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New heterogenized C_2-symmetric bis(sulfonamide)-cyclohexane-1,2-diamine-Rh^{III}Cp* complexes and their application in the asymmetric transfer hydrogenation (ATH) of ketones in water

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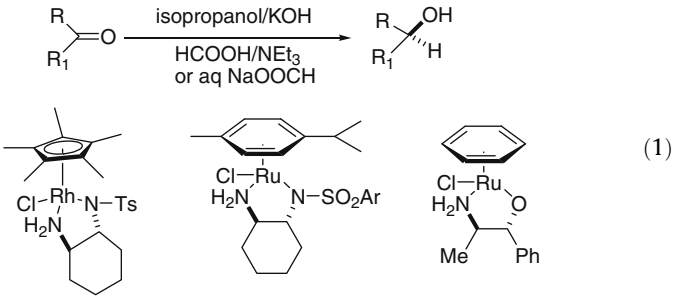
ABSTRACT

C_2-symmetric bis(sulfonamide) ligands derived from chiral *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine were immobilized on silica gel and on polystyrene resin, and complexed to Rh^{III}Cp*. The resulting complexes were used as catalysts in the asymmetric transfer hydrogenation (ATH) of acetophenone. The chiral secondary alcohol was obtained in high yields (>99%) and enantioselectivities (92%) with aqueous sodium formate as the hydride source. The immobilized catalysts were recycled with no loss in activity.

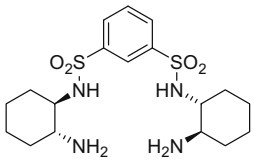
Asymmetric reduction of ketones to chiral secondary alcohols is an important chemical transformation providing chiral intermediates for the chemical manufacture of pharmaceuticals, animal health products, agrochemicals, fungicides, pheromones, flavors, and fragrances.[1–3] Reduction using molecular hydrogen or asymmetric transfer hydrogenation (ATH) using isopropanol/KOH, HCOOH/Et_3N has received much attention in recent years. The former requires molecular hydrogen under pressure leading to clean products and has found a niche in the fine chemicals manufacturing industry;[4] the latter (ATH), although involves a simple methodology, has been lagging behind due to lower TON, TOF, and the use of environmentally unfriendly solvents (Eq. (1)).[5–8] However, a number of recent reports have appeared which may reverse this, specially with the use of water-soluble ligands and heterogenized ligands in conjunction with Ru(II), Rh(III), and Ir(III) complexes as catalysts in aqueous sodium formate as the hydride source.[9]



(1)

Related to this we have reported the synthesis of C_2-symmetric bis(sulfonamide) ligand **1** and its use in the ATH of aromatic ketones, complexed to Rh^{III}Cp* in the presence of aqueous sodium formate as hydride source, giving the secondary alcohols in excellent enantioselectivities (>90%) and yields (>99%).[9a]

In this Letter, we report the immobilization of C_2-symmetric bis(sulfonamides) **1** and new ligand **2** on solid supports and their application as catalysts with Rh(III) in the ATH of aromatic ketones. Immobilized catalysts have been of great interest due to several advantages, such as simplification of product work-up, separation, isolation, and reuse of the catalyst.[10] 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.[10] 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.



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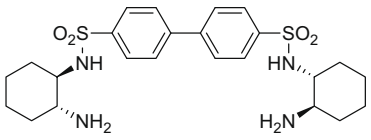

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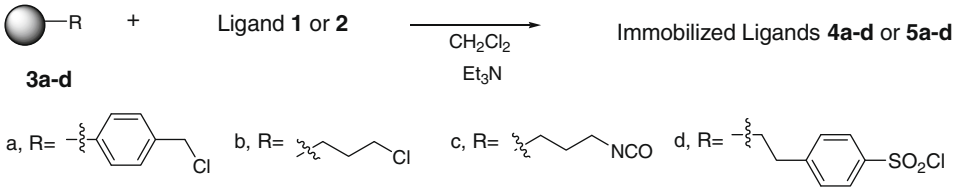
Commercially available (Sigma Aldrich) functionalized silica gels **3a–d** were stirred with ligand **1** or **2** (3 equiv) in dichloromethane using triethylamine as base at room temperature (Eq. (2)) to give immobilized ligands **4a–d** or **5a–d** (Fig. 1).



