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Dynamic kinetic resolution of secondary alcohols with a readily available ruthenium-based racemization catalyst

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Abstract—An easy to handle and stable racemization catalyst for secondary alcohols is obtained by an in situ mixture of readily available $[Ru(cymene)Cl_2]_2$ with chelating aliphatic diamines. Optimization of the reaction revealed that *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine as ligand racemizes aromatic alcohols completely within 5 h. This easy to handle and stable catalytic system is combined with a lipase-catalyzed resolution to provide an efficient dynamic kinetic resolution of secondary alcohols.

1. Introduction

The combination of biocatalysts with transition metal catalysis provides a great impact into the synthesis of chiral compounds in organic synthesis. Biocatalysts like lipases have proven to be very efficient catalysts for the enantioselective synthesis of esters or alcohols. As these hydrolysis or synthesis reactions are kinetic resolutions, they are limited to a yield of 50%. For this reason, deracemization strategies were developed to overcome this disadvantage.[1] In the case of dynamic kinetic resolution a racemization catalyst keeps the substrate racemic. For the racemization of secondary alcohols transition metal complexes have been proved to be very useful.[2] However, one of the major problems is the compatibility of both catalysts in one reaction system. The first example of such a dynamic kinetic resolution for secondary alcohols was given by Williams and co-workers. They catalyzed the acylation with vinylacetate and *Pseudomonas fluorescence* lipase in the presence of a rhodium complex.[3] For allylic alcohols palladium catalysts were successfully tested.[4] Bäckvall and co-workers have shown that ruthenium catalysts are even more effective in the dynamic kinetic resolution of secondary alcohols.[5] They took immobilized *Candida antarctica* lipase together with a dimeric Ru–H-complex as the catalytic system. The ruthenium complex also bears CO and hydroxytetraphenylcyclopentadienyl ligands. The acylation was done by *p*-chlorophenyl acetate, as the more conventional acyl donors such as vinyl acetate were not compatible with the ruthenium system. This catalyst is also very effective in the dynamic kinetic resolution of aliphatic mono- and di-alcohols.[6] Ruthenium complexes with indenyl-ligands are also suitable racemization catalysts. These complexes need triethylamine and molecular oxygen for its application in dynamic kinetic resolution.[7] An aminocyclopentadienyl-ruthenium chloride complex was presented as a very active catalyst even at room temperature by Kim and co-workers.[8] However, the ruthenium systems used are only available in multistep synthesis and are sensitive towards air and moisture. These results highlight the need for stable and readily available racemization catalysts for the dynamic kinetic resolution of secondary alcohols.

2. Results and discussion

2.1. Screening for an efficient racemization catalyst

2.1.1. Screening of different classes of neutral ligands. The aim of our investigation was the identification of an easy to handle and stable racemization catalytic system that fulfills industrial requirements. In

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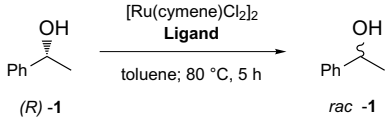
addition, the precursors and ligands were required to be readily available without high synthetic efforts. As a starting point for the development of a more practical ruthenium racemization catalyst we chose one of the most common ruthenium precursors $[Ru(cymene)Cl_2]_2$. It is also known that ruthenium–cymenechloride is a suitable catalyst in the dynamic kinetic resolution of allylic alcohols.[9] Thus, we wanted to find new ruthenium complexes to racemize even secondary non-allylic alcohols by ligand variation. In a first screen 12 readily available and structurally different phosphorus and nitrogen ligands were tested on (*R*)-1-phenylethanol as model system at 80 °C in toluene (Scheme 1).

The racemization activities of various ligands are listed in Table 1. The racemization capacity (Δee) is defined as the difference of the ee after the racemization beginning with an enantiopure compound. Phosphorus containing ligands such as aromatic, monochelating phosphines like triphenylphosphine (PPh_3) and tri-*o*-tolylphosphine ($P(o\text{-Tol})_3$) showed poor racemization. The aliphatic and more basic tri-*n*-butylphosphine (PBu_3) also did not lead to good performance. In addition, chelating phosphines like 1,4-bis(diphenylphosphino)-butane (dppb) or 1,1′-bis-(diphenylphosphino)ferrocene (dppf) as well as phosphites such as (tri-*n*-butylphosphite $P(O\text{-}n\text{-}Bu)_3$) resulted in non-significant racemization activity. Although in the case of nitrogen ligands neither the aromatic pyridine nor the chelating derivatives 2,2′-bipyridine nor 1,10-phenanthroline nor *N*,*N*,*N*′,*N*′-tetramethyl-1,8-naphthalenediamine (proton sponge®) gave positive results, we were pleased to find that *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (tmeda) led to a decrease of the ee from 100% to 50%.



