# VO(salen)(X) catalysed asymmetric cyanohydrin synthesis: an unexpected influence of the nature of anion X on the catalytic activity†

**Yuri N. Belokon,*[a] Victor I. Maleev,[a] Michael North*[b] and Dmitry L. Usanov[ab]**

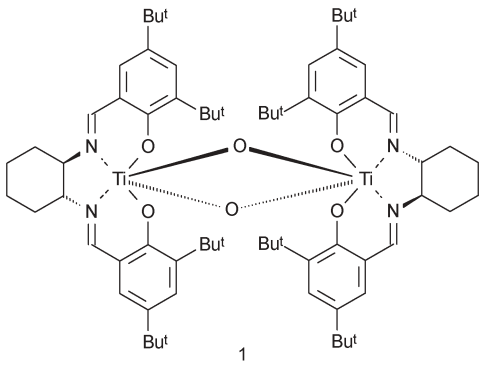
*Received (in Cambridge, UK) 5th July 2006, Accepted 24th August 2006*
*First published as an Advance Article on the web 26th September 2006*
**DOI: 10.1039/b609591g**

**The nature of the anionic ligand X (X = $EtOSO_3$, $BF_4$, Cl, Br, $OSO_2CF_3$, F or CN) in vanadium(V)salen complexes [$V^+O$(salen) $X^-$] was found to have a significant influence on the catalytic activity of the complexes, but not on their enantioselectivities; with the complexes in which X = Cl or F being most active and the complex with X = $OSO_2CF_3$ being totally inactive.**

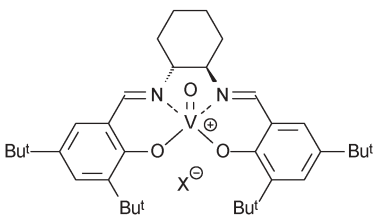
There is currently considerable interest in the design and development of asymmetric catalysts for cyanohydrin synthesis, due to the versatility of enantiomerically pure cyanohydrins in natural product synthesis and the synthesis of pharmaceutical intermediates.[1] In recent years we have reported[2] the development of a bimetallic titanium(salen) complex **1** and a vanadium(salen) complex **2** as highly effective catalysts for the asymmetric addition of trimethylsilyl cyanide,[3] potassium cyanide/acetic anhydride[4] and ethyl cyanoformate[5] to aldehydes and the use of complex **1** to catalyse the asymmetric addition of trimethylsilyl cyanide to ketones.[6] Other workers have shown that complex **1** can be used in conjunction with tertiary amines for the asymmetric synthesis of cyanohydrin acetates and ethyl carbonates[7] and that complexes **1** and **2** retain activity when polymerized[8] or attached to various insoluble supports.[9]

We have previously reported[10] detailed mechanistic studies on the asymmetric synthesis of cyanohydrin trimethylsilyl ethers using catalyst **1** which indicated that two metal ions were involved in the rate determining step and which were consistent with a mechanism in which cyanide was transferred intramolecularly within a bimetallic complex onto a coordinated carbonyl compound. Fewer mechanistic studies have been carried out on complex **2**,[11] but it was assumed that the mechanism would be closely analogous to that deduced for complex **1**. Although the enantioselectivity of **2** was much higher than that of **1**, the catalytic activity of the latter was greater by two orders of magnitude.[3b,4] Therefore, it was desirable to overcome the kinetic shortcomings of **2** by modification of its structure. Since the mechanistic studies on catalyst **1** indicated that the reaction mechanism involves rate limiting cleavage of the Ti(IV)–OCH(CN)R bond,[10] the sluggish reactivity of complex **2** might be related to the greater strength of the vanadium(V)–OCH(CN)R bond. Thus, anion X might not be a simple spectator of the catalysis, but its *trans*-influence might be a decisive factor in improving the catalytic activity of the vanadium based catalysts by promoting easier cleavage of the vanadium–cyanohydrin bond in the rate determining step of the reaction.

In this manuscript, we report the synthesis and catalytic activity of a series of complexes **3–8** which differ from complex **2** only in the nature of the anionic ligand. Kinetics results obtained with these complexes; and with catalysts **1** and **2** under identical conditions clearly demonstrate how the rate of reaction of vanadium based catalysts can be increased by orders of magnitude by tuning the nature of the X-ligand.




