Titanocene Dichloride as a Convenient Catalyst for the Diastereoselective Oxidation of 2-Substituted 1,3-Dithianes and 1,3-Dithiolanes

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Received 13 December 2001; revised 23 January 2002

Dedicated to the memory of Professor Guido Sodano, deceased on June 7th, 2001

Abstract: Cp₂TiCl₂ is an efficient catalyst for the diastereoselective mono-oxidation of 2-substituted 1,3-dithianes and 1,3-dithiolanes by tert-butyl hydroperoxide; comparable stereoselectivities and better yields than Ti(i-PrO)₄ were obtained. Activities are similar, provided activated 4Å molecular sieves are present in the titanocene-promoted process. Furthermore, Cp₂TiCl₂ is a more moisture stable compound than Ti(i-PrO)₄ and therefore can be used in catalytic amounts of 1 mol%.

Key words: diastereoselectivity, oxidations, metallocenes, sulfoxides, titanium

The d⁰ transition metal/alkyl hydroperoxide system has been extensively used for the oxidation of a number of organic compounds, in particular alkenes and thioethers. In several instances, fairly good diastereoselectivities can be obtained in the oxidation of allylic alcohols and thioethers containing a stereogenic center. The level of the stereoselectivity, however, is dependent on the metal catalyst and the substrate structure.

Ti(IV) alkoxides are commonly employed as catalysts in the diastereo- and enantioselective epoxidation of allylic and enantioselective epoxidation of allylic alcohols as well as in the enantioselective oxidation of thioethers.

Surprisingly, cyclopentadienyl Ti(IV) compounds, despite their great availability and wide employment as catalysts in many homogeneous processes, have been scarcely used in these oxidation reactions.

We have recently shown the applicability of titanocenes such as Cp₂TiCl₂, CpTiCl₃ and bis(cyclopentadienyl)titanium (IV) bis(trifluoromethanesulfonate) [Cp₂Ti(OTf)₂] in the diastereoselective epoxidation of allylic and bishomoallylic alcohols and in the enantioselective sulfoxidation using tert-butyl hydroperoxide (TBHP) as oxidant. The catalytic activity is markedly enhanced in the presence of activated 4Å molecular sieves.

As an extension of our work, we became interested in the diastereoselective oxidation of dithianes. A great deal of data is available in the literature on the oxidation of racemic 2-substituted 1,3-dithianes and 1,3-dithiolanes as models of cyclic thioethers. Except for enzymatic reactions, d⁰ transition metal/alkyl hydroperoxides proved to be the most stereoselective oxidizing systems for this type of substrates. However, the chiral Kagan and Modena catalyst, a Ti(i-PrO)₄/(+)-diethyl tartrate [(+)-DET] modified system, has been mostly used in stoichiometric amount to achieve a diastereo- and enantioselective process. The diastereoselectivity is merely associated with facial discrimination, whereas the enantioselectivity is a result of both facial selectivity and selection between the two enantiotopic sulfur atoms. In order to perform a diastereoselective transformation, a simple achiral transition-metal catalyst can be employed.

Very few systematic reports have appeared concerning the use of an achiral reagent for the diastereoselective oxidation of thioethers. Indeed, a catalytic (using minimal amount of catalyst) process would be highly desirable and the use of cheap, safe and stable catalysts should be highly preferable.

In the present work, we compare some simple achiral titanocenes with the traditional Ti(IV) catalyst, namely Ti(i-PrO)₄, as promoters in the TBHP oxidation of 2-substituted 1,3-dithianes and 1,3-dithiolanes (Scheme 1). Diastereoselectivity, yield, catalyst loading as well as its cost and ease of handling, were taken into account for each titanium compound.

