Available online at www.sciencedirect.com

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 17 (2006) 1625–1628

Tetrahedron: *Asymmetry*

An alternative model for the asymmetric addition of cyanide to aldehydes catalysed by titanium–salen complexes based on a structurally related iron–salen complex

Gennadiy Ilyashenko, Majid Motevalli and Michael Watkinson*

Walter Besant Building, School of Biological and Chemical Sciences, Queen Mary, University of London, Mile End, London E1 4NS, UK

Received 12 May 2006; accepted 5 June 2006

Abstract—X-ray crystallographic analysis of $[(\mathrm{Fe}(3,5\text{-}\mathrm{Bu}^t\text{-salen}))_2\mathrm{O}]$ **4** allied with comparison of structurally related analogues is used to support an alternative transition state in the titanium–salen catalysed addition of cyanide to aldehydes. Experimental conditions for the preparation and isolation of $[(\mathrm{Fe}(3,5\mathrm{Bu}^t\text{-salen}))_2\mathrm{O}]$ are also reported.

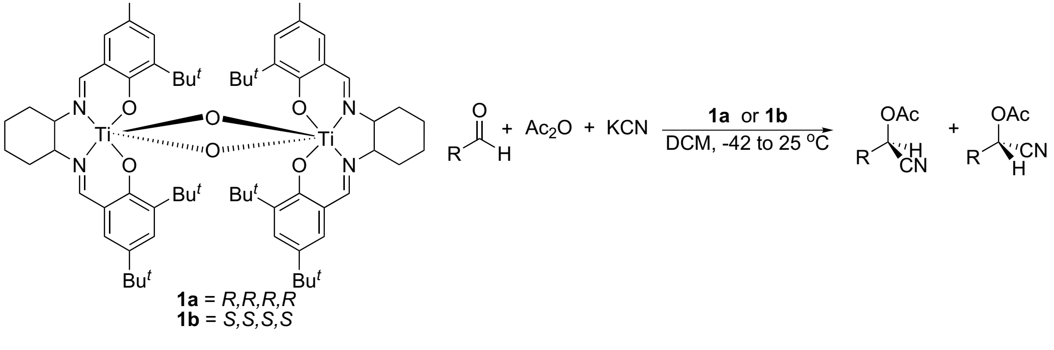
---

1. Introduction

Enantiomerically enriched cyanohydrins are versatile intermediates in organic synthesis[1–4] and many synthetic approaches towards their synthesis are being pursued.[5–7] Recently, Belokon et al. reported that bimetallic titanium catalyst **1** catalyses the asymmetric addition of potassium cyanide to aldehydes in the presence of acetic anhydride, leading to nonracemic cyanohydrin acetates as shown in Scheme 1.[8] This methodology uses only inexpensive reagents and leads to cyanohydrin esters in good yields and with good to excellent enantioselectivity.

2. Results and discussion

The initial results were shortly followed by a more detailed investigation into the mechanism of this asymmetric transformation.[9] North et al. provided a hypothesis, which was consistent with all of the observed data in which complex **1** acted as a pre-catalyst to the catalytically active species. The reaction was proposed to proceed via a transition state in which both of the salen ligands in a μ-oxo-bridged dimer adopt a β-*cis*-conformation, thereby creating a gap through which an aldehyde, but not a ketone, and the nucleophile may enter (Fig. 1). The initial bonding of the substrates

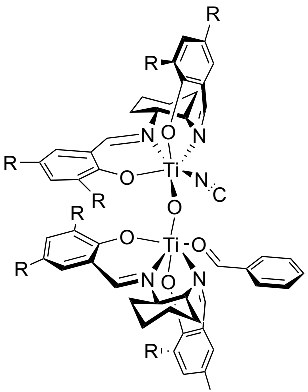


Scheme 1. The asymmetric addition of cyanide to aldehydes catalysed by titanium complex **1**.

---

* Corresponding author. Tel.: +44 (0)2078823263; fax: +44 (0)2078827427; e-mail: m.watkinson@qmul.ac.uk

0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.06.018

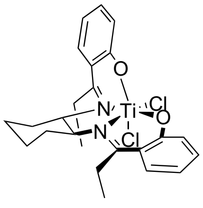


2

Figure 1. North's proposed transition state **2** for the catalytic reaction with both nucleophile and electrophile being bound to the catalytically active species.

to the catalyst was then proposed to be followed by intramolecular transfer of cyanide. Subsequent reaction with acetic anhydride gives the product and regenerates pre-catalyst **1**.

