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Ligand-free Stille cross-coupling reaction using Pd/CaCO₃ as catalyst reservoir

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Abstract—Stille reactions between halobenzenes and other substituted (hetero)arenes and tributylphenyltin were carried out in ethanol–water solution using Pd/CaCO₃ as catalyst in a ligand-free system. The catalyst could be recycled three times without any loss of activity. The ethanol–water solution, after removal of the catalyst and extraction of the product, was found to have catalytic activity, thus showing the presence of soluble Pd(0)/Pd(II) species that can be regarded as the true catalysts.
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In recent years there has been much focus and emphasis on the Stille reaction, the palladium catalyzed coupling of organotin compounds with haloarenes, for the construction of new carbon–carbon bonds.[1] Biaryls and their hetero analogs are an important class of organic compounds. The biaryl unit is present 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 from two monoaryl precursors in cross-coupling reactions have been developed over the last two decades.[2]

Our search for new processes involves the use of well-known heterogeneous catalysts, such as Pd/C[3] and other systems.[4] In cross-coupling reactions, particularly in the Stille reaction, Pd/C, Pd on KF/Al₂O₃, and Pd on modified silica have been used as catalysts.[5] Pd/CaCO₃ (Lindlar's catalyst), which is effective as a hydrogenation catalyst[6] has been rarely used in these reactions.

Recently, our group reported a study with Pd/CaCO₃ as a reservoir for the Miyaura–Suzuki cross-coupling reaction.[7] Our results showed that the production of biaryls in high yields and the catalyst could be reused up to

seven times without any noticeable loss of activity. Our results combined with the pioneering work of Genêt and co-workers,[8] who studied a Heck reaction involving diazonium salts and olefins using Pd/CaCO₃ as catalyst, indicated that this very insoluble catalyst could be of general interest.

In addition, the replacement of expensive, toxic, and flammable organic solvents by water or aqueous systems is highly desirable for reducing costs and for developing environmentally benign synthetic reactions that facilitate catalyst recycling.[9] Various previous examples of aqueous carbon–carbon bond formations including Suzuki,[10] Sonogashira,[11] Heck[12], and Stille[13] reactions have been reported. In our search for developing new processes for cross-coupling reactions,[14] this present Letter reports our results concerning the use of Pd/CaCO₃ as a catalyst in the Stille cross-coupling reaction for a ligand-free aqueous system.

Our initial investigation started with the cross-coupling reaction of iodobenzene and tributylphenyltin[15] as a model system (Scheme 1). The reaction was carried
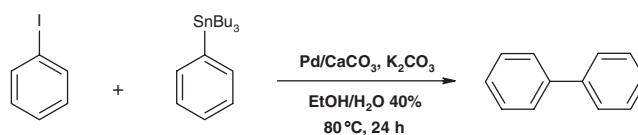
Scheme 1. Stille reaction between iodobenzene and tributylphenyltin.

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Table 1. Stille reaction using catalytic Pd/CaCO$_3$ system[a]

Entry	Pd/CaCO$_3$ (mol %)	Yield[b] (%)
1	5	100
2	1	99
3	0.5	93
4[c]	5	33

[a] 1.0 mmol iodobenzene, 1.1 mmol tributylphenyltin, 2 mmol K$_2$CO$_3$, Pd/CaCO$_3$ in 30 mL of 40% EtOH/H$_2$O at 80 °C for 24 h.
[b] Determined by GC–MS using an external standard.
[c] Room temperature.

out in the presence of different amounts of Pd/CaCO$_3$ as a catalyst reservoir, in a ligand-free system, in 40% aqueous ethanol at 80 °C for 24 h. Our results are summarized in Table 1.

The Stille reaction between iodobenzene and tributylphenyltin furnished high yields of biphenyl with very low loadings of Pd/CaCO$_3$ (Table 1). High yields were obtained with 5 and 1 mol % of catalyst (entries 1 and 2). Reduction of the catalyst loading to 0.5 mol % resulted in a small reduction of the yield (entry 3). The Stille reaction was also carried out using 5 mol % Pd/CaCO$_3$ at room temperature but the result was not satisfactory (entry 4), showing that heating is necessary. Due to the very low solubility of CaCO$_3$ the addition of K$_2$CO$_3$ to the reaction medium is also required. To generalize our method, other aryl halides were tested using tributylphenyltin, K$_2$CO$_3$ and 1 mol % Pd/CaCO$_3$ in aqueous ethanolic solution under reflux for 24 h.[16] The results are described in Table 2.

