Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 879–884

TETRAHEDRON: *ASYMMETRY*

Efficient ruthenium-catalyzed racemization of secondary alcohols: application to dynamic kinetic resolution

Arné Dijksman, Jeoffrey M. Elzinga, Yu-Xin Li, Isabel W. C. E. Arends and Roger A. Sheldon*

Biocatalysis and Organic Chemistry, Department of Biotechnology, Delft University of Technology, Julianalaan 136, 2628 BL Delft, The Netherlands

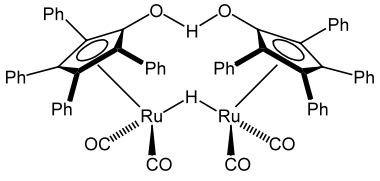
Received 8 April 2002; accepted 18 April 2002

Abstract—Three new ruthenium-based catalytic systems are described which are capable of catalyzing the racemization of chiral secondary alcohols. In addition, one of these systems, $[TosN(CH_2)_2NH_2]RuCl(p\text{-cymene})$/TEMPO, was able to catalyze the in situ racemization during enzymatic resolution, i.e. dynamic kinetic resolution.

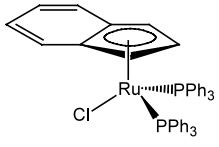
1. Introduction

Enantiomerically pure secondary alcohols are important synthetic intermediates and chiral auxiliaries.[1] They can be prepared in high enantiomeric purity by asymmetric hydrogenation[2] or transfer hydrogenation[3,4] of prochiral ketones using well-designed chiral Ru(II) complexes as catalysts. Alternatively, chiral Ru(II) complexes can also be conveniently employed in the kinetic resolution of a racemic alcohol using either aerobic oxidation[5] or transfer hydrogenation with acetone.[6] In both cases, one of the enantiomers is converted to the corresponding ketone.

Higher enantiomeric excesses (e.e.s) can be obtained, however, in the kinetic resolution of alcohols via lipase-catalyzed[7] or aminoacylase-catalyzed[8] acylation. One major limitation with both the ruthenium-catalyzed and enzymatic resolution method is that the maximum yield is 50% based on the racemate. As a method to overcome this limitation, dynamic kinetic resolution processes (or second-order asymmetric transformations) have been introduced for secondary alcohols, in which the alcohols are continuously racemized with metal catalysts during an enzymatic resolution.[9] For example, $[RuH(CO)_2(\eta^5\text{-}Ph_4C_4CO)]_2$ **1**[10] and $(\eta^5\text{-indenyl})RuCl(PPh_3)_2$ **2**[11] have been shown to catalyze in situ racemization of alcohols. However, the major drawback of these systems is the requirement for large amounts of additives, i.e. up to 1 equiv. of acetophenone and 3 equiv. of triethylamine, based on the substrate, to achieve their activity. In addition, at least three column-extractions are required to purify complex **1**.



1



2

Herein, we report on the development of readily accessible ruthenium catalysts for the efficient racemization of chiral secondary alcohols without a requirement for substantial amounts of additives.

2. Results and discussion

2.1. Combination of $RuCl_2(PPh_3)_3$ and TEMPO

For our initial experiments, we selected (*S*)-1-phenylethanol as the test substrate and a $RuCl_2(PPh_3)_3$/TEMPO system as the racemization catalyst. $RuCl_2(PPh_3)_3$/TEMPO was previously shown by us to be an efficient catalyst for the aerobic oxidation of alcohols.[12]

As shown in Table 1, $RuCl_2(PPh_3)_3$ alone is inactive in the racemization of (*S*)-1-phenylethanol (entry 1).

