

# Multimetallic catalysed cross-coupling of aryl bromides with aryl triflates

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The advent of transition-metal catalysed strategies for forming new carbon-carbon bonds has revolutionized the field of organic chemistry, enabling the efficient synthesis of ligands, materials, and biologically active molecules<sup>1–3</sup>. In cases where a single metal fails to promote a selective or efficient transformation, the synergistic cooperation<sup>4</sup> of two distinct catalysts—multimetallic catalysis—can be used instead. Many important reactions rely on multimetallic catalysis<sup>5–10</sup>, such as the Wacker oxidation of olefins<sup>6–8</sup> and the Sonogashira coupling of alkynes with aryl halides<sup>9,10</sup>, but this approach has largely been limited to the use of metals with distinct reactivities, with only one metal catalyst undergoing oxidative addition<sup>11,12</sup>. Here, we demonstrate that cooperativity between two group 10 metal catalysts—(bipyridine)-nickel and (1,3-bis(diphenylphosphino)propane)palladium—enables a general cross-Ullmann reaction (the cross-coupling of two different aryl electrophiles)<sup>13–15</sup>. Our method couples aryl bromides with aryl triflates directly, eliminating the use of arylmetal reagents and avoiding the challenge of differentiating between multiple carbon-hydrogen bonds that is required for direct arylation methods<sup>16,17</sup>. Selectivity can be achieved without an excess of either substrate and originates from the orthogonal reactivity of the two catalysts and the relative stability of the two arylmetal intermediates. While (1,3-bis(diphenylphosphino)propane)palladium reacts preferentially with aryl triflates to afford a persistent intermediate, (bipyridine)nickel reacts preferentially with aryl bromides to form a transient, reactive intermediate. Although each catalyst forms less than 5 per cent cross-coupled product in isolation, together they are able to achieve a yield of up to 94 per cent. Our results reveal a new method for the synthesis of biaryls, heteroaryls, and dienes, as well as a general mechanism for the selective transfer of ligands between two metal catalysts. We anticipate that this reaction will simplify the synthesis of pharmaceuticals, many of which are currently made with pre-formed organometallic reagents<sup>1–3</sup>, and lead to the discovery of new multimetallic reactions.

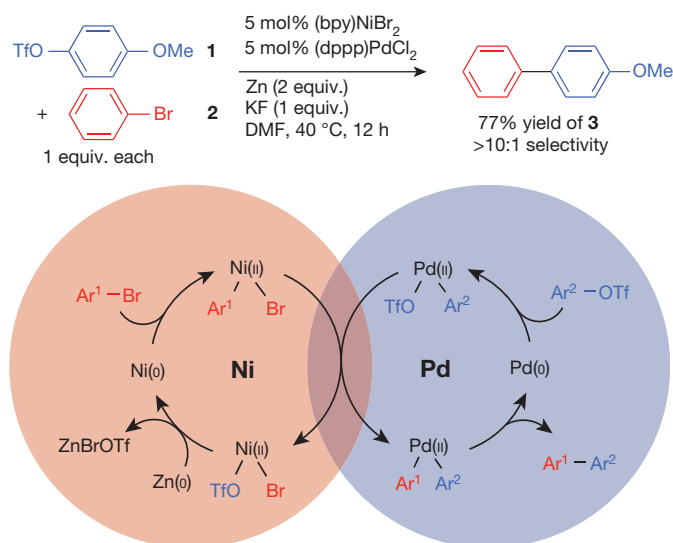
We envisaged that a general solution to the cross-Ullmann reaction could be realized through multimetallic catalysis if, first, each of the two catalysts activated only one of the two substrates (**1** and **2** in Fig. 1); second, selective transmetalation (the transfer of ligands from one metal to another) could be achieved (overlap of circles in Fig. 1); and third, the catalysts were redox compatible<sup>18</sup>. Based on Hayashi's work<sup>19</sup>, we chose an electron-rich palladium(0) (Pd) catalyst with a bidentate phosphine ligand, 1,3-bis(diphenylphosphino)propane (dppp), to react preferentially with aryltrifluoromethylsulfonate esters (aryl triflates) over aryl bromides<sup>19</sup>. From our own studies<sup>20</sup>, we chose a bipyridine (bpy) nickel(0) (Ni) catalyst to react selectively with aryl bromides in preference to aryl triflates.

