In Situ Formation of Heterobimetallic Salen Complexes Containing Titanium and/or Vanadium Ions

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A combination of high-resolution electrospray mass spectrometry and ^{1}H NMR spectroscopy has been used to prove that when a mixture of [(salen)TiO]$_2$ complexes containing two different salen ligands (salen and salen') is formed, an equilibrium is established between the homodimers and the heterodimer [(salen)TiO$_2$Ti(salen')]. Depending upon the structure and stereochemistry of the two salen ligands, the equilibrium may favor either the homodimers or the heterodimer. Extension of this process to mixtures of titanium(salen) complexes [(salen)TiO]$_2$ and vanadium^V(salen') complexes [(salen')VO]$^+$Cl$^-$ allowed the in situ formation of the heterobimetallic complex [(salen)TiO$_2$V(salen')]$^+$X$^-$ to be confirmed for all combinations of salen ligands studied except when the salen ligand attached to titanium contained highly electron-withdrawing nitro-groups. The rate of equilibration between heterobimetallic complexes is faster than that between two titanium complexes as determined by line broadening in the ^{1}H NMR spectra. These structural results explain the strong rate-inhibiting effect of vanadium^V(salen) complexes in asymmetric cyanohydrin synthesis catalyzed by [(salen)TiO]$_2$ complexes. It has also been demonstrated for the first time that the titanium and vanadium complexes can undergo exchange of salen ligands and that this is catalyzed by protic solvents. However, the ligand exchange is relatively slow (occurring on a time scale of days at room temperature) and so does not complicate studies aimed at using heterobimetallic titanium and vanadium salen complexes as asymmetric catalysts. Attempts to obtain a crystal structure of a heterobimetallic salen complex led instead to the isolation of a trinuclear titanium(salen) complex, the formation of which is also consistent with the catalytic results obtained previously.

Introduction

Metal complexes bearing chiral ligands have numerous applications as Lewis acids in asymmetric catalysis.[1] In most cases, the metal complex is (or at least is assumed to be) a monometallic species in which one or more chiral ligands are attached to a single metal ion. Recently however, it has been found that catalytic species which were previously assumed to be monometallic actually form bimetallic (or

higher nuclearity) complexes in situ.[2] As a result, a number of chiral ligand systems specifically designed to bind to two identical metal ions have been prepared.[3,4] However, for many potential catalytic applications, it would be desirable to have a bimetallic complex containing two different metal ions which are capable of carrying out different catalytic

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roles. Unfortunately, the design and synthesis of such heterobimetallic complexes is a challenging undertaking.[5–7]

Over the last ten years, we have developed bimetallic titanium(salen) and monometallic vanadium(salen) complexes **1** and **2** as highly active asymmetric catalysts for the addition of a range of cyanide sources to aldehydes and ketones, resulting in the synthesis of highly enantiomerically enriched cyanohydrins.[8] This is now a commercial process for the synthesis of enantiomerically pure cyanohydrins and their derivatives.[9] Subsequently, we showed that when complexes **1** and **2** of opposite absolute configurations were mixed, the catalytic properties of the resulting mixture could be explained on the basis of the in situ formation of a heterobimetallic complex containing both titanium and vanadium ions.[10] In particular, reactions between benzaldehyde and trimethylsilyl cyanide catalyzed by complex **1** are over one hundred times faster than those catalyzed by complex **2**. In spite of this, when complexes **1** and **2** were

Scheme 1. Synthesis of Mandelonitrile Trimethylsilyl Ether Using Catalysts **1** and/or **2**
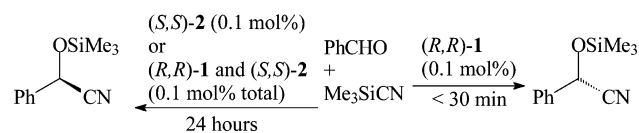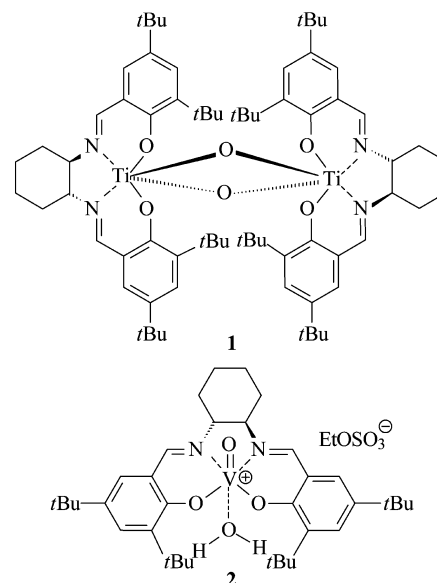
mixed, it was the stereochemistry of the salen ligand attached to the vanadium ion which determined the stereochemistry of the cyanohydrin product (Scheme 1). Recently, we have extended this work to the use of mixtures of chiral and achiral salen ligands and again obtained results which indicated the in situ formation of catalytically active heterobimetallic complexes.[11]

In this paper, we present the first direct experimental evidence for the formation of bimetallic complexes containing two titanium ions with a different salen ligands attached to each ion; or one titanium and one vanadium ion with either the same or a different ligand attached to each metal ion. The occurrence of dynamic processes involving ligand exchange between the metal ions is also discussed, as is the use of the complexes in asymmetric cyanohydrin synthesis.

Results and Discussion

Synthesis of Homometallic Complexes. The salen ligands **3−8** used in this work were prepared from (R,R)- or (S,S)-1,2-diaminocyclohexane or 1,2-diaminoethane and the appropriate salicylaldehyde derivative according to literature procedures.[12] The ligands were complexed to titanium to

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Scheme 2. Synthesis of Titanium^{IV} and Vanadium^{V}(Salen) Complexes **1**, **9–18**
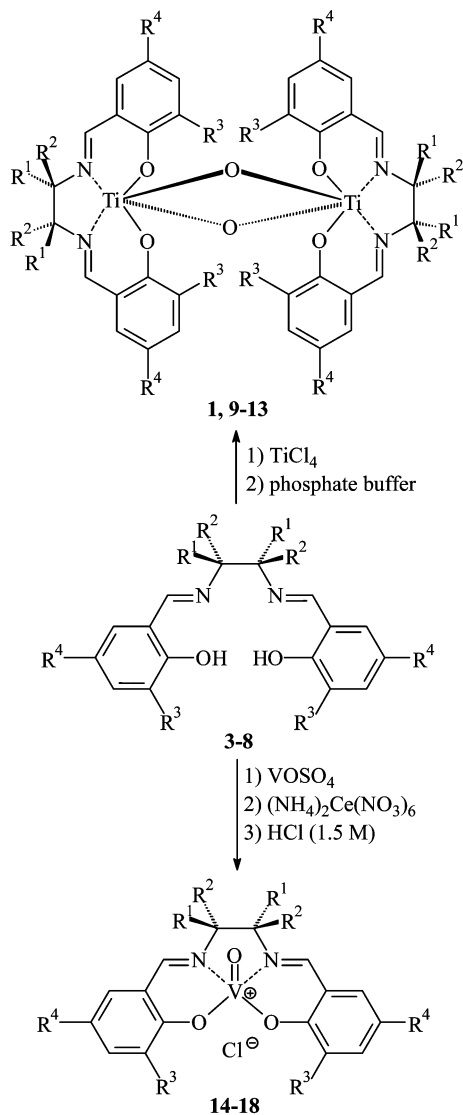
1,3,14: R^1 = H; R^2-R^2 = (CH$_2$)$_4$; R^3 = R^4 = ^{t}Bu

4,9,15: R^1-R^1 = (CH$_2$)$_4$; R^2 = H; R^3 = R^4 = ^{t}Bu

5,10,16: R^1 = H; R^2-R^2 = (CH$_2$)$_4$; R^3 = ^{t}Bu; R^4 = OMe

6,11: R^1 = H; R^2-R^2 = (CH$_2$)$_4$; R^3 = ^{t}Bu; R^4 = NO$_2$

7,12,17: R^1 = H; R^2-R^2 = (CH$_2$)$_4$; R^3 = R^4 = H

8,13,18: R^1 = R^2 = H; R^3 = R^4 = ^{t}Bu

form bimetallic complexes **1**, **9–13** by the two-step process we have previously developed[13] for the synthesis of complex **1** as shown in Scheme 2. To form the corresponding vanadium^V complexes **14–18**, ligands **3–5**, **7**, **8** were first treated with vanadyl sulfate to form a vanadium^{IV}(salen)

(15) For a general discussion of the oxidation of vanadium^{IV} (salen) complexes to the corresponding vanadium^V complexes see Bonadies, J. A.; Butler, W. M.; Pecoraro, V. L.; Carrano, C. J. *Inorg. Chem.* **1987**, *26*, 1218–1222.

