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Tetrahedron Letters 44 (2003) 7537–7540

TETRAHEDRON LETTERS

Selective catch and release of a synthetically useful phosphine ligand

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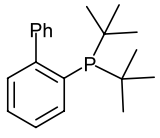
Received 19 June 2003; revised 30 July 2003; accepted 31 July 2003

Abstract—The selective catch and release of the synthetically useful (*o*-biphenyl)(*t*-butyl)$_2$P from basic and non basic compounds, utilizing solid phase supported sulfonic acid sources is demonstrated.

The synthetic versatility of sterically hindered alkyl phosphine ligands in palladium-catalyzed reactions has been the focus of several recent publications.[1] Chromatography has been used to isolate the products and recycle the costly phosphine ligand, thus making these reactions impractical for a solution phase parallel synthesis protocol. Upon performing catch and release purification on synthesis products containing basic functionality, it was observed that (*o*-biphenyl)(*t*-butyl)$_2$P ligand **1** in the reaction mixture was also effectively scavenged by the polystyrene bound sulfonic acid. It occurred to us that selective catch and release of phosphine **1** from the synthesis products would offer a convenient method for parallel purifications as well as a means of ligand recycling. Herein, we describe the selective catch and release of the (*o*-biphenyl)(*t*-butyl)$_2$P ligand **1** from other compounds and synthesis products.



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Reaction solvent can be an important component in palladium-catalyzed reaction optimization, therefore, a systematic study of solvent compatibility was undertaken to assess the usefulness of this catch and release methodology with solvents commonly used for such reactions. Phosphine **1** was effectively scavenged using 2% cross-linked polystyrene bound sulfonic acid,[2] or Silicycle® sulfonic acid functionalized silica gel in a variety of solvents (Table 1). All of these experiments were performed open to air. Phosphine **1** was completely scavenged with a minimum of 2.0 equiv. of silica supported sulfonic acid, while only 1.6 equiv. was needed for complete capture with polystyrene bound sulfonic acid (Table 1, entries 1 and 3). Similar conditions failed to capture triphenylphosphine (Table 1, entries 2 and 4). These results can be understood in terms of the greater basicity of **1** compared to triphenylphosphine.[3] While phosphine **1** was completely captured on polystyrene bound sulfonic acid resin when methanol or DME was used as the solvent (Table 1, entries 3 and 5), incomplete capture was observed in THF, DCM and DMF (Table 1, entries 9–11), and no apparent capture was observed when ethyl acetate, dioxane, or diethyl ether was used as solvent (Table 1, entries 6–8). These results are probably best explained by the increased ability of methanol and DME to swell the highly polar resin. Although phosphine **1** showed only partial capture on silica based solid support sulfonic acid when DMF was used as solvent (Table 1, entry 18), complete capture was achieved with DME, ethyl acetate, dioxane, diethyl ether, THF, and DCM (Table 1, entries 12–17). Therefore, the Silicycle® sulfonic acid functionalized silica is a versatile solid support for catch and release of phosphine **1** due to its extensive solvent compatibility.

The selective capture of compounds with a broad variety of basic functionality and phosphine **1** was

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doi:10.1016/j.tetlet.2003.07.004

Table 1. Solvent effects on scavenging of phosphines with solid phase supported sulfonic acid

Entry	Phosphine	Solvent	Sulfonic acid support	Sulfonic acid (equiv.)	Phosphine scavenged[a]
1	**1**	MeOH	Silica	2.0[b]	Yes
2	Ph_3P	MeOH	Silica	2.5	No
3	**1**	MeOH	Polystyrene	1.6[b]	Yes
4	Ph_3P	MeOH	Polystyrene	2.5	No
5	**1**	DME	Polystyrene	3.0	Yes
6	**1**	EtOAc	Polystyrene	3.0	No
7	**1**	Dioxane	Polystyrene	3.0	No
8	**1**	Ether	Polystyrene	3.0	No
9	**1**	THF	Polystyrene	3.0	60%[c]
10	**1**	DCM	Polystyrene	3.0	80%[c]
11	**1**	DMF	Polystyrene	3.0	80%[c]
12	**1**	DME	Silica	3.0	Yes
13	**1**	EtOAc	Silica	3.0	Yes
14	**1**	Dioxane	Silica	3.0	Yes
15	**1**	Ether	Silica	3.0	Yes
16	**1**	THF	Silica	3.0	Yes
17	**1**	DCM	Silica	3.0	Yes
18	**1**	DMF	Silica	3.0	40%[c]