Although this transition state appears entirely reasonable, close inspection of related structures suggests that this conformation of tetradentate Schiff base ligands is in fact very rare. In 1999 a single crystal X-ray structure of the structurally related complex **3** was reported.[10]



3

Here the ligand adapts a β-*cis*-arrangement which is similar to that proposed by North. However, the same report notes that 'substantial steric effects within the ligand are required to achieve a folding of the ligand such that it takes up a *cis*-geometry'.[10] Moreover, there are only a further two examples of single crystal X-ray structures of complexes of salen based ligands in which the ligand adopts this β-*cis*-conformation that have been reported, $[Co(salen)(acac)]\cdot 0.7H_2O$[11] and $[W(salen)(Bu^tN)_2]$[12] In both cases the salen ligand is forced into the β-*cis*-conformation by ligands that were already coordinated to the metal centre. These cases exemplify the fact that β-*cis* coordination is not favourable for salen ligands and we wondered whether there was an alternative to North's hypothesis. Indeed close inspection of the tetradentate Schiff base ligand in the titanium complex that formed the basis of North's mechanistic revealed that the ligands did not adopt a β-*cis*-arrangement.[7] As part of our long-term interest in metallo–salen complexes, we prepared and crystallised complex **4**[13] and were able to obtain its single crystal X-ray structure. By analogy with the related titanium system an alternative transition state model is proposed, which, while broadly similar to North's original proposal, does not involve β-*cis* coordination of the Schiff base ligand.

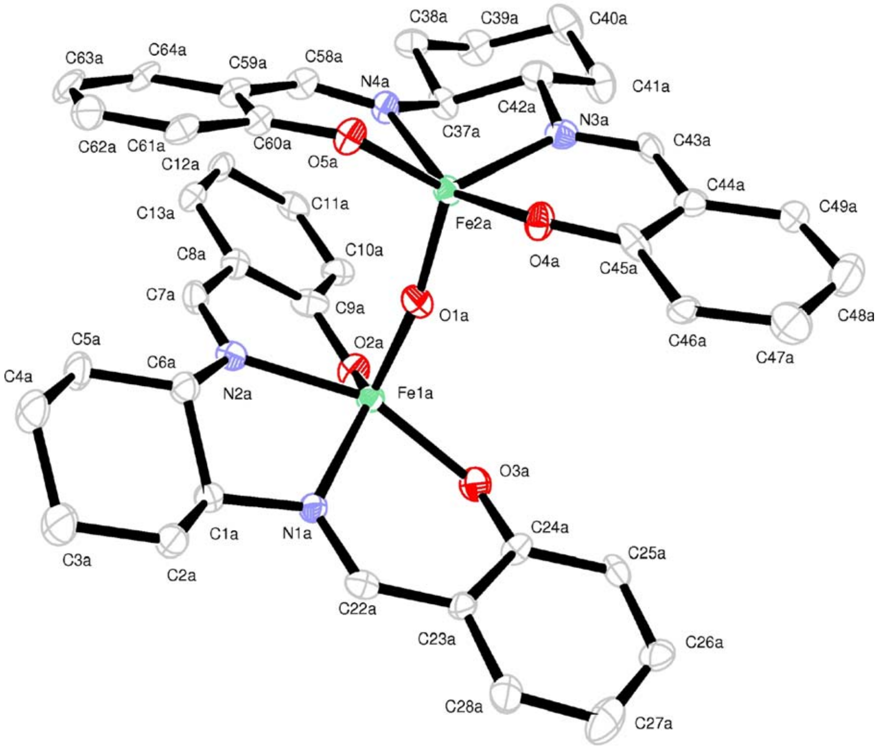


Figure 2. ORTEP[14] plot of the single crystal X-ray structure of the binuclear iron complex **4**, (the 3,5-Bu^t groups have been omitted for clarity from both ligands).

Crystals of **4** suitable for X-ray crystallography were obtained from a dichloromethane solution of **4** layered with *n*-heptane which revealed the presence of two iron(III)salen units linked via a μ-oxo bridge forming a dimer (Fig. 2). Selected bond lengths and angles are listed in Tables 1 and 2.

