Chemodivergence Between Electrophiles in Cross-Coupling Reactions

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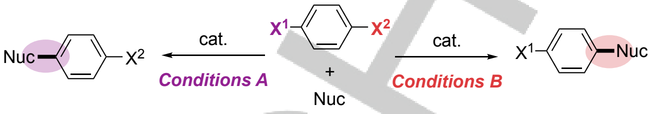
Abstract: Chemodivergent cross-couplings are those in which either one of two (or more) potentially reactive functional groups can be made to react based on choice of conditions. In particular, this review focuses on cross-couplings involving two different (pseudo)halides that can compete for the role of the electrophilic coupling partner. The discussion is primarily organized by pairs of electrophiles including chloride vs. triflate, bromide vs. triflate, chloride vs. tosylate, and halide vs. halide. Some common themes emerge regarding the origin of selectivity control. These include catalyst ligation state and solvent polarity or coordinating ability. However, in many cases, further systematic studies will be necessary to deconvolute the influences of metal identity, ligand, solvent, additives, nucleophilic coupling partner, and other factors on chemoselectivity.

Introduction and Scope

Catalytic cross-coupling reactions have been the subject of extensive research for half a century. This strategy for forming C—C and C—heteroatom bonds has proven instrumental to the synthesis of pharmaceuticals, agrochemicals, organic materials, natural products, and other classes of organic compounds. In recognition of the importance of this reaction class, the 2010 Nobel Prize was awarded to Suzuki, Negishi, and Heck for their work on C—C bond-forming cross-couplings.[1] Cross-coupling reactions typically involve an organo(pseudo)halide electrophile that couples with a nucleophilic partner such as an organometallic reagent, an alkene, or a heteroatom. The most common transition metal catalysts are palladium and nickel, and their reactivity is frequently modulated by phosphines, *N*-heterocyclic carbenes, or other ancillary ligands.

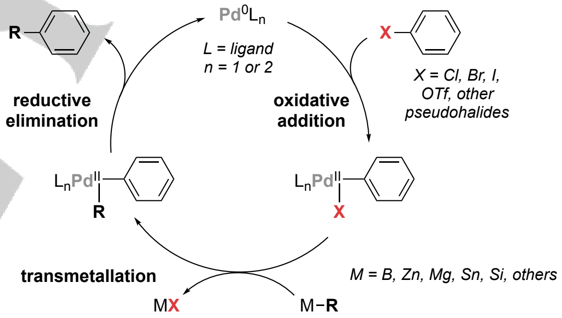
The presence of two or more (pseudo)halides on the substrates introduces selectivity as a critical challenge. If selectivity can be controlled, then both (pseudo)halides can be utilized effectively in iterative or sequential cross-coupling reactions to construct increasingly complex molecules.[2] Alternatively, it can be desirable to achieve reaction of only one (pseudo)halide, leaving the other(s) intact in a final product. For example, chloride is a common substituent in pharmacologically relevant products,[3,4] so methods that enable selective reaction at a different (pseudo)halide without touching an aryl chloride can be useful.

In this review, we focus on the emerging topic of chemodivergence in cross-coupling reactions. Here, we define chemodivergent couplings as those in which two or more potentially reactive (pseudo)halides are present on the substrate, but selectivity between these functional groups can be controlled through some aspect of the reaction conditions (Scheme 1). We limit our discussion to *chemo*divergent cross-couplings (two *different* (pseudo)halides) as opposed to regio- or site-divergent couplings (two identical (pseudo)halides). An excellent review on regioselective cross-couplings of substrates bearing two or more identical halides was recently published by Spivey et al.[5] Chemodivergence between nucleophilic coupling partners[6] or different bonds of a single functional group[7] is also possible but will not be explored here. Numerous general[8] and specialized[9] reviews have also already covered many other aspects of cross-coupling reactions.



Scheme 1. Chemodivergent cross-couplings.

Cross-coupling reactions involving organometallic nucleophiles typically proceed through the general catalytic cycle in Scheme 2. Examples include the Suzuki, Negishi, Kumada, Stille, and Hiyama reactions. Other cross-couplings, such as the Heck, Sonogashira, and Buchwald-Hartwig reactions, have catalytic mechanisms that diverge from this general cycle after oxidative addition takes place. As such, to a first approximation, traditional cross-coupling reactions involve oxidative addition as the first step. During a typical oxidative addition, the metal inserts into a C—(pseudo)halide bond with concomitant oxidation of the catalyst by 2 electrons.[10] Because of the direction of electron flow, oxidative addition is typically accelerated by more electron-deficient substrates or a more electron-rich metal. In known examples of chemodivergent cross-couplings, the oxidative addition step is most likely selectivity-determining.



Scheme 2. General catalytic cycle for cross-couplings involving organometallic reagents depicted with Pd^0 as the catalyst.

Strategies for controlling cross-coupling chemoselectivity include catalyst, solvent, additive, and substrate control. As will be discussed, the most common way that catalysts influence selectivity is through choice of ancillary ligand. In a few examples, different metals can also effect divergent selectivity. Solvents and additives can often influence chemoselectivity but, from a mechanistic perspective, their effect can sometimes be attributed to catalyst speciation. As such, the effect of solvents and additives might also be categorized as catalyst control. Finally, substrate steric or electronic biases can (de)activate certain sites and thereby enable atypical chemoselectivity.

In this minireview, we begin our discussion with early examples of cross-couplings that established conventional reactivity patterns of (pseudo)halides and demonstrated that reaction conditions can dramatically affect chemoselectivity. Subsequent examples of chemodivergent couplings are organized by pairs of competing electrophiles. Particular attention is given to studies that present mechanistic insight into selectivity.

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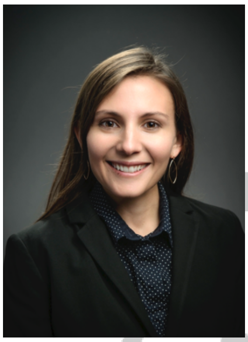
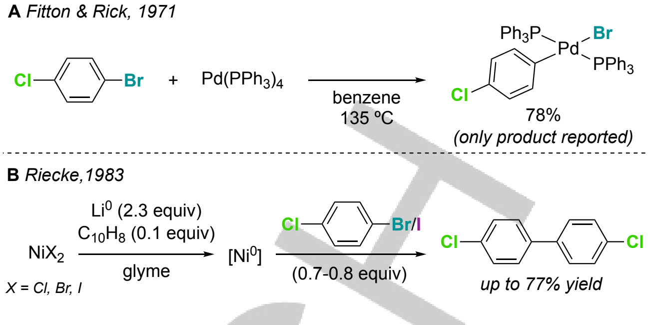


Early Chemoselectivity Studies

The first examples of chemodivergent cross-couplings stemmed from early efforts to establish the order of reactivity of aryl halides with Pd(0). In 1971, Fitton and Rick showed that halobenzenes undergo oxidative addition into $Pd(PPh_3)_4$ with the reactivity order PhI > PhBr > PhCl.[11] This trend mirrors C—X bond strength, whereby the weakest C—X bond is the quickest to break. Based on this trend, a natural starting point for exploring chemoselectivity was to attempt oxidative addition of a more reactive halide while leaving a less reactive one untouched. Indeed, Fitton and Rick can be credited with the first example of chemoselective oxidative addition. They reported that *p*-bromochlorobenzene reacts with $Pd(PPh_3)_4$ to form (4-chlorophenyl)$PdBr(PPh_3)_2$ (Scheme 3A).

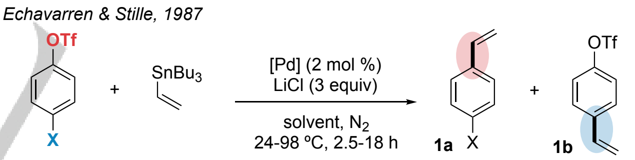
In 1983, Riecke reported the first chemoselective metal-mediated coupling reaction.[12] *p*-Bromo and *p*-iodochlorobenzene were shown to undergo homocoupling in the presence of activated nickel powder to afford 4,4′-dichlorobiphenyl (Scheme 3B). Coupling occurs selectively through cleavage of the weaker C—X bond (Br or I) without affecting the stronger C—Cl bond. Because aryl bromides were found to require longer reaction times than iodides, this work also confirmed that nickel follows the same reactivity pattern as palladium, where ArI > ArBr > ArCl.



Scheme 3. (A) First example of chemoselective oxidative addition at Pd(0).[11] (B) First chemoselective metal-mediated coupling reaction.[12]

As metal catalyzed coupling reactions grew in popularity, the behavior of trifluoromethylsulfonate (triflate)—a quintessential "pseudohalide"—became a question of interest. The relative reactivity of aryl triflates versus bromides and iodides was unknown until 1987, when Echavarren and Stille investigated the Pd-catalyzed cross-coupling of bromo- and iodophenyl triflate with a vinylstannane (Table 1).[13] They discovered what appears to be the first example of chemo*divergent* cross-coupling. In particular, the product distribution in the cross-coupling of 4-bromophenyl triflate was found to depend on the reaction conditions. The use of $Pd(PPh_3)_4$ in dioxane, especially in the absence of LiCl, favors C—Br cleavage to afford **1b** (entries 1-2).[14] In contrast, catalysis with $PdCl_2(PPh_3)_2$ in DMF leads to C—OTf cleavage (entries 3-4).[15] Unlike 4-bromophenyl triflate, the iodo analogue reacts at iodide regardless of conditions (entries 5-6). As such, this work established a reactivity order of I > Br ≈ OTf, where the relative order of Br and OTf depends on conditions.

Table 1. First examples of chemodivergent cross-coupling: selectivity depends on reaction conditions.[13]



entry	X	cat.	solvent	temp (°C)	time (h)	major product	1a : 1b
1	Br	$Pd(PPh_3)_4$	dioxane	98	7	1b	1 : 6
2[a]	Br	$Pd(PPh_3)_4$	dioxane	98	2.5	1b	1 : 33
3	Br	$PdCl_2(PPh_3)_2$	DMF	70	3	1a	5 : 1
4	Br	$PdCl_2(PPh_3)_2$	DMF	24	18	1a	n.r.[b]
5[a]	I	$Pd(PPh_3)_4$	dioxane	98	16	1b	n.r.[b]
6	I	$PdCl_2(PPh_3)_2$	DMF	24	7	1b	n.r.[b]

[a]Without LiCl. [b]Ratio not reported (single product described).

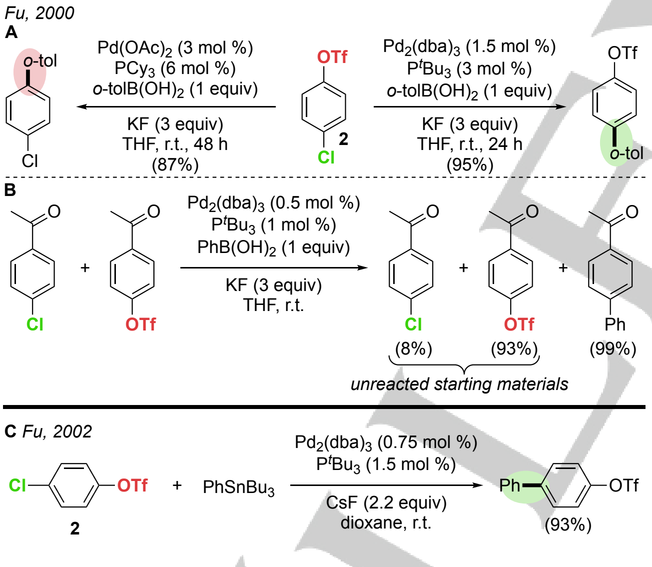
To explain the divergent selectivity between bromide and triflate, Echavarren and Stille proposed that a triflate oxygen could direct oxidative addition by interacting with coordinatively unsaturated $Pd(PPh_3)_2$ generated from $PdCl_2(PPh_3)_2$. However, much later mechanistic work discounts this hypothesis and instead highlights the orthogonal effects of nonpolar and polar coordinating solvents, such as dioxane and DMF, on the chemoselectivity of haloaryl triflate cross-coupling reactions (*vide infra*). Indeed, it was later found that $PdCl_2(PPh_3)_2$ favors reaction at *bromide* when a nonpolar solvent is used,[16] as described in the "Bromide vs. Triflate" subsection below.

Divergent Selectivity Between a Halide and a Pseudohalide

Following Echavarren and Stille's studies, a few more examples of divergent selectivity between bromide and triflate emerged in the '80s and '90s (and several more recently). The first instance of chemodivergent cross-coupling of *chloro*aryl triflates was not described until 2000. Nevertheless, here we first discuss Cl vs. OTf selectivity even though the initial discoveries in this area were chronologically later than much of the Br vs. OTf work. The reason for this organization is that the Cl/OTf systems have produced the most fruitful mechanistic studies so far. Other types of chemoselectivity are perhaps most profitably viewed through the lens of the Cl/OTf mechanistic work.

