

Crystal Structure of an Imine-TiCl₄ Complex formed in Catalytic Aziridination Reactions. Scope and Mechanistic Considerations

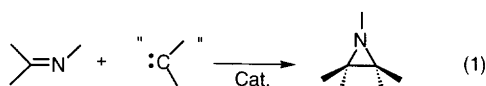
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A dimeric imine-titanium(IV) complex formed in the TiCl₄-catalyzed aziridination of imines has been isolated and characterised by X-ray diffraction. The structure is discussed and a mechanistic rationale is presented based on the enantiomeric excess obtained in catalytic aziridination of imines using alkyl diazoacetates as the carbene fragment donor in the presence of chiral TiX₂-TADDOLate complexes.

Aziridines are fundamental building blocks in organic chemistry.¹ In recent years the focus has been on catalytic formation of aziridines from imines and alkenes and a carbene or nitrene precursor, respectively, in the presence of a metal complex.^{2,3}

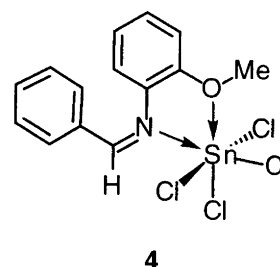


The catalytic procedure for the formation of aziridines from imines and diazo compounds, e.g., ethyl diazoacetate (EDA), as the carbene fragment donor can proceed by two different mechanisms depending on the metal acting as catalyst [reaction (1)].² The metal catalyst can act as a Lewis acid activating the imine by coordination leading to intermediate 1 [(i) Scheme 1]. The coordination of the Lewis acid to the imine leads to activation of the imine towards nucleophilic attack by EDA followed by elimination of N₂ giving the aziridine 3. The second mechanism [(ii) Scheme 1] comprises initial reaction of EDA with the metal complex with elimination of N₂ leading to the formation of a metal-carbene intermediate 2, which then transfers the carbene fragment to the imine with formation of the aziridine 3.

A variety of Lewis acid complexes, such as titanium(IV),^{2i,m} zinc(II),^{2h,i} ytterbium(III),²ⁱ tin(IV),^{2d,m,4} silicon(IV),^{2j} boron(III),^{2j,m} and methylrhenium trioxide^{2e} and rhodium- and manganese-exchanged montmorillonite K10 clays^{2k} can catalyze the

formation of aziridines from imines by Lewis acid activation of the imine as shown in (i) Scheme 1.

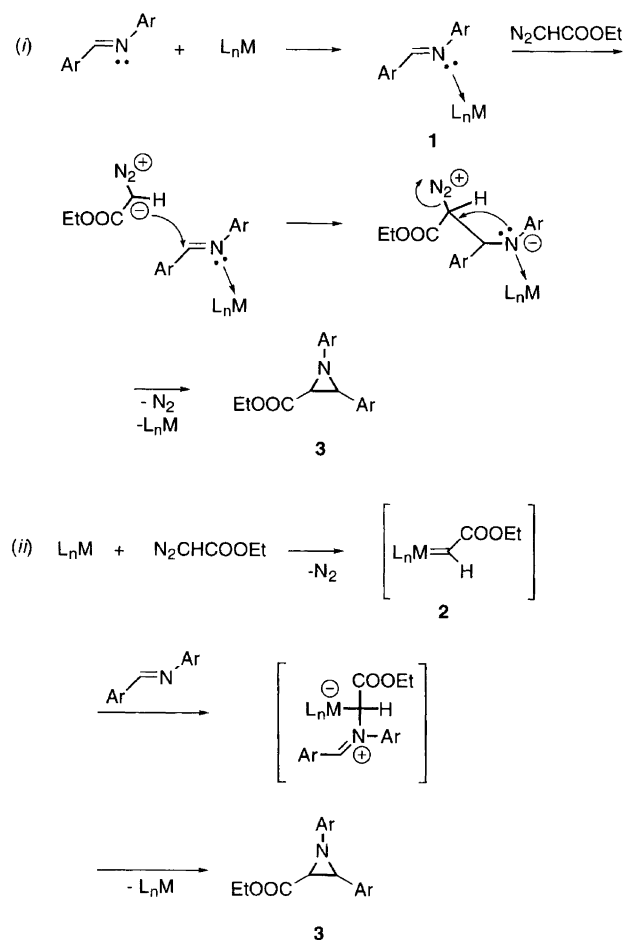
Recently an imine-Lewis acid intermediate complex, 4, in a tin(IV)-catalyzed aziridination, consisting of the imine coordinated in a bidentate fashion to SnCl₄, has been isolated and characterised by X-ray diffraction.⁴



