C—O Selective Cross-Coupling of Chlorinated Phenol Derivatives

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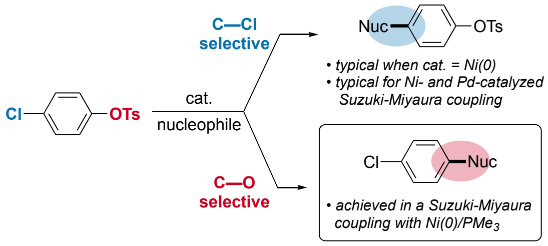

• typical when cat. = Ni(0)
• typical for Ni- and Pd-catalyzed Suzuki-Miyaura coupling

• achieved in a Suzuki-Miyaura coupling with Ni(0)/PMe$_3$

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Abstract Chemoselective cross-coupling of phenol derivatives is valuable for generating products that retain halides. Here we discuss recent developments in selective cross couplings of chloroaryl phenol derivatives, with a particular focus on reactions of chloroaryl tosylates. The first example of a C—O-selective Ni-catalyzed Suzuki-Miyaura coupling of chloroaryl tosylates is discussed in detail.

Key words Nickel, Cross-Coupling, Oxidative addition, Chemoselectivity, DFT

Introduction

Phenols represent an abundant, accessible precursor to electrophilic substrates for cross-coupling reactions. Although cross-couplings typically employ aryl halides as the electrophilic coupling partner, phenol derivatives as alternatives to aryl halides have a few notable advantages: (1) because the main source of phenols is fossil fuels, they are widely available and often inexpensive; (2) an emerging source of phenols is lignin biomass, which is considered to be sustainable and renewable;[1] (3) many phenol derivatives are robust enough to be carried through multiple synthetic steps; and (4) some phenol derivatives are able to direct other transformations (such as *ortho*-metalation, electrophilic aromatic substitution, and C—H functionalization)[2,3,4] prior to being used as the electrophile for a cross-coupling reaction. Particularly relevant to this paper, a fifth advantage of phenol derivatives is that their reactivity toward oxidative addition at low-valent metals is sometimes complementary to that of aryl halides. As such, one can envision selective cross-coupling through cleavage of the C—O bond of a halogenated phenol derivative, resulting in an elaborated product that retains an aryl halide (as a possible handle for subsequent transformations or because the halide is desired in the final product).

Because both C—O and C—halogen bonds can react in cross-coupling processes, it is valuable to develop *chemoselective* methods to achieve reaction of only the desired bond of halogenated phenol derivatives. Such methods can facilitate sequential or iterative cross-coupling steps. Alternatively, the ability to selectively react at a C—O bond of a chlorinated phenol derivative allows for synthesis of a final product that contains an aryl chloride functionality. Many such products are pharmacologically relevant.[5,6] For reference, approximately 250 chlorine-containing drug molecules are FDA-approved.[7] Figure 1 depicts examples of medically relevant structures that contain aryl chlorides in addition to bond(s) that could conceivably be formed through cross-coupling.[8]

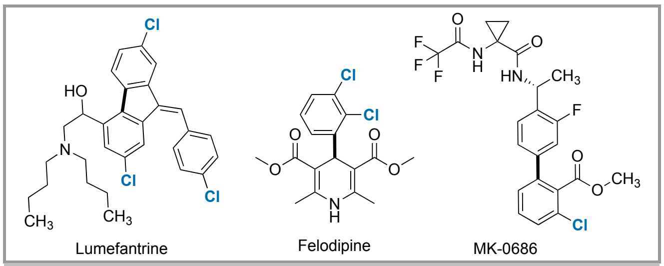


Figure 1 Examples of pharmacologically relevant molecules containing both aryl–chloride bonds and bonds that could be formed by cross-coupling.

