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Homogeneous and heterogeneous ruthenium catalysts in the synthesis of fine chemicals

Wolfgang Mägerlein [a,*], Claus Dreisbach [a], Herbert Hugl [a], Man Kin Tse [b], Markus Klawonn [b], Santhosh Bhor [b], Matthias Beller [b]

[a] *Saltigo GmbH, D-51369 Leverkusen, Germany*
[b] *Leibniz-Institut für Katalyse e.V., Albert-Einstein-Str. 29a, D-18059 Rostock, Germany*

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Abstract

Two examples of the application of ruthenium catalysts in fine chemical synthesis are given in this paper. In the first part, protocols for both asymmetric and non-asymmetric epoxidation reactions of olefins employing hydrogen peroxide as a ''green'' re-oxidant are described. Ruthenium pyridine-2,6-dicarboxylate complexes containing tridentate *N*-donor ligands are used as homogeneous catalysts. In the second part, a method for the stereoretentive hydrogenation of α-amino acids with water as a solvent is presented. The use of heterogeneous ruthenium catalysts, modified with rhenium, permits the efficient synthesis of the respective amino alcohols with high enantiomeric excess.

Keywords: Ruthenium catalysts; Epoxidation; Hydrogen peroxide; Chiral ligands; Hydrogenation; Amino alcohols

1. Introduction

Ruthenium compounds constitute a versatile class of catalysts for important synthetic transformations in organic chemistry [1]. Several aspects make ruthenium interesting as a catalyst metal. First, its ability to access 11 different oxidation states, ranging from –II (d^{10}) up to +VIII (d^0) is (besides osmium) a unique feature within the periodic table. Furthermore, ruthenium can accommodate a large variety of ligands (e.g. carbonyl, phosphines, cyclopentadienyl, arenes, carbenes) in various coordination geometries which gives rise to numerous different metal complexes. Finally – especially interesting from an industrial point of view – ruthenium is much less expensive compared to other platinum metals:

Ru 4.79 €/g
Pd 9.79 €/g
Pt 29.78 €/g
Rh 121.89 €/g

(all numbers refer to the unfabricated metal; data from 2006-04-10 [2])

Throughout the last three decades important synthetic methods employing ruthenium catalysts have been developed. The scope of these reactions comprises (transfer) hydrogenations, olefin metathesis reactions, oxygenations and dehydrogenations, Lewis-acid-catalyzed reactions, C–C bond forming reactions, C–H bond activations, reactions with CO or CO_2 and many more [1].

Here, we present two examples of ruthenium-catalyzed reactions relevant for the synthesis of fine chemicals. In the context of ''green'' chemistry and for technical purposes it is an important goal to develop environmentally benign catalytic processes permitting the use of clean and cost efficient reagents and solvents. The first example, which originates from a joint collaboration between the Leibniz-Institut für Katalyse e.V. and Saltigo GmbH (the former Business Unit Fine Chemicals of LANXESS), deals with the homogeneously ruthenium-catalyzed epoxidation of olefins using H_2O_2 as oxidant. The development of efficient asymmetric and non-asymmetric protocols using biomimetic Ru complexes is presented.

The second example covers a method for the stereoretentive hydrogenation of α-amino acids using heterogeneous Ru/Re catalysts with water as a ''green'' solvent. This process has been developed at Saltigo.

* Corresponding author. Tel.: +49 214 3052285; fax: +49 214 3095952285.
E-mail address: wolfgang.maegerlein@saltigo.com (W. Mägerlein).

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2. Homogeneous Ruthenium-catalyzed epoxidation of olefins

Oxidation reactions constitute core technologies for the synthesis of chemical intermediates in the production of both high-tonnage commodities [3] and high-value fine chemicals, such as agrochemical and pharmaceutical precursors. One of the most important oxidative processes is the selective conversion of olefins into the respective epoxides since those compounds serve as valuable intermediates for further transformations, e.g. towards diols or amino alcohols. Traditionally, epoxides can be synthesized by reaction of olefins with peracids. A drawback of this method is the limited use for acid-labile olefins and epoxides and the generation of stoichiometric amounts of waste (salts). Therefore, in order to achieve higher atom efficiency and selectivity control, transition metal-catalyzed epoxidations have been developed. By using optically active catalysts, asymmetric reactions of olefins to yield chiral epoxides have become possible [4].

The efficiency and applicability of a catalytic epoxidation process is fundamentally influenced by the kind of the re-oxidizing agent which is characterized by its cost, availability, toxicity and side-production of waste [5]. Obviously, molecular oxygen is the ideal oxidant in this respect. However, the direct olefin epoxidation with O_2 has only been applied to the epoxidation of ethylene and 1,3-butadiene (leading to oxirane and 3,4-epoxy-1-butene, respectively) in the presence of Ag catalysts on a commercial scale so far [6]. Higher olefins like propylene containing allylic C–H bonds don't react selectively enough. Improvements along this line have been made with Au/C catalysts on a laboratory scale [7]. Apart from molecular oxygen, hydrogen peroxide, H_2O_2, is an environmentally benign oxidant. It can reach up to 47% atom efficiency in epoxidation reactions and generates only water as a byproduct [8]. Due to its availability (million metric ton-scale) and low price (ca. 1.0 $/kg of 100% H_2O_2) [9] H_2O_2 is attractive for epoxidations on large scale [10], as demonstrated by the propylene oxide processes employing titanium(IV)-silicalite (TS-1) catalysts [11]. A general method to epoxidize alkenes under mild, pH-neutral conditions is provided by the well-known methyltrioxorhenium (MTO) catalyst system [12]. With regard to the synthesis of fine chemicals, H_2O_2 can be conveniently used in liquid-phase oxidations in stirred vessels. When using H_2O_2 it has to be considered that the reaction takes place in the presence of water, either in two-phase systems or in polar solvents. Such systems suffer from the inherent disadvantage that polar molecules, particularly water and alcohols, may retard catalytic oxidations by competing with the substrate (and/or oxidant) for coordination sites on the metal.

The objective of our joint research project was to develop catalytic epoxidation methods with H_2O_2 as oxidant permitting an efficient conversion of a wide range of olefins with high selectivity and productivity. Furthermore, an extension towards catalyst systems for enantioselective epoxidation reactions was a focus of our work.

Regarding the epoxidation catalyst metal we chose ruthenium. The potential of ruthenium as epoxidation catalyst arises from its extensive redox chemistry and its propensity to form high-valent oxo complexes. Due to the capability of ruthenium to form complexes with a variety of organic ligands, it is possible to modulate the reactivity of these oxometal intermediates and thus enhance the epoxide selectivity of the catalytic reaction. Chiral modification of these ruthenium complexes should give the opportunity to develop enantioselective catalytic epoxidation protocols.