The structure of the complex 4 shows that imine utilises both the nitrogen and oxygen lone-pair electrons for coordination to tin(IV). Furthermore, the imine isomerises from a *trans* geometry in *N*-benzylidene-*o*-anisidine substrate to a *cis* geometry by reaction with SnCl₄.⁴

In an attempt to develop a selective aziridination reaction of imines catalyzed by transition metal complexes our attention has been focused especially on titanium(IV) as the catalyst, as a variety of different chiral ligands are available for titanium. This paper presents the isolation and characterisation of a complex in the titanium(IV)-catalyzed aziridination of imines. Asymmetric aziridination using TiX₂-TADDOLate complexes as catalysts is also presented and the mechanistic aspects are discussed.

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Scheme 1.

Results and discussion

The imine–titanium(IV) complex **8** was formed together with the *cis*-aziridine **7** in the aziridination of *N*-benzylidene-*o*-anisidine **5** with EDA **6** in the presence of TiCl₄ as the catalyst [reaction (2)]. The spectroscopic evidence

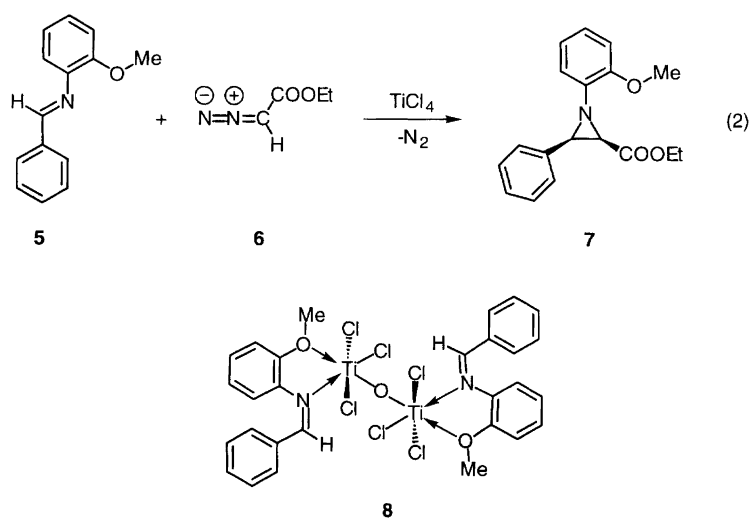
for the formation of **8** in solution comes primarily from ¹³C NMR spectroscopy. The chemical shift for the imine and methoxy carbon atoms changes from 161.3 to 171.7 ppm and 55.8 to 64.4 ppm, respectively, on coordination to TiCl₄.

The complex **8** can also be prepared by addition of TiCl₄ (19.5 μl, 0.178 mmol) to a solution of imine **5** (37.6 mg, 0.178 mmol) in CDCl₃. The mixture is kept for several days to give air- and moisture-sensitive red crystals. The structure of **8**, determined by X-ray diffraction, is depicted in Fig. 1.

The structure of complex **8** is a dimeric imine–titanium(IV) complex bridged by an oxygen atom, which is *trans* to the oxygen atoms of the imines. The origin of the bridging oxygen atom is not clear. It is probable that it comes from ‘traces’ of H₂O in the solvent or that has penetrated through the rubber septum, although the reaction was performed under ‘dry’ conditions. The structure of **8** in Fig. 1 shows that (i) imine **5** changes from *trans* to *cis* by reaction with TiCl₄, (ii) the imine C(1)=N bond [1.286(3) Å] is not affected by the coordination to titanium and (iii) the two aromatic groups are twisted relative to each other. The *trans* to *cis* isomerisation reduces the steric repulsion between the *C*-phenyl substituent and the equatorial chloride at the titanium. The Ti–N, Ti–O(7) and Ti–O bond lengths are 2.198(2), 2.223(2) and 1.788(1) Å, respectively.

Complex **8** reacts with EDA to give the *cis*-aziridine **7** in relatively low yield. The low yield of **7** is due to decomposition of the product as TiCl₄ is present in stoichiometric amounts. Thus, e.g., a chloride-induced ring-opening of **7** is observed.

