Pergamon

TETRAHEDRON

Tetrahedron 58 (2002) 3943–3949

Hydrolytic kinetic resolution of terminal epoxides catalyzed by fluorous chiral Co(salen) complexes

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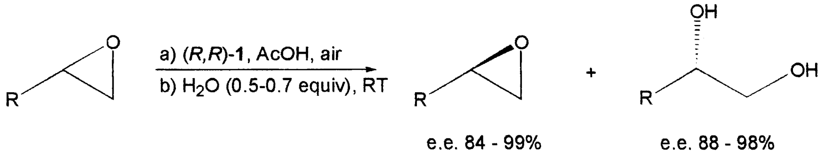
Received 14 November 2001; revised 10 January 2002; accepted 16 January 2002

Abstract—Cobalt complexes of fluorous chiral salen ligands have been synthesized and tested as catalysts in the hydrolytic kinetic resolution of terminal epoxides. Whereas the activity of heavily fluorinated complexes was found to be rather low, a 'light fluorous' complex was shown to be an efficient and highly selective catalyst for this asymmetric ring-opening reaction. Several strategies for the isolation of reaction products and the recovery of the fluorous catalyst are also discussed. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

Asymmetric homogeneous catalysis is a powerful tool for the efficient synthesis of enantiomerically enriched chiral compounds.[1] Application of this methodology on a wide scale is often prevented by issues relating to purification of the reaction products and recyclability of the precious chiral catalysts. The immobilization of chiral catalysts onto insoluble supports (both organic and inorganic) is an attractive, but still challenging, strategy for overcoming these limitations.[2] Indeed, immobilized chiral catalysts often show lower enantioselectivities and/or efficiencies than their homogeneous parallels. In the case of homogeneous catalysts covalently attached to the support, the practical advantages expected from heterogenization should also compensate for the additional synthetic efforts required to modify the structure of the chiral ligand.

Enantioselective reactions were recognized as a potential target at a very early stage of development of fluorous chemistry.[3] Four years later, we succeeded in demonstrating that the fluorous biphase (FB) approach can be applied to the immobilization of chiral catalysts.[4] The asymmetric epoxidation of alkenes was chosen as a model reaction in view of its considerable importance and also because the reported immobilization strategies for Mn(salen) complexes, the most efficient chiral catalyst for this reaction, presented several drawbacks.[5] It was found that chiral Mn(salen) complexes featuring perfluoroalkyl substituents (R_F) in the 3,3′- and 5,5′-positions in the ligand could be utilized for enantioselective epoxidation reactions carried out under FB conditions. The fluorous layer in which the catalyst was dissolved could be readily recovered and reused, but good enantioselectivities were obtained for indene only.[6] The scope of the FB epoxidation has been recently widened thanks to the synthesis of second-generation Mn(salen) complexes that were designed taking into account the possible role of steric and electronic effects arising from the presence of R_F substituents in the proximity of the coordination sites of the ligand.[7] These catalysts can be used in the FB asymmetric epoxidation of several substrates, affording results that compare favorably to those obtained with other immobilized catalytic systems.[8] The fluorous phase could be used up to four times before significant decline in yield and enantioselectivity was observed. Nevertheless, effective recycling of Mn(salen) complexes through a very high number of reaction runs is limited by the tendency of these compounds to undergo oxidative decomposition under the reaction conditions. Application of a FB methodology can avoid this inconvenience only to some extent.



Scheme 1.

Keywords: cobalt and compounds; diols; epoxides; fluorine and compounds.

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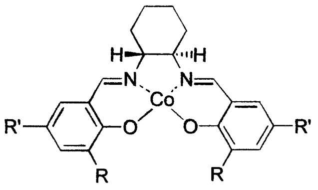
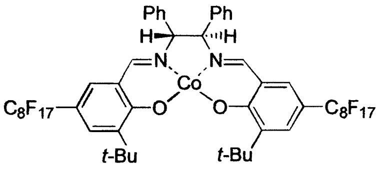
PII: S0040-4020(02)00216-8



(*R*,*R*)-**1** R = R' = *t*-Bu

(*R*,*R*)-**2** R = R' = C_8F_{17}

(*R*,*R*)-**4** R = *t*-Bu, R' = C_8F_{17}



(*R*,*R*)-**3**

Figure 1.