* Corresponding author. Tel.: +31 152782675; fax: +31 152781415; e-mail: r.a.sheldon@tnw.tudelft.nl

0957-4166/02/$ - see front matter
PII: S0957-4166(02)00187-8

Table 1. Ru/TEMPO-catalyzed racemization of (*S*)-1-phenylethanol[a]

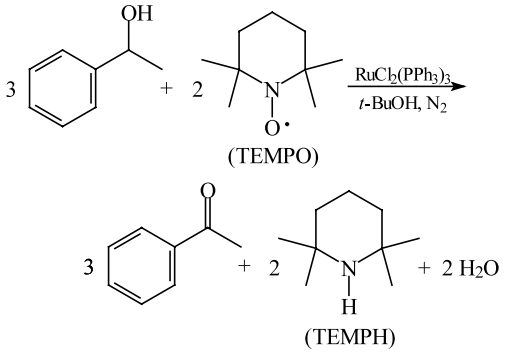
Entry	Solvent	E.e. (%)[b]
1[c]	*tert*-Butanol	99
2	*tert*-Butanol	38 (0)
3	Chlorobenzene	78
4	1,2-Dimethoxyethane	88
5	Toluene	82 (74)
6	Ethyl acetate	73
7	[bmim]BF_4[d]	88

[a] Reaction conditions: (*S*)-1-phenylethanol (1 mmol), $RuCl_2(PPh_3)_3$ (10 μmol), TEMPO (30 μmol), solvent (3 mL), N_2 atmosphere, $T=70°C$, 24 h.

[b] E.e.s[13] based on HPLC results; numbers in parentheses are e.e.s after 48 h.

[c] No TEMPO.

[d] (1-Butyl-3-methylimidazolium)tetrafluoroborate.

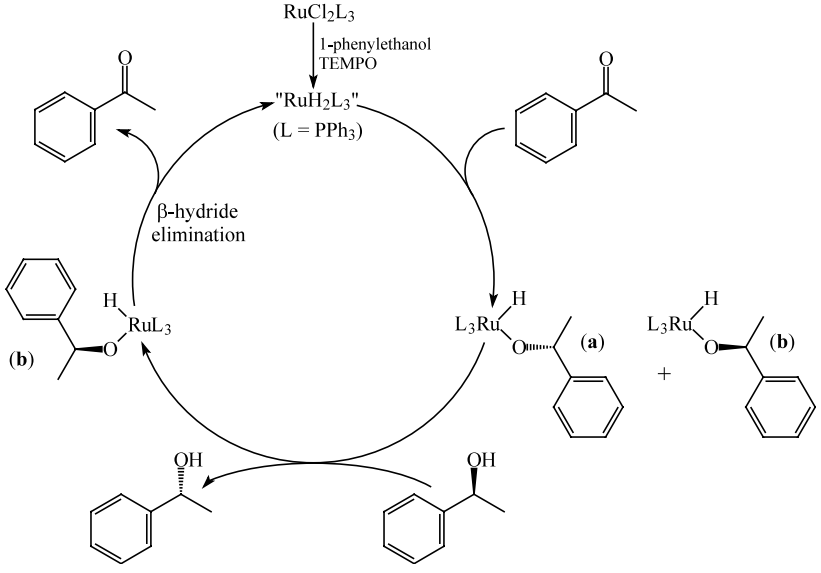


Scheme 1. Ru-catalyzed oxidation of benzyl alcohol with TEMPO as oxidant.

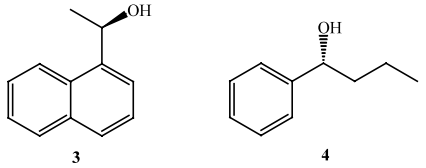
Addition of TEMPO (3 mol%), which itself is also inactive, to $RuCl_2(PPh_3)_3$ leads to a substantial increase in activity (entry 2). The use of *tert*-butanol as solvent was found to be quite essential, i.e. racemization in other solvents resulted in much lower activities (entries 3–7).

