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Asymmetric Carboxycyanation of Aldehydes by Cooperative AlF / Onium Salt Catalysts: from Cyanoformate to KCN as Cyanide Source

Daniel Brodbeck,[a] Sonia Álvarez-Barcia,[b] Jan Meisner,[b] Florian Broghammer,[a] Julian Klepp,[a] Delphine Garnier,[a] Wolfgang Frey,[a] Johannes Kästner,*[b] and René Peters*[a]

Abstract: Asymmetric 1,2-additions of cyanide yield enantioenriched cyanohydrins as versatile chiral building blocks. Next to HCN, volatile organic cyanide sources are usually used. Among them cyanoformates are more attractive on technical scale than TMSCN for cost reasons, but catalytic productivity is usually lower. Here we describe the development of a new strategy for cyanations by which this activity disadvantage is overcome. A Lewis acidic Al center cooperates with an aprotic onium moiety within a bifunctional Al–F-salen complex which is remarkably robust. This allowed for unprecedented TONs of up to 10^4. DFT studies suggest an unexpected unique trimolecular pathway in which the ammonium bound cyanide attacks the aldehyde which itself is activated by the carbonyl group of the cyanoformate binding to the Al center. In addition, a novel practical carboxycyanation method was developed which makes use of KCN as the sole cyanide source. The use of a pyrocarbonate as carboxylating reagent provided the best results.

Introduction

Nucleophilic cyanations of aldehydes are among the most important 1,2-addition reactions and are widely employed both in academic laboratories as well as for technical scale production processes due to the synthetic versatility of chiral cyanohydrine derivatives.[1-3] Industrial scale applications usually make use of enzyme catalyzed additions of hydrogen cyanide.[4,5] Nevertheless, employing HCN bears serious risks due to the combination of its high volatility and toxicity. In academic studies less volatile cyanation reagents such as trimethylsilyl cyanide and ethyl cyanoformate are usually preferred.[2,6,7] These reagents also offer the advantage that O-protected cyanohydrin products less easily undergo a racemization, because the addition reaction becomes irreversible.[Fehler! Textmarke nicht definiert.] However, for many cost-sensitive technical scale applications the use of TMSCN is too expensive in terms of follow-up costs.[8] In this respect, cyanoformates appear to be much more attractive as cyanide source. As an additional benefit, the carboxy groups are not necessarily protecting groups only,[9] but they also served for elegant further transformations like [3,3]-rearrangements and enantiospecific allylic substitutions.[10] Nevertheless, the most attractive cyanide source for a user should be inorganic cyanide salts like KCN, which combines a low price and low volatility. To the best of our knowledge, highly enantioselective catalytic carboxycyanations of aldehydes using KCN as the exclusive cyanide source have, in contrast to acylcyanations,[11] not been reported to date.

A general issue for carboxycyanations has been a significantly lower catalytic activity compared to cyanosilylations,[12,13] thus requiring catalyst loadings in a range of 1-10 mol% for the best reported catalyst systems.[2a] This might be partly explained by catalyst inhibition by the Lewis basic carboxy protective groups. In the development of these latter methods cooperative catalysts emerged which often provided significantly higher enantioselectivity and catalytic activity compared to more traditional catalysts lacking cooperative activation modes.[14-16] Recently, we reported a new strategy for the carboxycyanation of aldehydes to permit unprecedented TONs.[17] In this approach a Lewis acidic Al center cooperates with an internal ammonium salt moiety.[18] The idea behind was that a loosely bound cyanide should be highly reactive in the 1,2-addition step to a Lewis-acid-activated aldehyde.[18] We found that very high catalyst efficiency was enabled by a considerably Lewis-acidic Al–F unit which at the same time leads to an extraordinarily stable catalyst. In this full paper we provide full account of this synthetic development.

Detailed computational studies provided insight into possible reaction mechanisms and revealed that besides the initially anticipated catalytic product formation pathway an unexpected trimolecular pathway might play a role. Furthermore, we present the development and application of a new, operationally attractive method that forms the carboxycyanation product with KCN as the sole cyanide source.

Results and Discussion

1. Development of a Highly Active Carboxycyanation Catalyst using a Cyanoformate as Cyanide Source and Mechanistic Studies

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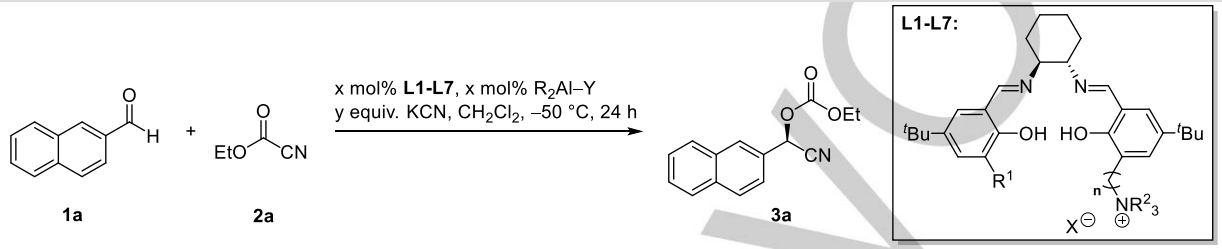
The Al-salen catalysts were formed *in situ* in our early studies using Me_3Al as Al-source and ligands such as **L1**, which were equipped with two ammonium bromide side chains. The solubility of these catalysts is problematic at low temperatures. In CH_2Cl_2 at –50 °C activity and enantioselectivity were low (Table 1, entry 1). Because (1) we were speculating that a competition between both ammonium moieties might take place leading to different enantioface differentiations in the 1,2-addition step and (2) in order to increase the solubility of the complexes, we were then studying catalysts bearing only one ammonium bromide salt side chain.[18d] By that change the solubility issue was successfully addressed. However, the activity was still not useful and the enantioselectivity only marginally improved (entry 2).

Because a cyanide/bromide exchange would be necessary in the ammonium salt moiety to allow for the targeted mechanism, the presence of KCN salt as additive was studied and allowed for quantitative yields and a significant improvement of the enantioselectivity (entry 3).

Table 1. Development of a potent cooperative bifunctional Lewis-acid / onium salt catalyst for the carboxycyanation of aldehydes.



