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Readily available catalysts for demanding Suzuki–Miyaura couplings under mild conditions

Oleg M. Demchuk *, Katarzyna Kapłon, Liliana Mazur, Dorota Strzelecka, K. Michał Pietrusiewicz

Department of Organic Chemistry, Maria Curie-Sklodowska University, 33 Gliniana St., 20614 Lublin, Poland

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ABSTRACT

A straightforward synthesis of a sterically hindered and electron rich bidentate monophosphine biaryl ligand *Sym*-Phos of C,P-type of complexation was realised in a high yield starting from simple substrates in easily affordable conditions. In combination with a palladium source, the obtained ligand formed a highly active catalyst mediating sterically demanding Suzuki–Miyaura coupling reactions in aqueous media even at 60 °C and with no need to protect the reaction mixture by an inert gas.

1. Introduction

Sterically demanding Suzuki–Miyaura coupling reactions have been considered a significant challenge for the organic chemist and chemical industry.[1–4] Many tri- and tetra-*ortho* substituted (in relation to aryl–aryl bond) biaryls are associated with biologically active and natural compounds[5–10] and constitute a core of efficient ligands in homogenous catalysis,[11–16] as well as of functional materials.[17]

The palladium complexes of phosphorus ligands are typical catalysts for cross-coupling reactions.[18] The catalytic efficiency of such catalysts is closely associated with the basicity of the phosphorus atom and the steric hindrance created by its substituents. The electron density at phosphorus atom in the transition metal complexes is transmitted to the transition metals,[14,19] and increases their nucleophilicity and reactivity towards organohalides at the oxidative addition reaction step.[20–22] At the same time the presence of the bulky substituents on the phosphorus atom are also crucial.[23] The bulky groups at phosphorus atom in the ligand structure play a multi-fold role—they facilitate formation of the catalytically active low coordinating transition metal complexes with a single phosphorus ligand bonded, and accelerate the last reaction step of reductive elimination of the product. In certain cases the presence of the bulky substituents on the phosphorus atom are important to keep the ligand in the oxygen resistant conformation,[24] or conformation suitable for the high level of asymmetric induction.[15,25,26]

Results of the extensive number of complementary studies of many research groups indicate that the phosphorus ligands of less typical C,P-type of complexation (Fig. 1),[27,28] such ligands as Hayashi's MOP, Kočovský's MAP and Buchwald's *S*-Phos and similar,[27–31] are superior over the other types of phosphorus, nitrogen and sulfur ligands in challenging cross-coupling reactions.

Recent developments in synthetic organic chemistry allow sterically demanding couplings to take place thanks to the new and very efficient catalysts used. Such reactions are usually run in anhydrous conditions at high temperatures.[28,29,32–37] However, the substrate scope for the synthesis of tetra-*ortho*-substituted biaryls is not wide and usually limited to small alkyl and alkoxy substituted

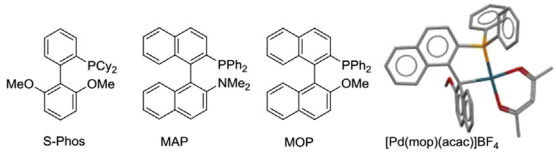

Fig. 1. Illustrative examples of C,P-ligands and complexes.

* Corresponding author. E-mail address: Oleh.Demchuk@UMCS.Lublin.pl (O.M. Demchuk).

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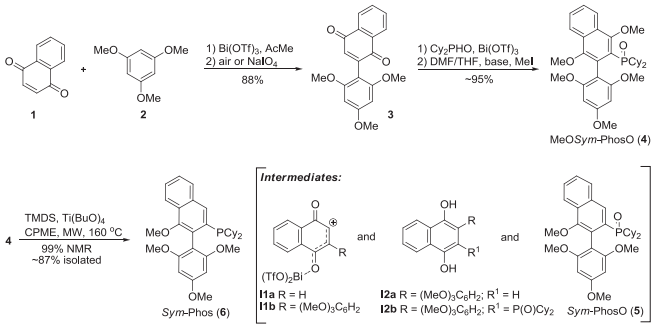
aromatics.[28] An additional challenge for the pharmaceutical and fine chemical industries is sustainable catalysis.[38,39] It could be very attractive to perform advanced Suzuki–Miyaura couplings in water at near to ambient temperatures. Water does not usually solubilise substrates nor products, but the inorganic 'by-products' of the reaction are soluble in water, and in combination with high yields of the reaction it makes the procedure of product isolation very simple. At the same time, the medium of the reaction could be used several times without purification (the reaction is not sensitive to inorganic salts present in the aqueous phase) and it could be used for the simplification of the process of recovering of used halogens.

The Suzuki–Miyaura coupling reactions, mediated by palladium complexes recently announced in a communication,[40,41] bulky and electron rich chelating monophosphorus biaryl ligand *Sym*-Phos (**6**), had been used to confront this challenge. Thus, herein we present the results of our comprehensive studies on the synthesis of sterically hindered biaryls performed in environmentally friendly conditions.[25,30,31,40,42] Assessed, in comparison with other excellent ligands, efficiency of palladium complexes of *Sym*-Phos in Suzuki–Miyaura and Heck coupling reaction in combination with the improved, notably simpler, fast, high-yielding and inexpensive synthesis could make *Sym*-Phos a ligand of choice in a variety of challenging cross-coupling reaction based syntheses.