We propose that the Ru/TEMPO-catalyzed racemization involves initial ruthenium-catalyzed oxidation of the alcohol, to the corresponding ketone, with TEMPO as the stoichiometric oxidant (Scheme 1). By analogy with the $RuCl_2(PPh_3)_3$-catalyzed hydrogen-transfer reactions[14] and the $RuCl_2(PPh_3)_3$/TEMPO-catalyzed aerobic oxidation of alcohols,[15] we propose that $RuH_2(PPh_3)_3$ is the active intermediate in the Ru/TEMPO-catalyzed racemization (Scheme 2). This ruthenium hydride subsequently reacts with the in situ generated acetophenone to form an alkoxyruthenium(II) complex that consists of a 1:1 mixture of (**a**) and (**b**) in which the alkoxy ligand has (*R*)- or (*S*)-configuration, respectively. Reaction of complex (**a**) with a molecule of (*S*)-1-phenylethanol affords (*R*)-1-phenylethanol and complex (**b**). The latter undergoes β-hydride elimination to afford acetophenone and $RuH_2(PPh_3)_3$ to complete the catalytic cycle. The overall result is racemization of the alcohol. The observation that catalytic amounts of $RuH_2(PPh_3)_4$ and acetophenone gave the same results, i.e. complete racemization in 2 days, is consistent with the proposed mechanism.

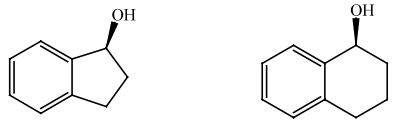
The use of $RuCl_2(PPh_3)_3$/TEMPO as racemization catalyst was then applied to some other chiral secondary (benzylic) alcohols. Using a substrate/ruthenium ratio of 100, alcohols **3**, **4** and **5** were moderately active and e.e.s of 45, 51 and 25%, respectively, could be obtained within 48 h. Fortunately, extended reaction time (3–5 days) led to full racemization in all cases,[16] indicating that the catalyst was not deactivated with time.



Scheme 2. Proposed mechanism for the Ru/TEMPO catalyzed racemization of (*S*)-1-phenylethanol.



3 4

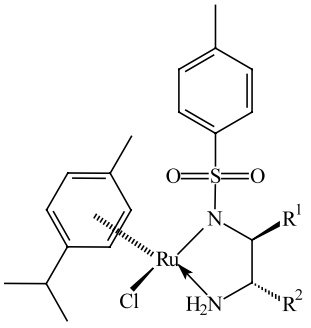


5 6

Although the Ru/TEMPO-catalyzed racemization of chiral secondary (benzylic) alcohols is potentially interesting, it is still rather slow and requires the coaddition of 3 mol% of rather expensive TEMPO for the in situ formation of catalytic quantities of the corresponding ketone. This prompted us to search for other ruthenium catalysts for the racemization of chiral alcohols.

2.2. Ruthenium complex with bidentate nitrogen ligand

Chiral ruthenium(II) compounds with general structure **7** have been extensively reported as catalysts for the asymmetric transfer hydrogenation of prochiral ketones.[4,6] These complexes are synthesized from $[RuCl_2(p\text{-cymene})]_2$ and a chiral bidentate nitrogen ligand. We reasoned, therefore, that the corresponding achiral ruthenium complex **8** ($R^1=R^2=H$) would be likely to be an efficient catalyst for the racemization of alcohols.



7

As the results in Table 2 show, compound **8** alone is inactive as a catalyst for the racemization of (*S*)-1-phenylethanol (entry 1). Addition of a base (KOH) as co-catalyst (which itself is inactive as a catalyst) to **8** leads to a substantial increase in activity (entries 2 and 3). The choice of base was found to be essential. For example, racemization of (*S*)-1-phenylethanol with **8** in the presence of other bases resulted in much lower activities (entries 7–11). In addition, TEMPO could also be used as co-catalyst although the activity was found to be lower than with KOH (entry 12).

