ORGANIC LETTERS

2005
Vol. 7, No. 11
2085−2088

Superparamagnetic Nanoparticle-Supported Catalysis of Suzuki Cross-Coupling Reactions

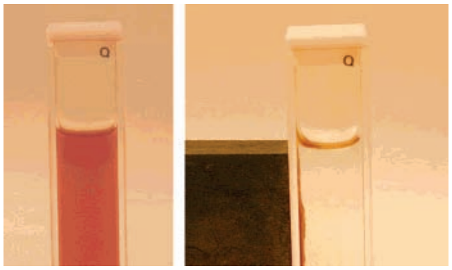
Philip D. Stevens,[†] Jinda Fan,[†] Hari M. R. Gardimalla,[†] Max Yen,[‡] and Yong Gao*,[†]

Department of Chemistry and Biochemistry, Mailcode 4409, Southern Illinois University, Carbondale, Illinois 62901-4409, and Materials Technology Center, Southern Illinois University, ENGR A-120, Carbondale, Illinois 62901-6603

ygao@chem.siu.edu

Received February 2, 2005 *(Revised Manuscript Received April 17, 2005)*

ABSTRACT



Emulsion polymerization was examined as a novel route for the synthesis of core/shell superparamagnetic nanoparticles consisting of a highly crystalline γ-Fe2O3 core and a very thin polymeric shell wall. These nanoparticles were used as soluble supports for immobilizing Pd catalysts to promote Suzuki cross-coupling reactions. Recovery of catalysts was facilely achieved by applying a permanent magnet externally. Isolated catalysts were reused for new rounds of reactions without significant loss of their catalytic activity.

Recycling of homogeneous catalysts is a task of great economic and environmental importance in chemical and pharmaceutical industries, especially when expensive and/or toxic heavy metal complexes are employed.[1] Immobilization of homogeneous catalysts on various insoluble supports, especially porous materials with high surface areas, is usually the method of choice since the immobilized catalysts can be facilely recovered via a simple filtration process after reactions. However, a substantial decrease in activity and selectivity of the immobilized catalysts is frequently observed due to the heterogeneous nature of these support materials in reaction media. The loaded catalysts also encounter other problems in solid-phase-supported organic reactions:[2] nonlinear kinetic behavior, unequal access to chemical reactions, and synthetic difficulties in transferring standard solution-phase reactions to the solid phases.

During recent years, development of novel soluble matrixes for supporting solution-phase organic reactions has received a great deal of research attention.[3] Many of the aforementioned problems associated with heterogeneous insoluble matrixes can be addressed by adopting a soluble support. JandaJel,[4] perfluorinated tags,[5] ROMP gels,[6] and other types of synthetic soluble polymers[7] have been well explored for immobilizing catalysts, reagents, and scavengers.

[†] Department of Chemistry and Biochemistry.

[‡] Materials Technology Center.

(1) For a review: Cole-Hamilton, D. J. *Science* **2003**, *299*, 1702.

(2) For a review: Vaino, A. R.; Janda, K. D. *J. Comb. Chem.* **2000**, *2*, 579.

(3) For some recent reviews: (a) Tzschucke, C. C.; Markert, C.; Bannwarth, W.; Roller, S.; Hebel, A.; Haag, R. *Angew. Chem., Int. Ed.* **2002**, *41*, 3964. (b) Bergbreiter, D. E. *Chem. Rev.* **2002**, *102*, 3345. (c) Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Chem. Rev.* **2002**, *102*, 3301. (d) Dickerson, T. J.; Reed, N. N.; Janda, K. D. *Chem. Rev.* **2002**, *102*, 3325. (e) Fan, Q.-H.; Li, Y.-M.; Chan, A. S. C. *Chem. Rev.* **2002**, *102*, 3385. (f) Yoshida, J.-i.; Itami, K. *Chem. Rev.* **2002**, *102*, 3693.

(4) Gambs, C.; Dickerson, T. J.; Mahajan, S.; Pasternack, L. B.; Janda, K. D. *J. Org. Chem.* **2003**, *68*, 3673.

(5) (a) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766. (b) Dinh, L. V.; Gladysz, J. A. *Chem. Commun.* **2004**, *8*, 998.

