DOI: 10.1002/adsc.200900523

Asymmetric *meso*-Epoxide Ring-Opening with Trimethylsilyl Cyanide Promoted by Chiral Binuclear Complexes of Titanium. Dichotomy of C–C versus C–N Bond Formation

Yuri N. Belokon,[a,*] Denis Chusov,[a] Alexander S. Peregudov,[a] Lidia V. Yashkina,[a] Galina I. Timofeeva,[a] Victor I. Maleev,[a] Michael North,[b] and Henri B. Kagan[c]

[a] A.N. Nesmeyanov Institute of Organo-Element Compounds Russian Academy of Sciences, Vavilov 28, 119991 Moscow, Russian Federation
Fax: (+7)-499-135-5085; e-mail: yubel@ineos.ac.ru
[b] School of Chemistry and University Research Centre in Catalysis and Intensified Processing, Newcastle University, Bedson Building, Newcastle upon Tyne, NE1 7RU, U.K.
[c] Laboratoire de Catalyse Moléculaire, Institut de Chimie Moléculaire et des Matériaux d'Orsay, UMR 8182, Université Paris-Sud, 91405 Orsay, France

Received: July 28, 2009; Revised: October 28, 2009; Published online: December 2, 2009

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.200900523.

Abstract: In the presence of chiral catalysts derived from the same chiral hexadentate ligand and aluminium, zinc or titanium ions, the reaction between cyclohexene oxide and trimethylsilyl cyanide can be controlled to give predominantly either the nitrile (up to 99% *ee*) or the isonitrile product (up to 94% *ee*). The metal ion, ligand stereochemistry and base concentration all play a role in determining the product ratio.

Keywords: asymmetric ring-opening; binuclear catalysts; *meso*-epoxides; N/C dichotomy; trimethylsilyl cyanide

Introduction

Epoxides are widely utilized as versatile synthetic intermediates.[1] Their reactions generally involve the cleavage of the strained three-membered ring by a wide range of nucleophiles to give β-substituted alcohols. In particular, the asymmetric ring opening (ARO) of epoxides is a rational and effective way to form two or even three contiguous stereogenic centers.[2]

Catalytic ARO is of particular interest because it is an efficient method to convert readily available chemicals into non-racemic products.[3] *meso*-Epoxides have been successfully employed in ARO reactions with a large variety of heteroatom-based nucleophiles such as azides,[4] alcohols,[5] water,[6] thiols,[7] selenols,[8] amines,[9] and halides.[10] In contrast, only five papers describe asymmetric ring opening of *meso*-epoxides by trimethylsilyl cyanide (TMSCN) as a C-nucleophile.[2,11,12a,13]

Recently we developed an asymmetric cyanohydrin synthesis and ARO of *meso*-epoxides using TMSCN promoted by new titanium complexes of the hexadentate ligands (R_aSS)-**1** and (S_aSS)-**2** (Figure 1) as catalysts.[12] These complexes catalyzed the asymmetric addition of TMSCN to aldehydes under mild reaction

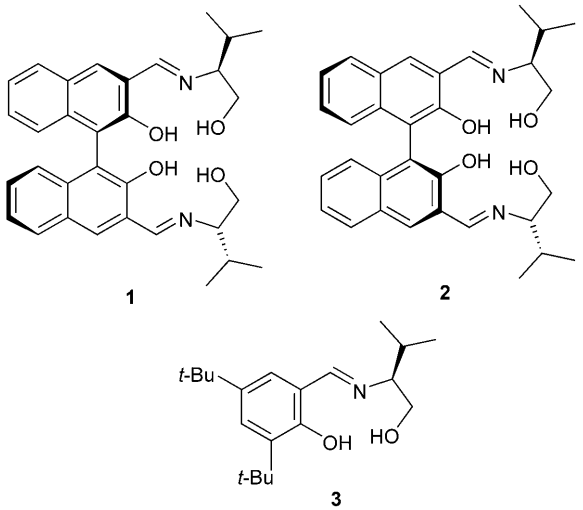
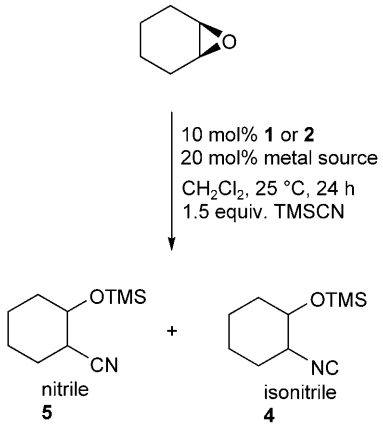


Figure 1. Hexadentate and tridentate ligands.



Scheme 1. Asymmetric ring-opening of cyclohexene oxide with TMSCN.

conditions furnishing cyanohydrins in excellent chemical yields and in higher enantiomeric purity, as compared with the complex derived from a tridentate ligand **3**.[12] According to preliminary data, ARO of *meso*-cyclohexene oxide with TMSCN (Scheme 1) was also catalyzed by the complexes, leading predominantly to β-trimethylsilyloxy cyanide (89% *ee*). However, the rate of the reaction was very slow and there were some unidentified products formed.[12]

In this work we studied the ARO reaction of *meso*-cyclohexene oxide with TMSCN in more mechanistic detail in order to improve both the stereoselectivity of the reaction and its rate. In addition, as ARO is an irreversible reaction, both hydroxy isonitrile (**4**) and hydroxy nitrile (**5**) formation could be expected, depending on the hardness/softness of the catalyst metal ions.[14] It was of significant interest to test if the nitrile/isonitrile ratio could also be varied by changing the structure of the ligands rather than that of the metal.

Results and Discussion

The synthesis of ligands (R_aSS)-**1** and (S_aSS)-**2** (Figure 1) was described earlier.[12] All the complexes derived from **1** and **2** were prepared *in situ* in dichloromethane. The zinc complexes were prepared by the interaction of 2 equivalents of diethylzinc with **1**, the aluminium precatalysts were synthesized by the reaction of the ligands with 2 equivalents of aluminium triisopropoxide and titanium-based precatalysts were obtained from 2 equivalents of titanium tetraisopropoxide. Other precatalysts **6** and **7** (Figure 2) were previously shown to be highly efficient at promoting asymmetric TMSCN addition to aldehydes.[15] The structure of the titanium complex **8** derived from ligand (R_aSS)-**1** is rather complicated. Its ^{1}H NMR spectrum in CD_2Cl_2 showed several sets of resonances

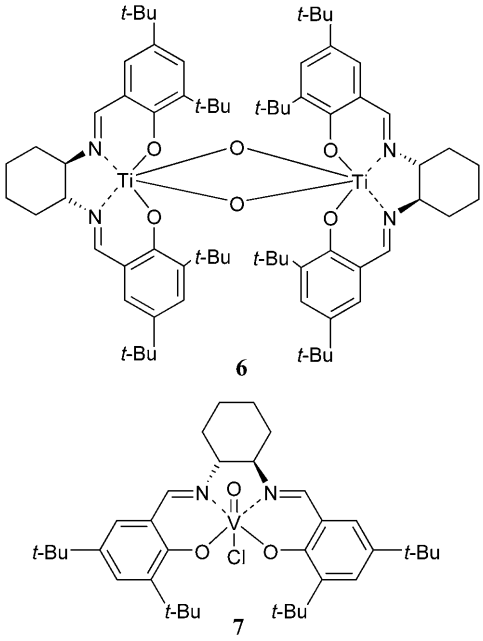


Figure 2. Structures of titanium and vanadium complexes.

instead of a simple set of signals reflecting C_2 symmetry. Estimation of the molecular weight of the complex in dichloromethane by the ultracentrifugation method[12b] gave a value of 1430 ± 70 which was, evidently, much greater than that expected for the simple dinuclear complex of (R_aSS)-**1** and 2 equivalents of titanium tetraisopropoxide (MW 840).

