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Magnetically Separable Pd Catalyst for Carbonylative Sonogashira Coupling Reactions for the Synthesis of α,β-Alkynyl Ketones

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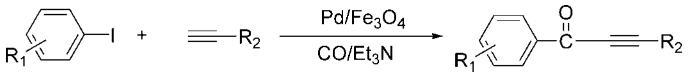
ABSTRACT



A magnetically separable palladium catalyst was simply synthesized through a wet impregnation incorporating palladium nanoparticles and superparamagnetic Fe_3O_4 nanoparticles in KBH_4 solution, which is a highly efficient catalyst for the carbonylative Sonogashira coupling reaction of aryl iodides with terminal alkynes under phosphine-free conditions. This catalyst is completely magnetically recoverable due to the super paramagnetic behavior of Fe_3O_4 and can be reused with sustained selectivity and activity.

Transition-metal-catalyzed carbonylation reactions have become a straightforward and powerful method in organic synthesis. This protocol has been repeatedly modified and improved to prepare aromatic carbonyl compounds which cannot be easily or efficiently formed using classical transformations, including esters, acids, α-keto amide, and α,β-alkynyl ketones.[1,2] Of particular interest among these important carbonyl intermediates are the α,β-alkynyl ketones because they appear in many biologically active molecules and also play crucial roles as intermediates in the synthesis of natural products. A direct method to prepare α,β-alkynyl ketones involves the alkynyl organometallic reagent with acid chlorides.[3,4] An alternative route for these compounds is the Pd-catalyzed carbonylative coupling reaction of terminal alkynes or the metalated derivatives with aryl idodes in the presence of carbon monoxide under mild conditions.[5a]

After the early reports on the carbonylative Sonogashira coupling reaction, a variety of modifications were reported for this reaction.[5] But the most restricting aspect of these

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(1) (a) Tafesh, A. M.; Weiguny, J. *Chem. Rev.* **1996**, *96*, 2035. (b) Tietze, L. F.; IIa, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (c) Gabriele, B.; Salerno, G.; Costa, M.; Chiusoli, G. P. *Curr. Org. Chem.* **2004**, *8*, 919. (d) Morimoto, T.; Kakiuchi, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 5580.

(2) Chowdhury, C.; Kundu, N. G. *Tetrahedron* **1999**, *55*, 7011.

(3) (a) Kalinin, V. N.; Shostakovsky, M. V.; Ponamaryov, A. B. *Tetrahedron Lett.* **1990**, *31*, 4073. (b) Ciattini, P. G.; Morera, E.; Ortar, G.; Rossi, S. S. *Tetrahedron* **1991**, *47*, 6449. (c) Torri, S.; Okumoto, H.; Xu, L.-H.; Sadakane, M.; Shostakovsky, M. V.; Ponomaryov, A. B.; Kalinin, V. N. *Tetrahedron* **1993**, *49*, 6773. (d) Bernard, D.; Daniel, C.; Robert, L. *Tetrahedron Lett.* **1996**, *37*, 1019. (e) Dodero, V. I.; Koll, L. C.; Faraoni, M. B.; Mitchell, T. N.; Podesta, J. C. *J. Org. Chem.* **2003**, *68*, 10087. (f) Marco-Contelles, J.; de Opazo, E. *J. Org. Chem.* **2002**, *67*, 3705. (g) Vong, B. G.; Kim, S. H.; Abraham, S.; Theodorakis, E. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3947. (h) Trost, B. M.; Ball, Z. T. *J. Am. Chem. Soc.* **2004**, *126*, 13942.

(4) (a) Sheng, H.; Lin, S.; Huang, Y. *Tetrahedron Lett.* **1986**, *27*, 4893. (b) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301. (c) Matsuo, K.; Sakaguchi, Y. *Heterocycles* **1996**, *43*, 2553. (d) Jeevandandam, A.; Narkunan, K.; Cartwright, C.; Ling, Y.-C. *Tetrahedron Lett.* **1999**, *40*, 4841. (e) Cabarrocas, G. *Tetrahedron: Asymmetry* **2000**, *11*, 2483. (f) Kel'in, A. V.; Sromek, A. W.; Gevorgyan, V. *J. Am. Chem. Soc.* **2001**, *123*, 2074. (g) Chang, K.-T.; Choi, S.-H.; Kim, S.-H.; Yoon, Y.-J.; Lee, W. S. *J. Chem. Soc., Perkin Trans. I* **2002**, 207. (h) Kel'in, A. V.; Gevorgyan, V. *J. Org. Chem.* **2002**, *67*, 95.

