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Discrete *versus In Situ*-Generated Aluminum-Salen Catalysts in Enantioselective Cyanosilylation of Ketones: Role of Achiral Ligands

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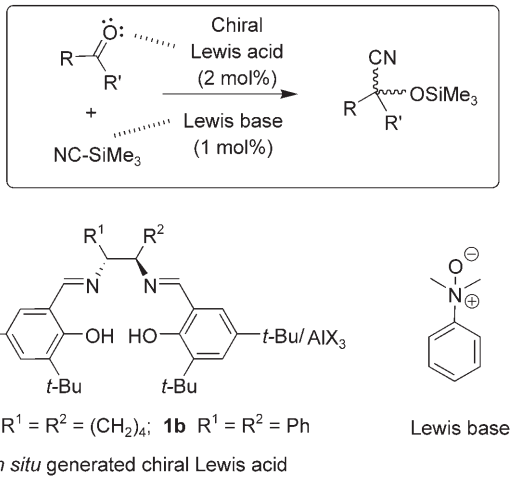
Abstract: The monometallic species {Salen}AlX (X = Me, **2a**,**b**; X = Cl, **4a**,**b**; O-*i*-Pr, **5a,b**) and open bimetallic species {Salen}$[AlMe_2]_2$ (**3a**,**b**) that result from binary combinations between an aluminum precursor [trimethylaluminum, dimethylaluminum chloride, aluminum tris(isopropoxide)] and a diprotio {Salen}H_2 pro-ligand **1a**,**b** (**a** = 1*R*,2*R*-cyclohexyl-salen; **b** = 1*R*,2*R*-diphenylethylene-salen) have been isolated. The crystal structures of **3b**, **4b** and of μ-oxo species [{diphenylethylene-salen}Al]$_2$O (**6b**) are reported. The discrete species **2–5a,b** have been individually evaluated in the asymmetric cyanosilylation of acetophenone. It is shown that, in several cases, these discrete catalysts display dramatically different performances than the catalyst systems *in situ*-generated from the binary combinations. The influence of the achiral ligand X on both the enantioselectivity and activity of the cyanosilylation reaction has been investigated, resulting in the definition of a highly active and productive hexafluoro-2-propoxide-based catalyst for a variety of aryl alkyl ketones (TON up to 470, TOF up to 140 h^{-1} at −20 °C for acetophenone).

Keywords: aluminum; asymmetric catalysis; cyanosilylation; homogeneous catalysis; Salen ligands

Introduction

Enantioselective cyanosilylation of ketones is a common route for the preparation of cyanohydrins with a quaternary stereocenter,[1] a much valuable class of intermediates in organic synthesis.[2] Those reactions are catalyzed, e.g., by a metal-based Lewis acid,[3] which activates the ketone substrate. An important development of such reactions, with wider implications across the field of asymmetric catalysis, consists in "double-activation catalysis".[3d–k,4] In this process, an extra Lewis base further activates the cyanosilylation agent [Me_3SiCN] and facilitates cyanide delivery to the activated substrate (Scheme 1). This principle of double-activation catalysis was initially demonstrated with quite sophisticated bifunctional Lewis-basic/chiral ligands.[3d–f,4] Looking for simpler catalyst systems, Feng and co-workers investigated the cyanosilylation of ketones in the presence of Lewis acid complexes based on commercially available ligands in combination with achiral Lewis base additives.[3g–j] Effective *in situ* combinations of an aluminum precursor AlX_3 (or AlX_2X') with a readily available {Salen}H_2 pro-ligand and *N,N*-dimethylaniline *N*-oxide (DMAO) were thus recently identified (Scheme 1).[3j] This practical approach gives substantially higher *ee* values than the related bifunctional catalysts for a range of ketones (up to 94% *ee* for acetophenone). The reaction times were, however, slightly extended due to modest catalyst activity. Also, the exact nature of the actual active species or catalyst precursors in these *in situ* systems was not thoroughly investigated, hampering the establishment of clear structure-activity-selectivity relationships.

In this work we have studied the organometallic outcome of the catalyst systems *in situ*-generated from an aluminum precursor AlX_3 (or AlX_2X') and a diprotio {Salen}H_2 pro-ligand. The different species that result from these binary combinations have been isolated, characterized and individually evaluated in the asymmetric cyanosilylation of acetophenone. It is shown that, in some cases, these discrete catalysts dis-



Scheme 1.

play dramatically different performances than the binary systems which are assumed to generate them. The influence of the achiral ligand on both the enantioselectivity and activity of the reaction has been investigated, resulting in the definition of a highly active hexafluoro-2-propoxide-based catalyst.

