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Cyanosilylation of aldehydes catalyzed by *N*-heterocyclic carbenes

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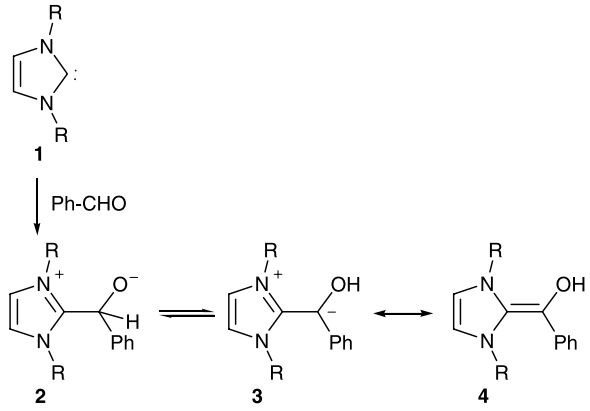
Abstract—*N*-Heterocyclic carbenes produced in situ from salts of imidazolium, benzimidazolium, pyrido[1,2-*c*]imidazolium, imidazolinium, thiazolium, and triazolium catalyze the addition of trimethylsilylcyanide to aldehydes to yield cyanohydrin trimethylsilyl ethers. The use of C_2-symmetric imidazolidenyl carbene derived from (*R*,*R*)-1,3-bis[(1-naphthyl)ethyl]imidazolium chloride led to enantioselective cyanosilylation.

1. Introduction

Cyanohydrin trimethylsilyl ethers are versatile intermediates because they can be transformed into a number of important building blocks such as α-hydroxyacids and β-hydroxyamines. One of the common methods to prepare silylated cyanohydrins is the addition reaction of trimethylsilylcyanide (TMS-CN) to aldehydes. It has been known that Lewis acids catalyze the cyanosilylation of aldehydes by activating them,[1] while Lewis bases catalyze the reaction by the activation of TMS-CN.[2] In this paper, we report *N*-heterocyclic carbenes (NHCs) **1** as catalysts for the cyanosilylation of aldehydes.

NHCs are excellent σ-donors, and their use as ligands for transition metal catalysts enhances catalytic performance and stability.[3] In addition, they are effective organocatalysts for important reactions such as benzoin condensation,[4,5] Stetter reactions,[6] and acylation/transesterification reactions.[7] Our research group has reported NHC-catalyzed reactions such as nucleophilic aroylation and asymmetric acylation.[5,8,9]

In benzoin condensation, the nucleophilic addition of the NHC to a carbonyl carbon atom of an aldehyde produces intermediate **2** (Scheme 1). A tautomer of **2** is an acyl anion equivalent **4**, which reacts with another aldehyde to produce benzoin. We anticipated intermediate **2** to react with TMS-CN to produce cyanosilyl ethers and the NHCs to catalyze the cyanosilylation reaction.



Scheme 1.

2. Results and discussion

To examine the catalytic ability of the NHCs for cyanosilylation, a reaction of *p*-chlorobenzaldehyde (**5a**) and TMS-CN was carried out in the presence of 1,3-dibenzylimidazolinylidene (5 mol%) generated in situ from imidazolium bromide **6** (Table 1, entry 1). After the mixture of **6** and potassium *tert*-butoxide in tetrahydrofuran was stirred at room temperature to generate the carbene, **5a** and TMS-CN were added. The reaction mixture was stirred continuously at room temperature, and the generation of cyanohydrin trimethylsilyl ether **7a** was observed by silica gel thin-layer chromatography. The reaction mixture was treated with dilute HCl, and the product was isolated as a form of cyanohydrin **8a** (80%). The cyanosilylation reaction of other aromatic aldehydes **5b–e**, conjugated aldehyde **5f**, and aliphatic aldehydes **5g–i** also proceeded to produce

