^{2+} and TfO− slow reduction at Zn surface
LiCl recovers activity

III-OTf $E_{1/2}$ = -0.86 V vs. SCE

I

III-Cl $E_{1/2}$ = -0.86 V vs. SCE

Chemical Reduction of (L)Ni[II](X_2) to (L)Ni[0](cod)[b]

Additive	Yield from III-OTf	Yield from III-Cl
none	0% yield	37% yield
ZnCl_2	2% yield	5% yield
LiCl (40 equiv)	44% yield	86% yield

C. Optimized reaction conditions

5 mol% PdCl_2/dppb
5 mol% NiCl_2(dme)/dtbbpy
LiCl (2 equiv), Zn (2 equiv)
1:1 NMP/DMF
80 °C, 24 h

1a 1 equiv each   2a   3a

entry	change from the optimized conditions[c]	3a (%)[d]
1	none	84
2	NaCl instead of LiCl	62
3	LiBr instead of LiCl	59
4	Bu_4NCl instead of LiCl	53
5	TMSCl instead of LiCl	16
6	no LiCl	<10
7	Mn instead of Zn	62
8	Mn instead of Zn, LiBr instead of LiCl	77
9	without PdCl_2 and dppb	44
10	without NiCl_2(dme) and dtbbpy	<5
11	reaction set up on the benchtop[e]	80
12	1.2 equiv of 2a	90 (89[f])

[a]In DMF. See the Supporting Information for details on electrochemical studies. [b]Reduction of III was conducted in DMF at a concentration of 0.025 M with Zn powder (40 equiv). Cyclooctadiene (0.125 M) was added to stabilize the product. Salts (1−40 equiv) were added in some cases. See the Supporting Information for additional results and experimental details. [c]Reactions were run on a 0.5 mmol scale in 2 mL of solvent. NMP = N-methyl-2-pyrrolidinone. [d]GC yield vs dodecane as an internal standard. [e]The reaction was set up under air with dry solvent. [f]Isolated yield.

inhibited (Table 1A). Arylpalladium (**IV**) will not consume aryl triflate without arylnickel (**II**) present. The inhibition could arise from slow oxidative addition (**I** to **II**),[17] slow reduction (**III** to **I**), or an off-cycle loss of nickel catalyst.
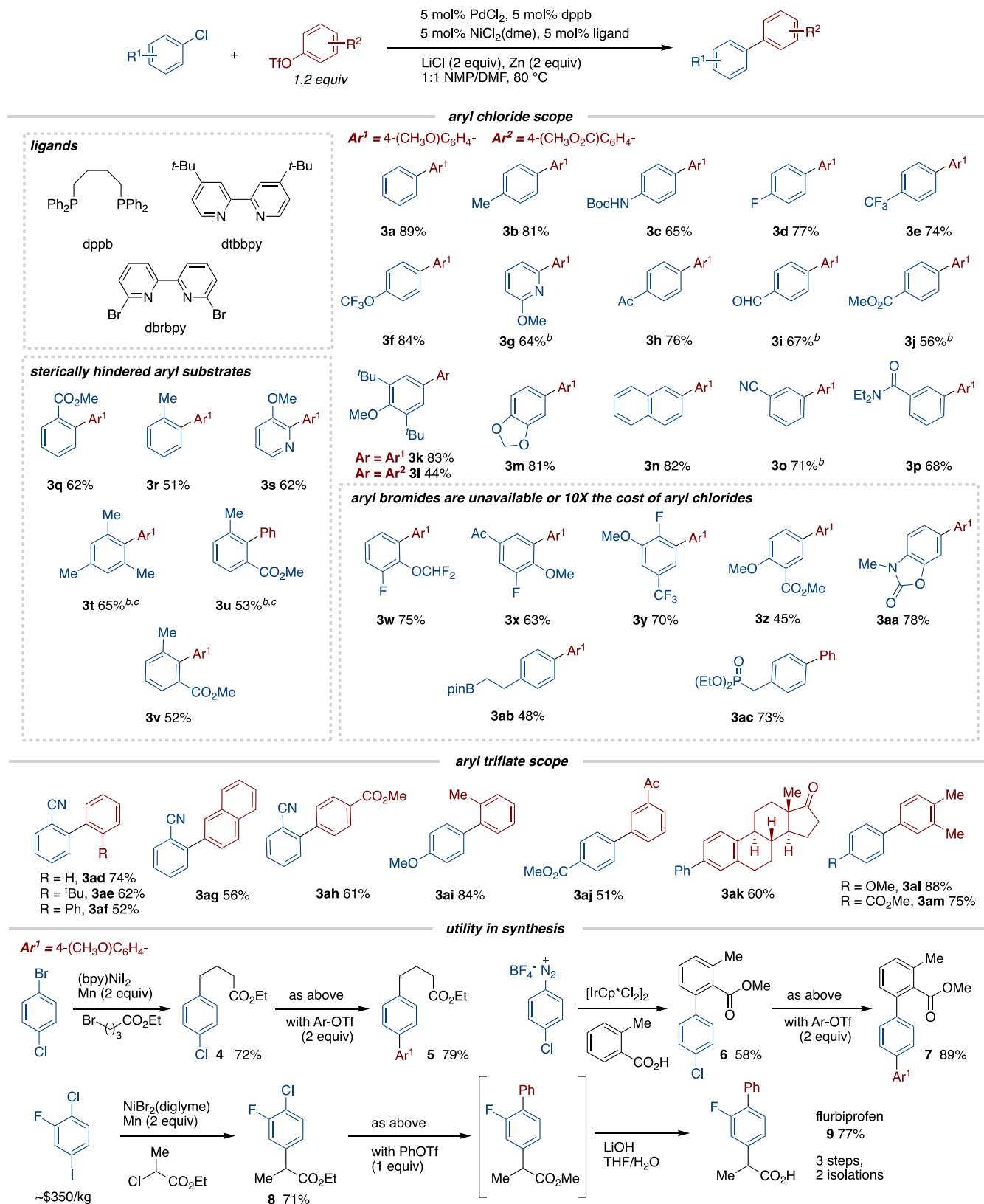
Reduction of the (dtbbpy)Ni[II]X_2 complexes **III-Cl** and **III-OTf** was studied by both electrochemical and chemical methods (Table 1B). Cyclic voltammetry (CV) studies, which are commonly used to assess the ease of reduction of metal complexes,[18] showed no difference between **III-Cl** and **III-OTf** (Table 1B and Figures S7 and S8 in the Supporting