Since nitrogen-containing chiral ligands are increasingly used in asymmetric catalysis,[9] we decided to explore the use of the readily accessible fluorous salen ligands in reactions other than the epoxidation of alkenes. In the frame of this program, it was shown that the hydrogen transfer reduction of ketones in a mixture perfluoroalkane/isopropanol proceeds in the presence of $[Ir(COD)Cl]_2$ associated with chiral fluorous salen ligands, affording optically active carbinols with ees up to 60%.[10,11] Herein we report the promising application of fluorous chiral Co(salen) complexes to the hydrolytic kinetic resolution (HKR) of terminal epoxides (Scheme 1).[12] Due to the mild conditions under which the HKR is performed, decomposition of the catalyst is a minor problem with respect to epoxidation reactions. The separation of the products from the catalyst can be conducted by both fluorous and standard techniques.

2. Results and discussion

The HKR of terminal epoxides in the presence of chiral Co(salen) complexes, discovered by Jacobsen in 1997, provides a convenient access to both highly enantioenriched terminal epoxides and 1,2-diols.[12] The cobalt complex (*R*,*R*)-**1** (Fig. 1) and closely related polystyrene- or silica-bound chiral Co(salen) complexes proved to be highly efficient and enantioselective catalysts for this reaction.[13,14]

Two distinct sets of fluorous chiral salen ligands were available from our previous studies.[6–8] One is characterized by a relatively low fluorine content (F<50%) and by the presence of bulky *t*-butyl substituents in the 3,3′-positions, as in the reference catalyst (*R*,*R*)-**1**. Ligands of this kind can be described as 'light' or 'minimally' fluorous compounds.[15,16] The second set is richer in fluorine (F>60%) thanks to the presence of more R_F substituents. This allows the ligands to be selectively soluble in perfluorocarbons, as required by FB applications, but the presence of R_F substituents in the 3,3′-positions can also have detrimental effects on the enantioselectivities of the catalysts obtained from these ligands, as exemplified by the behavior of fluorous Mn(salen) complexes in epoxidation reactions. In the case of HKR, however, the enhanced Lewis acidity of the metal site induced by the strongly electron-withdrawing R_F substituents might have a positive effect on the catalyst activity.[13] Therefore, cobalt complexes of ligands belonging to both groups were prepared and tested (Fig. 1).

Co(II) complexes (*R*,*R*)-**2**–(*R*,*R*)-**4** were readily obtained by adding a solution of $Co(OAc)_2\cdot 4H_2O$ in EtOH to the corresponding fluorous ligand dissolved in hot toluene and stirring the mixture for 3 h.[17] The complexes were isolated after crystallization from EtOH in 90–98% yield and were characterized by UV–vis, FT-IR and elemental analysis. As expected, the 'light-fluorous' complexes (*R*,*R*)-**3** and (*R*,*R*)-**4** (F=45.3 and 48.6%, respectively) were found to be soluble in common organic solvents such as CH_2Cl_2 and toluene and insoluble in perfluorocarbons at room temperature. The solubility behavior of (*R*,*R*)-**2** (F=63.0%) is less straightforward, the complex being insoluble in common organic solvents, but also very slightly soluble in perfluorocarbons at room temperature (e.g. 6.8×10^{-5} M in perfluorooctane as evaluated by UV–vis spectroscopy).[8]

The three complexes were examined for their efficacy in the HKR of racemic 1-hexene oxide (Table 1). In a first series of experiments (entries 2–4), the fluorous Co(II) complexes were oxidized by air prior to the reaction in the presence of acetic acid, an effective promoter for the aerobic

Table 1. Hydrolytic kinetic resolution of 1-hexene oxide catalyzed by fluorous chiral Co(salen) complexes previously oxidized to the Co(III) state in the presence of a promoter

Entry	Catalyst	Promoter	Time (h)	Conversion (%)[a]	ee diol (%)[b]	ee epoxide (%)[c]
1[d]	(*R*,*R*)-**1**	CH_3COOH	5	50[e]	98	98
2	(*R*,*R*)-**2**	CH_3COOH	24	10	81.4	10.3
3	(*R*,*R*)-**3**	CH_3COOH	32	0	–	–
4	(*R*,*R*)-**4**	CH_3COOH	18	43	96.9	72.4
5	(*R*,*R*)-**2**	$C_8F_{17}COOH$	24	29	84.8	32.6
6	(*R*,*R*)-**3**	$C_8F_{17}COOH$	12	10	62.4	7.0
7	(*R*,*R*)-**4**	$C_8F_{17}COOH$	6	46	≥99	91.2

Reaction conditions: racemic epoxide=25 mmol (3 ml); H_2O=17.5 mmol (0.32 ml); catalyst=0.05 mmol. Molar ratio epoxide/catalyst=500.

