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Communication

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

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*Supporting Information Placeholder*

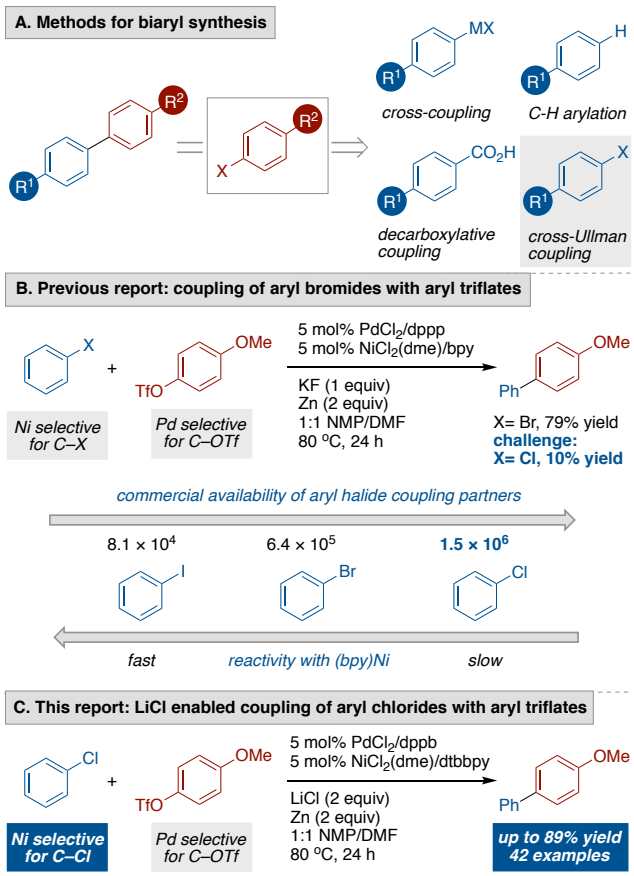
**ABSTRACT:** While the synthesis of biaryls has advanced rapidly in the past decades, cross-Ullman couplings of aryl chlorides, the most abundant aryl electrophiles, have remained elusive. Reported here is the first general cross-Ullman coupling of aryl chlorides with aryl triflates. The selectivity challenge associated with coupling an inert electrophile with a reactive one is overcome using a combination of two catalysts: nickel and palladium. 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, agrochemical, 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, however 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 12,13,14] *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 faster rate than aryl triflates; the Pd catalyst activated aryl triflates at a faster 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 activated aryl chlorides were used, an erosion in catalyst selectivity led to homocoupling

**Scheme 1. Cross-Ullman Reaction in Biaryl Synthesis.**




rather than effective cross-coupling. 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).

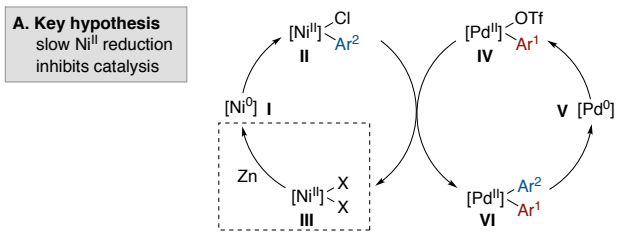
Based upon the mechanism proposed in our earlier studies with nickel and palladium co-catalysis (Table 1A),[8] the slow consumption of the *aryl chloride and aryl triflate* suggested that arylnickel (**II**) formation was being inhibited (Table 1A). Arylpalladium (**IV**) will not consume aryl triflate without arylnickel (**II**) present. The inhibition could come from slow oxidative addition (**I** to **II**),[17] slow reduction (**III** to **I**), or an off-cycle loss of nickel catalyst.

Reduction of (dtbbpy)$Ni^{II}X_2$ complexes **III-Cl** and **III-OTf** was studied by both electrochemical and chemical methods (Table 1B). 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 Supporting Information Figures S7 and S8). 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 flake in the presence or absence of additives showed that **III-OTf** is not reduced unless chloride salts are present (Table 1B and 1C; Supporting Information Figures S8 and S9; Table S2). There is also a cation effect: while LiCl enhances the rate of reduction of both nickel complexes **III-OTf** and **III-Cl**, $ZnCl_2$ did 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 is generally the most useful additive studied (Table 1, entries 1-6 and Supporting Information Table S2).[22,23] While we found that reduction of octyl bromide to octylzinc bromide was also inhibited by zinc salts,[24,21d] reduction of palladium(II) phosphine complexes to palladium(0) was fast with or without added LiCl or Zn (Supporting Information Figures S11-S16).[25,26]

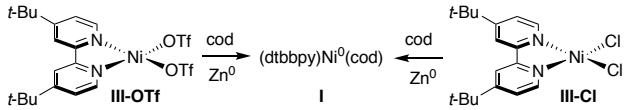
These studies show that the low reactivity observed for the coupling of aryl chlorides with aryl triflates (Scheme 1B) is due to autoinhibition: the zinc salts ($ZnCl_2$ and $Zn(OTf)_2$) formed in reduction of **III** to **I** inhibit subsequent reductions of **III**. While it had previously been noted 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 have not been previously reported. This result has broad implications for cross-electrophile coupling reactions that rely upon metallic reductants.