Selective cross-coupling of C—O bonds in the presence of aryl chlorides (and, for some types of coupling, aryl bromides)[9] has been achieved under palladium catalysis when the oxygen-containing leaving group is triflate.[10,11,12] However, triflates are notoriously challenging to carry through other synthetic steps due to facile hydrolysis. As such, it is desirable to develop methods for selective cross-coupling of other less-labile chlorinated phenol derivatives. The best-studied non-triflate C—O electrophile for cross-coupling is perhaps tosylate. Until a recent publication of ours,[13] chemoselective cross coupling of aryl tosylates in the presence of chlorides had not been systematically explored, although several isolated examples are scattered in the literature.[12]

In many reports, competition between an aryl tosylate and an aryl chloride leads to preferential cross-coupling at chloride (Table 1). These chloride-selective reactions include Suzuki couplings,[3,14] direct arylations,[15] decarboxylative couplings,[16] and a Hiyama coupling.[17] However, there are also several instances of tosylate-selective reactions including carbonylative Suzuki couplings,[18] Kumada,[19] Hiyama,[20] and Sonogashira couplings,[21] a decarboxylative cross-coupling,[22] a cross-coupling with umpolung aldehydes,[23] a reductive homocoupling[24] and a cross-electrophile coupling,[25] an amination,[26] a Mizoroki-Heck coupling,[27] and an alkoxycarbonylation.[28] Nearly all reported cross-couplings of chloroaryl tosylates involve palladium catalysts.[29,30,31] Careful review of the literature suggests a trend in ligand effects on the chemoselectivity of Pd-catalyzed cross couplings of chloroaryl tosylates. In particular, all of the reported chloride-selective examples employ bulky monodentate ligands (Table 1). In contrast, the vast majority of instances of tosylate-selective reactions involve bidentate ligands (Table 2). Although this trend has not been rigorously evaluated, it suggests that the chloride vs. tosylate chemoselectivity with palladium mirrors that of chloride vs. triflate selectivity.[12] Monoligated palladium (promoted by bulky ligands) has been shown to favor oxidative addition at chloride over triflate, while bisligated palladium (promoted by smaller or bidentate ligands) displays the opposite selectivity.[10b]

Table 1 Chloride-selective Pd-catalyzed cross-coupling reactions of chloroaryl tosylates.

reference	reaction type	E^+	nuc.	ligand
Buchwald 2003 [3]	Suzuki-Miyaura	**1**	**4**	**14**
Wu 2007 [14a]	Suzuki-Miyaura	**1**	**5**	**15**
Ackermann 2010 [14b]	Suzuki-Miyaura	**1**	**4**	**16**
Shao 2012 [14c]	Suzuki-Miyaura	**1**	**6**	**17**
Zou 2014 [14d]	Suzuki-Miyaura[a]	**1,2**	**7**	**18**
Liu 2011 [16a]	Decarboxylative coupling	**1**	**8**	**19**
Liu 2011 [16b]	Decarboxylative coupling	**1**	**9**	**14**
Buchwald 2007 [15a]	Direct arylation	**3**	**10**	**19**
Ackermann 2008 [15b]	Direct arylation	**1**	**11**	**20**
Kalyani 2017 [15c]	Direct arylation	**3**	**12**	**14**
Wu 2008 [17]	Hiyama	**1**	**13**	**14**

[a] Reaction catalyzed by Ni instead of Pd.

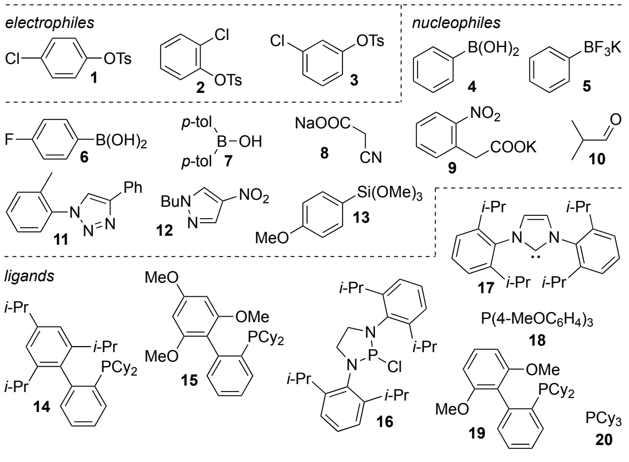
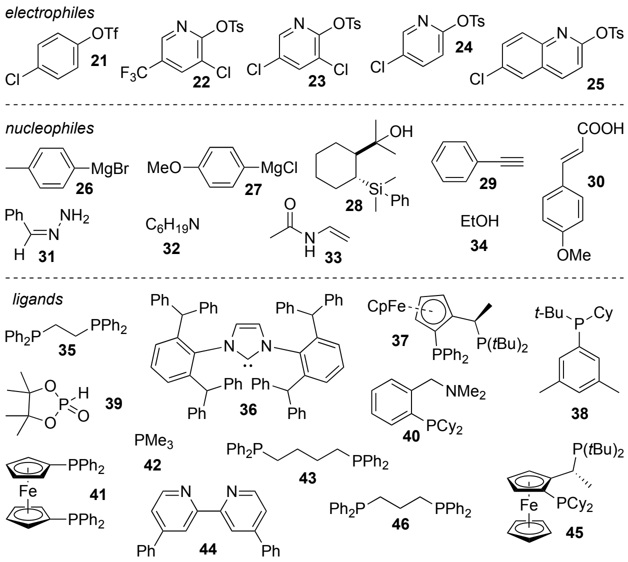


