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Stille cross-coupling reaction using Pd/$BaSO_4$ as catalyst reservoir

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Stille cross-coupling reactions between iodobenzene and tributylphenyltin were carried out in ethanol/water solution using different amounts of Pd/$BaSO_4$ as catalyst reservoir in a ligand-free system and high yields were obtained. Other substituted biaryls were obtained with good yields. The catalyst can be reused up to three times with some loss in activity. Filtration of the catalyst and product extraction yielded a solution that kept its activity, showing the presence of Pd(0)/Pd(II) species that can be regarded as the true catalysts. Interestingly, both 2-bromotiophene and chlorobenzene yielded the desired corresponding reaction products. Copyright © 2007 John Wiley & Sons, Ltd.

Keywords: Stille reaction; Pd/$BaSO_4$; ligand-free system; biaryls

Introduction

Biaryls and their hetero analogs are important classes of organic compounds. The biaryl unit is presented in several compounds of current interest including natural products, polymers and molecules of medicinal interest. In view of the importance of biaryls, a number of catalytic methods for forming these molecules in cross-coupling reactions have been developed over the last two decades.[1–6] The palladium-catalyzed Stille cross-coupling[7–11] of aryl halides with organotin reagents is an important carbon–carbon bond forming reaction that has found wide application in natural product synthesis. The popularity associated with this reaction stems from the fact that the organostannane reagents tolerate a variety of functional groups, and are stable to both moisture and oxygen.

The search for new processes involves the use of well-known heterogeneous catalysts, such as Pd/C[12–15] and other systems.[16–18] In cross-coupling reactions, particularly in the Stille reaction, Pd/C, Pd on KF/Al_2O_3 and Pd on modified silica have been used as catalysts.[19] Pd/$CaCO_3$ (Lindlar's catalyst) which is effective as a catalyst in hydrogenation,[20–22] is rarely used in these reactions and Pd/$BaSO_4$ (Rosemund's catalyst), which is effective as a catalyst in hydrogenation,[20–22] has not been tested so far in the Stille reaction.

Recently, our group reported some studies with Pd/$CaCO_3$ as a catalyst reservoir in carbon–carbon cross-coupling.[23] Our results showed the production of the desired C–C coupling compounds with good to high yields; and we proved that the catalyst can be reused seven times without any noticeable loss of activity.

Based on the work of Beller and Kühlein, who carried out a Heck reaction involving diazonium salts and olefins using several heterogeneous catalysts, including Pd/$BaSO_4$,[24] and Genêt and co-workers, who carried out a Heck reaction involving diazonium salts and olefins using Pd/$CaCO_3$ as catalyst[25] (applied by us to the Stille reaction), we decided to investigate the use of the very insoluble Pd/$BaSO_4$ as a catalyst in the Stille reaction.

Results and Discussion

Our initial investigation started with the cross-coupling reaction of iodobenzene and tributylphenyltin as a model system (Scheme 1). The reaction was carried out in the presence of different amounts of Pd/$BaSO_4$ as catalyst, in 40% aqueous ethanolic solution at 80 °C for 24 h. Our results are summarized in Table 1.

The Stille cross-coupling reaction between iodobenzene and tributylphenyltin in an aqueous system, for 24 h, furnished high yields. High yields were obtained with 5.0 and 1.0 mol% (based on Pd) catalyst (entries 1 and 2). Decrease to 0.5 mol% resulted in a slight reduction in reaction yield (entry 3) with increasing TON. Room temperature resulted in low yield (entry 4), showing that heat is necessary for this reaction. Testing a base-free system resulted in lower (although still good) yield (entry 5), showing the need for a base to neutralize HI from the hydrolysis of the resulting Bu_3SnI from transmetallation.

To generalize our method, other aryl halides were tested using tributylphenyltin, K_2CO_3 and 1 mol% Pd/$BaSO_4$ in aqueous ethanolic solution under reflux for 24 h. The results are described in Table 2.

Coupling 4-nitroiodobenzene and tributylphenyltin using 0.5 mol% of Pd/$BaSO_4$ resulted in the desired biphenyl at 82% yield (entry 1). Increasing loading to 1.0 mol% catalyst for this reaction gave 95% yield (entry 2). Owing to this result, it was decided to use this amount of catalyst for other systems (entries 2–7). Using 4-iodoanisole (entry 3) resulted in a high yield, showing that the electron donnor group did not affect the reaction yield. The use of bromobenzene did not result in decreasing yields when compared with iodobenzene (entry 4), while chlorobenzene, a normally very

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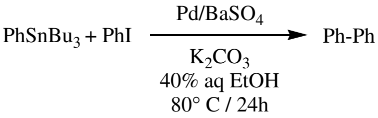
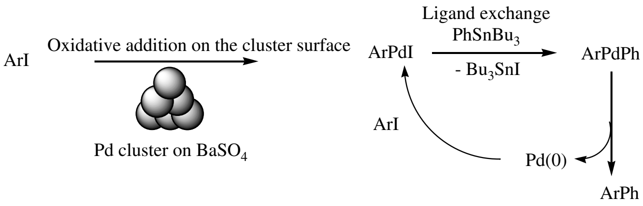


$$\mathrm{PhSnBu_3 + PhI} \xrightarrow[\substack{K_2CO_3\\ 40\%\ \mathrm{aq\ EtOH}\\ 80^\circ\ \mathrm{C}\ /\ 24\mathrm{h}}]{\mathrm{Pd/BaSO_4}} \mathrm{Ph\text{-}Ph}$$

Scheme 1. Stille reaction between iodobenzene and tributylphenyltin.