We began our investigation of this multimetallic system by combining a 1:1 mixture of bromobenzene (substrate **2**) and 4-methoxyphenyltriflate (substrate **1**) in the presence of both of the catalysts and a zinc reducing agent (Fig. 2b). Remarkably, we observed a high selectivity for formation of the cross-product, 4-methoxybiphenyl (product

**3**; 70% yield), in preference to the dimers biphenyl (product **4**; 17%) and bianisole (product **5**; 10%). When each catalyst was allowed to react independently with the two aryl electrophiles, however, no such 'cross-selectivity' was observed. (Bpy)NiBr<sub>2</sub> formed exclusively biphenyl (**4** in Fig. 2a) from bromobenzene (**2**) before reacting with 4-methoxyphenyltriflate (**1**) (Fig. 2c), while (dppp)PdCl<sub>2</sub> 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. 2d). Only when the two catalysts were combined did a selective reaction occur.

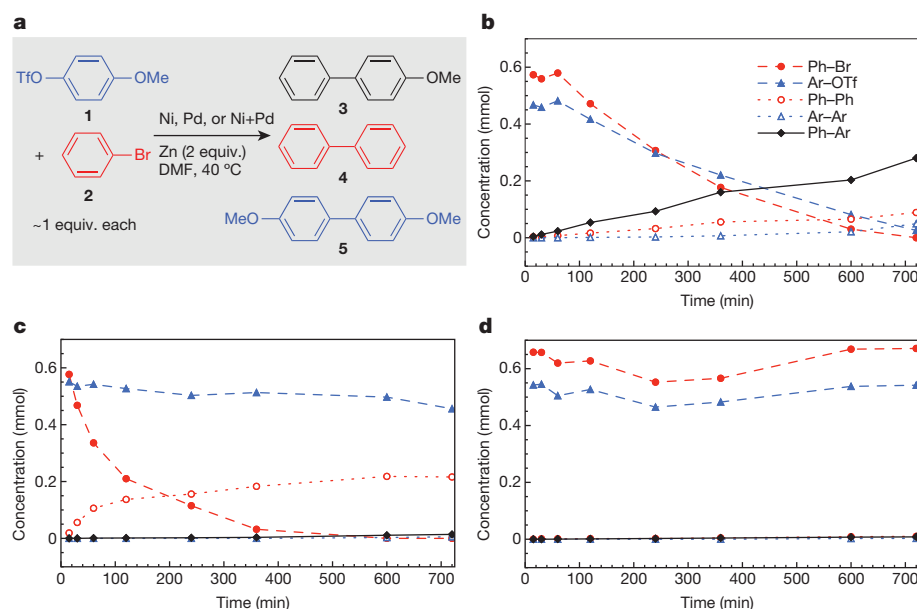
To ensure that the cross-product observed was the result of synergy between the two proposed metal catalysts, we examined the reactivity of alternative catalysts that could be formed *in situ* via exchange of the supporting ligands dppp and bpy<sup>21</sup>. Our results (Table 1, entries 5, 7–9) demonstrate that the two alternative catalysts, (dppp)NiBr<sub>2</sub> and (bpy)PdCl<sub>2</sub>, are poorly reactive and form primarily biphenyl (**4**) rather than cross-product (**3**). These findings are consistent with product arising from our proposed mechanism, and with symmetrical biaryl products arising 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 versus 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)



**Figure 1 | A general cross-Ullmann reaction catalysed by a combination of nickel and palladium.** **1**, 4-methoxyphenyltriflate; **2**, bromobenzene; **3**, the main cross-product, 4-methoxybiphenyl. Although a nickel(0/II) and palladium(0/II) cycle is depicted, alternative mechanisms are also possible, such as a nickel(I/III) cycle<sup>30</sup>. OTf, triflate; DMF, *N,N*-dimethylformamide (solvent).