Initially, we performed a set of preliminary experiments on 2-phenyl-1,3-dithiane (1a) as model compound (Table 1) using our previously reported procedure for the titanocene-promoted sulfoxidation. For the titanocene-catalyzed oxidation an aqueous workup (Method A: see
The stereochemical outcome for all the Ti(IV)-catalyzed oxidations was similar, while Cp₂TiCl₂ furnished a good conversion after 22 hours at room temperature (run 3), a 1 mol% catalytic amount of Cp₂TiCl₂ worked better in the presence of molecular sieves. In fact, under the same conditions, at 0 °C and 5 mol% catalyst loading, the diastereoselectivity was slightly decreased. According to what we reported in our previous paper, 11 Cp₂Ti(OTf)₂ worked better than Cp₂TiCl₂ (runs 5–7). From this point of view it is interesting to note that in the oxidation of 1c Cp₂TiCl₂/MS is superior to Mo(VI) catalyst and be-}

**Table 1** Ti(IV)-Catalyzed Oxidation of 1a by TBHP

<table>
<thead>
<tr>
<th>Run</th>
<th>Catalyst (% mol)</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Yield of 2a (%)</th>
<th>trans/cis Ratio (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ti(i-PrO)₄ (5)</td>
<td>0</td>
<td>3</td>
<td>72</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cp₂TiCl₂ (5)</td>
<td>0</td>
<td>22</td>
<td>81</td>
<td>99:1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Cp₂TiCl₂ (1)</td>
<td>r.t.</td>
<td>22</td>
<td>79</td>
<td>97:3</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Cp₂TiCl₂/MS (5)</td>
<td>0</td>
<td>5</td>
<td>86</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Cp₂TiCl₂/MS (1)</td>
<td>0</td>
<td>21</td>
<td>84</td>
<td>98:2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Cp₂Ti(OTf)₂ (1)</td>
<td>0</td>
<td>5</td>
<td>42</td>
<td>96:4</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Cp₂Ti(OTf)₂/MS (1)</td>
<td>0</td>
<td>5</td>
<td>76</td>
<td>99:1</td>
<td></td>
</tr>
</tbody>
</table>

* Isolated yield.
* Determined by ¹H NMR analysis (400 MHz) on the crude reaction mixture.
* MS = 4Å molecular sieves. Ratio of titanocene to MS = 1 mmol/3.5 g experimental section) or a simple filtration through a silica gel pad (Method B), could be indifferently used.

At 0 °C and in 5 mol% catalytic amount, Ti(i-PrO)₄ reacted faster than Cp₂TiCl₂ (runs 1 and 2), the former required a short reaction time to reach a good conversion, while a better yield was obtained using the more chemoselective titanocene. Comparable stereoselectivities were observed.

As expected, 10,11 titanocene activity was improved by adding activated 4Å molecular sieves. In fact, under the same conditions, at 0 °C and 5 mol% catalyst loading, the reaction time and the stereoselectivity were comparable in those obtained with Ti(i-PrO)₄, yield being still higher (runs 4 and 5). In the presence of molecular sieves, simply prolonging the reaction time (runs 4 and 5), the amount of titanocene can be lowered to 1 mol% without affecting the yield and the facial selectivity.

According to what we reported in our previous paper, 11 Cp₂Ti(OTf)₂ worked better than Cp₂TiCl₂ (runs 5–7). However, because of its higher cost and lower moisture stability, the bis-triflate complex is less convenient than the dichloride.

Once we had recognized the best conditions for the titanocene-promoted oxidation, we investigated variously 2-substituted substrates 1b–f (Table 2).

The stereochemical outcome for all the Ti(IV)-catalyzed reactions was similar, while Cp₂TiCl₂ furnished systematically higher yields than Ti(i-PrO)₄. The trans/cis ratios slightly decreased changing the R group from Ph to Me (1b), a result that can be ascribed to the less sterically demanding Me group. Again (runs 2 and 3), as a general rule, Cp₂TiCl₂ worked better in the presence of molecular sieves. Furthermore, we confirmed that with prolonged reaction time, a reduced 1 mol% catalyst loading can be used without altering the efficiency and the diastereoselectivity (run 4).