Keywords: Cyanosilylation; Cyanohydrin; *N*-Heterocyclic carbene; Organocatalysis; Asymmetric cyanosilylation.
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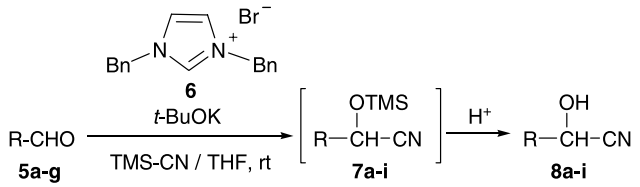
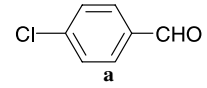
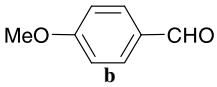
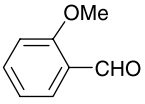
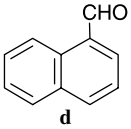
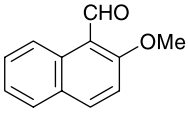
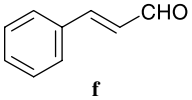
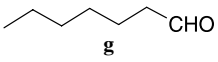
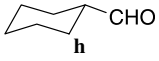
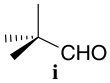
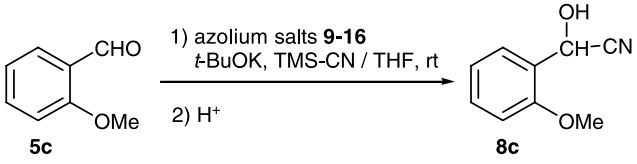
Table 1. Cyanosilylation of aldehydes catalyzed by 1,3-dibenzylimidazolidenyl carbene

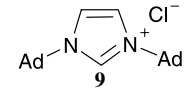
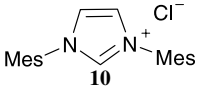
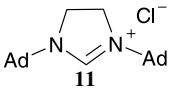
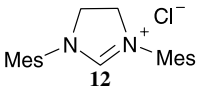
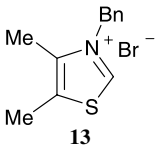
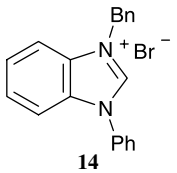
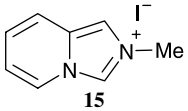
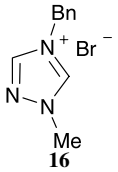


Entry	5	Time (h)	Yield (%)[a]
1	 **a**	2	80
2	 **b**	0.5	69
3	 **c**	0.5	93
4	 **d**	0.5	94
5	 **e**	3	85
6	 **f**	0.5	75
7	 **g**	0.5	77
8	 **h**	0.5	81
9	 **i**	0.5	65

[a] Isolated yield as a cyanohydrin.

Table 2. Cyanosilylation of *o*-methoxybenzaldehyde



Entry	Azolium salt	Time (h)	Yield (%)[a]
1	 **9**	8	85
2	 **10**	1.5	98
3	 **11**	8	65
4	 **12**	1.3	96
5	 **13**	20	59
6	 **14**	20	60
7	 **15**	2	82
8	 **16**	2	87

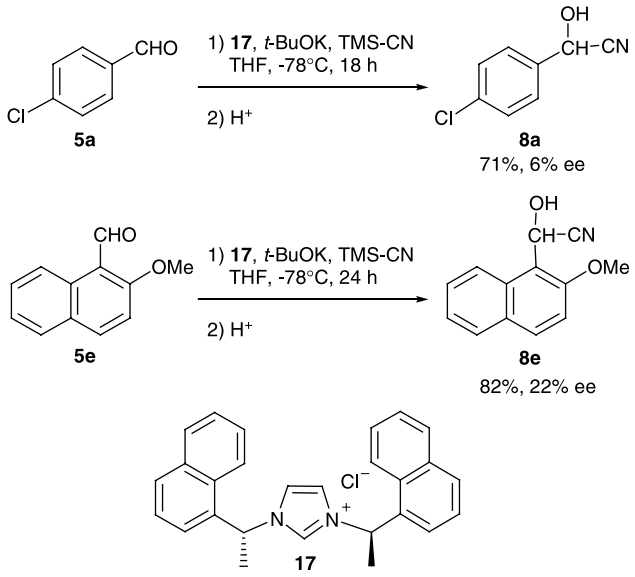
[a] Isolated yield as a cyanohydrin.

corresponding cyanohydrins **8b–i** in good yields (Table 1, entries 2–8).

