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Heterogeneous Palladium Catalysts for a New One-Pot Chemical Route in the Synthesis of Fragrances Based on the Heck Reaction

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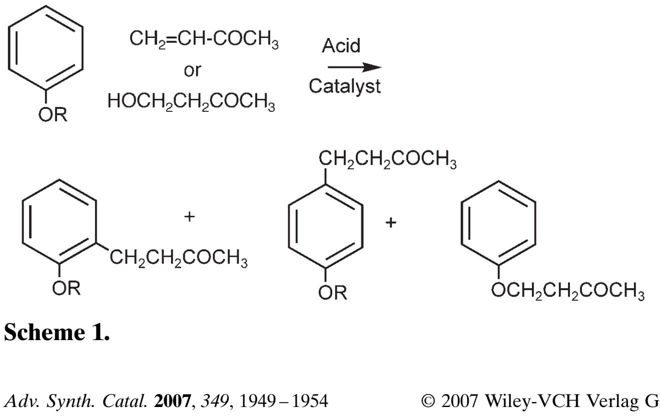
Abstract: The one-pot synthesis of the fragrance 4-(*p*-methoxyphenyl)butan-2-one, with raspberry scent, has been carried out using palladium on different supports such as magnesium oxide (MgO), hydrotalcite, hydroxyapatite (HA), aluminium oxide (γ-Al_2O_3) and titanium dioxide (TiO_2). The first pathway consists of a Heck coupling between 4-methoxy-iodoanisole and methyl vinyl ketone followed by hydrogenation. Palladium supported on titanium dioxide showed the best performance for carrying out both consecutive steps giving 4-(*p*-methoxyphenyl)-butan-2-one with high yields and selectivity. The Pd-TiO_2 catalyst is more active than a homogeneous palladium complex that is well accepted in the literature as being highly active for performing Heck reactions.

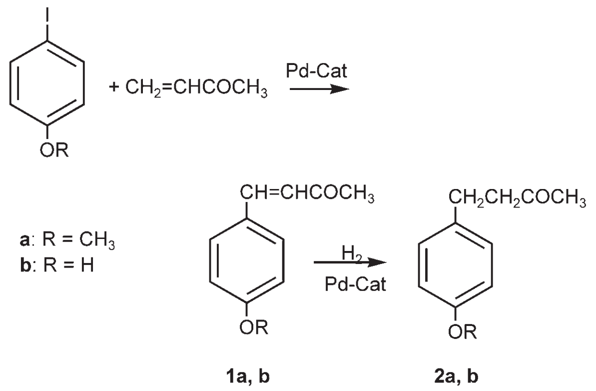
Keywords: fragrances; Heck reaction; one-pot reaction; palladium; raspberry scent; supported catalysts

Introduction

4-(*p*-Methoxyphenyl)butan-2-one (**2a**) and 4-(*p*-hydroxyphenyl)butan-2-one (**2b**) are odorous products with raspberry scent obtained by extraction from *Aloe* wood, which have been approved by the FDA for food use at a level of 25 ppm. Commercially they have been prepared by Friedel–Crafts alkylation of anisole or phenol with 4-hydroxybutan-2-one or methyl vinyl ketone using acid catalysts such as concentrated sulfuric, phosphoric, and hydrochloride acids.[1] It is known that the Friedel–Crafts alkylation of phenol or anisole with 4-hydroxybutan-2-one or methyl vinyl ketone in the presence of Lewis or Brønsted homogeneous acid catalysts produces many side reactions such as transalkylations, isomerization, polyalkylation and polymerization (Scheme 1). Thus, cation exchanged resins have been reported in the patent literature as heterogeneous catalysts to perform this alkylation.[2] More specifically, Dowex-50 was used for the alkylation of phenol with 4-hydroxybutan-2-one and a selectivity of 60–70% for **2b** is claimed, while, no conversion data are reported. In a more recent work the preparation of **2a** has been described by Friedel–Crafts alkylation of anisole with 4-hydroxybutan-2-one or methyl vinyl ketone in the presence of a cation exchanged montmorillonite. However, in that case the yield of **2a** was only 25% at 373 K after 48 h reaction time.[3] We thought that an alternative catalytic process for the synthesis of **2a** could consist in reacting aryl halides with methyl vinyl ketone through a Heck reaction in the presence of a homogeneous or heterogeneous palladium catalyst. This will give the intermediate **1a**, which can be hydrogenated to give product **2a** (Scheme 2). Since both reactions are compatible following our process, we will show that it is possible to obtain excellent yields and selectivities of the desired product by means of a one-pot reaction. The search for uni- or multisite catalysts that allow the introduction of new cascade or one-pot processes, avoiding intermediate separation and purifications, is a matter of much interest from the fundamental and technological points of view.[4] In fact, this methodology based on consecutive Heck coupling followed by hydrogenation, has been reported for the synthesis of dibenzyl and 2-styrylphenylamine using Pd/C as catalyst.[5]



