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Nanocrystalline Titania-Supported Palladium(0) Nanoparticles for Suzuki–Miyaura Cross-Coupling of Aryl and Heteroaryl Halides

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Abstract: The Suzuki cross-coupling reaction of various aryl and heteroaryl halides with arylboronic and heteroarylboronic acids was studied using a titania-supported palladium(0) catalyst at room temperature under air. The conversion and selectivity results obtained for many substrates were excellent and similar to those provided by more active or even homogeneous catalysts. The methodology is similarly effective using 2-bromo-3,4,5-trimethoxybenzaldehyde as the coupling partner and gave products in good yield. Furthermore, it has been shown that it is useful for the synthesis of terphenyl and tetraphenyls. The catalyst is quantitatively recovered from the reaction by simple filtration and reused for a number of cycles without significant loss of activity. Inductively coupled plasma (ICP) mass-spectrometric analysis of the filtrate from the reaction mixture demonstrated that the palladium metal hardly leached into the solution within the limits of the detector (1 ppm), thus suggesting that the present Suzuki–Miyaura reaction proceeded by heterogeneous catalysis.

Keywords: aryl halides; arylboronic acids; heteroaryl halides; palladium; Suzuki–Miyaura coupling; titania

Introduction

The biaryl moiety is an important structural motif in a great number of biologically active compounds and functional molecules,[1] which include the natural products[2] Biphenomycin, the pharmaceuticals[3] Valsartan, Telmisartan, Felbinac, Losartan, Imatinib, the agrochemical Boscalid,[4] liquid crystals for LCD screens,[5] chiral ligands for catalysis[6] and organic functional materials. The palladium-catalyzed Suzuki–Miyaura cross-coupling reaction is one of the most useful methods for the synthesis of biaryl molecules.

Consequently, considerable effort has been directed to the development of efficient and selective methods for the Suzuki–Miyaura cross-coupling reaction. Generally phosphine ligands are used to complex and activate the palladium species, and excellent results have been reported for the palladium-catalyzed Suzuki–Miyaura cross-coupling reaction.[7,8] The use of such ligands is undesirable because of their toxicity and air- as well as moisture-sensitive nature with conversion to, for example, phosphine oxide species. However, few phosphine-free N-based ligands, such as N-heterocyclic carbenes,[9] N,O- or N,N-bidentate ligands,[10] aryloximes,[11] arylimines,[12] *N*-acylamidines,[13] and simple amines,[14] have been used in the Suzuki cross-coupling reaction. Despite the synthetic elegance and high turnover numbers, the non-reusability of the precious palladium precludes wide synthetic applications in the pharmaceutical industry. In view of the above, it is desirable to develop a ligand-free and reusable catalytic system for the Suzuki coupling. Heterogeneous catalysis is particularly attractive as it allows the production and ready separation of large quantities of products with the use of a small amount of catalyst. In recent years, numerous heterogeneous supported palladium catalysts were successfully employed in Suzuki cross-coupling reactions.[15]

Metal nanoparticles are attractive for catalysis because of their large surface area-to-volume ratio, which allows the effective utilization of expensive metals.[16] Palladium nanoparticles, particularly with a dimension of less than 10 nm, exhibit unexpectedly high catalytic activities toward different types of reactions, a property not revealed in bulk palladium.[17] Unfortunately, however, aggregation of naked nanoparticles often prohibits tailoring of particle size.[18] To overcome this problem, palladium nanoparticles are

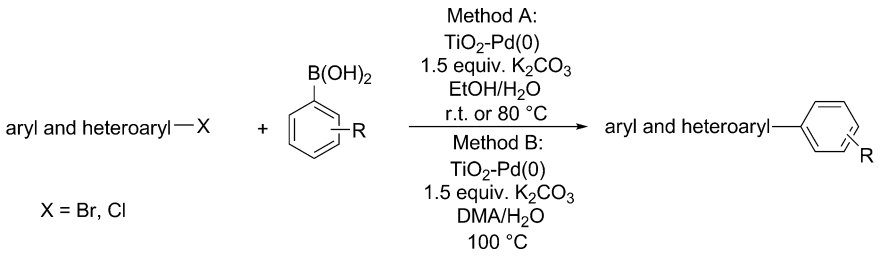
generally dispersed on support materials, among which nano metal oxides are commonly used.[19] This is because when the size of the support materials is decreased to the nanometer scale, the surface area of nanoparticles will increase dramatically. As a consequence, nanoparticle supports could have higher catalyst loading capacity than many conventional support matrixes, leading to the improved catalytic activity of the nanoparticle-supported catalysts. Among many nanomaterials, titanium dioxide is a material with outstanding chemical and physical properties, which are of interest for a wide variety of different applications in gas sensing,[20] catalysis,[21] photocatalysis,[22] optics,[23] photovoltaics,[24] and pigmentation.[25] Titanium dioxide is a useful support because it is inexpensive, inert, and non-toxic, as well as having an electronic band structure suitable for the aforementioned applications. One of the major areas of current research in the field of catalysis is the synthesis of surface-modified nanoparticles with appropriate surface-modifying agents and these surface-modified nanoparticles can be used as noble metal supports to prepare heterogeneous catalysts that are more accessible to the reactants as compared to conventional heterogeneous systems.[26]

In this article we report that nanocrystalline TiO_2-supported palladium(0) is an effective catalyst for the Suzuki–Miyaura cross-coupling of aryl and heteroaryl halides with aryl and heteroaryl boronic acids under aqueous conditions (Scheme 1). This catalyst also showed outstanding reusability without loss of significant activity.

