Asymmetric Transfer Hydrogenation of Prochiral Ketones in Aqueous Media with Chiral Water-Soluble and Heterogenized Bifunctional Catalysts of the RhCp*-Type Ligand

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ABSTRACT Asymmetric transfer hydrogenation (ATH) of prochiral aromatic ketones was carried out with a water-soluble complex of $Rh^{III}Cp^*$ and mononitrobenzenesulfonamide bidentate ligand (1*R*,2*R*)-*N*-(2-aminocyclohexyl)-4-nitrobenzenesulfonamide **1** derived from chiral cyclohexane-1,2-diamine. Aqueous sodium formate was used as the hydride source. The reaction afforded the chiral alcohols in good enantioselectivities (79–93%) and yields (>99%). The modified monosulfonamide ligand was also covalently immobilized on solid phase such as silica, resin, and mesoporous SBA-15 silica and then explored as a catalyst with $Rh^{III}Cp^*$ in the ATH of acetophenone. *Chirality 23:178–184, 2011.* © 2010 Wiley-Liss, Inc.

KEY WORDS: asymmetric transfer hydrogenation; aromatic ketones; chiral ligands; nitrobenzenesulfonamide; heterogenized ligands; $Rh^{III}Cp^*$; SBA-15

INTRODUCTION

Chiral secondary alcohols are valuable intermediates in the synthesis of physiologically active pharmaceuticals,[1–6] agrochemicals,[7] and flavor ingredients.[8] In response to the increasing demand for optically active secondary alcohols, a variety of powerful catalytic procedures have been developed. One such method involves the use of monotosylated 1,2-diamines or amino alcohols as ligands for ruthenium(II)-catalyzed asymmetric transfer hydrogenation (ATH) of ketones, a method developed by Noyori and coworkers.[9–17] These bifunctional catalysts deliver the hydrogen in a concerted six-membered transition state to the aromatic ketone, and the enantioselectivity is induced by the proton-π interaction between the aryl ring proton and the aromatic ring of the ketone.

Since this discovery, a significant number of new ligands have been reported for the ATH with ruthenium(II), iridium(III), and rhodium(III) complexes as catalysts in the ATH of ketones.[18–35] More importantly, the hydride source for the reaction has been changed from isopropanol/KOH or $HCOOH/NEt_3$ to a "greener" hydride source using sodium formate/water, a solvent system that is readily available, benign, and environmentally acceptable.[36–51] This has triggered an intense search for new and efficient water-soluble ligands that could be used with Ru(II) and Rh(III) complexes as catalysts in the ATH of ketones. Addressing this, we recently reported the synthesis of a number of chiral bis- and monosulfonamide ligands L*, derived from *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine, which were efficiently used with Ru(II) and Rh(III) as catalysts in the ATH of ketones in aqueous sodium formate (Fig. 1).[52–57] Continuing our search for a more efficient water-soluble catalyst, here we report the use of a ligand containing an aromatic nitro group in the homogeneous and heterogeneous ATH of prochiral ketones in aqueous media.

MATERIALS AND METHODS

Instrument and Measurements

Melting points were determined on a Fisher–Johns melting-point apparatus and are uncorrected. Infrared (IR) spectra were taken on a Perkin-Elmer FTIR 1600 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Nova 500 MHz and on Varian Mercury 200 spectrometers. Rotation was measured with a Perkin-Elmer 343 Polarimeter. Elemental analyses were conducted by NuMega, San Diego.

