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

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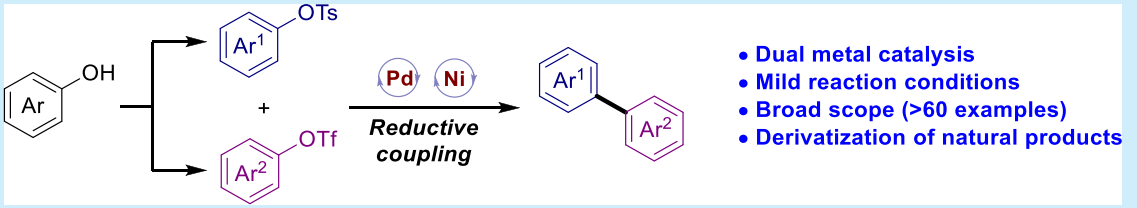

ABSTRACT: Cross-coupling between substrates that can be easily derived from phenols is highly attractive due to the abundance of phenols. Here, we report a dual nickel-/palladium-catalyzed reductive cross-coupling between aryl tosylates and aryl triflates; both substrates can be accessed in just one 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 allows for straightforward late-stage functionalization, illustrated with examples such as ezetimibe and tyrosine.

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 of these reactions rely on an organometallic reagent as one of the cross-coupling partners. Despite the widespread use 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 complementarity 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 is achieving cross-coupling selectivity and avoiding the competing homocoupling reactions. In 2015, Weix and co-workers 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 transmetalation 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) are more environmentally friendly.

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 where each metal catalyst is responsible for activating one of the substrates.

Our initial attempts at achieving the selective cross-electrophile coupling were hampered by fast palladium-catalyzed homocoupling of the aryl triflate. Nonetheless, we hypothesized that by varying the ligands on both metals, the rates of oxidative addition into the two different electrophiles could be matched. 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**,

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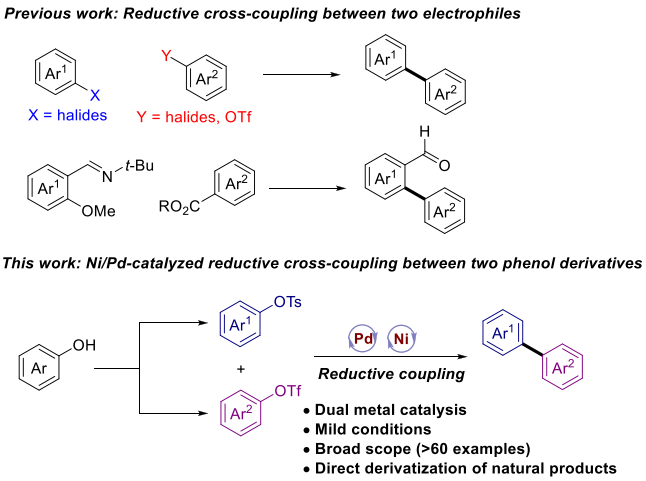
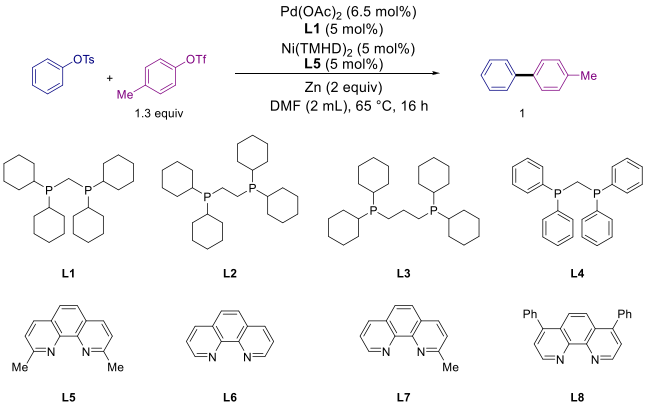


Figure 1. Comparison of existing reductive aryl−aryl cross-coupling reactions and the work reported here.

$Ni(TMHD)_2$ (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).[8] The use of equimolar amounts of palladium and **L1** leads to a slight decrease in yield (entry 2). Control experiments where either one of the metal sources is removed clearly showed that both metals are necessary for product formation (entries 3 and 4). This was further supported by experiments without either $Pd(OAc)_2$/**L1** or $Ni(TMHD)_2$/**L5** which also led to no formation of product (entries 5 and 6). Other reductants than zinc either led to a significantly reduced yield or no product formation (entries 7−9). Variation of the bidentate phosphine ligand, either in the linker length between the phosphorus atoms or in substituents on phosphorus, provided lower yields (entries 10−12). The same trend was observed for variations to the bidentate nitrogen ligand where different substitution patterns than 2,9-dimethyl led to reduced yields (entries 13−15). Screening of reaction temperatures ranging from 40 to 80 °C revealed that 65 °C provided the highest yield (entries 16−20). Finally, a range of other polar solvents were shown to decrease the yield of the desired cross-coupling product (entries 21−24).

