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Investigation of Lewis Acid versus Lewis Base Catalysis in Asymmetric Cyanohydrin Synthesis

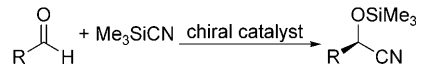
Michael North,* Marta Omedes-Pujol, and Courtney Williamson[a]

Abstract: The asymmetric addition of trimethylsilyl cyanide to aldehydes can be catalysed by Lewis acids and/or Lewis bases, which activate the aldehyde and trimethylsilyl cyanide, respectively. It is not always apparent from the structure of the catalyst whether Lewis acid or Lewis base catalysis predominates. To investigate this in the context of using salen complexes of titanium, vanadium and aluminium as catalysts, a Hammett analysis of asymmetric cyanohydrin synthesis was undertaken. When Lewis acid catalysis is dominant, a significantly positive reaction constant is observed, whereas reactions dominated by Lewis base catalysis give much smaller reaction constants. [{Ti(salen)O}$_2$] was found to show the highest degree of Lewis acid catalysis, whereas two [VO(salen)X] (X = $EtOSO_3$ or NCS) complexes both displayed lower degrees of Lewis acid catalysis. In the case of reactions catalysed by [{Al(salen)}$_2$O] and triphenylphosphine oxide, a non-linear Hammett plot was observed, which is indicative of a change in mechanism with increasing Lewis base catalysis as the carbonyl compound becomes more electron-deficient. These results suggested that the aluminium complex/triphenylphosphine oxide catalyst system should also catalyse the asymmetric addition of trimethylsilyl cyanide to ketones and this was found to be the case.

Keywords: asymmetric catalysis · cyanohydrin · Hammett analysis · Lewis acids · Lewis bases

Introduction

Over the last decade, there has been a substantial increase in interest in asymmetric cyanohydrin synthesis.[1] Most of this work utilises trimethylsilyl cyanide as the cyanide source and aldehydes as the electrophile to form non-racemic cyanohydrin trimethylsilyl ethers (Scheme 1), a reaction which has been shown to be catalysed by chiral Lewis acids[2] and chiral Lewis bases.[3] However, the relatively complex nature of chiral catalysts means that they almost always contain acidic and basic sites and it is then not clear what the mode of action of the catalyst is. In addition, it is well established that the most effective catalysts simultaneously employ acid and base catalysis to activate both components of the reaction.[2c,4] An illustrative example of this is the bis-N-oxide catalyst **1** developed by Feng et al. (see Scheme 2).[5] The N-oxides within catalyst **1** are proposed to act as Lewis bases to activate the trimethylsilyl cyanide, whereas one of the two secondary amides acts as an acid to activate the aldehyde, leading to the transition-state structure shown in Scheme 2.



Scheme 1. Asymmetric addition of trimethylsilyl cyanide to aldehydes.

For metal-based Lewis acids of general structure ML_n^*, the situation is particularly mechanistically complex as the ligands are only coordinated to the metal and dissociation of one of the L* units will inevitably produce a chiral Lewis base (L*) and increase the Lewis acidity of the metal. Thus, for any metal-based catalyst the issue arises as to the relative importance of Lewis acid and Lewis base catalysis. A particularly effective class of metal-based catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes are complexes of the salen ligand **2**.[2] We have shown that the bimetallic titanium complex **3** is a highly efficient catalyst[6] and subsequently developed the vanadium-based catalysts **4a** and **4b** as even more enantioselective catalysts.[6b,7]

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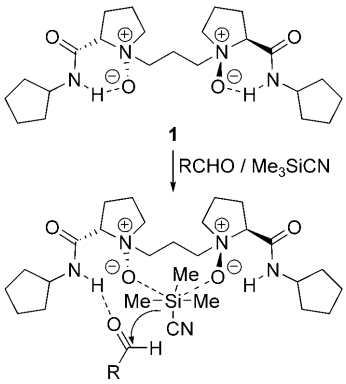
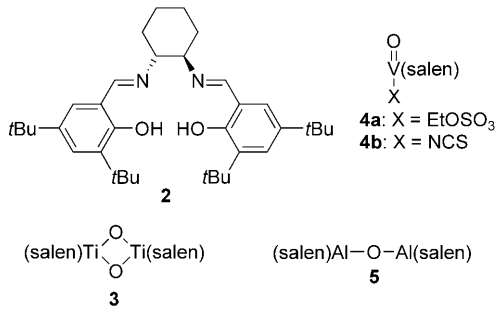


Scheme 2. Transition state for the asymmetric cyanohydrin synthesis catalysed by the bis-N-oxide **1**.

Most recently, we have shown that the combination of the bimetallic aluminium complex **5** and triphenylphosphine oxide forms an effective catalyst system.[8]



The mechanism of action of complexes **3**–**5** has been extensively investigated by a combination of kinetic studies and identification of reaction intermediates.[6b,9–12] However, this work has tended to focus on the role of the metal as a Lewis acid and the origin of the asymmetric induction. However, it has, become increasingly apparent that Lewis base catalysis is also of some importance in reactions catalysed by complexes **3**–**5**. This is most apparent in reactions catalysed by aluminium complex **5**, since addition of triphenylphosphine oxide resulted in a substantial increase in the rate and the enantioselectivity of cyanohydrin synthesis.[8] For vanadium-based complexes **4**, the rate of reaction, but not the degree of asymmetric induction, was found to depend on the Lewis basicity of the X group.[10] The most active catalyst **4b** had the most Lewis basic X group (NCS), whereas the complex with X = triflate was catalytically inactive despite having the most Lewis acidic vanadium centre. It is also known that the oxygen atom of the V=O bond has appreciable Lewis basicity[13] and this can lead to the formation of oligomeric complexes in solution,[6d,14] which are important for formation of the most active catalysts as suggested by the kinetic data. In the case of titanium complex **3**, the two bridging oxygen atoms are known to be Lewis basic, as we have shown that they are silylated by trimethylsilyl cyanide as part of the formation of the catalytically active species.[9] In addition, the phenolic oxygens of metal(salen) complexes are known to be Lewis basic,[15] which provides another opportunity for Lewis base catalysis in all complexes **3**–**5**. Thus, we decided to undertake a study to investigate the relative importance of Lewis acidity and Lewis basicity in the catalytic activity of complexes **3**–**5** and this paper presents the results of this study.

