Titanocene-Catalysed Enantioselective Opening of *meso*-Epoxides

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Abstract: A comparison of different titanium catalysts in the enantioselective opening of *meso*-epoxides has been carried out. The best catalyst is readily available in both enantiomers from menthol and allows for a highly enantioselective reaction.

Keywords: enantioselectivity; epoxides; diastereoselectivity; radical reactions; titanium

Epoxides are valuable starting materials in organic synthesis due to their easy accessibility and the high reactivity of the strained three-membered ring. The enantioselective opening of *meso*-epoxides *via* S_N2 reactions has become a major focus of enantioselective catalysis.[1] A different approach towards epoxide opening is constituted by electron transfer.[2] The resulting radical transformations are complementary to the S_N2 reactions in terms of chemoselectivity and constitute examples of reagent controlled radical reactions.[3] We have only recently developed the first catalytic[4] and the first catalytic enantioselective versions[5] of this type of reaction. A serious limitation of our previous system is, however, the limited accessibility of both enantiomers of the catalyst and its lengthy preparation, also the enantioselectivities are not ideal in all cases.[6] In this communication we describe the evolution of a catalyst that can be easily synthesised in both enantiomers and that is as least as efficient in terms of enantioselectivity and isolated yield of the product.

We decided to investigate chiral, non-racemic titanocene complexes that are readily available from simple starting materials and that have been used in enantioselective catalysis before.[7] The results are compared to the reactions with the previously described catalyst **3** and are summarised in Table 1. The complexes used in this study are shown in Figure 1. They were tested in the reductive opening of the epoxide **5** as shown in Figure 2. The absolute stereochemistry of **6** was established by comparison with a sample derived from (*S*)-malic acid.

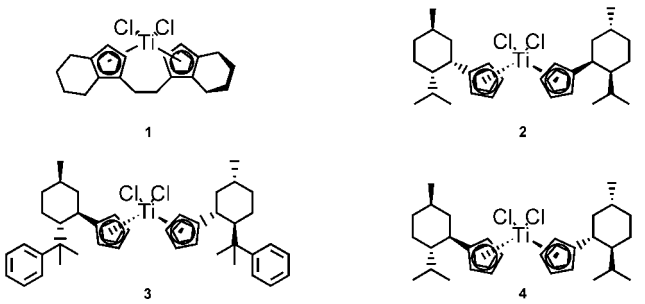

Figure 1. Titanocene complexes investigated in this study.

Table 1. Comparison of complexes **1** – **4** in the standard reaction of **5**.

Catalyst	Yield [%]	ee [%][a]
1	55	56[b]
2	45 – 51	20 – 52[b]
3	71	93[c]
4	76	94[c]

[a] By GC on a heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4) column.
[b] (*R*)-**6** formed preferentially.
[c] (*S*)-**6** formed preferentially.

ansa-Metallocene **1**[8] and its zirconium analogue, that are readily available in multi gram quantities, have recently been used with great success in enantioselective catalysis.[9,10,11] In our reaction, **1** proved to be less well suited. With 10 mol % of the catalyst, **6** was obtained in 55% yield and an enantiomeric excess of only 56%.

Complex **2** that can be synthesised in three steps from (−)-menthol without the necessity of column chromatography[12] gave variable and unsatisfactory results. Compound **6** was obtained in up to 51% yield and an ee of up to 52%. The reaction is highly sensitive to traces of oxygen and water.

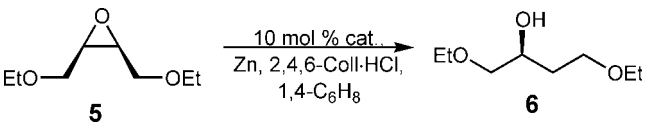

Figure 2. Standard test reaction for catalyst evaluation (for details, see Representative Procedure).

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In asymmetric synthesis with chiral auxiliaries it is well documented that a more efficient pattern than *neo*-menthol for achieving high selectivities is the 8-phenylmenthol arrangement.[13] Vollhardt and Halterman have prepared complex **3** containing the 8-phenylmenthol ligand from (+)-pulegone in six steps.[6] Unfortunately, the synthesis involves a tedious separation of diastereoisomers by column chromatography at an early stage. Additionally, only (+)-pulegone is available at reasonable price [6 € per g vs. 110 € per g for (−)-pulegone]. Alcohol **6** was gratifyingly obtained in 72% yield with an ee of 93% with 10 mol % **3**. The results of an X-ray analysis of **3** suggest that the high enantioselectivity is due to a conformational locking of the cyclopentadienyl ligand by the aryl group.[5b]

We then decided to synthesise **4**[12] in order to validate the importance of the phenyl group in **3** and were surprised to find that **4** gave a slightly better result than **3**. Similar to **3** the cyclopentadienyl ligand is conformationally locked but this time by an interaction with the 2-propyl group as determined by an X-ray analysis and NMR study. Although complexes **3** and **4** show similar conformational preferences the chiral pocket of **4** is somewhat wider.[5b]

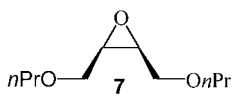
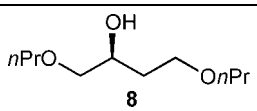
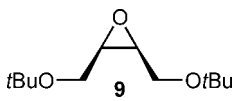
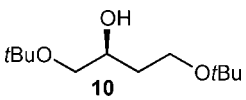
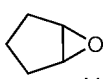
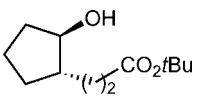
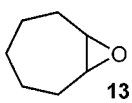
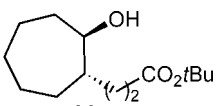
The usefulness of **4** could be of general interest for ligand design in asymmetric catalysis with metallocene catalysts because so far the phenylmenthyl group was regarded as being distinctly superior to the menthyl group.[13] From a practical point of view the use of **4** is clearly more advantageous, because it is readily accessible in both enantiomers from (+)- or (−)-*neo*-menthol without column chromatography, respectively.[12]

A direct comparison of **4** and **3** demonstrates the superiority of **4** as summarised in Table 2.