Comparable results to the titanocene-catalyzed oxidation of dithiane 1a were achieved for dithiane 1e and a better stereoselectivity was observed with respect to the Ti(i-PrO)₄ promoted process (runs 5 and 6). From this point of view it is interesting to note that in the oxidation of 1c Cp₂TiCl₂/MS is superior to Mo(VI) catalyst and behaves similarly to VO(acac)₂. 13a

According to the literature, 14,15 the oxidation of 2-carbonyl dithianes proceeds with low trans stereoselectivities; for example, in the oxidation of 1d, a diastereomeric ratio of 75:25 was reported using the Modena catalyst, whereas an almost completely stereospecific trans oxidation resulted on 1a and 1b. 15 The reason of the lower ste-
reochemical ratio was attributed to the enolizability of H-2 in the 2-carbonyl dithiane oxides. The diastereomeric mixture may be obtained with high stereoselectivity but, then the Lewis acidic titanium might equilibrate the isomeric mixture. Cp₂TiCl₂/MS and Ti(i-PrO)₄ produced lower diastereomeric ratios (runs 7–9), when compared with the oxidation of dithianes 1a and 1b. Interestingly, Ti(i-PrO)₄ showed to be, in this instance, more diastereoselective in the absence of (+)-DET ligand (run 7 and literature data¹⁵). In order to prevent the acid catalyzed equilibration of diastereomers a non-nucleophilic base, namely the 2,6-di-tert-butyl-4-methylpyridine, was added, but no significant improvement in the trans/cis ratio was observed (run 10).

Similarly, the more sterically hindered titanocene (±)-ethylene-bis-(4,5,6,7-tetrahydro-1-indenyl)dichlorotitanium(IV) [3, rac-(EBTHI)TiCl₂], (Figure 1) turned out to be less stereoselective and active catalyst (run 11). In the 2,2-disubstituted dithiane 1e, the ability of the catalyst to discriminate between the two faces of the ring is expectedly reduced. In fact, using Modena catalyst, a 85:15 trans/cis diastereomeric ratio was obtained in the oxidation of 1e¹³b while surprisingly, using the Kagan modification the stereospecific trans oxidation was reported.¹⁴ Since both faces of the ring are shielded, a lower reactivity is predictable. Our results confirmed these expectations (runs 12 and 13). Titanocene 3 did not lead to any improvement of the facial selectivity (run 14).

Figure 1  The structure of titanocene 3.

The hydroxymethyl dithiane 1f deserves some attention. So far the sulfoxidation of this substrate has never been reported. We envisioned a mechanism involving the initial coordination of the hydroxy group to the metal center, followed by an intramolecular oxygen transfer by the coordinated alkyl hydroperoxide. Such behaviour is, indeed, well documented for β-hydroxy sulfides.¹⁷ This transition state could have afforded a different stereochemical outcome compared to unfunctionalized 2-substituted dithianes. The oxidation of 1f catalyzed by Cp₂TiCl₂/MS under the usual conditions, furnished two main products as inseparable mixture by silica gel chromatography in 93:7 ratio (run 15). They were identified as the two geometric isomers of the monosulfoxide 2f.

A confirmation of their structure was gained by performing the synthetic sequence depicted in Scheme 2. The known 1:1 trans/cis mixture of monosulfoxide 2g was obtained by Ti(i-PrO)₄-catalyzed oxidation of commercially available 1,3-dithiane 1g. The reduction of 2g by DIBAL-H or NaBH₄, afforded a 1:1 mixture of the same compounds isolated after the titanocene oxidation of 1f, as confirmed by ¹H NMR analysis.

Scheme 2

Crystals suitable for X-ray analysis of the more abundant 2f diastereomer were obtained by slow evaporation from a benzene–CHCl₃ solution. X-ray structure analysis showed a trans relative configuration (Figure 2).

