



An Aluminum Fluoride Complex with an Appended Ammonium Salt as an Exceptionally Active Cooperative Catalyst for the Asymmetric Carboxycyanation of Aldehydes

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Dedicated to Professor Yoshito Kishi on the occasion of his 80th birthday

Abstract: Al–F bonds are among the most stable σ bonds known, exhibiting an even higher bond energy than Si–F bonds. Despite a stability advantage and a potentially high Lewis acidity of Al–F complexes, they have not been described as structurally defined catalysts for enantioselective reactions. We show that Al–F salen complexes with appended ammonium moieties give exceptional catalytic activity in asymmetric carboxycyanations. In addition to aromatic aldehydes, enal and aliphatic substrates are well accepted. Turnover numbers up to around 10^4 were achieved, whereas with previous catalysts 10^1 – 10^2 turnovers were typically attained. In contrast to Al–Me and Al–Cl salen complexes, the analogous Al–F species are remarkably stable towards air, water, and heat, and can be recovered unchanged after catalysis. They possess a considerably increased Lewis acidity as shown by DFT calculations.

Asymmetric 1,2-additions of cyanide to aldehydes have been intensively studied because the enantioenriched cyanohydrin products are valuable chiral building blocks.^[1–3] Although it is industrially employed in enzymatic processes,^[4,5] the direct use of HCN is difficult for safety reasons and thus less volatile HCN equivalents are often utilized, in particular trimethylsilyl cyanide and ethyl cyanoformate.^[2,6,7] Whereas addition of HCN is reversible, the O-protected products formed from TMSCN and EtO(C=O)CN are stable towards the reverse reaction and hence less prone to racemization.^[2] On a production scale, the use of EtO(C=O)CN appears more attractive for practical, safety, and cost reasons.^[8] The installed carboxy groups were also used for elegant further transformations like [3,3]-rearrangements.^[9]

Although very active catalysts have been developed that can be applied to cyanosilylations with very small catalyst

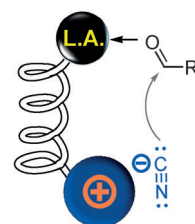
loadings,^[10] for carboxycyanations, the turnover numbers (TONs) are lower, with catalyst loadings usually in the range of 1–10 mol %.^[2a,11] As a general trend, cooperative catalysis has proven to be beneficial for both carboxy- and carbocyanations.^[12–14]

In this Communication, we report a new strategy for the carboxycyanation of aldehydes, which permits unprecedented TONs.^[2] In our approach, a Lewis acid catalyst cooperates with an internal ammonium salt moiety.^[15] The study was driven by the idea that a “naked” cyanide would facilitate the 1,2-addition to a simultaneously activated aldehyde while the ammonium should promote a face-selective attack.^[15] Key for the high catalyst efficiency is a robust Al–F unit that provides an extraordinarily stable and active catalyst.

Initial experiments (0.1 mmol scale) were conducted with ligands like **4** (5 mol %), which bear two ammonium units (Table 1, entry 1). The Al catalysts were formed in situ using AlMe₃. However, activity and *ee* were poor in CH₂Cl₂ at –50 °C. To improve the catalyst solubility, ligand **5** was studied, which bears a single ammonium unit (entry 2). The reactivity was massively improved by using KCN as an additive, which also has a positive impact on the *ee* (entry 3). A further *ee* enhancement was achieved with ligand **6**, which has a Et₂MeN⁺CH₂ residue (entry 4), and with BF₄[–] as X[–] in **7** (entry 5). The influence of longer linkers between the salen core and the ammonium group were studied (entries 6 and 7), and the best results were obtained with the (CH₂)₃ unit in ligand **9**.

“Non-nucleophilic” counterions X[–] initially had an unexpected impact. With triflate in ligand **10** (and also PF₆[–]) in place of BF₄[–], the enantioselectivity was nearly completely lost (entry 8). In contrast, when using ligand **10** but with Me₂AlCl for complexation, it was largely regained (entry 9). Solvent screening using the catalyst formed from **9** and AlMe₃ revealed that slightly better enantioselectivity is attained in CHCl₃. The amount of **2** and KCN could then be lowered without any negative effect (entry 10).

