Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b05409 • Publication Date (Web): 17 Jul 2017

Inverting Conventional Chemoselectivity in Pd-Catalyzed Amine Arylations with Multiply Halogenated Pyridines

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Supporting Information Placeholder

ABSTRACT: A new catalyst system is reported that has proven to be general for reversing conventional chemoselectivity in the Pd-catalyzed amination of multiply halogenated pyridines. A reaction optimization strategy employing ligand parameterization led to the identification of 1,1′-bis[bis(dimethylamino)phosphino]ferrocene "DMAPF" – a readily available yet previously unutilized diphosphine – as a uniquely effective ligand for this transformation.

In drug discovery, site- and chemoselective cross-coupling reactions offer efficient and versatile means of generating diversity. Such selectivity can be imparted through the strategic use of innate reactivity, although these methods often require sourcing of discrete and potentially expensive starting materials in order to access products with orthogonal connectivity. In contrast, catalyst controlled processes provide the opportunity to modulate disconnection tactics, allowing for more flexible synthetic strategies towards diversity. In this context, site-selectivity in heterocyclic ring systems bearing multiple identical halogens ($X_1 = X_2$) is typically determined by reaction at the most electrophilic position (Figure 1a, (i)),[1] although examples using catalyst-control to overcome substrate bias have been reported.[2] However, chemoselectivity in heteroarenes bearing non-identical halogens ($X_1 \neq X_2$) is, with few exceptions,[3] governed by bond dissociation enthalpies (Figure 1a, (ii)).[4] Depending on the relative positioning of the two halogens on the ring, the intrinsic polarization of the heterocycle can serve to either reinforce or oppose conventional, BDE-based chemoselectivity. In light of the expected narrowing of the free energy difference ($\Delta\Delta G^{\ddagger}$) between competing transition states in the latter scenario, we were intrigued by the possibility to enable orthogonal halogen reactivity through precise tuning of catalyst-substrate interactions. Specifically, a goal would be to develop a system in which activation of a C–Cl bond is enabled in the presence of a much weaker C–I/Br bond, as this would be synthetically attractive as a tool for heterocycle diversification. Additionally, successful development of such a protocol would raise significant fundamental questions regarding the interactions responsible for departure from established reactivity patterns. Herein, we present the realization of this concept – guided by a ligand parameterization enabled optimization strategy – and demonstrate a reversal of chemoselectivity in Pd-catalyzed aminations of a wide range of multihalogenated pyridines (Figure 1b).

We initially investigated the coupling of aniline to 5-bromo-2-chloropyridine (**1**) as our model reaction (Table 1). Initial evaluation of 75 structurally diverse phosphine ligands provided a preliminary dataset for elucidation of structure-selectivity relationships.[5] As expected, due to the poor electrophilicity of the heterocycle,[6,7] no background reaction was observed in the absence of palladium, and only trace (<2%) product formation was detected in the absence of added ligand (entries 1–2). Triaryl phosphines afforded no observed product, whereas trialkyl (**L1**) and dialkyl biaryl (**L2**/**L3**) phosphines each promoted selective formation of product **2**, derived from the expected oxidative addition of the C−Br bond (entries 3–5). With the exception of SIPr (**L4**, entry 6), NHC ligands proved ineffective for this transformation. Notably, IMes (**L5**), which was reported to afford modest Cl > Br selectivity in related aminations,[4,7] was indeed found to favor formation of product **3**, although the yield could not be improved beyond 15% (entry 7). Xantphos (**L6**) afforded exquisite selectivity for product **2** (entry 8) consistent with prior reports,[4,7] whereas DPEphos (**L7**), which is similar in structure and bite angle (β_n)[8] to **L6**, provided improved yields but lower selectivity (9:1, entry 9). This result indicated that conformational flexibility in the ligand backbone likely contributes to the formation of product **3**. Consistent with this hypothesis, ferrocenyl diphosphine DPPF (**L8**) yielded a greater fraction of product **3** (entry 10).[9,10] This ratio could be shifted to modestly favor **3** (3:1) by the use of its *t*-butyl congener, DTBPF (**L9**, entry 11). The use of 1,4-dioxane significantly enhanced both the yield (76%) and selectivity (>8:1, entry 12) as compared to the reaction in toluene.[11,12] Additional ferrocenyl diphosphines (**L8**–**L15**, entries 13–19) were evaluated in parallel, and although comparable levels of conversion could be achieved, the selectivity offered by DTBPF (**L9**) could not be