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complex, and this was then oxidized to the vanadium^V(salen) chloride by treatment with ceric ammonium nitrate followed by hydrochloric acid according to the method of Nakajima (Scheme 2).[14] The ceric ammonium nitrate oxidation was found to be more general[15] than the routes we have previously reported for the synthesis of complex **2** using oxygen[13] or cumene hydroperoxide[11,14] as the oxidant. By working-up the oxidation reaction with hydrochloric acid, vanadium complexes **14–18** were directly obtained with chloride counterions, which we have previously shown has a highly beneficial effect on the catalytic activity of the complexes.[16]
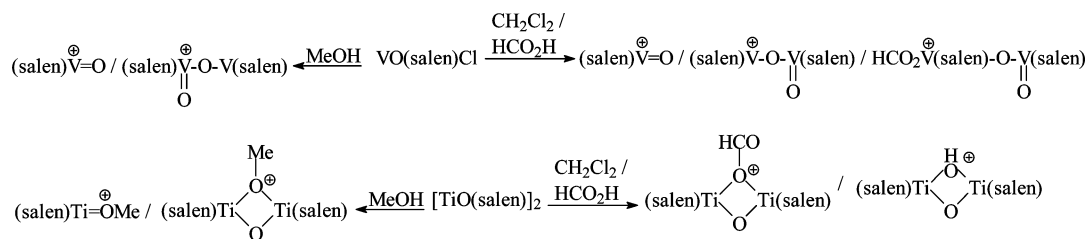
Analysis of Individual Homometallic Complexes. As a precursor to studies aimed at characterizing the species formed when complexes **1** and **9–18** were mixed, each complex was individually fully characterized, and useful structural information was obtained from both the ^{1}H NMR spectra and the high-resolution electrospray mass spectra of the complexes. In addition, the crystal structures of complexes **2**, **12**, and **13** have previously been published.[11,13,17] A detailed analysis of the ^{1}H NMR spectra of complexes **1** and **13** which provided information about the number and nature of species present in solution has previously been reported.[11] For the work described in this paper, all ^{1}H NMR spectra were recorded from samples in CD$_2$Cl$_2$, as in this solvent, the complexes gave a well defined set of peaks at room temperature, corresponding to a single major species. If peaks due to a second species were present, these were of very low intensity and so did not interfere with subsequent studies on the structures formed when the complexes were mixed. All of the titanium complexes gave NMR spectra consistent with the bimetallic structures **1**, **9–13** in which the salen ligands both adopt *cis-β* configurations,[11] while all of the vanadium complexes gave NMR spectra consistent with the square-based pyramidal (or octahedral if the chloride counterion is assumed to coordinate to the vanadium) monometallic structures **14–18**.[18]

The high-resolution electrospray mass spectra of complexes **1** and **9–18** were particularly informative and also very useful for the subsequent characterization of heterobimetallic complexes. The nature of the spectra obtained was very dependent on the method used to ionize the sample. In some cases, simply injecting a methanol solution of the complex into the ionization chamber gave satisfactory results, while for other complexes, injection of a dichloromethane solution of the sample to which 0.1% formic acid had been added gave good results. Important structural information could be obtained from both the high-resolution masses of the peaks in the molecular ion cluster and from the isotope pattern which could be matched to that predicted for a particular chemical composition. The nature of the species detected from titanium and vanadium(salen) complexes using both ionization methods are highlighted in Scheme 3.

Vanadium complexes (**14–18**) gave excellent mass spectrometry results using both injection systems and clearly showed

(18) Data contained in the supporting information.

Scheme 3. Species Detected in the Electrospray Mass Spectra of Titanium and Vanadium(Salen) Complexes

a molecular ion peak (M^+) along with evidence for the presence of dimeric species comprising one V^V(salen) unit and one V^{IV}(salen) unit.[19] The $2M^+$ peak was always of much higher intensity for spectra recorded from methanol solution than for spectra recorded from dichloromethane/formic acid solution, consistent with in situ oxidation of methanol being largely responsible for the reduction of V^V to V^{IV} as the ^{1}H NMR spectra of the complexes showed no evidence for the presence of paramagnetic V^{IV} species. Mass spectra recorded from dichloromethane/formic acid solutions showed an additional peak corresponding to the formate adduct of a dimer in which both vanadium ions were still in the +5 oxidation state (Scheme 3). Figure 1 illustrates the predicted and actual isotope distributions from a typical spectrum: that obtained from a methanol solution of complex **18**. The full spectrum is included in the Supporting Information. Corresponding spectra were obtained for complexes **14**–**17** and for complex **18** ionized from dichloromethane/formic acid.[18]

Further evidence that electron transfer processes occur during the acquisition of electrospray mass spectra of vanadium(salen)
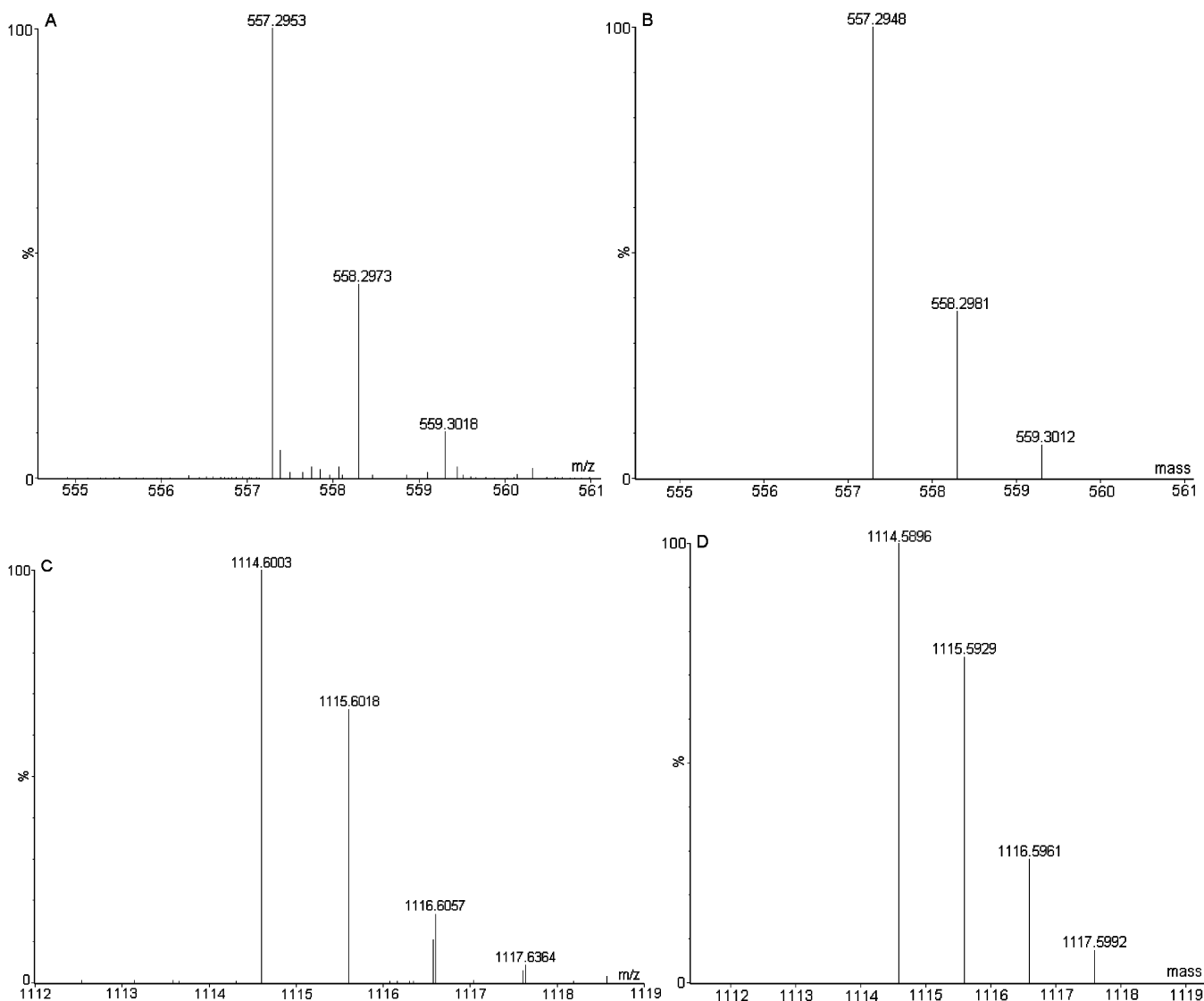
Figure 1. Electrospray ionization mass spectrum of complex **18** (obtained from a methanol solution). (A) Actual high-resolution data for monomeric species, (B) simulated isotope pattern for monomeric species, (C) actual high-resolution data for dimeric species, and (D) simulated isotope pattern for dimeric species.
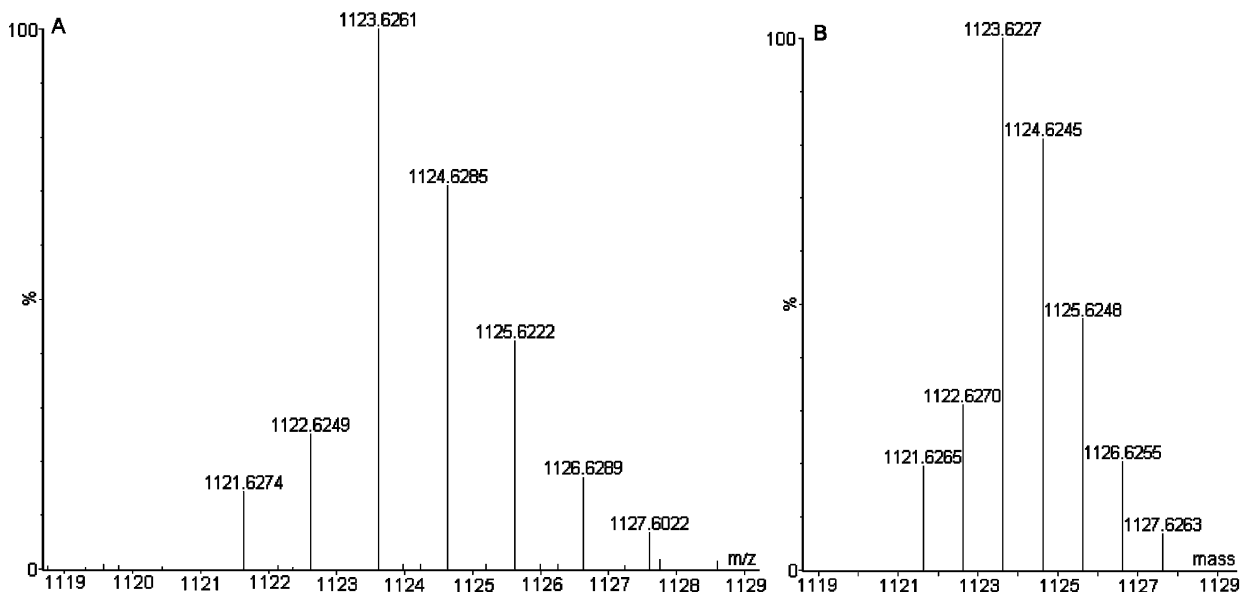
Figure 2. Electrospray ionization mass spectrum of complex **13** (obtained from a methanol solution). (A) Actual high-resolution data for complex **13** + Me and (B) simulated isotope pattern for **13** + Me.

complexes was obtained by recording the mass spectrum of a 1:1 mixture in methanol of vanadium[V](salen) complex **18** and the vanadium[IV](salen) complex derived from ligand **3** [(salen-**3**)VO].[18] This spectrum clearly shows ion clusters corresponding to both monometallic vanadium[V](salen) complexes (**14** at m/z 611 and **18** at m/z 557), to the dimers of both of these complexes (m/z 1222 and 1114, respectively), and to the mixed dimer formed from both monometallic species (m/z 1168). The formation of the monocharged dimers requires that the vanadium[IV](salen) complex derived from ligand **3** must have been partially oxidized to the corresponding vanadium[V](salen) complex **14**, while complex **18** must have been partially reduced to the corresponding vanadium[IV](salen) complex derived from ligand **8**. The electrospray mass spectrum of a 1:1 mixture in methanol of complexes **14** and **18** was also recorded.[18] This gave rise to the same mono- and bimetallic species as those obtained from the mixture of [(salen-**3**)VO] and **18**, but the peaks corresponding to the bimetallic vanadium[IV]-vanadium[V] species were much weaker in this case as the only source of vanadium[IV] ions was in situ reduction of vanadium[V] complexes using methanol as the reducing agent.