(5) (a) Ahmed, M. S. M.; Mori, A. *Org. Lett.* **2003**, *5*, 3057. (b) Liang, B.; Huang, M. W.; You, Z. J.; Xiong, Z. C.; Lu, K.; Fathi, R.; Chen, J. H.; Yang, Z. *J. Org. Chem.* **2005**, *70*, 6097. (c) Fukuyama, T.; Yamaura, R.; Ryu, I. *Can. J. Chem.* **2005**, *83*, 71. (d) Sans, V.; Trzeciak, A. M.; Luis, S.; Ziłˊkowski, J. J. *Catal. Lett.* **2006**, *109*, 37. (e) Liu, J. H.; Chen, J.; Xia, C. G. *J. Catal.* **2008**, *258*, 50. (f) Rahman, M. T.; Fukuyama, T.; Kamata, N.; Sato, M.; Ryu, I. *Chem. Commun.* **2006**, 2236. (g) Tambade, P. J.; Patil, Y. P.; Nandurkar, N. S.; Bhanage, B. M. *Synlett* **2008**, 886.

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studies is that they were focused on homogeneous catalytic systems together with phosphine ligands, wherein the expensive palladium catalysts are difficult to be separated and reused. This transformation was accomplished to overcome several significant limitations: (a) higher activity palladium-based catalyst, (b) copper-free and phosphine-free routes eliminated the noncarbonylative product, (c) the reusability of the Pd catalyst. In this regard, the development of an easily recoverable and recyclable heterogeneous catalyst is still in high demand, although a large number of supported Pd catalysts for C−C coupling reactions, in particular the Heck reaction, have been reported.[6] To overcome these limitations, magnetically nanosized catalysts are a better choice because their magnetic separation is an alternative to filtration or centrifugation as it prevents loss of catalyst and increases the reusability. Magnetically nanosized catalysts of palladium had been widely used in a variety of organic reactions, such as hydrogenation processes,[7] epoxide hydrogenolysis reactions,[8] and Suzuki, Heck, and Sonogashira cross-coupling reactions.[9,10] In most cases, palladium was immobilized onto the modified surface of the magnetic nanoparticles (MNP). Very recently, $Ru(OH)_x/Fe_3O_4$, ruthenium hydroxide was directly supported on the surface of Fe_3O_4 and showed excellent catalytic activities in both oxidation and reduction.[11]

In this paper, we demonstrate that the Pd/Fe_3O_4 catalyst, which could be easily prepared with a modified method according to Mizuno's procedure,[11] could act as an efficient catalyst in the Sonogashira carbonylative coupling reaction. To the best of our knowledge, this is the first report for the use of Pd/Fe_3O_4 for Sonogashira carbonylative coupling reactions with high efficiency. The catalyst could be easily separated from the reactant with the simple application of an external magnetic field, and its catalytic efficiency remains unaltered even after recycling seven times.

The catalyst was characterized by transmission electron microscopy (TEM). In the TEM images, iron oxide nanoparticles of 25−50 nm in diameter and palladium nanoparticles of 5 nm entrapped in iron oxide are observed (Figure 1a). Figure 1b shows that the Pd spectra contain two peaks with 335.8 and 341.1 eV. These two peaks are assigned to electron transitions of $3d_{5/2}$ and $3d_{3/2}$ of Pd^0, which indicates that the Pd^{2+} can be reduced to metallic Pd^0.[12]

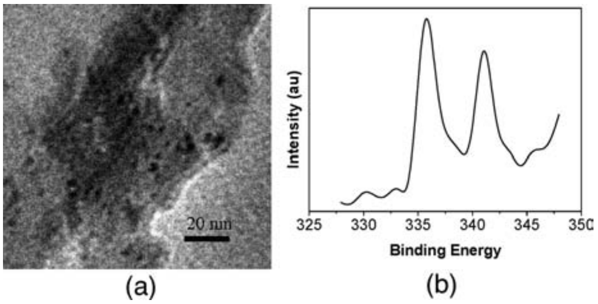
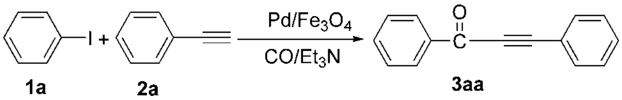


Figure 1. (a) TEM image of Pd/Fe_3O_4 catalyst. (b) XPS spectra of Pd/Fe_3O_4.

