

## New insight into the role of a base in the mechanism of imine transfer hydrogenation on a Ru(II) half-sandwich complex†

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Asymmetric transfer hydrogenation (ATH) of cyclic imines using [RuCl(η<sup>6</sup>-*p*-cymene)TsDPEN] (TsDPEN = *N*-tosyl-1,2-diphenylethylenediamine) was tested with various aliphatic (secondary, tertiary) and aromatic amines employed in the HCOOH–base hydrogen donor mixture. Significant differences in reaction rates and stereoselectivity were observed, which pointed to the fact that the role of the base in the overall mechanism could be more significant than generally accepted. The hydrogenation mixture was studied by nuclear magnetic resonance (NMR), Fourier transform ion cyclotron resonance mass spectrometry (FT-ICR MS) and vibrational circular dichroism (VCD) with infrared spectroscopy. The results suggested that the protonated base formed an associate with the active ruthenium-hydride species, most probably *via* a hydrogen bond with the sulfonyl group of the complex. It is assumed that the steric and electronic differences among the bases were responsible for the results of the initial ATH experiments.

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### Introduction

Enantiomerically pure compounds are of vital importance for a broad range of life sciences and fine chemical products, particularly for pharmaceuticals and agrochemicals. For the manufacture of chiral compounds starting from achiral precursors, enantioselective catalysis has become a valuable and versatile synthetic route.

Catalytic enantioselective synthesis is according to Rouhi<sup>1</sup> one of the most important synthetic methods for the production of chiral compounds. One of those methods, catalytic asymmetric hydrogenation, plays an outstanding role both on a laboratory and an industrial scale.<sup>2</sup> Enantioselective hydrogenation of the C=C double bond has historically attracted the most interest.

Nowadays, the asymmetric hydrogenation of ketones and imines plays comparably an important role from the practical point of view. The reduction can be conducted either by

gaseous hydrogen (asymmetric hydrogenation, AH), or by hydrogen obtained *in situ* from an organic molecule, such as propan-2-ol or formic acid, which is present in the reaction mixture (asymmetric transfer hydrogenation, ATH). The AH of functionalized ketones is typically carried out with the organometallic complexes of rhodium and ruthenium bearing diphosphine ligands.<sup>3</sup> Unfunctionalized ketones are efficiently reduced over ruthenium-diphosphine/β-diamine complexes.<sup>4</sup> For ATH, several active ruthenium-arene, iridium-Cp and rhodium-Cp (Cp = cyclopentadienyl) complexes based on β-diamines and β-amino alcohols have been described.<sup>5</sup>

There are a variety of mechanisms through which catalytic hydrogenation employing transition metals can operate.<sup>6</sup> ATH using [RuCl(η<sup>6</sup>-*p*-cymene)TsDPEN] (TsDPEN = *N*-tosyl-1,2-diphenylethylenediamine) (**1** in Scheme 1) with HCOOH requires the presence of a base such as *t*-BuOK or triethylamine (TEA), which serves as an acceptor of HCl from **1**.<sup>7</sup> A 16 e<sup>−</sup> unsaturated complex (**3**)<sup>8</sup> is formed, which can be *in situ* protonated and form a solvate (**4**).<sup>9</sup> In the presence of HCOOH, ruthenium hydride **2** is formed.<sup>8,10</sup> This species is capable of reducing prochiral ketones or imines (such as dihydroisoquinolines, DHIQs) to optically enriched alcohols or amines (tetrahydroisoquinolines, THIQs). The outcome is complex **4** (in an equilibrium with **3**), which is converted back to species **2** by reacting with the formate anion.

In the ATH of ketones it has been shown that selection of the base can affect the reaction's enantioselectivity.<sup>11</sup> However,

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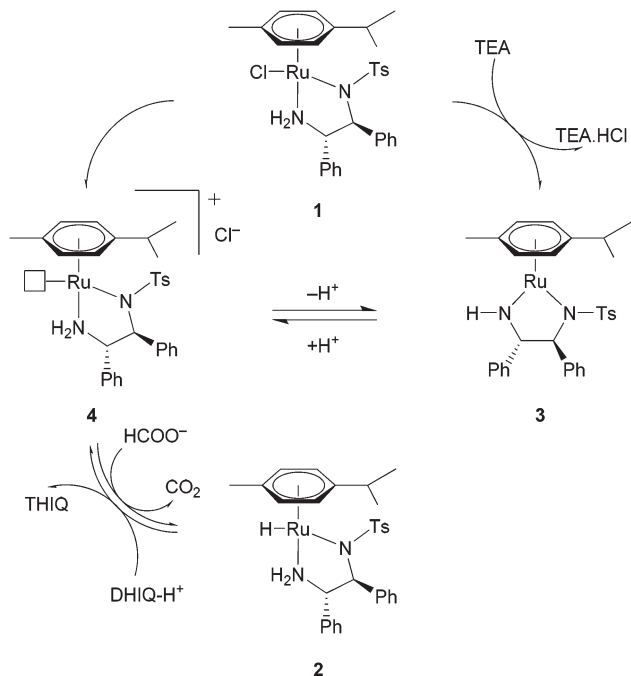
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**Scheme 1** Suggested catalytic cycle for the ATH of a protonated dihydroisoquinoline (DHIQ-H<sup>+</sup>) using catalyst **1**.

no mechanistic rationale was proposed and research in this direction has been rather limited. The presented work is focused on the influence of a base on the ATH of cyclic imines and is complemented with a mechanistic study.

## Results and discussion

### Kinetic experiments

We started our investigation by the ATH of (*R*)-1,4-dimethyl-3,4-dihydroisoquinoline ((*R*)-**5**) followed *in situ* by NMR. Diastereomeric products formed during the reaction were readily distinguishable by <sup>1</sup>H NMR. Several bases were tested in combination with HCOOH as a hydrogen source and the results are summarized in Table 1.

