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Article

Systematic Variation of Ligand and Cation Parameters Enables Site-Selective C–C and C–N Cross-Coupling of Multiply Chlorinated Arenes through Substrate–Ligand Electrostatic Interactions

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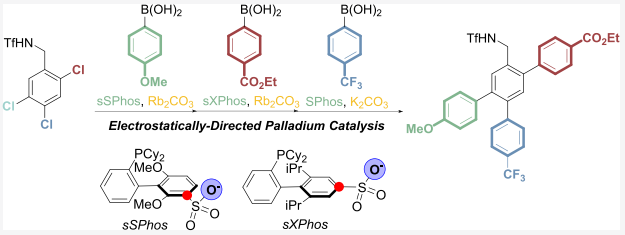
ABSTRACT: Use of attractive noncovalent interactions between ligand and substrate is an emerging strategy for controlling positional selectivity. A key question relates to whether fine control on molecules with multiple, closely spaced reactive positions is achievable using typically less directional electrostatic interactions. Herein, we apply a 10-piece "toolkit" comprising of two closely related sulfonated phosphine ligands and five bases, each possessing varying cation size, to the challenge of site-selective cross-coupling of multiply chlorinated arenes. The fine tuning provided by these ligand/base combinations is effective for Suzuki–Miyaura coupling and Buchwald–Hartwig coupling on a range of isomeric dichlorinated and trichlorinated arenes, substrates that would produce intractable mixtures when typical ligands are used. This study develops a practical solution for site-selective cross-coupling to generate complex, highly substituted arenes.



INTRODUCTION

Established guidelines relating to chemoselectivity enable synthetic chemists to reliably predict which functional group in a molecule is likely to undergo reaction in a given context.[1] The challenge of site-selectivity presents itself in molecules which possess two or more instances of the same functional group. Sometimes electronic or steric factors may dispose one to be more reactive than others, but in many cases, mixtures of isomers as well as overreaction typically preclude practically useful procedures.[2] Consequently, synthetic chemists will intuitively incorporate numerous extra synthetic steps into a planned route to avoid a site-selectivity challenge which could risk derailment. The uncalculated cost, both economically and environmentally, resulting from the paucity of methods for carrying out common chemical transformations in a site-selective manner is likely to be large indeed. One of the most widely utilized reaction classes in contemporary synthetic chemistry is cross-coupling.[3] Cross-coupling reactions of arenes should be of particular value if able to be carried out in a site-selective manner because aryl halides, chlorides in particular, are remarkably inert to many other reaction types and can be retained during many synthetic steps. Strong electronic biases mean that cross-coupling selectivity trends in heteroarenes have been well documented.[4] In recent years, much progress, particularly from Schoenebeck and co-workers,[5] has been made in the development of catalysts that are able to carry out highly chemoselective cross-coupling of arenes that possess several different (pseudo)halides.[6] However, in these cases, differentially di- or tri(pseudo)-halogenated arene precursors are required, in which the respective halogens must be regioselectively incorporated and the synthesis of which can be challenging. There are remarkably few ways to tackle the inherent challenge of site-selective coupling of arenes that have the same chloride located at two or more positions.[7] In notable work, Manabe and co-workers developed an elegant catalyst-controlled strategy, although this requires strong organometallic bases and is restricted to Kumada and Sonogashira couplings, two of the lesser used cross-coupling reactions.[8] This paucity of methods is regrettable considering the much greater ease of accessing multiply chlorinated arenes when compared with differentially di- or trihalogenated arenes. This ease of access is reflected in a simple comparison of commercial availability between these types of compounds in the context of benzylamines that are relevant to this study (Figure 1a).

Catalyst designs which incorporate attractive, noncovalent interactions between ligand and substrate are rapidly gaining traction as powerful approaches for influencing site selectivity in transition metal catalysis.[9] While hydrogen-bonding interactions have been the focus of most studies, electrostatic interactions remain underexplored.[10,11] A likely reason is concern related to the low directionality of electrostatic interactions, particularly when an application demands precise