[a] Determined by GC analysis of the reaction mixture. See Section 4.

[b] Determined by capillary GC analysis of the isolated product on a HP Chiral—20% permethylated β-cyclodextrin column.

[c] Optical purity of the isolated epoxide.

[d] See Ref. 13: H_2O=0.55 equiv. Molar ratio epoxide/catalyst=240.

[e] Based on the ee of the recovered epoxide and diol. See Ref. 14.

Table 2. Hydrolytic kinetic resolution of terminal epoxides catalyzed by (*R*,*R*)-**4** previously oxidized to the Co(III) state in the presence of $C_8F_{17}COOH$

Entry	R	Time (h)	Diol		Epoxide	
			Isolated yield (%)[a]	ee (%)[b]	Isolated yield (%)[a]	ee (%)[c]
1	CH_3	15	49	75.2	–	–
2	$CH_3(CH_2)_3$	6	41	≥99	55	91.2
3	$CH_3(CH_2)_5$[d]	15	47	≥99	51	≥99
4	$ClCH_2$[e]	15	40	98.3	56	90.6
5	C_6H_5	15	46	79.4	51	76.3

Reaction conditions: racemic epoxide=25 mmol; H_2O=17.5 mmol; catalyst=0.05 mmol. Molar ratio epoxide/catalyst=500.

[a] Products isolated by fractional distillation. See Section 4.

[b] Determined by capillary GC analysis of the isolated product on a HP Chiral—20% permethylated β-cyclodextrin column.

[c] Optical purity of the isolated epoxide.

[d] Racemic 1,2-hexanediol (20 mol%) was added as a co-solvent. See Ref. 12.

[e] CH_2Cl_2 (3 ml) was added as a co-solvent.

oxidation of (*R*,*R*)-**1** and related compounds to the corresponding catalytically active Co(III) species.[14] Whereas the literature procedure was suitable for the oxidation of (*R*,*R*)-**3** and (*R*,*R*)-**4**, the Co(III) complex corresponding to (*R*,*R*)-**2** could be obtained only after prolonged treatment of a suspension of the heavily fluorinated compound in a boiling mixture toluene/acetic acid 9/1, v/v. Once formed, the catalysts were isolated by removing the solvent under reduced pressure. Rather surprisingly, the three fluorous Co(III) complexes were soluble in neat 1-hexene oxide at 1.66×10^{-2} M, a concentration yielding a molar ratio epoxide/catalyst=500 as used by Jacobsen in the HKR of propylene oxide.[12] Therefore, reactions could be carried out at room temperature without addition of any co-solvent. A sub-stoichiometric amount of water (0.7 equiv. with respect to the epoxide) was added to the homogeneous solutions that were gently stirred under aerobic conditions. The progressive consumption of the epoxide was followed by GC analysis, the only detectable products being (*S*)-1,2-hexanediol and lower amounts of its *R* enantiomer.

The Co(III) complex generated from (*R*,*R*)-**4** (entry 4) proved to be an efficient catalyst for the HKR of the model compound, affording the enantiomerically enriched epoxide and diol with ee=72.4 and 96.9%, respectively, and conversion=43%. For sake of comparison, literature data for the HKR of 1-hexene oxide catalyzed by the Co(III) complex generated from (*R*,*R*)-**1** are reported (entry 1). The promising results obtained with (*R*,*R*)-**4** stand in deep contrast with those obtained with (*R*,*R*)-**3** (entry 3), also bearing *t*-butyl and R_F substituents in the 3,3′-positions and 5,5′-positions of the ligand, respectively. In that case, the Co(III) species did not catalyze at all the epoxide ring-opening reaction, even on an extended time scale. It appears that the nature of the 1,2-diamine moiety of the ligand is utterly important in determining the catalytic activity, as also demonstrated by the results obtained with complex (*R*,*R*)-**2**, derived from (*R*,*R*)-1,2-diaminocyclohexane as (*R*,*R*)-**4** (entry 2). Although, contrary to our expectations, the introduction of R_F substituents in the 3,3′-positions is not beneficial for the catalyst activity, a certain degree of enantioselection was achieved even in the absence of the sterical hindrance provided by the *t*-butyl groups.

