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Short Communication

Asymmetric transfer hydrogenation of 1-phenyl dihydroisoquinolines using Ru(II) diamine catalysts

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ABSTRACT

A new [Ru(II)(η^6-*p*-cymene)(1*R*,2*R*)-*N*-((1*S*,2*S*)-borneol-10-sulfonyl)-1,2-diphenylethylenediamine] catalyst for the asymmetric transfer hydrogenation of both 1-alkyl and 1-aryl dihydroisoquinolines has been isolated. For the first time in this type of reaction, the catalyst employs an N-alkylsulfonyl group instead of N-arylsulfonyl.

1. Introduction

Chiral amines are important building blocks in the fine-chemical, agrochemical and pharmaceutical industries. As the natural resources of optically pure substances are limited, their synthesis from achiral precursors is strongly in demand. The asymmetric reduction of corresponding imines is nowadays a prevalent procedure of their preparation [1].

Chiral ruthenium(II)-diamine catalysts (for instance **1a** and **1b** in Fig. 1) together with the formic acid-triethylamine azeotropic mixture (HCOOH-TEA) as a hydrogen donor represents an efficient and popular system for the asymmetric transfer hydrogenation (ATH) of various imines and ketones [2–4]. Regarding imine substrates, this catalytic system is capable of reducing the C=N double bonds of aryl-*N*-benzyl imines, β-carbolines and 1-alkyl- or 1-benzyl-3,4-dihydroisoquinolines (DHIQs). On the other hand, the ATH of 1-phenyl-DHIQs represents a considerable challenge since catalysts bearing the *N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine (TsDPEN) ligand (like **1a**) fail to catalyze this reduction under standard reaction conditions.

Some homogeneous catalysts have been described for the asymmetric hydrogenation of 1-phenyl substituted DHIQs, such as Rh(III)-diamine catalysts structurally similar to **1a** [5] and Ir(III)-phosphine complexes [6,7]. Catalytic activity was also reached in aqueous environment with the substrate in the form of iminium over modified **1a** [8], and with **1a** upon activation with $AgSbF_6$/La(OTf)$_3$ [9]. Among ruthenium-based catalysts, there is only one example of a complex which is able to catalyze the ATH of 6,7-dimethoxy-1-phenyl-DHIQ (**2a**) to corresponding tetrahydroisoquinoline under the original conditions. Catalyst **1a**, bearing the *N*-naphthalene-1-sulfonyl-DPEN ligand (NpsDPEN), was first proposed and tested by Noyori [10] and subsequently used by Vedejs and Boros [11–13].

Although the original Noyori-type ATH catalysts always bear an N-arylsulfonyl substituent, Ohkuma et al. [14], Ikariya et al. [15] and others [16–18] showed that Ir and Ru catalysts containing methanesulfonyl-DPEN (MsDPEN) hydrogenate various aryl-*N*-benzyl imines, N-sulfonylimines and aryl ketones with molecular hydrogen. Carreira and co-workers followed with their work on the ATH of β-keto esters in water catalyzed by an Ir(III)-MsDPEN complex [19]. The MsDPEN ligand belongs to a very small group of N-alkylsulfonyl diamines that proved utilizable in asymmetric (transfer) hydrogenation. Another such ligand is alicyclic *N*-(camphor-10-sulfonyl)-DPEN (CsDPEN) that has been employed in the ATH of various ketones [20–23]. However, to the best of our knowledge, no N-alkylsulfonyl diamines have applied in the ATH of imines such as DHIQs.

We report here a CsDPEN-based Ru(II) catalyst that is suitable for the reduction of both 1-alkyl- and 1-phenyl-DHIQ substrates.

2. Experimental

2.1. General information

[RuCl(η^6-*p*-cymene)(1*R*,2*R*)-*N*-((1*S*,2*S*)-borneol-10-sulfonyl)-1,2-diphenylethylenediamine] (**5**) and [RuCl(η^6-benzene) (1*R*,2*R*)-*N*-

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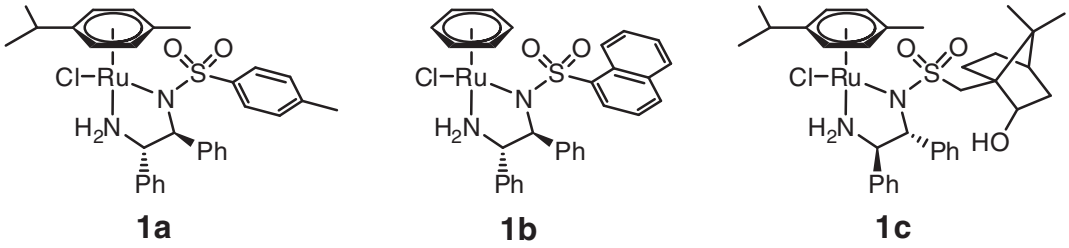


Fig. 1. Structures of Ru(II) half-sandwich complexes **1a**–**1c** used in this work.