No.	ligand (x)	NR^2_3	X^-	n	R^1	R_2Al-Y	equiv. **2a**	y	yield [%][a]	*ee* [%][b]
1	**L1** (5.0)	NMe_2Bn	Br^-	1	CH_2NMe_2Bn/Br	Me_2Al–Me	4	0	9	12
2	**L2** (5.0)	NMe_2Bn	Br^-	1	^{t}Bu	Me_2Al–Me	4	0	20	15
3	**L2** (5.0)	NMe_2Bn	Br^-	1	^{t}Bu	Me_2Al–Me	4	2	100	39
4	**L3** (5.0)	NEt_2Me	Br^-	1	^{t}Bu	Me_2Al–Me	4	2	100	53
5	**L4** (5.0)	NEt_2Me	BF_4^-	1	^{t}Bu	Me_2Al–Me	4	2	100	85
6	**L5** (5.0)	NEt_2Me	BF_4^-	2	^{t}Bu	Me_2Al–Me	4	2	63	66
7	**L6** (5.0)	NEt_2Me	BF_4^-	3	^{t}Bu	Me_2Al–Me	4	2	100	88
8[c]	**L6** (5.0)	NEt_2Me	BF_4^-	3	^{t}Bu	Me_2Al–Me	2	1	100	90
9	**L7** (5.0)	NEt_2Me	$F_3CSO_3^-$	3	^{t}Bu	Me_2Al–Me	4	2	99	12
10[c,d]	**L7** (5.0)	NEt_2Me	$F_3CSO_3^-$	3	^{t}Bu	**Me_2Al–F**	2	1	100	90
11[c,d]	**L7** (1.0)	NEt_2Me	$F_3CSO_3^-$	3	^{t}Bu	**Me_2Al–F**	1	0.1	100	92
12[c,d,e]	**L7 (0.1)**	NEt_2Me	$F_3CSO_3^-$	3	^{t}Bu	**Me_2Al–F**	**1**	**0.1**	**100**	**93**
13[c,d]	**L7** (1.0)	NEt_2Me	$F_3CSO_3^-$	3	^{t}Bu	Me_2Al–Cl	1	0.1	12	69

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

Further rises in enantioselectivity were achieved by (1) switching to a diethylmethylammonium side arm (entry 4) and (2) by changing to a BF_4^- counterion (entry 5). The last result appeared logical, because cyanide might more easily replace a weakly binding counterion like BF_4^-.

In addition, different $(CH_2)_n$-linkers between the salen core and the onium moieties were used with n = 1-3 (entries 5-7). The best results in terms of enantioselectivity (*ee* = 88%) were obtained for n = 3 (ligand **L6**, entry 7). In contrast, for n = 2 the enantioselectivity was significantly lower (ligand **L5**, entry 6). A catalyst decomposition via β-elimination in the ammonium side arm, forming a resonance stabilized styrene derivative, seems likely. With n = 3 ligand/catalyst decompositions are probably less problematic and despite the high flexibility of the onium arm the attained enantioselectivity was high.

Investigation of various solvents using the catalyst formed *in-situ* from **L6** and Me_3Al revealed $CHCl_3$ to be superior (entry 9). In this case, the relative amounts of **2a** and KCN could be decreased while still allowing a quantitative yield and an improved enantioselectivity (entry 8).

Surprising results were then obtained with complexes of this type carrying a different 'non-nucleophilic' counterion X^-. Replacing BF_4^- by triflate ($F_3CSO_3^-$, OTf^-) in ligand **L7** led to almost racemic product (entry 9).

To find out more about the influence and role of the 'non-nucleophilic' counterions X^- like BF_4^- and triflate, spectroscopic studies were performed. They revealed that the less selective catalyst generated from the triflate containing ligand **L7** and Me_3Al was essentially one defined species. In contrast, the much more selective catalyst formed from the BF_4^- containing ligand **L6** and Me_3Al proved to be a complex mixture consisting of a number of species as judged by $^1H/^{19}F$ NMR. We hypothesized that an {Al–F} catalyst might have been formed in this case which might be much more active. The presumed necessary methyl/fluoride exchange could be supported by HR-MS data. In addition, crystallization attempts allowed to generate single crystals of one of these species, which could be analyzed by X-ray crystallography. This revealed a dimeric aggregate with an anionic F–Al–F–Al–F axis (Figure 1, *top*).[19]

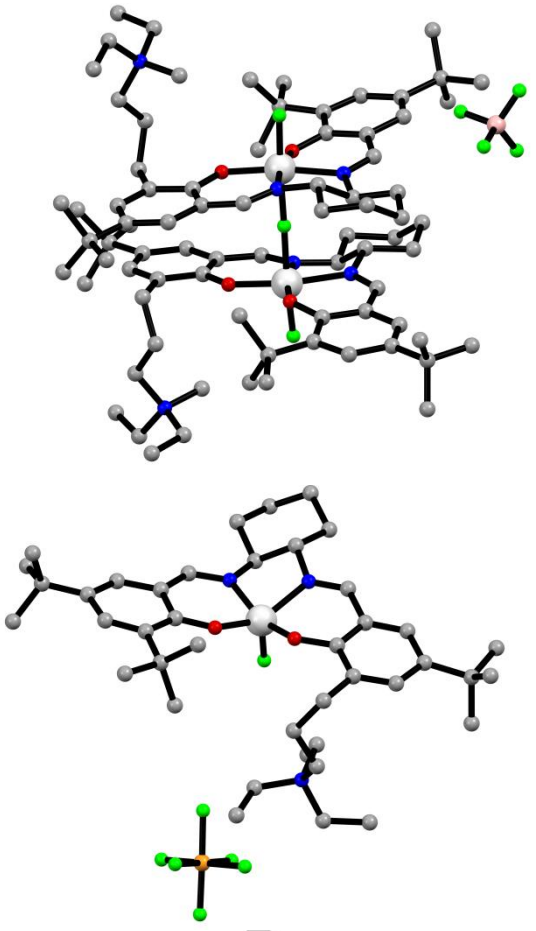


Figure 1. X-ray single crystal structure analyses of **{Al$_2$F$_3$}BF$_4$** (*top*) containing a F–Al–F–Al–F axis and **{Al–F}PF$_6$** (*bottom*). H atoms, included solvent molecules and a second monomer per unit cell (for b), see SI) have been omitted for clarity.

To get a monomeric Al-salen complex containing an Al–F bond, which would offer a free coordination site necessary for catalytic activity, Me_2AlF[20] was prepared and used for complexation to provide the monomeric complex **{Al–F}OTf**.

The solid state structure of the closely related **{Al–F}PF$_6$** could be determined by X-ray single crystal structure analysis.[19] Two different species with different configurations at the stereogenic Al centers were identified in the solid state. Only one of them is depicted in Figure 1, *bottom*. Two different species were also present in chlorinated solvents at room temperature as determined by NMR. The ^{19}F NMR spectra provided 2 signals of the Al coordinated F atoms. The detection of a coalescence in ^1H, ^{13}C and ^{19}F NMR at higher temperatures, leading to one set of signals, is a strong indication of interconversion between the two isomers that is slower than NMR scale. While the two {Al–F} ^{19}F signals merge directly above room temperature ($T_{coalescence}$ (^{19}F) = 303 K) into one broad, temperature-dependent signal, coalescence in ^1H-NMR was observed at much higher temperature ($T_{coalescence}$ (^1H) = 363 K).

PGSE (Pulsed Gradient Spin Echo) NMR experiments[21] performed on both **{Al$_2$F$_3$}** and **{Al–F}OTf** indicate that **{Al$_2$F$_3$}** retains (almost entirely) a dimeric structure in $CHCl_3$, whereas **{Al–F}OTf** is monomeric (the Supporting Information contains the details and results of the NMR experiments).

