Magnetic Nanoparticles as an Orthogonal Support of Polymer Resins: Applications to Solid-Phase Suzuki Cross-Coupling Reactions

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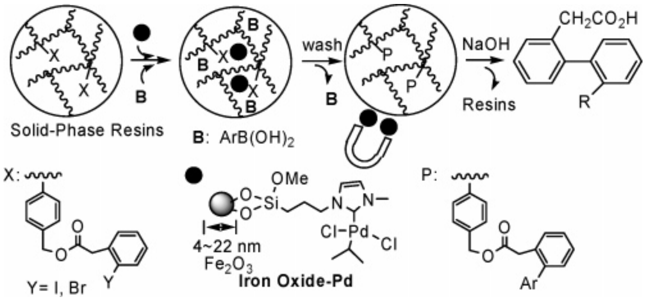

Most of the reactants immobilized on conventional solid-phase resins are buried inside the interiors of lightly cross-linked polystyrene beads. An orthogonal support of solid-phase resins needs to be small enough to penetrate the interpolymeric chain spaces of a swollen resin to reach reaction sites. In this paper, we report the use of magnetic nanoparticles (∼4 nm) as an orthogonal matrix to assist solid-phase reactions. A magnetic nanoparticle-supported homogeneous Pd catalyst was employed for promoting the Suzuki cross-coupling of an aryl halide on resins and an excessive arylboronic acid in solution. The workup separating three components (the catalyst, product, and remaining arylborate) is a chromatography-free process. The Pd catalyst was magnetically isolated and recycled from the reaction mixture by applying an external magnetic field. Then, a filtration process was followed to recover the excess borate reagent from the resins/product. Our work here presents the first example of an orthogonal matrix of solid-phase resins and shows the promise of employing nanomaterials in organic synthesis.

Introduction

Starting with the pioneer work of Merrifield,[1] solid-phase resins such as lightly cross-linked polystyrene have been implemented in a wide range of organic synthetic methodologies. During recent years, especially following the rapid development of combinatorial chemistry, the use of polymeric supports in organic synthesis has moved beyond the traditionally automated synthesis of biopolymers (e.g., peptide, DNA, and RNA)[2] and become common practice in constructing small organic molecules.[3] Together with high-throughput screening formats and efficient data management, solid-phase organic synthesis has been utilized as a synthetic method of choice in the combinatorial discovery of new materials, catalysts, and drug candidates in many research laboratories worldwide. The increasing importance of solid-phase organic synthesis is partially due to polymer supports allowing rapid product purification and the ability to drive a given reaction to completion through the use of an excess of reagents in solution.[4,5] During workup, a simple filtration process can be employed to separate the product on resins from the filtration

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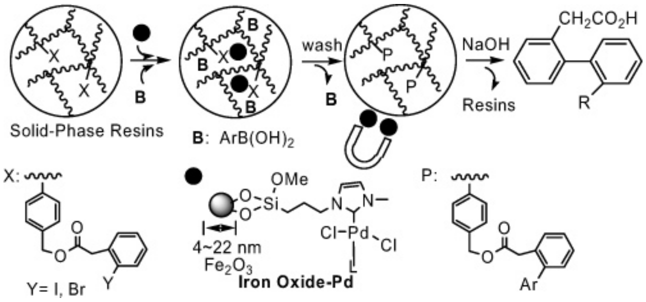
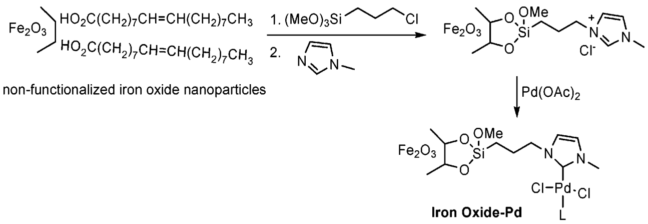
10.1021/jo051861z CCC: $33.50

SCHEME 1. Schematic Representation of Magnetic Nanoparticle Facilitated Solid-Phase Suzuki Cross-Coupling Reactions



SCHEME 2. Immobilization of Pd-NHC Complexes onto the Surface of Iron Oxide Nanoparticles



mixture. This will circumvent time-consuming and laborious purification steps and allow solid-phase organic synthesis amenable to automation.