The mass spectra of titanium complexes (**1**, **9–13**) were highly dependent on the method used to insert the sample into the ionization chamber. When the complex was introduced in a dichloromethane/formic acid solution, peaks corresponding to protonated and formylated [(salen)Ti-μ-O-μ-(HCO$_2$)$^+$-Ti(salen)] bimetallic complexes were observed as the major and sometimes only significant peaks in the spectrum (Scheme 3). In contrast, when the sample was injected from a methanol solution, peaks corresponding to the methylated complexes [(salen)Ti=OMe$^+$] and [(salen)Ti-μ-O-μ-O$^+$Me-Ti(salen)] were observed because of the replacement of one of the bridging oxygen atoms of complexes **1**, **9–13** by a methoxy unit (Scheme 3). Methanol adduct peaks were also sometimes observed, and the methylated monometallic complex was always the major species present,

which is consistent with previous work by Katsuki on the solvent dependence of the structure of Ti(salen)O complexes.[20] The mass spectrum of complex **13** (obtained from methanol[18]) illustrates the presence of methylated complex **13** (m/z = 1123) (Figure 2), the methanol adduct of methylated **13** (m/z = 1155), and the methylated monometallic version of complex **13** [(salen)Ti = OMe; m/z = 569]. The corresponding spectra for complexes **1**, **9–12** displayed similar features.[18]

Analysis of Homobimetallic Complexes Derived from Two Different Ti[IV](Salen) Complexes. When two of the titanium complexes **1**, **9–13** were mixed in equimolar amounts in CD$_2$Cl$_2$, an equilibrium was established between the two homodimers and the heterodimer derived from one of each TiO(salen) unit. The mass spectrometric evidence for the formation of each of the heterodimeric complexes is summarized in Table 1, and the analysis of the mixture obtained from complexes **9** and **13** (Scheme 4) is discussed in detail. Expansions of the aromatic and imine region of the ^{1}H NMR spectra (in CD$_2$Cl$_2$) of compounds **9**, **13**, and the mixture of compounds **9** and **13** are shown in Figure 3 (the full spectra are contained in the Supporting Information along with those of the other mixtures detailed in Table 1), and the high-resolution electrospray mass spectrum corresponding to complex **19** obtained from the mixture of complexes **9** and **13** in dichloromethane/formic acid is shown in Figure 4. For all of the complexes derived from two different titanium(salen) complexes, ionization from dichloromethane/formic acid gave much better quality mass spectra[18] than ionization from methanol.

(19) No evidence for the formation of bimetallic complexes containing two vanadium[V] ions was detected. Such a species would have a charge of 2, and hence would have the same m/z ratio as a mononuclear structure. However, the isotope peaks for the hypothetical dimer would occur at half-integer values and hence be clearly distinguishable from the mononuclear species. The spectra in the supporting information show no evidence for the formation of such a species.
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Table 1. Spectroscopic Evidence for the Formation of Mixed Titanium(Salen) Complexes

| first complex	second complex	m/z of center of observed ion clusters (ionized from CH₂Cl₂/formic acid)	equilibrium populations determined by ¹H NMR
9	**13**	1138 (complex **13** + CHO); 1192 (complex **19** + CHO); 1246 (complex **9** + CHO).	**9:13:19** = 2:6:3
10	**13**	1111 (MH⁺ for all three complexes); 1139 (M + CHO for all three complexes.	**10:13**:mixed dimer = 3:5:6
10	**11**	1142 (complex **10** + CHO); 1172 (mixed complex + CHO).	**10:11**:mixed dimer = 2:3:4
1	**10**	1142 (complex **10** + CHO); 1194 (mixed complex + CHO); 1246 (complex **1** + CHO).	**1:10**:mixed dimer = 5:3:1
9	**10**	1142 (complex **10** + CHO); 1194 (mixed complex + CHO); 1246 (complex **1** + CHO).	**9:10**:mixed dimer = 4:3:2
1	**11**	1224 (mixed complex + CHO); 1246 (complex **1** + CHO).	**1:11**:mixed dimer = 4:9:4
9	**11**	1246 (complex **1** + CHO).	**9:11**:mixed dimer = 1:2:20

Scheme 4. Equilibration between Complexes **9**, **13**, and **19**
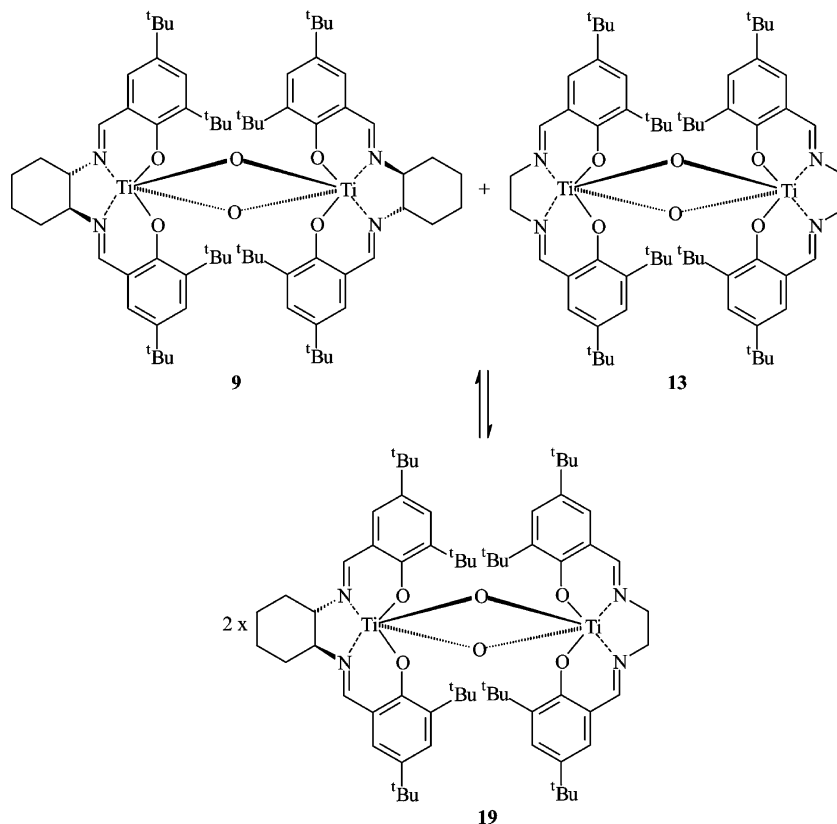
The ¹H NMR spectra in Figure 3 clearly demonstrate that the mixture of compounds **9** and **13** contains peaks assignable to both of these complexes, as well as peaks corresponding to the in situ formation of a new species. The mass spectrum[18] confirms the presence of complexes **9** and **13** in the mixture and indicates that the new species is the mixed dimer **19** (M + CHO, m/z = 1191, Figure 4). Compound **19** should give rise to four imine signals in its ¹H NMR spectrum, and these are clearly visible above 8 ppm in Figure 3c. Of the eight ArCH signals required by structure **19**, only three are clearly visible. The remaining signals are coincident with those of complexes **9** and **13** as indicated by integration of the ¹H NMR spectrum and a ¹H–¹H COSY spectrum. The peaks in Figure 3c do not show evidence of line broadening, which indicates that the rate of exchange of Ti(salen) units between complexes **9**, **13**, and **19** is slow on the NMR time scale. Integration of the signals in Figure 3c indicates that the equilibrium ratio of complexes **9**, **13**, and

19 is 2:6:3, respectively, which does not coincide with the statistical ratio (1:1:2). The ratio of complexes **9** and **13** in the mixture was not 1:1, which can be explained on the basis of the second complex present perturbing the equilibrium between the dimeric and monomeric [(salen)Ti=O] forms of the complexes. We have previously shown that this equilibrium exists[11,21] and the same effect was seen for all other combinations of two titanium(salen) complexes (Table 1).

In general, the electrospray mass spectra (obtained from a dichloromethane/formic acid solution) of the combinations of titanium complexes **1**, **9**–**13** showed (M + CHO)⁺ ions corresponding to the species present (Scheme 3). However, the combination of complexes **10** and **13** was exceptional in that it also contained a signal corresponding to MH⁺, and the base peak was a doubly charged ion [(salen)TiOTi-