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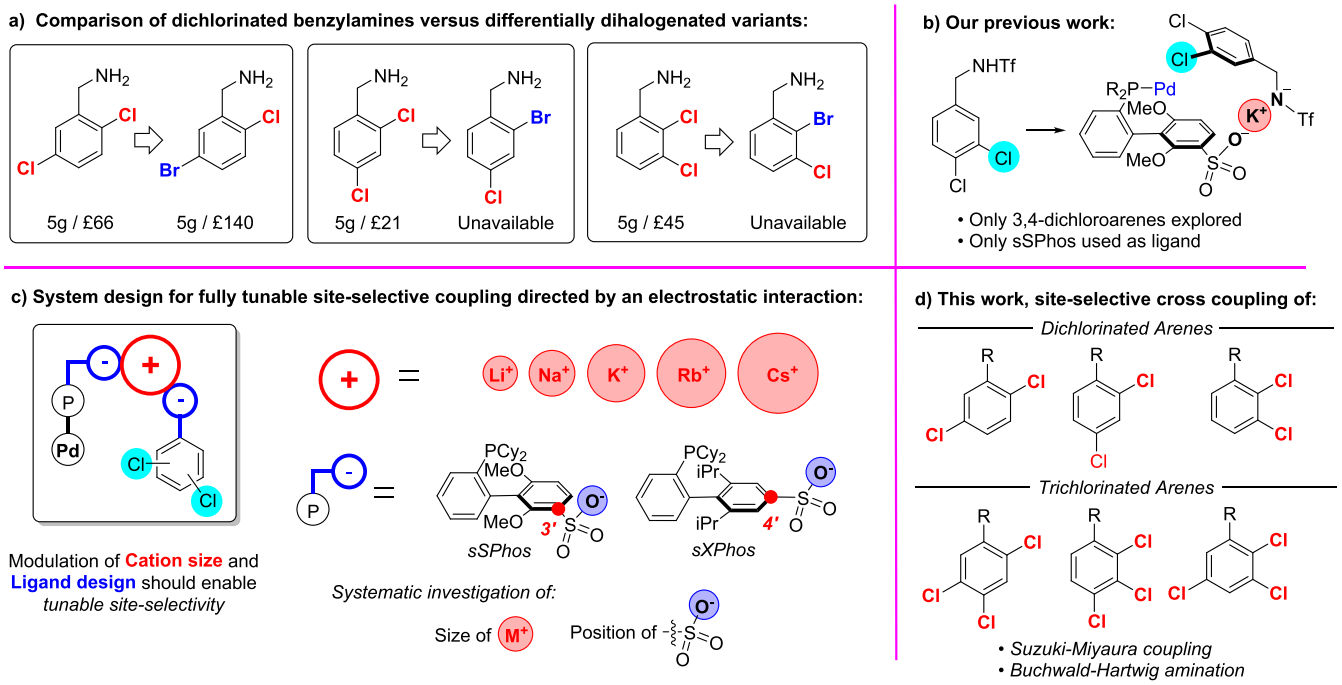

Figure 1. Site-selective cross-coupling of multiply chlorinated arenes guided by ligand−substrate electrostatic interactions. (A) Greater accessibility of multiply chlorinated arenes versus differentially halogenated variants. Prices in GBP from Fluorochem as of Oct 2020. (B) Our previous work on site-selective cross-coupling of 3,4-dichloroarenes using sSPhos. (C) Outline of the design plan for a fully tunable system, based on an electrostatic interaction, to control site selectivity in oxidative addition of palladium. (D) This study.

spatial control. Yet many common functional groups can act as participants in attractive electrostatic interactions and if these can be harnessed present exciting but untapped opportunities for exploitation in control of site-selective catalysis.

In an initial proof-of-concept study with this goal in mind, we recently disclosed that sSPhos, a sulfonated version of the common ligand SPhos, originally developed by Anderson and Buchwald for performing cross-couplings in water,[12] could be repurposed as a bifunctional ligand for controlling site-selective cross-coupling.[13] This was demonstrated on 3,4-dichlorinated arene substrates that contained suitable functionality with which to interact with the catalyst sulfonate group. We hypothesized that the interaction was electrostatic in nature and involved the alkali metal cation of the deprotonated substrate sitting between it and the anionic sulfonate group of the ligand (Figure 1b). High levels of site-selectivity for cross-coupling at the chlorine located at the *meta* position were observed, while SPhos resulted in no selectivity. While that study provided proof-of-concept for ligand-directed cross-coupling at distal positions, we only explored the 3,4-dichloroarene motif in combination with sSPhos (depicted), and it was unclear whether the success in this limited context would translate to other substitution patterns or higher orders of halogenation, factors which would be crucial for this approach to be applied in a generally applicable and synthetically useful manner.

We used our mechanistic hypothesis to identify two key factors that we anticipated, if systematically varied, could feasibly impact site-selectivity for any given substrate. The first factor was the size of the alkali metal cation, arising from the exogenous base used, and modulation of which should impact the positioning between the ligated palladium metal center and any particular carbon−halogen bond on the substrate (Figure 1c, top row). The second was the positioning of the sulfonate group on the lower ring of the dialkylbiaryl phosphine scaffold. It is well established that the palladium metal typically resides over this lower ring, and we anticipated that whether the sulfonate is at the 3′ or 4′ position will have a small but significant effect on the crucial distance between the sulfonate and the palladium metal center (Figure 1c, middle row).[14] sSPhos and sXPhos are both commercially available, and while sulfonation occurs at the 3′ position of SPhos, on XPhos an *ipso*-sulfonation occurs, substituting the *i*Pr group at the 4′ position.[12] This regiodivergence between the two scaffolds conveniently provides two closely related ligands between which the site of sulfonation on the lower aryl ring is varied in the desired manner. At the outset of this study, we envisaged that a ligand/base "toolkit" comprising both sSPhos and sXPhos together with bases containing the five most common alkali metal cations could be readily screened against a given substrate and the optimum combination leading to site-selectivity be quickly identified. This would tackle the question of whether fine control of position selectivity is viable using electrostatic interactions as well as provide a much needed approach to site-selective coupling of di- and trichloroarenes using the most commonly used protocols of Suzuki−Miyaura coupling and Buchwald−Hartwig amination (Figure 1d).