Chloride vs. Triflate

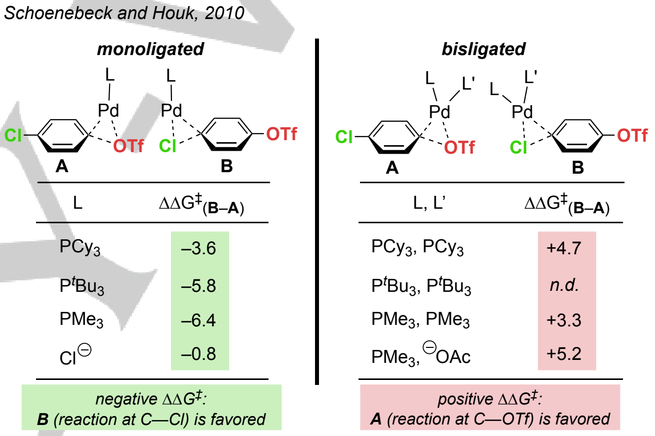
The first example of chemodivergent cross-coupling of a chloroaryl triflate was reported in 2000 by Fu in a paper that focused on the utility of P^tBu_3 for Pd-catalyzed Suzuki-Miyaura cross-coupling of aryl chlorides.[17] At the time, chlorides were considered to be poorly reactive. As such, it was surprising that the use of a Pd/P^tBu_3 catalytic system led to exclusive coupling of **2** through C—Cl cleavage, leaving a reactive triflate intact (Scheme 4A, right). Similarly, an aryl chloride was found to react preferentially in an intermolecular competition with an aryl triflate under these conditions (Scheme 4B). This chloride-selectivity was also upheld in a Stille coupling (Scheme 4C).[18] In contrast to P^tBu_3, the use of PCy_3 led to reversal of selectivity of the Suzuki coupling (Scheme 4A, left).[17]



Scheme 4. (A) First chemodivergent cross-coupling of a chloroaryl triflate; selectivity is determined by ligand identity. P^tBu_3 also effects preferential C—Cl cleavage in (B) an intermolecular competition during a Suzuki coupling[17] and (C) an intramolecular competition during a Stille coupling.[18]

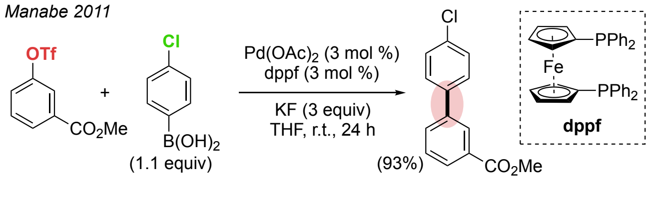
The divergent catalytic systems in Scheme 4A differ not only in ligand identity, but also in palladium source and the ratio of ligand to Pd. Control experiments showed that the Pd source ($Pd(OAc)_2$ vs $Pd_2(dba)_3$) does not affect selectivity, while the phosphine:Pd stoichiometry does.[17] The selectivity for reaction of triflate is eroded when the PCy_3:Pd ratio is decreased to 1.2:1 instead of 2:1. Although P^tBu_3 stoichiometry does not influence selectivity,[19] the cross-coupling *rate* is much slower when the ratio of P^tBu_3:Pd is increased to 2:1 instead of 1:1.[17,19]

Ten years later, Schoenebeck and Houk conducted DFT calculations that provided critical insight into the origins of this ligand-controlled selectivity (Scheme 5).[20] They found that monoligated $Pd(PCy_3)$ inserts more easily into the C—Cl bond of **2**, a prediction that is not consistent with the experimentally observed selectivity with this ligand during cross-coupling. However, bisligated $Pd(PCy_3)_2$ reacts faster at C—OTf, suggesting that bisligated Pd is the experimentally relevant active catalyst with PCy_3. Monoligated $Pd(P^tBu_3)$ also prefers to react at chloride, which is the experimentally favored site with this ligand. Transition structures using bisligated $Pd(P^tBu_3)_2$ could not be located in Schoenebeck and Houk's original report. However, Schoenebeck later found that the use of dispersion-containing functionals enabled such structures to be located, and they were disfavored over those involving just one P^tBu_3 ligand.[21] Taken together, these results indicate that the active catalyst is ligated by a different number of phosphines depending on whether PCy_3 or P^tBu_3 is used. The trend that monoligated Pd reacts more easily at chloride and bisligated Pd reacts more easily at triflate was upheld for other catalysts examined computationally, including $Pd(PMe_3)$ or $[PdCl]^-$ vs. $Pd(PMe_3)_2$ or $[Pd(PMe_3)(OAc)]^-$.



Scheme 5. DFT studies suggest that monoligated Pd reacts preferentially at C—Cl, while bisligated Pd reacts at C—OTf. n.d. = not determined.[20]

The divergent selectivity of mono- and bisligated Pd was rationalized by Schoenebeck and Houk in terms of distortion and interaction energies.[20] Oxidative addition of C—Cl involves a smaller (more favorable) distortion energy than at C—OTf, and monoligated palladium's selectivity for reaction at C—Cl is distortion-controlled. In contrast, bisligated palladium's selectivity is more influenced by interaction energy: PdL_2 is much more electron-rich, and thus has a stronger favorable interaction with the more electrophilic carbon of C—OTf (C—O bonds are more polar than C—Cl bonds). These results are consistent with the optimal Pd:phosphine ratios in Fu's experimental system, where a 1:1 ratio is best for Pd/P^tBu_3 but a 1:2 ratio is best for Pd/PCy_3. Also consistent with the ligation state hypothesis, Manabe later showed that the bidentate ligand dppf can be used instead of PCy_3 to achieve triflate-selective cross-coupling (Scheme 6).[22]

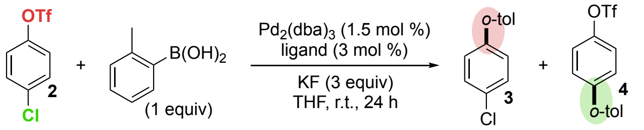


Scheme 6. A bidentate phosphine promotes selective C—OTf cleavage.[22]

Additional insight into ligand effects was provided in 2016, when Sigman tested a variety of other monodentate phosphines in the Suzuki cross-coupling shown in Table 2.[19] Although these reactions were often low-yielding, the product ratios were in good agreement with those predicted by a parameterized model. Of the nearly 40 phosphines evaluated, only 6 were found to favor C—Cl oxidative addition when used in a 1:1 ratio with Pd. All of the phosphines that promote reaction at chloride contain at least one (usually two) *tert*-butyl or adamantyl groups. Taken together with Schoenebeck and Houk's studies,[20] it is likely that these six bulky ligands favor a monoligated active catalyst, while the other phosphines favor a bisligated catalyst. Interestingly, although P^tBu_2Ph favors chloride activation, JohnPhos [(2-biphenyl)di-*tert*-butylphosphine]—which features an essentially identical environment around phosphorus—promotes triflate activation. A possible explanation for JohnPhos' behavior could relate to the ability of *o*-biphenylphosphines to coordinate in a bidentate manner through a hemilabile Pd-π interaction.[9b]

Table 2. Cl vs. OTf chemoselectivity promoted by monodentate phosphines; most phosphines favor C—OTf cleavage.[19]

Sigman 2016



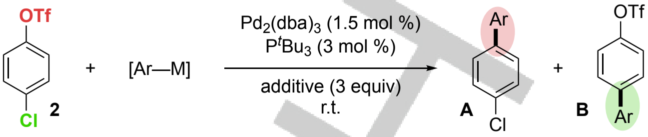
phosphine	$\Delta\Delta G^{\ddagger}_{(\mathbf{4}-\mathbf{3})}$ (kcal/mol)	phosphine	$\Delta\Delta G^{\ddagger}_{(\mathbf{4}-\mathbf{3})}$ (kcal/mol)	phosphine	$\Delta\Delta G^{\ddagger}_{(\mathbf{4}-\mathbf{3})}$ (kcal/mol)
PMe_2Ph	4.00	PCy_2*o*Tol	0.94	$P^nBu(1\text{-}Ad)_2$	–1.43
PEt_3	3.75	$PCy_2(pNMe_2C_6H_4)$	2.60	$P^tBu_2(pCF_3C_6H_4)$	–1.46
$PEtPh_2$	3.57	SPhos	4.15	$P^iPr_2{}^tBu$	–0.31
P*m*Tol_3	3.12	$PMePh_2$	3.70	P^nPr_3	3.11
PPh_3	2.64	$P(pOMeC_6H_4)_3$	3.49	PCy_2Ph	2.08
P^iPr_3	1.02	P*p*Tol_3	3.33	PCy_2Et	1.09
$P(oOMeC_6H_4)_3$	4.77	PCy_3	1.94	$PPh_2(pC_6H_4C_2H_3)$	3.12
PBn_3	4.20	P^tBu_2Ph	–1.26	$PPh_2{}^iPr$	3.01
P^tBuPh_2	2.36	JohnPhos	2.91	PPh_2allyl	3.23
P*o*Tol_3	1.42	CyJohnPhos	3.32	PEt_2Ph	3.49
P^cPent_3	0.59	RuPhos	4.25	Cy-vBRIDP	4.22
P^nBu_3	2.40	XPhos	3.53		
P^tBu_3	–2.72	$PBn(1\text{-}Ad)_2$	–1.35		

*A negative value of $\Delta\Delta G^{\ddagger}_{(\mathbf{4}-\mathbf{3})}$ means **4** (reaction at C—Cl) is favored. Cy-vBRIDP = dicyclohexyl(1-methyl-2,2-diphenylvinyl) phosphine.*

In 2011, Schoenebeck discovered that the Cl vs. OTf selectivity in Fu's system using Pd/P^tBu_3 is solvent dependent.[23] Fu's original Suzuki coupling with P^tBu_3 was performed in THF, and as discussed above, gave exquisite selectivity for C—Cl cleavage.[17] However, Schoenebeck showed that moving away from the nonpolar solvents THF and toluene to the much more polar solvents DMF and MeCN effects an impressive switch in selectivity with this catalytic system (Table 3 entries 1-3). Changing the identity of the implicit solvent in DFT calculations did not provide any clues about the experimentally observed selectivity switch: monoligated $Pd(P^tBu_3)$ was calculated to favor reaction at chloride regardless of implicit solvent polarity. The possibility of solvent coordination to Pd to provide a bisligated active complex was also considered, but the calculations suggested that oxidative addition at $Pd(P^tBu_3)$(solvent) is too high-energy to be realistic. However, it is worth noting that these calculations were performed with a dispersion-free functional, and consideration of dispersion is now well-known to lower the energy of crowded transition structures, including those for oxidative addition at bisligated Pd.[21] A similar solvent effect was also observed using a $[(P^tBu_3)PdBr]_2$ catalyst, wherein Suzuki cross-coupling of **2** proceeds through C—Cl cleavage in THF, but through C—OTf cleavage in MeCN.[24]

Table 3. Solvent and additive effects on the chemoselectivity of Pd/P^tBu_3-catalyzed Suzuki and Stille cross-coupling of a chloroaryl triflate.[23]

Schoenebeck 2011

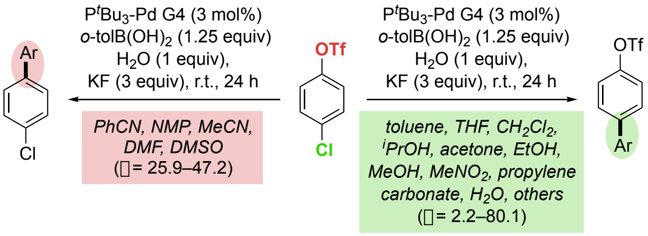


entry	solvent	[Ar—M]	additive	**2** : **A** : **B**
1	toluene	*o*-tol$B(OH)_2$	KF	20 : — : 70
2	MeCN	*o*-tol$B(OH)_2$	KF	— : 74 : 3
3	DMF	*o*-tol$B(OH)_2$	KF	37 : 22 : 3
4	DMF	$PhSnBu_3$	KPF_6	45 : 8 : 47
5	DMF	$PhSnBu_3$	KF	18 : 51 : 30
6	DMF	$PhSnMe_3$	CsF	— : 79 : 21

Interestingly, a Pd/P^tBu_3-catalyzed Stille coupling led to C—Cl cleavage, regardless of solvent (Table 3, entry 4).[23, 25] To rationalize the different solvent effects in the Suzuki vs. Stille couplings, Schoenebeck proposed that polar solvents stabilize an anionic bisligated $[Pd(P^tBu_3)(X)]^–$ active catalyst in the Suzuki system (X = fluoride, deprotonated boronic acid, or other anion).[23] DFT calculations indicated that $[Pd(P^tBu_3)(X)]^–$ should prefer to react at triflate over chloride, consistent with the observed selectivity in the Suzuki coupling in DMF or MeCN (entries 2-3). In the Stille system using the additive KPF_6, no coordinating anions are available to allow formation of such species. Indeed, when KF or CsF is added to the Stille coupling in DMF, the selectivity behaves more like the Suzuki coupling and favors the product of C—OTf cleavage (entries 5-6).