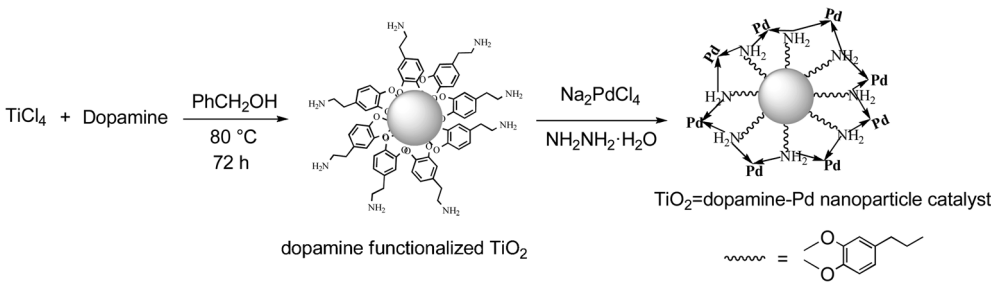
Results and Discussion

Preparation of Nanocrystalline TiO_2-Supported Pd(0) Catalyst

Preparation of the catalyst was carried out as outlined in Scheme 2. In the first step of the synthesis, titanium tetrachloride is added dropwise and under vigorous stirring to a mixture of benzyl alcohol and dopamine and the dark red reaction mixture is aged at room temperature for about 2 h and subsequently heated to 80 °C for 72 h. The dopamine-functionalized TiO_2 is recovered by centrifugation and subsequently washed with chloroform or dichloromethane and dried at 60 °C to furnish a pale brown powder in good yield.[27] 1 g of the dried dopamine-functionalized titania powder was dissolved in water, titania with dopamine ligands having positively charged terminal amine groups results in particle-particle repulsion and leads to a stable aqueous colloidal solution. To this solution Na_2PdCl_4 solution in water was added to the mixture to get 10 wt% of Pd. A dilute solution of hydrazine monohydrate was added drop wise to adjust the pH to 9. The reaction mixture was stirred overnight at room temperature and then allowed to settle. Herein hydrazine monohydrate acts as a reducing agent to reduce Pd(II) into Pd(0) during the reaction. The product Pd(0) on titania was washed several times with water, centrifuged and dried at room temperature and the product is referred as TiO_2-Pd(0).



Scheme 1.



Scheme 2. Preparation of TiO_2-supported palladium catalyst.

Characterization of Ti-Pd(0)

The prepared catalyst was well characterized with IR, TGA-MS, XRD, TEM, XPS and ICP-AES.

The FT-IR spectra of pure dopamine, surface-functionalized TiO_2 nanoparticles, and TiO_2-Pd(0) are given in the Supporting Information. From the FT-IR spectrum of surface-functionalized TiO_2 nanoparticles the peak at 3383 cm^{-1} has been assigned to the surface-adsorbed water and the peak at 1623 cm^{-1} is due to the N–H bending. The peak at 1489 cm^{-1} is due to C–H bending of aromatic groups, whereas peaks at 1259 cm^{-1} and 1156 cm^{-1} are due to C–O stretching and aliphatic C–H bending, respectively. The presence of these peaks in the TiO_2-Pd(0) catalyst clearly suggests that the functionalizing agent is intact in the final catalyst. Furthermore, the presence of dopamine in TiO_2-Pd(0) catalyst was confirmed by TGA-MS analysis. When the TiO_2-Pd(0) catalyst was subjected to TGA-MS, an evolved gas fragment 44 a.m.u was observed which can be attributed due to the fragment $-CH_2-CH_2-NH_2$, a side chain present in dopamine, and this also is consistent with the XPS and FT-IR observations confirming the synthesis of dopaminefunctionalized TiO_2-Pd(0) catalyst (please see Supporting Information). The amount of palladium in the catalyst was determined using inductively coupled plasma-atomic emission spectroscopy (ICP-AES) technique and it was found to be 0.16 mmol g^{-1}. The XRD peaks of TiO_2-Pd(0) clearly show the anatase form of TiO_2[27] and the appearance of peak at 39.86° confirms the presence of palladium in metallic state (Figure 1). Furthermore, the catalyst was characterized by transmission electron microscopy (TEM). From the TEM images of both the fresh and used catalysts, it is seen that the average size of TiO_2 nanoparticles is in the range of 10–15 nm in diameter and palladium nanoparticles of about 2–3 nm and are uniformly dispersed on TiO_2 nanoparticles (the size distributions for both TiO_2 and Pd nanoparticles are shown in Supporting Information). Although we followed the same procedure as Niederberger et al.,[27] the size of TiO_2 particles is larger. possibly due to the difference in the aging times. This clearly confirms that there is no change in the morphology even after five cycles [Figure 2 (**b**)]. X-ray photoelectron spectroscopic (XPS) investigation of TiO_2-Pd nanoparticles of used and fresh catalysts was carried out. XPS survey scans of both fresh and used catalyst showed characteristic peaks of Ti 2*p*, O 1*s* and Pd 3*d* along with C 1*s* peak (please see Supporting Information). High resolution narrow scans for Pd 3*d* level show peaks at 335.08 eV and 340.41 eV and 334.92 eV and 340.26 eV for Pd $3d_{5/2}$ and Pd $3d_{3/2}$, respectively, which clearly indicates that the palladium is in the zero oxidation state (Figure 3) even after five catalytic cycles. Two peaks were observed for O 1*s* at 529.79 eV and 531.94 eV for the fresh and 529.60 eV and 531.69 eV for the used catalyst. The peak at 529 eV is attributed to the oxygen bonding in TiO_2 whereas the 531.6 eV peak is due to OH present in dopamine. This observation

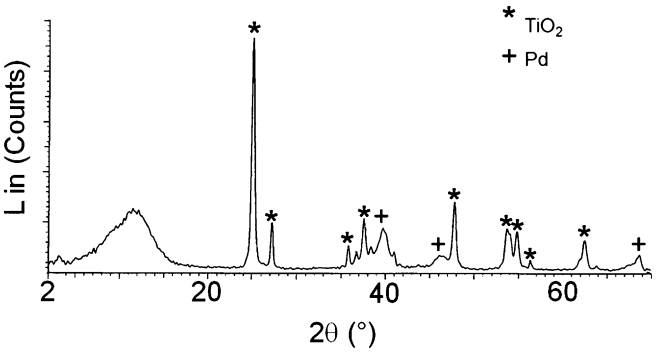


Figure 1. XRD spectrum of TiO_2-Pd(0) nanoparticles.