RESULTS AND DISCUSSION

We commenced our study by examining the three other nonsymmetrical dichlorinated isomers of *N*-triflated benzylamine: 2,3-, 2,4-, and 2,5-dichloro (Figure 2, **1**−**3**). For each isomer, the whole ligand/base toolkit was evaluated—sSPhos and sXPhos in combination with each of the carbonate bases of the first five group 1 metals. For the purpose of establishing a reliable measure of site-selectivity, a limiting amount of boronic acid (0.5 equiv) was used to avoid formation of

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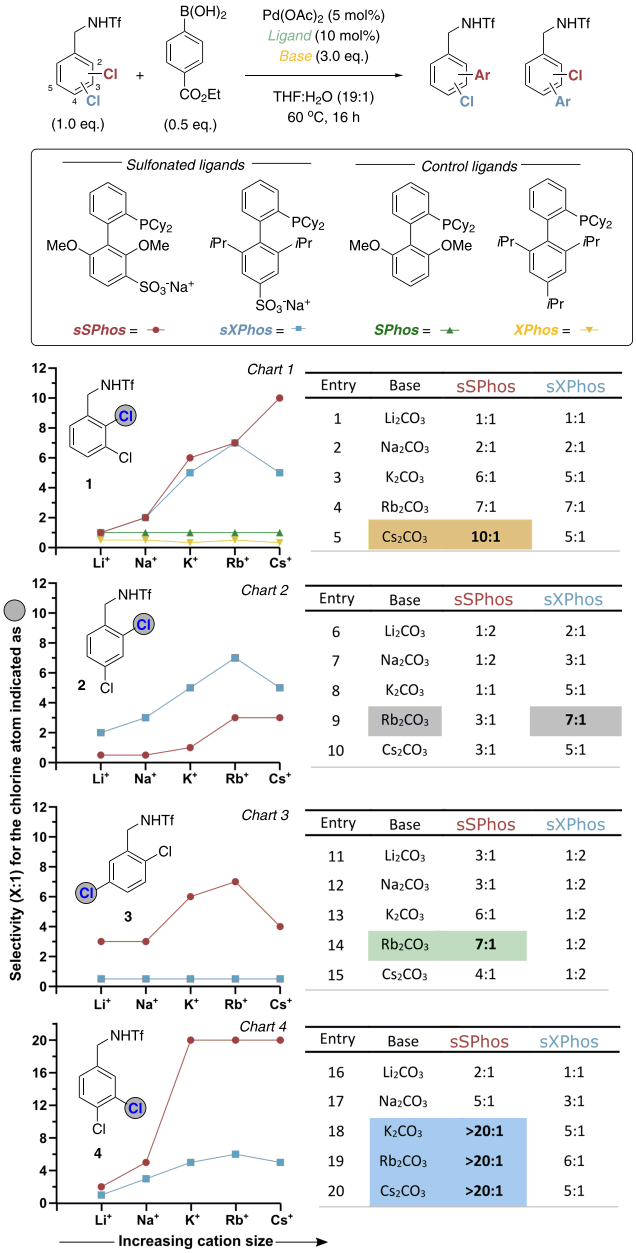

Entry	Base	sSPhos	sXPhos
1	Li_2CO_3	1:1	1:1
2	Na_2CO_3	2:1	2:1
3	K_2CO_3	6:1	5:1
4	Rb_2CO_3	7:1	7:1
5	Cs_2CO_3	**10:1**	5:1

Entry	Base	sSPhos	sXPhos
6	Li_2CO_3	1:2	2:1
7	Na_2CO_3	1:2	3:1
8	K_2CO_3	1:1	5:1
9	Rb_2CO_3	3:1	**7:1**
10	Cs_2CO_3	3:1	5:1

Entry	Base	sSPhos	sXPhos
11	Li_2CO_3	3:1	1:2
12	Na_2CO_3	3:1	1:2
13	K_2CO_3	6:1	1:2
14	Rb_2CO_3	**7:1**	1:2
15	Cs_2CO_3	4:1	1:2

Entry	Base	sSPhos	sXPhos
16	Li_2CO_3	2:1	1:1
17	Na_2CO_3	5:1	3:1
18	K_2CO_3	**>20:1**	5:1
19	Rb_2CO_3	**>20:1**	6:1
20	Cs_2CO_3	**>20:1**	5:1

Figure 2. Systematic evaluation of ligand/base combinations with all four dichlorinated isomers of *N*-triflated benzylamine. Ratios and conversions determined by ^{1}H NMR analysis with reference to internal standard.

dicoupled product, which could mask the true site-selectivity of the combination under assessment.