Figure 2  Crystal structure of the more abundant 2f diastereoisomer (ORTEP plot). Thermal ellipsoids are drawn at 30% probability level.
ities achieved with both the Ti(IV) catalysts are similar in most of the examples.

The employment of a compound in minimal amounts is one of the main goals of green chemistry. In this respect Cp₂TiCl₂ is preferable to Ti(i-PrO)₄. The former is very cheap and moisture stable compound, 19 so it can be used in catalytic amount of 1 mol%, whereas for the more sensitive Ti(i-PrO)₄, less than 5 mol% has never been reported.

Moreover, with Cp₂TiCl₂/MS only a simple filtration is needed to remove the catalyst (Method B: see experimental section).

All reactions were carried out under dry N₂. Glassware was flame-dried (0.05 Torr) before use. The solvents employed were freshly distilled and dried. Temperatures were measured externally; reactions were monitored by TLC on Merck silica gel plates (0.25 mm) and visualized by UV light and by exposition to I₂ vapours. 

Method B (Products 2a–e, 13a, 13c, 15, 1a, 1b, 1c, 1d, 1g, 1H NMR (400 MHz, CDCl₃): δ = 7.46–7.34 (m, 5 H, Ar-H), 4.77 (s, 1 H, H-2), 3.22 (m, 1 H), 3.05 (m, 1 H), 2.81–2.61 (m, 3 H), 1.87 (m, 1 H).

1C NMR (100.6 MHz, CDCl₃): δ = 135.5, 129.1, 128.9, 128.4, 64.7, 47.4, 30.0, 13.9.

cis-2-Phenyl-1,4,3-dithian-1-one (cis-2a)
1H NMR (400 MHz, CDCl₃): δ = 7.46–7.34 (m, 5 H, Ar-H), 4.77 (s, 1 H, H-2), 3.22 (m, 1 H), 3.05 (m, 1 H), 2.81–2.61 (m, 3 H), 1.87 (m, 1 H).

1C NMR (100.6 MHz, CDCl₃): δ = 135.5, 129.1, 128.9, 128.4, 64.7, 47.4, 30.0, 13.9.

trans-2-Methyl-1,4,3-dithian-1-one (trans-2b)
1H NMR (400 MHz, CDCl₃): δ = 7.46–7.34 (m, 5 H, Ar-H), 4.77 (s, 1 H, H-2), 3.22 (m, 1 H), 3.05 (m, 1 H), 2.81–2.61 (m, 3 H), 1.87 (m, 1 H).

1C NMR (100.6 MHz, CDCl₃): δ = 135.5, 129.1, 128.9, 128.4, 64.7, 47.4, 30.0, 13.9.

trans-2-Phenyl-1,4,3-dithiolan-1-one (trans-2c)
1H NMR (400 MHz, CDCl₃): δ = 7.46–7.34 (m, 5 H, Ar-H), 4.77 (s, 1 H, H-2), 3.22 (m, 1 H), 3.05 (m, 1 H), 2.81–2.61 (m, 3 H), 1.87 (m, 1 H).

1C NMR (100.6 MHz, CDCl₃): δ = 135.5, 129.1, 128.9, 128.4, 64.7, 47.4, 30.0, 13.9.
**trans-2-(Hydroxymethyl)-1,4,3-dithian-1-one (trans-2f)**

White needles from MeOH; mp 179–181 °C.

IR (KBr/nujol): 3233, 1424, 1083, 982, 720, 668 cm⁻¹.

1H NMR (400 MHz, CDCl₃); δ = 4.27 (dd, 1 H, J = 12.3, 4.1 Hz, CH1HOH), 4.02 (dd, 1 H, J = 12.3, 2.8 Hz, CH1HOH), 3.94 (dd, 1 H, J = 4.1, 2.8 Hz, H-2), 3.52 (m, 1 H, H-6), 2.88 (dddd, 1 H, J = 14.0, 12.3, J₂ = 2.6 Hz, H-4), 2.80 (ddd, 1 H, J = 13.3, 12.4, 2.9 Hz, H-6), 2.67 (m, 1 H, H-4'), 2.55–2.46 (m, 1 H, H-5), 2.31–2.18 (m, 1 H, H-5').