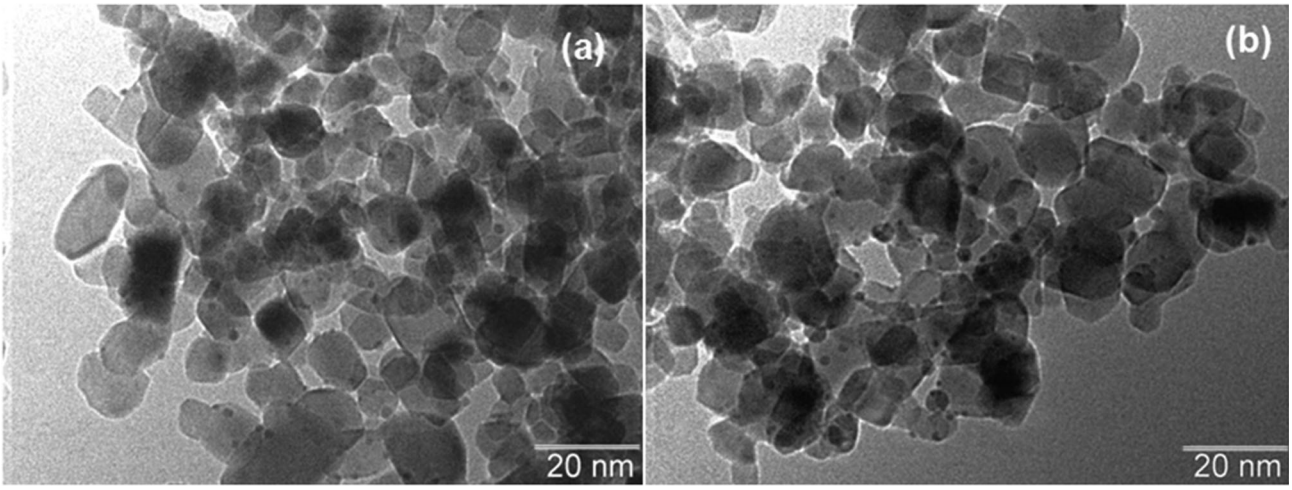


Figure 2. TEM images of TiO_2-Pd(0) nanoparticles before (**a**) and after (**b**) catalysis as observed at 120 kV.

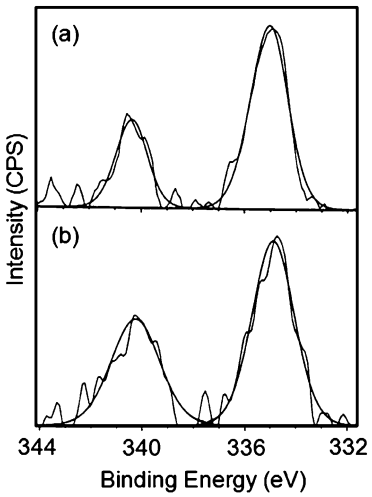


Figure 3. High resolution XPS scan of Pd 3*d* in (**a**) fresh and (**b**) used catalyst – TiO_2-Pd(0) nanoparticles.

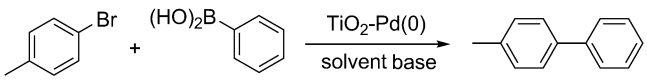
also suggests that TiO_2 is functionalized with dopamine in the present catalytic system. Furthermore, the BET surface area of TiO_2-Pd(0) is found to be 142 m^2g^{-1}(please see Supporting Information).

Suzuki–Miyaura Cross-Coupling using Ti-Pd(0)

In an endeavor to identify the best catalytic system for Suzuki coupling, various bases in combination with different solvents were investigated using 4-bromotoluene and phenylboronic acid as the model substrates and the results are presented in Table 1. The solvent has a pronounced effect in these reactions out of which ethanol/water (1:1) has been proven to the best solvent. Ethanol, methanol and methanol/water (1:1) gave the product in moderate yield, whereas 2-propanol, *n*-butanol and water gave the product in low yield. However, water with TBAB (1.2 equiv.) at 80 °C proved to be equally good as ethanol/water (1:1) and gave the product 4-methylbiphenyl in good yield within 2 h (Table 1, entries 1–9). Among the various bases screened in ethanol/water (1:1), the relatively weak and less expensive K_2CO_3 gave the best result. Reactions with other bases such as Na_2CO_3, K_3PO_4 and Cs_2CO_3 generate the desired product in good yields (Table 1, entries 10, 11and 14), whereas, *t*-BuOK and NaOH gave the product in low yield (Table 1, entries 12 and 13).

We are gratified to observe that the best conditions developed for phenylboronic acid and 4-bromotoluene were found to be broadly applicable for a variety of neutral, electron-rich, and electron-poor arylboronic acids and heteroarylboronic acids proving the scope and generality of TiO_2-Pd-prompted Suzuki–Miyaura reaction to afford the corresponding biaryls in high to excellent yields and our preparative results

Table 1. Optimization of reaction conditions for Suzuki–Miyaura cross-coupling.[a]



Entry	Base	Solvent	Time [h]	Yield [%][b]
1	K_2CO_3	H_2O	10	30
2	K_2CO_3	H_2O/TBAB	6	65
3	K_2CO_3	H_2O/TBAB	2	86[c]
4	K_2CO_3	EtOH	4	82
5	K_2CO_3	MeOH	4	75
6	K_2CO_3	2-propanol	6	48
7	K_2CO_3	*n*-butanol	10	25
8	K_2CO_3	EtOH/H_2O	4	92
9	K_2CO_3	MeOH/H_2O	4	90
10	Na_2CO_3	EtOH/H_2O	4	85
11	K_3PO_4	EtOH/H_2O	4	80
12	*t*-BuOK	EtOH/H_2O	4	56
13	NaOH	EtOH/H_2O	6	30
14	Cs_2CO_3	EtOH/H_2O	4	90

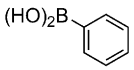
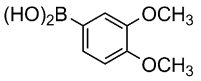
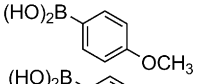
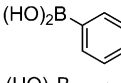
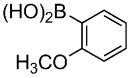
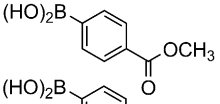
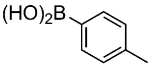
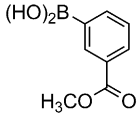
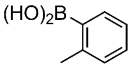
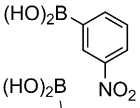
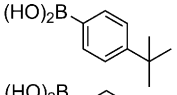
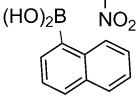
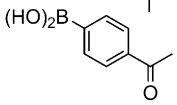
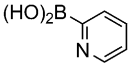
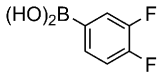
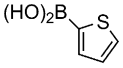
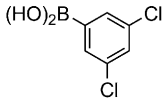
[a] *Reaction conditions:* 4-bromotoluene (1 mmol), phenylboronic acid (1.2 mmol), catalyst (0.8 mol%), base (1.5 equiv.), solvent (2 mL), room temperature.
[b] Yield after column chromatography.
[c] Reaction conducted at 80 °C.

