

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

Ilya V. Kuchurov*, Andrei A. Vasiliev, Sergei G. Zlotin

N.D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky Prosp. 47, 119991
Moscow, Russia

E-mail: ilya.kuchurov@gmail.com Fax: +7 499 1355328

ABSTRACT

An efficient green-chemistry procedure for Pd-catalyzed Suzuki–Miyaura cross-coupling between chloroarenes and arylboronic acids in the presence of a system comprising of Pd(OOCF₃)₂, Buchwald phosphine ligand and inorganic base in supercritical carbon dioxide has been developed. Reactions were carried out at 110 bar and 110–130 °C. Cesium carbonate or potassium phosphate (carbonate) were used as bases and 18-crown-6 as phase-transfer catalyst (PTC). Up to four chlorine atoms in starting chloroarenes could be replaced by aryl groups by the developed procedure. The method is suitable for non-activated chloroarenes and hopefully can be used for the synthesis of practically valuable aromatic compounds from commercially available chlorinated materials.

INTRODUCTION

The Suzuki–Miyaura cross-coupling reaction between arylboronic acids and aryl halides is one of the most efficient methods for the formation of carbon-carbon bonds [1, 2]. It is applied at the key steps in total syntheses of natural compounds and other valuable substances, in particular porphyrins, amino acids, peptides, polymers and dendrimers [3, 4]. Commonly, it is performed in the presence of various Pd/ligand complexes in organic solvents [5]. However, intensive studies aiming at the development of more environment-friendly and efficient versions of this reaction are carrying out recently [6]. Among them, studies aiming at the replacement of volatile and often toxic organic solvents for alternative environment-safe mediums such as water, ionic liquids, or supercritical fluids are a priority from green and sustainable chemistry viewpoints [7, 8]. Over the last decade, supercritical fluids, especially supercritical carbon dioxide (scCO₂), found wide application in synthetic organic chemistry due to their useful properties [9, 10]. Examples of Pd-catalyzed homogeneous cross-coupling in scCO₂ are known [11–16], however the reported procedures have some limitations. As a rule, active iodoarenes should be used as the starting compounds and the reactions should be performed in the presence of expensive fluorinated, or air-sensitive phosphine ligands.

Herein we report a new convenient procedure for the Suzuki–Miyaura cross-coupling in scCO₂, which is applicable for available chloroarenes and is characterized by the combined use of Buchwald phosphine ligands, inorganic bases and crown ether as additive to promote the reactions of non-activated chloroarenes.

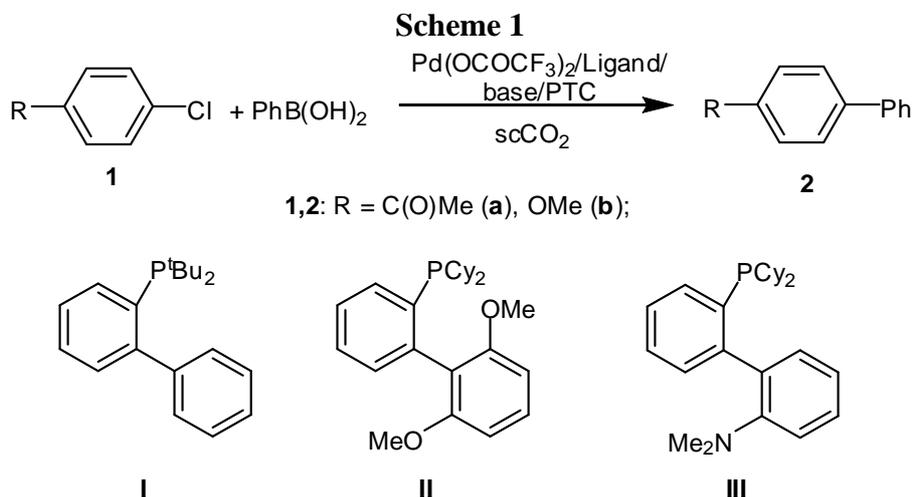
MATERIALS AND METHODS

Commercially available Buchwald phosphine ligands were purchased from DALCHEM (Russia). 4-Chloroacetophenone, 4-chloroanizole, polychloroarenes, arylboronic acids, Pd(OCOCF₃)₂ and inorganic bases were purchased from Aldrich.