2. Results and discussion

2.1. Synthesis of the *Sym*-Phos ligand

Approach to the synthesis of *Sym*-Phos (**6**) (Scheme 1) is based on a variation of the previously reported protocol we had applied in the synthesis of *Nap*-Phos ligand.[29] Taking into consideration that the most costly step of the *Nap*-Phos synthesis was naphthoquinone arylation realised by means of Suzuki–Miyaura coupling, in the optimised protocol leading to even more electron rich *Sym*-Phos ligand we used an alternative procedure of formal direct cross dehydrogenative coupling of naphthoquinone with 1,3,5-trimethoxy-benzene.[43] In such a way, the key intermediate **3** was obtained in 88% yield. The arylation reaction starts with the activation of **1** by coordination of oxophilic bismuth(III) (Scheme 1, intermediate **I1a**), and subsequently dihydroxynaphthalene **I2a** is formed according to the Friedel–Crafts mechanism. Next, intermediate **I2a** undergoes the spontaneous oxidation by **1**, used in excess, or atmospheric dioxygen to arylnaphthoquinone **3** (the 60% of **3** have spontaneously crystallised from the reaction mixture at this point). To accelerate the oxidation process, sodium periodate could be added to the reaction mixture when the arylation is completed (the 88% of **3** could be chromatographically isolated from the reaction mixture at this point). Next improvement was made at the phosphorylation step. The classical approach to Michael addition of secondary phosphine oxides to EWG substituted olefins is based on the activation of phosphorus nucleophile by the strong base driven deprotonation of phosphine oxide. Such an approach suffers from its air sensitivity and possibility of base promoted side reactions. To override this problem we have developed an alternative Lewis acid catalysed procedure, according to which the treatment of **3** with dicyclohexylphosphine oxide (Cy_2PHO) in the presence of $Bi(OTf)_3$ leads to the formation of intermediate **I2b**, which can be isolated by filtration. Without the isolation, **I2b** was subjected to the methylation reaction with dimethyl sulfate or methyl iodide run in the presence of sodium hydride and caesium carbonates in DMF giving MeO*Sym*-PhosO (**4**). Since **4** does not undergo the deoxygenation reaction in the presence of usual P=O reducing reagents,[29,44] the formed in situ titanium hydride reagent was applied in the synthesis of target *Sym*-Phos phosphine (**6**). The tandem conversion of MeO*Sym*-PhosO (**4**) to *Sym*-Phos (**6**) was realised in sealed pressure-resistant reactors under a microwave heating with the utilisation of reducing mixture $(Me_2SiH)_2O$ and $Ti(BuO)_4$ in CPME (cyclopentyl methyl ether) for 5 h at 160 °C in almost quantitative ^{31}P NMR yield. $(EtO)_3SiH$ or even $PhSiH_3$ could be used instead of TMDS; moreover, their utilisation resulted in some shortening of the reaction time. (Attention!) The significant amounts of flammable gases caused the rapid rise of the pressure inside the sealed reactors. Thus, in the cases of a full-scale synthesis the pressure was released after 1 h of reaction run. The pure phosphine **6** is crystallised from the chilled reaction mixture in 72% yield. An additional 15% of **6** could be chromatographically isolated from the residue. To omit the necessity to work with pressured microwave reactors, a two-steps produce leading from **4** to **6** in some lower yield could be also applied.[41] The demethoxylation of **4**, carried out under the reflux conditions in THF, in the presence of $PhSiH_3$ or $(Me_2SiH)_2O$ and $(i\text{-}PrO)_4Ti$, leads to **5** in reasonably high 75–80% yield. The deoxygenation of *Sym*-PhosO carried out in toluene at 100 °C by application of standard $HSiCl_3/Et_3N$ reductant furnish **6** in 85% isolated yield. The isolation of **6** include an alkalisation of the reaction mixture with 15% aqueous sodium hydroxide, filtration and washing with hot ethanol in a sealed vial. The *Sym*-Phos (**6**) is an air- and humidity resistant odour- and colourless phosphine, soluble in not polar organic solvents and weakly soluble in acetone and methanol. Exposed to air, diluted solutions of **6** undergo slow oxidation to form **5**.



Scheme 1. Synthesis of *Sym*-Phos (**6**).

2.2. Palladium complexes of *Sym*-Phos

The *Sym*-Phos ligand is structurally similar to the highly efficient ligands of *S*-Phos (and their analogues), while at the same time it is significantly more electron rich and spatially developed. These additional features of *Sym*-Phos allow us to expect that it will be also highly efficient in cross-coupling reaction. The pre-catalysts based on *Sym*-Phos were obtained in reaction of latter with bis(acetonitrile)dichloropalladium(II) in DCM. Applying different stoichiometry of the reagents, [Pd(*sym*-phos)$_2$Cl$_2$] and [Pd(*sym*-phos)Cl$_2$] complexes were obtained selectively. The ^{31}P NMR (CD_2Cl_2) spectra of the complexes contained signals at 48 and 61 ppm, respectively. This allows to make an assumption that the palladium atom in a complex with a single ligand is more charged than in a complex with two coordinated ligands. Thus, in the bisphosphine complex, two phosphorus ligands may donate more electron density to the palladium atom than a single phosphorus ligands together with an aromatic system participating in C,P-complexation. The pure monophosphine complex had been re-crystallised from DCM-Et_2O solution. At the same time, the bisphosphine complex was less stable and in the solution in weakly coordinating solvents (such as CD_2Cl_2, $CDCl_3$) it always underwent a partial dissociation to free *Sym*-Phos and [Pd(*sym*-phos)Cl$_2$]. The ^1H and ^{31}P NMR spectra of [Pd(*sym*-phos)Cl$_2$] recorded at 22 °C in $CDCl_3$ contained additional minor signals of equal amounts of free phosphine and [Pd(*sym*-phos)Cl$_2$]. Addition of some excess of *Sym*-Phos allows to shift equilibrium in the direction of complete formation of [Pd(*sym*-phos)$_2$Cl$_2$].