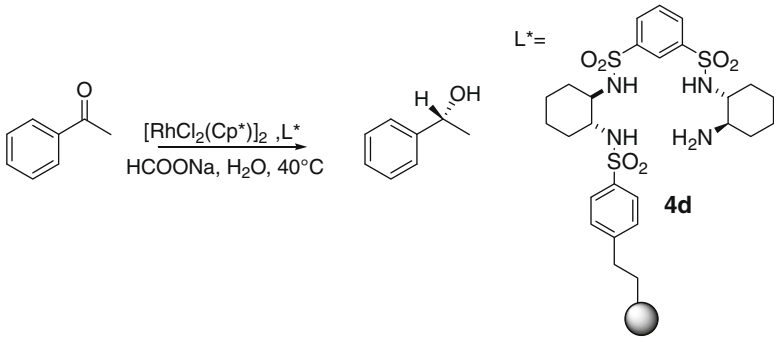
(2)

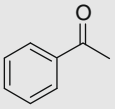
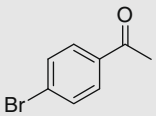
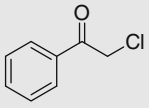
Initially, in order to compare the catalytic activity of homogeneous systems versus that of heterogeneous systems, the immobilized chiral ligand **4d** was complexed in situ with $[RhCl_2(Cp^*)]_2$ and reacted with acetophenone in water at 40 °C for 1 h. The chiral alcohol was obtained in >99% conversion and 91% enantioselectivity (Table 1, entry 2). The ligand **4d**–Rh(III) complex also efficiently reduced functionalized ketones (Table 1, entries 4 and 6) to alcohol in >99% conversion and 89–99% enantioselectivities.

Results show that the catalytic activity (ee and yield) of heterogeneous ligand **4**–Rh(III) complex was comparable to that of homogeneous ligand **1**–Rh(III) complex, except for the total run time and TOF. The immobilized catalyst was recycled three times with no change in activity.

Attempting to improve the performance of the heterogenized-metal complex **4d**, we explored the possibility of moving the catalytically active center away from solid surface with a spacer or linker, hoping it will enhance the activity. To test this, applying this technique to our ligand, we synthesized ligand **2** from 4,4′-bis(biphenylsulfonyl) chloride and *trans*-(1*R*,2*R*)-cyclohexane-1,2-diamine, and immobilized it using silica gel **3d** to give ligand

Table 1
Catalytic activity of homogeneous systems versus that of heterogeneous systems



Entry	Ketone	Ligand	Run	*t* (h)	ee[a,b] (%)	Yield (%)	Conf. abs.[c]
1		**1**[d]	1	0.25	92	>99	*R*
2		**4d**	3	16	91	>99	*R*
3		**1**	1	0.25	90	98	*R*
4		**4d**	3	12	89	>99	*R*
5		**1**	1	6	90[e]	100	*S*
6		**4d**	3	12	92	>99	*S*

[a] The substrate to metal ratio (S/C) was 100:1 and all reactions were carried out at 40 °C.
[b] Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.
[c] Absolute configurations were assigned by comparing optical rotations with literature values.[9d,f]
[d] Homogeneous reactions, carried out at 25 °C.
[e] The substrate to metal ratio (S/C) was 3000:1.

