# Dual Nickel/Palladium-Catalyzed Reductive Cross-Coupling Reactions Between Two Phenol Derivatives

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**Abstract:** Cross-coupling between substrates that can be easily derived from phenols is highly attractive due to the abundance and low cost of phenols. Here, we report a dual nickel/palladium-catalyzed reductive cross-coupling between aryl tosylates and aryl triflates; both substrates can be accessed in just one step from readily available phenols. The reaction has a broad functional group tolerance and substrate scope (>60 examples). Furthermore, it displays low sensitivity to steric effects demonstrated by the synthesis of a 2,2'-disubstituted biaryl and a fully substituted aryl product. The widespread presence of phenols in natural products and pharmaceuticals allow for straightforward late-stage functionalization, illustrated with examples such as Ezetimibe and tyrosine. NMR spectroscopy and DFT calculations indicate that the nickel catalyst is responsible for activating the aryl triflate, while the palladium catalyst preferentially reacts with the aryl tosylate.

The biaryl motif is widespread in natural products and pharmaceutical compounds.[1] Accordingly, the development of convenient and efficient methods for forging aryl−aryl bonds has been a long-term interest of chemists.[2] Transition-metal-catalyzed cross-coupling reactions are arguably the most powerful tools for constructing $C(sp^2)-C(sp^2)$ bonds, as highlighted by the extensive use of Suzuki, Negishi, Kumada, and Hiyama-Denmark cross-coupling reactions.[3] All these reactions rely on an organometallic reagent as one of the cross-coupling partners. Despite the widespread of the traditional cross-coupling reactions, this requirement for a nucleophilic organometallic reagent can impose limitations on the substrate scope, including difficulties with derivatization of advanced synthetic intermediates and natural products.

Recently, reductive cross-coupling reactions have received increasing attention due to the complementary to traditional cross-coupling reactions and the avoidance of nucleophilic organometallic coupling partners.[4] Given that reductive cross-coupling reactions take place between two electrophiles, the biggest challenge for reductive cross-coupling reactions is achieving cross-coupling selectivity and avoiding the competing homo-coupling reactions. In 2015, Weix and coworkers disclosed a dual Ni/Pd-catalyzed reductive cross-coupling reaction, in which nickel and palladium selectively undergo

oxidative addition into different aryl electrophiles.[5] An ensuing transmetallation places both aryl groups on palladium, and a subsequent reductive elimination affords the desired biaryl product. The presence of zinc facilitates the reduction of nickel thus allowing for the use of catalytic amounts of nickel. Following the initial report, reductive cross-coupling reactions have been demonstrated to proceed between two different aryl halides, aryl halides and aryl triflates, and between aryl esters and aryl ethers bearing a directing group (Figure 1).[6] Compared to aryl halides, electrophiles that can be directly derived from the aryl alcohol (phenols) feature wider commercial availability, are cheaper, and are more environmentally friendly.

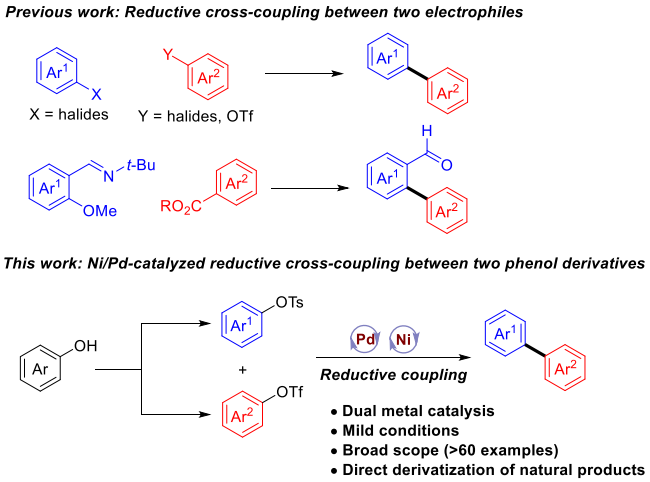
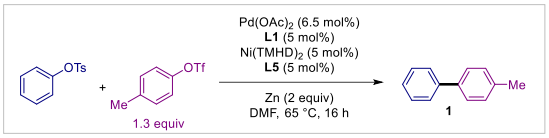