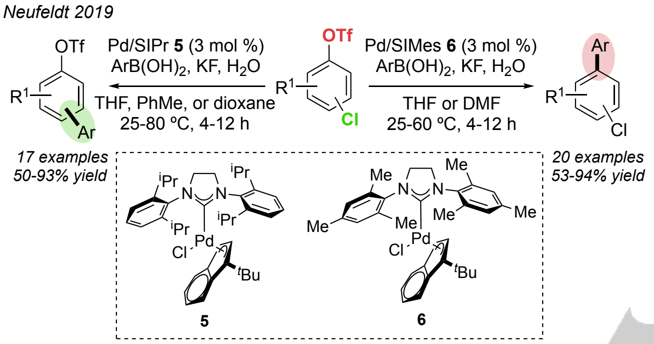
The hypothesis that polar solvents promote oxidative addition at anionic bisligated palladium is consistent with the experimentally observed difference between the Suzuki vs. Stille coupling in DMF. However, Neufeldt and coworkers recently reported the puzzling observation that selectivity in the Pd/P^tBu_3-catalyzed Suzuki coupling of **2** does not necessarily trend with solvent polarity (Scheme 7).[26] Some very polar solvents such as acetone, propylene carbonate, water, and alcohols provide the same chloride-selectivity as nonpolar solvents like THF and toluene. In fact, DMF, MeCN, and a few other solvents (NMP, DMSO, PhCN) that promote reaction at triflate are apparent outliers. These observations suggest that anionic bisligated Pd may not be the active catalyst in all polar solvents. Once again, DFT calculations using implicit solvent are unable to account for the observed selectivity differences. It is interesting to note that all of the solvents that promote triflate selectivity are classically considered to be "coordinating", and so a closer examination of the role of explicit solvent coordination on selectivity is warranted.

Neufeldt 2020



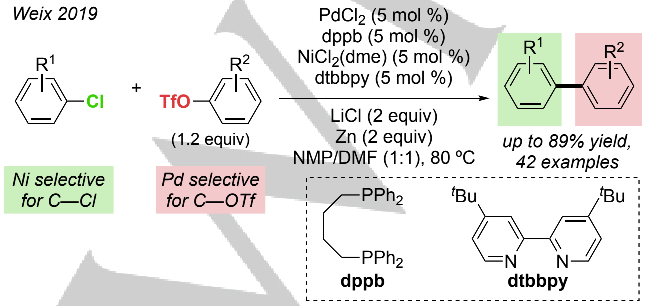
Scheme 7. Nonpolar and many polar non-coordinating solvents promote Suzuki coupling at chloride with Pd/P^tBu_3, while only polar coordinating solvents favor reaction at triflate.[26]

The vast majority of chemodivergent cross-coupling examples involve phosphine ligands for palladium. However, in 2019, the Neufeldt group described the first instance of *N*-heterocyclic carbene (NHC) ligand-controlled chemodivergent cross-coupling (Scheme 8).[27] During a Pd-catalyzed Suzuki coupling, chloroaryl triflates were shown to react preferentially at chloride with SIPr (the NHC ligand on precatalyst **5**), but at triflate with SIMes (the NHC ligand on **6**). DFT calculations indicate that monoligated Pd^0(NHC) prefers to react at chloride, regardless of whether NHC = SIPr or SIMes. This result suggests that a monoligated catalyst is active with SIPr, which favors C—Cl cleavage, but not with SIMes, which favors reaction at C—OTf. Transition structures involving bisligated $Pd(SIMes)_2$ could not be located and may be unrealistic due to SIMes' steric bulk. However, bisligated anionic species such as $[Pd(SIMes)(OH)]^-$ were calculated to prefer reaction at triflate. Such species might be responsible for the selectivity with IMes, although further mechanistic studies are needed.



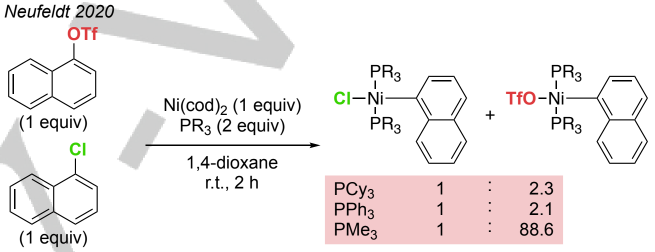
Scheme 8. NHC ligand-controlled chemodivergent Suzuki coupling of chloroaryl triflates.[27]

The examples discussed thus far have involved a palladium catalyst supported by phosphine or NHC ligands. However, reports by Weix in 2015 and 2019 also provided insight into *nickel's* selectivity for Cl vs. OTf.[28,29] Weix used a two-catalyst system to achieve highly selective cross-Ullmann coupling of an aryl chloride with an aryl triflate (Scheme 9). In this system, palladium—supported by the bidentate ligand dppb—reacts selectively with the aryl triflate, as expected based on what was already known about the behavior of bisligated palladium. On the other hand, nickel, supported by a bidentate bipyridine ligand (dtbbpy), was found to react much faster with the chloride electrophile than with the triflate. As such, Pd/dppb and Ni/bpy display complementary chemoselectivity, and this behavior was exploited to develop a robust cross-electrophile coupling.



Scheme 9. Ni- and Pd-catalyzed cross-Ullmann coupling that exploits these metals' complementary chemoselectivities. Here, nickel reacts faster with an aryl chloride than a triflate.[29]

Nickel's preference for reaction at C—Cl in Weix's system is consistent with prior reports by Liu[30] and by Sproules and Nelson.[31] Liu's DFT calculations with monoligated $Ni(PMe_3)$ and Sproules and Nelson's experimental studies with Ni(dppf) indicated that oxidative addition at these complexes is faster for aryl chlorides than triflates. However, additional data provided in a recent report by Neufeldt confirms that the relative rate of oxidative addition of aryl electrophiles at Ni(0) is ligand-dependent.[32] Ni/PCy_3 and Ni/PPh_3 react slightly faster with an aryl triflate in an intermolecular competition reaction (about 2x the rate of reaction of an aryl chloride, Scheme 10). Furthermore, Ni/PMe_3 reacts with an aryl triflate about 90x faster than an aryl chloride (based on product distribution), showing complete reversal of the chemoselectivity reported by Weix using Ni/bpy. Although this experimental observation contradicts Liu's calculations with monoligated $Ni(PMe_3)$,[30] additional DFT studies suggest that nickel is most likely bisligated during oxidative addition with PMe_3 (as well as with PCy_3 and PPh_3).[33] The origin of nickel's chemoselectivity trends is not fully understood, but calculations suggest that both ligand electronics and sterics can affect the barriers to oxidative addition of C—sulfonate bonds.

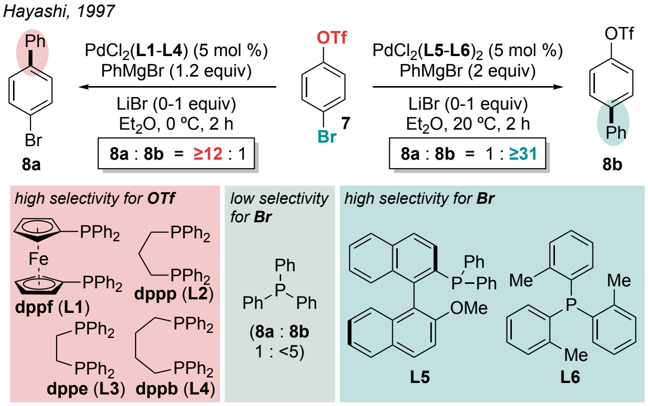


Scheme 10. Nickel's preference for Cl vs. OTf oxidative addition is ligand-dependent. Here, nickel reacts faster with an aryl triflate than a chloride.[32]

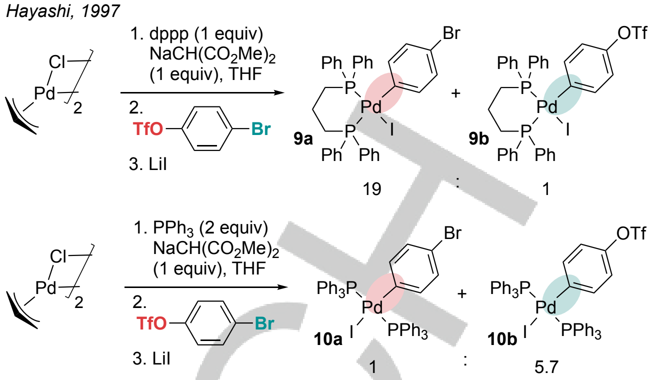
Overall, the work described in this section provides strong evidence that oxidative addition selectivity can depend on the metal's ligation state and other ligand characteristics. At least for palladium, a monoligated catalyst prefers to react at chloride rather than triflate, while a bisligated complex preferentially inserts into C—OTf bonds. With this paradigm in mind, we next turn to bromide vs. triflate selectivity. As discussed in the next section, the circumstantial evidence suggests that Br vs. OTf selectivity using palladium catalysts is governed by similar principles as Cl vs. OTf.

Bromide vs. Triflate

Since Echavarren and Stille first described the effect of solvent and precatalyst on bromophenyl triflate cross-coupling selectivity, multiple other reports established that selectivity between bromide and triflate can also be influenced by ancillary phosphine ligands. In 1997, Hayashi described a systematic study of ligand effects on the selectivity of a Pd-catalyzed Kumada coupling.[16] When palladium is supported by bidentate ligands **L1**-**L4** (Scheme 11), reaction of 4-bromophenyl triflate proceeds by C—OTf cleavage to afford product **8a** with good selectivity (≥12 : 1) and up to 97% isolated yield. Conversely, the bulky monodentate phosphines **L5**-**L6** lead to highly selective C—Br cleavage to provide **2b** in up to 68% isolated yield. The selectivity for bromide exhibited by **L5** was further demonstrated with five other substrates, including *ortho*- and *meta*-bromophenyl triflate.



Scheme 11. Ligand-controlled chemodivergent Kumada coupling of a bromoaryl triflate.[16]



Scheme 12. Stoichiometric studies showing that ligand-controlled chemoselectivity between Br and OTf is determined during the oxidative addition step.[16]

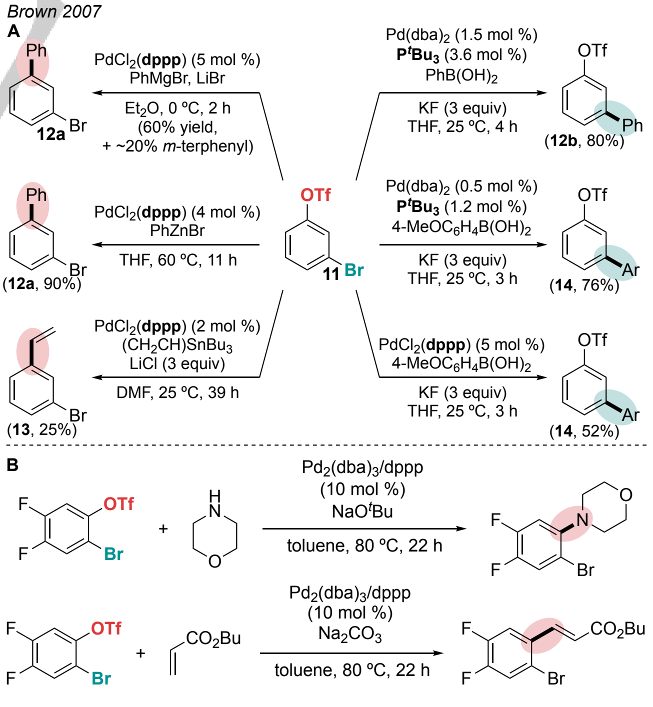
Importantly, Hayashi's studies controlled for solvent effects by using the same nonpolar solvent (Et_2O) with all ligands. The role of the additive LiBr on selectivity was examined, and the results suggest that this salt slightly promotes reaction of triflate. With dppp (**L2** in Scheme 11), selectivity appears to be independent of the additive LiBr and preferential C—OTf cleavage always gives **8b**. However, with bulky monodentate **L5**, addition of LiBr leads to slight erosion of selectivity. In particular, the ratio of terphenyl—the product of diarylation—to **8b** increases to 0.16 : 1 compared to 0.05 : 1 without LiBr, indicating that more C—OTf cleavage occurs in the presence than absence of LiBr. The origin of this effect was not discussed in Hayashi's report. However, in light of the later mechanistic studies on Cl/OTf selectivity (*vide supra*) one possible explanation could be that addition of LiBr enables some amount of anionic bisligated $[Pd(\mathbf{L5})(Br)]^-$, a species that would be expected to promote reaction of triflate, to become catalytically relevant.

Like the other monodentate phosphines **L5** and **L6**, Hayashi found that PPh_3 [introduced as $PdCl_2(PPh_3)_2$] favors reaction at bromide in Et_2O, albeit with only modest selectivity. This result contrasts with Echavarren and Stille's report that catalysis with $PdCl_2(PPh_3)_2$ in DMF favors C—OTf cleavage. Most likely, the critical difference between these two studies is solvent. For example, a bisligated palladium complex may be the dominant active catalyst in a polar coordinating solvent (DMF), while a nonpolar solvent (Et_2O) might allow the activity of monoligated $Pd(PPh_3)$ to significantly contribute to product distribution. However, PPh_3 has also been reported to promote selective C—OTf cleavage in a nonpolar solvent (benzene) when the competition is between a vinyl triflate and an aryl bromide.[34] Innate reactivity differences between vinyl and aryl electrophiles likely account for these results,[35] which run counter to Hayashi's observations.