are presented in Table 2. Notably, even electron-deficient arylboronic acids, which are known to be usually reluctant to give Suzuki–Miyaura products very likely because they are less nucleophilic than their electron-neutral analogues and consequently tend to transmetalate more slowly, gave the desired derivatives in excellent yields (Table 2). Arylboronic acids bearing *ortho* substituents can also be used to prepare hindered cross-coupling products in high yield (Table 2, entries 3 and 5). Furthermore, heteroaryl boronic acids such as pyridine-2-boronic acid and thiophene-2-boronic acid underwent the reaction smoothly to give the desired product in good yield under the optimized reaction conditions (Table 2, entries 16 and 17).

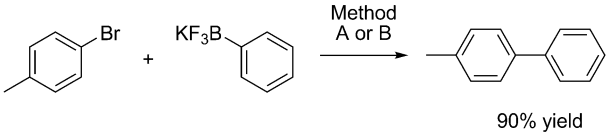
Moreover, the potassium organofluoroborate also reacted smoothly to give the desired product in excellent yield by using TiO_2-Pd(0) as the catalyst (Scheme 3).

However, unfortunately, this catalyst was ineffective for the reaction of alkylboronic acid (cyclohexylboronic acid) with 4-bromotoluene even under harsh reaction conditions (Scheme 4).

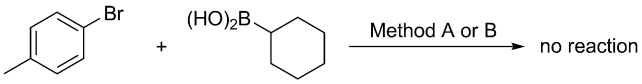
Table 2. TiO_2-Pd(0) catalyzed Suzuki–Miyaura cross coupling of 4-bromotoluene with different arylboronic acids.[a]

Entry	Boronic acid	Time [h]	Yield [%][b]	Entry	Boronic acid	Time [h]	Yield [%][b]
1		6	87	10		5	96
2		6	92	11		5	96
3		8	90	12		6	87
4		5	92	13		6	83
5		6	90	14		8	91
6		6	95	15		6	88
7		6	85	16		10	82
8		6	90	17		10	76
9		6	92				

[a] *Reaction conditions:* 4-bromotoluene (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (1.5 mmol), and ethanol/water mixture(1:1) (2 mL), room temperature.
[b] Yield after column chromatography.



Scheme 3. Suzuki–Miyaura cross-coupling of bromotoluene with potassium trifluoroborates.

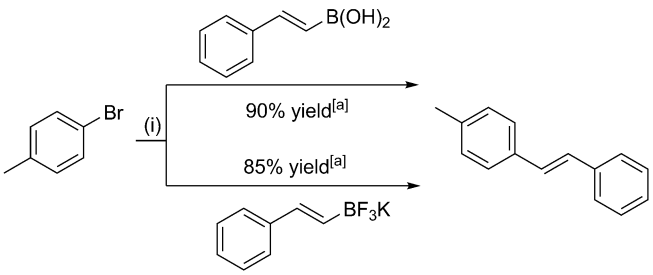


Scheme 4.

The optimized conditions could also be extended to the Suzuki–Miyaura coupling reaction of both β-styrylboronic acid and β-styryl trifluroborates with 4-bromotoluene to form the Suzuki–Miyaura coupling product with 95% and 90% yields, respectively (Scheme 5.

Encouraged by these results, we next investigated the scope of the reaction with respect to the aryl halide substrate. We tested a variety of substituted aryl bromides under the optimized reaction conditions with phenylboronic acid as cross-coupling counterpart. Various aryl bromides, including the deactivated aryl bromides, were readily converted to the corresponding coupled products in excellent yields as shown in Table 3.

Unsubstituted as well as 4-methyl-, 4-methoxy-substituted bromobenzenes underwent smooth reaction with good yields when compared to 2-methyl- and 2-methoxybromobenzenes (Table 3, entries 1–6). Furthermore, the reaction was extended to other aryl halides having electron withdrawing groups to generate biaryl products in good to excellent yields (Table 3, entries 7–11). It is interesting to note that coupling of 3,5-dibromobenzaldehyde with phenylboronic acid gave 3-phenyl-5-bromobenzaldehyde in 73% along with 10% diphenyl product and when we used 2 equivalents of phenylboronic acid the reaction underwent smoothly to afford terphenyl in 83% yield (Table 3, entry 11). As terphenyls are known to possess biological activities with potential therapeutic value,[28] we have tested the TiO_2-Pd(0) catalyst for the preparation of *o*-, *m*-, and *p*-terphenyls under standard reaction conditions (Table 4). To our delight



Scheme 5. *Reaction conditions:* (i) 4-bromotoluene (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (1.5 mmol) and ethanol/water mixture-(1:1) (2 mL), room temperature. [a] Yield after column chromatography.

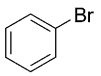
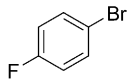
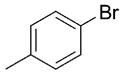
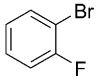
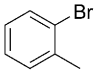
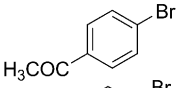
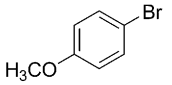
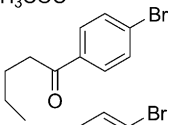
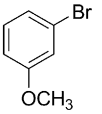
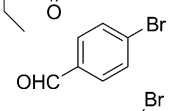
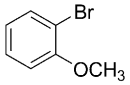
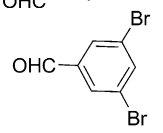
1,3- and 1,4-dibromobenzenes undergo cross-coupling with *o*-methylphenylboronic acid smoothly to give the desired products in good yields (Table 4, entries 1 and 2). Further as shown in Table 4, the coupling of 1,2-dibromobenzene and 1,3,5-tribromobenzenes with *p*-methylphenylboronic acid also gave terphenyl and tetraphenyl, respectively (Table 4, entries 3 and 4).