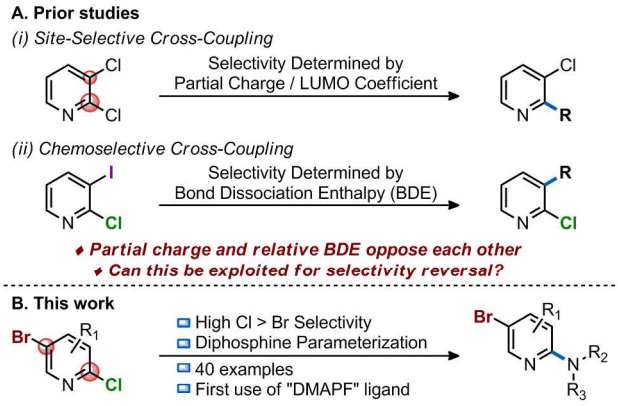
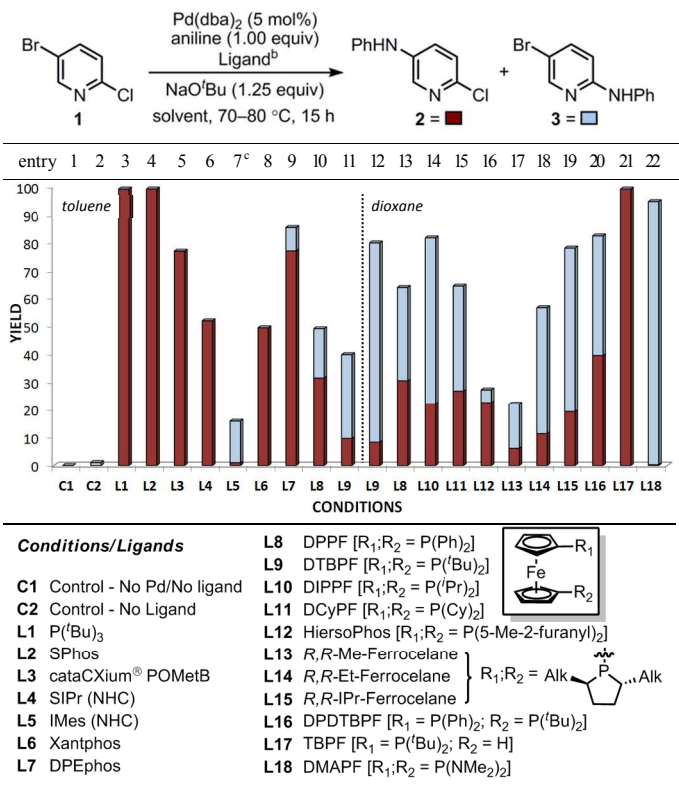


Figure 1. Ligand-enabled cross-coupling selectivity reversal.

Table 1. Reaction Optimization[a]



[a]Yields determined by HPLC-MS vs. internal standard. See Supporting Information for more details. [b]Monodentate ligands were loaded at 12 mol%, bidentate at 6 mol%. [c]Reaction was heated to 120 °C.

improved. Interestingly, the dissymmetric ligand **L16** (entry 20) increased overall yield, but did not significantly alter the product ratio as compared to DPPF (**L8**), while monophosphine **L17** (entry 21) favored Br-coupling, reasserting the importance of bidentate coordination in selective C–Cl oxidative addition.

