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# Asymmetric transfer hydrogenation of imines catalyzed by a Noyori-type Ru(II) complex—a parametric study

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ABSTRACT

We present, to the best of our knowledge, the first parametric study of the asymmetric transfer hydrogenation of imines catalyzed by a Noyori-type catalytic complex based on ruthenium. A model imine for this study was 1-methyl-3,4-dihydroisoquinoline, and a well-known complex RuCl($\eta^6$-*p*-cymene)((1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine) was chosen as the model catalyst. The reactions were performed in the presence of a formic acid–triethylamine mixture as the source of hydrogen.

The parameters examined include general parameters, for example, concentration, temperature, and substrate-to-catalyst molar ratio, as well as parameters specific to this particular reaction, such as the amount of the hydrogenation mixture used, the ratio of its components, or the inhibitive effect of carbon dioxide. During this study, several unexpected parameters worth further investigation have emerged.



## 1. Introduction

The increasing demand for enantiomerically pure compounds arising mainly from the pharmaceutical industry provokes new enantioselective synthetic methods to be sought, particularly when the synthesis of a racemic mixture followed by chiral separation is not economically feasible. The asymmetric transfer hydrogenation (ATH) of C=N and C=O double bonds presents an alternative to classical reduction procedures using gaseous hydrogen allows the formation of enantiomerically enriched alcohols and amines.[1]

Ruthenium-based complexes comprising of chiral diamine ligands can effectively catalyze this reaction and achieve good efficiency and excellent enantioselectivity. These Noyori-type complexes work for both ketones and imines.[2] For ketones, the hydrogen donor can be either a mixture of formic acid and an organic base, or a mixture of a strong inorganic base and a primary or a secondary alcohol.[3] In the case of imines, on the other hand, only a mixture of formic acid and a base is effective.[4]

The mechanism of the reduction of ketones was proposed by Noyori[5] and supported by means of a theoretical study.[6] In this case, both hydrogen atoms are transferred simultaneously and the transition state has the form of a six-membered cycle.

For imines, this mechanism does not plausibly explain some of the observed phenomena, in particular the need for the imine to be either protonated or at least activated by a Lewis acid to undergo the reduction,[7] and also the formation of the opposite configuration of the amine product. A mechanistic study of the ATH of imines was conducted by Martins et al. and a different, 'ionic', mechanism was suggested.[8] In this case, a protonated imine would undergo the reduction, while only one hydrogen atom would be transferred. The transition state is therefore acyclic.

The origin of the enantioselectivity is another important aspect of the mechanism. For ketones, an explanation was proposed by Yamakawa et al. A weak interaction between the CH group of the Ru-$\eta^6$-coordinated aromatic ligand and the aromatic part of the substrate was considered to stabilize the favorable transition state leading to the preferred product. The disfavored transition state would lack such a stabilizing interaction and would be less preferred.[9]

A theoretical study concerning the ATH of imines was recently carried out by Václavík et al., focusing on this CH–$\pi$ interaction. The reaction coordinates for several different interactions were calculated and their stabilization effects were enumerated, supporting the hypothesis on the stabilizing effect of this interaction[10] (Fig. 1).

In contrast to the efforts made to explain the mechanism of the ATH, very few studies describing the influence of the reaction conditions on the course of the reaction presently exist. Kinetic studies of ATH of acetophenone in water on Ru-based complexes have

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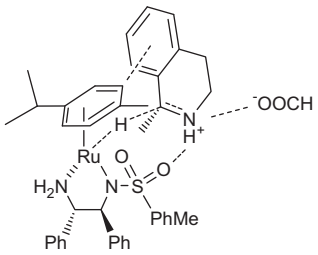



**Figure 1.** A transition state of hydrogen transfer during the ATH of 3,4-dihydroisoquinolines as investigated by Václavík et al. The $NH^{+}\cdots O–S–O$ hydrogen bond and CH–π interaction are depicted.

been conducted both with common complexes[11] and their 'tethered' modifications.[12]