(21) Belokon, Y. N.; Blacker, A. J.; Carta, P.; Clutterbuck, L. A.; North, M. *Tetrahedron* **2004**, *60*, 10433–10447.
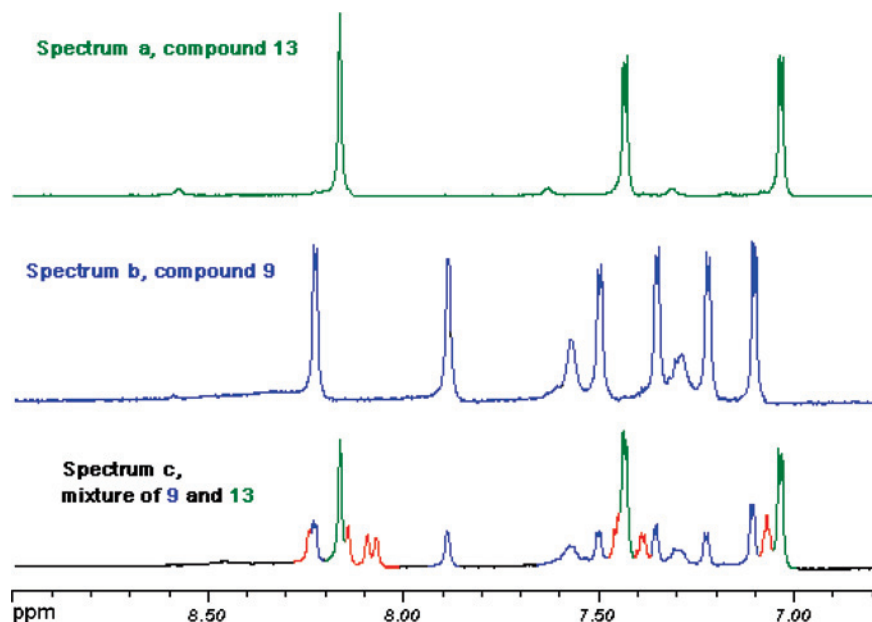
Figure 3. Expansion of the ^{1}H NMR spectra (in CD_2Cl_2) of complexes **13** (spectrum a), **9** (spectrum b), and a mixture of complexes **9** and **13** with peaks corresponding to complex **19** highlighted in red (spectrum c).
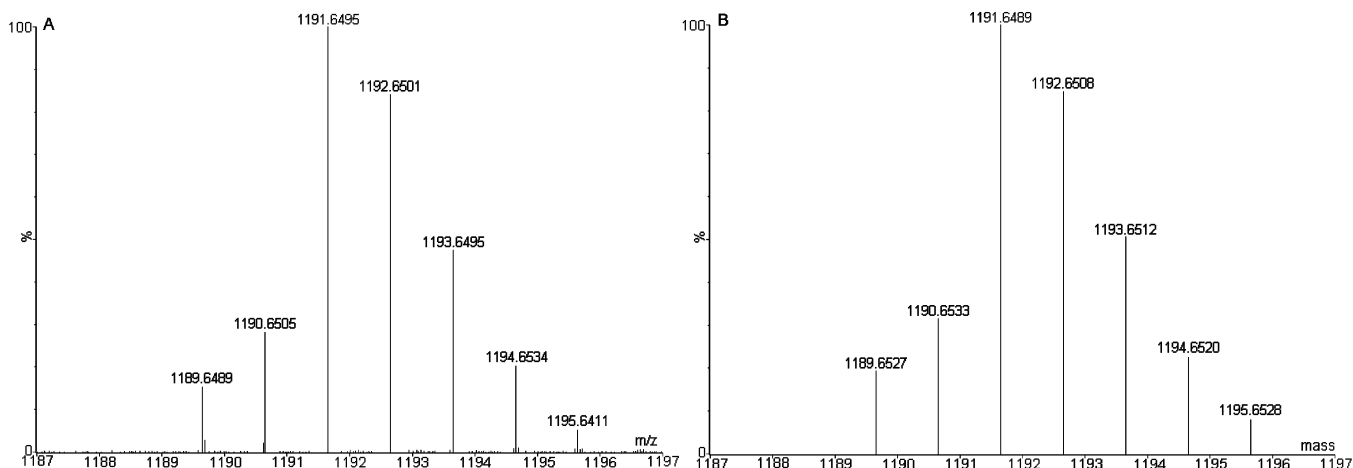

Figure 4. Electrospray ionization mass spectrum of a mixture of complexes **9** and **13** in dichloromethane/formic acid. (A) Actual data for complex **19** + CHO and (B) simulated isotope pattern for complex **19** + CHO.

(salen)]$^{2+}$. No evidence for doubly charged ions was present in the mass spectra of any of the other complexes. The peak intensities in the electrospray mass spectra of the bimetallic complexes could not be used to determine equilibrium populations as the intensities were very dependent on the electronic nature of the salen ligand. In particular, ions derived from salen ligand **6** which contains nitro-groups were of particularly low intensity whichever method was used to ionize the complexes. Thus, the mixed dimer obtained from complexes **1** and **11** could only just be detected in the mass spectrum of the mixture of complexes **1** and **11**, and the diastereomeric complex derived from complexes **9** and **11** could not be detected at all by mass spectrometry, even though it is the major species present in CD_2Cl_2 as determined by ^{1}H NMR spectroscopy (Table 1).

The data in Table 1 indicate considerable variability in the equilibrium for formation of the mixed dimeric complexes. Thus, whereas complexes **10** and **13** favor formation of the mixed dimer, a mixture of complexes **10** and **1** favors

formation of the homodimers, and only a relatively small amount of the mixed dimer is formed. In all cases, however, the NMR spectra of the mixed complexes showed no evidence of line-broadening, indicating that equilibration between the complexes occurs slowly on the NMR time scale. Comparison of the last four entries in Table 1 shows that the relative stereochemistry of the complexes does have a significant influence on the relative stabilities of the dimers. Thus, the combination of complex **10** with the enantiomeric complexes **1** or **9** gave twice as much mixed dimer in the latter case, indicating that the heterochiral mixed dimer is more stable than the homochiral mixed dimer. This is consistent with our previous theoretical analysis of the factors that determine the stability of bimetallic metal(salen) complexes.[11] The effect is even more pronounced in the case of complex **11** with the same enantiomeric complexes **1** or **9** where twenty times as much heterochiral dimer was present at equilibrium as homochiral dimer.
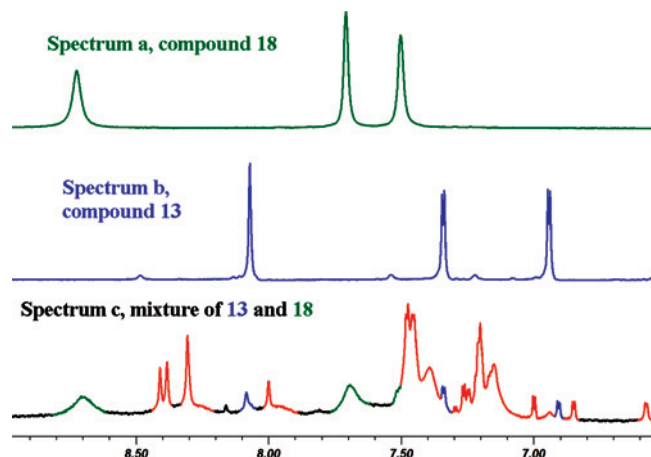
Figure 5. Expansion of the ^{1}H NMR spectra (in CD$_2$Cl$_2$) of complexes **18** (spectrum a), **13** (spectrum b), and a mixture of complexes **13** and **18** with peaks corresponding to complex **20** highlighted in red (spectrum c).

Scheme 5. Equilibration between Complexes **13**, **18**, and **20**
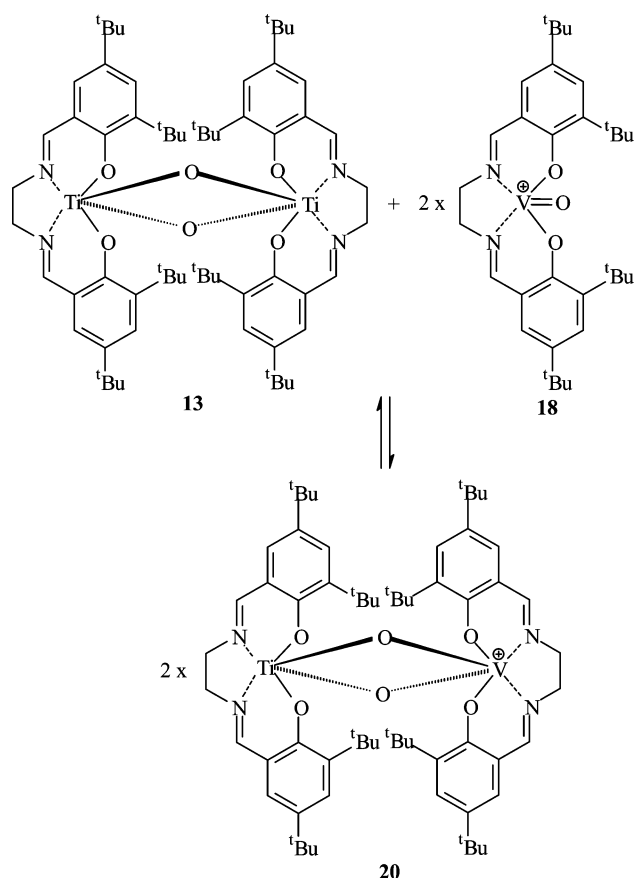
Analysis of Heterobimetallic Units Derived from Ti^{IV}(Salen) and V^V(Salen) Complexes. When various combinations of Ti^{IV}(salen) and V^V(salen) complexes were mixed, the resulting ^{1}H NMR and electrospray mass spectra always showed evidence for the in situ formation of heterobimetallic complexes. Figure 5 shows the ^{1}H NMR spectrum obtained from an equimolar mixture of complexes **13** and **18**, while Figure 6 shows the corresponding high-resolution mass spectrum recorded from methanol. In this case, the electrospray mass spectrum clearly shows the presence of the mixed dimer **20** (Scheme 5) by the presence of an ion cluster at m/z 1126 which both the isotope pattern and the high-

Table 2. Mass Spectrometric Evidence for the Formation of Heterobimetallic Salen Complexes

titanium complex	vanadium complex	m/z of center of observed ion clusters
13	**18**	1112 (complex **20** + H); 1114 (dimer of complex **18**); 1126 (complex **20** + Me)[a]
1	**18**	1114 (dimer of complex **18**); 1180 (mixed dimer + Me)[a]
1	**15**	1220 (mixed dimer); 1223 (dimer of complex **15**); 1246 (complex **1** + CHO); 1268 (dimer of complex **15** + CHO$_2$); 1294 (mixed dimer + CHO + CHO$_2$)[b]
10	**15**	1142 (complex **10** + CHO); 1168 (mixed dimer); 1223 (dimer of complex **15**); 1242 (mixed dimer + CHO + CHO$_2$); 1268 (dimer of complex **15** + CHO$_2$)[b]
11	**15**	1213 (mixed dimer + Me); 1223 (dimer of complex **15**)[a]
		1173 (complex **11** + H); 1198 (mixed dimer); 1223 (dimer of complex **15**); 1268 (dimer of complex **15** + CHO$_2$)[b]
13	**15**	1180 (mixed dimer + Me); 1223 (dimer of complex **15**)[a]
		1138 (complex **13** + CHO); 1166 (mixed dimer); 1240 (mixed dimer + CHO + CHO$_2$); 1268 (dimer of complex **15** + CHO$_2$)[b]
1	**14**	1223 (dimer of complex **14**); 1231 (complex **1**); 1234 (mixed dimer + Me)[a]
10	**14**	1182 (mixed dimer + Me); 1223 (dimer of complex **14**)[a]
		1142 (complex **10** + CHO); 1168 (mixed dimer); 1223 (dimer of complex **14**); 1268 (dimer of complex **15** + CHO$_2$)[b]
11	**14**	1213 (mixed dimer + Me); 1223 (dimer of complex **14**)[a]

[a] Ionization from methanol solution. [b] Ionization from dichloromethane/formic acid.

resolution masses indicate corresponds to complex **20** + Me$^+$. Ion clusters corresponding to both monomeric complexes (**13** at 569 and **18** at 557) are also present. The ion cluster at m/z 1114 is actually two separate peaks as shown in the expansion. The major species in this region is the monocharged dimer of complex **18** (see Figure 1 for the simulated isotope pattern of this species), while a minor species present around m/z 1112 corresponds to protonated complex **20**. Interestingly however, no peak corresponding to the dimeric titanium complex **13** at m/z 1123 (see Figure 2 and Supporting Information) was present in the spectrum despite the presence of the monomeric version of this complex.