Although the yield and selectivity for product **3** afforded by **L9** were serviceable, both were considerably diminished when challenged with various steric and electronic perturbations on the coupling partners (vide infra). To address this, we employed linear regression analysis comparing molecular descriptors to chemoselectivity[13] – a tool that we have recently applied in the evaluation of monodentate phosphine ligands.[14] Unfortunately, we were unable to identify simple multivariate models using the ligand descriptor database compiled by Fey and co-workers.[15,16] However, a positive correlation (R^2 = 0.88) between measured selectivity (represented here as the free energy difference [$\Delta\Delta G^{\ddagger}$]), and the computed Pd–Cl bond lengths (Å) of the corresponding L_2PdCl_2 complexes was ultimately found (Figure 2a).[16c] This relationship suggested that *trans*-influence, and therefore σ-donor ability of the ligand, is important for selective coupling of the C–Cl bond.

Given the unique ability of 1,1′-ferrocenyl diphosphines to provide both a meaningful range of $\Delta\Delta G^{\ddagger}$ and synthetically useful yields, we focused on further correlating the selectivity observed using this ligand class (**L8–L15**). Initially, a simple correlation was identified between the measured ^{31}P NMR chemical shifts (δ) of the free ligands and the observed selectivity (Figure 2b), again, possibly implicating ligand electronics. However, since the theoretical underpinnings of isotropic phosphorus chemical shifts are rather complex, truncated forms of each ligand were calculated in order to delineate the relative importance of steric and electronic influences. Each ferrocenyl phosphine was abridged to a phenyl ring with the appropriate R substituents to effectively render it a monodentate phosphine. The corresponding phosphine selenide

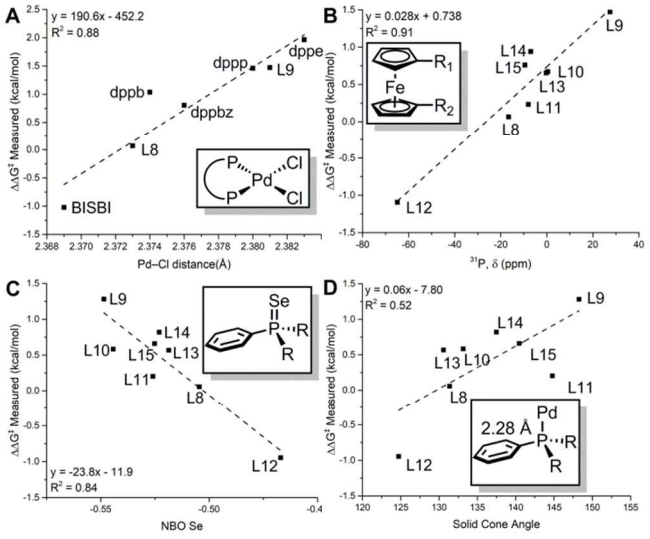
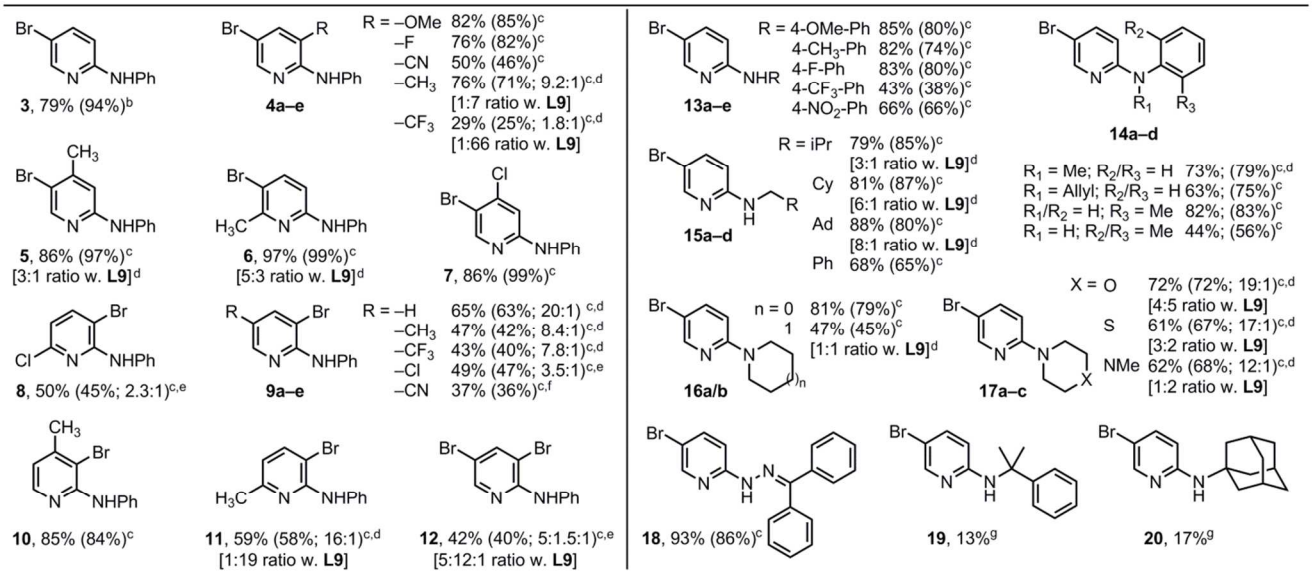


