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The first Lewis acid mediated asymmetric Torgov cyclisation

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Abstract

The first catalytic enantioselective Torgov cyclisation has been achieved in 72% yield and up to 70% ee by using a chirally modified Ti complex. The new bis-steroidal ligands were found to be clearly superior to BINOL.

1. Introduction

In a previous paper we reported on the successful application of bis-steroidal phosphines as chiral ligands for the enantioselective hydrogenation of alkenes.[1] As a part of our ongoing efforts to broaden the scope of these ligands, we have investigated their potential as chiral modifiers in Lewis acid mediated asymmetric ene cyclisations.[2,3] Herein we present our preliminary results of the catalytic asymmetric cyclisation of methyl secone **1**, the key process in the Torgov synthesis of estrone.[4]

2. Results and discusion

Our study was initiated by the observation that methyl secone **1** smoothly cyclized to (±)-**2**[5] (10%) and (±)-**3**[6,7] (90%) on treatment (30 min, 0°C) with 20 mol% (i-PrO)$_2$TiCl$_2$[8] in dichloromethane (Scheme 1).[†]

This result encouraged us to repeat the reaction with the chiral (R)-BINOL–Ti complex **4**[9] as a catalyst (Scheme 2). We were pleased to observe that treatment of **1** with 20 mol% of catalyst **4** in CH$_2$Cl$_2$ at −20°C in the presence of 4 Å MS afforded a mixture of (S)-**3** (62% yield, 26% ee) and compound **2**

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[†] The same cyclisation occurs with some other Lewis acids (Et$_2$AlCl, La(OTf)$_3$ or RuCl$_3$).

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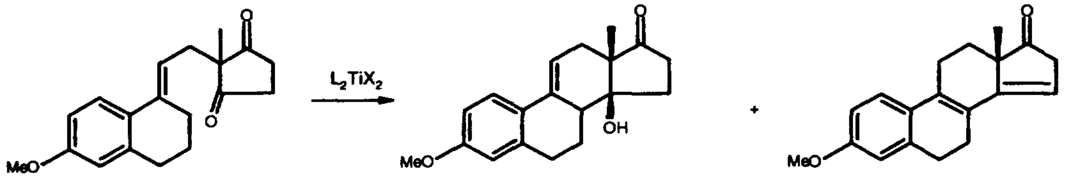
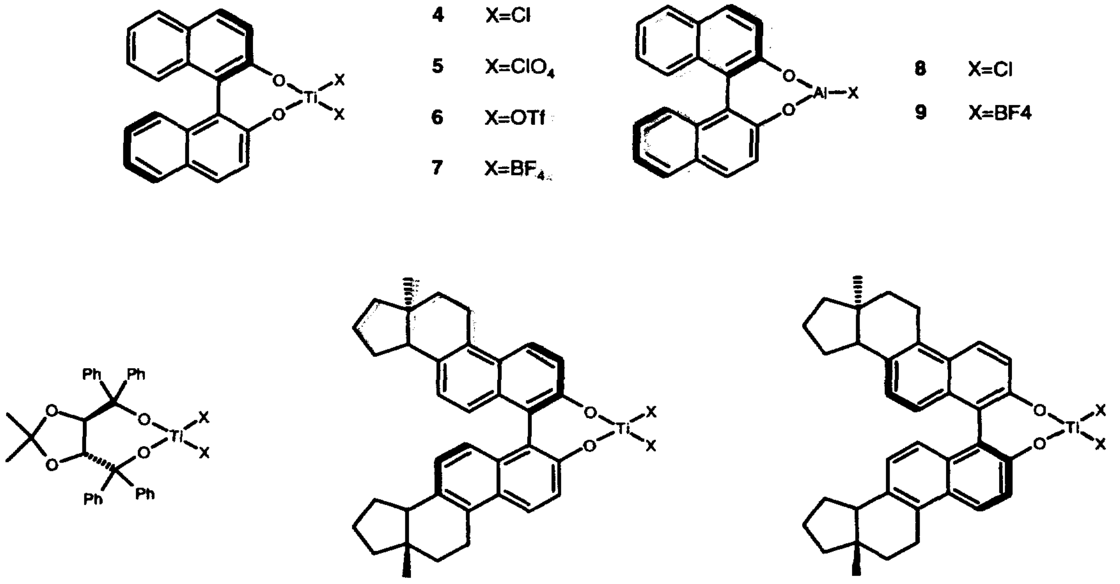


