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Tetrahedron Letters 48 (2007) 8048–8051
Tetrahedron Letters

# Polyfluorinated phosphine ligands in the room temperature Suzuki cross-coupling reactions

Shahla Yekta, Lawrence Cheung and Andrei K. Yudin*

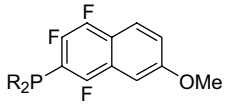
*Davenport Research Laboratories, Department of Chemistry, University of Toronto 80 St. George Street, Toronto, Ontario, Canada M5S 3H6*

Received 22 July 2007; revised 31 August 2007; accepted 4 September 2007
Available online 8 September 2007

**Abstract**—Polyfluorinated phosphine ligands can be obtained by regioselective nucleophilic aromatic substitution on tetrafluoronaphthalene derivatives. The ligand efficiency has been demonstrated in the room temperature Suzuki coupling reactions of aryl bromides and aryl boronic acids. The described process allows access to a new class of highly versatile fluorinated phosphine ligands.

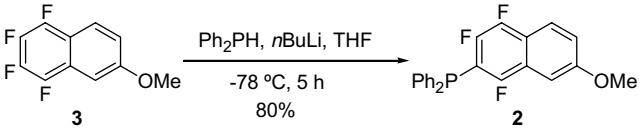

The development of new ligands for transition metal catalysis is of ever growing importance in a field searching for cheaper, faster and environmentally friendlier methods of making new molecules. A plethora of phosphine ligands have been designed to aid metal-catalyzed cross-coupling reactions that form carbon–carbon as well as carbon-heteroatom bonds.[1] The most commonly used phosphine ligands are triaryl substituted as they are readily available and do not require inert atmosphere for storage. Fluorinated ligands, and in particular fluorinated phosphine ligands have found applications in catalysis as fluorine substitution does not affect the steric properties of a ligand, however, greatly modifies its electronic characteristics.[2,3] Fluorine substituents have also been shown to participate in hydrogen bonding with neighbouring atoms.[4]

Here, we describe the synthesis of polyfluorinated phosphine ligands (Fig. 1) and their application in the room temperature Suzuki reaction of aryl bromides and boronic acids. Ligands **1** and **2** are air-stable and can be stored on the bench. We previously showed that a variety of oxygen and carbon nucleophiles regioselectively displace fluorine at the 7-position of the 2-alkoxy substituted tetrafluorinated naphthalene rings.[5] Using lithiated phosphine nucleophiles, the ligands can be prepared from the corresponding tetrafluoronaphthalene **3** (Scheme 1).




**1** R = Cyclohexyl
**2** R = Phenyl

**Figure 1.** Polyfluorinated phosphine ligands.




**Scheme 1.**

While ligand **2** can be directly synthesized from lithium diphenylphosphide at −78 °C, dicyclohexylphosphine needed to be protected following Grubbs' procedure prior to deprotonation with base.[6] The metallated phosphine species was generated at −78 °C and then allowed to react with **3**. Since no product was observed after a few hours at room temperature, the reaction was heated to reflux and stirred for 16 h to give the desired product **4** in 60% yield. Unlike nucleophilic aromatic substitutions with carbon and oxygen nucleophiles that generally result in a mixture of 6- and 7-substituted products, which are often difficult to separate by flash column chromatography, only one product, the 7-substituted phosphine was formed in this case. Phosphine

* Corresponding author. Tel.: +1 416 946 5042; fax: +1 416 946 7676; e-mail: ayudin@chem.utoronto.ca

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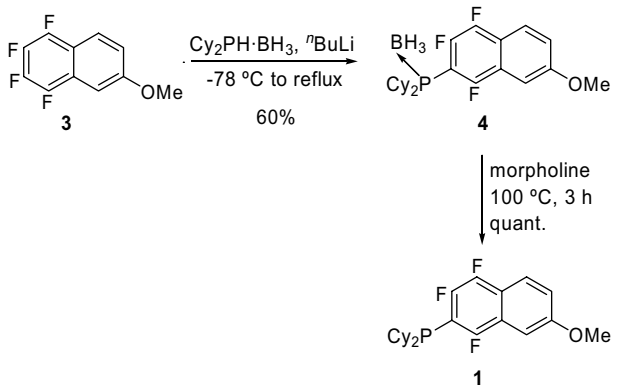
doi:10.1016/j.tetlet.2007.09.016



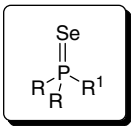

**Scheme 2.**

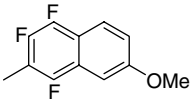
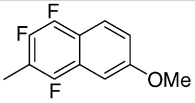
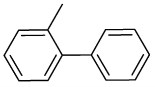
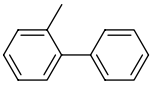
deprotection occurs in the presence of morpholine at 110 °C (Scheme 2).

