

# Sulfonate Versus Tosylate: Nickel and Palladium Multimetallic Cross-Electrophile Coupling of Aryl Triflates with Aryl Tosylates

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**ABSTRACT:** While phenols are frequent and convenient aryl sources in cross-coupling, typically as sulfonate esters, the direct cross-Ullmann coupling of two different sulfonate esters is unknown. We report here a general solution to this challenge catalyzed by a combination of Ni and Pd with Zn reductant and LiBr as an additive. The reaction has broad scope, as demonstrated in 33 examples (65% ± 11% average yield). Mechanistic studies show that Pd strongly prefers the aryl triflate, the Ni catalyst has a small preference for the aryl tosylate, aryl transfer between catalysts is mediated by Zn, and Pd improves yields by consuming arylzinc intermediates.

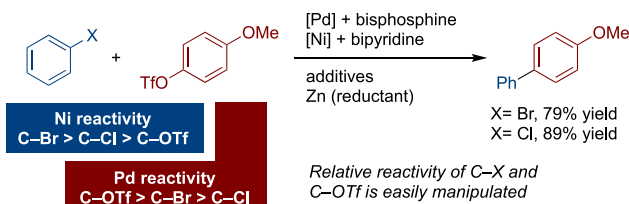
The development of palladium-catalyzed cross-coupling has led to biaryls becoming a cornerstone of pharmaceutical and medicinal chemistry.<sup>1</sup> The significance of biaryls has driven the development of new cross-coupling approaches involving different transition-metal catalysts<sup>2</sup> or even eschewing a metal catalyst.<sup>3</sup> One major challenge for all cross-coupling approaches is the availability of starting materials.<sup>4</sup> The low commercial availability of aryl nucleophiles has led to the development of improved methods to access them<sup>5</sup> as well as C–H arylation methods<sup>6</sup> and cross-Ullmann methods<sup>7,8</sup> that avoid them.<sup>4</sup>

A central challenge of cross-Ullmann reactions is achieving selectivity for the heterocoupling product over homocoupling products.<sup>7</sup> We introduced a new, multimetallic approach<sup>9</sup> based upon the different order of reactivity of palladium bisphosphine catalysts and nickel bipyridine catalysts with aryl halides and aryl triflates (Scheme 1A): the nickel catalyst prefers the C–Cl/Br bonds, while the palladium catalyst prefers C–OTf bond.<sup>10</sup> While this strategy has proven general, it was not clear whether it could be extended beyond coupling aryl triflates with aryl halides. We were particularly interested in the cross-Ullmann coupling of phenol derivatives because of their importance in cross-coupling<sup>11</sup> and the ubiquity of phenols in nature.<sup>12</sup> The most-used phenol derivatives in cross-coupling are sulfonate esters, yet the cross-Ullmann coupling of two different aryl sulfonate esters is unknown.<sup>13–16</sup> In exciting, concurrent work, Zeng recently reported on the cross-Ullmann coupling of different phenol derivatives using a different, directing-group-based approach.<sup>17</sup>

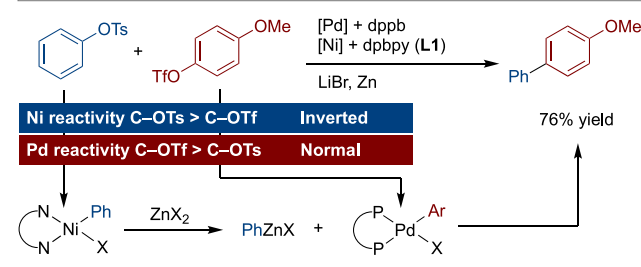
Our multimetallic strategy would appear to be incompatible with this goal: while the relative reactivity between aryl halides and aryl triflates can be manipulated for selective coupling at either bond (Scheme 1A),<sup>10</sup> the analogous inversion of selectivity between two different sulfonate esters has not been reported.<sup>18</sup> Although there are relatively few studies on this topic, aryl tosylates are generally considered less reactive than aryl triflates.<sup>19,20</sup> We report here a solution to this challenge via a nickel catalyst with unusual sulfonate selectivity<sup>18</sup> (Scheme 1B)

## Scheme 1. Cross-Ullmann Approaches to Biaryls Using Sulfonate Esters

### A. Previous Studies: Differentiation Between Sulfonate Esters and Halides



### B. This Work: Differentiation Between Two Different Sulfonate Esters



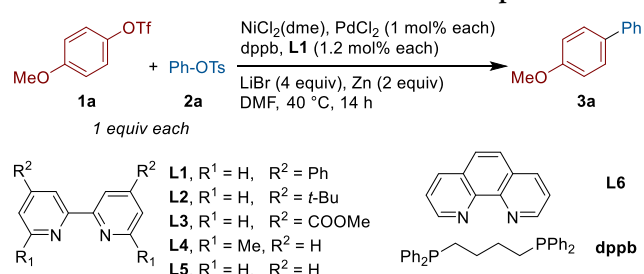
as well as studies that shed light on the mechanism of the reaction.