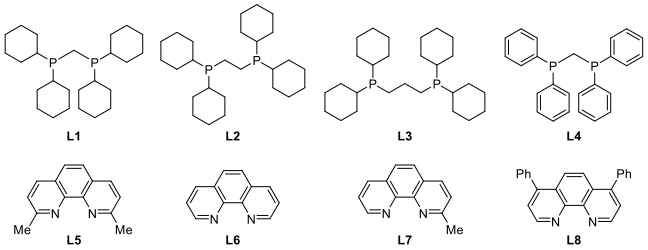

**Figure 1.** Comparison of existing reductive aryl–aryl cross-coupling reactions and the work reported here.

Herein, we report the reductive cross-coupling reaction between two different electrophiles, aryl tosylates and aryl triflates, which can both easily be derived from phenols. The mild reaction conditions in combination with the availability of substrates provides an attractive novel route for biaryl synthesis.[7] The methodology relies on dual nickel/palladium catalysis were each metal catalyst is responsible for activating one of the substrates.

After extensive optimization, we succeeded in identifying reaction conditions which provided a high yield for the selective cross-coupling of an aryl tosylate and an aryl triflate used in near-stoichiometric amounts (Table 1). The optimized reaction conditions consists of $Pd(OAc)_2$ with bidentate ligand **L1**, $Ni(TMHD)_2$ (TMHD = 2,2,6,6-tetramethyl-3,5-heptanedionate) with bidentate ligand **L5**, aryl tosylate as limiting reagent, a small excess of aryl triflate (1.3 equiv), zinc as reductant and DMF as solvent at 65 °C (entry 1). The use of equimolar amounts of palladium and **L1** leads to a slight decrease in yield (entry 2). Control experiments without either $Pd(OAc)_2$/**L1** or $Ni(TMHD)_2$/**L5** led to no formation of product highlighting the importance of both catalysts in the reaction (entries 3–4). Other reductants than zinc either led to a significantly reduced yield or no product formation (entries 5–7). Variation to the bidentate phosphine ligand, either in the linker length between the phosphorus atoms or in substituents on phosphorus, provided lower yields (entries 8–10). The same trend was observed for variations to the bidentate nitrogen ligand were different substitution patterns than 2,9-dimethyl led to reduced yields (entries 11–14). A change in reaction temperature of +/-5 °C only had a small impact on the yields (entries 15–16). Finally, a range of other polar solvents were shown to decrease the yield of the desired cross-coupling product (entries 17–20).

**Table 1.** Effect of various reaction parameters on the outcome of the reductive cross-coupling reaction between aryl tosylates and aryl triflates[a]




| Entry | Deviation from standard conditions | Yield of **1** [%][b] |
|---|---|---|
| 1 | none | 90 |
| 2 | 5 mol% $Pd(OAc)_2$ instead of 6.5 mol% $Pd(OAc)_2$ | 81 |
| 3 | Without $Pd(OAc)_2$, **L1** | nd |
| 4 | Without $Ni(TMHD)_2$, **L5** | nd |
| 5 | Mn instead of Zn | 49 |
| 6 | Mg instead of Zn | nd |
| 7 | Sn instead of Zn | nd |
| 8 | **L2** instead of **L1** | 57 |
| 9 | **L3** instead of **L1** | 30 |
| 10 | **L4** instead of **L1** | 17 |
| 11 | **L6** instead of **L5** | 15 |
| 12 | **L7** instead of **L5** | 42 |
| 14 | **L8** instead of **L5** | 36 |
| 15 | 70 °C instead of 65 °C | 85 |
| 16 | 60 °C instead of 65 °C | 82 |
| 17 | DMA instead of DMF | 56 |
| 18 | DMSO instead of DMF | 40 |
| 19 | THF instead of DMF | nd |
| 20 | MeCN instead of DMF | nd |

[a] The reactions were performed on 0.2 mmol scale. [b] Yields were determined by GC analysis using n-dodecane as internal standard. THMD = 2,2,6,6-tetramethyl-3,5-heptanedionate.