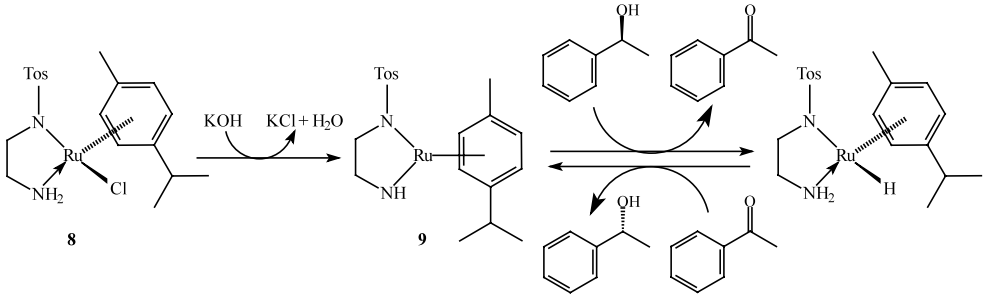
Table 2. Racemization of (*S*)-1-phenylethanol with **8** as catalyst[a]

Entry	Co-catalyst[b]	Solvent	E.e. (%)[c]
1	–	*tert*-Butanol	99
2	KOH (10)	*tert*-Butanol	22 (0)
3	KOH (20)	*tert*-Butanol	0
4	KOH (10)	*tert*-Amyl alcohol	3 (0)
5	KOH (10)	Toluene	84
6[d]	KOH (30)	Toluene	13 (10)
7	K_2CO_3 (10)	*tert*-Butanol	96
8	DBU (10)[e]	*tert*-Butanol	55
9	DABCO (10)[f]	*tert*-Butanol	80
10	Triethylamine (10)	*tert*-Butanol	75
11	Pyridine (10)	*tert*-Butanol	98
12[d]	TEMPO (45)	*tert*-Butanol	79
13[d]	TEMPO (45)	*tert*-Amyl alcohol	75 (48)
14[d]	TEMPO (45)	Toluene	41 (15)

[a] Reaction conditions: (*S*)-1-phenylethanol (1 mmol), catalyst **8** (10 μmol), co-catalyst, solvent (3 mL), N_2 atmosphere, $T=70°C$, 24 h.
[b] Numbers in parentheses are amounts added in μmol.
[c] E.e.s[13] based on HPLC results; numbers in parentheses are e.e.s after 48 h.
[d] Catalyst **8** (15 μmol).
[e] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[f] 1,4-Diazabicyclo[2.2.2]octane.

The requirement for a strong base, such as KOH, can be rationalized on the basis of Scheme 3. The role of the base is to abstract a proton from the amino-group of the ligand, resulting in the formation of the active catalyst **9**. However, when in the racemization the preformed compound **9** was used, less activity was observed, i.e. 50% e.e. was obtained with **9** after 24 h compared to the 22% in the case of the in situ formed catalyst. Analogous to Ru/TEMPO, we propose that this interesting system is also based on a hydrido-metal mediated hydrogen transfer mechanism (Scheme 3).

As with the Ru/TEMPO system, the solvent played an important role (Table 2; entries 2, 4 and 5).[17] The best results were obtained in *tert*-amyl alcohol. In contrast,



8 9

Scheme 3. Racemization catalyzed by active catalyst **9**.

toluene proved to be the best solvent when TEMPO was used as co-catalyst (entries 12–14). Based on the results presented above, we selected KOH as the co-catalyst and *tert*-amyl alcohol as the solvent and performed the ruthenium-catalyzed racemization of some chiral secondary benzylic alcohols,[18] other than (*S*)-1-phenylethanol. For (*S*)-indan-1-ol **5** and (*S*)-α-tetralol **6**, complete racemization was observed within 48 h. On the other hand, in the racemization of (*R*)-1-(1′-naphthyl)-ethanol **3** and (*R*)-1-phenylbutan-1-ol **4** e.e.s of 20 and 35%, respectively, were obtained. Fortunately, these alcohols could also be fully racemized by prolonging the reaction time to 4 days.

Another interesting application is the *cis*/*trans* isomerization of cyclic alcohols. For example, *cis*-4-*tert*-butylcyclohexanol was converted to a *cis*/*trans* (55/45) mixture within 24 h. We are currently examining the scope of the cis/trans isomerization of cyclic alcohols.