Synthesis of Ligands

[(1*R*,2*R*)-*N*-2-Aminocyclohexyl]-4-nitrobenzenesulfonamide (1). Monosulfonamide ligand **1** was obtained as reported in the literature[40] from the corresponding commercially available *p*-nitrobenzenesulfonyl chloride with chiral (1*R*,2*R*)-1,2-cyclohexanediamine. Pale yellow solid (0.195 g, 80%); mp 146–149°C; IR (KBr) 3358, 3297, 2945, 2860, 1528, 1450, 1351, 1160, 1091 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$ + DMSO-d_6) δ 8.34 (d, J = 9.0 Hz, 2H), 8.11 (d, J = 9.0 Hz, 2H), 6.28 (d, J = 7.5 Hz, 1H), 2.64–2.80 (m, 3H), 2.43 (m, 1H), 1.95–2.14 (m, 2H), 1.65–1.82 (m, 2H), 1.15–1.22 (m, 2H), 1.04–1.14 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO-d_6) δ 149.9, 147.4, 128.3, 124.5, 60.9, 54.4, 34.1, 32.7, 31.0, 24.6. Anal. Calcd. for $C_{12}H_{17}N_3O_4S$: C, 48.15%; H, 5.72%. Found: C, 48.10%; H, 5.68%.

(1*R*,2*R*)-[2-(4-Nitro-benzenesulfonylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (2). Ligand **1** was selectively mono-tert-Butyl carbamate (BOC) protected using the method given in the literature.[58] mp 150–155°C; IR (KBr) 3105, 2975, 2936, 1686, 1605, 1530, 1349, 1165 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 8.33 (d, J = 8.8 Hz, 2H), 8.04 (d, J = 8.8 Hz, 2H), 6.23 (d, J = 5.8 Hz, 1H), 4.40 (d, J = 7.6 Hz, 2H), 3.35 (m, 1H), 2.95 (m, 1H), 1.97 (m, 2H), 1.69 (m, 2H), 1.44 (s, 9H), 1.09–1.38 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 157.2, 149.7, 147.5, 128.1, 124.2, 80.3, 60.4, 53.6, 34.0, 32.6, 28.4, 24.6, 24.3. Anal. Calcd. for $C_{17}H_{25}N_3O_6S$: C, 51.11%; H, 6.31%. Found: C, 51.18%; H, 6.35%.

Crystallographic data for the structure reported in this article have been deposited with the Cambridge Crystallographic Data Centre (CCDC 764962).
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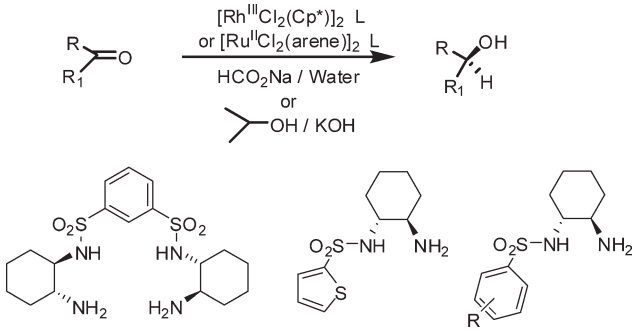


Fig. 1. ATH of prochiral ketones using chiral bis- and mono-sulfonamide ligands derived from *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine.

(1*R*,2*R*)-[2-(4-Amino-benzenesulfonylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (3). A number of methods were explored in reducing the aromatic nitro compound to the corresponding amine: Zinc/HCl, Pd/C/H_2, and Pd/ammonium formate. The latter method[59] gave the amine in 96% yield. $[\alpha]_D^{25} = +53^\circ$ (c = 22 mg/100 ml MeOH). mp 165–168°C; IR (KBr) 3374, 2977, 2936, 2860, 1686, 1631, 1597, 1505, 1153 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.62 (d, J = 8.4 Hz, 2H), 6.66 (d, J = 8.4 Hz, 2H), 5.33 (d, J = 5.8 Hz, 1H), 4.48 (d, J = 7.4 Hz, 1H), 4.12 (br s, 2H), 3.26 (m, 1H), 2.81 (m, 1H), 1.98 (m, 2H), 1.68 (m, 2H), 1.45 (s, 9H), 1.05–1.37 (m, 4H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 156.7, 152.0, 129.1, 127.9, 114.0, 79.6, 58.4, 54.3, 33.9, 32.9, 28.4, 24.6, 24.5. Anal. Calcd. for $C_{17}H_{27}N_3O_4S$: C, 55.26%; H, 7.37%. Found: C, 55.32%; H, 7.42%.