Results and Discussion

Since a Lewis acid will activate the aldehyde, whereas a Lewis base activates the trimethylsilyl cyanide, a Hammett plot[16] based on substituted aromatic aldehydes provides a way of assessing the importance of Lewis acid and Lewis base activation to the rate of asymmetric cyanohydrin synthesis. Lewis acid catalysis implies that an aldehyde activated by coordination to the Lewis acid is involved in the rate-determining step of the reaction. Therefore, if Lewis acid catalysis is dominant, a Hammett plot with a large positive reaction constant will be expected, since the Lewis acid withdraws electron density from the carbonyl bond. Thus, an aldehyde, which is already electron-deficient, will be made even more reactive by coordination to the Lewis acid, whereas a very electron-rich aldehyde will form a more stable and hence, less reactive complex with the Lewis acid. In contrast, a reaction proceeding entirely by Lewis base catalysis would be expected to have a reaction constant of zero, since the rate-determining step of the mechanism involves activation of the trimethylsilyl cyanide and the aldehyde is only involved after the rate-determining step. Hammett plots have previously been used to determine the Lewis acidity of palladium complexes,[17] to study achiral Lewis acid-[18] or base-catalysed[19] reactions and to study asymmetric Lewis acid-catalysed,[20] Lewis base-catalysed[21] and carbene insertion reactions,[22] but do not appear to have previously been used to determine the relative importance of Lewis acid and Lewis base catalysis.

In previous work,[8,9a,10b,12] we have determined the kinetics of the asymmetric addition of trimethylsilyl cyanide to benzaldehyde catalysed by complexes **3**, **4a**, **4b** and **5** and have shown that the reactions obey the rate equations shown in Equations (1)–(4), respectively.

$$\text{rate} = k[\mathbf{3}]^{1.3}[\text{Me}_3\text{SiCN}] = k_{\text{obs}}[\text{Me}_3\text{SiCN}] \quad (1)$$

$$\text{rate} = k[\mathbf{4a}]^{0.6}[\text{Me}_3\text{SiCN}][\text{PhCHO}] = k_{\text{obs}}[\text{Me}_3\text{SiCN}][\text{PhCHO}] \quad (2)$$

$$\text{rate} = k[\mathbf{4b}]^{1.2}[\text{Me}_3\text{SiCN}][\text{PhCHO}] = k_{\text{obs}}[\text{Me}_3\text{SiCN}][\text{PhCHO}] \quad (3)$$

$$\text{rate} = k[\mathbf{5}][\text{Ph}_3\text{PO}][\text{Me}_3\text{SiCN}] = k_{\text{obs}}[\text{Me}_3\text{SiCN}] \quad (4)$$

It is apparent from Equations (1)–(4), that reactions catalysed by complexes **3** and **5** follow first-order kinetics with

the reaction rate being independent of the benzaldehyde concentration. In contrast, reactions catalysed by vanadium complexes **4a** and **4b** follow second-order kinetics with the reaction rate depending on the concentrations of benzaldehyde and trimethylsilyl cyanide.

All of the kinetics measurements throughout this work were obtained by monitoring the UV absorbance at $\lambda = 240$–315 nm of unreacted aldehyde in samples periodically removed from reactions carried out at 0 °C, as we have previously described.[8,9a,10b,12] Every kinetics experiment was carried out in duplicate and the average rate constant used to construct the Hammett plot.[23] The aldehydes were chosen to provide as wide a range of substituent constants as possible; though for titanium complex **3**, highly electron-deficient aldehydes (3,4-dichloro-, 3,5-difluoro- and 4-(trifluoromethyl)benzaldehyde) reacted so quickly (100 % conversion in ≈5 s) that it was not possible to monitor the kinetics and this restricted the range of positive substituent constants that could be studied. The results obtained with ten aldehydes by using 0.1 mol % of complex **3** as catalyst are shown in Table 1. All of the aldehydes were found to follow the same first-order kinetic equation [Eq. (1)] previously found for the use of benzaldehyde as substrate. As the data in Table 1 show, the kinetics experiments showed good reproducibility and when converted into a Hammett plot (Figure 1) produced a good fit to a straight line with a slope of 2.4.

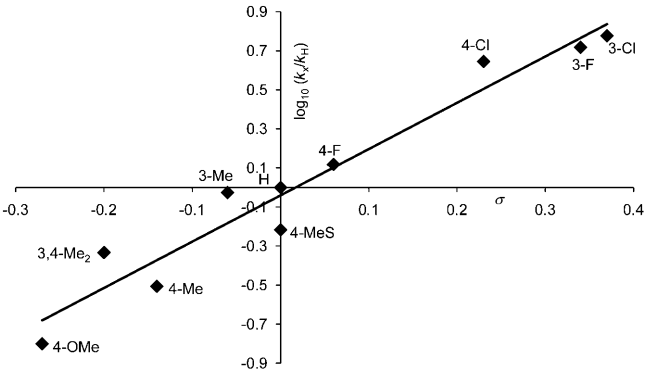
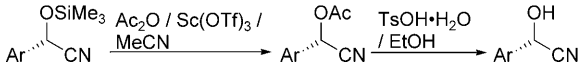


Figure 1. Hammett plot for the asymmetric addition of trimethylsilyl cyanide to different benzaldehydes catalysed by complex **3** ($y = 2.3715x - 0.0409$, $R^2 = 0.9427$). For abbreviations see Table 1.



Scheme 3. Synthesis of cyanohydrin acetates and free cyanohydrins for stereochemical analysis (Ts = *para*-toluenesulfonyl).