Substantially different reaction rates were observed with various bases. The highest was for tertiary amines, *i.e.* TEA, *N,N*-diisopropyl(ethyl)amine (DIPEA) and 1,4-diazabicyclo[2.2.2]octane (DABCO). In the case of TEA, the rate was over four times higher than in the trial with DIPEA. Secondary amines (morpholine, piperidine and pyrrolidine) performed with even lower rates. The rate was surprisingly high for pyrrole (an aromatic heterocycle) when compared to pyrrolidine because the rates obtained with other aromatic bases (imidazole and pyridine) were very low.

Selection of a base also distinctively affected the asymmetric bias of the reaction. The lowest diastereomeric excess (de) was observed for DIPEA, followed by TEA and DABCO. Secondary amines (piperidine, morpholine and pyrrole) performed with around 65% de and the highest value was obtained for pyrrolidine, which is one of the smallest

molecules in the set. The diastereoselectivity was also within the range of 65–70% de for aromatic bases (pyrrole, pyridine), but the use of imidazole showed zero selectivity. Based on these results, we assumed that the differences in diastereoselectivity were related to the steric requirements of the bases applied.

A similar experiment was conducted with 1-methyl-3,4-dihydroisoquinoline (**6**). The differences in reaction rates were very significant and also followed the groups of tertiary, secondary and aromatic bases. However, in this case the rate with DIPEA was slightly higher than with TEA. Interestingly, enantioselectivity was not changed appreciably when various bases were used. This is in contrast with the observations made with substrate (*R*)-**5**.

It was clear that the base dramatically influenced the reaction performance for no apparent reason. We therefore set out to investigate the observed phenomena closely by utilizing spectroscopic methods.


### Spectroscopic studies

To get further information concerning the structure of species present in the solution, a mixture of complex **1**, HCOOH and TEA was studied by NMR spectroscopy. Different ratios of TEA and HCOOH ranging from pure HCOOH to 1 : 10 were examined (Fig. 1).

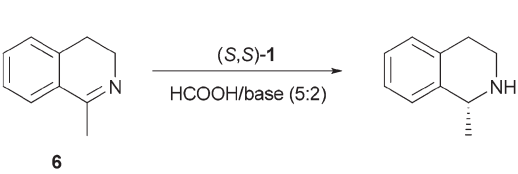
When only HCOOH (1 eq.) was added to **1**, the Ru hydride species (**2**) could be detected but it underwent rapid decomposition. Adding excess HCOOH led to catalyst breakdown, although after a certain period of time complex **1** reappeared, meaning that HCOOH did not destroy the catalyst irreversibly. Addition of TEA had a positive effect on the formation of hydride **2** (Fig. 1) but increasing the TEA : HCOOH ratio above 5 : 1 did not lead to any appreciable increase of the concentration of **2**. Under such conditions, the aromatic region of <sup>1</sup>H NMR spectra consisted of three sets of four individual signals belonging to three different *p*-cymene moieties, which can be attributed to (a) hydride **2**, (b) a compound identified as ruthenium formate [Ru(HCOO<sup>-</sup>)(η<sup>6</sup>-*p*-cymene)TsDPEN]<sup>10a</sup> and (c) a species that was assumed to be a second diastereomer of the ruthenium hydride. The latter has also been observed in the case of ruthenium tethered complexes<sup>12</sup> and the hypothesis is further supported by the fact that no second hydridic species was observed with an achiral *p*-toluenesulfonylethylenediamine ligand as shown by Ikariya *et al.*<sup>10a</sup> In contrast, in the <sup>1</sup>H NMR spectrum of precatalyst **1**, all protons of the *p*-cymene moiety resonated in a narrow region (Fig. S1†<sup>13</sup>). One interpretation of such significant changes might be that the coordination mode of *p*-cymene was changed. However, the <sup>1</sup>J<sub>C-H</sub> direct interaction constants of *p*-cymene in complexes **1** and **2** were very similar (Table S1†<sup>13</sup>) and the slight differences were therefore ascribed to different electron-donating abilities of the chloride and hydride ligands. This measurement thus disproved our initial assumption of *p*-cymene decoordination since more profound changes of <sup>1</sup>J<sub>C-H</sub> constants would be expected. An explanation based on subsequent experiments is proposed at the end of this study (*vide infra*).



**Table 1** Results of the asymmetric transfer hydrogenation of (*R*)-**5** and **6** using catalyst **1** and HCOOH with various bases



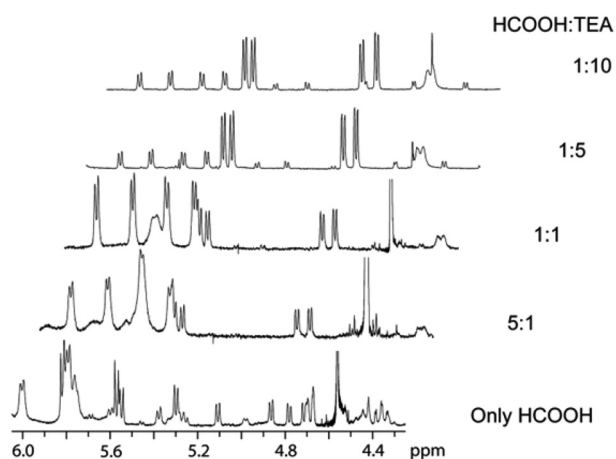
(*R*)-**5**



**6**

Amine type	Amine	$pK_{a1}$	Substrate ( <i>R</i> )- <b>5</b>		Substrate <b>6</b>	
			$k^a$	de <sup>b</sup> [%]	$k^a$	ee <sup>c</sup> [%]
Tertiary	TEA <sup>d</sup>	10.8	1.0000	55.5	1.0000	83.9
	DIPEA <sup>e</sup>	11.4	0.2442	46.1	1.1650	84.0
	DABCO <sup>f</sup>	8.7	0.2335	63.8	0.4932	82.7
Secondary	Morpholine	8.3	0.2144	65.6	0.1156	78.9
	Piperidine	11.0	0.2059	65.1	0.2383	82.1
	Pyrrolidine	11.2	0.0594	71.5	0.2726	79.2
Aromatic	Pyrrole	0	0.1423	65.5	0	—
	Imidazole	7.0	0.0042	0	0	—
	Pyridine	5.2	0.0064	69.3	0.0006	n.d. <sup>g</sup>