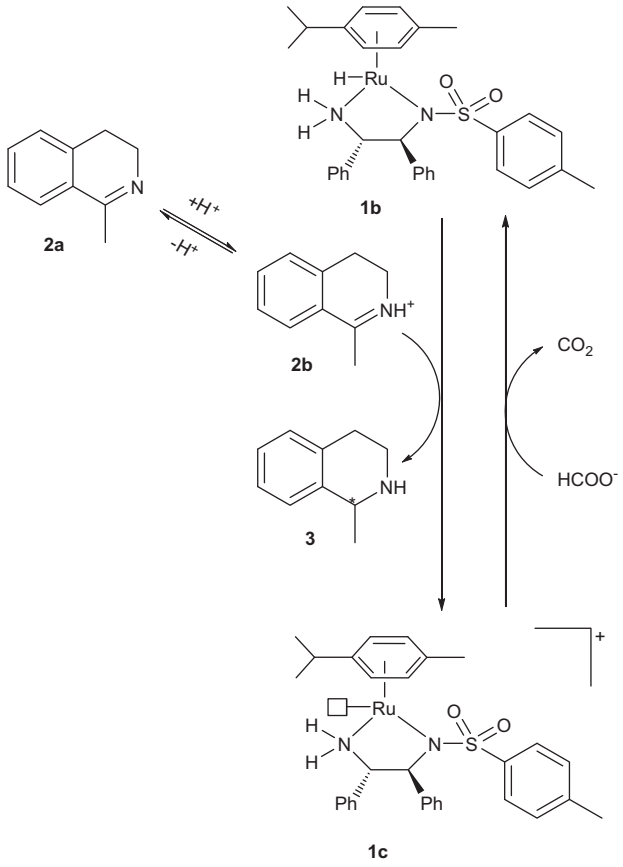
To the best of our knowledge, the only kinetic study of the ATH of imines published so far was conducted on a Rh-based catalytic complex analogous to Noyori's catalyst.[13]

The aim of this study was to provide an insight into the parameters influencing the asymmetric transfer hydrogenation of imines catalyzed by Noyori's Ru-based catalytic complexes. A well-known Noyori-type complex RuCl(η$^6$-*p*-cymene)((1*S*,2*S*)-*N*-*p*-toluenesulfonyl-1,2-diphenylethylenediamine) **1a** was chosen as the model catalyst and a simple prochiral imine 1-methyl-3,4-dihydroisoquinoline **2a** was chosen as the model substrate. The hydrogenations were performed in acetonitrile in the presence of a formic acid–triethylamine mixture.

The first step of the reaction is an in situ transformation of inactive chloride **1a** into the active hydride species **1b**. Haack et al. described the base-induced elimination of hydrogen chloride under strongly basic conditions in alcohol (as in the ATH of ketones).[2] The exact mechanism of this reaction under the aforementioned conditions remains, as yet, unclear (Scheme 1).

In the case of imines, the protonation of substrate **2a** occurs in the acidic reaction mixture. Iminium salt **2b** can then enter the transition state in which the hydrogen transfer takes place. The transition state is stabilized by a relatively strong ion-dipole interaction between the $NH^{+}$ group of the protonated substrate and the sulfonyl group of **1b**.[10] After the hydrogen transfer, when the positive charge on the NH group has disappeared, this interaction weakens and 1-methyl-1,2,3,4-tetrahydroisoquinoline **3** can leave the active site. Species **1b** is regenerated from the coordinatively unsaturated Ru complex **1c** and a formate ion, giving carbon dioxide as a by-product (Scheme 2).

The composition of the reaction mixture denominates most parameters necessary to describe the entire catalytic system. They include the concentration of the reaction mixture, temperature, substrate-to-catalyst (S/C) molar ratio, amount of hydrogenation mixture, and the ratio of the components of the mixture. The results indicate that the course of the reaction is strongly dependent on these parameters and that their careful choice can considerably improve the activity and, to a certain extent, selectivity of the reaction as well.




**Scheme 2.** Suggested pathway of **1b**–catalyzed ATH of **2a** affording **3**.

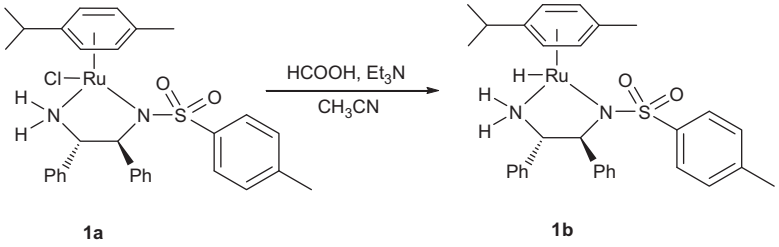
## 2. Results and discussion

The main goal of the work presented herein was to devise a set of parameters describing as many aspects of the system as possible. Subsequent variations of these parameters (preferably one at a time—a goal not always achievable) were then employed in order to determine their influence on the course of the reaction.

### 2.1. Concentration of the reaction mixture

The principal parameter influencing every chemical reaction is the concentration of the reaction mixture (or the partial pressure of the reactants in the case of reactions in the gaseous phase). Two experiments were performed in round-bottom flasks with two different S/C molar ratios. Other important molar ratios were: FA/TEA = 2.5, HM/S = 8.8, and the temperature was 30 °C (Table 1 and Fig. 2).