We had found previously that the solubility of charged Mn(III) fluorous complexes in perfluorocarbons can be strongly enhanced by choice of a fluorinated counterion.[7] (*R*,*R*)-**2** was thus oxidized by air in the presence of 2 equiv. of perfluorononanoic acid, affording the corresponding Co(III)(salen)($C_8F_{17}COO$) complex. Unfortunately, also this species was found to be preferentially soluble in neat 1-hexene oxide, the partition coefficient between the epoxide and *n*-perfluorooctane determined by UV–vis spectroscopy at 25°C being >100, and so a possible application of the FB approach was ruled out. The identity of the counterion for the catalytically active Co(III) complex had been proved to be important in the case of the kinetic resolution of terminal epoxides with phenols.[18] In that context, the presence of a perfluorinated anion ($(CF_3)_3CO^-$) enhances the activity of the Co(III) complex generated from (*R*,*R*)-**1**. A similar effect was observed in the HKR of racemic 1-hexene oxide: the presence of the fluorinated counterion $C_8F_{17}COO^-$ plays a beneficial role, with the fluorous Co(III) complexes consistently displaying increased activities (entries 5,6,7 vs 2,3,4). Again, the best results were obtained with the Co(III) complex generated from (*R*,*R*)-**4** which gave the enantiomerically enriched *R*-epoxide and *S*-diol with ee=91.2 and ≧99%, respectively, at 46% conversion in 6 h.

Other terminal epoxides were subjected to HKR under the optimized solvent-free conditions described above, and results are summarized in Table 2. Reaction products were isolated in good yields by fractional distillation, and the configurations of the enantiomerically enriched epoxides and diols (established by comparison with authentic samples) always corresponded to those reported in Scheme 1.

The catalytic system based on the fluorous complex (*R*,*R*)-**4** usually gave clean reactions with no detectable traces of by-products, affording highly selective kinetic resolutions over reasonable reaction times even at a low catalyst loading. In the case of epichlorohydrin, the diol could be obtained in good enantiomeric purity, but the reaction was sluggish and a low conversion of the epoxide (15.3%) was observed. The low catalytic activity of the system was ascribed to the low solubility of the fluorous catalyst in the reaction mixture, since partial precipitation of the fluorous complex as a brown slurry was observed just after the diol started to form. Addition of CH_2Cl_2 as a solvent allowed to overcome this problem and the ring-opening reaction proceeded in 15 h with conversion=44% (entry 4). It must be noted that epichlorohydrin is

Table 3. Hydrolytic kinetic resolution of 1-hexene oxide catalyzed by (*R*,*R*)-**4** previously oxidized to the Co(III) state in the presence of $C_8F_{17}COOH$. Recycling of the catalyst after fractional distillation of the reaction mixture

Cycle	Time (h)	Conversion (%)[a]	ee diol (%)[b]	ee epoxide (%)[c]
1	6	46	≥99	91.2
2	6	44	97.2	90.6
3	6	45	97.4	90.8
4	8	46	96.9	90.5

Reaction conditions: racemic epoxide=25 mmol (3 ml); H_2O=17.5 mmol (0.32 ml); catalyst=0.05 mmol. Molar ratio epoxide/catalyst=500.

[a] Determined by GC analysis of the reaction mixture. See Section 4.

[b] Determined by capillary GC analysis of the isolated product on a HP Chiral—20% permethylated β-cyclodextrin column.

[c] Optical purity of the isolated epoxide.

susceptible to racemization upon distillation of the reaction mixture.[14] Accordingly, the optical purity of the isolated epoxide was found to be 90.6% against ee=97% as measured by chiral GC analysis of the reaction mixture.