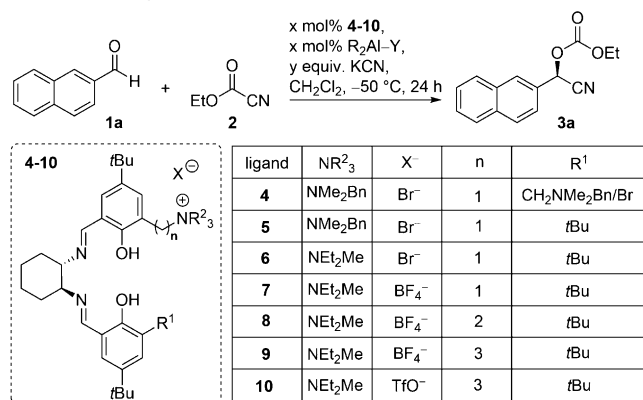
The so far most selective catalyst formed in situ from **9** (X[–] = BF₄[–]) and AlMe₃ proved to be a complex mixture of several species as judged by ¹H-/¹⁹F NMR. Our speculation that a much more active [Al–F] catalyst might have been



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Table 1: Development of the model reaction.

Entry	Ligand (<i>x</i>)	R_2Al-Y	2 (equiv)	γ	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	4 (5.0)	Me ₂ Al-Me	4	0	9	12
2	5 (5.0)	Me ₂ Al-Me	4	0	20	15
3	5 (5.0)	Me ₂ Al-Me	4	2	100	39
4	6 (5.0)	Me ₂ Al-Me	4	2	100	53
5	7 (5.0)	Me ₂ Al-Me	4	2	100	85
6	8 (5.0)	Me ₂ Al-Me	4	2	63	66
7	9 (5.0)	Me ₂ Al-Me	4	2	100	88
8	10 (5.0)	Me ₂ Al-Me	4	2	99	12
9	10 (5.0)	Me ₂ Al-Cl	4	2	99	79
10 ^[c]	9 (5.0)	Me ₂ Al-Me	2	1	100	90
11 ^[c,d]	10 (5.0)	Me ₂ Al-F	2	1	100	90
12 ^[c,d]	10 (1.0)	Me ₂ Al-F	1	0.1	100	92
13 ^[c,d,e]	10 (0.1)	Me ₂ Al-F	1	0.1	100	93
14 ^[c,d]	10 (1.0)	Me ₂ Al-Cl	1	0.1	12	69

[a] Determined by ¹H-NMR of the crude product using an internal standard. [b] Determined by HPLC. [c] The reaction was performed in $CHCl_3$. [d] Preformed catalyst was used. [e] Reaction time: 48 h.

formed in the presence of a BF_4^- counterion through a methyl/fluoride exchange was supported by HR-MS and X-ray crystal structure analysis of one of these species (Figure 1, left), which revealed a dimeric aggregate with an anionic F-Al-F-Al-F axis.

A monomeric {Al-F}OTf salen complex featuring a free coordination site was then synthesized from ligand **10** and Me_2AlF .^[16] X-ray crystal structure analysis (Figure 1, right) and PGSE (Pulsed Gradient Spin Echo) NMR experiments

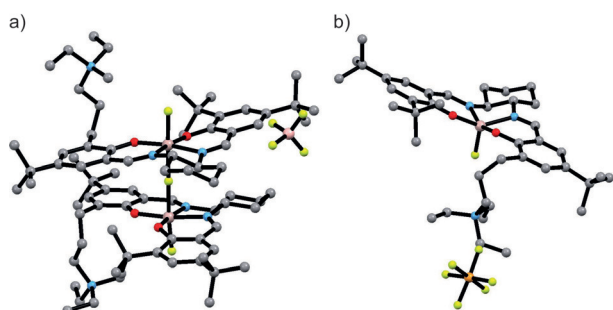


Figure 1. X-ray crystal structure analyses of dimeric $[Al_2F_3]BF_4$ (a) and monomeric $[Al-F]PF_6$ (b) complexes. H atoms, included solvent molecules and a second monomer per unit cell (for (b); see the Supporting Information) are omitted for clarity.

