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trans-$Pd(OAc)_2(Cy_2NH)_2$ catalyzed Suzuki coupling reactions and its temperature-dependent activities toward aryl bromides

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Abstract—A new catalytic system based on Pd-simple amines for Suzuki coupling reactions of aryl bromides is described. A well-defined air-stable complex, *trans*-$Pd(OAc)_2(Cy_2NH)_2$ effectively promotes Suzuki couplings of aryl bromides with a range of aryl boronic acids to give diaryl products in high yields. It also exhibits temperature-dependent activity toward aryl bromides bearing different electronic substituents under reaction conditions.

The palladium-catalyzed Suzuki coupling reaction, involving cross-coupling of aryl halides with aryl boronic acids, is one of the most powerful and convenient synthetic methods for preparation of biaryl compounds.[1] The reaction is normally promoted by a palladium catalyst precursor, a ligand that binds to the palladium center to stabilize the catalyst during the reaction process, and a base that captures the boronic acid moiety. The choice of the right ligand is a pivotal factor in determining the rate of the reaction. Triaryl phosphines are traditionally employed as ligands for the reaction.[1a] Recently electron-rich, bulky phosphines[2–5] and phosphine oxides[6] have been reported to be effective ligands. Moreover, a number of important developments with phosphine-free ligands, such as C-based heterocyclic carbenes,[7] C,N-based 2-aryl-2-oxazolines,[8] aryloximes,[9] arylimines,[10] and *N*,*N*-based diazabutadienes[11] have been reported. These non-phosphine ligands have the potential to overcome the problems of catalyst sensitivity to air and environmental concerns. However, most of these new ligands are not commercially available and some are cumbersome to synthesize; of those that are commercially available many are quite expensive. It is desirable to have simple, inexpensive, easily accessible and stable catalysts for these reactions. We report here a new in-situ Pd-simple amine based catalytic system for the Suzuki coupling reaction and the first well-defined single-component $Pd(OAc)_2$–amine complex as an efficient catalyst and its temperature-dependent catalytic behavior toward aryl bromides with different electronic substituents.

Simple amines have not been reported as ligands for Suzuki coupling reactions although *t*-butylammonium bromide has been used as a promoter for the reaction in a stoichiometric amount.[12] In our continuing efforts to develop new non-phosphine based catalysts for the Suzuki coupling reaction,[8] we have screened several simple and commercially available amines as ligands for the coupling reaction of 4-bromoanisole and phenylboronic acid in the presence of 2 mol% of $Pd(OAc)_2$, 4 mol% amine, and 2 equiv. of Cs_2CO_3 in dioxane at 80°C. Triethylamine, aniline, pyridine and diisopropylethylamine (DIPEA) showed no or low activity for the reaction (Fig. 1). However, Cyclohexylamine afforded the product in 83% yield. This encouraging result prompted us to test the effectiveness of dicyclohexylamine (DCyA) since sterically bulky phosphines have been reported as efficient ligands.[2,3,5] DCyA was indeed an excellent choice since the coupling product was obtained in a nearly quantitative yield after 3 h. Another bulky 1° amine, 1-$AdNH_2$, gave a comparable result. However, bulky 3° amines, such as dicylohexylmethylamine and DIPEA, gave somewhat lower yields, compared to DCyA and diisopropylamine, respectively (Fig. 1). These results indicate that commercially available bulky 1° and 2° amines can be used as ligands for the reaction. Thus we have identified an effective, simple amine-based palladium catalytic system for the Suzuki coupling reaction.

Many in situ catalytic systems are available, however, only few are well-defined.[6,7e,10a,13] Consequently, we

