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SHORT COMMUNICATION

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Highly Chemoselective Mono-Suzuki Arylation Reactions on All Three Dichlorobenzene Isomers and Applications Development

Ehsan Ullah,[a] James McNulty,*[a] and Al Robertson[b]

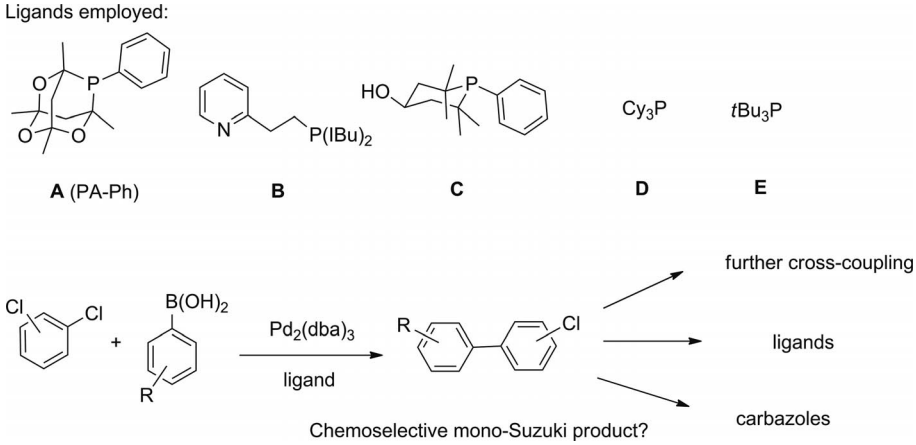
Keywords: Palladium / Cross-coupling / Biaryls / Chemoselectivity / Azides / Fused-ring systems

A Pd catalyst system is described that allows very high chemoselective monoarylation on all three isomers of dichlorobenzene. Direct application of these commodity chemicals to high-value ligands, anilines, azides, and carbazoles was achieved through this process discovery.

Introduction

Palladium-catalyzed C–C bond-forming reactions have become among the most versatile tools used in organic synthesis.[1] In particular, the Suzuki–Miyaura cross-coupling reaction of aryl or vinyl halides and equivalents with boronic acids has become a standard method for the construction of sp^2–sp^2 and sp^2–sp^3 carbon–carbon bonds.[2] Aryl bromides and iodides are very reactive and easily converted into biphenyls with many palladium catalysts. From both industrial and economic view points, aryl chlorides are attractive because of their availability, structural diversity, and lower cost and have become attractive substrates for cross-coupling reactions.[3] While activation of aryl chlorides is more challenging, many systems have now been developed by employing the use of specialized ligands.[3]

Polyhalogenated arene and heteroarene substrates have also been employed in various cross-coupling processes allowing for chemoselective activation at the more reactive position (generally I > Br >> Cl), as well as site-selective sequential cross-coupling reactions in polybromo and mixed halogenated species.[4] Our laboratory has investigated the design and synthesis of new phosphane ligands for coupling reactions over the last few years, including the activation of challenging aryl chlorides.[5] Palladium complexes of the ligand *P*-phenyl-1,3,5,7-tetramethyl-2,4,8-trioxa-6-phosphaadamantane **A** (Scheme 1, PA-Ph)[5e,5f] and P,N and P,O ligands **B**[5a] and **C**,[5b] respectively, were shown to be highly effective in a variety of Pd-mediated processes, including activation of hindered electron-rich aryl chlorides.



Scheme 1. Selective mono-Suzuki cross-coupling reactions of dihalobenzenes and the phosphane ligands employed.

In view of these considerations, we became interested in the potential for chemoselective monofunctionalization of

