N-Alkoxy carbonyl / carbamoylmethyl substituted 1H-imidazol-2-ylidene-Pd (II) complexes as highly efficient catalysts for Suzuki-Miyaura cross-coupling reaction

Meliha ÇETİN KORUKÇU *
Bursa Uludağ University, Faculty of Arts and Science, Department of Chemistry, 16059 Bursa / TURKEY

Abstract

N-Alkoxy carbonyl / carbamoylmethyl substituted 1H-imidazol-2-ylidene-Pd (II) complexes (Cat-1-5) were used for the first time as catalysts in the Suzuki-Miyaura reaction between aryl bromides and arylboronic acids. All complexes screened were found to be excellent catalysts in the selected coupling between 4-bromobenzaldehyde and phenylboronic acid at room temperature. Cat-3 was shown to be the most efficient one and used for the optimisation of the reaction conditions and determining the substrate scope. The application of the optimised method provided a series of biaryl (3a-l) in excellent isolated yields. With these promising results the catalysts could be applied successfully to some other classic cross-coupling reactions such as Sonogashira, Stille and Buchwald-Hartwig.

1. Introduction

Suzuki-Miyaura cross-coupling reaction is one of the most powerful reactions used to form C-C bonds in organic chemistry. It is a mild and facile route to prepare biaryl from the reaction of an aryl halide (vinylhalide or sulfonate) with an arylboronic acid (or ester) by using catalytic amounts of Pd compounds [1]. It is most frequently used in the formation of biaryls (one of the major skeletons in organic chemistry) which take place in many pharmaceuticals, agrochemicals and biologically active natural compounds [2]. Biaryls have also been used recently in the area of material chemistry for the preparation of functional molecules such as organic light emitting diodes (OLEDs) [3], molecular wires, liquid crystals, conducting polymers etc [4].

Since the palladium complexes involving tertiary phosphine ligands used in Suzuki-Miyaura coupling are toxic, often air, oxygen and water sensitive and require high temperature [5], the use of less toxic catalysts and more environmentally friendly conditions like aqueous organic solvents (as DMF:H₂O, toluene-H₂O etc.) and working at room temperature have become the determining factors of the reaction [6].

N-heterocyclic carbenes, the imidazol-2-ylidene, are convenient ligands [7] that have been used in Suzuki-Miyaura reaction in the last decades [8]. Their palladium complexes, in particular, have been used successfully not only in Suzuki-Miyaura but also in many other coupling reactions such as Heck-Mizoroki, Negishi, Sonogashira, Hiyama, Buchwald-Hartwig etc [9]. Apart from that, they have various properties and interesting areas of usage [10].

In one of the our previous works we reported the preparation of a new type of bidentate N-heterocyclic carbene enolates (NHCE) and their palladium complexes via transmetallation of silver complexes [11]. First we treated 1,4-diaryl and 1,2,4-triaryl imidazoline N-oxides with dimethyl acetylenedicarboxylate (DMAD) to get isoxazolines. Rearrangement of these isoxazolines under reflux in toluene provided the 1,4-diaryl or 1,2,4-triaryl imidazolines and corresponding 3H-imidazol-1-ium ylides. The reaction of ylides (with no substituent at C-2) with silver nitrate and triethylamine at room conditions provided C-2 metallated N-heterocyclic carbene ylides (Ag(NHCY)(Et₃N)). The treatment of these precursors with equimolar amounts of Pd(CH₂CN)₂Cl₂ in CH₂Cl₂ provided mono Pd(II)-NHCE complexes that are in equilibrium with their bis-Pd(II)-NHCE analogues [12]. All the new complexes were fully characterized with IR, NMR, elemental analysis and thermogravimetric analysis (TGA). In the same study, we also tried these newly prepared Pd complexes in a model Heck-Mizoroki and in a model Suzuki-Miyaura reactions and showed that they were...
pretty good as catalysts. We also used the Hammett type correlations in order to reveal the substituent effect on the aryl halides, catalysts, styrenes and arylboronic acids.