Interpretation of the ^{1}H NMR spectra of the heterobimetallic complexes was complicated by line broadening due to dynamic exchange processes between the various complexes present and between the configurations of these complexes occurring on the NMR time scale. Spectra recorded in other solvents (CDCl$_3$ or C$_6$D$_6$) also showed significant line broadening. Therefore, it was not possible to calculate the equilibrium populations of the various complexes from integration of the spectra. However, the ^{1}H NMR spectrum of a mixture of complexes **13** and **18** (Figure 5) showed the presence of all three complexes **13**, **18**, and **20** (Scheme 5), though only a very minor amount of complex **13** was present in the mixture compared with complexes **18** and **20**. As achiral complexes **13** and **18** give relatively simple ^{1}H NMR spectra, in this case it was possible to determine that complex **20** was present as a mixture of two diastereomers (ΔΔ/ΛΛ
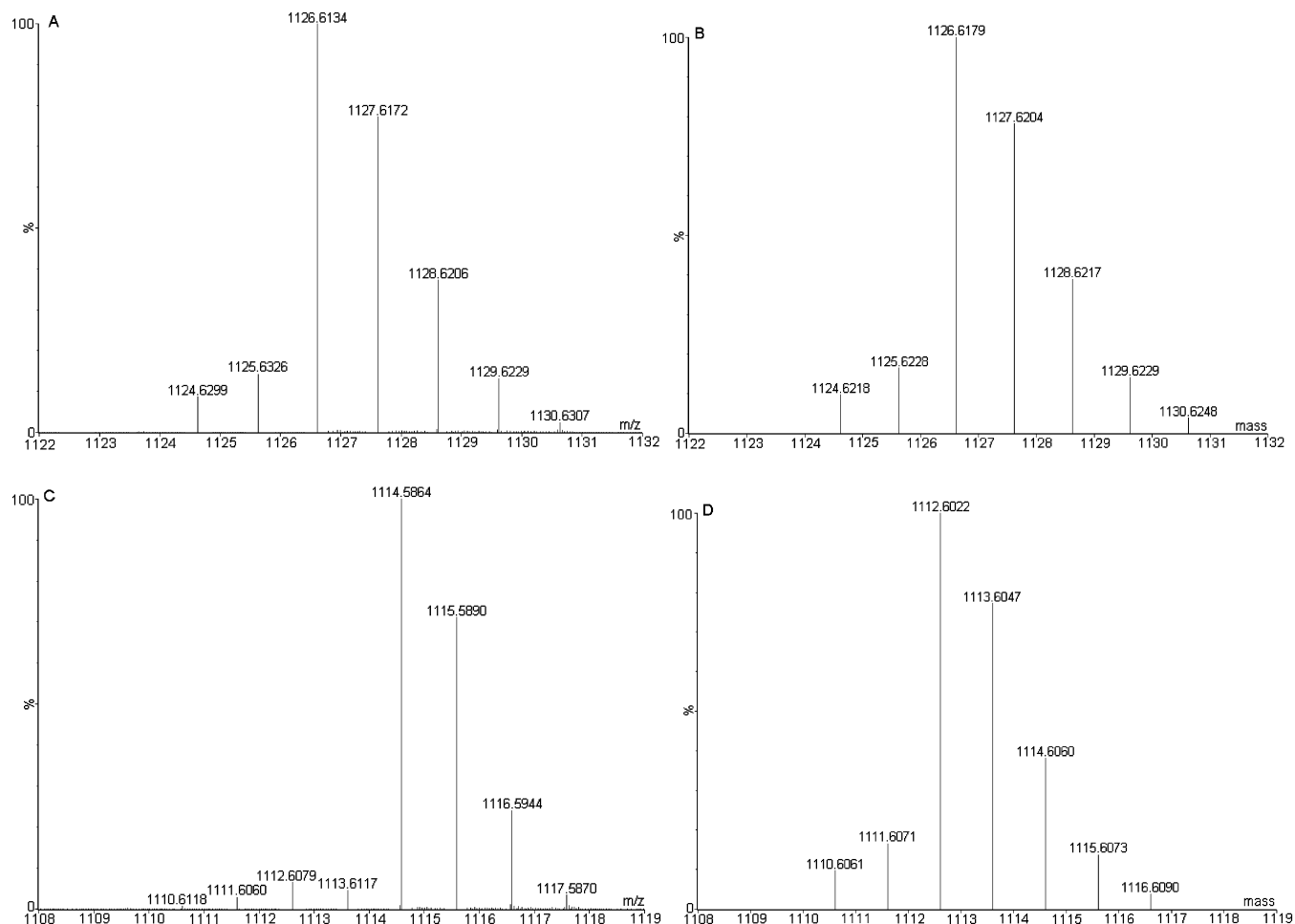
Figure 6. High-resolution electrospray ionization mass spectrum of a mixture of complexes **13** and **18** in methanol. (A) Actual data for complex **20** + Me, (B) simulated isotope pattern for complex **20** + Me, (C) actual data for complex **20** + H and the dimer of complex **18**, and (D) simulated isotope pattern for complex **20** + H.

and ΔΛ/ΛΔ). The major isomer was assigned the hetero-chiral (ΔΛ) configuration on the basis of literature precedent with related compounds and previously established rules for the determination of the relative stability of the configurations of bimetallic salen complexes.[11] The ^{1}H NMR spectrum of a mixture of complexes **13** and **18** was highly temperature dependent,[18] but even at –80 °C line broadening was still observed which combined with signal overlap, prevented a more detailed analysis of the spectrum.

Key data for the other combinations of titanium and vanadium complexes studied are summarized in Table 2, and copies of all of the NMR spectra and mass spectra are included in the Supporting Information. The heterobimetallic complexes were detected as (M + Me)$^+$ and MH$^+$ ions in spectra obtained from methanol, indicating that the vanadium ion had been reduced in situ to V^{IV}, but as M$^+$ and (M + CHO + CHO$_2$)$^+$ in spectra obtained from dichloromethane/formic acid, corresponding to the vanadium ion still being in the +5 oxidation state. Peaks corresponding to the homobimetallic titanium (when present in the spectrum) and vanadium dimers, ionized as indicated in Scheme 3, were also observed in the spectra.

Only in the case of a mixture of complexes **1** and **14** was the peak for the bimetallic titanium complex detected in the mass spectrum recorded from methanol on a time of flight

(TOF) spectrometer, and in this case modeling of the isotope pattern corresponding to the overlapping signals for the mixed dimer and complex **1** suggested that complex **1** accounted for just 14% of the mixture. In all other spectra obtained from methanol, only peaks corresponding to the dimeric vanadium complex and the heterobimetallic complex were detected on the TOF spectrometer, though peaks corresponding to monometallic titanium and vanadium complexes were always present in the spectra and the bimetallic titanium complex could be detected as a minor species on a more sensitive Fourier transform mass spectrometer (FTMS). Similarly, in every case except the combination of titanium complex **11** with enantiomeric vanadium complexes **14** or **15**, the ^{1}H NMR spectrum of a mixture of titanium and vanadium complexes showed only very small signals for the titanium dimer or these signals were completely absent from the spectra. It appears that the bimetallic titanium complexes are destabilized in the presence of vanadium complexes, possibly by formation of linear oligomeric or polymeric complexes (the crystal structure of such an oligomeric complex is reported later in this paper). This is consistent with previous work on asymmetric cyanohydrin synthesis using mixtures of titanium and vanadium complexes, where addition of even a small amount of vanadium complex (relative to the amount of titanium

complex present) significantly reduced the rate of reaction, apparently by sequestering the catalytically active bimetallic titanium complexes.[10] Mass spectra recorded from dichloromethane/formic acid did, however, show the presence of bimetallic titanium complexes in the mixtures (detected as their formylated or protonated species as shown in Scheme 3), a result which is again consistent with previous work by Katsuki, indicating that for Ti(salen)O complexes, monomeric species predominate in methanol while dimeric species are more prevalent in dichloromethane.[20]

The ^{1}H NMR spectra of mixtures containing complex **11** were exceptional as they showed no evidence for the formation of a mixed dimer.[18] This suggests that the electron-withdrawing nitro groups present in complex **11** destabilize the mixed dimer (which would also have a positive charge on the vanadium atom) relative to the homodimer **11**. The electrospray mass spectra of mixtures of complex **11** with complexes **14** or **15** did show a peak at $m/z = 1198$ (spectrum recorded from dichloromethane/formic acid) or 1213 (spectrum recorded from methanol) whose high-resolution masses and isotope distribution pattern corresponded to those required for the mixed dimer and methylated mixed dimer, respectively.[18] However, these species have the vanadium ion in the +4 oxidation state and so are not as electron-deficient as the unreduced mixed dimer formed from complexes **11** and **14** or **15**. The fact that complex **11** exists as a dimeric complex and that it forms mixed bimetallic complexes with other titanium(salen) complexes (Table 1) further supports the hypothesis that it is the combination of electron-withdrawing groups on the salen ligand attached to titanium and a positive charge on the vanadium ion which destabilize the heterodimers derived from complex **11** and vanadium(salen) complexes.