The molecular symmetry of the free ligand normally approaches C_2, however, in the metal complexes this symmetry is lost.[15,16] In the present case, a further complication is added due to the formation of the dimer between the two square-based pyramidal units via the μ-oxo bridge. Where the substituents on the ligand are small, and thus less sterically demanding, the two salen units can become more or less eclipsed (Figs. 3 and 4).[17,18]

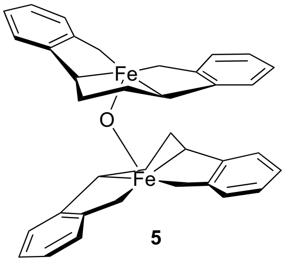
In the present case, however, the bulky substituents on the ligand do not allow for such an eclipsed conformation (Fig. 4) and a propeller conformation is adopted instead.

The sterically demanding nature of the *tert*-butyl groups also has a profound effect on the angle of the μ-oxo bridge between the two iron centres. Whilst the Fe–O–Fe bond angle in other closely related structures ranges from 139° to 160°, in this case the angle is as high as 175.59°, which is comparable to that observed in the similarly bulky complex **8**[15] (Table 3). However, the other bond lengths and angles are very similar to the previously reported examples.[15–23]

By combining the experimental evidence provided by North and the structural data obtained from the analysis of the crystal structure of **4**, a subtly different transition state model can be postulated (Fig. 5) that does not involve the disfavoured β-*cis* conformation.

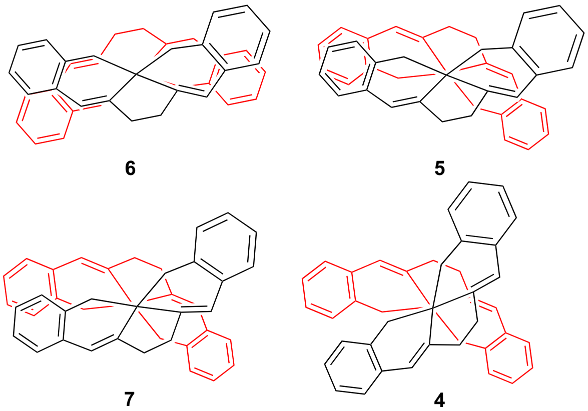
Table 1. Selected bond lengths (Å) for **4** with esds

	Bond length (Å)		Bond length (Å)
Fe(1A)–O(1A)	1.777(3)	Fe(1B)–O(1B)	1.779(3)
Fe(1A)–O(2A)	1.930(3)	Fe(1B)–O(2B)	1.909(3)
Fe(1A)–O(3A)	1.941(3)	Fe(1B)–O(3B)	1.946(3)
Fe(1A)–N(1A)	2.109(3)	Fe(1B)–N(1B)	2.112(3)
Fe(1A)–N(2A)	2.102(3)	Fe(1B)–N(2B)	2.111(3)
Fe(2A)–O(1A)	1.774(3)	Fe(2B)–O(1B)	1.767(3)
Fe(2A)–O(5A)	1.921(3)	Fe(2B)–O(5B)	1.913(3)
Fe(2A)–O(4A)	1.929(3)	Fe(2B)–O(4B)	1.937(3)
Fe(2A)–N(3A)	2.106(3)	Fe(2B)–N(3B)	2.117(3)
Fe(2A)–N(4A)	2.092(3)	Fe(2B)–N(4B)	2.099(3)



5

Figure 3. The molecular structure of $[\mathrm{Fe(salen)}]_2\mathrm{O}$ dimer **5** reported by Gerloch et al. side-on view.[17]


6

5

7

4

Figure 4. Schematic representations of iron(salen) complexes **4**–**7**; the bottom Fe–salen units in the dimers are indicated in red.

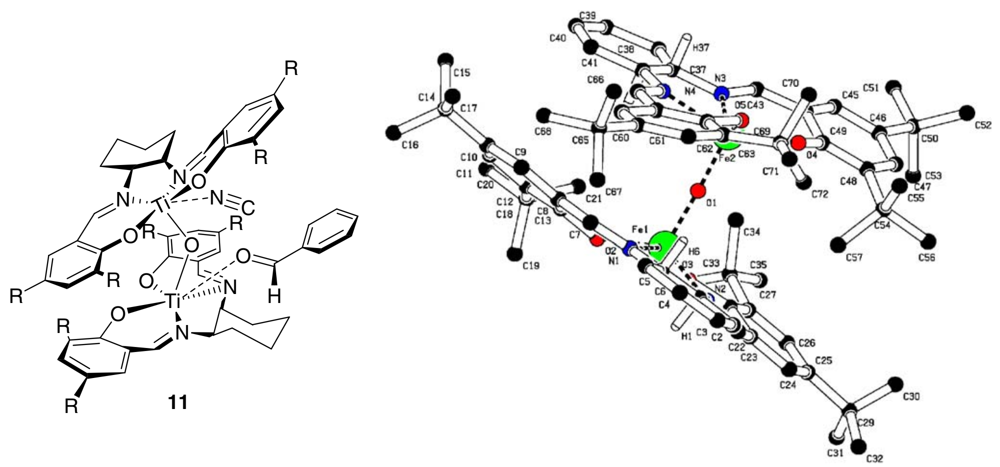
Table 3. Selected examples of structurally related μ-oxo bridged iron(III) complexes and the Fe–O–Fe bond angles