As hypothesized, the **{Al–F}OTf** catalyst showed a much higher activity than the catalysts prepared from Me_3Al (entries 10-12). For that reason, it was possible to (1) reduce the KCN amounts from stoichiometric to catalytic (10 mol%), (2) to avoid any excess of **2a**, and (3) to reduce the catalyst loading from 5 to 0.1 mol%. Under these conditions the product was still formed in quantitative yield and the *ee* value was improved to 93% (entry 12. The fluoride ligand effect is unique. For instance, the Al–Cl counterpart to **{Al–F}OTf** was found to be much less active and enantioselective (entry 13).

Using **{Al–F}OTf** the reaction scope was then investigated. A catalyst loading of 0.1 mol% was used if not indicated otherwise (Table 2).[22] In general, it can be stated that the catalyst performance is not very sensitive towards electronic effects. Aromatic aldehydes with σ- and π-donors were well tolerated (entries 2, 5-10, 12-13). Donor substituents in *ortho*-positions resulted in a small decrease of the *ee* value, whereas the reactivity was useful to high (entries 7, 12). Nearly quantitative yields were obtained for substrates equipped with σ- or π-acceptor substituents (entries 11, 13-18) as well as with 2-furylcarbaldehyde (entry 19).

The reaction is not limited to aromatic aldehydes. In particular, for enals high yields and enantioselectivities were attained. (*E*)-Cinnamaldehyde gave product **3p** in >99% yield and with 96% *ee* (entry 20). A *p*-OMe group as a π-donor substituent only slightly reduced the reactivity (entry 21). An aromatic substituent in β-position is not crucial. γ-Acidic enals equipped with alkyl residues at the β-C atom work as well. Even the slim crotonaldehyde **1v**, in which steric interaction with the catalysts might be reduced to a minimum, is well accepted (entry 22).

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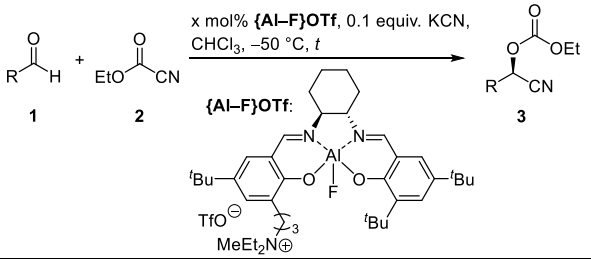
Table 2. Investigation of the substrate scope.



No.	1/3	R	catalyst loading x [mol%]	*t* [h]	yield [%][a]	*ee* [%][b]
1	**a**	2-naphthyl-	0.1	24	>99	93
2	**b**	6-MeO-2-naphthyl-	0.1	24	92	93
3	**c**	1-naphthyl-	0.1	24	80	79
4	**d**	Ph-	0.1	24	99	91
5	**e**	4-Me-C_6H_4-	0.1	72	85	88
6	**f**	3-Me-C_6H_4-	0.1	48	98	90
7	**g**	2-Me-C_6H_4-	0.1	48	99	82
8	**h**	4-*t*Bu-C_6H_4-	0.5	72	51	85
9	**i**	3,4-Me_2-C_6H_3-	0.1	72	83	86
10	**j**	4-MeO-C_6H_4-	0.5	72	78	93
11	**k**	3-MeO-C_6H_4-	0.1	24	>99	92
12	**l**	2-MeO-C_6H_4-	0.1	48	61	84
13	**m**	3,4-$(MeO)_2$-C_6H_3-	0.5	72	97	96
14	**n**	4-Cl-C_6H_4-	0.1	48	>99	89
15	**o**	3-Cl-C_6H_4-	0.1	24	93	79
16	**p**	4-F-C_6H_4-	0.1	48	>99	89
17	**q**	3-F-C_6H_4-	0.1	24	98	78
18	**r**	3-MeO_2C-C_6H_4-	0.1	48	99	80
19	**s**	2-furyl-	0.1	48	98	82
20	**t**	(*E*)-Ph-CH=CH-	0.1	48	>99	96
21	**u**	(*E*)-4-MeO-C_6H_4-CH=CH-	0.1	48	90	97
22[c]	**v**	(*E*)-Me-CH=CH-	0.1	72	96	94
23[d]	**v**	(*E*)-Me-CH=CH-	**0.01**	**72**	>99	**93**
24[c]	**w**	Me-	0.1	48	>99	80
25[c]	**x**	Et-	0.1	72	99	81
26[c]	**y**	*n*Pr-	0.1	72	89	78
27[c]	**z**	$PhCH_2CH_2$-	0.1	72	99	90
28[c]	**za**	*t*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 °C. [d] 0.05 equiv. of KCN.

For crotonaldehyde we studied if a further cutback of the catalyst amount might be still feasible. In fact, the catalyst performance was not disturbed by a catalyst loading of just 0.01 mol% of **{Al–F}OTf**. In that case, a highly enantioenriched product was isolated in quantitative yield, being equivalent to a turnover number of 10000 (entry 23).

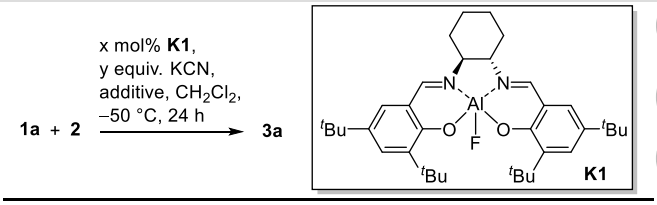
Also, other enolizable substrates such as acetaldehyde **1w**, propanal **1x**, butanal **1y** and dihydrocinnamaldehyde **1z** (entries 24-27), as well as non-enolizable bulky aliphatic substrates like pivaldehyde **1za** (entry 28) are well accommodated. Particularly noteworthy is the *ee* value of 80% attained with the very volatile acetaldehyde **1w**, since *ee* values reported in literature for any kind of asymmetric 1,2-cyanide addition reaction using this substrate were to the best of our knowledge ≤ 45% so far.[23]

A gram scale experiment using cinnamaldehyde **1t** was conducted to demonstrate the preparative value of **{Al–F}OTf**. The reaction was otherwise performed under the conditions described in Table 2, entry 20. **3t** was isolated in quantitative yield and with 96% *ee*. To ascertain a high efficiency, it is crucial to vigorously and continuously stir the reaction mixture. We ascribe this to the phase transfer catalysis (PTC) character of this reaction, in which solid KCN needs to deliver cyanide counterions to form the active species of the catalyst. Another practical benefit is the ease of recycling **{Al–F}OTf** which was recovered unchanged in 72% yield by simple precipitation from the reaction mixture using **1u** as substrate as proven by ^{1}H-/^{19}F-NMR & HR-MS. It was reused under identical conditions giving **3u** in quantitative yield and with 95% *ee*.