Table 2 Tosylate-selective Pd-catalyzed cross-coupling reactions of chloroaryl tosylates.

reference	reaction type	E^+	nuc.	ligand
Chang 2016 [18a]	Suzuki-Miyaura	**1**	**4**	**35**
Lu 2015 [18a]	Suzuki-Miyaura	**1**	**4**	**36**
Hartwig 2005 [19a]	Kumada	**1**	**26**	**37**
Li 2019 [19c]	Kumada[a]	**1**	**26**	**38**
Ackermann 2006 [19b]	Kumada	**1**	**27**	**39**
Nakao 2016 [20]	Hiyama	**1**	**28**	**40**
Shen 2014 [21]	Sonogashira	**1**	**29**	**36**
Zhang 2019 [22]	Decarboxylative coupling[b]	**1**	**30**	**41**
Li 2018 [23]	Umpolung aldehyde coupling[a]	**1**	**31**	**42**
Liu 2017 [24]	Reductive homocoupling	**1,2**	--	**41**
Weix 2020 [25]	Cross-electrophile coupling[a]	**1,21**	--	**43,44**
Hartwig 2008 [26]	Amination	**1,3**	**32**	**45**
Skrydstrup 2009 [27]	Mizoroki-Heck	**22-25**	**33**	**41**
Sugi 1998 [28]	Alkoxycarbonylation	**1**	**34**	**46**

[a] Reaction catalyzed by Ni instead of Pd. [b]Copper was used as a co-catalyst.



Although palladium has demonstrated success in catalyzing cross-couplings of aryl tosylates,[12,32] nickel has developed a reputation for reacting more easily with strong C—O bonds due to its smaller size and increased nucleophilicity.[33] Despite a flurry of reports on Ni-catalyzed cross-couplings of phenol derivatives in the last ~20 years, nearly none of these methods allowed for selective cleavage of a C—O bond in the presence of aryl-halogen bonds.[33,34,35] As such, we have been interested in systematically exploring the influence of ligands on nickel's chemoselectivity, with a particular interest in achieving C—O-selective Suzuki coupling of chlorinated phenol derivatives.

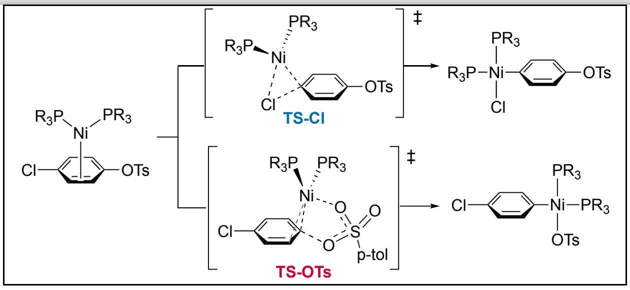
This selectivity had not been previously achieved for Suzuki couplings of non-triflate phenol derivatives using nickel catalysts. We recently published a paper that describes the first Ni-catalyzed Suzuki cross-coupling of phenol derivatives (mostly aryl tosylates) in the presence of aryl chloride bonds.[13] Interestingly, our mechanistic studies suggest that the ligand effects on the selectivity of oxidative addition at nickel differ from palladium. Whereas circumstantial literature evidence indicates that palladium's preference for tosylate versus chloride depends on its ligation state (coordination number),[12] this does not seem to be the case for nickel. Instead, bisligated nickel(0) can favor reaction at either chloride or tosylate depending on the sterics and electronics of its ligands.[13] Herein, we give an overview of our recent work in this area and include expanded discussions about the relationship between computation and experiment as well as about the effect of reaction conditions on the catalytic cross-coupling.