3. Results and discussion [13]

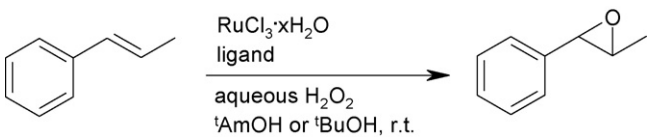
At the outset of our research we focused on non-asymmetric epoxidations. As a model system to evaluate the influence of critical reaction parameters, especially the type of ligand, on the catalyst productivity we chose the reaction of (*E*)-β-methylstyrene with aqueous H_2O_2 in the presence of $RuCl_3$ (Scheme 1).

From literature it is known that olefins like (*E*)-stilbene, cyclohexene or octadec-9-enoic acid can be epoxidized with high selectivity by using $RuCl_3$ together with electron-donating ligands, such as 2,2′-bipyridine, phenanthrolines or triphenylphosphine in the presence of various oxidants [14,15]. With these ligands, alkene cleavage can be minimized. When H_2O_2 was employed, the reaction was plagued by the competing non-productive decomposition of H_2O_2 (ruthenium is an excellent catalyst for the cleavage of H_2O_2 into O_2 and H_2O [16]) and a 100-fold excess of H_2O_2 had to be used [14].

In order to circumvent this problem in our investigations, we added a stoichiometric amount of the oxidant continuously within 12 h by using a syringe pump.

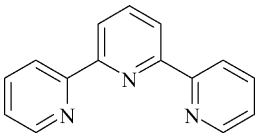
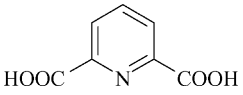
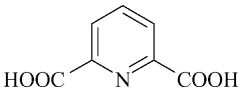
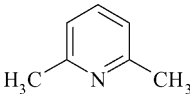
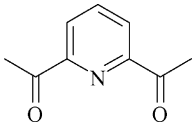
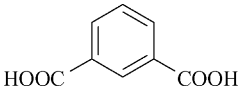
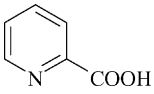
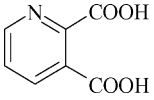
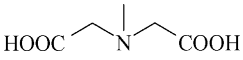
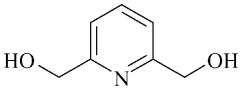
Our first study aimed at examining the performance of pyridine-type *N*-donor ligands [17]. In general, the reactions were run at room temperature in the presence of 1 mol% $RuCl_3{\cdot}xH_2O$ and 10 mol% of the respective ligand with tertiary alcohols, such as *t*-amyl alcohol or *t*-butyl alcohol, as solvents.

As shown in Table 1 (entry 1), $RuCl_3{\cdot}xH_2O$ alone gave only unspecific decomposition of H_2O_2 and (*E*)-β-methylstyrene. In the presence of unmodified pyridine or terpyridine (tpy) (Table 1, entries 2, 3), essentially no olefin conversion was observed. However, if pyridine-2,6-dicarboxylic acid (H_2-pydic) was employed as ligand, a remarkable increase in catalyst activity and selectivity led to a nearly quantitative yield of the desired epoxide (Table 1, entry 4). Using H_2-pydic without the metal or using pyridine and acetic acid as mimic of H_2-pydic (Table 1, entries 5, 6), no reaction occurred at all. If the carboxylic groups in H_2-pydic were replaced with methyl or acetyl groups or if the pyridine ring was replaced, the epoxide yield dropped to 0% (Table 1, entries 7–9). Interestingly, even in the presence of pyridine-2-carboxylic acid no epoxide formation was observed (Table 1, entry 10), demonstrating the



Scheme 1. Epoxidation of (*E*)-β-methylstyrene with aqueous H_2O_2 in the presence of $RuCl_3$.

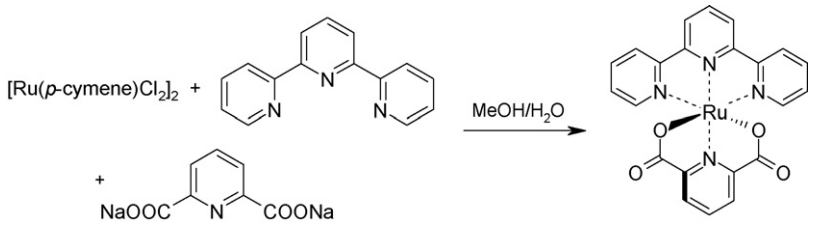
Table 1
Epoxidation of (*E*)-β-methylstyrene with H_2O_2 in the presence of different catalysts[a]

Entry	Ligand	Conversion (%)	Selectivity (%)
1	None	34	0
2[b]		0	0
3		3	0
4		100	99
5	 Without $RuCl_3$	0	0
6[b]	Pyridine/acetic acid	0	0
7		20	0
8		26	0
9		29	0
10		5	0
11		30	83
12		56	82
13		100	96

[a] General conditions: 0.5 mmol (*E*)-β-methylstyrene, 1 mol% $RuCl_3 \cdot xH_2O$ in 9 ml *t*-AmOH, 10 mol% ligand, 12 h addition of 3.0 equiv. 30% H_2O_2 in 1 ml *t*-AmOH, room temperature.
[b] 1 equiv. of ligand.

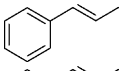
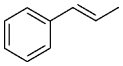
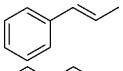
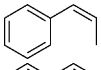
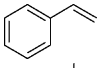
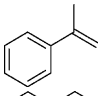
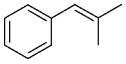
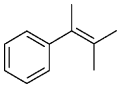
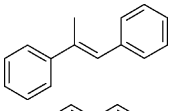
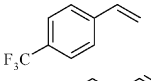
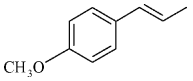
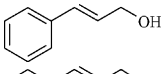
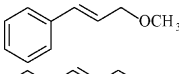
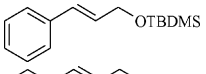
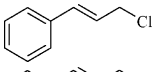
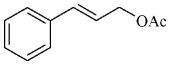
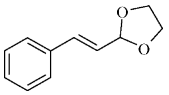
importance of a tridentate coordination around the metal center. High epoxide selectivity, however at low conversions, were obtained with pyridine-2,3-dicarboxylic acid and an aliphatic analogue of H_2-pydic (Table 1, entries 11, 12). 2,6-Bis(hydroxymethyl)pyridine gave almost the same yield as H_2-pydic (Table 1, entry 13), because it is likely to be oxidized to H_2-pydic under the reaction conditions. In case of successful transformations we observed a color change from initially light brown through dark brown upon addition of oxidant to finally violet near or after finishing the reaction.

The $RuCl_3/H_2$-pydic/H_2O_2 catalyst system has proven to efficiently epoxidize a variety of aliphatic acyclic and cyclic



Scheme 2. Development of an improved ruthenium catalyst ([Ru(tpy)(pydic)]).