In Hayashi's studies, the lower selectivity with PPh_3 compared to **L5** and **L6** may be rationalized by the differences in ligand steric bulk. For example, the cone angle of $P(o\text{-tol})_3$ (**L6**) is 194° while that of PPh_3 is only 145°.[36] A larger cone angle would promote ligand dissociation to give mono-ligated transition states, but palladium can easily accommodate two monophosphines that have small cone angles during oxidative addition.

Hayashi also showed that the selectivity of stoichiometric oxidative addition in the absence of a nucleophilic coupling partner is ligand-controlled and matches the selectivity observed under catalytic conditions. Reaction of Pd/dppp with 4-bromophenyl triflate in THF gave primarily **9a** after trapping with LiI, while reaction of Pd/PPh_3 gave mostly **10b** (Scheme 12). These results demonstrate that selectivity is determined during the oxidative addition step.

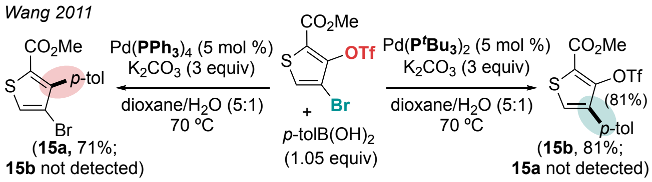
In light of Hayashi's stoichiometric studies, one might expect that cross-coupling chemoselectivity should be independent of nucleophilic coupling partner. However, in 2007 Brown reported the surprising finding that Suzuki couplings of bromoaryl triflates do not exhibit the same chemoselectivity pattern as other types of couplings.[37] In the presence of $PdCl_2$(dppp), substrate **11** undergoes cross-coupling with an organomagnesium, -zinc, or -tin reagent to selectively provide the product of C—OTf cleavage (**12a** and **13** in Scheme 13A). Similar selectivity was also observed in a Heck coupling and a Buchwald-Hartwig amination (Scheme 13B), and several years later, Weix demonstrated that Pd/dppp also preferentially reacts at triflate during a cross-electrophile coupling between aryl bromides and triflates (*vide infra*).[28] In stark contrast however, Suzuki coupling with an arylboronic acid results in selective C—Br cleavage, regardless of whether a bulky monodentate (P^tBu_3) or bidentate (dppp) ligand is used (**12b** and **14** in Scheme 13A).[37]



Scheme 13. The bidentate ligand dppp promotes C—OTf cleavage in Kumada, Negishi, Stille, Buchwald-Hartwig, and Heck couplings, but Suzuki coupling proceeds through C—Br cleavage independent of ligand.[37]

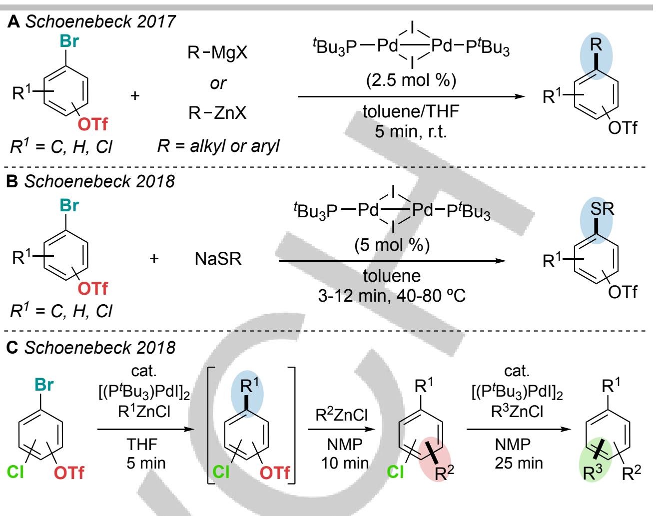
Together with Hayashi's earlier report,[16] these results suggest that ligand choice may determine Br vs. OTf selectivity in most cross-couplings except for Suzuki. Unlike the other reactions, selectivity in the Suzuki coupling of bromophenyl triflates is ligand-independent and apparently always favors C—Br cleavage.[38] This result contrasts to the ligand-dependence of Suzuki couplings of chloroaryl triflates.[17] Brown speculated that the anomalous behavior of the Suzuki reaction of bromoaryl triflates could mean that the boronic acid or its byproducts are involved in the selectivity-determining oxidative addition.[37]

At least two counterexamples to the 'Suzuki-Miyaura anomaly' have been reported. In 2011, Wang demonstrated ligand-controlled chemoselectivity in the Suzuki coupling of 3-bromo-4-trifloylthiophenes (Scheme 14).[39] A bulky monodentate phosphine (P^tBu_3) promotes C—Br cleavage to give **15b**, but use of the smaller phosphine PPh_3 leads to C—OTf cleavage (**15a**). König showed that 8-bromo-1-trifloyldibenzofurans, substrates that are electronically activated toward oxidative addition at C1, also undergo Suzuki-Miyaura cross-coupling with ligand-dependent selectivity.[40] Clearly, substrate structure can determine the extent to which ligands influence chemoselectivity.



Scheme 14. Br vs. OTf chemoselectivity is ligand-controlled in a Suzuki coupling of 3-bromo-4-trifloylthiophenes.[39]

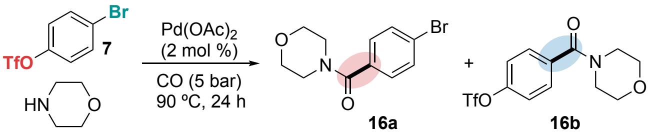
Studies on the catalytic utility of a Pd^I/Pd^I dimer reported by Schoenebeck in 2017 further illustrate that P^tBu_3 promotes C—Br cleavage during Kumada and Negishi couplings of bromo(hetero)aryl triflates (Scheme 15A).[41,42] In these systems, oxidative addition was proposed to proceed at either the Pd^I dimer or at coordinatively unsaturated $Pd^0(P^tBu_3)$. In either case, it was suggested that the especially high selectivity is related to the very fast reaction time, such that cross-coupling outcompetes conversion of the catalyst into less selective species. Similar selectivity was later reported in the cross-coupling of bromo(hetero)aryl triflates with organothiolates using the same Pd^I dimer (Scheme 15B).[43] Although substituents *ortho* to Br tend to erode selectivity with this catalyst,[41] a striking exception to this trend was reported by Schoenebeck in 2020.[44] Bromoaryl triflates bearing adamantyl groups *ortho* to bromide undergo highly selective Negishi couplings through C—Br cleavage. The selectivity with this substrate class was attributed to attractive dispersion interactions between the adamantyl group and the P^tBu_3 ligand. A nonpolar solvent (toluene or THF) was used in all of these bromide-selective couplings.[41,42,43,44] In 2018, Schoenebeck showed that after reacting at the bromide of a bromoaryl triflate, the resulting triflate-containing product could be further cross-coupled through C—OTf cleavage using the same Pd^I dimer catalyst.[45] The optimized conditions for triflate coupling used NMP as a solvent, and the authors proposed that this polar solvent might promote formation of an anionic active catalyst. As such, a single catalyst could be used for three sequential cross-coupling reactions in the order Br > OTf > Cl (Scheme 15C). In competition reactions between C—Br and C—OSO_2F, fluorosulfonate was found to behave analogously to triflate.[46] Accordingly, $[(P^tBu_3)PdI]_2$-catalyzed Negishi and Kumada couplings, as well as thiolation, were found to be selective for C—Br over C—OSO_2F cleavage, and the fluorosulfonate could subsequently undergo coupling upon the addition of NMP.



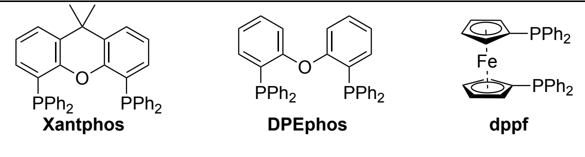
Scheme 15. A Pd(I) dimer supported by P^tBu_3 effects selective C—Br cleavage in (A) Kumada and Negishi-type couplings[41,42] and (B) thiolation reactions.[43] (C) Addition of NMP allows the same catalyst to be effective for C—OTf coupling in the absence of a competing C—Br bond.[45]

In 2017, Jiao and Wu described results that shed light on solvent effects in the chemoselectivity of cross-coupling of bromoaryl triflates.[47] The product distribution in the Pd-catalyzed carbonylative amination of **7** was shown to depend on the combination of ligands and solvent (Table 4). With Xantphos, a bidentate phosphine with a large bite angle, selective C–Br cleavage occurs in toluene (entry 1). However, selectivity with this ligand is greatly eroded when DMSO is used as the solvent (entry 2). Conversely, dppf—also a bidentate ligand, but with a smaller bite angle—in combination with DMSO (entry 5), DMF, or NMP (not shown) leads to high selectivity for reaction of triflate. When dppf is used in toluene, poor selectivity is observed (entry 4). As such, high chemoselectivity for reaction at either site can be obtained with the right match between ligand and solvent; a mismatch between these two variables leads to low selectivity. The optimized ligand/solvent combinations were also applied to a chemodivergent carbonylative Suzuki coupling.[47]

Table 4. Synergistic ligand and solvent effects on the chemoselectivity of a carbonylative amination.[47]



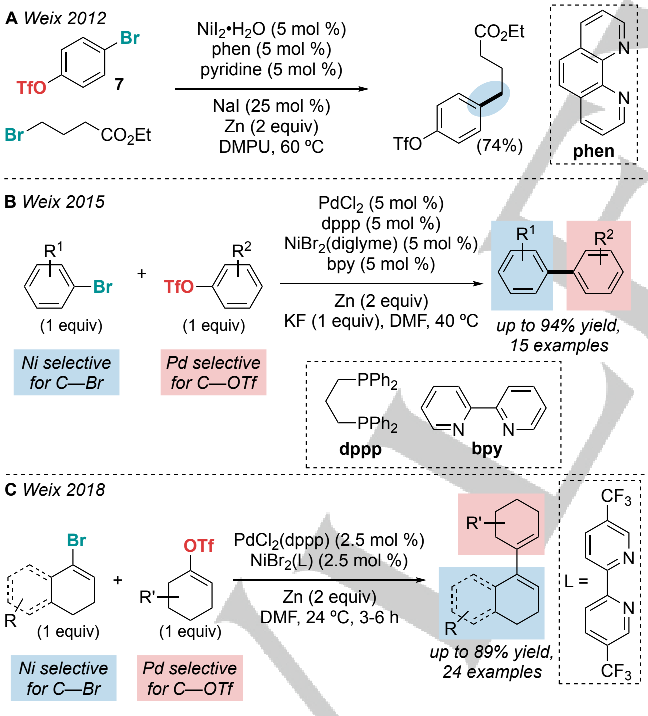
entry	ligand	solvent	% conversion of 7	16a	:	16b
1	Xantphos	toluene	>99	1	:	>99
2	Xantphos	DMSO	32	50	:	50
3	DPEphos	toluene	75	31	:	69
4	dppf	toluene	41	55	:	45
5	dppf	DMSO	>99	99	:	<1
6	$BuPAd_2$	toluene	>99	1	:	>99
7	$BuPAd_2$	DMSO	94	1	:	>99
8	P^tBu_3•HBF_4	toluene	>99	1	:	>99
9	P^tBu_3•HBF_4	DMSO	42	1	:	>99



Jiao and Wu's data show that reaction at triflate is facilitated by polar solvents such as DMSO, DMF, and NMP. A possible explanation for this solvent effect was suggested by DFT calculations, which revealed a much greater charge separation during the calculated transition structures for oxidative addition at triflate compared to Br. As such, the more polar C—OTf oxidative addition transition state is better stabilized by polar solvents.

While the selectivity influence of Xantphos and dppf proved to be solvent-sensitive, the use of bulky monodentate phosphines P^tBu_3 or $BuPAd_2$ led to exclusive C—Br cleavage independent of solvent during the carbonylative amination (Table 4, entries 6-9). In this respect, the behavior of bromoaryl triflates appears to differ from that of chloroaryl triflates. As described above, the selectivity of Pd/ P^tBu_3-catalyzed cross-couplings of chloroaryl triflates can be solvent-dependent, where nonpolar solvents promote chloride coupling and polar coordinating solvents favor triflate coupling. However, it is important to note that this solvent effect has only been demonstrated in Suzuki-Miyaura couplings and has not been evaluated in carbonylative aminations of chloroaryl triflates.

The examples described in this section so far have dealt with palladium catalysts, but a few reports have also helped to establish the Br vs. OTf selectivity of *nickel* complexes. In 2012, Weix reported that **7** reacts selectively through the C—Br bond in a Ni/phen-catalyzed reductive alkylation (Scheme 16A).[48,49] This selectivity preference was later exploited for the development of multimetallic cross-electrophile couplings between aryl bromides and triflates (Scheme 16B)[28] or between vinyl bromides and triflates (Scheme 16C).[50] In these reactions, Pd supported by a bidentate phosphine reacts selectively with triflate, while Ni supported by a dinitrogen ligand reacts preferentially with bromide.