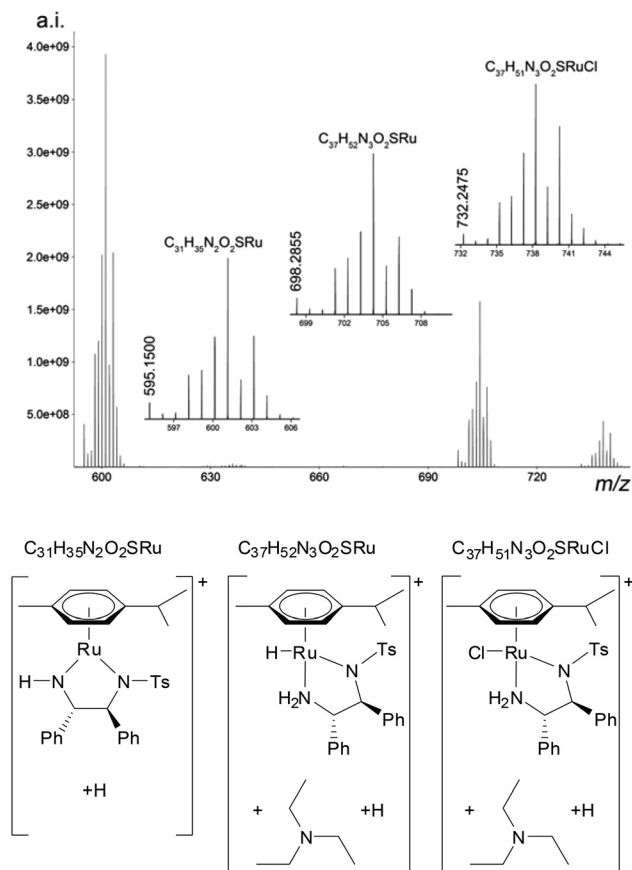
<sup>a</sup> Zero order rate constants relative to TEA. From the time-conversion plot, the linear region was used for the least squares linear regression analysis to determine the  $k$  values. <sup>b</sup> Diastereomeric excess, determined by NMR. <sup>c</sup> Enantiomeric excess, determined by GC after pre-column derivatization. <sup>d</sup> Triethylamine. <sup>e</sup> *N,N*-Diisopropyl(ethyl)amine. <sup>f</sup> 1,4-Diazabicyclo[2.2.2]octane. <sup>g</sup> The amount of the product was too low to determine ee.

**Fig. 1** Spectra of **1** upon adding pure HCOOH or a mixture of HCOOH and TEA in various ratios.

In the next stage, we utilized Fourier transform ion cyclotron resonance mass spectrometry with electrospray ionization in positive mode (ESI<sup>+</sup>-FT-ICR MS) to observe active hydride species **2**. Since the NMR experiments showed that it was formed in the prevalence of TEA, similar conditions were applied (TEA : HCOOH = 5 : 2).

The mass spectrum contained three isolated ion clusters (Fig. 2 and Table 2). The most intense ion cluster in the spectrum contained a monoisotopic ion with  $m/z$  595.1500. Analyzing the ion cluster and the isotope relative ratio allowed us to reveal the molecular formula  $C_{31}H_{35}N_2O_2RuS$ , which well agreed with the measured data (Table 2). The species was identified as a  $[M - H]^+$  ion of the 16 e<sup>-</sup> Ru complex (**3**) that is formed from **1** by elimination of HCl.<sup>14</sup> The second most intense ion cluster in the spectrum contained a monoisotopic ion with  $m/z$  698.2855 reflecting the elemental composition  $C_{37}H_{52}N_3O_2RuS$ .



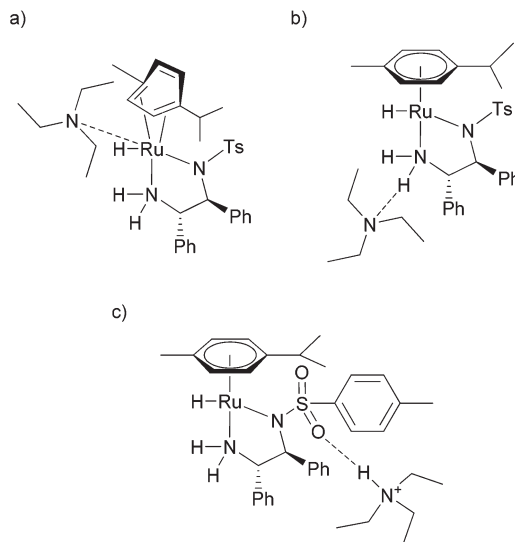


**Fig. 2** ESI<sup>+</sup>-FT-ICR MS spectrum of species formed from **1** in the presence of HCOOH and TEA.

**Table 2** Monoisotopic masses obtained from ESI<sup>+</sup>-FT-ICR MS measurements with TEA, DIPEA and DABCO

Monoisotopic mass ( <i>m/z</i> )		Error [ppm]	Formula	Identified species
Measured	Theoretical			
<b>TEA</b>				
595.1500	595.1490	1.7	C <sub>31</sub> H <sub>35</sub> N <sub>2</sub> O <sub>2</sub> RuS	<b>3</b>
698.2855	698.2851	0.6	C <sub>37</sub> H <sub>52</sub> N <sub>3</sub> O <sub>2</sub> RuS	2 + base
732.2475	732.2466	1.2	C <sub>37</sub> H <sub>51</sub> N <sub>3</sub> O <sub>2</sub> RuSCL	1 + base
<b>DIPEA</b>				
595.1499	595.1490	1.5	C <sub>31</sub> H <sub>35</sub> N <sub>2</sub> O <sub>2</sub> RuS	<b>3</b>
726.3150	726.3164	1.9	C <sub>39</sub> H <sub>56</sub> N <sub>3</sub> O <sub>2</sub> RuS	2 + base
760.2756	760.2779	3.0	C <sub>39</sub> H <sub>55</sub> N <sub>3</sub> O <sub>2</sub> RuSCL	1 + base
<b>DABCO</b>				
595.1499	595.1490	1.5	C <sub>31</sub> H <sub>35</sub> N <sub>2</sub> O <sub>2</sub> RuS	<b>3</b>
709.2662	709.2647	2.1	C <sub>37</sub> H <sub>49</sub> N <sub>4</sub> O <sub>2</sub> RuS	2 + base
743.2256	743.2262	0.8	C <sub>37</sub> H <sub>48</sub> N <sub>4</sub> O <sub>2</sub> RuSCL	1 + base