Table 3. Racemization of (*S*)-phenylethanol in the presence of additives[a]

Entry	Co-catalyst[b]	Solvent	Additive[c]	E.e. (%)[d]
1	KOH	*tert*-Amyl alcohol	–	0
2			Nov435	99 (99)
3			AcD	99 (96)
4		Toluene	–	13 (10)
5			Nov435	4 (0)
6			AcD	89 (79)
7	TEMPO	Toluene	–	42 (15)
8			Nov435	63 (45)
9			AcD	72 (63)

[a] Reaction conditions: (*S*)-1-phenylethanol (1 mmol), catalyst **8** (15 μmol), *tert*-butanol (3 mL), N_2 atmosphere, $T=70$°C.
[b] KOH (30 μmol) or TEMPO (45 μmol).
[c] Nov435 = 50 mg Novozym 435; AcD = 2 mmol *p*-chlorophenyl acetate.
[d] E.e.s[13] based on HPLC results; numbers in parentheses are e.e.s after 48 h.

2.3. Dynamic kinetic resolution

Both $RuCl_2(PPh_3)_3$/TEMPO and [$TosN(CH_2)_2NH_2$]-RuCl(*p*-cymene)/KOH are active and selective catalysts for the racemization of chiral secondary (benzylic) alcohols. Initial attempts to combine lipase-catalyzed acylation with these catalytic racemization systems in either *tert*-amyl alcohol or *tert*-butyl alcohol were not successful, i.e. only enantioselective acylation and no racemization-activity was observed. It was subsequently shown that both the lipase and the acyl donor had a negative influence on the ruthenium-catalyzed racemization. The ruthenium catalyst was deactivated by the enzyme as well as the acyl donor in alcoholic solvents as was shown in separate experiments (Table 3; entries 1–3).

Because of this we re-examined the racemization results and decided to repeat the experiments mentioned above in the more apolar solvent toluene. Unfortunately no improvements were observed for $RuCl_2(PPh_3)_3$/TEMPO. On the other hand, racemization was observed in the presence of either the lipase or the acyl donor using [$TosN(CH_2)_2NH_2$]RuCl(*p*-cymene)/KOH as the catalytic system (Table 3; entries 4–6). However, in the desired dynamic kinetic resolution, again only enantioselective acylation was observed (Table 4, entries 2 and 3).

As discussed above (Table 2), TEMPO can be used instead of KOH as the co-catalyst in combination with [$TosN(CH_2)_2NH_2$]RuCl(*p*-cymene) **8**. With this combination, racemization was observed in the presence of either lipase or acyl donor (Table 3; entries 7–9). Moreover, in contrast to the other two systems, in situ racemization occurred in the desired dynamic kinetic resolution (Table 4; entries 4–5).

3. Conclusion

In summary, we have developed three new catalytic systems which are capable of catalyzing the racemization

Table 4. Dynamic kinetic resolution of 1-phenylethanol[a]

Entry	Catalytic system	Conv. (%)[b] 1-phenylethanol	Yield[b,c] 1-phenylethyl acetate (%)
1	$RuCl_2(PPh_3)_3$/TEMPO[d]	61	56
2	**8**/KOH[e]	61	55
3	**8**/KOH[f]	68	57
4	**8**/TEMPO[g]	79	63
5	**8**/TEMPO[d]	91	76

[a] Reaction conditions: 1-phenylethanol (1 mmol), *p*-chlorophenyl acetate (3 mmol), Ru-catalyst (50 μmol), KOH (30–50 μmol) or TEMPO (50–150 μmol), Novozym 435 (50 mg), toluene (3 mL), *p*-cymene (0.2 mmol-internal standard), N_2 atmosphere, $T=70$°C, 48 h.
[b] Conversion and yield based on GC results; conversion corresponds to total phenylethanol (PE) disappeared after 48 h relative to internal standard, conv. = {[(mmol PE)$_{t=0\ h}$–(mmol PE)$_{t=48\ h}$]/(mmol PE)$_{t=0}$}×100%; yield corresponds to {mmol (1-phenylethyl acetate)$_{t=48\ h}$/(mmol PE)$_{t=0}$}×100%. Difference between conversion of PE and yield of ester is accounted for by oxidation of 1-phenylethanol to acetophenone. Mass balance obtained was close to 100% in all cases.
[c] E.e. of 1-phenylethyl acetate >99% in all cases.
[d] TEMPO (150 μmol).
[e] **8** (15 μmol) and KOH (30 μmol).
[f] KOH (50 μmol).
[g] TEMPO (50 μmol).