In a different study, we reported the synthesis and characterisations of another group of Pd (II)-NHC complexes starting from appropriate imidazolium salts [13]. All the new complexes were characterized with spectral methods and elemental analysis and their thermal behaviours were investigated in detail. We also screened the new complexes for their catalytic activities in Heck-Mizoroki coupling and revealed the catalysts to be highly efficient.

As a continuation of our last research, in this study catalysts 1-5 are used in Suzuki-Miyaura cross-coupling for the first time, with very low catalyst loadings, in an aqueous solvent, at room temperature, in very short time with extremely high yields and easy isolation method.

2. Materials and Methods

2.1. Apparatus

An Electrothermal Digital melting point apparatus was used for determining the melting points of the compounds. $^1$H and $^{13}$C NMR experiments were performed on an Agilent 400 MHz spectrometer. The preparative TLC was performed with silica gel 60 HF254 (90% < 45 μm). All of the reagents and solvents used in this work were provided commercially and used without any further purifications.

2.2. Synthesis of the biphenyls (3)

**General procedure:** Aryl bromide (0.2 mmol) and arylboronic acid (0.3 mmol) are stirred in N,N-dimethylformamide-water (1:1, v/v, 0.6 mL) with Cs₂CO₃ (0.4 mmol, 0.132 g) and cat-3 (0.0002 mmol, 0.12 mg) in screwed vials at room conditions. The reactions are monitored with thin layer chromatography (ethyl acetate-petroleum ether (EA-PE, 1:3)). Once the reaction is completed 2 mL of water is added and aqueous mixture is extracted with CHCl₃ (3 X 2 mL). After combining the organic extracts they are washed with 3 mL of water and dried over anhydrous Na₂SO₄. The solvent is evaporated under vacuum. The pure biphenyls are isolated from preparative TLC (EA-PE / 1:3 as eluent system) and crystallized from diethyl ether-petroleum ether (1:2). The identity of the products was proved comparing with the physical and spectral characteristics of the original samples. $^1$H and $^{13}$C NMR data of the biphenyls are given in Table 1.

3. Results and Discussion

3.1. Preparation of the catalysts

The catalysts used in this study were prepared according to our reported work mentioned above [13]. The reactions of appropriate imidazolium salts with Ag₂O (or with AgNO₃ and Et₃N) in CH₂Cl₂ at room temperature provides Ag-metallated complexes. Treatment of these Ag-complexes with Pd(CH₂CN)₂Cl₂ in CH₂Cl₂ provides catalysts 1-5 at room temperature in high yields. The NMR, IR and elemental analysis data of the compounds are matching with those in the literature. Structures of the catalysts are given in Figure 1.

![Figure 1. Structures of the catalysts (1-5) used in this study.](image-url)
There was no conversion with K$_3$CO$_3$, NaHCO$_3$ and NaOAc as a base and 1 mol % cat-3. There was no conversion with K$_2$CO$_3$, for the reactions performed with Cs$_2$CO$_3$, Na$_2$CO$_3$, NaHCO$_3$ and NaOAc the isolated yields were 44, 16, 17 and 22 % respectively (Table 2, entries 6-10).
Due to its higher performance, Cs₂CO₃ was used in the experiments to investigate the best solvent and the reactions were performed with 1 mol % catalyst loading in seven different solvents.

There was no conversion in formamide. The reaction in DMF-H₂O (1:1) occurred very fast (the reaction finished within 5 minutes). The reactions in DMF and H₂O also occurred with pretty good results in 2.5 and 24 hours respectively (Table 2, entries 11-17). After determination of the lead catalyst, solvent and the base, concentration studies were performed with different mol % concentrations (0.1, 0.01, 0.001 and 0.0001) of the catalyst. The isolated yields of the reactions were 96, 97, 18 and 10 % and the TONs are 0.96x10³, 0.97x10³, 1.8x10⁴ and 10⁵ respectively (Table 2, entries 18-21).