The IR spectra of the mixture did not contain strong absorptions in the region of 800–690 cm^{-1} which is typical for Ti–O–Ti bridges. Attempts to produce a crystal suitable for X-ray structure determination failed. However, a Schiff base analogue derived from (R_a)-2,2′-dihydroxy-3,3′-diformyl-1,1′-binaphthalene and (*S*)-valine surprisingly produced a dimeric coordinatively saturated complex, containing two Ti ions per two hexadentate ligands instead of the expected four Ti atoms (the X-ray stucture was published earlier[12b]). The four phenolate oxygen atoms of the complex were well situated to function as chelate donor atoms. Possibly, the predominant solution structure of **8** contained a coordinatively saturated core with two titanium atoms and two other titanium tetraisopropoxide moieties associated with the phenolic oxygen atoms of the core (Figure 3). This would give a molecular weight for **8** equal to 1680. An admixture of this complex with the simple monomeric complex with a **1**:Ti(O-*i*-Pr)$_4$ ratio of 1:2 would account for the molecular weight data. The structure of **8** was easily modified in the presence of strong donor solvents such as methanol, producing a dimeric complex with the expected two titanium atoms for each ligand (see the Supporting Information).

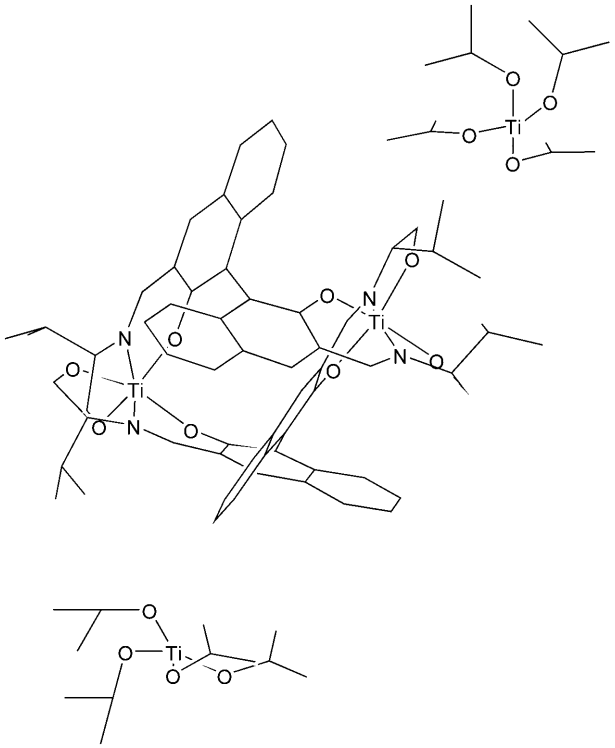


Figure 3. Possible predominant structure of tetranuclear titanium complex **8** derived from (R_aSS)-**1** in CH_2Cl_2.

The chosen model reaction was that of cyclohexene oxide ring opening with TMSCN (Scheme 1) in DCM at 25 °C (or −20 °C). No spontaneous reaction was observed under the experimental conditions. The chemical yields of the products after 24 h reaction, their enantiomeric purities and percentage of nitrile *vs.* isonitrile are summarized in Table 1. As can be seen from the data, the soft zinc(II) complex promoted the formation of only racemic isonitrile **4** (Table 1, run 1), whereas the use of the aluminium(III) complex led to the exclusive formation of racemic nitrile **5** (Table 1, run 2).

Both titanium complexes derived from (R_aSS)-**1** and (S_aSS)-**2** were much less active than those of zinc and aluminium (Table 1, runs 3 and 4). (1*S*,2*R*)-2-Cyanocyclohexan-1-ol derivative **5** was formed predominantly in the case of the **1**-Ti_2 complex with 89% *ee* (determined by chiral GC, Table 1, run 3) and in the case of **2**-Ti_2 the (1*R*,2*S*)-nitrile (*ee* 30%) was formed (Table 1, run 4). The configuration of **5** was assigned according to the sign of its optical rotation (see Experimental Section). A sizable amount of β-trimethylsilyloxy isonitrile **4**, apparently resulting from *N*-nucleophilic ARO by cyanide, was also found in the reaction mixture after detailed analysis by ^{1}H, ^{13}C NMR and IR-spectroscopy (Table 1, runs 3 and 4).[14,16] The absolute configuration of **4** was assigned according to the sign of the optical rotation of the 2-amino alcohol derived from **4** by hydrolysis[17] (see Experimental Section) and its *ee* was determined by chiral GC of the amino alcohol.[18] A reaction catalyzed by titanium(salen) complex **6** was slow and gave only nitrile with 40% *ee* (Table 1, run 5). Vanadium oxo(salen) chloride complex **7** gave no detectable amount of any products of ARO with TMSCN (Table 1, run 6). A mononuclear catalyst derived from **3** gave only racemic nitrile **5** in low yield (Table 1, run 7).

The results of runs 1, 2, 3, and 5 seemed to be easily rationalized by the hard/soft theory, as the soft zinc complex generated isonitrile, whereas aluminium and titanium complexes produced predominantly nitriles.[2,11,13,14] Unexpectedly however, there was a sig-

Table 1. ARO of *meso*-cyclohexene oxide (Scheme 1) with TMSCN in DCM.[a]

Run	Precatalyst	Conversion [%][b]	Nitrile:isonitrile[b]	*ee* of nitrile [%] (configuration)[c]	*ee* of isonitrile [%][d] (configuration)
1	**1**+2 equiv. of $ZnEt_2$	>99	only isonitrile[f]	–	0
2	**1**+2 equiv. of Al(O-*i*-Pr)$_3$	>99	>99:1	0	–
3	**1**+2 equiv. of Ti(O-*i*-Pr)$_4$	60	12:1	89 (1*S*,2*R*)	86 (1*S*,2*S*)
4	**2**+2 equiv. of Ti(O-*i*-Pr)$_4$	83	2:1	30 (1*R*,2*S*)	27 (1*R*,2*R*)
5	**6**	56	>99:1	40 (1*R*,2*S*)	–
6[e]	**7**	no reaction	–	–	–
7	**3**+1 equiv. of Ti(O-*i*-Pr)$_4$	20	>99:1	0	–

[a] The ligand (10.0 mg, 19.5 μmol), metal precursor (39 μmol) [in case of **3** it was 0.2 equiv. of the ligand and 0.2 equiv of Ti(O-*i*-Pr)$_4$ with respect to cyclohexene oxide], TMSCN (40 μL, 298 μmol) with respect to cyclohexene oxide (20 μL, 200 μmol) under Ar, stirring for 24 h in DCM (0.55 mL).

[b] Determined by ^{1}H NMR spectroscopy.

[c] Determined by chiral GC on a β-DM column.

[d] The isonitrile was hydrolyzed to give the β-hydroxy amine which was reacted with trifluoroacetic anhydride. The enantiomeric excess of the trifluoroacetate derivative was determined by chiral GC analysis.[18]

[e] No product of ARO with TMSCN was found by ^{1}H NMR spectroscopy.

