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Tetrahedron 61 (2005) 7289–7293
Tetrahedron

An efficient Stille cross-coupling reaction catalyzed by $Pd(OAc)_2$/DAB-Cy catalytic system

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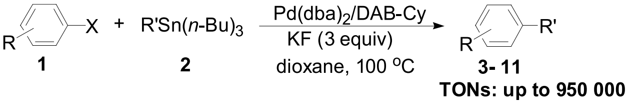
Received 22 February 2005; revised 27 April 2005; accepted 30 April 2005

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.

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 cross-coupling reaction.[1–5] Generally, the combination of palladium catalysts with various phosphine ligands results in excellent yields and high efficiency.[1,2] However, phosphine ligands and their palladium complexes are often air-sensitive and are object to P–C bond degradation at elevated temperature.[6] Thus, the use of other supporting ligands for the Stille cross-coupling reaction emerged as an attractive alternative to the phosphine ligands.[3–5] 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 cross-coupling reaction.[5] 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[2a,2c,2n–p,3a,3e–g] (general 1 to 5 mol% Pd).[1] For these reasons, the development of new and efficient phosphine-free palladium catalytic systems remains an interesting area for organic chemists.[3–5] Herein, we report a stable and efficient $Pd(dba)_2$/DAB-Cy (1,4-dicyclohexyl diazabutadiene) catalytic system for the Stille reactions of aryl halides with organotin compounds (Eq. 1).



(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 $Pd(dba)_2$ 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 $Pd(dba)_2$ (entries 3 and 8). The use of n-Bu_4NF as

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Keywords: $Pd(dba)_2$/DAB-Cy; Stille cross-coupling reaction; Aryl halide; Organotin compound; Turnover number.

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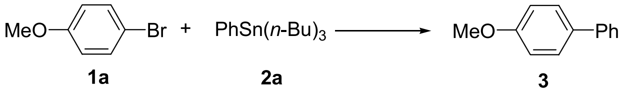
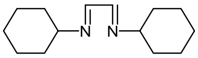
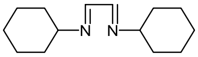
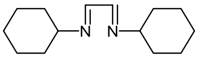
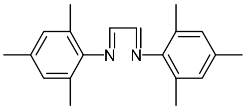
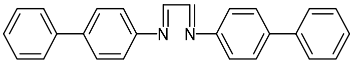
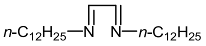
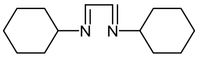
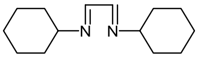
doi:10.1016/j.tet.2005.04.073

Table 1. Palladium-catalyzed Stille cross-coupling reaction of 4-bromoanisole (**1a**) with phenyltributyltin (**2a**)[a]



Entry	Pd	Ligand	Time (h)	Yield (%)[b]
1	$Pd(dba)_2$	—	22	45
2[c]	$Pd(dba)_2$		18	78
3	$Pd(dba)_2$		18	93
4[d]	$Pd(dba)_2$		18	94
5	$Pd(dba)_2$		22	20
6	$Pd(dba)_2$		20	79
7	$Pd(dba)_2$		21	72
8	$Pd(OAc)_2$		22	70
9[e]	$Pd(dba)_2$		18	32

[a] 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_2.

[b] Isolated yield.

[c] Ligand (3 mol%).

[d] Ligand (12 mol%).

[e] n-Bu_4NF (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).[7]

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 mol% of $Pd(dba)_2$, 6 mol% of DAB-Cy, and 3 equiv of KF. The results indicated that $Pd(dba)_2$/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 $Pd(dba)_2$ (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 $Pd(dba)_2$/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_4NF 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).

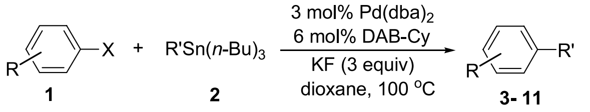
2.3. Screening the catalytic efficiency of the palladium-catalyzed Stille coupling reaction

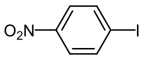
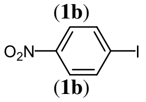
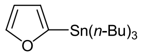
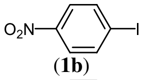
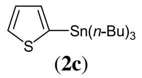
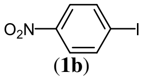
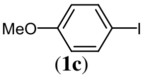
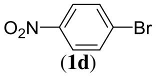
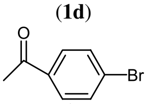
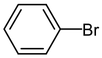
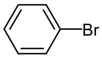
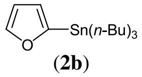
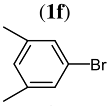
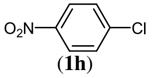
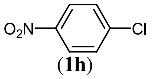
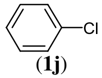
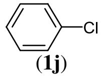
As shown in Table 3, the catalytic efficacy of $Pd(dba)_2$/DAB-Cy was further evaluated. For coupling of aryl bromides **1a** and **1d** with **2a**, respectively, satisfied yields could still be obtained after prolonged reaction time when the catalyst loading was reduced to 0.1 mol% (entries 1 and 7). 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 $Pd(dba)_2$/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 cross-coupling 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