(naphthalene-1-sulfonyl)-1,2-diphenylethylenediamine] (**1b**) were prepared from corresponding diamine ligands and $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and $[RuCl_2(\eta^6\text{-benzene})]_2$, respectively, as described previously [10]. All starting materials were of commercial origin (Sigma-Aldrich, Germany or Penta, Czech Republic). ^1H and ^{13}C NMR spectra were recorded on Bruker AVANCE III 400 MHz, 600 MHz and 700 MHz spectrometers with reference to the residual signal of solvent as an internal standard. Kinetic samples were analyzed by a GC instrument with an FID detector and Varian VF-1 non-polar capillary column. Enantiomeric excess (*ee*) was determined by GC using pre-column derivatization with (*R*)-(−)-menthyl chloroformate. For complete NMR data please refer to the supporting information.

X-ray diffraction data were measured at 190 K on a four-circle CCD diffractometer Gemini of Oxford Diffraction Ltd. with graphite monochromated CuKα radiation (λ = 1.5418 Å). Data reduction including empirical absorption correction by using spherical harmonics was performed with CrysAlis-Pro (Oxford Diffraction, England). The crystal structure was solved by the charge-flipping method using the program Superflip [24] and refined with the Jana2006 program package [25] by full-matrix least-squares technique on F. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were positioned geometrically and refined by using the riding model. The molecular-structure plots were prepared by using ORTEP III [26] and the intermolecular interactions were viewed in Mercury software [27].

2.2. Synthesis of chiral ligands and catalysts

2.2.1. Synthesis of (1R,2R)-N-((S)-camphor-10-sulfonyl)-1, 2-diphenylethylenediamine (ligand for catalyst **1c**)

(*S*)-Camphor-10-sulfonic acid (500 mg, 2.15 mmol) was treated with $SOCl_2$ (0.625 mL, 8.61 mmol) for 1.5 h at 120 °C to get (*S*)-camphor-10-sulfonyl chloride. Excess $SOCl_2$ was evaporated twice with toluene (5 mL) at reduced pressure.

The solution of (*S*)-camphor-10-sulfonyl chloride (215 mg, 0.85 mmol) in acetonitrile (20 mL) was added dropwise into a solution of (*R*,*R*)-1,2-diphenylethylene-1,2-diamine (DPEN; 200 mg, 1.1 eq) and triethylamine (TEA; 240 μL, 4 eq) in acetonitrile (40 mL) at 0 °C for 30 min. After further 60 min of the reaction, the white precipitate of TEA·HCl was filtered off and the reaction mixture was diluted with dichloromethane and evaporated at 40 °C at reduced pressure. The product was dissolved in 0.1 M solution of NaOH (30 mL) and extracted with dichloromethane (3 × 10 mL). Combined extracts were dried over anhydrous Na_2SO_4 and evaporated. The crude product was purified by flash column chromatography using Silicagel 60 and mobile phase consisting of ethyl acetate/hexane/TEA (1/1/0.02) yielding ochre crystals of pure (1*R*,2*R*)-*N*-((*S*)-camphor-10-sulfonyl)-1,2-diphenylethylene-1, 2-diamine. Yield: 280 mg, 77%; purity: 98%.

2.2.2. Synthesis of (1R,2R)-N-(naphthalene-1-sulfonyl)-1, 2-diphenylethylenediamine (ligand for catalyst **1b**)

The compound was prepared according to the procedure described above using commercial naphthalene-1-sulfonyl chloride. Yield: 722 mg, 49%; purity: 97%.