Table 1. Rate constants and enantioselectivities for the synthesis of cyanohydrin trimethylsilyl ethers catalysed by bimetallic titanium complex **3**.[a]

Entry	Aldehyde	Abbrev.	k_a [min^{-1}]	k_b [min^{-1}]	k_{avg} [min^{-1}]	*ee* [%][b]
1	PhCHO	H	0.4506	0.4060	0.4283 ± 0.0223	84
2	4-ClC$_6$H$_4$CHO	4-Cl	1.8688	1.9131	1.89095 ± 0.02215	87
3	3-ClC$_6$H$_4$CHO	3-Cl	2.5318	2.5923	2.56205 ± 0.03025	84
4	4-FC$_6$H$_4$CHO	4-F	0.5142	0.6080	0.5611 ± 0.0469	88
5	4-MeC$_6$H$_4$CHO	4-Me	0.1471	0.1201	0.1336 ± 0.0135	79
6	4-MeOC$_6$H$_4$CHO	4-MeO	0.0699	0.0658	0.06785 ± 0.00205	46[c]
7	3,4-Me$_2$C$_6$H$_3$CHO	3,4-Me$_2$	0.1971	0.2006	0.19885 ± 0.00175	57[d]
8	4-MeSC$_6$H$_4$CHO	4-MeS	0.2382	0.2806	0.2594 ± 0.0212	55
9	3-FC$_6$H$_4$CHO	3-F	2.2268	2.2496	2.2382 ± 0.0114	87
10	3-MeC$_6$H$_4$CHO	3-Me	0.4344	0.3721	0.40325 ± 0.03115	95

[a] All reactions were carried out in duplicate (to give k_a and k_b, respectively) in dichloromethane at 0 °C with $[\text{aldehyde}]_0 = 0.5$ M, $[Me_3SiCN]_0 = 0.55$ M and [**3**] = 0.5 mM. [b] Determined by chiral GC analysis of the cyanohydrin acetate unless stated otherwise. [c] Determined by comparison of the specific rotation with literature data.[27] [d] Determined by ^{1}H NMR spectroscopy in the presence of (*R*)-mandelic acid and dimethylaminopyridine (DMAP).

Where possible, the enantiomeric excesses of the cyanohydrin trimethylsilyl ethers shown in Table 1 were determined by chiral GC analysis[23] after conversion into the corresponding acetates by the method of Kagan (Scheme 3).[24] In two cases, no separation of enantiomers was achieved by chiral GC. Therefore, the enantiomeric excess of the cyanohydrin derived from 3,4-dimethylbenzaldehyde was determined by ^{1}H NMR analysis[23] of the free cyanohydrin obtained by hydrolysis of the acetate,[25] in the presence of (*R*)-mandelic acid and DMAP.[26] The cyanohydrin derivative obtained from 4-methoxybenzaldehyde was found to racemise on hydrolysis, so the enantiomeric purity was determined by comparison of the specific rotation of the trimethylsilyl ether with literature data.[26] In each case, the *S* enantiomer of the cyanohydrin derivative was obtained from complex **3** derived from (*R*,*R*)-diaminocyclohexane, which is consistent with previous work.[6] The enantiomeric excesses obtained for the cyanohydrins confirm that the reaction being monitored was that catalysed by complex **3** rather than any uncatalysed reaction leading to racemic products.

The kinetics results obtained by using thirteen aromatic aldehydes and 0.1 mol % of the vanadium-based catalyst **4a** are shown in Table 2. In this case, the reactions were significantly slower than those catalysed by complex **3**, so more electron-deficient aldehydes could be used (Table 2, entries 11–13), which allowed the Hammett plot to be extended to more positive σ values. All of the substrates obeyed second-order kinetics (first-order in the aldehyde and in trimethylsilyl cyanide).[23] The kinetics results again showed good reproducibility and when incorporated into a Hammett plot (Figure 2) produced a good fit to a straight line with a slope of 1.9. The enantiomeric excesses of the cyanohydrin trimethylsilyl ethers were again found to always be > 50 %,[23] confirming that the reaction being monitored was the catalysed rather than uncatalysed reaction.

In the case of asymmetric cyanohydrin synthesis catalysed by the isothiocyanatovanadium complex **4b**, fourteen aldehydes were used as substrates (Table 3) and again second-order kinetics was observed in all cases.[23] However, 4-methoxybenzaldehyde (Table 3, entry 6) was found to display an anomalously slow rate of cyanation in reactions catalysed by complex **4b**. This was attributed to coordination of the methoxy group to the vanadium ion of the catalyst, thus, inhibiting the catalysis. Support for this hypothesis came from reactions that use 4-*tert*-butoxybenzaldehyde as substrate (Table 3, entry 11), which when incorporated into a Hammett plot (Figure 3) produced a reasonable fit to a straight line that had a slope of 1.6. The enantiomeric excesses of the cyanohydrin trimethylsilyl ethers were all $>56\,\%$,[23] again confirming that they were produced by a catalysed rather than uncatalysed process.

Table 4 presents the kinetic data obtained for the asymmetric trimethylsilylcyanation of fifteen aldehydes by using 2 mol% of the aluminium-based catalyst **5** and 10 mol% of triphenylphosphine oxide as catalysts. These reactions all obeyed first-order kinetics,[23]

Table 2. Rate constants and enantioselectivities for the synthesis of cyanohydrin trimethylsilyl ethers catalysed by vanadium complex **4a**.[a]

Entry	Aldehyde	Abbrev.	k_a [$M^{-1}min^{-1}$]	k_b [$M^{-1}min^{-1}$]	k_{avg} [$M^{-1}min^{-1}$]	*ee* [%][b]
1	PhCHO	H	0.0037	0.0042	0.0040 ± 0.0003	86
2	4-ClC_6H_4CHO	4-Cl	0.0078	0.0091	0.0084 ± 0.0007	86
3	3-ClC_6H_4CHO	3-Cl	0.0177	0.0213	0.0195 ± 0.0018	72
4	4-FC_6H_4CHO	4-F	0.0053	0.0049	0.0051 ± 0.0002	89
5	4-MeC_6H_4CHO	4-Me	0.0014	0.0013	0.00135 ± 0.00005	68
6	3,4-$Me_2C_6H_3CHO$	3,4-Me_2	0.0010	0.0009	0.00095 ± 0.00005	65[c]
7	4-BrC_6H_4CHO	4-Br	0.0073	0.0068	0.0071 ± 0.0003	84
8	3-FC_6H_4CHO	3-F	0.0166	0.015	0.0158 ± 0.0008	88
9	3-MeC_6H_4CHO	3-Me	0.0019	0.002	0.00195 ± 0.00005	86
10	4-*t*$BuOC_6H_4CHO$	4-O*t*Bu	0.0014	0.0007	0.00105 ± 0.00035	58
11	4-$F_3CC_6H_4CHO$	4-CF_3	0.0172	0.0145	0.01585 ± 0.00135	77
12	3,5-$F_2C_6H_3CHO$	3,5-F_2	0.0344	0.03	0.0322 ± 0.0022	82
13	3,4-$Cl_2C_6H_3CHO$	3,4-Cl_2	0.0855	0.0904	0.08795 ± 0.00245	78[c]

[a] All reactions were carried out in duplicate (to give k_a and k_b, respectively) in dichloromethane at 0 °C with $[aldehyde]_0=0.5$ M, $[Me_3SiCN]_0=0.55$ M and [**4a**] = 1.0 mM. [b] Determined by chiral GC analysis of the cyanohydrin acetate unless stated otherwise. [c] Determined by ^1H NMR spectroscopy in the presence of (*R*)-mandelic acid and DMAP.