of chiral secondary alcohols. However, only one of these systems, [TosN(CH_2)$_2$$NH_2$]RuCl(*p*-cymene)/TEMPO, is able to catalyze the in situ racemization of chiral secondary alcohols during enzymatic acylation. Using this system, enantiomerically pure (>99% e.e.) 1-phenylethyl acetate was obtained in 83% selectivity at 91% conversion. The only side product observed was acetophenone, formed by oxidation of the substrate by the TEMPO co-catalyst.

4. Experimental

4.1. General

$RuCl_2(PPh_3)_3$[19] and [$RuCl_2$(*p*-cymene)]$_2$[20] were prepared according to literature. TEMPO was purchased from the Aldrich Chemical Co. and used without further purification. Novozym 435 is a commercially available immobilized *Candida Antarctica* Lipase B.

4.2. *N*-*p*-Toluenesulfonylethylenediamine

A mixture of *p*-toluenesulfonyl chloride (1.91 g, 10 mmol) in dichloromethane (25 mL) was slowly added to a stirred solution of ethylenediamine (6.0 g, 100 mmol) in dichloromethane (25 mL). The resulting mixture was stirred for another 15 min, washed twice with distilled water (25 mL) and dried over CaH_2. The solvent was removed in vacuo to give a fine white powder (1.62 g, 76%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.75 (d, 2H, $^3J_{HH}$=8.1 Hz, 2H^{ortho}), 7.31 (d, 2H, $^3J_{HH}$=8.4 Hz, 2H^{meta}), 2.95 (dd, 2H, $^3J_{HH}$=7.2 Hz and $^3J_{HH}$=6.0 Hz, TosNHCH_2), 2.79 (dd, 2H, $^3J_{HH}$=7.2 Hz and $^3J_{HH}$=6.3 Hz, C$H_2$$NH_2$), 2.43 (s, 3H, C$H_3$), 1.40 (broad, 2H, N$H_2$).

4.3. [*N*-*p*-Toluenesulfonylethylenediamine]RuCl-(*p*-cymene) 8

A mixture of *N*-*p*-toluenesulfonylethylenediamine (0.22 g, 1.0 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (0.31 g, 0.5 mmol) and triethylamine (0.28 mL) in 2-propanol (30 mL) was heated under reflux for 1 h. After cooling to ambient temperature, 2-propanol and the excess of triethylamine were removed in vacuo and the residue was dissolved in dichloromethane (30 mL). The resulting orange solution was washed two times with water (15 mL) and dried over Na_2SO_4. The solvent was removed in vacuo to give an orange powder (0.32 g, 66%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.76 (d, 2H, $^3J_{HH}$=8.4 Hz, 2{*p*-tosyl}H^{ortho}), 7.31 (d, 2H, $^3J_{HH}$=8.1 Hz, 2{*p*-tosyl}H^{meta}), 5.70 (broad, 2H, 2{*p*-cymene}H^{meta}), 5.50 (broad, 2H, 2{*p*-cymene}H^{ortho}), 3.02 (broad, 2H, TosNCH_2), 2.80 (m, 1H, {*p*-cymene}CH(CH_3)$_2$), 2.75 (broad, 2H, C$H_2$$NH_2$), 2.34 (s, 3H, {*p*-tosyl}CH_3), 2.15 (s, 3H, {*p*-cymene}CH_3), 1.57 (s, 2H, NH_2), 1.27 (d, 6H, $^3J_{HH}$=6.6 Hz, {*p*-cymene}CH(CH_3)$_2$).