The reaction rates related to the amount of the catalyst were slightly lower in the case of S/C = 200 and this difference increased




**Scheme 1.** Activation of catalyst **1a**.

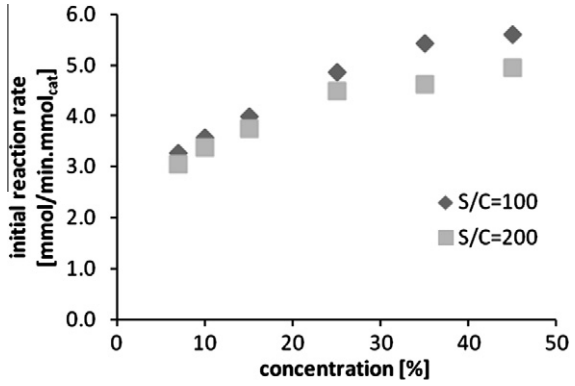



**Figure 2.** Dependence of the initial reaction rate on the concentration of the reaction mixture for each of the S/C ratios.

**Table 1**
Reaction rate and selectivity achieved with different concentrations of the reaction mixtures

| Concentration[a] (%) | Initial reaction rate[b] (mmol/min mmol$_{cat}$) | Conversion[c] (%) | ee[c] (%) |
|---|---|---|---|
| *S/C = 100* | | | |
| 45 | 5.60 | 99.8 | 86 |
| 35 | 5.42 | 99.9 | 86 |
| 25 | 4.87 | 99.8 | 86 |
| 15 | 3.99 | 99.2 | 85 |
| 10 | 3.57 | 97.6 | 84 |
| 7 | 3.26 | 95.8 | 83 |
| *S/C = 200* | | | |
| 45 | 4.95 | 98.4 | 86 |
| 35 | 4.63 | 99.4 | 86 |
| 25 | 4.49 | 95.6 | 86 |
| 15 | 3.74 | 85.3 | 85 |
| 10 | 3.38 | 80.4 | 85 |
| 7 | 3.06 | 76.1 | 86 |

[a] Concentration is defined by the following formula: concentration = (mass of **2a** + mass of **1a** + mass of formic acid + mass of triethylamine)/mass of solvent.
[b] Initial reaction rates were calculated from the linear part of each conversion curve.
[c] Conversion and ee are given after 50 min.

with increasing concentration. A possible cause of this behavior is that some constant amount of the catalyst is not active during the reaction (not regenerated yet, blocked by the base or by the product), and for the S/C = 200 reactions, a larger fraction of the total amount of the catalyst is blocked than for the S/C = 100 reactions, which results in a lower reaction rate related to the total amount of the catalyst.

The influence of concentration was found to be significant. One can obtain up to 80% increase in the reaction rate by using a more concentrated reaction mixture. We can also see that with each of the S/C ratios, the rate increase per unit of concentration increase diminishes with increasing concentration. A possible explanation is that at higher concentrations, the reaction rate is no longer limited by the frequency of effective collisions between hydride **1b** and the protonated molecules of substrate **2b**, but by the total amount of **1b** present in the mixture.

## 2.2. S/C Ratio

The differences of the reaction rates related to the mass of the catalyst with different S/C ratios were examined further, as the S/C ratio is a parameter that generally affects the course of catalytic reactions. For this experiment, a concentration of 15% was chosen because more apparent differences in the reaction rates were expected. Other important molar ratios were: FA/TEA = 2.5, HM/S = 8.8, temperature 30 °C (Table 2 and Fig. 3).

**Table 2**
Initial reaction rate and selectivity with various S/C ratios

| S/C[a] | Initial reaction rate[b] (mmol/min mmol$_{cat}$) | Conversion[c] (%) | ee[c] (%) |
|---|---|---|---|
| 75 | 4.17 | 99.7 | 82 |
| 100 | 3.99 | 99.2 | 84 |
| 130 | 3.83 | 94.9 | 84 |
| 170 | 3.44 | 89.6 | 85 |
| 200 | 3.34 | 76.5 | 85 |
| 225 | 3.24 | 68.9 | 86 |

[a] The S/C ratios are molar.
[b] Initial reaction rates were calculated from the linear part of each conversion curve.
[c] Conversion and ee are given after 50 min.