Figure 2. Representative computed (**A**, **C**, **D**) and measured (**B**) descriptors suggest that product selectivity is governed by electronic (**A**, **B**, **D**) rather than steric (**C**) properties of the ligand. $\Delta\Delta G^{\ddagger} = 0.001986 \times 343.15\ln([\text{yield } \mathbf{3}]/[\text{yield } \mathbf{2}])$.

was computed as a proxy for ligand electronics (Figure 2c),[17] while the solid cone angle of the corresponding Pd-complex was calculated as a representation of steric effects (Figure 2d).[18,19] Analysis of these surrogates revealed relatively poor correlations to steric measurements. Conversely, the calculated natural bond orbital (NBO) charges of the phosphine selenides trended well to selectivity; greater electron density at selenium correlated with enhanced formation of **3**. This correlation further substantiates that bidentate ferrocene ligands with increased σ-donation promote oxidative addition of the C–Cl bond despite the presence of the C–Br bond. Following this logic, DTBPF (**L9**) is the best performing ligand in our initial screen as well as in any virtual prediction using alternative dialkyl-ferrocenyl phosphines.

On the basis of the preceding correlations, we considered heteroatom substituents at phosphorus. Unlike phosphonites ([$RP(OR')_2$]), which are uniformly weak σ-donors and strong π-acceptor ligands,[20] the electronic properties of the corresponding bis(dialkylamino)phosphines are highly tunable. For instance, the Tolman electronic parameter (υ_{CO}) measured for *trans*-$L_2Rh(CO)Cl$ spans from 2007 cm^{-1} for $PhP(pyrrolyl)_2$ to 1949 cm^{-1} for ^{t}BuP(pyrrolidinyl)$_2$.[21] Yet, the use of these putative ligands in catalysis has scarcely been explored.[22] Two ferrocene derivatives – DMAPF (**L18**, Table 1) and its ethyl analogue, DEAPF – are commercially available.[23] Analysis of the appropriate surrogate structure for DMAPF indicated a possible modest improvement according to the Se NBO charge correlation (Figure 2c) as compared to DTBPF (-0.5505 versus -0.5486). Similarly, the ^{31}P-NMR chemical shift of **L18** was measured at 95.4 ppm, which according to our best model (Figure 2b) was predicted to afford a $\Delta\Delta G^{\ddagger}$ of 3.41 kcal·mol^{-1} (cf. 1.47 kcal·mol^{-1} for **L9** or >10-fold increase in selectivity). Gratifyingly, the reaction of pyridine **1** with aniline in the presence of **L18** afforded a 95% assay yield of coupling products with 315:1 selectivity ($\Delta\Delta G^{\ddagger}$ = 3.93 kcal·mol^{-1}, Table 1, entry 22) in favor of product **3**. This corresponds to a 35-fold improvement in selectivity over the previous best result from a screen of 75 commonly applied ligands. The origin of this dramatic observation warrants further mechanistic examination outside of the scope of this report. It is interesting to note that these structures have not previously been used as ligands in transition metal-catalyzed processes.[24,25] Fortunately, Fey and coworkers computed **L18** despite its limited representation in the literature, and the correlation to Pd–Cl