Another five reactions were performed on a 200 mg scale under the same conditions. The results were similar to those on the 0.1 mmol scale reported in Table 2 [**1a** (72 h): 100%, 93% *ee*; **1d** (72 h): 98%, 91% *ee*; **1f** (48 h): 100%, 90% *ee*; **1t** (72 h): 100%, 96% *ee*; **1u** (72 h): 92%, 96% *ee*].

Control experiments were performed with the simple chiral Al-salen complex **K1** which is not equipped with an appended ammonium moiety (Table 3). Previously, Jacobsen *et al.* have shown that salen Al-complexes are very efficient catalysts in the cyanation of other substrates than aldehydes.[24]

Table 3. Control experiments.



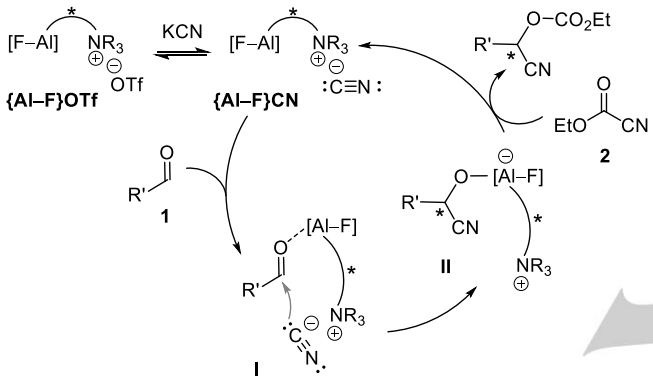
No.	x	equiv. **2**	y (equiv.)	additive (mol%)	yield [%][a]	*ee* [%][b]
1	5	2.0	0.5	-	12	17
2	0.1	1.0	0.2	$[Et_4N]$OTf (0.1)	31	2
3	-	1.0	0.2	$[Et_4N]$OTf (0.1)	23	-

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

Even at high catalyst loadings **K1** gave very small amounts of **3a** with low *ee*, despite working with an excess of **2** and

relatively large amounts of KCN (entry 1). In the presence of $[Et_4N]OTf$ as catalytic additive the reactivity could be increased, but the product was nearly racemic, while the catalytic activity was much lower than with the bifunctional **{Al–F}OTf** (entry 2). $[Et_4N]OTf$ also shows some activity in the absence of **K1** (entry 3). The control experiments thus support the importance of the ammonium moiety in the dual activation catalyst **{Al–F}OTf**.

In Scheme 1 the initially expected mechanism is shown. KCN is probably improving the reactivity by generation of **{Al–F}CN**.[25] The aldehyde substrate **1** could be activated by coordination to the Al center, facilitating a quasi-intramolecular attack of cyanide. The absence of a non-linear effect (see the Supporting Information) is in agreement with a mechanism in which only one catalyst molecule is involved. Product release and catalyst regeneration would be achieved by carboxylation with **2**.



Scheme 1. Initially expected simplified mechanism.

The unique performance of **{Al–F}OTf** is probably also a consequence of its increased stability and *Lewis* acidity compared to other Al-salen complexes. For Al–F bonds bond energies of 659-672 kJ/mol have been reported.[26] They are thus among the most stable σ-bonds. As a consequence, **{Al–F}OTf** exhibits a high robustness. It is remarkably stable against water, against air over several months at room temperature and melted under air without decomposition as judged by $^1H/^{19}F$ NMR at 221 °C. As described above and in contrast to the related **{Al–Cl}** and **{Al–Me}** catalysts it could be recovered unchanged after the title reaction.

2. Computational Investigations

The Al–F bond was studied by means of density functional theory (DFT)[27] and Intrinsic Bond Orbitals (IBOs)[28] which lead to useful Lewis structures and are appropriate to interpret quantum chemical calculations.[29] Structurally simplified Al-salen complexes **K2** were investigated to clarify 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 solid state structure (1.688-1.702 Å). The IBO analysis shows that the Al–F σ-bond is strongly polarized towards the F atom and only 0.23 of the corresponding bond charge (12%) is located at the Al atom. For Cl and Me values of 0.38 and 0.50, respectively, were calculated. As a consequence, the central metal in the Al–F complex possesses a higher partial charge (+1.26) than in the Cl and Me complexes (+1.09 and +1.11, respectively), confirming a higher Lewis acidity. The same trend was found by a Mulliken population analysis as shown in the Supporting Information. The Al–F bond thus has a stronger ionic character than in the Al–Cl and Al–Me bonds. This is in agreement with 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, respectively.

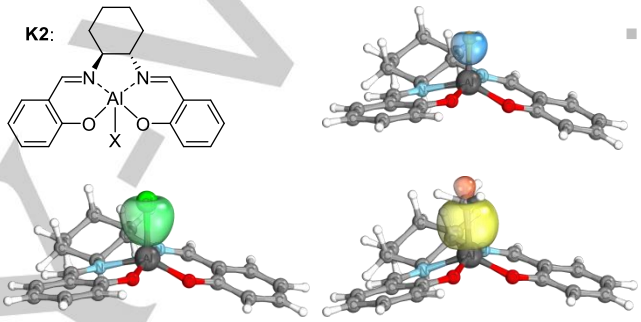
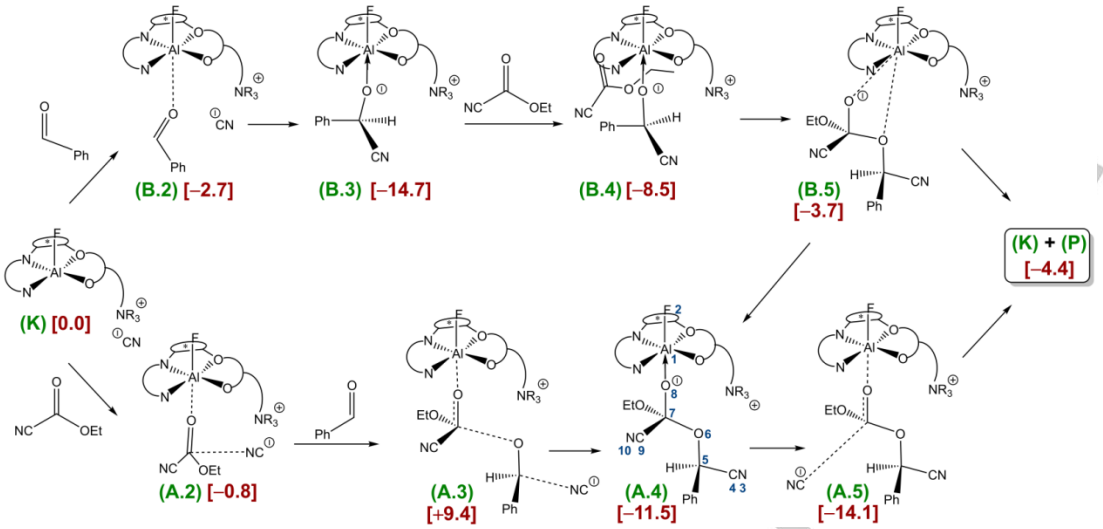


Figure 2. IBOs for the Al–X bonds of complexes **K2**: *top*/*right*: Al–F; *bottom*/*left*: Al–Cl; *bottom*/*right*: Al–Me.