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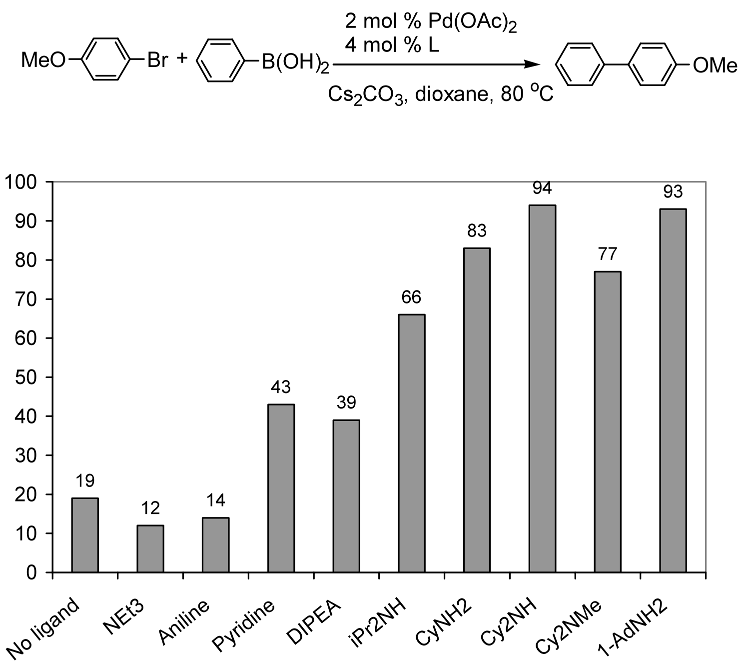


Figure 1. Effect of ligands on a model reaction.

sought to isolate and characterize the single-component complex of DCyA and $Pd(OAc)_2$. The complex, *trans*-$Pd(OAc)_2(Cy_2NH)_2$, (DAPCy) was readily prepared from $Pd(OAc)_2$ and 2 equiv. of DCyA in dioxane at rt in 91% yield (Eq. (1)). It is a yellow solid which is stable at room temperature and can be weighed in air. Its structure is confirmed by ^1H, ^{13}C NMR, elemental analysis and X-ray crystallography.[14]

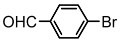
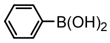
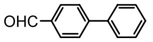
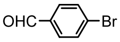
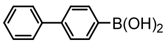
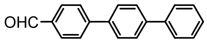
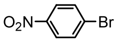
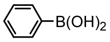
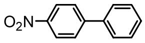
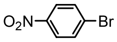
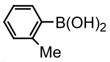
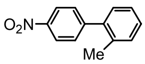
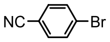
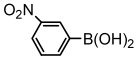
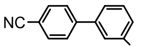
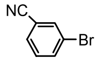
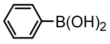
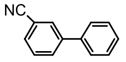
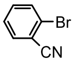
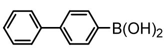
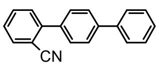
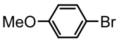
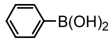
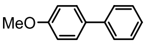
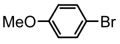
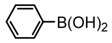
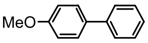
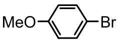
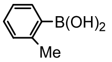
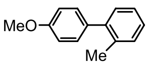
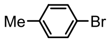
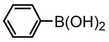
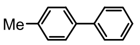
$$Pd(OAc)_2 + 2\ Cy_2NH \xrightarrow[\text{Dioxane}]{\text{RT}} trans\text{-}(Cy_2NH)_2(OAc)_2Pd \qquad (1)$$

In order to begin to define the utility of this new complex as a useful catalyst we have initiated studies with various coupling reactions. Table 1 summarizes our preliminary results for Suzuki coupling reactions. DAPCy exhibits unusual temperature-dependent catalytic activities toward the Suzuki coupling reaction of aryl bromides with different electronic substituents. It catalyzes the coupling reactions of electron-poor aryl bromides with boronic acids *at room temperature*; however, electron-rich ones require *an elevated temperature*. The reactions of aryl bromides with electron-withdrawing groups present gave the coupling products in good to excellent yields (entries 1–7) in the presence of 2 mol% DAPCy in 10–30 h at room temperature. Those reactions involving aryl bromides with electron-donating groups (such as 4-bromoanisole), did not proceed at room temperature (entry 8). But, they did proceed to completion to give the coupling product in 94% yield after 3 h at 80°C (entry 9). The other electron-rich bromides also afforded the corresponding coupling products in good yields (entries 10 and 11) at the higher temperature. This indicates that DAPCy has the unusual ability to distinguish between electron-rich and -poor aryl bromides in the coupling reaction. It is well documented that electronic-poor halides are more reactive than electronic-rich ones for the Suzuki couplings and that the same catalytic system shows different activities toward different halides, such as bromides and chlorides. However, to our knowledge, a catalytic system which can distinguish aryl bromides with different electronic substituents has not been previously described. Further studies of the scope of this observation are underway. While the electronic property of the bromides greatly influenced the rate of coupling reactions, that of the boronic acids has little effect. Both electron-poor and electron-rich boronic acids reacted with different bromides to give the coupling products in good to excellent yields. It should be noted that reactions at both room temperature and 80°C are tolerant to sensitive groups like CN, NO_2, CHO, etc. Finally, it is also noted that DAPCy represents the first N-based mono-Pd centered catalyst for the Suzuki reaction. A number of the defined C,N-, C,P-based palladacycle catalysts[6,10a,13] exist in binuclear forms. Mono-Pd centered catalysts are rare, only recently being reported for very bulky P-based[3c] and C-based catalysts.[7e]