Scheme 2. The proposed mechanism.

unreactive, although abundant and low-priced feedstock, afforded moderate yield (entry 5). Using 4-bromoacetophenone (entry 6) resulted in good yield and 2-bromothiophene (entry 7) also afforded a good yield. All products were analyzed and characterized by GC-MS, ^{1}H NMR and ^{13}C NMR.

Recycling experiments were carried out as previously described.[23] Recycling the whole reaction media showed some loss in reaction yields (Table 3). Recycling of the solution was carried out by decanting the solid catalyst, and recycling the ethanol–water solution after extraction furnished a yield of 89% (Table 3), thereby showing the presence of soluble Pd(0)/Pd(II) species in solution as these catalysts. The solution was recycled once more, resulting in a 64% yield.

A dimethylglioxime test for Pd species in the ethanol–water solution after decantation and product extraction gave a positive,

Table 1. Stille reaction using catalytic Pd/BaSO$_4$ system[a]

Entry	Mol% Pd/BaSO$_4$	Yield[b] (%)	TON
1	5.0	100	20
2	1.0	100	100
3	0.5	92	200
4[c]	5.0	37	8
5[d]	5.0	63	12

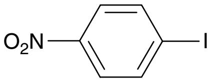
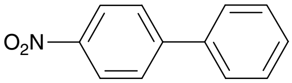
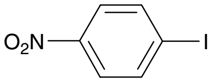
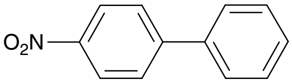
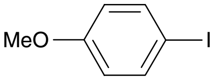
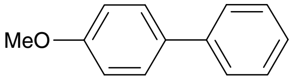
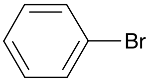
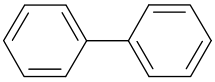
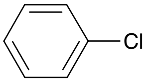
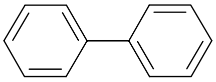
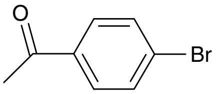
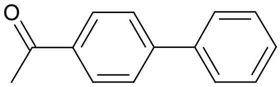
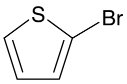
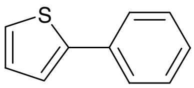
[a] 1.0 mmol PhI, 1.1 mmol PhSnBu$_3$, 2 mmol K$_2$CO$_3$, Pd/BaSO$_4$ in 30 ml 40% aq EtOH at 80 °C for 24 h.
[b] Determined by GC-MS using a external standard.
[c] Room temperature.
[d] Without base.

Table 3. Recycling of whole reaction media and recycling of solution of the Stille reaction

Entry	Run	Recycling of whole reaction media (%)[a,b]	Recycling of solution (%)[a–c]
1	First	91	89
2	Second	77	64
3	Third	63	–

[a] 1.0 mmol iodobenzene and 1.1 mmol tributylphenyltin at 80 °C for 24 h.
[b] Determined by GC-MS using external standard.
[c] Decanting the catalyst after centrifugation.

Table 2. Stille reaction between different aryl halides and tributylphenyltin[a]

Entry	Aryl halide	Product	Yield[b] (%)
1[c]			82
2			95
3			91
4			93
5			67
6			85
7			78

[a] 1.0 mmol PhI, 1.1 mmol PhSnBu$_3$, 2 mmol K$_2$CO$_3$, 1mol% Pd/BaSO$_4$ in 30 ml 40% aq EtOH at 80 °C for 24 h.
[b] Determined by GC-MS using a external standard.
[c] 0.5 mol% of Pd/BaSO$_4$.

yellow result. Atomic absorption analysis carried out in this solution showed the presence of soluble Pd species at 0.65 mg l^{-1} (0.0061 mM) concentration. The use of 30 ml of this solution in the recycling experiments and 89% reaction yield gave an impressive (TON) Turnover number - number of mol/number of catalyst of about 5000.

Quite recently Eberlin's group[26] disclosed their results on the investigation of the mechanism of the Stille reaction and detected several different intermediates, including palladium-containing phosphines, including $Pd(PPh_3)_2$ species,[27] and palladium complexes with acetonitrile. The present reaction pathway must be very similar, although it was proved in the present paper that the reaction proceeded well in the absence of phosphines (Scheme 2). Further investigation on the mechanism of this reaction in the present conditions is needed.