However, despite tremendous progress on solid-phase organic synthesis, to the best of our knowledge, no orthogonal supports assisting solid-phase reactions have yet been reported. The design of matrixes orthogonal to solid-phase resins still remains a scientifically intriguing challenge. This is partially because most (>99%) of the sites of attachment of solid-phase resins are not on the surface of a bead, but are actually buried inside the interiors of the polymeric resins instead.[6] A chemical reagent and its carrier (orthogonal support) need to penetrate the interpolymeric chain spaces of a bead swollen in an organic medium to react. As a consequence, the pore-like structures and topography of a swollen solid-phase bead present three-dimensional steric restrictions to incoming orthogonal matrixes.[6]

In this paper, we would like to report the use of magnetic nanoparticles (~4 nm) as the first example of an orthogonal support of the solid-phase resins (Scheme 1). In our study, the Pd catalyst was immobilized on the surface of magnetic nanoparticles[7] for catalyzing the solid-phase Suzuki cross-coupling of an aryl halogen on resins and an arylboronic acid in the solvent phase.[8,9] Due to their small dimensions (~4 nm), magnetic nanoparticles can penetrate the pores of resins and bring the attached catalytic groups to close proximity of the immobilized reagents buried inside the beads; and because of the maghemite (γ-Fe_2O_3) core magnetism, nanoparticles with their immobilized Pd catalyst can be magnetically separated from resins via applying an external magnetic field after reaction.[10]

Results and Discussion

The maghemite nanoparticle-supported Pd catalyst **Iron Oxide-Pd**, used for promoting solid-phase Suzuki reactions (Scheme 1), was synthesized via multiple steps from nonfunctionalized 4 nm iron oxide nanocrystals (Scheme 2).[11a] Organic silane groups were utilized for immobilization of Pd-NHC complexes to the surface of maghemite nanoparticles because silanes were known to have a large affinity for under-coordinated surface sites of metal oxide particles.[12] Elemental analysis determined the Pd loading capacity of **Iron Oxide-Pd** (4 nm) to be about 0.29 mmol/g. Aryl halogens were also immobilized onto the 1% divinylbenzene-cross-linked polystyrene resins (Acros Organics, 200−400 mesh). The loading capacity of the resins was found to be 0.87 mmol/g via elemental analysis. A typical Suzuki cross-coupling reaction involved an aryl halogen (1 mmol) on resins (1.22 g), an arylboronic acid (2 mmol), and

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[4] For selected reviews on solid-phase resins see: (a) Vaino, A. R.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 579. (b) Sherrington, D. C. *Chem. Commun.* **1998**, 2275. (c) Svec, F.; Fréchet, J. M. J. *Science* **1996**, *276*, 782. (d) Bergbreiter, D. E. *Med. Res. Rev.* **1999**, *19*, 439.

[5] For selected recent reviews on solid-phase supported catalysis see: (a) Leadbeater, N. E.; Marco, M. *Chem. Rev.* **2002**, *102*, 3217. (b) McNamara, C. A.; Dixon, M. J.; Bradley, M. *Chem. Rev.* **2002**, *102*, 3275. (c) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325. (d) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3275. (e) Song, C. E.; Lee, S.-g. *Chem. Rev.* **2002**, *102*, 3495. (f) Wight, A. P.; Davis, M. E. *Chem. Rev.* **2002**, *102*, 3589. (g) Bräse, S.; Kirchhoff, J. H.; Köbberling, J. *Tetrahedron* **2003**, *59*, 885.

[6] Numerous studies have been carried out using various techniques such as NMR, IR, fluorescence, Raman, and EPR for studying the resin structures. For some recent publications see: (a) Marchetto, R.; Cilli, E. M.; Jubilut, G. N.; Schreier, S.; Nakaie, C. R. *J. Org. Chem.* **2005**, *70*, 4561. (b) Gambs, C.; Dickerson, T. J.; Mahajan, S.; Pasternack, L. B.; Janda, K. *J. Org. Chem.* **2003**, *68*, 3673. (c) Warrass, R.; Wieruszeski, M.; Bouitillon, C.; Lippens, G. *J. Am. Chem. Soc.* **2000**, *122*, 1789. (d) Zhao, T. J.; Beckham, H. W.; Gibson, H. W. *Macromolecules* **2003**, *13*, 4833. (e) Kress, J.; Zanaletti, R.; Rose, A.; Frey, J. G.; Brockesby, W. S.; Ladlow, M.; Bradley, M. *J. Comb. Chem.* **2003**, *5*, 28. (f) McAlpine, S. R.; Schreiber, S. L. *Chem. Eur. J.* **1999**, *5*, 3528.

