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The Suzuki–Miyaura cross-coupling of bromo- and chloroarenes with arylboronic acids in supercritical carbon dioxide

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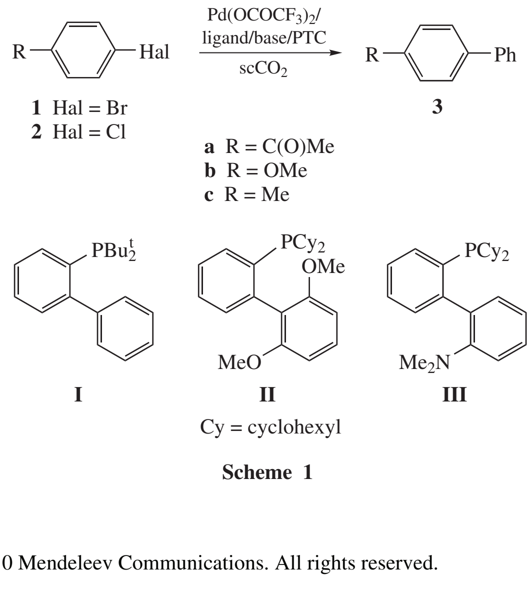
Haloarenes ArHal (Hal = Br, Cl) react with arylboronic acids in supercritical carbon dioxide in the presence of a system comprising $Pd(OCOCF_3)_2$/Buchwald phosphine ligand/potassium carbonate (phosphate)/18-crown-6 to yield the corresponding cross-coupling products in high yields; all chlorine atoms in di- and tetrachloroarenes are replaced by aryl groups under the proposed conditions.

The development of environmentally friendly chemical processes with the use of alternative solvents such as water,[1] ionic liquids[2] and supercritical fluids[3] is a promising area of green chemistry. In recent years, supercritical carbon dioxide ($scCO_2$) has attracted attention as a green neoteric solvent since it is a nontoxic, inflammable, thermally stable, cheap and readily available compound of nearly an inexhaustible supply. It has low critical temperature ($T_c = 31.1$ °C) and pressure ($P_c = 73.8$ bar) and, therefore, can be easily transferred into the supercritical state.

In the last decade, $scCO_2$ has been used in hydrogenation,[4] hydroformylation,[5] oxidation,[6] polymerization[7] and cross-coupling reactions.[8–19] However, its application to Pd-catalyzed cross-coupling has some limitations. As a rule, active iodoarenes should be used as the starting compounds[10–16,19] and the reactions should be performed in the presence of expensive fluorinated,[5(b),14] or air-sensitive phosphine ligands[11–16] and rather expensive organic amines[11,15,16,19] or cesium carbonate.[15]

Herein, we report a new convenient procedure for the Suzuki–Miyaura cross-coupling in $scCO_2$, which is applicable for bromo- and chloroarenes and is characterized by the combined use of Buchwald phosphine ligands, cheap inorganic bases, such as potassium carbonate, and a crown ether. At first, we studied model reactions between bromoarenes **1a**–**c** bearing electron-withdrawing or donating groups at the *para*-position of the aromatic ring and phenylboronic acid (Scheme 1, Table 1). The reactions were performed at 110 bar and 110 °C in the presence of $Pd(OCOCF_3)_2$ which has better solubility in $scCO_2$ than conventional $Pd(OAc)_2$[3(c),15] and air-stable and easy to handle phosphine ligands **I**–**III**.[20] Potassium or cesium carbonates, potassium phosphate and organic amines were examined as bases.



Scheme 1

4-Bromoacetophenone **1a** readily reacted with phenylboronic acid in $scCO_2$ in the presence of $Pd(OCOCF_3)_2$, ligand **I** or **II**, and a base (K_2CO_3 or K_3PO_4) to afford cross-coupling product **3a** in quantitative yield (Table 1, entries 1, 2).† 4-Bromoanisole **1b** is less active under these conditions (entries 3, 4). The yield of product **3b** can be improved either by carrying out the reaction in the presence of Cs_2CO_3 instead of K_3PO_4 or K_2CO_3 (entries 5, 6) or by raising the temperature to 120 °C (entry 8). Further temperature elevation to 130 °C resulted in a somewhat lower yield of compound **3b** (entry 9). Organic bases, such as DIPEA and TEA, in contrast to the reported data,[11,15,16,19] were highly inefficient (entries 10, 11), and their use led to decomposition of phenylboronic acid.