2.2.3. Synthesis of $[RuCl(\eta^6\text{-}p\text{-cymene})$ (1R,2R)-N-((1S,2S)-borneol-10-sulfonyl)-1,2-diphenyl-ethylenediamine] (**1c**)

$[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ (139 mg, 0.227 mmol), (1*R*,2*R*)-*N*-((*R*)-camphor-10-sulfonyl)-1,2-diphenylethylenediamine (168 mg, 0.394 mmol) and TEA (126 μL; 0.91 mmol) were dissolved in propan-2-ol (5 mL) and heated for 3 h at 85 °C under an argon atmosphere. The resulting dark red solution was evaporated to dryness and crude product was washed with water (20 mL) on sintered glass and dried in a desiccator for a period of 2 days. The catalyst was recrystallized from boiling ethanol:methanol (1:1) mixture and red crystals were washed with a small amount of cold solvents. Yield: 125.5 mg (after recrystallization), 43%.

2.2.4. $[RuCl(\eta^6\text{-benzene})$(1R,2R)-N-(naphthalene-1-sulfonyl)-1,2-diphenyl-ethylenediamine] (**1b**)

The compound was prepared according to the procedure described above using (1*R*,2*R*)-*N*-(naphthalene-1-sulfonyl)-1,2-diphenyl-ethylenediamine. Yield: 104 mg, 50%.

2.3. General procedure for asymmetric transfer hydrogenation

The formic acid-triethylamine azeotropic mixture (218 μL; 6.3 eq of formic acid with respect to the imine) was charged into a round-bottom flask (10 mL), followed by the catalyst (0.01 eq) dissolved in acetonitrile (1 mL). The resulting mixture was stirred for 10 min to activate the catalyst. The imine (0.42 mmol) dissolved in acetonitrile (1 mL) was introduced at once and the mixture was stirred at 30 °C. The samples of the reaction mixture (60 μL) were collected at 10, 20, 30, 40, 50, 90, 120 and 180 min.

Each sample was quenched by using saturated solution of Na_2CO_3 (1 mL) and extracted with diethyl ether (3 × 1 mL). Combined extracts were dried over anhydrous sodium sulfate and the solvent was stripped off in a stream of nitrogen. The dry sample was dissolved in acetonitrile (1 mL) and analyzed.

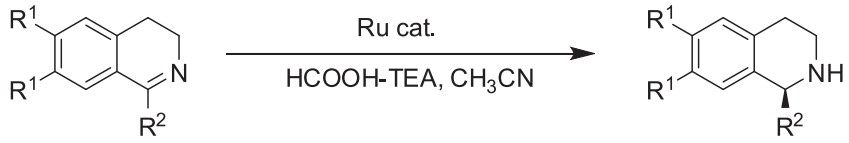
3. Results and discussion

3.1. Catalyst development and performance

At the beginning of our study, we tested catalyst **1b** in the ATH of a series of 1-phenyl-DHIQs **2a**–**2d** and two 1-alkyl-DHIQs (**2e** and **2f**) (Table 1, entries 1–6). We found out that this system showed significantly lower catalytic activity (expressed as turnover frequency, TOF) and selectivity (expressed by *ee*) in the ATH of 1-alkyl-DHIQs (**2e** and **2f**) compared to catalyst **1a** (entries 7 and 8), which, however, does not reduce 1-phenyl-DHIQs (**2a**–**2d**).

The change of the N-arylsulfonyl substituent from *p*-toluenesulfonyl (present in **1a**) to naphthalene-1-sulfonyl in **1b** thus enabled the catalytic activity in the ATH of substrates **2a**–**2d**. Noyori et al. showed that catalysts bearing N-benzoyl and N-acetyl DPEN ligands are inactive in ATH [10]. Our computational studies revealed that the sulfonyl group plays a crucial role in the reaction mechanism by forming an N – H···S═O hydrogen bond with the protonated imine [28]. The low reactivity of 1-aryl DHIQs is attributed to the fact that the aromatic ring and the

Table 1
ATH of 1-phenyl (**2a**–**2d**) and 1-methyl (**2e** and **2f**) substituted DHIQs over catalysts **1a**–**1c**.



2a–2f

2a: R^1 = MeO, R^2 = Ph
2b: R^1 = H, R^2 = Ph
2c: R^1 = H, R^2 = 4-(CF_3)-C_6H_5
2d: R^1 = H, R^2 = 4-(CH_3)-C_6H_5
2e: R^1 = H, R^2 = CH_3
2f: R^1 = MeO, R^2 = CH_3

Entry	Substrate	Catalyst	TOF (h^{-1})	*ee* (%)
1	**2a**	**1b**	4.1	73
2	**2b**	**1b**	3.8	39
3	**2c**	**1b**	4.8	40
4	**2d**	**1b**	5.7	49
5	**2e**	**1b**	5.9	61
6	**2f**	**1b**	45	80
7	**2e**	**1a**	171	82
8	**2f**	**1a**	261	94
9	**2a**	**1c**	3.7	74
10	**2b**	**1c**	<1	–[a]
11	**2c**	**1c**	<1	–[a]
12	**2d**	**1c**	6.7	63
13	**2e**	**1c**	226	82
14	**2f**	**1c**	265	87
15	Acetophenone	**1c**	11.5	97

[a] *ee* was not determined due to low conversion.