[7] Magnetic nanoparticles have been used as a novel matrix for supporting catalysts: (a) Stevens, P. D.; Fan, J.; Gardimalla, H. M. R.; Yen, M.; Gao, Y. *Org. Lett.* **2005**, *7*, 2085. (b) Yoon, T.-J.; Lee, W.; Oh, Y.-S.; Lee, J.-K. *New J. Chem.* **2003**, *27*, 227.

[8] For selected publications on Pd-mediated cross-coupling reactions see: (a) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437. (b) Zapf, A.; Ehrentraut, A.; Beller, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 4153. (c) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 3387. (e) Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290. (f) Miura, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2201. (g) Lebel, H.; Janes, M. K.; Charette, A. B.; Nolan, S. P. *J. Am. Chem. Soc.* **2004**, *126*, 5046. (h) Altenhoff, G.; Goddard, R.; Lehmann, C.; Glorius, F. *J. Am. Chem. Soc.* **2004**, *126*, 15196. (i) Batey, R. A.; Shen, M.; Lough, A. J. *Org. Lett.* **2002**, *4*, 1411. (j) Hadei, N.; Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Org. Lett.* **2005**, *7*, 1991.

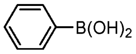
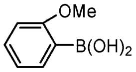
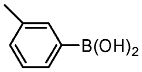
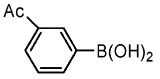
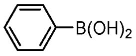
[9] Recent examples of supported Pd catalysts for cross-coupling reactions include: (a) Byun, J.-W.; Lee, Y.-S. *Tetrahedron Lett.* **2004**, 1837. (b) Berteina, S.; Wendeborn, S.; Brill, W. K.-D.; De Mesmaeker, A. *Synlett* **1998**, *6*, 676. (c) Wang, Y.; Sauer, D. R. *Org. Lett.* **2004**, *6*, 2793. (d) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *Org. Lett.* **2002**, *4*, 3371. (e) Zhang, T. Y.; Allen, M. J. *Tetrahedron Lett.* **1999**, *40*, 5813. (f) Yamada, Y. M. A.; Takeda, K.; Takahashi, H.; Ikegami, S. *J. Org. Chem.* **2003**, *68*, 7733.

[10] Usually about 83% of **Iron Oxide-Pd** (based on the weights) could be separated from resins via a magnetic concentration step. However, repeated magnetic separation steps were needed to ensure complete removal of **Iron Oxide-Pd** out of resins. A picture of magnetic concentration using a permanent magnet is included in the Supporting Information. During magnetic separation, the mixture was then vigorously shaken followed by applying an external permanent magnet. **Iron Oxide-Pd** was accumulated on the sidewall of a cuvette. Excessive borate and suspended resins in solution were transferred out of the cuvette by using a pipet.

[11] (a) Hyeon, T.; Lee, S. S.; Park, J.; Chung, Y.; Na, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 12798. (b) Park, J.; An, K.; Hwang, Y.; Park, J.-G.; Noh, H.-J.; Kim, J.-Y.; Park, J.-H.; Hwang, N.-M.; Hyeon, T. *Nat. Mater.* **2004**, *3*, 891.

[12] (a) Rajh, T.; Chen, L. X.; Lukas, K.; Liu, T.; Thurnauer, M. C.; Tiede, D. M. *J. Phys. Chem. B* **2002**, *106*, 10543. (b) Kohler, N.; Fryxell, G. E.; Zhang, M. *J. Am. Chem. Soc.* **2004**, *126*, 7206. (c) Lu, Y.; Yin, Y.; Mayers, B. T.; Xia, Y. *Nano Lett.* **2002**, *2*, 183.

TABLE 1. Suzuki Cross-Coupling of Aryl Halogens (on Resins) and Arylboronic Acids (in Solution) under Iron Oxide-Pd (4 nm) (Scheme 1)[a]

entry	Y	borate	Suzuki product[b]	
			yield (%)[c]	purity (%)[d]
1	*o*-I		78	>99
2	*o*-I		63	>99
3	*o*-I		71	>99
4	*o*-I		77	>99
5	*o*-Br		62	>99

[a] Reaction conditions: resins (1.22 g) loaded with an aryl halogen (1 mmol) were added to a mixture of the arylboronic acid (2 mmol) and K$_2$CO$_3$ (2 mmol) in 20 mL of DMF containing **Iron Oxide-Pd** (4 nm) (30 mg, 0.87 mol %) at 80 °C for 6 days. [b] Suzuki products were cleaved from resins and purified via recrystallization steps. [c] Average of at least two runs. [d] Purity was determined by HPLC analyses and the structures of Suzuki products were confirmed by ^{1}H NMR and MS.