The molecular formula of **2** is C<sub>31</sub>H<sub>36</sub>N<sub>2</sub>O<sub>2</sub>SRu, which differs from the ion cluster by C<sub>6</sub>H<sub>16</sub>N. Because the reaction mixture contained TEA (C<sub>6</sub>H<sub>15</sub>N), this cluster could be explained as **2** associated with TEA. Similarly, the third cluster (*m/z* 732.2475) was assigned to precatalyst **1** associated with TEA.



**Fig. 3** Three hypothetical associates of TEA with **1**. The amine (a) coordinates to the Ru atom of **1**, (b) forms a hydrogen bond with the NH<sub>2</sub> group of the ligand, or (c) forms a hydrogen bond with the sulfonyl group.

Application of ESI as an ion source can be accompanied by formation of artificial in-source ions as a consequence of ion-ion or ion-solvent reactions. However, they can be eliminated by dilution and no substantial changes in the MS spectrum after a 1000-fold dilution of the measured solution with pure acetonitrile were detected (Fig. S2<sup>†</sup>). Therefore, we believe that the detected ions reflected the true solution composition.

To support our hypothesis based on the association of the base with the complex, we repeated the ESI<sup>+</sup>-FT-ICR MS measurements with DIPEA and DABCO. In both cases, three clusters were observed (Table 2, Fig. S3 and S4<sup>†</sup>). The one corresponding to **3** was present in both spectra. The second and third clusters showed the presence of “2-base” and “1-base” associates, respectively. Thus, it was further confirmed that also other bases could bind to the Ru complex.

Although the experiments pointed to catalyst-base associates, it was not clear how the amines could be bound to **1** and **2**. Three hypothetical situations were initially considered (see Fig. 3):

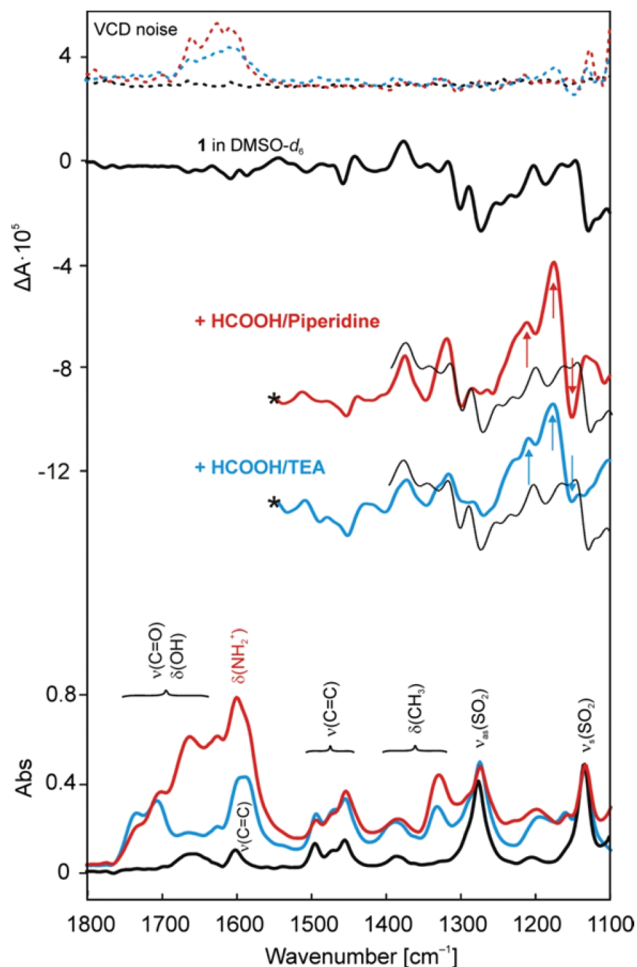
(a) The base coordinates to the ruthenium central atom.

(b) The base forms an N...H-N hydrogen bond with the NH<sub>2</sub> group of the TsDPEN ligand.

(c) The base is protonated and forms an N<sup>+</sup>-H...O=S hydrogen bond with the sulfonyl group of the TsDPEN ligand.

Hydride **2** is a coordinatively saturated complex and thus one of its ligands would have to decoordinate in order to accept the base as a ligand. Since both hydride and TsDPEN ligands are required to maintain the catalytic activity of the complex, the only remaining situation would be a ring slippage, *e.g.* η<sup>6</sup> to η<sup>4</sup> (ref. 10a and 15) as depicted in Fig. 3a. However, this scenario was ruled out by NMR measurements as the <sup>1</sup>J<sub>C-H</sub> interaction constants of *p*-cymene would necessarily change upon its decoordination (*vide supra*).





**Fig. 4** VCD and IR absorbance spectra of **1** in DMSO- $d_6$  and upon addition of HCOOH/piperidine (5/2) and HCOOH/TEA (5/2) mixtures. VCD noise is depicted in dashed lines.

Options (b) and (c) required further investigation and therefore we directed our experiments towards vibrational circular dichroism (VCD). VCD spectra were measured together with IR absorption as the method enables simultaneous acquisition of both (Fig. 4). The rather low signal-to-noise ratio in VCD was inevitably caused by an intensive stream of gaseous  $\text{CO}_2$  that was formed when **1** was mixed with the HCOOH–base mixtures. Due to a high level of spectral noise within  $1700\text{--}1550\text{ cm}^{-1}$ , the VCD spectra were not interpreted in this region.