(see the Supporting Information) confirm a monomeric structure for the {Al-F}X complexes.^[17]

{Al-F}OTf provided **3a** in a quantitative yield with good *ee* (entry 11). Its superior performance permitted us to employ a catalytic amount of KCN (0.1 equiv) and obviated the need for an excess of **2**, while at the same time improving the *ee* through a reduced catalyst load (entry 12). A quantitative yield was still obtained with 0.1 mol% of {Al-F}OTf (TON = 1000, entry 13). A comparison of {Al-F}OTf with its Al-Cl counterpart revealed that the latter is much less active (entry 14).

The optimized conditions with a standard {Al-F}OTf loading of 0.1 mol% were applied to various aldehydes (Table 2).^[18] Both σ and π donors on aromatic aldehydes were well tolerated (entries 2, 4–7, 9–11). In the case of an *ortho*-positioned donor, the *ee* was slightly reduced, but the reactivity was still useful to high (entries 6, 9). Substrates bearing σ or π acceptors (entries 8, 12–14), as well as 2-furylcarbaldehyde (entry 15), furnished nearly quantitative yields. The catalyst performance is thus not very sensitive towards electronic effects.

High yields and *ee* values were also attained with enals. With (*E*)-cinnamaldehyde, the product was formed in more

Table 2: Investigation of the substrate scope.

Reaction scheme showing the investigation of the substrate scope. Aldehyde **1** reacts with nitrile **2** in the presence of *x* mol% of {Al-F}OTf, 0.1 equiv. KCN, in $CHCl_3$ at $-50^\circ C$ for *t* to form product **3**.

Structure of {Al-F}OTf is shown as a monomeric complex with a central Al-F-Al-F axis. The ligand consists of two salen-like ligands coordinated to two aluminum centers, which are bridged by fluorine atoms. The ligand has a central nitrogen atom coordinated to the aluminum centers, and a central carbon atom coordinated to the fluorine atoms. The ligand is substituted with tBu groups and a central R^1 group.

Entry	1/3	R-	<i>x</i>	<i>t</i> [h]	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	a	2-naphthyl-	0.1	24	> 99	93
2	b	6-MeO-2-naphthyl-	0.1	24	92	93
3	c	Ph-	0.1	24	99	91
4	d	4-Me-C ₆ H ₄ -	0.1	72	85	88
5	e	3-Me-C ₆ H ₄ -	0.1	48	98	90
6	f	2-Me-C ₆ H ₄ -	0.1	48	99	82
7	g	4-MeO-C ₆ H ₄ -	0.5	72	78	93
8	h	3-MeO-C ₆ H ₄ -	0.1	24	> 99	92
9	i	2-MeO-C ₆ H ₄ -	0.1	48	61	84
10	j	3,4-Me ₂ -C ₆ H ₃ -	0.1	72	74	86
11	k	3,4-(MeO) ₂ -C ₆ H ₃ -	0.5	72	97	96
12	l	4-Cl-C ₆ H ₄ -	0.1	48	> 99	89
13	m	4-F-C ₆ H ₄ -	0.1	48	> 99	89
14	n	3-MeO ₂ C-C ₆ H ₄ -	0.1	48	99	80
15	o	2-furyl-	0.1	48	98	82
16	p	(<i>E</i>)-Ph-CH=CH-	0.1	48	> 99	96
17	q	(<i>E</i>)-4-MeO-C ₆ H ₄ -CH=CH-	0.1	48	90	97
18 ^[c]	r	(<i>E</i>)-Me-CH=CH-	0.1	72	96	94
19 ^[d]	r	(<i>E</i>)-Me-CH=CH-	0.01	72	98	93
20 ^[c]	s	Et-	0.1	72	99	81
21 ^[c]	t	PhCH ₂ CH ₂ -	0.1	72	99	90
22 ^[c]	u	<i>t</i> Bu-	0.1	72	99	78