10.1021/ol050218w CCC: $30.25

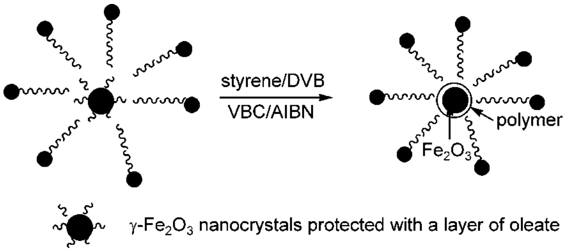
By replacing insoluble resins with these soluble scaffolds, the solution-phase reaction conditions will be reinstated. After reactions, a second solvent is usually introduced for the selective precipitation of matrixes out of the reaction mixtures (JandaJel and ROMP gels) or for the extraction of the scaffolds into the orthogonal liquid phase (perfluorinated tags). Although tremendous progress has been made in this area, there is still a need to develop new types of soluble supports, especially those that can be widely employed in chemical and pharmaceutical industries. The large-scale introduction of a second solvent in an industrial process can potentially increase the costs and generate more waste, leading to environmental concerns.

Nanoparticles have emerged as alternative soluble matrixes for supporting homogeneous organic reactions.[8] This is because when the size of the support materials is decreased to the nanometer scale, the surface area of nanoparticles will increase dramatically. As a consequence, nanoparticle supports could have higher catalyst loading capacity than many conventional support matrixes, leading to the improved catalytic activity of the nanoparticle-supported catalysts. In addition, catalysts are usually immobilized on the surface of nanoclusters. Reactants in solution have easy access to the active sites on the surface of nanoparticles, avoiding the problems encountered in many heterogeneous support matrixes where a great portion of catalysts are present deep inside the matrix backbones and reactants have the limited access to the catalytic sites. Among many nanomaterials, monolayer-protected Au nanoclusters (Au MPCs) have received particular research attention due to their stability and solubility in organic solvents. Recent studies have confirmed the high catalytic activity of Au MPC-supported catalysts.[8c] However, facile isolation and recycling of nanoparticle supports from reaction media have remained a challenge. Additional laboratory work is usually required for the judicious selection of addition of a second solvent to selectively precipitate Au nanoparticles out of the reaction medium.

Superparamagnetic nanoparticles are a new type of soluble matrix that potentially can address the isolation and recycling problems encountered in Au MPCs and other soluble supports for immobilization of homogeneous catalysts. These magnetic nanoparticles usually have a core/shell structure[9] consisting of a magnetic iron oxide core surrounded by a layer of lightly cross-linked polymeric shell wall. The organic polymer shells stabilize nanoparticles by preventing aggregation of inorganic cores and offer a platform for immobilization of catalysts. For the solubility of nanoparticles in organic media, shell walls are usually thin (~nm) and the shell polymers are preferred to have low molecular weights.[10] Iron oxide cores will respond to a magnetic field but retain no magnetization properties when the field is removed. The lack of magnetic remanence prevents nanoparticles from forming magnetized clumps in the reaction media. In addition, unusually high magnetization moments of "super"paramagnetic materials allow the use of low-field magnets to efficiently concentrate magnetic nanoparticles. In this paper, we would like to report our preliminary studies demonstrating the feasibility of using this new class of materials for supporting homogeneous catalysts. The Pd catalysts immobilized on magnetic core/shell nanoparticles can be facilely recovered by using an external permanent magnet that is readily available at a low cost from many commercial vendors.

The core/shell iron oxide/polymer nanocrystals used for immobilizing Pd catalysts were synthesized via a novel emulsion polymerization approach (Scheme 1).[11] Vigorous stirring facilitated the formation of micelles of pluronic surfactant P-123 in an aqueous medium. Highly crystalline and monodisperse γ-Fe_2O_3 nanocrystals (~11 nm) coated with a layer of oleate[12] were encapsulated inside the interior cores of micelles due to the hydrophobic alkyl chains of the oleate molecules. Styrene, 4-vinylbenzene chloride (VBC), and 1,4-divinylbenzene (DVB) were added and entrapped

Scheme 1. Emulsion Polymerization Synthesis of Core/Shell Iron Oxide/Polymer Nanocrystals[a]



[a] Organic polymeric shell consists of lightly cross-linked polymers of styrene and VBC. DVB: 1,4-divinylbenzene. VBC: 1,4-vinylbenzyl chloride.