The bidentate imine **5** was used in an attempt to obtain the more rigid imine–titanium(IV) intermediate, which could bring about catalytic asymmetric aziridinations. Attention was focused on the use of TiX₂–TADDOLate complexes **9**, which are very useful asymmetric catalysts for a variety of reactions.⁵ The catalysts **9** were prepared from the chiral TADDOLate ligand and TiCl₂(O^{*i*}Pr)₂ in



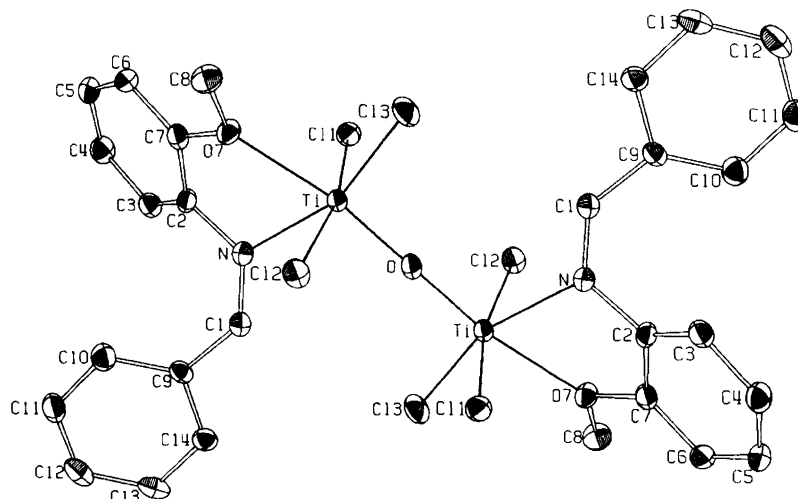
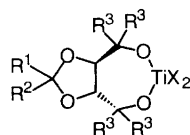


Fig. 1. The X-ray structure of the dimeric imine-titanium complex **8**. C-H hydrogen atoms are not shown. Selected distances (Å) and angles (°) for **8**: Ti-N 2.198(2), Ti-O 1.788(1), Ti-O(7) 2.223(2) Ti-Cl(1) 2.301(1), Ti-Cl(2) 2.313(1), Ti-Cl(3) 2.268(1), N-C(1) 1.286(2), N-C(2) 1.434(3), C(7)-O 1.387(3), O-C(8) 1.453(3), N-Ti-O(7) 70.93(7), O-Ti-O(7) 169.05(5), Cl(1)-Ti-Cl(2) 168.13(3), Cl(1)-Ti-Cl(3) 94.08(4), Cl(2)-Ti-Cl(3) 93.33(3) Ti-O-Ti 180.0.

the presence of 4 Å molecular sieves and used directly in the reactions. In some of the reactions, chloride was replaced with other counter-anions. The reaction of imine **5** with EDA **6** in the presence of the various TiX_2 -TADDOLate complexes **9** as catalysts (10 mol%) proceeded to give, very selectively, the *cis*-aziridine **7** in yields in the range 40–60%. Unfortunately, the ee of **7** was in all cases very low (0–10%).



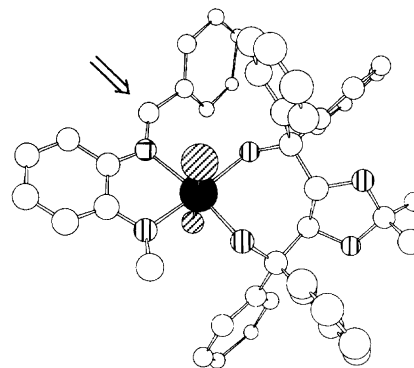
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R ¹	R ²	R ³	X	Aziridine 7 <i>cis</i> : <i>trans</i>	ee (%)
Me	Me	3,5-Dimethylphenyl	Cl	>25:1	≈5
Me	Me	2-Naphthyl	Cl	>50:1	≈5
Me	Ph	Ph	Cl	>50:1	10
Me	Me	Ph	BF ₄	>50:1	≈5
Me	Me	Ph	Ts	>50:1	≈0

In order to improve the ee of the aziridination in the presence of TiX_2 -TADDOLate complexes **9** as catalysts, the reaction was performed with (–)- and (+)-menthyl diazoacetate. However, it turned out that no significant improvement in selectivity was found. In relation to these doubly diastereoselective reactions it should be noted that aziridination with (–)-menthyl diazoacetate as the carbene fragment donor proceeded to give a diastereomeric excess of 18% according to ¹H NMR spectroscopy and HPLC. Thus, the stereodifferentiation of the chiral diazoacetate is larger than that for the reaction of EDA

in the presence of the chiral TiX_2 -TADDOLate complexes **9** as catalysts.