Iron complex	Fe–O–Fe angle (°)
4	169.61(18) and 175.59(18)
$[\mathrm{Fe(salen)}]_2\mathrm{O}\cdot 2\mathrm{py}$, **5**	139.1[17]
$[\mathrm{Fe(salen)}]_2\mathrm{O}\cdot \mathrm{CH_2Cl_2}$, **6**	142.4[19]
$[\mathrm{Fe(salen)}]_2\mathrm{O}$, **7**	144.6[21]
$[\mathrm{Fe(5Bu^{t}saltmen)}]_2\mathrm{O}$, **8**	173.4[15]
$[\mathrm{Fe(tsalen)}]_2\mathrm{O}$, **9**	159[22]
$[\mathrm{Fe(acen)}]_2\mathrm{O}$, **10**	150.7[23]

A parallel between both structures **4** and **11** can be drawn. In both cases the ligands are arranged to accommodate the substrate and the electrophile in the gap between their planes. Furthermore, the slight difference in the Fe–O–Fe

Table 2. Selected angles (°) for **4** with esds

	Angle (°)		Angle (°)
Fe(2A)–O(1A)–Fe(1A)	169.61(18)	Fe(2B)–O(1B)–Fe(1B)	175.59(18)
O(2A)–Fe(1A)–N(1A)	132.28(12)	O(2B)–Fe(1B)–N(1B)	148.37(13)
O(2A)–Fe(1A)–O(3A)	95.67(13)	O(2B)–Fe(1B)–O(3B)	93.22(14)
O(3A)–Fe(1A)–N(2A)	157.92(12)	O(3B)–Fe(1B)–N(2B)	143.99(12)
N(2A)–Fe(1A)–N(1A)	76.93(12)	N(2B)–Fe(1B)–N(1B)	76.73(14)
O(4A)–Fe(2A)–N(3A)	86.30(13)	O(4B)–Fe(2B)–N(3B)	84.10(12)
N(4A)–Fe(2A)–N(3A)	76.99(13)	N(4B)–Fe(2B)–N(3B)	76.30(12)
O(5A)–Fe(2A)–N(4A)	84.99(13)	O(5B)–Fe(2B)–N(4B)	86.67(13)
O(5A)–Fe(2A)–O(4A)	94.65(14)	O(5B)–Fe(2B)–O(4B)	95.55(13)



11

Figure 5. A possible alternative transition state model, **11**, for the catalytic addition of cyanide to aldehydes in which both the nucleophile and the electrophile are bound to the catalyst which does not require β-*cis* coordination of the Schiff base ligand by comparison with the structure of iron complex **4** (PLUTON).[24]

angle (ca. 6°) between the two units of the crystal structure of complex **4** is indicative that there is a degree of flexibility in the μ-oxo bridge. It means that upon binding of the nucleophile and electrophile the gap between the ligands widens making the Fe–O–Fe angle smaller, which is sterically demanding. Once the reaction is complete, the product is expelled from the catalyst and the complex can return to the original 'closed' conformation. We believe that this new alternative transition state based on the crystal structure of **4** provides a credible explanation for the reactivity and selectivity of the catalytic reaction, assuming that the ground state conformation plays a major role on the outcome of this process.

Acknowledgements

We are grateful to Overseas Research Council for support and The University of London for the provision of an Elsie Idea Leas studentship (to G.I.). We are also grateful to the EPSRC for its mass spectrometry service, University of Wales, Swansea, and its X-ray crystallographic service, University of Southampton.