1 **(±)-2** **(±)-3**

Scheme 1.

(18%, 16% ee) (Table 1, entry 1).[‡] The exchange of CH_2Cl_2 by toluene resulted in the racemic product **3** with less than 10% yield (entry 3).



4 X=Cl
5 $X=ClO_4$
6 X=OTf
7 $X=BF_4$

8 X=Cl
9 X=BF4

10 X=Cl
11 X=BF4

(R,S)-**12** $X=BF_4$

(S,S)-**13** $X=BF_4$

Scheme 2.

Some effort was made to improve the enantioselectivity by varying the nature of the catalyst (Scheme 2). According to Mikami's protocol,[10] the corresponding in situ prepared derivatives of (*R*)-BINOL–Ti complex **4** with ClO_4^-, TfO^- and BF_4^- as counteranions were tested as catalysts for the cyclisation. As can be seen from Table 1, the replacement of Cl^- with ClO_4^- or TfO^- produced the very active but not selective catalysts **5** and **6** (entries 4 and 5).[§] In contrast, the exchange of Cl^- with BF_4^- afforded catalyst **7** with the same activity as **4** but higher enantioselectivity (entry 6). Additionally in this

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[‡] Performing the reaction below −20°C decreased the rate of the cyclisation without significant improvement of ee. Above −20°C the ee of the product was drastically decreased.

[§] Surprisingly, the application of a stoichiometric amount of titanium catalyst did not improve either yield or ee of the Torgov cyclisation, but triggered the formation of side and/or decomposition products instead.

Table 1
Asymmetric cyclisation of **1** at −20°C

entry	catalyst	solvent	time (h)	conversion[a]	**3** yield (%)[b]	ee (%)[c] /confg[d]
1	(*R*)-**4**	CH_2Cl_2	54	90%	62	26/(S)
2	(*S*)-**4**	CH_2Cl_2	54	90%	61	26/(R)
3	(*R*)-**4**	toluene	54	<15%	<10%	racemic
4	(*R*)-**5**	toluene	8	>95%	80	racemic
5	(*R*)-**6**	toluene	12	>95%	82	racemic
6	(*R*)-**7**	CH_2Cl_2	54	91%[e]	43	36/(S)
7	(*R*)-**7**	toluene	54	90%[f]	63	47/(S)
8	(*R*)-**8**	toluene	48	80%	60	racemic
9	(*R*)-**9**	toluene	54	<10%	<8%	racemic
10	(+)-**10**	CH_2Cl_2	54	<4%	<2%	racemic
11	(+)-**10**	toluene	54	<2%	traces	racemic
12	(+)-**11**	toluene	48	70%	40	racemic
13	(*R*,*S*)-**12**	toluene	54	98%[g]	72	**70/(S)**
14	(*S*,*S*)-**13**	toluene	54	92%[h]	70	54/(R)

[a] based on ^{1}H-NMR of the crude reaction mixture. [b] isolated yield. [c] enantioselectivity was determined by chiral HPLC (Chiralcel OJ). [d] based on rotation. [e] compound **2**- 20% yield, 22% ee. The ee of the compound **2** was determined indirectly: it was converted to **3** by treatment with Amberlist-15 in toluene and determined by HPLC (Chiralcel OJ). [f] compound **2** - 23% yield, 28% ee. [g] compound **2** - 20% yield, 36% ee. [h] compound **2** - 20% yield, 30% ee.

case the ee of the product could be improved by performing the cyclisation in toluene instead of CH_2Cl_2 (entry 7).