1



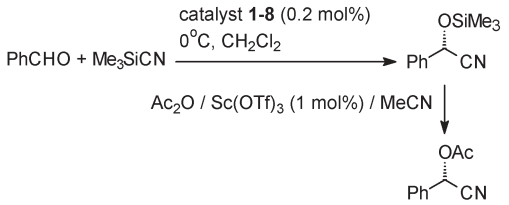

**2**: X = $EtOSO_3$
**3**: X = $BF_4$
**4**: X = Cl
**5**: X = Br
**6**: X = $CF_3SO_3$
**7**: X = F
**8**: X = CN

Complexes **3–6** were prepared by ion-exchange chromatography using Dowex® 1X8-400 resin starting from ethyl sulfonate complex **2**, the synthesis of which we have previously reported.[4] Complex **2** was first converted into tetrafluoroborate complex **3** by passing it through a column of Dowex® 1X8-400 which had previously been thoroughly treated with sodium tetrafluoroborate. Complexes **2** and **3** were well separated by TLC and by gel phase chromatography on Sephadex LH20, thus allowing the extent of ion-exchange to be monitored. Complex **3** then served as the precursor for complexes **4–6** since it underwent ion-exchange when passed through a column of Dowex® 1X8-400 which had previously been saturated with the appropriate sodium salt. This procedure was more convenient than direct ion-exchange from

[a] *A. N. Nesmeyanov Institute of Organo-Element Compounds, Russian Academy of Sciences, 119991, Moscow, Vavilov 28, Russian Federation. E-mail: yubel@ineos.ac.ru; Fax: 7-495-135-63-56; Tel: 7-495-135-50-85*
[b] *School of Natural Sciences, Bedson building, Newcastle University, Newcastle upon Tyne, UK NE1 7RU. E-mail: michael.north@ncl.ac.uk; Fax: +44 (0)870 131 3783; Tel: +44 (0)191 222 7128*

† Electronic supplementary information (ESI) available: Experimental details and characterizing data for complexes **3–6**. Graphical analyses of the kinetic data for complexes **1–8**. See DOI: 10.1039/b609591g




**Scheme 1** Standard conditions for the use of complexes **1–8** in the synthesis and analysis of *O*-trimethylsilyl mandelonitrile.

complex **2** to complexes **4–6** since these complexes could not be chromatographically distinguished. Alternatively, chloride complex **4** could also be prepared by treating the salen ligand directly with vanadium(V) oxychloride. Unfortunately, the corresponding fluoride or cyanide complexes **7** and **8** could not be prepared in this way. Instead, mixtures of **2** and potassium fluoride or potassium cyanide were tested as catalysts in the reaction, anticipating that ion exchange would take place and form the target complexes *in situ*.

To allow a direct comparison to be made between complexes **1–8**, they were each tested as catalysts for the asymmetric addition of trimethylsilyl cyanide (1.1 equivalents) to benzaldehyde at 0 °C in dichloromethane as shown in Scheme 1. In each case, 0.2 mol% of complexes **1–8** was used and the progress of the reaction was determined by UV spectrophotometry through monitoring the disappearance of the benzaldehyde adsorption at 246 nm. Under these conditions, benzaldehyde was cleanly converted into mandelonitrile trimethylsilyl ether and no catalyst decomposition took place on the timescale of the reaction. To allow the enantiomeric excess of the mandelonitrile trimethylsilyl ether to be determined, the crude *O*-trimethylsilyl mandelonitrile was treated with acetic anhydride in the presence of catalytic scandium triflate according to the method of Kagan[12] to produce the corresponding *O*-acetyl mandelonitrile which could be easily analysed by chiral GC.

Precatalyst **6** was catalytically inactive. All the other precatalysts were most active only if an air atmosphere was maintained in the reaction vessel. The reaction was severely retarded under an argon atmosphere (Fig. 1). Kinetic plots of the reaction catalysed by **1–5** and **7–8** are presented in Fig. 2. Table 1 records the time taken for 50% of the benzaldehyde to be consumed in these reactions along with the enantiomeric excess of the *O*-acetyl mandelonitrile.