Having established the effectiveness of (*R*,*R*)-**4** as a catalyst precursor, recycling of this light fluorous complex was investigated. A methodology analogous to that proposed by Jacobsen and coworkers for the reference complex (*R*,*R*)-**1** was applied at first (Table 3).[13] The non-volatile residue obtained after distillation of the reaction mixture deriving from the HKR of 1-hexene oxide was taken up in toluene and treated with $C_8F_{17}COOH$ in air. The Co(III) species was thus regenerated as shown by UV–vis spectroscopy. Evaporation of the solvent under reduced pressure afforded a dark brown material that was dissolved in a new batch of racemic 1-hexene oxide. Water was added to the solution that was stirred 6 h at room temperature. GC analysis of the organic phase showed the almost complete consumption of the reactive *S*-epoxide and the formation of the *S*-diol with 97.2% ee (entry 2). As judged by comparison with the results obtained with fresh (*R*,*R*)-**4** (entry 1), the catalyst could be recycled as described at least 3 times with only minor loss in activity and selectivity.

This simple and effective recycling procedure, however, presents some limitations, as in the case of products prone to racemization or non-volatile. Moreover, fractional distillation of certain reaction mixtures is a delicate and time-consuming task. The use of polymer-supported chiral Co(salen) complexes has been proposed as a solution to these problems.[14] Polystyrene-bound catalysts could be isolated from product mixtures by simple filtration and continuous-flow reaction systems based on silica-bound catalysts were also tested. Alternative solutions based on the fluorous character of the catalyst can be envisaged. A wide range of fluorous techniques complementary to the standard FB approach have been introduced, providing new options for separating reaction mixtures.[19] Our interest for these techniques was stimulated by the finding that a chiral light fluorous phosphine can be conveniently used in Pd(0)-catalyzed asymmetric allylic substitutions. It was shown that these reactions could be carried out under homogeneous conditions in common organic solvents, the products being subsequently recovered by simple liquid–liquid extraction with a perfluorocarbon.[20] Unluckily, neither the catalyst nor the ligand could be recycled, as also observed by Curran and co-workers in the case of phosphine-based light fluorous platinum complexes used as catalysts in the allylation of benzaldehydes.[15] This drawback is probably related to the sensitivity of the ligands used and (*R*,*R*)-**4** seemed to be a better candidate for testing the value of light fluorous techniques, due to its proved stability under the reaction conditions here employed.

Three different fluorous separation methods were compared, using again the HKR of 1-hexene oxide as a model reaction:

(A) liquid–liquid extraction at room temperature, in the presence of a fluorinated co-solvent;
(B) liquid–liquid extraction in a continuous extractor;
(C) solid phase extraction.

The results obtained are summarized in Table 4.

As discussed above, complex (*R*,*R*)-**4** is insoluble in *n*-perfluorooctane at room temperature and rather soluble in 1-hexene oxide. However, the solubility of the spent catalyst in the products mixture is decreased by the presence of the more polar 1,2-hexanediol and can be further decreased by addition of CH_3CN, a fluorophobic solvent able to dissolve both reaction products. When 10 ml of *n*-perfluorooctane

Table 4. Hydrolytic kinetic resolution of 1-hexene oxide catalyzed by (*R*,*R*)-**4** previously oxidized to the Co(III) state in the presence of $C_8F_{17}COOH$. Recycling of the catalyst using fluorous techniques

Entry	Method[a]	Time (h)	Conversion (%)[b]	ee diol (%)[c]	Co loss (%)
1[d]	–	6	46	≥99	–
2	A	24	50	≥99	16[e]
3	B	15	47	95.2	14[f]
4	C[g]	50	36	≥99	50[h]
5	C[i]	36	41	90.9	33[h]

Reaction conditions: racemic epoxide=25 mmol (1.5 ml); H_2O=17.5 mmol (0.32 ml); fresh catalyst=0.05 mmol (66 mg); $C_8F_{17}COOH$=0.1 mmol (46 mg). Initial molar ratio epoxide/catalyst=500.

[a] See main text.

[b] Determined by GC analysis of the reaction mixture. See Section 4.

[c] Determined by capillary GC analysis of the reaction mixture on a HP Chiral—20% permethylated β-cyclodextrin column.

[d] Fresh catalyst.

[e] Colorimetric essay of the fluorous extract after the first reaction cycle. See Ref. 8 for the method used.

[f] ICP analysis of the recovered material after the second reaction cycle.

[g] Extraction of the spent catalyst adsorbed on a fluorous reverse phase silica with cold toluene.

[h] ICP analysis of the extracted silica.