K$_2$CO$_3$ (2 mmol) in DMF in the presence of **Iron Oxide-Pd** (4 nm, 0.87 mol %) at 80 °C (Table 1). HPLC analyses were utilized for tracking reaction progress by closely monitoring the consumption of the arylborate reagent with use of an internal standard. During workup, **Iron Oxide-Pd** was magnetically concentrated and removed by applying an external permanent magnet (LifeSep 50sx magnetic separator from Dexter Magnetic Technologies). About 83% of **Iron Oxide-Pd** (based on the weights) could be separated from resins via a magnetic concentration step. However, repeated magnetic separation steps were needed to ensure complete removal of **Iron Oxide-Pd** out of resins. Then, the Suzuki product on solid-phase resins was separated from the excess borate in solution via a filtration process. The filtrate was acidified with dilute HCL and extracted with toluene for the recovery of the remaining arylboronic acid (purity $>99\%$). Saponification of resins with NaOH yielded a mixture of the Suzuki product and the unreacted aryl halogen. The purity of the Suzuki product could be further improved via a simple recrystallization step, using EtOH/H$_2$O. Table 1 listed the yields and purity of isolated Suzuki products of several test reactions shown in Scheme 1. An average of 70% isolation yield with high purity ($>99\%$) was obtained via this approach in five Suzuki cross-coupling reactions.

Considerable research efforts have been focused on establishing the catalytic roles of **Iron Oxide-Pd** in these solid-phase Suzuki cross-coupling reactions. Due to the size restrictions of resin pores, a smaller catalytic fragment generated through dissociation from **Iron Oxide-Pd** under reaction conditions could be a preferred catalyst over the nanoparticle–Pd complexes to reach reaction sites inside resins. For example, Pd(OAc)$_2$ was known to catalyze Suzuki cross-coupling reactions.[13] We were concerned about the possibility that trace amounts of Pd(OAc)$_2$ physically adsorbed on the surface of magnetic nanoparticles during our synthesis of **Iron Oxide-Pd** were actually dissociated from the nanoparticles and entered resin reaction sites to promote the solid-phase Suzuki reactions. However, our subsequent experiments ruled this possibility out and supported the catalytic roles of **Iron Oxide-Pd** inside reaction sites. Elemental analysis showed that recovered **Iron Oxide-Pd** of 4 nm contained $\sim$0.284 mmol/g of Pd, comparable to that (0.29 mmol/g) of freshly prepared catalysts. In addition, recovered **Iron Oxide-Pd** showed similar catalytic activity to that of the freshly prepared 4-nm **Iron Oxide-Pd**. A subsequent solution-phase Suzuki cross-coupling of iodobenzene and phenylboronic acid in DMF at 50 °C promoted by recovered and freshly prepared **Iron Oxide-Pd** (30 mg, 0.87 mol %) led to isolation yields of 88% and 91%, respectively. Elemental analysis of the Suzuki products did not find detectable Pd contaminations. After removal of **Iron Oxide-Pd** and solid-phase resins from a Suzuki reaction,[14] the filtrate was introduced to a new round of the same reaction between resin-supported 2-iodophenylacetic acid and phenylboronic acid in solution in the absence of **Iron Oxide-Pd**. No conversion of phenylboronic acid was found. Apparently, the Pd catalyst was retained on the surfaces of nanoparticles during our solid-phase Suzuki reactions and workups.

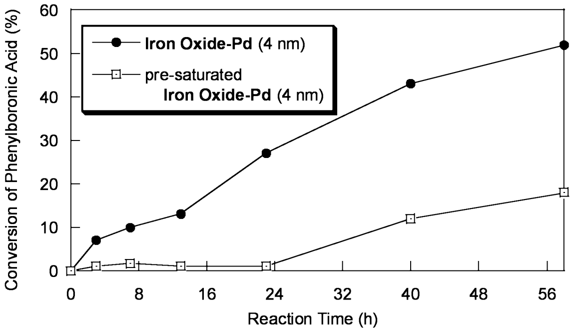


FIGURE 1. Comparative kinetics study of two solid-phase Suzuki reactions of 2-iodophenylacetic acid (on resins) and phenylboronic acid (in solution). **Iron Oxide-Pd** (4 nm): resins (1.2 g) were mixed with phenylboronic acid (2 mmol) and K$_2$CO$_3$ (2 mmol) in 40 mL of DMF containing 260 mg of **Iron Oxide-Pd** (4 nm, 3.7 mol %) at 80 °C. Presaturated **Iron Oxide-Pd** (4 nm): resins (1.2 g) were mixed with 4-nm maghemite nanoparticles (bearing no Pd catalytic groups) (180 mg), phenylboronic acid (2 mmol), and K$_2$CO$_3$ (2 mmol) in 40 mL of DMF at 80 °C. After 48 h, 260 mg of **Iron Oxide-Pd** (4 nm, 3.7 mol %) was added.