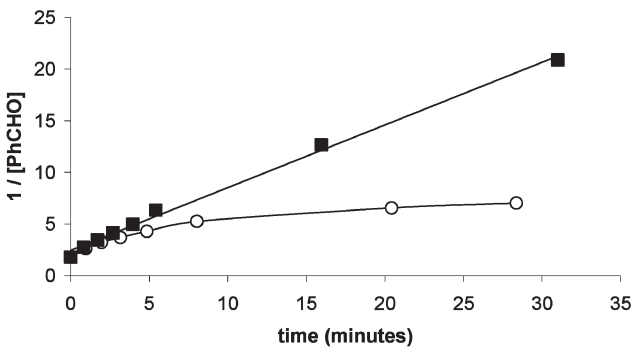



**Fig. 1** Second order kinetics plots for the addition of trimethylsilyl cyanide to benzaldehyde catalysed by complex **4** at 20 °C in dichloromethane in the presence (filled squares) or absence (open circles) of air.

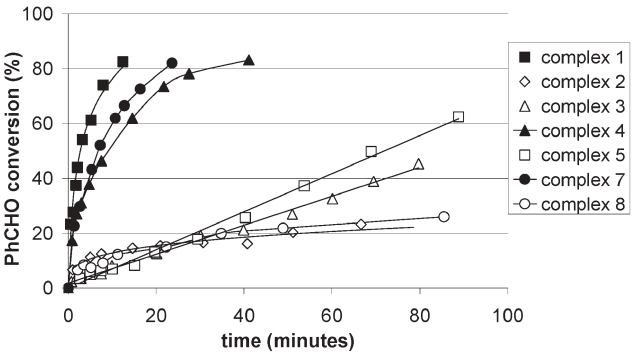



**Fig. 2** Plots of benzaldehyde conversion *vs.* time for the addition of trimethylsilyl cyanide to benzaldehyde catalysed by complexes **1–5** and **7–8** at 0 °C in dichloromethane.

From the data in Fig. 2 and Table 1, it is apparent that the enantiomeric excess of the product (90–94%) was not significantly influenced by the nature of the counterion. This suggests that the stereodetermining step of the reaction and the structure of the transition state leading to C–C bond formation is the same throughout the series of catalysts **2–8** and does not involve any anion participation.

In contrast, the counterion within the catalyst has a major impact on the kinetics of the trimethylsilylation reaction. The catalytic activity of the complexes increases as the basicity of the anions increases, thus: X = F > Cl > Br > $BF_4$ > CN > $EtOSO_3$ ⋙ $CF_3SO_3$ (see Table 1, entries 2–8). Complex **4** was the most active isolable catalyst, and was also found to catalyse the reaction of other aldehydes with trimethylsilyl cyanide as shown in

**Table 1** Comparison of catalysts **1–8** in the synthesis of *O*-trimethylsilyl mandelonitrile[a]

| Entry | Precatalyst | $t_{50\%}$/min | ee (%)[b] |
|---|---|---|---|
| 1 | **1** | 3.4 | 87 |
| 2 | **7** | 7.6 | 94 |
| 3 | **4** | 8.6 | 93 |
| 4 | **5** | 50.3 | 94 |
| 5 | **3** | 78.2 | 90 |
| 6 | **8** | 201.9 | 91 |
| 7 | **2** | 370.0 | 91 |
| 8 | **6** | No reaction | |

[a] Reaction conditions: benzaldehyde concentration 0.5–0.7 M, ratio of benzaldehyde–trimethylsilyl cyanide = 1/1.1; precatalyst loading 0.2 mol%; 0 °C, dichloromethane. For **1**: 0.2 mol% of metal ions corresponds to 0.1 mol% of the dimeric complex. [b] Determined by chiral GC with an error of ± 3%. Mandelonitrile of (*S*)-configuration was invariably formed from (*R,R*) complexes.

**Table 2** Cyanohydrin synthesis catalysed by complex **4**[a]

| Entry | Aldehyde | *T*/°C | Time/h | Conversion (%) | *ee* (%)[b] |
|---|---|---|---|---|---|
| 1 | 2-$ClC_6H_4CHO$ | −40 | 24 | >95% | 91 |
| 2 | 2-$ClC_6H_4CHO$ | 0 | 0.5 | >95% | 87 |
| 3 | 2-$ClC_6H_4CHO$ | 20 | 0.5 | >95% | 82 |
| 4 | $Me_2CHCHO$ | 0 | 0.5 | >95% | 83 |
| 5 | $Me_3CCHO$ | 0 | 0.5 | >95% | 83 |

[a] Reaction conditions: aldehyde concentration 0.5–0.7 M, ratio of aldehyde/trimethylsilyl cyanide = 1/1.1; catalyst **4** loading 0.2 mol%; 0 °C, dichloromethane. [b] Determined by chiral GC.