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. First, 21 different aryl triflates were examined leading to products **2**−**22** (Figure 2). 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 (**7**−**10**). Notably, no significant difference in yields were observed for the ortho-, meta-, and para-methoxy-substituted aryl triflates.[9] Anilines including an acetyl protected aniline with a free NH moiety[10] afforded good yields of the desired products (**11** and **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 tolerated (**18** and **19**).[11] Substrates containing an aryltrimethylsilyl group and a dihydrobenzofuran could also undergo the reductive cross-coupling reaction (**20** and **21**). Finally, a Boc-protected indole afforded a high yield of the desired product (**22**).

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 $Pd(OAc)_2$	nd
4	without $Ni(TMHD)_2$	nd
5	without $Pd(OAc)_2$, **L1**	nd
6	without $Ni(TMHD)_2$, **L5**	nd
7	Mn instead of Zn	49
8	Mn instead of Zn	nd
9	Sn instead of Zn	nd
10	**L2** instead of **L1**	57
11	**L3** instead of **L1**	30
12	**L4** instead of **L1**	17
13	**L6** instead of **L5**	15
14	**L7** instead of **L5**	42
15	**L8** instead of **L5**	36
16	40 °C instead of 65 °C	55
17	50 °C instead of 65 °C	73
18	60 °C instead of 65 °C	82
19	70 °C instead of 65 °C	85
20	80 °C instead of 65 °C	72
21	DMA instead of DMF	56
22	DMSO instead of DMF	40
23	THF instead of DMF	nd
24	ACN 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.

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**). Quinoline substrates and a biphenyl tosylate were well-tolerated leading to good yields of the desired products (**27**−**29**). Aryl ketone substrates smoothly underwent the reductive cross-coupling, and 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 on the aryl tosylate, such as nitrile, ester, sulfonyl, cyclic ketone, amides, indole, trifluoromethyl, and fluoride produced good to high yields (**33**−**40**). Substrates containing aliphatic esters, ketone, and nitriles also

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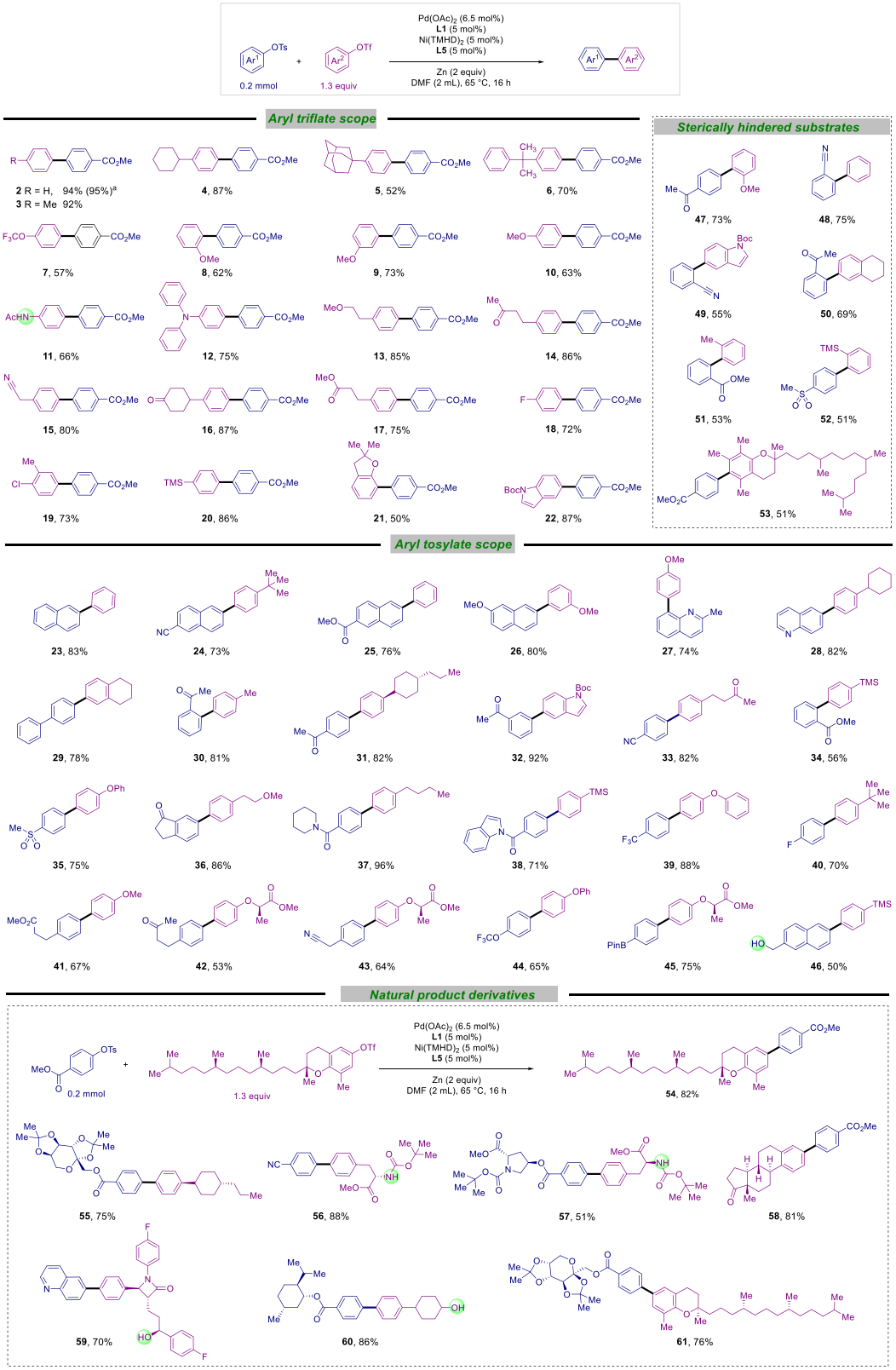

