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Dual Lewis Acid−Lewis Base Activation in Enantioselective Cyanation of Aldehydes Using Acetyl Cyanide and Cyanoformate as Cyanide Sources

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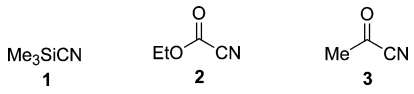
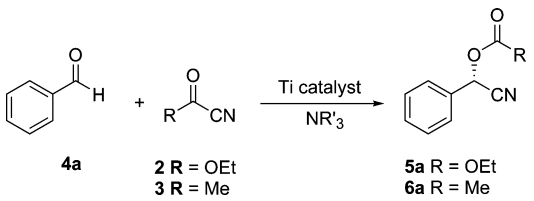
Enantiomerically pure cyanohydrins serve as highly versatile synthetic building blocks.[1] Much effort has, therefore, been devoted to the development of catalytic systems for enantioselective cyanation of aldehydes and prochiral ketones.[2]



Trimethylsilyl cyanide (**1**) has most commonly been used as the source of cyanide ions. Due to its toxicity and high price, access to alternative cyanation reagents is desirable. Particularly useful are reagents providing direct access to O-functionalized derivatives, which themselves are important synthetic targets.[1b] Addition of cyanoformic esters (**2**) to aldehydes, affording O-alkoxycarbonyl-functionalized cyanohydrins, has been achieved together with binol-[3] and salen-based[4] catalysts, as well as in the presence of inorganic bases[5] and Lewis bases,[6] although in the latter case, large amounts of catalyst and prolonged reaction times are often required. Acetyl cyanide (**3**), affording O-acetylated cyanohydrins, has so far not been used for enantioselective cyanation of aldehydes, although nonselective reactions in the presence of potassium carbonate[5] and using DABCO[7] or tributyltin cyanide[8] as catalyst[9] have been reported.

Scheme 1



Being interested in having access to enantioenriched O-acetylated cyanohydrins, we decided to study the reaction of benzaldehyde and **3** in the presence of **7**, known to afford cyanation products of high enantiomeric purity from both trimethylsilyl cyanide and cyanoformic esters.[10] No reaction occurred between **3** and benzaldehyde at −40 °C when **7** alone was used as catalyst, however, and at room temperature, only a slow unselective reaction took place (entries 1 and 2, Table 1).

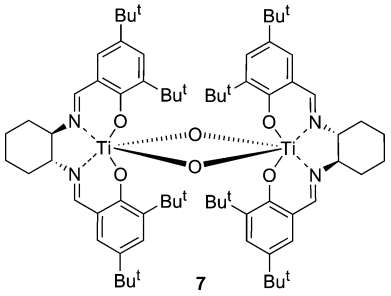
Simultaneous Lewis acid activation of an electrophile and Lewis base activation of a nucleophile have been achieved in cyanations employing silyl cyanide and cyanoformic esters[3,11] as well as in other types of catalytic processes.[12] We decided to explore whether dual Lewis acid−Lewis base activation would improve the reactivity of **3**. Gratifyingly, we found that in the presence of DMAP, the reaction proceeded smoothly to give the product with 94% ee after 6 h at −40 °C (entry 3). Increasing the amount of DMAP (entries 4 and 5) or the temperature (entries 6 and 7) resulted in increased rates, but in the latter case in a decrease in enantioselectivity. Lowering the amount of **3** resulted in a slower reaction (entry 8).