The catalytic reaction behaved as expected from the stoichiometric studies: the addition of LiCl enabled turnover (Table 1C, entries 1-6, Supporting Information Figures S1-S2).[30] Consistent with previous reports,[8] these reactions were still promoted by the cooperativity between two metal catalysts: reactions without palladium were poorly selective and reactions without nickel did not consume starting materials

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




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

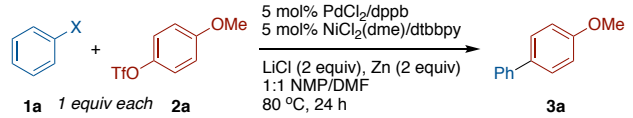



$E_{1/2}$ = -0.86 V vs. SCE $E_{1/2}$ = -0.86 V vs. SCE

**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**




**1a** *1 equiv each* **2a** **3a**

| entry | change from 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 benchtop[e] | 80 |
| 12 | 1.2 equiv of **2a** | 90(89[f]) |

[a] In DMF. See 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 to 40 equiv) were added in some cases. See Supporting Information for additional results and experimental details. [c] Reactions were run on 0.5 mmol scale in 2 mL of solvent. NMP = *N*-methyl-2-pyrrolidinone. [d] GC yield vs dodecane as internal standard. [e] Reaction was set up under air with dry solvent. [f] Isolated yield.

(entries 9 and 10). Similar to other cross-electrophile coupling reactions,[28a] the reaction was tolerant of adventitious dioxygen, allowing reactions to be set up on the benchtop (Table 1, entry 11), albeit $O_2$ in the reaction headspace resulted in an induction period (Supporting Information 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 Supporting Information Figure S5).[20a] Finally, while dtbbpy and dppb were generally the best pair of ligands for this coupling, $PCy_3$ was also effective (Supporting Information 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, 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 employing the hindered, electron-poor 6,6′-dibromo-2,2′-bipyridine ligand (**3g**, **3i**, **3j**, **3o**, **3t**, and **3u**). Under these reaction conditions ortho-substitution (**3q-s**) and 2,6-disubstitution on aryl bromides and chlorides (**3t-v**) were also coupled efficiently. In contrast, steric hinderance 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 ligand did not improve yields. 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 analog synthesis.[36]

This report shows how the nickel and palladium co-catalyst 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.

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

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### Author Contributions

The manuscript was written through contributions of all authors.

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(16) Qian reported one example of the coupling of 3,4,5-trimethoxybromobenzene with 4-chloroanisole in 58% yield, see reference 7d. It is not clear if this approach is general and no further reports have appeared on this monometallic strategy.

(17) Our own studies and those of others have shown that aryl chlorides react rapidly with $(N–N)Ni^0$ complexes of the type used in this study. For example, carboxylation of aryl chlorides using similar catalysts and

reductants is known. For two examples, see: (a) Fujihara, T.; Nogi, K.; Xu, T.; Terao, J.; Tsuji, Y. Nickel-Catalyzed Carboxylation of Aryl and Vinyl Chlorides Employing Carbon Dioxide. *J. Am. Chem. Soc.* **2012**, *134*, 9106-9109; (b) Charboneau, D. J.; Brudvig, G. W.; Hazari, N.; Lant, H. M. C.; Saydjari, A. K. Development of an Improved System for the Carboxylation of Aryl Halides through Mechanistic Studies. *ACS Catalysis* **2019**, *9*, 3228-3241.

(18) Cyclic voltammetry studies on the reduction of **III** showed only an apparent two-electron reduction at -0.86 V vs SCE (Supporting Information Figure S7). The observed reduction potential did not depend upon the counterion on 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 electrocatalyzed by the precursor NiX(2)(bpy) with X(-)=Cl-, Br- or MeSO(3)(-) and bpy equals 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 on nickel(0) complexes and their reactivity. We previously reported this approach (with LiBr over Mn surfaces, reference 20a).

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(21) The effect of LiCl on reduction of *organic halides* has been studied in some detail: (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 the following reference.