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**Figure 2 | Selectivities of nickel and palladium catalysts.** **a**, The substrates and three possible products. **1**, 4-methoxyphenyl triflate (Ar-OTf); **2**, bromobenzene (Ph-Br); **3**, 4-methoxybiphenyl (Ph-Ar); **4**, biphenyl (Ph-Ph); **5**, 4,4'-dimethoxybiphenyl (Ar-Ar). **b**, (dppp)PdCl<sub>2</sub> and (bpy)NiBr<sub>2</sub> (10 mol% each); **c**, (bpy)NiBr<sub>2</sub> (10 mol%); and **d**, (dppp)PdCl<sub>2</sub> (10 mol%) were used along with approximately 0.5 mmol of each starting material. Concentrations of products were determined by gas chromatography analysis, corrected with an internal standard. The low mass balance in **c** is due to the formation of benzene (0.13 mmol) from hydrodehalogenation of substrate **2**.

or a tridentate ligand (2,2':6',2''-terpyridine) all formed reasonably selective multimetallic catalytic systems with (dppp)PdCl<sub>2</sub> (47–69% yield; Extended Data Fig. 1). By 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 might arise from improved desired reactivity with palladium or from diminished undesired reactivity with nickel. We also expected the ratio of nickel to palladium to be important to selectivity, considering the vastly different reactivities of the individual complexes, but we found that reactions using 2/1, 1/1, or 1/2 Pd/Ni ratios provided similar yields and selectivities (Table 1,

entries 11 and 12 versus entries 2 and 3; see also Supplementary Information, Chart S6). Together, these results suggest that the transmetallation step between the two catalysts is inherently selective.

In many cases, the ratio of substrates also had minimal effect on the final yield of product. In previously reported cross-Ullmann reactions catalysed by a single metal, two or more equivalents of one reactant were required to produce yields that were consistently greater than 60%, and ratios closer to 1/1 usually resulted in dramatically lower yields<sup>22</sup>. However, in our multimetallic cross-Ullmann reaction, an excess of aryl triflate did not dramatically alter the yield of cross-product, although in some cases an excess of aryl bromide did improve our results. For example, three equivalents of 3-bromothiophene improved the cross-coupled yield from 64% 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 one 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 substrate **2** was consumed at 24 hours, producing a 62% yield of product **3**. In the presence of KF, however, 91% conversion of **2** occurred in 11 hours with a 77% yield of **3** (Table 1, entry 2). The beneficial effect of KF seen here is consistent with observations of other cross-coupling reactions that are catalysed by nickel<sup>23</sup> and palladium<sup>24,25</sup>. In nickel catalysis, KF can reduce the amount of dimeric products formed; in palladium catalysis, KF can alter the oxidative addition selectivity for carbon–triflate bonds over carbon–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 in enhancing catalysis. Although optimization was performed in an inert-atmosphere glove box, reactions could be set up on the bench top 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), demonstrating that zinc itself is slow to react with the aryl electrophiles under these conditions and arguing against an intermediary role of arylzinc reagents in this cross-Ullmann reaction. (For further details on reaction condition optimization, see Supplementary Information, Charts S4–S9).

Applying these reaction conditions to a variety of aryl electrophiles demonstrates the generality of this method (Fig. 3). Both