Scheme 1.



Scheme 2.

The Heck reaction[6] is a selective method to form C–C bonds in organic synthesis. The reaction involves the coupling of olefins that can contain a variety of multifunctional groups, with aryl or vinyl halides in the presence of soluble palladium Pd(II) or Pd(0) complexes as catalysts, tertiary amine as a base, and an aprotic polar liquid (such as, for instance, dimethylformamide or dimethylacetamide) as solvent. A generally accepted mechanism involves oxidative addition of aryl halide to Pd(0), addition of olefin to Pd complex, beta-hydride elimination of the product and regeneration of the Pd catalyst by reduction. Usually a precatalyst in the Pd(II) oxidation state is used and this is presumed to be reduced to Pd(0) *in situ* allowing the oxidative addition of the aryl halide to form a Pd(II) intermediate.[7]

The use of different homogeneous[8] and solid catalysts[9] containing palladium for the Heck reaction has recently attracted considerable interest. Thus, palladium supported on carbon,[10] mesoporous material (MCM-41),[11] molecular sieves,[12] oxides (MgO, TiO_2, ZnO, Al_2O_3),[13] layered double hydroxide,[14] basic zeolites and sepiolites,[15] silica,[16] and alumina[17] have been applied to the Heck reaction.

In the first part of this work, the synthesis of **2a** has been carried out using palladium on different supports. As supports we have chosen high surface area, basic solid catalysts such as MgO, hydrotalcite (HT), and hydroxyapatite (HA), as well as γ-Al_2O_3 and TiO_2. In the second part of the work results with a homogeneous catalyst will be revealed.

Results and Discussion

A new route to obtain 4-(p-methoxyphenyl)butan-2-one (**2a**) of raspberry scent is proposed here that involves the Heck reaction between 4-methoxyiodobenzene and methyl vinyl ketone followed by the one-pot hydrogenation of intermediate **1a** in the presence of different solid catalysts (see Scheme 2).

In order to study the possibilities of this new route for synthesizing the raspberry scent, we have prepared different palladium-based catalysts by supporting Pd on different metal oxide supports. The catalysts, with 0.2 wt % of Pd, were tested in the first reaction step, that is, the Heck reaction, using a methyl vinyl ketone/iodoanisole molar ratio of 2, dimethylformamide as a solvent and 393 K as reaction temperature. After 5 h reaction time, the reactor was pressurized with H_2 (5 bar) and the reaction continued during 15 h at 393 K. Moreover, for comparison purposes, a commercial Pd/C (5 wt%) was also tested. The amount of Pd/C catalyst was adjusted in such way the Pd content was the same as that in the case of the other heterogeneous catalysts. In Table 2 the conversions and yields obtained in each reaction step with the different Pd catalysts are given.

The catalytic results show that TiO_2 containing 0.2 wt % of Pd provided the most active catalyst for the Heck reaction, achieving 98 % yield of product 4-(p-methoxyphenyl)-3-buten-2-one (**1a**) in 5 h of reaction time. In the second reaction step the hydrogenation of **1a** takes place but the yield of 4-(p-methoxyphe-

Table 2. Results of the Heck reaction and hydrogenation steps obtained using palladium supported (0.2 wt %) on different oxides.