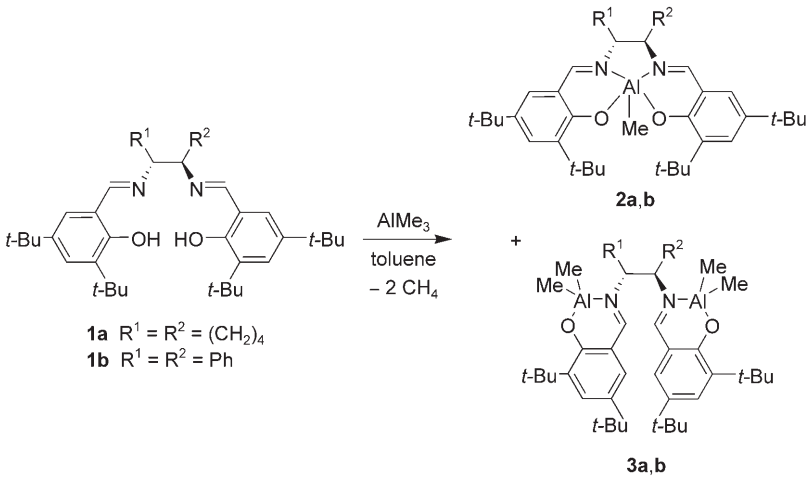
Results and Discussion

Reaction of {Salen}H_2 Pro-ligands with Aluminum Precursors

The reaction of {Salen}H_2 pro-ligands with one equiv. of a trialkylaluminum was first investigated (Scheme 2). This reaction is anticipated to provide the corresponding {Salen}AlR complex (**2**) as the major (exclusive) product *via* methane elimination.[5] However, Atwood and co-workers previously reported that open bimetallic complexes of the type {Salen}-$[AlR_2]_2$ (**3**) can also be cleanly produced upon using two equiv. of trialkylaluminum per {Salen}H_2 pro-ligand.[5,6] In fact, we observed that the 1:1 reactions of $AlMe_3$ and {Salen}H_2 pro-ligands derived from *trans*-1*R*,2*R*-cyclohexyldiamine (**1a**) and *trans*-1*R*,2*R*-diphenylethylenediamine (**1b**), under the conditions used for the *in situ* generation of "{Salen}AlR″-type catalysts, that is, at room temperature in toluene solution, led in both cases to mixtures of **2a,b** and **3a**,**b**, as revealed by NMR spectroscopy. Unexpectedly enough, the open bimetallic complexes **3a**,**b** were often the major products observed in these reactions.

The influence of the parameters that may vary in such a protocol, that is, the introduction order and concentration of reagents, the reaction temperature and reaction time, was systematically investigated. Some representative results are summarized in Table 1. No significant influence of the addition rate of the second reagent on the overall reaction time was noticed on the **2**/**3** relative proportions. Not surprisingly, addition of pro-ligands **1a**,**b** onto $AlMe_3$ afforded the open bimetallic complexes **3a**,**b** in high yield or as the exclusive product (entries 1 and 6). Reversal of the addition order, however, did not significantly affect the outcome. Improved selectivity for the desired five-coordinated monometallic complexes **2a**,**b** was obtained upon increasing the reagent concentrations (compare entries 3 and 4) and even more upon increasing the reaction temperature. Only at high temperature (i.e., much higher than that used for the *in situ* generation) could **2a**,**b** be obtained in high yields, but were still contaminated by **3a**,**b**.

Complexes **2a**,**b** and **3a**,**b** were separated and isolated in good yields from these mixtures by recrystallization at low temperature. As no crystal structure of Salen complexes derived from the 1,2-diphenylethylene backbone has been reported so far, X-ray diffrac-



Scheme 2.

Table 1. Reaction of {Salen}H_2 pro-ligands **1a**,**b** with $AlMe_3$.[a]

Entry	Temp [°C]	Time [h]	[reagent] [mol/L]	Addition order of reagents	**2**:**3**
1	20	14	0.10	1. $AlMe_3$, 2. **1a**	12:88
2	20	14	0.10	1. **1a**, 2. $AlMe_3$	27:73
3	20→110	4	0.04	1. **1a**, 2. $AlMe_3$	55:45
4	20→110	4	0.14	1. **1a**, 2. $AlMe_3$	68:32
5[b]	110	4	0.14	1. **1a**, 2. $AlMe_3$	91:9
6	20	14	0.03	1. $AlMe_3$, 2. **1b**	0:100
7	20	14	0.03	1. **1b**, 2. $AlMe_3$	13:87
8	20→110	4	0.14	1. **1b**, 2. $AlMe_3$	47:53

[a] Reactions conducted in toluene solutions; complete conversion of the reagents was observed in all cases.
[b] Solutions of both reagents were pre-heated before addition.

tion studies were conducted in this series. The molecular structure of open bimetallic complex **3b** is shown in Figure 1. Crystallographic details are available in the Supporting Information (Table S1). The Al centers in **3b** are in a slightly distorted tetrahedral environment and the main geometric characteristics are essentially similar to those reported for the related {cyclohexyl-salen} complex **3a**.[6b]

Following similar alcohol or alkane elimination protocols, pro-ligands **1a**,**b** react with Al(O-*i*-Pr)$_3$ or $AlMe_2Cl$ in toluene to give the corresponding {Salen}AlX (X = Cl, **4a,b**; O-*i*-Pr, **5a,b**) complexes (Scheme 3). In these cases, no other species than those expected were detected in the crude reaction mixtures by NMR spectroscopy. Thus, all complexes were isolated in pure form in high yields by simply concentrating the reaction mixture under vacuum and washing the final solid residue with hexanes. {Cyclohexyl-salen} complexes **4a**[7] and **5a**[8] were described previously, while complexes **4b** and **5b** that have a 1,2-diphenylethylene backbone are new. The latter complexes were fully characterized by NMR, elemental analyses and an X-ray diffraction study for **4b**. The solid state structure of **4b** (Figure 2 and Supporting Information, Table S1) contains two independent molecules per unit cell, whose geometric data (bond distances and angles) are slightly different (see Legend of Figure 2), but the general features are essentially similar. Overall, these two molecules compare very