Table 3. Rate constants and enantioselectivities for the synthesis of cyanohydrin trimethylsilyl ethers catalysed by vanadium complex **4b**.[a]

Entry	Aldehyde	Abbrev.	k_a [$M^{-1}min^{-1}$]	k_b [$M^{-1}min^{-1}$]	k_{avg} [$M^{-1}min^{-1}$]	*ee* [%][b]
1	PhCHO	H	0.204	0.2452	0.2246 ± 0.0206	87
2	4-ClC_6H_4CHO	4-Cl	0.4035	0.3709	0.3872 ± 0.0163	84
3	3-ClC_6H_4CHO	3-Cl	0.4983	0.4866	0.4925 ± 0.0059	77
4	4-FC_6H_4CHO	4-F	0.2904	0.2876	0.2890 ± 0.0014	85
5	4-MeC_6H_4CHO	4-Me	0.1284	0.1058	0.1171 ± 0.0113	85
6	4-$MeOC_6H_4CHO$	4-MeO	0.0187	0.0161	0.0174 ± 0.0013	96[c]
7	3,4-$Me_2C_6H_3CHO$	3,4-Me_2	0.0789	0.0734	0.0762 ± 0.0028	76[d]
8	4-$MeSC_6H_4CHO$	4-MeS	0.1373	0.1903	0.1638 ± 0.0265	57
9	3-FC_6H_4CHO	3-F	0.6461	0.6663	0.6562 ± 0.0101	86
10	3-MeC_6H_4CHO	3-Me	0.2102	0.2238	0.2170 ± 0.0068	78
11	4-*t*$BuOC_6H_4CHO$	4-O*t*Bu	0.0726	0.0746	0.0736 ± 0.0100	78
12	4-$F_3CC_6H_4CHO$	4-CF_3	0.6312	0.5717	0.6015 ± 0.0298	75
13	3,5-$F_2C_6H_3CHO$	3,5-F_2	1.9063	2.0289	1.9676 ± 0.0613	75
14	4-BrC_6H_4CHO	4-Br	0.4243	0.4194	0.4219 ± 0.0025	81

[a] All reactions were carried out in duplicate (to give k_a and k_b, respectively) in dichloromethane at 0 °C with $[aldehyde]_0=0.5$ M, $[Me_3SiCN]_0=0.55$ M and [**4b**] = 1.0 mM. [b] Determined by chiral GC analysis of the cyanohydrin acetate unless stated otherwise. [c] Determined by comparison of the specific rotation with literature data.[27] [d] Determined by ^1H NMR spectroscopy in the presence of (*R*)-mandelic acid and DMAP.

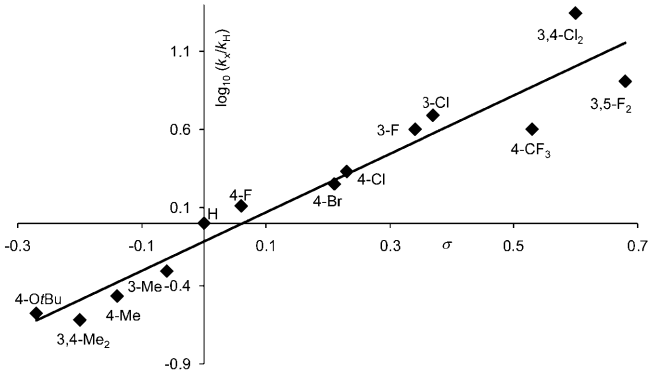


Figure 2. Hammett plot for the asymmetric addition of trimethylsilyl cyanide to different benzaldehydes catalysed by complex **4a** ($y=1.8724x-0.1167$, $R^2=0.9252$) For abbreviations see Table 2.

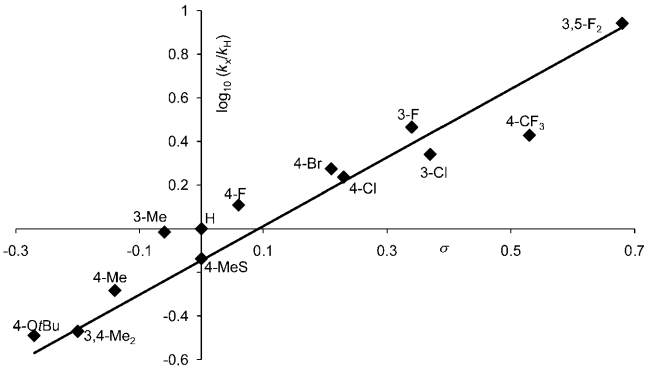


Figure 3. Hammett plot for the asymmetric addition of trimethylsilyl cyanide to different benzaldehydes catalysed by complex **4b** ($y=1.5705x-0.1448$, $R^2=0.8511$) For abbreviations see Table 3.