13C NMR (100.6 MHz, CDCl₃); δ = 72.5, 1(4) Å, V = 725.1(4) Å³, μ(CuKα) = 60.68 cm⁻¹. A suitable crystal of 2f was selected and mounted on a glass fiber. Diffraction measurements were performed at room temperature on a Rigaku AFC7S diffractometer using graphite monochromated CuKα radiation (λ = 1.54178 Å). Intensity data were corrected for Lorentz, polarization, and absorption effects (w-scan). No decay correction was applied.

The structure was solved by direct methods using SIR92 and refined by means of full matrix least-squares procedure based on F² with SHELXL97. Eightyone variable parameters against 584 reflections were considered in the final refinement cycle. Anisotropic displacement factors were used for all non-hydrogen atoms. Hydrogen atoms were included (considering a riding model) but not refined. Maximum and minimum residual density were respectively 0.34 eÅ⁻³ and -0.45 eÅ⁻³. Final disagreement indices are R₁ = 0.033 (I>2σ(I)) and R_w = 0.082 (all 584 data).²²

**Mixture of cis- and trans-2-(Hydroxymethyl)-1,4,3-dithian-1-one (cis-trans-2f)**

1H NMR (400 MHz, CDCl₃); δ (distinct signals) = 4.15 (dd, AB system, 1 H, J = 7.7, 6.1 Hz, H-6), 3.88 (dd, 1 H, J = 11.9, 7.7 Hz, CH1HOH), 3.83 (dd, AB system, 1 H, J = 11.9, 6.1 Hz, CH1HOH), 3.21 (ddd, 1 H, J = 14.3, 6.5 Hz, 2.6 Hz), 2.04–1.92 (m, 1 H).

**Ethyl 1-Oxo-1,4,3-dithiane-2-carboxylate (2g), trans/cis-Mixture**

To a stirred mixture of Ti(i-PrO)₄ (74 mg, 0.26 mmol) in anhyd CH₂Cl₂ (2 mL), at r.t. were added sequentially a 5–6 M solution of TBHP in degane (1.13 mL, 6.2 mmol) and dithiane 1g (1 g, 5.2 mmol). After 6 h, the reaction was quenched by pouring the mixture into a beaker containing sat.aq Na₂SO₄. After stirring for 10 min, the mixture was extracted with EtOAc; the combined extracts were dried (MgSO₄) and filtered, and then the solvent was removed in vacuo. The crude product was purified by flash chromatography on silica gel (eluens: CHCl₃ to CHCl₃–MeOH). Final agreement indices are R₁ = 0.033 (I>2σ(I)) and R_w = 0.082 (all 584 data).²²

**NaBH₄ Reduction of 2g, trans/cis-Mixture**

To a stirred solution of nearly 1:1 trans/cis-2g (72 mg, 0.35 mmol) in EtOH (1.5 mL) was added NaBH₄ (26 mg, 0.70 mmol). After 4 h, the reaction mixture was filtered through a Celite pad and washed with EtOH. After evaporation of the solvent a crude mixture was obtained whose 1H NMR spectrum revealed, as main products, a nearly 1:1 mixture of the stereoisomers obtained by oxidation of 1f and identified as trans/cis-2f.

**Acknowledgement**

MURST and CNR are gratefully acknowledged for financial support.

**References**


(19) The same batch of Cp₂TiCl₂ was used for several months without taking any particular precaution.


(23) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no CCDC-175498. Copies of data may be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: +44(1223)33603; e-mail: deposit@ccdc.cam.ac.uk].