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Phosphine mono- and bis-ylide palladacycles as homogeneous molecular precatalysts: Simple and efficient protocol greatly facilitate Suzuki and Heck coupling reactions

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ABSTRACT

Moisture/air-stable and robust phosphine mono- and bis-ylide palladacycles as catalyst precursors were used in Suzuki and Heck cross-coupling reactions with different aryl halides including electron-rich and electron-deficient substituents. These coupling reactions could proceed smoothly in air under optimized reaction conditions (Suzuki coupling: 0.001 mol% of palladacycle, Cs_2CO_3 in DMF at 110 °C; Heck coupling: 0.001 mol% of palladacycle, K_2CO_3 in NMP at 130 °C), affording the corresponding products in mostly good to excellent yields. Filtration experiments and poisoning studies indicate that the phosphine-ylide palladacycles decompose under reaction conditions to form active Pd (0) homogeneous species. These homogenous catalysts were exhibited high catalytic activities in the presence of low catalyst loadings, providing high yields of desired products. Applications of five-member palladacycle [(PĈ)$PdCl_2$] (**1**) in these coupling reactions produced comparable catalytic activities of seven-member analogs [(CĈ)$PdCl_2$] (**2**). We found that the palladacycle complexes containing bulky, symmetrical and unsymmetrical phosphorus ylides are the active catalysts in the appropriate Suzuki and Heck cross-coupling reactions.

1. Introduction

Palladium-catalyzed C–C coupling reactions have been recognized as powerful tools and major area of interest in multiple organic synthesis [1–3], natural products [4,5] and material science [6,7]. Coupling of aryl halides with arylboronic acids (Suzuki reaction) and alkenes (Heck reaction) have significant importance, and are well-established methodologies in modern organic synthesis [8,9]. Indeed, various efficient palladium precatalysts have been developed in recent years that allow aryl halides to be effectively coupled with aryl boronic acids [10a,b] and olefins [10c,d] under mild reaction conditions. Palladium complexes incorporating phosphine ligands are the most intensively investigated due to the fact that their catalytic activities can be effectively modulated by the electronic and steric properties of the ligands [2,10e, 11–15]. In recent years, various homogeneous palladium-phosphine catalysts have been developed for the efficient cross-coupling reactions [16–22], but most of them did not have good results about the coupling of less reactive aryl halides as substrates in Suzuki and Heck coupling reactions. Furthermore, high loading of catalysts and an inert atmosphere in most reactions especially involving phospha–palladacycles are generally required for achieving better conversions [23].

Serrano et al. [24a] reported imine–palladacycles containing imidate "Pseudohalide" ligands which catalyzed Suzuki cross-coupling reactions of both aryl and benzyl bromides with phenylboronic acid in the presence of 1 mol% catalyst. Wu and coworkers [24b] synthesized ferrocenylimines cyclopalladated [PdCl{[(η^5-C_5H_5)]Fe[(η^5-C_5H_3)–CCH_3]=N[(n-$C_{12}H_{25}$)$_2$]}(PPh_3)] precatalysts which promote the Suzuki and Heck coupling reactions. In the reaction of chlorobenzene with ethyl acrylate using 0.1 mol% of catalyst, only trace amount of ethyl cinnamate was obtained after 12 h in 140 °C. While, the reaction of aryl bromides with phenyl boranic acid using 0.001 mol% were completed in 45 min at 110 °C. Bedford et al. [24c] evaluated Suzuki and Stille couplings by using of orthopalladated complexes. Under argon atmosphere, low isolated yields were obtained from the reaction of some aryl chlorides with phenylboronic acid or butyl acrylate after long reaction times [24c]. It has been found that phosphine complexes as catalysts are not only comparable with other catalysts but, in some cases, are also better than them in the presence of same aryl halide [24]. The coupling of aryl bromides and chlorides, which are the cheapest and most abundant among the aryl halides, has been addressed in the recent past using such complexes as catalysts [25]. Thus,

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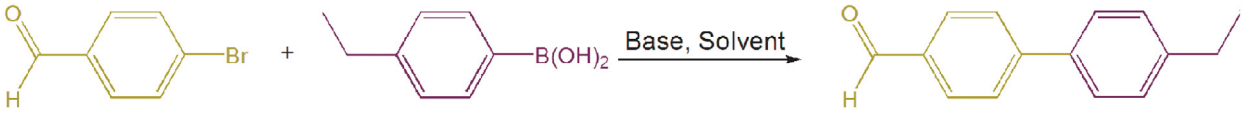
Table 1
Optimization of base and solvent for Suzuki reactions of 4-bromobenzaldehyde with 4-ethylphenylboronic acid.[a]