Catalysts	Heck reaction[a]			Hydrogenation:[b,c] Yield [%] of products			
	Conversion of iodoanisole [%]	Yield of **1a** [%]	Selectivity **1a** [%]	**1a**	Anisole	**2a**	others
0.2 Pd-HA	44	43	97	87	13	0	0
0.2 Pd-Al_2O_3	53	52	98	83	15	1	1
0.2 Pd-MgO	60	60	100	53	42	5	0
0.2 Pd-HAT	56	56	100	21	18	55	6
0.2 Pd-TiO_2	99	98	99	80	0	20	0
0.2 Pd/C	64	63	98	72	1	5	18

[a] *Reaction conditions:* 4.4 mmol p-iodomethoxybenzene, 8.8 mmol MVK, 5.4 mmol of sodium carbonate, 4.5 mL DMF, 300 mg of catalyst, 5 h reaction time at 393 K.
[b] Hydrogen flow 5 mL min^{-1} (5 bar), after 15 h reaction time at 393 K.
[c] 100 % conversion of iodoanisole is achieved.

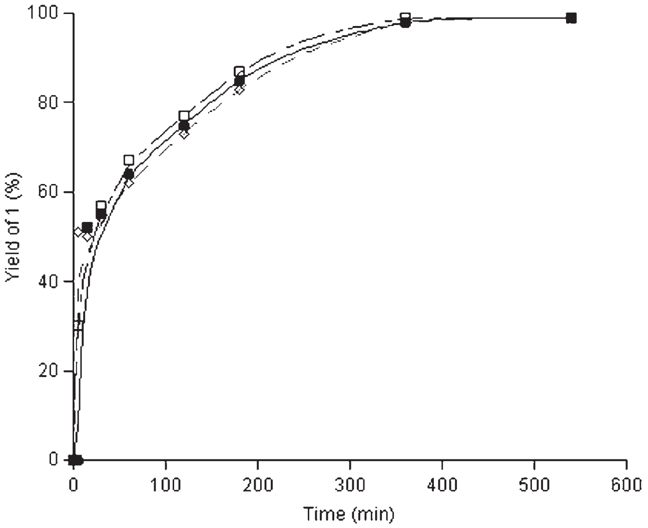


Figure 1. Time yield of **1a** plot for the Heck reaction in the presence of fresh 0.2 Pd-TiO_2 (□), reuse 1 (■), reuse 2 (◇).

nyl)butan-2-one (**2a**) with a raspberry scent was still low.

Results from Table 2 also indicate that selectivity for the coupling reaction is very high regardless of the selected support. Nevertheless, Pd/C, Pd/MgO and especially Pd on TiO_2 give higher activity. These results can be explained, taking into account previous work[18] that reports on the influence of the acid/base properties of the support and metal dispersion on Pd activity for the Heck reaction.

Kinetic results for the first step, that is, the Heck reaction catalyzed by 0.2 Pd-TiO_2 are given in Figure 1, and therefrom a turnover frequency (TOF) of 4557 h^{-1} has been calculated by dividing the initial reaction rate by the total Pd content. It should be taken into account that the real TOF will always be larger that the one calculated by considering all the Pd in the sample, since only the Pd at the crystal surface and/or that in the solution will be active.

On the other hand, it is interesting to point out that during the hydrogenation step only the 0.2 Pd-TiO_2 catalyst gives full selectivity to the final hydrogenated product (**2a**) while with the other less active catalysts, anisole is formed in appreciable proportions due to the dehydrohalogenation of the 4-iodoanisole remaining in the reaction (see Table 2). It should be pointed out that during the hydrogenation step the Pd/C catalyst only gives a 5% of the desired product (**2a**), the Heck adduct (**1a)** and the compound coming from Heck coupling between **1a** and iodoanisole being the main products. According to this, and from the results of the hydrogenation step given in Table 2, the 0.2 Pd-TiO_2 catalyst appears to be a good candidate for performing the first (Heck coupling) and second (hydrogenation reaction) steps.