In our initial screens, more reaction parameters, such as temperature and CO pressure, were investigated. The results are summarized in Table 1. The desired product, 1,3-diphenylprop-2-yn-1-one, was formed in a 92% isolated yield, when toluene was selected as solvent under 2.0 MPa pressure of CO at 130 °C, in the presence of 50 mg of Pd/Fe_3O_4. Low reaction temperature resulted in low yield in forming the carbonylative Sonogashira coupling product (Table 1, entries 1−3). We also investigated the effect of the pressure of CO: 2.0 MPa of CO led to a nearly quantitive transformation. Several solvents were also screened, and toluene proved to be the best choice for the carbonylative Sonogashira coupling reaction. Next, an evaluation of a variety of bases in the carbonylative Sonogashira coupling confirmed that Et_3N exhibited superior selectivity and activity than other tested bases (Table 1, entry 1). DABCO gave a

Table 1. Carbonylative Sonogashria Coupling Reaction of Iodobenzene under Different Conditions[a]



entry	solvent	base	temp (°C)	yield (%)[b]
1	toluene	Et_3N	130	98 (92[c])
2	toluene	Et_3N	110	79
3	toluene	Et_3N	120	94
4[d]	toluene	Et_3N	130	68
5[e]	toluene	Et_3N	130	93
6	DME	Et_3N	130	49
7	THF	Et_3N	130	63
8	1,4-dioxane	Et_3N	130	51
9	CH_3CN	Et_3N	130	64
10	toluene	DABCO	130	79
11	toluene	K_3PO_4	130	6.5
12	toluene	Cs_2CO_3	130	5.7

[a] Reactions were carried out in 5.0 mL of solvent under 2.0 MPa pressure of CO at 130 °C for 4 h with 2.5 mmol iodobenzene, 3.0 mmol phenylacetylene, 7.2 mmol Et_3N, and Pd/Fe_3O_4 catalyst (Pd, 1.04 wt %), 50 mg (Pd/substrate = 1/511). [b] Determined by GC. [c] Isolated yield. [d] 1.0 MPa of CO. [e] 1.5 MPa of CO.

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(6) For reviews, see: (a) Astruc, D.; Lu, F.; Aranzaes, J. R. *Angew. Chem., Int. Ed.* **2005**, *44*, 7852. (b) de Vries, J. G. *Dalton Trans.* **2006**, 421. (c) Köhler, K.; Kleist, W.; Pröckl, S. *Inorg. Chem.* **2007**, *46*, 1876. (d) Astruc, D. *Inorg. Chem.* **2007**, *46*, 1884.

(7) (a) Guin, D.; Baruwati, B.; Manorama, S. V. *Org. Lett.* **2007**, *9*, 1419. (b) Hu, A.; Yee, G. T.; Lin, W. *J. Am. Chem. Soc.* **2005**, *127*, 12486. (c) Yi, K. D.; Lee, S. S.; Ying, Y. J. *Chem. Mater.* **2006**, *18*, 2459. (d) Abu-Reziq, R.; Wang, S.; Post, M.; Alper, H. *Chem. Mater.* **2008**, *20*, 2544.

(8) Kwon, M. S.; Park, I. S.; Jang, J. S.; Lee, J. S.; Park, J. *Org. Lett.* **2007**, *9*, 3417.

(9) (a) Stevens, P. D.; Fan, J.; Gardimalla, H. M. R.; Yen, M.; Gao, Y. *Org. Lett.* **2005**, *7*, 2085. (b) Stevens, P. D.; Li, G.; Fan, J.; Yen, M.; Gao, Y. *Chem. Commun.* **2005**, 4435. (c) Baruwati, B.; Guin, D.; Manorama, S. V. *Org. Lett.* **2007**, *9*, 5377.