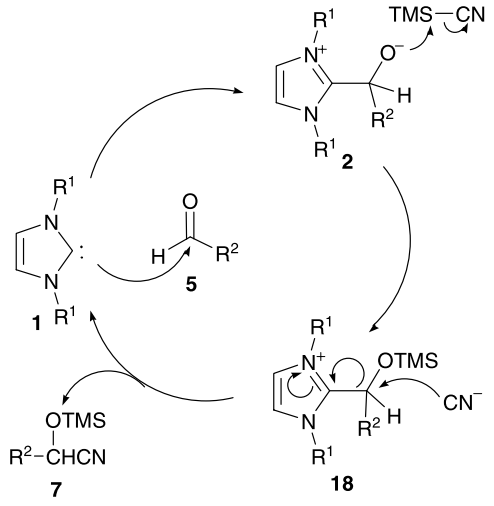
In the acylation reaction of alcohols, imidazolidinylidenes (derived from imidazolinium salts) were reported to exhibit less catalytic ability than imidazolinylidenes (derived from imidazolium salts).[10] To compare the catalytic abilities of imidazolidinylidenes and imidazolinylidenes, the cyanosilylation of *o*-methoxybenzaldehyde (**5c**) was examined using imidazolium and imidazolinium salts **9–12** with adamantyl and mesityl groups as *N*-substituents (Table 2, entries 1–4) because imidazolidinylidenes without bulky substituents gradually dimerize.[11] In contrast to the acylation of alcohols, the NHCs generated from imidazolium and imidazolinium chlorides with the same *N*-substituents exhibited comparable catalytic abilities in the cyanosilylation of **5c**.

The cyanosilylation of **5c** was also conducted by using other azolium salts **13–16** (Table 2, entries 5–8). The reaction rates were low and the yields were moderate with thiazolium salt **13** and benzimidazolium salt **14** (entries 5 and 6). Reactions with pyrido[1,2-*c*]imidazolium salt **15** and triazolium salt **16** produced cyanohydrin **8c** in good yields (entries 7 and 8).

Many reports have described asymmetric reactions catalyzed by chiral NHCs such as asymmetric benzoin condensation and the Stetter reaction.[9,12–15] The cyanosilylation of aldehyde **5a** was carried out in the presence of chiral NHC generated from imidazolium salt **17**[16] at −78 °C for 18 h (Scheme 2). Cyanohydrin **8a** was obtained with a yield



Scheme 2. Asymmetric cyanosilylation catalyzed by chiral NHC.

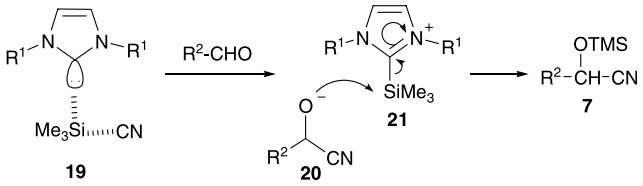


Scheme 3. Postulated reaction pathway.

of 71% and 6% ee. The reaction of **5e** at −78 °C for 24 h produced **8e** with a yield of 82% and 22% ee.

A possible reaction pathway of cyanosilylation is shown in Scheme 3. The formation of intermediate **2** has been widely accepted in NHCs' catalysis.[12,15b,17] Intermediate **2** reacts with TMS-CN to produce intermediate **18** and cyanide anion. The cyanide anion nucleophilically attacks a carbon atom (derived from aldehyde carbonyl carbon) of **18**. The imidazolium moiety of **18** acts as a leaving group, and nucleophilic substitution occurs to produce cyanohydrin silyl ether **7**. In the case of the chiral NHC, **1** added to **5** face selectively to produce diastereoisomeric intermediates **2** with an excess of a favored isomer.

It should be noted that an alternative catalytic mechanism possibly exists. In particular, the NHCs activate TMS-CN by coordination (Scheme 4). The chemical behavior of the NHCs is similar to those of tertiary amines and phosphines. All these species are used as ligands, nucleophilic reagents, and catalysts. Tertiary amines and phosphines catalyze the cyanosilylation of aldehydes by activating TMS-CN.[2] Mukaiyama et al. reported that the reaction of TMS-CN with cyclohexanecarboxyaldehyde in the presence of a catalytic amount of chiral amine, (+)-cinchonine, produced optically active cyanohydrin.[18]



Scheme 4. Alternative reaction pathway.

Song et al. reported NHC-catalyzed trifluoromethylation of carbonyl compounds.[19] They implied NHCs catalyze trifluoromethyl transfer by activation of trifluoromethyltrimethylsilane (TMS-CF_3). There are also two types of mechanism proposed for NHC-catalyzed transesterification. One mechanism involves a nucleophilic attack of NHC to a carbonyl carbon.[7] The other involves an activation of alcohols by NHCs.[20]

3. Conclusion

We have shown that the NHCs catalyze the cyanosilylation reaction between aldehydes and TMS-CN. In addition, we have proposed possible reaction mechanisms. One involves the nucleophilic addition of the NHCs to the carbonyl carbon atoms of aldehydes, followed by O-silylation and the replacement of an azolium moiety with a cyano group by S_N2 substitution. The other involves the activation of TMS-CN by coordination of NHCs. Although the optical yield was not satisfactory, the use of chiral NHC resulted in asymmetric cyanosilylation. Further investigations to clarify the reaction mechanism and increase optical yields in asymmetric cyanosilylation are in progress.