Table 1. Cyanation of Benzaldehyde with **3** Catalyzed by **7** in the Presence of Lewis Bases

entry	% **7**	Lewis base (%)	equiv of **3**	*T* (°C)	time (h)	% conv[a]	% ee (*S*)[b]
1	5		2	−40	24	0	n.d.
2	5		2	25	24	30	53
3	5	DMAP (10)	2	−40	6	57	94
4	5	DMAP (15)	2	−40	6	67	91
5	5	DMAP (20)	2	−40	6	76	91
6	5	DMAP (10)	2	−10	6	78	89
7	5	DMAP (10)	2	25	4	97	67
8	5	DMAP (10)	1	−10	6	63	90
9	5	DABCO (10)	2	−40	9	67	92
10	5	Et_3N (10)	2	−40	8	96	94
11	5	DIEA (10)	2	−40	8	97	81
12	5	sparteine (10)	2	−40	8	93	65
13	5	cinchonidine (10)	2	−40	9	78	96
14	5	quinine (10)	2	−40	9	80	92
15	5[c]	sparteine (10)	2	−40	8	96	−67
16	5[c]	cinchonidine (10)	2	−40	9	75	−92
17	5[c]	quinine (10)	2	−40	9	73	−95

[a] Determined by GC−MS. [b] Determined by chiral GC. [c] *ent*-**7** was used.

The activation by different achiral and chiral Lewis bases was then studied. Activation by DABCO, Et_3N, diisopropylethylamine (DIEA), and sparteine was effective, but the use of DIEA and sparteine led to decreased selectivities (entries 9−12). Use of chiral bases had little effect on the enantioselectivity (entries 13 and 14), and consequently, replacement of **7** with *ent*-**7** had no larger influence on the reaction outcome (entries 15−17).



Reaction with only base as catalyst resulted in low conversion and for the chiral bases low enantioselectivity, demonstrating that dual activation is required for the reaction to proceed efficiently (Table 2).

With these results in hand, we decided to study the effect of Lewis bases in the reaction of ethyl cyanoformate with benzaldehyde catalyzed by **7**, which is normally a quite sluggish reaction requiring 18 h reaction time at −42 °C.[4] In the presence of 10 mol % of DMAP, the reaction of benzaldehyde with 2 equiv of **2** catalyzed by 5 mol % of dimer **7** occurred smoothly within 4 h at −40 °C, with only a minor loss in selectivity (from 95 to 93% ee, entries 1 and 3, Table 3). Increasing the amount of DMAP allowed the reaction time to be further reduced, at the expense of a slight loss in enantiomeric excess (entries 4 and 5). The presence of

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Table 2. Cyanation of Benzaldehyde with **3** Catalyzed by Lewis Bases[a]

entry	Lewis base (%)	equiv of **3**	time (h)	% conv[b]	% ee (*S*)[c]
1	DMAP (10)	2	8	<1	
2	DABCO (10)	2	8	<1	
3	Et_3N (10)	2	8	13	
4	DIEA (10)	2	8	16	
5	sparteine (10)	2	8	23	0
6	cinchonidine (10)	2	8	9	40
7	quinine (10)	2	8	2	15

[a] All reactions were run at −40 °C. [b] Determined by GC−MS. [c] Determined by chiral GC.

Table 3. Cyanation of Benzaldehyde with **2** Catalyzed by **7** in the Presence of Lewis Bases at −40 °C

entry	% **7**	Lewis base (%)	equiv of **2**	time (h)	% conv[b]	% ee (*S*)[c]
1[a]	5		2	18	100	95
2[a]	1		2	19	100	83
3	5	DMAP (10)	2	4	99	93
4	5	DMAP (15)	2	3	96	91
5	5	DMAP (20)	2	2	93	86
6	1	DMAP (2)	2	8	78	95
7	5	DMAP (10)	1.2	8	95	94
8	5	DABCO (10)	1.2	7	90	90
9	5	Et_3N (10)	1.2	3	97	92
10	5	DIEA (10)	1.2	3	96	89
11	5	sparteine (10)	1.2	3	98	78
12	5	cinchonidine (10)	1.2	4	98	94
13	5	quinine (10)	1.2	4	93	93
14	5[d]	sparteine (10)	1.2	3	98	−79
15	5[d]	cinchonidine (10)	1.2	7	93	−94
16	5[d]	quinine (10)	1.2	7	97	−94

[a] Reactions were run at −42 °C. [b] Determined by GC−MS. [c] Determined by chiral GC. [d] *ent*-**7** was used.