[f] No traces of nitrile were found in the proton NMR spectrum which means that there is less than 0.5% of nitrile in the mixture.

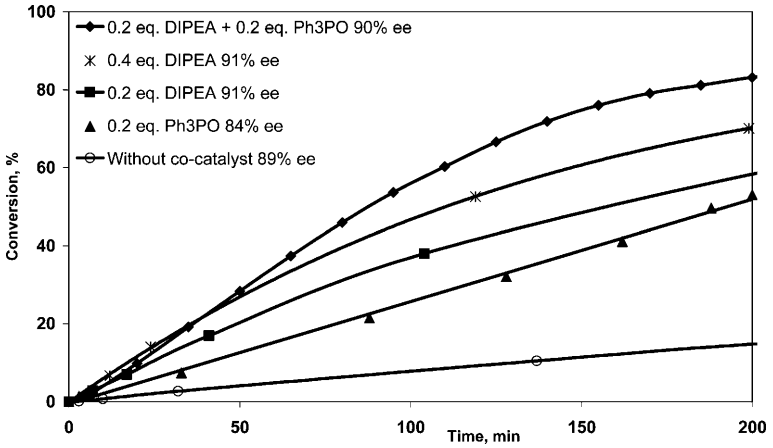


Figure 4. The rate of the ARO of *meso*-cyclohexene oxide with TMSCN promoted by titanium-catalysts generated from (R_aSS)-**1** and Ti(O-*i*-Pr)$_4$ with different quantities of Hunig's base and/or Ph_3PO added (equivalents relative to cyclohexene oxide), as monitored by ^{1}H NMR spectroscopy in CD_2Cl_2 (600 MHz).

nificant difference in the ratio of nitrile/isonitrile formed when reaction was promoted by the two diastereoisomeric complexes of titanium with ligands (R_aSS)-**1** (entry 3) and (S_aSS)-**2** (entry 4). Thus, there are three observations that had to be rationalized:

1) The relatively low activity of the titanium-based catalytic systems derived from **1** and **2**, as compared with the corresponding zinc- and aluminium-based systems (Table 1, runs 1, 2 and 3, 4). The accepted Lewis acidity order of the ions is opposite to the observed activity of the complexes.

2) It appeared that alteration of the steric arrangement of the ligand could result in a six-fold change in the nitrile/isonitrile ratio (Table 1, runs 3 and 4). Clearly, this was not accounted for by the hard/soft metal centre theory.

3) The nitrile and isonitrile formed under **1**-Ti$_2$ catalysis had the same stereochemistry (Table 1, entries 3 and 4). The difference in absolute configuration at C-2 is simply due to the differences in priorities in the Cahn–Ingold–Prelog priority rules.

In order to rationalize these observations, kinetic studies were undertaken. The consumption of the epoxide was monitored by following the disappearance of the resonances at 3.1 ppm. The appearance of the products was followed by the increase of the resonances at 2.4 ppm (nitrile) and 3.3 ppm (isonitrile).

The addition of bases and, in particular, Hunig's base (*N*,*N*-diisopropylethylamine, DIPEA) to the reaction mixture accelerated the reaction promoted by **1**-Ti$_2$ (Figure 4) and the increase in the rate was proportional to the amount of the base added (Figure 4). The enantioselectivity of the process increased to 91% when the ratio between the Hunig's base and titanium atoms reached 1:1. Addition of more base did not lead to a change in enantioselectivity, but unexpectedly, led to an increased amount of isonitrile product (see Table 2).

Table 2. ARO of cyclohexene oxide promoted by dinuclear titanium complexes derived from ligand (R_aSS)-**1** or (S_aSS)-**2** at room temperature in DCM.[a]

Entry	DIPEA	Nitrile-isonitrile[b]	*ee* **5** [%][c]	*ee* **4** [%][d]
1	0	12:1	89 (1*S*,2*R*)	nd
2	0.2 equiv.	6.1:1	91 (1*S*,2*R*)	nd
3	0.4 equiv.	5.2:1	91 (1*S*,2*R*)	nd
4	2.0 equiv.	4.0:1	91 (1*S*,2*R*)	nd
5[e]	0.2 equiv.	3.3:1	96 (1*S*,2*R*)	nd
6[f]	0.2 equiv.	2.1:1	93 (1*S*,2*R*)	90 (1*S*,2*S*)
7[g]	2.0 equiv.	1.2:1	13 (1*R*,2*S*)	nd
8[e,g]	2.0 equiv.	0.8:1	42 (1*R*,2*S*)	24 (1*R*,2*R*)

[a] 0.1 equiv of ligand (10.0 mg, 19.5 μmol), 0.2 equiv of Ti(O-*i*-Pr)$_4$ (11.4 μL, 39 μmol), 1.5 equiv. of TMSCN (40 μL, 298 μmol) with respect to cyclohexene oxide (20 μL, 200 μmol) in 0.55 mL of DCM.
[b] Determined by NMR spectroscopy.
[c] Enantiomeric excesses were determined by chiral GC.
[d] The isonitrile was hydrolyzed to give the β-hydroxy amine which was reacted with trifluoroacetic anhydride. The enantiomeric excess of the trifluoroacetamide derivative was determined by chiral GC analysis.[18]
[e] The reaction was carried out at −20 °C.
[f] 3.0 equiv. (80 μL, 596 μmol) of TMSCN were used.
[g] Ligand (S_aSS)-**2** was used instead of ligand **1**.

Some σ-donors, such as Ph_3PO, DMF and others, also accelerated the reaction, but after adding one equivalent of the donor relative to each titanium atom, no further increase in the rate was observed. In addition, both the base and the donor operated in concert, increasing the rate of the reaction (Figure 4) to a greater extent than each of them separately. Evidently, the mechanisms of their action are different.

The function of the donor might be to coordinate to the titanium ions in the complex, leading to the dissociation of the initial inactive tetrameric structure

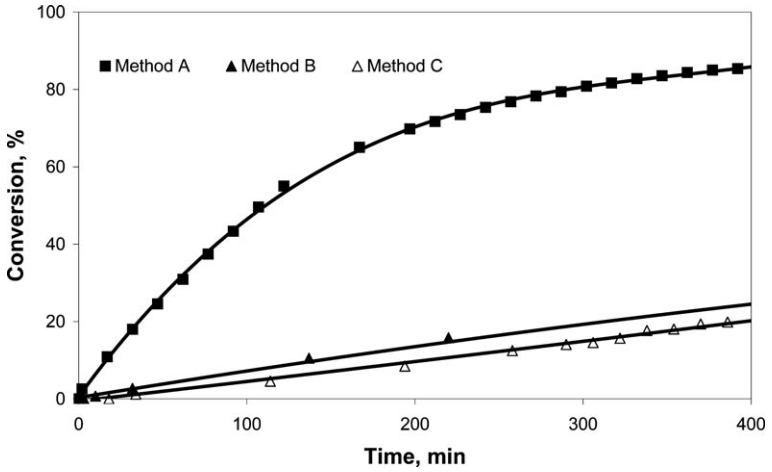


Figure 5. Reaction was monitored by ^{1}H NMR (600 MHz). Method A: 0.1 equiv. of ligand (10.0 mg, 19.5 μmol), 0.2 equiv. of Ti(O-*i*-Pr)$_4$ (11.4 μL, 39 μmol), 0.2 equiv. of DIPEA (6.8 μL, 39 μmol), 1.5 equiv. of TMSCN (40 μL, 298 μmol), 1 equiv. of cyclohexene oxide (200 μmol) with respect to the epoxide were added sequentially in CD_2Cl_2. Method B: the same as Method A but without DIPEA added. Method C: the same amount of the ligand and Ti(O-*i*-Pr)$_4$ were dissolved in CD_2Cl_2, the solvent was evaporated and the residue redissolved in CD_2Cl_2, 0.2 equiv. of DIPEA (6.8 μL, 39 μmol), 1.5 equiv. of TMSCN (40 μL, 298 μmol), and 1 equiv. of cyclohexene oxide were added sequentially in CD_2Cl_2.

