Site-Selective Cross-Coupling of Remote Chlorides Enabled by Electrostatically-Directed Palladium Catalysis

William A. Golding, Robert Pearce-Higgins and Robert J. Phipps*

Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, United Kingdom.

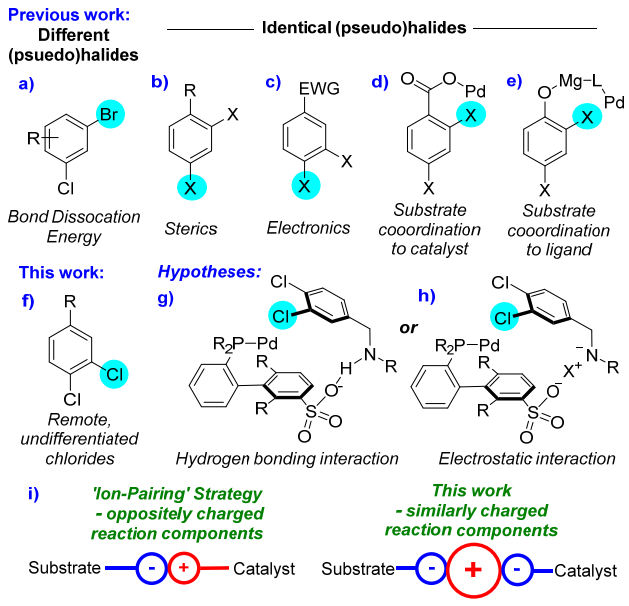
Supporting Information Placeholder

ABSTRACT: Control of site-selectivity in chemical reactions that occur remote from existing functionality remains a major challenge in synthetic chemistry. We describe a strategy that enables three of the most commonly used cross-coupling processes to occur with high site-selectivity on dichloroarenes which bear acidic functional groups. We have achieved this by repurposing an established sulfonylated phosphine ligand to exploit its inherent bifunctionality. Mechanistic studies suggest that the sulfonate group engages in attractive electrostatic interactions with the associated cation of deprotonated substrate, guiding cross-coupling to the chloride at the arene *meta*-position. This counterintuitive combination of anionic ligand and anionic substrate demonstrates an alternative design principle when considering applying non-covalent interactions to direct catalysis.

Transition metal-catalyzed cross coupling has become a key tool in the synthetic chemist's arsenal.[1] A key feature is its predictability with regard to which functional group undergoes reaction. In simple cases, with only a single (pseudo)halide and a single organometallic, the outcome is certain. In more complex substrates bearing multiple halides, particularly heteroarenes, it can be less obvious.[2] For standard arenes, C-X Bond dissociation energy is the strongest indicator of reactivity towards oxidative addition, in some cases allowing iterative cross coupling of substrates bearing several different halides (Figure 1, a).[3,4,5] An often more challenging scenario involves arenes bearing the same halide at multiple sites. For specific substitution patterns it may be possible to differentiate them according to steric (b) and/or electronic (c) considerations, as typically the least hindered and most electron deficient C-X bonds will be most reactive.[3b, 6] In some cases, it has been possible to invert intrinsic selectivity by employing a directing group to interact with either the palladium catalyst (d)[7] or a bifunctional ligand for palladium which complexes with a magnesium salt of the substrate after deprotonation of both with strong base (e).[8] However, these strategies have only resulted in coupling *proximal* to the directing group, at the *ortho* position.

Arguably the greatest challenge in this area, which remains largely unaddressed, is that of how to achieve remote site-selective coupling on arenes with minimal steric or electronic bias (f).[9,10] Access to polyhalogenated arenes bearing multiple identical halogens is typically more straightforward than regioselectively accessing variants bearing non-identical halogens. Thus development of catalyst-controlled methods to differentiate identical, remote halogens could rapidly add value and complexity to readily available building blocks. We hypothesized that this challenge might be met using bifunctional phosphine ligands that bear a remote functional group able to interact with the substrate though a non-covalent interaction.[11,12] With the proper scaffold, a pseudo-intramolecular transition state could realize site-selective oxidative addition through either hydrogen bonding or electrostatic interactions (Fig 1, g or h). A variety of sulfonylated phosphine ligands are known, for the purposes of carrying out catalysis in water[13] and we envisaged these may be repurposed to exploit their inherent bifunctionality. In particular, electrostatic interactions have been under-explored as directing elements for site-selective catalysis.[14,15] We recently demonstrated that an anionic sulfonate-bearing bipyridine ligand can direct C-H borylation through electrostatic interactions with a cationic substrate.[16] The pairing together of