Strong bands in the IR absorption spectrum of **1** at  $1275$  and  $1133\text{ cm}^{-1}$  were assigned to asymmetric and symmetric vibrations of the  $\text{SO}_2$  group of TsDPEN. In the VCD spectrum, these vibrations were identified as negative patterns at  $1272$  and  $1129\text{ cm}^{-1}$ . When the HCOOH–base mixtures were added, two pronounced changes were observed. Firstly, a new band appeared in VCD at  $1211$  and  $1213\text{ cm}^{-1}$  for TEA and piperidine, respectively, which was assigned to asymmetric stretching of the  $\text{SO}_2$  group combined with another vibration of a group nearby. Secondly, an exciton couplet appeared in VCD with a positive signal at  $1178$  and  $1176\text{ cm}^{-1}$  for TEA and

piperidine, respectively, and a negative signal at  $1153\text{ cm}^{-1}$ , which was identified as C–N stretching vibration of the protonated base. However, the C–N vibrations are typically located at lower wavenumbers. The observed shift may be explained by the fact that the base was bound to the Ru complex. Moreover, as the protonated base is not chiral itself and cannot be observed in a VCD spectrum, the VCD signal supported the hypothesis of a complex–base associate. In combination with the distinct change of the vibrations of the  $\text{SO}_2$  group observed in VCD, this observation suggested a hydrogen bond of the  $\text{N}^+\text{--H}\cdots\text{O}=\text{S}$  type connecting the  $\text{SO}_2$  group of TsDPEN and the protonated base. For the sake of completeness, additional assignment of the measured VCD signal is given in ESI.†

Hypothesis (c) was conditional on the presence of a protonated base that could form a hydrogen bond. In the case of piperidine, deformation vibrations of the  $\text{NH}_2^+$  group were observed in the IR spectrum at  $1600\text{ cm}^{-1}$  (Fig. 4). Since the N–H bond of protonated TEA can only undergo stretching vibrations at shorter wavelengths, the deformation vibrations could not be expected in VCD spectra. Therefore, additional FT-IR spectra were measured for **1** and **1** + HCOOH/TEA in the range of  $4000\text{--}2000\text{ cm}^{-1}$  (Fig. S5†<sup>13</sup>). Unfortunately, we refrained from drawing conclusions based on these data due to their unsatisfactory quality. Protonation of TEA was therefore assumed from its similarity with piperidine regarding structure and acidic properties.

The stark difference between the  $^1\text{H}$  NMR spectra of **1** (Fig. S1†<sup>13</sup>) and **1** + HCOOH/TEA (Fig. 1) was also interpreted based on the knowledge obtained. TEA, presumably bound to the complex, changed the proton shielding and symmetry of the system, which resulted in the *p*-cymene ligand being manifested as four individual doublets instead of a narrow multiplet.

Diffusion ordered spectroscopy (DOSY) and NOE-based NMR measurements were carried out to examine the base–catalyst interaction. Unfortunately, no conclusive results could be obtained due to several complications arising from the composition of the mixture. The HCOOH–triethylamine mixture is in excess to the catalyst and therefore we were usually confronted with very strong ridges in the spectra coming from intense signals of TEA. Further, the lifetime of **2** is relatively short (about 8–10 hours), which prevented us from running experiments that are long enough to get a reasonable signal-to-noise ratio for the catalyst present as a minority. Finally, the complex-bonded TEA does not exhibit separate resonances different from the HCOOH–TEA complex, which prevented us from performing some selective experiments and/or selective suppression of the intense signals.

Therefore, the higher amount of the HCOOH–triethylamine mixture over the catalyst was detrimental to the DOSY experiments. The processing of a DOSY experiment consists of the analysis of the NMR signal attenuation of particular mixture components. The loss of signal intensity depends on the power of magnetic gradients and the slope is proportional to the diffusion coefficient. We expect the presence of bonded and non-bonded TEA species, which both possess NMR



signals of the same chemical shifts. Therefore, the analysis of the DOSY spectrum would require a detection of minor changes in the attenuation curve of the signals of TEA caused by bonded TEA, which is unrealistic in the case of predominating non-bonded TEA. The DOSY spectra, which were measured, demonstrated mainly TEA signals with no unequivocal demonstration of TEA being bonded to the complex. When the complex and HCOOH–triethylamine were in an equimolar ratio, the conversion of **1** to **2** was not complete and the mixture composition no longer corresponded to the reaction conditions.

The NOE measurements were likewise complicated by the excess of triethylamine. Since only a small part of the total amount of triethylamine forms the described associate with the Ru complex, it could not be observed under such conditions.

Eventually, the findings allowed us to offer an explanation for the differences in reactivity and/or selectivity observed in the ATH of (*R*)-**5** and **6**. Similarly to the base, the substrate is also protonated and enters the transition states from an energetic minimum in which it is bonded to the oxygen atom of the sulfonyl group (Fig. 5a).<sup>16</sup> The base can compete with the substrate for this site, which might explain its influence on the reaction rate.<sup>17</sup>

Enantioselectivity is a result of a fine interplay between the substrate and the  $\eta^6$ -aromate of the catalyst, which is based on CH– $\pi$  interactions. The presence of a base in the vicinity of the aromatic ligand and the substrate molecule (Fig. 5b) may affect the free energy of Si ( $G_S^\ddagger$ ) and/or Re ( $G_R^\ddagger$ ) transition states (sterically, electronically, or by a combination of both), thereby changing the enantioselectivity since the ee value is factually dependent on the difference  $\Delta G_{R/S}^\ddagger$ . Regarding different trends of de and ee in the case of (*R*)-**5** and **6**, respectively, it is

speculated that the molecules of the catalytic complex and (*R*)-**5** are structurally more prone to interfere with the base, resulting in more apparent influence of the base on the reaction performance.

## Conclusions

Together with the aforementioned results we can draw a conclusion that it is likely that the base binds to the catalytic complex by forming an  $N^+ \cdots H \cdots O=S$  hydrogen bond with the  $SO_2$  group of the ligand. As a consequence, the selection of the base can have an influence on the reaction rate and enantioselectivity of the ATH of cyclic imines. The influence of the base on the enantioselectivity of the ATH of ketones, as observed earlier,<sup>11</sup> can be explained in the same fashion.