Coupling of Ligand 3 to Solid Supports

(1*R*,2*R*)-[2-(4-Amino-benzenesulfonylamino)-cyclohexyl]-carbamic acid *tert*-butyl ester (3). (0.22 g, 0.6 mmol) was dissolved in CH_2Cl_2 (5 ml), and added sequentially, triethylamine (0.2 mmol) and derivatized resin or silica with 4-ethyl benzene sulfonyl chloride (0.2 g, 0.2 mmol). The reaction mixture was then stirred for 48 h at room temperature. The supported ligand was filtered, rinsed sequentially with CH_2Cl_2 (20 ml) and a mixture of CH_2Cl_2:acetone (20 ml, 1:1 v/v), and finally dried under vacuum.

BOC deprotection of solid-supported materials. Sulfonamide tethered to resin **4** or silica **5** was stirred with CH_2Cl_2:TFA (5%) for 5 h, and then the product was centrifuged, washed with dichloromethane (three times), and dried in a vacuum oven for 24 h before use.

Grafting Benzenesulfonyl Chloride on SBA-15 Mesoporous Silica

Organically modified chlorosulfonylphenyl-SBA-15 molecular sieve was prepared by functionalization of silicate SBA-15 solid with 2-(4-chlorosulfonylphenyl ethyltrimethoxysilane). SBA-15 mesoporous solid was synthesized according to reported procedures.[60] The nonionic triblock copolymer Pluronic P123 (EO20-PO70-EO20, MWav. 5750; BASF) was used as the surfactant template, and tetraethylorthosilicate (TEOS, 98% Aldrich) was the source of the silica. Molar compositions of the sol–gels were $Si(OEt)_4$:P123:HCl:H_2O = 1:2.9:0.017:200. The surfactant was dissolved in acidic media and stirred at 40°C. After the addition of TEOS, the mixture was stirred for 24 h to allow the onset of hydrolysis and the mesostructure formation to take place. Finally, the mixture was transferred to a Teflon bottle and hydrothermal treatment applied at 100°C for 48 h enabling further condensation of the silica framework. The resulting solid was washed with H_2O, filtered, air dried, and rendered porous by solvent extraction (three washings: refluxing with EtOH 50 ml/g, 8 h). Grafting of 2-(4-chlorosulfonylphenyl ethyltrimethoxysilane) was achieved by stirring 3 g of 2-(4-chlorosulfonylphenyl ethyltrimethoxysilane under reflux conditions with 4 g of solvent-extracted SBA-15 in methanol.

TABLE 1. Crystal data and structure refinement parameters for ligand 1[a]

Empirical formula	$C_{12}H_{17}N_3O_4S$
Formula weight	299
Crystal system	Orthorhombic
a (Å)	7.3706(8)
b (Å)	9.8596(11)
c (Å)	19.515(3)
V (Å^3)	1418.2(3)
Space group	$P2_12_12_1$
T (K)	298
Radiation, λ (Å)	Mo Kα
Final R indices[b]	R_1 = 6.72%
	wR_2 = 15.21%

[a]Data collected at 294 K using highly oriented graphite crystal monochromated Mo Kα radiation. The structure was solved by direct methods, and nonhydrogen atoms were refined anisotropically. Structure solutions were performed by direct methods, and structure refinement was done with the program SHELXS.[61]

[b]$R_1 = \sum \frac{||F_0|-|F_c||}{|F_0|}$; $wR_2 = [\sum[w(F_0^2 - F_c^0)^2]/\sum[w(F_0^2)^2]]^{1/2}$.