Our attempts to apply the *in situ* prepared chiral Al complexes **8** and **9**[11] failed as the cyclisation with **8** afforded racemic **3** in 80% yield (Table 1, entries 8 and 9). The corresponding BF_4^- modified catalyst turned out to be virtually inactive affording racemic **3** in less than 8% yield (entry 9).

Finally, three additional chiral ligands, (+)-TADDOL[12] and both diastereomers of our bis-steroidal ligands[1] were used for the preparation of catalysts **10**, **11**, **12** and **13**. The results revealed some interesting points in terms of structure–enantioselectivity relationships for the ligand used in Ti complexes. The catalyst **10** derived from TADDOL, which has previously been reported to provide a high level of catalytic activity in enantioselective Diels–Alder reactions[13] did not, in practice, induce any cyclisation at −20°C (entries 10 and 11). Most probably the lack of reactivity in this case is due to the decreased electrophilicity of Ti in the complex **10** (lower acidity of TADDOL in comparison with BINOL[9]). The addition of 2 equiv. of $AgBF_4$ to **10** afforded catalyst **11** which was more active than **10** but did not induce any enantioselectivity.

More significantly, the incorporation of the (*R*,*S*)-bis-steroid as a ligand into catalyst **12** was found to afford a remarkably increased level of enantiocontrol (72% yield 70% ee), the highest ee observed so far (entry 13). Additional recrystallisation from ethanol afforded virtually enantiomerically pure **3** in 41% yield. In contrast, the diastereomeric bis-steroid (*S*,*S*)-**13** yielded the opposite enantiomer with moderate (54% ee) selectivity. In both cases the bis-steroid containing catalysts afforded **3** with higher enantiomeric excess than the corresponding BINOL derived catalysts. Yet this is the first time that we not only observe an influence of the bis-steroid backbone on the level of enantioselectivity, but also a remarkable difference between the two ligands in terms of selectivity.