---

(6) (a) Harned, A. M.; He, H. S.; Toy, P. H.; Flynn, D. L.; Hanson, P. R. *J. Am. Chem. Soc.* **2005**, *127*, 52. (b) Ralph, C. K.; Akotsi, O. M.; Bergens, S. H. *Organometallics* **2004**, *23*, 1484. (c) Enholm, E. J.; Gallagher, M. E. *Org. Lett.* **2001**, *3*, 3397. (d) Årstad, E.; Barrett, A. G. M.; Hopkins, B. T.; Köbberling, J. *Org. Lett.* **2002**, *4*, 1975.

(7) For some recent references: (a) Bergbreiter, D. E.; Osburn, P. L.; Smith, T.; Li, C.; Frels, J. D. *J. Am. Chem. Soc.* **2003**, *125*, 6254. (b) Lau, K. C. Y.; He, H. S.; Chiu, P.; Toy, P. H. *J. Comb. Chem.* **2004**, *6*, 955. (c) Hebel, A.; Haag, R. *J. Org. Chem.* **2002**, *67*, 9452. (d) Zhong, J.-H.; Fishman, A.; Lee-Ruff, E. *Org. Lett.* **2002**, *4*, 4415.

(8) (a) Templeton, A. C.; Hostetler, M. J.; Warmoth, E. K.; Chen, S.; Hartshorn, C. M.; Krishnamurthy, V. M.; Forbes, M. D. E.; Murray, R. W. *J. Am. Chem. Soc*. **1998**, *120*, 4845. (b) Fan, J.; Chen, S.; Gao, Y. *Colloids Surf., B* **2003**, *28*, 199. (c) Marubayashi, K.; Takizawa, S.; Kawakusu, T.; Arai, T.; Sasai, H. *Org. Lett*. **2003**, *5*, 4409. (d) Kell, A. J.; Stringle, D. L. B.; Workentin, M. S. *Org. Lett*. **2000**, *2*, 3381. (e) Yoon, T.-J.; Lee, W.; Oh, Y.-S.; Lee, J.-K. *New J. Chem.* **2003**, *27*, 227.

(9) (a) Li, G.; Fan, J.; Jiang, R.; Gao, Y. *Chem. Mater*. **2004**, *16*, 1835. (b) Vestal, C. R.; Zhang, Z. J. *J. Am. Chem. Soc*. **2002**, *124*, 14312. (c) Wang, Y.; Teng, X.; Wang, J.-S.; Yang, H. *Nano Lett*. **2003**, *3*, 789. (d) Kohler, N.; Fryxell, G. E.; Zhang, M. *J. Am. Chem. Soc*. **2004**, *126*, 7206. (e) Dyal, A.; Loos, K.; Noto, M.; Chang, S. W.; Spagnoli, C.; Shafi, K. V. P. M.; Ulman, A.; Cowman, M.; Gross, R. A. *J. Am. Chem. Soc.* **2003**, *125*, 1684. (f) Gu, H.; Ho, P.-L.; Tsang, K. W. T.; Wang, L.; Xu, B. *J. Am. Chem. Soc.* **2003**, *125*, 15702.

(10) Commercial magnetic beads with a size over several microns are usually suspended in most organic media due to the high molecular weights of their shell walls.

(11) Similar approach was used for the synthesis of polystyrene nanoparticles using micelle templates: Jang, J.; Ha, H. *Langmuir* **2002**, *18*, 5613.

(12) (a) Hyeon, T.; Lee, S. S.; Park, J.; Chung, Y.; Na, H. B. *J. Am. Chem. Soc.* **2001**, *123*, 12798. (b) Lu, J.; Fan, J.; Xu, R.; Roy, S.; Ali, N.; Gao, Y. *J. Colloid Interface Sci.* **2003**, *258*, 427.

into the micellar cores. 2,2′-Azobis(2-methylpropionitrile) (AIBN) was used as a free radical initiator for the formation of a layer of organic polymers surrounding the iron oxide core inside a micelle. VBC served as a linkage point for immobilization of catalysts. A small amount (1%) of DVB was used to cross-link the shell polymers slightly to improve the mechanical strength of the formed core/shell particles.[13]

The generated core/shell nanoparticles were isolated by applying an external permanent magnet (LifeSep 50sx magnetic separator from Dexter Magnetic Technologies). Iron oxide nanparticles were magnetically concentrated, while P-123 surfactants and other excessive reagents remained in the aqueous medium. Removal of the reaction solution out of the flask separated nanoparticles from the reaction mixtures. A TEM micrograph (Figure 1) has confirmed the formation of such a core/shell structure in these iron oxide nanoparticles. Very thin polymer shells (~2 nm) could be observed at the edge of a hole on a TEM grid, while the iron oxide cores were found to possess a diameter of about 11 nm. Apparently, polymerization reactions did not alter the size of the iron oxide cores, and the thickness of the polymeric shell walls was decided by the dimension of the interior cores of micellar templates.