DFT Studies on Oxidative Addition at Ni(0)

We began by conducting density functional theory (DFT) calculations on the oxidative addition of a chloroaryl tosylate at Ni(0) to explore the effect of the ligand on this step.[36] To simplify the calculations, PMe_3 was used as a model phosphine: we rationalized that this would be a reasonable simple model for more complex trialkyl phosphines such as PCy_3. Two PMe_3 ligands were included because previous DFT studies on nickel suggest that bis-phosphine ligation is likely favored during oxidative addition (even for phosphines as bulky as PCy_3) when dispersion is included.[37]

To our surprise—and naively, to our dismay—the initial calculations contradicted previous experimental results in the literature on nickel-catalyzed cross-couplings of chloroaryl tosylates.[34] Whereas prior literature reported poor selectivity or reactivity that strongly favored C—Cl cleavage, our calculations using the "model ligand" PMe_3 predicted that oxidative addition of C—OTs was significantly easier than C—Cl (Table 3, entry 1). At this level of theory, the difference in activation free energies between the transition structures for tosylate vs. chloride oxidative addition (3.0 kcal/mol) suggests a ~160:1 selectivity for reaction of C—OTs. We had anticipated that PMe_3 should be a reasonable model for the commonly employed trialkylphosphine PCy_3, but a reported example of Ni/PCy_3-catalyzed Suzuki cross-coupling gave a meager 2:1 selectivity (for reaction at OTs:Cl) along with poor yields.[34a]

Table 3 Comparison of calculated activation free energies for oxidative addition of C—Cl or C—OTs at NiL_2.[a]

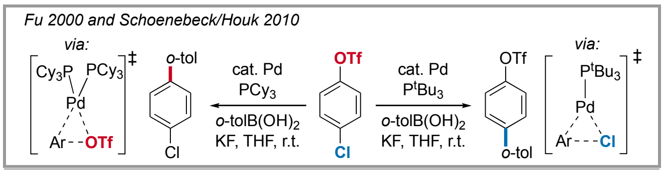


entry	PR_3	TS-Cl $\Delta G^‡$	TS-OTs $\Delta G^‡$	$\Delta\Delta G^‡_{OTs—Cl}$	selectivity OTs : Cl[b]
1	PMe_3	16.1	13.1	-3.0	160 : 1
2	PCy_3	10.2	9.0	-1.2	7 : 1
3	PPh_3	12.6	14.6	2.0	1 : 30

[a] Activation free energies given in kcal/mol and measured from the preceding Ni-arene π-complex. The geometry of TS-OTs is illustrated as the lowest energy geometry when PR_3 = PMe_3, but differs slightly for the other ligands. [b] Estimated selectivity for reaction at tosylate : chloride based on $\Delta\Delta G^‡$ (calculated with the Eyring equation at 298 K).

It seemed plausible that our DFT method was merely a poor choice for obtaining accurate energies for this system; alternatively, PMe_3 could be a poor model for PCy_3. To begin to evaluate these possibilities, we switched to running calculations in which we employed the full ligand PCy_3 instead of PMe_3 (Table 3, entry 2). Interestingly, the predictions with PCy_3 were fairly consistent with experimental results: these calculations predicted a ~7:1 OTs:Cl selectivity based on $\Delta\Delta G^‡$. (Note: the temperature specified for the calculations was 25 ºC, although the experimental results in the literature[34a] were obtained at 130 ºC.) Furthermore, calculations using PPh_3 predicted about a 1:30 OTs:Cl selectivity (Table 3, entry 3), consistent with the high chloride-selectivity reported experimentally for Ni-catalyzed Suzuki cross couplings using arylphosphines.[34f] We also repeated our calculations with several other functionals.[13] For the most part, these other methods all consistently indicated that PMe_3 should give better selectivity than PCy_3 for OTs, whereas PPh_3 should favor reaction at chloride.