Suzuki–Miyaura reaction in scCO₂ (Typical procedure): Chloroarene (0.5 – 1.0 mmol), arylboronic acid (1.2 – 2.5 mmol), Pd(OCOCF₃)₂ (7 – 14 mg, 0.02 – 0.04 mmol), ligand **I–III** (0.04 – 0.08 mmol), base (1.5 – 3.0 mmol) and 18-crown-6 (0.075 – 0.15 mmol, in the case of K₂CO₃ or K₃PO₄) were placed in a 10 mL stainless steel cell equipped with magnetic stirring bar. The cell was sealed, pressurized to approximately 55 bar, heated to 110–130 °C, and the pressure was then adjusted to 110 bar by adding more CO₂. Temperature, pressure and duration of reactions are specified in Tables 1, 2 and Schemes 2–4. The cell was cooled, and once CO₂ was carefully released through the valve, it was opened. The residue was washed out with toluene (4×5 mL). The combined extracts were washed with water and dried (Na₂SO₄). An aliquot of the solution was analyzed by GC or GC/MS. The retention times of products **2a,b** were identical to those of the authentic samples. Products **5** and **6** were isolated by column chromatography (silica gel, eluent 10→20% CH₂Cl₂ in light petroleum) in yields ca. 10–15% lower than those measured by GC.

RESULTS AND DISCUSSION

At first, we studied model reactions between chloroarenes **1a,b** 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(OCOCF₃)₂ which has better solubility in scCO₂ than conventional Pd(OAc)₂ [12] and air-stable and easy to handle phosphine ligands **I–III** [17 – 19]. Potassium or cesium carbonates, potassium phosphate and organic amines were examined as bases.



4-Chloroacetophenone (**1a**) readily reacted with phenylboronic acid in scCO₂ in the presence of the Pd(OCOCF₃)₂, ligand **I–III** and Cs₂CO₃ to afford cross-coupling product **2a** (Table 1, entries 1–3). Ligand **II** which showed the highest activity was used in further reactions between substrate **1a** and phenylboronic acid in the presence of various bases. Inorganic bases K₃PO₄ and K₂CO₃ acted similar to Cs₂CO₃ in the studied reaction (entries 4, 5) whereas organic bases, such as DIPEA and TEA, in contrast to the reported data [13, 14]

were essentially inefficient (entries 6, 7), and their use led to decomposition of phenylboronic acid.

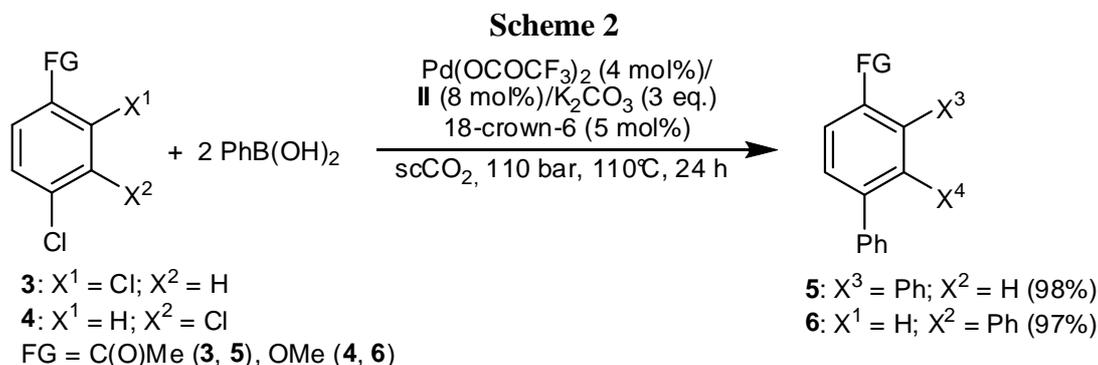
Table 1. Cross-coupling of chloroarenes **1a-c** with PhB(OH)₂ in scCO₂.^a