Table 2
Epoxidation of various alkenes with H_2O_2 in the presence of [Ru(tpy)(pydic)][a]

Entry	Alkene	Catalyst loading (mol%)	Conversion (%)	Selectivity (%)
1		1	100	96
2		0.1	100	95
3		0.01[b]	93	95
4		0.5	100	99
5		0.5	100	71
6		0.5	100	88
7		0.5	100	99
8		0.5	100	96
9		0.5	100	95
10		0.5	90	99
11		0.5	100	99
12		0.5	100	97
13		0.5	100	96
14		0.5	100	99
15		0.5	100	94
16		0.5	100	98
17		0.5	100	62
18		0.5	100	84

[a] General conditions: 0.5 mmol alkene, [Ru(tpy)(pydic)] in 9 ml *t*-AmOH, 12 h addition of 3.0 equiv. 30% H_2O_2 in *t*-AmOH, room temperature.
[b] At the outset, 0.1 mol% tpy and 0.1 mol% H_2-pydic were added.

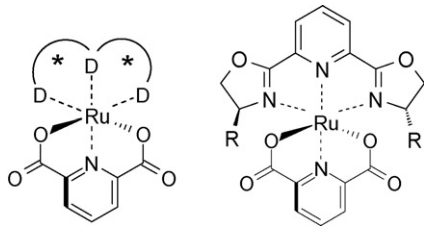


Fig. 1. Variation of terpyridine ligand.

olefins as well as styrene derivatives with catalyst productivities up to 10.000 [17]. The drawbacks of this procedure are the relatively high amount of H_2-pydic ligand (10 mol%) and limitations in the substrate scope due to the acidic reaction conditions. Thus, olefins bearing acid-sensitive functional groups might lead to lower selectivity of the desired epoxides. In the case of reactive styrene oxides, the oxirane ring is prone to ring-opening reactions under these conditions.

Therefore, we developed an improved ruthenium catalyst by replacing the chloro ligands in a Ru(II) precursor with the dianion of pyridine-2,6-dicarboxylic acid and adding terpyridine to yield [Ru(tpy)(pydic)] (Scheme 2).

This biomimetic complex with its dual meridional ligand system was first introduced by Nishiyama et al. and applied for alkene epoxidation [18]. However, in the original protocol with dichloromethane as solvent, oxidants like *t*-BuOOH and high-valent iodine compounds were used and high catalyst loadings and low activity were reported.

By using our oxidation reaction conditions with *t*-amyl alcohol as the solvent and 30% aqueous H_2O_2 as the oxidant, we were able to dramatically lower the catalyst/substrate ratio and run epoxidations within 12 h at room temperature [19]. Thus, with (*E*)-β-methylstyrene as a model substrate, the epoxide yield was 88% at a ruthenium/olefin ratio of 1:10.000, corresponding to a TON of 8.800 (Table 2, entry 3).

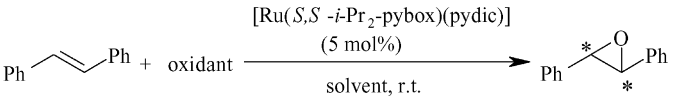
A wide variety of other alkenes can be epoxidized with this catalyst system in good to excellent yields. All substitution patterns of aromatic olefins, such as monosubstituted, 1,1-disubstituted, 1,2-*E*/*Z*-substituted, 1,1,2-trisubstituted and finally tetrasubstituted alkenes gave the corresponding epoxides in high yields (Table 2, entries 1–9). The examples with ring-substituted styrenes (Table 2, entries 10, 11) indicate that electron rich olefins display a higher reactivity compared to an electron poor olefins, underlining the fact that the reaction mechanism is electrophilic. The compatibility of this epoxidation protocol with functional groups, such as –OH, –OR, –OTBDMS, halogen and acetal is noteworthy (Table 2, entries 12–17). Aliphatic olefins like 1-methylcyclohexene also react under these conditions (Table 2, entry 18), although the $RuCl_3$/H_2-pydic-catalyst system is generally preferred for this class of substrates.

Due to the excellent performance of [Ru(tpy)(pydic)] in racemic epoxidations we started to explore an enantioselective procedure by variation of the terpyridine ligand. As depicted in Fig. 1 (left), the replacement of tpy with chiral tridentate donor ligands should give access to a variety of optically active Ru complexes.

Previous to our work, ruthenium catalyst systems for the asymmetric olefin epoxidation have been described, but they are not sufficient in terms of catalyst activity, selectivity, substrate scope and oxidant [18,20]. Up to now, transition metal complexes based on titanium (Sharpless epoxidation) and manganese (Jacobsen–Katsuki epoxidation) have been used most successfully as catalysts [4]. However, in spite of extensive research efforts, the development of a general and catalytic asymmetric epoxidation method using hydrogen peroxide has not been achieved so far [21].

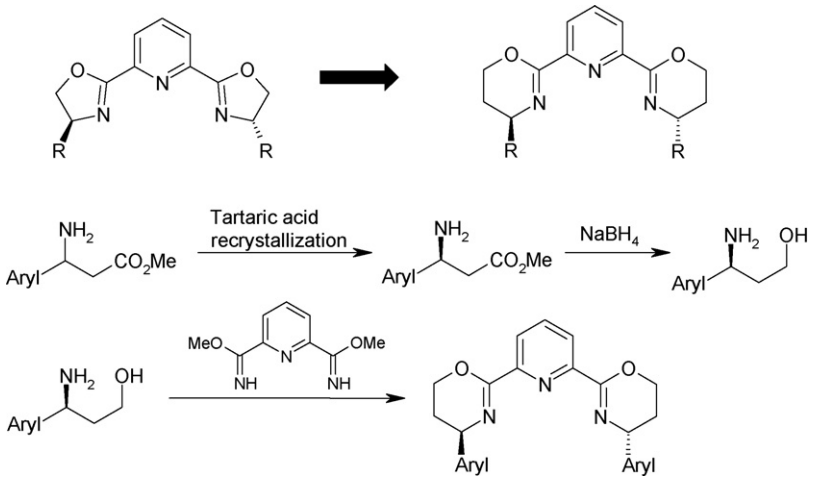
At the outset of our investigation, we employed Nishiyama's Ru-pyridine-2,6-dicarboxylate complex which is modified with the bis(4,5-dihydro-1,3-oxazol-2-yl)-substituted pyridine ligand (*S*,*S*-*i*-Pr_2-pybox in the case of R = *i*-propyl) as a model catalyst (Fig. 1, right) [18]. Advantageously, pybox ligands are readily accessible from chiral amino alcohols and can be easily modified in terms of substitution pattern and structure.