We succeeded in improving the yield of product **3b** to 87–91% by running the reaction in the presence of 18-crown-6 (5 mol% with respect to the base) that supposedly acted as a phase-transfer catalyst (PTC) facilitating the migration of the potassium salt into a $scCO_2$ solution (entries 12, 13). Note that crown ethers have not been used earlier in cross-coupling reac-

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† *Suzuki–Miyaura reaction in supercritical CO_2 (typical procedure).* A haloarene (0.5–1.0 mmol), arylboronic acid (1.2–2.5 mmol), $Pd(OCOCF_3)_2$ (7–14 mg, 0.02–0.04 mmol), ligand **I**–**III** (0.04–0.08 mmol), a base (1.5–3.0 mmol) and 18-crown-6 (0.075–0.15 mmol, in the case of K_2CO_3 or K_3PO_4) were placed in a 10 ml stainless steel cell equipped with a magnetic stirring bar. The cell was sealed, pressurized to approximately 55 bar, heated to 110–120 °C, and the pressure was then adjusted to 110 bar by adding more CO_2. The temperature, pressure and duration of reactions are specified in Tables 1, 2 and Schemes 2–4. The cell was cooled, and once CO_2 was carefully released through the valve, it was opened. The residue was washed out by toluene (4×5 ml). The combined extracts were washed with water and dried (Na_2SO_4). An aliquot of the solution was analyzed by GC or GC/MS. The retention times of products **3a**–**c** were identical to those of the authentic samples. Products **5** and **7** were isolated by column chromatography (silica gel, eluent 10→20% CH_2Cl_2 in light petroleum) in yields ~10–15% lower than those measured by GC.

Using smaller amounts of catalysts resulted in lowering the conversion of the starting haloarenes into the cross-coupling products. The expected by-products, biphenyl or bi(*p*-tolyl) resulting from homocoupling of arylboronic acids, were detected only in a scarce number of experiments in quantities not higher than 2% (since the boronic acids were used as excess reactants, the fractions of such by-products were neglected while calculating the yields of target products).

Table 1 Cross-coupling of bromoarenes **1a–c** with $PhB(OH)_2$ in $scCO_2$.[a]

Entry	ArBr	Ligand	Base	PTC[b]	GC yield (%)
1	**1a**	**I**	K_3PO_4	—	100
2	**1a**	**II**	K_2CO_3	—	100
3	**1b**	**II**	K_3PO_4	—	78
4	**1b**	**II**	K_2CO_3	—	46
5	**1b**	**I**	Cs_2CO_3	—	100
6	**1b**	**II**	Cs_2CO_3	—	100
7	**1b**	**III**	Cs_2CO_3	—	67
8	**1b**	**II**	K_2CO_3	—	95[c]
9	**1b**	**II**	K_2CO_3	—	89[d]
10	**1b**	**II**	DIPEA	—	6
11	**1b**	**II**	TEA	—	1
12	**1b**	**II**	K_3PO_4	18-crown-6	87
13	**1b**	**II**	K_2CO_3	18-crown-6	91
14	**1b**	**II**	K_2CO_3	Bu_4NBr	58
15	**1c**	**II**	K_3PO_4	—	56
16	**1c**	**II**	K_2CO_3	—	25
17	**1c**	**II**	K_3PO_4	18-crown-6	100
18	**1c**	**II**	K_2CO_3	18-crown-6	100

[a] Reaction conditions: $PhB(OH)_2$ (1.2 equiv.), $Pd(OCOCF_3)_2$ (2 mol%), ligand (4 mol%), base (1.5 equiv.), 110 °C, 110 bar, 10 h; [b] 5 mol%. [c] At 120 °C. [d] At 130 °C.

Table 2 Cross-coupling of chloroarenes **2a–c** with $PhB(OH)_2$ in $scCO_2$.[a]

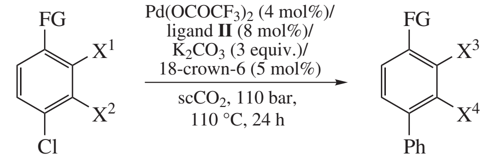
Entry	ArCl	Base	Time/h	GC yield (%)
1	**2a**	K_3PO_4	5	100
2	**2b**	K_3PO_4	10	80
3	**2b**	K_2CO_3	10	61
4	**2b**	K_2CO_3	18	94[b]
5	**2c**	K_2CO_3	10	44
6	**2c**	K_2CO_3	18	81[b]

[a] Reaction conditions: $PhB(OH)_2$ (1.2 equiv.), $Pd(OCOCF_3)_2$ (2 mol%), ligand **II** (4 mol%), 18-crown-6 (5 mol%), base (1.5 equiv.), 110 °C, 110 bar. [b] At 120 °C, 4 mol% $Pd(OCOCF_3)_2$ and 8 mol% ligand **II**.

tions in $scCO_2$ medium. Surprisingly, in the presence of Bu_4NBr instead of 18-crown-6, the yield of product **3b** (entry 14) dropped. This fact differentiates $scCO_2$ from organic solvents where Bu_4NBr and 18-crown-6 show similar efficacy.[21] A 18-crown-6 additive noticeably intensified the reactions of 4-bromotoluene **1c** with phenylboronic acid in $scCO_2$ (Table 1, entries 17, 18), resulting in significantly higher yields of the corresponding product **2c** compared to the control experiments (entries 15, 16).

Then, the optimal conditions were applied to the cross-coupling of chloroarenes **2a–c** (Scheme 1, Table 2). 4-Chloroacetophenone **2a** appeared to react with phenylboronic acid in the presence of the $Pd(OCOCF_3)_2$/ligand **II**/K_2CO_3 (or K_3PO_4)/18-crown-6 system to give 4-acetylbiphenyl **3a** in ~100% yield (Table 2, entry 1). Chloroarenes **2b** and **2c** containing electron-donating groups afforded corresponding products **3b** and **3c** in lower yields (entries 2, 3, 5). However, they were significantly improved by raising the catalyst loading to 4 mol% and the reaction temperature to 120 °C (entries 4, 6).