Having established reactions conditions that provided a high yield for the selective reductive cross-coupling of the simple aryl tosylate and aryl triflate substrates in Table 1, we set out to thoroughly evaluate the substrate scope and functional group compatibility (Figure 2). First, 21 different aryl triflates were examined leading to products **2**–**22**. While the unsubstituted phenyl tosylate led to a high yield, substrates bearing different unfunctionalized aliphatic substituents on the aryl triflate in general led to good yields (**2**–**6**). Trifluoromethoxy as well as methoxy groups were tolerated, and, notably, no significant difference in yields were observed for ortho-, meta-, and para-methoxy-substituted aryl triflates[8] (**7**–**10**). Anilines including an acetyl protected aniline with a free NH moiety[9] afforded good yields of the desired products (**11**–**12**). The presence of various common aliphatic functional groups such as ether, ketones, nitrile, and ester did not affect the reaction outcome, and high yields were obtained (**13**–**17**). An aryl fluoride and even an aryl chloride were well-tolerated (**18**–**19**). Substrates containing an aryltrimethylsilyl group and a dihydrobenzofuran could also undergo the reductive cross-coupling reaction (**20**–**21**). Finally, a Boc-protected indole afforded a high yield of the desired product (**22**).

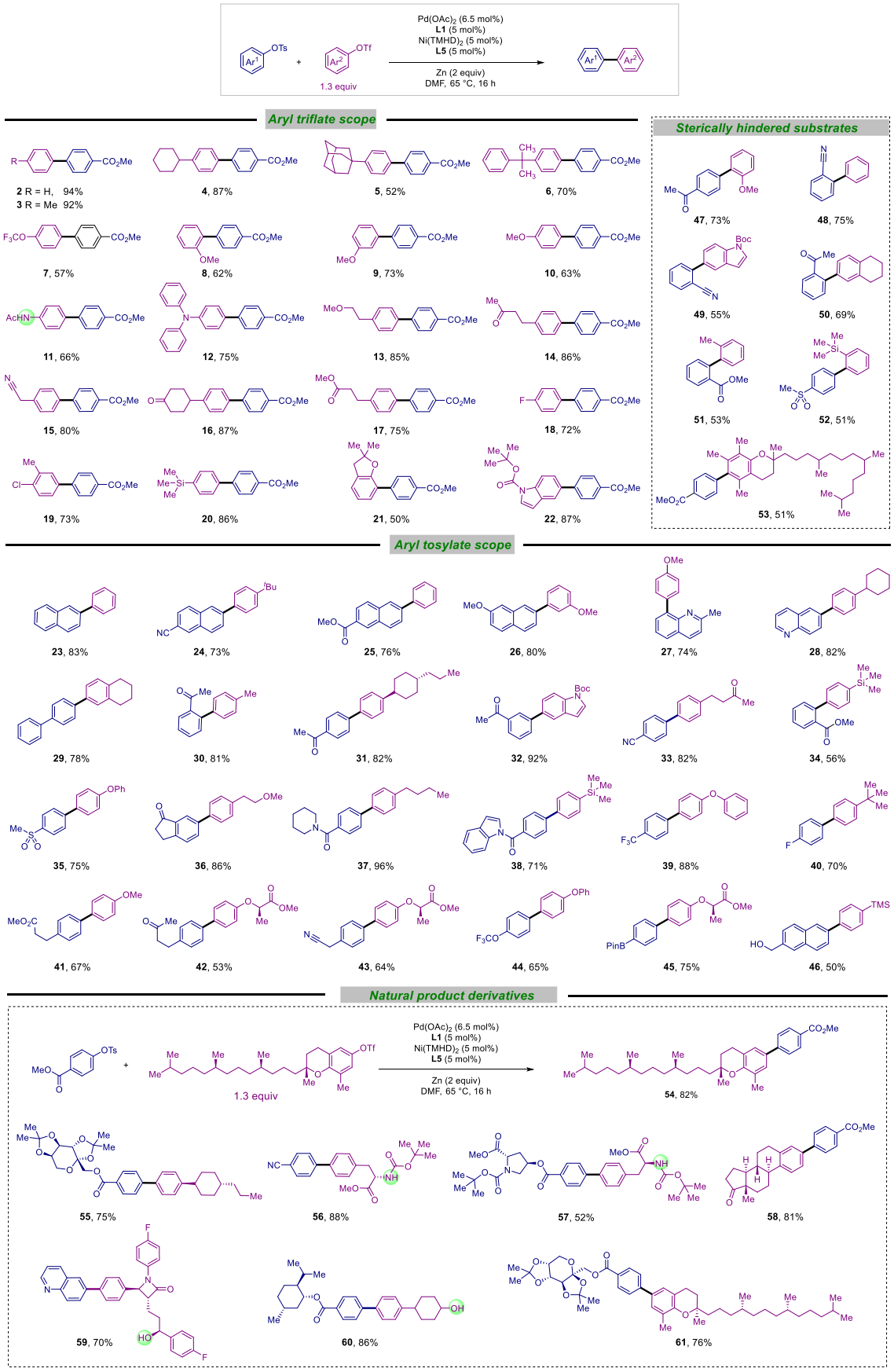



**Figure 2.** Substrate scope investigation for the reductive cross-coupling reaction between aryl tosylates and aryl triflates. Listed yields are isolated yields.

Next, 24 aryl tosylates were examined leading to cross-coupling products **23**–**46**. A simple naphthyl tosylate led to 83% yield, and the introduction of electron-withdrawing or electron-donating groups on the naphthyl moiety only had a minor influence on the yield (**23**–**26**). Notably, quinoline substrates were well-tolerated leading to good yields of the desired products (**27**–**28**). A biphenyl tosylate also led to a good yield (**29**). Aryl ketone substrates smoothly underwent the reductive cross-coupling, and, just as observed for the aryl triflates, no significant difference in yields were observed between the ortho-, meta-, and para-substituted substrates (**30**–**32**). A range of substrates bearing common functional groups directly connected to the aryl tosylate, such as nitrile, ester, sulfonyl, cyclic ketone, amides (including an indole), trifluoromethyl, and fluoride produced good-to-high yields (**33**–**40**). Substrates containing aliphatic esters, ketone, and nitriles also afforded the desired cross-coupling products (**41**–**43**). Finally, it was demonstrated that a trifluoromethoxy group, an arylboronic ester,[10] and even an unprotected primary aliphatic alcohol[11] are tolerated during the reductive cross-coupling reaction (**44**–**46**).

To evaluate the sensitivity to steric effects, combinations of sterically hindered aryl tosylates and aryl triflates were examined (**47**–**53**). Notably, when both substrates contain an ortho-substituent, the desired cross-coupling product **51** could still be obtained in 53% yield. Furthermore, a vitamin E derived substrate bearing two ortho-substituents also led to product formation affording a fully substituted aromatic ring (**53**).

Overall, the broad functional group tolerance for both coupling partners, including electrophilic functional groups, heterocycles, aryl chloride, and arylboronic ester highlights the mild reaction conditions of the developed protocol for the reductive cross-coupling reaction. Encouraged by the results, we continued to examine applications for functionalization of compounds, which, for the most part, can be derived in one step from natural products and pharmaceuticals. First, we demonstrated that the triflate from a tocopherol could be directly arylated in 82% yield (**54**). Also, a protected fructose substrate afforded the desired reductive cross-coupling product in a good yield (**55**). The arylation of tyrosine went smoothly, and two amino acids could be connected using our protocol (**56**–**57**). The steroid scaffold, estratrien, was well-tolerated (**58**). Even the installation of a heterocycle directly on the drug Ezetimibe (treatment of high cholesterol) proceeded in 70% yield without the need for protecting the pendant aliphatic alcohol (**59**). The presence of an unprotected aliphatic alcohol was also tolerated for a benzoyl derivative of L-(–)-menthol (**60**). Finally, it was demonstrated that protected fructose and a tocopherol could be connected using the reductive cross-coupling reaction (**61**). The successful cross-coupling either directly on or in the presence of natural products and pharmaceuticals highlights the mild reaction conditions and the potential for late-stage functionalization using the developed protocol.