Table 3
Effect of solvent, water and oxidant on the Ru-catalyzed asymmetric epoxidation of (*E*)-stilbene[a]



Entry	Solvent	Oxidant	Equiv. of oxidant (related to olefin)	Time (h)	Conv. (%)	Selec. (%)	*ee* (%)[b]
1	Toluene	$PhI(OAc)_2$	3	96	97	82	63
2	Toluene/H_2O	$PhI(OAc)_2$	3	6	82	77	29
3	Toluene/H_2O	$PhI(OAc)_2$	6	4	100	75	46
4	*t*-BuOH/toluene/H_2O	$PhI(OAc)_2$	6	1	100	84	57
5	*t*-BuOH/toluene/H_2O	NaOCl	1.1	1	10	0	0
6	*t*-BuOH/toluene/H_2O	*t*-BuOOH	1.1	18	30	90	28
7	*t*-BuOH/toluene/H_2O	*t*-BuOOH	6	66	98	99	21
8	*t*-BuOH/toluene/H_2O	H_2O_2	3	18	28	89	64
9	*t*-BuOH/toluene/H_2O	H_2O_2	6	6	45	100	48
10	*t*-Amyl alcohol/toluene/H_2O	H_2O_2	3	16	58	98	57
11	*t*-Amyl alcohol/H_2O	H_2O_2	3	12	100	100	54

[a] General conditions: 0.025 mmol catalyst and 0.5 mmol (*E*)-stilbene in 9 ml of the appropriate solvent, addition of oxidant. Monitoring of the reaction by GC-FID.
[b] The major enantiomer of (*E*)-stilbene oxide had (1*S*,2*S*) configuration.



Scheme 3. Pyboxazine ligand family and its facile synthesis starting from β-amino acids.

With this Ru catalyst moderate epoxide yields and *ee* values were reported for the conversion of (*E*)-stilbene, however the reaction system in toluene had several drawbacks, such as low catalyst activity (96 h reaction time) and the use of expensive hypervalent iodine reagents as stoichiometric oxidants (Table 3, entry 1) [18].

In our first attempts to increase the reaction rate of the system we tested the influence of the solvent [22]. Surprisingly, it turned out that upon addition of defined amounts of water, the conversion was completed within 6 h, albeit with loss of enantioselectivity (Table 3, entries 2, 3). The *ee* could be increased to 57% if *t*-BuOH was added (Table 3, entry 4). The use of alternative oxidants like sodium hypochlorite or TBHP either led to a pronounced decrease in catalyst activity or low *ee* values (Table 3, entries 5–7). To our delight, we found that H_2O_2 permitted very good epoxidation reaction rates with yields up to 100% and an *ee* of 54% (Table 3, entries 8–11).

In order to further elaborate this catalyst system we focused our attention on the H_2O_2-catalyzed epoxidation of styrene which is amongst the more challenging asymmetric epoxidation reactions both with regard to chemo- and enantioselectivity [23]. To this end, we tested the influence of various substituted pybox-type ligands. Furthermore, we introduced a new class of chiral tridentate *N*-donor ligands by enlargement of the oxazoline ring in pybox to a six-membered 5,6-dihydro-4*H*-1,3-oxazine moiety. The resulting pyboxazine ligand family is depicted in Scheme 3 along with a facile synthesis starting from β-amino acids. The latter compounds are accessible e.g. by homologization of α-amino acids *via* the well-known Arndt–Eistert protocol.

The metal complexes [Ru{(*S*,*S*)-R_2pyboxazine}(pydic)] can be easily synthesized according to [Ru(tpy)(pydic)] (cf. Scheme 2) starting from [{Ru(*p*-cymol)Cl_2}$_2$].

The results we obtained in the enantioselective epoxidation of styrene with H_2O_2 in the presence of Ru-pybox and Ru-pyboxazine catalysts are disclosed in Table 4 [23].

All the Ru complexes catalyzed the reaction in good to excellent chemical yield. It turned out that by replacing the *i*-propyl- with a phenyl-substituent on the oxazoline ring, the *ee* went up from 19 to 31% and the catalyst productivity increased (Table 4, entries 1, 2). Considering this result, π–π interactions between the ligand and the substrate are conceivable. When the phenyl group was moved from the 4- to the 5-position the enantioselectivity dropped significantly (Table 4, entries 2 and 3) indicating that the stereoinformation should be close to the metal center. Moreover, the flexibility of the aryl substituent seems to be essential (Table 4, entries 2 and 4) for the enantioselectivity. A direct comparison of the 4-phenyl-pybox ligand with our newly developed 4-phenyl- or 4-naphthyl-substituted pyboxazine ligands revealed that the latter led to an increase of the enantioselectivity up to 48% (Table 4, entries 2 and 5–7).

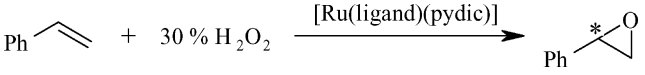
Using the β-naphthyl-substituted pyboxazine as the best ligand, different aromatic olefins were epoxidized in the presence of H_2O_2 (Table 5) [23].

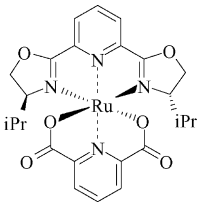
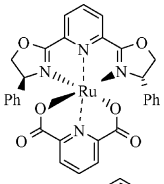
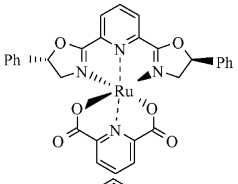
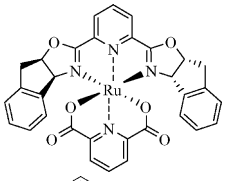
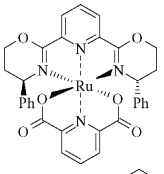
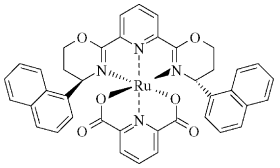
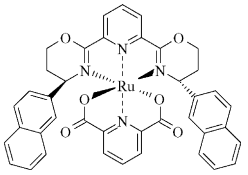
In the case of styrene, it was found that the epoxide yield increased to 85% and the *ee* value increased to 59% (Table 5, entries 1, 2) when 20 mol% of acetic acid (HOAc) was added as a co-catalyst. Mechanistic studies indicated that HOAc accelerates the reaction, possibly by stabilizing the active intermediates against self-degradation. With ring-substituted styrene derivatives *ee* values up to 64% were observed (Table 5, entries 3–7). This catalytic system has also been applied successfully to mono-, di- and trisubstituted aromatic olefins (Table 5, entries 8–12). The best results are obtained with (*E*)-disubstituted and trisubstituted olefins. Hence, our new procedure complements the known manganese-catalyzed asymmetric epoxidation protocols. The highest *ee* value (84%) was obtained with 2-methyl-1-phenylpropene at 0 °C (Table 5, entry 12).