Table 4. Rate constants and enantioselectivities for the synthesis of cyanohydrin trimethylsilyl ethers catalysed by the bimetallic aluminium complex **5**.[a]

Entry	Aldehyde	Abbrev.	k_a [min^{-1}]	k_b [min^{-1}]	k_{avg} [min^{-1}]	*ee* [%][b]
1	PhCHO	H	0.0015	0.0016	0.00155±0.00005	64
2	4-ClC$_6$H$_4$CHO	4-Cl	0.0021	0.0020	0.00205±0.00005	61
3	3-ClC$_6$H$_4$CHO	3-Cl	0.0024	0.0019	0.00215±0.00025	54
4	4-FC$_6$H$_4$CHO	4-F	0.0019	0.0024	0.00215±0.00025	69
5	4-MeC$_6$H$_4$CHO	4-Me	0.0016	0.0015	0.00155±0.00005	65
6	4-MeOC$_6$H$_4$CHO	4-MeO	0.0007	0.0006	0.00065±0.00005	71[c]
7	3,4-Me$_2$C$_6$H$_3$CHO	3,4-Me$_2$	0.0010	0.0012	0.0011±0.00005	68[d]
8	4-MeSC$_6$H$_4$CHO	4-MeS	0.0011	0.0013	0.0012±0.0001	40
9	3-FC$_6$H$_4$CHO	3-F	0.0033	0.0028	0.00305±0.00025	61
10	3-MeC$_6$H$_4$CHO	3-Me	0.0015	0.0017	0.0016±0.0001	73
11	4-*t*BuOC$_6$H$_4$CHO	4-O*t*Bu	0.0008	0.0010	0.0009±0.0001	58
12	4-F$_3$CC$_6$H$_4$CHO	4-CF$_3$	0.0020	0.0021	0.00215±0.00005	49
13	3,5-F$_2$C$_6$H$_3$CHO	3,5-F$_2$	0.0025	0.0035	0.0030±0.0005	38
14	4-BrC$_6$H$_4$CHO	4-Br	0.0018	0.0016	0.0017±0.0001	60
15	3,4-Cl$_2$C$_6$H$_3$CHO	3,4-Cl$_2$	0.0017	0.0019	0.0018±0.0001	50[d]

[a] All reactions were carried out in duplicate (to give k_a and k_b, respectively) in dichloromethane at 0°C with [aldehyde]$_0$ = 0.5 M, [Me$_3$SiCN]$_0$ = 0.55 M, [**5**] = 1.0 mM and [Ph$_3$PO] = 5.0 mM. [b] Determined by chiral GC analysis of the cyanohydrin acetate unless stated otherwise. [c] Determined by comparison of the specific rotation with literature data.[27] [d] Determined by ^{1}H NMR spectroscopy in the presence of (*R*)-mandelic acid and DMAP.

and 4-methoxybenzaldehyde (Table 4, entry 6) was again found to react with an anomalously slow rate, whereas 4-*tert*-butoxybenzaldehyde (Table 4, entry 11) gave kinetic data that were more consistent with the other substrates. For this catalyst system, it was impossible to fit the rate data to a single linear Hammett plot (Figure 4). The enantiomeric excesses of the cyanohydrin derivatives obtained by using complex **5** and triphenylphosphine oxide were generally lower than those obtained by using the other catalysts, but were still >35%,[23] thus, confirming that the kinetics being monitored were for the catalysed reaction.

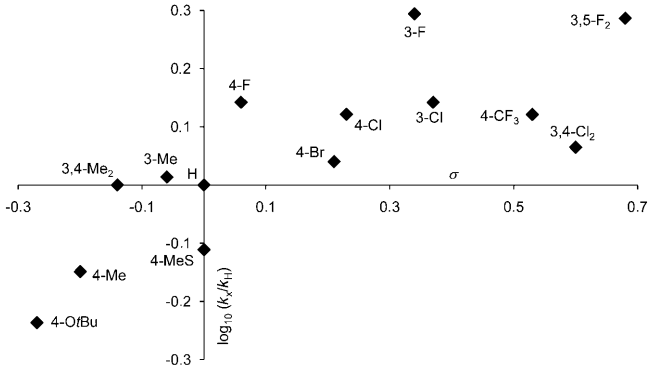


Figure 4. Hammett plot for the asymmetric addition of trimethylsilyl cyanide to different benzaldehydes catalysed by complex **5**. For abbreviations see Table 4.

The Hammett data for asymmetric cyanohydrin synthesis catalysed by complex **3** can simply be interpreted in terms of catalysis entirely by Lewis acid catalysis. There is clearly a linear correlation between how electron-deficient the aldehyde is and the rate with which it reacts (Figure 1). The linear correlation observed for all aldehydes with substituent constants between −0.3 and +0.4 suggests that all substrates are capable of coordinating to the Lewis acidic titanium ion and that, in doing so, they are activated towards addition of cyanide to the carbonyl group. The reaction constant (+2.4) observed for the addition of trimethylsilyl cyanide to aldehydes catalysed by complex **3** is almost identical to that obtained for the uncatalysed addition of cyanide to aldehydes (+2.3) and for the hydrolysis of methyl esters (+2.2),[16] indicating that nucleophilic addition to the carbonyl bond is the rate-determining step in each case.

The vanadium-based catalysts **4a** and **b** gave linear Hammett plots with reaction constants of 1.9 and 1.6, respectively (Figure 2 and Figure 3). These are lower reaction constants than that found for the titanium-based complex **3** and suggest that some Lewis base catalysis may also occur in these reactions. However, Lewis acid catalysis is still dominant as all aldehydes with substituent constants of −0.3 to +0.7 fitted the Hammett plot, indicating that they were all activated by coordination to the vanadium ion. The small degree of Lewis base catalysis occurring in both of these reactions may be due to the V=O bond,[13] and the greater degree of Lewis base catalysis in the case of complex **4b** may be due to Lewis base catalysis by the isothiocyanate counterion. There is a vast difference in the absolute rate of catalysis by complexes **4a** and **4b** since the second-order rate constant for catalysis by complex **4b** is 100 times higher than the corresponding rate constant for complex **4a**.[10b] The Hammett data indicate that this difference in rate of catalysis is partly due to Lewis base catalysis by the counterion, but may also be due to differences in the oligomeric nature of species formed in the reaction mixture.[6d,10b,11b,14]

The data for the aluminium-based catalyst **5** are clearly very different to the data obtained for the titanium- and vanadium-based catalysts. This is not too surprising, since a Lewis base (triphenylphosphine oxide) is specifically added to reactions catalysed by complex **5**. The failure of all of the aldehydes to fit a linear Hammett plot (Figure 4) is consistent with aluminium(III) being a weaker Lewis acid than titanium(IV) or vanadium(V). Thus, only the more electron-rich aldehydes (those with $\sigma < +0.35$) are capable of coordinating to the metal and of being activated by Lewis acid catalysis. The more electron-deficient aldehydes show evidence of predominant Lewis base catalysis, since there is no correlation between the substituent constant of the aldehyde and the reaction rate. However, the aldehyde must still be at least weakly bound to the aluminium, since asymmetric cya-

nohydrin synthesis is occurring within the sphere of influence of the chiral salen ligands as evidenced by the asymmetric induction observed (Table 4). In this system, both Lewis acid and Lewis base catalysis are operative, with Lewis acid catalysis being more important for electron-rich aldehydes than for electron-deficient substrates.