Ligand Exchange Studies. In all the structural analysis so far, it has been assumed that the salen ligands remain attached to the metal to which they were originally bound. The formation of heterobimetallic complexes containing both titanium and vanadium and possessing two different salen ligands allowed this assumption to be probed. In the absence of ligand exchange, a combination of [Ti(salen)O]$_2$ and [V(salen′)O]$^+$ complexes can lead to only one new bimetallic complex (ignoring the possible formation of Δ and Λ stereoisomers) as shown in Scheme 6. However, if the two salen ligands are allowed to migrate from one metal to another then many additional new mono- and bimetallic complexes may be formed. The NMR spectra of mixtures of titanium and vanadium salen complexes were too complex to allow possible ligand exchange to be detected. However, as the various complexes shown in Scheme 6 have different molecular weights and isotope patterns, high-resolution electrospray mass spectrometry did allow this process to be probed.

The possible occurrence of ligand exchange was studied in detail using a combination of complexes **13** and **15**. These ligand exchange studies were carried out on a FT mass spectrometer, and the extra sensitivity of the FTMS instrument did allow the molecular ion cluster corresponding to **13** + Me$^+$ to be detected in the spectrum of the mixture.

**Scheme 6.** Formation of Ligand-Exchanged Species from Metal(Salen) Complexes
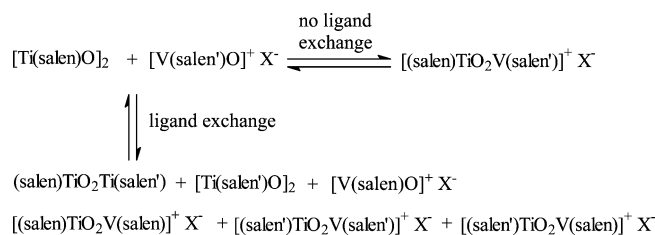
The complexes were mixed in dichloromethane, then diluted a thousand-fold with methanol prior to analysis by electrospray mass spectrometry at various times after the methanol dilution. A mass spectrum run immediately after the dilution showed a characteristic isotope pattern around m/z 1123 corresponding to the presence of **13** + Me$^+$ and identical to the isotope pattern obtained when pure complex **13** was analyzed (Figure 2). However, when the sample was reanalyzed over a period of 13 days, the relative intensities of the peaks in the cluster changed, indicating the formation of a new species with m/z 1126.[18] Both the high-resolution masses and the isotope distribution of this peak indicated that it corresponded to heterobimetallic complex **20** in which both of the metal ions are attached to salen ligand **8** (see Figure 6 and Scheme 5). This complex can be formed only if the two different salen ligands (**4** and **8**) attached to the two different metals are scrambled in methanol solution over a period of 13 days. The spectra also showed other evidence of ligand exchange. Thus, in spectra recorded between 8 and 13 days after the methanol solution was prepared, a peak at m/z 1168 was present in increasing intensity which corresponds to the mixed vanadium dimer formally derived from complexes **15** and **18**. Complex **18** can only be formed by a ligand exchange process. Finally, a peak at m/z 623 corresponding to the monomeric form of the titanium complex of ligand **4** [(salen-**4**)Ti=OMe] was present in spectra recorded after 8 days.

Subsequently, this experiment was repeated except that the mixture of complexes **13** and **15** was left in pure dichloromethane for 6 days. The electrospray mass spectrum of the mixture was recorded daily with a sample being diluted with methanol immediately prior to analysis. Under these conditions, no change in the ion cluster centered on m/z 1123 was detected, indicating that no ligand exchange occurred. Thus, the ligand exchange process occurs only in the presence of a protic species. It has previously been shown that metal ions retard the hydrolysis of Schiff bases[22] and that ligand exchange in uranyl(Schiff base) complexes is catalyzed by the presence of free amines.[23] Thus, the role of the protic solvent is probably to induce partial decomposition of complex **13** and/or **15** to give 3,5-di-*tert*-butylsalicyl-aldehyde and 1,2-diaminoethane and/or 1,2-diaminocyclo-hexane which then induces the ligand exchange process.

(22) Suh, J.; Min, D. W. *J. Org. Chem.* **1991**, *56*, 5710–5712.
(23) (a) For leading references see Mubarak, A. T. *Spectrochim. Acta, Part A* **2006**, *65*, 1197–1207. (b) Bharara, M. S.; Tonks, S. A.; Gorden, A. E. V. *Chem. Commun.* **2007**, 4006–4008.
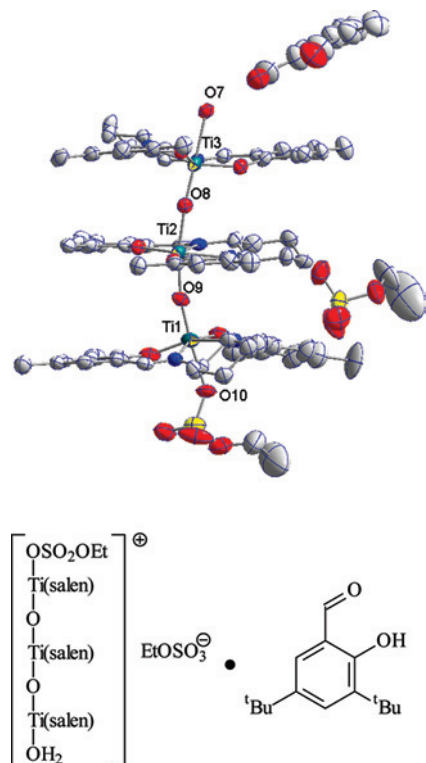
Figure 7. Structure of complex **21** (without hydrogen atoms). The uncoordinated ethyl sulfate anion is to the right, and the cocrystallized salicylaldehyde molecule at the top. Methyl carbon atoms of all *tert*-butyl groups have been omitted for clarity. Displacement ellipsoids are shown at the 50% probability level. Titanium and oxygen atoms of the helical chain of the cation are labeled.

The occurrence of ligand exchange in methanol solution was also detected in other cases when the sample was allowed to stand overnight prior to analysis. Thus, analysis of a mixture of complexes **1** and **18** immediately after the sample had been prepared showed no evidence of species formed by ligand exchange (Table 2).[18] However, when the sample was allowed to stand in methanol overnight prior to analysis, the following additional ion clusters were observed because of the presence of complexes formed by ligand exchange processes: 569 (monomer of complex **13** + Me),[18] 1126 (complex **20** + Me, see Figure 6), 1168 (**14** + **18**), and 1234 (the heterodimer + Me derived from complexes **1** and **14**).[18] Similarly, the electrospray mass spectra of a mixture of titanium complexes **10** or **11** with vanadium complex **15** recorded 18 h after the samples were prepared both showed an ion cluster at m/z 623 corresponding to the monometallic version of complex **9** [(salen-**4**)Ti=OMe] formed by ligand exchange from vanadium complex **15**.[18]

Solid-State Study. Numerous attempts were made to obtain crystals of a mixed dimer from any combination of titanium and vanadium(salen) complexes. However, in no case was this possible. Either just one of the initial complexes crystallized or decomposition occurred. Only when a mixture of (*R,R*)-**1** and (*S,S*)-**2** was allowed to crystallize slowly from a solution of deuterated dichloromethane were crystals of a new complex suitable for X-ray analysis obtained. The structure (Figure 7) was that of complex **21**, containing three titanium(salen) units. The structure also contains two ethyl sulfate groups derived from complex **2** and a cocrystallized

molecule of 3,5-di-*tert*-butylsalicylaldehyde which presumably is obtained by hydrolytic decomposition of complex **2**. There are also substantial voids within the structure, capable of holding solvent molecules, but no discrete atoms could be modeled and the contribution of this highly disordered solvent was treated by a diffuse scattering model. Within structure **21**, each titanium ion is coordinated by a salen ligand of (*R,R*)-configuration and these are oriented so as to form a (*P*)-helical structure; the absolute configuration is unambiguously established from anomalous scattering effects. Interestingly, the structure contains two different ethyl sulfate groups. One of these is directly coordinated to one of the terminal titanium ions while the other is uncoordinated, and the coordination of the other terminal titanium ion is completed by a water molecule as observed for complex **2**. This is the first example of a chiral trinuclear titanium(salen) complex, though the crystal structures of achiral trimeric Ti(salen) complexes have previously been reported,[24] as have related polymeric Ti(salen) structures derived from achiral salen ligands.[25] The in situ formation of oligomeric complexes such as **21** provides an explanation for previous results obtained on asymmetric cyanohydrin synthesis using a mixture of titanium(salen) and vanadium(salen) complexes as discussed earlier.

The metal centers in structure **21** are assigned as titanium rather than vanadium or a mixture on the following grounds. Charge balance requires a total of 12+ for the three metal ions, appropriate for Ti[IV] (or V[IV]) but not for V[V]. The initial titanium complex contained the (*R,R*)-ligand. The Ti–N bond lengths span the fairly narrow range of 2.126–2.157 Å, which is a better match to the mean Ti–N bond length of 2.151 Å for 41 salen complexes found in a search of the Cambridge Structural Database (CSD; Version 5.29 of November 2007)[26] than to the mean V–N bond length of 2.066 Å for 107 salen complexes in a corresponding search of the CSD (bond lengths to salen-oxygen atoms are more variable for each of these metals, and the mean values in the CSD are almost identical at 1.887 Å for Ti–O and 1.893 Å for V–O).

The hydrogen atoms of the coordinated water molecule form hydrogen bonds; one is to the 3,5-di-*tert*-butylsalicylaldehyde molecule, which also has an intramolecular O–H···O hydrogen bond, and the other is to an oxygen atom of the coordinated ethyl sulfate ligand of a symmetry-equivalent trinuclear cation, thus generating helical hydrogen-bonded chains of cations. The uncoordinated ethyl sulfate anion does not act as an acceptor of any hydrogen bonds.