4. Conclusion

In summary, general protocols for the ruthenium-catalyzed epoxidation of olefins with H_2O_2 as the oxidant have been developed. Thus, by using $RuCl_3$ as a simple ruthenium salt and pyridine-2,6-dicarboxylic acid as a ligand, a variety of aliphatic and aromatic olefins with different substitution patterns were

Table 4
Effect of ligands on the Ru-catalyzed asymmetric epoxidation of styrene using H_2O_2[a]



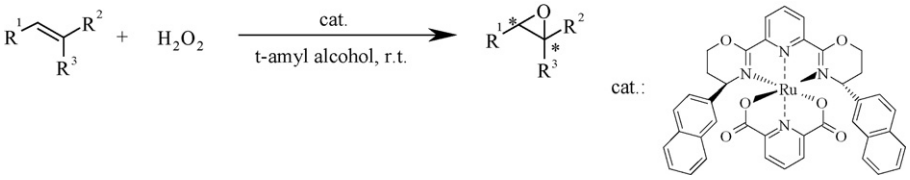
Entry	Ligand	Time (h)	Conv. (%)	Selec. (%)	*ee* (%)
1		20	72	63	19[b]
2		12	99	70	31[b]
3		12	100	66	3[c]
4		20	91	65	18[b]
5		12	81	69	48[b]
6		12	100	65	38[b]
7		12	82	72	48[b]

[a] General conditions: 0.025 mmol catalyst and 0.5 mmol styrene in 9 ml *t*-AmOH, 12 h addition of 3.0 equiv. 30 % H_2O_2 in 830 μl *t*-AmOH, room temperature.
[b] (*R*)-(+)-styrene oxide was the major enantiomer.
[c] (*S*)-(−)-styrene oxide was the major enantiomer.

converted to the respective racemic epoxides in good to excellent yields at room temperature. Modification of the Ru-pydic-catalyst with a terpyridine ligand allowed us to run the epoxidation under pH-neutral conditions thus extending the substrate scope to acid-labile olefins and epoxides. With both systems catalyst turnover numbers of up to 10.000 were achieved.

By replacing the terpyridine ligand with chiral tridentate *N*-donor ligands, such as pybox and pyboxazine, a general ruthenium-catalyzed asymmetric H_2O_2-epoxidation protocol was developed. The combination of both the pydic and the pybox/pyboxazine ligands in the biomimetic catalyst plays a crucial role to provide reactivity and enantioselectivity. With the new pyboxazine ligand class *ee* values of up to 84% were

Table 5
Asymmetric epoxidation of aromatic olefins with H_2O_2 in the presence of a [Ru(pyboxazine)(pydic)]-catalyst[a]



Entry	Substrate			Time (h)	Conv. (%)	Selec. (%)	*ee* (%)
	R_1	R_2	R_3				
1	Ph	H	H	12	82	72	48[b]
2	Ph	H	H	12	100	85	59[b,c]
3	*p*-F-C_6H_4	H	H	12	100	82	60[c]
4	*p*-CF_3-C_6H_4	H	H	12	65	88	55[c]
5	*p*-CH_3-C_6H_4	H	H	12	100	80	58[c]
6	*o*-CH_3-C_6H_4	H	H	12	100	>99	64[c]
7	*o*-Cl-C_6H_4	H	H	12	86	91	58[c]
8	Ph	Ph	H	12	100	100	54[d]
9	Ph	CH_3	H	12	100	95	72[e]
10	*p*-CH_3O-C_6H_4	CH_3	H	12	100	>99	53
11	Ph	1,1-Cyclohexyl		12	100	>99	79
12	Ph	CH_3	CH_3	26	94	97	84[c,f]

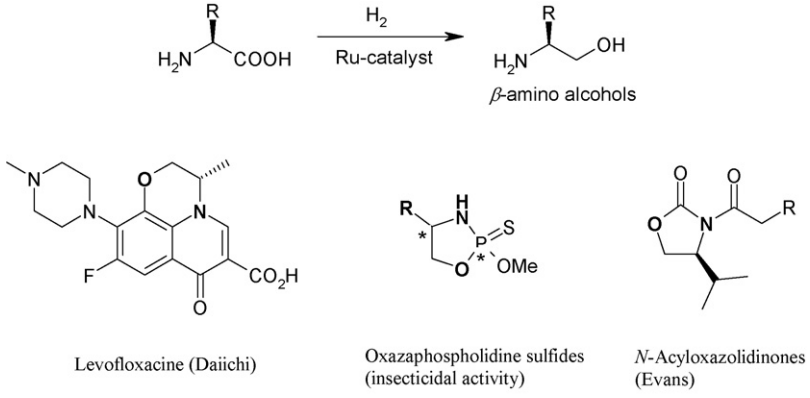
[a] General conditions: 0.025 mmol catalyst and 0.5 mmol olefin in 9 ml *t*-AmOH, 12 h addition of 3.0 equiv. 30% H_2O_2 in 830 μl *t*-AmOH, room temperature.
[b] (*R*)-(+)-styrene oxide was the major enantiomer.
[c] 20 mol% of HOAc was added.
[d] (*S*,*S*)-(−)-stilbene oxide was the major enantiomer.
[e] (*R*,*R*)-(+)-1-Phenylpropylene oxide was the major enantionmer.
[f] 12 h addition of 1.5 equiv. 50% H_2O_2 in 949 μl *t*-AmOH, 0 °C.

obtained. It is expected that these ligands will complement the catalytic behavior of the well-known pybox derivatives [24]. The use of two different ligands significantly simplifies structural variations on the catalyst thus allowing easy tuning of the catalyst properties and further improvement of the enantioselectivity.

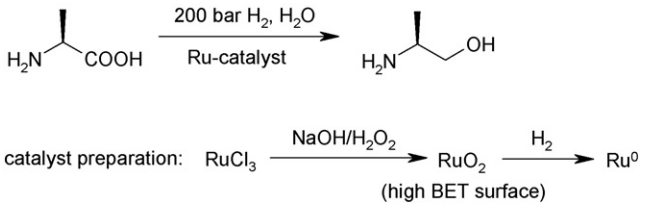
5. Heterogeneous ruthenium-catalyzed hydrogenation of α-amino acids

As a second example for the application of ruthenium catalysts in fine chemicals synthesis a method for the stereoretentive hydrogenation of α-amino acids to amino alcohols is presented. Ruthenium complexes are extensively used in hydrogenation reactions. The most prominent areas in this field are homogeneously catalyzed asymmetric hydrogenations of C=C and C=O double bonds, e.g. with Ru-BINAP complexes [1]. However, also heterogeneous supported Ru catalysts constitute valuable tools for hydrogenation processes in the fine chemicals industry. Noteworthy in this respect are Ru-catalyzed ring saturation reactions of arenes and heteroarenes and the conversion of carboxylic acids to primary alcohols [25].

In our research project we were interested in the application of heterogeneous Ru catalysts for the hydrogenation of a special class of carboxylic acids, i.e. α-amino acids. The direct hydrogenation of these substrates would provide a straightforward entry to synthetically useful enantiopure vicinal amino alcohols from the chiral pool (Scheme 4).