Preliminary studies examined the coupling of *p*-anisyl triflate (1a) with phenyl tosylate (2a) in the presence of nickel and palladium catalysts, salt additives, and reductants (Table 1). The optimal conditions were with 1 mol % of each catalyst (1:1.2 metal/ligand ratio), Zn reductant, and LiBr at 40 °C overnight

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**Table 1. Sulfonate Cross-Ullmann Reaction Optimization<sup>a</sup>**

entry	variations from above conditions	3a <sup>b</sup> (%)
1	none	76
2	without NiCl <sub>2</sub> (dme) and L1	<5 <sup>c</sup>
3	without PdCl <sub>2</sub> and dppb	58
4	Mn instead of Zn or without Zn	<5 <sup>c</sup>
5	without LiBr	8 <sup>c</sup>
6	2.0 equiv instead of 4.0 equiv of LiBr	63
7	NaBr instead of LiBr	72
8	KBr instead of LiBr	73
9	<i>n</i> -Bu <sub>4</sub> NBr instead of LiBr	54
10	ZnBr <sub>2</sub> instead of LiBr	<5 <sup>c</sup>
11	L2 instead of L1	32
12	L3 instead of L1	12
13	L4 instead of L1	8 <sup>c</sup>
14	L5 instead of L1	65
15	L6 instead of L1	62
16	0.5 mol % [Ni]/[Pd], 0.6 mol % dppb/L1	73 <sup>d</sup>
17	Reaction setup on benchtop using standard glassware and Schlenk line	73 <sup>e</sup>

<sup>a</sup>Reactions on a 0.25 mmol scale in 1.0 mL of DMF. <sup>b</sup>Gas chromatography yield vs dodecane. <sup>c</sup>More than 75% of both **1a** and **2a** remained. <sup>d</sup>Reaction on a 0.5 mmol scale in 1.0 mL DMF. <sup>e</sup>Isolated yield.

(Table 1, entry 1). Unless otherwise noted (footnote c in Table 1), low yields were accompanied by larger amounts of dimeric biaryls (biphenyl and bianisole).

Salts were added to facilitate catalyst turnover<sup>9c</sup> (by activating the zinc surface and converting nickel triflate to nickel bromide), to stabilize potential arylpalladium(II) intermediates,<sup>20</sup> and to modulate transmetalation.<sup>21</sup> A variety of bromide salts were effective (Table 1, entries 5–9), but ZnBr<sub>2</sub> was inhibitory<sup>9c</sup> (entry 10). However, Zn reductant was essential and could not be replaced with Mn (entry 4).

While a variety of phosphines and bipyridines supported the coupling, the best yields were obtained with 1,4-bis(diphenylphosphino)butane (dppb) and 4,4'-diphenyl-2,2'-bipyridine (L1, dpbpy) (Table 1 and Table S1 in Supporting Information). A variety of phosphines other than dppb resulted in moderate yields of **3a** (29–61% yield, Table S1) due to decreased selectivity for cross-coupling over homocoupling; **1a** and **2a** were completely consumed. In contrast, the results with nitrogen ligands had a strong dependence on electronics (Table 1, entries 1 and 11–15). The optimal ligand, L1, bears mildly electron-withdrawing groups. Reactions with simple 2,2'-bipyridine (bpy) (L5) or phenanthroline (phen) (L6) consumed both starting materials and formed cross-product **3a** in 65 and 62% yields. Reactions with ligands that were more electron-rich (L2) and more sterically hindered (L4) provided lower yields of **3a** due to slow conversion of both **1a** and **2a**. Reactions with a more electron-poor ligand (L3) resulted in primarily bianisole from homocoupling of **1a** and slow

consumption of **2a**. The catalyst loading in some cases can be lowered to 0.5 mol %, the lowest reported for Ni/Pd multimetallic cross-Ullmann reactions (entry 16 and Scheme 2, **3d**, **3p**, **3w**, **3af**).<sup>9</sup>