The mechanistic understanding of other examples of chemoselective cross-couplings in the literature involves differences in catalyst ligation state as shown in Scheme 1 (i.e., different chemoselectivity is obtained depending on whether the catalyst is mono- or bisligated during oxidative addition).[10,38] Consistent with this, reported instances of chemoselective *palladium*-catalyzed cross-couplings of chloroaryl tosylates display a trend in which bulky monodentate ligands (which can promote monoligated Pd) favor reaction at chloride[3,14a-c] while bidentate ligands promote reaction at tosylate.[18] However, this trend does not seem to hold for the predicted selectivity of oxidative addition at Ni(0). Furthermore, calculations suggest that bisligated oxidative addition transition structures are lower energy than monoligated ones for all three phosphines PPh_3, PCy_3, and PMe_3 (even though these provide very different selectivities).[37]



Scheme 1 Previous experimental and computational studies into chemodivergent oxidative addition at Pd(0), controlled by the metal's ligation state.

The high tosylate-selectivity of PMe_3 compared to the chloride-selectivity of PPh_3 could relate to the greater electron donating character of PMe_3.[39] Nickel is calculated to be more negatively charged when coordinated to PMe_3 than PPh_3 (Figure 2). A more electron-rich nickel species should have a stronger attractive interaction with the carbon attached to OTs compared to the carbon attached to Cl (the carbon of C—OTs has a larger positive charge). Indeed, a distortion-interaction analysis supports this hypothesis.[13] However, electronics do not easily explain why PCy_3 provides poor selectivity for oxidative addition at tosylate. If anything, nickel may be *more* electron-rich when supported by PCy_3 compared to PMe_3 (Figure 2).

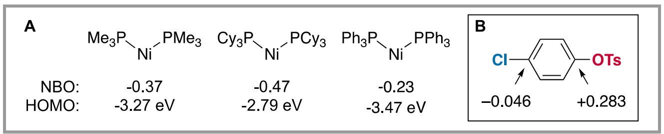


Figure 2 (A) Calculated NBO charges and HOMO energy at nickel for NiL_2 complexes. (B) Calculated NBO charges at the electrophilic carbons of 4-chlorophenyl tosylate.

Instead, the critical difference between PMe_3 and bulkier alkyl phosphines like PCy_3 appears to be sterics. Oxidative addition at C—O can take place through one of two mechanisms: either a 'nucleophilic displacement' mechanism in which there is no direct interaction between nickel and tosylate or a 5-centered transition structure in which a sulfonyl oxygen interacts with nickel (Figure 3). For PMe_3, the 5-centered transition structure is lower in energy. However, that mechanism is destabilized with PCy_3 because the sulfonyl oxygen cannot get as close to nickel due to the phosphine ligand's steric hindrance. As such, both the electronics and the small size of PMe_3 contribute to its unusual tosylate selectivity.

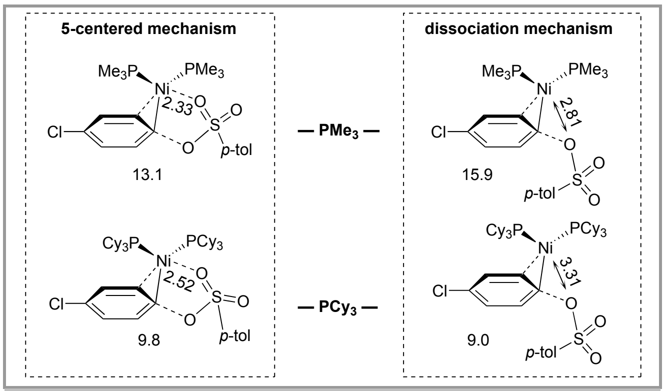
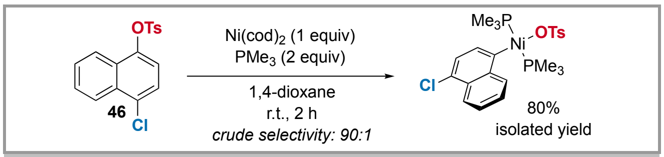


Figure 3 Transition structure geometries for oxidative addition at C—OTs. The distance between Ni and the closest sulfonyl oxygen is labeled (units are Ångstroms). Activation free energies are given in kcal/mol.