The mechanism was investigated by density functional theory simulations to provide atomistic understanding of the reaction. One of the two diastereomers of the catalyst **AlF{PF_6}** which were identified by X-ray single crystal analysis (Figure 1, *bottom*) was used In combination with benzaldehyde **1d** as substrate. Scheme 2 provides a summary of the most probable reaction paths identified in the simulations (main pathways A and B). The intermediates are labeled consecutively with the respective letter. The catalyst without substrates or reactants is labeled **K** and the product is labeled **P**. Path B is equivalent to the initially assumed simplified mechanism depicted in Scheme 1.[17] Path A is an alternative possible mechanism which was found during the computational studies. Relative free energies at 223 K (–50 ºC) of all intermediates are given in Scheme 2. Additional data (e.g., tables of bond lengths) are provided in the Supporting Information.



Scheme 2. Proposed mechanisms for the carboxycyanation of aldehydes (paths B (*top*) and A (*bottom*)). Relative free energies ΔG(223 K) in kcal/mol with respect to structure **K** are shown in brackets. Important atom numbers for the discussion are depicted in blue.

The energetic profile of the alternative path A is shown in Figure 3 while the calculated 3D structures of intermediates **A.2-A.5** are shown in Figure 4.

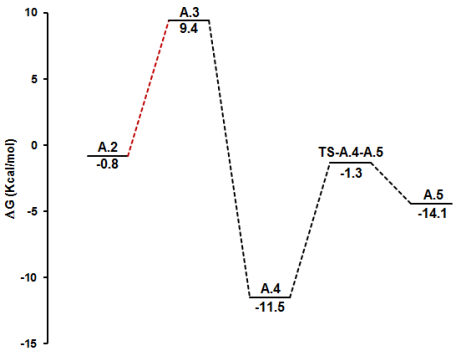


Figure 3. Energy profile of reaction path A. Relative free energies ΔG(223 K) in kcal/mol with respect to structure **K** are given. The red line indicates that a barrierless step is assumed since no bond breaking/formation takes place.

In this path EtO(CO)CN and not the aldehyde coordinates to the catalyst, forming structure **A.2**, in which the carbonyl oxygen weakly interacts with the Al-center ($d(Al_{[1]}\text{-}O_{[8]})$ = 2.97 Å). Cyanide is simultaneously stabilized by the onium moiety ($d(N\text{-}N)$ = 4.17 Å). In the next step, the aldehyde weakly coordinates with its carbonyl oxygen to the carbonyl carbon of EtO(CO)CN to form structure **A.3**. At the same time, a weak coordination of the cyanide anion, which is held in close proximity to the aldehyde by the onium moiety takes place ($d(N_{[3]}\text{-}C_{[5]})$ = 2.72 Å). Since no bonds are broken or formed, it is assumed that this step possesses a negligible barrier, the increase in the free energy is of purely entropic origin. The distance $d(Al_{[1]}\text{-}O_{[8]})$ = 2.32 Å in structure **A.3** is rather large. In the barrierless and exothermic (20.9 kcal/mol) transition to the tetrahedral intermediate **A.4**, the attack of the cyanide at the aldehyde creates the stereocenter.

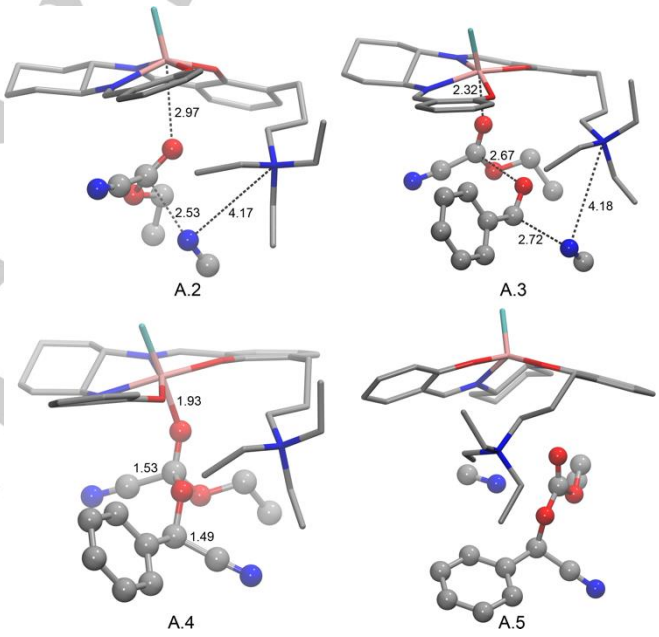


Figure 4. Geometries of the intermediates of path A. Hydrogen atoms are omitted for clarity. Distances are indicated in Å.

In this concerted trimolecular reaction, the aldehyde is cyanated ($d(C_{[4]}\text{-}C_{[5]})$ = 1.49 Å in **A.4**) and the adduct simultaneously undergoes a protection reaction with EtO(CO)CN which is facilitated by the catalyst. In **A.4**, the resulting product is strongly bound to the catalyst ($d(Al_{[1]}\text{-}O_{[8]})$ = 1.93 Å).
By overcoming a barrier of 10.2 kcal/mol during the elimination of a cyanide anion from the tetrahedral intermediate ($d(C_{[7]}\text{-}C_{[9]})$ = 2.76 Å), structure **A.5** ($d(Al_{[1]}\text{-}O_{[8]})$ = 4.11 Å, $d(C_{[4]}\text{-}C_{[5]})$ = 1.48 Å) is formed, in which the product **P** is only weakly

bound to the Al-center. Product release requires a free energy of 9.8 kcal/mol.

In path B (Scheme 2, *top* and Figures 5 and 6), the aldehyde initially weakly coordinates to the Al-center, forming structure **B.2** (d($Al_{[1]}$-$O_{[8]}$) = 2.90 Å).

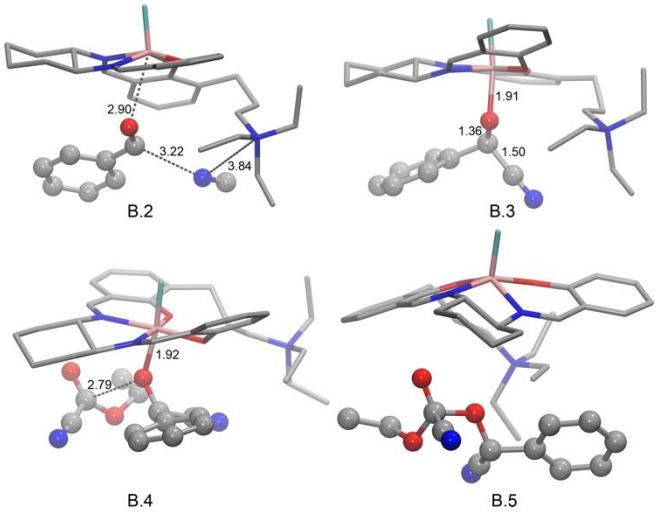


Figure 5. Geometries of the intermediates of path B. Hydrogen atoms are omitted for clarity. Distances are indicated in Å.