A presaturated solid-phase Suzuki reaction was also employed to confirm **Iron Oxide-Pd** catalysis inside solid-phase beads (Figure 1). Resins (1.2 g) loaded with 2-iodophenylacetic acid were mixed with nonfunctionalized iron oxide nanocrystals of 4 nm (bearing no Pd catalytic groups)[11a] (180 mg) and K$_2$CO$_3$ (2 mmol) in 40 mL of DMF. The temperature was raised to 80 °C. After 48 h, 260 mg of **Iron Oxide-Pd** (4 nm, 3.7 mol %) and phenylboronic acid (2 mmol) were added to the mixture. Reaction progress was monitored by HPLC analyses after the

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(13) For example, palladium acetate was known to catalyze Suzuki cross-coupling reactions: (a) Liu, L.; Zhang, Y.; Wang, Y. *J. Org. Chem.* **2005**, *70*, 6122. (b) Goodson, F. E.; Wallow, T. I.; Novak, B. M. *Org. Synth.* **1998**, *75*, 61. (c) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, 466.

(14) Repeated magnetic concentration and centrifugation steps were employed for complete removal of nanoparticle-supported Pd catalysts. TEM experiments were used to ensure complete removal of **Iron Oxide-Pd** from the filtrate.

TABLE 2. Yields of Solid-Phase Suzuki Reactions between 2-Iodophenylacetic Acid (on Resins) and Phenylboronic Acid (in Solution) under Iron Oxide-Pd of Different Dimensions[a]

	catalyst			
	4 nm[b]	12 nm[b]	22 nm[b]	**Resin-Pd**[c]
yield (%)[d]	87	56	32	0

[a] Reaction conditions: resins (1.22 g) loaded with an aryl halogen (1 mmol) were added to a mixture of the arylboronic acid (2 mmol) and K_2CO_3 (2 mmol) in 20 mL of DMF containing **Iron Oxide-Pd** (4 nm) (30 mg, 0.87 mol %) at 80 °C for 6 days. [b] The average core dimensions of **Iron Oxide-Pd**. [c] **Resin-Pd**: the Pd-NHC complexes immobilized on solid-phase microbeads (0.87 mol % of Pd) (Scheme 3). [d] Yields were determined by HPLC analyses. Average of at least two runs.

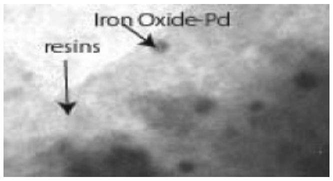
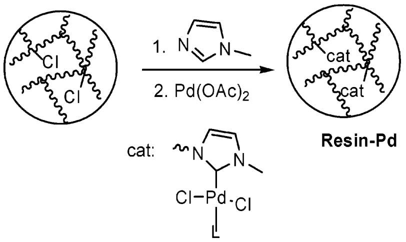


FIGURE 2. TEM micrograph of **Iron Oxide-Pd** (12 nm) encapsulated inside a solvent-swollen polystyrene solid-phase bead (partial). The swollen polystyrene polymers were deposited at the edge of a hole on a lacey TEM grid for improved imaging contrasts.

introduction of **Iron Oxide-Pd** and phenylborate. Conversion of phenylboronic acid in this presaturated reaction was compared with that of the same solid-phase reaction under **Iron Oxide-Pd** directly without being preincubated with nonfunctionalized iron oxide nanocrystal competitors. Figure 1 showed that during the first 24 h after the introduction of **Iron Oxide-Pd**, the presaturated reaction converted only 1% of phenylboronic acid into the product while its counterpart led to approximately 30% of conversion. Afterward, the re-saturated reaction began to accelerate and reached a conversion yield of 15% in 58 h. Diffusion of a catalyst in and out of the reaction sites is usually believed to be the rate-limiting step in solid-phase reactions. The presence of a large number of nonfunctionalized nanoparticles inside resins in our presaturated experiment denied and/or slowed the access of **Iron Oxide-Pd** into reaction sites. It was known that maghemite nanoparticles themselves (bearing no Pd catalytic groups) do not catalyze Suzuki cross-coupling reactions.[15] **Iron Oxide-Pd** served as a catalyst and the low concentration of **Iron Oxide-Pd** inside resins led to the initially slow conversion of phenylboronic acid. As the reaction time was prolonged, **Iron Oxide-Pd** gradually replaced nonfunctionalized iron oxide nanoparticles inside resins and the presaturated reaction started to accelerate leading to a faster conversation of phenylboronic acid into the Suzuki product than that during the first 24 h.