(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 vs 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 Supporting Information 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: (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 on iodide additives in nickel-catalyzed cross-electrophile coupling, see reference 28a and references cited therein. For the effect of $MgCl_2$ and LiBr on the reduction of nickel complexes at metal surfaces, see references 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 non-coordinating anions also appeared to be inhibitory, such as $BF_4$ and $PF_6$. While zinc appears to be inhibitory ($ZnCl_2$ slowed reduction), both $LiCl_2$ and $Bu_4NCl$ accelerated reduction, suggesting that there is not a special lithium effect, but rather a special zinc effect. See Supporting Information Table S2 for additional data.

(30) A mixture of solvents was used to help with solubility of pre-catalyst solutions. DMF provided the same yields and selectivities as the mixture. See Supporting Information 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**, 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: (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.

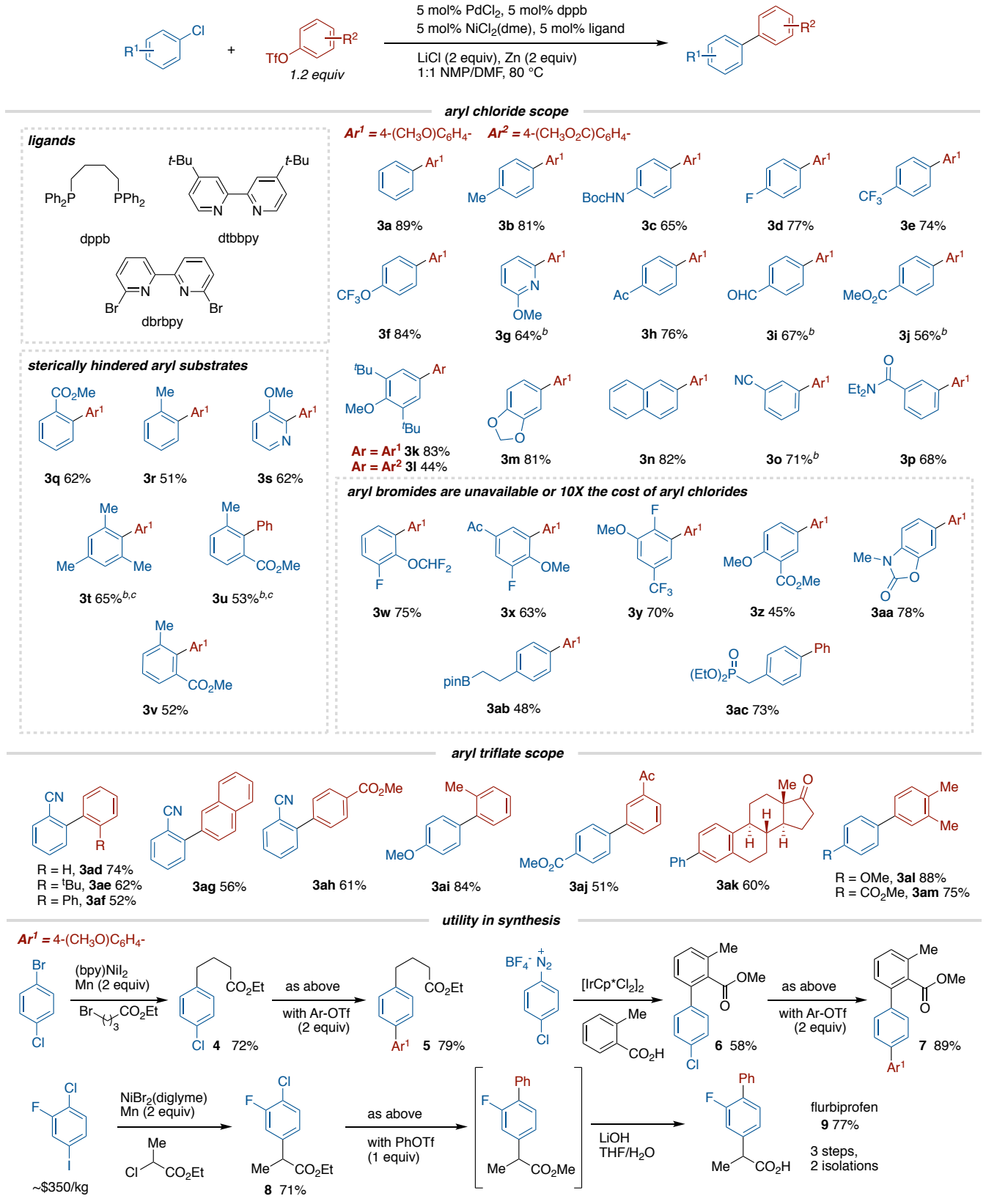
(34) (a) Carini, D. J.; Duncia, J. V.; Aldrich, P. E.; Chiu, A. T.; Johnson, A. L.; Pierce, M. E.; Price, W. A.; Santella, J. B.; Wells, G. J. Nonpeptide angiotensin II receptor antagonists: the discovery of a series of N-(biphenylylmethyl)imidazoles as potent, orally active antihypertensives. *J. Med. Chem.* **1991**, *34*, 2525-2547; (b) Kubo, K.; Kohara, Y.; Yoshimura, Y.; Inada, Y.; Shibouta, Y.; Furukawa, Y.; Kato, T.; Nishikawa, K.; Naka, T. Nonpeptide angiotensin II receptor antagonists. Synthesis and biological activity of potential prodrugs of benzimidazole-7-carboxylic acids. *J. Med. Chem.* **1993**, *36*, 2343-2349; (c) Wexler, R. R.; Greenlee, W. J.; Irvin, J. D.; Goldberg, M. R.; Prendergast, K.; Smith, R. D.; Timmermans, P. B. M. W. M. Nonpeptide Angiotensin II Receptor Antagonists: The Next Generation in Antihypertensive Therapy. *J. Med. Chem.* **1996**, *39*, 625-656.