C═N bond are in conjugation, which affects its electron density and polarization. This effect is further manifested through the N–H···S═O interaction which has an impact on the catalytic activity. These considerations led us to the idea of changing the structure of the catalyst in order to enhance its activity and selectivity for both 1-alkyl and 1-aryl DHIQs.

The camphor fragment was selected as the substituent of the sulfonyl group due to its inherent chirality. By reacting (*S*)-camphor-10-sulfonyl chloride with (*R*,*R*)-DPEN, we obtained (1*R*,2*R*)-*N*-((*S*)-camphor-10-sulfonyl)-DPEN (CsDPEN). The ligand was further reacted with [Ru(II)$Cl_2(\eta^6$-*p*-cymene$)]_2$. During the reaction, the complex underwent stereoselective transfer auto-hydrogenation of the carbonyl group in the *N*-camphorsulfonyl part of the molecule to give a complex of *N*-borneolsulfonyl-DPEN. As the reaction was performed in propan-2-ol, the solvent served as a hydrogen source. The isolated crystalline material contained only one isomer (borneolsulfonyl, not isoborneolsulfonyl as evidenced from the crystallographic analysis, *vide infra*). This ligand has been shown applicable in the ATH of a ketone [21] but its isolated complex has not been characterized. The reaction conditions towards the non-reduced analog were not examined since the synthesis of such complex has already been reported [20].

The resulting complex, [Ru(II)Cl(η^6-*p*-cymene)(1*R*,2*R*)-*N*-((1*S*,2*S*)-borneol-10-sulfonyl-DPEN)] (**1c**), was tested in the ATH of a series of DHIQs and a ketone (Table 1, entries 9–15). In the reduction of 1-phenyl-DHIQs containing electron-donating groups (**2a** and **2d**, entries 9 and 12), the catalyst's performance was comparable with that of **1b** (entries 1, 4, 9 and 12). On the contrary, substrates lacking electron-donating groups (**2b**, entry 10) or even containing an electron withdrawing group (**2c**, entry 11) displayed very low catalytic activity. In the case of 1-phenyl-DHIQs, the catalytic activity (dependent on the electronic distribution in the C═N bond) was hampered by the conjugation of the C═N bond with the aromatic ring. When electron-donating groups like CH_3O- and CH_3- were present in the molecule, the catalytic activity was higher than in an opposite case. The sensitivity of **1c** to this effect was evidently more pronounced than in the case of **1b**.

In the ATH of imines **2e** and **2f**, the reactivity was much higher than with **1b**, and slightly exceeding the activity of **1a**. The catalyst was also active in the ATH of acetophenone (entry 11). The reactivity was rather low despite very high *ee*. The reduction of other ketones has been reported elsewhere [20–23].

3.2. XRD structure analysis of **1c**

The single crystal structure of compound **1c** is built up by discrete moieties in the orthorhombic space group $P2_12_12_1$ with one formula unit in the asymmetric unit. Basic crystallographic information is given in Table 2.

The Ru atom in **1c** has a pseudo-octahedral geometry, being coordinated to a η^6-*p*-cymene occupying three facial coordination sites, a five-membered chelate ring with neutral amine and anionic sulfonamide moieties (occupying two coordination sites) and a chloride ligand. The chelate ring is formed by two-carbon-symmetric bidentate diphenylethylenediamine ligand. The distance of the Ru atom from the center of the η^6-*p*-cymene ring is 1.676 Å and the average Ru–C distance is 2.191 Å. The Ru1–C28 distance is significantly longer than the rest of Ru–C bonds (2.227 Å compared to 2.17–2.19 Å). The borneolsulfonyl group is connected to the N1 atom by a three-membered S-shaped chain S1–C15–C16 and contains a strong

Table 2
Crystal data and structure refinement of catalyst **1c**.