**Table 1 | Conditions for the multimetal-catalysed cross-Ullmann reaction**

**1**

**2**

+

**w** mol% NiBr<sub>2</sub>(diglyme)

**x** mol% bpy

**y** mol% PdCl<sub>2</sub>

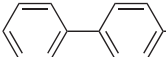
**z** mol% dppp

Zn

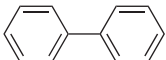
DMF

→

+

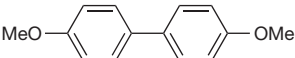


**3**



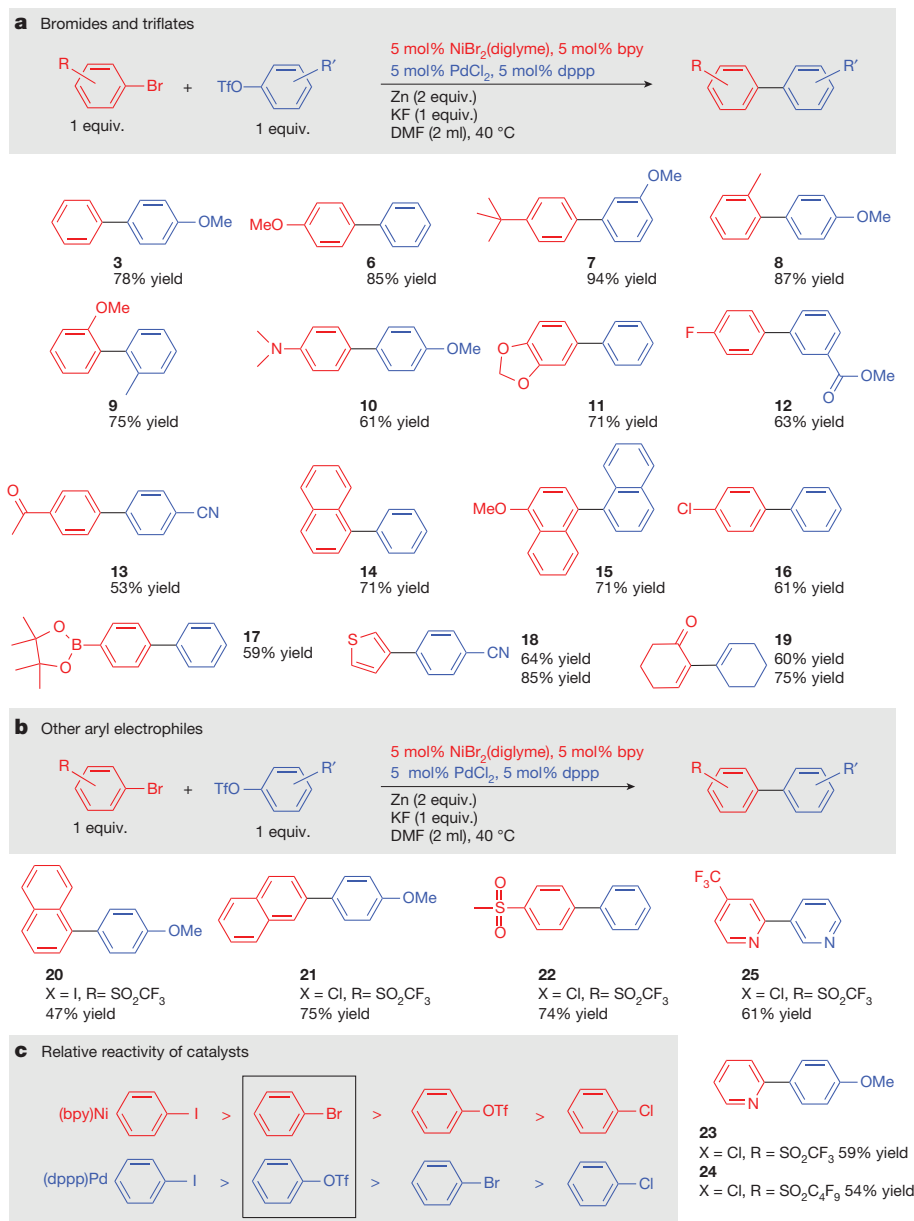
**4**

+



**5**

Entry	w	x	y	z	3*	4*	5*
1†	5	5	5	5	77	7	4
2	5	5	5	5	62	21	14
3	10	10	10	10	70	17	10
4	0	0	10	10	3	4	1
5	0	10	10	0	0	15	0
6	10	10	0	0	6	42	6
7	10	0	0	10	1	1	0
8	0	5	10	5	4	7	1
9	10	5	0	5	1	16	0
10‡	10	10	10	10	67	13	12
11	5	5	10	10	61	20	14
12	10	10	5	5	66	18	13
13§	10	10	10	10	65	12	10
14	0	0	0	0	0	0	0



**Figure 3 | Substrate scope.** **a**, Reactions of aryl and vinyl bromides with aryl and vinyl triflates. **b**, Reactions of other aryl electrophiles. **c**, Relative reactivity of the palladium and nickel catalysts. To generate products **18**, **23**, **24** and **25**, no KF was used. For product **18**, yield was increased from 64% to 85% when three (rather than one) equivalents of 3-bromothiophene were used. For product **19**, yield was increased from 60% to 75% when two equivalents of 2-bromocyclohexenone were used. The reaction to produce product **3** was replicated independently by three different researchers in our group using the procedure given in the Supplementary Information.

