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Microwave-mediated ruthenium-catalyzed asymmetric hydrogen transfer

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Abstract—Ru-catalyzed hydrogen transfer from propan-2-ol to acetophenone under microwave conditions using monotosylated (*R*,*R*)-diphenylethylenediamine as the chiral source afforded (*R*)-1-phenylethanol in >90% yield and 82% e.e. within 9 min, while use of ephedrine or norephedrine gave the same compound in high yield with 70 and 46% e.e., respectively. *t*-Butylphenylketone was reduced to (*R*)-2,2-dimethyl-1-phenyl-1-propanol under the same conditions in close to quantitative yield, although with low enantioselectivity.

1. Introduction

The enantioselective reduction of ketones is an important transformation affording synthetically useful enantiopure chiral secondary alcohols.[1] Among the available methods for the process, asymmetric hydrogen transfer reduction is particularly attractive, being operationally simple and economically advantageous. Several combinations of metal complexes, ligands and hydrogen sources have been employed in the process with varying degrees of success.[2] Some recent examples include the use of Ru, Co, Rh and Ir complexes of thiourea derivatives,[3] Ru complexes of tridentate bisoxazolines,[4] 2-azanorbornyl alcohols[5] and phosphinooxazolines,[6] and Ir complexes of sulfoxides[7] and perfluorinated imine ligands.[8] Catalysts prepared from $[RuCl_2(\eta^6\text{-arene})]_2$ and a variety of amino alcohols[9] or (1*S*,2*S*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine[10] have proven to be particularly versatile in combination with formic acid[11] or propan-2-ol as the hydrogen source, and a base.[12] The mechanism for the latter process has recently been elucidated via theoretical studies.[2,9b]

In addition to the selectivity, the rate and turn over frequency are factors of importance in asymmetric catalysis. Although the monotosylated diphenylethylenediamine introduced by Noyori has several advantages, exhibiting high enantioselectivity and being simple to prepare from commercially available starting materials, its reactions are rather slow. Recently, we have successfully employed microwave irradiation to accelerate enantioselective metal-catalyzed reactions.[13] We decided to investigate the effect of microwave irradiation on the hydrogen transfer process. Use of formic acid as the hydrogen source results in the evolution of CO_2, and was not considered appropriate for reactions under microwave conditions as they are performed in closed vessels. We were thus limited to using propan-2-ol as the hydrogen source, although it has the disadvantage that the reaction is reversible, deteriorating the enantioselectivity.

2. Results and discussion

The catalyst needed for the hydrogen transfer process was conveniently prepared by heating a mixture of $[RuCl_2(\eta^6\text{-}p\text{-cymene})]_2$ and (1*R*,2*R*)-*N*-(*p*-toluenesulfonyl)-1,2-diphenylethylenediamine **1** (Ru/L = 1/2) in propan-2-ol under air for 1 min in the microwave cavity at 100 W; the published procedure requires heating at 80°C for 20 min under Ar.[10] In order to find optimum conditions for the catalytic process, the reaction time and the power were varied. All optimization reactions were completed using 0.5 M solutions of acetophenone in propan-2-ol, 1 mol% of the catalyst and 5 mol% of KOH (Scheme 1). All reactions were performed under air; identical results were obtained from reactions run under N_2. A high yield (87%) of (*R*)-1-phenylethanol with moderate enantioselectivity (e.e. = 48%) was obtained after only 5 min at 80 W (entry 1, Table 1). Heating for 9 min at lower power of 60 W, afforded the product in up to 90% yield with 82% e.e. (entry 2).

