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Green and Efficient Synthesis of Sulfonamides Catalyzed by Nano-Ru/Fe_3O_4

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Abstract: The environmentally benign synthesis of carbon−nitrogen bonds continues to be an active and challenging field of chemical research. Here, a novel, environmentally benign method for the direct coupling of sulfonamides and alcohols is described. Despite the importance of sulfonamide derivatives as intermediates in drug synthesis, till now such transformations are rarely known. For the first time a domino dehydrogenation-condensation-hydrogenation sequence of alcohols and sulfonamides has been realized in the presence of a nanostructured catalyst. The magnetic property of the catalyst system allows for convenient isolation of the product and efficient recycling of the catalyst. A variety of coupling reactions of benzylic alcohols and sulfonamides including various heterocycles were successfully realized, often with >80% isolated yield. Advantageously, only one equivalent of the primary alcohol is consumed in the process. Mechanistic investigations of the competitive reactions of benzyl alcohol and d_7-benzyl alcohol with *p*-toluenesulfonamide revealed a kinetic isotope effect (k_H/k_D) of 2.86 (±0.109) for the dehydrogenation of benzyl alcohol and 0.74 (±0.021) for the hydrogenation of *N*-benzylidene-*p*-toluenesulfonamide intermediate, which suggests dehydrogenation of the alcohol to be the rate determining step.

Introduction

Carbon−nitrogen bonds present in many biologically active molecules are key moieties.[1] To generate molecular diversity, the development of versatile methods for C−N bond formation constitutes to be a major topic in chemical synthesis.[2−5] In this respect, the synthesis of sulfonamides is also a vital area.[6−9] Until to date sulfonamides have been extensively used as antibacterials, diuretics, anticonvulsants, hypoglycemics, and HIV protease inhibitors.[10−14] The preparation of this class of compounds typically proceeds via reaction of the corresponding amine with sulfonyl chlorides.[15,16] Clearly, this method is efficient and has proven its versatility on small laboratory scale; however, the usage of sulfonyl chlorides causes severe storage and handling problems as well as significant waste generation.[17,18] Although several other synthetic methods[19−21] such as cross-coupling of sulfonamides with aryl halides[22−25] and the reaction of activated sulfonate esters with amines[26] have been reported, all these procedures create at least stoichiometric amounts of unwanted side-products.

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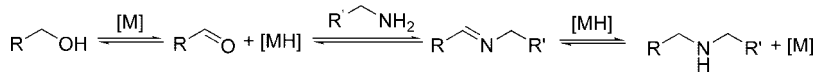
Scheme 1. C−N Bond Formation from Alcohol and Amine



More recently, the salt-free synthesis of secondary amines from amines and alcohols via hydrogen-borrowing methodology has attracted significant interest (Scheme 1). So far relatively few metal complexes based on ruthenium, iridium, rhodium, and nickel have been studied as catalysts.[27−33] Intrinsically, this reaction is environmentally friendly as it produces only water as byproduct and does not need special high pressure equipment.

Thus, it is apparent that the preparation of sulfonamides using alcohols as alkylation reagents should be attractive because of their ready availability, easy handling, low price, and toxicity. Nevertheless, apart from the coupling reactions of sulfonamides and secondary benzylic and allylic alcohols in the presence of Lewis acids,[34−38] which pass through a carbocation mechanism, little is known.

In comparison with homogeneous catalysts, heterogeneous catalysts have advantages with respect to product and catalyst isolation, catalyst reuse, and operational handling. Recently, we and others have demonstrated that nanostructured iron catalysts are close in catalytic activity to the corresponding homogeneous catalyst, but more easy to isolate and reuse.[39,40] Here, we report our new findings about an iron-supported nanoruthenium catalyzed coupling reaction of sulfonamides with alcohols.