SCHEME 3. Immobilization of Pd-NHC Complexes onto Solid-Phase Resins



In addition, we examined relationships between the core sizes of **Iron Oxide-Pd** and reaction yields to confirm **Iron Oxide-Pd** catalysis of solid-phase Suzuki cross-couplings (Table 2). To this end, transformations of 2-iodophenylacetic acid on resins and phenylboronic acid in solution under **Iron Oxide-Pd** of different iron oxide core dimensions (4, 12, and 22 nm ≤ ±10%)[11] were investigated. Each reaction contained 0.87 mol % of Pd. A control experiment involving the same reaction under a resin-supported Pd-NHC catalyst (**Resin-Pd**) (Scheme 3) for a solid−solid reaction was also listed in Table 2. We found that reaction yields strongly depended on the core dimensions of nanoparticle catalysts (Table 2). For example, **Iron Oxide-Pd** of 4 nm gave a yield of 87% while its 22 nm counterpart led to a yield of 32%. Apparently, smaller **Iron Oxide-Pd** could have easier access to reaction sites than the larger ones due to the size restrictions of resin pores. The resin-supported Pd-NHC (**Resin-Pd**) was too big to enter the interior spaces of another bead and thus no detectable products were found in the solid−solid reaction. The matrix size-dependent reaction yields in Table 2 strongly suggested the catalytic roles of **Iron Oxide-Pd** in our solid-phase transformations. Additional evidence supporting **Iron Oxide-Pd** catalysis came from a TEM study of the mixture of resins and 12-nm **Iron Oxide-Pd**. The TEM micrograph in Figure 2 showed the encapsulation of iron oxide nanoparticles inside a swollen bead (partial). Elemental analysis of this specimen confirmed the presence of both iron and palladium inside a polystyrene resin.[16]

Conclusions

This proof-of-concept work presents the first example of using magnetic nanoparticles as a novel matrix orthogonal to polymer resins for supporting solid-phase organic synthesis. Our research efforts have been focused on establishing the catalytic roles of **Iron Oxide-Pd**. Preliminary investigations employing various techniques including TEM microscopy supported the **Iron Oxide-Pd** catalysis of solid-phase Suzuki reactions. The matrix size-dependent reaction yields in Table 2 demonstrated the advantages of nanoparticle supports over their micrometer-sized counterparts in solid-phase organic transformations and showed the promise of applying nanomaterials to organic synthesis. In addition, our investigations found that employment of two orthogonal supports[17] has facilitated final separation/purification steps, without employing a chromatographic separation technique. Such chromatography-free workup processes could be useful in the robotic synthesis of combinatorial libraries and can potentially be adopted to fully automated organic syntheses. This orthogonal support strategy may also find its applications in process chemistry. Complicated separation and purification steps have frequently become a bottleneck in large-scale industrial processes that involve millions of tons of solvents, reagents, and catalysts. Facile recovery and recycling of expensive homogeneous catalysts and excess reagents will cut

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[15] Stevens, P. D.; Li, G.; Fan, J.; Yen, M.; Gao, Y. *Chem. Commun.* **2005**, 4435.

[16] Encapsulation of nanoparticles inside the large pores of resins has been utilized for chromatographic separation and purification of nanomaterials. For example: (a) Novak, J. P.; Nickerson, C.; Franzen, S.; Feldheim, D. L. *Anal. Chem.* **2001**, *73*, 5758. (b) Jimenez, V. L.; Leopold, M. C.; Mazzitelli, C.; Jorgenson, J. W.; Murray, R. W. *Anal. Chem.* **2003**, *75*, 199. (c) Krueger, K. M.; Al-Somali, A. M.; Falkner, J. C.; Colvin, V. L. *Anal. Chem.* **2005**, *77*, 3511.