[a] Department of Chemistry and Chemical Biology, McMaster University,
1280 Main Street West, Hamilton, Ontario, L8S 4M1, Canada
Fax: +1-905-522-2509
E-mail: jmcnult@mcmaster.ca
[b] Cytec Canada Inc.,
P.O. Box 240, Niagara Falls, Ontario, L2E 6T4, Canada
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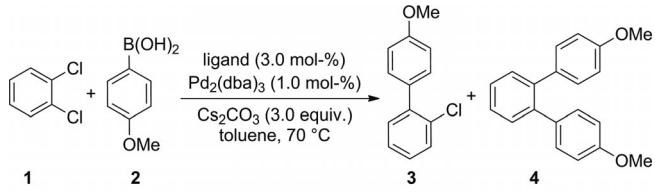
the isomers of dichlorobenzene. All three isomers of dichlorobenzene are readily available in quantity and are inexpensive commodity chemicals. The chemoselective site-selective monofunctionalization and subsequent elaboration would be expected to lead to a wide array of synthetic intermediates and products (Scheme 1). Nonetheless, these substrates have proved challenging in terms of selective mono-cross-coupling reactions. While site-selective mono-Suzuki reactions have been reported for dibromobenzene[4o] and bromo- and chlorobenzenes,[4l] no reports of such a process have been reported on dichlorobenzene substrates. Ackermann reported a domino NH/CH annulation onto a series of 1,2-dihalobenzenes, including two examples of *ortho*-dichlorobenzene,[4m] leading to functionalized carbazoles. More recently, Jin[6a] and Zlotin[6b] have independently reported double, triple, and quadruple Suzuki cross-coupling reactions with di-, tri-, and tetrachlorobenzene derivatives. The intermediate mono-cross-coupled derivatives were reported to be "scarcely formed" or produced in "minor quantity" resulting only in the formation of polysubstituted arenes. In this communication we report the discovery of a process for the chemoselective mono-Suzuki–Miyarua cross-coupling reaction on all three isomeric dichlorobenzenes. The utility of this selective cross-coupling process is also initially demonstrated through elaboration of the *ortho*-mono-coupled arene to Buchwald-type biaryl ligands as well as to a collection of structurally diverse carbazoles (Scheme 2).

Table 1. Chemoselective mono-Suzuki cross-coupling reactions of 1,2-dichlorobenzene with 1.1 and 2.2 equiv. of 4-methoxyphenylboronic acid by using $Pd_2(dba)_3$ and ligands **A**–**E**.[a]



Entry	Ligand	Boronic acid (equiv.)	Products (% yield)[b] Mono	Bis
1	A	**2** (1.1)	**3** (82)	**4** (0)
2	A	**2** (2.2)	**3** (74)	**4** (5)
3	B	**2** (1.1)	**3** (70)	**4** (7)
4	B	**2** (2.2)	**3** (55)	**4** (30)
5	C	**2** (1.1)	**3** (60)	**4** (13)
6	C	**2** (2.2)	**3** (45)	**4** (29)
7	D	**2** (1.1)	**3** (68)	**4** (16)
8	D	**2** (2.2)	**3** (36)	**4** (46)
9	E	**2** (1.1)	**3** (80)	**4** (12)
10	E	**2** (2.2)	**3** (40)	**4** (52)

[a] Reaction conditions: 1,2-dichlorobenzene (0.34 mmol, 1.0 equiv.), 4-methoxyphenylboronic acid [0.37 mmol, 1.1 (or 2.2 equiv.)], Cs_2CO_3 (1.02 mmol, 3.0 equiv.), $Pd_2(dba)_3$ (1.0 mol-%), ligand **A**–**E** (3.0 mol-%), PhMe (1 mL), 3–8 h, 70 °C. [b] Isolated yield after column chromatography.

Results and Discussion

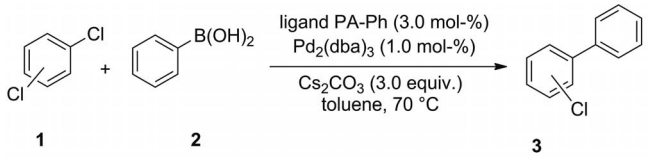
We began our study by investigating the selectivity of arylation on 1,2-dichlorobenzene with 4-methoxyphenylboronic acid as the model reaction (Table 1). In this case, monoarylated chlorobenzene product **3** is readily separable from double substitution product **4** by both thin-layer chromatography and column chromatography over silica gel.