Next, we sought to gain insight into the reaction mechanism of the reductive cross-coupling reaction. NMR spectroscopy confirmed that the phosphine ligand **L1** binds to palladium while the nitrogen ligand **L5** binds to nickel.[12] Based on this knowledge, DFT calculations were performed to identify which metal complex reacts with each electrophile. All calculations were performed at SMD/B3LYP/6-311+G(d,p)/LANL2DZ//B3LYP/6-31G(d)/LANL2DZ level with Gaussian 16 program.[12] The free energies of oxidative addition complexes **A** and **B** were found to be lower than those of oxidative addition complexes **C** and **D** by 1.7 kcal/mol (Figure 3a). Accordingly, the DFT calculations suggest that the nickel(0) catalyst undergoes oxidative addition to the aryl triflate, while the palladium(0) catalyst undergoes oxidative addition to the aryl tosylate. Based on these preliminary results, our current hypothesis for the reaction mechanism is shown in Figure 3b. Following the selective oxidative additions to the aryl tosylate and aryl triflate by palladium and nickel, respectively, transmetallation between the two metal catalysts would position both aryl groups on palladium. An ensuing reductive elimination forms the cross-coupling product and regenerates palladium(0). Nickel(0) is regenerated by reduction with zinc.[5]

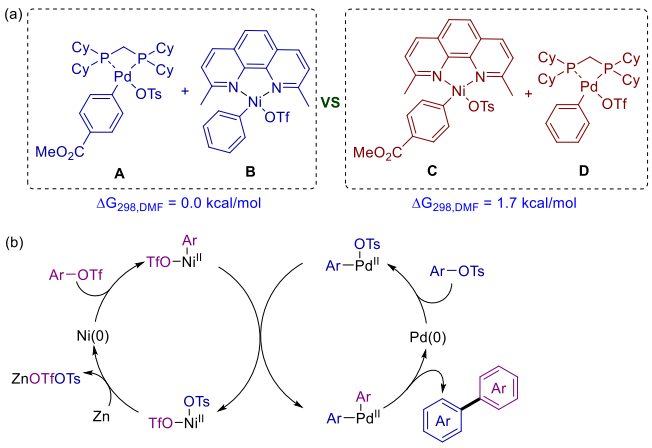



**Figure 3.** (a) Relative energies of combinations of oxidative addition complexes obtained by DFT calculations. (b) Proposed reaction mechanism for the reductive cross-coupling reaction between aryl tosylates and aryl triflates. Ligands are omitted for clarity.

In summary, we have developed a dual nickel/palladium-catalyzed cross-coupling reaction between two easily accessible phenol derivatives, aryl tosylates and aryl triflates. The mild reaction conditions allow for broad functional group tolerance and scope (>60 examples). Other features include low sensitivity to sterical hindrance and straightforward late-stage functionalization of the pharmaceutical Ezetimibe. Preliminary DFT calculations indicate that the nickel catalyst is responsible for activating the aryl triflate while the palladium catalyst activates the aryl tosylate. Given the broad functional group tolerance and the abundance of phenols, the method reported here is a powerful alternative to traditional cross-coupling reactions. An in-depth mechanistic investigation of the reductive cross-coupling reaction is currently ongoing in our groups.


## Acknowledgements

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Keywords: Reductive Cross-Coupling • Dual Catalysis • Nickel Catalysis • Palladium Catalysis • Phenols



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[12] See supporting information for the details.

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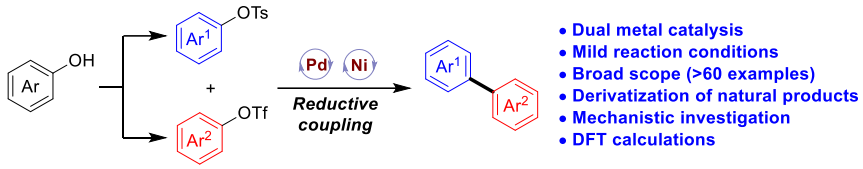


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