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PEG_{350}-based di-(2-pyridyl)methylamine as a ligand in the Pd-catalyzed water Suzuki–Miyaura reaction of aryl chlorides

Ouissam Adidou [a,b], Catherine Goux-Henry [a], Mohamed Safi [b], Mohamed Soufiaoui [c], Eric Framery [a,*]

[a] ICBMS, UMR-CNRS 5246, Equipe Synthèse Asymétrique, Université de Lyon, Université Lyon 1, 43 Bd du 11 Novembre 1918, F-69622 Villeurbanne Cedex, France
[b] Faculté des Sciences et Techniques, BP 146, Cité Yasmina, Mohammedia, Morocco
[c] Université Mohamed V, Faculté des Sciences, Avenue Ibn Batouba, Rabat, Morocco

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ABSTRACT

The synthesis of new hydrosoluble PEG-based ligand derived from di-(2-pyridyl)methylamine has been developed. The catalytic performance of this ligand is demonstrated in Suzuki–Miyaura reactions between aryl chlorides and arylboronic acids and using water as solvent.

The biaryl compounds constitute one of the most important building blocks for the synthesis of pharmaceuticals, herbicides, polymers, materials, liquid crystals, and ligands. And one of the most attractive synthetic routes for the preparation of these compounds is the palladium-catalyzed cross-coupling reaction of aryl halides with boronic acids, so-called Suzuki–Miyaura reaction.[1]

From an environmental as well from an economic point of view, an alternative to the organic solvents is the use of water,[2] or the immobilization of the catalyst in a liquid phase such as ionic liquids.[3] The ionic liquids are very expensive, and their toxicity and environmental effect are for the most part unknown. The catalytic reactions performed in water require water-soluble catalysts. Among numerous water-soluble ligands,[4] sulfonated ligands are probably the most known. Another way is the use of poly(ethylene glycol) (PEG) and its monomethyl ethers.[5] They are known to be inexpensive, thermally stable, and nontoxic. They can be used to recover catalysts and ligands in organic synthesis,[6] or used as an alternative solvent. For example, PEG_{400},[7] PEG_{2000},[8] and PEG_{6000}[9] have been used as solvent in the Suzuki–Miyaura reactions with catalysts derived or not from PEG.

The N,N-ligands (Fig. 1), like di-2-pyridylamine-derived ligands **1**,[10] have proven to be efficient catalysts for C–C and C–N bond forming reactions. And the Pd-complexes based on ligand **2** derived from di-2-pyridylmethylamine are also efficient catalysts for Heck, Suzuki–Miyaura, and Sonogashira reactions in organic or aqueous solvent under homogeneous conditions.[11] This last type of Pd-complexes have been anchored to an organic or inorganic matrix like styrene-maleic anhydride copolymer[12] or silica matrix.[13] These functionalized materials provide recyclable catalysts for these C–C bond formation reactions.

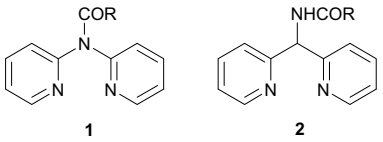

Figure 1. Bipyridine ligands.

Prompted by the results of the ligands based on di-2-pyridylmethylamine, we propose to functionalize the same ligand with a PEG arm, in order to use it in the Suzuki–Miyaura reaction with water as solvent. Here, we describe the preparation of the PEG_{350}-based di-2-pyridylmethylamine ligand **3** from commercial di-(2-pyridyl)methanone **4** (Scheme 1).

According to literature,[14] the di-2-pyridylmethylamine **5** was prepared in two steps from derivative **4**: preparation of the oxime followed by Zn-reduction of the oxime. After Jones' oxidation of polyethylene glycol monomethylether with an average molecular weight of 350 g/mol (PEG_{350}, purchased to Alfa Aesar Company), the corresponding carboxylic acid was coupled with amino compound **5** in a THF–CH_2Cl_2 solution in the presence of 1-[3-dimethylaminopropyl]-3-ethylcarbodiimide hydrochloride (EDC·HCl), 1-hydroxybenzotriazole (HOBT), and $NaHCO_3$, afforded PEG_{350}-based

* Corresponding author. Tel.: +33 472 446 263; fax: +33 472 448 160.
E-mail address: framery@univ-lyon1.fr (E. Framery).