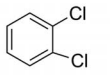
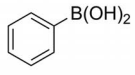
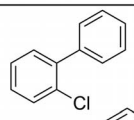
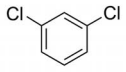
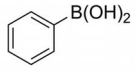
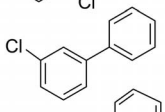
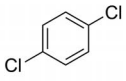
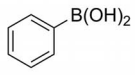
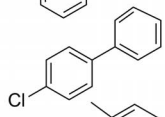
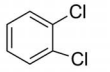
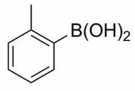
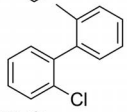
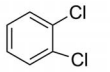
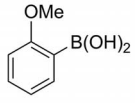
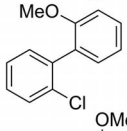
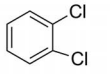
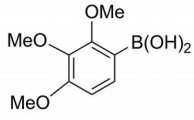
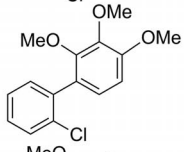
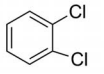
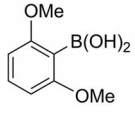
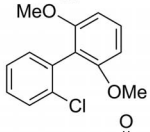
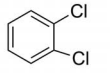
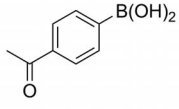
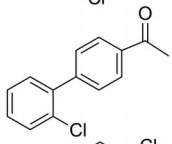
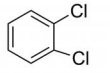
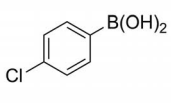
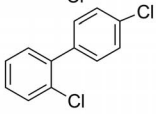
The selective monofunctionalization employing ligands **A**, **B**, and **C** and two standards, sterically hindered, electron-rich phosphane ligands tricyclohexylphosphane **D** and tri-*tert*-butylphosphane **E** (Scheme 1), were included in the study. The yields reported in Table 1 are of gravimetrically determined isolated yields of at least duplicate experiments. In order to gauge the chemoselectivity of the monoarylation process, the reaction with each ligand was initially conducted with 1.05 equiv. of the boronic acid relative to 1,2-dichlorobenzene at 70 °C in toluene, and the overall results are shown in Table 1. To our delight, PA-Ph ligand **A** reacted with very high selectivity when 1.1 equiv. of **2** was employed, yielding exclusively monoarylation product **3**, which was isolated reproducibly in 82–85% yield (Table 1, Entry 1). All other ligands provided moderate to poor chemoselectivity under the same conditions with 5–16% of the bisarylated adduct being formed (Table 1, odd-numbered entries). The chemoselectivity of the cross-coupling process was now challenged further by using an excess amount of **2** (2.20 equiv.) relative to **1**. Under these conditions, the Pd-PA-Ph catalyst was shown to be superior for the selective monoarylation, yielding only a trace amount (≈5%) of doubly arylated product **3a** (Table 1, Entry 2). In contrast, the other ligands proved to be poorly selective, yielding a mixture of monoarylated product **3** contaminated with 29–52% of bisarylated product **4** (Table 1, even-numbered entries). All reactions performed with an excess amount of boronic acid were conducted under identical conditions and no attempt was made to push the reactions to completion. As evidenced by the odd-numbered entries in Table 1, all five ligands investigated proved competent in the initial activation of 1,2-dichlorobenzene. Further activation of intermediate **3** is considerably slower when the Pd-PA-Ph catalyst is employed. The precise reason for this selectivity is, as of yet, unclear; however, the chemoselectivity for monoarylation observed with the use of the PA-Ph ligand is unprecedented, allowing access to the synthetically useful monoarylated intermediates (vide infra).

The reaction was next investigated with a range of reaction partners that expanded the scope and provided mechanistic insight (Table 2). For example, under the standard conditions described with the use of the Pd-PA-Ph catalyst, the reaction of phenylboronic acid (1.1 equiv.) proved to be chemoselective for all three isomers of dichlorobenzene (Table 2, Entries 1–3). High isolated yields (80–86%) were realized for isomeric mono-cross-coupled aryl chlorides **3**. This result demonstrates that steric factors alone are not

responsible for the reduced reactivity of the intermediate monoarylated aryl chloride using this catalyst. A series of hindered *ortho*-methyl- and methoxy-substituted phenylboronic acids (Table 2, Entries 4–7) as well as electronically deactivated derivatives (Table 2, Entries 8 and 9) also reacted selectively with 1,2-dichlorobenzene to yield the monoarylated intermediates, demonstrating consistency in the chemoselectivity of the reaction.