These conditions are compatible with a variety of functional groups (Scheme 2), including ketones (**3e** and **3m**), esters (**3f** and **3g**), dimethylaniline (**3i**), trifluoromethoxy (**3i**), alkyl chloride (**3j**), aryl chloride (**3k**), Boc-protected alkyl amine (**3l**), and arylboronic acid pinacol ester (**3m**). More sterically hindered pairings could also be coupled, using slightly modified conditions: a higher reaction temperature (60 °C) and an additional 0.5 equiv of aryl tosylate (**3n–3t**). Scaling the synthesis of **3w** 10-fold (from 0.5 to 5.0 mmol) provided a similar yield of product (73% yield at 0.5 mmol vs 68% yield at 5.0 mmol).

The ability to cross-couple two phenol derivatives can provide extra flexibility in synthesis, because phenols are more abundant than arylmetal reagents, and in some cases phenols are the most convenient arene source (see Supporting Information Table S2).<sup>4,22</sup> For example, we coupled a variety of aryl triflates and tosylates derived from natural products (**3w**, **3x**, **3y**, **3ab**, **3ac**, **3ad**, **3ae**, **3af**, **3ag**), drug intermediates (**3u**, **3v**, **3z**, **3aa**, **3ad**, **3af**, **3ag**), or precursors to common materials (**3aa**, **3ab**, **3ae**).

Another feature of this biaryl synthesis is that a pair of phenols can be coupled in two different ways, providing another approach to improve yields. More electron-rich aryl triflates provided higher yields (**3a** vs **3b**, 72% vs 62% yield), but there was no trend with aryl tosylate electronics (Tables S7–S9 in the Supporting Information).

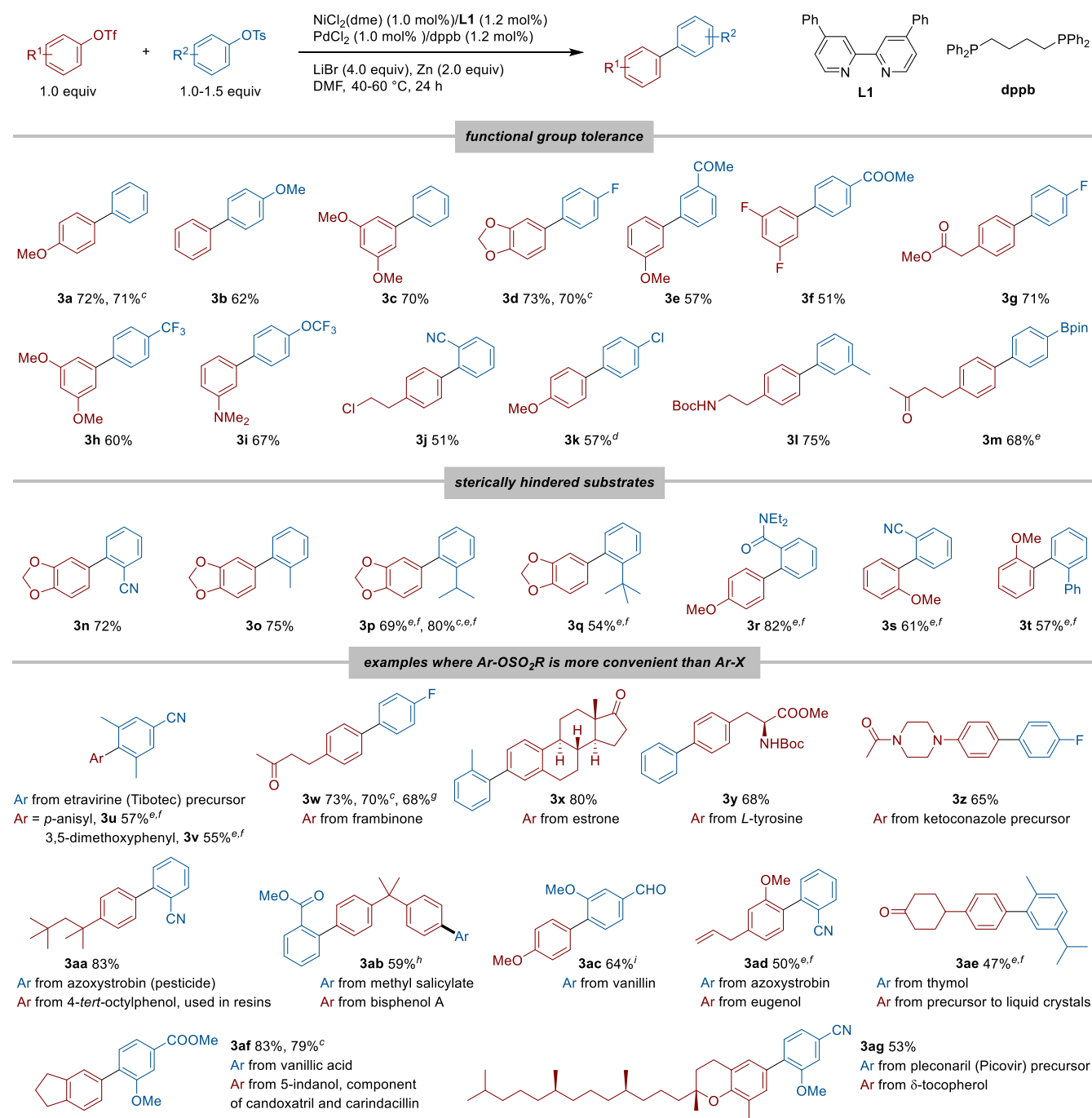
Mechanistically, we focused on three questions: (1) determining the reactivity preference of each catalyst for the substrates,<sup>18–20</sup> (2) the mechanism of aryl transfer between catalysts, and (3) the role of Pd in the reaction given that nickel alone also forms product (Table 1, entries 1–3). The collected data are consistent with the Pd catalyst reacting preferentially with the aryl triflate and the Ni catalyst reacting with both substrates but slightly preferring the aryl tosylate. The evidence shows that Zn mediates the aryl transfer between Ni and Pd. Finally, Pd improves yields by helping to balance the rate of consumption of aryl zinc reagents with the rate of their formation.