[a] Yield of isolated product after column chromatography. [b] Determined by HPLC. [c] Reaction in $CH_2Cl_2/CHCl_3$ (1:1) at $-80^\circ C$. [d] 0.05 equiv of KCN.

than 99% yield and in highly enantioenriched form (entry 16). A π donor slightly affected the product yield (entry 17). Moreover, the small, linear γ -acidic crotonaldehyde was well accepted (entry 18). It was shown that even lower catalyst loadings are possible without disturbing the catalyst performance. When using as little as 0.01 mol % of {Al-F}OTf, a highly enantioenriched product was formed in an almost quantitative yield (TON = 9800, entry 19). The method is also applicable to enolizable substrates like propanal and dihydrocinnamaldehyde (entries 20–21), as well as bulky aliphatic substrates like pivaldehyde (entry 22).

To study the preparative value of {Al-F}OTf, gram-scale experiments were conducted using cinnamaldehyde in analogy to Table 2, entry 16. The product was again isolated in quantitative yield and with 96% *ee*. Efficient stirring proved to be essential to maintain high yields, which is ascribed to the phase-transfer catalysis (PTC) character of this reaction. {Al-F}OTf was recovered unchanged (characterized again by ^1H -/ ^{19}F -NMR and HR-MS) in 72% yield through precipitation from the reaction mixture and reused under identical conditions, providing **3p** in 88% yield and with 95% *ee*. The lower yield is ascribed to an incomplete precipitation of the tiny catalyst amount. The catalyst recycling needs to be technically optimized, but the data establish a proof of principle.

Moreover, five additional experiments were conducted on a 200 mg scale at -50°C using 0.1 mol % {Al-F}OTf and almost identical results were obtained as on the 0.1 mmol scale reported in Table 2 [**1a** (72 h): 100%, 93% *ee*; **1c** (72 h): 98%, 91% *ee*; **1e** (48 h): 100%, 90% *ee*; **1p** (72 h): 100%, 96% *ee*; **1q** (72 h): 92%, 96% *ee*].

Control experiments were conducted with the chiral Al salen complex **11**, which lacks an appended ammonium moiety (Table 3).^[19] **11** furnished very small amounts of nearly racemic **3a**, even at high catalyst loadings and working with an excess of **2** and relatively large amounts of KCN (entry 1). By adding [Et₄N]OTf, the reactivity was increased. However, nearly no enantioselectivity was found and the reactivity was much lower than with the bifunctional {Al-F}OTf (entry 2). [Et₄N]OTf also catalyzed the reaction in the absence of **11**, but with decreased activity (entry 3). The results support the essential role of the ammonium moiety in the dual activation catalyst {Al-F}OTf.

Table 3: Control experiments.

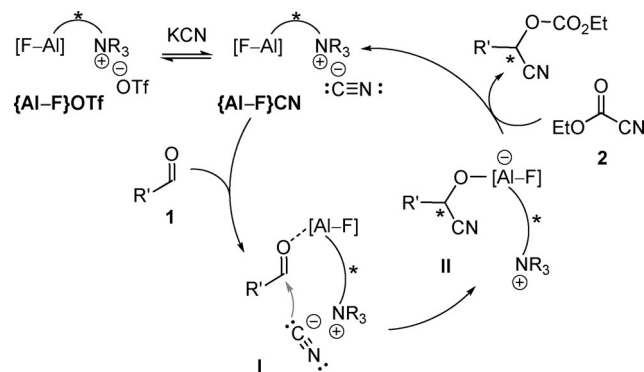
$\text{1a} + \text{2} \xrightarrow[\text{-50 } ^\circ\text{C, 24 h}]{\substack{x \text{ mol\% } \textbf{11}, \\ y \text{ equiv. KCN,} \\ \text{additive, CH}_2\text{Cl}_2}}$

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Entry	<i>x</i>	2 (equiv)	γ (equiv)	additive (mol %)	Yield [%] ^[a]	<i>ee</i> [%] ^[b]
1	5	2.0	0.5	–	12	17
2	0.1	1.0	0.2	[Et ₄ N]OTf (0.1)	31	2
3	–	1.0	0.2	[Et ₄ N]OTf (0.1)	23	–

[a] Determined by ^1H -NMR of the crude product using an internal standard. [b] Determined by HPLC.