4.4. [*N*-*p*-Toluenesulfonylethylenediamine]Ru(*p*-cymene) 9

A mixture of *N*-*p*-toluenesulfonylethylenediamine (0.22 g, 1.0 mmol), [$RuCl_2$(*p*-cymene)]$_2$ (0.31 g, 0.5 mmol) and KOH (0.40 g, 7.1 mmol) in dichloromethane (7 mL) was stirred for 5 min at room temperature. Water (7 mL) was added and the two layers were separated. The organic layer was washed with water (7 mL) and dried over CaH_2. The solvent was removed in vacuo to give a purple powder (0.35 g, 77%). ^{1}H NMR (300 MHz, $CDCl_3$, TMS) δ 7.73 (d, 2H, $^3J_{HH}$=8.4 Hz, 2{*p*-tosyl}H^{ortho}), 7.25 (d, 2H, $^3J_{HH}$=8.4 Hz, 2{*p*-tosyl}H^{meta}), 5.70 (broad, 2H, 2{*p*-cymene}H^{meta}), 5.50 (broad, 2H, 2{*p*-cymene}H^{ortho}), 3.02 (broad, 2H, TosNCH_2), 2.83 (m, 1H, {*p*-cymene}CH(CH_3)2), 2.75 (broad, 2H, C$H_2$$NH_2$), 2.40 (s, 3H, {*p*-tosyl}CH_3), 2.32 (s, 3H, {*p*-cymene}CH_3), 1.23 (d, 6H, $^3J_{HH}$=6.9 Hz, {*p*-cymene}CH(CH_3)$_2$).

4.5. General procedure and analysis for the racemization of secondary (benzylic) alcohols

A typical reaction was carried out as follows: (*S*)-1-phenylethanol (121 μL, 1.0 mmol), $RuCl_2(PPh_3)_3$ (10 μmol; 9.6 mg) and TEMPO (30 μmol; 4.7 mg) were dissolved in *tert*-butanol (3 mL) and heated under a nitrogen atmosphere to 70°C. The reaction was monitored with time by taking samples (50 μL). The samples were diluted with *n*-hexane (1 mL), dried over Na_2SO_4 and centrifuged. The e.e. of the alcohol was determined using HPLC-analysis (CHIRALCEL OD or OB-H 25 cm×0.46 cm column; eluent: *n*-hexane/*iso*-propanol (95/5 or 90/10 v/v); flow rate: 0.6 mL/min). On the other hand, the selectivity of the reaction was determined using GC-analysis (50 m×0.53 mm CP-WAX 52 CB column).

4.6. General procedure for the dynamic kinetic resolution of 1-phenylethanol

A typical reaction was carried out as follows: A mixture of 1-phenylethanol (1.0 mmol; 121 μl), Ru complex **8** (15 μmol, 7.3 mg), TEMPO (45 μmol, 7.0 mg), 50 mg Novozym 435 and *p*-chlorophenyl acetate (3.0 mmol) in toluene (3 mL) was heated under a nitrogen atmosphere to 70°C. The reaction was monitored with time by taking samples (50 μL). The samples were diluted with *n*-hexane (1 mL), dried over Na_2SO_4 and centrifuged. For analysis see Section 4.5. Use of *p*-chlorophenyl acetate, *iso*-propenyl acetate and vinyl acetate did not lead to satisfactory results.

Acknowledgements

We gratefully acknowledge the IOP (Innovation-Oriented Research Program) for financial support.

References

1. (a) Sheldon, R. A. *Chirotechnology*, *Industrial Synthesis of Optically Active Compounds*; Dekker: New York, 1993; (b) Laumen, K.; Breitgoff, D.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1988**, 1459–1461.