Under the same reaction conditions, a number of bromonaphthalenes and 9-bromophenanthroline were also found to be reactive with *p-tert*-butylphenylboronic acid and gave the products in good yield (Table 5).

Given the remarkably high levels of catalytic activity displayed with TiO_2-Pd(0) catalyst, we investigated its use for the preparation of hindered biaryls from 2-bromomesitylene and different phenylboronic acids. As can be seen from Table 6, arylboronic acids with electron-donating groups such as methoxy, hydroxy, *tert*-butyl, 3,4-dimethoxy and 3,4-methylenedioxy groups (Table 6, entries 1–6) underwent smooth reaction with excellent yields compared to those with electron-withdrawing group (Table 6, entry 7) present in the phenylboronic acid ring.

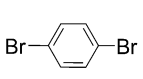
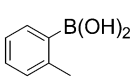
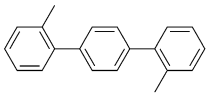
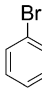
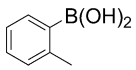
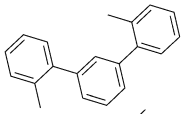
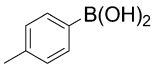
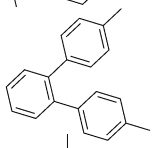
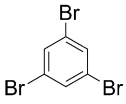
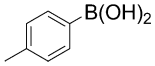
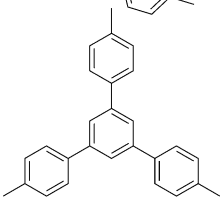
To explore the scope and limitations of the coupling reaction fully, the coupling of a number of substituted arylboronic acids with 2-bromo-3,4,5-trimethoxybenzaldehyde was studied as the resulting products are present in number of bioactive compounds (Figure 4)[29] and the results are summarized in Table 7. Arylboronic acids with substituents at the *para* and *meta* positions were well tolerated and gave the products in yields comparable to their unsubstituted phenylboronic acid (Table 7, entries 1–6). In addition, electronic effects associated with the substituent did not manifest themselves in either the yields of product obtained or the conditions required to achieve the coupling. However, coupling efficiency was significantly altered when strong electron-withdrawing substituents are present on the aromatic ring (Table 7, entries 7–9) and this effect is not observed with the dichloro and difluoro substitutions (Table 7, entries 10 and 11). Furthermore, β-styrylboronic acid underwent the cross-coupling reaction smoothly and gave the desired product in good yield (Table 7, entry 12).

Table 3. Nano-TiO_2-Pd(0) catalyzed Suzuki–Miyaura cross coupling of different bromoarenes with phenylboronic acid.[a]

Entry	Aryl bromide	Time [h]	Yield [%][b]	Entry	Aryl bromide	Time [h]	Yield [%][b]
1		4	95	7		6	94
2		6	92	8		6	91
3		8	88	9		4	98
4		6	96	10		4	94
5		6	95	11		4	95
6		6	75	12		8	75

[a] *Reaction conditions:* aryl halide (1 mmol), phenylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (1.5 mmol), and ethanol/water mixture(1:1) (2 mL), room temperature.
[b] Yield after column chromatography.

Table 4. Synthesis of different *o*-, *m*-, *p*-terphenyls and tetraphenyls.[a]

Entry	Aryl halide	Boronic acid	Product	Time [h]	Yield [%][b]
1				8	90
2				8	86
3				8	85
4[c]				10	85

[a] *Reaction conditions:* aryl halide (1 mmol), arylboronic acid (2.5 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (3 mmol), and ethanol/water mixture(1:1) (3 mL), room temperature.

[b] Yield after column chromatography.

[c] *Reaction conditions:* aryl halide (1 mmol), arylboronic acid (3.5 mmol), TiO_2-Pd(0) catalyst (1.2 mol%), K_2CO_3 (4.5 mmol) and ethanol/water mixture(1:1) (5 mL), room temperature.

However, this catalyst was ineffective for the reaction of alkyl halide (2-phenylethyl bromide) with phenylboronic acid under the optimized reaction conditions.

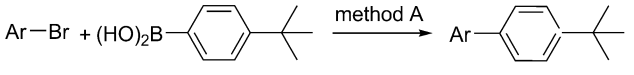
Owing to the stability of the carbon-chlorine bond, aryl chlorides are challenging substrates for various coupling reactions. Encouraged with these results we chose to investigate heterogeneous TiO_2-Pd(0) catalyst to activate aryl chlorides for Suzuki–Miyaura cross coupling. Unfortunately the catalytic system was less effective for the aryl chlorides. However, best results were obtained by increasing the temperature to 100 °C and changing the solvent from H_2O/EtOH to H_2O/DMA and K_2CO_3 as the base. Under the above conditions, the TiO_2-Pd(0) possessed good catalytic activity for aryl chlorides.

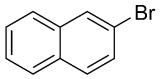
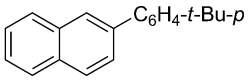
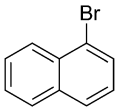
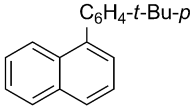
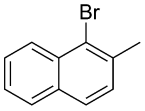
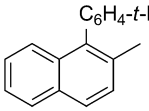
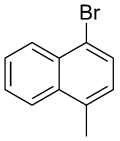
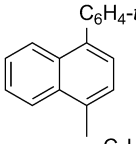
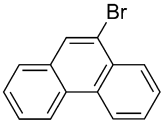
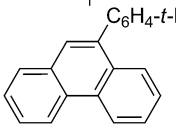
Unsubstituted as well as 4-methyl-, 4-methoxychlorobenzenes and (4-chlorophenyl) (methyl) sulfane underwent reaction with moderate to good yields of the biphenyl products (Table 8, entries 1–4). On the other hand, chloroarenes with electron-withdrawing substituents underwent the reaction smoothly to generate biphenyl products in good to excellent yields (Table 8, entries 5–9).