We initially studied the coupling between 4-nitro-iodobenzene and tributylphenyltin using 0.5 mol % of Pd/CaCO$_3$ that furnished the expected product in 75% yield (entry 1). Increasing the loading to 1 mol % of catalyst for this reaction gave 93% yield (entry 2). Due to this result the same catalyst loading was used in the other reactions (entries 2–7). Using 4-iodoanisole (entry 3) resulted in a lower yield due to the electron donating group effect. The use of bromobenzene did not result in a decreased yield when compared to iodobenzene (entry 4), while chlorobenzene, a normally very unreactive, although abundant and low priced feedstock, afforded a satisfactory yield (entry 5). The 4-bromoaceto-

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

Entry	Halide	Product	Yield[b] (%)
1[c]	4-IC$_6$H$_4$NO2	4-O$_2$NC$_6$H$_4$C$_6$H$_5$	75
2	4-IC$_6$H$_4$NO2	4-O$_2$NC$_6$H$_4$C$_6$H$_5$	93
3	4-IC$_6$H$_4$OMe	4-MeOC$_6$H$_4$C$_6$H$_5$	81
4	BrC$_6$H$_5$	Biphenyl	98
5	ClC$_6$H$_5$	Biphenyl	60
6	4-BrC$_6$H$_4$COCH$_3$	4-CH$_3$COC$_6$H$_4$C$_6$H$_5$	66
7[d]	2-Bromopyridine	2,2′-Bipyridyl	92

[a] 1.0 mmol aryl halide, 1.1 mmol tributylphenyltin, 2 mmol K$_2$CO$_3$ and 1 mol % Pd/CaCO$_3$ in 30 mL of 40% EtOH/H$_2$O.
[b] Determined by GC–MS using external standard.
[c] 0.5 mol % Pd/CaCO$_3$.
[d] Homocoupling product.

phenone (entry 6) gave a surprisingly moderate yield and 2-bromopyridine (entry 7) furnished only the homocoupled product. As 1 mmol of reagents were used and 0.01 mmol of Pd, then TONs between 60 and 98 were obtained. All compounds were characterized and analyzed by GC–MS, ^{1}H NMR, and ^{13}C NMR.[17]

Recycling experiments were carried out as previously described.[7] The whole reaction medium was recycled after extraction of the product. Three cycles were possible with no effect upon the yield (Table 3). To witness the role of Pd/CaCO$_3$ as a catalyst reservoir, revealing that leaching occurred to give rise to the true catalytic species, the solid catalyst source was separated from solution by centrifugation (5000 rpm) and decantation of the solution after extraction of the reaction products. This solution could be reused twice giving yields of 94% each time. Thus confirming the presence of soluble Pd(0)/Pd(II) species in solution (also detected via dimethylglyoxime yellow testing) as the true catalysts.

Mechanistically (Scheme 2), an active intermediate is formed upon very slow oxidative addition of ArI to the Pd(0), nanoparticles, on the support surface. This addition would result in the intermediate ArPdI, which after ligand exchange would form ArPdAr and then the final product, Ar–Ar, and a very active 'mononuclear' Pd(0) species that would react faster with ArI thus resulting in a homogeneous catalytic cycle. Thus, Pd/CaCO$_3$ is really acting as a source of soluble Pd(0)/Pd(II) species.

Table 3. Recycle of the Stille reaction

Run	Yield[a,b] (%)
1st	94
2nd	98
3rd	98

[a] 1.0 mmol iodobenzene and 1.1 mmol tributylphenyltin at 80 °C for 24 h.
[b] Determined by GC–MS using external standard.
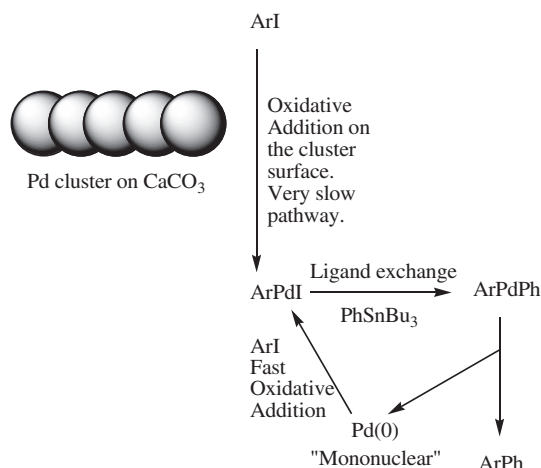
Scheme 2. Mechanism of the Stille reaction using Pd/CaCO$_3$ as a catalyst source.

The concentration of Pd(0)/Pd(II) species was determined via atomic absorption and a level of 1.1 mg L^{-1} (0.010 mM solution) Pd was found, that is, only 0.17% Pd(II) was leached from the Pd source.