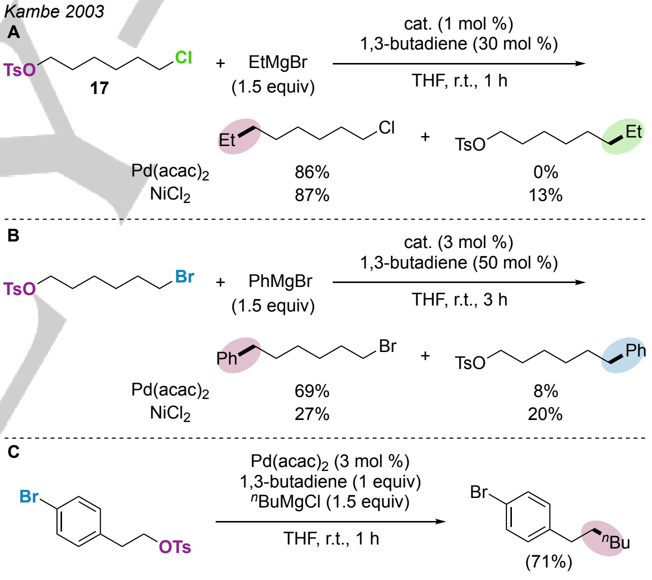


Scheme 16. (A) Nickel supported by a dinitrogen ligand reacts preferentially with an aryl bromide over a triflate.[48] The complementary chemoselectivity of Pd and Ni has been exploited to achieve cross-electrophile couplings of (B) aryl bromides with aryl triflates[28] and (C) vinyl bromides with vinyl triflates.[50]

Chloride vs. Tosylate

Aryl tosylates are usually considered to be less reactive electrophiles than triflates or other fluorinated sulfonates.[46, 51] Consistent with this perception, most reported instances of Pd-catalyzed Suzuki couplings of chloroaryl tosylates proceed through C—Cl cleavage, even though chloroaryl *triflates* tend to react at C—O with most ligands.[19] In contrast, reported Kumada couplings of chloroaryl (or alkyl) tosylates react through C—OTs cleavage. A superficial analysis suggests that tosylate vs. chloride selectivity tends to correlate with the class of cross-coupling (i.e., the nucleophilic coupling partner), but this apparent correlation is likely coincidental. Collectively, the evidence suggests that selectivity is more influenced by ligand choice. The origin of tosylate vs. chloride selectivity is further discussed below after a survey of examples in which this type of chemoselectivity has been described.

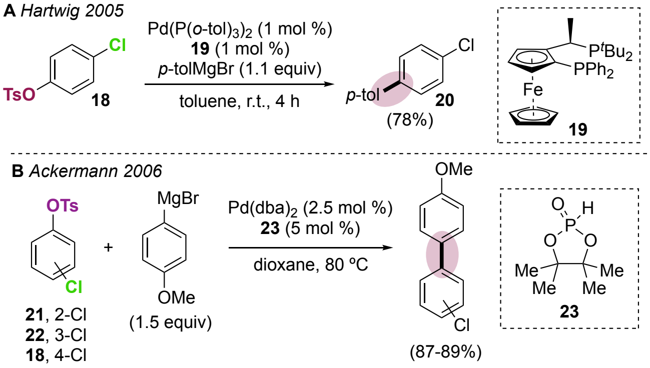
Although rare, literature reports of Kumada, Buchwald-Hartwig, and Heck couplings indicate that tosylates are more reactive than chlorides in these classes of reactions. In apparently the first example of a cross-coupling reaction that favored C—OTs over C—Cl cleavage, Kambe reported the results of a Kumada coupling of **17**.[52] With a Pd catalyst supported by 1,3-butadiene, substitution of the alkyl tosylate was exclusively observed in the coupling of **17** with ethyl Grignard (Scheme 17A). A nickel catalyst was found to also favor C—OTs cleavage, albeit with worse selectivity. Interestingly, an alkyl tosylate was more reactive than even an alkyl or aryl bromide in this reaction using the Pd catalyst (Scheme 17B-C).



Scheme 17. Pd-catalyzed Kumada coupling favors reaction of an alkyl tosylate over (A) an alkyl chloride, (B) an alkyl bromide, or (C) an aryl bromide. Nickel is less selective than palladium in these couplings.[52]

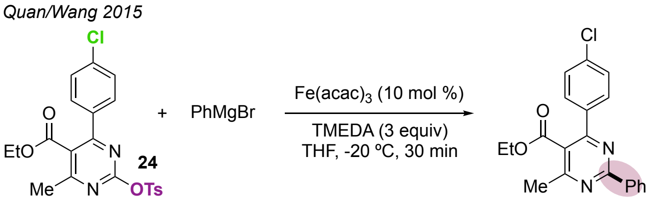
In 2005 Hartwig described an intramolecular competition between an aryl tosylate and chloride in a Pd-catalyzed Kumada coupling.[53] Substrate **18** reacts with an aryl Grignard reagent in the presence of a Pd/Josiphos catalytic system to provide product **20**, resulting from coupling at the tosylate group (Scheme 18A). Ackermann described a similar outcome in Pd/PinP(O)H-catalyzed Kumada couplings of *ortho*-, *meta*-, and *para*-chlorophenyl tosylate (Scheme 18B).[54]

In one report by Quan and Wang, an Fe catalyst was found to promote Kumada coupling of a tosylate over a chloride (Scheme 19); however, the two possible leaving groups of substrate **24** are in very different chemical environments so it is not possible to say whether this chemoselectivity is general.[55]


A *Hartwig 2005*

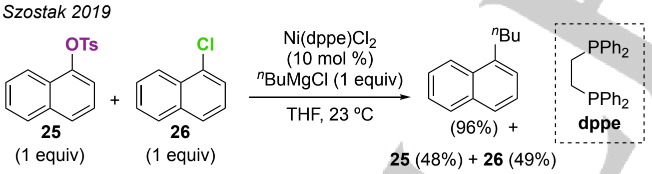
B *Ackermann 2006*

Scheme 18. Pd-catalyzed Kumada couplings of chloroaryl tosylates proceed through C—OTs cleavage.[53,54]


Quan/Wang 2015

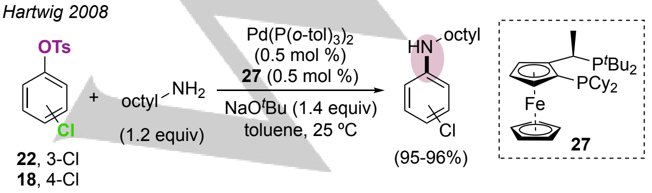
Scheme 19. An Fe-catalyzed Kumada coupling favors reaction at a 2-pyrimidinyl tosylate over an aryl chloride.[55]

Kambe's 2003 report suggested that nickel is less selective than Pd in Kumada couplings of chloroalkyl (or bromoalkyl) tosylates.[52] This observation was corroborated by a separate study by Szostak in 2019.[56] In the presence of a Ni/dppe catalyst, 1-chloronaphthalene and 1-naphthyl tosylate react with an alkyl Grignard reagent at essentially identical rates, resulting in about 50% recovery of each starting material (Scheme 20).


Szostak 2019

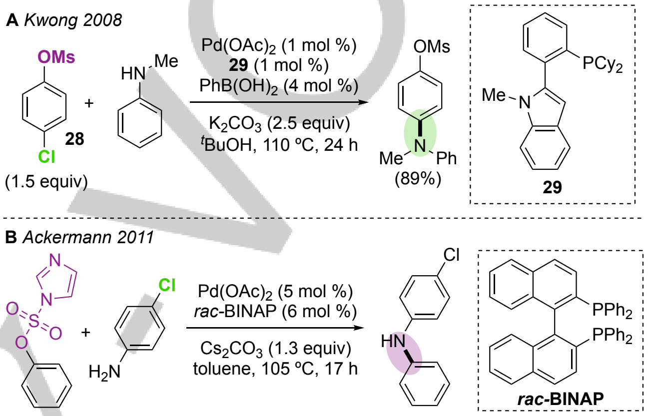
Scheme 20. A nickel/dppe-catalyst does not discriminate between an aryl tosylate and chloride during a Kumada coupling.[56]

In 2008, Hartwig reported that amination of 3- or 4-chlorophenyl tosylate proceeds through C—OTs cleavage in the presence of a Pd/Josiphos catalytic system (Scheme 21).[57] As such, the chemoselectivity in this Buchwald-Hartwig coupling is consistent with that observed earlier in a Kumada coupling also catalyzed by a Pd/Josiphos system (Scheme 18A).[53]


Hartwig 2008

Scheme 21. An isolated example of Buchwald-Hartwig amination of chlorophenyl tosylates proceeds through C—OTs cleavage.[57]

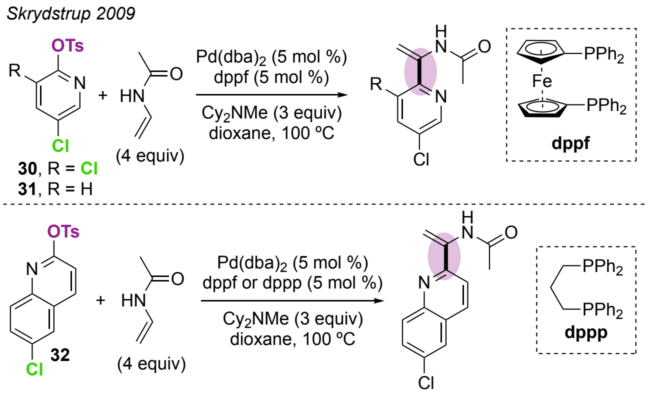
This single report from Hartwig is insufficient to conclude that tosylate selectivity in Buchwald-Hartwig aminations is general; for example, selectivity might be ligand-dependent. In support of this possibility, a chloride proved to be more readily displaced than a mesylate group, which is related to tosylate, in the Buchwald-Hartwig amination of **28** catalyzed by Pd/**29** (Scheme 22A).[58] On the other hand, Pd/BINAP-catalyzed amination of an aryl imidazolylsulfonate with chlorophenylamine provides the product of C—O cleavage, with the C—Cl bond intact (Scheme 22B).[59]


A *Kwong 2008*

B *Ackermann 2011*

Scheme 22. (A) A palladium catalyst supported by bulky monodentate phosphine **29** favors react at chloride over mesylate in a Kumada coupling.[58] (B) Pd supported by diphosphine BINAP enables Kumada coupling through C—O cleavage of an imidazolylsulfonate, leaving a C—Cl bond intact.[59]

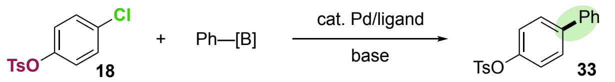
There has been one report examining the Cl vs. OTs chemoselectivity of a Heck coupling. The Pd/dppf-catalyzed coupling between **30**, **31**, or **32** and an alkene provides products resulting from C—OTs cleavage (Scheme 23).[60] However, it is notable that the tosylate in these examples resides at a privileged site: the C2 position is usually the most reactive site toward cross-coupling of poly(pseudo)halogenated pyridines.[5]


Skrydstrup 2009

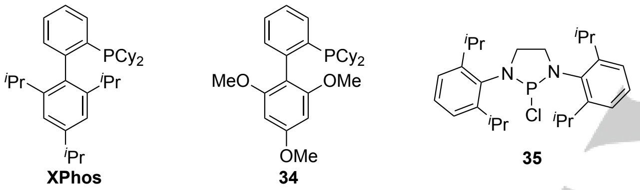
Scheme 23. Examples of Pd-catalyzed Heck couplings that favor reaction of tosylate, albeit with electronically biased substrates.[60]

In 2003, Buchwald reported the first general conditions for Pd-catalyzed Suzuki couplings of aryl tosylates.[61] Using a Pd/XPhos catalytic system, a variety of aryl tosylates could be coupled with aryl boronic acids in high yields. However, when the reactivity of the C—OTs bond is challenged in an intramolecular competition against a C—Cl bond, substrate **18** reacts exclusively through C—Cl cleavage to afford the tosylate-containing product **33** (Table 5, 1st entry). Wu reported a similar outcome in the Pd-catalyzed cross-coupling of **18** with $PhBF_3K$ in the presence of the Buchwald ligand **34** (2nd entry).[62] Whereas this catalytic system is effective for coupling a variety of aryl tosylates with potassium aryltrifluoroborates, the C—Cl bond of **18** proved to be more reactive than the C—OTs bond. Similarly, **18** couples exclusively at the chloride position in a Pd/diaminochlorophosphine-catalyzed Suzuki coupling (3rd entry).[63]

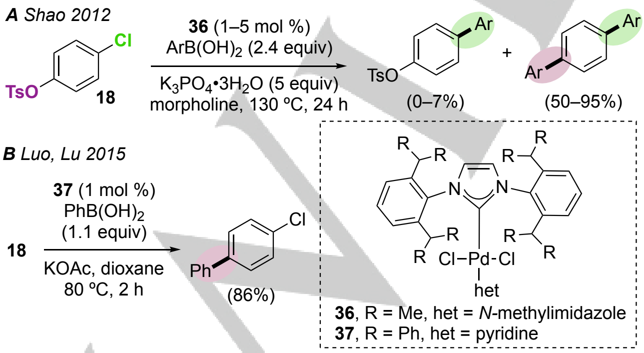
Table 5. Pd reacts at chloride during Suzuki couplings of chloroaryl tosylate **18**.[61,62,63]



reference	[Pd]	ligand	coupling partner	base	solvent, temp, time	33 (% yield)
Buchwald 2003	$Pd(OAc)_2$ (2 mol %)	**XPhos** (5 mol %)	$PhB(OH)_2$ (1.3 equiv)	K_3PO_4•H_2O (3 equiv)	THF, r.t., 2 h	88
Wu 2007	$Pd(OAc)_2$ (2 mol %)	**34** (4 mol %)	$PhBF_3K$ (1.1 equiv)	Et_3N (3 equiv)	EtOH, 80 °C, 6 h	84
Ackermann 2010	$Pd_2(dba)_3$ (1 mol %)	**35** (4 mol %)	$PhB(OH)_2$ (1.5 equiv)	CsF (3 equiv)	1,4-dioxane, 80 °C, 18 h	72