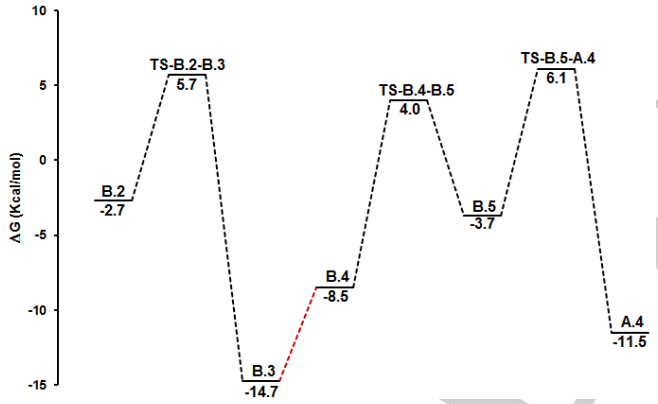


Figure 6. Energy profile of reaction path B. Relative free energies Δ*G*(223 K) in kcal/mol with respect to structure **K** are given. The red line indicates that a barrierless step is assumed since no bond breaking/formation takes place. A connection between B.5 and A.4 is also shown.

The activated aldehyde is subsequently attacked by a cyanide anion which is stabilized at the onium moiety, forming structure **B.3** by overcoming a barrier of 8.4 kcal/mol. In structure **B.3**, the tetrahedral intermediate is coordinating to the Al-center via the oxygen with a bond length d($Al_{[1]}$-$O_{[6]}$) = 1.91 Å. For a subsequent reaction with EtO(CO)CN, the cyanation product might have to leave the metal center. It is questionable how stable the anionic addition product is at low temperatures and how fast it will undergo the reverse reaction to form the aldehyde via elimination of a cyanide anion. A stabilizing role of onium moieties for anionic reaction intermediates in the copolymerization of CO_2 and propylene oxide to form polycarbonates has already been postulated in the literature.[30] The authors proposed that a growing, anionic carbonate chain is cleaved from the catalyst's Co center after each propagation step and is held in constant proximity of the Lewis acid by Coulomb interactions with an onium moiety. In our system, a favored cleavage of the anionic addition product and stabilization at the positively charged onium moiety would in principle be possible. However, no such structure could be optimized, even when EtO(CO)CN is in close proximity to the Al-center, as in structure **B.4**. The association of EtO(CO)CN to the adduct to form **B.4** is favored and enthalpically barrierless. The rising free energy is of purely entropic origin. The nucleophilic attack of the addition product at EtO(CO)CN yields structure **B.5** which is 4.8 kcal/mol higher in energy via an endergonic step with a calculated reaction barrier of 12.5 kcal/mol. Thus, the formation of **B.5** from **B.4** and **B.3** constitutes the rate-determining step, with an estimated barrier of 18.7 kcal/mol. In **B.5**, the tetrahedral intermediate leading to product **P** is already detached from the Al-center (d($Al_{[1]}$-$O_{[6]}$) = 4.71 Å, d($Al_{[1]}$-$O_{[8]}$) = 4.41 Å), which explains the increase in energy despite the formation of a σ-bond. By elimination of a cyanide anion the final product **P** is formed. A possible reaction path connecting **B.5** to **A.4** was identified using the NEB approach (nudged elastic band), exhibiting an estimated barrier of 9.8 kcal/mol relative to **B.5**.

In summary, the computational investigations yield the following information. In pathway A, the estimated rate-limiting barrier (10.2 kcal/mol) is significantly lower than the one for pathway B (18.7 kcal/mol). However, the enantioface differentiation in pathway A is influenced only in the periphery by the sterical and electrostatic constraints of the enantioselective catalyst. It is possible that in complex **A.2** a chiral pocket is created via the catalyst's core, the onium moiety and EtO(CO)CN (see Figure 4). The substrate may preferably enter this pocket in only one orientation, which allows for an enantioselective reaction (structure A.3). Surprisingly, for pathway B no structures could be optimized in which the catalyst-internal onium moiety favors the cleavage of the anionic addition product from the Al-center by Coulomb interactions. It is unclear how stable the deprotonated cyanohydrin is at low temperatures and if the latter would rapidly decay to the aldehyde and a cyanide anion after detachment from the catalyst. The control experiments (Table 3), however, showed that the presence of an internal onium moiety is essential for both high activity and selectivity in the presented carboxycyanation reactions. The absence of an NLE is in agreement with both paths A and B.

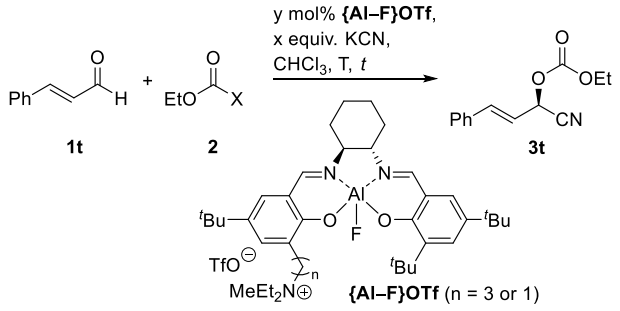
3. Development of a Synthetic Protocol with KCN as the Sole Cyanide Source

As shown above (see subchapter 1.), the presence of solid KCN in catalytic amounts was essential for a high catalytic efficiency in the first-generation carboxycyanation protocol. It is likely that the ammonium moiety acts as a phase transfer catalyst transporting cyanide anions into solution. Nevertheless, this anion exchange could not be confirmed spectroscopically. Even

using $K^{13}CN$ for the anion exchange, a cyanide anion was not detected by ^{13}C NMR. Also, by IR this exchange could not be verified. Probably the equilibrium between the corresponding ammonium triflate and ammonium cyanide is far on the side of ammonium triflate.[31] For that reason, the triflate containing catalyst could be recovered above in pure form after its use.

On the other hand, the fact that excellent results were only obtained in the presence of KCN pointed to the possibility of employing KCN as the exclusive cyanide source, thus avoiding any volatile and thus particularly hazardous organic cyanation reagents.[11] In addition, the use of KCN would be economically attractive. Table 4 summarizes the development of such a protocol.

Table 4. Development of a protocol with KCN as the sole cyanide source.