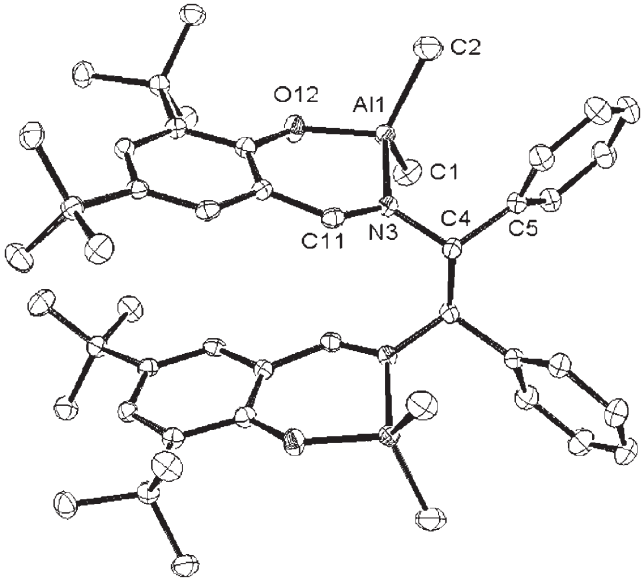
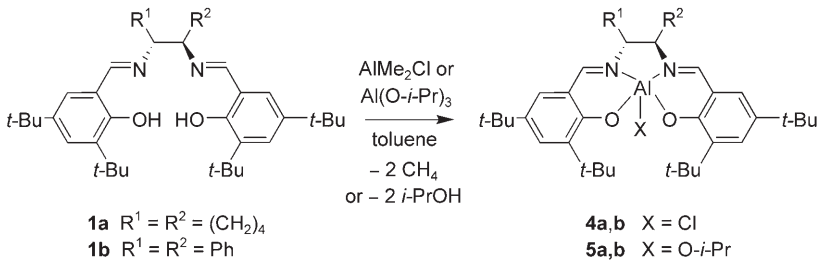


Figure 1. Molecular structure of **3b** (60% ellipsoids; all H atoms removed). Main bond distances (Å) and angles (deg): Al(1)–O(12), 1.7748(10), Al(1)–C(2), 1.9552(16); Al(1)–C(1), 1.9602(15), Al(1)–N(3), 1.9795(11); O(12)–Al(1)–C(2), 111.25(6); O(12)–Al(1)–C(1), 106.27(6); C(2)–Al(1)–C(1), 120.04(7); O(12)–Al(1)–N(3), 93.63(5); C(2)–Al(1)–N(3), 110.94(6); C(1)–Al(1)–N(3), 111.41(6); N(3)–C(4)–C(5), 108.98(10); dihedral angle C(5)–C(4)–C(4′)–C(5′), 54.5(1).



Scheme 3.

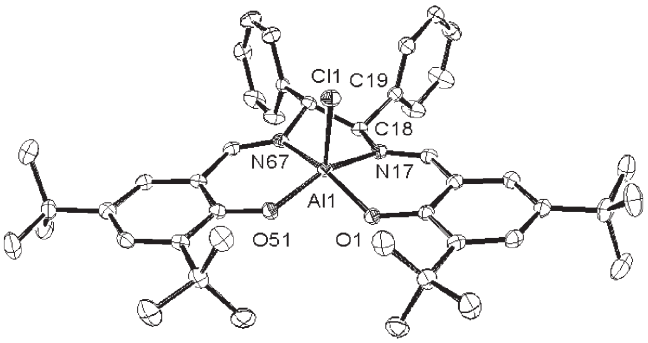
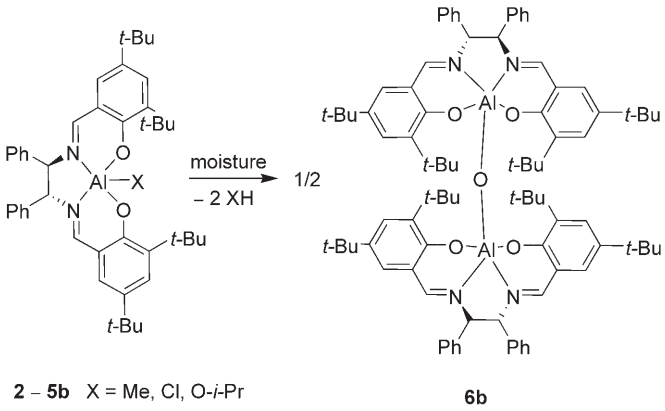


Figure 2. Moleculat structure of **4b** (50% ellipsoids; all H atoms removed; only one of the two independent molecules is shown). Main bond distances (Å) and angles (deg) [data in square brackets refer to the second independent molecule, not shown]: Al(1)–O(51), 1.7758(12) [1.7814(12)]; Al(1)–O(1), 1.7991(12) [1.7870(12)]; Al(1)–N(17), 1.9970(15) [1.9927(14)]; Al(1)–N(67), 2.0080(14) [1.9989(14)]; Al(1)–Cl(1), 2.1723(6) [2.1701(6)]; O(51)–Al(1)–O(1), 90.79(5) [90.42(5)]; O(51)–Al(1)–N(17), 148.59(6) [141.21(6)]; O(1)–Al(1)–N(17), 89.05(6) [89.22(5)]; O(51)–Al(1)–N(67), 88.77(5) [88.62(5)]; O(1)–Al(1)–N(67), 155.81(6) [161.61(6)]; N(17)–Al(1)–N(67), 79.01(6) [80.15(5)]; O(51)–Al(1)–Cl(1), 109.97(5) [112.82(4)]; O(1)–Al(1)–Cl(1), 102.83(4) [101.78(4)]; N(17)–Al(1)–Cl(1), 100.66(4) [105.19(4)]; N(67)–Al(1)–Cl(1), 100.03(4) [95.50(4)]; N(17)–C(18)–C(19), 116.63(13) [116.80(13)]; dihedral angle C(19)–C(18)–C(18′)–C(19′), 59.3(2) [58.4(2)].

well with other five-coordinated {Salen}AlCl complexes previously described.[5,7,9]