In order to determine the nucleophilicity of the phosphine ligands, selenium coupling constants were obtained and compared with the literature results as well as with other structurally related phosphine ligands (Table 1). To our surprise, fluorinated phosphine ligand **1** is very similar in nucleophilicity to the commercially available dicyclohexylphosphino-1,1′-biphenyl (Table 1, entries 5 and 6). The ligand **2** (R = Ph, entry 4) exhibited a much higher value, close to diphenylthienyl and diphenylfuryl phosphines (Table 1, entries 2 and 3).

Interaction between the phosphorous centre of ligand **1** and $Pd(OAc)_2$ is revealed by considering $^{19}F$ and $^{31}P$ NMR shifts of the corresponding peaks.[7,8] $^{19}F$ NMR of the same solution after 10 h showed unaltered resonances, confirming that palladium does not insert into C—F bonds of the ligand, as has been shown possible with some fluorinated ligands.[9] The structure of a complex obtained from a 1:1 mixture of ligand with

**Table 1.** s-Character on the phosphorous lone pair




| Entry | R | $R^1$ | $^1J(^{31}P–^{77}Se)$ |
|---|---|---|---|
| 1 | Ph | Ph | 732 |
| 2 | Ph |  | 743 |
| 3 | Ph |  | 754 |
| 4 | Ph |  | 756 |
| 5 | Cy |  | 729 |
| 6 | Cy |  | 733 |
| 7 | $^t$Bu |  | 703 |

$PdCl_2(BnCN)_2$ was solved using X-ray diffraction and is shown in Figure 2. The complex has a trans, square planar geometry with a centre of inversion about the Pd atom in which the fluorinated aryl group of the ligand points away from the crowded palladium centre. The X-ray structure of **1** reveals a hydrogen bond between the fluorine on C10 and a hydrogen of the cyclohexyl group on phosphorous.

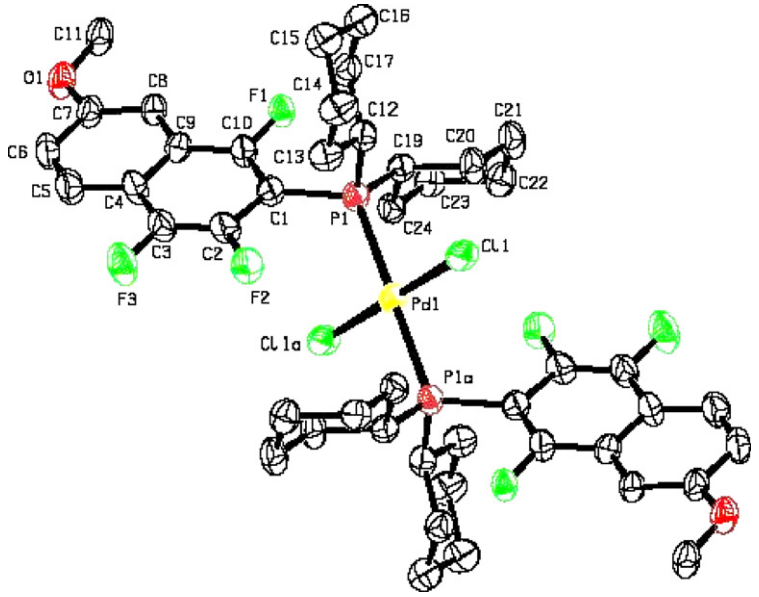
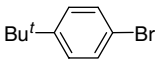
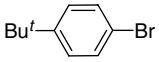
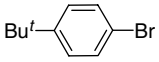
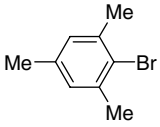
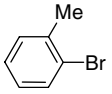
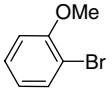
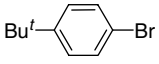
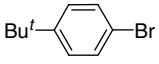
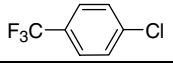



**Figure 2.** X-ray structure of **1** and $PdCl_2(BnCN)_2$ complex.

**Table 2.** Application of polyfluorinated ligands in Suzuki-type reactions

$$\mathrm{Ar{-}X + PhB(OH)_2} \xrightarrow[\mathrm{K_3PO_4,\ toluene}]{\mathrm{Pd(OAc)_2/ligand\ (1:2)}} \mathrm{Ph{-}Ar}$$

| Entry | Ar–X | Time (h) | Temperature (°C) | Yield[a] (%) | Ligand |
|---|---|---|---|---|---|
| 1 |  | 3 | rt | 85 | **1** |
| 2 |  | 3 | rt | 50[c] | **5** |
| 3 |  | 5 | 110 | 88 | **5** |
| 4 |  | 12 | 50 | 79 | **1** |
| 5 |  | 5 | rt | 91 | **1** |
| 6 |  | 5 | 50 | 78 | **1** |
| 7 |  | 5 | 50 | 82 | **1** |
| 8 |  | 8 | 50 | 80[b] | **1** |
| 9 |  | 8 | rt | 8[c] | **2** |
| 10 |  | 12 | 80 | 27[d] | **1** |

[a] Typical reaction condition used 5 mol % $Pd(OAc)_2$.
[b] 1 mol % $Pd(OAc)_2$ was used.
[c] Conversion.
[d] 2 mol % $Pd(OAc)_2$ was used.