Application to Asymmetric Cyanohydrin Synthesis. Each of complexes **1** and **9**–**18** along with a selection of in situ generated mixed bimetallic catalysts were tested as catalysts for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde (Scheme 1) under standard conditions (dichloromethane solution, 0.1 mol % catalyst, 20 °C, 24 h

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(25) (a) Gallo, E.; Solari, E.; Franceschi, F.; Floriani, C.; Chiesi-Villa, A.; Rizzoli, C. *Inorg. Chem.* **1995**, *34*, 2495–2496. (b) Tsuchimoto, M. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 2101–2105.

(26) Allen, F. A. *Acta Crystallogr., Sect. A* **2002**, *58*, 380–388.

Table 3. Asymmetric Synthesis of Mandelonitrile Trimethylsilyl Ether Using Combinations of Complexes 1, 9–18[a]

first complex	second complex										
	1	9	10	11	12	13	14	15	16	17	18
1	100[b] (82 S)	100 (0)	35 (64 S)	24 (30 S)	87 (52 S)	20[b] (34 S)	79[b] (90 S)	76[c] (79 R)	55 (77 S)	47 (67 S)	100[b] (18 S)
9		100 (85 R)	34 (6 R)	34 (38 R)	82 (50 R)	28 (42 R)	72 (79 S)	73 (80 R)	40 (54 R)	28 (62 R)	100 (12 R)
10			41 (58 S)	31 (33S)		32 (18 S)	82 (90 S)	87 (62 R)			25 (19 S)
11				8 (19 S)		17 (12 S)	52 (78 S)	83 (80 R)			
12					35 (49 S)	30 (27 S)	71 (85 S)	55 (85 R)	43 (49 S)	25 (12 S)	
13						34[b] (0)	88 (92 S)	75[c] (88 R)	45 (89 S)	11 (0)	54 (0)
14							73 (93 S)				
15								77[b] (91 R)			
16									54 (92 S)		
17										9 ([d])	
18											86[b] (0)

[a] Data are presented as conversion (determined by ^{1}H NMR spectroscopy) followed by enantioselectivity and absolute configuration in brackets (determined by chiral GC after conversion to mandelonitrile acetate). [b] Data taken from ref 11. [c] These results differ slightly from those reported in ref 11 because of the different counterion (chloride rather than ethyl sulfate) present in the complex. [d] Too little product formed to determine the enantioselectivity.

reaction time). For reactions involving mixtures of catalysts, 0.05 mol % of each titanium complex and 0.1 mol % of each vanadium complex was used. The conversions and enantioselectivities obtained with each catalyst or catalyst combination are summarized in Table 3.

In most cases, the conversions and enantioselectivities obtained using mixtures of catalysts were intermediate between those of the two parent catalysts. However, in a few cases the mixture displayed catalytic activity which is only consistent with catalysis by a heterobimetallic complex formed in situ. The most obvious examples are the combination of vanadium complex **14** with either of the titanium complexes **10** or **13**. In both cases, the enantioselectivity was essentially identical to that obtained using complex **14** alone, but the conversion obtained using the mixture of catalysts was significantly higher than that obtained in reactions catalyzed by either of the parent complexes.

Vanadium complex **17** had such low catalytic activity that, in the absence of heterobimetallic complex formation, it would not have been expected to have any influence on reactions involving catalysis by titanium complexes. However, as Table 3 shows, use of a mixture of complex **17** with any of the titanium complexes **1**, **9**, **12**, and **13** did substantially reduce both the conversion and the enantioselectivity, the effect being particularly pronounced for the combination of complexes **9** and **17**. The same effect was apparent from the combination of the two titanium complexes **1** and **11**.

Conclusions

A combination of NMR spectroscopy and mass spectrometry has provided the first proof of the in situ formation of mixed bimetallic complexes of general form [(salen)TiO$_2$-Ti(salen')] from the corresponding homobimetallic complexes, and heterobimetallic complexes of the form [(salen)-TiO$_2$V(salen')]$^+$ X$^-$ from a combination of [(salen)TiO]$_2$ and [VO(salen')]$^+$ X$^-$. The equilibrium between the various mono- and bimetallic complexes present depends upon the nature of both the metal ions and the salen ligands and formation of [(salen)TiO$_2$V(salen')]$^+$ X$^-$ is disfavored if electron-withdrawing nitro groups are present in the salen ligand bound to the titanium ion.

The occurrence of ligand exchange processes involving tetradentate salen ligands within complexes of general form [(salen)TiO$_2$V(salen')]$^+$ X$^-$ has been demonstrated for the first time by mass spectrometry. Ligand exchange occurs only in protic media and even then on a time scale of days so that it does not interfere with the use of heterobimetallic-(salen) complexes as asymmetric catalysts for cyanohydrin synthesis. Use of various combinations of [(salen)TiO]$_2$ and [VO(salen')]$^+$ X$^-$ complexes as catalysts for the asymmetric addition of trimethylsilyl cyanide to benzaldehyde gave results which in some cases could only be explained on the basis of at least partial catalysis by the mixed bimetallic complexes formed in situ. All of the structural and reactivity data are consistent with the previously proposed mechanism for asymmetric cyanohydrin synthesis by [(salen)TiO]$_2$ and [(salen)TiO$_2$V(salen')]$^+$ X$^-$ complexes, and the identification by X-ray crystallography of a trimetallic titanium(salen) complex formed in situ from a mixture of [(salen)TiO]$_2$ and [VO(salen)]$^+$ EtOSO$_3$$^-$, complexes (**1** and **2**), provides an explanation for the large reduction in the rate of catalysis observed when even small amounts of [VO(salen')]$^+$ X$^-$ complexes are combined with [(salen)TiO]$_2$ complexes.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 spectrometer ([1]H 300 MHz, [13]C 75 MHz). Variable-temperature spectra were recorded at 500 MHz on a Jeol spectrometer. The solvent for a particular spectrum is given in parentheses. Spectra were referenced to the residual solvent peak and chemical shift (δ) values, expressed in parts per million (ppm), are reported downfield of tetramethylsilane (TMS). The multiplicity of signals is reported as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), broad (br), or a combination of any of these.

Low- and high-resolution electrospray mass spectra (ES) were recorded on a Waters LCT Premier MS (TOF) or on a Bruker Apex III (FTMS) using positive ion mode. Samples were injected directly into the spectrometer from a syringe pump in the solvent specified. The major fragment ions are reported, and the molecular ions and other characteristic ions are assigned. Low- and high-resolution electron ionization (EI) and chemical ionization (CI) spectra were recorded by the EPSRC national mass spectrometery service.

Infrared spectra were recorded on a Varian 800 FT-IR fitted with an ATR attachment. Optical rotations were recorded on a Perkin-Elmer 343 polarimeter in a thermostatted cell of length 0.25 dm using the sodium D-line, and a suitable solvent that is reported along with the concentration (in g/100 mL) and temperature.

Chromatographic separations were performed with silica gel 60 (230–400 mesh) and thin-layer chromatography was performed on

polyester-backed sheets coated with silica gel 60 F254, both supplied by Merck. Chiral gas chromatography (GC) was carried out on a Hewlett-Packard 5890 gas chromatograph fitted with a thermal conductivity detector, using a γ-CD butyryl, fused silica capillary column (30 m x 0.25 mm) and hydrogen as the carrier gas. The following conditions were used for the analysis of mandelonitrile acetate: initial temperature 100 °C, hold at initial temperature for 2 min then a ramp rate of 5 °C/minute to 180 °C. Flow rate 1.6 mL/minute. Retention times 15.25 min (*R*)-enantiomer and 15.43 min (*S*)-enantiomer.

Ligand 6. (*R,R*)-1,2-diaminocyclohexane dihydrochloride (0.42 g, 2.24 mmol) and 2-hydroxy-5-nitro-3-*tert*-butylbenzaldehyde[27] (1.0 g, 4.48 mmol) were dissolved in methanol (25 mL) and ethanol (25 mL). Sodium methoxide (4.48 mmol, 0.242 g) was added and the mixture heated at reflux for 3 h. The solvents were evaporated in vacuo, and the residue taken up in CH_2Cl_2 (80 mL), washed with water (2 × 50 mL) and brine (50 mL), then dried (Na_2SO_4) and evaporated in vacuo to give compound **6** (1.09 g, 94%) as a bright yellow powder. $[\alpha]_D^{22}$ –161 (c 0.1, CH_2Cl_2); ν_{max}(ATR) 2945, 2865, 2360, 2341, 1612, and 1524 cm^{-1}; δ_H(CDCl$_3$) 8.35 (2H, s), 8.15 (2H, d *J* 2.7 Hz), 8.00 (2H, d *J* 2.7 Hz), 3.5–3.4 (2H, m), 2.1–2.0 (2H, m), 2.0–1.9 (2H, m), 1.9–1.7 (2H, m), 1.40 (18H, s) 1.3–1.2 (2H, m); δ_C(CDCl$_3$) 167.35, 164.59, 139.67, 138.61, 126.22, 125.00, 116.81, 71.24, 35.17, 32.43, 28.86, 20.31; m/z (CI) 525 (MH$^+$, 95), 320 (70), 290 (100); Found (ES) 525.2691, $C_{28}H_{37}N_4O_6$ (MH$^+$) requires 525.2713.

Reaction of Ligand 6 with TiCl$_4$. Ligand **6** (0.5 g, 0.953 mmol) was dissolved in CH_2Cl_2 (50 mL), and a solution of titanium tetrachloride in CH_2Cl_2 (0.94 mL of 1.0 M solution) was added. The solution was stirred for an hour, then the solvent was evaporated in vacuo leaving a brown solid which was taken up in diethyl ether (30 mL) and stirred for 5 min. The ether layer was decanted, and 50:50 hexane/diethyl ether (40 mL) was added to the residue, stirred briefly, and decanted to leave an orange powder which was dried in vacuo to leave the titanium dichloride complex of ligand **6** (0.60 g, 100%) as an orange powder. $[\alpha]_D^{22}$ –464 (c 0.05, CH_2Cl_2); ν_{max}(ATR) 2957, 2931, 1621, 1594, and 1520 cm^{-1}; δ_H(CDCl$_3$) 8.49 (2H, s), 8.45 (2H, s), 7.23 (2H, s), 4.1–4.0 (2H, m), 2.7–2.6 (2H, m), 2.2–2.1 (2H, m), 1.7–1.5 (4H, br m), 1.56 (18H, s); δ_C(CDCl$_3$) 166.19, 159.88, 142.19, 140.27, 129.35, 129.04, 125.91, 68.88, 36.30, 29.91, 29.08, 24.39; m/z (ES) 607 ((^{37}Cl)M$^+$ − Cl, 10), 605 ((^{35}Cl) M$^+$ − Cl, 20), 242 (100); Found (EI) 640.1328, $C_{28}H_{34}N_4O_6Ti^{35}Cl_2$ requires 640.1329.