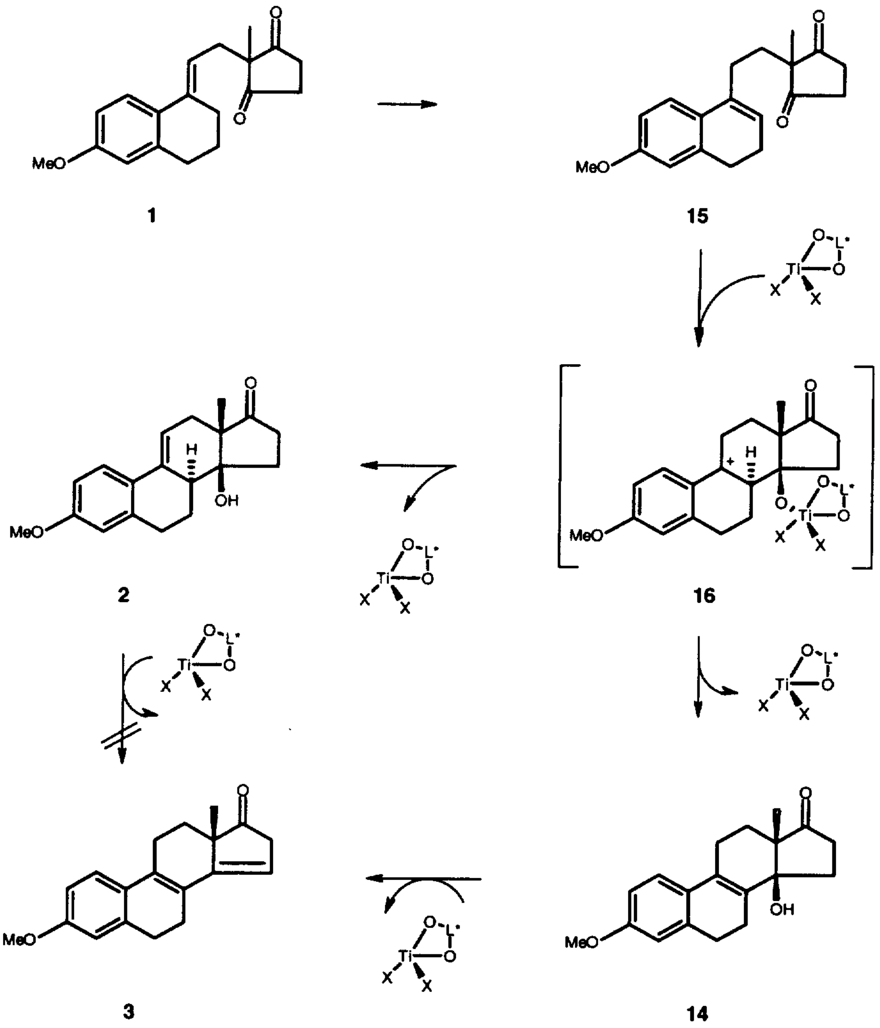
Initially, our mechanistic explanation for the formation of compounds **2** and **3** was based on an ene type cyclisation of **1** to the alcohol **2** followed by dehydration and isomerisation to **3**. However there were two facts which required further explanation. The first one was that approximately 20% of the compound **2** remained unreacted even after 54 hours. The extension of the reaction time (up to 15 days) did not give any additional conversion. One could speculate that this is due to gradual decomposition of the catalyst caused by the liberated water from the reaction. The other astonishing point was that at the end of the reaction the ee of compound **2** was lower than the ee of compound **3**. If we assumed that compound **2** appeared as an intermediate, one explanation could be that the observed enantioselectivity did not arise directly from a desymmetrisation of **1**, but from a kinetic resolution in the course of transformation of **2** to **3**. To check this assumption, compound (±)-**2** (0.3 g) was treated with a catalytic amount of **12** under the reaction conditions, but after 3 days only 9% of racemic **3** was isolated together with 82% of unreacted starting material. This result clearly showed that **3** did not arise directly from **2**, additionally excluding a kinetic resolution as an explanation for the observed difference in the ees of compounds **2** and **3**.

The real precursor of **3** was isolated from the reaction of **1** with 5 mol% $(i\text{-PrO})_2TiCl_2$ in toluene at −20°C (see Experimental). After 24 h, compounds (±)-**2** (18%) and (±)-**3** (47%) together with (±)-**14**[14,15] (18%) and traces of **15**[16] (5%) were isolated from the reaction mixture. Exposure of racemic **14** (0.3 g) to a catalytic amount of **12** (20 mol%, −20°C) resulted in a 70% conversion after 1 hour to racemic **3**.

All our results can be explained in terms of a multiple-step cationic cyclisation (Scheme 3). After initial isomerisation of **1** to **15**, the chiral Lewis acid induces a Prins type cyclisation to the chiral cation **16**. Subsequently, the regioselective elimination of **16** results in the formation of the two isomers **2** and **14** with different ees.[17] Dehydration of the latter yields ketone **3**.

In the above-mentioned mechanism, the question which still remains open is how the isomerisation of **1** to **15** proceeds. To the best of our knowledge there is no precedent for such an isomerisation by the Ti complex itself. Therefore we assume that traces of acid liberated from the decomposition of the catalyst are responsible for this isomerisation.

In conclusion, we have developed an efficient one-step asymmetric Torgov cyclisation to estrone derivative **3**[12] based on asymmetric catalytic desymmetrization of methyl secone **1**. It has to be pointed out that in terms of yield and ee this method is better than existing microbiological as well as chemical methods for the enantioselective synthesis of **3**.[18–20] Especially intriguing to us was the fact that this new cyclisation opens the path to the asymmetric synthesis of steroidal compounds based on the self-reproduction of the chirality of a small amount of an enantiomerically pure steroid catalyst.