We opted to apply the ligand in the palladium-catalyzed Suzuki couplings of aryl bromides and aryl boronic acids. The reactions were found to occur at room temperature and products were obtained in good yields (Table 2). A GC conversion/time study shows that while **1**/$Pd(OAc)_2$ catalyzed the coupling of 4-*tert*-butylphenyl bromide and phenyl boronic acid at room temperature in 3 h, the catalyst system based on commercially available dicyclohexylphosphino-1,1′-biphenyl [ligand **5**, with a similar $^1J(^{31}P{-}^{77}Se)$] required heating up to 80 °C for complete conversion of the starting material (Table 2, entries 1–3).[10]

When smaller amounts of Pd were used, heating was required for the reaction to go to full conversion (entry 8). Heating (50 °C) was also required for the substrates with *ortho*-substituents (entries 4, 6 and 7). 2-Bromothiophene reacted with phenylboronic acid at room temperature to give the desired biaryl in excellent yield (entry 5). When the diphenylphosphine ligand **2** was used in the Suzuki coupling of 4-*tert*-butylphenyl bromide and phenyl boronic acid, 8% conversion was observed at room temperature after 24 h (entry 9). This result is not surprising considering the high $^1J(^{31}P{-}^{77}Se)$ coupling constant of **2**, as well as the need for the right balance of electron-rich phosphines with steric hindrance to facilitate oxidative addition and reductive elimination.[11] Unfortunately, aryl chlorides and phenyl boronic acid gave low conversions even at high temperatures (entry 10).

We have also demonstrated that ligand **2** can catalyze the Suzuki cross-coupling of naphthyl bromides and naphthyl boronic acids (Table 3). In this case, heating to 80 °C was required and although coupling of compounds with *ortho*-substituents was possible, full conversion was not achieved. When both coupling partners had *ortho*-substituents, no reaction occurred even at elevated temperatures (100 °C).

**Table 3.** Scope of ligand **2** in the Suzuki coupling of naphthyl bromides[a]

$$\mathrm{Ar^1X\ (X = OTf,\ Br)} + \mathrm{Ar^2B(OH)_2} \xrightarrow[\mathrm{K_3PO_4,\ toluene}\ 80\ ^\circ\mathrm{C},\ 24\ \mathrm{h}]{\mathrm{Pd(OAc)_2/\mathbf{2}\ (1:2)}} \mathrm{Ar^1{-}Ar^2}$$

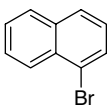
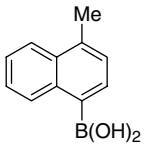
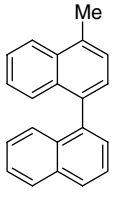
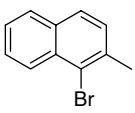
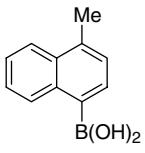
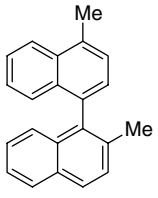
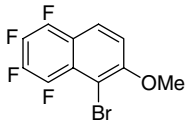
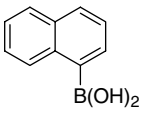
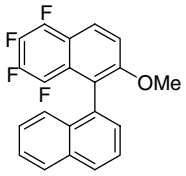
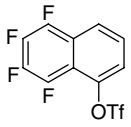
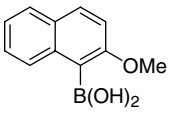
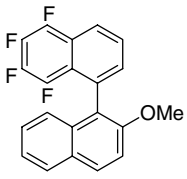
| Entry | $Ar^1X$ | $Ar^2B(OH)_2$ | Product | Conv. (%) | Yield (%) |
|---|---|---|---|---|---|
| 1 |  |  |  | 100 | 60 |
| 2 |  |  |  | 83 | 51 |

**Table 3** (*continued*)

| Entry | $Ar^1X$ | $Ar^2B(OH)_2$ | Product | Conv. (%) | Yield (%) |
|---|---|---|---|---|---|
| 3 |  |  |  | 64 | 50[b] |
| 4 |  |  |  | 69 | 55 |

[a] Reaction conditions: 5 mol % $Pd(OAc)_2$/10 mol % ligand, 1 equiv $Ar^1Br$, 1.5 equiv $Ar^2B(OH)_2$, 2 equiv $K_3PO_4$.
[b] GC yield (product was not separable from starting aryl bromide by flash chromatography).

In conclusion, we have shown that the steric and electronic balance at the phosphorous centre of polyfluorinated phosphine ligands allows for room temperature palladium-catalyzed cross-coupling reaction of aryl bromides and aryl boronic acids. These fluorinated ligands are readily accessible and can be synthesized on a gram scale. The versatility of the synthetic methodology allows access to a series of ligands with different substituents having a variety of substitution patterns.

## Acknowledgements

We thank NSERC, CFI, ORDCF, and Amgen for financial support. We also thank Dr. A. Lough for X-ray structure analysis.

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