Entry	ArCl	Ligand	Base	PTC ^b	GC yield of 2 , %
1	1a	I	Cs ₂ CO ₃	-	40
2	1a	II	Cs ₂ CO ₃	-	100
3	1a	III	Cs ₂ CO ₃	-	68
4	1a	II	K ₃ PO ₄	-	100
5	1a	II	K ₂ CO ₃	-	100
6	1a	II	DIPEA	-	7
7	1a	II	TEA	-	2
8	1b	II	Cs ₂ CO ₃	-	16
9	1b	II	K ₃ PO ₄	-	7
10	1b	II	K ₂ CO ₃	-	6
11	1b	II	K ₃ PO ₄	18-crown-6	80
12	1b	II	K ₂ CO ₃	18-crown-6	61
13	1b	II	K ₃ PO ₄	Bu ₄ NBr	46
14	1b	II	K ₂ CO ₃	18-crown-6	91 ^c
15	1b	II	K ₂ CO ₃	18-crown-6	81 ^d

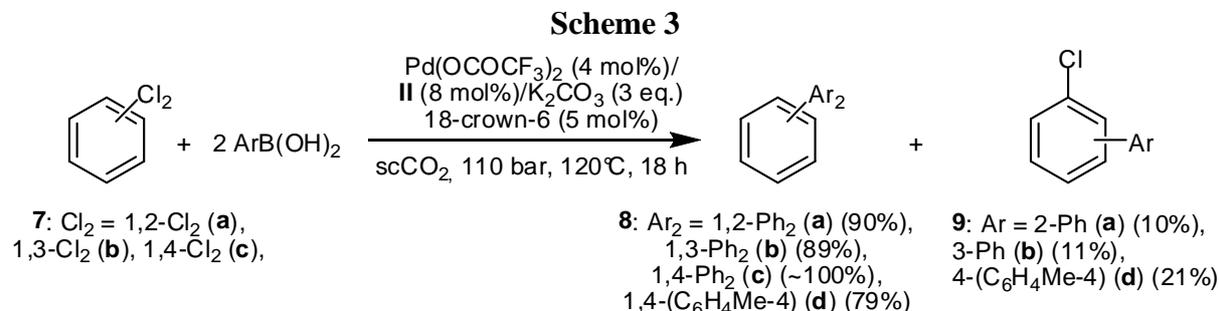
^a Reaction conditions: PhB(OH)₂ (1.2 equiv.), Pd(OCOCF₃)₂ (2 mol%), ligand (4 mol%), base (1.5 equiv.), 110 °C, 110 bar, 10 h.; ^b 5 mol%; ^c At 120 °C; ^d At 130 °C.

4-Chloroanisole (**1b**) was less active under studied conditions (entries 8-10). We succeeded in improving the yield of product **2b** 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 scCO₂ solution (entries 11, 12). It should be noted that crown ethers have not been used earlier in cross-coupling reactions in scCO₂ medium. Surprisingly, in the presence of Bu₄NBr instead of 18-crown-6, the yield of product **2b** (entry 13) dropped. This fact differentiates scCO₂ from organic solvents where Bu₄NBr and 18-crown-6 show similar efficacy [20]. The yield of product **2b** can be further improved by raising the temperature to 120 °C (entry 14). Further temperature elevation to 130 °C resulted in a somewhat lower yield of compound **3b** (entry 15).

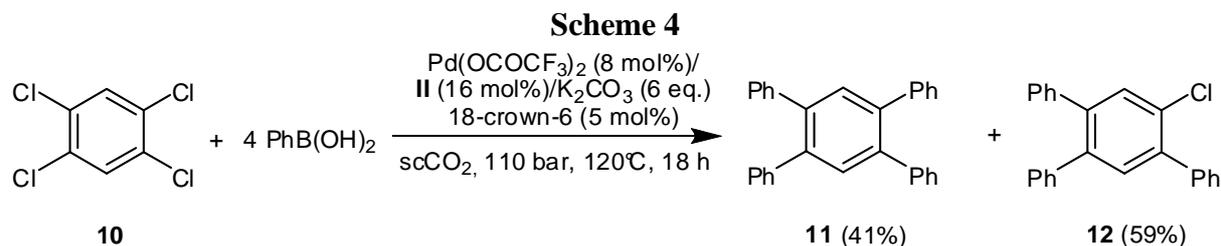
An advantage of the proposed procedure is its applicability to reactions of polychloroarenes. In the presence of an excess of phenylboronic acid both chlorine atoms in functionalized dichloroarenes **3** and **4** could be replaced by phenyl groups to afford the corresponding substituted terphenyls **5** and **6** in nearly quantitative yields (Scheme 2).