2. (a) Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703–1707; (b) Ohkuma, T.; Ishii, D.; Takeno, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 6510–6511.
3. (a) Alonso, D. A.; Brandt, P.; Nordin, S. J. M.; Andersson, P. G. *J. Am. Chem. Soc.* **1999**, *121*, 9580–9588; (b) Alonso, D. A.; Nordin, S. J. M.; Roth, P.; Tarnai, T.; Andersson, P. G. *J. Org. Chem.* **2000**, *65*, 3116–3122; (c) Petra, D. G. I.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; van Loon, A. M.; de Vries, J. G.; Schoemaker, H. E. *Eur. J. Inorg. Chem.* **1999**, 2335–2341; (d) Petra, D. G. I.; Reek, J. N. H.; Handgraaf, J.-W.; Meijer, E. J.; Dierkes, P.; Kamer, P. C. J.; Brussee, J.; Schoemaker, H. E.; van Leeuwen, P. W. N. M. *Chem. Eur. J.* **2000**, *6*, 2818–2829; (e) Gao, J.-X.; Ikariya, T.; Noyori, R. *Organometallics* **1996**, *15*, 1087–1089; (f) Sammakia, T.; Stangeland, E. L. *J. Org. Chem.* **1997**, *62*, 6104–6105.
4. Haack, K.-J.; Hashiguchi, S.; Fujii, A.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 285–288.
5. Masutani, K.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* **2000**, *41*, 5119–5123.
6. Hashiguchi, S.; Fujii, A.; Haack, K.-J.; Matsumara, K.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 288–290.
7. (a) Kichner, G.; Scollar, M. P.; Klibanov, A. M. *J. Am. Chem. Soc.* **1985**, *107*, 7072–7076; (b) Schmid, R. D.; Verger, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1608–1633; (c) Castaing-Degueil, M.; de Jeso, B.; Drouillard, S.; Maillard, B. *Tetrahedron Lett.* **1987**, *28*, 953–954; (d) Wang, Y. F.; Landonde, J. J.; Momongan, M.; Bergbreiter, D. E.; Wong, C. H. *J. Am. Chem. Soc.* **1988**, *110*, 7200–7205; (e) Rotticci, D.; Ottosson, J.; Norin, T.; Hult, K. *Methods Biotech.* **2001**, *15*, 261–276; (f) Thiel, F. *Methods Biotech.* **2001**, *15*, 277–289.
8. Bakker, M.; Spruijt, A. S.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1801–1808.
9. (a) El Gihani, M. T.; Williams, J. M. J. *Curr. Opin. Chem. Biol.* **1999**, *3*, 11–15; (b) Dinh, P. M.; Howarth, J. A.; Hudnott, A. R.; Williams, J. M. J. *Tetrahedron Lett.* **1996**, *37*, 7623–7626.
10. (a) Larsson, A. L. E.; Persson, B. A.; Bäckvall, J.-E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1211–1212; (b) Persson, B. A.; Larsson, A. L. E.; Le Ray, M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1999**, *121*, 1645–1650.
11. (a) Koh, J. H.; Jeong, H. M.; Park, J. *Tetrahedron Lett.* **1998**, *39*, 5545–5548; (b) Koh, J. H.; Jung, H. M.; Kim, M.-J.; Park, J. *Tetrahedron Lett.* **1999**, *40*, 6281–6284.
12. Dijksman, A.; Arends, I. W. C. E.; Sheldon, R. A. *Chem. Commun.* **1999**, 1591–1592.
13. $$\text{E.e. } (\%) = \frac{([S]-[R])}{([S]+[R])} \times 100$$
14. Aranyos, A.; Csjernyik, G.; Szabó, K. J.; Bäckvall, J.-E. *Chem. Commun.* **1999**, 351–352.
15. Dijksman, A.; Marino González, A.; Mairata i Payeras, A.; Arends, I. W. C. E.; Sheldon, R. A. *J. Am. Chem. Soc.* **2001**, *123*, 6826–6833.
16. For detailed studies, see table 5 in the supplementary material.
17. See table 6 in the supplementary material for a detailed study on the solvent effect.
18. For detailed studies, see table 7 in the supplementary material.
19. Hallman, P. S.; Stephenson, T. A.; Wilkinson, G. *Inorg. Synth.* **1970**, *12*, 237–240.
20. Bennett, M. A.; Huang, T.-N.; Matheson, T. W.; Smith, A. K. *Inorg. Synth.* **1982**, *21*, 74–78.