[17] (a) Andrews, S. P.; Stepan, A. F.; Tanaka, H.; Ley, S. V.; Smith, M. D. *Adv. Synth. Catal.* **2005**, *347*, 647. (b) Davies, I. W.; Matty, L.; Hughes, D. L.; Reider, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 10139.

costs and minimize chemical wastes—providing environmental protection benefits in the chemical industry.[18] However, our research work here only proves the possibility of using magnetic nanoparticles as an orthogonal support in solid-phase reactions and continuous work is still needed in this area to address these two challenges: (1) slow reaction rates of our three-phase reactions (more than 6 days needed to complete reactions, which is presumably due to the slow diffusion of **Iron Oxide-Pd** in to and out of the resin pores) and (2) the solubility of **Iron Oxide-Pd** in organic media. Our **Iron Oxide-Pd** is only partially soluble in DMF and repeated magnetic separation steps were needed to completely remove the catalyst from the resins. Novel solid-phase supports such as monolithic materials having pore dimensions as large as several micrometers and magnetic nanoclusters with improved solubility in organic media will presumably reduce reaction times and facilitate separation of solid-phase resins and magnetic nanoparticles. Our progress in this area will be reported in due course.

Experimental Section

Synthesis of Iron Oxide-Pd. About 60 mg of 4-nm γ-Fe_2O_3 nanocrystals coated with oleate[11a] in 50 mL of chloroform was treated with (3-chloropropyl)trimethoxysilane (1 mL, 5.48 mmol). The resulting solution was then brought to reflux. After 12 h, the solution was cooled to ambient temperature. Nanoparticles were magnetically concentrated by using an external permanent magnet (LifeSep 50sx magnetic separator) and washed with toluene (2 × 50 mL), 0.1 M HCL (2 × 50 mL), and methanol (2 × 50 mL). The resulting nanoclusters were air-dried. Such nanoparticles were redissolved in 45 mL of dry toluene and then *N*-methylimidazole (0.75 mL, 9.41 mmol) in 5 mL of toluene was added. The resulting solution was brought to reflux and after 16 h, it was cooled to room temperature. Nanoparticles were then magnetically concentrated and washed with toluene, HCl, and methanol sequentially.

About 100 mg of the aforementioned magnetic nanoparticles were redissolved in a mixture of DMF (2 mL) and Na_2CO_3 aqueous solution (0.5 M, 2 mL) in the presence of $Pd(OAc)_2$ (22 mg, 98 μmol). After 16 h at 50 °C, the mixture was cooled to room temperature. The nanoparticle−Pd composites were magnetically concentrated and washed with water (3 × 50 mL), 0.1 M HCl (3 × 50 mL), and methanol (3 × 50 mL) and air-dried. The amount of Pd on the nanoparticles was determined by elemental analysis. Both 12 and 22 nm **Iron Oxide-Pd**[11b] were synthesized similarly by following the procedures above. The formed **Iron Oxide-Pd** was partially soluble in DMF.

Loading of Aryl Halogens onto Solid-Phase Resins. To a suspension of chloromethylated polystyrene beads (1% divinylbenzene cross-linked, 200−400 mesh) (2.0 g) in DMF (30 mL) was added an aryl halogen such as 2-iodophenylacetic acid (3 mmol) and K_2CO_3 (5 mmol). The mixture was stirred gently at 85 °C for 24 h. Then the resins were filtered off and washed with DMF (5 × 100 mL), methanol (5 × 100 mL), water (5 × 100 mL), and methanol (5 × 100 mL) again. The beads were then dried by air. IR (KBr) showed the attachment of 2-iodophenylacetic acid to the resins: $\nu_{C=O}$ 1732 cm^{-1}, ν_{C-O} 1149 cm^{-1}. Elemental analysis of iodine confirmed the loading of about 0.87 mmol of 2-iodophenylacetic acid in 1 g of the resins. The procedure here was also employed for loading other aryl halogens onto resins.