References

1. Sawada, D.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2000**, *122*, 10521.
2. Yabu, K.; Masumoto, S.; Yamasaki, S.; Hamashima, Y.; Kanai, M.; Du, W.; Curran, D. P.; Shibasaki, M. *J. Am. Chem. Soc.* **2001**, *123*, 9908.
3. Musamoto, S.; Suzuki, M.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 8647.
4. Yabu, K.; Masumoto, S.; Kanai, M.; Curran, D. P.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 2923.
5. Gregory, J. H. *Chem. Rev.* **1999**, *99*, 3649.
6. North, M. *Tetrahedron: Asymmetry* **2003**, *14*, 147.
7. Belokon, Y. N.; Caveda-Cepas, S.; Green, B.; Ikonnikov, N. S.; Khrustalev, V. N.; Larichev, V. S.; Moskalenko, M. A.; North, M.; Orizu, C.; Tararov, V. I.; Tasinazzo, M.; Timofeeva, G. I.; Yashina, L. V. *J. Am. Chem. Soc.* **1999**, *121*, 3968.
8. Belokon, Y. N.; Gutnov, A. V.; Moskalenko, M. A.; Yashkina, L. V.; Lesovoy, D. E.; Ikonnikov, N. S.; Larichev, V. S.; North, M. *Chem. Commun.* **2002**, 244.
9. Belokon, Y. N.; Green, B.; Ikonnikov, N. S.; Larichev, V. S.; Lokshin, B. V.; Moskalenko, M. A.; North, M.; Orizu, C.; Peregudov, A. S.; Timofeeva, G. I. *Eur. J. Org. Chem.* **2000**, 2655.
10. Corden, J. P.; Errington, W.; Moore, P.; Wallbridge, M. G. H. *Chem. Commun.* **1999**, 323.
11. Calligaris, M.; Manzini, G.; Nardin, G.; Randaccio, L. *J. Chem. Soc., Dalton Trans.* **1972**, 542.
12. Motevalli, M.; Parkin, B. C.; Ramnauth, R.; Sullivan, A. C. *J. Chem. Soc., Dalton Trans.* **2000**, 2661.
13. NEt_3 (2.5 cm^3, 18.4 mmol, 10 equiv) was added to a suspension of $FeCl_3$ (0.30 g, 1.84 mmol, 1.0 equiv) and ligand (1.00 g, 1.84 mmol, 1.0 equiv) in methanol (30 cm^3) at room temperature. The resulting brown-orange solution was stirred for further 12 h. The orange precipitate was collected and redissolved in dichloromethane (30 cm^3). The solution was then washed with water (3×20 cm^3), brine (30 cm^3), dried over $MgSO_4$ and concentrated under reduced pressure to approximately 5 cm^3. *n*-Hexane (ca. 2 cm^3) was then carefully layered over DCM solution and the mixture was left for 12 h until deep red crystals appeared. The crystals were collected and dried (0.66 g, 60%) CCDC 602998. All other spectroscopic and analytical data for the crystals were the same as previously reported. Leung, W.; Chan, E. Y. Y.; Chow, E. K. F.; Williams, I. D.; Peng, S. *J. Chem. Soc., Dalton Trans.* **1996**, 1862.
14. Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.
15. Murkherjee, R. N.; Abrahamson, A. J.; Patterson, G. S.; Stack, T. P. D.; Holm, R. H. *Inorg. Chem.* **1988**, *27*, 2137.
16. Gerloch, M.; Mabbs, F. E. *J. Chem. Soc. (A)* **1967**, 1900.
17. Gerloch, M.; McKenzie, E. D.; Towl, A. D. C. *J. Chem. Soc. (A)* **1969**, 2850.
18. Gerloch, M.; Mabbs, F. E. *J. Chem. Soc. (A)* **1967**, 1598.
19. Coggon, P.; McPhail, A. T.; Mabbs, F. E.; McLachlan, V. N. *J. Chem. Soc. (A)* **1971**, 1014.
20. Davies, J. E.; Gatehouse, B. M. *Acta Crystallogr.* **1973**, *B29*, 1934.
21. Marini, P. J.; Murray, K. S.; West, B. O. *J. Chem. Soc., Dalton Trans.* **1983**, 143.
22. Corrazza, F.; Floriani, C.; Zehnder, M. *J. Chem. Soc., Dalton Trans.* **1987**, 709.
23. Kurtz, D. M. *Chem. Rev.* **1990**, *90*, 585.
24. Spek, A. *Acta Crystallogr., Sect. A* **1990**, *46*, C34.