The chemistry of chloro- and isopropoxy-Al-{Salen} complexes (**4** and **5**) confirms to be simpler than that of methyl-Al-{Salen} complexes (**2** and **3**). However, all three complexes may also adventitiously generate a fourth type of species, that is hydrolysis products. In fact, we observed that products **2–5** are all quite sensitive to moisture, which might be present either in reaction or recrystallization solvents, or might have partly altered aged aluminum precursors as well. Thus, in a couple of reactions starting from Al(O-*i*-Pr)$_3$ or in some recrystallizations of **2–5b**, the formation of a small amount of crystals differently shaped than the main product was noticed (Scheme 4). Although the quality of these crystals was always poor, which was reflected in the X-ray diffraction data [thus not reported in detail; $R = 0.097$, $wR2 = 0.2584$], the latter technique allowed us to establish this product to be the μ-oxo species [{diphenylethylene-salen}-Al]$_2$O (**6b**) (Figure 3). The overall structure of **6b** is reminiscent to those of [{ethylene-salen$^{t\text{-Bu}}$}Al]$_2$O[10] and [{ethylene-salen^{H}}Al]$_2$O.[11] The most noticeable differences lie in the significantly more obtuse Al–O–Al angle [168.6(2)° in **6b** *vs.* 159.5(5) and 152.0(3)°, respectively], which is attributable to the presence of the bulky 1,2-phenyl groups; these bulky groups prob-



Scheme 4.

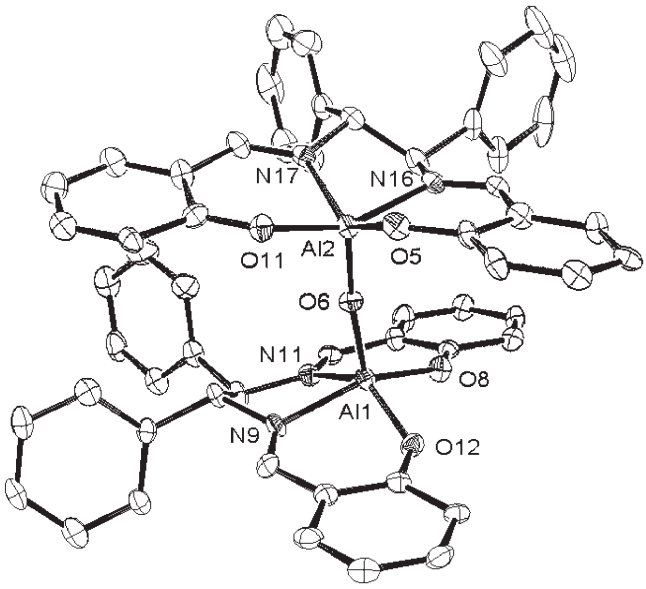


Figure 3. Molecular structure of **6b** (50% ellipsoids; all H atoms and *t*-Bu groups on phenyl rings removed for clarity). Main bond distances (Å) and angles (deg): Al(1)–O(6), 1.699(3); Al(1)–O(12), 1.802(3); Al(1)–O(8), 1.833(3); Al(1)–N(11), 2.014(4); Al(1)–N(9), 2.035(3); Al(2)–O(6), 1.699(3); Al(2)–O(5), 1.794(3); Al(2)–O(11), 1.824(3); Al(2)–N(16), 2.026(4); Al(2)–N(17), 2.029(4); Al(2)–O(6)–Al(1), 168.6(2); O(6)–Al(2)–O(5), 116.64(17); O(6)–Al(2)–O(11), 107.00(15); O(5)–Al(2)–O(11), 89.33(14); O(6)–Al(2)–N(16), 95.71(15); O(5)–Al(2)–N(16), 87.66(15).

ably also account for the nearly perpendicular arrangement of the two salen moieties in **6b**, while the salen moieties are more eclipsed in [{ethylene-salen$^{t\text{-Bu}}$}Al]$_2$O and [{ethylene-salen^{H}}Al]$_2$O.

Discrete *versus in situ*-Generated Catalysts in Cyanosilylation of Acetophenone

The catalytic performances of the different discrete complexes isolated in the previous section were evalu-

ated and compared to those of the corresponding *in situ* combinations.[3j] The cyanosilylation of acetophenone with 2 equiv. of TMSCN at −20 °C was chosen as the model reaction; *N,N*-dimethylaniline *N*-oxide (DMAO, 1.0 mol%) was selected as the Lewis base (Scheme 1). Representative results are summarized in Table 2.

We first investigated alkyl-Al systems. The *in situ*-generated systems derived from either $AlEt_3$[3j] or $AlMe_3$ with **1a** were found to afford similar catalytic activity (as judged from the final conversion of acetophenone) and enantioselectivity[12] (Table 2; entries 1 and 2). On the other hand, quite different performances were observed for the corresponding discrete species produced from these mixtures. As compared to the *in situ* system, monometallic complex **2a** leads to significantly enhanced activity and enantioselectivity (entry 3), whatever the solvent used (entries 4 and 5), while the bimetallic complex **3a** is much less active and less enantioselective (entry 6). The observation of an "averaged" activity for the *in situ* system is consistent with the abovementioned formation of both **2a** and **3a** from $AlMe_3$/**1a** combinations (Table 1). The lower enantioselectivity of the *in situ* system suggests that less or non stereoselective species other than **2a** and **3a**, for example, unreacted $AlMe_3$, contribute also to a significant extent to the cyanosilylation process. The same activity trend was observed for *in situ* catalysts based on **1b** and the corresponding discrete species **2b** and **3b** (entries 7–10); i.e., the monometallic complex is a much more active catalyst (or precursor) than its bimetallic congener. With this ligand system, all *in situ*-generated and discrete catalyst systems afford similar enantioselectivity, and the intervention of active species other than **2b** and **3b** can be discarded *a priori*.

