Enantioselective Cyanoformylation of Aldehydes Catalyzed by a Chiral Quaternary Ammonium Salt and Triethylamine

Dan Peng,[a] Hui Zhou,[a] Xiaohua Liu,[a] Liwei Wang,[a] Shikui Chen,[a] Xiaoming Feng*[a,b]

[a] Key Laboratory of Green Chemistry & Technology (Sichuan University), Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, P. R. of China

[b] State Key Laboratory of Biotherapy, Sichuan University, Chengdu 610041, P. R. of China
Fax +86(28)85418249; E-mail: xmfeng@scu.edu.cn

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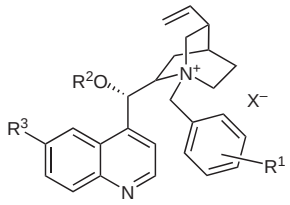
Abstract: An efficient enantioselective cyanoformylation of aldehydes with ethyl cyanoformate, catalyzed by a chiral quaternary ammonium salt and triethylamine, has been developed. The reaction can be carried out in excellent yields (up to 97%) with moderate enantioselectivity (up to 72% ee).

Key words: cyanation, aldehyde, ethyl cyanoformate, quaternary ammonium salt, organocatalysis

Asymmetric cyanation of aldehydes has become a powerful tool to synthesize various chiral compounds, which serve as highly versatile building blocks in biologically active products.[1] During the last two decades, HCN, K(Na)CN, and TMSCN have been widely used as the cyanide source to realize this goal.[2,3] For their stabilization and less toxicity, cyanoformate esters (ROCOCN), acetyl cyanide, and diethyl cyanophosphonate have been investigated as the promising candidates in recent years. Tremendous efforts have been devoted to this field, illustrated by Deng,[4] Shibasaki,[5] Sansano, Nájera and Saá,[6] Belokon and North,[7] Moberg,[8] and our group.[9] To date, to our best knowledge, the majority of chiral catalysts used in this reaction are chiral ligands in the presence of metal ions.[10] Herein, we wish to report the first organocatalytic enantioselective cyanation of aldehydes with $EtCO_2CN$ (ethyl cyanoformate).

Recently we reported the cyanosilylation of ketones catalyzed by quaternary ammonium salt combined with *N*-oxide.[11] Therefore, we speculated that the quaternary ammonium salt together with a Lewis base may catalyze the cyanation of aldehydes with $NCCO_2Et$.

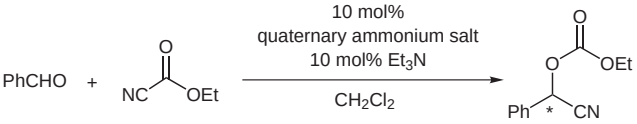
In a preliminary study, we investigated the addition of $NCCO_2Et$ to benzaldehyde in the presence of chiral quaternary ammonium salt **2g** (10 mol%) and *N*,*N*-dimethylaniline *N*-oxide (10 mol%). To our delight, the corresponding product was obtained in 63% yield with 40% ee after 48 hours at –15 °C. It was noted that **2g** alone could not promote this addition reaction. When Et_3N was used in place of *N*,*N*-dimethylaniline *N*-oxide, the reaction was complete in ten hours with 43% ee (Table 1, entry 7). Therefore Et_3N was selected as the Lewis base for the reaction.



2a: R^1 = 4-O_2N, R^2 = allyl, R^3 = H, X = Br
2b: R^1 = 4-O_2N, R^2 = H, R^3 = H, X = Br
2c: R^1 = 2,3,4-trifluoro, R^2 = H, R^3 = MeO, X = Br
2d: R^1 = 4-CF_3, R^2 = H, R^3 = MeO, X = Br
2e: R^1 = 4-O_2N, R^2 = H, R^3 = MeO, X = Br
2f: R^1 = 3,4,5-trifluoro, R^2 = H, R^3 = MeO, X = Br
2g: R^1 = 3,5-bis(CF_3), R^2 = H, R^3 = MeO, X = Br
2h: R^1 = 3,5-bis(CF_3), R^2 = H, R^3 = MeO, X = MeCOO

Figure 1 Quaternary ammonium salts evaluated for asymmetric addition of ethyl cyanoformate to benzaldehyde

Table 1 Asymmetric Cyanation of Benzaldehyde Catalyzed by the Combination of Quaternary Ammonium Salt (Figure 1) and Et_3N[a]



1a **3a**

Entry	Catalyst	Time (h)	ee (%)[b]
1	**2a**	10	6
2	**2b**	10	13
3	**2c**	10	13
4	**2d**	10	17
5	**2e**	10	19
6	**2f**	10	24
7	**2g**	10	43
8	**2h**	1	44

[a] All reactions were performed with benzaldehyde (0.1 mmol) and $NCCO_2Et$ (0.15 mmol) in CH_2Cl_2 (1 mL) at –15 °C. All reactions gave quantitative yield.
[b] Determined by HPLC on a Chiralcel OD-H column. The absolute configuration was *R*, determined by comparison with the sign of the reported optical rotation value.[5c]