Conclusion

In conclusion, $Pd/BaSO_4$ proved to be a suitable catalyst for the Stille cross-coupling reaction in a ligand-free aqueous system. Substituted biaryls were obtained with good yields in this method. The catalyst was recycled up to three times with some loss in activity. Use of the ethanol–water solution after decanting the catalyst and extracting the product afforded high yields, indicating that the true catalyst was soluble Pd(II)/Pd(0) species formed upon slow oxidative addition to the insoluble catalyst and repeated eliminative reduction/oxidative addition in solution. Chlorobenzene and 2-bromothiophene were shown to be important substrates in this reaction. Other cross-coupling reactions utilizing $Pd/BaSO_4$ as catalyst are under study in our group.

Experimental

The ^1H NMR and ^{13}C NMR spectra were recorded on Bruker 200 and 50 MHz NMR spectrometers in $CDCl_3$. The mass spectra were obtained using a Shimadzu instrument GCMS-QP2010S. The reagents were obtained from commercial sources and used without purification.

General procedure for reaction of tributylphenyltin[28]

In a 200 ml reaction flask containing *n*-BuLi 1.6 M (83.6 mmol, 52 ml), the temperature was cooled to −78 °C and bromobenzene (75.96 mmol, 8 ml) was added slowly, for 15 min, under vigorous stirring. The reaction was maintained for 40 min at −78 °C under continuous stirring. During this step, the color of the reaction passed from yellowish to colorless. Later, the $SnBu_3Cl$ (1.1 mmol, 0.35 ml) was added over 15 min and the reaction left overnight. The reaction mixture was neutralized with saturated solution of $(NH_3)_2SO_4$ and the aqueous phase was extracted with hexane. The tributylphenyltin was purified by Kugelrohr distillation.

Tributylphenyltin

Colorless oil, 7.6 g (81%). ^1H NMR ($CDCl_3$, 200 MHz) δ 0.87–0.92 (t, 9 H), 1.03–1.09 (q, 6 H), 1.31–1.38 (q, 6 H), 1.50–1.61 (m, 6 H), 7.31–7.40 (m, 3 H), 7.46–7.48 (m, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 7.55, 13.8, 27.5, 29.2, 128.3, 136.6, 142.2.

General procedure for the Stille reaction

In a 25 ml reaction flask containing iodobenzene (1 mmol; 0.204 g), tributylphenyltin (1.1 mmol; 0.2 ml g), $Pd/BaSO_4$ (0.01 mmol; 0.021 g) and K_2CO_3 (2 mmol; 0.280 g) were suspended in 30 ml $EtOH/H_2O$ 40% at 80 °C for 24 h. The reaction mixture was extracted with hexane. The organic phase was washed with water, brine and 1 M KF solution, and dried over anhydrous magnesium sulfate. The solution was filtered under celite®, solvent was evaporated and crude product was analyzed by GC-MS, ^1H NMR and ^{13}C NMR.

Biphenyl

^1H NMR ($CDCl_3$, 200 MHz) δ 7.56 (d, 4 H), 7.40 (dd, 4 H), 7.29 (d, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 140.8, 128.4, 126.9, 126.8. GC-MS: 154 *m/z*, 77 *m/z*.

4-Nitro-biphenyl

^1H-RMN ($CDCl_3$, 200 MHz) δ 8.30 (d, 2 H), 7.74 (d, 2 H), 7.64 (d 2 H), 7.52–7.44 (m, 3 H). ^{13}C-NMR ($CDCl_3$, 50 MHz) δ 147.6, 147.1, 138.8, 129.2, 128.9, 127.8, 127.4, 124.1. GC-MS: 199 *m/z*, 183 *m/z*, 169 *m/z*, 152 *m/z*.

4-Methoxy-biphenyl

^1H RMN ($CDCl_3$, 200 MHz) δ 7.54 (t, 4 H), 7.42 (t, 2 H), 7.31 (t, 1 H), 6.98 (d, 2 H), 3.86 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 159.1, 140.8, 133.7, 128.7, 128.1, 126.7, 126.6, 114.2, 55.3. GC-MS: 184 *m/z*, 169 *m/z*, 141 *m/z*, 115 *m/z*.

1-Biphenyl-4-yl-ethanone

^1H RMN ($CDCl_3$, 200 MHz) δ 8.09 (d, 2 H), 7.63 (d, 2 H), 7.58 (d, 2 H), 7.40 (m, 2 H), 7.37 (m, 1 H), 2.63 (s, 3 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 197.7, 145.7, 139.8, 135.9, 128.9, 128.1, 127.3, 26.2. GC-MS: 196 *m/z*, 181 *m/z*, 153 *m/z*, 77 *m/z*.

2-Phenylthiophene

^1H RMN ($CDCl_3$, 200 MHz) δ 7.61 (d, 1 H), 7.37–7.16 (m, 5 H), 7.02–6.99 (m, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 128.9, 127.9, 127.9, 127.4, 125.9, 124.8, 123.0, 29.7. GC-MS: 160 *m/z*, 82 *m/z*, 77 *m/z*.

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