Results and Discussion

Coupling Reaction of Benzyl Alcohol and *p*-Toluenesulfonamide. In 2007, we discovered that maghemite (γ-Fe_2O_3) catalyzes the oxidation of benzyl alcohol to benzaldehyde using H_2O_2 as an environmentally benign oxidant.[40] As a starting point for this work, we observed in control experiments that dehydrogenation of benzyl alcohol to afford benzaldehyde proceeds even without oxidant! However, elevated temperatures are needed for the generation of hydrogen. Best results are observed applying magnetite Fe_3O_4 as catalyst (TON ≈ 3−5, 150−180 °C, 12 h).

Scheme 2. Possible Mechanism for the Coupling Reaction of Alcohols and Sulfonamides

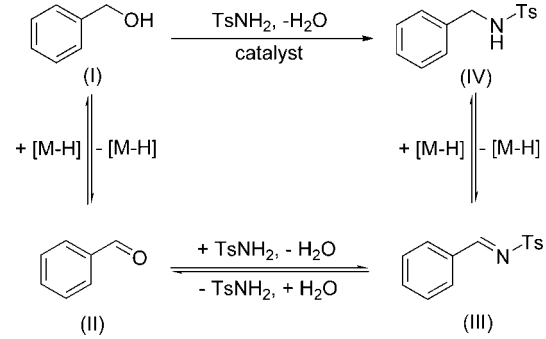


Table 1. Coupling of *p*-Toluenesulfonamide and Benzyl Alcohol Catalyzed by Ru/Fe_3O_4[a]

entry	catalyst	base	mol%	*T*/°C	*t*/h	Conv./%[b]	Sel./%[c]
1	Fe_3O_4	−	−	160	20	12	<1
2	Ru/Fe_3O_4	−	−	160	24	94	73
3	Ru/Fe_3O_4	Na_2CO_3	2.0%	140	6	60	80
4	Ru/Fe_3O_4	Cs_2CO_3	2.0%	140	6	60	93
5	Ru/Fe_3O_4	K_2CO_3	2.0%	140	6	67	97
6	Ru/Fe_3O_4	K_2CO_3	2.0%	150	6	82	98
7	Ru/Fe_3O_4	K_2CO_3	2.0%	150	12	98	98
8	Ru/Fe_3O_4	K_2CO_3	1.0%	150	12	91	98
9	5 wt %Ru/C	K_2CO_3	2.0%	150	12	84	76
10	5 wt %Ru/Al_2O_3	K_2CO_3	2.0%	150	12	86	76
11[d]	$RuCl_3 \cdot H_2O/Fe(NO_3)_3 \cdot 9H_2O$	K_2CO_3	2.0%	150	12	47	5

[a] Reaction conditions: 5 mmol (855 mg) p-toluenesulfonamide, 20 mmol (2160 mg) benzyl alcohol, 40 mg Ru/Fe_3O_4 (0.4 mol% Ru), with argon bubbling. [b] Conversion of *p*-toluenesulfonamide directly obtained from GC-MS peak area without modification. [c] Selectivity to *N*-benzyl-*p*-toluenesulfonamide directly obtained from GC-MS peak area without modification. [d] Same mol amount of ruthenium and iron as in our Ru/Fe_3O_4 catalyst were used.

Inspired by this interesting result, we envisioned that iron-based catalysts may be also suitable for the synthesis of amides or amines through the dehydrogenation-condensation-hydrogenation sequence shown in Scheme 2. To the best of our knowledge such carbon−nitrogen bond formation has not been described in the literature.