For the 2,3-dichloro substrate **1**, we observed that using the larger alkali metal cations, good selectivity for cross-coupling at the most proximal chlorine, at the 2-position, could be obtained (Chart 1, Figure 2). While this was true for both sSPhos (red line) and sXPhos (blue line), the former gave the highest ratio at 10:1 Cl_2:Cl_3 when Cs_2CO_3, possessing the largest cation, was used (entry 5). Importantly, control experiments with both SPhos (green line) and XPhos (yellow line) gave no selectivity with any base, demonstrating that there is no intrinsic selectivity bias and that the sulfonate group of the phosphine is playing a crucial role. We next examined an *ortho* versus *para* competition in the form of the 2,4-dichlorinated isomer **2** (Chart 2, Figure 2). Here, the most proximal chlorine, at the 2-position, was again favored, but in contrast, sSPhos performed relatively poorly, even with the larger metal cations. It was solidly outperformed by sXPhos, which gave 7:1 selectivity for coupling at Cl_2 when used in combination with Rb_2CO_3 in a clear standout combination (entry 9). A similar trend was observed with sXPhos as in the Cl_2 vs Cl_3 competition: once the cation became too large (Cs), the selectivity decreased (entry 10). In the Cl_2 vs Cl_5 competition of **3**, sXPhos showed a weak preference for the Cl_2-coupled product (Chart 3, Figure 2). However, sSPhos together with Rb_2CO_3 gave 7:1 selectivity, this time for the more remote chlorine at C_5. To complete this systematic study, we finally returned to the Cl_3 vs Cl_4 competition from our initial report, where both chlorines are at remote positions in substrate **4** (Chart 4, Figure 2). In this case, sSPhos was far superior, showing the highest levels of selectivity (>20:1) with every cation larger than sodium. sXPhos showed a similar trend as it had with other substrates (Charts 1 and 2, Figure 2) but peaked at a much lower level than sSPhos (6:1).

Having applied the toolkit in a screening capacity to identify the optimal ligand/base combinations for each dichlorinated isomer of the *N*-triflated benzylamine, we next evaluated the reaction on a preparative scale under practically relevant conditions with the dichloroarene as the limiting reagent. We were initially concerned that dicoupling may be problematic, but this was not the case—only small amounts were typically observed, allowing isolation of good to excellent yields of the desired monocoupled products (Scheme 1). The low levels of overcoupling are again an indicator of a high degree of catalyst control in the process. The isomeric ratios observed in the crude reaction mixtures were often higher than the values in Charts 1−3, Figure 2, and we attribute this to formation of small amounts of dicoupled product, wherein the minor isomer is apparently being consumed preferentially in some cases, enhancing the observed selectivity. Advantageously, upon isolation, the isomeric ratio was further improved in some cases (isolated ratio quoted in parentheses). All three dichlorinated isomers were coupled each with two different aryl boronic acids and a heteroaryl boronic acid, demonstrating the practical utility of this procedure following identification of the optimal ligand/base combination from the initial screen. The few cases where selectivity did appear to vary between boronic acids most likely reflects differences in the amount of dicoupled product being formed in those particular cases due to differing conversion.

We next sought to explore Buchwald−Hartwig coupling given the importance of this disconnection for C−N bond formation.[15] On the assumption that oxidative addition of Pd to the C−Cl bond is irreversible and selectivity determining, we initially attempted to use the same ligand/base combinations that had been optimal for each substrate in the Suzuki−Miyaura couplings. From our previous experience in transitioning from Suzuki to Buchwald−Hartwig couplings we were aware that to obtain reactivity we would need to use higher reaction temperatures (60−110 °C) and accordingly change solvent (THF to 1,4-dioxane), factors which could affect the finely tuned ligand/base combinations. Gratifyingly, the original optimal combination of sSPhos with Rb_2CO_3 was still highly effective for the 2,5-dichloro substrate **3**, and we proceeded to couple three electronically distinct anilines with very good site selectivity for coupling at the *meta* position (Scheme 2, top row). Usefully, the minor isomer was able to be removed during purification, giving isomerically pure