In the mechanistic pathways described so far, the base solely serves as an acceptor of the chloride ligand from the  $Ru^{II}$  precatalyst. The implications of this work thus supplement those parts of the reaction mechanism that have already been clarified, and allow for a rational optimization of the ATH reaction conditions that would suit concrete substrates.

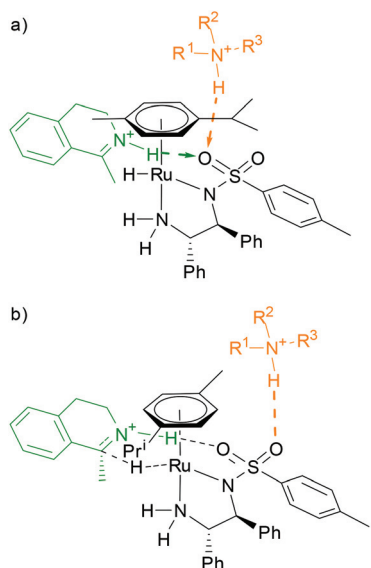
## Experimental

### Chemicals

[ $RuCl(\eta^6-p\text{-cymene})TsDPEN$ ], (*2R*)-2-phenylpropan-1-amine (99%), phosphorus oxychloride (99%), acetanhydride ( $\geq 98\%$ ), formic acid ( $\geq 96\%$ ), triethylamine ( $\geq 99\%$ ), *N,N*-diisopropyl(ethyl)amine (99.5%), 1,4-diazabicyclo[2.2.2]octane ( $\geq 99\%$ ), pyridine ( $\geq 99.0\%$ ), pyrrole (98%), imidazole ( $\geq 99\%$ ), pyrrolidine ( $\geq 99\%$ ), morpholine ( $\geq 99\%$ ), piperidine (99%) were purchased from Sigma-Aldrich (Steinheim, Germany). DMSO- $d_6$  (99.8 atom%D),  $CD_3CN$  (99.5 atom%D), and  $CDCl_3$  (99.8 atom%D) were purchased from ARMAR Chemicals. Toluene (p.a.), chloroform (p.a.), acetonitrile (p.a.), xylene (p.a.) and diethyl ether (p.a.) were obtained from Penta (Czech Republic).

### Instrumentation

**NMR.** NMR spectra were measured on a Varian UNITY Inova-400 spectrometer (399.89 MHz for  $^1H$  and 100.55 MHz for  $^{13}C$ ), a Bruker AVANCE III 400 MHz spectrometer (400.00 MHz for  $^1H$  and 100.58 MHz for  $^{13}C$ ) and a Bruker AVANCE III 600 MHz spectrometer (600.23 MHz for  $^1H$  and 150.93 MHz for  $^{13}C$ ) in  $CD_3CN$ , DMSO- $d_6$ , and  $CDCl_3$  at 303 K. The residual signal of the solvent was used as an internal standard ( $CD_3CN$ :  $\delta_H$  1.931 ppm,  $\delta_C$  1.265 ppm, DMSO- $d_6$ :  $\delta_H$  2.500 ppm,  $\delta_C$  39.60 ppm,  $CDCl_3$ :  $\delta_H$  7.265 ppm,  $\delta_C$  77.00 ppm).  $^1H$  NMR,  $^{13}C$  NMR, COSY, gHMQCAD, and gHMBCAD spectra were measured using standard manufacturers' software (Varian Inc., Palo Alto, U.S.A. and Topspin 2.1, Bruker Biospin GmbH, Rheinstetten, Germany). 1D NMR spectra were zero filled to fourfold data points and multiplied by window function (for  $^1H$  NMR with two-parameter double-exponential Lorentz–Gauss function, for



**Fig. 5** (a) The base hinders the substrate by competing for the sulfonyl site; (b) the base is involved in the supramolecular structure of the diastereomeric transition state, thus affecting its free energy.



$^{13}\text{C}$  NMR line broadening 1 Hz was applied) before Fourier transformation to improve resolution. Chemical shifts are given in  $\delta$  scale [ppm] and coupling constants in Hz. Digital resolution enabled us to report chemical shifts of protons to 3 and coupling constants to 1 and carbon chemical shifts to 2 decimal places.

**FT-ICR MS.** Mass spectrometric experiments were performed on a commercial APEX-Ultra FTMS instrument equipped with a 9.4 T superconducting magnet and a Dual II ESI/MALDI ion source (Bruker Daltonics, Billerica, MA) using electrospray ionization in the positive mode (ESI<sup>+</sup>). The flow rate was 1  $\mu\text{L min}^{-1}$  and the temperature of dry gas (nitrogen) was set to 200 °C. Mass spectra were obtained by accumulating ions in the storage hexapole for 0.1 s and running the quadrupole mass filter in non mass-selective (Rf-only) mode so that ions of a broad  $m/z$  range (200–2500) were passed to the FTMS analyzer cell. The accumulation time in a collision cell was set to 0.2 s, the ICR cell was opened for 1500  $\mu\text{s}$  and 8 experiments were collected for one spectrum. The instrument was externally calibrated using singly charged arginine clusters and as a result, the typical mass accuracy was  $\leq 3.0$  ppm. After the analysis the spectra were apodized using sin apodization with one zero fill. The interpretation of mass spectra was done using the DataAnalysis version 3.4 software package (Bruker Daltonics, Billerica MA) and mMass.<sup>18</sup>

**Circular dichroism.** The VCD spectra were measured using a Bruker IFS-66/S spectrometer equipped with a PMA 37 VCD/IRRAS module containing a BaF<sub>2</sub> polarizer, a ZnSe photoelastic modulator, an MCT detector and a filter restricting frequencies to  $<1800\text{ cm}^{-1}$ , as described previously.<sup>19</sup> For all measurements an A145 Bruker cuvette with BaF<sub>2</sub> windows and a 100  $\mu\text{m}$  pathlength were used. All spectra were measured at a resolution of 8  $\text{cm}^{-1}$ , averaging 8 blocks, each containing 2240 interferometric scans with a zero filling factor of 4.