According to a recent MDL Drug Data Report, pyridines are the most common heterocycles in pharmaceutically active compounds.[30] A useful synthetic tool for the modification of such compounds is the Suzuki–Miyaura coupling,[31] which has been applied for the preparation of arylpyridines,[32] bipyridines,[33] arylpyrimidines,[34] and the synthesis of nucleosides.[35] Unfortunately, nitrogen-containing heterocycles are difficult substrates for Suzuki–Miyaura cross-coupling reactions.[36] In this regard, we next wanted to demonstrate the generality of the optimized reaction conditions for Suzuki–Miyaura reactions of heteroaryl chlorides with arylboronic acids using nano TiO_2-Pd(0) as the catalyst.

The coupling of both electron-rich and electron-poor arylboronic acids proceeded smoothly with 2-chloropyridine and a quantitative yield of 2-phenylpyridines were obtained in the presence of TiO_2-Pd(0) at 100 °C (Table 9, entries 1 and 2). 2-Chloro-6-methoxypyridine also underwent the desired reaction and gave the product in good yield (Table 9, entry 3). Furthermore, as shown in Table 9, the Suzuki–Miyaura coupling was also successful with other heterocycles including quinoline, pyrimidines, quinazoline and thiazoles. Excellent results were obtained in each case as the reactions were complete within three hours, affording 82–95% yields of the corresponding products. Amexol reacted even faster to give the desired products in excellent yields (Table 9, entries 4–7). It was also found that this method could be readily

Table 5. Nano-TiO_2-Pd(0)-catalyzed Suzuki–Miyaura cross-coupling of different bromonaphthlenes with *p-tert*-butylphenylboronic acid.[a]



Entry	Aryl halide	Product	Time [h]	Yield [%][b]
1			4	85
2			4	82
3			6	75
4			6	80
5			6	69

[a] *Reaction conditions:* aryl halide (1 mmol), 4-*tert*-butylphenylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (1.5 mmol) and ethanol/water mixture(1:1) (2 mL), room temperature.

[b] Yield after column chromatography.

applicable to 2-chlorothiazole to afford the corresponding product in good yield (Table 9, entry 8).

The heterogeneity of the catalyst was also evaluated to study whether the reaction using solid Pd catalysts occurred on the solid surface or was catalyzed by Pd species in the liquid phase. To address this issue, we conducted two separate experiments with 4-bromotoluene and phenylboronic acid. In the first experiment, the reaction was terminated after 1 h, and the conversion of 4-bromotoluene was found to be 34%. At this juncture, the catalyst was separated from the reaction mixture and the reaction was continued with the filtrate for an additional 5 h. In the second experi-

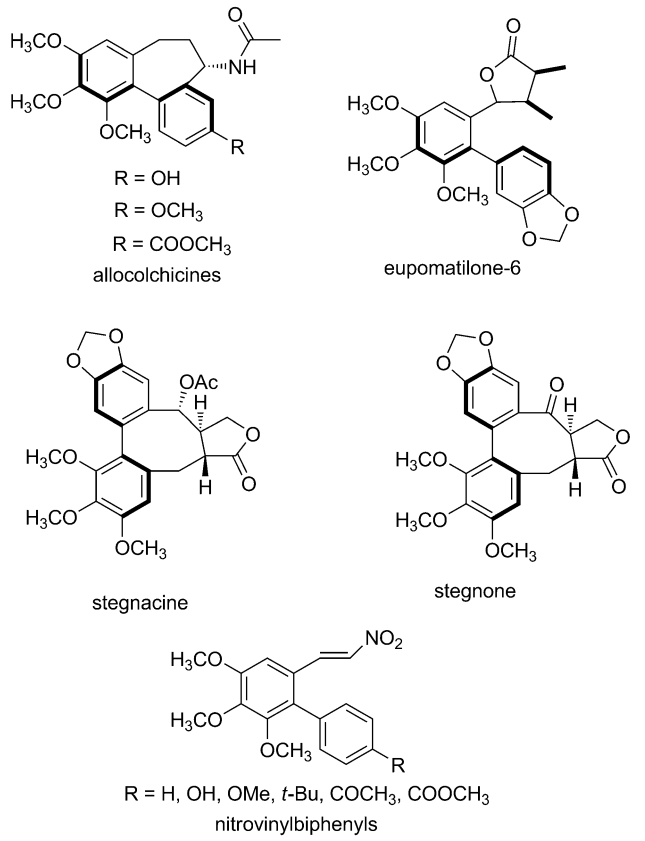
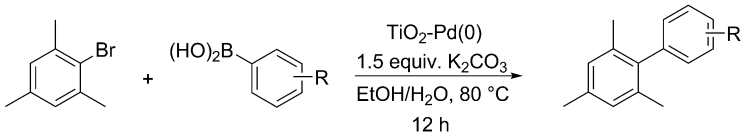


Figure 4.

Table 6. Synthesis of hindered biaryls using Nano-TiO_2-Pd(0)-catalyzed Suzuki–Miyaura cross-coupling.[a]

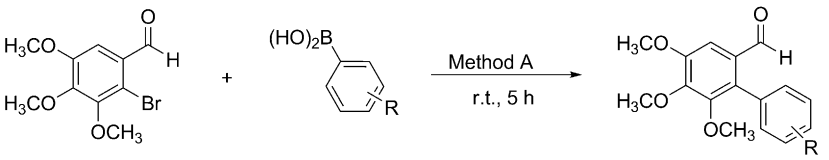


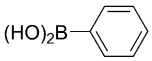
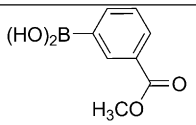
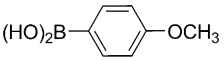
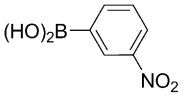
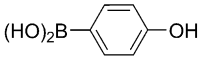
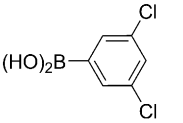
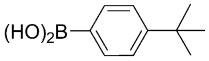
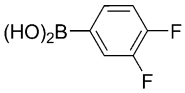
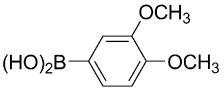
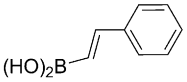
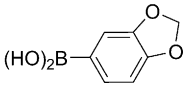
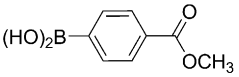
Entry	1	2	3	4	5	6	7
R	H	4-OCH_3	4-OH	4-$C(CH_3)_3$	3,4-OCH_2O	3,4-$(OCH_3)_2$	4-$COOCH_3$
Yield [%][b]	86	91	88	90	92	89	82

[a] *Reaction conditions:* 2-bromomesitylene (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (1.5 mmol), and ethanol/water mixture(1:1) (2 mL).