Scheme 1. Screening reaction of the racemization of 1-phenylethanol with $[Ru(cymene)Cl_2]_2$ and different ligands.

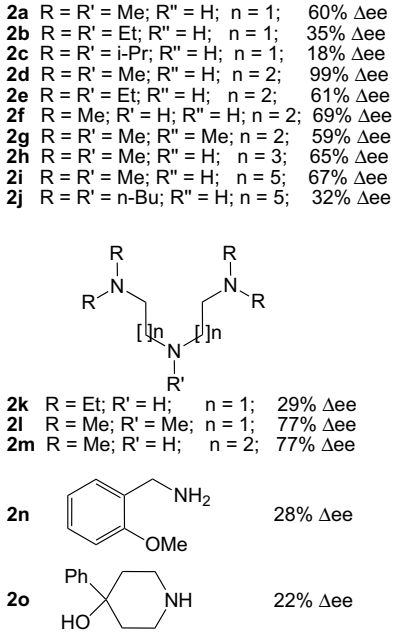
Table 1. Racemization activity of various ligands in an in situ mixture with $[Ru(cymene)Cl_2]_2$ for (*R*)-1-phenylethanol[a]

Entry	Ligand	Equiv	Δee [%]
1	PPh_3	2	3
2	$P(o\text{-Tol})_3$	2	4
3	PBu_3	2	4
4	dppb	1	3
5	dppf	1	4
6	$P(O\text{-}n\text{-}Bu)_3$	2	4
7	pyridine	2	4
8	2,2′-bipyridine	1	4
9	1,1′-phenanthroline	1	3
10	proton sponge®	2	8
11	tmeda	1	50
12	—	—	1

[a] Reagents and conditions: 0.025 mmol $[Ru(cymene)Cl_2]_2$, 0.8 mmol enantiopure (*R*)-**1**, 5 h, 80 °C, toluene.

2.1.2. Screening of different aliphatic amine ligands. It appears that chelating aliphatic diamine ligands transform $[Ru(cymene)Cl_2]_2$ into an active racemization catalyst. To prove this assumption, we tested a variety of readily available aliphatic nitrogen ligands (Scheme 2).

All tested amine ligands gave significant racemization. As an overall trend it can be noticed that a methyl group is more effective than an ethyl group on the nitrogen. This fact is obvious in the case of *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (**2a**) with a Δee of 60% compared to *N*,*N*,*N*′,*N*′-tetraethylethylenediamine (**2b**) with 35%. Steric hindrance can explain this trend, as the *iso*-propyl group of **2c** reduces the racemization. The optimal chelate ring size is obtained with a bridge size of three carbon atoms. Thus, the tetramethyl derivatives of the ethyl bridge in **2a** and the 1,3-butyl bridge in **2g** as well as the 1,4-butyl bridge in **2h** and the 1,6-hexyl group in **2i** show a Δee in the range of 60–70% ee. The relatively low racemization activity in *N*,*N*,*N*′,*N*′-tetra-*n*-butyl-1,6-hexanediamine (**2j**) is affected by the *n*-butyl groups rather than by the size of the ring. The far most active ligand contains the combination of methyl groups on the nitrogen and the 1,3-propyl bridge (**2d**) so that complete racemization is achieved. It is also important to avoid NH-bonds, as it is seen in *N*,*N*,*N*′-trimethyl-1,3-propanediamine (**2f**), lacking only one methyl group but lowering the Δee from 99% to 69%. Tris-chelating ligands like *N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine (**2l**) and *N*,*N*,*N*′,*N*′-tetramethyldipropylenetriamine (**2m**) show the second best performance with about 77% Δee, but under the precondition that the nitrogen contains methyl groups, not ethyl groups like **2k**. It can be assumed that the diamine coordinates to the $[Ru(cymene)Cl_2]_2$ in analogy to ethylenediamine[10] to form $[Ru(cymene)Cl(diamine)]^+Cl^-$, which should be the



Scheme 2. Racemization of (*R*)-1-phenylethanol with $[Ru(cymene)Cl_2]_2$ in combination with various amine ligands.

active racemization catalyst. This is also in accordance with the racemization activity of a cymene ruthenium system with tosylated diamine as bidentate nitrogen ligand introduced by Sheldon and co-workers.[11]

2.1.3. Scopes and limitations of ruthenium diamine racemization of secondary alcohols. Having identified the very efficient in situ mixture of $[Ru(cymene)Cl_2]_2$ and *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (**2d**) we varied the metal:ligand ratio (Table 2). As seen in Table 2 at 0.5 mmol of **2d** (metal:ligand ratio = 1:20) the Δee was even enhanced in the model reaction to 99.9% whereas a lower ligand ratio gives only 91% racemization. This confirms that the ligand transforms the ruthenium precursor into an active racemization catalyst.