Feng and co-workers reported very poor catalytic performances for *in situ*-generated isopropoxide-Al systems based on **1b** (entry 15).[3j] We did also observe very poor yield and enantioselectivity for the analogous $Al(O\text{-}i\text{-}Pr)_3$/**1a** combination (entry 11). In contrast, discrete complexes **5a** and **5b**, and even the μ-oxo complex **6b**,[13] proved to be quite effective for the cyanosilylation of acetophenone, leading to high

Table 2. Cyanosilylation of acetophenone with *in situ*-generated and discrete catalyst systems.[a]

Entry	Catalyst system	Time [h][b]	Conversion [%][c]	*ee* [%][d]
1[e]	{cyclohexyl-salen}H_2 (**1a**) + $AlEt_3$	78	45	51
2	{cyclohexyl-salen}H_2 (**1a**) + $AlMe_3$	48	41	54
3	{cyclohexyl-salen}AlMe (**2a**)	48	59	76
4[f]	{cyclohexyl-salen}AlMe (**2a**)	48	62	75
5[g]	{cyclohexyl-salen}AlMe (**2a**)	48	51	70
6	{cyclohexyl-salen}$[AlMe_2]_2$ (**3a**)	48	6	66
7[e]	{diphenylethylene-salen}H_2 (**1b**) + $AlEt_3$	78	45	83
8	{diphenylethylene-salen}H_2 (**1b**) + $AlMe_3$	48	52	80
9	{diphenylethylene-salen}AlMe (**2b**)	48	81	84
10	{diphenylethylene-salen}$[AlMe_2]_2$ (**3b**)	48	8	81
11	{cyclohexyl-salen}H_2 (**1a**) + $Al(O\text{-}i\text{-}Pr)_3$	48	7	23
12	{cyclohexyl-salen}AlO-*i*-Pr (**5a**)	48	89	86
13[h]	{cyclohexyl-salen}AlO-*i*-Pr (**5a**)	48	>99	80
14[i]	{cyclohexyl-salen}AlO-*i*-Pr (**5a**)	48	46	84
15[e]	{diphenylethylene-salen}H_2 (**1b**) + $Al(O\text{-}i\text{-}Pr)_3$	78	17	14
16	{diphenylethylene-salen}AlO*i*Pr (**5b**)	48	71	81
17	[{diphenylethylene-salen}Al]$_2$(μ-O) (**6b**)	48	98	80
18	{cyclohexyl-salen}H_2 (**1a**) + $AlMe_2Cl$	48	4	41
19	{cyclohexyl-salen}AlCl (**4a**)	48	51	83
20[e]	{diphenylethylene-salen}H_2 (**1b**) + $AlEt_2Cl$	78	traces	(87)
21	{diphenylethylene-salen}AlCl (**4b**)	48	41	75

[a] Reactions carried out at −20 °C with acetophenone (0.81 mmol, at 0.8 M in THF), TMSCN (1.62 mmol, 2 equiv.), Al (2.0 mol%), DMAO (1.0 mol%), unless otherwise stated.
[b] Reaction time was not necessarily optimized.
[c] Conversion of acetophenone to the cyanohydrin silyl ether, as determined by ^1H NMR and GLC.
[d] The *ee* was determined by GLC with a CHIRASIL DEX.CB column; the major enantiomer has always a *S* configuration, as determined from the specific optical rotation.
[e] Results from ref.[3j]
[f] Reaction run in dichloromethane.
[g] Reaction run in toluene.
[h] Reaction run at 0 °C.
[i] Reaction run at −40 °C.

yields and *ee*s up to 86% (entries 12–14, 16 and 17). In the same line, *in situ*-generated chloro-Al systems based on **1a** and **1b** are poorly active (entries 18 and 20),[3j] while discrete complexes **4a** and **4b** afford the cyanosilylation product in 41–51% yields (entries 19 and 21).

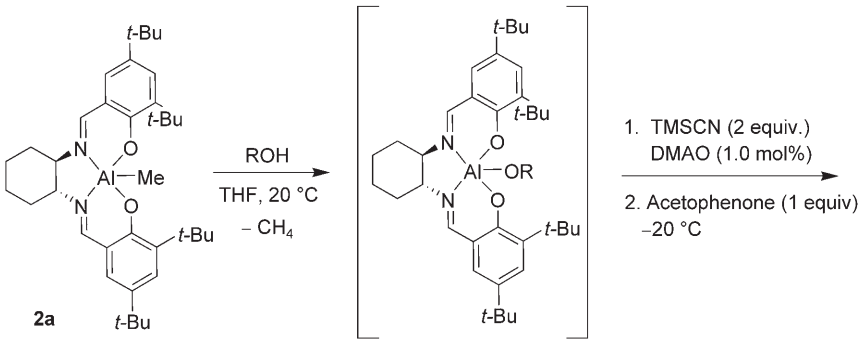
These results clearly evidence that *in situ* combinations of aluminum precursors with {salen}H_2 pro-ligands do not necessarily afford equivalent catalyst systems to discrete complexes. This is especially the case for Al(O-*i*-Pr)$_3$/**1a,b** combinations,[3j] since these systems require relatively harsh conditions to afford the desired {salen}Al(O-*i*-Pr) complexes (*vide supra*). Thus, the "*in situ* approach", although enabling fast screening of potentially diverse systems, can lead to erroneous conclusions and/or choices for further catalyst development.

Another well-established feature in asymmetric catalysis that is further confirmed from the performances of discrete catalysts **2**, **4**, **5a**,**b** is that the achiral X ligand (X = Me, Cl, O-*i*-Pr) can affect significantly not only the activity[14] but also the enantioselectivity of the catalyst. Indirectly, these results demonstrate that the X ligand remains in the coordination sphere of the active metal center throughout the cyanosilylation reaction. Due to the larger availability, diversity and lower cost of such X ligands as compared to chiral {salen}H_2 pro-ligands, the nature of the X ligand is obviously a most interesting parameter for catalyst tuning. In light of the valuable catalytic performances of discrete isopropoxide complexes **5a** and **5b** (Table 2; entries 12–14 and 16), unrevealed in the initial study[3j] for the aforementioned reason, we became interested in varying the alkoxide ligand in those series of complexes. The cyclohexyl (**a**) ligand framework was selected for this study.