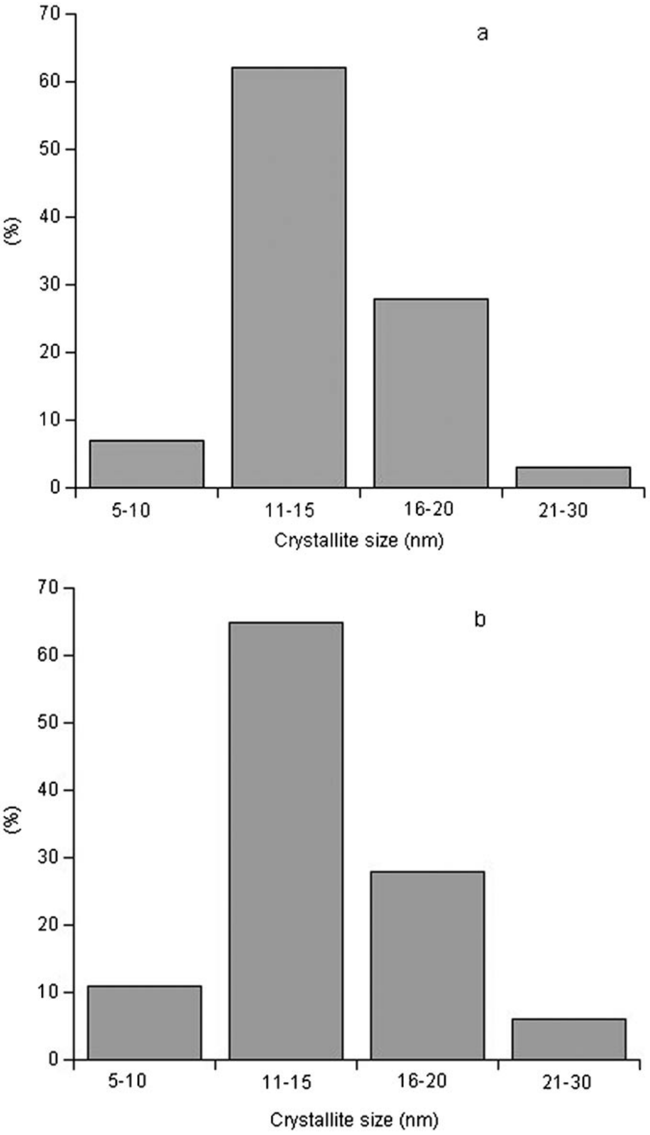


Figure 2. Percentage of the crystallite size measured from TEM images of 0.2 Pd-TiO_2 catalysts before (**a**) and after reuse (**b**).

The stability of 0.2 Pd-TiO_2 was studied by reusing it for the coupling reaction which is the most sensitive to metal leaching. Then, after the first use, the catalyst was filtered hot and washed with dichloromethane and water. After the washing, the solid was dried at 523 K under vacuum for 2 h. The results obtained for the consecutive reaction-regeneration experiments are given in Figure 1. A very small decrease of activity, only observable at shorter reaction times, occurs and suggests that either some Pd leaching and/or metal agglomeration on the support has occurred. Measurement of the distribution of the crystallite size from TEM images of the 0.2 Pd-TiO_2 catalyst fresh and after reuses are presented in Figure 2 a and b, respectively, and show no metal agglomeration. At this

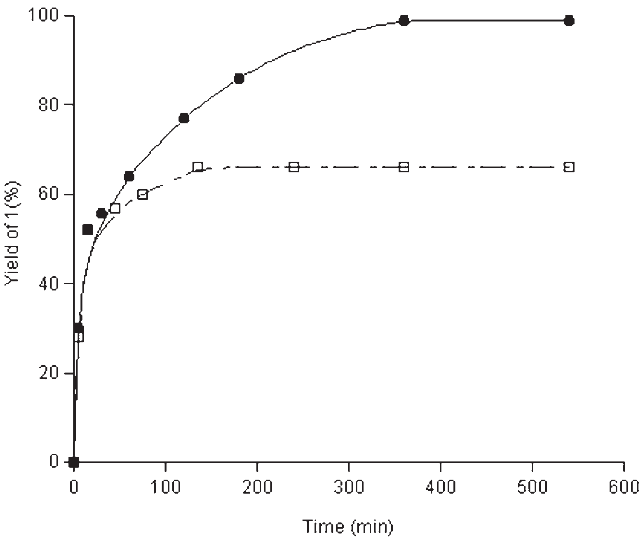


Figure 3. Yield-conversion plot for the Heck reaction in the presence of 0.2 Pd-TiO_2 catalyst (■) and when the catalyst was filtered hot and the solution was allowed to continue the reaction (□).

