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Ruphos-mediated Suzuki cross-coupling of secondary alkyl trifluoroborates

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ABSTRACT

A Ruphos-mediated Suzuki cross-coupling between (hetero)aryl bromides and secondary alkyltrifluoroborates is described using palladium catalysis. The Ruphos ligand showed superior properties as compared to S-Phos in this type of reaction. This method constitutes a valuable extension to current methods for the straightforward production of secondary-alkylated (hetero)aryl derivatives.

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Palladium-catalysed cross-coupling chemistry is of great importance in the synthesis of a variety of chemical entities. In the past three decennia, a plethora of reports have been published about the applications of this chemistry, including carbon–carbon and carbon–heteroatom bond forming reactions. Noteworthy are the Kumada, Negishi, Stille and Suzuki reactions for the formation of carbon–carbon bonds[1] and the Buchwald–Hartwig methodology for creating a carbon–heteroatom bond, for example, carbon–nitrogen, carbon–oxygen or carbon–sulfur.[2] Suzuki cross-coupling[3] is often the preferred reaction in carbon–carbon bond formation because it has several advantageous features. In general, starting materials are stable and commercially available, it runs under mild conditions and no toxic materials are formed in the course of the reaction. These features make the Suzuki cross-coupling amenable for large scale synthesis.[4] Since the first publications,[5] significant optimisation chemistry has been described, especially in the area of ligand choice,[6] whose efforts have resulted in a tremendous extension of its scope. Recently, we were encouraged by some articles from Buchwald[7] wherein S-Phos was disclosed (Fig. 1) as a novel ligand, broadening the existing scope of the Suzuki cross-coupling reaction. Their reported catalytic system is applicable for reactions with aryl- and heteroaryl chlorides, aryl- and heteroarylboronic acids and esters. Beside this, the effect of steric hindrance does not seem to disturb the reaction. Intriguingly, primary alkylboronic acids—in general a problematic class of compounds in the Suzuki reaction—were shown to react smoothly. The interest in the identification of a universal catalyst system for the Suzuki reaction prompted us to explore the use of the S-Phos ligand in more detail. Although the reported results in general are satisfying, the Suzuki reaction with secondary alkylboronic acids remains troublesome. Under the conditions described by Buchwald, it turned out to be difficult to couple secondary alkylboronic acids—such as cyclohexylboronic acid, cyclopentylboronic acid or isopropylboronic acid—with aryl bromides.

Although a few Suzuki reactions with secondary alkylboronic acids have been reported,[8] the majority of them failed to yield the desired products.[9] A notable exception is the Suzuki reaction with cyclopropylboronic acids.[10] This phenomenon has been

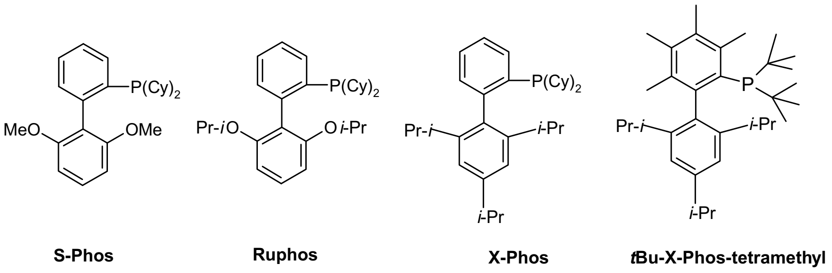

Figure 1.

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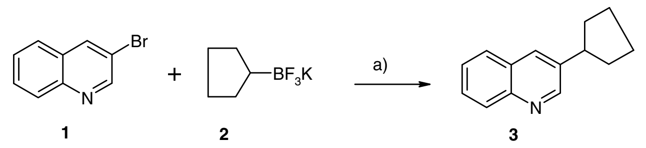
rationalised by invoking the partial sp^2 character of the cyclopropyl carbon atoms. The troublesome results with secondary alkylboronics may be explained by their instability during the course of the reaction and a diminished nucleophilicity which adversely influences the transmetallation step. In addition, the sluggish reductive elimination step in general leads to β-hydride elimination, thereby resulting in reduction of the aryl halide and alkene formation. We decided to switch to the potassium secondary alkyltrifluoroborates instead of their corresponding boronic acids in order to circumvent these difficulties.

The use of potassium organotrifluoroborates in organic synthesis has gained popularity during the last 10 years.[11] This class of compounds is easy to prepare and much more stable than their boronic acid counterparts. Their satisfactory use in the Suzuki cross-coupling[12] has been reported. The Suzuki cross-coupling with functionalised potassium primary alkyltrifluoroborates[13]—which opens a new way for introducing functionalised alkyl groups into aromatics and heteroaromatics—is particularly noteworthy. To the best of our knowledge, the use of potassium secondary alkyltrifluoroborates in the Suzuki reaction has not been reported. Therefore, a dedicated program was initiated to explore this reaction. 3-Bromoquinoline **1** and the commercially available potassium cyclopentyltrifluoroborate **2** (Aldrich) served as the starting materials (Scheme 1).

