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

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*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, 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, C–H arylation, and decarboxylative cross-coupling.

The relative abundance of aryl electrophiles (Scheme 1B) would make the cross-Ullman reaction 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. 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 or late-stage coupling on complex molecules.

Although significant advances in the use of aryl chlorides in cross-coupling have been made recently, there are no general methods for the direct cross-coupling of electron-neutral or electron-rich aryl chlorides with other aryl electrophiles. 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 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 triolate. Herein we report a general multimetallic solution that achieves the selective coupling of a variety of aryl chlorides with aryl triflates (Scheme 1C).

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

| Additive                  | Yield from II−OTf (%) | Yield from III−Cl (%) |
|--------------------------|-----------------------|-----------------------|
| none                     | 2%                    | 5%                    |
| LiCl                     | 5%                    | 3%                    |
| LiBr                     | 3%                    | -                     |
| Bu4NCl instead of LiCl   | 27%                   | 96%                   |
| TMSCI instead of LiCl    | -                     | -                     |
| no LiCl                  | -                     | -                     |
| Mn instead of Zn         | 2%                    | 8%                    |
| Mn instead of Zn, LiBr   | -                     | -                     |
| without PdCl2 and dppb   | 5%                    | 8%                    |
| without NiCl3(dme) and dbbpy | -                   | -                     |
| reaction set up on the benchtop | -                   | -                     |

"In DMF. See the Supporting Information for details on electrochemical studies. Reduction of III was conducted in DMF at a concentration of 0.025 M with Mn 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. Reactions were run on a 0.5 mmol scale in 2 mL of solvent. NMP = N-methyl-2-pyrrolidinone. GC yield vs dodecane as an internal standard. The reaction was set up under air with dry solvent. 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), slow reduction (II to I), or an off-cycle loss of nickel catalyst.

Reduction of the (dibbpy)NiX2 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, showed no difference between III−Cl and III−OTf (Table 1B and Figures S3 and S4) but suggested a significant difference in the rate of the reaction.

Chemical Reduction of (L)NiX2 to (L)NiII(cod)6

| Entry | Change from the optimized conditions | Yield 3a (%) |
|-------|-------------------------------------|--------------|
| 1     | none                                | 84           |
| 2     | NaCl instead of LiCl                | 62           |
| 3     | LiBr instead of LiCl                | 59           |
| 4     | Bu4NCl instead of LiCl              | 53           |
| 5     | TMSCI 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 PdCl2 and dppb              | 44           |
| 10    | without NiCl3(dme) and dbbpy        | <5           |
| 11    | reaction set up on the benchtop     | 80           |
| 12    | 1.2 equiv of 2a                     | 90 (89%)     |

These studies show that the low reactivity observed for the coupling of arylicl halides with arylicl triflates (Scheme 1B) is due to autoinhibition: the zinc salts (ZnCl2 and Zn(OTf)2) in the reduction of III to I inhibit subsequent reductions of III. While it had previously been noted that halide anions accelerate reduction of NiX2 intermediates at zinc surfaces, the inhibitory effect of less-coordinating anions (OTf−, BF4−, PF6−) 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). Consistent with previous reports, 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, the reaction was tolerant of adventitious O2, allowing reactions to be set up on the benchtop (Table 1, entry 11), although O2 in the reaction headspace resulted in an induction period (Figure S6). 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). Finally, while dbbpy and dppb were generally the best pair of ligands for this coupling, PCy3 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 fluorne-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
and chlorides (3t−v) were also coupled efficiently. In contrast, steric hindrance was not as well tolerated in our previous report. 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 (3I), 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 alky halide (8), C–H arylation (7), and reduction of 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 reduciant choice as much as the ligand choice: salts formed in the reaction may be autoinhibitory, and new reduciant combinations can unlock new reactivity.

**ASSOCIATED CONTENT**

* Supporting Information
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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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Biochemistry To Form Highly Substituted 1,3-Dienes.

J. Multimetallic Ni- and Pd-Catalyzed Cross-Electrophile Coupling

2,2 functionalized aryl and pyridine halides catalyzed by nickel bromide

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(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.

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