With knowledge of the structure of the imine-titanium complex **8** and a characterised substrate- TiCl_2 -TADDOLate complex⁶ it might be possible to understand why the ee in the aziridination reaction catalyzed by the complexes **9** is low. A possible intermediate in the aziridination reaction of *N*-benzylidene-*o*-anisidine **5** catalyzed by **9** (R¹=R²=Me, R³=Ph) is structure **10**. The EDA attacks the imine functionality as indicated by the arrow and it appears that the discrimination of the imine functionality by the TADDOLate ligand is minimal.



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The present investigation shows that it is possible to isolate and characterise a complex in the titanium(IV)-catalyzed aziridination of an imine coordinated to the metal in a bidentate fashion. The structure is a dimeric imine-titanium complex with a bridging atom. On the basis of attempts to perform enantioselective aziridination using TiX_2 -TADDOLate complexes as chiral cata-

lysts, which takes place with low selectivity, and the structure of the imine–titanium complex, a model for the intermediate is proposed, which accounts for the low enantioselectivity.

Experimental

¹H and ¹³C NMR spectra were recorded on a Varian 300 MHz Gemini spectrometer. CDCl₃ was used as the solvent and reported δ values are relative to tetramethylsilane (TMS).

Crystal data. C₂₈H₂₆Cl₆N₂O₃Ti₂ · 2 CHCl₃, M_w = 985.85, monoclinic, space group P2₁/n, a = 11.3012(2) Å, b = 14.8012(2) Å, c = 11.9017(2) Å, β = 90.145(1) Å, V = 1990.8131 Å³, Z = 2, d_{calc} = 1.64 g cm⁻³, F(000) = 988, λ (Mo Kα) = 0.71073 Å, μ = 1.24 mm⁻¹, red crystal, 0.5 × 0.2 × 1 mm. Data collection: Siemens SMART diffractometer, narrow frames up to θ = 28.5, T = 120 K. 11 086 reflections measured, 4682 unique, (R_{int} = 0.047) 3964 significant [I > 3σ(I)]. Structure solved by direct methods and refined by full matrix least-squares with anisotropic atomic displacement factors for nonhydrogen atoms. Hydrogens refined. Final agreement R = 0.037, R_w = 0.55 for 3964 reflections with 280 parameters. The authors have deposited atomic coordinates, bond lengths, bond and torsion angles, and thermal parameters for the structure at the Cambridge Crystallographic Data Centre (UK).

Reactions conditions. A 0.1 M solution of TiCl₂(OⁱPr)₄ in CH₂Cl₂ (500 μl) and 0.06 mmol of the chiral ligand were added to 1 ml CH₂Cl₂ containing 4 Å molecular sieves in a 10 ml Schlenk flask which was evacuated and filled twice with Ar. *N*-Benzylidene-*o*-anisidine (180 μl, 0.9 mmol) and EDA (65 μl, 1.0 mmol) were added at room temperature. When the evolution of N₂ had ceased the reaction mixture was filtered through a plug of silica gel, which was washed with additional 3 ml CH₂Cl₂. The solvent was evaporated off *in vacuo* and the crude product was analyzed by ¹H and ¹³C NMR spectroscopy. The crude product was purified by flash chromatography on silica gel using 2–10% EtOAc–petroleum ether to give the pure aziridines. The ee was determined by chiral HPLC. ¹H and ¹³C NMR data for **7**: δ_H 0.95 (t, J 7.2, 3 H), 3.09 (d, J 6.5, 1 H), 3.59 (d, J 6.5, 1 H), 3.82 (s, 3 H), 3.93–4.12 (m, 2 H), 6.85–6.89 (m, 2 H), 6.94–7.03 (m, 2 H), 7.28–7.36 (m, 3 H) and 7.54–7.57 (m, 2 H). δ_C 13.9, 45.9, 47.6, 55.4, 60.8, 111.0, 119.8, 120.6, 123.9, 127.6, 127.8, 127.9, 134.8, 140.8, 152.1 and 168.1. *m/z* 297.133 (C₁₈H₁₉NO₃ requires 297.133, 19%), 252 (13%) and 224 (100%).

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