The differences between the Hammett plots for catalysts **3**–**5** are emphasised in Figure 5 in which all of the data are plotted on the same vertical axis. On this scale, all the data

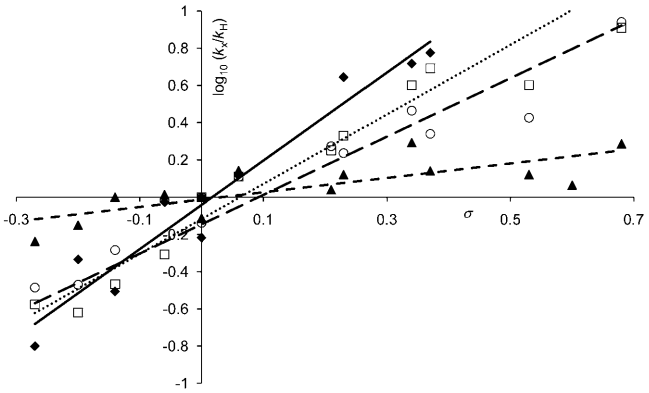


Figure 5. Superimposition of the Hammett plots for catalysts **3**–**5**. [◆ = **3** (——, $y=2.3715x-0.0409$), □ = **4a** (•••••, $y=1.8724x-0.1167$), ○ = **4b** (– – –, $y=1.5705x-0.1448$); ▲ = **5** (-----, $y=0.3888x-0.0131$)].

for complex **5** appears to fit a linear correlation that is almost horizontal compared to the data for catalysts **3**, **4a** and **4b**. This emphasises the high degree of Lewis base catalysis in reactions catalysed by complex **5**/triphenylphosphine oxide. The difference in slope (ρ) between catalysts **3** and **5** (2.4 and 0.4, respectively) is particularly marked, with the data for the vanadium-based catalysts **4a** and **4b** having an intermediate slope of 1.9–1.6.

Previously, we have shown that the titanium-based catalyst **3** is capable of inducing the asymmetric addition of trimethylsilyl cyanide to ketones,[6b,c] but the vanadium-based catalysts **4a** and **4b** do not accept ketones as substrates.[10b] In light of the results presented above, this can be rationalised in terms of the titanium-based catalyst **3** being a sufficiently good Lewis acid to active ketones, whereas the vanadium-based catalysts **4a** and **4b** are less Lewis acidic and so cannot activate the ketone. The alternative mode of catalysis involving Lewis base activation of the trimethylsilyl cyanide is also apparently not sufficiently effective to allow complexes **4a** and **4b** to catalyse the asymmetric addition of trimethylsilyl cyanide to ketones. Since the Hammett data for the asymmetric addition of trimethylsilyl cyanide to aldehydes catalysed by complex **5** and triphenylphosphine oxide suggested that Lewis base catalysis was significant for all substrates, we reasoned that the complex **5**/triphenylphosphine oxide catalyst system might be capable of catalysing the asymmetric addition of trimethylsilyl cyanide to ketones by a mechanism that involves predominantly Lewis base rather than Lewis acid catalysis.

To test this hypothesis, the asymmetric addition of trimethylsilyl cyanide to eight methyl ketones was investigated. A reaction carried out with acetophenone as substrate at −40 °C by using 1.6 equivalents of trimethylsilyl cyanide, 2 mol % of complex **5** and 10 mol % of triphenylphosphine oxide gave a conversion of just 12 % after a reaction time of 16 h. Increasing the reaction temperature to room temperature and increasing the reaction time to 48 h improved the conversion to 85 % and gave the (*S*)-cyanohydrin trimethylsilyl ether with 51 % enantiomeric excess. Increasing the amount of complex **5** to 4 mol % did not improve either the conversion or the enantioselectivity. Hence, all subsequent reactions were carried out by using 2 mol % of complex **5** and 10 mol % of triphenylphosphine oxide at room temperature for two days. As shown in Table 5 (entries 1–7), all of the acetophenone derivatives gave the corresponding cyanohydrin trimethylsilyl ether with an enantiomeric excess between 47 and 55 %,[23] though the conversion varied significantly between the substrates, with electron-rich aromatic ketones giving low conversions (entries 6 and 7), whereas halogenated acetophenones gave conversions >90 %. Pentan-2-one also gave the corresponding cyanohydrin trimethylsilyl ether with complete conversion under these conditions, but with a reduced enantioselectivity of just 44 % (Table 5, entry 8).

Table 5. Asymmetric addition of trimethylsilyl cyanide to acetophenones catalysed by aluminium complex **5** and triphenylphosphine oxide.

Entry	Ketone	Conversion [%][a]	*ee* [%][b]
1	PhCOMe	85	51 (*S*)
2	4-ClC_6H_4COMe	99	51 (*S*)
3	3-ClC_6H_4COMe	99	47 (*S*)
4	4-BrC_6H_4COMe	99	49 (*S*)
5	4-FC_6H_4COMe	91	55 (*S*)
6	4-MeC_6H_4COMe	62	50 (*S*)
7	4-$MeOC_6H_4COMe$	54	55 (*S*)
8	$MeCH_2CH_2COMe$	100	44 (*S*)

[a] Determined by ^{1}H NMR analysis of the reaction mixture. [b] Determined by ^{1}H NMR spectroscopy in the presence of (*R*)-mandelic acid and DMAP.[26]

Attempts to extend the chemistry to other ketones were not successful as no conversion was observed with propiophenone, and 1-tetralone gave just 21 % conversion (*ee* not determined). Attempts were also made to use the vanadium-based complexes **4a** and **4b** to catalyse the asymmetric addition of trimethylsilyl cyanide to acetophenone in the presence of triphenylphosphine oxide. However, no reaction was observed. It may be that the triphenylphosphine oxide coordinates to the vanadium(V) complex, thus, preventing it from acting as a Lewis acid.