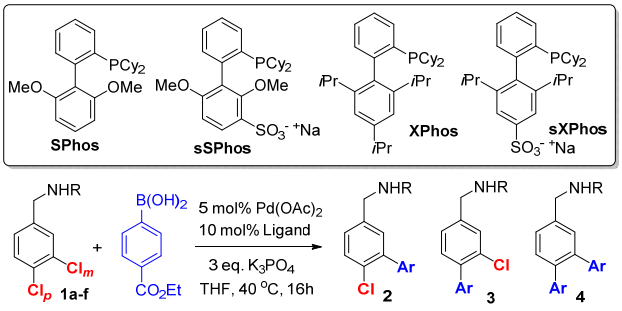
Figure 1. Site-selective cross-coupling of dihaloarenes



oppositely charged components in an 'ion-pairing' strategy, is an intuitive way to invoke attractive electrostatic interactions but this combination may not always be practical. In this work we present a distinct mechanistic concept for utilizing electrostatic interactions in which an anionic substrate and anionic catalyst are able to be united through putative interaction with a bridging alkali metal cation (Fig 1, i).

An important criterion at the outset was to develop a protocol that would be effective on aryl chlorides, given their greater availability than the corresponding bromides or iodides.[17] Accordingly, we sought to use derivatives of the dialkylbiaryl phosphine ligand family pioneered by Buchwald,[18] in which the lower aryl ring offers several positions for functionality. In 2005, Anderson and Buchwald reported sodium salts of sulfonylated **SPhos** and **XPhos**, **sSPhos** and **sXPhos**, for cross-coupling of aryl chlorides in water, which have since been used widely and are commercially available.[19,20] To probe their ability to act as bifunctional ligands, we evaluated **sSPhos** and **sXPhos** in the Suzuki coupling of *N*-Acetyl-3,4-dichlorobenzylamine (**1a**) alongside standard **SPhos** and **XPhos** (Table 1), initially to probe whether a hydrogen bonding interaction may result in site-selectivity (Figure 1,g). As expected, **SPhos** and **XPhos** gave equal coupling at the *meta* and *para* chlorides (entries 1 and 2). In contrast, **sSPhos** gave an encouraging 3.8:1 ratio, favoring Cl_m (entry 3) whilst

Table 1. Evaluation of ligand/substrate parameters[a]



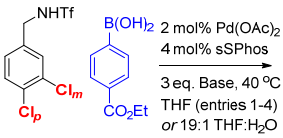
Entry	R	Ligand	% Yield 2	3	4	2:3	% Conv.
1	Ac (**1a**)	**SPhos**	19	18	17	1.1:1	65
2	Ac	**XPhos**	41	32	10	1.3:1	100
3	Ac	**sSPhos**	38	10	5	3.8:1	54
4	Ac	**sXPhos**	42	22	6	1.8:1	70
5	TFA (**1b**)	**sSPhos**	39	20	14	1.9:1	73
6	Boc (**1c**)	**sSPhos**	17	11	8	1.5:1	34
7	Ts (**1d**)	**sSPhos**	48	6	4	7.5:1	53
8	*p*Ns (**1e**)	**sSPhos**	48	2	<1	>20:1	50
9	Tf (**1f**)	**sSPhos**	78	<1	9	>20:1	91
10[b]	Tf	**sSPhos**	63	<1	31	>20:1	100
11[b,c]	Tf	**sSPhos**	60	<1	31	>20:1	100
12[b,c,d]	Tf	**sSPhos**	88 (82)	<1	11	>20:1	100
13[b,c,d]	Tf	**SPhos**	30	19	30	1.6:1	75
14[b,c,d]	Tf	**sXPhos**	67	9	10	7:1	91
15[b,c,d]	Tf	**XPhos**	40	33	22	1.2:1	88

[a] Yields determined by ^{1}H-NMR with internal standard except in parentheses (isolated) [b] Solvent used: 19:1 THF:H_2O. [c] 2 mol% $Pd(OAc)_2$ and 4 mol% ligand used. [d] 1.2 Equivalents boronic acid used.