A brief survey of the reaction conditions led to some interesting results. The initial conditions (3 mol % Pd(OAc)$_2$, 6 mol % S-Phos, 3 equiv K$_2$CO$_3$, 1 equiv **1** and 1.5 equiv **2** in MeOH at reflux temperature), yielded, unfortunately, only a trace of the coupling product **3** after 24 h. Replacement of MeOH by toluene/water 10:1 (v/v) and changing the base from K$_2$CO$_3$ to K$_3$PO$_4$ gave **3** in a yield of 16%. Trace amounts of quinoline and **1** were detected in the crude reaction mixture. In addition, some cyclopentene was detected which is indicative of a competitive β-hydride elimination reaction. Increased amounts of Pd catalyst and ligand (Pd(OAc)$_2$ and S-Phos, respectively) resulted in a slightly higher yield. For example, 20 mol % of Pd catalyst and 40 mol % of ligand led to a yield of 25% (Table 1, entry 1). Neither extension of the reaction time nor raising the temperature to 130 °C (in xylene/water 10:1 (v/v)) had a beneficial effect on the isolated yields. Changing the base from K$_3$PO$_4$ to Cs$_2$CO$_3$ turned out to be detrimental.

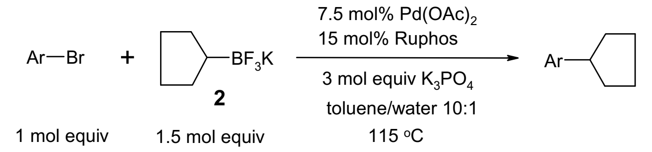
The observation of β-hydride elimination as a side reaction prompted the application of more sterically hindered ligands because it is known that these can suppress concurrent β-hydride elimination.[14] Therefore, X-Phos[15] and the P(*tert*-butyl)$_2$ tetramethyl analogue derived from X-Phos[16] (Fig. 1) were applied, but unfortunately with disappointing results. To our surprise, the combination of 7.5 mol % Pd(OAc)$_2$ with 15 mol % Ruphos,[17] provided a much better result. Compound **3** was isolated in 40% yield after 20 h and in a yield of 60% after a prolonged reaction time of 88 h (Table 1, entries 2 and 3, respectively). It can be concluded that in contrast with S-Phos, extension of the reaction time with Ruphos increases the yield of **3** significantly.

Whereas the yields in the corresponding reaction with S-Phos were disappointing and not influenced by the applied reaction temperature, a clear temperature effect on the yield was observed with Ruphos. Compound **3** could be isolated in a yield of 55% after 20 h reaction at 130 °C in xylene/water 10:1 (v/v) (Table 1, entry 4). The formation of small quantities of quinoline as a by-product—caused by the competitive β-hydride elimination reaction which is presumably due to the increased reaction temperature—was observed. It is interesting to note that the use of *tert*-amyl alcohol/water or *tert*-amyl alcohol/toluene as alternative solvents[18] in order to suppress the competitive β-hydride elimination reaction gave a negligible yield of **3**.



Scheme 1. Reagents and conditions: (a) See the detailed description in the text.

Table 1

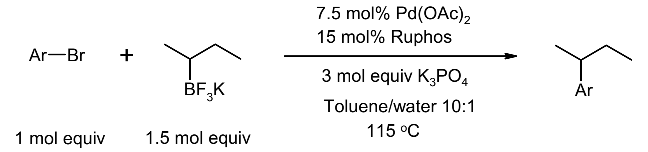


Entry	Ar–Br	Time (h)	Yield[a] (%)
1	3-Bromoquinoline	20	25[b]
2	3-Bromoquinoline	20	40
3	3-Bromoquinoline	88	60
4	3-Bromoquinoline	20	55[c]
5	4-Bromobenzophenone	44	70
6	4-Bromobiphenyl	43	53
7	4-Bromonitrobenzene	20	58
8	4-Bromobenzonitrile	67	62
9	4-Bromobenzotrifluoride	90	85
10	3-Bromopyridine	40	15[d]
11	3-Bromopyridine	40	40

[a] Isolated yields of pure compounds.
[b] Using 20 mol % Pd(OAc)$_2$ and 40 mol % S-Phos.
[c] Xylene/water 10:1 at 130 °C.
[d] S-Phos instead of Ruphos.