Information). While CV provides information on the thermodynamic driving force for a reduction, it does not account for the complex kinetic picture of reduction at a metal surface.[19,20] Indeed, the reduction of complexes **III-OTf** and **III-Cl** over zinc flakes in the presence or absence of additives showed that **III-OTf** is not reduced unless chloride salts are present (Table 1B,C, Figures S8 and S9, and Table S2). There is also a cation effect: while LiCl enhances the rate of reduction of both nickel complexes **III-OTf** and **III-Cl**, ZnCl_2 does not. In fact, zinc chloride and zinc triflate, salts formed during the reaction, inhibit reduction of (dtbbpy)Ni[II]Cl_2 (37% yield with no salt, 2−5% yield with 1 equiv of ZnCl_2 or Zn(OTf)_2). Lithium chloride[21] can overcome zinc inhibition and was generally the most useful additive studied (Table 1, entries 1−6, and Table S2).[22,23] While we found that reduction of octyl bromide to octylzinc bromide was also inhibited by zinc salts,[21d,24] reduction of palladium(II) phosphine complexes to palladium(0) was fast with or without added LiCl or Zn (Figures S11−S16).[25,26]

These studies show that the low reactivity observed for the coupling of aryl chlorides with aryl triflates (Scheme 1B) is due to autoinhibition: the zinc salts (ZnCl_2 and Zn(OTf)_2) formed in the reduction of **III** to **I** inhibit subsequent reductions of **III**. While it had previously been noted that halide anions accelerate reduction of NiX_2 intermediates at zinc surfaces,[27,28] the inhibitory effect of less-coordinating anions (OTf−, BF_4−, PF_6−)[29] and zinc salts has not been previously reported. This result has broad implications for cross-electrophile coupling reactions that rely upon heterogeneous metallic reductants.

The catalytic reaction behaved as expected from the stoichiometric studies: the addition of LiCl enabled turnover (Table 1C, entries 1−6, and Figures S1 and S2).[30] Consistent with previous reports,[8] these reactions were still promoted by the cooperativity between the two metal catalysts: reactions without palladium were poorly selective, and reactions without nickel did not consume starting materials (Table 1, entries 9 and 10). Similar to other cross-electrophile coupling reactions,[28a] the reaction was tolerant of adventitious O_2, allowing reactions to be set up on the benchtop (Table 1, entry 11), although O_2 in the reaction headspace resulted in an induction period (Figure S6).[31] Both Zn and Mn could be utilized as reductants. As in our previous report, LiBr was superior to LiCl with Mn (Table 1, entries 7 and 8, and Figure S5).[20a] Finally, while dtbbpy and dppb were generally the best pair of ligands for this coupling, PCy_3 was also effective (Figures S2 and S3). While 6,6'-dibromo-2,2'-bipyridine was not an effective ligand for the model reaction, it was effective for couplings of electron-poor aryl chlorides (Scheme 2).