General Procedure for the Asymmetric Transfer Hydrogenation of Ketones in Water (S/C 300)

A mixture of the metal precursor $[Rh^{III}Cl_2Cp^*]_2$ (0.0039 mmol) and the chiral ligand (0.0075 mmol) was heated in water (2 ml) at 40°C for 1 h in air without a base. HCOONa (5.7 mmol) and the substrate were subsequently added (2.28 mmol). The reaction mixture was stirred at 40°C for the time indicated in Table 2 for each individual reaction. The reaction mixture was extracted with ether (3 × 10 ml). The ether layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue containing the alcohol was acetylated using acetic anhydride.

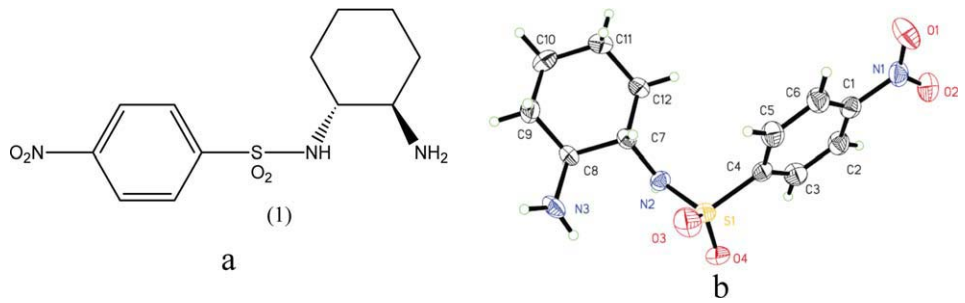
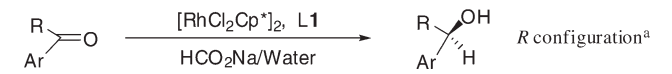
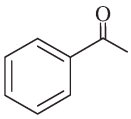
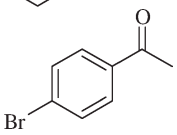
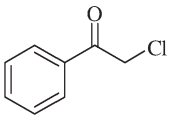
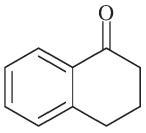
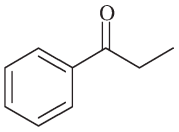
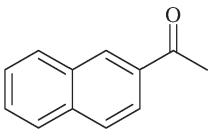
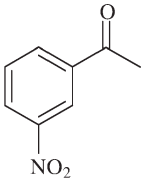
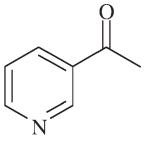


Fig. 2. (**a**) Structure of ligand **1** and (**b**) X-ray structure of the ligand **1**. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

TABLE 2. Reduction of aromatic ketones with Rh^{III}-ligand complex



Ketones	Yield (%)[b]	*ee* (%)[b]	*T* (h)[c]
	>99	93	0.30
	>99[d]	90[d]	3[d]
	>99	91	0.30
	>99	88	0.30
	85	88	0.30
	>99	89	0.30
	93	81	0.30
	>99	81	0.30
	20	58	0.30

[a]Absolute configurations are all *R*, assigned by comparing optical rotations with literature values,[36,39] except for 2-chloroacetophenone[63] [compared with a chloro alcohol sample from Aldrich Sigma, rotation (−) for configuration (*R*), based on rotation (+), the configuration (*S*) is assigned].
[b]Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.
[c]Reaction conditions: 40°C. S/C = 300.
[d]Reaction conditions: 40°C. S/C = 100.

General Procedure for the Transfer Hydrogenation of Ketones Using Supported Ligands in Water

The supported ligand (0.0068 mmol) and $[Rh^{III}Cl_2Cp^*]_2$ (0.002 mmol) were stirred in H_2O (1 ml) for 1 h at 40°C. Then, HCOONa (3.4 mmol) and the ketone (0.68 mmol) were added, and the mixture was stirred at 40°C and was monitored by Thin Layer Chromatography (TLC). After completion of the reaction, hexane:ether (1:1) was added and the mixture was centrifuged for 1 min (2000 rpm), and then the solution was removed with a syringe. The recovered alcohol was acetylated using acetic anhydride. The catalyst was then washed twice with hexane (1 ml), and then the hexane was removed. A new reaction could be conducted adding ketone (0.68 mmol) along with 1 equiv HCOONa in turn to the recovered catalyst.