electronically similar and electronically disparate aryl bromides and triflates couple with good yields, but the coupling of a highly activated substrate with a deactivated substrate results in a low yield. Aryl substrates with *ortho*-substitution can be coupled (Fig. 3a, **8** and **14**), and the synthesis of 2,2'-disubstituted biaryls and 2,2'-binaphthyls can also be achieved (Fig. 3a, **9** and **15**). The tolerance of this multimetallic method to different functional groups—including amine, ether, ester, aldehyde, sulfone, and acetal groups—is promising. In addition, boronic acid ester containing 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 Supplementary Information, Charts S1–S3), we found several synthetically useful exceptions. While reactions with aryl iodides generally resulted in rapid formation of biaryl (see Supplementary Information, Chart S3; both palladium and nickel react with aryl iodides more quickly than with aryl triflates), naphthyl iodide could be coupled to form product **20** with 47% yield (Fig. 3b). Similarly, 2-naphthyl chloride could be coupled to form product **21** with 75% yield, suggesting that the nickel catalyst has a

strong affinity for naphthyl substrates that is not shared by the palladium catalyst<sup>26</sup>. The higher yield of the coupled product obtained when using naphthyl chloride rather than naphthyl iodides suggested 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 product **22**. By contrast, reactions of unactivated aryl chlorides formed large amounts of symmetric biaryl from the aryl triflate. Bromothiophene and pyridyl halides and triflates coupled with reasonable yield, including the synthesis of 2,3'-bipyridine (product **25**). Finally, the chemistry could be extended to the synthesis of diene (product **19**) from  $\alpha$ -bromocyclohexenone and cyclohexenyl triflate. To our knowledge, this is the first cross-Ullmann 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). We propose that, after the two arylmetal intermediates are formed by oxidative addition, a mechanism analogous to the 'persistent radical effect' allows for the observed cross-selectivity in transmetalation<sup>27,28</sup>. 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(Ar<sup>2</sup>) triflate is stable to further reaction with itself (Fig. 2d) and accumulates in solution. By contrast, (bpy)Ni(Ar<sup>1</sup>) bromide is a transient intermediate that quickly reacts with itself (Fig. 2c) or with (dppp)Pd(Ar<sup>2</sup>) triflate (Fig. 2b). Selectivity arises from the relative concentrations of these two complexes in solution, similar to what occurs during multimetallic reactions with group 11 organometallic intermediates, which are generally slow to homocouple<sup>11</sup>. Consistent with our observations (Table 1), the selectivity of this cross-Ullmann reaction is predicted to be independent of the amount of palladium and nickel added. Furthermore, our proposed mechanism suggests that the formation of (bpy)Ni(Ar<sup>1</sup>) bromide would limit the rate of product formation. Therefore, a higher concentration of nickel, but not of palladium, should result in a higher rate of product formation. We found this to be the case: reactions that were run with a higher concentration of nickel were faster (24% yield versus 7% yield at 4 hours for 25 mM versus 12.5 mM nickel), but the concentration of palladium did not affect the rate of product formation (11% yield versus 7% yield at 4 hours for 25 mM versus 12.5 mM palladium). We are now 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-Ullmann coupling, such as C–H arylation<sup>29</sup>.