With these modified reaction conditions and an effective way to promote aryl chloride reactivity, we examined the couplings of a variety of aryl chlorides and triflates containing an array of functional groups and steric environments (Scheme 2). Electron-poor fluorine-containing substrates as well as electron-neutral and electron-rich substrates were well-tolerated, including sensitive functionalities such as a Boc-protected amine (**3c**), an aldehyde (**3i**), an alkyl Bpin ester (**3ab**), and a phosphonate ester (**3ac**). More reactive aryl halides, such as aryl chlorides bearing strongly electron-withdrawing groups, heteroaryl halides, or aryl bromides, could be selectively coupled with an aryl triflate by the use of the hindered, electron-poor ligand 6,6'-dibromo-2,2'-bipyridine (**3g**, **3i**, **3j**, **3o**, **3t**, and **3u**). Under these reaction conditions, ortho-substituted (**3q−s**) and 2,6-disubstituted aryl bromides

Scheme 2. Reaction Scope and Applications[a]

aryl chloride scope

ligands

dppb   dtbbpy   dbrbpy

Ar¹ = 4-(CH₃O)C₆H₄-   **Ar²** = 4-(CH₃O₂C)C₆H₄-

3a 89%   **3b** 81%   **3c** 65%   **3d** 77%   **3e** 74%

3f 84%   **3g** 64%[b]   **3h** 76%   **3i** 67%[b]   **3j** 56%[b]

sterically hindered aryl substrates

3q 62%   **3r** 51%   **3s** 62%

Ar = Ar¹ **3k** 83%
Ar = Ar² **3l** 44%

3m 81%   **3n** 82%   **3o** 71%[b]   **3p** 68%

3t 65%[b,c]   **3u** 53%[b,c]

3v 52%

aryl bromides are unavailable or 10X the cost of aryl chlorides

3w 75%   **3x** 63%   **3y** 70%   **3z** 45%   **3aa** 78%

3ab 48%   **3ac** 73%

aryl triflate scope

R = H, **3ad** 74%
R = ᵗBu, **3ae** 62%
R = Ph, **3af** 52%

3ag 56%   **3ah** 61%   **3ai** 84%   **3aj** 51%   **3ak** 60%

R = OMe, **3al** 88%
R = CO₂Me, **3am** 75%

utility in synthesis

Ar¹ = 4-(CH₃O)C₆H₄-

4 72%   **5** 79%   **6** 58%   **7** 89%

~$350/kg   **8** 71%   flurbiprofen **9** 77%

3 steps, 2 isolations

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[a]Reactions were run on a 0.5 mmol scale in 2 mL of solvent for 2−24 h. [b]Using 5 mol % 6,6′-dibromo-2,2′-bipyridine instead of dtbbpy. [c]The aryl bromide was used instead of the aryl chloride.

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and chlorides (**3t−v**) were also coupled efficiently. In contrast, steric hindrance was not as well tolerated in our previous

report.[32,33] The ability to couple unactivated aryl chlorides can be beneficial in synthesis when the corresponding aryl bromide

is either more expensive or not commercially available (**3w–ac**). The most challenging combination was electron-rich aryl chlorides with electron-poor aryl triflates (**3l**), which suffered from lower selectivity (about 2.5:1 biaryl to product).

The scope of the aryl triflate was also examined (Scheme 2), demonstrating good yields with both electron-donating and electron-withdrawing substituents (**3ad–am**). The lower yields observed for the coupling of electron-poor aryl triflates with electron-poor aryl chlorides (**3ah** and **3aj**) were due to competing homodimer formation. In these cases, the use of 6,6′-dibromo-2,2′-bipyridine as the ligand did not improve the yield. The couplings with 2-cyano-1-chlorobenzene form biaryls that could be useful for the synthesis of angiotensin II receptor antagonists (**3ad–ah**).[34]

Besides their improved availability and lower cost, an additional benefit of using aryl chlorides is that their lower reactivity facilitates multistep synthesis (Scheme 2). For example, cross-electrophile coupling with an alkyl bromide (**5**), C−H arylation (**7**), and reductive α-arylation (**9**) can all be conducted while preserving the C−Cl bond.[35] As an example of how this can be applied in synthesis, a concise three-step synthesis of flurbiprofen (**9**) was demonstrated that would be amenable to rapid analogue synthesis.[36]

This report shows how the nickel and palladium system can be rationally modulated to couple less reactive substrates: an unselective multimetallic reaction was made selective with the use of an additive, LiCl, that facilitates the reduction of the nickel catalyst at the zinc surface. Combined with our previous reports, these results suggest that the Ni/Pd system is general and that multimetallic catalysis may have broad generality. Finally, this work demonstrates how reactivity in cross-electrophile coupling reactions can be influenced by the reductant choice as much as the ligand choice: salts formed in the reaction may be autoinhibitory, and new reductant combinations can unlock new reactivity.

ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b05461.

> Materials, methods, compound characterization, and supplementary figures, schemes, and tables (PDF)

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Notes

The authors declare no competing financial interest.

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(18) Cyclic voltammetry studies of the reduction of **III** showed only an apparent two-electron reduction at −0.86 V vs SCE (Figure S7). The observed reduction potential did not depend upon the counterion of nickel (Cl⁻ or OTf⁻) or the electrolyte (Bu_4NPF_6 or Bu_4NCl), suggesting that all of these species were ionized in solution. These results match those previously reported for related catalysts: (a) Durandetti, M.; Devaud, M.; Périchon, J. Investigation of the reductive coupling of aryl halides and/or ethylchloroacetate electro-catalyzed by the precursor NiX_2(bpy) with X⁻ = Cl⁻, Br⁻ or $MeSO_3^−$ and bpy = 2,2′-dipyridyl. *New J. Chem.* **1996**, 20, 659−667. (b) Mikhaylov, D.; Gryaznova, T.; Dudkina, Y.; Khrizanphorov, M.; Latypov, S.; Kataeva, O.; Vicic, D. A.; Sinyashin, O. G.; Budnikova, Y. Electrochemical nickel-induced fluoroalkylation: synthetic, structural and mechanistic study. *Dalton Trans.* **2012**, 41, 165−172.

(19) This strategy for evaluating the reduction of nickel(II) to nickel(0) grew out of our studies of nickel(0) complexes and their reactivity. We previously reported this approach (with LiBr over Mn surfaces).[20a]

(20) (a) Huang, L.; Olivares, A. M.; Weix, D. J. Reductive Decarboxylative Alkynylation of N-Hydroxyphthalimide Esters with Bromoalkynes. *Angew. Chem., Int. Ed.* **2017**, 56, 11901−11905. (b) Ni, S.; Muñoz Padial, N.; Kingston, C.; Vantourout, J. C.; Schmitt, D. C.; Edwards, J. T.; Kruszyk, M.; Merchant, R. R.; Mykhailiuk, P. K.; Sanchez, B.; Yang, S.; Perry, M.; Gallego, G. M.; Mousseau, J. J.; Collins, M. R.; Cherney, R. J.; Lebed, P. S.; Chen, J. S.; Qin, T.; Baran, P. S. A Radical Approach to Anionic Chemistry: Synthesis of Ketones, Alcohols, and Amines. *J. Am. Chem. Soc.* **2019**, 141, 6726−6739.

(21) The effect of LiCl on reduction of *organic halides* has been studied in some detail. See: (a) Krasovskiy, A.; Malakhov, V.; Gavryushin, A.; Knochel, P. Efficient Synthesis of Functionalized Organozinc Compounds by the Direct Insertion of Zinc into Organic Iodides and Bromides. *Angew. Chem., Int. Ed.* **2006**, 45, 6040−6044. (b) Koszinowski, K.; Böhrer, P. Formation of Organozincate Anions in LiCl-Mediated Zinc Insertion Reactions. *Organometallics* **2009**, 28, 771−779. (c) Feng, C.; Cunningham, D. W.; Easter, Q. T.; Blum, S. A. Role of LiCl in Generating Soluble Organozinc Reagents. *J. Am. Chem. Soc.* **2016**, 138, 11156−11159. (d) Jess, K.; Kitagawa, K.; Tagawa, T. K. S.; Blum, S. A. Microscopy Reveals: Impact of Lithium Salts on Elementary Steps Predicts Organozinc Reagent Synthesis and Structure. *J. Am. Chem. Soc.* **2019**, 141, 9879−9884.

(22) These results do not conclusively show that nickel(0) is the operative oxidation state of the nickel catalyst. Love and Schaefer have recently shown that alkene ligands can influence the relative stability of nickel(I) and nickel(II/0) (see ref 23).

(23) Beattie, D. D.; Lascoumettes, G.; Kennepohl, P.; Love, J. A.; Schafer, L. L. Disproportionation Reactions of an Organometallic Ni(I) Amidate Complex: Scope and Mechanistic Investigations. *Organometallics* **2018**, 37, 1392−1399.