sXPhos was inferior (entry 4). Variation of the *N*-group on the amine revealed that while trifluoroacetyl and Boc gave poor selectivity (entries 5 and 6), Tosyl increased to 7.5:1 and p-Nosyl to >20:1, albeit with moderate conversion (entries 7 and 8). Continuing the electronic trend, triflate provided excellent selectivity and now with excellent conversion (entry 9). A small amount of water as co-solvent increased conversion without reducing site-selectivity (entry 10) and Pd loading could be reduced to 2 mol% (entry 11). Reducing the boronic acid to 1.2 eq. gave less di-coupled byproduct **4** (entry 12). A control experiment on this substrate using **SPhos** demonstrated that in the absence of the sulfonate group on the ligand there is essentially no selectivity (entry 13). Under these optimized conditions, **sXPhos** gave 7:1 *m:p*, inferior to **sSPhos** (entry 14), whilst **XPhos** was non-selective (entry 15). Analysis as the reaction progressed revealed that site-selectivity remained constant over time.[21]

Given the striking increase in selectivity as the *N*-protecting groups became more electron-withdrawing, we considered whether the potassium phosphate base may be deprotonating **1f** to form a potassium salt. Indeed, stirring **1f** in d^8-THF with K_3PO_4 showed complete deprotonation by ^{1}H-NMR within 30 mins at room temperature, whilst no such changed was observed for **1a**. This suggests that the superior site-selectivity observed with the *N*-Tf group may be best rationalized by invoking an electrostatic interaction of the potassium salt of **1f** with the sulfonate group of the ligand (Figure 1,h). We sought to test this hypothesis by addition of an appropriately sized crown ether, which should disrupt this putative interaction by sequestration of the potassium cation.[12, 22] Accordingly, in the presence of 18-crown-6, site-selectivity was completely eroded, but as the crown ether became too small to complex K^+, selectivity was restored, providing support for the importance of the uncomplexed potassium cation (Scheme 1, entries 1-4). Systematic variation of the cation size suggested that it should be of a minimum ionic radius in order to achieve high selectivity (entries 5-8).

Scheme 1. Effect of crown ethers and cationic radius

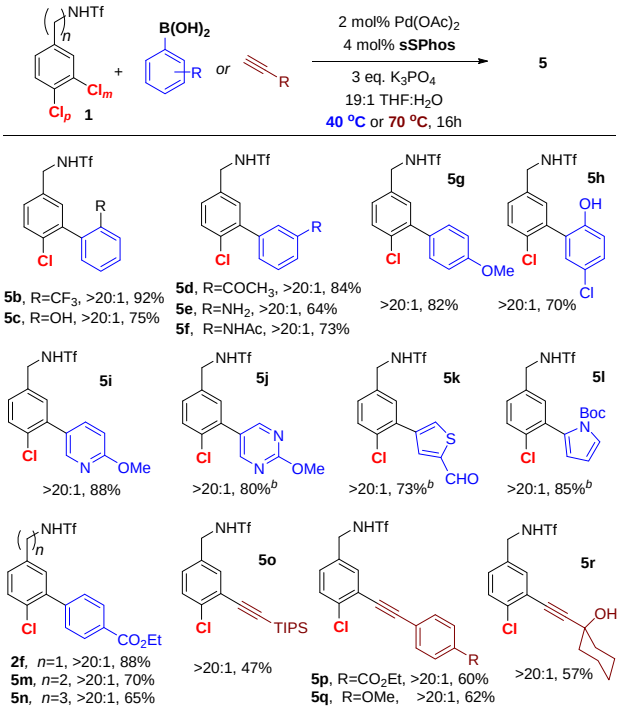


Entry	Additive (3 eq.)	Base	Selectivity (*m*/*p*)	% Conv.
1	None	K_3PO_4	>20:1	89
2	18-Crown-6	K_3PO_4	1.5:1	60
3	15-Crown-5	K_3PO_4	3.5:1	51
4	12-Crown-4	K_3PO_4	>20:1	88
5	None	Li_2CO_3	1.8:1	38
6	None	Na_2CO_3	3.8:1	68
7	None	K_2CO_3	>20:1	77
8	None	Cs_2CO_3	>20:1	60