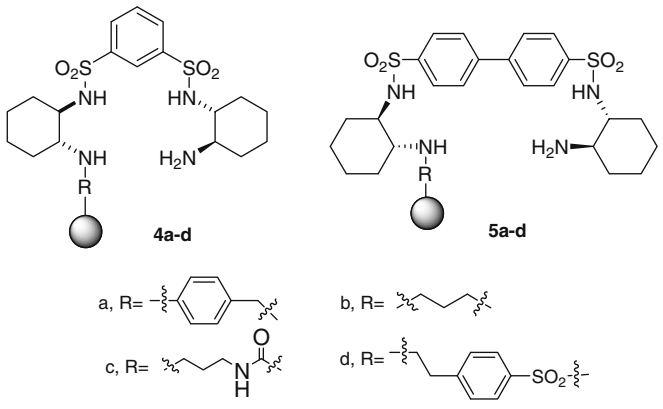
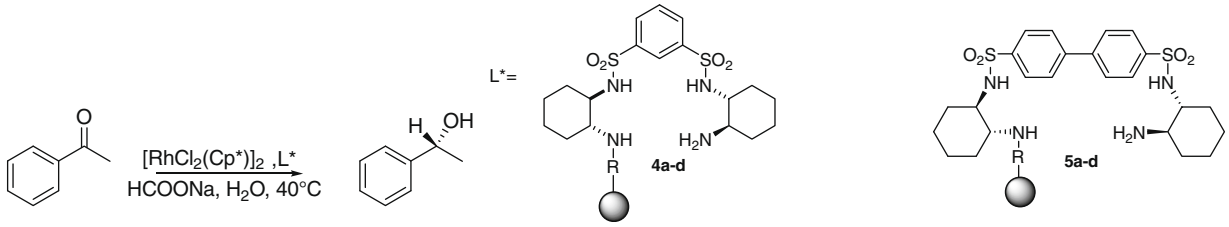


Figure 1. Supported ligands derived from ligands **1** and **2**.

5d, where the active center is moved away from any silica surface interaction. Results indicate that moving the active center by a linker did not produce any dramatic difference in the enantioselectivity and yield (Table 2, entries 9 and 10). However, the ligand–**5d**-catalyst was recycled seven times with no change in activity.

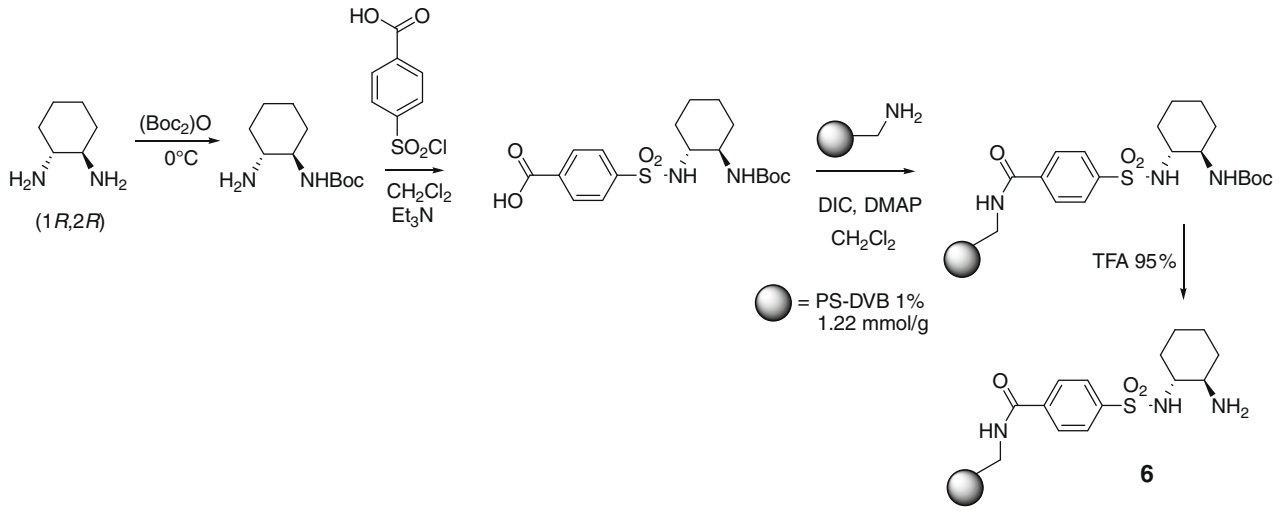
Having demonstrated that the catalytic activity of heterogenized ligand–metal complexes is comparable to that of the homogeneous ligand–metal complexes, we turned to explore other derivatized silica gels as sources of solid support. Derivatized silica gels with benzyl chloride **3a**, propyl chloride **3b** and isocyantes **3c** were coupled to the ligands **1** and **2** using standard procedures to give heterogenized ligands **4a**–**c** and **5a**–**c**. The application of these immobilized ligand–Rh(III) complexes in the reduction of acetophenone under ATH conditions was studied. Results are shown in Table 2. The results clearly indicate that the ligands immobilized