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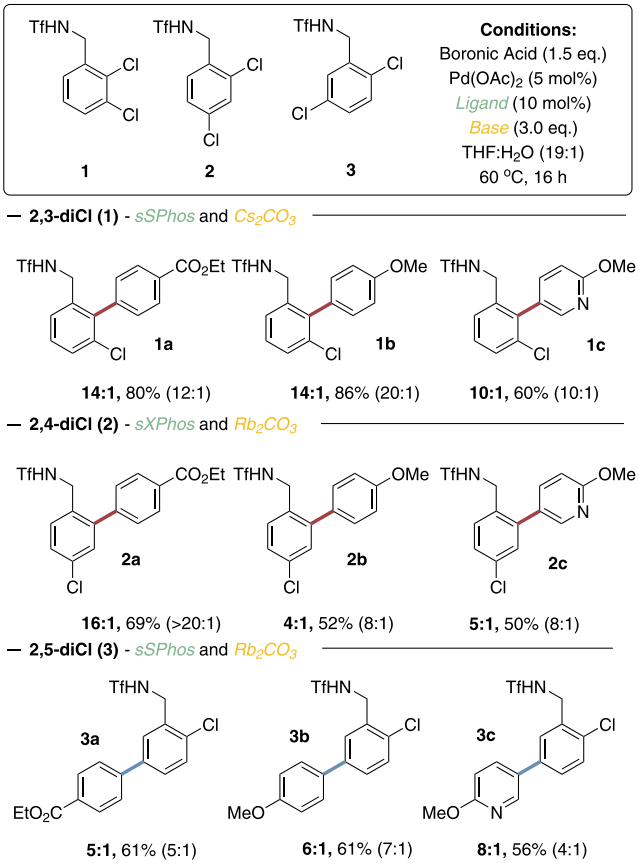
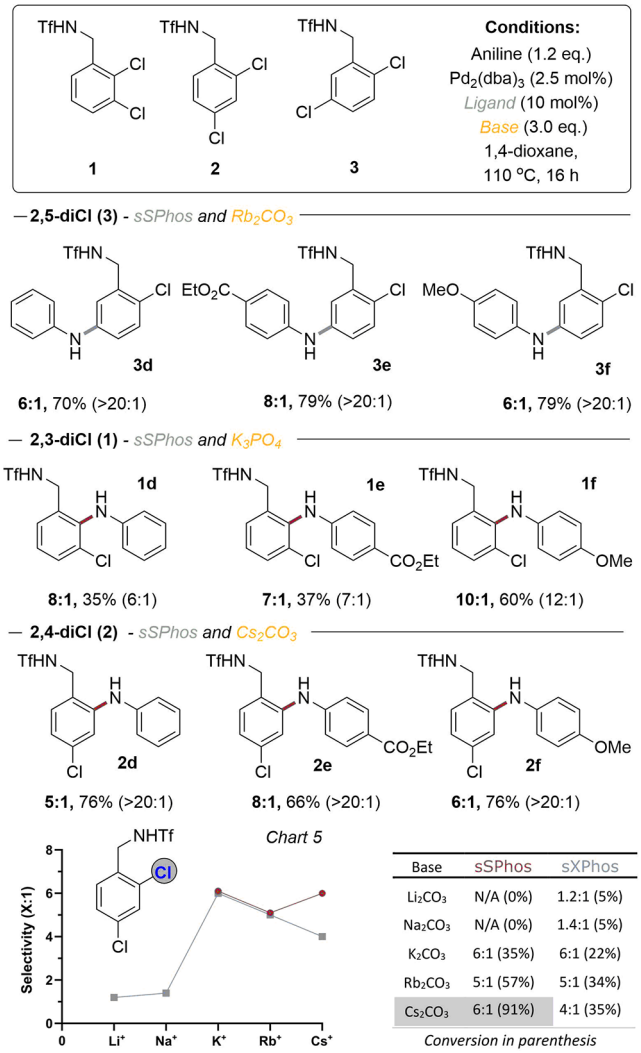
Scheme 1. Preparative Reactions Using Three Boronic Acid Partners in Suzuki Couplings with Isomeric Dichloro Substrates 1−3[a]



[a]Bold ratios were determined from the crude ^{1}H NMR. Yields given are isolated, and the isomeric ratio in parentheses is that of the isolated material.

product in all cases. The crude isomeric ratio is denoted first, with the isolated ratio in parentheses. Disappointingly, low conversion was observed using the original ligand/base combinations identified for both the 2,3-dichloro (**1**, sSPhos and Cs_2CO_3) and the 2,4-dichloro (**2**, sXPhos and Rb_2CO_3) substrates, and further optimization was required. The complete ligand/base toolkit was screened afresh against the 2,3-isomer **1**, but in all cases, very low product formation was observed (<10% in all cases, see SI for full details). We discovered that switching the conjugate anion of the base to phosphate was crucial for promoting reactivity with this substrate and that K_3PO_4 gave acceptable conversion, allowing a moderate yield of the C_2-coupled isomer to be isolated, with good site-selectivity (**1d**). It is important to note here that the moderate yields are due to incomplete conversion rather than formation of any other isomers. Two other anilines were demonstrated as effective partners in addition (Scheme 2, middle row). Application of the complete toolkit to the 2,4-dichloro isomer **2** revealed that switching both ligand to sSPhos and base to Cs_2CO_3 gave uniquely high conversion as well as 6:1 selectivity for coupling at Cl_2 (Chart 5, Scheme 2). This effect was found to be consistent across all three anilines tested, and indeed, the *ortho*-coupled isomer could be isolated in >20:1 isomeric purity in all cases in good yields (Scheme 2, lower row).

Scheme 2. Variation of the Aniline Partner in Buchwald−Hartwig Couplings with Dichloro Substrates 1−3



Having used our ligand/base toolkit to achieve site-selective cross-couplings on dichlorinated isomers of benzylamine, we next turned to the challenge of trichlorinated arenes to explore whether catalyst control could be maintained in these extremely challenging systems. Trichlorinated benzylamines bearing three nonsymmetrical substation patterns (2,3,4 (**5**), 2,4,5 (**6**), and 2,3,5 (**7**)) were examined in their *N*-triflated form (Scheme 3). In these coupling reactions there are seven possible products: three mono products which could all undergo further coupling to afford an additional three regioisomers of dicoupled product and finally the tricoupled product. Standard cross-coupling conditions would be expected to result in complex, intractable mixtures. Importantly, these isomerically pure, trichlorinated arenes are readily accessible in a few steps from cheap, commercially available compounds at low cost (see SI for details).