(24) Huo, S. Highly Efficient, General Procedure for the Preparation of Alkylzinc Reagents from Unactivated Alkyl Bromides and Chlorides. *Org. Lett.* **2003**, *5*, 423−425.

(25) As determined by ^{31}P NMR spectroscopy versus an internal standard. The DMF/THF solvent mixture was used because the palladium complexes were poorly soluble in pure DMF. The catalytic reaction works well in DMF/THF mixtures. For detailed conditions, see the Figures S9−S12.

(26) Another alternative hypothesis is insertion of zinc into Ar−Cl or Ar−OTf bonds to form arylzinc reagents. This does not happen under our conditions, consistent with the literature. See: (a) Jin, M.-Y.; Yoshikai, N. Cobalt−Xantphos-Catalyzed, LiCl-Mediated Preparation of Arylzinc Reagents from Aryl Iodides, Bromides, and Chlorides. *J. Org. Chem.* **2011**, *76*, 1972−1978. (b) Fillon, H.; Gosmini, C.; Périchon, J. New chemical synthesis of functionalized arylzinc compounds from aromatic or thienyl bromides under mild conditions using a simple cobalt catalyst and zinc dust. *J. Am. Chem. Soc.* **2003**, *125*, 3867−3870. (c) Klatt, T.; Markiewicz, J. T.; Sämann, C.; Knochel, P. Strategies To Prepare and Use Functionalized Organometallic Reagents. *J. Org. Chem.* **2014**, *79*, 4253−4269. (d) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. Recent Developments in Negishi Cross-Coupling Reactions. *ACS Catal.* **2016**, *6*, 1540−1552.

(27) For a thorough discussion of iodide additives in nickel-catalyzed cross-electrophile coupling, see ref 28a and references cited therein. For the effect of MgCl$_2$ and LiBr on the reduction of nickel complexes at metal surfaces, see refs 28b and 20, respectively.

(28) (a) Everson, D. A.; Jones, B. A.; Weix, D. J. Replacing Conventional Carbon Nucleophiles with Electrophiles: Nickel-Catalyzed Reductive Alkylation of Aryl Bromides and Chlorides. *J. Am. Chem. Soc.* **2012**, *134*, 6146−6159. (b) Wang, X.; Ma, G.; Peng, Y.; Pitsch, C. E.; Moll, B. J.; Ly, T. D.; Wang, X.; Gong, H. Ni-Catalyzed Reductive Coupling of Electron-Rich Aryl Iodides with Tertiary Alkyl Halides. *J. Am. Chem. Soc.* **2018**, *140*, 14490−14497.

(29) Other noncoordinating anions, such as BF$_4$ and PF$_6$, also appeared to be inhibitory. While zinc appears to be inhibitory (ZnCl$_2$ slowed the reduction), both LiCl and Bu$_4$NCl accelerated the reduction, suggesting that there is not a special lithium effect but rather a special zinc effect. See Table S2 for additional data.

(30) A mixture of solvents was used to help with solubility of precatalyst solutions. DMF provided the same yields and selectivities as the mixture. See Table S1.

(31) While most isolated reactions were run for 24 h for convenience, the reaction in Table 1 was 90% complete in 2 h and finished in less than 8 h when run under nitrogen.

(32) The homodimerization of hindered aryl bromides with nickel has been reported. See the following reference and references cited therein: Hong, R.; Hoen, R.; Zhang, J.; Lin, G.-Q. Nickel-catalyzed Ullmann-type Coupling Reaction to Prepare Tetra-ortho-substituted Biaryls. *Synlett* **2001**, *2001*, 1527−1530.

(33) Biaryls with four different ortho substituents are still not coupled in high yield. For these types of substrates, cross-coupling with organometallic reagents is the best approach. See: (a) Altenhoff, G.; Goddard, R.; Lehmann, C. W.; Glorius, F. An N-Heterocyclic Carbene Ligand with Flexible Steric Bulk Allows Suzuki Cross-Coupling of Sterically Hindered Aryl Chlorides at Room Temperature. *Angew. Chem., Int. Ed.* **2003**, *42*, 3690−3693. (b) Valente, C.; Çalimsiz, S.; Hoi, K. H.; Mallik, D.; Sayah, M.; Organ, M. G. The Development of Bulky Palladium NHC Complexes for the Most-Challenging Cross-Coupling Reactions. *Angew. Chem., Int. Ed.* **2012**, *51*, 3314−3332.

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