We next evaluated the scope with regard to the boronic acid component, for which excellent site-selectivity was retained (>20:1 in all cases, Scheme 2). This included electron-deficient (**2f, 5b**) and electron-rich (**5c, 5e, 5g**) aromatics. Versatile functional groups are tolerated, including a methyl ketone (**5d**) and a free aniline (**5e**). Notably, several groups that could potentially engage in hydrogen bonding interactions with the catalyst (eg. phenol **5c** and acetamide **5f**) are tolerated well, suggesting that the presumed electrostatic mode of catalyst direction has orthogonality with potential hydrogen bonding interactions. Furthermore, a boronic acid bearing a chloride could be coupled selectivity with little evidence of further coupling of the product (**5h**), demonstrating the high level of catalyst control over which site un-

dergoes oxidative addition. Heterocyclic boronic acids including pyridine (**5i**), pyrimidine (**5j**), thiophene (**5k**) and pyrrole (**5l**) also gave excellent site-selectivity. For the latter three substrates, commercially available precatalyst **sSPhos-PdG2** was required, due to the sensitivity of the boronic acids.[23,24] Longer chain lengths did not result in reduction of site-selectivity, despite their greater flexibility (**5m**, **5n**). We evaluated whether Sonogashira coupling, to form sp^2-sp C-C bonds, would be compatible with our ligand-directed approach. This worked well under copper-free conditions giving excellent selectivity for coupling at the *meta*-chloride.[25] Several alkynes were evaluated: TIPS-acetylene (**5o**), two arylacetylenes (**5p**, **5q**), and a cyclohexanol-substituted acetylene (**5r**).

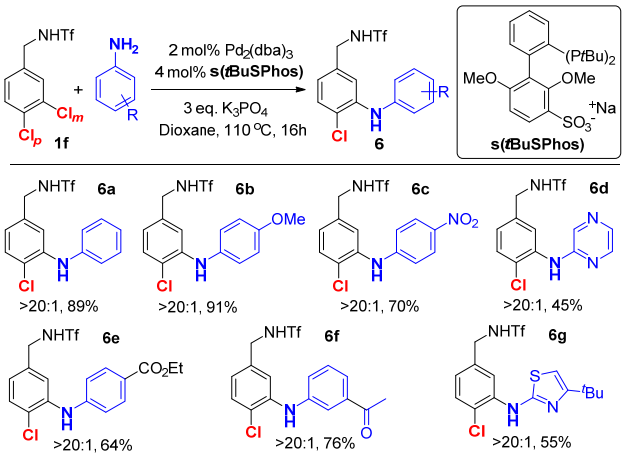
Scheme 2. Scope of Site-Selective Suzuki-Miyaura and Sonogashira couplings[a]



[a] Yields shown are isolated. Ratios of coupling at Cl_m:Cl_p were determined by ^{1}H-NMR. [b] **sSPhosPdG2** (2 mol%) was used.

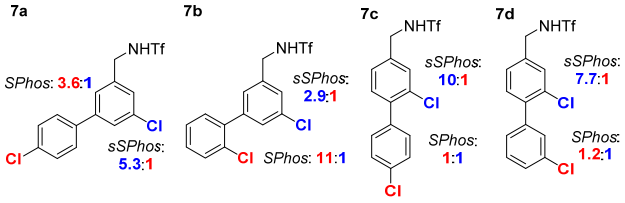
Given the importance of C-N bond-formation, we next investigated whether Buchwald-Hartwig amination would be feasible. Gratifyingly, aniline could be selectively coupled with **1f** and after optimization we found that the novel ligand **s(*t*BuSPhos)**, the P-(tBu)$_2$ version of **sSPhos,** gave superior reactivity (Scheme 3).[26] A range of electron rich (**6a, 6b**) and poor (**6c, 6e, 6f**) anilines participated as well as several aromatic heterocyclic amines (**6d** and **6g**). As previously, control experiments with standard **SPhos** gave very low selectivity.[21]

Scheme 3. Site-selective Buchwald-Hartwig coupling



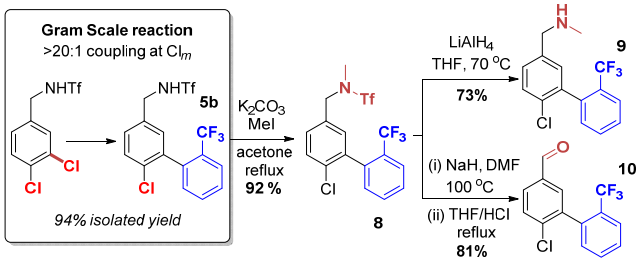
For Suzuki coupling we also examined several substrates that bear chlorides on different aromatic rings, comparing any intrinsic selectivity (**SPhos**) with directed-selectivity (**sSPhos**) (Scheme 4). In all cases, the directing effect of the ligand had a large impact on the intrinsic selectivity, pulling it dramatically towards the *meta*-chloride. Intrinsic selectivity was either reversed (**7a**, **7b**) and or went from non-selective to highly selective (**7c, 7d**). These results highlight the potential for this method in the late stage functionalization of more complex molecules that bear multiple chlorides.

