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Short Communication

Ligandless Suzuki–Miyaura reaction in neat water with or without native β-cyclodextrin as additive

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ABSTRACT

Efficient green ligand-free Suzuki cross coupling in neat water was developed by using low loading of catalyst (0.5 mol%) in neat water in the presence or not of β-cyclodextrin (0.5 mol%) as additive at 25 °C and 100 °C respectively.

1. Introduction

Among the carbon–carbon bond-forming reactions using palladium: the Suzuki–Miyaura reaction, the Heck reaction, the Kumada reaction, the Stille reaction, the Negishi reaction, and the Sonogashira reaction, the palladium-catalyzed Suzuki coupling reaction has found wide applications in modern synthetic organic chemistry for the preparation of unsymmetrical biaryl compounds. The major advantages of the Suzuki–Miyaura reactions were the low-cost and commercial availability of a large number of boronic acids, as well as their nontoxic nature and stability to heat, air, and moisture. These reactions are usually carried out with palladium in the presence of auxiliary ligands using heterogeneous catalytic systems [1,2] and homogeneous catalytic systems [3]. Although the use of homogeneous catalysis provided environmental and economic problems in large scale-synthesis, it also afforded high reactivity, high turnover numbers, and milder reaction conditions. For example, a large variety of organic molecules was obtained in different scales from academic laboratories and industries such as Felbinac, Losartan, Boscalid, and Diovan.

Due to recent efforts in developing green chemistry and sustainable development for academic and industrial research, chemists have recently established a catalytic Suzuki–Miyaura protocol based on atom economy, less hazardous chemical syntheses, safer solvents and auxiliaries. In this respect, the Suzuki–Miyaura reaction was developed in safe, economical and environmentally benign aqueous media such as a cosolvent mixture in water [4] or neat water [5–8]. When the initial substrates were unsoluble in water, the most attractive choice was the use of surfactants [9] or inverse phase-transfer catalysts such as cyclodextrin [10–12] or calixarene [12] permitting the phase transfer of water-insoluble substrates.

In regard with the 12 green chemistry principles, the development of a ligandless protocol in an aqueous medium was recently reported [13–21]. Different mixtures such as EGME–water [13], PEG–water [14,15], ethanol–water [16], NMP–water [17,18], acetone–water [19], THF–water [20] and DMF–water [21] were successfully investigated. Only few ligandless Suzuki–Miyaura reactions in neat water with high yield were described. Starting from arylbenzoic acid and methyl arylbenzoate, the use of tetraalkylborate as a new type of borate source in the presence of palladium charcoal-catalyzed Suzuki coupling reaction in water and without ligand could be achieved in good yield [22]. A reverse order of addition of reagents was developed starting from arylbenzoic acid and the corresponding methyl ester [23]. Recently, Mondal and Bora described an efficient protocol for palladium-catalyzed ligand-free Suzuki–Miyaura coupling in water with or without an additive [24]. The primary advantage of the ligandless methodology is its ability to eliminate one reagent (e.g., phosphine derivatives). This provides less hazardous chemical syntheses and atom economy. The second key advantage is a marked improvement in reaction efficiency that allows for shorter reaction time, milder conditions and greater catalytic turnover.

To the best of our knowledge, only one report has described the Suzuki–Miyaura reaction in neat water using water unsoluble starting materials and ligand-free in the presence of modified α-cyclodextrin-capped palladium nanoparticles [25]. In this work, Antunes et al. used

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2-hydroxypropyl-α-cyclodextrin as a reductant and capping agent for the Suzuki–Miyaura reaction and obtained different unsymmetrical biaryl compounds in high yields with a significant catalytic activity [25]. Starting from modified α-cyclodextrin a phase transfer was not permitted due to the little size of the hydrophobic internal cavity. In an attempt to expand the sustainable aspect of the Suzuki–Miyaura reaction, our group developed a successful ligand-free water-based method by using a natural β-cyclodextrin (β-CD) promoter.

2. Experimental

2.1. General

All reactants were obtained from Acros Organics and were used as received without further purification. Solvents were purchased from Carlo Erba and were dried and freshly distilled under nitrogen. Water (deionized) was degassed by sparging with nitrogen. Chromatography was performed on a neutral silica gel. All reactions and workup procedures were performed under an inert atmosphere by using conventional vacuum-line and glasswork techniques.

2.2. Characterization

NMR spectra of Suzuki coupling products were recorded on a Bruker instrument operating at 400.13 MHz for proton and 100.62 MHz for carbon. The qualitative and quantitative analyses of the reactants and products were performed by gas chromatography. Products were identified by a comparison with authentic samples. Conversion and GC yields were calculated with dodecane as an internal standard. NMR spectra for the complexation analysis were recorded on a Bruker instrument operating at 600.17 MHz.

An isothermal calorimeter (ITC_{200}, MicroCal Inc., USA) was used for determining the stoichiometry and the binding constant of the complex between the different substrates and the cyclodextrin. Aliquots (0.5 µL to 2 µL) of titrant solution (11.1 to 38.3 mM) were added with a syringe to the titrate solution (200 µL, 0.38 to 2.83 mM) at 25 °C. Data analysis was carried out by using Origin 7 software.

Samples for TEM analyses were prepared by depositing one drop of diluted nanoparticle aqueous dispersion on PVP-coated copper grids. After drying, the images were obtained by a Hitachi H 600 transmission electron microscopy (100 kV).

