Recycling of homogeneous Pd catalysts using superparamagnetic nanoparticles as novel soluble supports for Suzuki, Heck, and Sonogashira cross-coupling reactions†

Philip D. Stevens,[a] Guifeng Li,[a] Jinda Fan,[a] Max Yen[b] and Yong Gao*[a]

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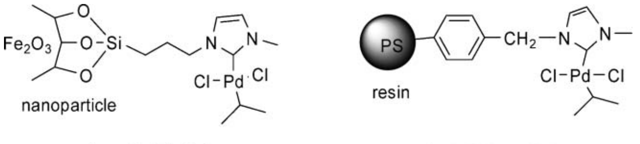
Recycling of homogeneous catalysts could be achieved by using magnetic nanoparticles and solid-phase beads, but nanoparticle-supported catalysis proceeded much faster than its counterpart on resins.

Homogeneous catalysts offer some important advantages over their heterogeneous counterparts.[1,2] Such catalysts can usually be dissolved in reaction media making all catalytic sites accessible to reactants in solution. In addition, many homogeneous catalysts demonstrate high selectivity and can be utilized for controlling the stereochemistry and regiochemistry of the reaction products. Because of these advantages, tremendous progress has been made in the field of homogeneous catalysis during recent years. For example, palladium-catalyzed coupling reactions of aryl halides for C–C formation have been receiving tremendous research interest[3] leading to a group of highly active Pd–ligand homogeneous catalysts.[4] However, despite these advantages and progress, homogeneous catalysis has a share of less than 20% in industrial processes, significantly lower than that of heterogeneous catalysis.[1] This is due to the difficulty in separating the soluble catalyst from the product and any reaction solvent. Heavy metal contamination of a product is undesirable and must be limited to ppm or lower levels. In addition, many transition metals used in homogeneous catalytic systems are quite expensive. Industrial processes based on these new inventions are less attractive unless a new and practical strategy for recycling active catalysts is found.

Consequently, numerous approaches, for example, thermal or chemical recovery, membrane processes and multiple phase transfers, have been investigated for the separation and recycling of homogeneous catalysts.[2] Among these strategies, immobilization of the catalyst on a supporting matrix, especially soluble supports, has been receiving particular research interest.[5] By replacing insoluble resins with soluble scaffolds, the solution-phase reaction conditions will be reinstated and supported catalytic reactions will proceed under homogeneous conditions. During recent years, JandaJel,[6] perfluorinated tags,[7] ROMP gels[8] and other types of synthetic soluble polymers[9] have been extensively explored for immobilizing catalysts, reagents and scavengers. Isolation of the immobilized catalyst is usually achieved by the judicious selection of a second solvent for the selective precipitation of matrices out of the reaction mixtures or extraction of the scaffolds into an orthogonal liquid phase. These strategies have achieved great success for supporting many organic transformations on the laboratory scale. However, alternative immobilization strategies are still needed. An ideal soluble matrix for industrial homogeneous catalyses should be easily concentrated, if possible, without introducing an additional solvent. This will save millions of tons of solvents and minimize the environmental impact of industrial processes.

In this paper, we report the use of superparamagnetic nanoparticles as a new type of matrices for supporting catalytic homogeneous Suzuki, Heck and Sonogashira cross-coupling reactions. These Pd-catalyzed C–C coupling reactions are ranked today amongst the most general transformations in organic synthesis, which have great industrial potential for the synthesis of chemicals, therapeutic drugs and their intermediates. The complexes of Pd and *N*-heterocyclic carbenes (NHCs) were chosen to coat magnetic maghemite (γ-Fe_2O_3) cores to form Iron Oxide–Pd (Fig. 1) because NHC–Pd bonding interactions are known to be chemically and thermodynamically inert towards cleavage.[10] Because of their very small dimensions (~ 11 nm) and organic coating, Iron Oxide–Pd can be partially dissolved in many organic media. This is in contrast to the much larger magnetic counterparts previously reported for supporting organic transformations, which are practically insoluble in organic solvent systems.[11] The superparamagnetism of the maghemite core allows the catalyst to be magnetically concentrated and re-dispersed without forming permanent magnetized clumps in the reaction media.

Immobilization of NHC–Pd complexes onto the surface of soluble magnetic nanoparticles to generate Iron Oxide–Pd (Fig. 1) was achieved *via* three steps (ESI†). Maghemite nanoparticles coated with oleate possessing an average γ-Fe_2O_3 core dimension of 11 nm and narrow size distributions ($\leqslant \pm 10\%$)[12] were used as the starting material. In each step, isolation and purification of



Iron Oxide-Pd **Solid Phase-Pd**

Fig. 1 Structures of maghemite nanoparticle-supported NHC–Pd complexes (Iron Oxide–Pd) and polystyrene (PS) resin-supported NHC–Pd catalyst (Solid Phase–Pd).