Scheme 1 shows a possible mechanism. Addition of KCN likely improves the reactivity by generating {Al-F}CN.^[20,21] **1** is activated through coordination to the Al center, thereby facilitating a quasi-intramolecular attack by cyanide.^[22] Product release and catalyst regeneration are achieved through carboxylation by **2**.



Scheme 1. Possible mechanism.

The superior performance of {Al-F}OTf is ascribed to two factors: increased stability and Lewis acidity. Al-F bonds are among the most stable σ bonds, with reported bond energies of 659–672 kJ mol⁻¹.^[23] This stability is reflected by the high robustness of {Al-F}OTf, which is remarkably stable to water, air (over several months at room temperature), and melted without decomposition (judged by ^1H -/ ^{19}F NMR) at 221 $^\circ\text{C}$. In contrast to the related {Al-Cl} and {Al-Me} catalysts, it can be recovered unchanged after the title reaction.

The Al-F bond was investigated by means of density functional theory (DFT)^[24] and intrinsic bond orbitals (IBOs)^[25] which lead to useful Lewis structures and are appropriate to interpret quantum chemical calculations.^[26] The structurally reduced Al salen complexes **12** were studied to describe the binding situation around the aluminum center for X = F, Cl and Me (Figure 2).

The calculated Al-F distance of 1.69 Å is in very good agreement with the crystal structure (1.688–1.702 Å). The IBO analysis shows that the Al-F σ bond is strongly polarized towards the F atom: only 0.23 of the corresponding bond charge (12%) is located at the Al atom (for Cl 0.38, for Me

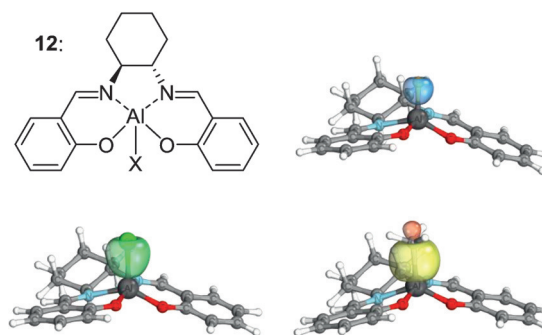


Figure 2. Intrinsic bond orbitals for the Al-X bonds in complexes **12**: top right: Al-F; bottom left: Al-Cl; bottom/right: Al-Me.

0.50). It follows that the Al atom in the Al–F complex possesses a higher partial charge (+1.26) than in the respective Cl and Me complexes (+1.09 and +1.11), thus confirming a higher Lewis acidity. A Mulliken population analysis shows the same trend, as shown in the Supporting Information. This suggests that the Al–F bond is more ionic than the Al–Cl and Al–C bonds. This is supported by the lower Wiberg bond order of 0.58 for the Al–F bond compared to 0.77 and 0.74 for the Al–Cl and Al–C bonds.

In conclusion, we have reported an exceptionally active, broadly applicable catalyst for the asymmetric carboxycyanation of aldehydes, which gives unprecedented TONs of up to around 10^4 . Our results suggest that a Lewis acidic Al center cooperates with an internal ammonium salt moiety. Key for the high efficiency is the Al–F unit. This is explained by 1) a high Lewis acidity as found by DFT studies and 2) a remarkable catalyst stability, which also allows catalyst recovery. As a result of these advantages, [Al–F] catalysts might be of technical interest. To our knowledge, this is the first application of a structurally defined Al catalyst containing an Al–F σ bond in asymmetric catalysis. Even higher enantioselectivity might be possible with alternative catalyst cores. We expect that Al–F catalysts will find wide application.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Al–F bond · cyanide · dual activation · ion pairs · phase transfer catalysis

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