Scheme 4. Competition substrates bearing chlorides on different rings



The chemistry works very effectively on gram-scale and we demonstrate several synthetic manipulations of the products involving removal of the triflate group (Scheme 5).[27]

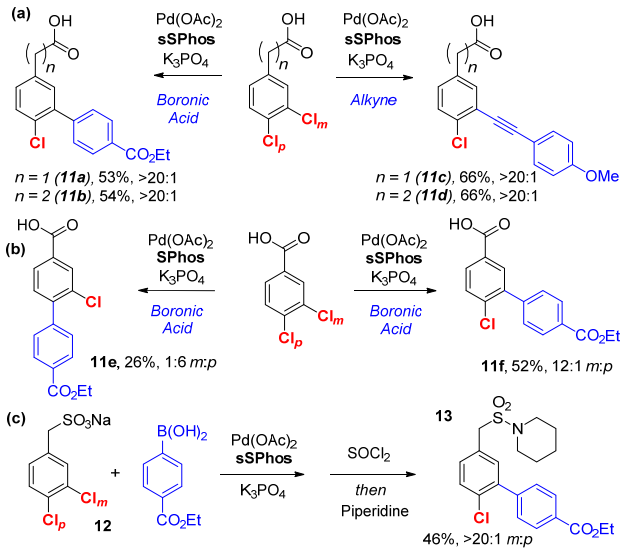
Scheme 5. Gram-scale reaction and manipulations



If our mechanistic hypothesis regarding the origin of selectivity is correct (Figure 1h), we reasoned that arenes bearing Brønsted acidic groups other than triflamide may also participate effectively as they would readily form potassium salts under the reaction conditions. Not only would this broaden the scope of the process, but also provide a further test of the

proposed mechanism. Accordingly, we evaluated 3,4-dichlorophenylacetic acid in Suzuki-Miyaura coupling using **sSPhos** and were happy to observe that, in line with our hypothesis, >20:1 site-selectivity for the *meta* chloride was again achieved (Scheme 6a, **11a**), whilst **SPhos** gave none.[21] Conversely, **sSPhos** gave poor selectivity with the corresponding methyl ester of the carboxylic acid.[21] High selectivity was maintained with the longer chain of a hydrocinnamic acid (**11b**), and Sonogashira couplings were also compatible with both (**11c, 11d**). Interestingly, 3,4-dichlorobenzoic acid undergoes preferential coupling at the *para*-Cl using standard **SPhos**, due to electronic effects (Scheme 6b, **11e**). In contrast, **sSPhos** completely switches site-selectivity to the *meta*-Cl (**11f**). Further validating the mechanistic hypothesis, sodium sulfonate **12,** derived from the corresponding benzyl chloride, also underwent site-selective coupling (Scheme 6c). The product could be converted directly to sulfonamide **13**, a group used extensively in medicinal chemistry, or alternatively transformed directly back to a benzyl chloride.[21]

Scheme 6. Coupling of carboxylic acids and benzylsulfonates[a]



[a] For carboxylic acids, yields shown are isolated after conversion to methyl esters with TMS-diazomethane.

In conclusion, we have demonstrated that a commercially available sulfonylated phosphine ligand, in which the sulfonate group is conventionally used to engender water solubility, can be 'repurposed' as a bifunctional ligand to enable a range of site-selective cross couplings at remote positions. We propose that selectivity arises due to a key electrostatic interaction between the alkali metal cation of a deprotonated substrate and the anionic sulfonate group of the ligand. This counterintuitive combination of anionic ligand and anionic substrate demonstrates an alternative design principle when considering applying non-covalent interactions to direct catalysis. The process effectively controls site-selectivity in three of the most widely used cross-coupling processes (Suzuki-Miyaura, Sonogashira and Buchwald-Hartwig)[28] and has been demonstrated on substrates bearing three different acidic functional groups.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures, additional reaction optimization, and characterization data (pdf).

AUTHOR INFORMATION

Corresponding Author

*rjp71@cam.ac.uk

Notes

The authors declare no competing financial interests.