When testing the coupling reaction of benzyl alcohol with different amines and amides, to our delight, conversion is observed applying *p*-toluenesulfonamide as the nitrogen source although only *N*-benzylidene-*p*-toluenesulfonamide was formed as the major product, Table 1, entry 1. Apparently, dehydrogenation of benzyl alcohol with subsequent condensation reaction with *p*-toluenesulfonamide occurred. This result suggested us to incorporate a noble metal into the catalyst system for the hydrogenation step of the coupling reaction. Hence, a cooperative ruthenium-magnetite catalyst may be suitable. Advantageously, such a catalyst may contain the function of dehydrogenation and hydrogenation as well as magnetic recycling ability. Indeed, preparing and using a magnetite supported nanoruthenium catalyst system, the conversion of *p*-toluenesulfonamide reached to 94% with 73% selectivity to the desired product, entry 2. The only side product observed was

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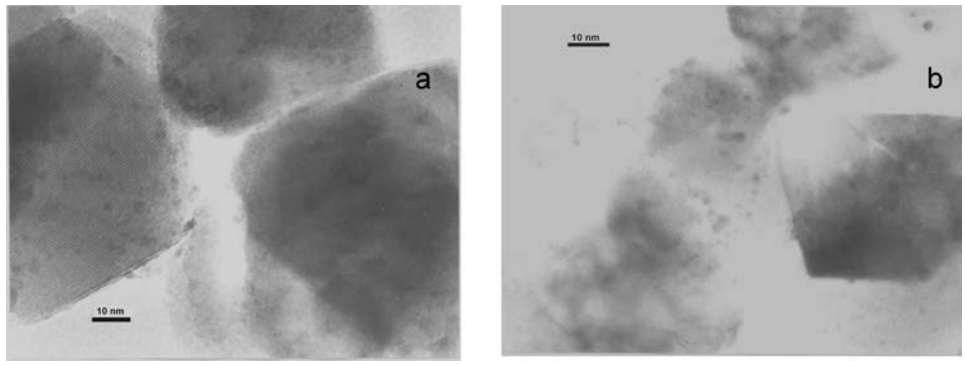


Figure 1. TEM pictures of Ru/Fe_3O_4 (a) before and (b) after 5 runs usage.

N-benzylidene-*p*-toluenesulfonamide. Addition of a catalytic amount of base as cocatalyst, that is, two mol% K_2CO_3, resulted in >98% conversion and selectivity for the model reaction, entries 3−8.

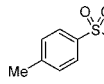
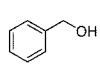
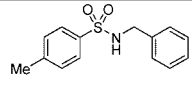
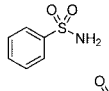
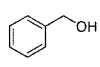
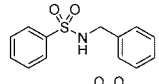
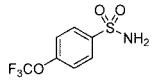
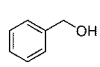
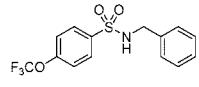
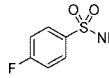
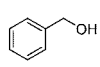
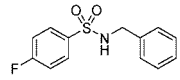
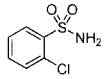
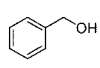
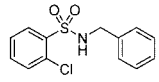
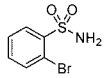
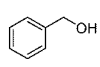
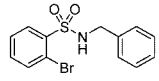
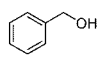
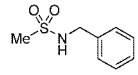
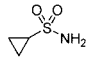
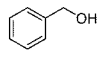
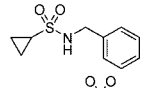
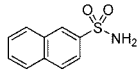
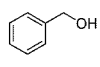
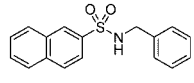
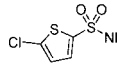
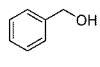
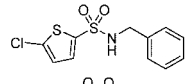
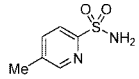
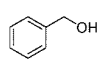
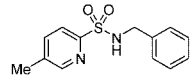
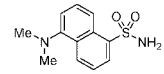
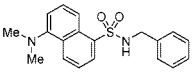
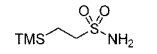
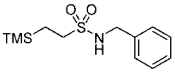
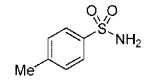
Interestingly, *N*-benzylidene-*p*-toluenesulfonamide is observed as the major product at the initial stage of the reaction. A close monitoring of the reaction by GC-MS showed that the amount of *N*-benzylidene-*p*-toluenesulfonamide decreased during the reaction and more than 98% *N*-benzyl-*p*-toluenesulfonamide are formed, entry 7. Simultaneously, benzaldehyde is also detected in the early stage of the reaction. These results indicate that *N*-benzylidene-*p*-toluenesulfonamide is an intermediate product, which is formed via condensation of benzaldehyde and sulfonamide. Subsequent hydrogenation gave the desired product in high yield. Notably, the concentration of benzaldehyde is low (∼1%) during the whole reaction. More importantly, only 1 equiv of benzyl alcohol is consumed making the reaction highly atom-efficient. Commercially available supported ruthenium catalysts, such as Ru/Al_2O_3 and Ru/C, gave also high conversion of the sulfonamide, but the selectivity was relatively low, entries 9 and 10. This further confirms that our novel supported nano-Ru/Fe_3O_4 works in a cooperative manner. The application of $RuCl_3 \cdot H_2O/Fe(NO_3)_3 \cdot 9H_2O$ as homogeneous catalyst gave lower conversion (47%) and the selectivity was only 5%, entry 11. Apparently, the real catalyst for this coupling reaction is the magnetite supported ruthenium but not the leached ruthenium and iron in the reaction solution.