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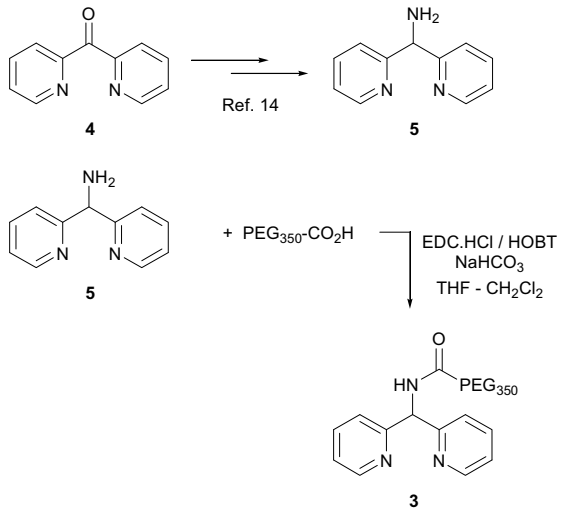
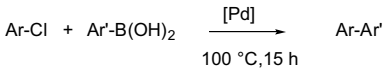


Scheme 1. Preparation of PEG-based di-2-pyridylmethylamine ligand **3**.

di-2-pyridylmethylamine ligand **3** in 76% yield evaluated from the elemental analysis.[15] On the ^{1}H and ^{13}C NMR spectra, the signals corresponding to the proton and carbon of the di-2-pyridylmethylamine were observed in addition to the signals of the PEG, and several changes before and after condensation can be cited (seeSupplementary data). The chemical shifts of the proton linked to C-1 of di-(2-pyridyl)methylamine's unit moved δ 5.32 to 6.29 ppm. The chemical shifts of both carbons C-1 and C-2 of di-(2-pyridyl)methylamine's unit moved δ 62.5 to 59.2 ppm and δ 162.8 to 159.3 ppm, respectively, confirming that the di-(2-pyridyl)methylamine's part and the PEG arm were well linked together.

Knowing that the water influences favorably the activity of Suzuki–Miyaura catalyst,[16] the cross-coupling reaction in this solvent was investigated using various aryl halides and arylboronic acids. The results are summarized in Table 1. The reactions[17] were carried out in water (0.08 M) at 100 °C for 15 h, and were catalyzed with 0.1 or 0.01 mol % of Pd-catalyst prepared in situ from $Pd(OAc)_2$ and ligand **3**, in the presence of 2 equiv of K_2CO_3 as a base, and of 0.5 equiv of tetrabutylammonium bromide (TBAB) as an additive as described in the literature.[11a] Since the molecular weight of the PEG_{350} is not well defined, in order to prepare the Pd-catalyst, the amount of ligand **3** was determined from the nitrogen analysis.

Table 1
Suzuki–Miyaura cross-coupling reactions of aryl chlorides and arylboronic acids with $Pd(OAc)_2$/**3**[a]



Entry	Ar–Cl	Ar′–B(OH)$_2$	Yield[b] (%)	TON
1[c]	4-NO_2	H	0	0
2	4-NO_2	H	99	990
3	4-MeCO	H	98	980
4	4-CN	H	99	990
5[d]	4-CN	H	98	9800
6	2-NO_2	H	99	990
7	4-Me	H	90	900
8	4-NO_2	4-MeO	99	990
9	4-NO_2	4-Me	93	930
10	4-CN	4-Me	86	860
11	2-NO_2	4-Me	85	850
12	2-NO_2	2-Me	85	850

[a] [Ar–Cl] = 0.08 M, [Ar–Cl]/[Ar–B(OH)$_2$]/[K_2CO_3]/[$Pd(OAc)_2$]/[Ligand]/[TBAB] = 1.0:1.1:2.0:0.001:0.001:0.5.
[b] Isolated chemical yield after column chromatography.
[c] Reaction performed without ligand.
[d] Reaction performed with 0.01 mol % of Pd-catalyst.

Before testing the potential of the PEG_{350}-based di-2-pyridylmethylamine ligand **3**, we studied the cross-coupling of 1-chloro-4-nitrobenzene (Table 1, entry 1) with 1.1 equiv of phenylboronic acid using a 'ligandless' palladium catalyst. No reaction occurred. It is well known that the ligand-free Pd(OAc) is able to catalyze the coupling reaction of aryl iodides and activated or desactivated aryl bromides;[18] however, in the case of aryl chlorides, temperatures higher than 150 °C or microwave assistance are necessary in order to perform efficiently this cross-coupling reaction.[19] Using ligand **3**, aryl chlorides bearing electron-withdrawing or electron-donating groups reacted with various arylboronic acids affording the corresponding biaryl compounds in excellent yields (>85%) (Table 1, entries 2–12). When compared with the ligands derived from di-2-pyridylmethylamine described in the literature,[11a,b,12,13] the same reactivity was observed, with good TON values up to 9800 when the reaction was performed with 0.01 mol % of Pd-catalyst (Table 1, entry 5).