Table 2. Reaction Scope[a]



[a]Isolated yields of major isomer at 1 mmol scale. Internal standard yields of duplicate reactions shown in parentheses. For product ratios the first value corresponds to the structure drawn. See Supporting Information for more details. [b]Yield determined by HPLC-MS using internal standard. [c]Yield determined by ^{1}H-NMR using internal standard. [d]Ratio determined by HPLC-MS. [e]Ratio determined by ^{1}H-NMR. [f]A weak background reaction (15%) was detected. [g]Internal standard yield not determined.

bond length (Figure 2a) was supported upon inclusion of the measured $\Delta\Delta G^{\ddagger}$ for **L18** ($R^2 = 0.86$).

Experimental and computational investigations have found selectivity in such transformations to be influenced by numerous reaction variables.[26–30] The pronounced observed effects imparted by ligand electronics and backbone may be best explained by the activation strain model presented by Bickelhaupt, Houk and coworkers ($\Delta E^{\ddagger} = \Delta E^{\ddagger}_{dist} + \Delta E^{\ddagger}_{int}$).[31] The most selective ligands for Ar-Br functionalization generally form monoligated Pd-complexes,[32] which cause substrate contributions to the distortion energy ($\Delta E^{\ddagger}_{dist}$ α relative BDE) to control the selectivity. Inverting reactivity toward Cl-activation requires the use of strongly donating bidentate ligands with flexible backbones. This is consistent with the activation strain model in which stabilizing secondary back-bonding ($d_\pi \rightarrow \pi^*$) interactions ($\Delta E^{\ddagger}_{int}$) are able to compensate for disparities in $\Delta E^{\ddagger}_{dist}$. Within the bidentate ligand series, strong σ-donation is expected to increase the magnitude of $\Delta E^{\ddagger}_{int}$, while conformational flexibility would minimize the endergonic penalty (contributing to $\Delta E^{\ddagger}_{dist}$) of bite angle ($\beta_n$) compression during oxidative addition.[33]

With a highly selective catalyst system identified, we investigated the scope of the transformation (Table 2). The generality of the developed conditions for a range of substrate combinations is striking, particularly when directly compared to analogous reactions using DTBPF (**L9**). Using DMAPF (**L18**), the coupling remained Cl-selective even for substrates where the 2-position was electronically deactivated (**4a**) or sterically encumbered (**4a–e**) as compared to the bromide. Notably, *ortho*- methyl substitution (**4d**) was not tolerated using **L9**, and while the reasons for the decreased yield and selectivity observed for the CF_3-substituted pyridine **4e** are unclear at this time, the use of **L9** with this substrate was both low yielding and favored coupling at the bromide (1:66 ratio). Substitution *ortho*- to the bromide (**5/6**) served only to enhance the yield and selectivity for Cl-coupling under these conditions, whereas **L9** again afforded inferior product ratios. The trihalogenated precursor to **7** coupled with complete selectivity at the 2-position, and the regioisomeric precursor to **8** coupled with moderate preference for the more hindered chloride, further supporting that the observed selectivity is electronically rather than sterically determined. We were pleased to find that 3-bromo-2-chloropyridine derivatives also coupled with modest yields and selectivities under the optimized conditions (**9–11**). To again contrast **L9** with **L18**, the Br/Cl selectivity for the precursor to product **11** was reversed when applying **L9**. Perhaps most impressively, product **12** is formed with reasonable selectivity in the presence of two bromides.