Catalyst Characterization. Magnetite and magnetite-supported ruthenium catalysts were characterized by XRD, XPS, BET and TEM. XRD analysis of fresh and used Ru/Fe_3O_4 confirmed the formation of magnetite as the only crystalline product (Figure S1, Supporting Information), No Ru could be detected by XRD, most probably due to the small size of the Ru particles, which is shown by TEM to be 1.5−5 nm while the magnetite itself shows particles of ∼100 nm, Figure 1a. XPS analysis revealed almost equal binding energies of 461.7 and 461.9 eV for the Ru $3p_{3/2}$ peaks of fresh and used catalysts which are well in the range of those expected for metallic Ru, Figure S2, Supporting Information. The Ru/Fe ratio is slightly higher for the used catalyst which may suggest slight increase in Ru dispersion upon 5 times use. BET analysis showed that the surface area of the Ru/Fe_3O_4 catalyst does virtually not change, being 14.36 m^2/g before and 13.80 m^2/g after 5 times use. All these results clearly indicate that the catalysts contain Ru^0 nanoparticles immobilized on the surface of crystalline Fe_3O_4 which remain stable and highly dispersed during use in the catalytic reaction.

Scope and Limitations. The magnetite-supported ruthenium-catalyzed coupling reactions of various alcohols and sulfonamides were further investigated as shown in Table 2. The standard coupling of benzyl alcohol and *p*-toluenesulfonamide proceeded smoothly with 97% isolated yield, entry 1. Notably, the catalyst is easily separated from the reaction mixture by adhering it onto the magnetic stirrer bar in just several seconds. After washing with acetone and drying in air, the catalyst was directly reused without any other treatment. Noteworthy, 96% yield is still maintained even when the catalyst is reused for 5 times and the TON reached to 1100 mol/mol. TEM analysis of the recycled catalyst indicated that the ruthenium nanoparticles are stable enough under our reaction conditions. Almost the same particle size as in the fresh sample, 1.5−6 nm, is maintained, Figure 1b and Figure S1b, Supporting Information. Next, sulfonamides with various functional groups were further tested. For 4-(trifluoromethoxy)benzenesulfonamide, 96% yield is obtained, entry 2; 92−96% yields are achieved for halide-containing sulfonamides, entries 4−6. The coupling of benzyl alcohol with methanesulfonamide gave also an excellent yield (98%), entry 7. These results suggested that the presence of functional groups on the aromatic ring of the sulfonamide or modification of the aromatic ring to an aliphatic group does not have any inferior effects on the catalytic activity. Interestingly, a good yield (86%) is achieved with cyclopropanesulfonamide as the starting material, entry 8. The cyclopropane group is stable enough under our reaction conditions although ring-opening often occurred in the presence of base. A 93% yield is obtained with naphthaline-2-sulfonamide as the starting material, entry 9. In addition, the coupling reaction of benzyl alcohol with heterocycle- and heteroatom-containing sulfonamides, such as 5-chlorothiophene-2-sulfonamide, 5-methylpyridine-2-sulfonamide, 5-(dimethylamino)naphthalene-1-sulfonamide and 2-(trimethylsilyl)ethane-sulfonamide were also successful with 49% to 95% isolated yield, entries 10−13. On the other hand, excellent results are obtained with aliphatic or halogen substituents on the aromatic ring of benzyl alcohols, entries 14−18. Finally, 80−98% yield are achieved for the coupling reactions of 3-pyridinemethanol and 2-thiophenemethanol with *p*-toluenesulfonamide, entries 19−20. Even the coupling reaction of 5-(dimethylamino)naphthalene-1-sulfonamide with 2-thiophenylmethanol is realized with 82% yield, entry 21.