(Figure 3) into more active monomeric units. One possibility was that DIPEA neutralized the HCN evolved by the reaction of liberated *i*-PrOH with TMSCN, producing reactive cyanide ions. The propensity of cyanide ions to activate silicon derivatives *via* supravalent complex formation is documented.[19]

This concept was supported by several experiments the results of which are presented graphically in Figure 5. Method A corresponds to an experiment where DIPEA was added to the reaction mixture with a combination of (R_aSS)-**1** and Ti(O-*i*-Pr)$_4$ already present. Method C corresponds to the experiment where a mixture of (R_aSS)-**1** and Ti(O-*i*-Pr)$_4$ in dichloromethane was evaporated under vacuum to remove the liberated *i*-PrOH. Then, dichloromethane, DIPEA, cyclohexene oxide, and TMSCN were added sequentially to the residue. In this case, the rate of the reaction dropped significantly and was similar to that of the reaction without any DIPEA added (Method B). The *ee* of the product (58%) was also low, compared to the 91% *ee* obtained in experiments without *i*-PrOH removal.

The rate of formation of the reaction product under the standard reaction conditions with cyclohexene oxide added last (see the legend to Figure 5) was best described by a first order rate equation in spite of the only 1:1.5 ratio of the reagents (epoxide and TMSCN).

There was a decrease in the rate of product formation if the amount of cyclohexene oxide was increased

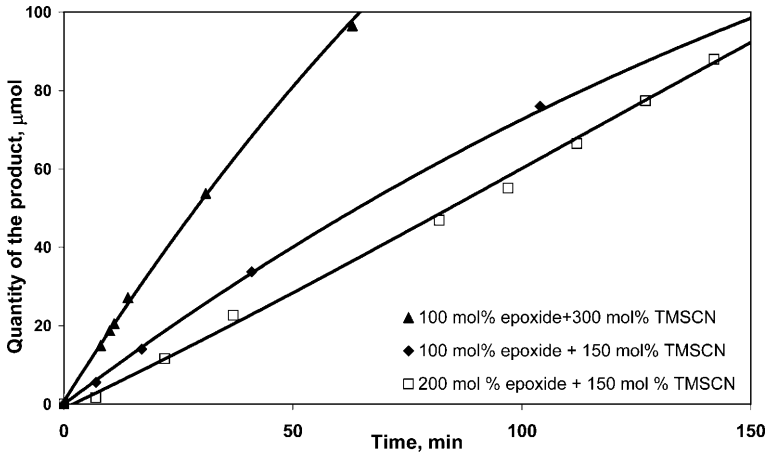
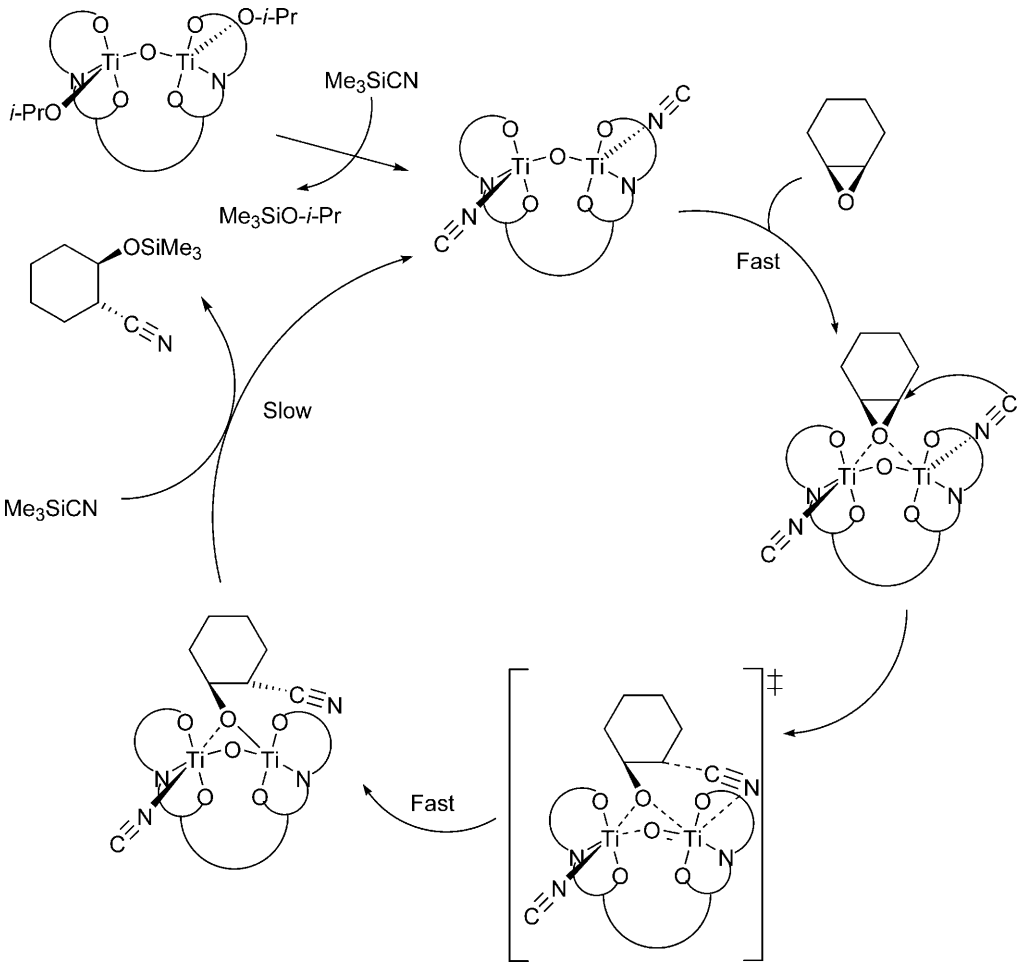


Figure 6. The dependence of reaction rate on the concentration of epoxide and TMSCN (in CD_2Cl_2). In all cases catalyst derived from (R_aSS)-**1** and DIPEA was added.



Scheme 2. Proposed mechanism for the epoxide ring-opening.

twofold (Figure 6). This can be rationalized by possible saturation of coordination positions of the titanium ions by the substrate. At the same time, a twofold increase in the concentration of TMSCN led to a two-fold acceleration of the reaction (Figure 6). A mechanistic scheme that may account for the observed data is shown in Scheme 2. Accordingly, the first stage of the reaction is the interaction of the initial complex with TMSCN, producing a catalytic cyanide complex.

The next stage is cyclohexene oxide complexation, which is a fast step. The intramolecular attack of cyanide on the complexed substrate is also fast and facilitated by the charge compensating breaking of the oxygen bridge. As a result, a new complex is formed with the intermediate alkoxide strongly held by the two titanium ions. The slow step is regeneration of the catalytic species with formation of the final silylated hydroxy nitrile. Such a scheme explains why there is almost no dependence of the reaction rate on the concentration of the substrate and the observed first order dependence on the concentration of TMSCN. In addition, it explains the apparent contradiction – poor catalysis by a strong Lewis acid (titanium ion), as compared to good catalysis by a weak Lewis acid (zinc ion), as documented in Table 1. Evidently, the regeneration of the catalyst from the intermediate, strongly held by two titanium cations, makes the total reaction rate slow in comparison with the zinc- or aluminium-based catalysts.