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[a] *Department of Chemistry and Biochemistry, Mailcode 4409, Southern Illinois University, Carbondale, IL 62901-4409, USA.*
E-mail: ygao@chem.siu.edu; Tel: +1 (618)453-4904
[b] *Materials Technology Center, Southern Illinois University, ENGR A-120, Carbondale, IL 62901-6603, USA*

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nanoclusters were achieved *via* magnetic concentration using a small permanent magnet externally (LifeSep™ 50sx magnetic separator from Dexter Magnetic Technologies). Elemental analysis confirmed that Iron Oxide–Pd has a Pd loading capacity of about 1.5 mmol g^{-1}. Similarly, the NHC–Pd complexes were also immobilized on polystyrene resins (Solid Phase–Pd) (Fig. 1) *via* multiple synthetic steps (ESI) with a loading capacity of 0.29 mmol g^{-1}.[13]

Iron Oxide–Pd was tested for catalyzing three types of carbon–carbon bond formation reactions—Suzuki (Table 1), Heck (Table 2) and Sonogashira (Table 3) cross-coupling reactions. After several kinds of reaction variables such as the temperature and reaction time were surveyed, the reaction conditions were optimized. For example, our Suzuki reactions typically involved an aryl halide and an arylboronic acid in DMF in the presence of Iron Oxide–Pd (7.3 mol%) at 50 °C for about 12 h. During workup, a permanent magnet (LifeSep™ 50sx magnetic separator) was applied externally and the nanoparticle-supported catalyst was magnetically concentrated on a side wall of the flask. Reaction solutions were removed from the flask and then subjected to GC analyses. The products were purified *via* flash chromatography and characterized by spectroscopic methods such as IR, ^1H NMR, ^{13}C NMR and high-resolution mass spectrometry. The isolated Pd catalyst was washed with various solvents several times and air-dried. More than 97% of Iron Oxide–Pd could usually be recovered (based on the weights of Iron Oxide–Pd).

Table 1 Maghemite nanoparticle-supported Suzuki cross-coupling reactions

Entry	R	X	Yield[a,b] (%)	Isolated yield[c] (%)
1	*o*-Me	I	95	87
2	*o*-Me	Br	93	84
3	*m*-OMe	I	99	91
4	*m*-OMe	Br	94	90
5	*p*-Ac	I	99	93

[a] All reactions were carried out in DMF using 1.0 equiv. of aryl halide, 1.1 equiv. arylboronic acid and 2.0 equiv. of sodium carbonate in the presence of Pd–NH complexes (7.3 mol%) at 50 °C for 12 h. [b] Yields determined by GC analyses. [c] Yields after isolation.

Table 2 Maghemite nanoparticle-supported Heck reactions

Entry	R	X	Yield[a,b] (%)	Isolated yield[c] (%)
1	*o*-Me	I	97	90
2	*o*-Me	Br	95	88
3	*m*-OMe	I	95	89
4	*m*-OMe	Br	96	90
5	*p*-Ac	I	96	88

[a] All reactions were carried out in DMF using 1.0 equiv. of aryl halide, 1.1 equiv. of *n*-butyl acrylate and 2.0 equiv. of sodium carbonate in the presence of Pd–NH complexes (7.3 mol%) at 50 °C for 12 h. [b] Yields determined by GC analyses. [c] Yields after isolation.

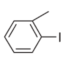
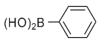
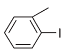
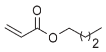
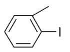
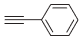
Table 3 Maghemite nanoparticle-supported Sonogashira cross-coupling reactions

Entry	R	X	Yield[a,b] (%)	Isolated yield[c] (%)
1	*o*-Me	I	94	89
2	*o*-Me	Br	94	91
3	*m*-OMe	I	96	88
4	*m*-OMe	Br	95	93
5	*p*-Ac	I	96	91

[a] All reactions were carried out in DMF using 1.0 equiv. of aryl halide, 1.1 equiv. of phenylacetylene, 0.15 equiv. of CuI and 2.0 equiv. of sodium carbonate in the presence of Pd–NH complexes (7.3 mol%) at 50 °C for 12 h. [b] Yields determined by GC analyses. [c] Yields after isolation.