Table 2. Palladium-catalyzed Stille coupling reaction in the presence of DAB-Cy[a]



Entry	ArX	R′Sn(*n*-Bu)$_3$	Time (h)	Yield (%)[b]
1	 (**1b**)	PhSn(*n*-Bu)$_3$ (**2a**)	16	98 (**4**)
2	 (**1b**)	 (**2b**)	16	100 (**5**)
3	 (**1b**)	 (**2c**)	16	100 (**6**)
4	 (**1b**)	$Ph-C\equiv C-Sn(n\text{-}Bu)_3$ (**2d**)	16	100 (**7**)
5	 (**1c**)	PhSn(*n*-Bu)$_3$ (**2a**)	16	100 (**3**)
6	 (**1d**)	PhSn(*n*-Bu)$_3$ (**2a**)	18	96 (**4**)
7	 (**1e**)	PhSn(*n*-Bu)$_3$ (**2a**)	23	70 (**8**)
8	 (**1f**)	PhSn(*n*-Bu)$_3$ (**2a**)	22	85 (**9**)
9	 (**1f**)	 (**2b**)	20	52 (**10**)
10	 (**1g**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	82 (**11**)
11	 (**1h**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	Trace (**4**)
12[c]	 (**1h**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	45 (**4**)
13	 (**1j**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	Trace (**9**)
14[c]	 (**1j**)	PhSn(*n*-Bu)$_3$ (**2a**)	24	22 (**9**)

[a] Under otherwise indicated, the reaction conditions were as follows: **1** (0.30 mmol), **2** (0.40 mmol), Pd(dba)$_2$ (3.0 mol%), DAB-Cy (6.0 mol%), KF (3 equiv), and dioxane (5 mL) at 100 °C under N$_2$.

[b] Isolated yield.

[c] *n*-Bu$_4$NF (3 equiv) instead of KF.

Table 3. Screening the catalytic efficiency of the palladium-catalyzed Stille coupling reaction of **1** with **2**[a]

Entry	ArX	R′Sn(*n*-Bu)$_3$	Pd (mol%)	Yield (%)[b]	TON
1	**1a**	**2a**	0.1	65 (**3**)	650
2	**1a**	**2a**	0.001	28 (**3**)	28,000
3	**1b**	**2a**	0.0001	95 (**4**)	950,000
4	**1b**	**2b**	0.001	96 (**5**)	96,000
5	**1b**	**2b**	0.0001	90 (**5**)	900,000
6	**1c**	**2a**	0.0001	90 (**3**)	900,000
7	**1d**	**2a**	0.1	73 (**8**)	730

[a] Under otherwise indicated, the reaction conditions were as follows: **1** (0.30 mmol), **2** (0.40 mmol), Pd(dba)$_2$/DAB-Cy (1:2), KF (3 equiv), and dioxane (5 mL) at 100 °C under N$_2$ for 48 h.

[b] Isolated yield.

corresponding biaryls and alkyne in good to excellent yields (maximum TONs up to 950,000 for the reaction of 1-iodo-4-nitrobenzene and phenyltributyltin). Currently, further efforts to extend the application of these ligands and this protocol in organic synthesis are underway in our laboratory.

4. Experimental

4.1. General methods

^{1}H and ^{13}C NMR spectra were recorded on an INOVA-400 (Varian) spectrometer or a Bruker AMX-300 spectrometer with $CDCl_3$ as the solvent. All reagents were directly used as obtained commercially. All the products **3–11** are known.[8–12]

4.2. Typical experimental procedure for the palladium-catalyzed Stille cross-coupling reaction

A mixture of aryl halide **1** (0.30 mmol), organotin **2** (0.40 mmol), $Pd(dba)_2$ (3.0 mol%), DAB-Cy (6 mol%), KF (3 equiv), and dioxane (5 mL) was added to a sealed tube. Then the mixture was stirred at 100 °C under N_2 for desired time until complete consumption of starting material as judged by TLC. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography (hexane or hexane/ethyl acetate) to afford **3–11**.

4.3. Typical experimental procedure for 0.0001 mol% of Pd and 0.0002 mol% of DAB-Cy-catalyzed Stille cross-coupling reaction of 1-iodo-4-nitrobenzene (1b) and phenyltributyltin (2a) (entry 3 in Table 3)

First, $Pd(dba)_2$ (4.5 mg, 0.02 mmol) was dissolved in 200 mL of dioxane, and DAB-Cy (4.5 mg, 0.04 mmol) was also dissolved in another 200 mL of dioxane. Then 3 μL of $Pd(dba)_2$ dioxane solution and 6 μL of DAB-Cy dioxane solution were added to a mixture of 1-iodo-4-nitrobenzene (**1b**) (0.30 mmol), phenyltributyltin (**2a**) (0.40 mmol), KF (3 equiv), and dioxane (5 mL) in a sealed tube (by syringe). The mixture was stirred at 100 °C under N_2 for 48 h determined by TLC. After the mixture was filtered and evaporated, the residue was purified by flash column chromatography (hexane/ethyl acetate) to afford 95% yield of **4** (TONs: 950,000).

Acknowledgements

We thank the National Natural Science Foundation of China (No. 20202002) for the financial support.

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