Empirical formula	$C_{34}H_{45}ClN_2O_3RuS$
Formula weight	698.4
Wavelength (Å)	1.5418
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	
a (Å)	12.4647 (2)
b (Å)	16.3344 (3)
c (Å)	17.1478 (5)
Volume ($Å^3$)	3491.35 (13)
Z	4
Calculated density	1.3282
Absorption coefficient	5.16
F(000)	1456
Reflections collected/unique	45295/7330
R1, wR2	0.0409, 0.0543

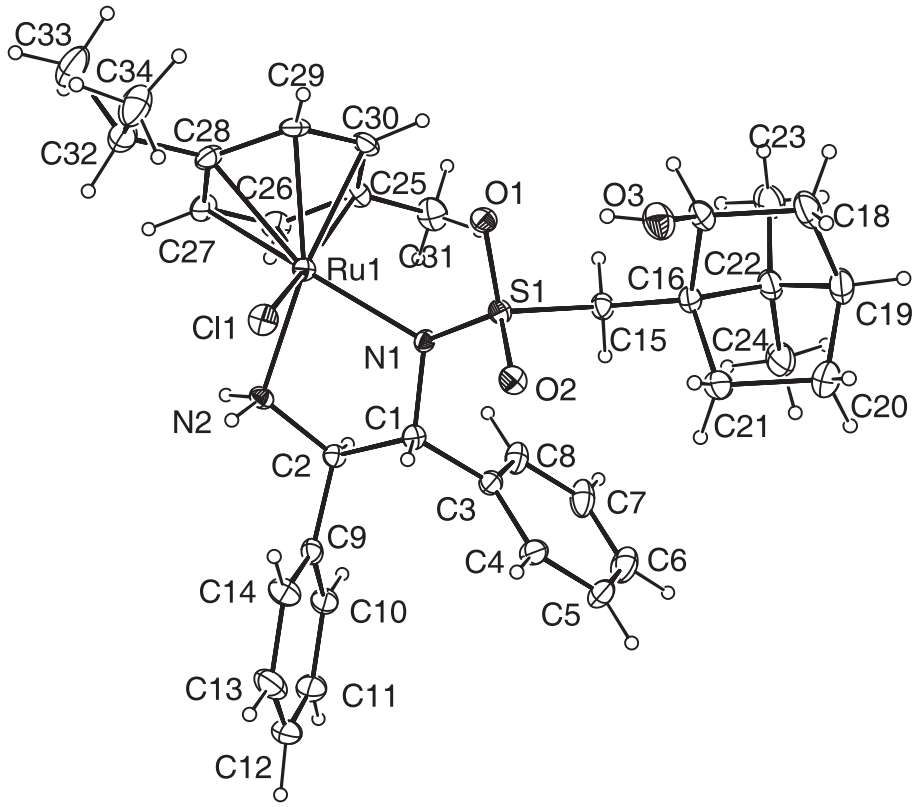


Fig. 2. Solid-state molecular structure of **1c** (25% probability ellipsoids).

intramolecular hydrogen bond O1 – H1O3···O3 with the H···A distance of 2.33(7) Å. This hydrogen bond makes the system more rigid and causes a synergistic effect with other steric and electronic properties leading to the catalytic results achieved. The X-ray crystallographic structure is given in Fig. 2 and selected bond lengths and angles are summarized in Table 3.

4. Conclusions

In conclusion, the novel ruthenium-arene complex containing (1*R*,2*R*)-*N*-((1*S*,2*S*)-borneol-10-sulfonyl)-DPEN proved to be a robust ATH catalyst since it is able to reduce both 1-methyl and 1-phenyl-DHIQs with performance comparable with the reported catalysts. To the best of our knowledge, this is the first N-alkylsulfonyl-DPEN catalyst which can catalyze the ATH of cyclic imines. This study opens the way to other active and selective Ru catalysts for the asymmetric hydrogen transfer reductions of imines and ketones.

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Table 3
Selected bond lengths [Å] and bond angles [°] in **1c**.

Ru1 – C27	2.185(5)	Cl1 – Ru1 – N1	87.46(1)
Ru1 – Cl1	2.4247(1)	Ru1 – N1 – S1	120.19(2)
Ru1 – N1	2.138(3)	O1 – S1 – N1	110.45(2)
Ru1 – N2	2.117(4)	N1 – S1 – C15	106.4(2)
S1 – N1	1.615(4)	S1 – C15 – C16	116.00(1)
S1 – O1	1.450(4)	N1 – Ru1 – N2	79.29(1)
S1 – O2	1.448(3)		
S1 – –15	1.808(4)		
O1 – H1O3	2.331(6)		

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.03.004.

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