(35) (a) Johnson, K. A.; Biswas, S.; Weix, D. J. Cross-Electrophile Coupling of Vinyl Halides with Alkyl Halides. *Chem.—Eur. J.* **2016**, *22*, 7399-7402; (b) Huang, L.; Hackenberger, D.; Gooßen, L. J. Iridium-Catalyzed ortho-Arylation of Benzoic Acids with Arenediazonium Salts. *Angew. Chem., Int. Ed.* **2015**, *54*, 12607-12611; (c) Durandetti, M.; Gosmini, C.; Périchon, J. Ni-catalyzed activation of α-chloroesters: a simple method for the synthesis of α-arylesters and β-hydroxyesters. *Tetrahedron* **2007**, *63*, 1146-1153.

(36) (a) Peretto, I.; Radaelli, S.; Parini, C.; Zandi, M.; Raveglia, L. F.; Dondio, G.; Fontanella, L.; Misiano, P.; Bigogno, C.; Rizzi, A.; Riccardi, B.; Biscaioli, M.; Marchetti, S.; Puccini, P.; Catinella, S.; Rondelli, I.; Cenacchi, V.; Bolzoni, P. T.; Caruso, P.; Villetti, G.; Facchinetti, F.; Del Giudice, E.; Moretto, N.; Imbimbo, B. P. Synthesis and Biological Activity of Flurbiprofen Analogues as Selective Inhibitors of β-Amyloid1-42 Secretion. *J. Med. Chem.* **2005**, *48*, 5705-5720; (b) Quasdorf, K. W.; Riener, M.; Petrova, K.

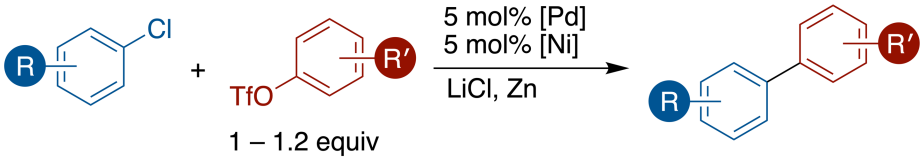
V.; Garg, N. K. Suzuki–Miyaura Coupling of Aryl Carbamates, Carbonates, and Sulfamates. *J. Am. Chem. Soc.* **2009**, *131*, 17748-17749.

**Scheme 2. Reaction Scope and Applications.**[a]




[a] Reactions were run on 0.5 mmol of scale in 2 mL solvent for 2 to 24 h. $Ar^1$ = 4-$(CH_3O)C_6H_4$-. $Ar^2$ = 4-$(MeO_2C)C_6H_4$-. [b] Using 5 mol% 6,6'-dibromo-2,2'-bipyridine instead of dtbbpy. [c] Aryl bromide was used instead of aryl chloride.

**TOC Graphic**




**42 examples**
**68% ave yield**

**R R′ includes**

| | |
|---|---|
| aldehyde | NHBoc |
| ketone | $CF_3$ |
| ester | $OCF_3$ |
| $P(O)(OEt)_2$ | $OCHF_2$ |
| carbamate | Bpin |

**Role of LiCl**

$[Ni^{II}]OTf_2 \xrightarrow{Zn} [Ni^0]$

*w/o LiCl, no reaction*
*w/LiCl, fast reduction*