For this purpose, we decided to pursue another route to the preparation of {cyclohexyl-salen}Al(OR) complexes, that is the alcoholysis of methyl complex **2a** with one equiv. of appropriate dry alcohols in THF. The validity of this *in situ* protocol was evaluated directly in the cyanosilylation of acetophenone (Scheme 5). The results reported in Table 3 (entry 4) show that the **2a**/*i*-PrOH combination affords identical results (within experimental uncertainty) to those obtained with discrete **5a** (Table 2, entry 12). One may thus reasonably assume that this alcoholysis protocol effectively generates the desired {cyclohexyl-salen}Al(OR) complexes, at least for secondary alcohols.[15]

The influence of steric and electronic factors was next investigated with a variety of alcohols (Table 3). All the alcohols tested afforded systems more active than the initial methyl-Al precursor **2a**. The only exception was for tributoxysilanol, which led to a completely inactive system (entry 16). Primary and simple secondary alcohols afforded high yields (80–100%) of the cyanosilylation product. L- and D-menthol and *tert*-butyl alcohol afforded somewhat less active catalysts (65–69% yields), which likely reflects the detrimental influence of excess steric bulkiness of the alkoxy ligand on this process. Major enhancements on catalytic activity were obtained by the introduction of electron-withdrawing substituents. Only a slight increase in the final yield was observed moving from ethanol ($pKa = 16$) to trifluoroethanol ($pKa = 12$) (entries 2 and 11). The influence was much more pronounced by replacing 2-propanol ($pKa = 17$) with hexafluoro-2-propanol ($pKa = 9$) (entries 12–15). With this system, thus far unprecedented turnover frequencies up to 140 (mol acetophenone)$(\text{mol Al})^{-1}(\text{h})^{-1}$ (at 70% conversion) and turnover numbers up to 470 (mol acetophenone)$(\text{mol Al})^{-1}$ were achieved at −20 °C (Table 3, Figure 4). Enhanced Lewis acidity of the metal center induced by the electron-withdrawing CF_3 groups most likely accounts for the observed higher catalytic activity and productivity.

The maximal enantioselectivity was observed for the 2-propoxide catalyst system. Less bulky alkoxides (ethoxide, benzyloxide) or bulkier alkoxides (*tert*-butoxide, menthoxide, *sec*-butoxide) led to decreased enantioselectivities.[12] Interestingly, the presence of a chiral center in the alkoxide (menthoxide, *sec*-butoxide) ligand was found to be of marginal importance, as judged by the similar catalytic performances observed from both enantiomers in each case; in fact,



Scheme 5.

Table 3. Cyanosilylation of acetophenone with alkoxide catalyst systems *in situ*-generated from complex **2a** and ROH.[a]

Entry	ROH	*pKa*	Time [h][b]	Conversion [%][c]	*ee* [%][d]
1	-	-	48	59	76
2	ethanol	16	48	81	68
3	benzyl alcohol	14	48	89	71
4	isopropyl alcohol	17	48	85	83
5	*tert*-butyl alcohol	18	48	68	77
6	L-menthol	15	48	65	74
7	D-menthol	15	48	69	75
8	(*R*)-*sec*-butanol	17	48	86	78
9	(*S*)-*sec*-butanol	17	48	84	82
10	*(R)*-2-phenylethanol	14	48	99	67
11	2,2,2-trifluoroethanol	12	48	88	66
12	hexafluoro-2-propanol	9	48	100	73
13[e]	hexafluoro-2-propanol	9	3	90	73
14[f]	hexafluoro-2-propanol	9	14	83	76
15[g]	hexafluoro-2-propanol	9	48	94	75
16	tributoxysilanol	6	48	0	-

[a] Reactions carried out at −20 °C with acetophenone (0.81 mmol, at 0.8 M in THF), TMSCN (1.62 mmol, 2 equiv.), Al (2.0 mol%), ROH (2.0 mol%), DMAO (1.0 mol%), unless otherwise stated.
[b] Reaction time was not necessarily optimized.
[c] Conversion of acetophenone to cyanohydrin silyl ether as determined by ^{1}H NMR and GLC.
[d] The *ee* was determined by GLC with a CHIRASIL DEX.CB column; the major enantiomer has always a *S* configuration, as determined from the specific optical rotation.
[e] 1.0 mol% Al; 1.0 mol% ROH; 0.5 mol% DMAO.
[f] 0.5 mol% Al; 0.5 mol% ROH; 0.25 mol% DMAO.
[g] 0.2 mol% Al; 0.2 mol% ROH; 0.1 mol% DMAO.