XPS studies were carried out in a Kratos Axis Ultra DLD spectrometer equipped with a monochromatic Al Ka-X-ray source ($h\nu = 1486.6$ eV) operating at 150 W, a multi-channel plate and delay line detector under 1.0×10^{-9} Torr vacuum. The survey and high-resolution spectra were collected at fixed analyzer pass energies of 160 and 20 eV, respectively. The instrument work function was calibrated to give an Au4f7/2 metallic gold binding energy of 83.95 eV. The spectrometer dispersion was adjusted to give a binding energy of 932.63 eV for metallic Cu 2p3/2. Samples were mounted in a floating mode in order to avoid differential charging, and charge neutralization was required for all samples. Binding energies were referenced to the C 1s binding energy of adventitious carbon contamination which was taken to be 284.80 eV [26,27]. The data were analyzed with a commercially available software, CasaXPS. The individual peaks were fitted by a Gaussian (70%)–Lorentzian (30%) (GL30) function after the Shirley type background subtraction.

2.3. Typical procedure for the Suzuki–Miyaura reaction

A 10 mL Schlenk flask was charged with bromoarene (0.25 mmol), phenylboronic acid (0.375 mmol, 1.5 eq), base (0.5 mmol, 2 eq), β-cyclodextrin ($1.25\,10^{-3}$ mmol, 0.5 mol%). A solution of Pd ($1.25\,10^{-3}$ mmol, 0.5 mol%) in water (2 mL) was added. The mixture was flushed with nitrogen, capped and placed in a pre-heated oil bath. The reaction mixture was stirred at the specified temperature for the specified time. Then the reaction mixture was extracted with ethyl acetate (3×3 mL) and the combined organic layers were dried over $MgSO_4$, filtered and evaporated under reduced pressure. The crude product was analyzed by GC or purified by flash chromatography on silica gel.

3. Results and discussion

β-CDs are a family of cyclic oligosaccharides composed of α-(1→4)-linked D-glucopyranose units in $^4C_1$ chair conformation that have seven glucopyranose units. As a consequence of the non-modified β-CD structure, the molecule is hydrophilic and features a conical cavity that is essentially hydrophobic in nature with a size of the internal cavity permitting the phase transfer of water-unsoluble substrates. The best method consisted of obtaining an inclusion complex between a model initial substrate such as 4-bromacetophenone (**1**) and native β-CD and not or weak inclusion complex between the target compounds such as 4-acetylbiphenyl (**3**) and β-CD. NMR spectroscopy is one of the most reliable techniques for studying β-CD inclusion complexes. In our case, the ^{1}H NMR spectra of the native β-CD, β-CD-4-bromoacetophenone (**1**) mixture and β-CD-4-acetylbiphenyl (**3**) mixture were realized in D_2O. The mixture of the β-CD and 4-bromoacetophenone (**1**) showed apparent chemical shift changes of the β-CD cavity protons, H-3 and H-5. The H-3 and H-5 protons were shifted downfield in the range from 3.889 ppm; 3.782 ppm to 3.782 ppm; 3.661 ppm respectively. In contrast, the shifts of β-CD outside H-2 and H-4 could be neglected. The analysis of the ^{1}H NMR spectrum showed that the 4-bromoacetophenone (**1**) or a part of it was included into the β-CD cavity, thus, confirming the formation of an inclusion complex.

The T-ROESY spectrum of the β-CD (10 mM) and 4-bromoacetophenone (**1**) (10 mM) mixture showed that the proton peaks of the phenyl core (a, b) were highly correlated with the proton peaks of β-CD (H-3 and H-5). This confirmed that the phenyl ring was included into the β-CD cavity. In this case, two potent inclusion complexes could exist depending on the orientation of the 4-bromoacetophenone (**1**) inside the cavity; one with the bromide atom oriented in the primary face and the other with the bromide atom in the secondary face. The same experiments were realized with the replacement of 4-bromoacetophenone (**1**) by 4-acetylbiphenyl (**3**) in D_2O. The ^{1}H NMR spectrum of the mixture did not show apparent chemical shift change. To gain a better insight into the complexation phenomena, experiments were also conducted with isothermal titration calorimetry (ITC) [28].

Fig. 1 describes the ITC enthalpogram for the addition of β-CD with 4-bromoacetophenone (**1**) in pure water at 25 °C. Negative peaks were observed for each addition as a consequence of the formation of the inclusion complex. The intensities decreased as such association weakens as the host concentration inside the cell increased. The fit of these data to the theoretical model allowed the determination of the thermodynamic parameters. The stoichiometry was 1:1 and the association constant was equal to 634 (±19) M^{-1} at 25 °C. In our hands, the same experiments performed with 4-acetylbiphenyl (**3**) used as a guest in pure water failed. However in a mixture of water and acetone (50:50), a low value of inclusion constant could be obtained (155± 36 M^{-1} at 25 °C).

Even if the structure of compound **3** could form an inclusion complex the association constant was low in our conditions. These results demonstrated that native β-CD could be used as a mass transfer promoter for the initial compound in the Suzuki reaction. The results also showed that the target hydrophobic biphenyl core could be easily extracted.

In the first set of experiments, the reaction of 4-bromoacetophenone (**1**) (1 equiv) with phenylboronic acid (**2**) (1.5 equiv) was carried out as a model reaction in sole water at 100 °C with K_2CO_3 (2 equiv) using $Pd(OAc)_2$ (0.5 mol%) as the catalyst and native β-CD (0.5 mol%) (Table 1, entry 1). It was notable that in the literature the amount of