Table 3. Results of the Heck reaction and hydrogenation steps obtained using TiO_2 with different amounts of palladium loading and in the presence of a homogeneous catalyst (Pd-AO).[a]

Catalysts	Heck reaction		Hydrogenation[e]
	Conversion of iodoanisole [%]	Yield **1a** [%]	Yield **2a** [%]
0.2 Pd-TiO_2	99	99	30[d]
1 Pd-TiO_2	100	100	97[d]
2 Pd-TiO_2	100[b]	100	97[e] (99)
Pd-AO	98[c]	98	18[d]

[a] *Reaction conditions:* 4.4 mmol iodoanisole, 8.8 mmol MVK, 5.4 mmol of sodium carbonate 4.5 mL DMF, 2 h, 300 mg of catalyst, 413 K.

[b] 1 h.

[c] 7 h.

[d] 15 h.

[e] 10 h; in brackets results at 24 h.

[f] Hydrogen flow 5 mL min^{-1} (5 bar) at 413 K.

point we tested the 0.2 Pd-TiO_2 catalyst for leaching by analyzing the Pd content in the accumulated filtered liquid, and 0.4 ppm Pd were detected. This would be in agreement with the very small increase in conversion observed after filtration of the catalyst when the reaction achieved 57 % conversion, and allowing the reaction in the filtrate to proceed further (see Figure 3). In any case, the amount of leached active species and solid recovery are high, resulting in a useful catalytic process.

While the 0.2 Pd-TiO_2 catalyst gives high conversion and selectivity for the coupling reaction, the progress of the consecutive hydrogenation reaction was slow. Thus, in order to improve the yield of the second step, reaction conditions and metal content (1 and 2 wt %) of the catalyst were modified. The results in Table 3 clearly show that for a 1 wt % Pd on TiO_2 catalyst and working at 413 K, not only the coupling is completed in 2 h, but the consecutive hydrogenation reaction was practically completed in 15 hours, giving a 97 % final yield of the desired product **2a**. Better results were obtained by further increasing the Pd content up to 2 wt % (see Table 3). The 2 wt % Pd catalyst was regenerated after the hydrogenation step, and reused in a second cycle for coupling plus hydrogenation with the same catalytic activity.

For comparative purposes, we have prepared a homogeneous Pd catalyst, that is, the acetophenone oxime-derived palladacycle complex (Pd-AO), which has been successfully for carrying out several Heck coupling reactions.[19] The reaction between *p*-methoxyiodobenzene and MVK, was performed using acetophenone oxime-palladium complex with an amount of Pd content equivalent to that present in 300 mg of 0.2 Pd-TiO_2 catalyst, in DMF as solvent and 413 K reaction temperature. The results presented in Table 3 show that under the same reaction conditions and on the basis of the same Pd content, the homogeneous catalyst is less active than the heterogeneous 0.2 Pd-TiO_2 for the Heck reaction, achieving with the former 98 % yield after 7 h reaction time. Notice that as occurred before with the heterogeneous catalyst, the palladacycle complex homogeneous catalyst does not hydrogenate completely the intermediate **1a**, its activity being similar to that of 0.2 Pd-TiO_2. If we add to this the problems associated for catalyst recovering and the high cost of the starting Pd salt for making the homogeneous catalyst, we find no advantage for using the homogeneous *versus* the heterogeneous catalyst for this reaction.

Conclusions

We have showed, taking as an example the synthesis of a fine chemical, that is, 4-(*p*-methoxyphenyl)butan-2-one with raspberry scent, that a less selective, acid-catalyzed Friedel–Crafts reaction (maximum selectivity that we are aware of is 70 %[2]), could be replaced by one-pot highly selective Heck coupling plus hydrogenation of the intermediate using Pd-supported catalysts. For performing these reactions, not only the metal is important but the support plays an important role by dispersing and stabilizing the metal towards leaching. The Pd-TiO_2 catalyst presented here is more active than a homogeneous Pd complex that is well accepted in the literature as being highly active for performing Heck reactions.

The new catalytic route proposed here has the advantage of taking place in one-pot in which two reactions taking place through consecutive steps are carried out, in our case with very high yield, without the necessity of intermediate separations and purifications.