Scheme 4. Hydrogenation of α-amino acids to β-amino alcohols: a straight-forward entry to synthetically useful enantiopure vicinal amino alcohols from the chiral pool.



Scheme 5. Hydrogenation of L-alanine over Ru black and simple representation of catalyst preparation.

The benefits of this method in the context of "green chemistry" are its high atom efficiency and the fact that only water is produced as a byproduct. Advantageously, hazardous and expensive stoichiometric reagents like $LiAlH_4$ or $NaBH_4$/acid which are difficult to handle on larger scale can be avoided. From a technical point of view, it is worth mentioning that this hydrogenation method is basically amenable to continuous processing.

The resulting chiral amino alcohols are important building blocks in the synthesis of active pharmaceutical [26] or agrochemical ingredients [27] (Scheme 4). Furthermore, they are frequently used in important chiral auxiliaries [28] and chiral ligands in organic synthesis (see first part of this paper).

A closer look at the Ru-catalyzed hydrogenation method we were aiming at revealed certain challenges we had to deal with: In order to achieve technically interesting space-time-yields, the hydrogenation reaction has to run at a reasonable rate. However, Ru catalysts usually display sufficient reactivity only at higher reaction temperatures which could lead at least to a partial racemisation.

Therefore, the objective of this work was to develop a catalyst system permitting an efficient hydrogenation of amino acids with high yields and without any racemisation ($ee \geq 99.5\%$).

6. Results and discussion [29]

In our first studies we used L-alanine as a model substrate and tested ruthenium black as a simple "first-generation"-catalyst. The catalyst was prepared by hydrogen reduction of Ru(IV)-oxide-hydrate (BET surface ca. 210 m^2/g) which was obtained from $RuCl_3$ by precipitation/oxidation (Scheme 5) [30].

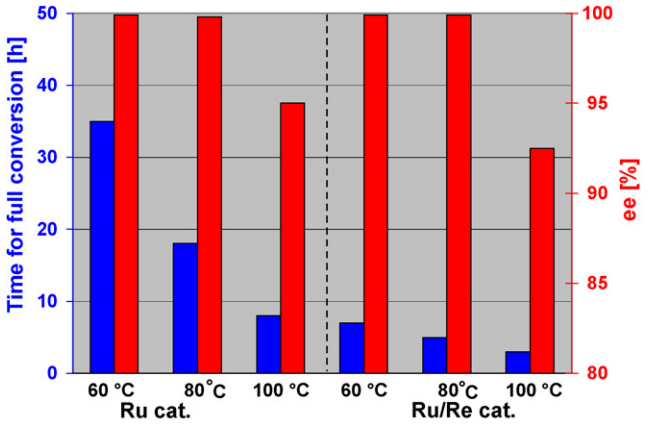


Fig. 2. Hydrogenation of L-alanine over Ru/Re catalyst (comparison with monometallic Ru catalyst).

However, under various reaction conditions we tested, the catalyst activity was low and partial racemisation was observed. A certain improvement was achieved by the addition of a mineral acid to the reaction mixture in order to protonate the amino acid zwitterion at the carboxylate group [31]. This led to an increase of the reaction rate and the *ee* values, but the efficiency of the catalyst system was still not satisfactory. Consequently, the catalyst had to be modified. A breakthrough was achieved by changing the monometallic Ru catalyst to a bimetallic Ru/Re system. The bimetallic Ru/Re catalyst is prepared by adding high-surface RuO_2-hydrate to Re(VII)-oxide in water and reducing the mixture at 120 °C with hydrogen [32]. The resulting Ru/Re catalyst is characterized by a high BET surface and by close contact of the Ru and Re particles.

The Ru/Re catalyst was employed in the hydrogenation of L-alanine and compared with the monometallic Ru catalyst in terms of enantioselectivity and catalyst activity (measured as the time required for full conversion) (Fig. 2).

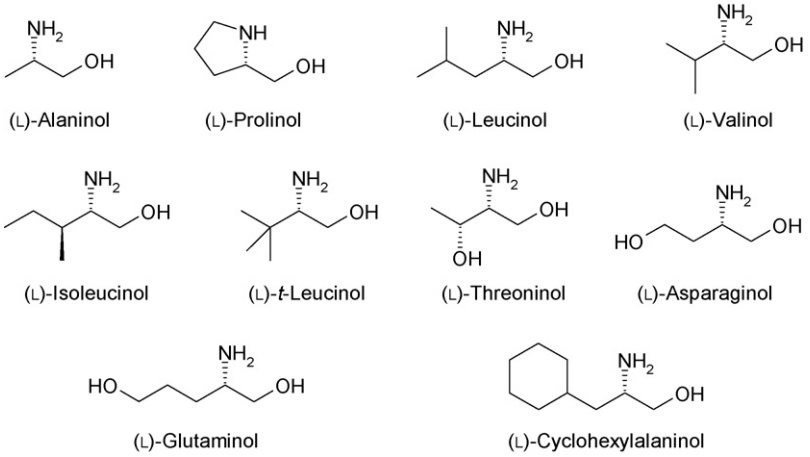
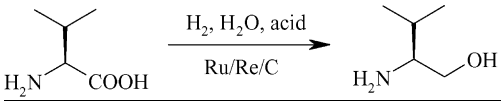


Fig. 3. Enantiopure amino alcohols obtained in good to excellent yields over Ru/Re catalyst.

Table 6
Hydrogenation of (L)-valine with a Ru/Re/C catalyst: temperature-dependency of the ee value



Entry	Hydrogenation temperature (°C)	*ee* (%)
1	150	89.4
2	120	97.7
3	100	99.0
4	80	99.7

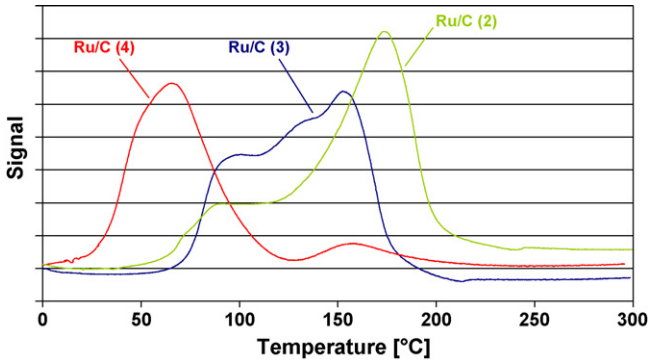


Fig. 4. TPR profiles of Ru/C (2), Ru/C (3) and Ru/C (4).

With the Ru catalyst a reasonable reaction time below 10 h could only be obtained at 100 °C. However, at this temperature the *ee* value of the reaction product, (L)-alaninol, dropped to 95%. In contrast, the Ru/Re system showed a much higher catalyst activity and enabled a rapid, technically interesting conversion even at 60 or 80 °C. At these temperatures no racemisation was observed.