Entry	Base	Solvent	Time (h)/Temp. (°C)	(Yield %)[b]
1	Cs_2CO_3	Dioxane	10/110	60
2	Cs_2CO_3	NMP	3/130	71
3	Cs_2CO_3	Methanol	6/60	40
4	Cs_2CO_3	CH_3CN	8/80	53
5	Cs_2CO_3	Toluene	10/110	65
6	Cs_2CO_3	H_2O	12/100	N.R.[c]
7	Cs_2CO_3	DMF	1.5/110	85
8	Et_3N	H_2O	12/100	N.R.
9	K_2CO_3	DMF	1.5/110	75
10	Na_2CO_3	DMF	1.5/110	52
11	NaOAc	DMF	12/110	47
12	NaF	DMF	12/110	32
13	Et_3N	DMF	12/110	Trace

[a] *Reaction conditions*: 4-bromobenzaldehyde (0.75 mmol), 4-ethylphenylboranic acid (1 mmol), base (1.5 mmol), solvent (2 ml), catalyst **2** (0.001 mol%), under air.
[b] Isolated yields.
[c] No reaction.

the investigations for new palladium catalysts have been received much attention particularly for the use of less reactive aryl halides as substrates at low Pd loading, under aerobic conditions.

Other issue that complicates analyses is that in some cases soluble palladium species are produced *in situ* and redeposit back onto the solution which varies efficiencies during Suzuki and Heck reactions [26]. Thus, standard tests for recognizing homogeneous vs. heterogeneous catalysts such as filtration experiments and poisoning studies for palladium can be used to discriminate between soluble and insoluble catalysts [26a,27].

In view of these findings and our continuing interest in the synthesis of palladacycle complexes [28–33] and the applications of these systems [34–36]; we encouraged to use five- and seven-membered palladacycles 1 and 2 which were synthesized in our previous works [35,36] (Scheme 1) as catalyst precursors in Suzuki and Heck cross-coupling reactions. Also, we report our results in this work regarding to the nature of the active species involved in the Suzuki and Heck coupling reactions promoted by these palladacycles.

2. Results and discussion

2.1. Suzuki cross-coupling reactions

With these new palladium (II) catalyst precursors in hand, we envisioned to apply them in the construction of C–C bond via cross-coupling reaction. We commenced our studies using catalysts **1** and **2** for Suzuki cross-coupling reactions. Suzuki cross-coupling reaction represents a powerful method for the C–C bond formation [37,38]. Construction of biaryl compounds via the palladium-catalyzed Suzuki reaction is an interesting area in organic synthesis. The importance of biaryl units as molecular components in pharmaceuticals, herbicides and natural products, as well as in engineering materials such as conducting polymers, molecular wires and liquid crystals, have attracted enormous interest [39–41].

2.1.1. Optimization of base and solvent

We first investigated the effect of various solvents on the model reaction of 4-bromobenzaldehyde with 4-ethylphenylboronic acid catalyzed by 0.001 mol% of catalyst **2** under air (Table 1). Cs_2CO_3 was used as a base in this reaction. Generally moderate product yields were observed when the reactions were performed in solvents of low polarity, such as dioxane and toluene (Table 1, entries 1 and 5). High yields were observed when highly polar solvents, such as dimethylformamide (DMF), N-methylpyrrolidone (NMP) were used as reaction medium for Suzuki reactions. The reaction could not proceed in water and no yield was observed even when reaction prolonged after 12 h at 100 °C (Table 1, entry 6). As shown in Table 1, DMF gave the highest yield (entry 7, 85%) after 90 min at 110 °C. After selecting DMF as the optimal solvent, we investigated the influence of various bases (Table 1, entries 7–13) on the Suzuki reaction between of 4-bromobenzaldehyde and 4-ethylphenylboronic acid (0.001 mol% of catalyst **2** under air). Under otherwise identical reaction conditions the change of base, such as Cs_2CO_3, Et_3N, K_2CO_3, Na_2CO_3, NaOAc and NaF led to considerable variation in levels of isolated yields. However, only Cs_2CO_3 and K_2CO_3 gave acceptable results with DMF as a solvent. According to the results shown in Table 1, Cs_2CO_3 gave excellent yield (entry 7, 85%) under best reaction conditions.

2.1.2. Optimization [Pd] loading

Various catalyst concentrations were also tested and showed in Table 2. A control experiment indicated that the coupling reaction did not occur in the absence of catalyst (entry 1). The results in Table 2 show that 0.001 mol% of the catalyst loading gave the best results (entries 4 and 8).

Table 2
Optimization of catalyst concentrations.[a]

Entry	Catalyst (mol%)	Time (h)	Yield[b] (%)
1	None	12	N.R.[c]
2	**1** (0.1)	1.5	88
3	**1** (0.01)	1.5	85
4	**1** (0.001)	1.5	84
5	**1** (0.005)	1.5	85
6	**1** (0.0005)	5	65
7	**2** (0.1)	1.5	95
8	**2** (0.01)	1.5	91
9	**2** (0.001)	1.5	90
10	**2** (0.005)	1.5	90
11	**2** (0.0005)	5	71

[a] *Reaction conditions*: 4-bromobenzaldehyde (0.75 mmol), 4-ethylphenylboranic acid (1 mmol), Cs_2CO_3 (1.5 mmol), DMF (2 ml), 110 °C.
[b] Isolated yields.
[c] No reaction.