Solid-Phase Suzuki Cross-Coupling Reactions. A typical solid-phase Suzuki cross-coupling reaction was as following: the aforementioned resins (1.22 g) loaded with an aryl halogen (1 mmol) were added to a mixed suspension of the arylboronic acid (2 mmol) and K_2CO_3 (2 mmol) in 20 mL of DMF containing **Iron Oxide-Pd** (4 nm) (30 mg, 0.87 mol %). The mixture was heated to 80 °C and was maintained at this temperature for 6 days. **Iron Oxide-Pd** was magnetically concentrated by using an external permanent magnet. To this end, the mixture was vigorously shaken. A permanent magnet (LifeSep 50sx magnetic separator) was then applied externally. Magnetic nanoparticles were concentrated on the sidewalls of the tube (horizontal direction) while resins were suspended in solution or precipitated at the bottom of the tube (vertical). The suspended and precipitated resins as well as the solution were transferred out of the tube by using a pipet. This process usually needed to be repeated to ensure that most of the nanoparticles were removed from resins. **Iron Oxide-Pd** was then washed with methanol (10 × 200 mL). Afterward, magnetic nanoparticles were further washed with water (5 × 100 mL) and methanol (5 × 100 mL). The nanoparticles were then air-dried and used directly for a new round of Suzuki reaction.

The resins and excessive arylborate were separated via filtration. The beads were recovered as the filter and subsequently washed with methanol (5 × 100 mL) and water (5 × 100 mL). The cleavage of the Suzuki product out of the resins was achieved by adding the solid-phase beads (1.18 g) and NaOH (2 mmol) to a mixture of ethanol (15 mL) and water (15 mL). The mixture was heated to reflux and stirred at this temperature for 2 days. After cooling to ambient temperature, resins were filtered off and the filtrate was neutralized with 1 M HCl to pH 7. Solvents were removed in vacuo and the residues were extracted with ethyl acetate (10 × 50 mL). The combined organic solutions were dried over anhydrous Na_2SO_4 and subjected to HPLC and NMR analyses. A simple recrystallization step was also employed, using EtOH/H_2O to improve the purity of the Suzuki product. The solid-phase Suzuki reactions employing **Iron Oxide-Pd** of different sizes (12 and 22 nm) were following similar procedures as above with catalyst amounts of 0.87 mol %. The structures of isolated Suzuki products were determined by ^1H NMR, IR, and high-resolution MS.[7a] HPLC analyses of isolated products after recrystallization showed that high purity (>99%) was obtained. A UV detector with a fixed wavelength of 254 nm was employed for signal detection. A typical HPLC analysis program used a solvent gradient starting from 40% H_2O in CH_3CN to 10% H_2O in CH_3CN in 6 min followed by 10% H_2O in CH_3CN for an additional 9 min with a flow rate of 0.5 mL/min.

Kinetics Study of Nanoparticle-Supported Solid-Phase Reactions. The resins (1.3 g) loaded with 2-iodophenylacetic acid (1.14 mmol) were mixed with phenylboronic acid (2 mmol) and K_2CO_3 (2 mmol) in 40 mL of DMF containing 260 mg of **Iron Oxide-Pd** (4 nm, 3.7 mol %). The mixture was heated to 80 °C and stirred at this temperature during our kinetics study. For the HPLC study, an aliquot of 0.5 mL of the reaction mixture was taken out. **Iron Oxide-Pd** was removed from the sample with an external magnetic field and the beads were filtered out. A portion of the filtrate (100 μL) was mixed with 100 μL of 0.01 M 1,3-dintrobenzene in acetonitrile. 1,3-Dintrobenzene was used as the internal standard for HPLC analyses. A typical HPLC analysis program used a solvent gradient starting from 40% H_2O in CH_3CN to 10% H_2O in CH_3CN in 6 min followed by 10% H_2O in CH_3CN for an additional 9 min with a flow rate of 0.5 mL/min. A UV detector with a fixed wavelength of 254 nm was employed for signal detection. A second ELSD detector was also utilized in some HPLC experiments.

The presaturation experiment was carried out as following: the resins (1.2 g) loaded with 2-iodophenylacetic acid were mixed with 4-nm maghemite nanoparticles (bearing no Pd catalytic groups)[11a] (180 mg), phenylboronic acid (2 mmol), and K_2CO_3 (2 mmol) in 40 mL of DMF. The temperature was raised to 80 °C. After 48 h, 260 mg of **Iron Oxide-Pd** (4 nm, 3.7 mol %) was added to the mixture. During our kinetics study, an aliquot of 0.5 mL of the reaction mixture was taken out periodically. **Iron Oxide-Pd** was removed from the sample with an external magnetic field and the beads were filtered out. A portion of the filtrate (100 μL) was mixed

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[18] Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702.

with 100 μL of 0.01 M 1,3-dintrobenzene in acetonitrile for HPLC analyses.

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Supporting Information Available: TEM micrographs of nonfunctionalized maghemite nanoparticles (4, 12, and 22 nm) and a detailed description of materials and instruments. This material is available free of charge via the Internet at http://pubs.acs.org.

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