A series of enantiopure amino alcohols were obtained in generally good to excellent yields in that way (Fig. 3).

It is worth mentioning that hydrogenation of aromatic amino acids with the Ru/Re catalyst yielded the corresponding cycloaliphatic amino alcohols, e.g. (L)-cyclohexylalaninol.

With regard to the scale-up of this catalytic hydrogenation protocol, the Ru/Re sponge catalyst has disadvantages concerning handling properties. Thus, the filtration behavior is not satisfactory for technical demands and the spent catalyst loses activity. Besides, there are safety issues to consider with larger amounts of reduced ruthenium metal. Therefore, we focused our attention on supported Ru/Re catalysts which should circumvent these disadvantages. Additionally, by fixing the metals on a support, a higher degree of utilization of the metals should be achieved, since it is conceivable that in the metal sponge only the surface atoms are catalytically active whereas the bulk metal atoms remain unused. In addition, supported catalysts offer more possibilities for fine tuning, e.g. by varying the metal dispersion and the support properties. As a support we preferred charcoal in order to avoid abrasion problems when using the catalyst in a production plant.

The Ru/Re/C catalysts were prepared by impregnation of commercial Ru/C catalysts with aqueous Re_2O_7 and subsequent hydrogen reduction. As an example, we studied the hydrogenation of (L)-valine (Table 6) and evaluated the racemisation behavior at different temperatures. In analogy to (L)-alanine it turned out that 80 °C is the upper temperature limit for a racemisation-free hydrogenation.

In the case of (L)-valine we observed a considerably lower catalyst activity as compared to less sterically hindered substrates like (L)-alanine. Therefore, we examined the correlation of certain catalyst properties with its activity in order to enable higher reaction rates also for amino acids like (L)-valine. As can be seen in Table 7 (entries 1, 2), a catalyst which contains only 20 wt.% Re (related to Ru) displays a significantly lower acitivity than a catalyst based on the same Ru/C precursor but with a five times higher Re loading.

Not unexpectedly, the type of Ru/C has a great influence on the catalyst performance, too. Thus, using different Ru/C precursors, hydrogenation times from 23 up to 64 h were observed, with the Ru/Re sponge catalyst ranging in the medium region (Table 7, entries 2–6). Comparable trends concerning Re content and type of Ru/C were obtained with (L)-proline (Table 7, entries 7–11). In this case, Ru/C (4) with a Re:Ru ratio of 1:1 (wt.) led to the catalyst with the highest activity, the hydrogenation being finished within 13 h (Table 7, entry 9). In order to gain deeper insight into the structure-activity relationship of the catalyst, we determined certain characteristics of the Ru/C precursors. As an example, the TPR profiles (1 K/min; 7.5% H_2 in Ar) of Ru/C (2), Ru/C (3) and Ru/C (4) are depicted in Fig. 4.

Table 7
Hydrogenation of (L)-valine and (L)-proline in the presence of different Ru/Re/C catalysts at 80 °C

Entry	Amino acid	Catalyst	Ratio Re:Ru (wt.)	Hydrogenation time (h)	*ee* (%)
1	(L)-Valine	Ru/C (1)/Re_2O_7	0.2	41	99.7
2	(L)-Valine	Ru/C (1)/Re_2O_7	1	29	99.7
3	(L)-Valine	Ru/C (2)/Re_2O_7	1	64	99.8
4	(L)-Valine	Ru/C (3)/Re_2O_7	1	23	99.7
5	(L)-Valine	Ru/C (4)/Re_2O_7	1	24	99.6
6	(L)-Valine	Ru/Re sponge	1	38	99.2
7	(L)-Proline	Ru/C (2)/Re_2O_7	1	32	99.5
8	(L)-Proline	Ru/C (3)/Re_2O_7	1	26	99.7
9	(L)-Proline	Ru/C (4)/Re_2O_7	1	13	99.5
10	(L)-Proline	Ru/C (4)/Re_2O_7	0.2	22	99.5
11	(L)-Proline	Ru/C (4)/Re_2O_7	0	42	99.3

The patterns reveal that all three precursors contain different oxidic Ru species. The temperature peak of Ru/C (4), leading to the most active catalyst in the (L)-proline hydrogenation, occurs at the lowest temperature (30–100 °C), whereas most of the Ru of the least active catalyst precursor, Ru/C (2), is only reduced above 130 °C. These TPR findings point to a higher Ru dispersion (i.e. smaller Ru particle size) for the most active Ru/C (4) precursor, which was further supported by CO chemisorption measurements.

7. Conclusion

In summary, a procedure for the stereoretentive direct hydrogenation of amino acids to the respective chiral vicinal amino alcohols has been developed. The protocol is characterized by using highly active heterogeneous bimetallic Ru/Re sponge catalysts which allow to run the process at relatively low temperatures. These conditions are crucial in order to prevent any racemisation. The catalyst system was improved from a practical point of view by supporting the metals on charcoal. In the context of "green chemistry", the atom efficiency of this process is worth mentioning along with the fact that water is used as the solvent. Studies directed towards a further improvement and recycling of the catalyst are in progress.