[i] Extraction in continuous of the spent catalyst adsorbed on a fluorous reverse phase silica with warm toluene.

and 2 ml of α,α,α-trifluorotoluene were added to the reaction mixture diluted with 30 ml of CH_3CN, two distinct layers formed. After stirring for 30 min at room temperature, the mixture was poured into a separating funnel. The upper layer was subjected to a second extraction and the combined brown fluorous layers were collected, washed with 10 ml of CH_3CN and evaporated to dryness under reduced pressure. The recovered catalyst was regenerated by treatment with $C_8F_{17}COOH$ as previously described, and used in a second run (entry 2). Quantitative colorimetric analysis of a diluted solution of the recovered Co(III)(salen) species taken before the second reaction cycle showed an absorption decrease of 16% with respect to a fresh catalyst solution.[8] The partial loss of catalyst during the extraction was confirmed by the results of the second run. Although the enantioselectivities in epoxide and diol were not affected, a significant reduction of activity was observed, 50% conversion of the racemic epoxide being achieved only after 24 h.

Crich and co-workers suggested the use of a jacketed continuous extraction apparatus to overcome the low tendency to partition in the fluorous phase of light fluorous compounds.[16] This method was tested after diluting the reaction mixture with CH_3CN (7.5 ml) as in the case of liquid–liquid extraction at room temperature, but this time no co-solvent was added to *n*-perfluorooctane (35 ml) that was refluxed in the receiver flask. Cold water kept the two phases cold and immiscible in the jacketed return arm of the apparatus, but a brown solid was clearly visible at the interface of the two layers. The extraction was halted after a period of 2 h and evaporation of the fluorous phase afforded only a few milligrams of an orange solid which was identified as a Co(II)(salen) complex by the presence of two characteristic UV–vis absorption bands at 407 and 344. Better results were obtained with a common continuous extractor the upper part of which became progressively hotter as the extraction proceeded. Hot *n*-perfluorooctane readily dissolved the brown solid when crossing the interface between the organic and the fluorous layers. After 2 h the *n*-perfluorooctane solution in the receiver flask was cooled to room temperature affording an orange precipitate (92 mg against 112 mg of (*R*,*R*)-**4** plus $C_8F_{17}COOH$ initially used). Ten milligrams of pale-orange solid was also obtained from the liquid phase after evaporation under reduced pressure. The recovered material was reoxidized and recycled as described before. However, reduction of the catalytic activity was still observed (entry 3). Elemental analysis (ICP) of the solid recovered after the second reaction cycle showed a Co loss of 14 % with respect to the fresh catalyst.

Fluorous compounds can be quickly separated from standard organic molecules using a particular kind of solid–liquid extraction based on the adsorbing properties of 'fluorous reverse phase silica gel'.[21] In a third series of recycling experiments, the crude reaction mixture was charged to 1 g of silica gel modified with a perfluoroalkyl residue, placed in a plastic syringe.[22] Elution with 6 ml of CH_3CN removed 1-hexene oxide and 1-2-hexanediol in a few minutes, with no trace of Co(salen) detectable by UV–vis spectroscopy. However, only a fraction of the fluorous catalyst was recovered by a second elution with a different, more fluorophilic solvent (e.g. CH_2Cl_2, toluene or Et_2O). In the case of toluene, the best solvent among those tested, 50% of the initial cobalt remained attached to the silica as determined by elemental analysis. The recovered material still showed catalytic activity, but as expected reaction rate was reduced (entry 4). Extraction in continuous of the fluorous silica gel with toluene in a Sohxlet apparatus also gave disappointing results: elemental analysis of the extracted silica showed that 33% of the cobalt initially introduced was still adsorbed and this was associated with both decreased catalytic activity and enantioselectivity (entry 5).