Experimental Section

The supports were supplied by Degussa (TiO_2), Merck (Al_2O_3), Aldrich (MgO), while hydrotalcite was prepared according toRef[20] and hydroxyapatite was synthesized by precipitation ccording to the literature procedure.[21]

Palladium on activated carbon (Pd/C) catalyst (Pd 5 wt%, Degussa type E101NO/W, 50% water) was purchased from Sigma–Aldrich.

Samples with 0.2 wt% of supported palladium were prepared by impregnation of the support with an aqueous solution of dichlorobis(benzonitrile)palladium (28 mg) in acetone (300 mL) which wasd added to 4.0 g of oxide support. The mixture was stirred for 5 h at room temperature and the solid was filtered and dried overnight under vacuum. The samples were calcined 2 h at 673 K with an N_2 flow of 100 mL min^{-1}. Samples were activated after calcination at 723 K with a mixture of hydrogen and nitrogen (H_2/N_2: 90/10) at a flow rate of 100 mL min^{-1} during 2 h. The main characteristics of the catalysts are given in Table 1.

N_2 adsorption/desorption isotherms were performed at 77 K in an ASAP 2010 apparatus from Micromeritics, after pre-treating the samples under vacuum at 673 K overnight and the BET surfaces were obtained using the BET methodology. Physicochemical characteristics of the catalysts are presented in Table 1.

Reaction Procedure

The reaction was carried out as follows: a mixture of 4-methoxyiodobenzene (4.4 mmol), methyl vinyl ketone (8.8 mmol), Na_2CO_3 (5.39 mmol), in 4.5 mL of DMF and catalyst (300 mg) were added to an autoclave. The resultant suspension was heated a 393 K at atmospheric pressure under vigorous stirring. The autoclave was heated with an oil bath equipped with an automatic temperature control system while the reaction temperature was measured in the autoclave. When the Heck reaction was completed the autoclave was pressurized with H_2 (5 bar) with a hydrogen flow of 5 mL min^{-1}, and the product from the first reaction step was hydrogenated at 393 K to give compound **2a** with a raspberry fragrance. Samples were taken at a regular intervals and analyzed by GC using an FID detector and a column (Equiyt^{TM}-5 Fused Silica capillary column 30 m × 0.25 mm, 0.25 μm film thicknesses). Reaction products were identified by GC-MS (Hewlett–Packard 5988 A) and ^{1}H NMR spectroscopy (Varian Gemenis- 300 MHz, $CDCl_3$ as solvent).

Table 1. Main characteristics of different oxides used in the preparation of **2a**.

Catalysts	Surface area (m^2 g^{-1})	Pore volume (cm^3 g^{-1})
0.2 Pd-HA	77	0.30
0.2 Pd-Al_2O_3	135	0.18
0.2 Pd-MgO	177	0.50
0.2 Pd-HT[a]	253	0.47
0.2 Pd-TiO_2	52	0.22

[a] Relation molar Al/Al + Mg = 0.25.

Study of Pd Leaching

Application of the hot filtration test in order to study Pd leaching was carried out in the reaction of methoxyiodobenzene with methyl vinyl ketone at 393 K using Pd-TiO_2 as catalyst. After 15 min of reaction time the hot reaction mixture was filtered and the solid catalyst removed. 5.39 mmol of base were added to the liquid phase mixture and the reaction was continued during 9 h with the composition of the reaction mixture being analyzed at different time points.

Recycling of Catalyst

After running the reaction of *p*-methoxyiodobenzene with MVK according to the general procedure, the catalyst was removed by filtration, washed several times with water to remove the base and finally with dichloromethane. The catalyst was dried at 523 K under vacuum (2 torr) during 2 h and then activated at 723 K with a mixture of hydrogen and nitrogen (H_2/N_2: 90/10) at a flow rate of 100 mL min^{-1} during 2 h.