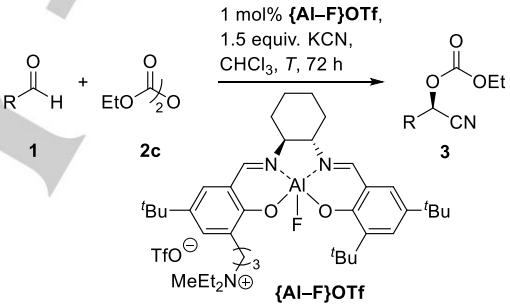
No.	**2** (equiv.)	X	x	y	n	*T* [°C]	*t* [h]	yield [%][a]	*ee* [%][b]
1	**2b** (2.0)	Cl	2.0	0.1	3	–50	72	44	69
2	**2b** (2.0)	Cl	4.0	0.1	3	–50	72	75	40
3	**2c** (2.0)	O(CO)OEt	2.0	0.1	3	–50	48	96	86
4	**2c** (2.0)	O(CO)OEt	2.0	1.0	3	–50	72	92	90
5	**2c** (1.0)	O(CO)OEt	1.0	1.0	3	–50	48	64	83
6	**2c** (2.0)	O(CO)OEt	1.1	1.0	3	–40	72	99	91
7	**2c** (4.0)	**O(CO)OEt**	**1.5**	**1.0**	**3**	**–60**	**72**	**100**	**92**
8	**2c** (4.0)	O(CO)OEt	1.5	1.0	1	–60	72	89	87

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

Initial studies were performed with chloroformate **2b**. In the presence of 0.1 mol% of the standard **{Al-F}OTf** catalyst and an excess of KCN and **2b** (each 2.0 equiv.) the product was slowly formed at –50 °C with moderate enantioselectivity (entry 1). A larger KCN excess led to a higher yield at the cost of an erosion of enantioselectivity (entry 2). Much more interesting results were obtained with diethyl pyrocarbonate **2c**, which delivers the same stable products as with the previous protocol. Under the conditions of entry 1 with 0.1 mol% of **{Al-F}OTf** the product was formed in nearly quantitative yield and with promising enantioselectivity (*ee* = 86%, entry 3). Slightly better enantioselectivity was attained with 1.0 mol% of catalyst (*ee* = 90%, entry 4). Avoiding an excess of both the carboxylating reagent and KCN had a negative influence on activity and enantioselectivity (entry 5). On the other hand, an almost quantitative yield and high enantioselectivity could also be achieved with just 1.1 equiv. of KCN at –40 °C (entry 6). The highest *ee* value of 92% was obtained at –60 °C with 1.5 equiv. of KCN and 4.0 equiv. of **2c** (entry 7). Interestingly, using these conditions but NaCN instead, only trace amounts of product were formed. Noteworthy from a practical point of view is also the result shown in entry 8 with an **{Al-F}OTf** catalyst in which the salen core and the ammonium moiety are linked by only one methylene group (rather than three in the standard catalyst), because this catalyst is more rapidly and easily synthesized.

The conditions of Table 4, entry 7 were then selected to investigate the substrate scope (Table 5).

Table 5. Investigation of the substrate scope of the second-generation carboxycyanation protocol.



No.	**1/3**	R	*T* [°C]	yield [%][a]	*ee* [%][b]
1	**a**	2-naphthyl-	–60	96	93
2	**b**	6-MeO-2-naphthyl-	–60	93	93
3[c]	**d**	Ph-	–60	92	88
4[c]	**e**	4-Me-C_6H_4-	–80	85	90
5	**f**	3-Me-C_6H_4-	–60	98	91
6	**g**	2-Me-C_6H_4-	–60	>99	82
7	**i**	3,4-Me_2-C_6H_3-	–60	98	90
8	**j**	4-MeO-C_6H_4-	–60	99	93
9	**k**	3-MeO-C_6H_4-	–60	>99	85
10	**l**	2-MeO-C_6H_4-	–60	>99	90
11	**m**	3,4-$(MeO)_2$-C_6H_3-	–60	90	96
12	**n**	4-Cl-C_6H_4-	–60	>99	89
13	**o**	3-Cl-C_6H_4-	–60	>99	80
14	**p**	4-F-C_6H_4-	–60	>99	91

15	**r**	3-MeO_2C-C_6H_4-	–60	92	82
16 [c]	**s**	2-furyl-	–80	93	90
17	**s'**	2-thiophenyl-	–60	91	80
18	**t**	(*E*)-Ph-CH=CH-	–60	>99	92
19	**u**	(*E*)-4-MeO-C_6H_4-CH=CH-	–60	99	93
20 [d]	**v**	(*E*)-Me-CH=CH-	–60	90	95
21 [e]	**v**	(*E*)-Me-CH=CH-	–60	81	94
22	**w**	Me-	–60	>99	55
23 [c]	**z**	$PhCH_2CH_2$-	–80	95	69

[a] Yield of isolated product after column chromatography. [b] Determined by HPLC. [c] Reaction in CH_2Cl_2/$CHCl_3$ (1:1). [d] 0.5 mol% of catalyst was used. [e] 0.1 mol% of catalyst was used.

Overall, it can be stated that the results and tendencies are similar to the first-generation approach presented above, albeit the activity is somewhat lower than using ethyl cyanoformate. It is possible that $EtOCO_2^-$ and/or EtO^- (formed by decarboxylation temporarily inhibit the Al center. In addition KCN is an almost insoluble solid, whereas the cyanoformate is completely dissolved. Naphthyl derivatives (entries 1-2), benzaldehyde (entry 3), aromatic aldehydes carrying alkyl groups as σ-donors (mono and disubstituted, entries 4-7, respectively), π-donors (entries 8, 10, 11), σ-acceptors (entries 9, 11-15) and π-acceptors (entry 15) were all well accepted. As before, *ortho*-substituted substrates yielded slightly lower enantioselectivities (entries 6, 10). Also, heteroaromatic substrates were tolerated (entries 16-17) and even higher enantioselectivities could be attained than with the first-generation protocol. With enals like *trans*-cinnamaldehyde or -crotonaldehyde a similar efficiency was found for both protocols (entries 18-21). For crotonaldehyde we demonstrated that a high catalytic efficiency is maintained with reduced catalyst loadings. For instance, with a reduced catalyst loading of 0.1 mol% a yield of 81% and 94% *ee* was obtained (entry 21).

In contrast to aromatic aldehydes and enals, aliphatic substrates were less well accommodated in terms of enantioselectivity, whereas the product yields were still high to excellent (entries 22-24).

Conclusions

We have developed an exceptionally active and broadly applicable bifunctional dual activation catalyst for the asymmetric carboxycyanation of aldehydes. This catalyst allowed for unprecedented turnover numbers of up to 10^4. Control experiments suggest that a Lewis acidic Al–F center cooperates with an internal ammonium salt moiety. The necessity of the fluoride ligand for exceptional activity is explained by an increased Lewis acidity as found by DFT studies and a noteworthy catalyst stability, which is unprecedented for Al-salen complexes and allowed for catalyst recovery and reuse. This appears to be the first application of a structurally defined Al catalyst containing the extraordinarily strong Al–F σ-bond in asymmetric catalysis.