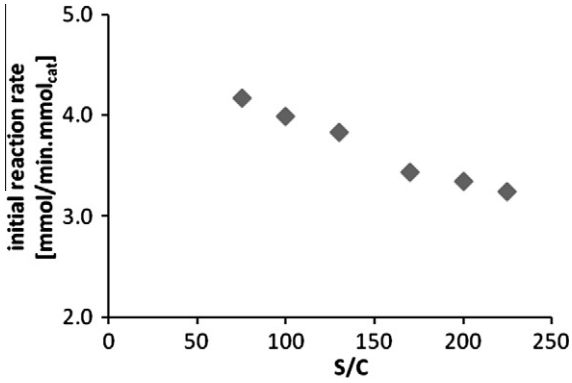



**Figure 3.** Dependence of the initial reaction rate on the S/C ratio.

It was confirmed that varying the S/C ratio leads to different reaction rates even when these are relative to the amount of the catalyst. The difference supports the hypothesis of the 'inactive fraction' of the catalyst (3.1).

## 2.3. Temperature

Temperature is another basic parameter influencing chemical reactions. For this reaction, the measurement of its effect on both the reaction rate and enantioselectivity was conducted in the range of 10–50 °C. The concentration was 7% in all cases and other molar ratios were also constant: S/C = 100, FA/TEA = 2.5; HM/S = 8.8 (Table 3 and Fig. 4).

An increase in the reaction rate with increasing temperature was expected and is rather common.

**Table 3**
Reaction rates and selectivity for the reactions performed at different temperatures

| Temperature (°C) | Initial reaction rate[a] (mmol/min mmol$_{cat}$) | Conversion[b] (%) | ee[b] (%) |
|---|---|---|---|
| 10 | 0.37 | 18.2 | 89 |
| 20 | 1.54 | 71.4 | 87 |
| 30 | 3.14 | 95.5 | 85 |
| 40 | 5.27 | 95.9 | 84 |
| 50 | 7.64 | 96.8 | 82 |

[a] Initial reaction rates were calculated from the linear part of each conversion curve.
[b] Conversion and ee are given after 50 min.

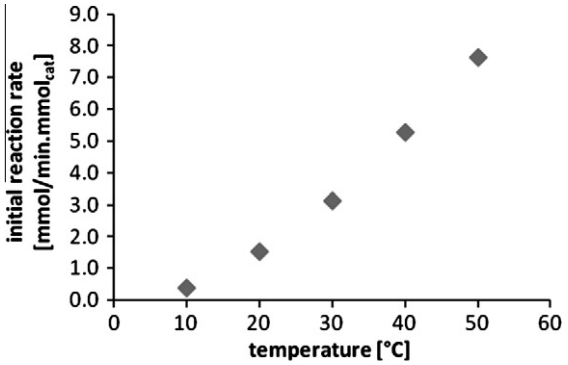



**Figure 4.** Dependence of the initial reaction rate on temperature.

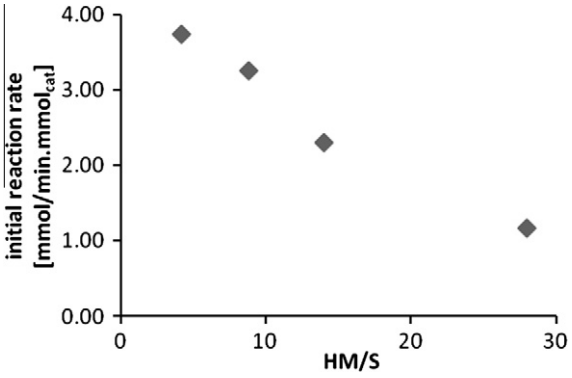



**Figure 5.** Dependence of the initial reaction rate on the amount of the hydrogenation mixture used.

The decrease in enantioselectivity can be explained by Yamakawa's theory on the cause of the selectivity. Yamakawa stated (and supported this statement by ab initio molecular modeling) that two different transition states exist.[9] One would lead to the preferred configuration of the product; the other would lead to the other configuration. For catalyst **1b** and substrate **3**, this has been further elaborated by Václavík et al., who calculated the actual energy difference between these transition states.[10] This difference would make the first transition state favorable and its formation would be advantageous in comparison with the other, disfavorable transition state.[14] Obviously, molecules with higher energy (as in the higher temperature) would overcome this barrier to a greater extent than molecules with lower energy and the non-preferred product would become more abundant, as we can see from Table 3.

### 2.4. Amount of the hydrogenation mixture

The mixture of formic acid and triethylamine provides hydrogen for the reduction. The most commonly used ratio of these two is 5/2 and this mixture exhibits azeotropism,[15] therefore it is commonly referred to as the azeotropic mixture. Variation of its amount was expected to have a major influence on the course of the reaction. Several hydrogenation mixture/substrate ratios were tested. Concentration of the reaction mixture was 7% in all cases, as well as S/C = 100, FA/TEA = 2.5, and temperature 30 °C (Table 4 and Fig. 5).

