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Multimetallic Catalysis Enabled Cross-Coupling of Aryl Bromides with Aryl Triflates

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Abstract

Transition metal-catalyzed strategies for the formation of new C-C bonds have revolutionized the field of organic chemistry, enabling the efficient synthesis of ligands, materials, and biologically active molecules.^{1–3} In cases where a single metal fails to promote a selective or efficient transformation, the synergistic cooperation⁴ of two distinct catalysts – multimetallic catalysis – can be employed instead. Many important reactions rely on multimetallic catalysis,⁵ including the Wacker oxidation of olefins^{6–8} and the Sonogashira coupling of alkynes with aryl halides.^{9–10} However, the application of this strategy, even in recently developed methods¹¹, has largely been limited to the use of metals with distinct reactivities, with only one metal catalyst undergoing an oxidative addition.¹² In this manuscript, we demonstrate that cooperativity between two d10 metal catalysts, (bipyridine)nickel and (1,3-bis(diphenylphosphino)propane)palladium, enables a general cross-Ullman reaction.^{13–15} Our method couples aryl bromides with aryl triflates directly, eliminating the use of arylmetal reagents and avoiding the challenge of differentiating between multiple C–H bonds that is required for many C–H activation methods.^{16–17} The selectivity does not require an excess of either substrate and originates from the orthogonal activity of the two catalysts and the relative stability of the two arylmetal intermediates. While (dppp)Pd reacts preferentially with aryl triflates to afford a persistent intermediate, (bpy)Ni reacts preferentially with aryl bromides to form a transient, reactive intermediate. Although each catalyst forms less than 5% cross product in isolation, together they are able to achieve up to 94% yield. Our results reveal a new, general method for the synthesis of biaryls, heteroaryls, and dienes, as well as a new mechanism for selective transmetalation between two catalysts. We anticipate that this reaction will simplify the synthesis of pharmaceutical agents, many of which are currently made with pre-formed organometallic reagents,^{1–3} and lead to the discovery of new multimetallic reactions.

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Author Contributions

D.J.W. conceived of the idea. L.K.G.A. performed experiments and analyzed the results with assistance from M.M.L. Both D.J.W. and L.K.G.A. proposed the experiments, discussed the data, and wrote the manuscript.

Additional Information

Supplementary information and chemical compounds information are available in the online version of the paper. Reprints and permissions information is available at www.nature.com/reprints. Correspondence and requests for materials should be addressed to D.J.W.

Competing Financial Interests

The authors declare no competing financial interests.

We envisioned that a general solution to the cross-Ullman reaction (the cross-coupling of two different aryl electrophiles) could be realized through multimetallic catalysis if 1) the two catalysts each selectively activated one of the two substrates (**1** and **2** in Fig. 1), 2) selective transmetalation could be achieved (overlap of circles in Fig. 1), and 3) the catalysts were redox compatible¹⁹. Based upon literature precedent, an electron rich palladium(0) catalyst with a bidentate phosphine ligand, 1,3-bis(diphenylphosphino)propane (dppp) was chosen to preferentially react with aryltrifluoromethylsulfonate esters (aryl triflates, Ar-OTf) over aryl bromides²⁰ (Ar-Br). And from our own studies, a bipyridine (bpy) nickel(0) catalyst was chosen to react selectively with aryl bromides over aryl triflates²¹.

We began our investigation of this multimetallic system by combining a 1:1 mixture of bromobenzene and 4-methoxyphenyltriflate in the presence of both catalysts and a zinc reducing agent (Fig. 2A). Remarkably, a high cross selectivity was observed in the formation of 4-methoxybiphenyl (70%) over the dimers biphenyl (17%) and bianisole (10%). When each catalyst was allowed to react independently with the two aryl electrophiles, however, no cross selectivity was observed. (Bpy)NiBr₂ formed exclusively biphenyl (**4**) from bromobenzene (**2**) before reacting with 4-methoxyphenyltriflate (**1**) (Fig. 2(B)), while (dppp)PdCl₂ was unreactive under these conditions, consuming only a minimal amount of substrate and forming trace amounts of benzene, anisole, bianisole (**5**), and product (**3**) (Fig. 2(C)). Only when the two catalysts were combined, did a selective reaction occur.

To ensure that the cross product observed was a result of a synergy between the two proposed metal catalysts, we examined the reactivity of alternate catalysts that could be formed *in situ* via ligand exchange²². Our results (Table 1, entries 5, 7–9) demonstrate that the two alternate catalysts, (dppp)NiBr₂ and (bpy)PdCl₂ are poorly reactive and form primarily biphenyl **4** rather than cross-product **3**. These studies are consistent with product arising via our proposed mechanism and symmetric biaryl products may arise from “mismatched” metal-ligand combinations. Interestingly, when all of the reagents were added together at the beginning of the reaction, the results were nearly identical to reactions in which pre-formed catalysts were used (Table 1, entry 3 vs. entry 10).