Bimetallic Titanium Complex 11. The titanium dichloride complex of ligand **6** (0.5 g, 0.745 mmol) was dissolved in CH_2Cl_2 (200 mL), sodium phosphate buffer (60 mL of a solution obtained by dissolving $Na_2HPO_4.7H_2O$ (8.70 g) and $NaH_2PO_4.2H_2O$ (3.0 g) in distilled water (500 mL)) was added, and the mixture stirred vigorously for 1 h after which time the buffer was removed and replaced by a fresh portion (60 mL) with vigorous stirring for a further hour. The organic layer was separated, washed with water (2 × 100 mL), dried (Na_2SO_4), and evaporated *in vacuo* to give complex **11** (0.502 g, 99%) as a light orange solid. $[\alpha]_D^{24}$ –370 (c 0.1, CH_2Cl_2); ν_{max}(ATR) 2945, 2865, 2359, 2342, 1632, 1594, 1570, and 1506 cm^{-1}; δ_H(CD$_2$Cl$_2$) 8.37 (2H, s), 8.34 (4H, d *J* 2.1 Hz), 8.24 (4H, d *J* 2.1 Hz), 8.12 (2H, s), 3.8–3.7 (2H, m), 2.9–2.8 (2H, m), 1.9–1.8 (2H, m), 1.8–1.7 (2H, m), 1.6–1.2 (6H, m), 1.2–1.0 (6H, m, Cy*H*), 1.42 (18H, s), 1.13 (18H, s); m/z(ES, MeOH) 1187 (M + Me$^+$, 5), 601 ((salen)Ti=OMe$^+$, 100); Found (ES, MeOH) 1187.4108, $C_{57}H_{71}N_8O_{14}Ti_2$ (M + Me$^+$) requires 1187.4063.

Reaction of Ligand 5 with TiCl$_4$. Ligand **5** (0.5 g, 1.01 mmol) was dissolved in CH_2Cl_2 (30 mL), and a solution of titanium tetrachloride in CH_2Cl_2 (1.1 mL of 1.0 M solution) was added. The solution was stirred for 30 min, then the solvent was evaporated in vacuo leaving a red/brown solid which was washed with ether (2 × 50 mL) and with 1:1 hexane/ether (50 mL) and dried in vacuo to leave the titanium dichloride complex of ligand **5** (0.59 g, 95%) as a red powder. $[\alpha]_D^{22}$ + 979 (c 0.03, CH_2Cl_2); ν_{max}(ATR) 2881, 2869, 1616, 1597, and 1563 cm^{-1}; δ_H(CDCl$_3$) 8.24 (2H, s), 7.15 (2H, d *J* 3.0 Hz), 6.84 (2H, d *J* 3.0 Hz), 4.1–4.0 (2H, m), 3.82 (6H, s), 2.6–2.5 (2H, m), 2.1–2.0 (2H, m), 1.6–1.4 (4H, m, Cy*H*), 1.50 (18H, s); δ_C(CDCl$_3$) 173.48, 171.75, 160.01, 139.49, 129.41, 121.76, 115.50, 67.74, 55.96, 35.63, 29.89, 29.57, 29.28; m/z(EI) 610 (M$^+$, 27), 575 (M$^+$ − Cl, 100); Found (EI) 610.1831, $C_{30}H_{40}N_2O_4Ti^{35}Cl_2$ (M$^+$) requires 610.1839.

Bimetallic Titanium Complex 10. The titanium dichloride complex of ligand **5** (0.5 g, 0.818 mmol) was dissolved in CH_2Cl_2 (200 mL) and sodium phosphate buffer (60 mL of a solution obtained by dissolving $Na_2HPO_4.7H_2O$ (8.70 g) and $NaH_2PO_4.2H_2O$ (3.0 g) in distilled water (500 mL)) was added and the mixture stirred vigorously for 1 h after which time the buffer was removed and replaced by a fresh portion (60 mL) with vigorous stirring for a further hour. The organic layer was separated, washed with water (2 × 100 mL), dried (Na_2SO_4) and evaporated in vacuo to give complex **10** (0.46 g, 99%) as a yellow solid. $[\alpha]_D^{24}$ –296 (c 0.05, CH_2Cl_2); ν_{max}(ATR) 2937, 2860, 1628, 1605, 1555, and 1506 cm^{-1}; δ_H(CD$_2$Cl$_2$) 8.21 (2H, s), 7.91 (2H, s), 7.10 (2H, d *J* 2.1 Hz), 6.96 (2H, d *J* 2.1 Hz), 6.75 (2H, d *J* 2.1 Hz), 6.65 (2H, d *J* 2.1 Hz), 4.0–3.9 (1H, m), 3.83 (6H, s), 3.76 (6H, s), 3.9–3.7 (1H, m), 2.8–2.7 (1H, m), 2.5–2.3 (1H, m), 1.2–0.8 (16H, m), 1.44 (18H, s), 1.16 (18H, s); m/z(ES, MeOH) 1159 (M + MeOH + Me$^+$, 30), 1127 (M + Me$^+$, 30), 571 ((salen)Ti=OMe$^+$, 100); Found (ES, MeOH) 1127.5037, $C_{61}H_{83}N_4O_{10}Ti_2$ (M + Me$^+$) requires 1127.5083.

Vanadium Complex 16. Vanadium oxychloride (1.11 mmol, 0.11 mL) was added to a solution of ligand **5** (0.5 g, 1.01 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was heated at reflux for 4 h, then allowed to cool to room temperature and stirred overnight. The resulting solution was purified by flash chromatography eluting with CH_2Cl_2 (100 mL) followed by 2:1 ethyl acetate/methanol (150 mL). Complex **16** (0.27 g, 45%) was obtained from the ethyl acetate/methanol fraction as a dark green solid. $[\alpha]_D^{24}$ + 1650 (c 0.08, CH_2Cl_2); ν_{max}(ATR) 2947, 2867, 1621, 1600, 1559, and 1532 cm^{-1}; δ_H(CD$_2$Cl$_2$) 8.60 (1H, s), 8.37 (1H, s), 7.27 (1H, s), 7.22 (1H, s), 6.98 (1H, s), 6.90 (1H, s), 3.80 (3H, s), 3.77 (3H, s), 2.6–2.4 (2H, m), 2.0–1.3 (8H, m), 1.45 (18H, s); m/z(ES, MeOH) 1118 (2M$^+$, 5), 559 (M$^+$, 100); Found (ES, MeOH) 559.2383, $C_{30}H_{40}N_2O_5V$ (M$^+$) requires 559.2377.

General Procedure for Preparation of Mixed Bimetallic Complexes. The appropriate titanium **1, 9–13** (0.45 μmol) and/or vanadium **14–18** (0.9 μmol) catalyst(s) were dissolved in CH_2Cl_2 (3 mL). The resulting solution was used directly for asymmetric cyanohydrin synthesis reactions or for analysis by mass spectrometry. For ^{1}H NMR analysis, the same procedure was used with CD$_2$Cl$_2$.

General Procedure for the Synthesis of Mandelonitrile Trimethylsilyl Ether. Benzaldehyde (0.1 mL, 0.94 mmol) was added to the catalyst or mixture of catalysts (0.001equiv) in distilled CH_2Cl_2 (3 mL). Trimethylsilyl cyanide (0.16 mL, 1.03 mmol) was added, and the reaction stirred at room temperature overnight. The resulting solution was filtered through a silica-filled Pasteur pipet to give mandelonitrile trimethylsilyl ether as a colorless oil. The

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conversion was determined from the intensities of the ^{1}H NMR signals corresponding to the HC=O of benzaldehyde and CHO of the product.

Mandelonitrile Acetate. A sample of mandelonitrile trimethylsilyl ether was dissolved in acetonitrile (3 mL), and scandium(III) trifluoromethanesulfonate (4.7 mg, 0.0094 mmol) was added followed by acetic anhydride (0.18 mL, 1.88 mmol). The resulting solution was stirred at room temperature for 30 min and then filtered through a silica-filled pipet. The solvent was removed in vacuo, and the residue analyzed by chiral gas chromatography.

X-ray Crystallography. Crystal data for **21**: $C_{111}H_{162}N_6O_{13}$-$STi_3^+C_2H_5O_4S^-\cdot C_{14}H_{22}O_2$ (ignoring disordered solvent), $M = 2312.7$, hexagonal, space group $P6_5$, $a = 27.380(2)$, $c = 38.033(3)$ Å, $V = 24692(3)$ Å^3, $T = 120$ K, $Z = 6$; 59945 reflections measured (Bruker APEX2 diffractometer, synchrotron radiation, $\lambda = 0.6709$ Å, crystal size $0.18 \times 0.06 \times 0.06$ mm), 17038 unique, $R_{int} = 0.075$; 1452 refined parameters, R (F, $F^2 > 2\sigma$) = 0.055, R_w (F^2, all data) = 0.138, goodness of fit (F^2) = 0.992, absolute structure parameter[28] = 0.00(3), final difference map extremes + 0.54 and −0.19 e Å^{-3}. The *tert*-butyl group of the cocrystallized 3,5-di-*tert*-butylsalicylaldehyde molecule is disordered over two orientations in an approximate 3:2 ratio. Hydrogen atoms were positioned geometrically and refined as riding, except for those of the water molecule, which were located in a difference map and refined with geometrical restraints. Discrete atomic sites with sensible molecular geometry could not be assigned in substantial voids of the crystal structure; they are probably occupied by highly disordered solvent (dichloromethane) molecules, and the contribution of these to the diffraction was treated by the SQUEEZE procedure of PLATON.[29]

Supporting Information Available: ^{1}H NMR spectra of samples dissolved in CD$_2$Cl$_2$, high-resolution electrospray mass spectra and simulated molecular ion cluster intensities for complexes **1**, **9**–**18** and for all in situ formed heterobimetallic complexes (PDF); crystallographic details for complex **21** in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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