**FT-IR.** Infrared spectra were obtained on an FT-IR NICOLET 6700 spectrometer. Measurements were conducted within the range of 4000–2000  $\text{cm}^{-1}$  with 32 scans per spectrum. Spectra were obtained and interpreted using OMNIC v7.3 software.

## Spectroscopic studies

**Kinetic experiments.** Procedure for the ATH of (*R*)-5: A stock solution of **1** (28  $\text{mg mL}^{-1}$ ) was prepared. HCOOH (83  $\mu\text{L}$ , 2.2 mmol) and a base (2.5 eq.) were premixed in DMSO-*d*<sub>6</sub> to a total volume of 600  $\mu\text{L}$  and a solution of **1** (10  $\mu\text{L}$ ) was added thereto. The mixture was transferred into the NMR tube and placed in the NMR.  $^1\text{H}$  NMR spectra were measured using the WET pulse sequence for presaturation of strong signals. During the initial period, an appropriate saturation waveform was generated for elimination of signals of HCOOH and the base. Then substrate (*R*)-5 (7.0 mg, 44  $\mu\text{mol}$ ) dissolved in DMSO-*d*<sub>6</sub> was added to reach a total volume of 700  $\mu\text{L}$ .  $^1\text{H}$  spectra were acquired at regular intervals. Conversion and de were determined by integration.

Procedure for the ATH of **6**: A stock solution of **1** (5.2  $\text{mg mL}^{-1}$ ) was prepared. HCOOH (62  $\mu\text{L}$ , 2.2 mmol) and a base (2.5 eq.) were premixed in CD<sub>3</sub>CN, the mixture was transferred

into an NMR tube and a solution of **1** (97  $\mu\text{L}$ ) was added thereto. Then substrate **6** (12 mg, 83  $\mu\text{mol}$ ) dissolved in CD<sub>3</sub>CN was added to reach a total volume of 800  $\mu\text{L}$ .  $^1\text{H}$  spectra were acquired at regular intervals. Conversion was determined by integration. After the reaction, a saturated solution of sodium carbonate (1 mL) was added to the reaction mixture, which was subsequently extracted with diethyl ether, dried over magnesium sulfate and evaporated to dryness. The residue was reconstituted to acetonitrile (1 mL), (1*R*)-(–)-menthyl chloroformate (10.0  $\mu\text{L}$ , 0.13 mmol) and triethylamine (20.0  $\mu\text{L}$ , 0.14 mmol) were added and the sample was analyzed on GC for the determination of enantiomeric excess (ee).

**FT-ICR MS.** Catalyst **1** (5.1 mg) was dissolved in acetonitrile (550  $\mu\text{L}$ ) and water (40  $\mu\text{L}$ ). The base (triethylamine: 9.2  $\mu\text{L}$ , 66  $\mu\text{mol}$ ; DIPEA: 11.6  $\mu\text{L}$ , 66  $\mu\text{mol}$ ; DABCO: 7.4 mg, 66  $\mu\text{mol}$ ) and HCOOH (0.5  $\mu\text{L}$ , 13  $\mu\text{mol}$ ) were added thereto and the solution was stirred for 5 minutes. Prior to the FT-MS measurement an aliquot (1  $\mu\text{L}$ ) of the solution was dissolved in pure acetonitrile (1 mL).

**Circular dichroism.** A stock solution of **1** (21.0 mg) was prepared by dissolving it in DMSO-*d*<sub>6</sub> (300  $\mu\text{L}$ ) and VCD and IR absorbance spectra of the solution (75  $\mu\text{L}$ ) were measured. The base (triethylamine: 2.30  $\mu\text{L}$ , 16.5  $\mu\text{mol}$ ; piperidine: 1.63  $\mu\text{L}$ , 16.5  $\mu\text{mol}$ ) and HCOOH (1.56  $\mu\text{L}$ , 0.04 mmol) were added to the sample and spectra of the resulting mixtures were acquired.

**FT-IR.** A stock solution of **1** in CHCl<sub>3</sub> (66  $\text{mg mL}^{-1}$ ) was prepared. The solution of **1** (0.5 mL) was mixed with triethylamine (72.5  $\mu\text{L}$ , 0.52 mmol) and HCOOH (49.0  $\mu\text{L}$ , 1.30 mmol). IR spectra of pure **1** and of the mixture were measured in a cuvette with a path length of 0.1 mm.

## Preparative procedures

**Synthesis of [(*R*)-2-phenylpropyl]acetamide.** (*R*)-2-Phenylpropane-1-amine (3.00 g, 22.2 mmol) was dissolved in toluene (12 mL). Under stirring, acetic anhydride (2.40 mL, 22.2 mmol) was added dropwise. The solution was then refluxed for 2 hours. The remaining oil was distilled (bp 142–145 °C at 2–3 mmHg) to afford the product. Yield: 3.73 g, 95%.  $^1\text{H}$  NMR (399.87 MHz, CDCl<sub>3</sub>, 303 K):  $\delta_{\text{H}}$  1.265 (3H, d,  $J = 7.0$  Hz, H-6), 1.892 (3H, s, H-1), 2.934 (1H, m, H-5), 3.227 (1H, ddd,  $J = 4.9, 8.7, 13.5$  Hz, H-4u), 3.621 (1H, ddd,  $J = 6.1, 6.9, 13.5$  Hz, H-4d), 5.554 (1H, br s, H-3), 7.198 (2H, m, H-ortho), 7.229 (1H, m, H-para), 7.323 (2H, m, H-meta);  $^{13}\text{C}$  NMR (100.55 MHz, CDCl<sub>3</sub>, 303 K):  $\delta_{\text{C}}$  19.34 (q, C-6), 23.06 (q, C-1), 39.58 (d, C-5), 46.14 (t, C-4), 126.65 (d, C-para), 127.10 (d, C-ortho), 128.65 (d, C-meta), 143.98 (s, C-*ipso*), 170.38 (s, C-2).