(10) Zhu, Y.; Peng, S. C.; Emi, A.; Su, Z.; Monalisa; Kempd, R. A. *Adv. Synth. Catal.* **2007**, *349*, 1917.

(11) Kotani, M.; Koike, T.; Yamaguchi, K.; Mizuno, N. *Green Chem.* **2006**, *8*, 735.

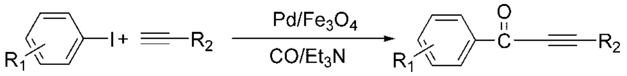
(12) The X-ray diffraction spectrum of Pd/Fe_3O_4 shows only a broad peak at $2\theta = 40.45°$ between Fe_3O_4 and Pd/Fe_3O_4 that is characteristic of amorphous Pd (see Supporting Information).

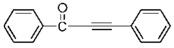
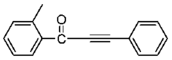
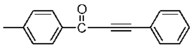
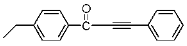
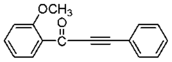
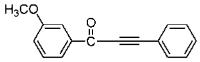
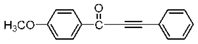
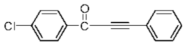
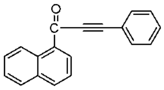
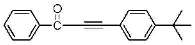
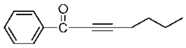
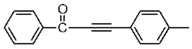
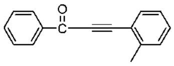
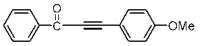
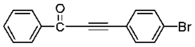
moderate yield. Poor selectivity and activity were observed, when inorganic bases such as K_3PO_4 and Cs_2CO_3 were applied (Table 1, entries 11 and 12). The nanocatalyst displays a high turnover number (TON) for iodobenzene and phenylacetylene (Table 1, entry 1, TON is about 501), a great increase when compared to the results obtained with the homogeneous palladium catalysts.[5] The turnover frequencies (TOF) reached 125 mol/mol/h.

To explore the generality and scope of the carbonylative Sonogashira coupling reaction, the reaction of various aryl iodides and terminal alkynes was carried out under the above conditions, and the results are summarized in Table 2. Aryl iodides bearing an electron-withdrawing group or an electron-donating group in the para, meta, and ortho positions afforded the corresponding substituted α,β-alkynyl ketones in good yields. When 2-methoxy-1-iodobenzene, 3-methoxy-1-iodobenzene, and 4-methoxy-1-iodobenzene were employed in the reaction with phenylacetylene (**2a**), the desired products were isolated in high yields (Table 2, entries 5−7). The reaction of 4-iodo-1-chlorobenzene and phenylacetylene (**2a**) also afforded the corresponding product in satisfactory yield (Table 2, entry 8). We also investigated the reactions of several phenylacetylenes containing different groups on the aromatic ring. All substituted phenylacetylenes were coupled with iodobenzene to afford the α,β-alkynyl ketones in good to excellent yields (Table 2, entries 10 and 12−14). The reaction of 1-hexyne with iodobenzene only proceeded to yield 50% of the carbonylative coupling product. The carbonylative Sonogashira coupling reaction of aryl bromides or chlorides with phenylacetylene using Pd/Fe_3O_4 under the optimal conditions was also investigated, and no corresponding α,β-alkynyl ketones were observed. Indeed, aryl bromides or chlorides may served as substrates in the Sonogashira coupling reaction.[13,14] Until now, these compounds could not be successfully applied to the carbonylative Sonogashira coupling reaction.[5]

Finally, catalyst cycles were run to investigate the stability of the catalytic activity and recycling. In each cycle, the catalyst was separated by magnetic separation. The separated catalyst was then washed several times with ethanol and dried under vacuum to remove the residual solvent (Figure 2, (b) reactants containing Pd/Fe_3O_4 catalyst, (c) recycled Pd/Fe_3O_4 catalyst in ethanol). As shown in Figure 2a, the catalyst could be reused seven times only with a slight loss of activity for the carbonylative Sonogashira coupling of iodobenzene and phenylacetylene. For the carbonylative Sonogashira coupling reaction catalyzed by the Pd/Fe_3O_4 catalyst, the mechanism is quasi-homogeneous. In the catalytic process, the actual active species is a small palladium species in solution.[6] The results also show that the active Pd catalyst is dissolved from the Pd/Fe_3O_4 catalyst during the reaction and partially or completely reprecipitated onto the support at the end of the reaction.[6,15,16]