Scheme 3.

3. Experimental section

The following procedure is illustrative for the asymmetric cyclisation of **1** with catalyst **12**. To a solution of the (*R*,*S*)-bis-steroid (0.094 g, 0.19 mmol) in dry toluene (5 ml) was added at RT 4 Å MS (0.600 g, beads 1 mm) and $AgBF_4$ (0.075 g, 0.39 mmol) under Ar and the mixture was sonicated for 10 min in the dark. Then a solution of $(i\text{-PrO})_2TiCl_2$ (0.62 ml, 0.302 M in toluene, 0.19 mmol) was added and the resulting dark red solution was stirred at room temperature in the dark for 1 hour. The mixture was cooled to −22°C and a solution of **1** (0.300 g, 1 mmol) in toluene (1 ml) was added dropwise. The reaction mixture was then allowed to stand at −20°C (freezer) for 3 days and then quenched with 20% Na_2CO_3. Work up in the usual way followed by flash chromatography gave **2** (0.06 g, 20%, 36% ee[15]), m.p. 162.5–163°C (EtOH), $[\alpha]_D$=+26.9 (c=0.2 in THF); IR (KBr): 3550, 2940, 2850, 1740, 1620, 1590 cm^{-1}; UV (EtOH): 275 nm; ^1H-NMR (DMSO-d_6): 7.44 (1H, d, *J*=8.5 Hz), 6.72 (1H, dd, *J*=8.5, 2.7 Hz), 6.62 (1H, d, *J*=2.7 Hz), 5.95 (1H, t, *J*=1.2 Hz), 4.7 (1H, s, OH), 3.75 (3H, s), 2.78–2.85 (2H, m), 2.25–2.40 (3H, m), 2.15 (1H, brd, *J*=11.5 Hz), 2.0–2.09 (1H, m), 1.93–1.85 (2H, m), 1.52 (1H, ddd, 17.5, 11.5, 5.5 Hz), 0.98 (3H, s); ^{13}C-NMR (DMSO-d$_6$): 218.5 (s), 158.3 (s), 137.5 (s), 134.9 (s), 128.5 (s), 125.0 (d), 113.0 (d), 112.5 (d), 76.9 (s), 55.1 (d), 51.2 (s), 42.8 (q), 32.1 (t), 32.3 (t), 31.2 (t), 30.5 (t), 24.7 (t), 16.3 (q); MS-EI: 289 (M$^+$, 72), 242 (37), 186 (100), 171 (65). Calculated for $C_{19}H_{22}O_3$ C 76.5%, H 7.4%. Found C 76.3%; H 7.3%. The relative stereochemistry of C-7, C-13 and C-14 stereogenic centers was confirmed by NOESY experiments.

Compound **3** (0.17 g, 72%, 70% ee), $[\alpha]_D=-70.9$ (c=0.12 in THF). Recrystallisation from EtOH afforded pure **3** (0.098 g, 41%, 99% ee), m.p. 110.3°C, $[\alpha]_D=-102$ (c=0.1 in THF). IR (KBr): 3060, 2940, 2850, 1740, 1600 cm^{-1}; UV (EtOH): 235 nm; ^{1}H-NMR: (CDCl$_3$): 7.24 (1H, d, *J*=8.5 Hz), 6.75 (1H, dd, *J*=8.5, 2.7 Hz), 6.70 (1H, d, *J*=2.7 Hz), 5.85 (1H, t, *J*=1.2 Hz), 3.80 (3H, s), 3.32 (1H, d, *J*=23.5 Hz), 2.90 (1H, dd, *J*=23.5, 3 Hz), 2.8–2.7 (2H, m), 2.6–2.5 (3H, m), 2.4–2.3 (1H, m), 2.05–2.0 (1H, m), 1.6–1.5 (1H, m), 1.12 (3H, s), ^{13}C-NMR (CDCl$_3$): 220.0 (s), 158.7 (s), 146.9 (s), 138.2 (s), 129.9 (s), 128.6 (s), 125.3 (s), 124.1 (d), 114.7 (d), 113.6 (d), 111.4 (d), 55.3 (q), 49.1 (s), 41.9 (t), 28.4 (t), 27.3 (t), 22.9 (t), 22.8 (t), 20.6 (q); MS-EI: 280 (M$^+$, 95), 252 (100), 238 (38), 223 (10), 178 (13), 165 (20). Calculated for $C_{19}H_{20}O_2$ C 81.4%, H 7.2%. Found C 81.3%; H 7.2%.