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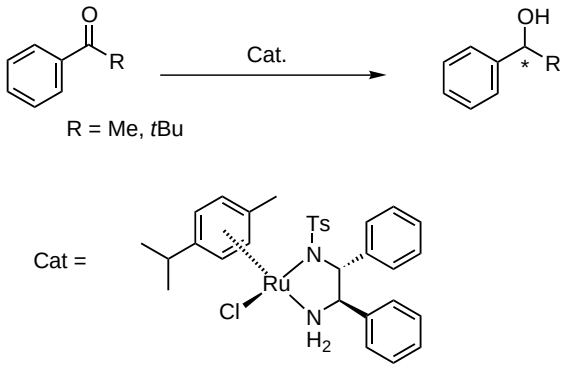
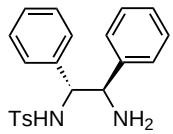


Scheme 1.

Prolonging the reaction time to 12 min instead of 9 min gave the product in somewhat lower yield with similar enantioselectivity (entry 3), whereas additional heating for 5 min at 80 W resulted in a decrease in enantioselectivity (63% e.e., entry 4). Decreasing the catalyst concentration resulted in lower yield under the standard conditions 9 min/60 W (entry 5).

Due to the reversible nature of the hydrogen transfer employing propan-2-ol as the hydrogen source, an increase in acetophenone concentration normally results in loss of enantioselectivity. Under our conditions, a two-fold increase of the concentration resulted in only a minor loss of e.e. (76%, entry 6). When the ligand/Ru ratio was decreased from 2/1 to 1/1, the product was still obtained in high yield, but with considerably lower e.e. (29%, entry 7). Increasing the ratio to 4/1 gave results identical to those obtained when a 2/1 ratio was employed (entry 8). Exchange of KOH for potassium *t*-butoxide did not have any significant effect on the outcome of the reaction, but the yield increased with increasing amount of the base (entries 9–11). However, high yield was obtained with a lower amount of potassium *t*-butoxide and an increased catalyst concentration (entry 12). The addition of water, previously shown to result in increased enantioselectivity,[14] had no effect under the conditions used here.



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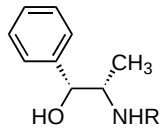

2 R = CH_3
3 R = H

These reactions were run using constant microwave power. The temperature profiles for the preparation of the catalyst at 100 W and for reaction involving ligand **1** at 60 W (Fig. 1) show that the reaction mixtures are superheated beyond the normal boiling point of propan-2-ol (82°C).

Some experiments were also performed with either ephedrine **2** and norephedrine **3** as the ligand in place of **1**. With these ligands the catalytic reaction proceeded faster than with **1**; using **2** an 84% yield of (*R*)-1-phenylethanol with 70% e.e. was obtained after 3 min at 60 W (entry 13) and with **3** the product was obtained in 96% yield and 46% e.e. after 4 min at 60 W (entry 14).

Finally, some other metal ions were tested in the process. Ru(II) has been found to be the most efficient metal ion for the catalytic hydrogen transfer reaction.

Table 1. Asymmetric reduction of acetophenone by chiral Ru(II) complexes in propan-2-ol under microwave irradiation

Entry	Ligand	Conditions (time/power)	Catalyst concentration (mol%)	Yield[a] (%)	E.e.[b] (%)
1	**1**	5 min/80 W	1	87	48 (*R*)
2	**1**	9 min/60 W	1	90	82 (*R*)
3	**1**	12 min/60 W	1	79	80 (*R*)
4	**1**	9 min/60 W + 5 min/80 W	1	81	63 (*R*)
5	**1**	9 min/60 W	0.5	24	70 (*R*)
6[c]	**1**	9 min/60 W	1	82	76 (*R*)
7[d]	**1**	9 min/60 W	1	90	29 (*R*)
8[e]	**1**	9 min/60 W	1	84	82 (*R*)
9[f]	**1**	9 min/60 W	1	65	82 (*R*)
10[g]	**1**	9 min/60 W	1	85 (83[h])	82 (*R*)
11[i]	**1**	9 min/60 W	1	95	80 (*R*)
12[g]	**1**	9 min/60 W	2	97	80 (*R*)
13	**2**	3 min/60 W	1	84	70 (*R*)
14	**3**	4 min/60 W	1	96	46 (*R*)

[a] Yield determined by GLC unless otherwise indicated.
[b] Analyzed by HPLC (Chiralcel OD-H column, eluent 1:9 propan-2-ol:hexane, flow rate 0.5 mL/min).
[c] A 1.0 M solution of acetophenone.
[d] Lig/M ratio 1.
[e] Lig/M ratio 4.
[f] 2.5 mol% *t*-BuOK used as base.
[g] 5 mol% *t*-BuOK used as base.
[h] Yield of isolated product.
[i] 10 mol% *t*-BuOK used as base.