Table 2. Sonogashira Carbonylative Coupling of Alkynes and Aryl Iodides[a]



entry	aryl-I	RC≡CH	product	yield (%)[b]
1	Ph **1a**	Ph **2a**	 **3aa**	92
2	*o*-Me-Ph **1b**	Ph **2a**	 **3ba**	94
3	*p*-Me-Ph **1c**	Ph **2a**	 **3ca**	92
4	*p*-Et-Ph **1d**	Ph **2a**	 **3da**	90
5	*o*-MeO-Ph **1e**	Ph **2a**	 **3ea**	93
6	*m*-MeO-Ph **1f**	Ph **2a**	 **3fa**	86
7	*p*-MeO-Ph **1g**	Ph **2a**	 **3ga**	95
8	*p*-Cl-Ph **1h**	Ph **2a**	 **3ha**	95
9	1-Nap **1j**	Ph **2a**	 **3ia**	95
10	Ph **1a**	*p*-*t*-Bu-C_6H_4 **2b**	 **3ab**	90
11	Ph **1a**	*n*-C_4H_9 **2c**	 **3ac**	50
12	Ph **1a**	*p*-Me-Ph **2d**	 **3ad**	84
13	Ph **1a**	*o*-Me-Ph **2e**	 **3ae**	80
14	Ph **1a**	*p*-MeO-Ph **2f**	 **3af**	92
15	Ph **1a**	*p*-Br-Ph **2g**	 **3ag**	71

[a] Reactions were carried out in 5.0 mL of toluene under 2.0 MPa pressure of CO at 130 °C for 4 h with 2.5 mmol aryl iodides, 3.0 mmol phenylacetylene alkynes, 7.2 mmol Et_3N, and Pd/Fe_3O_4 catalyst (Pd, 1.04 wt %), 50 mg (Pd/substrate = 1/511). [b] Isolated yield.

In summary, we have developed a highly efficient Pd(0) catalyst immobilized on Fe_3O_4 nanoparticles highly suitable

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(13) (a) Choudary, B. M.; Madhi, S.; Chowdari, N. S.; Kantam, M. L.; Sreedhar, B. *J. Am. Chem. Soc.* **2002**, *124*, 14127. (b) Lipshutz, B. H.; Chung, D. W.; Rich, B. *Org. Lett.* **2008**, DOI: 10.1021/ol801589p.

(14) For recent reviews, see: (a) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874. (b) Doucet, H.; Hierso, J.-C. *Angew. Chem., Int. Ed.* **2007**, *46*, 834.

(15) Diallo, A. K.; Ornelas, C.; Salmon, L.; Aranzaes, J. R.; Astruc, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 8644.

(16) After the first catalytic run, about 0.03 mg of Pd was determined in the reaction solution by atomic absorption spectroscopy. After the seventh catalytic run, about 0.01 mg of Pd was determined in the reaction solution.

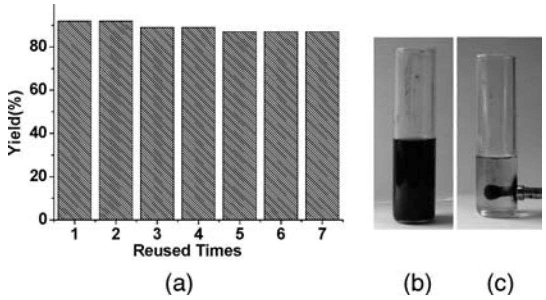

Figure 2. Recycle of the Pd/Fe_3O_4 catalyst.

for a carbonylative Sonogashira coupling reaction of aryl iodides. During the reaction, the palladium is leached and served as the active catalyst, and at the end of the reaction, palladium is redeposited onto the support. As a result, the catalyst is recoverable and could be reused seven times without significant loss in catalytic activity and selectivity. The Pd/Fe_3O_4 catalyst not only solves the basic problems of catalyst separation and recovery but also avoids the use of phosphine ligands in comparison with the homogeneous Pd catalyst system.

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Supporting Information Available: Experimental section, XPS, XRD, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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