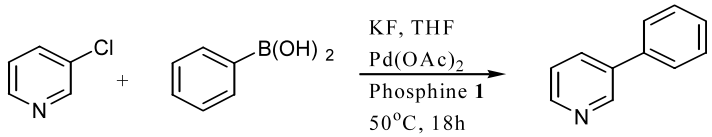
[a] The phosphine solution (0.1 M) was agitated with sulfonic acid resin for 15 min, the mixture was filtered, and the resin was washed with the same solvent. The combined filtrate and wash was analysed by LC-MS. 'Yes' denotes complete capture (<2% remaining) by LC-MS as compared to biphenyl internal standard, 'No' denotes no noticeable change in compound peak compared to biphenyl internal UV standard.
[b] Experimentally determined effective minimum equiv. of solid phase supported sulfonic acid for complete capture.
[c] Approximate percentage of phosphine scavenged relative to a biphenyl internal UV standard as determined by LC-MS.

achieved with 3 equiv. of either polystyrene or silica supported sulfonic acid in methanol (Table 2). The two supports gave identical results in these examples. Complete capture was achieved for amines **2**, **3**, and **4** while leaving phosphine **1** in solution (Table 2, entries 1–3). Subsequent release of compounds **2**, **3**, and **4** with 2.0 M methanolic ammonia resulted in 83, 74, and 78% recovery, respectively, with no detectable contamination of phosphine **1** (Table 2, entries 1–3). Three equiv. of solid supported sulfonic acid failed to capture diarylamine **5**, however, phosphine **1** was preferentially scavenged from the mixture (Table 2, entry 4). Treatment of the sulfonic acid support with 2.0 M methanolic ammonia recovered phosphine **1** without detection of diarylamine **5** (Table 2, entry 4). Three equiv. of solid supported sulfonic acid affected the partial capture of aniline **6** and pyrazole **7** along with partial capture of phosphine **1** (Table 2, entries 5 and 6). This result prompted us to increase the amount of sulfonic acid and investigate conditions for selective release.

Six equiv. of solid supported sulfonic acid in methanol was sufficient to effect the complete capture of compounds **2**, **3**, **4**, **6**, and **7** as well as phosphine **1**, while compound **5** remained in solution. No difference was observed between silica and polystyrene sulfonic acid source in all instances. Selective release of phosphine **1** from amines **2**, **3**, and **4**, was achieved with 30% pyridine in methanol, with each resulting phosphine solution containing no detectable amount of amines **2**, **3**, or **4** (Table 3, entries 1–3). Subsequent treatment of the solid support with 2.0 M methanolic ammonia liberated amines **2**, **3**, and **4** with no detectable phosphine contaminant (Table 3, entries 1–3). Aniline **6** and pyrazole **7** were selectively released from the solid support with 5% pyridine in methanol and were uncontaminated with phosphine **1** (Table 3, entries 5 and 6). Complete release of phosphine **1** was then achieved with 2.0 M methanolic ammonia, and compounds **6** and **7** were not detectable in the phosphine solution.

A Suzuki[4] reaction between a 3-chloropyridine and phenylboronic acid was performed to highlight the utility of this catch and release methodology in a common cross-coupling reaction (Eq. (1)). In such a reaction, the desired product would typically be isolated by aqueous work-up and chromatography. Instead,

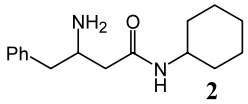
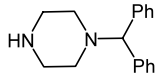
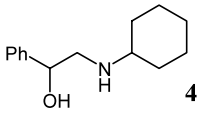
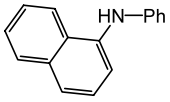
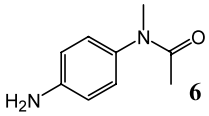
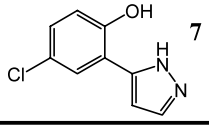
Suzuki Cross-Coupling Reaction



(1)

Reaction conditions: See footnote 5.

Table 2. Selective capture with 3 equiv. of solid supported sulfonic acid[a]

Entry	Basic Compound[b]	Capture of Compound[c]	Capture of Phosphine 1[c]	% Recovery[d]
1	 **2**	Yes	No	83%
2	 **3**	Yes	No	74%
3	 **4**	Yes	No	78%
4	 **5**	No	Yes	98%
5	 **6**	Partial	Partial	nd
6	 **7**	Partial	Partial	nd

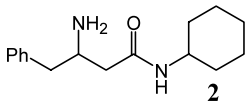
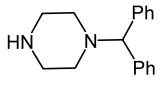
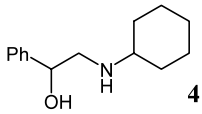
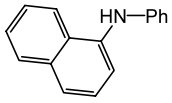
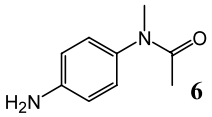
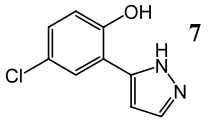
[a]All experiments were performed with a 0.1:1:3 molar ratio of phosphine, amine, and polymer-supported sulfonic acid in methanol, with biphenyl as an internal standard. After agitating for 15 minutes the mixture was filtered, the resin was washed with methanol, and the combined filtrate and wash was analysed by LC-MS. The resin was then treated with excess 2 M methanolic ammonia. Silica and polystyrene sulfonic acid resin gave identical results in all instances. [b]Compounds **2** to **7** are commercially available. [c]'Yes' denotes complete capture or undetectable by LC-MS as compared to biphenyl standard, 'No' denotes no noticeable change in compound peak compared to biphenyl standard, and 'Partial' denotes incomplete capture of basic compound and phosphine **1**. [d]Isolated mass to mass recovery of basic compound, 'nd' denotes recovery not determined.