Additional support for the mechanism comes from ^{1}H NMR monitoring of the reaction mixture in CD_2Cl_2 (Figure 7). The reaction was conducted with TMSCN added first to complex **8** and 0.2 equivalents of DIPEA followed by cyclohexene oxide. The formation of the silylated product in the solution was monitored, following the appearance of resonances at 0.18 ppm (resonances of the Me_3SiO group of silylated hydroxy nitrile and silylated hydroxy isonitrile). The relative amount of coordinated alkoxide was calculated from the difference of the total amount of the nitrile formed (silylated and non-silylated), assessed by resonances at 2.4 ppm, and that of the silylated products (Figure 7). As can be seen from the data, an

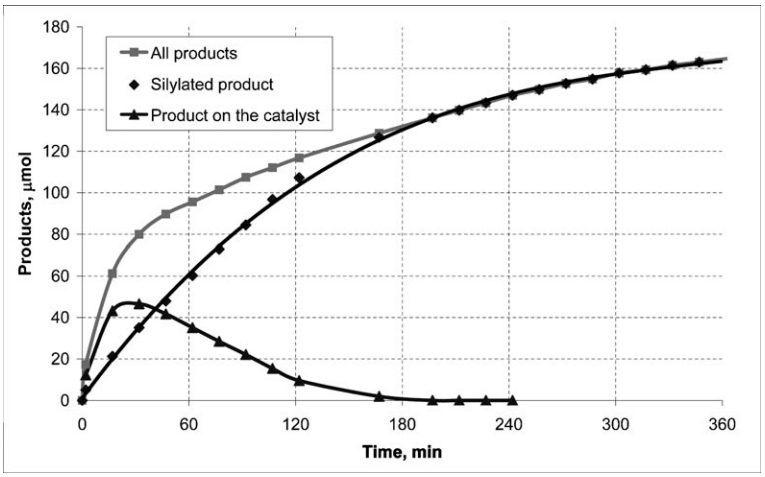


Figure 7. The variation of the silylated product and product on the catalyst (oxynitrile on the catalyst) with time during the ARO of *meso*-cyclohexene oxide with TMSCN promoted by (R_aSS)-**1** and Ti(O-*i*-Pr)$_4$ in DCM. Order of addition: 1) 5 mol% of **8**, 2) 20 mol% of DIPEA, 3) 150 mol% of TMSCN, 4) 100 mol% (195 μmol) of epoxide.

unsilylated product was accumulated at the beginning of the reaction. After 25 min (Figure 7, the maximum on the triangle marked curve) the complex was recovered by precipitation with hexane. Treatment of the precipitate with TMSCl furnished approximately one equivalent of silylated hydroxy nitrile for each titanium atom and the product had >99% *ee* [(1*S*,2*R*)-configuration]. No traces of isonitrile were found in the product, according to ^{1}H NMR analysis.

All these findings corroborate the early stage of the reaction, according to Scheme 2. At the beginning of the reaction, when most of the complex was converted to its CN form, the formation of coordinated alkoxide occurred very rapidly. The next step, silylation of the alkoxide and the regeneration of the catalytic species, was slow.

However, the accumulation of the product in solution (Figure 7, curve with square markers) had no induction period, as would have been expected had the rapidly formed complex with two coordinated alkoxides been the real catalytic intermediate.

Evidently, the intermediate was just a side product and not a catalytic intermediate. No accumulation of such an intermediate complex was observed if the order of addition of the reagents was changed to first adding the epoxide. This suggests that the real catalytically active species had a very low concentration in the reaction mixture and most likely had only one alkoxide coordinated to both titanium atoms (Scheme 2).

This experiment also seemed to indicate that the intramolecular attack of coordinated cyanide on the epoxide resulted in the exclusive formation of hydroxy nitrile. This raises the question as to how the isonitrile was formed. Furthermore, as detailed in Table 2 and Figure 5, the addition of Hunig's base to the reaction mixture accelerated the reaction promoted by the titanium complex generated from **1**.

The enantioselectivity of the process increased to 91% when the ratio between the base and titanium atoms reached 1:1 (Table 2, entry 2). Addition of more base did not lead to a change in enantioselectivity (Table 2, entries 3 and 4) but, unexpectedly, led to an increased amount of isonitrile product (Table 2, entries 1–4). The ratio of nitrile/isonitrile changed from 12/1 (Table 2, entry 1) to 6/1 (Table 2, entry 2) with the addition of 0.2 equivalents of DIPEA.

An additional increase in the amount of base to 0.4 and 2.0 equivalents at room temperature gave nitrile/isonitrile ratios of 5/1 and 4/1, respectively (Table 2, entries 3 and 4). Lowering of the reaction temperature to −20 °C with 0.2 equivalents of base further increased the proportion of isonitrile, furnishing a 2/1 ratio of nitrile/isonitrile (Table 2, run 5). As expected, the titanium complex generated from (S_aSS)-**2** gave an even greater ratio of nitrile/isonitrile equal to 0.8/1 with 2.0 equivalents of base at −20 °C (Table 2, entry 8).

It appeared that both nitrile and isonitrile formation occurred within the same chiral coordination sphere of the titanium complexes, as both products had almost the same (90%) *ee* values (Table 2, entry 6). In addition, the stereochemistry of the isonitrile formed was the same as that of the nitrile in the case of both Ti-**2** and Ti-**1** precatalysts (Table 2, entries 6 and 8). This suggests that there is no difference in the orientation of the coordinated substrate within the coordination sphere of the Ti complex relative to the attacking nucleophile in the transition states leading to nitrile- and isonitrile-containing products.

Undoubtedly, the hard/soft metal center principle had to be modified to account for the observations

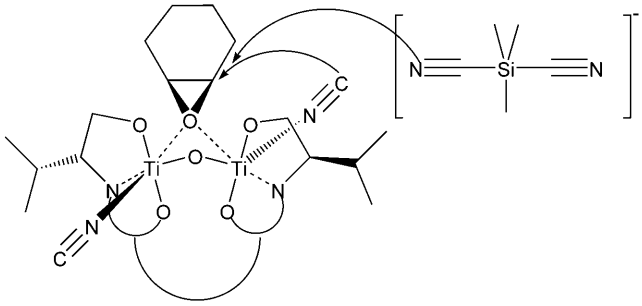


Figure 8. Rationalization of the nitrile/isonitrile dichotomy.

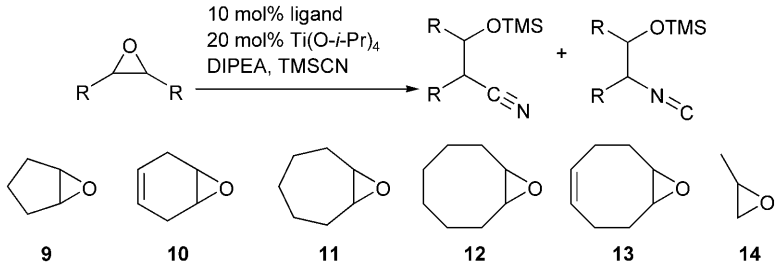
and a mechanistic model devised to rationalize the unusual effect of the reaction conditions on the **5**/**4** ratio.