RESULTS AND DISCUSSION

Asymmetric Transfer Hydrogenation of Ketones

Ligand **1** was prepared to compare the ATH of ketones with rhodium(III) complex as catalysts in homogeneous and heterogeneous reaction conditions. Ligand **1** was synthesized from the commercially available *p*-nitrobenzenesulfonyl chloride with chiral (1*R*,2*R*)-1,2-cyclohexanediamine and was characterized by comparing the spectroscopic data with those previously reported in the literature.[40] Single crystals suitable for X-ray structure analysis were obtained by slow evaporation from a concentrated solution in chloroform at 298 K (Fig. 2). Crystallographic data are presented in Table 1.

Ligand **1** complexed with $Rh^{III}Cp^*$ gave a water-soluble complex, catalyzing the reduction of aromatic ketones to chiral secondary alcohols in good yields (85 to >99%) and enantioselectivities (81–93%; except for methyl 3-pyridyl ketone, probably due to N-coordination with the metal), with S/C ratio of 300 and in 18 min using aqueous sodium formate as the hydride source (Table 2). Mohar and coworkers[62] have used a similar ligand with the nitrobenzenesulfonamide moiety [*N*-(*p*-nitrobenzenesulfonyl)-1,2-diphenylethylenediamine] to reduce aromatic α-ketoesters using $HCOOH/NEt_3$ in DMF as the hydride source in good yields (44–100%) and moderate enantioselectivities (27–86%), with a reaction time of 4–24 h.

In contrast with the results of Mohar's group,[62] we were able to get good yields and enantioselectivities using aqueous sodium formate as the hydride source in a much shorter reaction time of 0.30 h, using an environmentally more friendly solvent system. On the basis of the water solubility of ligand **1**, we were able to improve the substrate/catalyst ratio from 300 to 1000, with acetophenone as the substrate, obtaining high yield (>99%) and good enantioselectivity (90%) in 3 h of reaction (Table 2).

Immobilized Ligand on Resin or Silica Gel Solid Supports and Their Application in the ATH of Ketones

Having established the usefulness of compound **1** as a water-soluble ligand in the ATH of ketones, we turned our attention to immobilizing the ligand on solid surfaces and study their application in the ATH of ketones. Immobilized catalysts have been of great interest because of several advantages such as simplification of product work up, separation, isolation, and reuse of the catalyst.[64] However, their use in organic synthesis has been rather limited because in many cases, immobilized catalysts are less active than the corresponding original homogeneous catalysts. More importantly, recent interest in environmentally benign chemical processes reducing waste and high-throughput organic synthesis has triggered renewed interest in the chemistry of immobilization of homogeneous catalysts.[64] The NO_2 group on the aromatic ring in ligand **1** provides a useful functionality that can be reduced to the corresponding amine and derivatized with commercially available sulfonyl chlorides immobilized on resin or silica gel solid supports. Ligand **3** was immobilized on commercially available polystyrenesulfonyl chloride (Polystyrene-Divinylbenzene (PS-DVB) 8.5%, mesh