Mechanistic Studies. Labeling experiments revealed that the reaction mechanism is consistent with a dehydrogenation-condensation-hydrogenation mechanism. GC-MS analysis of the experiment between *N*-benzyl *p*-toluenesulfonamide and d_7-benzyl alcohol showed the formation of d_7-*N*-benzyl-*p*-toluenesulfonamide and d_6-*N*-benzylidene-*p*-toluenesulfonamide. Simultaneously, a small amount of nondeuteriated benzaldehyde

Table 2. Scope and Limitation of Coupling of Sulfonamides and Alcohols[a]

entry	sulfonamide	alcohol	product	yield/%[b] (TON)[c]
1				97/95[d]/96[e] (220/1100[e])
2				94 (214)
3				96 (218)
4[f]				96 (218)
5				92 (209)
6				95 (216)
7				98 (223)
8				86 (195)
9				93 (211)
10[f,g]				81 (184)
11[g]				49 (111)
12[g]				91 (207)
13				95 (216)
14				92 (209)
15[f]				97 (220)
16[f]				96 (218)
17[g]				90 (205)
18				98 (223)
19[g]				80 (182)
20[g,h]				84 (191)
21[g]				82 (186)

[a] Reaction conditions: 5mmol sulfonamide, 20 mmol alcohol (30 mmol alcohol is used in entries 10, 11, 12 and 21), 40 mg Ru/Fe_3O_4 (0.4 mol% Ru), 13.8 mg K_2CO_3 (0.10 mmol), 150 °C under argon bubble for 12 h. [b] Isolated yield. [c] Turn over numbers: mol product produced per mol ruthenium. [d] Catalyst is reused for the 2nd run. [e] Catalyst is reused for the 5th run; turn over numbers for 5 runs. [f] 24 h. [g] 138 mg K_2CO_3 (1.0 mmol). [h] Another 20 mmol thiophenemethanol is added after 12 h.

Scheme 3. Reaction of *N*-Benzyl *p*-Toluenesulfonamide and d_7-Benzyl Alcohol

Scheme 4. Reaction of d_7-Benzyl Alcohol and *p*-Toluenesulfonamide

is produced, Scheme 3 and Figure S3, Supporting Information. All these observations are in agreement with the dehydrogenation-condensation-hydrogenation mechanism and the whole process should be reversible, Scheme 2.

In the reaction of d_7-benzyl alcohol with *p*-toluenesulfonamide no significant scrambling of NH or OH with deuterium is observed. At the same time, no deuterium incorporation is monitored in the aromatic ring of *p*-toluenesulfonamide, Scheme 4 and Figure S4, Supporting Information. According to the GC-MS analysis of the competitive reaction of benzyl alcohol and d_7-benzyl alcohol with *p*-toluenesulfonamide, a primary kinetic isotope effect (KIE = k_H/k_D) of 2.86 ± 0.109) is observed for the dehydrogenation step, Scheme 5 and Scheme S1, Supporting Information, indicating the benzylic C−H bond breaking being the rate determining step. The kinetic isotope effect is in good agreement with the combined KIE (2.7 ± 0.25) of transfer hydrogenation of imines with the Ru-based Shvo's catalyst,[41] but far smaller compared to hydrogen atom abstraction by other metal-oxo-complexes.[42−45] An inverse secondary kinetic isotope effect (k_H/k_D) of 0.74 (±0.021) is obtained for the hydrogenation step.