Synthesis of Acetophenone Oxime-Palladium Complex (Pd-AO)

The acetophenone oxime-derived palladacycle complexe catalyst (Pd-AO) was synthesized according to reference.[19] To a solution of Li_2PdCl_4 (1 mmol) in methanol (10 mL) a methanolic solution (5 mL) of the acetophenone oxime (5 mmol) and sodium acetate (0.1 mmol) were added, and the solution was stirred for 3 days at room temperature. After this time, the mixture was filtered, and after additon of water to the liquid filtrate the cyclopalladate complexe was precipitated. The palladium complex was recovered by filtration and dried at room temperature under vacuum during 4 h. The structure of the catalyst was confirmed by ^{1}H NMR spectroscopy (Varian Gemenis 300 MHz, DMF-*d* as solvent).

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References

[1] R. Fischer, W. Koernig, (Badische-Anilin and Soda-Fabrick AG), *German Patent* DE 2,145,308, **1973**.

[2] Chisso Corp Japan, *Japanese Patent* 55,151,530, **1980**.
[3] J. Tateiwa, H. Horiuchi, K. Hashimoto, T. Yamauchi, S. Uemura, *J. Org. Chem.* **1994**, *59*,5901.
[4] A. Corma, M. Renz, *Angew. Chem. Int. Ed.* **2007**, *46*, 298.
[5] M. Gruber, S. Chouzier, K. Koehler, L. Djakovitch, *Appl. Catal. A: General* **2004**, *265*, 161.
[6] R. F. Heck, J. P. Nolley Jr., *J. Org. Chem.* **1972**, *37*, 2320.
[7] N. T. S. Phan, M. V. D. Sluys, C. W. Jones, *Adv. Synth. Catal.* **2006**, *348*, 609.
[8] J. P. Wolfe, R. A. Singer, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9550.
[9] Y. Ji, S. Jain, R. J. Davis, *J. Phys. Chem. B* **2005**, *109*, 17232.
[10] K. Kholer, R. G. Heidenreich, J. G. E. Krauter, J. Pietssch, *Chem.Eur. J.* **2002**, *8*, 622.
[11] C. P. Mehnert, D. W. Weaver, J. Y. Ying, *J. Am. Chem. Soc.* **1998**, *120*, 12289.
[12] M. Dams, L. Drijkoningen, B. Pauwels, G. Van Tendeloo, D. E. De Vos, P. A. Jacobs, *J. Catal.* **2002**, *209*, 225; L. Djakovitch, K. Koehler *J. Am. Chem. Soc.* **2001**, *123*, 5990, and references cited therein.
[13] K. Kaneda, M. Higuchi, T. Imanaka, *J. Mol. Catal.* **1990**, *63*, L33; M. Wagner, K. Kohler, L. Djakovitch, S. Weinkauf, V. Hagen, M. Muhler, *Top. Catal.*, **2000**, *13,* 319; K. Kohler, M. Wagner, L. Djakovitch, *Catal. Today* **2001**, 66, 105.
[14] B. M. Choudary, M. L. Kantam, N. M. Reddy, N. M. Gupta, *Catal. Lett.* **2002**, *82*, 79.
[15] A. Corma, H. Garcia, A. Leiva, A. Primo, *Appl. Catal. A: General* **2003**, *247*, 41; Corma, H. Garcia, A. Leiva, A. Primo, *Appl. Catal. A: General* **2004***, 257*, 77;Y. Y. Ji, S. Jain, R. J. Davis, *J. Phys. Chem.* **2005**, *109*, 17232.
[16] J. H. Clark, J. Macquarie, E. B. Mubofu, *Green Chem.* **2000**, *2*, 53.
[17] K. Okitsu, A. Yue, S. Tanabe, H. Matsunoto, *Chem. Mater.* **2000**, *12*, 3006.
[18] A. Wali, S. M. Pillai, V. K . Kaushik, S. Sathis, *Appl. Catal. A* **1996**, *135*, 83; A. Wali, S. M. Pillai, V. K. Kaushik, S. Sathis, *React. Kinet. Catal. Lett.* **1997**, *60*, 189.
[19] D. A. Alonso, C. Nájera, M. C. Pacheco, *Adv. Synth. Catal.* **2002**, *344*, 172.
[20] M. J. Climent, A. Corma, S. Iborra, A. Velty, *J. Catal.* **2004**, *221*, 474.
[21] S. Sugiyama, T. Minami, H. Hayashi, M. Tanaka, N. Shigemoto, J. B. Moffat, *J. Chem. Soc., Faraday Trans.* **1996**, *92*, 293.