To shed light on the mechanism, we compared reactions with both catalysts to reactions with a single catalyst (Figure 1). In particular, time-course studies on the coupling of *p*-anisyl triflate (**1a**) with phenyl tosylate (**2a**) were conducted under standard conditions (A, Figure 1-I), nickel-only conditions (B, Figure 1-II), and palladium-only conditions (C and D). We visualized the total concentration of Ph-M and Ar-M (M = NiX,<sup>23</sup> PdX, ZnX; Ar = *p*-anisyl) by quenching reaction aliquots with iodine.<sup>24</sup>

The data in Figure 1 show strong evidence for a low, steady-state concentration of PhZnX (Z-1) under standard reaction conditions (Figure 1-I, Condition A). This phenylzinc species is derived from phenyl tosylate (**2a**) and visualized as **8** after iodination. Together with experiments using either catalyst alone (Conditions B, C, and D), we can confirm that some of **8** in Condition A is derived from a phenylzinc intermediate, that nickel has a slight selectivity for **2a**, and that palladium is selective for **1a**.

Our reasoning:

- (1) The reaction catalyzed by nickel catalyst alone (Condition B, Figure 1-II; Tables S12 and S13) forms a

Scheme 2. Substrate Scope for the Cross-Coupling of Aryl Triflates with Aryl Tosylates<sup>a,b</sup>