A mechanism to explain these results is shown in Figure 8. This is based on the fact that nitrile formation followed an intramolecular reaction pathway with the cyanide coordinated by its nitrogen atom to titanium ion (hard acid/hard base), attacking the coordinated epoxide activated by the two titanium ions (Scheme 2). The result is C–C bond formation to give the nitrile, as predicted by the hard/soft principle. A parallel reaction pathway was assumed to involve the direct attack of TMSCN (or cyanide ion pair $[HDIPEA]^+CN^-$) at the coordinated epoxide. As TMSCN exists predominantly as the NC–TMS isomer, this results in C–N bond formation to give isontrile. The positive effect of the addition of Hunig's base can be explained by an increase in the amount of cyanide ion generated from the base and HCN (formed from TMSCN and isopropyl alcohol). Thus, the overall increase in the reaction rate is partly due to the rate of direct TMSCN addition which results in a greater proportion of isonitrile being formed.

The great difference in the stereoselectivities of ARO in cases of (R_aSS)-**1** and (S_aSS)-**2** catalysis (Table 1, runs 3 and 4, Table 2, runs 6 and 8) could be rationalized by a simple stereochemical model of the transition state (see the Supporting Information).

The amount of catalytic Ti–NC species in solution should be constant and independent of the TMSCN

Table 3. ARO of different epoxides promoted by dinuclear complexes generated from (R_aSS)-**1** or **2**.[a]



9 **10** **11** **12** **13** **14**

Entry	Ligand	Epoxide	Conversion [%]	Nitrile/isonitrile	*ee* (nitrile) [%]	*ee* (isonitrile) [%]
1[a]	**1**	**9**	98	4:1	94	93
2[a]	**2**	**9**	70	1.3:1	−7	−25
3[a]	**1**	**10**	81	4:1	90	nd
4[b]	**2**	**10**	93	1.6:1	−26	nd
5[a]	**1**	**10**	>99	4:1	94	94
6[a]	**2**	**10**	78	1.6:1	−26	nd
7[a]	**1**	**11**	>99	5:1	96	nd
8[a]	**2**	**11**	70	1.2:1	−18	nd
9[b]	**1**	**11**	65	3:1	91	nd
10[b]	**2**	**11**	79	2.5:1	−12	nd
11[a]	**1**	**12**	no reaction	–	–	–
12[a]	**1**	**13**	54	5:1	91	nd
13[c]	**1**	**13**	10	only nitrile	>99	–
14[d]	**1**	**14**	37	only nitrile	75	–

[a] The order of addition: 1) 10 mol% of the catalyst, 2) 200 mol% DIPEA, 3) 100 mol% of the epoxide, 4) 200 mol% of TMSCN, 118 h, −15 °C, CH_2Cl_2.

[b] 1) 10 mol% of the catalyst, 2) 20 mol% of the co-catalyst, 3) 100 mol% of the epoxide, 4) 150 mol% of TMSCN, 24 h, room temperature, CH_2Cl_2.

[c] 1) 10 mol% of the catalyst, 2) 20 mol% DIPEA, 3) 100 mol% of the epoxide, 4) 300 mol% of TMSCN, 72 h, −20 °C, CH_2Cl_2.

[d] 1) 10 mol% of the catalyst, 2) 20 mol% of the co-catalyst, 3) 200 mol% of the epoxide, 4) 100 mol% of TMSCN, 24 h, room temperature, CH_2Cl_2, the attack occurred at the least hindered end of the epoxide.

concentration. Therefore, the relative rate of formation of nitrile had also to be independent of this factor. On the other hand, the rate of formation of isonitrile should increase as the concentration of TMSCN increased. This was found to be the case and a three-fold increase in the amount of isonitrile formed was observed when the concentration of TMSCN was doubled (Table 2, entries 2 and 6).

Some other epoxides were also tested in the same reaction. As expected, in the case of epoxides **9**–**11** the catalyst derived from (R_aSS)-**1** with DIPEA was more active and stereoselective than the catalyst derived from (S_aSS)-**2** with DIPEA (Table 3, entries 1–10). However, a catalyst based on ligand (S_aSS)-**2** gave more isonitrile product (Table 3, entries 1, 3, 5, 7 *vs.* 2, 4, 6, 8). In the case of epoxides having smaller rings than cyclooctene oxide, the catalysts are active and highly enantioselective with *ee*s of both nitrile and isonitrile of 93–96%. For the reaction of cyclooctene oxide with TMSCN, the catalysts are completely inactive (Table 3, entry 11), but if cyclooctene oxide is changed to cyclooctadiene oxide, the reaction proceeds with moderate yield but very high *ee*. In all cases nitrile and isonitrile can by easily separated (see the Supporting Information).

Run 14 clearly indicates a potential of the catalyst to resolve racemic epoxides. The reaction could generate different regio- and stereoisomers, but for propylene oxide at room temperature, only one 2-hydroxy nitrile product was found in the reaction mixture with 75% *ee* and in 37% chemical yield (max. 50% yield).

Conclusions

In conclusion, we have elaborated a highly efficient Ti-based dinuclear catalytic system for the ARO of epoxides with TMSCN. The unprecedented dichotomy of C–C versus N–C bond formation in the reaction was traced to intra- *versus* intermolecular catalytic reactions observed in this dinuclear system. Studies on the further application of this catalytic system are in progress and will be reported in due course.

Experimental Section

Specific rotations were measured on a Perkin–Elmer 241 polarimeter and are reported as follows: $[\alpha]_{\lambda}^{T}$: $[\alpha]^{T}_{\lambda}$ (concentration in g/100 mL, solvent). Enantiomeric excesses were determined by GLC. Analytical ultracentrifugation was conducted using a MOM 3180 (Hungary) ultracentrifuge with differential Philpot-Svensson's optics.[12a]

^{1}H NMR spectra were recorded on Bruker Avance 300 (300 MHz) and Avance 600 (600 MHz) spectrometers and are reported in parts per million using the solvent as internal standard. Data are reported as s = singlet, d = doublet, dd = double doublet, t = triplet, q = quartet, m = multiplet, b = broad; coupling constant(s) in Hertz, integration. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker Avance 300 (75.5 MHz) spectrometer and are reported in parts per million using the solvent as internal standard.

Dichloromethane (or CD_2Cl_2) was distilled under argon from P_2O_5 and dried over 3 Å molecular sieves (1 g sieves per 1 mL dichloromethane). All reagents were purchased from Aldrich or Acros, and used without purification unless otherwise stated.

Ligands **1**, **2**, **3**, and complexes **7** and **8** were available from our previous work.[12,15]

Asymmetric Ring-Opening of Epoxides with TMSCN (General Procedure).

Ti(O-*i*-Pr)$_4$ (11.4 μL, 39 μmol) was added to a solution of the ligand **1** (or **2**) (10 mg, 19.5 μmol) in DCM (0.5 mL). If an additive was present it was added next. Epoxide (195 μmol) was added to the reaction mixture. After 2 min TMSCN (40 μL, 298 μmol) was added. Reaction time depends on the additive. The solvent was evaporated and hexane (or petroleum ether) (3 mL) was added, The precipitated complex was filtered off and the solution was evaporated under vacuum and analyzed by GC to determine the enantiomeric excess of the nitrile. To asses the enantiomeric purity of the isonitrile (2-isocyanocyclohexyloxy)trimethylsilane, **4** was converted into the amino alcohol by refluxing the reaction mixture with 6 M HCl in methanol for 16 h. The reaction mixture was evaporated and washed with chloroform. The residue was reacted with TFAA to produce the derivative for GLC analysis. GLC analysis: β-DM column $T_{(column)} = 120\,^{\circ}C$, $T_{(evaporator)} = T_{(detector)} = 230\,^{\circ}C$; pressure of the He = 15 psi; $T_R = 19.1$ min (1*R*,2*R*)-isomer, $T_R = 21.3$ min (1*S*,2*S*)-isomer.