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Subsequently, a series of chiral quaternary ammonium salts derived from quinidine or cinchonine combined with Et_3N was examined. As shown in Table 1, it was noteworthy that the skeleton of the quinidine has a perceptible influence on the enantioselectivity, as compared to cinchonine (Table 1, entries 2 and 5). The hydroxyl group from quinidine (Table 1, entries 1 and 2) and the electron-withdrawing group on benzyl bromide (Table 1, entries 3–7) were crucial for the chiral induction. Quaternary ammonium salt derived from quinidine and 3,5-bis(trifluoromethyl)benzyl bromide afforded the best architecture (Table 1, entries 7 vs. 3–6). When the anion Br^- was replaced by $MeCOO^-$,[12,13] the rate of the reaction was enhanced further (Table 1, entries 7 vs. 8).

In order to improve the enantioselectivity, we optimized the reaction conditions by changing the solvent and reaction temperature (Table 2). Et_2O, THF and CH_2Cl_2 showed a similar level of enantioselectivity at –15 °C (Table 2, entries 5–7). Relatively lower enantioselectivity was obtained from toluene, MeCN, hexane (Table 2, entries 2–4). Surprisingly, DMF gave a racemate mixture (Table 2, entry 1). CH_2Cl_2 exhibited an excellent tolerance to the low temperature employed and the asymmetric induction was increased as the temperature decreased (Table 2, entries 7–9). Particularly in CH_2Cl_2 when the temperature was decreased to –78 °C, the high reactivity was maintained and a 67% ee was obtained (Table 2, entry 10).

Encouraged by the result obtained for benzaldehyde, we investigated a series of aldehydes under the optimized conditions (Table 3). Almost all aromatic aldehydes tested gave moderate to excellent yields (up to 97%) and similar enantioselectivities (up to 72% ee) compared to those obtained from benzaldehyde. The presence of methyl group on the *ortho*, *para*, and *meta* positions of benzaldehyde showed a slight influence on the enantioselectivity (Table 3, entries 2–4). Halogen-substituted benzaldehyde, 1-naphthaldehyde and heliotropin gave similar results (Table 3, entries 5, 6, 8 and 10). *p*-Methoxybenzaldehyde gave the corresponding product with increased enantioselectivity, but a loss in reactivity was noted (Table 3, entry 9). 2-Naphthaldehyde gave the highest enantioselectivity (72% ee) and the enantiomeric excess could be increased to 95% after a single recrystallization (Table 2, entry 7). Nevertheless, unsatisfactory results were obtained for aliphatic aldehydes.[15]

At present the mechanistic detail of this conversion remains unknown. We speculate that triethylamine might function as a Lewis base that activates ethyl cyanoformate,[4,6,8,9b,c] and the quaternary ammonium salt might activate the carbonyl group with the positively charged nitrogen atom and the free hydroxyl group.[11,16]

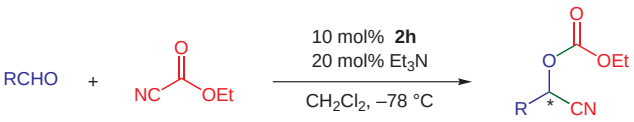
In summary, we have demonstrated the first enantioselective catalytic cyanation of aldehydes with $NCCO_2Et$ through a metal-free process. By using chiral quaternary ammonium salt and triethylamine, the reactions pro-

Table 2 Optimization of the Addition of Ethyl Cyanoformate to Benzaldehyde in the Presence of **2h** and Et_3N[a]

Entry	Solvent	Temperature (°C)	Yield (%)[b]	ee (%)[c]
1	DMF	–15	40	0
2	MeCN	–15	89	10
3	hexane	–15	97	29
4	toluene	–15	95	35
5	THF	–15	95	42
6	Et_2O	–15	96	45
7	CH_2Cl_2	–15	99	44
8[d]	CH_2Cl_2	–45	99	57
9	CH_2Cl_2	–78	96	65
10[e]	CH_2Cl_2	–78	96	67

[a] All reactions were performed with benzaldehyde (0.1 mmol) and $NCCO_2Et$ (0.15 mmol) in solvent (1 mL) with **2h** (10 mol%) and Et_3N (10 mol%) for 18 h, unless otherwise indicated.
[b] Isolated yield.
[c] Determined by HPLC on a Chiralcel OD-H column. The absolute configuration was *R*, determined by comparison with the sign of the reported optical rotation value.[5c,]
[d] Reaction time: 2 h.
[e] Benzaldehyde (0.1 mmol) and $NCCO_2Et$ (0.15 mmol) in CH_2Cl_2 (2 mL) with Et_3N (20 mol%) were employed for 18 h.