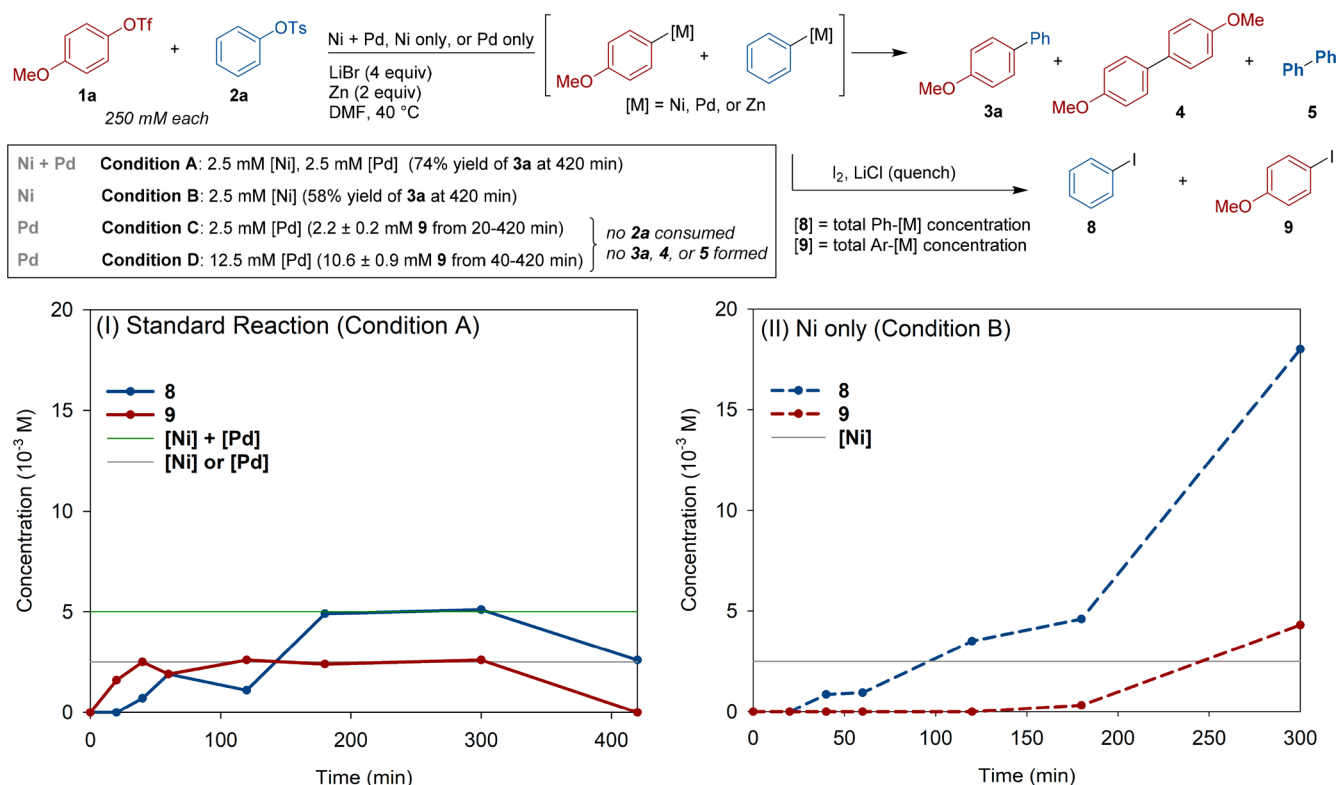
<sup>a</sup>Reactions on a 0.50 mmol scale in 2.0 mL of DMF. <sup>b</sup>Isolated yield of purified material. <sup>c</sup>Results at 0.5 mol % catalyst loading (as in Table 1, entry 16). <sup>d</sup>Reaction was run at 35 °C. <sup>e</sup>1.5 Equiv aryl tosylate was used. <sup>f</sup>Reaction was run at 60 °C. <sup>g</sup>Reaction was run on 5 mmol scale. <sup>h</sup>Reaction run with 2 equiv of ArOTs at 0.25 mmol scale. <sup>i</sup>Results at 5 mol % catalyst loading (5 mol % Ni + Pd, 6 mol % 4,4'-dimethoxy-2,2'-bipyridine + dppb).

concentration of **8** (24.4 mM at 420 min) that far exceeds the concentration of nickel catalyst (gray line, 2.5 mM, [8]/[Ni] = 9.8), confirming that nickel to zinc transmetalation is possible<sup>14</sup> and preferred over biaryl formation.<sup>7,8,25</sup>

- (2) The nickel catalyst alone (Condition B) consumes **1a** and **2a** at almost the same rate, with a slight preference for tosylate **2a** (Table S12, consumption of **2a/1a**  $\approx$  1.1 between 6% and 52% conversion). This is consistent with the stoichiometric reaction of (L1)Ni<sup>0</sup>(cod), where

tosylate **2a** reacted 3.2 times faster than triflate **1a**,<sup>26</sup> but contrary to most other reports, where triflates are much more reactive than tosylates.<sup>18–20</sup> This result further suggests that other steps in the catalytic cycle besides oxidative addition play a role in the selectivity for cross-product **3a** over dimeric biaryls.

- (3) In contrast, palladium(0) does not react with phenyl tosylate (**2a**) and instead oxidatively adds to *p*-anisyl triflate (**1a**) to form **9** after iodination (Conditions C and D, Tables S14–S16). We do not think that *p*-anisylzinc is



**Figure 1.** Assessment of organometallic reagents present in cross-Ullmann couplings. (I) Concentrations of 8 and 9 in Condition A vs time. (II) Concentrations of 8 and 9 in Condition B vs time. Concentrations of 8 and 9 were determined by gas chromatography analysis vs an internal standard after iodination of aliquots of the reaction mixtures. See Supporting Information Tables S10–S16 for further details, including data on Conditions C and D.