**Table 4**
Reaction rate and selectivity with different amounts of hydrogenation mixture used

| HM/S[a] | Initial reaction rate[b] (mmol/min mmol$_{cat}$) | Conversion[c] (%) | ee[c] (%) |
|---|---|---|---|
| 4.2 | 3.74 | 86.7 | 83 |
| 8.8 | 3.26 | 95.8 | 84 |
| 14.0 | 2.31 | 92.4 | 84 |
| 28.0 | 1.17 | 57.7 | 85 |

[a] The hydrogenation mixture/substrate ratios are molar: (amount of formic acid + amount of triethylamine)/amount of substrate.
[b] Initial reaction rates were calculated from the linear part of each conversion curve.
[c] Conversion and ee are given after 50 min.

Contrary to our original expectations, an increase in the amount of the azeotropic mixture leads to a decrease in the initial reaction rate.

We have come up with two working hypotheses to explain such behavior. One of them suggests that under strongly acidic conditions (if the word 'acidity' can be used in an aprotic solvent), the chiral diamine ligand becomes protonated and subsequently decoordinates from the Ru atom, which would lead to a loss of catalytic activity. The reaction would be then limited by the amount of the active catalytic species. Some other experimental results supported this hypothesis (vide infra), although no direct observation of the protonated ligand was made.

The other hypothesis states that in a large excess of the hydrogenation mixture, the protonated triethylamine is in a large excess over the protonated substrate. The triethylammonium cation is believed to be able to create a hydrogen bond with the sulfonyl group of the ligand, by means of which it sterically hinders the active site of the catalytic complex and prevents the substrate from reaching the active site. The reaction would then be limited by the amount of free active sites.[16] A theoretical calculation of such structure was performed and the stabilization caused by this bond was calculated to be $\Delta E$(DFT//MP2) = −89.4 kJ/mol and $\Delta G$(DFT//DFT) = −31.0 kJ/mol (Fig. 6).

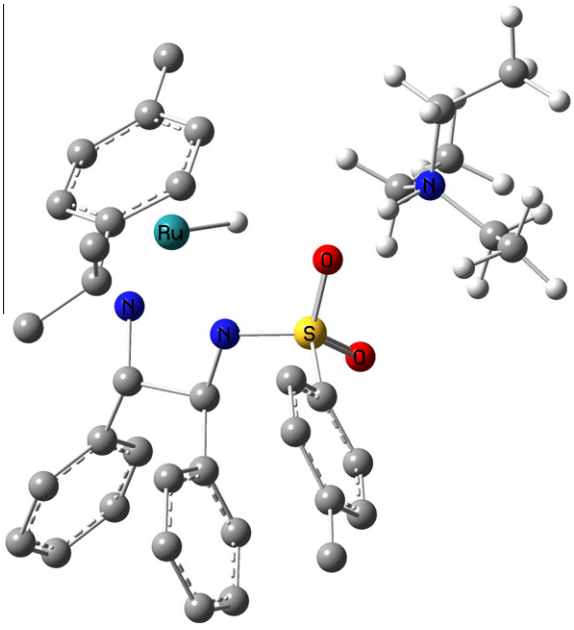



**Figure 6.** An associate of **1b** and the triethylammonium ion. The hydrogen atoms of the catalyst are omitted for clarity.

### 2.5. Ratio of formic acid and triethylamine

Variation of the ratio between formic acid and triethylamine, the two components of the hydrogenation mixture, could provide an insight into several subtle aspects of the reaction mechanism.

The following approach was used: the molar ratios of formic acid and triethylamine with respect to the substrate were taken from the standard experiment described in the experimental section (i.e., FA/S = 6.31, TEA/S = 2.52; entries 3 and 8). The ratio of one of the components to the substrate was held constant, while the ratio of the other one was varied and vice versa. The concentration of the reaction mixture was held constant at all times (7%), S/C ratio was 100 and temperature 30 °C. The HM/S ratio was inevitably varied throughout this experiment (Table 5).

During the experiments, significant color differences between the reaction mixtures were observed. Generally, the mixtures with higher formic acid/triethylamine ratio were yellowish to clear, whereas the more basic mixtures were orange, closely resembling the color of the stock solution of the catalyst. This could indicate some changes to the catalyst under acidic conditions.