Table 2
Heterogeneous asymmetric transfer hydrogenation of acetophenone in aqueous sodium formate



Entry	Ligand	*t* (h)	Run	ee[a,b] (%)	Yield (%)	Conf. abs.[c]
1	**1**[d]	0.25	1	92	>99	*R*
2	**2**[d]	0.3	1	94	>99	*R*
3	**4a**	16	1	75	89	*R*
4	**5a**	16	1	71	44	*R*
5	**4b**	16	1	70	53	*R*
6	**5b**	16	1	35	29	*R*
7	**4c**	16	1	26	43	*R*
8	**5c**	16	1	22	22	*R*
9	**4d**	16	3	91	99	*R*
10	**5d**	16	7	90	>99	*R*

[a] The substrate to metal ratio was 100:1 and all reactions were carried out at 40 °C.
[b] Measured by GC analysis of the acetylated alcohol with chiral capillary column β-DEX™ 120.
[c] Absolute configurations were assigned by comparing optical rotations with literature values.[9d,f]
[d] Homogeneous reactions, carried out at 25 °C.



Scheme 1. Synthesis of the immobilized ligand **6**.

via benzenesulfonyl chloride bound to silica gel give the best results (entries 9 and 10). Binding through isocyanate led to lower enantioselectivities and yields, probably due to the urea fuctional group inhibiting the diamine–metal binding.

Once our ligands were successfully immobilized on silica gel, we turned our attention to immobilization on polystyrene, since catalysts show improved stability in polymer matrix. Ligand **1** was immobilized on commercially available polystyrene sulfonyl chloride (PS–DVB 8.5%, mesh 70–90, loading 2.5–3.0 mmol/g) and was complexed to $Rh^{III}Cp^*$ and used as a catalyst in the reduction of acetophenone under ATH conditions (aqueous sodium formate as hydride source) to give the alcohol in 17% ee and 24% conversion. However, when the chiral (1*R*,2*R*)-diamine was tethered to aminomethylated polystyrene (1.22 mmol g^{-1}, DVB 1%) through a linker, ligand **6** (Scheme 1), the chiral secondary alcohol was obtained in 90% enantioselectivity and >99% conversion. The catalyst was recycled four times with a slight drop in the activity, indicating the amount of cross linking is critical in obtaining a good polystyrene tethered ligand.

In conclusion we have immobilized C_2-symmetric ligand–Rh(III) complexes to silica gel and polystyrene and showed that they are excellent catalysts in reducing aromatic ketones to chiral alcohols in good enantioselectivities and yields, using aqueous sodium formate as hydride source. The catalysts were recycled several times with only a slight loss in activity, showing potential practical application.

Acknowledgments

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Supplementary data

Supplementary data (Experimental procedures and spectroscopic and analytical data of compounds) associated with this Letter can be found, in the online version, at doi:10.1016/j.tetlet.2009.02.183.

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