The high affinity of the fluorous complex for the modified silica prompted us to explore the use of this material as an insoluble support for (*R*,*R*)-**4**, with the practical advantage that no modification of the ligand for the covalent attachment to the heterogeneous matrix was required. Two methods were tested in parallel: (a) adsorption of a solution of (*R*,*R*)-**4** in toluene onto the fluorous silica followed by aerobic oxidation in the presence of $C_8F_{17}COOH$, and (b) adsorption of the complex previously oxidized in solution to a Co(III) species. In both cases, the brown solid material was thoroughly rinsed with CH_3CN, CH_2Cl_2 and 1-hexene oxide and dried under vacuum before using it in the HKR of 1-hexene oxide. Elemental analysis indicated incorporation of 42 and 40 μmol of Co per gram of silica, respectively. Both heterogeneous materials were found to be devoid of catalytic activity, neither consumption of 1-hexene oxide nor formation of 1,2-diol being detected by GC analysis after 48 h, in striking contrast with the excellent results reported in the case of silica-bound Co(salen) complexes featuring the covalent attachment of the ligand to the inorganic support.[16] Site isolation resulting from the low catalyst loading on the fluorous silica might explain this remarkable difference. Indeed, the HKR of terminal epoxides is likely to proceed through a cooperative bimetallic mechanism, which is effective only in the case of physical proximity of the catalyst molecules. The access of water to the catalytically active Co(III) sites might be also difficult because of the hydrophobic character of the fluorous silica gel.

3. Conclusions

The hydrolytic kinetic resolution (HKR) of terminal epoxides can be performed under solvent-free conditions in the presence of small amounts of fluorous chiral Co(salen) complexes. The best results were obtained using a light fluorous catalyst featuring sterically hindered *t*-butyl substituents in the 3,3′-positions of the ligand. Catalytic activities and enantioselectivities were comparable to those reported for a similar non-fluorous catalytic system, and recycling of the spent catalyst could also be performed analogously. In addition, application of fluorous techniques provided alternative methods for the separation of the catalyst from reaction mixtures under mild conditions. Solid–liquid extraction was found to be the quickest and operationally simplest way to get rid of the catalyst: it did not require the use of a fluorous solvent and could be useful for parallel synthesis. Liquid–liquid extraction, both in the presence of a co-solvent and in a continuous extractor, was less effective. Indeed, the compounds here investigated are poorly soluble in perfluorocarbons despite the presence of long fluorous ponytails and their relatively high fluorine content. We are currently trying to extend this comparison to other chiral fluorous catalytic systems.

4. Experimental

Solvents were purified by standard methods and dried if necessary, except for *n*-perfluorooctane (Galden D-100, a generous gift from Ausimont S.p.A. Bollate, Italy), which was used as received. All commercially available reagents were used as received. TLC was carried out on silica gel 60 F_{254}. Column chromatography was carried out on SI 60 silica gel, mesh size 0.040–0.063, Merck, Darmstadt, Germany. Melting points (uncorrected) were determined with a Büchi SMP-20 capillary melting point apparatus. Optical rotations were measured using a Perkin–Elmer 241 polarimeter. UV–vis spectra were measured using a Lambda 6 Perkin–Elmer spectrometer. GC analyses were performed on a Hewlett-Packard 5890 instrument (column: 30 m×0.32 mm HP-5 5% phenyl methyl siloxane or 30 m× 0.25 mm HP Chiral—20% permethylated β-cyclodextrin column). Elemental analysis: Departmental Service of Microanalysis (University of Milano, C, H, N) and Redox S.n.c. (Monza, Italy, ICP determination of Co).

4.1. Synthesis of fluorous Co(II)(salen) complexes: general procedure

To a solution of salen ligand[6,8] (0.5 mmol) in toluene (7 ml) heated at 100°C under nitrogen was added dropwise $Co(OAc)_2 \cdot 4H_2O$ (0.25 g, 1 mmol) in aqueous 95%-ethanol (15 ml). The yellow solution turned orange and a precipitate was formed. The mixture was stirred for 4 h, after which the solvent was evaporated under reduced pressure. The residue was crystallized from EtOH (15 ml) affording the Co(II) complex as a bright orange solid.

4.1.1. Cobalt complex (*R*,*R*)-2. Yield=93.6%; $[\alpha]_D^{20}=-411$ (c=0.002, CCl_2FCClF_2); mp>250°C; UV–vis (6.8×10^{-5} M, CCl_2FCClF_2): λ_{max} (log ε)=403 (3.68), 353 (3.71), 243 (3.93); FT-IR (KBr): 3555, 2955, 1620, 1550, 1458, 1356, 1211, 1150 cm^{-1}; $C_{52}H_{16}CoF_{68}N_2O_2$ (2051.5): calcd C 30.44, H 0.79, N 1.37; found C 29.96, H 1.03, N 1.27.