**Online Content** Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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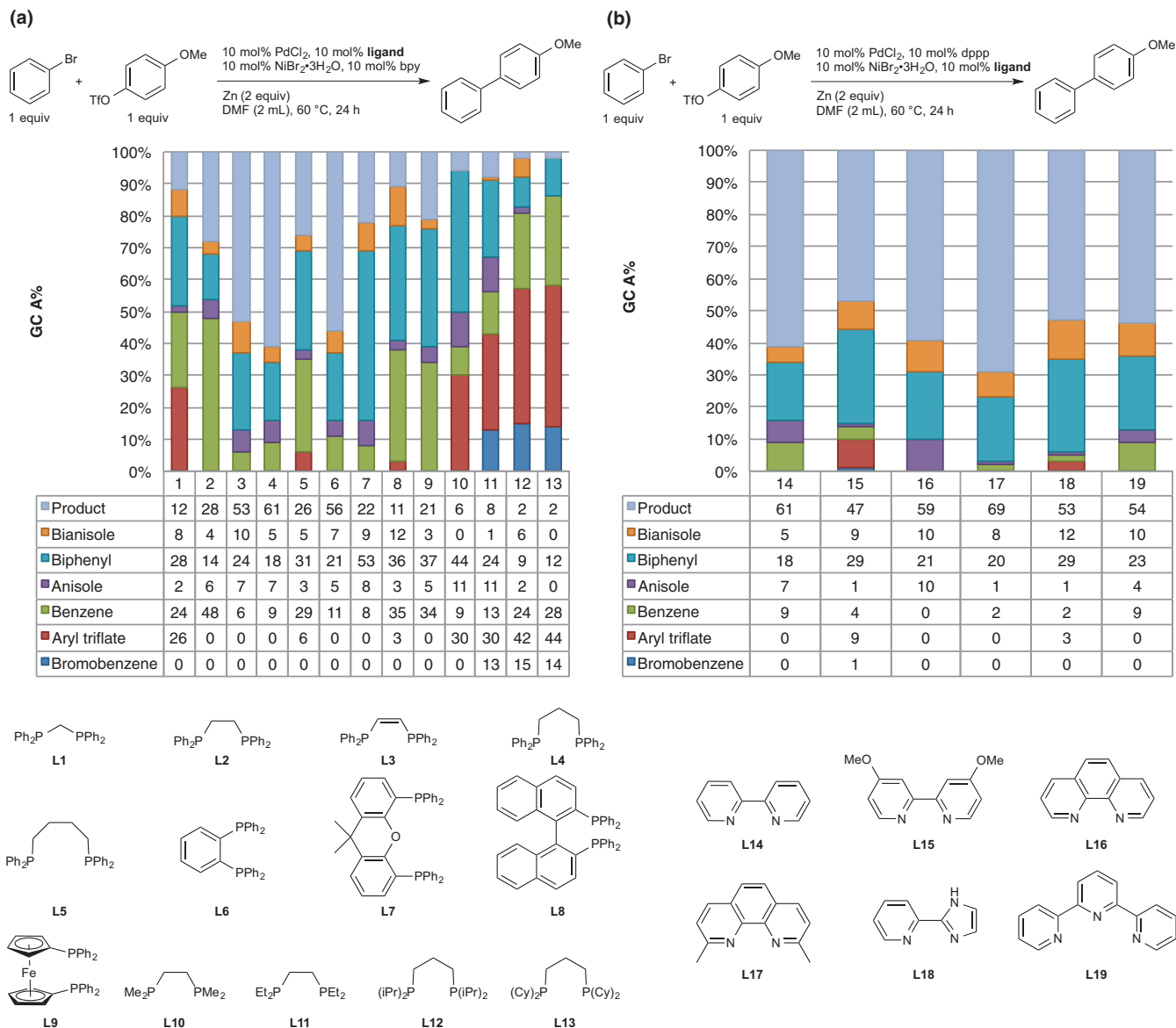
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**Supplementary Information** is available in the online version of the paper.

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**Author Contributions** D.J.W. conceived the idea. L.K.G.A. performed experiments and analysed 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.