We first attempted to draw analogy with the most closely related dichlorinated substrates in the hope that these would guide us to well-performing combinations for the trichlorinated compounds. In the case of the 2,3,4-trichlorinated substrate **5**, we used sXPhos and Rb_2CO_3, which had been optimal for the 2,4-dichlorinated substrate, and were happy to see that this gave a 4:1 ratio of the desired coupling at Cl_2 with respect to

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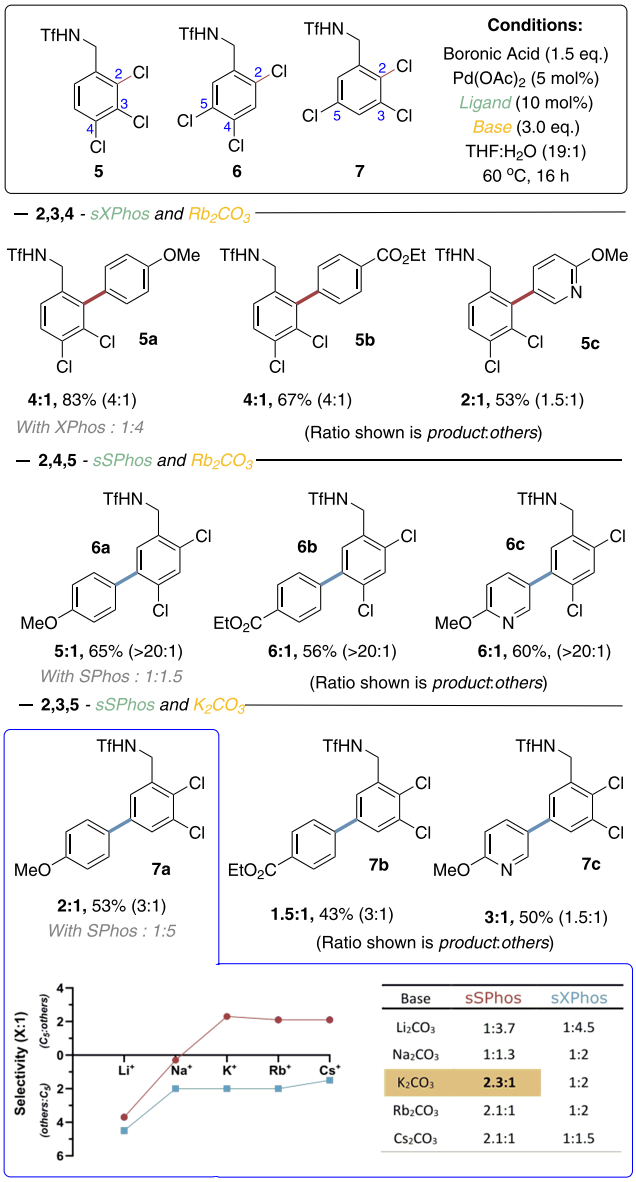
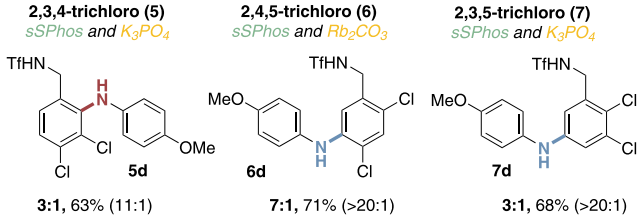
Scheme 3. Investigation of Site-Selective Suzuki−Miyaura Coupling with Trichlorinated Arenes 5−7



"others" (Scheme 3, top row, **5a**). In these compounds the benzylic peaks are highly diagnostic in the ^{1}H NMR spectra and constitute a reliable indicator of selectivity. To highlight how challenging this coupling is, a control reaction on this substrate combination using XPhos instead of sXPhos resulted in a 1:4 ratio, where "others" comprises five separate peaks, emphasizing the dramatic effect on site-selectivity that the sulfonated ligand has. Several different boronic acids were compatible, and similar selectivities were observed for these (**5b** and **5c**). We next examined the 2,4,5-trichlorinated isomer **6** and used sSPhos and Rb_2CO_3, a combination that had been optimal for Suzuki coupling on the 2,5-dichlorinated compound. This gave very good selectivity for coupling at Cl_5 (5:1−6:1 Cl_5:others) across the three boronic acids tested (Scheme 3, middle row, **6a−c**). Furthermore, in these cases the minor components could be easily removed by chromatography, allowing isolation of isomerically pure Cl_5-coupled compound in good yield. For comparison, the control was run for compound **6a** with SPhos, which gave a 1:1.5 ratio of Cl_5:others in which others comprised at least four compounds. Finally, we examined the 2,3,5-trichlorinated isomer **7** (Scheme 3, lower row). This was a very challenging substrate which required us to examine the full toolkit of ligands and bases (Chart 6, Scheme 3). This survey revealed that sSPhos with the larger metal cations gave the best outcomes, resulting in a 2.3:1 ratio of Cl_5:others using K_2CO_3. While this substrate arguably represents the limit of the current system, synthetically useful amounts of the *meta*-coupled product could still be obtained whereas standard ligands give truly intractable mixtures (1:5 Cl_5:others with SPhos for **7a**).