Due to its higher performance, Cs₂CO₃ was used in the experiments to investigate the best solvent and the reactions were performed with 1 mol % catalyst loading in seven different solvents.

Table 2. Optimisation studies of the Suzuki-Miyaura coupling between 4-bromobenzaldehyde and phenylboronic acid.

| Entry | Cat | Cat (mol %) | Base | Solvent | React Time (h) | Yield(%) |
|-------|-----|-------------|------|---------|---------------|----------|
| 1     | 1   | 1           | Cs₂CO₃ | 1,4-Dioxane | 24            | 33       |
| 2     | 2   | 1           | Cs₂CO₃ | 1,4-Dioxane | 24            | 35       |
| 3     | 3   | 1           | Cs₂CO₃ | 1,4-Dioxane | 24            | 45⁵      |
| 4     | 4   | 1           | Cs₂CO₃ | 1,4-Dioxane | 24            | 34       |
| 5     | 5   | 1           | Cs₂CO₃ | 1,4-Dioxane | 24            | 35       |
| 6     | 3   | 1           | Cs₂CO₃ | 1,4-Dioxane | 24            | 44⁵      |
| 7     | 3   | 1           | NaOAc  | 1,4-Dioxane | 24            | 16       |
| 8     | 3   | 1           | K₂CO₃  | 1,4-Dioxane | 24            | nr²      |
| 9     | 3   | 1           | NaHCO₃| 1,4-Dioxane | 24            | 17       |
| 10    | 3   | 1           | NaOAc  | 1,4-Dioxane | 24            | 22       |
| 11    | 3   | 1           | Cs₂CO₃ | 1,4-Dioxane | 24            | 47⁵      |
| 12    | 3   | 1           | Cs₂CO₃ | Formamide   | 24            | nr       |
| 13    | 3   | 1           | Cs₂CO₃ | DMF-H₂O⁴    | 5 min         | 95⁶      |
| 14    | 3   | 1           | Cs₂CO₃ | DMF         | 2.5           | 94       |
| 15    | 3   | 1           | Cs₂CO₃ | DMAc        | 24            | 16       |
| 16    | 3   | 1           | Cs₂CO₃ | NMP         | 24            | 19       |
| 17    | 3   | 1           | Cs₂CO₃ | H₂O         | 24            | 90       |
| 18    | 3   | 0.1         | Cs₂CO₃ | DMF-H₂O     | 5 min         | 96⁶      |
| 19    | 3   | 0.01        | Cs₂CO₃ | DMF-H₂O     | 2             | 97⁶      |
| 20    | 3   | 0.001       | Cs₂CO₃ | DMF-H₂O     | 48            | 18       |
| 21    | 3   | 0.0001      | Cs₂CO₃ | DMF-H₂O     | 48            | 10       |

¹Isolated yields. ²No reaction. ³4 eqs of base were used. ⁴The ratio of the solvents is 1:1 (v/v). ⁵The isolated yields from three different experiments. ⁶The reactions occur with quantitative conversion, the yields are isolated yields. (Abbreviations: DMF: N,N-Dimethylformamide, DMAc: N,N-Dimethylacetamide, NMP: N-Methyl-2-pyrrolidone)

Scheme 2. Suzuki-Miyaura cross-coupling reaction of aryl bromides with phenylboronic acids catalysed by Cat-3.