4. Experimental

4.1. General

Melting points are determined using a Yazawa Micro Melting Point Apparatus without correction. ^{1}H NMR (500 MHz) and ^{13}C NMR (126 MHz) spectra were recorded on a JEOL ECA-500 NMR spectrometer. IR spectra were recorded on a SHIMADZU IR Prestige-21. HRMS (FAB) spectra were recorded on a JEOL MStation JMS-700 mass spectrometer using *m*-nitrobenzyl alcohol as a matrix. Column chromatography was performed with Merck Silica Gel 60 and Silica Gel 60 N (spherical, neutral; Kanto Chemical Co., Inc.).

4.2. Typical procedure for cyanosilylation of aldehydes

To a suspension of azolium salt (0.05 mmol) in THF (2 mL), 1 M *t*-BuOK/THF (0.05 mmol) was added at room temperature, and the mixture was stirred for 30 min. Subsequently, the aldehyde (1 mmol) and TMS-CN (1.1 mmol) were added. This mixture was stirred at room temperature for the indicated time and then treated with dilute HCl. The crude product was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by silica gel chromatography using hexane/ethyl acetate as an eluent in order to produce cyanohydrin.

The enantiomeric excess of **8a**,**e** was determined by chiral HPLC analysis after the conversion to acetate.

4.2.1. 4-Chloromandelonitrile (8a).[21] Colorless granules (recrystallized from $CHCl_3$/hexane); Mp 35–37 °C; ^{1}H NMR ($CDCl_3$) δ: 3.16 (1H, br s, CHO*H*), 5.52 (1H, s, C*H*OH), 7.41 (2H, d, J=8.6 Hz), 7.46 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 63.0, 118.5, 128.1, 129.5, 133.6, 136.1; IR (KBr) 2255 (CN), 3401 (OH) cm^{-1}.

4-Chloromandelonitrile, acetate: Analytical chiral HPLC: Chiralcel OD-H column, 0.46×25 cm, hexane–2-propanol (99/1), 0.5 mL min^{-1}; 21.5, 25.2 min.

4.2.2. 4-Methoxymandelonitrile (8b).[22] Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 3.81 (3H, s, OCH_3), 5.44 (1H, s, C*H*OH), 6.92 (2H, d, J=4.6 Hz), 7.42 (2H, d, J=4.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 55.5, 63.2, 114.5, 119.3, 127.8, 128.4, 160.6; IR (neat) 2245 (CN), 3414 (OH) cm^{-1}.

4.2.3. 2-Methoxymandelonitrile (8c).[22] Colorless granules (recrystallized from CH_2Cl_2/hexane); Mp 64–67 °C; ^{1}H NMR ($CDCl_3$) δ: 3.62 (1H, d, J=8.9 Hz, CHO*H*), 3.94 (3H, s, OCH_3), 5.56 (1H, d, J=8.9 Hz, C*H*OH), 6.97 (1H, d, J=8.6 Hz), 7.01 (1H, t, J=7.5 Hz), 7.38–7.42 (2H, m); ^{13}C NMR ($CDCl_3$) δ: 55.9, 60.4, 111.3, 119.0, 121.2, 123.8, 128.2, 131.3, 156.8; IR (KBr) 2251 (CN), 3377 (OH) cm^{-1}.

4.2.4. α-Hydroxy-1-naphthaleneacetonitrile (8d).[21] Yellow oil; ^{1}H NMR ($CDCl_3$) δ: 2.93 (1H, d, J=6.3 Hz, CHO*H*), 6.18 (1H, d, J=6.3 Hz, C*H*OH), 7.51 (1H, dd, J=8.0, 7.5 Hz), 7.57 (1H, dd, J=8.0, 6.9 Hz), 7.61–7.64 (1H, m), 7.83 (1H, d, J=7.5 Hz), 7.91 (1H, d, J=8.6 Hz), 7.94 (1H, d, J=8.0 Hz), 8.15 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 62.2, 119.0, 123.0, 125.3, 125.8, 126.6, 127.5, 129.1, 130.0, 130.3, 131.0, 134.0; IR (neat) 2249 (CN), 3399 (OH) cm^{-1}.