Table 2. Particularly good enantiomeric excesses (Table 2, entries 4 and 5) were obtained for aliphatic aldehydes compared to those previously obtained (64–68%) for these substrates using catalysts **1** and **2**.[3,11]

Reactions involving complex **1** were found to obey first order kinetics as previously reported.[10] However, the vanadium based catalysts **2–8** gave reactions with different orders, which in some cases varied with temperature. It is for this reason that the rate data in Table 1 are quoted as $t_{50\%}$ rather than as rate constants. Thus, whilst reactions catalysed by each of complexes **2–5** and **8** displayed second order kinetics at 20 °C, at lower temperatures (10 °C and below for complex **3** and 0 °C and below for complex **5**), reactions catalysed by complex **3** and **5** exhibited zero order kinetics. Reactions catalysed by complex **7** exhibited first order kinetics.

Complexes **2–8** all have octahedral geometries. In the case of complex **2**, we have previously shown by X-ray crystallography[4] that the sixth coordination site is filled by a water molecule. Infrared spectroscopy and combustion analysis data indicate that this is also the case for complexes **4–6**, as does literature precedent.[13] However, in solution under the reaction conditions the anions can enter the coordination sphere of the vanadium ion, especially as TMSCN is a dehydrating agent.[14] In the case of complex **3** which has a tetrafluoroborate counterion, the crystal structure of an analogous achiral vanadium(V)(salen) tetrafluoroborate complex[15] indicates that one of the fluorine atoms of the tetrafluoroborate unit is coordinated to the vanadium, thus occupying the sixth coordination site. $^{19}$F NMR spectroscopy indicated that this coordination persisted in solution, and the $^{19}$F NMR spectrum of complex **3** similarly showed two peaks in a 3 : 1 ratio consistent with coordination of one of the fluorine atoms of the tetrafluoroborate to the vanadium.

If complexes **2–8** acted by a simple Lewis-acid catalysis mechanism, complex **6** (X = $CF_3SO_3$) should have had the highest catalytic activity, since in this case the positive charge is localized on the vanadium ion due to the non-coordinating counterion. If anion exchange, with formation of the CN-complex of vanadium(V) was responsible for the variation of the activity of the complexes, the *in situ* preformed cyanide complex **8** would have produced the most active catalyst. The mediocre performance of complex **8** (Table 1: entry 6) is however inconsistent with this hypothesis.

The catalytic data suggest that the anion X is not present in the catalytically active species during the stereodetermining C–C bond formation. Thus, all of the catalysts give the same level of asymmetric induction. The difference in rate observed for the complexes can be partly explained on the basis of the relative stabilities of the catalytically active vanadium(V) complexes with respect to the corresponding catalytically inactive vanadium(IV) complexes, produced *in situ* by benzaldehyde oxidation. The basic anions would be expected to stabilize the vanadium(V) complexes in solution. The zero order reaction observed at low temperatures in the case of complexes **3** and **5** could then be a result of oxygen induced oxidation of the inactive vanadium(IV) complex into the active vanadium(V) complex being the rate determining step. The first order kinetics observed for complex **7** suggest that a different process might be operating in this case. Thus, formation of a hypervalent complex of fluoride with trimethylsilyl cyanide, greatly increasing its activity, could change the rate determining step of the reaction from vanadium(V)–OCH(CN)R interaction with trimethylsilyl cyanide to that of the initial benzaldehyde–complex **7** interaction.

In conclusion, we have shown that the counterion present in vanadium(V)salen complexes has a significant influence on the effectiveness of the complex as a catalyst for asymmetric cyanohydrin synthesis. The mechanism is more complex for vanadium based catalysts **2–8** than that previously reported for dimeric titanium based catalyst **1**[10] due to the ability of vanadium to undergo redox reactions, and the ability of the counterion to change the rate determining step of the mechanism. The chloride complex **4** and *in situ* formed fluoride complex **7** are 50 times more reactive than the previously reported ethylsulfonate complex **2**, and have catalytic activities comparable with complex **1** whilst retaining the high levels of asymmetric induction associated with complex **2**.