References

[1] S.-I. Murahashi, Ruthenium in Organic Synthesis, Wiley-VCH, Weinheim, 2004.
[2] http://www.precious-metal.com/pmtrading.
[3] K. Weissermel, J.-J. Arpe, Industrial Organic Chemistry, Wiley-VCH, Weinheim, 2003.
[4] T. Katsuki, K. Muñiz, C. Bolm, W.R. Thiel, in: M. Beller, C. Bolm (Eds.), second ed., Transition Metals for Organic Synthesis, vol. 2, Wiley-VCH, Weinheim, 1998, p. 261.
[5] G.A. Barf, R.A. Sheldon, J. Mol. Catal. 102 (1995) 23.
[6] J.R. Monnier, Appl. Catal. A 221 (2001) 73.
[7] M.D. Hughes, Y.-J. Xu, P. Jenkins, P. McMorn, P. Landon, D.I. Enache, A.F. Carley, G.A. Attard, G.J. Hutchings, F. King, E.H. Stitt, P. Johnston, K. Griffin, C.J. Kiely, Nature 437 (2005) 1132.
[8] C.W. Jones, Applications of Hydrogen Peroxide and Derivatives, Royal Society of Chemistry, Cambridge, 1999.
[9] Chemical Market Reporter 267 (2005) 17.
[10] B.S. Lane, K. Burgess, Chem. Rev. 103 (2003) 2457.
[11] M.G. Clerici, G. Bellussi, U. Romano, J. Catal. 129 (1991) 159.
[12] W.A. Herrmann, R.W. Fischer, D.W. Marz, Angew. Chem. Int. Ed. 30 (1991) 1638.
[13] For experimental details, see the respective references.
[14] J.M. Fisher, A. Fulford, P.S. Bennett, J. Mol. Catal. 77 (1992) 229.
[15] (a) J.O. Turner, J.E. Lyons, Tetrahedron Lett. 29 (1972) 2903;
(b) G. Balavoine, C. Eskenazi, F. Meunier, H. Rivière, Tetrahedron Lett. 25 (1984) 3187;
(c) C. Eskenazi, G. Balavoine, F. Meunier, H. Rivière, J. Chem. Soc., Chem. Commun. (1985) 1111.
[16] M. Rüsch, Ph.D. Thesis, RWTH Aachen, 1993.
[17] M. Klawonn, M.K. Tse, S. Bhor, C. Döbler, M. Beller, J. Mol. Catal. A 218 (2004) 13.
[18] H. Nishiyama, T. Shimada, H. Itoh, H. Sugiyama, Y. Motoyama, Chem. Commun. (1997) 1863.
[19] M.K. Tse, M. Klawonn, S. Bhor, C. Döbler, G. Anilkumar, H. Hugl, W. Mägerlein, M. Beller, Org. Lett. 7 (2005) 987.
[20] Recent achievements in Ru-based asymmetric epoxidation see:
(a) R.I. Kureshy, N.H. Kahn, S.H.R. Abdi, K.N. Bhatt, Tetrahedron: Asymmetry 4 (1993) 1693;
(b) N. End, A. Pfaltz, Chem. Commun. (1999) 589;
(c) Z. Gross, S. Ini, Org. Lett. 1 (1999) 2077;
(d) R.M. Stoop, S. Bachmann, M. Valentini, A. Mezzetti, Organometallics 19 (2000) 4117;
(e) F. Pezet, H. Aït-Haddou, J.-C. Daran, I. Sadaki, G. Balavoine, Chem. Commun. (2002) 510.
[21] Selected examples of asymmetric epoxidation using H_2O_2 as oxidant:
(a) R. Sinigalia, R.A. Michelin, F. Pinna, G. Strukul, Organometallics 6 (1987) 728;
(b) T. Schwenkreis, A. Berkessel, Tetrahedron Lett. 34 (1993) 4785;
(c) R. Irie, N. Hosoya, T. Katsuki, Synlett (1994) 255;
(d) P. Pietikäinen, Tetrahedron Lett. 59 (1994) 1939;
(e) A. Berkessel, M. Frauenkron, T. Schwendreis, A. Steinmetz, J. Mol. Catal. 117 (1997) 339;
(f) C. Bolm, D. Kadereit, M. Valacchi, Synlett (1997) 687;
(g) M.B. Francis, E.N. Jacobsen, Angew. Chem. Int. Ed. 38 (1999) 937;
(h) R.M. Stoop, A. Mezzetti, Green Chem. 1 (1999) 39;
(i) R.M. Stoop, C. Bauer, P. Setz, M. Wörle, T.Y.H. Wong, A. Mezzetti, Organometallics 18 (1999) 5691;
(j) C. Bolm, N. Meyer, G. Raabe, T. Weyhermüller, E. Bothe, Chem. Commun. (2000) 2435;
(k) P. Pietikäinen, J. Mol. Catal. 165 (2001) 73;
(l) L. Shu, Y. Shi, Tetrahedron 57 (2001) 5213;
(m) R.I. Kureshy, N.-U.H. Khan, S.H.R. Abdi, S.T. Patel, R.V. Jasra, Tetrahedron: Asymmetry 12 (2001) 433.
[22] M.K. Tse, S. Bhor, M. Klawonn, C. Döbler, M. Beller, Tetrahedron Lett. 44 (2003) 7479.
[23] (a) M.K. Tse, C. Döbler, S. Bhor, M. Klawonn, W. Mägerlein, H. Hugl, M. Beller, Angew. Chem. Int. Ed. 43 (2004) 5255;
(b) M.K. Tse, S. Bhor, M. Klawonn, G. Anilkumar, H. Jiao, A. Spannenberg, C. Döbler, W. Mägerlein, H. Hugl, M. Beller, Chem. Eur. J. 12 (2006) 1855;
(c) M.K. Tse, S. Bhor, M. Klawonn, G. Anilkumar, H. Jiao, A. Spannenberg, C. Döbler, W. Mägerlein, H. Hugl, M. Beller, Chem. Eur. J. 12 (2006) 1875.
[24] For recent examples of catalysis with pybox derivatives see:
(a) A. Pfaltz, Acc. Chem. Res. 26 (1993) 339;
(b) H. Nishiyama, Y. Itoh, H. Matsumoto, S.-B. Park, K. Itoh, J. Am. Chem. Soc. 116 (1994) 2223;
(c) A.K. Ghosh, P. Mathivanan, J. Cappiello, Tetrahedron: Asymmetry 9 (1998) 1;
(d) G. Sekar, A. DattaGupta, V.K. Singh, J. Org. Chem. 63 (1998) 2961;
(e) J.S. Johnson, D.A. Evans, Acc. Chem. Res. 33 (2000) 325;
(f) C.-X. Zhao, M.O. Duffey, S.J. Taylor, P. Morken, Org. Lett. 3 (2001) 1829;
(g) J. Zhou, G.C. Fu, J. Am. Chem. Soc. 126 (2004) 1340;
(h) D. Cuervo, M.P. Gamasa, J. Gimeno, Chem. Eur. J. 10 (2004) 425.
[25] S. Nishimura, Handbook of Heterogeneous Catalytic Hydrogenation for Organic Synthesis, Wiley-Interscience, New York, 2001.
[26] S.B. Kang, S. Park, Y.H. Kim, Y. Kim, Heterocycles 45 (1997) 137.
[27] S. Wu, R. Takeya, M. Eto, C. Tomizawa, J. Pestic. Sci. 12 (1987) 221.
[28] G.M. Coppola, H.F. Schuster, Asymmetric Synthesis of Chiral Molecules using Amino Acids, Wiley-Interscience, New York, 1987.
[29] For experimental details, see:;
(a) S. Antons, B. Beitzke, EP Patent 0,696,575 (1997);
(b) S. Antons, A. Schulze Tilling, E. Wolters, US Patent 6,310,254 (2001);
(c) S. Antons, L. Frohn, J.-D. Jentsch, A. Schulze Tilling, E. Wolters, US Patent 6,376,414 (2002).
[30] L. Schuster, W. Franzischka, H. Hoffmann, S. Winderl, DE Patent 2,132,547 (1982).
[31] F.J. Tere, D.J. Miller, J.E. Jackson, Org. Lett. 5 (2003) 527.
[32] Temperature-programmed reduction (5 K/min; 7.5% H_2 in Ar) of unsupported Re(VII)-oxide showed that certain reduction processes started only at >280 °C, but the measurement was hampered by the volatility of the material at higher temperatures. However, in the presence of Ru the reduction of Re(VII) proceeds at much lower temperatures leading to elemental Re.