The reductive opening (C-H bond formation) was investigated for the epoxides **7** and **9**. The bis(*n*-propyl) epoxide **7** gave essentially the same ee with **3** and with **4**. The opening of the bulky substrate bis (*tert*-butyl) epoxide **9** is instructive: compound **4** gave a distinctly higher ee than **3** indicating that a wider chiral pocket is necessary for achieving better enantioselectivity in this case.

In the C–C bond forming reactions **4** proved to be more useful than **3** as well. For cyclopentene oxide **11** better enantioselectivity of epoxide opening was observed [81% (84% from analysis of the ^{19}F NMR spectra of the Mosher esters) vs. 74%] with **4** while in both cases the diastereoselectivity of the radical addition to *tert*-butyl acrylate was excellent (> 96 : < 4). With cycloheptene oxide **13** as substrate both catalysts performed essentially equally well concerning the enantioselectivity of epoxide opening and the diastereoselectivity of the addition reaction (*trans*:*cis* = 87:13). Thus, in both cases the bulky ligands induce approach of the acrylate to the radical from the face opposite of titanium.

Table 2. Performance of **3** and **4** in C-H and C-C bond-forming reactions.

Catalyst	Substrate	Product	Yield [%], ee [%]
3[a],[5a]	 **7**	 **8**	60, 92[b],
3	 **9**	 **10**	68, 74[c],
3[a],[5a]	 **11**	 **12**	69, 73[b], [e],
3[a],[5a]	 **13**	 **14**	60, 82[c], [f]
4	**7**	**8**	70, 91[c]
4	**9**	**10**	66, 86[b]
4	**11**	**12**	72, 81[b],[(e]
4	**13**	**14**	78, 80[d], [f]

[a] 5 mol % catalyst.
[b] By GC on an Ivadex 7/OV 1701; G/294 column.
[c] By GC on a heptakis(2,6-di-*O*-methyl-*O*-pentyl)-*β*-cyclodextrin/OV 1701 (1/4) column.
[d] By GC of the corresponding trifluoroacetate on a heptakis(2,6-di-*O*-methyl-*O*-pentyl)-*β*-cyclodextrin/OV 1701 (1/4) column.
[e] ds > 96:4.
[f] ds = 87:13 for both catalysts.

In summary, we have devised an efficient catalyst for the enantioselective opening of *meso*-epoxides via electron transfer. The catalyst is readily synthesised in both enantiomers from commercially available menthol or *neo*-menthol. The results should be of general interest for asymmetric catalysis because, in contrast to the usually observed selectivities,[13] the menthol-derived catalyst is superior to the phenylmenthol-derived complex.

Experimental Section

Representative Procedure: Synthesis of 3-[2-(*R*)-Hydroxycyclopent-1-(*S*)-yl]propanoic Acid *tert*-Butyl Ester (12)

To a suspension of collidine hydrochloride (394 mg, 2.5 mmol) in dry THF (10 mL) was added cyclopentene oxide (87 μL, 1.0 mmol; freshly distilled from CaH_2), 1,4-cyclohexadiene (94 μL, 1.0 mmol), *t*-butyl acrylate (290 μL, 2.0 mmol), **4** (53 mg, 0.1 mmol), and zinc dust (131 mg, 2.0 mmol) under Ar. The green suspension was stirred for 22 h and poured on MTBE (50 mL). The organic layer was washed with H_2O (30 mL), 2 N HCl (30 mL), H_2O (30 mL), saturated $NaHCO_3$ (30 mL), and H_2O (30 mL). After drying ($MgSO_4$) the volatiles were removed under vacuum and the residue (294 mg) was microdistilled (140 °C/10 mbar). Purification by SiO_2 chromatography (CH/EE 9 : 1) gave **12** as a colourless oil; yield: 154 mg (72%). $[\alpha]_D^{20}$: −19.6 ($c = 1$ in CH_2Cl_2). ^{1}H NMR (300 MHz, C_6D_6): δ = 3.51 (dd, $^3J \approx$ 11.9 Hz, $^3J \approx$ 5.7 Hz, 2′-H), 2.18 2.23 (m_c, 2-H_2), 1.27 1.77 (m, 3-H_2, 3′-H_2, 4′-H_2, 5′-H_2), 1.39 [s, C(CH_3)$_3$], 1.20 (br. s, 2′-OH), 0.91 (ddt, $^3J \approx$ 11.9 Hz, $J \approx$ 8.0 Hz, 1′-H). ^{13}C NMR (50 MHz, C_6D_6): δ = 173.16, 79.66, 78.67, 47.82, 34.87, 34.51, 30.13, 29.39, 28.14, 22.06; IR (film): ν = 3430, 2955, 2870, 1730, 1455, 1420, 1390, 1365, 1320, 1255, 1155, 1095, 1065, 970, 850, 755 cm^{-1}. GC data: heptakis(2,6-di-*O*-methyl-*O*-pentyl)-β-cyclodextrin/OV 1701 (1/4) column 95 °C, 70 kbar H_2 major enantiomer 119.4 min; minor enantiomer 122.7 min; anal. calcd. for $C_{12}H_{22}O_3$ (214.3): C 67.26, H 10.35; found: C 67.21, H 10.50.

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