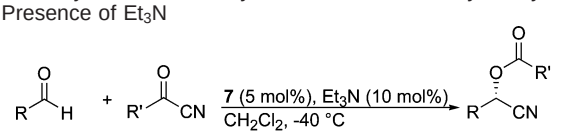
DMAP (2 mol %) in reactions using 1 mol % of **7** resulted in a product with higher enantiomeric excess (entries 2 and 6). Use of 5 mol % of catalyst, 10 mol % of DMAP, and a smaller excess, 1.2 equiv, of cyanoformate afforded 95% conversion and 94% ee within 7 h (entry 7).

Et_3N and DIEA were found to give essentially quantitative reactions within 3 h, with only minor decrease in selectivity (entries 9 and 10), whereas sparteine exhibited high reactivity but lower enantioselectivity (entry 11). The use of other chiral bases did not offer any major advantages (entries 12 and 13). Replacement of **7** by *ent*-**7** had only a marginal effect on the selectivity but resulted in slower reactions in the case of cinchonidine and quinine (entries 15 and 16).

Triethylamine was selected for further studies since it provided the product with high conversion and enantioselectivity. A variety of aromatic and aliphatic aldehydes were subjected to cyanation by both **2** and **3** using the combination of **7** and Et_3N. The results are summarized in Table 4. In all cases, the reaction readily took place giving O-protected cyanohydrins with high enantioselectivities and in high isolated yields.

The present methodology provides direct access to enantioenriched O-alkoxycarbonylated (**5**) and O-acetylated (**6**) cyanohydrins, which are important synthetic targets.[1b] The latter type of compounds are also accessible by the use of potassium cyanide and **7** in the presence of a trapping agent, such as an anhydride.[13] In our hands, this procedure, using the Ti−salen catalyst system, was less clean, resulting in the formation of several byproducts in addition to 1 equiv of potassium acetate. In contrast, higher selectivity and essentially quantitative conversion without formation of byproducts as well as perfect atom economy were achieved using our new dual activation protocol. In this case, a catalytically formed acetylated Lewis base probably serves as acetylating agent. The catalytic system employed, with the Lewis acidic and Lewis basic sites residing in different molecules, allows facile structural variations and, thereby, tuning of the catalytic properties. The scope and mechanism of this new dual Lewis acid−Lewis base activation are under investigation.

Table 4. Cyanation of Aldehydes with **2** and 3 Catalyzed by **7** in the Presence of Et_3N



4 **2** R' = OEt, **3** R' = Me → **5** R' = OEt, **6** R' = Me

entry		aldehyde (R)	**2**/**3**	product	time (h)	% yield[a]	% ee[b]
1	**4a**	Ph	**2**	**5a**	4	95	92
2	**4a**	Ph	**3**	**6a**	10	89	94
3	**4b**	4-CH_3−C_6H_4	**2**	**5b**	6	88	94
4	**4b**	4-CH_3−C_6H_4	**3**	**6b**	10	90	96
5	**4c**	4-CH_3O−C_6H_4	**2**	**5c**	6	79	94
6	**4c**	4-CH_3O−C_6H_4	**3**	**6c**	12	72	94
7	**4d**	4-Cl−C_6H_4	**2**	**5d**	4	90	93
8	**4d**	4-Cl−C_6H_4	**3**	**6d**	8	89	95
9	**4e**	(*E*)-PhCH═CH	**2**	**5e**	7	97	93
10	**4e**	(*E*)-PhCH═CH	**3**	**6e**	12	64	93
11	**4f**	$(CH_3)_3C$	**2**	**5f**	5	81	73
12	**4f**	$(CH_3)_3C$	**3**	**6f**	6	84	76
13	**4g**	$CH_3(CH_2)_4$	**2**	**5g**	5	83	89
14	**4g**	$CH_3(CH_2)_4$	**3**	**6g**	6	89	90

[a] Isolated yield. [b] Determined by chiral GC.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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