Isomeric dichlorobenzenes **7a-c** bearing no activating functional groups at the aromatic ring also reacted with phenyl- and 4-tolylboronic acids under proposed conditions yielding respective terphenyls **8a-d** in 74 – 100% yields. As a rule, minor quantities of monosubstitution products **9a,b,d** were detected along with compounds **8a-d** (Scheme 3).



Furthermore, 1,2,4,5-tetrachlorobenzene (**10**) underwent replacement of three or even four chlorine atoms by phenyl groups on treatment with phenylboronic acid in scCO_2 in the presence of the developed catalytic system affording two products **11** and **12** in comparable amounts (Scheme 4). It should be mentioned that 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 of polychlorinated compounds many of which are rather toxic from the reaction vessel into environment.



CONCLUSION

In summary, we have developed an efficient procedure for Pd-catalyzed Suzuki–Miyaura reaction of aryl chlorides in supercritical carbon dioxide. The method is suitable for non-activated chloroarenes and potentially can be used for synthetic utilization of polychlorinated aromatic compounds, in particular persistent organic pollutants [21, 22], by their transformation into valuable and safe products.

REFERENCES

- [1] Suzuki A. *J. Organomet.Chem.*, 576, **1999**, p. 147.
- [2] Miyaura N., Suzuki A. *Chem. Rev.*, 95, **1995**, p. 2457.
- [3] Molander G.A., Petrillo D.E., Landzberg N.R., Rohanna J.C., Biolatto B., *Synlett.*, **2005**, p. 1763.
- [4] Schluter A.D., *J. Polym. Sci., Part A: Polym. Chem.*, 39, **2001**, p. 1533.
- [5] Kotha S., Lahiri K., Kashinath D., *Tetrahedron*, 58, **2002**, p. 9633.
- [6] Bai L., Wang J.-X., *Curr. Org. Chem.*, 9, **2005**, p. 535.

- [7] Adams D.J., Dyson P.J., Tavener S.J., *Chemistry in Alternative Reaction Media*, Wiley-Interscience, Cambridge, **2004**.
- [8] Sheldon R.A., *Green Chem.*, **7**, **2005**, p. 267.
- [9] Jessop P.G., Leitner W., *Chemical Synthesis Using Supercritical Fluids*, Wiley-VCH, Weinheim, **1999**.
- [10] Jessop P.G., *J. Supercrit. Fluids*, **38**, **2006**, p. 211.
- [11] Carroll M.A., Holmes A.B., *Chem. Commun.*, **1998**, p. 1395.
- [12] Shezad N., Oakes R.S., Clifford A.A., Rayner C.M., *Tetrahedron Lett.*, **40**, **1999**, p. 2221.
- [13] Early T.R., Gordon R.S., Carroll M.A., Holmes A.B., Shute R.E., McConvey I. F., *Chem. Commun.*, **2001**, p. 1966.
- [14] Gordon R.S., Holmes A.B., *Chem. Commun.*, **2002**, p. 640.
- [15] Saffarzadeh-Matin S., Chuck C.J., Kerton F.M., Rayner C.M., *Organometallics*, **23**, **2004**, p. 5176.
- [16] Saffarzadeh-Matin S., Kerton F.M., Lynam J.M., Rayner C.M., *Green Chem.*, **8**, **2006**, p. 965.
- [17] Old D.W., Wolfe J.P., Buchwald S.L., *J. Am. Chem. Soc.*, **120**, **1998**, p. 9722.
- [18] Wolfe J.P., Singer R.A., Yang B.H., Buchwald S.L., *J. Am. Chem. Soc.*, **121**, **1999**, p. 9550;
- [19] Barder T.E., Walker S.D., Martinelli J.R., Buchwald S.L., *J. Am. Chem. Soc.*, **127**, **2005**, p. 4685.
- [20] Dehmlow E. V., Dehmlow S. S., *Phase Transfer Catalysis*, 3rd ed., VCH: Weinheim, **1993**.
- [21] Tundo P., Perosa A., Zecchini F., *Methods and Reagents for Green Chemistry*, Wiley Interscience, **2007**.
- [22] Lunin V. V., Lokteva E. S., *Russ. Chem. Bull.*, **45**, **1996**, p. 1609.