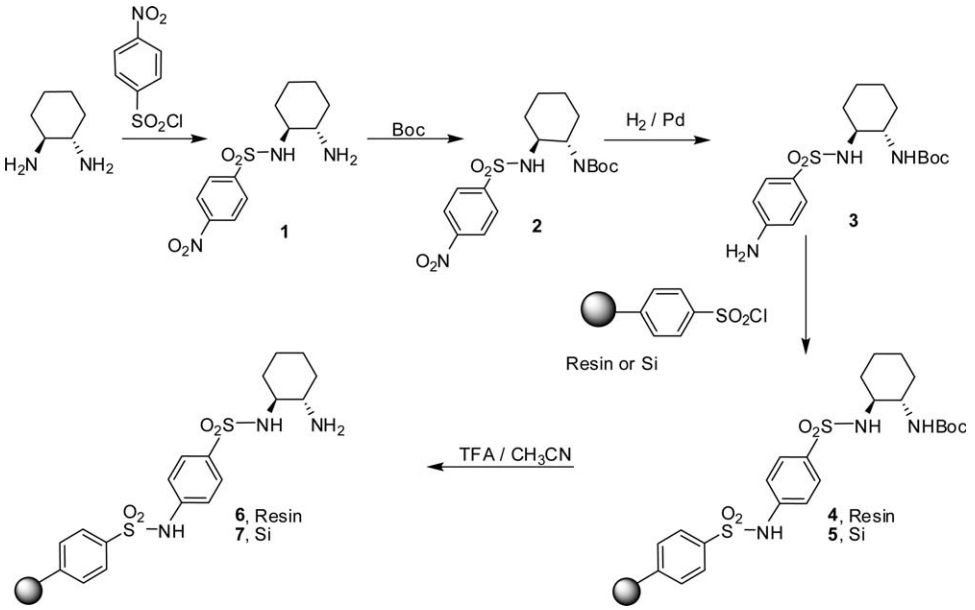


Fig. 3. Heterogenization of ligand **3**.

70–90, loading 2.5–3.0 mmol/g), and subsequent deprotection gave the ligand **6** (Fig. 3). Immobilized ligand **6** was complexed with $Rh^{III}Cp^*$ and used in the reduction of acetophenone under ATH conditions (aqueous sodium formate as the hydrogen source) to give the alcohol in 84% *ee* and 98% conversion. However, ligand **7** immobilized on silica gel gave better conversion (93%) but poor enantioselectivity (46%; Table 3).

The results of the heterogenized ligands indicate that the polymer-bound ligand **6** shows better catalytic properties when compared with the silica-bound material **7** under identical conditions. The poor results with silica may be due to the free Si—OH groups, which may interact with the metal center. Further, the flexible polymer-immobilized ligand **6** may offer tiny pockets within which the reaction may take place. Reusing the supported catalysts, **6** showed no significant decrement after the second run, while after the third run, the yield dropped to 31%, probably due to the ligand–metal leaching. These results with the resin-immobilized ligand **6** were comparable with our previously reported immobilized C_2 symmetry ligands.[55]

Immobilized Ligands on Mesoporous SBA-15 Silica and Their Application in the ATH of Ketones

Continuing on the same lines, we immobilized chiral diamine ligand **3** on mesoporous SBA-15 silica derivatized with sulfonyl group to obtain the functionalized mesoporous SBA-15 silica **8** (Fig. 4). The immobilized ligand **9** was subsequently complexed with $Rh^{III}Cp^*$ and used as a catalyst in the ATH of acetophenone under the same conditions as described above. The chiral alcohol was obtained in 45% yield and 42% enantioselectivity. Interestingly, when the chiral (1*R*,2*R*)-cyclohexane-1,2-diamine was attached directly to the SBA-15 sulfonyl derivative to obtain **10** (Fig. 4), and the addition of $Rh^{III}Cp^*$ to form the catalyst to be used in the ATH of acetophenone gave the chiral alcohol in a 70% yield and 52% enantioselectivity after a 24-h reaction time. This result suggests that the tethered spacer aromatic ring in ligand **9** probably sterically hinders the ligand-metal-Cp*coordination within the hexagonal pore of the mesoporous silica resulting in low yield and poor enantioselectivity. Literature reports on similar immobilized 1,2-diphenylethanediamine ligands gave a much higher conversion (>99%) and enantioselectivity (>93%) than those observed for ligand **10**.[22]