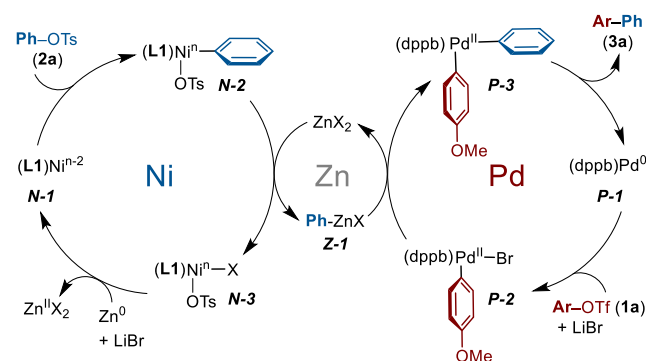
formed under these conditions, because  $[9]/[Pd]$  is between 0.15 and 1.01. The arylpalladium species is unreactive with itself, zinc, or zinc salts, because no biaryls (3a, 4, 5) are formed.

- (4) In Condition A (Figure 1-I; Tables S10 and S11), the combined concentration of 8 (5.1 mM) and 9 (2.6 mM) at 300 min indicates a total concentration of arylmetal species (7.7 mM) that exceeds the combined concentration of nickel and palladium catalysts (denoted with a green line, 5.0 mM). This confirms that phenylzinc is formed in productive reactions and suggests that both aryl and vinyl transfer in related multimetallic reactions is zinc-mediated.<sup>9</sup>

Upon the basis of these data and literature reports, we propose a mechanism for the nickel and palladium-catalyzed cross-Ullmann reaction of aryl triflate with aryl tosylate in Scheme 3.<sup>27</sup> The palladium catalyst (P-1) participates in an oxidative addition with the aryl triflate to form an arylpalladium(II) species<sup>20</sup> (P-2) that is unreactive with itself or zinc. The nickel catalyst reacts preferentially with aryl tosylate, presumably to form arylnickel (N-2), followed by transmetalation with zinc salts to form arylzinc Z-1 (Figure 1-II).<sup>14</sup> The arylzinc is present in a low, steady concentration when both catalysts are present (Figure 1-I,II) due to the efficient consumption of Z-1 by P-2 to form diarylpalladium (P-3).<sup>21,28</sup> Reductive elimination from P-3 forms cross-biaryl product 3a and regenerates palladium(0).<sup>29</sup> The nickel salt N-3 formed after arylzinc (Z-1) formation is reduced by zinc powder to regenerate low-valent nickel (N-1) with the assistance of LiBr.<sup>9c</sup>

While Ni is able to form and consume arylzinc reagents, Pd improves yields by ensuring full consumption of organozinc

### Scheme 3. Proposed Ni/Zn/Pd Mechanism for Cross-Ullmann Reaction of Aryl Triflates with Aryl Tosylates<sup>a</sup>



<sup>a</sup>Halide exchange is likely dynamic, X = Br, OTs, or OTf. Ar = *p*-anisyl. For nickel oxidation state,  $n = 2$  or 3.

reagents. Without Pd present, significant amounts of arylzinc reagents remain (Condition B, 10% yield 8, 6% yield 9), diminishing the yield of product 3a (58% for B, 74% for A).

In closing, we have found that the nickel and palladium system we first reported for the cross-coupling of aryl triflates with aryl bromides is capable of selectively cross-coupling aryl triflates with aryl tosylates.<sup>30</sup> This is the first cross-Ullmann reaction of two different sulfonate esters and suggests that methods to couple other “alike” electrophiles can be achieved. In this case, the nickel catalyst displays anomalous selectivity for the aryl tosylate over the aryl triflate. The reaction is general and will be especially useful in cases where phenols are the most convenient starting materials.

## ■ ASSOCIATED CONTENT

## SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacs.0c04670>.

Additional tables of optimization data, mechanistic studies, detailed experimental procedures, characterization of products, copies of product NMR spectra (PDF)

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## Notes

The authors declare no competing financial interest.

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(26) See Supporting Information Table S17. While this result is consistent with the slight preference of Ni for aryl tosylate (Table S12), 1,5-cyclooctadiene (cod) could alter the outcome of the reaction, and we cannot rule out nickel(I) intermediates. See ref 19 and Fang, S.; Wang, M.; Liu, J.; Li, B.; Liu, J. Theoretical Study on the Reaction Mechanism of “Ligandless” Ni-Catalyzed Hydrodesulfurization of Aryl Sulfide. *RSC Adv.* **2017**, *7*, 51475–51484.

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