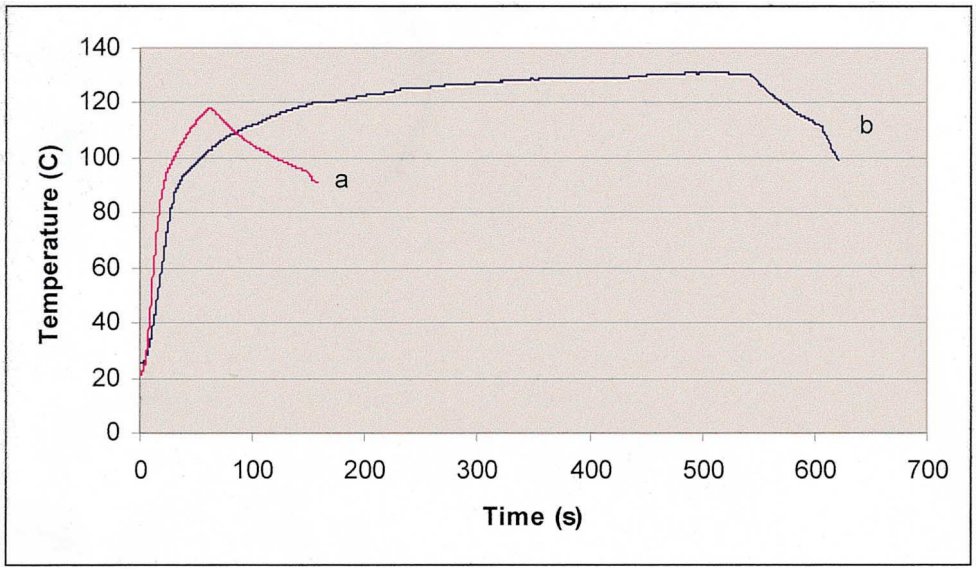

Figure 1. Temperature profiles for (a) catalyst preparation at 100 W, (b) catalytic reaction at 60 W (entry 2, Table 1).

$FeSO_4 \cdot 7H_2O$, $CoCl_2 \cdot 6H_2O$, $NiCl_2 \cdot 6H_2O$ and $[Rh(COD)Cl]_2$ when complexed to **1** all exhibited catalytic activity but provided essentially racemic product (e.e. $\leq 4\%$). In contrast to catalysts containing Ru, those with Fe, Co and Ni remained active after the reaction was terminated, forming additional product upon the addition of more acetophenone. With these metals, essentially no product was formed when **1** was replaced with **2** or **3**.

Sterically hindered ketones commonly result in low yield and low enantioselectivity under normal conditions, one exception being a reactive Ru complex of a thiourea compound, which in addition to giving high yields also affords the secondary alcohol from *t*-butylphenylketone with high enantioselectivity. Thus, using an amino alcohol ligand, the product was previously obtained in 22% yield and 49% e.e.[9] or in 46% yield and 64% e.e.,[5] depending on the structure of the ligand. We decided to exploit the reduction of *t*-butylphenylketone using microwave heating under conditions of constant temperature. With our system 71% yield and 14% e.e. of (*R*)-2,2-dimethyl-1-phenylpropanol was obtained after 3 min at 125°C (Table 2, entry 2); after 10 min we obtained a 99% yield of the product, but the e.e. was merely 13% (entry 3). With a shorter reaction time and higher temperature (3 min, 140°C) higher e.e. was observed (18%), but the yield was lowered (88%, entry 4). With 2 mol% of catalyst a faster reaction, giving similar e.e., was observed (entry 5). With ephedrine as ligand in place of **1**, the product was formed in 96% yield with 21% e.e. in 3 min at 115°C (entry 6).