The authors thank the EU (Descartes prize research fund) for financial support. Mass spectra were recorded by the EPSRC funded national service at the University of Wales, Swansea and use of the EPSRC's Chemical Database Service at Daresbury is also gratefully acknowledged.

## Notes and references

1 For recent reviews of the synthesis and applications of chiral cyanohydrins see: (*a*) M. North, *Tetrahedron: Asymmetry*, 2003, **14**, 147–176; (*b*) J.-M. Brunel and I. P. Holmes, *Angew. Chem., Int. Ed.*, 2004, **43**, 2752–2778.

2 For a review of the development and applications of catalysts **1** and **2** see: T. R. J. Achard, L. A. Clutterbuck and M. North, *Synlett*, 2005, 1828–1847.

3 (*a*) Y. N. Belokon, S. Caveda-Cepas, B. Green, N. S. Ikonnikov, V. N. Khrustalev, V. S. Larichev, M. A. Mosckalenko, M. North, C. Orizu, V. I. Taravov, M. Tasinazzo, G. I. Timofeeva and L. V. Yashkina, *J. Am. Chem. Soc.*, 1999, **121**, 3968–3973; (*b*) Y. N. Belokon, M. North and T. Parsons, *Org. Lett.*, 2000, **2**, 1617–1619.

4 Y. N. Belokon, P. Carta, A. V. Gutnov, V. Maleev, M. A. Moskalenko, L. V. Yashkina, N. S. Ikonnikov, N. V. Voskoboev, V. N. Khrustalev and M. North, *Helv. Chim. Acta*, 2002, **85**, 3301–3312.

5 Y. N. Belokon, J. Blacker, L. A. Clutterbuck and M. North, *Org. Lett.*, 2003, **23**, 4505–4507.

6 Y. N. Belokon, B. Green, N. S. Ikonnikov, M. North and V. I. Tararov, *Tetrahedron Lett.*, 1999, **40**, 8147–50.

7 S. Lundgren, E. Wingstrand, M. Penhoat and C. Moberg, *J. Am. Chem. Soc.*, 2005, **127**, 11592–11593.

8 (*a*) W. Huang, Y. Song, C. Bai, G. Cao and Z. Zheng, *Tetrahedron Lett.*, 2004, **45**, 4763–4767; (*b*) W. Huang, Y. Song, J. Wang, G. Cao and Z. Zheng, *Tetrahedron*, 2004, **60**, 10469–10477.

9 (*a*) C. Baleizão, B. Gigante, H. Garcia and A. Corma, *J. Catal.*, 2003, **215**, 199–207; (*b*) C. Baleizão, B. Gigante, D. Das, M. Alvaro, H. Garcia and A. Corma, *Chem. Commun.*, 2003, 1860–1861; (*c*) C. Baleizão, B. Gigante, H. Garcia and A. Corma, *Tetrahedron*, 2004, **60**, 10461–10468; (*d*) C. Baleizão, B. Gigante, H. Garcia and A. Corma, *J. Catal.*, 2004, **221**, 77–84.

10 Y. N. Belokon, B. Green, N. S. Ikonnikov, V. S. Larichev, B. V. Lokshin, M. A. Moscalenko, M. North, C. Orizu, A. S. Peregudov and G. I. Timofeeva, *Eur. J. Org. Chem.*, 2000, 2655–2661.

11 Y. N. Belokon, B. Green, N. S. Ikonnikov, M. North, T. Parsons and V. I. Tararov, *Tetrahedron*, 2001, **57**, 771–779.

12 S. Norsikian, I. Holmes, F. Lagasse and H. B. Kagan, *Tetrahedron Lett.*, 2002, **43**, 5715–5717.

13 (*a*) K. Nakajima, K. Kojima, M. Kojima and J. Fujita, *Bull. Chem. Soc. Jpn.*, 1990, **63**, 2620–2630; (*b*) N. F. Choudhary, P. B. Hitchcock and G. J. Leigh, *Inorg. Chim. Acta*, 2000, **310**, 10–20.

14 J. Blacker, L. A. Clutterbuck, M. R. Crampton, C. Grosjean and M. North, *Tetrahedron: Asymmetry*, 2006, **17**, 1449–1456.

15 K. Oyaizu, E. L. Dewi and E. Tsuchida, *Inorg. Chem.*, 2003, **42**, 1070–1075.