The results indicate that there is an optimal FA/TEA ratio for the reaction, and that the ratio is close to the azeotropic ratio of 5:2. With excessive formic acid, the reaction proceeded very slowly or even not at all, probably because the catalyst was destroyed by the formic acid. Protonation of the amino-group of the diamine ligand followed by its decoordination from the Ru atom seems to be a likely explanation of this phenomenon.[17]

With excess triethylamine, the reaction proceeded slowly as well. One explanation suggests that triethylamine neutralizes all of the formic acid prior to the reaction and then the substrate cannot be protonated, which has been reported to be of vital importance.[7] The aforementioned possibility of triethylamine's binding to the sulfonyl group through a hydrogen bond is another possible explanation.

The difference between entries 4 and 7 can be explained by these hypotheses because in the case of entry 7, the amount of free formic acid with respect to the catalyst is roughly twice the amount as in entry 4, and therefore the catalyst can be decomposed to a greater extent. The amount of triethylamine is also bigger in the case of entry 7, so more active sites can be blocked by coordinated triethylamine. The major difference between entries 2 and 9 can also be explained by these two hypotheses.

Low reaction rates in entries 1 and 10 can obviously be explained by the need of the substrate to be protonated. In these mixtures, most formic acid was consumed for the protonation of triethylamine, so the substrate was protonated to a small extent.

Extremely low rates in entry 5 and the absence of any product in entry 6 were probably caused by substantial damage that the catalyst had sustained under the strongly acidic conditions.

### 2.6. Atmosphere

ATH performed using a mixture of formic acid and triethylamine as the source of hydrogen has one by-product: carbon dioxide. Since this compound is a gas under standard conditions, the reaction is not strictly homogeneous and carbon dioxide can be assumed to have an influence on the course of the reaction. Four reactions employing the standard setting (S/C = 100, FA/TEA = 2.5, HM/S = 8.8, concentration 7%, temperature 30 °C) were carried out under different conditions: in an air atmosphere with magnetic stirring, in an air atmosphere with sonication degassing, in an inert argon atmosphere with stirring, and in $CO_2$ under atmospheric pressure (Table 6).

**Table 6**
Reaction rate and selectivity under different gas treatment

| Conditions | Initial reaction rate[a] (mmol/min mmol$_{cat}$) | Conversion[b] (%) | ee[b] (%) |
|---|---|---|---|
| Air, magnetic stirring | 3.41 | 96.2 | 83 |
| Air, sonication degassing | 3.40 | 96.7 | 83 |
| 1 atm Ar, magnetic stirring | 3.42 | 99.6 | 84 |
| 1 atm $CO_2$, magnetic stirring | 1.08 | 71.5 | 83 |

[a] Initial reaction rates were calculated from the linear part of each conversion curve.
[b] Conversion and ee are given after 50 min.

Carbon dioxide was confirmed to have a negative effect on the reaction rate. This can be attributed to its reported ability to form a complex with the catalyst, where it could prevent the active hydride species from being formed and block the active site.[18] These negative effects, however, can be completely overcome by stirring and no advanced techniques, such as sonication degassing or the use of an inert atmosphere proved more advantageous.

## 3. Conclusion

To sum up, we present the first evaluation of the parametric sensitivity of the asymmetric transfer hydrogenation of imines catalyzed by a Noyori-type ruthenium catalytic complex **1a** in the presence of a mixture of formic acid and triethylamine as a hydrogen source. During this study, several mechanistic aspects worth further investigation have emerged, most notably the low catalytic activity in overly acidic conditions as well as the possible interaction between **1a** and the base present in the hydrogenation mixture.

**Table 5**
Reaction rate and selectivity with various FA/TEA ratios

| Entry | FA/S[a] | TEA/S[a] | FA/TEA[a] | Initial reaction rate[b] (mmol/min mmol$_{cat}$) | Conversion[c] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | 6.31 | 12.60 | 0.5 | 0.10 | 4.6 | 80 |
| 2 | 6.31 | 6.31 | 1 | 0.12 | 8.4 | 67 |
| 3 | 6.31 | 2.52 | 2.5 | 3.16 | 95.8 | 85 |
| 4 | 6.31 | 1.26 | 5 | 0.49 | 26.6 | 87 |
| 5 | 6.31 | 0.63 | 10 | 0.02 | 0.6 | 81 |
| 6 | 25.20 | 2.52 | 10 | — | — | — |
| 7 | 12.60 | 2.52 | 5 | 0.04 | 1.5 | 83 |
| 8 | 6.31 | 2.52 | 2.5 | 3.16 | 95.8 | 85 |
| 9 | 2.52 | 2.52 | 1 | 0.48 | 20.2 | 81 |
| 10 | 1.26 | 2.52 | 0.5 | 0.03 | 1.4 | 73 |

[a] The ratios are molar.
[b] Initial reaction rates were calculated from the linear part of each conversion curve.
[c] Conversion and ee are given after 50 min.