3. Conclusion

Fast and efficient Ru-catalyzed hydrogen transfer from propan-2-ol to acetophenone was achieved using microwave irradiation. The enantioselectivity was, however, lower than that observed under standard conditions. Sterically hindered *t*-butylphenylketone, which normally is quite unreactive, was reduced in close to quantitative yield, albeit with low e.e.

Table 2. Asymmetric reduction of *t*-butylphenylketone by chiral Ru(II) complexes in propan-2-ol under microwave irradiation

Entry	Ligand	Conditions (time/temp.)	Yield[a] (%)	E.e.[b] (%)
1	**1**	1 day/rt	0	–
2	**1**	3 min/125°C	71	14 (*R*)
3	**1**	10 min/125°C	99	13 (*R*)
4	**1**	3 min/140°C	88	18 (*R*)
5[c]	**1**	1.5 min/125°C	95	15 (*R*)
6	**2**	3 min/115°C	96	21 (*S*)

[a] Isolated yield.
[b] Analyzed by HPLC (Chiralcel OD-H column, eluent 1:19 propan-2-ol:hexane, flow rate 1.0 mL/min).
[c] 2 mol% of catalyst.

4. Experimental

4.1. General

Microwave heating was performed in a MicroWell 10 single mode microwave cavity from Personal Chemistry AB, Sweden, producing continuous irradiation at 2.45 GHz. The reaction vessel was a round-bottomed 100 mm Duran™ glass tube with a Schott GL18 screw cap, provided with a Teflon septa as a pressure relief device. The temperature was recorded using an IR pyrometer sensor. After irradiation was complete, the samples were left in the microwave cavity for 1 min to allow for thermal equilibration before cooling in a water bath at rt. Ligand **1** was prepared according to published procedure.[15] All other reagents were used as received from Aldrich, Strem and Lancaster. The absolute configura-

tions of phenylethanol[16] and 2,2-dimethyl-1-phenylpropanol[3] were determined from their known optical rotations.

4.2. 1-Phenylethanol

Di-μ-chlorobis[(*p*-cymene)chlororuthenium(II)] (3.06 mg, 0.005 mmol, 1 mol%) and ligand **1** (7.32 mg, 0.02 mmol, 2 mol%) were added to a dry reaction vessel together with propan-2-ol (2.0 mL) and the mixture was irradiated for 1 min at 100 W. After addition of acetophenone (120 mg, 1.0 mmol) and KOH (2.8 mg, 0.05 mmol, 5 mol%), the resulting solution was irradiated at the appropriate time and effect (see Table 1). After evaporation of the solvent, the product was isolated by chromatography (eluent: ethyl acetate:dichloromethane 1:5). The e.e. was determined by HPLC using a Chiralcel OD-H column (eluent: propan-2-ol:hexane 10:90, flow rate 0.5 mL/min).

4.3. 2,2-Dimethyl-1-phenylpropanol

A solution of di-μ-chlorobis[(*p*-cymene)chlororuthenium(II)] (3.06 mg, 0.005 mmol, 1 mol%), 2,2-dimethylpropiophenone (132 mg, 1.0 mmol) and ligand **1** (7.32 mg, 0.02 mmol, 2 mol%) in propan-2-ol (2.0 mL) was irradiated for 1 min at 100 W. After addition of KOH (2.8 mg, 0.05 mmol, 5 mol%), the resulting solution was irradiated at the appropriate time and temperature (see Table 2). The solvent was removed in vacuo and the product was purified by chromatography (eluent: ethyl acetate:hexane 1:10). The e.e. was determined by HPLC using a Chiralcel OD-H column (eluent: propan-2-ol:hexane 5:95, flow rate 1.0 mL/min).

Acknowledgements

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