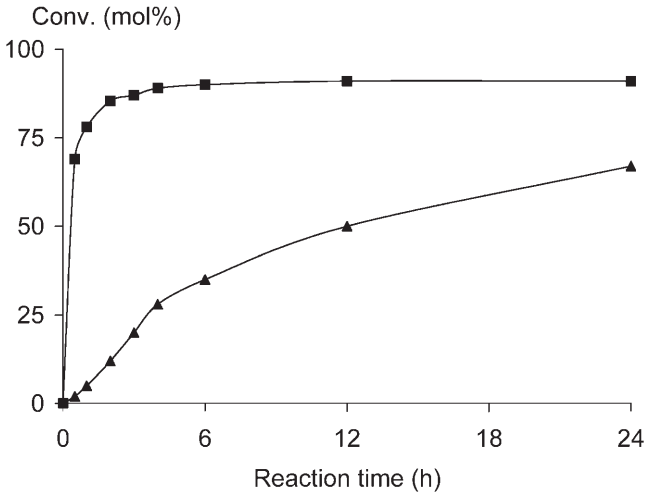
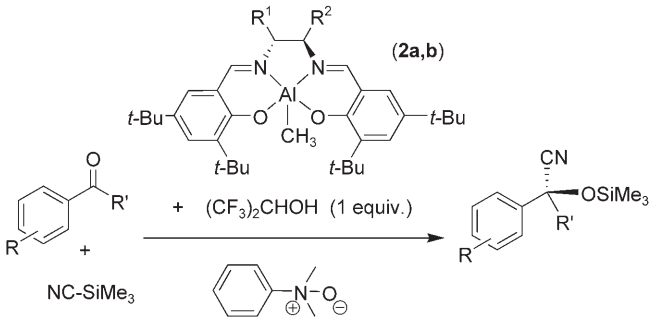


Figure 4. Kinetics of the cyanosilylation of acetophenone catalyzed by **2a**/*i*-PrOH (▲) and **2a**/$(CF_3)_2$CHOH (■) combinations. Reactions carried out at −20 °C with acetophenone (0.81 mmol, at 0.8 M in THF), TMSCN (1.62 mmol, 2 equiv.), **2a** (1.0 mol% *vs.* acetophenone), ROH (1.0 mol%), DMAO (0.5 mol%).

no obvious "matched-mismatched" effect could be observed. A relatively lower enantioselectivity was also observed with the hexafluoro-2-propoxide system, though in that case the influence of electronic effects (in addition to steric effects) cannot be discarded.[16]

The efficiency of such hexafluoro-2-propoxide systems was further demonstrated by generating the corresponding catalyst from the chiral cyclohexyl-bridged complex **2b** and using a variety of aryl alkyl ketones (Scheme 6). Representative results are summarized in Table 4. The reaction of acetophenone in the presence of the **2b**/$(CF_3)_2$CHOH (1:1) system proceeds as fast as with the analogous catalyst system derived from **2a**, with a conversion up to 81% after 1 h and a similar enantioselectivity (Table 4, entries 1 and 2). While 2-naphthyl methyl ketone reacts with similar performances as those observed for acetophenone (entry 3), the introduction of *ortho*-substituents (R = 2-Me,



Scheme 6.

Table 4. Cyanosilylation of aryl alkyl ketones RCOR' with hexafluoro-2-propoxide catalyst systems *in situ*-generated from complexes **2a,b** and $(CF_3)_2CHOH$.[a]

Entry	R	R′	Catalyst precursor	Time [h][b]	Conversion [%][c]	ee [%][d]
1	C_6H_5	Me	**2a**	48	100	73 (*S*)
2	C_6H_5	Me	**2b**	14[e]	100[e]	76 (*S*)
3	2-naphthyl	Me	**2a**	14	98	75 (−)
4	2-MeC_6H_4	Me	**2a**	14	100	72 (−)
5	2-$MeOC_6H_4$	Me	**2a**	14	100	70 (−)
6	2-ClC_6H_4	Me	**2a**	24	100	65 (−)
7	2-ClC_6H_4	Me	**2b**	14	100	71 (−)
8	4-MeC_6H_4	Me	**2a**	14	100	67 (*S*)
9	C_6H_5	Et	**2a**	14	96	81 (*S*)
10	C_6H_5	Et	**2b**	14	98	80 (*S*)
11	C_6H_5	*i*-Pr	**2a**	14	89	84 (−)
12	C_6H_5	*i*-Pr	**2b**	14	96	81 (−)

[a] Reactions carried out at −20 °C with the given aryl alkyl ketone (0.81 mmol, at 0.8 M in THF), TMSCN (1.62 mmol, 2 equiv.), Al (2.0 mol%), $(CF_3)_2CHOH$ (2.0 mol%), DMAO (1.0 mol%).
[b] Reaction time was not necessarily optimized.
[c] Conversion of the ketone to the cyanohydrin silyl ether as determined by ^1H NMR and GLC.
[d] Ee as determined by GLC with a CHIRASIL DEX.CB column.
[e] 81% conversion after 1 h.

OMe, Cl), and a *para*-substituent (R = 4-Me) as well, on acetophenone resulted in a slight erosion of the enantioselectivity (entries 4–8). On the other hand, improvement of enantioselectivity [more significant for the **2a** than for the **2b** system] was observed for aryl alkyl ketones bearing larger alkyl groups (R′ = Et, *i*-Pr) (entries 9–12). As anticipated for these bulky ketones, a slight decrease in activity was observed, although the hexafluoro-2-propoxide systems still allow high conversions within short reaction times.

Conclusions

In summary, we have shown that dramatically different catalytic performances can be obtained in the asymmetric cyanosilylation of acetophenone upon using either *in situ* combinations of an aluminum precursor AlX_3 (or AlX_2X') with a $\{Salen\}H_2$ pro-ligand or discrete {Salen}AlX complexes. Despite the anticipated high reactivity of alkyl- and alkoxide-aluminum precursors *versus* a quite acidic bis(phenol) pro-ligand, slow kinetics and above all undesired pathways may result in mixtures of complexes that feature significantly different catalytic activity and enantioselectivity than the {Salen}AlX species putatively generated. {Salen}Al alkoxide complexes have been found to be a valuable class of catalysts (or catalyst precursors) for the asymmetric cyanosilylation of acetophenone. Electronic tuning of the alkoxide ligand affords unprecedented high activity for cyanosilylation of aryl alkyl ketones with Al-based catalysts.