Conclusion

In conclusion, a new magnetite-immobilized nano-Ru catalyst was developed for the environmentally benign synthesis of

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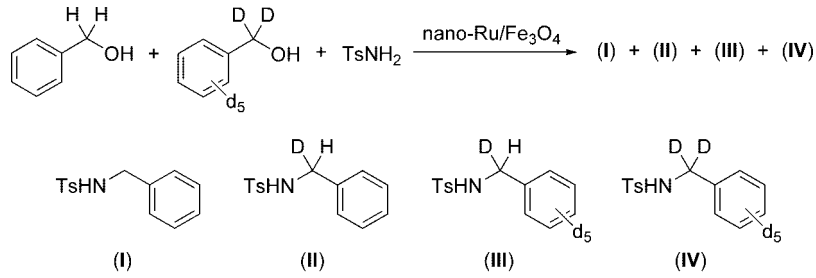
Scheme 5. Reaction of Benzyl Alcohol and d_7-Benzyl Alcohol with *p*-Toluenesulfonamide



(**I**) : (**II**) : (**III**) : (**IV**) = 6.38±0.249 : 3.01±0.087 : 2.28±0.023 : 1

sulfonamides. The underlying C−N bond formation reaction takes place with high selectivity giving only water as side-product. The catalyst is easily isolated and reused because of its magnetic property. In general, good to excellent yields are achieved using sulfonamides and alcohols containing various functional groups and heteroatoms. Mechanistic studies revealed that this heterogeneous catalyst catalyzes the reaction via a domino dehydrogenation-coupling-hydrogenation mechanism.

Materials and Methods

General. All solvents and chemicals were obtained commercially and were used as received. NMR spectra were measured using a Bruker ARX 300 or ARX 400 spectrometer at 300 or 400 MHz (^{1}H) and 75 or 100 MHz (^{13}C). All spectra were recorded in $CDCl_3$ or acetone-d_6 and chemical shifts (δ) are reported in ppm relative to tetramethylsilane referenced to the residual solvent peaks (38). Spectra were measured at room temperature unless otherwise stated. Mass spectra were in general recorded on an HP 6890/5973 GC-MS. Electron spray mass spectra were measured with an Agilent 1969A time-of-flight mass spectrometer (Waldbronn). In each case characteristic fragments with their relative intensities in percentages are shown. Elementary analyses were obtained by a Leco C/H/N/S-Analysator 932. Infrared spectra were recorded on a Nicolet 6700 spectrometer equipped with smart endurance using ATR-IR. Wave numbers (ν) are reported in cm^{-1}. Melting points were measured with a Staurt SMP3. TEM characterization was carried out with a transmission electron microscope CM20 STWIN (Philips). XRD analysis was measured by a STADI P automated transmission diffractometer (STOE). XPS analysis was performed with a VG ESCALAB220iXL spectrometer with Al Kα radiation (E = 1486.6 eV). BET surface area was obtained with a ASAP 2010 at 77 K. The ruthenium loading was measured with a Perkin-Elmer Analyst 300.