Characterization of Functionalized Mesoporous SBA-15 Silica 8

Elemental Carbon hydrogen and sulfur analysis (CHS) analysis of the organic functionalized mesoporous SBA-15 silica **8** yield 15.71% C, 2.43% H, and 4.19% S. The sulfur content of the sample suggests that the organic moieties were successfully grafted within the siliceous framework. To investigate the long-range order of the solid, the sample was analyzed by powder X-ray diffraction. The diffraction pattern of the solid (Fig. 5) shows the characteristic pattern of SBA-15 mesoporous solids with diffraction peaks 0.95°, 1.55°, and 1.76° at 2θ angles.[60] This result indicates that the hexagonal long-range order of the silicate material was conserved during the functionalization with 2-(4-chlorosulfonylphenyl)ethyltrimethoxysilane.

Nitrogen adsorption isotherm analysis of the solid (Fig. 6) displays type IV isotherm with well-defined hysteresis. Further analysis of the isotherm yield a Brunauer, Emmett and

TABLE 3. Reduction of acetophenone using immobilized ligands 6 and 7[a]

	6		7	
Run	Yield[b]	*ee*[b]	Yield[b]	*ee*[b]
1	98	84	93	46
2	78	80	93	44
3	31	81	—	—

[a]Absolute configuration is *R*, assigned by comparing optical rotations with literature values.[36,39] Reaction conditions: 40°C. S/C = 100.
[b]Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.

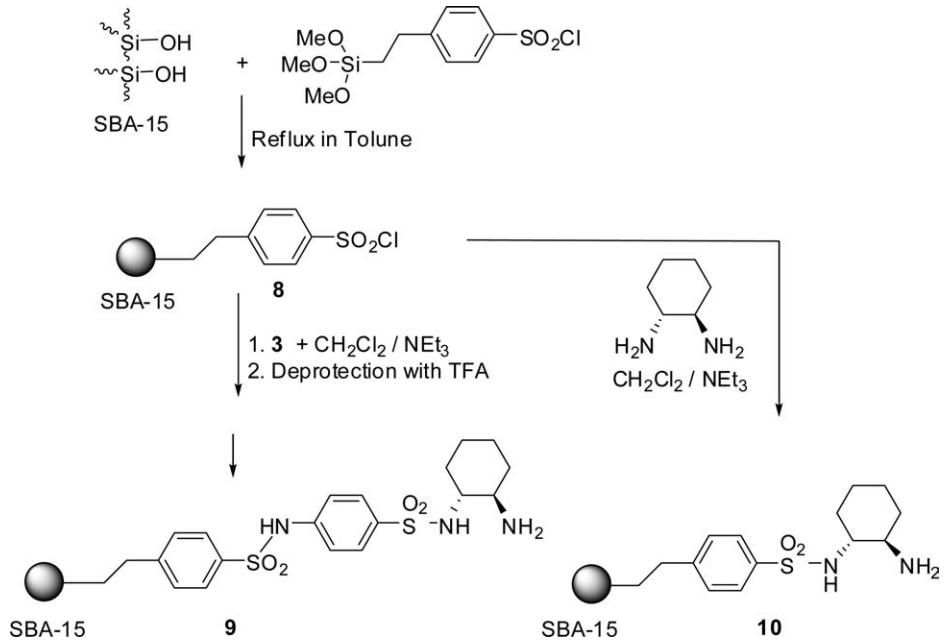


Fig. 4. Heterogenization of ligands on mesoporous SBA-15 silica.

Teller Theory (rule for the physical adsorption of gas molecules on a solid surface) (BET) surface area of 285 m^2/g, a Barret, Joyner and Halenda (The classical pore size model developed by) (BJH) pore size distribution of 55 Å, and a pore volume of 260 cm^3/g. These values are almost half of the reported values for siliceous nonfunctionalized SBA-15 mesoporous solids.[60] The reduction in pore volume, surface area, and pore size of our solid with respect to a pure silicate material suggest that the organic groups were successfully incorporated within the internal surface of the solid.