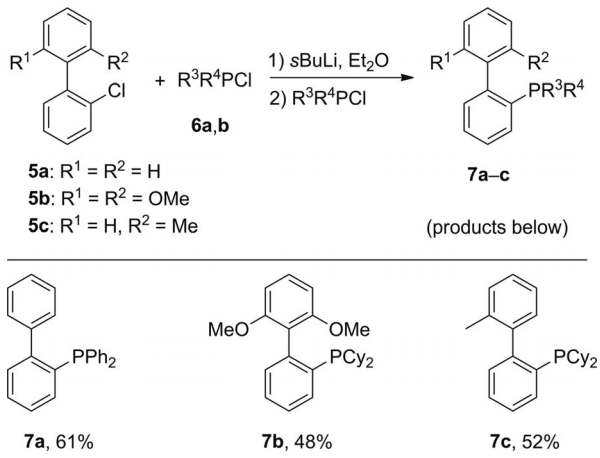
Table 2. Chemoselective monoarylation of dichlorobenzenes isomers by using the Pd-PA-Ph catalyst system.[a]



Entry	Cl-Ar-Cl	Boronic acid	Product **3**	% Yield[b]
1				86
2				80
3				83
4				76
5				72
6				66
7				60
8				96
9				64

[a] Reaction conditions: 1,2-dichlorobenzene (0.68 mmol, 1.0 equiv.), $PhB(OH)_2$ (0.75 mmol, 1.1 equiv.), Cs_2CO_3 (2.04 mmol, 3.0 equiv.), $Pd_2(dba)_3$ (1.0 mol-%), ligand **A** (3.0 mol-%), PhMe (2.0 mL), 70 °C. [b] Isolated yield after column chromatography.

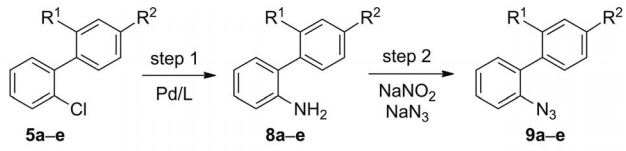
The utility of this monoarylation process was also investigated through elaboration of the 2-chlorobiphenyl product obtained from 1,2-dichlorobenzene. We first envisioned that such *ortho*-monochlorobiphenyls would readily be converted into useful Buchwald-type biaryl phosphane ligands through halogen–lithium exchange[7b] and subsequent trapping with suitable dialkyl or diaryl chlorophosphane **6**. This proved to be the case. Metalation of biaryl chlorides **5a**–**c**, produced by the chemoselective arylation process, proceeded without incident by using *s*BuLi in diethyl ether (Scheme 2). Lithiated **5a** was trapped with diphenylchlorophosphane to yield biaryl ligand **7a**, whereas trapping of the lithiated intermediates from **5b** and **5c** with dicyclohexylchlorophosphane yielded SPhos ligands **7b** and **7c** in good yields.

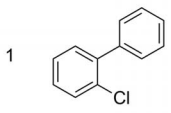
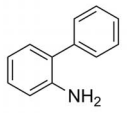
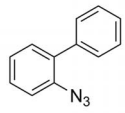
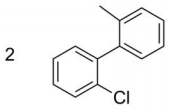
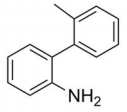
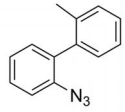
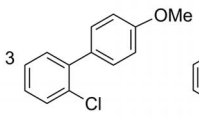
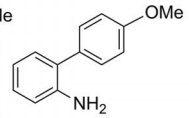
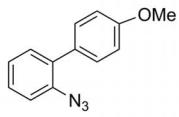
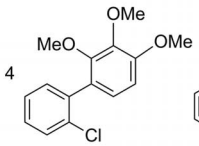
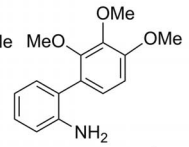
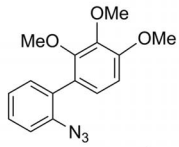
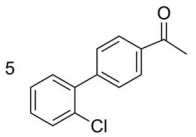
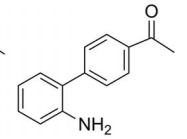
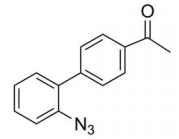


Scheme 2. Synthesis of biaryl phosphane ligands from 2-chlorobiphenyls. Reaction conditions: 2-chlorobiphenyl **5a**–**c** (0.26 mmol, 1.0 equiv.), *s*BuLi (0.65 mmol, 2.5 equiv.), chlorodiphenylphosphane (0.32 mmol, 1.25 equiv.), Et_2O (2.0 mL), –78 to 25 °C.