Recovery of Trimethylsilyl Derivative of (1*S*,2*R*)-2-Cyanocyclohexan-1-ol and Establishment of its Configuration

Ligand **1** (10.0 mg, 19.5 μmol) was dissolved in DCM (0.55 mL). Ti(O-*i*-Pr)$_4$ (11.4 μL, 39 μmol) was then added. The solution changed color from orange to orange-red. Then, DIPEA (Hunig's base, *N*,*N*-diisopropylethylamine) (6.8 μL, 39 μmol) and TMSCN (40 μL, 298 μmol) were added followed by cyclohexene oxide (20 μL, 195 μmol). After 25–30 min the reaction was stopped by adding hexane (3 mL) to precipitate the titanium complex, which was filtered, and treated with 4 equivalents of TMSCl in CH_2Cl_2 to recover the nitrile. The formed Cl–Ti complex was filtered, and washed with hexane. The filtrate and washings were combined and evaporated to give the silylated hydroxy nitrile with *ee* > 99%, according to chiral GLC. The product did not contain any trace of isonitrile. ^{1}H NMR ($CDCl_3$): $\delta = 0.17$ (s, 9H), 1.25–1.33 (m, 3H), 1.55–1.75 (m, 3H), 1.90–2.07 (m, 1H), 2.08–2.11 (m, 1H), 2.38–2.44 (m, 1H), 3.64–3.70 (m, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 0.18$, 23.3, 23.9, 28.2, 34.7, 37.7, 71.1, 121.6. *(1S,2R)-Isomer of 2-cyanocyclohexan-1-ol derivative [or (1R,2S)-2-trimethylsilyloxycyclohexane-1-carbonitrile]*; $[\alpha]_D^{25}$: +45.0 (*c* 0.42, DCM) for 99% *ee* {lit.[2]

$[\alpha]_D^{27}$: −38.5 (*c* 4.52, DCM) for *(1R,2S)-isomer of 2-cyanocyclohexan-1-ol derivative* of 91% *ee (or 1S,2R)-2-trimethylsilyloxycyclohexane-1-carbonitrile)*}.

Absolute Configuration of 4

(2-Isocyanocyclohexyloxy)trimethylsilane **4**: ^{1}H NMR ($CDCl_3$): $\delta = 0.2$ (s, 9H), 1.25–1.33 (m, 3H), 1.55–1.75 (m, 3H), 1.90–2.07 (m, 1H), 2.08–2.11 (m, 1H), 3.30–3.35 (m, 1H), 3.60–3.65 (m, 1H); ^{13}CNMR ($CDCl_3$): $\delta = 0.27$, 23.0, 23.2, 31.3, 33.4, 58.7, 72.9 155.1.

After hydrolysis of **4** the corresponding hydrochloride was converted to its free base as follows: To a solution of 0.5 M NaOMe in MeOH (0.5 mL) was added 2-aminocyclohexan-1-ol hydrochloride (36.5 mg, 0.24 mmol). The mixture was stirred for 1 h at room emperature. The precipitated NaCl was removed by filtration through Celite and washed with MeOH (5 mL). The solvent was removed under reduced pressure. The absolute configuration of the initial isonitrile was assumed to be the same as the amino alcohol and, consequently, it was determined by measuring the optical rotation of the amino alcohol and comparing the data with that in the literature.[17] *(1R,2R)-2-Aminocyclohexanol,* $[\alpha]_D^{27}$: −15.4 (*c* 0.2 MeOH) for 27% *ee* {lit.[17] $[\alpha]_D^{25}$: +48.8 (*c* 0.19 MeOH) (1*S*,2*S*)-isomer}.

General Method for *meso*-Epoxide Synthesis

Cyclooctadiene oxide: A solution of alkene (94 mmol) in DCM was cooled in an ice bath. *m*-CPBA (70%, 23 g, 93 mmol) was added over 3 h. The reaction mixture was stirred for 72 h at room temperature, then washed with a saturated aqueous solution of sodium bicarbonate (100 mL), water (100 mL) and dried with anhydrous magnesium sulfate. Solvent was evaporated under vacuum and the crude product was distilled under vacuum; yield: 64%. ^{1}H NMR (300 MHz, $CDCl_3$): δ_1.95–2.22 (m, 6H); 2.35–2.52 (m, 2H); 2.97–3.08 (m, 2H); 5.50–5.63 (m, 2H).

Cyclohexadiene oxide: A solution of cyclohexadiene (5 mL, 52 mmol) in DCM (300 mL) was cooled in an ice bath. *m*-CPBA (70%, 13 g, 52 mmol) was added over 0.5 h. The reaction mixture was stirred for 24 h at room temperature, then purified by flash chromatography on basic Al_2O_3 (eluent CH_2Cl_2). The product was then distilled under vacuum; yield: 4.0 g (85%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.30$–2.70 (m, 4H); 3.10–3.40 (m, 2H); 5.40–5.50 (m, 2H).

Cycloheptene oxide: A solution of cycloheptene (2 mL, 17.1 mmol) in DCM (150 mL) was cooled in an ice bath. *m*-CPBA (70%, 4.4 g, 18 mmol) was added over 0.5 h. The reaction mixture was stirred for 24 h at room temperature, then purified by flash chromatography on basic Al_2O_3 (eluent CH_2Cl_2). The product was then distilled under vacuum; yield: 1.64 g (84%). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.10$–1.70 (m, 6H); 1.80–2.05 (m, 4H); 3.05–3.12 (m, 2H).

Acknowledgements

We thank INTAS (05-1000008-7822) for financial support.

References

[1] C. Schneider, *Synthesis* **2006**, 3919–3944.

[2] S. E. Schaus, E. N. Jacobsen, *Org. Lett.* **2000**, *2*, 1001–1004.

[3] a) I. M. Pastor, M. Yus, *Current Organic Chemistry*, **2005**, *9*, 1–29; b) M. Pineschi, *Eur. J. Org. Chem.* **2006**, 4979–4988.

[4] a) H. Yamashita, *Bull. Chem. Soc. Jpn.* **1988**, *61*, 1213–1220; b) M. Hayashi, K. Kohmura, N. Oguni, *Synlett* **1991**, 774–776; c) W. A. Nugent, *J. Am. Chem. Soc.* **1992**, *114*, 2768–2769; d) B. W. McCleland, W. A. Nugent, M. G. Finn, *J. Org. Chem.* **1998**, *63*, 6656–6666; e) L. E. Martinez, J. L. Leighton, D. H. Carsten, E. N. Jacobsen, *J. Am. Chem. Soc.* **1995**, *117*, 5897–5898; f) K. B. Hansen, J. L. Leighton, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 10924–10925; g) R. G. Konsler, J. Karl, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 10780–10781; h) H. Adolfsson, C. Moberg, *Tetrahedron: Asymmetry* **1995**, *6*, 2023–2031; i) J. L. Leighton, E. N. Jacobsen, *J. Org. Chem.* **1996**, *61*, 389–390; j) J. F. Larrow, S. E. Schaus, E. N. Jacobsen, *J. Am. Chem. Soc.* **1996**, *118*, 7420–7421.