Stoichiometric Oxidative Addition Studies

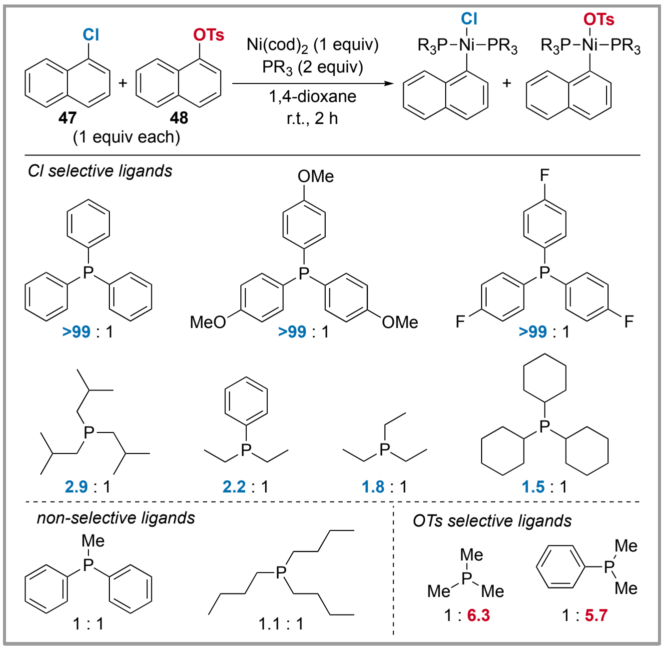
Based on these results, we decided to evaluate the use of PMe_3 in the lab. We had been resistant to exploring this ligand experimentally because it is a volatile, pungent, air-sensitive compound.[40] It has a tendency to spontaneously combust if exposed to air, yet it is a potent glovebox catalyst poison. Unsurprisingly, it is not a popular ligand in cross-coupling chemistry. To our knowledge, it had never been tested in Ni-catalyzed Suzuki couplings.[41,42] Nevertheless, the calculations clearly suggested that this ligand might enable the desired tosylate-selective cross coupling.[13] Furthermore, concurrent with our research, an isolated example of tosylate selectivity in a Ni/PMe_3 cross-coupling involving umpolung aldehydes was reported.[23]

Stoichiometric oxidative addition studies using a combination of $Ni(cod)_2$ and PMe_3 were performed. These reactions were analyzed by ^{31}P NMR. We conducted both intramolecular (Scheme 2) and intermolecular competitions (Scheme 3) between aryl chlorides and tosylates. Oxidative addition was determined to be complete within two hours, at which point a ^{31}P NMR spectrum was obtained. Gratifyingly, the experimental results were consistent with the DFT prediction that PMe_3 promotes preferential reaction at tosylate rather than chloride, with particularly high selectivity in the intramolecular competition using substrate **46** (Scheme 2). The selectivity in the reaction of **46** is about 90:1 in favor of tosylate oxidative addition. This selectivity is remarkably similar to the calculated selectivity using substrate **1**: a 90:1 selectivity corresponds to a $\Delta\Delta G^‡$ value of about 2.7 kcal/mol at room temperature, which is similar to the calculated $\Delta\Delta G^‡$ value of 3.0 kcal/mol.



Scheme 2. Stoichiometric oxidative addition in an intramolecular competition between Cl and OTs displays a strong preference for reaction at the C—OTs bond.

As expected based on computations and prior catalytic reports, the use of PCy_3 and PPh_3 led to poor selectivity and high selectivity for reaction at chloride, respectively, in intermolecular competitions between **47** and **48** (Scheme 3). A number of additional mono and bidentate phosphine ligands were also evaluated in this competition reaction.[13] In general, triarylphosphines promote reaction at chloride, while most alkyl phosphines give poor selectivity, typically slightly favoring reaction at chloride. Only the very smallest phosphines (bearing at least two methyl substituents) promote preferential reaction at tosylate: dimethylphenyl phosphine was the only ligand identified besides PMe_3 that favors oxidative addition at tosylate in the intermolecular competition (Scheme 3).

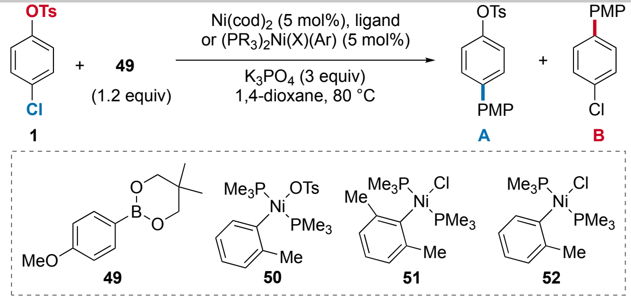


Scheme 3. The effect of phosphine ligands on the selectivity between C—Cl and C—OTs bonds during stoichiometric oxidative addition at Ni(0).