Experimental Section

Complementary details on instruments and measurements used, spectroscopic and analytical data for new complexes and cyanosilylation products, crystal structure determination of **3b**, **4b** and **6b**, and summary of crystal and refinement data for complexes **3b** and **4b**, are available as Supporting Information.

General Conditions

All manipulations requiring a dry atmosphere were performed under a purified argon atmosphere using standard Schlenk techniques or in a glovebox. Solvents (toluene, pentane, hexanes, diethylether, THF) were freshly distilled from Na/K alloy under nitrogen and degassed thoroughly by freeze-thaw-vacuum cycles prior to use. CH_2Cl_2 was dried over CaH_2, distilled twice and degassed by freeze-thaw-vacuum cycles prior to use. Deuterated solvents, except $CDCl_3$, were freshly distilled from Na/K amalgam under argon and degassed prior to use.

N,N-Dimethylaniline *N*-oxide,[17] pro-ligands $\{salen\}H_2$ **1a**,**b**[18] (1*R*,2*R*)-{cyclohexyl-salen}AlMe (**2a**),[19] (1*R*,2*R*)-{cyclohexyl-salen}$(AlMe_2)_2$ (**3a**),[6b] (1*R*,2*R*)-{cyclohexyl-salen}AlCl (**4a**),[7] and (1*R*,2*R*)-{cyclohexyl-salen}Al(O-*i*-Pr) (**5a**)[8] were synthesized following literature procedures. $AlMe_3$ (2.0 M solution in heptane), $AlMe_2Cl$ (1.0 M solution in hexane), and $Al(O\text{-}i\text{-}Pr)_3$ were purchased from Aldrich, Acros and Strem, and used as received. Ketones (Aldrich or Acros) and TMSCN (Aldrich) were dried over CaH_2 or activated molecular sieves (other ketones than acetophenone), distilled under argon and freshly degassed prior to use.

(1*R*,2*R*)-{Diphenylethylene-salen}AlMe (2b)

A solution of $AlMe_3$ (77 μL of a 2.0 M solution in heptane, 0.155 mmol) was added dropwise at room temperature onto

a solution of pro-ligand **1b** (100 mg, 0.155 mmol) in toluene (1 mL). The reaction mixture was refluxed for 4 h. Volatiles were removed under vacuum to leave a yellow solid which was recrystallized at −35 °C from toluene/hexane (2:1) to give **2b** as a yellow crystalline powder; yield 20 mg (39%).

(1*R*,2*R*)-{Diphenylethylene-salen}($AlMe_2$)$_2$ (3b)

A solution of pro-ligand **1b** (50 mg, 0.077 mmol) in toluene (2 mL) was added dropwise onto a solution of $AlMe_3$ (77.6 μL of a 2.0 M solution in heptane, 0.155 mmol) in toluene (3 mL). The reaction mixture was stirred for 12 h at room temperature. Volatiles were removed in vacuum and the yellow powder was washed several times with cold hexanes to give **3b**; yield: 98 mg (82%).

(1*R*,2*R*)-{Diphenylethylene-salen}AlCl (4b)

This complex was prepared as described above for **4a**, by the addition of a solution of pro-ligand **1b** (100 mg, 0.155 mmol) in toluene (5 mL) onto a solution of $ClAlMe_2$ (108 mg, 0.155 mmol) in toluene (2 mL). Reaction at room temperature for 14 h and usual work-up afforded **4b** as a yellow powder; yield: 90 mg (82%). Single crystals were obtained by recrystallization at −35 °C in toluene/hexane (2:1).

(1*R*,2*R*)-{Diphenylethylene-salen}Al(O*i*Pr) (5b)

This complex was prepared from pro-ligand **1b** (100 mg, 0.155 mmol), Al(O-*i*-Pr)$_3$ (31.7 mg, 0.155 mmol) in toluene (5 mL). The reaction mixture was stirred for 3 days at 80 °C. Volatiles were removed in vacuum and the residue was washed with cold hexanes (*ca.* 1 mL) to give **5b** as a yellow powder; yield: 102 mg (91%).

Typical Procedure for Acetophenone Cyanosilylation with Discrete Aluminum Catalysts

A 10-mL double wall Schlenk flask was charged with the Al complex (*ca.* 10 mg, 0.016 mmol, 2.0 mol% *vs.* acetophenone), THF (1 mL), and acetophenone (94 μL, 0.81 mmol). The reaction mixture was cooled to −20 °C. A solution *N,N*-dimethylaniline *N*-oxide (DMAO, 1.1 mg, 0.008 mmol) in THF (0.2 mL), previously treated for 1 h at room temperature with TMSCN (216 μL, 1.62 mmol), was then added dropwise. The reaction mixture was stirred at −20 °C for 48 h. Volatiles were removed under vacuum and the residue was analyzed by ^{1}H NMR to determine the conversion. The residue was purified by column chromatography (silica, CH_2Cl_2) to give 2-trimethylsilyloxy-2-phenyl-propanenitrile as a pale yellow oil.

Typical Procedure for Acetophenone Cyanosilylation with *in situ*-Generated Aluminum Catalysts

A 10-mL double wall Schlenk flask was charged with the complex **2a** (10.0 mg, 0.016 mmol), THF (1 mL), and the desired alcohol (0.016 mmol). Acetophenone (94 μL, 0.81 mmol) was next introduced, the mixture was cooled to −20 °C and the reaction was further carried out as described above.

Crystal Structures

Crystallographic data (excluding structure factors) for the structures of **3b, 4b** and **6b** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 669373, 669374 and 675685, respectively. Copies of the data can be obtained, free of charge from The Cambridge Crystalographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or from CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, [fax: +44-(0)1223–336033].

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