ACKNOWLEDGMENT

We are grateful to AstraZeneca for PhD studentships through the AZ-Cambridge PhD program (W.A.G. and R.P.), the Royal Society for a University Research Fellowship (R.J.P.), the EPSRC (EP/N005422/1) and the ERC (StG 757381). We thank the EPSRC UK National Mass Spectrometry Facility at Swansea University as well as Professors Steven V. Ley and Matthew J. Gaunt for support and useful discussion and Iain Cumming and Thomas McGuire (AstraZeneca). We are also very grateful to Professor Stephen L. Buchwald for useful discussion at the outset of this project.

REFERENCES

1. Meijere, A. d.; Bräse, S.; Oestreich, M., *Metal-Catalyzed Cross-Coupling Reactions and More*. Wiley-VCH Verlag GmbH & Co. KGaA: 2014.

2. For reviews, see: (a) Schröter, S.; Stock, C.; Bach, T., *Tetrahedron* **2005,** *61*, 2245-2267; (b) Fairlamb, I. J. S., *Chem. Soc. Rev.* **2007,** *36*, 1036-1045; (c) Almond-Thynne, J.; Blakemore, D. C.; Pryde, D. C.; Spivey, A. C., *Chem. Sci.* **2017,** *8*, 40-62; For selected examples: (d) Handy, S. T.; Zhang, Y., *Chem. Commun.* **2006**, 299-301; (e) Legault, C. Y.; Garcia, Y.; Merlic, C. A.; Houk, K. N., *J. Am. Chem. Soc.* **2007,** *129*, 12664-12665; (f) Garcia, Y.; Schoenebeck, F.; Legault, C. Y.; Merlic, C. A.; Houk, K. N., *J. Am. Chem. Soc.* **2009,** *131*, 6632-6639; (g) Dai, X.; Chen, Y.; Garrell, S.; Liu, H.; Zhang, L.-K.; Palani, A.; Hughes, G.; Nargund, R., *J. Org. Chem.* **2013,** *78*, 7758-7763; (h) Keylor, M. H.; Niemeyer, Z. L.; Sigman, M. S.; Tan, K. L., *J. Am. Chem. Soc.* **2017,** *139*, 10613-10616.

3. (a) Wang, J.-R.; Manabe, K., *Synthesis* **2009,** *2009*, 1405-1427; (b) Hassan, Z.; Patonay, T.; Langer, P., *Synlett* **2013,** *24*, 412-423; (c) Yamaguchi, M.; Manabe, K., Ligand-Controlled Site-Selective Cross-Coupling. In *Site-Selective Catalysis*, Kawabata, T., Ed. Springer International Publishing: Cham, 2016; pp 1-25.

4. (a) Kalvet, I.; Magnin, G.; Schoenebeck, F., *Angew. Chem. Int. Ed.* **2017,** *56*, 1581-1585; (b) Scattolin, T.; Senol, E.; Yin, G.; Guo, Q.; Schoenebeck, F., *Angew. Chem. Int. Ed.* **2018,** *57*, 12425-12429.

5. For a report in which standard halide reactivity in cross coupling is reversed using non-covalent catalysis, see: Pathak, T. P.; Miller, S. J., *J. Am. Chem. Soc.* **2013,** *135*, 8415-8422.

6. (a) Singh, R.; Just, G., *J. Org. Chem.* **1989,** *54*, 4453-4457; (b) Nawaz, M.; Khera, R. A.; Malik, I.; Ibad, M. F.; Abid, O.-U.-R.; Villinger, A.; Langer, P., *Synlett* **2010,** *2010*, 979-981; (c) Khera, R. A.; Nawaz, M.; Feist, H.; Villinger, A.; Langer, P., *Synthesis* **2012,** *44*, 219-234; (d) Dirk, S. M.; Price, D. W.; Chanteau, S.; Kosynkin, D. V.; Tour, J. M., *Tetrahedron* **2001,** *57*, 5109-5121; (e) Abid, O.-u.-R.; Ibad, M. F.; Nawaz, M.; Ali, A.; Sher, M.; Rama, N. H.; Villinger, A.; Langer, P., *Tetrahedron Lett.* **2010,** *51*, 1541-1544; (f) Nawaz, M.; Ibad, M. F.; Abid, O.-U.-R.; Khera, R. A.; Villinger, A.; Langer, P., *Synlett* **2010,** *2010*, 150-152.