In the literature,[12,13] the study of the recycling Pd-catalyst is only described when the catalyst is anchored to organic or inorganic matrix. Whatever the type of support used for the Pd-catalyst, in the case of the cross-coupling reaction with aryl chlorides and arylboronic acids, a significant decrease of conversion is observed from the second run. The recycling of the Pd-catalyst derived from PEG_{350}-based di-2-pyridylmethylamine ligand **3** was also studied in the case of the Suzuki–Miyaura reaction with 1-chloro-4-nitrobenzene and phenylboronic acid. Unfortunately, the yield of the coupling product decreased drastically to 30% from the second cycle. We explain it by the high solubility of Pd-catalyst in the both organic and aqueous phases. And after the first treatment, a large amount of Pd-catalyst was lost.

In conclusion, the synthesis of new hydrosoluble PEG-based ligand derived from di-(2-pyridyl)methylamine has been described. This ligand has been used in the palladium Suzuki–Miyaura cross-coupling reactions. The efficiency of this ligand has been demonstrated in a wide range of couplings between aryl chlorides and arylboronic acids. With only 1.1 equiv of arylboronic acid in relation to aryl chloride, the conversions and the chemical yields are generally high, with excellent TON up to 9800 when 0.01 mol % Pd-catalyst is used. Work is in progress actually in order to study recycling Pd-catalyst from new ligand derived of di-(2-pyridyl)methylamine with a PEG arm having an higher molecular weight in order to increase its solubility in water, and so to have a better extraction.

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Supplementary data

Supplementary data (^{1}H and ^{13}C NMR spectra of compounds **3** and **5**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.10.018.

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15. A mixture of **5** (4.3 mmol, 0.79 g), PEG_{350}–CO_2H (4.3 mmol, 1.50 g), EDC·HCl (6.9 mmol, 1.32 g), HOBT (8.6 mmol, 1.16 g), $NaHCO_3$ (6.9 mmol, 0.58 g), CH_2Cl_2 (5 mL), and THF (10 mL) was stirred at room temperature for 48 h. The solvents were evaporated, and the residue was dissolved in CH_2Cl_2 (30 mL), washed with 5% NaOH (10 mL) and with HCl 0.5 M (5 mL), then dried over $MgSO_4$. After filtration and evaporation, the residue was purified by flash chromatography on silica gel ($CHCl_3$/EtOH 10:1) to give compound **3** (1.85 g, 76%, based on elemental analysis) as a yellow oil (Found: C, 57.38; H, 7.54; N 7.40 giving a formula of $C_{27.1}H_{42.8}N_{3.0}O_{9.8}$); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.74 (1H, br d, *J* 7.0, NH), 8.52 (2H, d, *J* 4.7, H-6 of pyridine), 7.61 (2H, td, *J* 7.7 and 1.7, H-4 of pyridine), 7.42 (2H, d, *J* 7.7, H-3 of pyridine), 7.16 (2H, td, *J* 6.2 and 1.6, H-5 of pyridine), 6.29 (1H, d, *J* 7.0, C*H*NH), 4.08 (2H, s, CH_2 of PEG unit), 3.74–3.50 (30H, m, CH_2 of PEG unit), 3.35 (3H, s, CH_3O of PEG unit); δ_C (75 MHz; $CDCl_3$) 169.8, 159.3, 149.6, 137.2, 122.8, 122.5, 72.3, 71.6, 71.3, 71.1, 71.0, 70.9, 59.4, 59.0.
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17. Typical cross-coupling procedure: A flask was charged with $Pd(OAc)_2$ (1.3 mg, 6 μmol), **3** (3.4 mg, 18 μmol of nitrogen based on analysis), K_2CO_3 (1.66 g, 12.0 mmol), aryl chloride (6.0 mmol), arylboronic acid (6.6 mmol), TBAB (0.83 g, 3.0 mmol), and water (75 mL). The mixture was heated at 100 °C and stirred during 15 h. The mixture was cooled at room temperature, extracted with diethyl ether (2 × 50 mL), dried over $MgSO_4$, concentrated, and purified by flash chromatography on silica gel to afford the pure coupling product.
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