DFT studies also suggest that the initially assumed mechanism, in which the aldehyde substrate is activated by the Al center and subsequently attacked by an ammonium bound cyanide ion might be more difficult to realize than an alternative trimolecular pathway, in which the ammonium-bound cyanide attacks the aldehyde which itself is activated by the carbonyl group of the cyanoformate, whereas the latter is activated by the Al center. The originally assumed pathway seems to suffer from an energetically difficult carboxylation step.

Finally, a very practical carboxycyanation protocol was developed, which avoids the necessity of volatile organic and thus more dangerous cyanation reagents, making use of KCN as the exclusive cyanide source. This reagent, an inexpensive bulk chemical in salt form with low volatility, is very attractive for large scale applications. The use of a pyrocarbonate as carboxylation reagent provided the best results which are comparable to the first-generation approach in terms of yield and enantioselectivity.

Experimental Section

Computational Details. Geometries were optimized with density functional theory (DFT) using the functional M06-2X[32] and the basis set def2-SVP.[33] Frequencies were calculated at the same level. At fixed geometries, the energy was calculated using DLPNO-CCSD(T)/cc-pVTZ[34] and the solvation was accounted for using the COSMO solvation model[35] with $\varepsilon = 8.93$ (DCM as solvent) in combination with the augmented def2-SVPD basis set.[36] All geometry optimizations and the free-energy calculations using the rigid rotor, harmonic oscillator approximation at 223 K were performed in DL-FIND[37] in Chemshell,[38] DFT calculations were performed in Turbomole,[39] CCSD(T) calculations in Orca.[40] More details to the computational protocol are given in the Supporting Information.

General Procedure for the Formation and Isolation of Al–F-Salen-Catalysts (GP A)

Under a nitrogen atmosphere a Schlenk tube was charged with the respective ligand **L** (1.0 equiv.), which was dissolved in $CHCl_3$. A solution of dimethylaluminum fluoride[20] in toluene (2.53 M, 1.0 equiv.) was added dropwise and the resulting solution was stirred for 18 h at room temperature. The solvent was removed under reduced pressure and the residue was washed several times with *n*-pentane or an *n*-pentane/CH_2Cl_2 mixture.

General Procedure for the *In-Situ*-Formation of Al-Salen-Catalysts (GP B)

Under a nitrogen atmosphere a Schlenk tube was charged with the respective ligand **L** (1.0 equiv.), which was dissolved in the respective solvent solvent. A solution of the respective aluminum source (1.0 equiv., in the same solvent) was added dropwise and the resulting solution was stirred for 3 h at room temperature. The *in situ* formed catalysts were directly used without further purification.

General Procedure for the Asymmetric Carboxycyanation of Aldehydes Using EtO(CO)CN (GP C)

Catalyst **{Al–F}OTf** (2.05 mM in 1,2-dichloroethane, 0.1 mol%, 0.10 μmol, 0.08 mg, 49 μL) and KCN (0.1 equiv., 0.01 mmol, 0.7 mg) were placed in a Schlenk tube under a nitrogen atmosphere. $CHCl_3$ (0.2 mL) was added and the mixture was stirred for 10 min at room temperature. Then the solution was cooled to −50 °C. The respective aldehyde **1** (1.0 equiv., 0.10 mmol) was added as a solid or via syringe and flushed down with $CHCl_3$ (0.2 mL). EtO(CO)CN **2a** (1.0 equiv., 0.10 mmol, 10.0 mg, 10 μL) was added via syringe and the mixture was stirred for 24 h at −50 °C. The reaction mixture was filtered over a short pad of silica gel (petroleum ether/ethyl acetate 9:1) and the solvent was removed under reduced pressure to yield the respective cyanation product **3**.

General Procedure for the Asymmetric Carboxycyanation of Aldehydes Using KCN and $(EtO(CO))_2O$ (GP D)

Catalyst **{Al–F}OTf** (1.0 mol%, 4.00 μmol, 3.3 mg) and KCN (1.5 equiv., 0.60 mmol, 39.1 mg) were placed in a Schlenk tube under a nitrogen atmosphere. $CHCl_3$ (0.2 mL) was added and the mixture was stirred for 10 min at room temperature. Then the solution was cooled to −60 °C. The respective aldehyde **1** (1.0 equiv., 0.40 mmol) was added as a solid or via syringe and flushed down with $CHCl_3$ (0.2 mL). $(EtO(CO))_2O$ **2c** (4.0 equiv., 1.60 mmol, 267.5 mg, 243 μL) was added via syringe and the mixture was stirred for 72 h at −60 °C. The reaction mixture was filtered over a short pad of silica gel (DCM) and the solvent was removed under reduced pressure to yield the respective cyanation product **3**.

Preparation of (*R*,*E*)-1-Cyano-3-phenylallyl Ethyl Carbonate 3t with KCN and EtO(CO)CN on a 1 g Scale (GP C)

Compound **3t** was prepared according to GP5 using *trans*-cinnamaldehyde **1t** (1.0 equiv., 7.34 mmol, 1.00 g, 0.95 mL), $CHCl_3$ (29.4 mL), catalyst **{Al–F}OTf** (0.1 mol%, 7.34 μmol, 5.96 mg), KCN (0.1 equiv., 0.73 mmol, 47.80 mg) and EtO(CO)CN **2a** (1.0 equiv., 7.34 mmol, 734.67 mg, 733 μL) at −50 °C during a reaction time of 72 h to yield **3t** (7.32 mmol, 1.69 g, 100%, 96% *ee*) as a colorless oil.

Catalyst Recycling

The reaction mixture was transferred to a flask filled with 100 mL *n*-pentane at −50 °C. The resulting mixture was filtered over cotton and further washed with *n*-pentane. Flushing down with DCM and evaporation of the solvent yielded **{Al–F}OTf** (72%) in unchanged form (characterized again by ^1H and ^{19}F NMR, HR-MS).

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Keywords: Al–F σ-bond • bifunctional catalysis • nitriles • salen • trimolecular reaction

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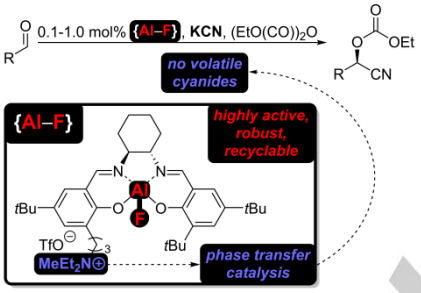
FULL PAPER

Trimolecular? The evolution of a robust, highly active catalyst for asymmetric aldehyde cyanations is reported, which in the final synthetic protocol uses inorganic KCN instead of volatile organic cyanation reagents. DFT studies for the initial protocol using a cyanoformate reagent suggest a unique trimolecular reaction pathway.



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Asymmetric Carboxycyanation of Aldehydes by Cooperative AlF-/Onium Salt Catalysts: from Cyanoformate to KCN as Cyanide Source