General Procedure for the Coupling Reaction. All reactions were carried out applying a multireactor (Carousel 12 station, RADLEYS). Typically, 5.0 mmol *p*-toluenesulfonamide (855 mg), 20.0 mmol benzyl alcohol (2160 mg), 40 mg nano-Ru/Fe_3O_4 (0.45 mol% Ru) catalyst and 0.10 mmol (13.8 mg) K_2CO_3 were added respectively to a glass vessel ~50 mL. Then, the reaction mixture was vigorously stirred (500−750 rpm) at 150 °C with argon bubbling. After 12 h, it was cooled down to room temperature. ~20 mL acetone was added to dissolve the reaction mixture and filtrated with celite. Then the acetone and benzyl alcohol were removed under vacuum and a yellow solid was obtained. It was further washed by diethyl ether/hexane to remove benzyl alcohol residue and other soluble impurities. After it was further dried under reduced pressure, white solid (1.26 g, 97%) was obtained. For the quantitative analysis of benzyl alcohol consumed in the reaction, 40 mmol (~3.52 g) dioxane was added and analyzed by GC-FID (HP 6890) with an external standard method. Three reactions were performed in parallel and the benzyl alcohol consumed was 5.42 mmol, 5.23 and 5.07 mmol, respectively (5.24 ± 0.175 mmol).

Reaction of d_7-Benzyl Alcohol and *N*-Benzyl-*p*-toluenesulfonamide. 0.1 mmol (26.1 mg) *N*-benzyl-*p*-toluenesulfonamide, 1.0 mmol (115.0 mg) d_7-benzylalcohol, 20 mg nano-Ru/Fe_3O_4, 0.05 mmol (6.9 mg) K_2CO_3 were added into a 5 mL tube. Then, it was sealed and reacted at 150 °C (oil bath temperature) for 15 h. After it was cooled to room temperature, the reaction mixture was dissolved in acetone and analyzed by GC-MS.

Reaction of d_7-Benzyl Alcohol and *p*-Toluenesulfonamide. 0.3 mmol (51.3 mg) *p*-toluenesulfonamide, 1.8 mmol (207 mg) d_7-benzylalcohol, 40 mg nano-Ru/Fe_3O_4, 0.1 mmol (13.8 mg) K_2CO_3 were added into a 5 mL tube. Then, it was sealed and reacted at 150 °C (oil bath temperature) for 18 h. After it was cooled to room temperature, the reaction mixture was dissolved in acetone and filtrated by celite. The acetone was removed under reduced pressure and the resulted mixture was washed by water and extracted by diethyl ether. Then the diethyl ether was removed under reduced pressure and a yellow solid was obtained. It was further washed by diethyl ether/hexane and white solid (67 mg, 83%) was obtained after it was dried under reduced pressure.

Isotope Effect Studies. All isotope effect studies were carried out in a 5 mL tube. Typically, 0.3 mmol (51.3 mg) *p*-toluenesulfonamide, 3.0 mmol (346 mg) d_7-benzylalcohol, 3.0 mmol (324 mg) benzylalcohol, 40 mg nano-Ru/Fe_3O_4, 0.1 mmol (13.8 mg) K_2CO_3 were added into a 5 mL tube. Then, it was sealed and reacted at 150 °C (oil bath temperature) for 6 h. After it was cooled to room temperature, the reaction mixture was dissolved in acetone and filtrated by celite. The acetone was removed under reduced pressure and the resulted mixture was washed by water and extracted by diethyl ether. Then the diethyl ether was removed under reduced pressure and a yellow solid was obtained. It was further washed by diethyl ether/hexane and white solid (44 mg, 57%) was obtained after it was dried under reduced pressure. The reaction was repeated 3 times. All samples were analyzed by GC-MS and ^{1}H NMR. The average results were used for analysis.

Acknowledgment. This work has been supported by the State of Mecklenburg-Western Pommerania, the Deutsche Forschungsgemeinschaft (SPP 1118 and Leibniz prize), and the BMBF. We thank Micromod GmbH for accessing a high temperature furnace in Warnemünde. F.S. thanks the Alexander-von-Humboldt-Stiftung for an AvH-Fellowship.

Supporting Information Available: Detailed information for characterization of catalysts, isotope effect testing, compound characterization and complete ref 12. This material is available free of charge via the Internet at http://pubs.acs.org.

JA807681V

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