In the case of ruthenium catalyzed racemization it is supposed that racemization occurs via an oxidative mechanism with the corresponding ketone as key intermediate. If the ketone is not formed in sufficient amount during the reaction, it has to be added even in stoichiometric amounts.[5] In the racemization of 1-phenylethanol by the ruthenium–cymene-complex with **2d** as ligand an addition of acetophenone (0.4 mmol) is prohibitive, as the Δee drops down from 99.9% to only 67%. Having tested a broad spectrum of different solvents the solvent of choice is toluene. Whereas diethyleneglycol–dimethylether was in the same range as toluene, ethyleneglycol hinders nearly completely the racemization which might be due to its hydroxy groups. Other high-boiling solvents like *N*,*N*-dimethylformamide or *N*-methyl-2-pyrrolidone as well as coordinating solvents like acetonitrile also lower the racemization tendency dramatically.

As far as additives are concerned, KOH increases the racemization activity of the in situ complex. A similar effect is observed with the cymene ruthenium tosylated diamine system and ruthenium–indenyl complexes.[11,12] Interestingly, also *p*-toluene sulfonic acid enhances the racemization, but not to the same extent as KOH. Further additives like LiBr or amines as well as ammonium ions hamper the racemization activity (Table 3).

Table 4 shows the substrate spectrum of this racemization catalyst. This system works very well for different aromatic alcohols like substituted 1-phenylethanol or naphthyl derivatives and especially 1-indanol is a very suitable substrate. However, aliphatic chains reduce the racemization activity as seen in the case of 1-phenyl-1-propanol. Pure aliphatic alcohols like 2-octanol are unfortunately poor racemization substrates.

Table 2. Variation of ligand amount in the racemization of (*R*)-**1** with $[Ru(cymene)Cl_2]_2$ and **2d**[a]

Entry	**2d** (mmol)	Yield [%]	Δee [%]
1	0.1	86	91
2	0.25	85	99
3	0.5	83	99.9

[a] Reagents and conditions: 0.025 mmol $[Ru(cymene)Cl_2]_2$, 0.8 mmol (*R*)-**1**, 5 h, 80 °C, toluene.

Table 3. Influence of additives in the racemization of (*R*)-**1** with $[Ru(cymene)Cl_2]_2$ and **2d**[a]

Entry	Additive (0.05 mmol)	Yield [%]	Δee [%]
1	KOH	78	98
2	*p*-toluene sulfonic acid	87	83
3	LiBr	89	54
4	triethylamine	86	62
5	tetraethylammoniumbromide	86	59

[a] Reagents and conditions: 0.025 mmol $[Ru(cymene)Cl_2]_2$, 0.25 mmol **2d**, 0.8 mmol (*R*)-**1**, 5 h, 80 °C, toluene.

Table 4. Racemization of various alcohols with $[Ru(cymene)Cl_2]_2$ and **2d**[a]

Entry	Alcohol	Yield [%]	Δee [%]
1	(*R*)-1-phenyl-1-propanol	94	38
2	(*R*)-1-indanol	90	99.9
3	(*S*)-methyl-2-naphthylmethanol	91	80
4	(*R*)-2-octanol	70	30
5	(*R*)-4-methoxy-1-phenylethanol	90	92
6	(*R*)-1-phenylethanol	85	99.5

[a] Reagents and conditions: 0.025 mmol $[Ru(cymene)Cl_2]_2$, 0.25 mmol **2d**, 0.8 mmol enantiopure alcohol (ee > 99%), 5 h, 80 °C toluene.

Overall, a new ruthenium-based racemization system of secondary alcohols was established. The main advantage is the convenient in situ formation of the catalyst by mixing the readily available ruthenium precursor $[Ru(cymene)Cl_2]_2$ and inexpensive *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine (**2d**). Furthermore, this system does not require inert conditions due to its stability to air and moisture.