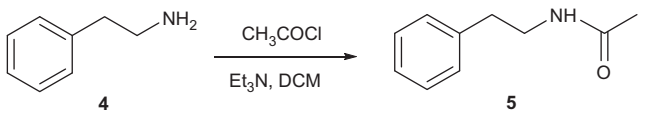
## 4. Experimental

### 4.1. General

The following chemicals were used: 2-phenethylamine (Fluka, 99%), acetylchloride (Sigma–Aldrich, 98%), triethylamine (Sigma–Aldrich, 98%), phosphorus(V) oxychloride (Fluka, 98%), phosphorus(V) oxide (Lachema, 99%), xylene (Penta, 99%), hydrochloric acid (Lachner, 36.4%), sodium hydroxide (Lachner, 99.6%), sodium sulfate (Lachner, 99.9%), diethyl ether (Sigma–Aldrich, 99%), toluene (Penta, 99%), acetonitrile (LC–MS grade, Sigma–Aldrich), RuCl(*p*-cymene)-(1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine (Sigma–Aldrich), formic acid (Fluka, 98%), sodium carbonate (Penta, 99%), magnesium sulfate (Lachner, 98%), and (−)-menthyl-chloroformate (Sigma–Aldrich, 99%). The synthesis of **2a** is based on a published procedure.[19]

### 4.2. Preparation of 2a

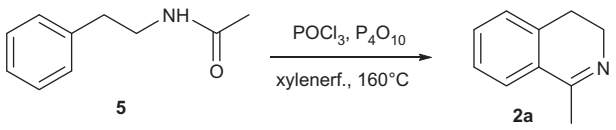
Phenethylamine **4** (18.0 g, 149 mmol) was dissolved in dichloromethane (375 ml) and triethylamine (25.0 ml, 180 mmol) was added. The flask was cooled on an ice bath to 0 °C and acetylchloride (12.7 ml, 178 mmol) was added dropwise (Scheme 3). After




**Scheme 3.** *N*-Acetylation of **4** affording **5**.

the addition, the reaction mixture was gradually heated to 40 °C for 15 min. After cooling down, water (165 ml) was added with intensive stirring for 15 min. The organic phase was separated, extracted with 5% aqueous solution of sodium carbonate (2 × 45 ml), then with 5% aqueous solution of hydrochloric acid (2 × 45 ml), again with 5% aqueous solution of sodium carbonate (1 × 45 ml) and finally with water (60 ml). The organic phase was dried over anhydrous magnesium sulfate and evaporated, affording 22.3 g (92%) of 2-phenethyl-acetamide **5**. Mass calcd: 163.10, measured: 163.16.

Compound **5** (21.8 g, 134 mmol) was mixed with phosphorus(V) oxychloride (47.0 ml, 502 mmol) and phosphorus(V) oxide (23.8 g, 168 mmol). The resulting mixture was refluxed in dry xylene (400 ml) for 4 h (Scheme 4). The cooled mixture was




**Scheme 4.** Bischler–Napieralski cyclization of **5** affording **2a**.

slowly hydrolyzed with warm water, until the addition of more water did not heat the reaction mixture. The aqueous phase was separated, concentrated HCl (25 ml) was added and the mixture was extracted with toluene (3 × 50 ml). The combined organic extracts were added to the separated organic phase, which was then extracted with 3.6% (w/w) HCl (1 × 110 ml). The extract was added to the previously separated water phase and the organic phase was discarded. The aqueous solution was cooled in an ice bath, alkalized by an addition of 400 ml concentrated solution of sodium hydroxide, allowed to cool down slightly and extracted with toluene (5 × 60 ml) and diethyl ether (4 × 30 ml). The extracts were combined and dried over anhydrous sodium sulfate. The dried extract was evaporated on a rotary evaporator, affording a reddish-brown oily substance which was then distilled in vacuo. The fraction of 95–97 °C (4 Torr) contained the desired **2a** (slightly yellowish oil). Yield: 12.5 g (64%), purity: 99% (GC). $^1$H NMR (400.00 MHz, $CDCl_3$, 303.2 K): $\delta$ 2.374 (3H, t, $J$ = 1.5 Hz, 1-$CH_3$), 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). $^{13}$C NMR (100.58 MHz, $CDCl_3$, 303.2 K): $\delta$ 23.17 (1-$CH_3$), 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). Mass calcd: 145.09; measured: 145.16.