7. (a) Houpis, I. N.; Huang, C.; Nettekoven, U.; Chen, J. G.; Liu, R.; Canters, M., *Org. Lett.* **2008,** *10*, 5601-5604; (b) Houpis, I. N.; Liu, R.; Wu, Y.; Yuan, Y.; Wang, Y.; Nettekoven, U., *J. Org. Chem.* **2010,** *75*, 6965-6968.

8. (a) Ishikawa, S.; Manabe, K., *Chem. Lett.* **2007,** *36*, 1304-1305; (b) Ishikawa, S.; Manabe, K., *Org. Lett.* **2007,** *9*, 5593-5595; (c) Ishikawa, S.; Manabe, K., *Angew. Chem. Int. Ed.* **2010,** *49*, 772-775; (d) Ishikawa, S.; Manabe, K., *Tetrahedron* **2011,** *67*, 10156-10163; (e) Yamaguchi, M.; Katsumata, H.; Manabe, K., *J. Org. Chem.* **2013,** *78*, 9270-9281; (f) Yamaguchi, M.; Manabe, K., *Org. Lett.* **2014,** *16*, 2386-2389; (g) Yamaguchi, M.; Akiyama, T.; Sasou, H.; Katsumata, H.; Manabe, K., *J. Org. Chem.* **2016,** *81*, 5450-5463.

9. For reviews, see: (a) Giuliano, M. W.; Miller, S. J., Site-Selective Reactions with Peptide-Based Catalysts. In *Site-Selective Catalysis*, Kawabata, T., Ed. Springer International Publishing: Cham, 2016; pp 157-201; (b) Shugrue, C. R.; Miller, S. J., *Chem. Rev.* **2017,** *117*, 11894-11951; (c) Toste, F. D.; Sigman, M. S.; Miller, S. J., *Acc. Chem. Res.* **2017,** *50*, 609-615.

10. For relevant studies addressing control of enantioselectivity rather than positional selectivity, see: (a) Kim, B.; Chinn, A. J.; Fandrick, D. R.; Senanayake, C. H.; Singer, R. A.; Miller, S. J., *J. Am. Chem. Soc.* **2016,** *138*, 7939-7945; (b) Chinn, A. J.; Kim, B.; Kwon, Y.; Miller, S. J., *J. Am. Chem. Soc.* **2017,** *139*, 18107-18114; (c) Kwon, Y.; Chinn, A. J.; Kim, B.; Miller, S. J., *Angew. Chem. Int. Ed.* **2018,** *57*, 6251-6255.

11. For reviews, see: (a) Raynal, M.; Ballester, P.; Vidal-Ferran, A.; van Leeuwen, P. W. N. M., *Chem. Soc. Rev.* **2014,** *43*, 1660-1733; (b) Dydio, P.; Reek, J. N. H., *Chem. Sci.* **2014,** *5*, 2135-2145; (c) Davis, H. J.; Phipps, R. J., *Chem. Sci.* **2017,** *8*, 864-877.

12. For application to site-selective C-H functionalization: Zhang, J.; Sha, S.-C.; Bellomo, A.; Trongsiriwat, N.; Gao, F.; Tomson, N. C.; Walsh, P. J., *J. Am. Chem. Soc.* **2016,** *138*, 4260-4266.

13. (a) Herrmann, W. A.; Kohlpaintner, C. W., *Angew. Chem. Int. Ed.* **1993,** *32*, 1524-1544; (b) Kevin, H. S.; Rebecca, B. D., *Curr. Org. Chem.* **2005,** *9*, 585-604; (c) Shaughnessy, K. H., *Chem. Rev.* **2009,** *109*, 643-710; (d) Dixneuf, P. H.; Cadierno, V., *Metal-Catalyzed Reactions in Water*. Wiley-VCH Verlag GmbH & Co. KGaA: 2013.

14. For early contributions, see: (a) Breslow, R.; Rajagopalan, R.; Schwarz, J., *J. Am. Chem. Soc.* **1981,** *103*, 2905-2907; (b) Breslow, R.; Heyer, D., *Tetrahedron Lett.* **1983,** *24*, 5039-5042.

15. (a) Chattopadhyay, B.; Dannatt, J. E.; Andujar-De Sanctis, I. L.; Gore, K. A.; Maleczka, R. E.; Singleton, D. A.; Smith, M. R., *J. Am. Chem. Soc.* **2017,** *139*, 7864-7871; (b) Ye, J.; Kalvet, I.; Schoenebeck, F.; Rovis, T., *Nat Chem* **2018,** *10*, 1037-1041.