After all, the reactions of substrate scope were carried on in DMF-H₂O (1:1) with Cs₂CO₃ and 0.1% mole of Cat-3 (Scheme 2). The reaction of bromobenzene, 4-bromotoluene, 4-bromoisocoumarin, 4-bromobenzaldehyde with phenylboronic acid occurred very fast so that it was not possible to observe any substituent effect of aryl bromides. Only the reaction with 3-bromobenzoaldehyde and phenylboronic acid was a little bit slower compared to the others. It might be from the meta substitution of formyl group (Table 3, entries 1-5). Then 4-bromobenzaldehyde was chosen as aryl bromide and the reactions performed with different arylboronic acids. All reactions occurred with quantitative conversions and excellent isolated yields (Table 3, entries 6-10). The reaction was also run with different matching. 4-Bromobenzaldehyde and 4-bromoisocoumarin were treated with 4-methoxyphenylboronic acid and the corresponding biphenyls obtained with pretty good yields (Table 3, entries 11-12)
With the courage from the results of aryl bromides the reactions were tried with aryl chlorides which are known to be less prone to this reaction. For that purpose 4-methoxyphenylboronic acid was chosen as arylboronic acid and a series of reactions were run with 4-chlorotoluene, 4-chloroanisole, 4-chlorobenzaldehyde, 4-chlorobenzonitrile and chlorobenzene in the same conditions. Unfortunately the desired biphenyls could not be obtained instead only self-coupling product of the 4-methoxyphenylboronic acid was observed. Increasing the catalyst amount and the reaction temperature did not change the result.

The mechanism of the Suzuki-Miyaura coupling is a well-known mechanism which includes palladium (0) and palladium (II) species. The probable mechanism for Suzuki-Miyaura reaction catalysed with Cat-3 is depicted in Scheme 3. When palladium (II) complexes are used, the mechanism starts with preactivation step to get palladium (0) complex A and goes on by the oxidative addition step to form organopalladium species B. The reaction of base with organopalladium species B gives intermediate C. Then the transmetallation step occurs and another organopalladium species D forms. After the reductive elimination step the desired product 3 and the starting palladium (0) compound A are emerged.

| Biphenyl (3) | R₁ | R₂ | React. Time (min) | Yield¹ (%) | Mp. (°C) | Lit. Mp. (°C) | Ref. |
|-------------|----|----|------------------|------------|----------|--------------|-----|
| a           | H  | H  | 5                | 98         | 69-70    | 69-70        | [12]|
| b           | 4-Me | H  | 5                | 98         | 40-41    | 41-42        | [11]|
| c           | 4-MeO | H  | 5                | 97         | 86-87    | 85-86        | [12]|
| d           | 4-CHO | H  | 5                | 98         | 61-62    | 59-60        | [12]|
| e           | 3-CHO | H  | 30               | 95         | 53-54    | 53-54        | [12]|
| f           | 4-CHO | 3-Me | 10               | 96         | 56-57    | 57-58        | [12]|
| g           | 4-CHO | 4-MeO | 10               | 98         | 103-104  | 103-104      | [12]|
| h           | 4-CHO | 4-CHO | 30               | 97         | 147-148  | 148-150      | [12]|
| i           | 4-CHO | 4-Cl  | 10               | 98         | 115-116  | 114-115      | [12]|
| j           | 4-CHO | 4-Br  | 10               | 96         | 142-143  | 135-140      | [14]|
| k           | 4-Me  | 4-MeO | 10               | 95         | 110-112  | 111-112      | [15]|
| l           | 4-MeO | 4-MeO | 10               | 95         | 177-178  | 178-180      | [15]|

¹Isolated yields from quantitative conversions. General conditions of the reaction: 1 (0.2 mmol) and 2 (0.3 mmol) were stirred in DMF:H₂O (1:1, v/v, 0.6 mL) with Cs₂CO₃ (0.4 mmol) and Cat-3 (0.1 % mmol) in screwed vials at room temperatures.
Scheme 3. Probable mechanism for Suzuki-Miyaura reaction catalysed with Cat-3.

4. Conclusion

The catalysts Cat-1-5 were screened in Suzuki-Miyaura cross-coupling reaction for the first time. The reactions occurred very fast with excellent yields in DMF-H₂O with Cs₂CO₃ and 0.1% mole of catalyst at room temperature (Scheme 4). With these promising results it is reasonably foreseeable that these catalysts could be applied successfully to some other classic cross-coupling reactions such as Sonogashira, Stille and Buchwald-Hartwig. Relevant studies are in progress.
Scheme 4. Suzuki-Miyaura reaction catalysed with Cat-3.

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**Conflicts of interest**

The author states that she did not have conflict of interests.

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