2.2. Dynamic kinetic resolution of secondary alcohols

The development of an effective racemization system for secondary alcohols was the prerequisite for the implementation of a dynamic kinetic resolution process. As the next step we chose an enzymatic resolution system. Besides the recently published use of proteases for the dynamic kinetic resolution of alcohols,[13] the most common enzymatic resolution system of alcohols in organic media is the acylation with *Candida antarctica* B lipase, which was available as Chirazyme® l-2. As an acyl donor we chose *p*-chlorophenyl acetate. This reagent is very mild and does not affect the ruthenium complex. Experiments with other acyl donors like, *tert*-butyl acetate or vinylesters, failed due to the low or in the case of vinyl esters the high acylation activity.[5,14]

In Table 5 the results for the dynamic kinetic resolution of alcohols are listed. Aromatic alcohols are resolved in very good yields and excellent enantioselectivities. Unsubstituted phenylethanol as well as the 4-methoxy derivative and the naphthyl system give yields of more than 60%. Interestingly, yield and enantioselectivity can be increased by adding the appropriate ketone in some amount. Thus, it was shown that this ruthenium-diamine racemization catalyst is very compatible with an enzymatic resolution system for providing an efficient

Table 5. Dynamic kinetic resolution of secondary alcohols[a]

Entry	Racemic alcohol	Additive[b]	Yield [%]	ee [%]
1	1-indanol	–	72	98
2	1-indanol	+	93	98
3	methyl-2-naphthylmethanol	–	58	98
4	methyl-2-naphthylmethanol	+	64	96
5	4-methoxy-1-phenylethanol	–	59	93
6	4-methoxy-1-phenylethanol	+	66	97
7	1-phenylethanol	–	72	96
8	1-phenylethanol	+	80	98

[a] Reagents and conditions: 0.025 mmol $[Ru(cymene)Cl_2]_2$, 0.25 mmol **2d**, 0.8 mmol *rac*-alcohol

[b] 0.4 mmol of the corresponding ketone.

dynamic kinetic resolution of aromatic secondary alcohols. With this easy to handle catalyst system nearly the same activities and selectivities were obtained compared to the catalytic systems introduced by Bäckvall, Kim or Sheldon. Our system has a strong preference to aromatic alcohols so that it complements the Bäckvall system with its preference for aliphatic alcohols and hydroxy esters.[15] Even the restriction to allylic alcohols, which was the limitation of ruthenium–cymene based catalysts, was overcome.[4,9] Furthermore, the herein introduced catalytic system is characterized by its simplicity of synthesis and its robustness.

3. Conclusion

In this letter we describe an alternative catalytic system for the dynamic kinetic resolution of secondary alcohols on ruthenium basis. At first, a racemization active in situ mixture consisting of the ruthenium precursor $[Ru(cymene)Cl_2]_2$ and readily available diamines was developed, which is distinguished by its easy synthesis and stability towards air and moisture. Especially *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine as ligand gives excellent racemization activity. This racemization catalyst is combined with lipase-catalyzed kinetic resolution using *p*-chlorophenyl acetate as acyl donor with good performance for the dynamic kinetic resolution of secondary alcohols.

4. Materials and methods

All chemicals were purchased at Sigma–Aldrich and used without prior purification. Chirazyme® l-2, c-f, lyo. was obtained from Roche and Biocatalytics. Yields and enantioselectivities were determined by GC-analysis with an Agilent 6890, CP-Chirasil-DEX-CB, 140 °C initial temperature, 200 °C final temperature, 15 °C/min. 0.1 mL hexadecane was used as internal standard.

4.1. Racemization experiments

In a Schlenk tube 15 mg (0.025 mmol) of di-μ-chlorobis((*p*-cymene)chlororuthenium(II)) are suspended in 2.5 mL toluene and supplemented with 0.25 mmol of diamine ligand. After 10 min 0.8 mmol of enantiopure alcohol is added and stirred at 80 °C for 5 h. Yields and enantioselectivities are determined by GC analysis.

4.2. Dynamic kinetic resolution

Fifteen milligrams (0.025 mmol) of di-μ-chlorobis((*p*-cymene)chlororuthenium(II)) is suspended in 2.5 mL toluene and supplemented with 0.25 mmol of *N*,*N*,*N*′,*N*′-tetramethyl-1,3-propanediamine. After 10 min 0.8 mmol of racemic secondary alcohol is added, if necessary 0.4 mmol of the corresponding ketone, 1.8 mmol *p*-chlorophenyl acetate and 60 mg of Chirazyme® l-2, c-f, lyo. The reaction mixture is stirred for 45 h at 80 °C. Yields and enantioselectivities are determined by GC analysis.

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