3.1. Reaction of 1 with 5 mol% (i-PrO)$_2$TiCl$_2$

To a mixture of **1** (3 g, 10 mmol) and 4 Å MS (5 g) in toluene (50 ml) was added at −20°C a solution of (*i*-PrO)$_2$TiCl$_2$ (1.5 ml, 0.302 M in toluene, 0.5 mmol) and the mixture was allowed to stand at −20°C (freezer) for 1 day. Work up and flash chromatography yielded **2** (0.55 g), **3** (1.4 g) and **14** (0.55 g): m.p. 136.5–137°C (ethyl acetate); IR (KBr): 3450, 2940, 2820, 1740, 1620, 1580 cm^{-1}; UV (EtOH): 265 nm; ^{1}H-NMR (CDCl$_3$): 7.12 (1H, d, *J*=9.0 Hz), 6.73 (1H, dd, *J*=9.0, 1.5 Hz), 6.71 (1H, d, 1.5), 3.80 (3H, s), 2.75 (2H, m), 2.0–2.6 (8H, m), 1.98 (1H, m), 1.55 (1H, m), 1.10 (3H, s); ^{13}C-NMR (CDCl$_3$): 220.5 (s), 158.8 (s), 137.7 (s), 132.6 (s), 130.3 (s), 128.5 (s), 124.0 (d), 113.3 (d), 111.1 (d), 79.5 (s), 55.3 (q), 52.2 (s), 34.9 (t), 31.0 (t), 29.2 (t), 27.3 (t), 22.8 (t), 22.4 (t), 17.2 (q); MS-CI: 299 (M$^+$+1, 10), 281 (M$^+$+1−H$_2$O, 100); MS-EI: 298 (M$^+$, 37), 280 (50), 252 (100), 237 (48), 223 (35), 178 (33), 165 (58). Calculated for $C_{19}H_{22}O_3$ C 76.5%, H 7.4%. Found C 76.2%; H 7.5%. **15** (0.16 g), semicrystals, IR (CHCl$_3$): 2940, 2820, 1730, 1610, 1570, 1500, 1225 cm^{-1}; UV (EtOH): 271 nm; ^{1}H-NMR (CDCl$_3$): 7.08 (1H, d, *J*=9.0 Hz), 6.75 (1H, dd, *J*=1.5, 9.0 Hz), 6.70 (1H, d, *J*=1.5 Hz), 5.65 (1H, t, *J*=2 Hz), 3.78 (3H, s), 2.6–2.9 (6H, m), 2.15–2.30 (4H, m), 1.88 (2H, m), 1.15 (3H, s); ^{13}C-NMR (CDCl$_3$): 216.4 (s), 158.4 (s), 133.5, (s), 127.2 (s), 123.6 (d), 123.3 (d), 114.0 (d), 110.9 (d), 56.7 (s), 55.2 (q), 35.2 (t), 34.6 (t), 28.7 (t), 28.0 (t), 22.9 (t), 19.6 (q); MS-EI: 298 (M$^+$, 60), 187 (52), 171 (40), 159 (100), 144 (30), 115 (20). Calculated for $C_{19}H_{22}O_3$ C 76.5%, H 7.4%. Found C 76.7%; H 7.2%.

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