**Synthesis of (*R*)-1,4-dimethyl-3,4-dihydroisoquinoline ((*R*)-5).** *N*-[(*R*)-2-Phenylpropyl]acetamide (3.57 g, 20.1 mmol) and phosphorus oxychloride (9.4 mL, 0.1 mol) were dissolved in dry xylene (100 mL) and stirred at 180 °C for 3 hours. The reaction mixture was carefully added to ice water and the solution was filtered. The filtrate was neutralized with water solution of NaOH (20%). The product was extracted with diethyl ether (3  $\times$  20 mL) and combined organic phases were washed with water (3  $\times$  20 mL), dried over anhydrous MgSO<sub>4</sub> and the



volatiles were concentrated in a vacuum to yield a dark oil. The crude product was distilled under reduced pressure (bp 104–110 °C/2–3 mmHg). Yield: 2.02 g, 63%. <sup>1</sup>H NMR (399.87 MHz, CDCl<sub>3</sub>, 303 K): δ<sub>H</sub> 1.232 (3H, d, *J* = 7.0 Hz, 4-CH<sub>3</sub>), 2.391 (3H, t, *J* = 1.5 Hz, 1-CH<sub>3</sub>), 2.825 (1H, m, H-4), 3.434 (1H, ddq, *J* = 1.5, 8.9, 15.5 Hz, H-3u), 3.726 (1H, ddq, *J* = 1.5, 5.8, 15.5 Hz, H-3d), 7.245 (1H, m, H-5), 7.284 (1H, m, H-7), 7.385 (1H, m, H-6), 7.478 (1H, m, H-8); <sup>13</sup>C NMR (100.55 MHz, CDCl<sub>3</sub>, 303 K): δ<sub>C</sub> 17.28 (q, 4-CH<sub>3</sub>), 23.15 (q, 1-CH<sub>3</sub>), 29.86 (d, C-4), 54.06 (t, C-3), 125.27 (d, C-8), 125.42 (d, C-5), 126.54 (d, C-7), 128.62 (s, C-8a), 130.78 (d, C-6), 142.23 (s, C-4a), 164.01 (s, C-1).

**Synthesis of *N*-(2-phenylethyl)acetamide.** Phenethylamine (5.0 g, 41 mmol) and triethylamine (7.3 mL, 51 mmol) were dissolved in dichloromethane (150 mL). The reaction mixture was stirred and acetyl chloride (3.6 mL, 50 mmol) was added dropwise during 15 min at 25 °C. The mixture was further stirred at 45 °C for 30 minutes. Water was added to the reaction mixture, which was cooled to room temperature. The organic phase was separated, washed with 5% hydrochloric acid (100 mL), 5% solution of sodium carbonate (100 mL) and water (100 mL), then dried over anhydrous magnesium sulphate and concentrated on a rotary evaporator (10 torr, 60 °C). The product was obtained in the form of honey-like oil. Yield: 6.5 g, 97%. <sup>1</sup>H NMR (399.87 MHz, CDCl<sub>3</sub>, 303 K): δ<sub>H</sub> 1.928 (3H, s, H-1), 2.811 (2H, t, *J* = 7.0 Hz, H-5), 3.498 (2H, dt, *J* = 5.8, 7.0 Hz, H-4), 5.813 (1H, br s, H-3), 7.186 (2H, m, H-ortho), 7.221 (1H, m, H-para), 7.301 (2H, m, H-meta); <sup>13</sup>C NMR (100.55 MHz, CDCl<sub>3</sub>, 303 K): δ<sub>C</sub> 23.11 (q, C-1), 35.55 (t, C-5), 40.64 (t, C-4), 126.42 (d, C-para), 128.55 (d, C-meta), 128.63 (d, C-ortho), 138.83 (s, C-ipso), 170.10 (s, C-2).

**Synthesis of 1-methyl-3,4-dihydroisoquinoline (6).** *N*-(2-Phenylethyl)acetamide (12.0 g, 73.6 mmol) and tetraphosphorus decaoxide (190 g, 0.67 mol) were dissolved in dry xylene (250 mL) under an argon atmosphere. The mixture was stirred at 160 °C for 6 hours and then hydrolyzed with water (200 mL) after cooling down to room temperature. The solution was acidified by addition of concentrated hydrochloric acid (20 mL). The aqueous phase was separated and washed with toluene (3 × 40 mL). Solid impurities were removed by filtration and the solution was alkalized with a concentrated solution of sodium hydroxide (280 g) in water. The product precipitated in the form of a milky emulsion, which was extracted with toluene (5 × 40 mL). Combined organic extracts were washed with water (50 mL) and brine (50 mL), dried over anhydrous magnesium sulfate and concentrated on a rotary evaporator (10 torr, bath temp. 65 °C). The obtained brown oil was distilled under reduced pressure (120 °C, 8 torr) to afford the product in the form of slightly yellowish oil. Yield: 5.2 g, 49%. <sup>1</sup>H NMR (400.00 MHz, CDCl<sub>3</sub>, 303.2 K): δ<sub>H</sub> 2.374 (3H, t, *J* = 1.5 Hz, 1-CH<sub>3</sub>), 2.689 (2H, m, H-4), 3.652 (2H, tq, *J* = 7.5, 1.5 Hz, H-3), 7.163 (1H, m, H-5), 7.275 (1H, m, H-7), 7.323 (1H, ddd, *J* = 7.4, 7.4, 1.4 Hz, H-6), 7.462 (1H, dd, *J* = 7.6, 1.4 Hz, H-8); <sup>13</sup>C NMR (100.58 MHz, CDCl<sub>3</sub>, 303.2 K): δ<sub>C</sub> 23.17 (1-CH<sub>3</sub>), 25.96 (C-4), 46.85 (C-3), 125.19 (C-8), 126.78 (C-7), 127.32 (C-5), 129.49 (C-8a), 130.45 (C-6), 137.32 (C-4a), 164.14 (C-1).

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