We next envisioned that the chloride "handle" present in 2-chlorobiphenyls such as **5a** would provide rapid entry to a series of functionalized anilines, azides, and carbazoles through an amination to azide sequence. Carbazoles are valuable heterocycles in view of their application in various areas of medicinal and materials chemistry[8] and have been prepared through transition-metal-catalyzed reactions.[9] Anilines and azides are valuable intermediates and substrates for Huisgen cycloaddition reactions.[12] Employing the method of Hartwig and Lee,[10] 2-chlorobiphenyl (**5a**) was coupled with $Zn[N(SiMe_3)]_2$ in the presence of LiCl by using $Pd(dba)_2$ as the Pd source and tri-*tert*-butylphosphane in THF to give aniline **8a** (Table 3). Diazotization of **8a** by using $NaNO_2$ at 0 °C in the presence of NaN_3 allowed smooth conversion to biaryl azide **9a**. Using this same two-step sequence, a series of functionalized biaryl chlorides, all produced from 1,2-dichlorobenzene, yielded the corresponding anilines **8a**–**e** and azides **9a**–**e** in excellent yield (Table 3, Entries 1–5). Finally, by using the method of Brown and co-workers,[11] azides **9a**–**e** underwent smooth thermal conversion in refluxing xylenes to yield the corresponding carbazoles **10a**–**e**, which were isolated in very high yields (Table 4).

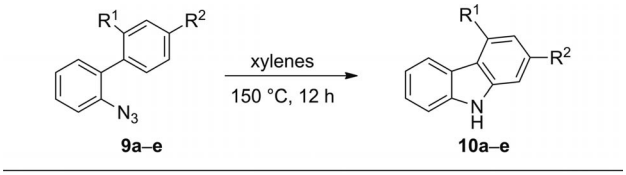
Table 3. Synthesis of biaryl azides using 2-chlorobiphenyl.[a]

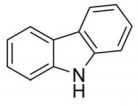


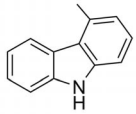
Entry	Ar-X	Ar-NH_2	% Yield	Ar-N_3	% Yield[b]
1			80		98
2			74		93
3			76		94
4			62		90
5			92		96

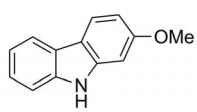
[a] General conditions: step 1: 2-chlorobiphenyl (0.50 mmol, 1.0 equiv.), $Zn[N(SiMe_3)]_2$, (0.50 mmol, 1.0 equiv.), LiCl (0.30 mmol, 0.6 equiv.), $Pd(dba)/P(tBu)_3$ (1.0 mol-%), THF (1.0 mL); step 2: 2-aminobiphenyl (0.53 mmol, 1.0 equiv.), $NaNO_2$ (0.74 mmol, 1.40 equiv.), NaN_3 (0.8 mmol, 1.50 equiv.), HOAc (3.0 mL), H_2O (1.5 mL), 0 °C to r.t., 30 min. [b] Isolated yield.

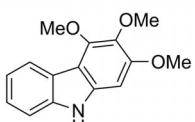
Table 4. Carbazole synthesis.[a]

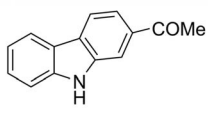



10a (92%)


10b (88%)


10c (90%)


10d (82%)


10e (96%)

[a] General conditions: Biphenyl azide in xylene (3 mL), 150 °C (oil bath), 12 h. [b] Isolated yield.

Conclusions

In summary, a Pd catalyst system has been discovered based on *P*-phenylphosphaadamantane ligand **A** that exhibits very high chemoselectivity for monoarylation of inexpensive dichlorobenzene substrates. Two applications of the methodology are reported that allow rapid access to biarylphosphane ligands as well as carbazole derivatives from commodity chemicals. The intermediate functionalized anilines have many uses in synthetic and medicinal chemistry, whereas functionalized azides are of much current interest as partners in Huisgen "click" chemistry.[12] Structure–activity studies with a series of ligands based on **A** to probe the ligand effect and applications development are under investigation.

Supporting Information (see footnote on the first page of this article): Experimental procedures and copies of the ^1H NMR and ^{13}C NMR spectra for all new compounds.

Acknowledgments

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