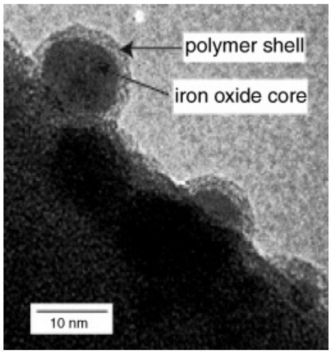
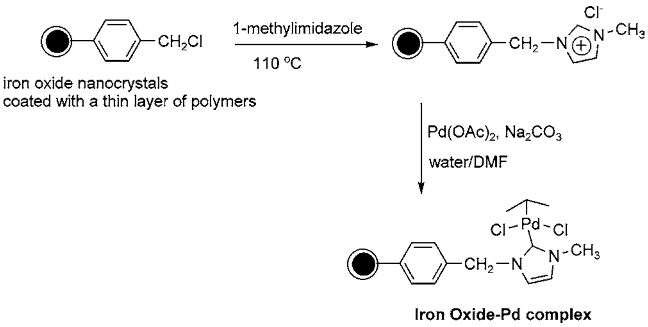


Figure 1. TEM micrograph of core/shell iron oxide/polymer nanoparticles. The lacey TEM grid consists of hollow woven-mesh-like holes and Cu supports that are covered with Formvar/carbon. Due to the lack of the Formvar/carbon coatings in the background, polystyrene shells of nanoparticles can be seen at the edge of a hole.

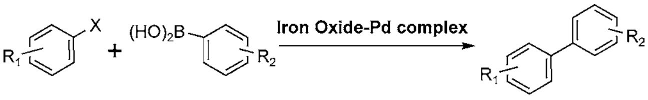
To immobilize Pd catalysts, we first loaded 1-methylimidazole onto the surface of core/shell nanoparticles by mixing nanoparticles with 1-methylimidazole in a refluxing toluene solution (Scheme 2). Then, Na_2CO_3 was used as a base for deprotonation of the imidazolium group to generate N-heterocyclic carbenes (NHCs) that can form strong complexes with Pd catalysts.[14] NHCs were chosen as a ligand for chelating Pd due to the fact that Pd−NHC bonding interactions were known to be chemically and thermodynamically inert toward cleavage.[14] Elemental analysis confirmed that about 0.72 mmol/g of Pd catalysts were loaded onto our nanoparticle supports. This is higher than the 0.29 mmol/g loading of Pd on chloromethyl polystyrene resins that were used for immobilization of Pd catalysts by forming similar Pd−methylimidazole NHC complexes.[15]

Scheme 2. Schematic Representation of the Preparation of Iron Oxide Nanoparticle-Supported Pd−NHC Complexes



Magnetic nanoparticle-supported Pd−NHC complexes were then examined for catalysis of a group of Suzuki cross-couplings of aryl halides with arylboronic acids (Scheme 3).

Scheme 3. Suzuki Cross-Couplings of Aryl Halides and Arylboronic Acids Using Iron Oxide Nanocrystal-Supported Pd−NHC Catalysts



After several kinds of reaction variables such as the temperature and reaction time were surveyed, the reaction conditions were optimized, which typically involved an aryl halide and an arylboronic acid in the mixed solution of DMF and 1% Na_2CO_3 aqueous solution in the presence of Pd−iron oxide nanoparticles (1.52×10^{-2} mol %) at 50 °C for about 12 h. After reaction, a permanent magnet (LifeSep 50sx magnetic separator) was applied externally, and nanoparticle-supported catalysts were magnetically concentrated at a side wall of the flask. The reaction solutions were separated from nanoparticles, and products were subjected to flash chromatography purification followed by spectroscopic characterizations using IR, ^1H NMR, ^{13}C NMR, and high-resolution mass spectrometry analyses (Supporting Information). The Pd catalysts were washed several times with various solvents and air-dried. More than 97% of Pd−iron oxide nanoparticles could usually be recovered (based on the weights of particles).