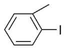
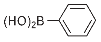
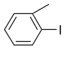
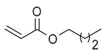
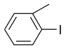
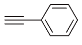
The feasibility of repeated use of Iron Oxide–Pd was also examined. In Table 4, we present results from the investigation of recycling of Iron Oxide–Pd for five consecutive rounds of the same reaction. After each round, nanoparticles were magnetically concentrated, washed, air-dried and used directly for the next round of reaction without further purification. No significant loss of the catalytic activity was observed for Iron Oxide–Pd in Suzuki (entry 1), Heck (entry 2) and Sonogashira (entry 3) reactions in Table 4. Similarly, Iron Oxide–Pd has been employed for three different types of reactions in sequence (Table 5). Iron Oxide–Pd was first used for promoting a Suzuki coupling of phenylboronic acid and 2-iodotoluene (entry 1). Then, the recovered catalyst was applied to a Heck reaction (entry 2) followed by a Sonogashira coupling reaction (entry 3). Iron Oxide–Pd was found to maintain its catalytic activity in all three reactions.

Table 4 Repeated uses of recovered Iron Oxide–Pd for catalyzing Suzuki, Heck, and Sonogashira cross-coupling reactions, respectively

			Yield of each round (%)[a]				
Entry	Reagent 1	Reagent 2	1	2	3	4	5
1			95	94	95	93	93
2			97	95	95	94	92
3			94	91	90	91	89

[a] Yields determined by GC analyses.

Table 5 Uses of recycled Iron Oxide–Pd for promoting three different types of reactions sequentially. The recovered catalyst after the Suzuki reaction (entry 1) was dried and used immediately for a Heck reaction (entry 2) followed by a Sonogashira coupling (entry 3) later

Entry	Reagent 1	Reagent 2	Reaction	Yield (%)[a]
1			Suzuki	94
2			Heck	95
3			Sonogashira	92

[a] Yields determined by GC analyses.

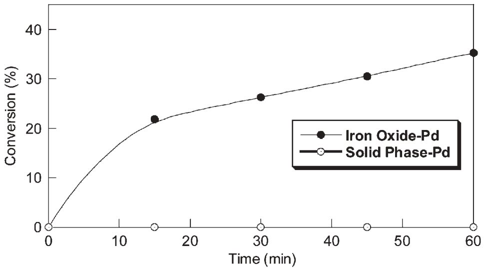


Fig. 2 Suzuki cross-couplings between 4-iodoacetophenone and phenylboronic acid catalyzed by Iron Oxide–Pd (nanoparticle supports) and Solid Phase–Pd (resin supports), respectively. All three reactions used 7.3 mol% of Pd at 50 °C. Our GC analyses did not find any detectable products in the resin-supported Suzuki reaction within 90 min.

We also carried out a comparative kinetic study of a Suzuki cross-coupling between 4-iodoacetophenone and phenylboronic acid under Iron Oxide–Pd and Solid Phase–Pd, respectively (Fig. 2). The experimental progress was closely monitored by GC analyses using anisole as an internal standard and all the reactions comprised the same amount (7.3 mmol%) of the NHC–Pd complexes. To minimize experimental errors, we repeated all experimental procedures at least twice. Fig. 2 showed that reactions catalyzed by Iron Oxide–Pd proceeded faster than that catalyzed by Solid Phase–Pd. For example, about 35% of 4-iodoacetophenone was converted into the product under Iron Oxide–Pd after 60 min of reaction. However, no detectable products were found in the same reaction catalyzed by Solid Phase–Pd until after 180 min of reaction (not shown in Fig. 2). The possibility that maghemite nanocrystals themselves served as a catalyst for the C–C formation can be ruled out. Our additional GC experiments found no detectable products of the same Suzuki reaction in the presence of iron oxide nanoparticles that bear no Pd atoms after 14 days. The catalyst on Iron Oxide–Pd is immobilized on the nanocluster surfaces. Reactants in solution have easy access to the active sites on the surface of nanoparticles, avoiding the problems encountered in heterogeneous support matrixes where a high proportion of the catalytic sites are present deep inside the matrix backbones and reactants have limited access to the catalyst.

In summary, magnetic nanoparticle-supported Suzuki, Heck and Sonogashira cross-coupling reactions have been examined. The Pd–NHC complex immobilized on maghemite nanocrystals demonstrated stability in organic media as reaction temperatures as high as 110 °C were used during the synthesis of Iron Oxide–Pd. Unlike other soluble matrices, recovery of the catalyst immobilized on partially soluble magnetic nanoparticles was achieved using an external permanent magnet—no need for adding a second solvent. This will be of significant importance in industrial processes since the use of additional millions of tons of solvents will be avoided. The feasibility of repeatedly employing the nanoparticle-supported catalyst for the same or a different type of reaction was confirmed. No significant loss of the catalytic activity of the immobilized catalyst was observed after several reaction cycles. More importantly, our comparative kinetic studies have shown that the nanoparticle-supported catalysis proceeded much faster than its counterpart on solid phases. Thereby, superparamagnetic nanoparticles are a new powerful tool for the synthesis of drug and chemical intermediates and hence open a new horizon for large-scale catalytic reactions in the chemical and pharmaceutical industries.

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