The ability of DAPCy to distinguish bromides with different electronic substituents is further demonstrated by a competitive coupling reaction carried out at room temperature. The reaction of 4-bromonitrobenzene (1.0 mmol) and 4-bromotoluene (1.0 mmol) with phenylboronic acid (1.5 mmol) gave 4-nitrobiphenyl in 93% yield, and without detection of the coupling product from the electron-rich bromide (Fig. 2). These initial results indicate that DAPCy could be used as a catalyst in Suzuki reactions to selectively couple electron-poor bromides with boronic acids in the presence of electron-rich ones.

In summary, we have described a new simple in situ amine/$Pd(OAc)_2$ catalytic system for the Suzuki coupling reaction of aryl bromides. The new single-compo-

Table 1. Temperature-dependent Suzuki reactions of aryl bromides catalyzed by DAPCy

Entry	Ar-Br	Ar'-B(OH)$_2$	Product[a]	Temp(°C)	Time (h)[b]	Yield (%)[c]
1				RT	16	89
2				RT	20	84
3				RT	10	98
4				RT	24	87
5				RT	10	92
6				RT	20	93
7				RT	30	90
8				RT	30	0
9				80	3	94
10				80	16	81
11				80	3	92

[a] Reaction conditions: 1.0 mmol of aryl bromide, 1.5 mmol of aryl boronic acid, 2.0 mmol of Cs_2CO_3, 2 mol% DAPCy, 3.0 mL of 1,4-dioxane.

[b] Reaction time not optimized.

[c] Isolated yield.

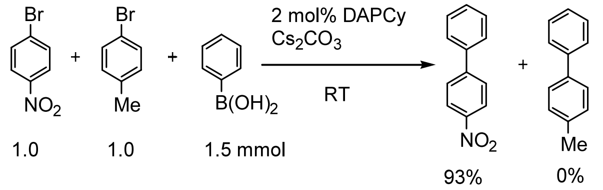


Figure 2. Selective coupling reaction by DAPCy.

nent catalyst, DAPCy, is easy to make, air-stable[15] and inexpensive.[16] It effectively catalyzes Suzuki coupling reactions of aryl bromides with aryl boronic acids in good to excellent yields. It also has the temperature-dependent property of coupling electron-poor bromides with boronic acids at room temperature and electron-rich bromides at elevated temperature. Further investigations of the utility of this catalyst are underway.

Acknowledgements

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14. Experimental procedure for preparation of DAPCy: Dicyclohexylamine (0.725 g, 4.0 mmol) was added into a solution of $Pd(OAc)_2$ (0.449 g, 2.0 mmol) in dioxane (20 mL) at rt. The mixture was stirred at rt for 3 h, during which a yellow precipitate occurred. The solvent was removed under reduced pressure. Crystallization from dichloromethane/hexanes gave DAPCy. Yield: 1.17 g (91%); mp 140°C (dec). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 6.94–6.92$ (m, 2H, NH), 2.82–2.79 (m, 4H, NHC of Cy), 2.48–2.36 (m, 4H, Cy), 1.91–1.66 (m, 30H, Cy), 1.29–1.17(m, 12H, Cy); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.5$ (C=O), 55.0 (NC of Cy), 32.1(Cy), 32.0 (Cy), 26.1 (Cy), 25.9 (Cy), 25.7 (Cy), 24.2 (CH_3). Anal. calcd for $C_{28}H_{52}N_2O_4Pd$: C, 57.27; H, 8.93; N, 4.77; found: C, 57.19; H, 8.98; N, 4.74. The X-ray data for DAPCy are unpublished results.
15. The catalyst retains the same activity after stored at room temperature over 4 months without any precautions to exclude air.
16. The Aldrich 2003–2004 catalog price for dicyclohexylamine is $26.10/500 g.