upon reaction completion, the addition of a 6-fold excess of Silicycle® sulfonic acid functionalized silica gel to the reaction mixture effectively captured both the desired product and phosphine **1**. The choice of the sulfonic acid functionalized silica gel was due to the fact that the reaction was performed in THF. After filtration, treatment of the solid support with 5% pyridine in methanol was sufficient to cleave the desired product which was obtained in 88% yield with no phosphine impurity. Subsequent treatment of the solid support with 2.0 M methanolic ammonia liberated phosphine **1** with 71% recovery. The entire reaction workup procedure was performed open to air, as the phosphine ligand is fairly resistant to air oxidation.

This procedure[5] proved to be a convenient method for the isolation of the desired product from the reaction mixture, as well as for the recovery of the ligand for future use.

In summary, we have demonstrated the effectiveness of using 2% cross-linked polystyrene sulfonic acid resin and Silicycle® sulfonic acid functionalized silica gel in the separate catch and selective release of (*o*-biphenyl)(*t*-butyl)$_2$P from various basic and non basic compounds. In addition, we have demonstrated the usefulness of this catch and release methodology in a cross-coupling reaction in which the product and the phosphine may be captured and each selectively liberated. This novel catch and release methodology is a potentially powerful procedure for purifications of palladium catalyzed reactions in addition to a convenient alternative to conventional ligand recycling techniques. Investigations to expand the scope of this methodology will be reported in due course.

Table 3. Selective catch and release with 6 equiv. of solid supported sulfonic acid[a]

Entry	Basic Compound[b]	Release of Compound	Release of Phosphine
1	 **2**	2.0 M NH_3	30% Pyridine
2	 **3**	2.0 M NH_3	30% Pyridine
3	 **4**	2.0 M NH_3	30% Pyridine
4	 **5**	n/a	2.0 M NH_3
5	 **6**	5% Pyridine	2.0 M NH_3
6	 **7**	5% Pyridine	2.0 M NH_3

[a] The experimental method is similar to that described in footnote a of Table 2 except that twice the amount of supported sulfonic acid is used and the 2 M methanolic ammonia treatment is preceded by a similar methanolic pyridine treatment. No difference was observed between silica and polystyrene sulfonic acid source in all instances. [b]Compounds **2** to **7** are commercially available.

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2. Bio-Rad AG® 50W-X2 200–400 mesh hydrogen form resin was washed with methanol and dried under vacuum at room temperature prior to use.
3. The absorption of **1** onto sulfonic acid resins presumably results from proton transfer from the sulfonic acid group to the basic phosphorus atom, followed by ion pairing of the phosphonium ion with the polymer-supported sulfonate group. In acetonitrile, the basicity of tri(*t*-butyl)phosphine is similar to that of morpholine, while that of triphenylphosphine is roughly similar to that of 4-(trifluoromethyl)aniline. Abdur-Rashid, K.; Fong, T. P.; Greaves, B.; Gusev, D. G.; Hinman, J. G.; Landau, S. E.; Lough, A. J.; Morris, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 9155–9171.
4. (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457; (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147.
5. A mixture of 4.5 mg (0.02 mmol) $Pd(OAc)_2$, 12 mg (0.04 mmol) of 2-(di-*t*-butylphosphino)biphenyl, 73 mg (0.6 mmol) of phenylboronic acid, and 70 mg (1.2 mmol) of KF in 2 mL of THF under nitrogen was treated with 45 uL (0.4 mmol) of 3-chloropyridine. The mixture was agitated for 14 h at 25°C and then it was filtered through a 13 mm PTFE syringe filter into an 8 mL vial. The solution was diluted with 5 mL of THF and then it was treated with 3.1 g (2.38 mmol) of Silicycle® sulfonic acid resin. The mixture was agitated for 1 h, filtered, and the resin was washed with 2 mL of methanol. The resin was treated with 7 mL of 5% methanolic pyridine (3.2 mmol) and the mixture was agitated for 10 min. The mixture was filtered and the resin was washed with 5 mL of 5% methanolic pyridine. Evaporation of the solvent gave an 88% yield of the known compound 3-phenylpyridine having >95% purity (LC-MS). Subsequent treatment of the resin with 2 M methanolic ammonia led to recovery of the ligand in 71% yield and >95% purity.