Table 1 lists a group of Suzuki cross-couplings of aryl halides with arylboronic acids that were investigated in our laboratory using nanoparticle-supported Pd catalysts (Scheme 3). An average isolation yield of 82% was obtained for 20

---

[13] Vigorous control of reaction conditions is needed, as sometimes the formation of aggregated insoluble nanoparticle composites was observed.

[14] For a review: Herrmann, W. A. *Angew. Chem., Int. Ed.* **2002**, *41*, 1290.

[15] Byun, J.-W.; Lee, Y.-S. *Tetrahedron Lett.* **2004**, 1837.

Table 1. Suzuki Cross-Couplings of Aryl Halides and Arylboronic Acids Using Nanoparticle-Supported Pd−NHC Complexes (Scheme 3)

entry	R_1	X	R_2	yield (%)[a]
1	H	I	*o*-Me	86
2	H	I	*m*-Me	88
3	H	I	*o*-OMe	84
4	H	I	*p*-OMe	83
5	H	I	*o*-Ac	89
6	H	I	*m*-Ac	89
7	H	I	naph[b]	82
8	H	I	*p*-CN	82
9	*o*-Me	I	H	87
10	*m*-Me	I	H	83
11	*p*-Me	I	H	88
12	*o*-OMe	I	H	74
13	*m*-OMe	I	H	81
14	*p*-OMe	I	H	83
15	*p*-Ac	I	H	80
16	*o*-Me	Br	H	77
17	*m*-Me	Br	H	74
18	*o*-OMe	Br	H	70
19	*m*-OMe	Br	H	72
20	*p*-OMe	Br	H	78

[a] Isolation yields after separation by flash chromatography; average of at least two runs. [b] Reagent is 1-naphthaleneboronic acid.

reactions. On the whole, nanoparticle-supported Pd catalysts showed better catalytic activity than chloromethyl polystyrene resin-supported counterparts reported in the literature.[15,16] For example, 1.52 × 10^{-2} mol % Pd catalyst was used to catalyze the reaction between *p*-iodotoluene and phenylboronic acid (entry 11 of Table 1) for an average 88% isolation yield, while more Pd catalyst (1.2 mol %) was needed to achieve a similar reaction efficacy using resin-supported catalysts.[15] We also investigated the possibility of repeated use of recovered catalysts for new rounds of reaction. To this end, iron oxide nanoparticle-supported Pd catalysts were examined for five consecutive rounds of reactions between *p*-iodotoluene and phenylboronic acid. After a reaction, catalysts were magnetically isolated, washed, air-dried, and used directly for a subsequent round of reaction without further purification. An isolation yield of 88 ± 3% was obtained each time. No significant loss of the catalytic activity was observed during five consecutive reactions.

In conclusion, core/shell iron oxide nanoparticles were prepared via an emulsion polymerization approach for immobilization of Pd−NHC catalysts. These nanoparticle-supported catalysts are stable and demonstrated high catalytic activity in promoting Suzuki cross-coupling reactions. More importantly, recovery of catalysts was facilely achieved by using a permanent magnet. Isolated catalysts were used for subsequent new rounds of reactions without significant loss of their catalytic activity. Our work here reveals the feasibility of using this new class of supports for immobilizing homogeneous catalysts. Such magnetic nanoparticlular matrixes offer potential advantages over some alternative soluble supports such as Au MPC in that they can be magnetically concentrated by applying an external magnet. There is no need to add a second solvent for the selective precipitation of matrixes. As a consequence, magnetic nanoparticles could be an ideal soluble support for immobilization of industrial homogeneous catalysts. More detailed investigations of nanoparticle structure effects on the catalytic activity of the immobilized catalysts are in progress and will be reported in due course.

Acknowledgment. This investigation was generously supported by partial funds provided by SIU Materials Technology Center, American Cancer Society, and the NSF through a career award to Y.G.

Supporting Information Available: Detailed experimental procedures and characterization studies of Suzuki cross-linking products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050218W

---

(16) Pd nanoparticles were known to catalyze Suzuki cross-coupling reactions: Li, Y.; Hong, X. M.; Collard, D. M.; El- Sayed, M. A. *Org. Lett.* **2000**, *2*, 2385. However, iron oxide nanoparticles alone are not an active catalyst for Suzuki coupling reactions. No detectable products were formed when iron oxide nanoparticles without Pd were used in our experiments.