Examination of different ligands for both nickel and palladium revealed that while many nitrogen-based ligands were effective, relatively few bisphosphines worked well. Nickel complexes derived from bidentate ligands (2,2'-bipyridine, 1,10-phenanthroline, 2-pyridylimidazole) or a tridentate ligand (2,2':6',2''-terpyridine) all formed reasonably selective multimetallic catalytic systems with (dppp)PdCl₂ (47–69% yield, Extended Data Fig. 1). In contrast, only two bisphosphine ligands besides dppp were effective: 1,2-bis(diphenylphosphino)benzene (56% yield) and (Z)-1,2-bis(diphenylphosphino)ethylene (53% yield). The performance of dppp could arise from improved reactivity with palladium or diminished undesired reactivity with nickel. The ratio of nickel to palladium was also expected to be important to selectivity, considering the vastly different reactivities of the individual complexes, but we found that reactions with 2:1, 1:1, and 1:2 Pd:Ni ratios provided similar yields and selectivities (Table 1, entries 11,12 versus entries 2,3; see also Chart S6 in the Supplementary Information). Together, these results suggest that the transmetalation step between the two catalysts is inherently selective.

In addition to the minor influence of the ratio of Pd:Ni on yield or selectivity, in many cases the ratio of substrates also had minimal effect on the final yield of product. In previously reported cross-Ullman reactions catalyzed by a single metal, 2 or more equivalents of one reactant were required for consistent yields above 60%, and ratios closer to 1:1 usually resulted in dramatically lower yields²³. In this multimetallic cross-Ullman, an excess of aryl triflate did not dramatically alter the yield of cross-product, but in some cases an excess of aryl bromide did improve our results. For example, 3 equivalents of 3-bromothiophene improved the cross-coupled yield from 65% to 85% (**18** in Fig. 3). However, an excess of aryl bromide did not improve yields with pyridine substrates.

The selectivity and rate of the reactions were also improved by the addition of potassium fluoride (KF). In all examples studied, the addition of 1 equivalent of KF accelerated the rate of the couplings, and with the exception of reactions with pyridyl chlorides and activated aryl bromides, a higher selectivity for cross product over dimerization was observed (Extended Data Fig. 2). In the coupling of bromobenzene with 4-methoxyphenyl triflate (Table 1, entry 1), 89% of **2** was consumed at 24 h with a 62% yield of **3**. In the presence of KF, however, 91% conversion of **2** occurred in 11 h with a 77% yield of **3** (Table 1, entry 2). The beneficial effect of KF is consistent with observations in other cross-coupling reactions of nickel²⁴ and palladium^{25–26}. In nickel catalysis, KF can reduce the amount of dimeric products formed, and in palladium catalysis, KF can alter the oxidative addition selectivity for C-OTf over C-X bonds through the formation of a palladium “ate” complex. In our preliminary studies, it appears that both the potassium ion and the fluoride ion play a role. Although optimization was performed in an inert-atmosphere glove box, reactions could be set up on the benchtop as long as standard air-free techniques were used (Table 1, entry 13). Reactions run without added catalysts did not consume starting materials (entry 14), arguing against the intermediacy of ArZnX reagents. For further details on reaction condition optimization, see Charts S9-S10 and S12-S15 in the Supplementary Information section.

Applying these reaction conditions to a variety of aryl electrophiles demonstrated the generality of this method (Fig. 3). Both electronically similar and electronically disparate aryl bromides and triflates couple in good yields, but the coupling of a highly activated substrate with a deactivated substrate results in a low yield at this time. Aryl substrates with *ortho*-substitution can be coupled (**8** and **14**) and the synthesis of 2,2'-disubstituted biaryls and 2,2'-binaphthyls can also be achieved (**9** and **15**). The functional group tolerance of this multimetallic method is promising and includes amine, ether, ester, aldehyde, sulfone, and acetal groups. In addition, boronic acid ester product **17** was formed without competing Suzuki coupling, despite the presence of palladium and KF, demonstrating complementarity with established cross-coupling methods. Although the combination of other halides and pseudohalides under these reaction conditions resulted in lower yields (see Charts S1 to S3 in the Supplementary Information), several synthetically useful exceptions were found. While reactions with aryl iodides generally resulted in rapid formation of biaryl (see Chart S3 in Supplementary Information; both Pd and Ni react with aryl iodides faster than aryl triflates), naphthyl iodide could be coupled to form **20** in 47% yield (Fig. 3B). Similarly, 2-naphthyl chloride could be coupled to form **21** in 75% yield, suggesting that the nickel catalyst has a strong affinity for naphthyl substrates that is not shared by the palladium

catalyst²⁷. The higher yield of the coupled product resulting from naphthyl chloride relative to naphthyl iodide, indicated the possibility of coupling other activated aryl chlorides with this system. Indeed, an aryl chloride with a sulfonyl group in the *para* position was successfully coupled with high selectivity to give **22**. In contrast, reactions of unactivated aryl chlorides formed large amounts of symmetric biaryl from the aryl triflate. Bromothiophene and pyridyl halides and triflates coupled in reasonable yield, including the synthesis of 2,3'-bipyridine **25**. In general, heteroaryl halides provided lower yields in reactions conducted with added KF. Finally, the chemistry could be extended to the synthesis of diene **19** from α -bromocyclohexenone and cyclohexenyl triflate. To our knowledge, this is the first cross-Ullman reaction to form a diene product.