[5] a) S. Matsunaga, J. Das, J. Roels, E. M. Vogl, N. Yamamoto, T. Iida, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 2252–2260; b) C. Schneider, A. R. Sreekanth, E. Mai, *Angew. Chem.* **2004**, *116*, 5809–5812; *Angew. Chem. Int. Ed.* **2004**, *43*, 5691–5694.

[6] a) C. A. G. M. Weijers, *Tetrahedron: Asymmetry* **1997**, *8*, 639–647; b) L. Zhao, B. Han, Z. Huang, M. Miller, H. Huang, D. S. Malashock, Z. Zhu, A. Milan, D. E. Robertson, D. P. Weiner, M. J. Burk, *J. Am. Chem. Soc.* **2004**, *126*, 11156–11157; c) J. M. Ready, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 2687–2688.

[7] a) H. Yamashita, T. Mukaiyama, *Chem. Lett.* **1985**, *14*, 1643–1646; b) T. Iida, N. Yamamoto, H. Sasai, M. Shibasaki, *J. Am. Chem. Soc.* **1997**, *119*, 4783–4784; c) M. H. Wu, E. N. Jacobsen, *J. Org. Chem*, **1998**, *63*, 5252–5254; d) J. Wu, X. L. Hou, L. X. Dai, L. J. Xia, M. H. Tang, *Tetrahedron: Asymmetry* **1998**, *9*, 3431–3436; e) Y.-J. Chen, C. Chen, *Tetrahedron: Asymmetry* **2007**, *18*, 1313–1319.

[8] M. Yang, C. Zhu, F. Yuan, Y. Huang, Y. Pan, *Org. Lett.* **2005**, *7*, 1927–1930.

[9] a) K. Arai, M. M. Salter, Y. Yamashita, S. Kobayashi, *Angew. Chem.* **2007**, *119*, 973–975; *Angew. Chem. Int. Ed.* **2007**, *46*, 955–957; b) R. I. Kureshy, S. Singh, N. H. Khan, S. H. R. Abdi, E. Suresh, R. V. Jasra, *Eur. J. Org. Chem.* **2006**, 1303–1309; c) F. Carree, R. Gil, J. Collin, *Org. Lett.* **2005**, *7*, 1023–1026; d) X. L. Hou, J. Wu, L. X. Dai, L. J. Xia, M. H. Tang, *Tetrahedron: Asymmetry* **1998**, *9*, 1747–1752; e) S. Sagawa, H. Abe, Y. Hase, T. Inaba, *J. Org. Chem.* **1999**, *64*, 4962–4965; f) A. Sekine, T. Ohshima, M. Shibasaki, *Tetrahedron* **2002**, *58*, 75–82; g) S. Azoulay, K. Manabe, S. Kobayashi, *Org. Lett.* **2005**, *7*, 4593–4595; h) C. Ogawa, S. Azoulay, S. Kobayashi, *Heterocycles* **2005**, *66*, 201–206; i) F. Carree, R. Gil, J. Collin, *Tetrahedron Lett.* **2004**, *45*, 7749–7751; j) R. I. Kureshy, S. Singh, N. Khan, S. H. R. Abdi, S. Agrawal, V. J. Mayani, R. V. Jasra, *Tetrahedron Lett.* **2006**, *47*, 5277–5279.

[10] a) W. A. Nugent, *J. Am. Chem. Soc.* **1998**, *120*, 7139–7140; b) S. E. Denmark, P. A. Barsanti, K. T. Wong, R. A. Stavenger, *J. Org. Chem.* **1998**, *63*, 2428–2429; c) B. Tao, M. M .C. Lo, G. C. Fu, *J. Am. Chem. Soc.* **2001**, *123*, 353–354; d) C. E. Garrett, G. C. Fu, *J. Org. Chem.* **1997**, *62*, 4534–4535; e) M. Nakaijama, M. Saito, M. Uemura, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 8827–8829; f) E. Tokuoka, S. Kotani, H. Matsunaga, T. Ishizuka, S. Hashimoto, M. Nakaijama, *Tetrahedron: Asymmetry* **2005**, *16*, 2391–2392; g) S. Bruns, G. Haufe, *J. Fluorine Chem.* **2000**, *104*, 247–254; h) G. Haufe, S. Bruns, *Adv. Synth. Catal.* **2002**, *344*, 165–171.

[11] a) B. M. Cole, K. D. Shimizu, C. A. Krueger, J. P. A. Harrity, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1996**, *108*, 1776–1779; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 15, 1668–1671; b) K. D. Shimizu, B. M. Cole, C. A. Krueger, K. W. Kuntz, M. L. Snapper, A. H. Hoveyda, *Angew. Chem.* **1997**, *109*, 1782–1785; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 1704–1707, 1703–1707.

[12] a) Y. N. Belokon, D. Chusov, D. A. Borkin, L. V. Yashkina, A. V. Dmitriev, D. Katayev, M. North, *Tetrahedron: Asymmetry* **2006**, *17*, 2328–2333; b) Y. N. Belokon, D. Chusov, T. V. Skrupskaya, D. A. Borkin, L. A. Yashkina, K. A. Lysenko, M. M. Ilyin, T. V. Strelkova, G. I. Timofeeva, A. S. Peregudov, M. North, *Russ. Chem. Bull.* **2008**, *57*, 1981–1988.

[13] B. Saha, M.-H. Lin, T. V. RajanBabu, *J. Org. Chem.* **2007**, *72*, 8648–8655.

[14] K. Imi, N. Yanagihara, K. Utimoto, *J. Org. Chem.* **1987**, *52*, 1013–1016.

[15] a) Y. N. Belokon, S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Larichev, M. A. Moscalenko, M. North, C. Orizu, V. I. Tararov, M. Tasinazzo, G. I. Timofeeva, L. V. Yashkina, *J. Am. Chem. Soc.* **1999**, *121*, 3968–3973; b) Y. N. Belokon, V. I. Maleev, M. North, D. L. Usanov, *Chem. Commun.* **2006**, 4614–4616;c) Y. N. Belokon, W. Clegg, R. W. Harrington, V. I. Maleev, M. North, M. O. Pujol, D. L. Usanov, C. Young, *Chem. Eur. J.* **2009**, *15*, 2148–2165.

[16] P. G. Gassman, T. L. Guggenheim, *J. Am. Chem. Soc.* **1982**, *104*, 5849–5850.

[17] F. G. Glansdorp, G. L. Thomas, J. K. Lee, J. M. Dutton, G. P. C. Salmond, M. Welch, D. R. Spring, *Org. Biomol. Chem.* **2004**, *2*, 3329–3336; A. Chaterjee, M. Sasikumar, N. N. Joshi, *Synth. Commun.* **2007**, *37*, 1727–1733; A. Nishida, F. Shirato, M. Nakagawa, *Tetrahedron: Asymmetry* **2000**, *11*, 3789–3805.

[18] a) C. Zhu, F. Yuan, W. Gu, Y. Pan, *Chem. Commun.* **2003**, 692–693; b) F. Yuan, C. Zhu, J. Sun, Y. Liu, Y. Pan, *J. Organomet. Chem.* **2003**, *682*, 102–107.

[19] Y. Belokon, E. Ishibashi, H. Nomura, M. North, *Chem. Commun.* **2006**, 1775–1777.