Steric and electronic perturbation of the aniline was well-tolerated (**13–14**), and primary aliphatic amines bearing various substituents at the β-position were uniformly high-yielding and selective (**15a–d**). The corresponding reactions using **L9** gave inferior product ratios. Furthermore, the loss in selectivity when using **L9** with secondary amines (**14a/b**, **16**/**17**) could be overcome using **L18**, although the cause of the low yield observed for piperidine **16b** is unclear at this time. Facile access to products such as **18** is potentially useful as its hydrolysis yields a hydrazine precursor for the preparation of 5-bromo-7-azaindole derivatives.[34] Finally, although low yielding under the current conditions, the system is capable of promoting the coupling of hindered *α,α,α*-trisubstituted primary amines with complete Cl-selectivity (**19–20**).[35]

In conclusion, selective chloride functionalization in the Pd-catalyzed amination of pyridines bearing traditionally more reactive bromides has been achieved. After an initial screen of diverse phosphine ligands, we were able to rapidly calculate descriptors on truncated ligands that provided relevant structure-selectivity models, allowing for extrapolation into unexplored ligand space. This workflow guided us to the discovery of DMAPF (**L18**), a previously unutilized diphosphine, which was uniquely selective for chloride functionalization. Reaction parameterization within this context has enlightened our understanding of the fundamental principles that govern selectivity in these systems and accelerated reaction development. The ability to diversify pyridines along orthogonal vectors further valorizes these scaffolds for early drug development campaigns, and efforts to extend these strategies to reaction optimization on other pharmaceutically relevant cores are underway.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI:

Experimental procedures, additional reaction optimization, and characterization data (PDF)

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Notes: The authors declare no competing financial interests.

ACKNOWLEDGMENTS

This work was supported by the Novartis Institutes for Biomedical Research (M.H.K.) and the NSF (Z.L.N. and M.S.S., CHE-1361296). The support and resources from the Center for High Performance Computing at the University of Utah are gratefully acknowledged. The authors thank Jinhai Gao for assistance with NMR structural determinations.

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(6) In the absence of additional activation and/or forcing conditions (high temperatures, excess amine) [ref. 7a], 2-halopyridines are resistant toward nucleophilic aromatic substitution (SNAr) as compared to their diazine counterparts (e.g. 2-chloropyridine is approximately 10^8 times less reactive toward nucleophiles than 2-chloropyrimidine) [ref. 7b].

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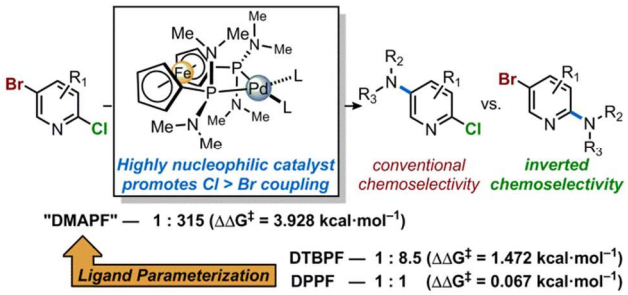

"DMAPF" — 1 : 315 ($\Delta\Delta G^{\ddagger}$ = 3.928 kcal·mol^{-1})

Ligand Parameterization

DTBPF — 1 : 8.5 ($\Delta\Delta G^{\ddagger}$ = 1.472 kcal·mol^{-1})

DPPF — 1 : 1 ($\Delta\Delta G^{\ddagger}$ = 0.067 kcal·mol^{-1})