We then turned our attention to site-selective Buchwald−Hartwig couplings on the three trichlorinated substrates **5**−**7**. Because we had found sSPhos to give superior reactivity to sXPhos in Buchwald−Hartwig couplings on the disubstituted substrates, we used this ligand in all cases. In addition, the 2,3-dichloro substitution pattern had required the use of phosphate base previously, and so this was used for **5** and **7**, which both contain this motif (Scheme 4). Considering the

Scheme 4. Site-Selective Buchwald−Hartwig Couplings on Trichlorinated Arenes 5, 6, and 7



challenges presented by these substrates, the observed ratios of major isomer:others of between 3:1 and 7:1 were highly encouraging. Upon purification, minor isomers could typically be removed to permit good isolated yields of largely single isomers to be obtained.

We next explored sequential Suzuki couplings and applied our ligands to 2,4,5-trichlorinated arene **6**, first carrying out a ligand-directed Cl_5-selective coupling using sSPhos/Rb_2CO_3 for boronic acid **A** (Figure 3a). We then switched to sXPhos with the same base to effect a site-selective Suzuki coupling with boronic acid **B** at Cl_2. Finally, a standard Suzuki coupling with boronic acid **C** on the final chlorine (Cl_4) gave the tricoupled product **6f** as a single regioisomer. Although in this case the sequence must be followed in the proper order of *meta* then *ortho* then *para*, in principle, any combination of coupled products could be achieved simply by varying the order in which the boronic acids are used. Given this success, we were keen to tackle the challenge of the tetrachlorinated isomer **8**, in which all four chlorines are in independent environments. Due to the complexity of this substrate and anticipating the potential for deleterious overcoupling, we first screened all 10 ligand/base combinations with limiting boronic acid in order to find that which gave the highest precision, expressed in terms of the ratio Cl_5:others (Figure 3b, Chart 7). This study showed sSPhos and Na_2CO_3 to be optimal, and we proceeded with this combination in a preparative manner with a slight excess of boronic acid **A** for the first step in the sequence, which enabled isolation of the monocoupled product in 40% yield with a 5:1 ratio of Cl_5:other isomers (Figure 3c). We believe that there is little precedent for carrying out a cross-coupling on such a highly halogenated substrate with this level of selectivity. This was carried forward in a Cl_2-selective

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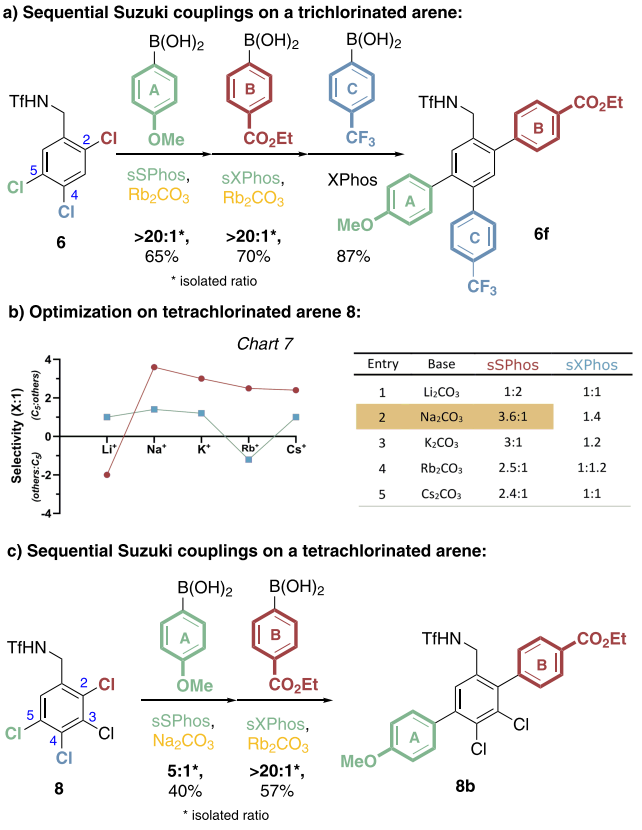

Figure 3. Sequential Suzuki coupling sequences demonstrated on trichlorinated arene **6** and tetrachlorinated arene **8**.

coupling using sXPhos and Rb_2CO_3, which proceeded smoothly with boronic acid **B** and allowed the product **8b** to be isolated in a 57% yield as a single isomer. We attempted selective Suzuki coupling on **8b**, but no selectivity between Cl_3 and Cl_4 was observed: we anticipate that the present ligand scaffold is not able to reach past an existing *ortho* substituent.

