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# An efficient Stille cross-coupling reaction catalyzed by Pd(OAc)<sub>2</sub>/DAB-Cy catalytic system

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**Abstract**—An efficient palladium-catalyzed Stille cross-coupling reaction has been developed. In the presence of 3 mol% of  $Pd(dba)_2$  and 6 mol% of DAB-Cy (1,4-dicyclohexyl-diazabutadiene), various aryl halides (iodides and bromides) were coupled with organotin compounds to afford the corresponding biaryls and alkyne in good to excellent yields. Furthermore, high TONs [turnover numbers, TONs up to 950,000 for the reaction of 1-iodo-4-nitrobenzene and tributyl(phenyl)stannane] for the Stille cross-coupling reaction were observed. © 2005 Elsevier Ltd. All rights reserved.

### 1. Introduction

The Stille cross-coupling reaction of organohalides with organotin compounds has been proven to be a useful synthetic method for carbon-carbon bond formation in organic synthesis. Consequently, many effective palladium catalytic systems have been developed for Stille crosscoupling reaction.<sup>1–5</sup> Generally, the combination of palladium catalysts with various phosphine ligands results in excellent yields and high efficiency.<sup>1,2</sup> However, phosphine ligands and their palladium complexes are often air-sensitive and are object to P-C bond degradation at elevated temperature.<sup>6</sup> Thus, the use of other supporting ligands for the Stille cross-coupling reaction emerged as an attractive alternative to the phosphine ligands.<sup>3-5</sup> Of these phosphine-free supporting ligands, only one paper has reported the use of diazabutadiene as the ligands combined with Pd(0) [Pd(Ar-BIAN)(dmfu)] to catalyze Stille crosscoupling reaction.<sup>5</sup> Compared with allyl halides and benzyl bromide, however, Pd(Ar-BIAN)(dmfu) showed low activity for the reaction of aromatic iodides. On the other hand, it is desirable to employ low catalyst loadings for pharmaceutical and industrial application. Although, many of the reported catalytic systems are effective, few reports employed the Stille reaction under <1 mol% loadings of palladium catalysts<sup>2a,2c,2n-p,3a,3e-g</sup> (general 1 to 5 mol% Pd).<sup>1</sup> For these reasons, the development of new and efficient phosphine-free palladium catalytic systems

remains an interesting area for organic chemists.<sup>3–5</sup> Herein, we report a stable and efficient Pd(dba)<sub>2</sub>/DAB-Cy (1,4-dicyclohexyl diazabutadiene) catalytic system for the Stille reactions of aryl halides with organotin compounds (Eq. 1).

#### 2. Results and discussion

### 2.1. Palladium-catalyzed Stille cross-coupling of 4-bromoanisole with phenyltributyltin

Initially, the efficiency of diazabutadienes as the ligands for the palladium-catalyzed Stille cross-coupling reaction was evaluated, and the results were summarized in Table 1. The results showed that DAB-Cy (1,4-dicyclohexyl-diazabutadiene) was the most effective ligand for the coupling reaction of 4-bromoanisole (1a) with phenyltributyltin (2a). Without any ligands, only a 45% yield of the corresponding cross-coupled product 3 was isolated in the presence of 3 mol% of Pd(dba)<sub>2</sub> and 3 equiv of KF (entry 1). Whereas, the yield of 3 was increased sharply to 93% when 6 mol% of DAB-Cy was added (entry 3). An identical yield was observed when the amount of DAB-Cy was further increased to 12 mol% (entry 4). Other diazabutadienes as the ligands were less effective than DAB-Cy (entries 3 and 5–7). The results also demonstrated that  $Pd(OAc)_2$  was inferior to Pd(dba)<sub>2</sub> (entries 3 and 8). The use of *n*-Bu<sub>4</sub>NF as

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<sup>a</sup> Under otherwise indicated, the reaction conditions were as follows: **1a** (0.30 mmol), **2a** (0.40 mmol), Pd (3 mol%), ligand (6 mol%), KF (3 equiv), and dioxane (5 mL) at 100 °C under N<sub>2</sub>.

<sup>b</sup> Isolated yield.

<sup>c</sup> Ligand (3 mol%).

<sup>d</sup> Ligand (12 mol%).

<sup>e</sup> n-Bu<sub>4</sub>NF (3 equiv) instead of KF. The reaction was not clean, and some side products were observed.

the base was also investigated, the reaction was not clean and resulted in a low isolated yield of **3** (entry 9).<sup>7</sup>

### **2.2. Palladium-catalyzed Stille cross-coupling of aryl** halides with organotins

As shown in Table 2, treatment of various aryl halides 1b-g with organotin compounds 2a-d, respectively, afforded good to excellent yields of the corresponding cross-coupled products 3-11 in the presence of  $3 \mod \%$  of  $Pd(dba)_2$ , 6 mol% of DAB-Cy, and 3 equiv of KF. The results indicated that Pd(dba)<sub>2</sub>/DAB-Cy was an efficient catalytic system for the Stille cross-coupling reactions. For example, aryl iodide 1b was reacted with organotin compounds including phenyltributyltin (2a), furan-2-yltributyltin (2b), thiophen-2-yltributyltin (2c), and 2-phenylethynyltri-butyltin (2d), respectively, to afford quantitative yields of the corresponding desired products 4-7 in the presence of Pd(dba)<sub>2</sub> (3.0 mol%), DAB-Cy (6 mol%), and KF (3.0 equiv) (entries 1-4). Coupling of aryl bromides 1d-g with organotin compounds 2a and 2b, respectively, was also carried out smoothly and efficiently to afford the desired cross-coupled products in moderate to good yields (entries 6-10). The Pd(dba)<sub>2</sub>/DAB-Cy/KF system was ineffective for the reaction of aryl chlorides 1h and 1i with 2a, respectively (entries 11 and 13). The use of n-Bu<sub>4</sub>NF as the base was further examined, the results showed that the activated aryl chlorides **1h** was coupled with **2a** smoothly to

afford 45% yield of **4** (entry 1 in Table 1; entries 11 and 12 in Table 2). A low yield was still observed from the reaction of **1i** with **2a** under the same catalytic system (entry 14).

### **2.3.** Screening the catalytic efficiency of the palladiumcatalyzed Stille coupling reaction

As shown in Table 3, the catalytic efficacy of Pd(dba)<sub>2</sub>/ DAB-Cy was further evaluated. For coupling of aryl bromides **1a** and **1d** with **2a**, respectively, satisfied yields could still be obtained after prolonged reaction time when the catalyst loading was reduced to 0.1 mol% (entries 1 and 7). Further reduction of the catalyst, loading to 0.01 mol% led to a low yield (28%, TONs=28,000, entry 2). For coupling of aryl iodides **1b** and **1c**, the catalytic efficiency of Pd(dba)<sub>2</sub>/DAB-Cy was also excellent. For example, **1b** was coupled with **2a** smoothly to afford 95% isolated yield for 48 h when the catalyst loading was decreased to 0.0001 mol% (TONs=950,000, entry 3).

#### 3. Conclusion

In summary, a stable and efficient  $Pd(dba)_2/DAB-Cy$  catalytic system for the palladium-catalyzed Stille crosscoupling reaction has been developed. In the presence of  $Pd(dba)_2$  (3.0 mol%), DAB-Cy (6 mol%), and KF (3.0 equiv), the reaction of aryl halides with organotin compounds were carried out smoothly to afforded the Download English Version:

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