Conclusion

A Hammett-plot analysis based on the substrate that potentially undergoes Lewis acid activation can be used to determine the relative importance of Lewis acid and Lewis base catalysis in asymmetric catalysis. Application of this methodology to a series of metal(salen) complexes, which all catalyse the asymmetric addition of trimethylsilyl cyanide to aldehydes, revealed major differences in the relative importance of Lewis acid and Lewis base catalysis, corresponding to activation of the aldehyde and trimethylsilyl cyanide, respectively. On the basis of this mechanistic analysis, the combination of the bimetallic aluminium salen complex **5** and triphenylphosphine oxide was predicted to accept ketones as substrates and this was found to be the case.

Experimental Section

General: Dichloromethane was distilled over CaH_2 under a nitrogen atmosphere immediately prior to use. For workup and chromatographic purification, commercial grade solvents were used. Trimethylsilyl cyanide and benzaldehyde were distilled on a Büchi B-580 Kugelrohr apparatus. Benzaldehyde was freshly distilled prior to use. Other commercially available chemicals (Alfa Aesar, Aldrich, Fluka, Riedel-de Haën) were used as received. Details of the instrumentation used to record the analytical data are given in the Supporting Information.

Synthesis of racemic cyanohydrin trimethylsilyl ethers

Racemic standards needed for enantiomeric excess analysis were prepared as follows: An aldehyde (0.985 mmol) was added to a solution of Bu_4NSCN (30 mg, 0.1 mmol) in CH_2Cl_2 (1.75 mL) at room temperature. To this solution, Me_3SiCN (116.5 mg, 1.182 mmol) was added and the reaction was stirred for 2 h. The solution then was passed through a silica plug eluting with CH_2Cl_2 and the solvent evaporated to leave the racemic cyanohydrin trimethylsilyl ether, which was used without further purification.

Synthesis of cyanohydrin acetates: An unpurified cyanohydrin trimethylsilyl ether was dissolved in MeCN (2 mL), and Ac_2O (1.5 mL, 1.58 mmol) and $Sc(OTf)_3$ (5 mg, 0.01 mmol) were added. The reaction was stirred for 30 min at room temperature, then the mixture was passed through a short silica plug and eluted with MeCN. The resulting solution was used for chiral GC analysis.[23]

Synthesis of cyanohydrins:[25] To a solution of a cyanohydrin acetate (0.985 mmol) in ethanol (3 mL), *p*-TsOH·H_2O (187 mg, 0.985 mmol) was added, and the mixture was stirred at room temperature for 2 days. The solvent was evaporated in vacuo and the residue was purified by column chromatography by eluting with a gradient from 1:15 EtOAc/hexane to 1:6 EtOAc/hexane to give the cyanohydrin. To determine the enantiomeric excess of the cyanohydrin, (*R*)-mandelic acid (2.74 mg, 18 μmol), DMAP (1.73 mg, 18 μmol) and $CDCl_3$ (0.6 mL) were mixed in an NMR tube. The cyanohydrin (18 μmol) was then added and the solution analysed by ^{1}H NMR spectroscopy.[23,26]

General method for kinetics experiments involving bimetallic titanium-(salen) complex 3: A solution of complex **3** (1.2 mg, 0.98 μmol) in dry CH_2Cl_2 (1.75 mL) was cooled to 0 °C in a water/ice bath. An aliquot (0.5 μL) was taken and diluted with CH_2Cl_2 (3.5 mL) to be used as the reference sample for the UV spectrophotometer. Then, freshly distilled aldehyde (0.985 mmol) was added to the reaction and another aliquot (0.5 μL) was taken and diluted with CH_2Cl_2 (3.5 mL). The absorbance of the sample at the wavelength corresponding to λ_{max} of the aldehyde was recorded. Me_3SiCN (116.5 mg, 1.182 mmol) was added to the reaction and aliquots (0.5 μL) were taken and quenched with CH_2Cl_2 (3.5 mL) at appropriate time intervals over a period of 1 min to 1 h, depending on the nature of the aldehyde. The remaining solution was then passed through a silica plug and eluted with CH_2Cl_2 and the solvent was evaporated to allow the enantiomeric excess of the cyanohydrin trimethylsilyl ether to be determined.

General method for kinetics experiments involving vanadium(salen) complexes 4a and 4b: A solution of catalyst **4a** or **4b** (1.96 μmol) in dry CH_2Cl_2 (1.75 mL) was cooled to 0 °C in a water/ice bath. An aliquot (0.5 μL) was taken and diluted with CH_2Cl_2 (3.5 mL) to be used as the reference sample for the UV spectrophotometer. Then, freshly distilled aldehyde (0.985 mmol) was added to the reaction and another aliquot (0.5 μL) was taken and diluted with CH_2Cl_2 (3.5 mL). The absorbance of the sample at the wavelength corresponding to λ_{max} of the aldehyde was recorded. Me_3SiCN (116.5 mg, 1.182 mmol) was added to the reaction and aliquots (0.5 μL) were taken and quenched with CH_2Cl_2 (3.5 mL) at appropriate time intervals over a period of 1 to 2 h (depending on the nature of the aldehyde) for reactions catalysed by complex **4b**, and 8 h for reactions catalysed by complex **4a**. The remaining solution was then passed through a silica plug and eluted with CH_2Cl_2 and the solvent was evaporated to allow the enantiomeric excess of the cyanohydrin trimethylsilyl ether to be determined.

General method for kinetics experiments involving bimetallic aluminium-(salen) complex 5: Catalyst **5** (10 mg, 8.8 μmol) and Ph_3PO (12 mg, 43.2 μmol) were dissolved in freshly distilled CH_2Cl_2 (1.75 mL) and the solution was cooled to 0 °C. A sample (0.50 μL) was removed and diluted with CH_2Cl_2 (3.0 mL) to be used as the reference sample for the UV spectrophotometer. Aldehyde (0.44 mmol) was added to the reaction mixture and another sample (0.50 μL) was removed and diluted with CH_2Cl_2 (3.0 mL). The absorbance of the sample at the wavelength corresponding to λ_{max} of the aldehyde was recorded. Me_3SiCN (69 mg, 0.7 mmol) was added to the reaction mixture and the kinetics monitored by taking samples (0.50 μL) and quenching them with CH_2Cl_2 (3.0 mL) at appropriate time intervals over a period of approximately 6 h. The remaining solution was then passed through a silica plug and eluted with CH_2Cl_2 and the solvent was evaporated to allow the enantiomeric excess of the cyanohydrin trimethylsilyl ether to be determined. Characterising data for known cyanohydrin trimethylsilyl ethers is given in the Supporting Information.