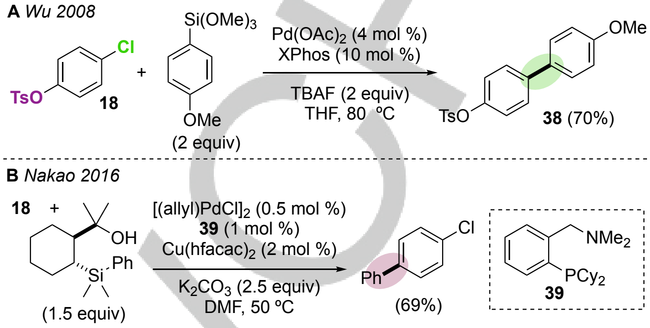


The selectivity of Pd-catalyzed Suzuki coupling in the presence of NHC ligands is less chloride-selective. The Pd/IPr (**36**)-catalyzed Suzuki coupling of **18** with an excess of boronic acid provides mostly the diarylated product resulting from both C—Cl and C—OTs cleavage (Scheme 24A).[64] The tosylate group is retained in the only monoarylated product observed, suggesting that this catalytic system is also perhaps slightly biased toward C—Cl cleavage. However, Luo and Lu reported that that a Pd/IPr* catalyst (**37**) promotes selective Suzuki coupling of **18** at tosylate (Scheme 24B).[65] This ligand was also used for a tosylate-selective cross-coupling of **18** with a terminal alkyne.[66]



Scheme 24. (A) A Pd/IPr catalyst effects diarylation of **18** under Suzuki coupling conditions using an excess of boronic acid[64] and (B) a Pd/IPr* catalyst promotes Suzuki coupling selectively at tosylate.[65]

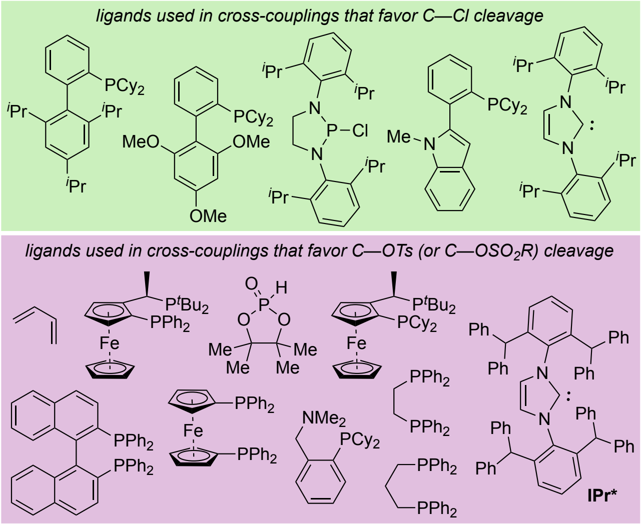
Hiyama-type couplings of **18** have shown variable chemoselectivity. Wu reported that the Pd/XPhos catalyzed coupling of **18** with a trimethoxy(aryl)silane leads to retention of the tosylate group to afford only product **38** (Scheme 25A).[67] However, cross-coupling of **18** with a phenyl silane in the presence of a P,N ligand (**39**) leads to preferential reaction at tosylate (Scheme 25B).[68]



Scheme 25. (A) Pd/XPhos-catalyzed Hiyama coupling proceeds through C—Cl, rather than C—OTs, cleavage, while (B) Pd/**39**-catalyzed coupling favors reaction at tosylate.[67,68]

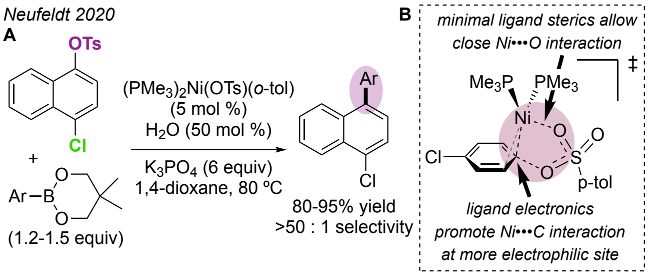
Selectivity has also been reported in a few other less traditional couplings of chlorophenyl tosylate **18**. For example, **18** undergoes tosylate-selective reaction in a Pd/dppe-catalyzed carbonylative Suzuki coupling,[69] a Pd/dppf-catalyzed reductive homocoupling,[70] and a Pd/dppf-catalyzed decarboxylative coupling with an α,β-unsaturated carboxylic acid.[71]

The different chemoselectivities of the Pd-catalyzed cross-couplings discussed so far in this section have not been systematically studied or explained. None of the chloride-selective and tosylate-selective couplings were evaluated using exactly the same ligand. However, close inspection of the ligands used in these studies reveals that bulky monodentate ligands were always used in the Pd-catalyzed reactions that favor C—Cl cleavage, while bidentate or smaller monodentate ligands were almost always used in those that favor C—O cleavage (a notable exception is IPr*,[65] Scheme 26).



Scheme 26. Bulky monodentate ligands were used in all reported Pd-catalyzed couplings that favor C—Cl cleavage, while bidentate ligands were used in almost all of those that favor C—OTs (or other sulfonate) cleavage. See the earlier schemes and text in this section for context.

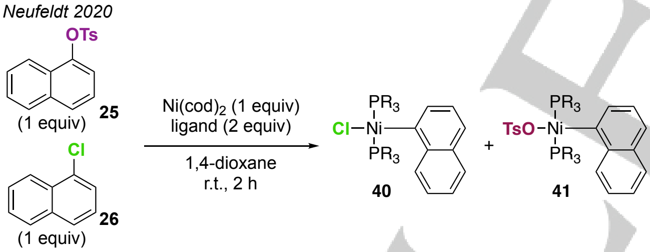
One recent study involving nickel catalysis provides evidence that ligand identity can be the determining factor in Cl vs. OTs selectivity. Neufeldt et al. showed that a Ni/PMe_3 catalytic system can promote highly selective Suzuki coupling of chloroaryl tosylates through C—O cleavage (Scheme 27A).[32] PMe_3 has also been reported to promote preferential reaction of tosylates in a Ni-catalyzed cross-coupling with umpolung aldehydes.[72]

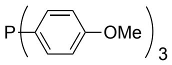
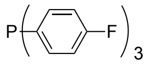
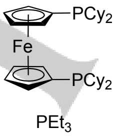


Scheme 27. (A) Nickel supported by PMe_3 ligands enables the first Suzuki coupling that is selective for reaction of tosylate over chloride. (B) DFT studies suggest the unique effect of PMe_3 relates to both sterics and electronics.[32]

The selectivity of oxidative addition at Ni/PR_3 was examined more closely in stoichiometric studies.[32] A variety of ligands were evaluated in an intermolecular competition between an aryl chloride and tosylate, and only PMe_3 and $PPhMe_2$ provide good selectivity for reaction of tosylate (Table 6). Triarylphosphines give high selectivity for reaction at chloride, while some other alkylphosphines give a mixture of products.

Table 6. Stoichiometric studies illustrate the effect of phosphine ligands on the selectivity of oxidative addition at Ni^0.[32]



entry	ligand	**40** : **41**	entry	ligand	**40** : **41**
1	PPh_3	>99 : 1	7	PCy_3	1.5 : 1
2		>99 : 1	8	$P(n\text{-}Bu)_3$	1.1 : 1
			9	$P(i\text{-}Bu)_3$	2.9 : 1
3		>99 : 1	10[a]		>99 : 1
4	$PPhMe_2$	1 : 5.7			
5	$PPhEt_2$	2.2 : 1	11	PEt_3	1.8 : 1
6	PPh_2Me	1 : 1	12	PMe_3	1 : 6.3

[a]With 1 equiv of bisphosphine.

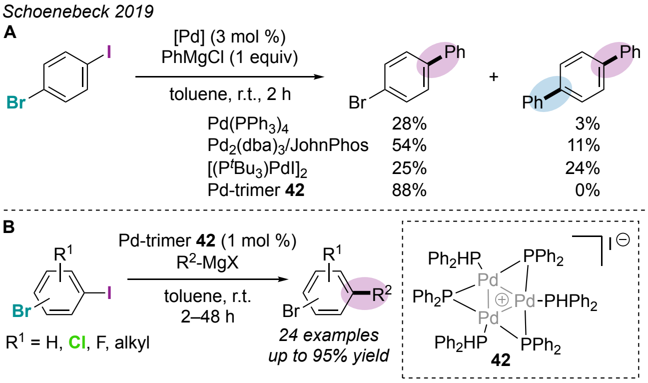
DFT calculations suggest that the unique selectivity of PMe_3 can be attributed to both steric and electronic factors (Scheme 27B). Interestingly, an isolated example from Weix and coworkers indicates that nickel supported by a bipyridine ligand can also favor reaction of tosylate over chloride in a Pd/Ni-catalyzed cross-electrophile coupling of a chloroaryl tosylate with an aryl triflate.[73] Taken together, the literature suggests that ligand identity can strongly influence Cl vs. OTs chemoselectivity. A systematic study comparing the use of identical ligands for different reaction classes would be necessary to disentangle the influences of ligand vs. nucleophilic coupling partner or other reaction conditions.

Divergent Selectivity Between Two Different Halides

The typical order of reactivity of arylhalides toward oxidative addition is I > Br > Cl. For this reason, the literature is replete with examples of selective cross-coupling at C—I and C—Br and bonds in the presence of C—Cl bonds. However, in this section we focus on examples of halide vs. halide selectivity that deviate from the conventional halide reactivity trend or that address challenges related to mono vs. difunctionalization of bromoiodoarenes.

Iodide vs. Bromide (Monofunctionalization)

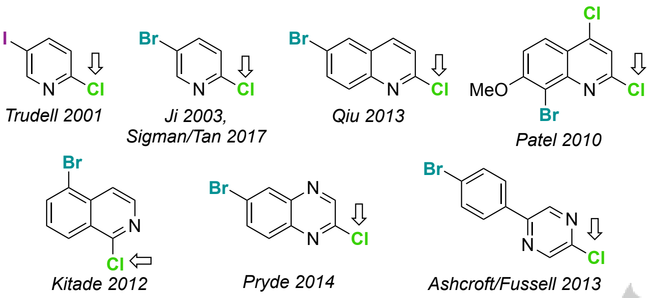
Complex molecule syntheses involving sequential cross-coupling reactions often exploit (hetero)aryl iodides as the electrophile in the first coupling step. This is because iodides are usually the most reactive of the (pseudo)halides due to the weak C—I bond strength, and selective coupling of an organoiodide can typically be achieved in the presence of chlorides and triflates (for one of myriad examples, see Scheme 3B). However, chemoselective cross-couplings of *bromo*iodoarenes can be challenging: the difference in C—I and C—Br bond strengths is not so large, and difunctionalized products are commonly formed in addition to the desired product of a single cross-coupling via C—I cleavage.[74] This challenge was highlighted in 2019 by Schoenebeck in a report showing that traditional Pd^0 or Pd^I/Pd^I catalysts perform poorly in the Kumada coupling of *p*-bromoiodobenzene (Scheme 28A).[75] Remarkably, however, high selectivity for the mono-coupled product can be achieved by using a cationic palladium trimer (Scheme 28B). DFT calculations show that the energy barriers for oxidative addition at the trimeric palladium catalyst are high compared to monomeric Pd-phosphine catalysts. While oxidative addition at C—I is still energetically accessible, C—Br and C—Cl activation are not. As a result, the trimeric Pd catalyst is highly selective for C—I insertion, even in the presence of other electrophilic functional groups.



Scheme 28. While traditional Pd^0 and Pd^I catalysts give low yields of mono-cross-coupled product, a Pd-trimer gives high selectivity for exclusive cross-coupling at iodide over bromide.[75]

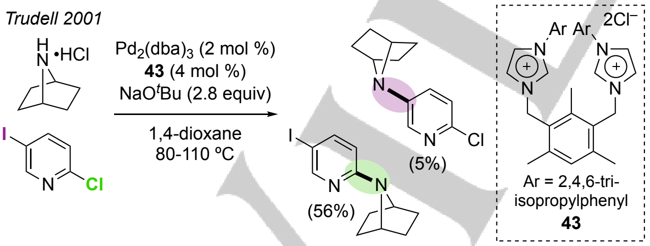
Chloride vs. Bromide and/or Iodide (Inverted Selectivity)

Although chlorides are usually less reactive electrophiles than bromides or iodides, several exceptions have been reported involving halogenated heteroaromatic substrates. These exceptions take advantage of electronic biases of the substrate, sometimes in combination with catalyst control, to achieve selective cross-coupling through cleavage of the conventionally less reactive C—Cl bond. In particular, although chemoselectivity between halides is usually determined by C—X bond strength, in some cases a stronger bond (C—Cl) can be preferentially cleaved when the chloride resides at the most electrophilic site of a heteroarene. For 6-membered azines, electronics generally favor oxidative addition at a carbon adjacent to nitrogen (e.g., C2 of pyridine).[5,76] Furthermore, azines are more electron-deficient than benzenes, and as such, electronics can favor oxidative addition of a heteroaryl–halide bond over an aryl–halide bond. These biases have been exploited to achieve selective cross-coupling through C—Cl cleavage of the substrates in Scheme 29. Of these examples, reactions with evidence for ligand-influenced selectivity are discussed in more detail below.