4.2.5. α-Hydroxy-1-(2-methoxynaphthalene)acetonitrile (8e). Colorless needles (recrystallized from CH_2Cl_2/hexane); Mp 95–97 °C; ^{1}H NMR ($CDCl_3$) δ: 3.94 (1H, d, J=9.7 Hz, CHO*H*), 4.09 (3H, s, OCH_3), 6.34 (1H, d, J=9.7 Hz, C*H*OH), 7.32 (1H, d, J=9.2 Hz), 7.41–7.44 (1H, m), 7.58–7.61 (1H, m), 7.84 (1H, d, J=8.0 Hz), 7.94 (1H, d, J=9.2 Hz), 8.04 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 56.6, 56.9, 112.9, 116.4, 119.3, 121.8, 124.5, 128.4, 129.1, 129.4, 130.8, 132.4, 155.6; IR (KBr) 2241 (CN), 3453 (OH) cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{11}NO_2$ (M^+): 213.0790, found: 213.0814.

α-Acetyloxy-1-(2-methoxynaphthalene)acetonitrile: colorless prisms (recrystallized from CH_2Cl_2/hexane); Mp 133–135 °C; ^{1}H NMR ($CDCl_3$) δ: 2.14 (3H, s, CH_3), 4.03 (3H, s, OCH_3), 7.28 (1H, d, J=9.2 Hz), 7.42–7.45 (1H, m), 7.53 (1H, s, C*H*OAc), 7.60–7.63 (1H, m), 7.83 (1H, d, J=8.0 Hz), 7.95 (1H, d, J=9.2 Hz), 8.25 (1H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 20.6, 55.1, 56.9, 112.2, 112.9, 116.9, 123.3, 124.4, 128.1, 129.0, 129.3, 131.8, 133.3, 155.6, 169.1; IR (KBr) 1749 (CO) cm^{-1}; HRMS (FAB) Calcd for $C_{15}H_{13}NO_3$ (M^+): 255.0895, found: 255.0875; Analytical chiral HPLC: Chiralcel OD-H column, 0.46×25 cm, hexane–2-propanol (98/2), 0.5 mL min^{-1}; 29.9, 40.3 min.

4.2.6. 2-Hydroxy-4-phenyl-3-butenenitrile (8f).[22] Pale yellow powder (recrystallized from CH_2Cl_2/hexane); Mp 71–74 °C; ^{1}H NMR ($CDCl_3$) δ: 2.65 (1H, d, J=6.3 Hz, CHO*H*), 5.17 (1H, t, J=6.3 Hz, C*H*OH), 6.26 (1H, dd, J=16.0, 6.3 Hz, olefinic H), 6.92 (1H, dd, J=16.0, 1.1 Hz, olefinic H), 7.30–7.40 (3H, m), 7.42 (2H, d, J=8.6 Hz); ^{13}C NMR ($CDCl_3$) δ: 62.0, 118.4, 122.3, 127.2, 129.0, 129.2, 134.8, 135.4; IR (KBr) 2253 (CN), 3358 (OH) cm^{-1}.

4.2.7. 2-Hydroxyoctanenitrile (8g).[23] Yellow oil; ^{1}H NMR ($CDCl_3$) δ: 0.87 (3H, t, J=6.9 Hz, Me), 1.24–1.38 (6H, m), 1.44–1.50 (2H, m), 1.81 (2H, q, J=6.9 Hz), 3.64 (1H, br s, CHO*H*), 4.44 (1H, t, J=6.9 Hz, C*H*OH); ^{13}C NMR ($CDCl_3$) δ: 14.1, 22.6, 24.6, 28.7, 31.6, 35.2, 61.3, 120.3; IR (neat) 2247 (CN), 3447 (OH) cm^{-1}.

4.2.8. 2-Cyclohexyl-2-hydroxyacetonitrile (8h).[21] Colorless oil; ^{1}H NMR ($CDCl_3$) δ: 1.01–1.28 (5H, m), 1.62–1.89 (6H, m), 3.87 (1H, br s, CHO*H*), 4.22 (1H, dd, J=6.3, 5.7 Hz, C*H*OH); ^{13}C NMR ($CDCl_3$) δ: 25.5, 25.5, 26.0, 27.9, 28.2, 42.2, 66.2, 119.6; IR (neat) 2245 (CN), 3435 (OH) cm^{-1}.

4.2.9. 2-Hydroxy-3,3-dimethylbutanenitrile (8i).[24] Yellow oil; ^{1}H NMR ($CDCl_3$) δ: 1.05 (9H, s, CH_3), 3.28 (1H, br s, CHO*H*), 4.11 (1H, s, C*H*OH). ^{13}C NMR ($CDCl_3$) δ: 25.0, 35.5, 70.6, 119.3.

References and notes

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