16. (a) Davis, H. J.; Mihai, M. T.; Phipps, R. J., *J. Am. Chem. Soc.* **2016,** *138*, 12759-12762; (b) Mihai, M. T.; Davis, H. J.; Genov, G. R.; Phipps, R. J., *ACS Catal.* **2018,** *8*, 3764-3769.

17. Littke, A. F.; Fu, G. C., *Angew. Chem. Int. Ed.* **2002,** *41*, 4176-4211.

18. (a) Martin, R.; Buchwald, S. L., *Acc. Chem. Res.* **2008,** *41*, 1461-1473; (b) Surry, D. S.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2008,** *47*, 6338-6361.

19. Anderson, K. W.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2005,** *44*, 6173-6177.

20. (a) Molander, G. A.; Ryu, D.; Hosseini-Sarvari, M.; Devulapally, R.; Seapy, D. G., *J. Org. Chem.* **2013,** *78*, 6648-6656; (b) Jiang, H.; Jia, T.; Zhang, M.; Walsh, P. J., *Org. Lett.* **2016,** *18*, 972-975; (c) Corr, M. J.; Sharma, S. V.; Pubill-Ulldemolins, C.; Bown, R. T.; Poirot, P.; Smith, D. R. M.; Cartmell, C.; Abou Fayad, A.; Goss, R. J. M., *Chem. Sci.* **2017,** *8*, 2039-2046; (d) Janusson, E.; Zijlstra, H. S.; Nguyen, P. P. T.; MacGillivray, L.; Martelino, J.; McIndoe, J. S., *Chem. Commun.* **2017,** *53*, 854-856; (e) Rojas, A. J.; Pentelute, B. L.; Buchwald, S. L., *Org. Lett.* **2017,** *19*, 4263-4266.

21. See supporting information for details.

22. (a) Gokel, G. W.; Leevy, W. M.; Weber, M. E., *Chem. Rev.* **2004,** *104*, 2723-2750; (b) Hoque, M. E.; Bisht, R.; Haldar, C.; Chattopadhyay, B., *J. Am. Chem. Soc.* **2017,** *139*, 7745-7748; (c) Sha, S.-C.; Tcyrulnikov, S.; Li, M.; Hu, B.; Fu, Y.; Kozlowski, M. C.; Walsh, P. J., *J. Am. Chem. Soc.* **2018**.

23. (a) Kinzel, T.; Zhang, Y.; Buchwald, S. L., *J. Am. Chem. Soc.* **2010,** *132*, 14073-14075; (b) Bruno, N. C.; Tudge, M. T.; Buchwald, S. L., *Chem. Sci.* **2013,** *4*, 916-920.

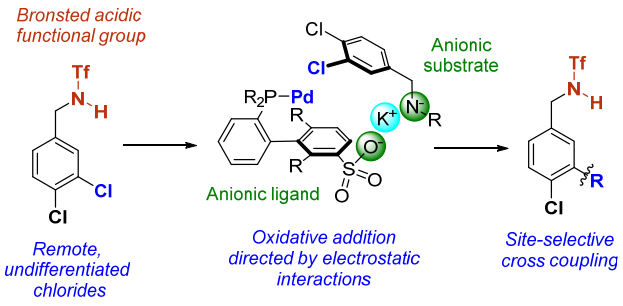
24. Sigma Aldrich catalogue number 763314.

25. Gelman, D.; Buchwald, S. L., *Angew. Chem. Int. Ed.* **2003,** *42*, 5993-5996.

26. Surry, D. S.; Buchwald, S. L., *Chem. Sci.* **2011,** *2*, 27-50.

27. Wang, X.; Mei, T.-S.; Yu, J.-Q., *J. Am. Chem. Soc.* **2009,** *131*, 7520-7521.

28. Brown, D. G.; Boström, J., *J. Med. Chem.* **2016,** *59*, 4443-4458.


Bronsted acidic functional group
Tf
N
H
Cl
Cl
Remote, undifferentiated chlorides
Cl
Cl
Anionic substrate
R2P–Pd
R
K+
N-
R
R
O-
S
O
O
Anionic ligand
Oxidative addition directed by electrostatic interactions
Tf
N
H
R
Cl
Site-selective cross coupling