A representative set of aryl bromides was used (Table 1, entries 5–9) to illustrate the preliminary scope of this novel method, using our optimised reaction conditions[19,20] (7.5 mol % Pd(OAc)$_2$, 15 mol % Ruphos, 1 equiv aryl bromide, 1.5 equiv **2**, 3 equiv powdered K$_3$PO$_4$, toluene/water 10:1 (v/v), 115 °C.) The reaction with *p*-bromobenzophenone resulted in a high yield of coupled product (70%) (Table 1, entry 5). In contrast, the corresponding reaction with cyclopentylboronic acid resulted in only a trace amount of product. The reaction of *p*-bromobiphenyl also proceeded well but the reaction product was contaminated with a trace amount of biphenyl which was removed by HPLC. Identically to the reaction between **1** and **2**, an increased temperature (130 °C, xylene/water 10/1 (v/v)) led to completion of the reaction in 17 h but also to a considerable amount of biphenyl (~25 mol %). 4-Bromonitrobenzene, 4-bromobenzonitrile and 4-bromobenzotrifluoride also reacted smoothly to give 4-(cyclopentyl)-nitrobenzene, 4-(cyclopentyl)-benzonitrile and 4-(cyclopentyl)-benzotrifluoride in isolated yields of 58%, 62% and 85%, respectively. 3-Cyclopentyl-

Table 2



Entry	Ar–Br	Time (h)	Yield[a] (%)
1	3-Bromoquinoline	48	37[b]
2	4-Bromobenzophenone	110	51[c]
3	4-Bromobenzophenone	24	30[d]
4	4-Bromobiphenyl	72	45

[a] Isolated yields of pure compounds.
[b] A reaction time of 112 h gave the same yield.
[c] Crude product contained a trace of benzophenone.
[d] Xylene/water 10:1 at 130 °C.

pyridine was accordingly prepared in a moderate yield (40%) from 3-bromopyridine. The corresponding reaction with S-Phos gave a poor yield of 15%.

We also explored briefly the Suzuki reaction with commercially available potassium isobutyltrifluoroborate (Aldrich) (Table 2). In comparison with the cyclic potassium cyclopentyltrifluoroborate, prolonged reaction times were required and it appeared that the starting aryl bromides were not fully consumed. Moreover, the β-hydride elimination turned out to be a more competitive side reaction. It should be emphasised that in all the studied cases, no isomerisation of the secondary butyl group into the *n*-butyl group occurred. This particular side reaction can be notorious for the Negishi cross-coupling reaction.[21] Increasing the reaction temperature by performing the reaction at 130 °C in xylene/water 10:1 (v/v) led to increased reaction rates, but unfortunately, to more by-product formation.

In conclusion, a Ruphos-mediated Suzuki cross-coupling between (hetero)aryl bromides and secondary alkyltrifluoroborates is described using palladium catalysis. This straightforward one-step reaction regioselectively produces secondary alkylated aryl- or heteroaryl derivatives in reasonable yields and as such, constitutes a valuable alternative for the synthesis of this type of compounds. Replacement of the S-Phos ligand with Ruphos was the key step in the optimisation of the reaction. Further work is in progress to broaden the scope of this efficient catalytic process.

Acknowledgments

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19. *General procedure for the Ruphos-mediated Suzuki cross-coupling of* **1** *with* **2** (Table 1, entry 3): A dried 50 ml, three-necked reaction vessel was charged with degassed toluene (20 ml) and degassed water (2 ml), followed by addition of **2** (260 mg, 1.5 mmol) and powdered K_3PO_4 (950 mg, 4.5 mmol). The mixture was magnetically stirred under a nitrogen atmosphere for 15 min at room temperature. After successively adding **1** (208 mg, 1 mmol), $Pd(OAc)_2$ (16.8 mg, 0.075 mmol) and Ruphos (70 mg, 0.15 mmol), the reaction mixture was heated in a pre-heated oil bath at 115 °C (LCMS, HPLC, TLC (diethyl ether) monitoring). After the indicated time (Table 1), the reaction mixture was allowed to attain room temperature. Water and diethyl ether were added and the resulting mixture was magnetically stirred for 5 min. The organic layer was separated, dried over Na_2SO_4, filtered and concentrated in vacuo. The obtained crude **3** was further purified by flash chromatography (Silica Gel 60 (0.040–0.063 mm, Merck)) with diethyl ether as eluent: ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.76–1.82 (m, 4H), 1.85–1.94 (m, 2H), 2.18–2.25 (m, 2H), 3.16–3.25 (m, 1H), 7.52 (t, *J* = 8 Hz, 1H), 7.64 (t, *J* = 8 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H), 7.94 (d, *J* = 2 Hz, 1H), 8.17 (d, *J* = 8 Hz, 1H), 8.84 (d, *J* = 2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.6, 34.4, 43.4, 126.6, 127.4, 128.2, 128.6, 129.1, 132.4, 139.0, 146.8, 151.6.
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