[b] Yield after column chromatography.

Table 7. Nano-TiO_2-Pd(0)-catalyzed Suzuki–Miyaura coupling of 2-bromo-3,4,5-trimethxy benzaldehyde with different arylboronic acids.[a,b]

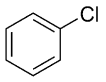
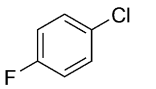
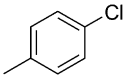
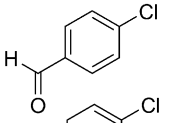
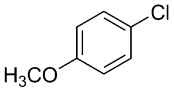
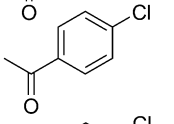
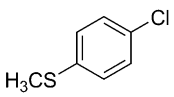
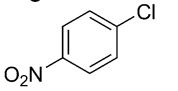


Entry	Boronic acid	Yield [%][b]	Entry	Boronic acid	Yield [%][b]
1		92	8		78
2		95	9		75
3		90	10		90
4		96	11		92
5		92	12		94
6		95			
7		85			

[a] *Reaction conditions:* 2-bromo-3,4,5-trimethoxybenzaldehyde (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (1.5 mmol), and ethanol/water mixture-(1:1) (2 mL), room temperature.

[b] Yield after column chromatography.

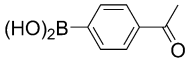
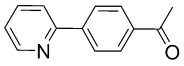
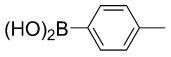
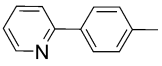
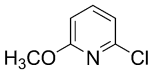
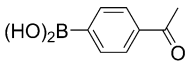
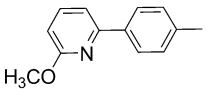
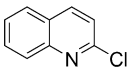
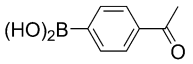
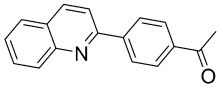
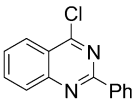
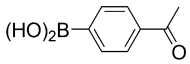
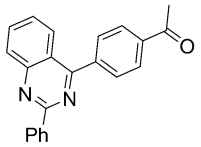
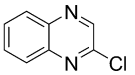
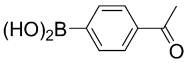
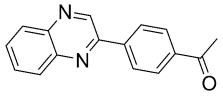
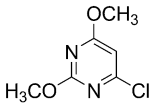
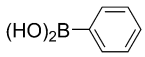
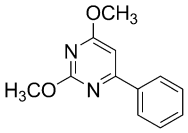
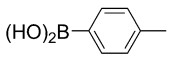
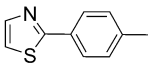
Table 8. Nano-TiO_2-Pd(0)-catalyzed Suzuki–Miyaura cross-coupling of chloroarenes with phenylboronic acid.[a]

Entry	Aryl chloride	Time [h]	Yield [%][b]	Entry	Aryl chloride	Time [h]	Yield [%][b]
1		24	78	5		24	82
2		48	65	6		24	80
3		48	68	7		24	86
4		48	51	8		16	94

[a] *Reaction conditions:* aryl chloride (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (1.5 mol%), K_2CO_3 (1.5 mmol), and DMA/water mixture(2:1) (3 mL), 100 °C, under air.

[b] Yield after column chromatography.

Table 9. Nano-TiO_2-Pd(0)-catalyzed Suzuki–Miyaura cross-coupling of different heteroaryl halides with arylboronic acids.[a]

Entry	Aryl chloride	Arylboronic acid	Product	Time [h]	Yield [%][b]
1				12	88
2				8	92
3				10	85
4				6	92
5				2	95
6				4	95
7				6	87
8				6	82

[a] *Reaction conditions:* heteroaryl chloride (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (1.5 mol%), K_2CO_3 (1.5 mmol), and DMA/water mixture(2:1) (3 mL), 100 °C, under air.

[b] Yield after column chromatography.

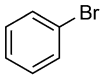
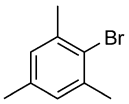
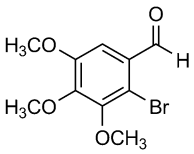
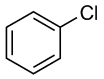
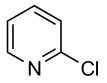
ment, the reaction was terminated after 2 h at 65% conversion, and the catalyst was removed. The reaction was continued with the filtrate for an additional 5 h. In both the cases, the conversion remained almost unchanged. Inductively coupled plasma (ICP) mass-spectrometric analysis of the filtrate from the reaction mixture demonstrated that the palladium metal hardly leached into the solution within the limits of the detector (1 ppm), thus suggesting that the present Suzuki–Miyaura reaction proceeded heterogeneously with palladium bound to the support throughout the reaction.

To check the reusability of the catalyst, as can be seen from Table 10, the reaction was performed with different aryl halides with phenylboronic acid under the optimized reaction conditions. After completion of the reaction the catalyst was separated from the reaction mixture by simple filtration and reused for five times showing partial loss in activity, i.e., between 4–7% yield depending on the substrate, which can also be attributed to the marginal increase in the size of the Pd nanoparticles as is seen from the histogram of size distribution (Figure 2 in Supporting Information).