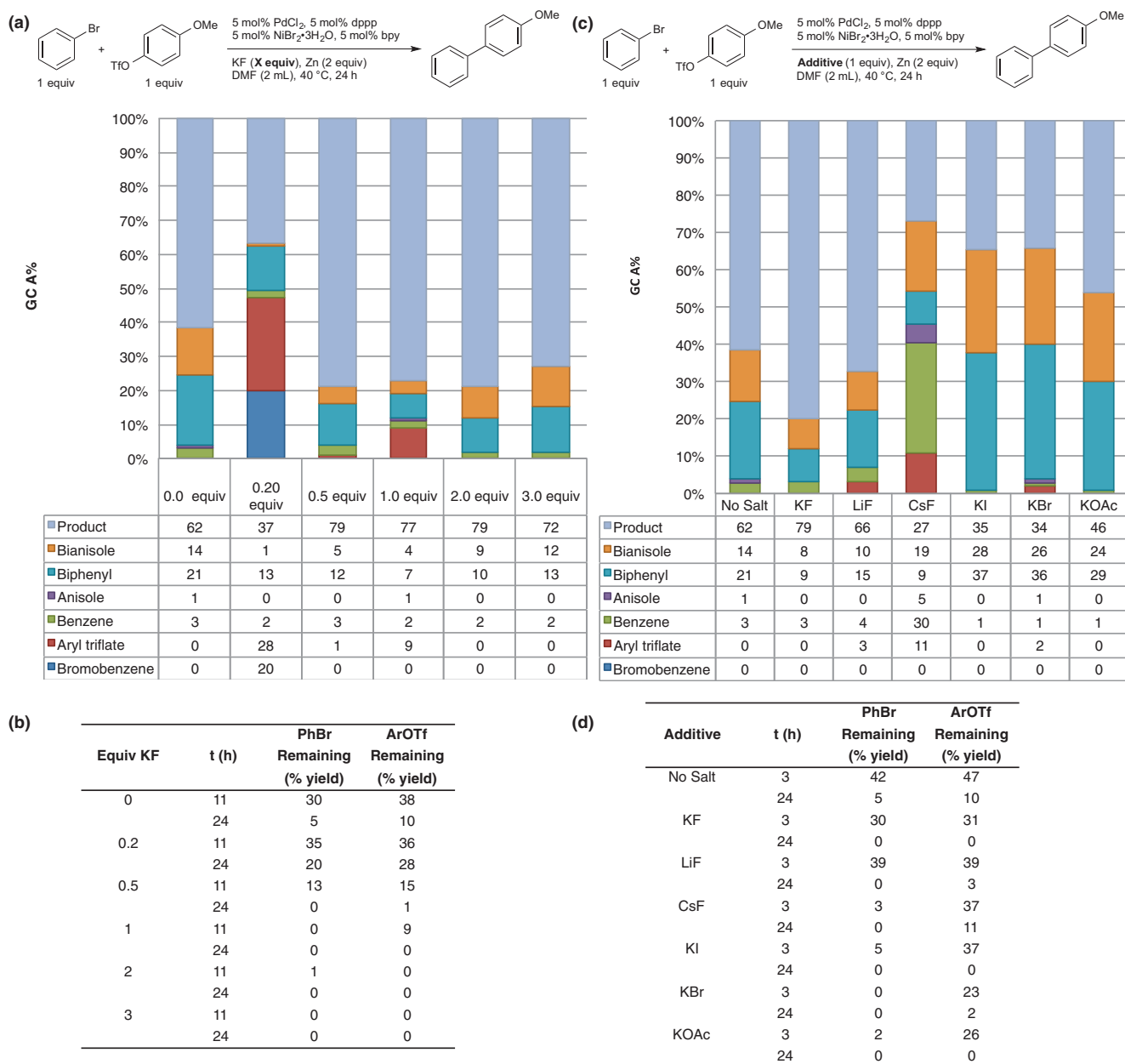
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**Extended Data Figure 1 | Varying ligands on the nickel and palladium catalysts.** Several different phosphine ligands for palladium (a) and amine ligands for nickel (b) were investigated. Although selectivity and yield of cross-product were sensitive to the identity of the phosphine ligand (a), a variety of

different amine ligands were effective (b). Reactions conducted with L15, L17, and L18 used 5 mol% catalyst loadings, were heated to 40 °C, and were monitored for 64 h. GC, gas chromatography; area per cent, uncorrected.





**Extended Data Figure 2 | The effect of potassium and fluoride salts on the selectivity of the multimetal-catalysed cross-Ullmann reaction.** The presence of potassium fluoride (KF) 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<sup>23,25</sup>. **a, b**, To investigate whether KF could be beneficial for the nickel and

palladium multimetallic system, we included various amounts of this additive under standard reaction conditions. The resulting selectivity and rate data are shown. **c, d**, Once the advantageous role of KF was confirmed, other potassium and fluoride salts were tested. The resulting selectivity and rate data are shown. 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 h to complete.)