An advantage of the proposed procedure is its applicability to reactions of polychloroarenes. In the presence of an excess of phenylboronic acid (2.2 equiv.), both chlorine atoms in functionalized dichloroarenes **4** and **5** could be replaced by phenyl groups to afford corresponding substituted terphenyls **6** and **7** in nearly quantitative yields[‡] (Scheme 2).



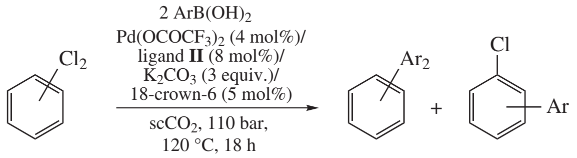
4 X^1 = Cl, X^2 = H
5 X^1 = H, X^2 = Cl

6 X^3 = Ph, X^4 = H (98%)
7 X^3 = H, X^4 = Ph (97%)

4, **6** FG = C(O)Me
5, **7** FG = OMe

Scheme 2

Isomeric dichlorobenzenes **8a–c** bearing no activating functional groups at the aromatic ring also reacted with phenyl- and 4-tolylboronic acids under proposed conditions yielding terphenyls **9a–d** in 74–100% yields. As a rule, minor quantities of monosubstitution products **10a**,**b**,**d** were detected along with compounds **9a–d** (Scheme 3).



8 **9** **10**

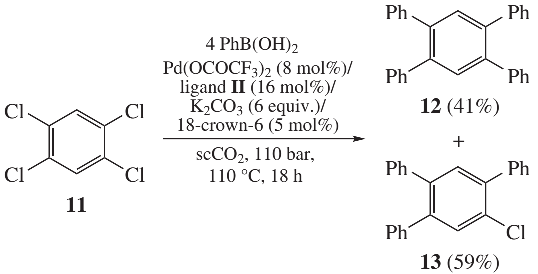
8a Cl_2 = 1,2-Cl_2
8b Cl_2 = 1,3-Cl_2
8c Cl_2 = 1,4-Cl_2

9a Ar_2 = 1,2-Ph_2 (90%)
9b Ar_2 = 1,3-Ph_2 (89%)
9c Ar_2 = 1,4-Ph_2 (~100%)
9d Ar_2 = 1,4-(p-MeC_6H_4)$_2$ (79%)

10a Ar = 2-Ph (10%)
10b Ar = 3-Ph (11%)
10d Ar = 4-(p-MeC_6H_4) (21%)

Scheme 3

Furthermore, in 1,2,4,5-tetrachlorobenzene **11** three or even four chlorine atoms were replaced by phenyl groups on treatment with phenylboronic acid (5 equiv.) in $scCO_2$ in the presence of the developed catalytic system to afford two products **12** and **13** in comparable amounts (Scheme 4). Note that the cross-coupling of polychloroarenes in $scCO_2$ have never been described so far. The procedure is simple and environmentally friendly as it minimizes the risk of leaching polychlorinated compounds, many of which are toxic, from the reaction vessel into the environment.



Scheme 4

In summary, we have developed an efficient procedure for the Pd-catalyzed Suzuki–Miyaura reaction of aryl bromides and chlorides in supercritical carbon dioxide. The method is suitable for non-activated chloroarenes and potentially can be used for synthetic utilization of polychlorinated aromatic com-

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[‡] *2,4-Diphenylacetophenone* **5**: mp 98–100 °C (lit.,[23] mp 104 °C). ^{1}H NMR ($CDCl_3$) δ: 2.08 (s, 3H), 7.38–7.53 (m, 8H), 7.61–7.72 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 30.3 (Me), 126.0 (CH), 127.2 (2CH), 127.9 (CH), 128.0 (CH), 128.6 (CH), 128.7 (2CH), 128.8 (2CH), 128.9 (2CH), 129.0 (CH), 139.3 (C), 139.8 (C), 140.8 (C), 141.2 (C), 143.6 (C), 204.1 (C). MS, m/z: M^+ 272.

3,4-Diphenylanisole **7**: mp 113–115 °C. ^{1}H NMR ($CDCl_3$) δ: 3.89 (s, 3H), 6.95–7.04 (m, 2H), 7.08–7.26 (m, 10H), 7.37 (d, 1H, J 8.8 Hz). ^{13}C NMR ($CDCl_3$) δ: 55.4 (Me), 113.0 (CH), 115.8 (CH), 126.0 (CH), 126.6 (CH), 127.8 (2CH), 127.9 (2CH), 129.8 (2CH), 129.9 (2CH), 131.7 (CH), 133.2 (C), 141.2 (C), 141.5 (C), 141.7 (C), 158.9 (C). MS m/z: M^+ 260. Found (%): C, 87.26; H, 6.34. Calc. for $C_{19}H_{16}O$ (%): C, 87.66; H, 6.19.

pounds, in particular persistent organic pollutants,[22] by their transformation into valuable and safe products.

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