Figure 2. Substrate scope investigation for the reductive cross-coupling reaction between aryl tosylates and aryl triflates. Listed yields are isolated yields. [a]Yield on 1.0 mmol scale in parentheses.

afforded the desired cross-coupling products (**41**−**43**). Finally, it was demonstrated that a trifluoromethoxy group, an arylboronic ester,[12] and even an unprotected primary aliphatic alcohol[13] 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

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(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. Interestingly, secondary amides and unprotected alcohols can sometimes be problematic in cross-electrophile coupling reactions, yet the substrate scope investigation indicated that this was not the case for our protocol. Encouraged by these 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** and **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 to protect 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 on natural products and pharmaceuticals highlights the mild reaction conditions and the potential for late-stage functionalization using the developed protocol.[14]

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 steric hindrance and straightforward late-stage functionalization of the pharmaceutical ezetimibe. Given the broad functional group tolerance and the abundance of phenols, the method reported here is a powerful alternative to traditional cross-coupling reactions. A mechanistic investigation of the reductive cross-coupling reaction is currently ongoing in our group.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02165.

Experimental procedures along with characterization data and copies of ^{1}H, ^{13}C and ^{19}F NMR spectra (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(7) During the finalization of this manuscript, a nickel/palladium-catalyzed cross-coupling reaction between aryl tosylates and aryl triflates appeared as "just accepted": Kang, K.; Huang, L.; Weix, D. J. *J. Am. Chem. Soc.* **2020**, *142*, 10634. However, our catalytic system is different from Weix's; for example, both ligands are different. Also, in our protocol, additives are not necessary, while without additive (LiBr, 4 equiv), only 8% yield of desired product was formed in Weix's report.

(8) Under the standard conditions, the cross-coupling product was formed in 90% yield, and the byproduct (homocoupling of ArOTf) was formed in 18% yield. When the amount of ArOTf was reduced to 1.0 equiv, the desired product was produced in 80% yield, while the byproduct (homocoupling of ArOTf) was produced in 19% yield and the second byproduct (homocoupling of ArOTs) was produced in 4% yield.

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(11) In compound **19**, C−Cl bond cleavage is a competing reaction. The methyl group in the *ortho* position inhibits the C−Cl bond cleavage due to its steric effect. Without the methyl group in the *ortho* position, the reaction afforded only 10% yield.

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(14) Other substrate classes were also examined. An aryl butane-1-sulfonate ester gave 34% yield of the desired cross-coupling product. A vinyl triflate did not afford any of the desired product.

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