It is well established that the *N*-triflyl group in benzylamines can be readily elaborated to a variety of useful functionalities, such as *N*-alkyl amines and aldehydes,[13,16] or subjected to nucleophilic displacement via the ditriflimide.[16b,17] Furthermore, we have previously shown that a number of anionic or Brønsted acidic functional groups are able to act as directing groups for the putative electrostatic interaction with the catalyst.[13,18] Accordingly, we sought to showcase several dichlorinated substrates which feature different directing groups for the electrostatic interaction and demonstrate that these can also be used together with the "toolkit approach" to rapidly identify the optimal ligand/base combination for each. We first selected the commercially available 2,3-dichlorinated hydrocinnamic acid **9** and evaluated the full ligand/base toolkit against it in a Suzuki coupling (Figure 4a). This revealed sSPhos to be the superior ligand, and all cations apart from lithium gave excellent selectivity for Cl_2 (Chart 8, Figure 4). When translated to a preparative reaction using excess boronic acid, this allowed compound **9a** to be isolated in an excellent yield, essentially as a single regioisomer. We then targeted 2,4-dichlorinated sulfamic acid **10**, which can be regarded as a temporarily protected amine and is readily rendered anionic by treatment with base.[19] A full evaluation showed that while sSPhos gave good outcomes, sXPhos was superior in this case and gave 15:1 selectivity for Cl_2 with the three largest cations.

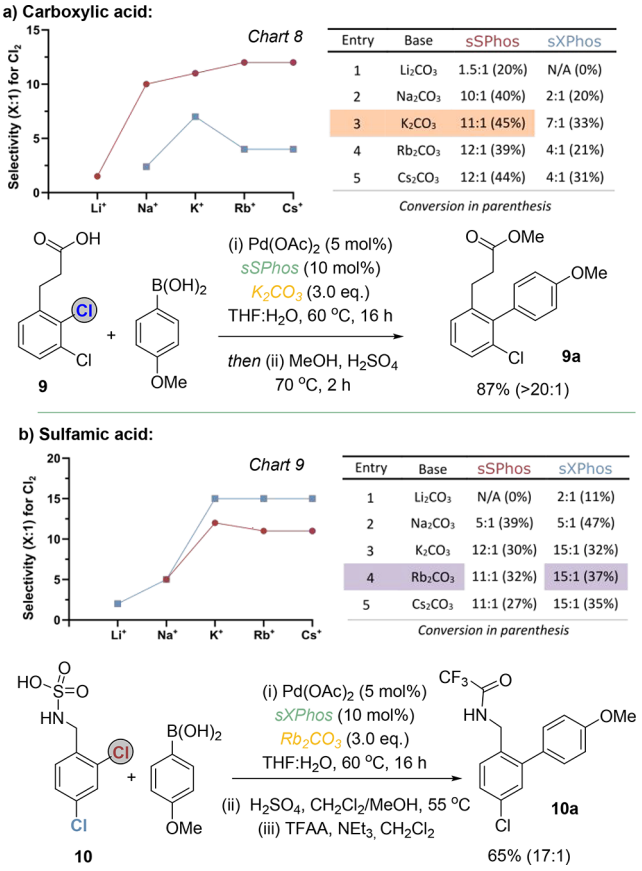

Figure 4. Application of the toolkit approach to two dichlorinated substrates bearing different Brønsted acidic functional groups.

Translated to preparative conditions, this resulted in isolation of **10a** in good yield and with 17:1 selectivity after acid-promoted cleavage of the sulfamate and trifluoroacetylation of the free amine to facilitate isolation.

CONCLUSIONS

Taking into account all of the substrates explored, one can derive a pattern of reactivity with this catalyst system if the properly fine-tuned ligand/base combination can be identified. A chloride at the *meta* position will couple first, so long as there is no *ortho* substituent adjacent to it, which would presumably impede access of the catalyst. Following this, a chloride at the *ortho* position is the second favored position. Chlorides at the *para* position and those that are *meta* but blocked by an *ortho* substituent are the least reactive with these sulfonated ligands, presumably as the catalyst is simply unable to reach. It should be emphasized that control experiments throughout this study using SPhos and XPhos demonstrate that the order outlined above is not an intrinsic order of reactivity toward cross-coupling in general in these substrates. The sulfonate group on the ligand is crucial to obtaining any kind of site-selectivity, but this must be fine tuned by modulation of the sulfonate position and the cation in order to achieve the optimal site-selectivity. On the basis of our current understanding, it is not possible to predict *de novo* exactly which ligand/base combination will be best, but we demonstrated that use of a toolkit of two commercially available ligands and five common bases allows this combination to be rapidly identified in most cases. We anticipate that this study will have practical application in

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streamlining the synthesis of complex polyarenes. More broadly, this demonstrates that fine tuning of precise electrostatic interactions is not only possible but can constitute a very powerful approach to engineering site-selective catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11056.

Experimental procedures and spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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