Development of a Tosylate-Selective Suzuki Coupling

Based on our computational and stoichiometric results, we were able to develop a catalytic system for tosylate-selective Suzuki cross-coupling of chloroaryl tosylates. The reaction was optimized with a combination of $Ni(cod)_2$ and PMe_3 or with a Ni(II) precatalyst (Table 4). The use of a precatalyst is appealing because it obviates the requirement for manipulating PMe_3 during the reaction setup. These precatalysts typically afforded better reproducibility than the $Ni(cod)_2$/PMe_3 combination, presumably due to difficulties in precisely measuring small quantities of free PMe_3. One of the precatalysts (**51**) is moderately air-stable. Our optimization studies reveal a few interesting trends.[13] First, the ratio of Ni:P is fairly important to success (Table 4, entries 1-4). Approximately a 1:2 ratio is ideal, and much lower or higher ratios lead to both lower yields and worse selectivity. Second, evaluation of a variety of phosphine ligands provides results that are consistent with the stoichiometric oxidative addition studies. For example, $PPhMe_2$ gives similar selectivity to PMe_3, while other alkyl phosphines give product ratios closer to 1:1 (entries 6–8). Another methylphosphine was identified that provides high tosylate selectivity [the bidentate ligand 1,2-bis(dimethylphosphino)ethane (dmpe), entry 9]; however the yield is quite poor. Third, the reaction yield is improved by the addition of a very small quantity of hydroxide or water (the latter gives better reproducibility, presumably due to better measurement accuracy, entries 10–13). Like palladium, nickel is believed to undergo transmetalation with organoboron reagents through a mechanism involving a hydroxy group that bridges between Ni and B.[43] Larger amounts of hydroxide are detrimental, presumably due to stabilization of off-cycle Ni-hydroxide dimers (compare entries 15-20).[43]

Table 4. Selected results of optimization trials for the tosylate-selective Suzuki-Miyaura cross-coupling.[a]

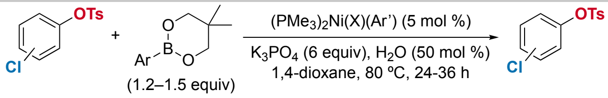


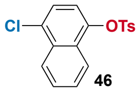
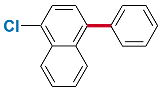
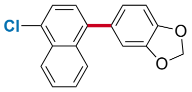
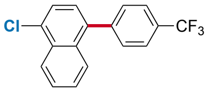
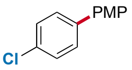
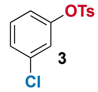
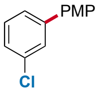
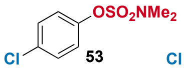
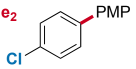
entry	additive (mol %)	[Ni]	L (mol%)	A (%)[b]	B (%)[b]
1[c]	--	$Ni(cod)_2$	PMe_3 (9)	6	62
2[c]	--	$Ni(cod)_2$	PMe_3 (10)	4	54
3[c]	--	$Ni(cod)_2$	PMe_3 (6)	7	39
4[c]	--	$Ni(cod)_2$	PMe_3 (15)	10	38
5	--	$Ni(cod)_2$	$PPhMe_2$ (9)	6	69
6	--	$Ni(cod)_2$	$PPhEt_2$ (9)	14	40
7	--	$Ni(cod)_2$	PPh_2Me (9)	32	17
8	--	$Ni(cod)_2$	PCy_3 (9)	4	4
9	--	$Ni(cod)_2$	dmpe (4.5)	1	15
10	--	**50**	--	3	60
11	H_2O (10)	**50**	--	3	67
12	H_2O (30)	**50**	--	3	75
13	H_2O (50)	**50**	--	2	88
14[d]	H_2O (50)	**51**	--	3	61
15	KOH (10)	**52**	--	2	66
16	KOH (20)	**52**	--	2	80
17	KOH (50)	**52**	--	2	55
18	KOH (100)	**52**	--	3	73
19	KOH (200)	**52**	--	1	39
20	KOH (300)	**52**	--	2	26

[a] PMP = p-methoxyphenyl. dmpe = 1,2-bis(dimethylphosphino)ethane. [b] Calibrated GC yield. [c] Boronic acid analog of 49 was used instead of the boronic ester. [d] Reaction was set up on the benchtop.