4.1.2. Cobalt complex (*R*,*R*)-3. Yield=98.4%; $[\alpha]_D^{20}=+192$ (c=0.01, CH_2Cl_2); mp=196°C; UV–vis (1.8×10^{-5} M, CH_2Cl_2): λ_{max} (log ε)=414 (4.12), 347 (4.14), 244 (4.40); FT-IR (KBr): 3365, 2958, 1619, 1601, 1540, 1292, 1246, 1205, 1148 cm^{-1}; $C_{52}H_{36}CoF_{34}N_2O_2$ (1425.7): calcd C 43.81, H 2.55, N 1.91; found C 43.54, H 2.61, N 1.88.

4.1.3. Cobalt complex (*R*,*R*)-4. Yield=89.6%; $[\alpha]_D^{20}=-534$ (c=0.01, CH_2Cl_2); mp=244°C; UV–vis (3.8×10^{-5} M, CH_2Cl_2): λ_{max} (log ε)=407 (4.05), 344 (4.10), 245 (4.67); FT-IR (KBr): 3441, 2955, 1607, 1543, 1210, 1151 cm^{-1}; $C_{44}H_{34}CoF_{34}N_2O_2$ (1327.6): calcd C 39.81, H 2.58, N 2.11; found C 39.73, H 2.70, N 1.93.

4.2. HKR of terminal epoxides: general procedure

The fluorous Co(II) complex (0.05 mmol) was dissolved in toluene (4 ml). Solid $C_8F_{17}COOH$ (46.4 mg, 0.1 mmol) was added and the mixture was stirred while open to the air for 1 h at room temperature. This procedure was carried out in refluxing toluene in the case of (*R*,*R*)-**2**. The solvent was removed by evaporation under reduced pressure and the brown residue was dried under vacuum. Racemic epoxide (25 mmol) was added and the mixture was stirred for 5 min. H_2O (0.32 ml, 17.5 mmol) was added in one portion and the mixture was stirred at room temperature. The outcome of the HKR was followed by GC analysis of aliquots taken at different times (column=HP-5). Conversion was evaluated by comparison of the relative area of the epoxide and diol peaks with a calibration curve built with mixtures of the two products in known amounts. The values obtained were found to be in good agreement with those calculated from GC measurement of the ee of the unreacted epoxide and formed diol (column HP-Chiral 20%).[14] After the reaction times reported in Tables 1 and 2, the products were isolated by fractional distillation of the reaction mixture in a Kugelrhor apparatus with dry-ice cooled receivers. The following compounds were distilled under vacuum: 3-chloro-1,2-propane diol (bp 83°C, 2 mmHg),[23] 1-octene oxide (bp 51–54°C, 10 mmHg),[24] 1,2-octane diol (bp 103–104°C, 0.5 mmHg),[25] 1-phenyl-1,2-ethane diol (bp 82°C, 1 mmHg).[26] The solid residue was recycled as described in the text if required.

4.3. Preparation of fluorous reverse phase silica gel

The procedure described in Ref. 22 was followed, with slight modifications. Flash chromatography grade silica (9 g, Silica Gel 40 μ, Mallinckrodt Baker) was dried at 120°C in a vacuum oven for 8 h and poured into a flask containing dry toluene (25 ml), imidazole (2.87 g, 42 mmol) and 1H,1H,2H,2H-perfluorooctyldimethylchlorosilane (15 g, 34 mmol). The mixture was heated for 80 h at 100°C and gently shaken with care occasionally. After cooling, the solid was filtered on a sintered glass filter, washed sequentially with toluene, MeOH, MeOH/H_2O, Et_2O, CH_3CN and dried at 120°C in a vacuum oven for 8 h to yield 13.5 g of fluorous reverse phase silica gel.

4.4. Solid–liquid extraction over fluorous reverse phase silica gel

A 5 ml plastic syringe fitted with a stopcock was packed with fluorous reverse phase silica (1 g) as described in Ref. 22. To this column the dark reaction mixture diluted with CH_3CN (1 ml) was loaded. A pale yellow liquid was eluted at first, while the top of the silica bed became almost black. The column was then eluted with further 6 ml of CH_3CN, thus completely removing 1-hexene oxide and 1-2-hexanediol.

Acknowledgements

The financial contribution of the European Commission through the Human Potential Programme (Contract no. HPRN-CT-2000-00002, Development of Fluorous

Phase Technology for Oxidation Processes) is gratefully acknowledged.

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