Scheme 29. Substrates that have been shown to undergo selective cross-coupling at the indicated chloride, despite the presence of a weaker C—Br or C—I bond.[77,78,79,80,81,82,83,84]

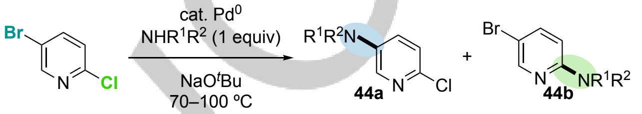
A few reports have examined the reactivity of 2-chloropyridine bearing a 5-bromo or -iodo substituent. For this substrate class, the chloride resides at the most electrophilic site of the pyridine ring, while the heavier halogen at C5 is at one of the least electrophilic positions. In 2001, Trudell reported that a Pd/bisimidazol-2-ylidene catalytic system is effective for *N*-arylation of 7-azabicyclo[2.2.1]heptane using 2-chloro-5-iodopyridine via preferential C—Cl cleavage (Scheme 30).[77]



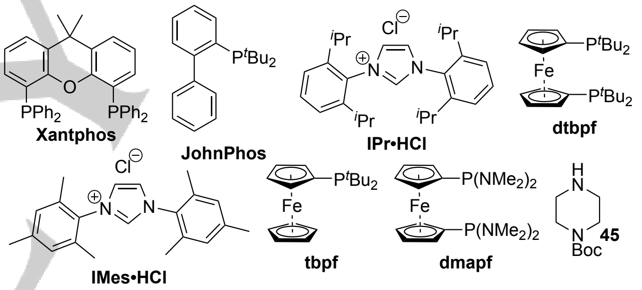
Scheme 30. Pd-catalyzed amination of 2-chloro-5-iodopyridine in the presence of a bisimidazol-2-ylidene ligand favors reaction of C—Cl over C—I.[77]

Although the role of the unusual bisimidazol-2-ylidene ligand in promoting this selectivity was not discussed, subsequent studies using 5-bromo-2-chloropyridine provide strong evidence that ligands influence the cross-coupling selectivity with this substrate (Table 7). In 2003, Ji examined a series of ligands for a Buchwald-Hartwig amination of 5-bromo-2-chloropyridine.[78] Most ligands studied in this paper promote C5—Br cleavage,[85] but the NHC ligand IMes was unusual in that it favors reaction of C2—Cl by about 3:1 over C5—Br. Sigman and Tan later used a ligand parameterization strategy for reaction optimization to identify dmapf as a diphosphine that promotes near-exclusive reaction at chloride in this system.[79] This ligand enables cross-coupling at C2 of a variety of substituted 5- or 3-bromo-2-chloropyridines with 1° and 2° amines. The authors provided evidence that ligand electronics were the most important factor in selectivity, and that a strongly donating diphosphine like dmapf promotes reaction at the electrophilic C2—Cl site by enhancing the interaction energy between catalyst and substrate during oxidative addition.

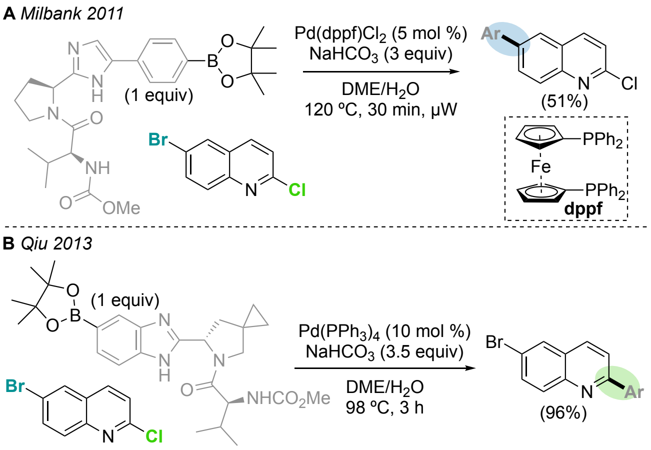
Table 7. The chemoselectivity of Pd-catalyzed amination of 5-bromo-2-chloropyridine is ligand-dependent.[78,79]



reference	ligand	solvent	amine	**44a** (%)	**44b** (%)
Ji 2003	Xantphos	toluene	**45**	70	0
	Johnphos	toluene	**45**	65	3
	IPr•HCl	toluene	**45**	79	8
	IMes•HCl	toluene	**45**	18	59
Sigman/ Tan 2017	P^tBu_3	toluene	$PhNH_2$	>99	0
	dtbpf	toluene	$PhNH_2$	10	30
	dtbpf	dioxane	$PhNH_2$	8	68
	tbpf	dioxane	$PhNH_2$	99	0
	dmapf	dioxane	$PhNH_2$	<1	94

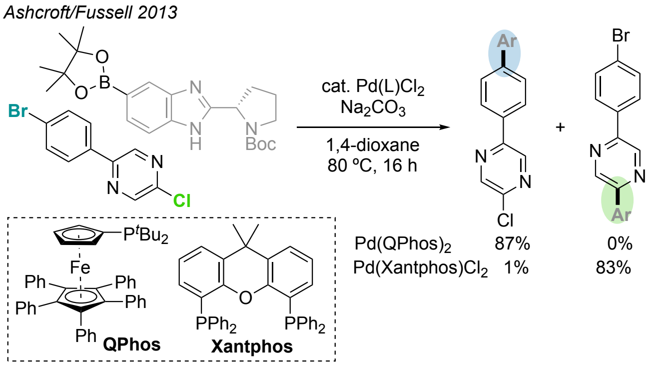


Another substrate that has been shown to undergo ligand-controlled chemodivergent cross-coupling is 6-bromo-2-chloroquinoline. In this case, the chloride is situated on the more electrophilic azine ring while bromide is on the carbocycle. Although Pd/dppf-catalyzed Suzuki coupling of this substrate proceeds through C—Br cleavage (Scheme 31A),[86] a Pd/PPh_3 system was reported to catalyze Suzuki coupling at chloride (Scheme 31B).[80]



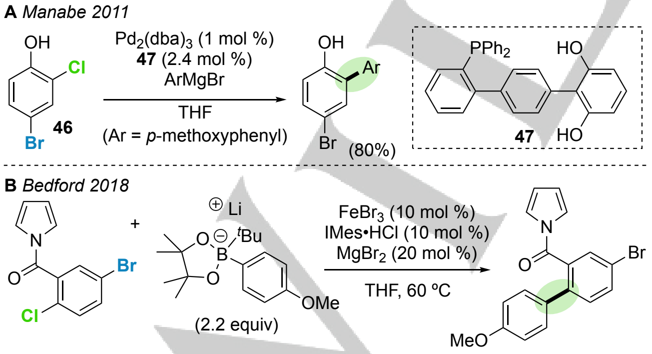
Scheme 31. Pd-catalyzed Suzuki coupling of 6-bromo-2-chloroquinoline proceeds through C—Br cleavage with dppf, but C—Cl cleavage with PPh_3.[86,80]

Finally, Suzuki cross-coupling of 2-(4-bromophenyl)-5-chloropyrazine also proceeds with ligand-controlled chemoselectivity. While QPhos strongly favors reaction of the bromide on the carbocycle, Xantphos promotes cross-coupling of the chloride on the pyrazine ring (Scheme 32).[84] An explanation for the divergent selectivity was not proposed, but the authors noted that chloride selectivity seems to benefit from the rigidity of the Xantphos ligand.



Scheme 32. Pd-catalyzed Suzuki coupling of 2-(4-bromophenyl)-5-chloropyrazine proceeds through C—Br cleavage with QPhos, but C—Cl cleavage with Xantphos.[84]

While the use of electronically-biased heteroarenes is by far the most common scenario for achieving selective cross coupling of C—Cl over C—Br, *ortho*-directing groups can also be effective at promoting reaction of the stronger C—X bond in dihalogenated arenes. Manabe demonstrated coupling of **46** with a Grignard reagent to provide primarily the product of C—Cl cleavage (Scheme 33A).[87] Selectivity was attributed to the directing effect of the *ortho*-hydroxyl group, which was proposed to interact with an oxygen of ligand **47** via a bridging Mg^{2+}. Bedford also reported an Fe-catalyzed Suzuki coupling involving selective reaction at chloride using a substrate that contained an amide *ortho* to Cl (Scheme 33B).



Scheme 33. Directing groups can promote selective reaction of chloride over bromide.

Conclusions and Outlook

The examples discussed in this minireview highlight the role of ligand, metal, solvent, additives, and substrate biases on the chemoselectivity of cross-couplings. Of these selectivity-influencing factors, the most promising area for further development lies in catalyst-controlled selectivity (metal or ligand). This is because catalyst-control has the potential to be much more general than other types of selectivity control. However, more systematic studies are needed to deconvolute the effects of catalyst, solvent, additives, and nucleophilic coupling partner on chemoselectivity between two or more different (pseudo)halides.

The best understood strategy for controlling chemoselectivity exists in the context of competing chloride and triflate electrophiles, where monoligated Pd favors reaction at chloride and bisligated Pd prefers to react at triflate. However, the origin of selectivity in many other instances of chemodivergence remains unclear. Additionally, besides the pairs discussed in this review, one could imagine other pairs of electrophiles for which chemodivergent couplings might be investigated in the future. One notable example is selectivity between two different C—O electrophiles. Exploration of this class of selectivity has only just begun with a seminal publication by Weix involving catalyst-controlled selectivity between aryl triflates and tosylates.[73, 88] Further development of the field of chemodivergent cross-coupling will not only expand the synthetic chemist's toolbox, but is certain to also inform future advances in other selective catalytic transformations.

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Keywords: chemoselectivity • cross-coupling • mechanism • palladium • nickel

References

[1] Johansson Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. *Angew. Chem. Int. Ed*. **2012**, *51*, 5062-5085.

[2] Dobrounig, P.; Trobe, M.; Breinbauer, R.; *Monatsh Chem.* **2017**, *148*, 3-35.

[3] Jiang, S.; Zhang, L.; Cui, D.; Yao, Z.; Gao, B.; Lin, J.; Wei, D. *Scientific Reports* **2016**, *6*, 34750.

[4] Hernandes, M. Z.; Cavalcanti, S. M. T.; Moreira, D. R. M.; De Azevedo Jr., W. F.; Leite, A. C. L. *Curr. Drug Targets* **2010**, *11*, 303-314.

[5] Almond-Thynne, J.; Blakemore, D. C.; Pryde, D. C.; Spivey, A. C. *Chem. Sci.* **2017**, *8*, 40-62.

[6] Selected examples: a) Afagh, N. A.; Yudin, A. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 262-310; b) Wang, J.; Seefeld, M. A.; Luengo, J. *Tetrahedron Lett.* **2011**, *52*, 6346-6348; c) Linshoeft, J.; Heinrich, A. C. J.; Segler, S. A. W.; Gates, P. J.; Staubitz, A. *Org. Lett.* **2012**, *14*, 5644-5647; d) Ueda, S.; Buchwald, S. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 10364-10367; e) Xu, T.; Alper, H.; *J. Am. Chem. Soc.* **2014**, *136*, 16970-16973; f) Kumar, K. A.; Kannaboina, P.; Rao, D. N.; Das, P. *Org. Biomol. Chem*. **2016**, *14*, 8989-8997.

[7] Selected examples: a) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc*. **2008**, *130*, 14468-14470; b) Shimasaki, T.; Tobisu, M.; Chatani, N. *Angew. Chem. Int. Ed.* **2010**, *49*, 2929-2932; c) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573-13576; d) Hong, X.; Liang, Y.; Houk, K. N. *J. Am. Chem. Soc.* **2014**, *136*, 2017-2025; e) Chatupheeraphat, A.; Liao, H.-H.; Srimontree, W.; Guo, L.; Minenkov, Y.; Poater, A.; Cavallo, L.; Rueping, M. J. Am. Chem. Soc. **2018**, *183*, 3724-3735; f) Halima, T.; B.; Zhang, W.; Yalaoui, I.; Hong, X.; Yang, Y.-F.; Houk, K. N.; Newman, S. G. *J. Am. Chem. Soc.* **2017**, *139*, 1311-1318.