Trimethylsilyloxy-(3,5-difluorophenyl)acetonitrile: $[\alpha]_D^{20} = -18.4$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 0.27$ (s, 9H), 5.47 (s, 1H), 6.84 (tt, ^3J(H,F) = 8.8, ^4J(H,H) = 2.4 Hz, 1H), 6.9–7.1 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = -0.4$, 62.4, 104.8 (t, ^2J(C,F) = 25.1 Hz), 109.3 (d, ^2J(C,F) = 26.9 Hz), 118.2, 140.0 (t, ^3J(C,F) = 9.1 Hz), 163.2 ppm (dd, ^1J(CF) = 249.4, ^3J(C,F) = 12.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$, $CFCl_3$): $\delta = -107.6$ ppm (t, ^3J(FH) = 7.5 Hz); IR (neat): $\tilde{\nu} = 3096$, 2962, 2903, 2243, 1626, 1602 cm^{-1}; MS (ESI): *m*/*z* (%): 259 (25) $[M+H_2O]^+$, 185 (100); HRMS (ESI): calcd for $C_{11}H_{13}NOF_2Si$ $[M]^+$: 241.0735; found: 241.0731; *ee* determined by chiral GC analysis of the corresponding acetate by using method 2:[23] $R_t = 14.8$ min (*R*), $R_t = 15.1$ min (*S*).

Trimethylsilyloxy-(3,4-dimethylphenyl)acetonitrile: m.p. 31–32 °C; $[\alpha]_D^{20} = -24.1$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 0.21$ (s, 9H), 2.26 (s, 3H), 2.28 (s, 3H), 5.41 (s, 1H), 7.1–7.3 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = -0.2$, 19.6, 19.8, 63.6, 119.4, 123.9, 127.6, 130.1, 133.7, 137.4, 138.0 ppm; IR (ATR): $\tilde{\nu} = 3017$, 2960, 2924, 2239 cm^{-1}; MS (ESI): *m*/*z* (%): 251 (100) $[M+H_2O]^+$, 207 (95) $[M-CN]^+$, 185 (40); HRMS (ESI): calcd for $C_{13}H_{19}NOSi$ $[M+H]^+$: 234.1314; found:234.1305; *ee* determined by ^{1}H NMR spectroscopy of the unprotected cyanohydrin in the presence of (*R*)-mandelic acid and DMAP: ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ_H(*R*-CHCN) = 5.36, δ_H(*S*-CHCN) = 5.31 ppm.

Trimethylsilyloxy-(4-tert-butoxyphenyl)acetonitrile: $[\alpha]_D^{20} = -17.4$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 0.22$ (s, 9H), 1.36 (s, 9H), 5.46 (s, 1H), 7.02 (d, ^3J(H,H) = 8.4 Hz, 2H), 7.36 ppm (d, ^3J(H,H) = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = -0.2$, 28.8, 63.4, 79.0, 119.3, 124.2, 127.2, 130.9, 156.4 ppm; IR (neat): $\tilde{\nu} = 3063$, 3036, 2978, 2904, 2240, 1608, 1508 cm^{-1}; MS (ESI): *m*/*z* (%): 278 (50) $[M+H]^+$, 276 (70), 242 (100); HRMS (ESI): calcd for $C_{15}H_{23}NO_2SiNa$ $[M+Na]^+$: 300.1396; found: 300.1371; *ee* determined by chiral GC analysis of the

corresponding acetate by using method 5:[23] $R_t = 72.9$ min (*R*), $R_t = 73.7$ min (*S*).

Trimethylsilyloxy-(3,4-dichlorophenyl)acetonitrile: $[\alpha]_D^{20} = -15.9$ ($c = 1.0$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, TMS): $\delta = 0.26$ (s, 9H), 5.44 (s, 1H), 7.31 (dd, $^3J(H,H) = 8.4$, $^4J(H,H) = 2.0$ Hz, 1H), 7.50 (d, $^3J(H,H) = 8.4$ Hz, 1H), 7.57 ppm (d, $^4J(H,H) = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, TMS): $\delta = -0.3$, 62.4, 118.4, 125.4, 128.3, 131.0, 133.3, 133.7, 136.3 ppm; IR (neat): $\tilde{\nu} = 3094$, 3025, 2961, 2901, 2242, 1595, 1568 cm^{-1}; MS (ESI): *m*/*z* (%): 296 (100) $[M+Na]^+$; HRMS (ESI): calcd for $C_{11}H_{13}NOCl_2SiNa$ $[M+Na]^+$: 296.0041; found: 296.0026; *ee* determined by ^1H NMR spectroscopy of the unprotected cyanohydrin in the presence of (*R*)-mandelic acid and DMAP: ^1H NMR (400 MHz, $CDCl_3$, TMS): δ_H-(*R*-CHCN) = 5.30 ppm, δ_H(*S*-CHCN) = 5.22 ppm.

General method for the asymmetric addition of trimethylsilyl cyanide to ketones: Ph_3PO (12 mg, 0.04 mmol) and catalyst **5** (10 mg, 8.4 μmol) were dissolved in CH_2Cl_2 (1.0 mL) and ketone (0.42 mmol) was added in one portion. Me_3SiCN (66 mg, 0.67 mmol) was then added and the resulting solution was stirred at room temperature for 48 h. After this time, the reaction mixture was passed through a silica plug and eluted with CH_2Cl_2. The solvent was removed under reduced pressure and the residue purified by column chromatography by eluting with Et_2O/petrol to give the trimethylsilyl protected cyanohydrin product. To determine the enantiomeric excess, the cyanohydrin trimethylsilyl ether was dissolved in CH_2Cl_2 (2 mL) and hydrochloric acid (1 mL) was added in one portion. The reaction was stirred vigorously at room temperature for one hour, then the organic layer was separated and the aqueous layer was washed with CH_2Cl_2 (2×2 mL). The combined organic layers were washed with brine (2 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure to leave the free cyanohydrin as an oil. The product was dissolved in $CDCl_3$ and (*R*)-mandelic acid (100 mg, 0.66 mmol) and a catalytic amount of DMAP were added. The sample was then analysed by ^1H NMR spectroscopy.[23] Characterising data for the cyanohydrin trimethylsilyl ethers is given in the Supporting Information.

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