Conclusions

In summary, we have developed a simple, general catalytic system for the Suzuki–Miyaura cross-coupling reaction with a broad substrate scope with an ability to make truly hindered biaryls, synthesis of terphenyls and the ability to operate at room temperature. Notably, the reaction is performed at room temperature with the use of a ligand-free heterogeneous palladium catalyst. This methodology is similarly suitable for the coupling of 2-bromo- and 3,4,5 trimethoxybenzaldehydes with different arylboronic acids and gave products in good yield. This catalytic system is also effec-

Table 10. Suzuki–Miyaura cross-coupling of different aryl halides with phenylboronic acid over five cycles.[a]

Entry	Aryl halide	Time [h]	Yield [%][d]				
			Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5
1[a]		4	92	90	90	87	88
2[a,b]		12	86	85	83	81	80
3[a]		5	92	93	91	89	85
4[c]		24	78	76	75	75	73
5[c]		8	90	90	88	86	85

[a] *Reaction conditions:* aryl bromide (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (0.8 mol%), K_2CO_3 (1.5 mmol), and ethanol/water mixture(1:1) (2 mL), room temperature, 4 h.
[b] Reaction conducted at 80 °C.
[c] *Reaction conditions:* aryl chloride (1 mmol), arylboronic acid (1.2 mmol), TiO_2-Pd(0) catalyst (1.5 mol%), K_2CO_3 (1.5 mmol) and DMA/water mixture (2:1) (3 mL), 100 °C, under air.
[d] Yield after column chromatography.

tive for Suzuki cross-couplings of both aryl and heteroaryl chlorides and heteroarylboronic acids, thus providing the desired products in generally good yields. The catalyst is quantitatively recovered from the reaction by simple filtration and reused for a number of cycles without significant loss of its catalytic activity. The simple procedure for catalyst preparation, easy recovery, and reusability of the catalyst is expected to contribute to its utilization for the development of benign chemical processes and products.

Experimental Section

General Remarks

All chemicals were purchased from Sigma–Aldrich and S.D Fine Chemicals, Pvt. Ltd. India and used as received. ACME silica gel (100–200 mesh) was used for column chromatography and thin-layer chromatography was performed on Merck-precoated silica gel 60-F_{254} plates. All the other chemicals and solvents were obtained from commercial sources and purified using standard methods. The IR spectra of all compounds were recorded on a Perkin–Elmer, Spectrum GX FTIR spectrometer. The IR values are reported in reciprocal centimeters (cm^{-1}). The ^1H, ^{13}C NMR spectra were recorded on Varian 400 MHz or Bruker-Avance 300 MHz spectrometers. Chemical shifts (δ) are reported in ppm, using TMS ($\delta = 0$) as an internal standard in $CDCl_3$. ESI mass spectra were recorded on a Finnigan LCQ Advantagemax spectrometer. EI mass spectra were recorded on a GC-MS QP2010 Plus (Shimadzu). The morphology, size and shape distribution of the Pd nanoparticles were recorded using a TECNAI FE12 TEM instrument operating at 120 kV. In each image more than 150 particles were analyzed using SIS imaging software to create the size distribution histogram. The diffraction patterns were recorded at selected area to determine the crystal structure and phases of crystals at 660 mm camera length. X-ray diffraction measurements of the Pd nanoparticles were recorded using a Rikagu diffractometer (Cu radiation, $\lambda = 0.1546$ nm) running at 40 kV and 40 mA (Tokyo, Japan). X-ray photoelectron spectroscopy (XPS) measurements were obtained on a KRATOS-AXIS 165 instrument equipped with dual aluminum-magnesium anodes using Mg Kα radiation ($h\nu = 1253.6$ eV) operated at 5 kV and 15 mA with pass energy 80 eV and an increment of 0.1 eV. The samples were degassed out for several hours in the XPS chamber to minimize air contamination to sample surfaces. In order to overcome the charging problem, a charge neutralizer of 2 eV was applied and the binding energy of C 1*s* core level (BE = 284.6 eV) of adventitious hydrocarbon was used as a standard. The XPS spectra were fitted using a non-linear square method with the convolution of Lorentzian and Gaussian

functions after a polynomial background was subtracted from the raw spectra. The amounts of Pd in the sample and filtrate are determined with an IRIS Intrepid II XDL inductively coupled plasma, atomic emission spectroscopy (ICPAES) instrument.

Preparation of the Dopamine-Functionalized TiO_2 Nanoparticles

In a typical synthesis, 1.89 g (10 mmol) of 3-hydroxytyramine hydrochloride was dispersed in 200 mL of benzyl alcohol in a glovebox. The vial was sealed and taken out of the box. 15 mL (137 mmol) of $TiCl_4$ were slowly added to the benzyl alcohol-ligand mixture under vigorous stirring at room temperature. The vial was sealed, and with continuous stirring heated to 80 °C for 72 h. The resulting pale brown suspension was centrifuged and the precipitate thoroughly washed twice with chloroform. After each washing step, the solvent was removed by centrifugation. The collected material was left to dry in air at room temperature and subsequently at 60 °C, yielding the dopamine-functionalized TiO_2 nanoparticles.

Preparation of the TiO_2-Pd(0) Catalyst

1 g of dopamine-functionalized TiO_2 nanoparticles was dispersed in water and Na_2PdCl_4 solution in water was added to the mixture to get 10 wt% of Pd. A diluted solution of hydrazine monohydrate was added dropwise to adjust the pH to 9. The reaction mixture was stirred overnight at room temperature and then allowed to settle. The product was washed several times with water, centrifuged and dried at room temperature.

Experimental Procedure for Room Temperature Suzuki–Miyaura Coupling of Bromoarenes (Method A)

An oven-dried, 10-mL, round-bottom flask was charged with aryl halide (1 mmol), phenylboronic acid (1.2 mmol), K_2CO_3 (1.5 mmol), TiO_2-Pd(0) (0.8 mol%), and ethanol/water mixture (1:1) (2 mL). The reaction mixture was stirred at room temperature (for 2-bromomesytylene at 80 °C) and the reaction was monitored by TLC. After the completion of the reaction as judged by TLC, the catalyst was separated by simple filtration and reused. The crude reaction mixture was extracted with ethyl acetate and chromatographed on silica gel using hexane/ethyl acetate as an eluent to afford the pure product.

Experimental Procedure for Suzuki–Miyaura Coupling of Aryl and Heteroaryl Chlorides (Method B)

An oven-dried, 10-mL, round-bottom flask was charged with aryl chloride (1 mmol), arylboronic acid (1.2 mmol), K_2CO_3 (1.5 mmol), TiO_2-Pd(0) (1.5 mol%), and *N*,*N*-dimethylacetamide/water (2:1) (3 mL). The reaction mixture was stirred at 100 °C under air and the reaction was monitored by TLC. After completion of the reaction as judged by TLC, the catalyst was separated by simple filtration and reused. The crude reaction mixture was extracted with ethyl acetate and chromatographed on silica gel using hexane/ethyl acetate as an eluent to afford the pure product.

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