Under the optimized conditions (Table 4, entry 13), a variety of chloroaryl tosylates and arylboronic esters were combined to give chloride-containing cross-coupled products (Table 5).[13] Good selectivity for reaction at C—O was also obtained using a chloroaryl sulfamate (entry 6) and a triflate.[13] Expansion to a more diverse scope of substrates, such as heteroaromatic compounds, is likely to require a better understanding of how to inhibit catalyst decomposition.

Table 5. Abbreviated scope of the C—O-selective Suzuki coupling.[a]



entry	substrate	major product	% GC yield (selectivity)[b]	isolated yield (%)
1[c]	 **46**		80 (>50:1)	72
2	**46**		86 (>50:1)	75
3[c]	**46**		87 (>50:1)	64
4[d]	**1**		88 (44:1)	72
5	 **3**		89 (30:1)	67
6[d]	 **53**		55 (8:1)	39

[a] PMP = p-methoxyphenyl. Entries 1-3: catalyst = **50**; entries 4 and 6: catalyst = $(PMe_3)_2Ni(OTs)$(1-naphthyl); entry 5: catalyst = **52**. Diarylated products observed in ≤10% estimated yield by GC unless otherwise noted. [b] Calibrated GC yield. Estimated selectivity based on calibrated GC yield of major product and uncalibrated GC yield of minor product. [c] ≤20% yield of the diarylated product detected by crude GC. [d] Selectivity based on calibrated GC yields of both the major and minor products.

Conclusion and Outlook

Our work in the area of chemoselective cross-coupling focuses on (a) chemodivergent couplings—the ability to select which functional group reacts depending on the conditions; (b) achieving chemoselectivity for the conventionally less reactive group; and (c) developing a mechanistic understanding of the origins of and strategies to control chemoselectivity. Our recently published nickel-catalyzed Suzuki-Miyaura coupling[13] reflects the latter two focus areas. With the exception of labile triflates, selective cross-coupling of phenol-derived electrophiles in the presence of aryl halides had not been systematically studied prior to our recent work. Although nickel is particularly adept at reacting with non-triflate C—O bonds, Ni-catalyzed cross-couplings of phenol derivatives are typically limited by their intolerance of aryl chlorides. We have developed an approach to selectively react at C—OTs bonds of chloroaryl tosylates in a Ni-catalyzed Suzuki-Miyaura cross-coupling. To the best of our knowledge, this work represents the first cross-coupling reaction developed to be intentionally selective for a non-triflate electrophile in the presence of an aryl halide. DFT studies accurately predicted the ligand trend for selectivity of oxidative addition at Ni(0), where preference for tosylate is in the order PMe_3 > PCy_3 > PPh_3. This trend was confirmed through stoichiometric studies. Tri- and dimethyl phosphines (PMe_3 and $PPhMe_2$) appear to be unique in their ability to promote selective reaction at tosylate in this system.[44] Proof of concept for a tosylate-selective Suzuki reaction catalyzed by Ni/PMe_3 was demonstrated with a variety of boronic ester coupling partners and aryl chlorotosylates. Unlike other literature examples of chemoselective cross-couplings, selectivity in this system does not appear to rely on ligation state. Instead, selectivity is controlled by both ligand steric and electronic factors. Further advancements in the area of Ni-catalyzed chemodivergent cross-coupling will be facilitated by developing better mechanistic understandings of catalyst inactivation pathways.

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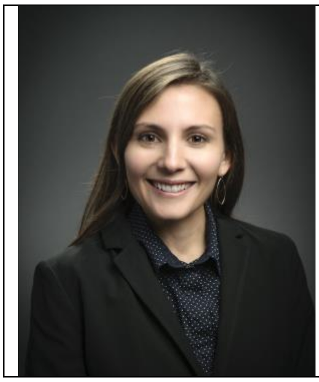
Biosketches



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