### 4.3. General protocol for reactions carried out in round-bottom flasks

A solution of substrate **2a** in acetonitrile (LC–MS grade) was prepared, so that its concentration was 150 mg/ml. A solution of catalyst **1a** was prepared by dissolving 5.4 mg of **1a** in 1 ml acetonitrile. A round-bottom flask was equipped with a magnetic stirrer and a septum with a needle, and pre-heated on a water bath. The initial volume of acetonitrile was transferred into the flask, the hydrogenation mixture (HM) consisting of formic acid (FA) and triethylamine (TEA) was added, followed by the solution of the catalyst. Active catalytic species **1b** was allowed to form by stirring the mixture for 5 min. After that, the solution of **2a** (S) was added. Standard reaction conditions: 0.11 mmol **2a**; **2a**/**1a** (S/C) ratio 100; HM/S ratio 8.83; FA/TEA ratio 2.5, total reaction mixture volume 1500 µl, concentration 7% (see Section 2.1), temperature 30 °C. All ratios are molar.

Samples were taken in the following way: the calculated amount of the reaction mixture containing approximately 2 mg total of **2b** and **3** was transferred into a vial containing saturated aqueous solution of sodium carbonate (1 ml). The mixture was shaken well and extracted with diethyl ether (3 × 1 ml). The extract was dried over anhydrous magnesium sulfate and stripped in a stream of argon to dryness. The residue was dissolved in acetonitrile (700 µl) and analyzed on GC for conversion. After that, triethylamine (20 µl) and (−)-menthyl-chloroformate **6** (10 µl) were added to the sample, affording a pair of diastereomeric carbamates **7a**, **7b**. The mixture was analyzed on GC for enantioselectivity (Scheme 5).

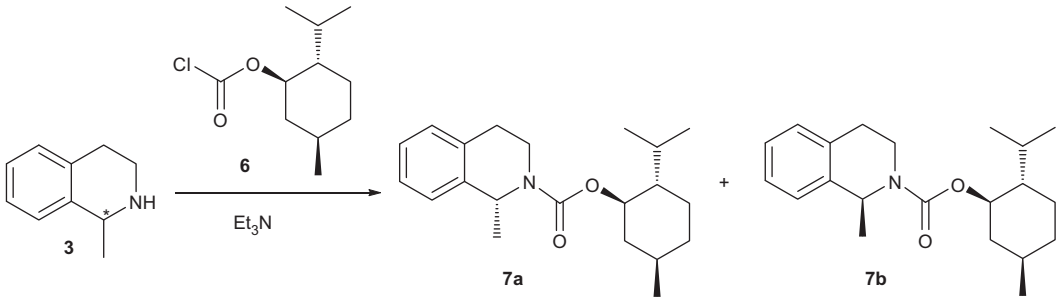
### 4.4. GC analyses

Varian CP-3800 gas chromatograph equipped with an 1177 injector, a Varian VF-1 column (length: 60 m, inner diameter: 0.25 mm, film thickness 0.25 µm, stationary phase: poly(dimethylsiloxane)), and an FID 11 flame-ionization detector was used. For the determination of conversion, the setting was as follows: injection volume 1 µl, injector temperature 250 °C, split ratio 25, column flow 0.5 ml/min, detector temperature 250 °C. Retention times: **3** 26.81 min, **2a** 27.06 min.

For enantioselectivity, the following setting was used: injection volume 1 µl, injector temperature 250 °C, split ratio 25, column flow 0.5 ml/min, detector temperature 250 °C. Retention times: carbamate **7a** derived from (*R*)-**3** 43.88 min, carbamate **7b** derived from (*S*)-**3** 44.31 min.

### 4.5. Theoretical computations

In performing the calculations of the catalyst-base associates (see Section 2.4), a DFT level of theory utilizing the novel restricted




**Scheme 5.** Formation of two diastereomeric carbamates during pre-column derivatization.

ωB97XD functional[20] was used in combination with the Def2-SVP basis set[21] for all atoms and additional effective core potential for the ruthenium atom.[22] The IEFPCM model was used to simulate solvation in acetonitrile. Frequency analyses were performed on optimized structures to obtain thermodynamic data, and so were the MP2-level calculations providing more accurate single-point energies.

### 4.6. NMR spectroscopy

NMR spectra were acquired using a Bruker Avance III 400 MHz spectrometer ($^1$H 400.00 MHz and $^{13}$C 100.58 MHz). $^1$H and $^{13}$C NMR spectra were measured in chloroform, whose residual signals ($\delta_H$ 7.265 ppm, $\delta_C$ 77.00 ppm) were used as internal standards for the chemical shift scale. Standard software was used, as supplied by the manufacturers (Bruker BioSpin GmbH, Rheinstetten, Germany).

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