Table 3 Asymmetric Cyanoformylation of Aldehydes with Ethyl Cyanoformate Catalyzed by Combination of **2h** and Et_3N[a]



Entry	Aldehyde	Time (h)	Yield (%)[b]	ee (%)[c] (config.)[d]
1	benzaldehyde	17	96	67 (*R*)
2	2-methylbenzaldehyde	29	97	65
3	3-methylbenzaldehyde	66	96	65 (*R*)
4	4-methylbenzaldehyde	93	85	67 (*R*)
5	4-fluorobenzaldehyde	48	82	63 (*R*)
6	4-chlorobenzaldehyde	40	61	61 (*R*)
7	2-naphthaldehyde	48	70	72 (95)[e]
8	1-naphthaldehyde	48	80	61 (*S*)
9[f]	4-methoxybenzaldehyde	160	65	70 (*R*)
10	heliotropin	70	57	61

[a] All reactions were performed with aldehyde (0.1 mmol) and $NCCO_2Et$ (0.15 mmol) in CH_2Cl_2 (2 mL) at –78 °C, unless otherwise indicated. For typical procedures, see ref. 14.
[b] Isolated yield.
[c] Determined by HPLC on a Chiralcel OD-H column.
[d] The absolute configurations were determined by comparison of optical rotations with those reported in the literature.[5c,7a,9a,]
[e] Yield after a single recrystallization with EtOAc–PE (1:15).
[f] Et_3N (30 mol%) was used.

ceeded smoothly with high yields and moderate enantioselectivities. Further effort should be devoted to the optimization of the catalyst to enhance the enantioselectivity.

Acknowledgment

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(12) **Procedure for Preparation of 2h**: To a solution of **2g** (0.100 g, 0.158 mmol) in CH_2Cl_2 (10 mL) at r.t. was added MeCOOAg (0.0277 g, 0.166 mmol, 1.05 equiv), and the mixture was stirred in the dark at r.t. for one week. The residue was centrifuged for half an hour. Then the precipitate was filtered off and the filtrate was concentrated under reduced pressure to afford a yellow solid; mp 142–143 °C; $[\alpha]_D^{25}$ 121 (c = 0.108, $CHCl_3$). IR (KBr): 3411, 2931, 2361, 1622, 1509, 1374, 1280, 1178, 1136, 905, 683 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.57 (d, J = 4.5 Hz, 1 H), 8.02 (s, 1 H), 7.66–7.81 (m, 4 H), 7.24–7.25 (m, 1 H), 6.94–6.98 (dd, J = 2.3, 9.2 Hz, 1 H), 6.49 (d, J = 12.5 Hz, 1 H), 6.37 (s, 1 H), 5.82–5.94 (sept, 1 H), 5.41 (d, J = 13.1 Hz, 1 H), 5.17–5.25 (m, 1 H), 4.70 (t, J = 10.5 Hz, 1 H), 4.52 (t, J = 10.1 Hz, 1 H), 4.15 (t, J = 8.9 Hz, 1 H), 3.72 (s, 3 H), 3.05 (t, J = 11.3 Hz, 1 H), 2.51–2.61 (q, 1 H), 2.30–2.39 (q, 1 H), 2.14 (t, J = 12.1 Hz, 1 H), 2.03 (s, 3 H), 1.70–1.87 (m, 3 H), 0.70–0.76 (m, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 175.1, 157.9, 147.9, 145.1, 144.2, 137.9, 135.1, 132.2, 131.9, 131.8, 131.4, 131.1, 130.8, 126.1, 125.0, 124.3, 122.3, 121.3, 121.0, 117.4, 102.9, 68.9, 64.2, 61.2, 56.1, 54.0, 37.6, 27.1, 24.9, 23.8, 21.2. HRMS (ESI): m/z [M^+ – MeCOO] calcd for $C_{29}H_{29}F_6N_2O_2$: 551.2128; found: 551.2020.

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(14) **Typical Procedure**: To a mixture of benzaldehyde (0.1 mmol), quaternary ammonium salt **2h** (0.01 mmol, 10 mol%) and Et_3N (0.01 mmol) in CH_2Cl_2 (2 mL) under a N_2 atmosphere, was added ethyl cyanoformate (0.15 mmol, 1.5 equiv) at –78 °C. The reaction was monitored by TLC, and after the reaction time indicated in Table 3, the residue was directly purified by silica gel column chromatography (PE–Et_2O, 10:1) to afford the title compound as a colorless oil in 96% yield with 67% ee as determined by HPLC analysis with a Chiralcel OD-H column [λ = 254 nm, hexane–2-propanol = 99:1, 1.0 mL/min, t_R(major) = 9.2 min, t_R(minor) = 10.9 min]; $[\alpha]_D^{25}$ = 6.49 (c = 0.154, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 7.53–7.56 (m, 2 H, ArH), 7.45–7.49 (m, 3 H, ArH), 6.27 (s, 1 H, OCHCN), 4.26–4.32 (m, 2 H, OCH_2), 1.34 (t, J = 7.1 Hz, 3 H, OCH_2CH_3).

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