Considering the use of 30 mL of this solution and 94% yield on solution recycling experiments an expressive TON of about 3000 can be calculated. This result is in agreement with our and other groups findings on the fact that Pd species leached from the nanoparticles, in our case from surface, are the true catalysts.[7,18,19] The concentration of Pd found is compatible to the results of De Vries[19] group who entitled such catalytic effect as homeopathic.

In conclusion, Pd/CaCO$_3$ proved to be a suitable catalyst source for Stille cross-coupling reactions in a ligand-free aqueous system. Substituted biaryls were obtained with good yields in this method. Chlorobenzene was found to be a convenient substrate. The catalyst could be recycled up to three times without any noticeable loss of activity. Use of the ethanol–water solution after decantation of the catalyst and product extraction, afforded high yields of product indicating that the true catalyst was a soluble species that was formed upon slow oxidative addition to the insoluble catalyst and repeated reductive elimination/oxidative addition in homogeneous solution. The present phosphine-free system can be regarded as of industrial interest.

Acknowledgments

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15. *General procedure for the production of tributylphenyltin:* In a 200 mL reaction flask containing 52 mL of *n*-BuLi 1.6 M (84 mmol) −78 °C, it was added bromobenzene (76 mmol; 8 mL) for 15 min, under vigorous stirring. The reaction was maintained for 40 min at −78 °C under continuous stirring, while the color of the reaction passed from yellowish to colorless. After that period, SnBuCl$_3$ (1.1 mmol; 0.35 mL) was added for 15 min and the reaction was left under stirring overnight. The reactional mixture was neutralized with saturated solution of (NH$_3$)$_2$SO$_4$ and the aqueous phase was extracted with hexane. The tributylphenyltin was purified by Kugelrohr distillation under reduced pressure. *Tributylphenyltin—* colorless oil, 7.6 g (81%). ^{1}H NMR (CDCl3, 200 MHz) δ 0.87–0.92 (t, 9H), 1.03–1.09 (q, 6H), 1.31–1.38 (q, 6H), 1.50–1.61 (m, 6H), 7.31–7.40 (m, 3H), 7.46–7.48 (m, 2H). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 7.55, 13.8, 27.5, 29.2, 128.3, 136.6, 142.2.

16. *General procedure for Stille reaction*: In a 25 mL reaction flask containing iodobenzene (1 mmol; 0.204 g) in 30 mL of EtOH/H$_2$O 40%, tributylphenyltin (1.1 mmol; 0.2 mL), Pd/CaCO$_3$ (0.01 mmol; 0.021 g) and K$_2$CO$_3$ (2 mmol; 0.280 g) were successively added. The reaction was then kept under stirring at 80 °C for 24 h. The reactional mixture was extracted with hexane. The organic phase was washed with water, brine and 1 M KF solution, and dried over anhydrous magnesium sulfate. Solution was filtered under Celite®, the solvent was evaporated and crude product was analyzed by GC–MS, ^{1}H NMR and ^{13}C NMR. *Biphenyl*—^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.56 (d, 2H), 7.40 (d, 2H), 7.29 (d, 2H). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 140.8, 128.4, 126.9, 126.8. GC–MS: *m/z* 154, 77.

17. *4-Nitro-biphenyl*—^{1}H NMR (CDCl$_3$, 200 MHz) δ 8.30 (d, 2H), 7.74 (d, 2H), 7.64 (d 2H), 7.52–7.44 (m, 3H). ^{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: *m/z* 199, 183, 169, 152. *4-Methoxy-biphenyl*—^{1}H NMR (CDCl$_3$, 200 MHz) δ 7.54 (t, 4H), 7.42 (t, 2H), 7.31 (t, 1H), 6.98 (d, 2H), 3.86 (s, 3H). ^{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: *m/z* 184, 169, 141, 115. *1-Biphenyl-4-yl-ethanone*—^{1}H NMR (CDCl$_3$, 200 MHz) δ 8.09 (d, 2H), 7.63 (d, 2H), 7.58 (d, 2H), 7.40 (m, 2H), 7.37 (m, 1H), 2.63 (s, 3H). ^{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: *m/z* 196, 181, 153, 77. *2,2'-Bipyridyl*—^{1}H NMR (CDCl$_3$, 200 MHz) δ 8.69 (m, 1H), 8.0 (m, 2H), 7.73 (m, 2H), 7.49 (m, 2H), 7.42 (m, 1H), 7.22 (m, 1H). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 157.3, 149.6, 139.3, 136.6, 128.8, 128.7, 126.8, 122.0, 120.4. GC–MS: *m/z* 156, 127, 78.

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