[8] Selected examples: a) Stille, J. K. *Angew. Chem. Int. Ed.* **1986**, *25*, 508-524; b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457-2483; c) Gildner, P. G.; Colacot, T. J. *Organometallics* **2015**, *34*, 5497-5508; d) Haas, D.; Hammann, J. M.; Greiner, R.; Knochel, P. *ACS Catal.* **2016**, *6*, 1540-1552; e) Biffis, A.; Centomo, P.; Del Zotto, A.; Zecca, M. *Chem. Rev.* **2018**, *118*, 2249-2295; f) Campeau, L.-C.; Hazari, N. *Organometallics* **2019**, *38*, 3-35.

[9] Selected examples: a) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed.* **2005**, *44*, 442-4489; b) Martin, R.; Buchwald, S. L.; *Acc. Chem. Res.* **2008**, *41*, 1461-1473; c) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev*. **2011**, *40*, 5151-5169; d) Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564-12649; e) Sherwood, J.; Clark, J. H.; Fairlamb, I. J. S.; Slattery, J. M. *Green Chem.* **2019**, *21*, 2164-2213.

[10] Labinger, J. A. *Organometallics* **2015**, *34*, 4784-4795.

[11] Fitton, P.; Rick, E. A.; *J. Organomet. Chem.* **1971**, *28*, 287-291.

[12] Matsumoto, H.; Inaba, S.-i.; Riecke, R. D. *J. Org. Chem.* **1983**, *48*, 840-843.

[13] Echavarren, A. M.; Stille, J. K. *J. Am. Chem. Soc.* **1987**, *109*, 5478-5486.

[14] These conditions also lead to C—Br cleavage in a Suzuki cross-coupling: Oh-e, T.; Miyaura, N.; Suzuki, A. *Synlett* **1990**, 221-223.

[15] A follow-up study indicates that the ratio of products formed under the conditions for Table 1 entry 4 is about 6.7 : 1; see Ansari, N. N.; Commings, M. M.; Söderberg, B. C. G. *Tetrahedron* **2018**, *74*, 2547-2560.

[16] Kamikawa, T.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 7087-7090.

[17] Littke, A. F.; Dai, C. Y.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020-4028.

[18] Littke, A. F.; Schwarz, L.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 6343-6348.

[19] Niemeyer, Z. L.; Milo, A.; Hickey, D. P.; Sigman, M. S. *Nature Chem*. **2016**, *8*, 610-617.

[20] Schoenebeck, F.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 2496-2497.

[21] Lyngvi, E.; Sanhueza, I. A.; Schoenebeck, F. Organometallics **2015**, 34, 805-812.

[22] Manabe, K.; Ohba, M.; Matsushima, Y. *Org. Lett.* **2011**, *13*, 2436-2439.

[23] Proutiere, F.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2011**, *50*, 8192-8195.

[24] Proutiere, F.; Aufiero, M.; Schoenebeck, F. *J. Am. Chem. Soc.* **2012**, *134*, 606-612.

[25] Proutiere, F.; Schoenebeck, F. *Synlett* **2012**, *23*, 645-648.

[26] Reeves, E. K.; Bauman, O. R.; Mitchem, G. B.; Neufeldt, S. R. *Isr. J. Chem.* **2020**, *60*, 406-409.

[27] Reeves, E. K.; Humke, J. J.; Neufeldt, S. R. *J. Org. Chem.* **2019**, 84, *18*, 11799-11812.

[28] Ackerman, L. K. G.; Lovell, M. M.; Weix, D. J. *Nature* **2015**, *524*, 454-457.

[29] Huang, L.; Ackerman, L. K. G.; Kang, K.; Parsons, A. M.; Weix, D. J. *J. Am. Chem. Soc*. **2019**, *141*, 10978-10978.

[30] Li, Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815-8823.

[31] Bajo, S.; Laidlaw, G.; Kennedy, A. R.; Sproules, S.; Nelson, D. J. *Organometallics* **2017**, *36*, 1662-1672.

[32] Entz, E. D.; Russell, J.; Hooker, L.; Neufeldt, S. R. *J. Am. Chem. Soc.* **2020**, *142*, 15454-15463.

[33] Hooker, L. V.; Neufeldt, S. R. *Tetrahedron* **2018**, *74*, 6717-6725.

[34] Saulnier, M. G.; Kadow, J. F.; Tun, M. M.; Langley, D. R.; Vyas, D. M. *J. Am. Chem. Soc.* **1989**, *111*, 8320-8321.

[35] Farina, V.; Krishnan, B.; Marshall, D. R.; Roth, G. P. *J. Org. Chem.* **1993**, *58*, 5434-5444.

[36] Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313-348.

[37] Espino, G.; Kurbangalieva, A.; Brown, J. M. *Chem. Commun.* **2007**, 1742-1744.

[38] See also: a) Hassan, Z.; Hussain, M.; Villinger, A.; Langer, P. *Tetrahedron* **2012**, *68*, 6305–6313; b) Yang, X.; Xu, G.; Tang, W. *Tetrahedron* **2016**, *72*, 5178–5183

[39] Wang, J.; Seefeld, M. A.; Luengo, J. *Tetrahedron Lett.* **2011**, *52*, 6346-6348.

[40] Wern, C.; Ehrenreich, C.; Joosten, D.; vom Stein, T.; Buchholz, H.; König, B. *Eur. J. Org. Chem.* **2018**, 5644-5656.

[41] Kalvet, I.; Magnin, G.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 1581-1585.

[42] Kalvet, I.; Sperger, T.; Scattolin, T.; Magnin, G.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2017**, *56*, 7078-7082.

[43] Scattolin, T.; Senol, E.; Yin, G.; Guo, Q.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2018**, *57*, 12425-12429.

[44] Kalvet, I.; Deckers, K.; Funes-Ardoiz, I.; Magnin, G.; Sperger, T.; Kremer, M.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 7721-7725.

[45] Keaveney, S. T.; Kundu, G.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2018**, *57*, 12573-12577.

[46] Mendel, M.; Kalvet, I.; Hupperich, D.; Magnin, F. Schoenebeck, F. *Angew. Chem. Int. Ed.* **2020**, *59*, 2115-2119.

[47] Shen, C.; Wei, Z.; Jiao, H.; Wu, X.-F. *Chem. Eur. J.* **2017**, *23*, 13369-13378.

[48] Everson, D.; Jones, B. A.; Weix, D. J. *J. Am. Chem. Soc.* **2012**, *134*, 6146-6159.

[49] For similar selectivity using Ni/bpy in a different coupling, see Zhao, Y.; Weix, D. J. *J. Am. Chem. Soc.* **2015**, *137*, 3237-3240.

[50] Olivares, A. M.; Weix, D. *J. Am. Chem. Soc.* **2018**, *140*, 2446-2449.

[51] Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 8704-8705.

[52] Jun, T.; Yoshitaka, N.; Hitoshi, K.; Nobuaki, K. *Chem. Lett.* **2003**, *32*, 890-891.

[53] Limmert, M. E.; Roy, A. H.; Hartwig, J. F. *J. Org. Chem.* **2005**, *70*, 9364-9370.

[54] Ackermann, L.; Althammer, A. *Org. Lett.* **2006**, *8*, 3457-3460.

[55] Chen, X.; Quan, Z.-J.; Wang, X.-C. *Appl. Organomet. Chem.* **2015**, *29*, 296-300.

[56] Piontek, A.; Ochędzan-Siodłak, W.; Bisz, E.; Szostak, M. *Adv. Synth. Catal.* **2019**, *361*, 2329-2336.

[57] Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 13848-13849.

[58] So, C. M.; Zhou, Z.; Lau, C. P.; Kwong, F. Y. *Angew. Chem. Int. Ed.* **2008**, *47*, 6402-6406.

[59] Ackermann, L.; Sandmann, R.; Song, W. *Org. Lett.* **2011**, *13*, 1784-1786.

[60] Gøgig, T. M.; Lindhardt, A. T.; Dehane, M.; Grouleff, J.; Skrydstrup, T. *Chem. Eur. J.* **2009**, *15*, 5950-5955.
[61] Nguyen, H. N.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 11818-11819.
[62] Zhang, L.; Meng, T.; Wu, J. *J. Org. Chem.* **2007**, *72*, 9346-9349.
[63] Ackermann, L.; Potukuchi, H. K.; Althammer, A.; Born, R.; Mayer, P. *Org. Lett.* **2010**, *12*, 1004-1007.
[64] Wang, Z.-Y.; Chen, G.-Q.; Shao, L.-X. *J. Org. Chem.* **2012**, *77*, 6608-6614.
[65] Tang, Y.; Yang, F.; Nie, S.; Wang, L.; Luo, Z.; Lu, H. *Chin. J. Org. Chem.* **2015**, *35*, 705-711.
[66] Lu, H.; Wang, L.; Yang, F.; Wu, R.; Shen, W. *RSC Adv.* **2014**, *4*, 30447-30452.
[67] Zhang, L.; Wu, J. *J. Am. Chem. Soc*. **2008**, *130*, 12250-12251.
[68] Ohgi, A.; Semba, K.; Hiyama, T.; Nakao, Y. *Chem. Lett.* **2016**, *45*, 973-975.
[69] Hao, C. Y.; Wang, D.; Li, Y. W.; Dong, L. L.; Jin, Y.; Zhang, X. R.; Zhu, H. Y.; Chang, S. *RSC Adv.* **2016**, *6*, 86502-86509.
[70] Zhong, S.; Chen, M.; Liu, G.; Sun, C.; Liu, W. *Appl. Organometal. Chem.* **2017**, *31*, e3705.
[71] Zhang, W.; Chen, G.; Wang, K.; Xia, R. *Appl. Organometal. Chem.* **2019**, *33*, e4914.
[72] Lv, L.; Zhu, D.; Tang, J.; Qiu, Z.; Li, C.-C.; Gao, J.; Li, C.-J. *ACS Catal.* **2018**, *8*, 4622-4627.
[73] Kang, K.; Huang, L.; Weix, D. J. *J. Am. Chem. Soc.* **2020**, *142*, 10634-10640.
[74] In one unusual example, *p*-bromoiodobenzene was reported to undergo Ni-catalyzed coupling with PhMgBr to provide 4-iodobiphenyl as the major product in about 40% yield; see: Styring, P.; Grindon, C.; Fisher, C. M. *Catal. Lett.* **2001**, *77*, 219-225.
[75] Diehl, C. J.; Scattolin, T.; Englert, U.; Schoenebeck, F. *Angew. Chem. Int. Ed.* **2018**, *58*, 211-215.
[76] Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N. *J. Am. Chem. Soc.* **2007**, *129*, 12664-12665.
[77] Chen, J.; Trudell, M. L. *Org. Lett.* **2001**, *3*, 1371-1374.
[78] Ji, J.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611-4614.
[79] Keylor, M. G.; Niemeyer, Z. L.; Sigman, M. S.; Tan, K. L. *J. Am. Chem. Soc.* **2017**, *139*, 10613-10616.
[80] Y. L. Qiu, C. Wang, X. Peng, H. Cao, L. Ying, X. Gao, B. Wang and Y. S. Or, WO2013052369 A1, **2013.**
[81] N. D. Patel, C. H. Senanayake, W. Tang, X. Wei and N. K. Yee, WO 2010129451 A1, **2010**.
[82] M. Kitade, S. Ohkubo and S. Yamashita, WO2012093708 A1, **2012.**
[83] Tran, T. D.; Wakenhut, F.; Pickford, C.; Shaw, S.; Westby, M.; Smith-Burchnell, C.; Watson, L.; Paradowski, M.; Milbank, J.; Brimage, R. A.; Halstead, R.; Glen, R.; Wilson, C. P.; Adam, F.; Hay, D.; Chiva, J.-Y.; Nichols, C.; Blakemore, D. C.; Gardner, I.; Dayal, S.; Pike, A.; Webster, R.; Pryde, D. C. *ChemMedChem* **2014**, *9*, 1378-1386.
[84] Ashcroft, C. P.; Fussell, S. J.; Wilford, K. *Tetrahedron Lett.* **2013**, *54*, 4529-4532.
[85] PPh_3 also promotes reaction at C—Br in a Suzuki cross-coupling of 5-bromo-2-chloropyridine; see Chamas, Z. E. A.; Marchi, E.; Modelli, A.; Fort, Y.; Ceroni, P.; Mamane, V. *Eur J. Org. Chem.* **2013**, 2316-2324.
[86] J. B. J. Milbank, D. C. Pryde and T. D. Tran, WO2011004276 A1, **2011**.
[87] Ishikawa, S.; Manabe, K. *Tetrahedron* **2011**, *67*, 10156-10163.
[88] See also (a) Xiong, B.; Li, Y.; Wei, Y.; Kramer, S.; Lian, Z. *Org. Lett.* **2020**, *22*, 6334-6338; (b) Tang, J.; Liu, L. L.; Yang, S.; Cong, X.; Luo, M.; Zeng, X. *J. Am. Chem. Soc.* **2020**, *142*, 7715-7720.

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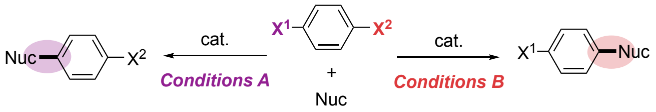

In cross-coupling reactions, chemoselectivity becomes a concern when two or more (pseudo)halides are present in the substrates. This minireview surveys cases in which divergent chemoselectivity between electrophiles can be achieved under different reaction conditions. Particular emphasis is placed on discussing the possible mechanistic origins of selectivity control.

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