Although we have not yet conducted a detailed study of the mechanism, current evidence is consistent with our original proposal (Fig. 1). After formation of the two arylmetal intermediates by oxidative addition, we hypothesize that a mechanism analogous to the "persistent radical effect" allows for the observed cross selectivity in transmetalation^{28–29}. In the persistent radical effect, one radical is unreactive with itself and stable, while the other radical is highly reactive and unselective. In our system, (dppp)Pd(Ar²)(OTf) is stable to further reaction with itself (Fig. 2C) and accumulates in solution. In contrast, (bpy)Ni(Ar¹)Br is a transient intermediate that quickly reacts with itself (Fig. 2B) or (dppp)Pd(Ar²)(OTf). Selectivity arises from the relative concentrations of these two complexes in solution, similar to multimetallic reactions with group 11 organometallic intermediates, which are generally slow to homocouple¹¹. Consistent with our observations (Table 1), the rate of this cross-Ullman is predicted to be independent of the amount of palladium and nickel added at the beginning of the reaction. Furthermore, our proposed mechanism suggests that the formation of (bpy)Ni(Ar¹)Br would be turnover-frequency limiting. Therefore, a higher concentration of nickel, but not palladium, should result in a higher rate of product formation. We found this to be the case: reactions run with a higher concentration of nickel were faster (24% yield vs. 7% yield at 4 h for 25 mM vs. 12.5 mM [Ni]), but the concentration of palladium did not have an impact on the rate of product formation (11% yield vs. 7% yield at 4 h for 25 mM vs. 12.5 mM [Pd]). We are presently working to further illuminate the mechanism of this reaction and the origin of the cross-selectivity.

After a century of developing strategies for the formation of biaryls, a general method to selectively form unsymmetrical biaryls directly from two aryl electrophiles has been realized. In addition to the immediate utility of this transformation, the general principle of selective transmetalation between a persistent catalytic intermediate and a transient, reactive organometallic intermediate should spur the development of new multimetallic reactions beyond the cross-Ullman coupling, such as C-H arylation³⁰.

Extended Data

Extended Data Fig. 1. Varying Ligands on the Nickel and Palladium Catalysts

Several different phosphine ligands for palladium (a) and amine ligands for nickel (b) were investigated. While selectivity and yield of cross-product were sensitive to the identity of the phosphine ligand (a), a variety of different amine ligands were nearly equally effective (b). Reactions conducted with **L15**, **L17**, and **L18** used 5 mol% catalyst loadings, were heated to 40 °C, and were monitored for 64 hours.

Extended Data Fig. 2. The Effect of Potassium and Fluoride Salts on the Selectivity of the Multimetallic Catalyzed Cross Ullman Reaction

The presence of potassium fluoride in cross couplings has been demonstrated to improve the product yield and rate of reactions while minimizing the formation of dimeric products. This “KF effect” can be attributed to a variety of different factors, including the formation of “ate” complexes, the removal of a halide from a metal complex, or the formation of a fluoride bridged complex, which could facilitate an oxidative addition or transmetalation step^{24,26}. To investigate whether KF could be beneficial for the nickel and palladium multimetallic system, various amounts of the additive were included under standard reaction conditions. The resulting selectivity and rate data are found in (a) and (b). Once the

advantageous role of KF was confirmed, other potassium and fluoride salts were subsequently tested. The resulting selectivity and rate data are found in (c) and (d). The presence of potassium resulted in faster reaction rates, while the presence of fluoride reduced the amount of bianisole and biphenyl byproducts, improving the yield of cross product. *Reactions without additives took 32 hours to complete.*

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1.

A general cross-Ullman reaction catalyzed by a combination of nickel and palladium. Although a nickel(0/II) and palladium (0/II) cycle is depicted, alternative mechanisms are also possible, such as a nickel(I/III) cycle¹⁸.

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Fig. 3. Substrate Scope. (a) Aryl and vinyl bromides with aryl and vinyl triflates. (b) Other aryl electrophiles. (c) Relative reactivity of the palladium and nickel catalysts

^a No KF was used. ^b Three equivalents of 3-bromothiophene were used. ^c Two equivalents of 2-bromocyclohexenone were used.

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