CONCLUSIONS

In conclusion, we have prepared a known water-soluble mono-*p*-nitrobenzenesulfonamide derived from cyclohexane-1,2-diamine (**1**) and demonstrated its application in the ATH of aromatic ketones under "green chemistry" conditions, using aqueous sodium formate, leading to the secondary alcohol in good yields and enantioselectivities. Reduction of acetophenone as the substrate with an S/C = 1000 gave a high yield (>99%) and good enantioselectivity (90%) within 3 h of reaction. We have also modified the nitroligand **1** and supported it on resin, silica, and mesoporous silica and demonstrated their application in the ATH of acetophenone. The resin-bound ligand **6** with $Rh^{III}Cp^*$showed better catalytic properties when compared with the silica-bound material **7**, but reuse of the supported catalyst **6** decreased the yield. ATH of acetophenone catalyzed by ligands **9** and **10** immobilized on mesoporous SBA-15 silica and complexed with $Rh^{III}Cp^*$ resulted in low yield and poor enantioselectivity. Elemental analysis of the organic-functionalized mesoporous SBA-15 silica **8** suggests that the functionalization with 2-(4-chlorosulfonylphenyl ethyltrimethoxysilane) was successfully grafted within the siliceous framework. Also, nitrogen adsorption isotherm analysis showed that the organic groups were successfully incorporated within the internal surface of the mesoporous SBA-15 silica.

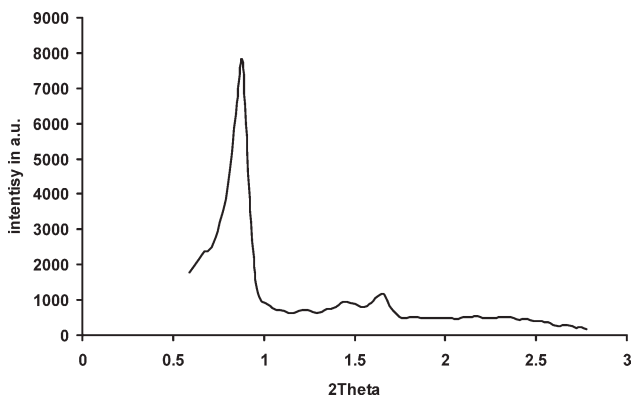


Fig. 5. X-ray diffraction pattern of 2-(4-chlorosulfonylphenyl)-functionalized SBA-15 mesoporous solid.

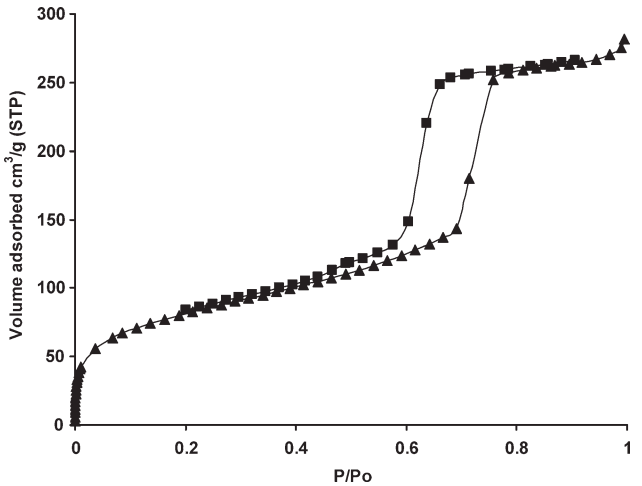


Fig. 6. Nitrogen adsorption isotherm of 2-(4-cholorosulfonylphenyl)-functionalized SBA-15 mesoporous solid. Triangles and squares denote adsorption and desorption, respectively.

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