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Discrimination of Reaction Pathways by a Simple Organoaluminum Compound, Me$_2$AlCl, in Lewis Acid Promoted Reactions of Aldehydes with Organosilicon Reagents

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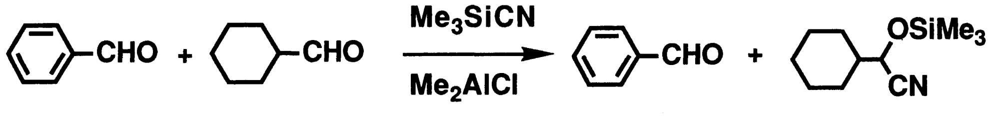
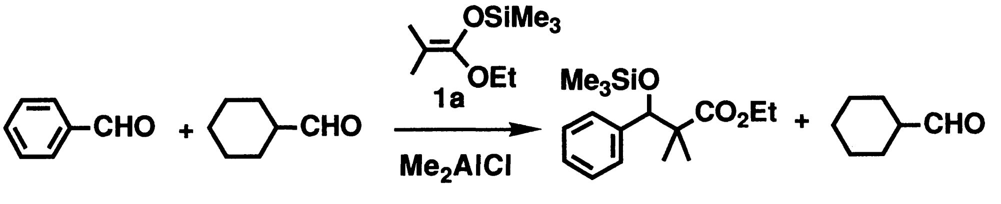
A novel character of a simple organoaluminum compound, dimethylaluminum chloride, concerning molecular recognition is demonstrated by the crossover reaction of aliphatic and aromatic aldehydes (benzaldehyde and cyclohexanecarbaldehyde) with organosilicon reagents, ketene trimethylsilylacetal and cyanotrimethylsilane in the presence of dimethylaluminum chloride (20-50 mol%) to afford the corresponding aldol adduct of benzaldehyde and cyanohydrin of cyclohexanecarbaldehyde exclusively.

Lewis acid promoted reactions of carbonyl and the related compounds with various nucleophiles have extensively been studied in recent years with respect to both synthetic utility and mechanistic character.1) One of the final goals in synthetic organic chemistry is the complete control of reactivities and selectivities by Lewis acids to obtain desired products. In particular, the control of chemoselectivity in Lewis acid mediated reactions involving aldehyde vs ketone,2) carbonyl vs acetal3) etc. has been an important problem as well as the stereochemical control. We herein wish to disclose a novel character of a simple Lewis acid, dimethylaluminum chloride to discriminate the reactivity between aromatic and aliphatic aldehydes with organosilicon reagents.

During the course of our recent studies on asymmetric cyanosilylation of aldehydes with cyanotrimethylsilane (TMSCN) promoted by peptide-aluminum complex as a chiral Lewis acid catalyst,4,5) we found that aliphatic aldehydes generally reacted much faster than aromatic aldehydes. On the other hand, inverted results are reported on aldol condensations with enol silyl ethers or ketene silyl acetals in the presence of various Lewis acids, in which the reaction of aromatic aldehydes are faster than those of aliphatic aldehydes.6) These adverse preferences encouraged us to undertake further investigation on the difference of reactivity in Lewis acid mediated reactions of aldehydes with the organosilicon reagents.



(1)

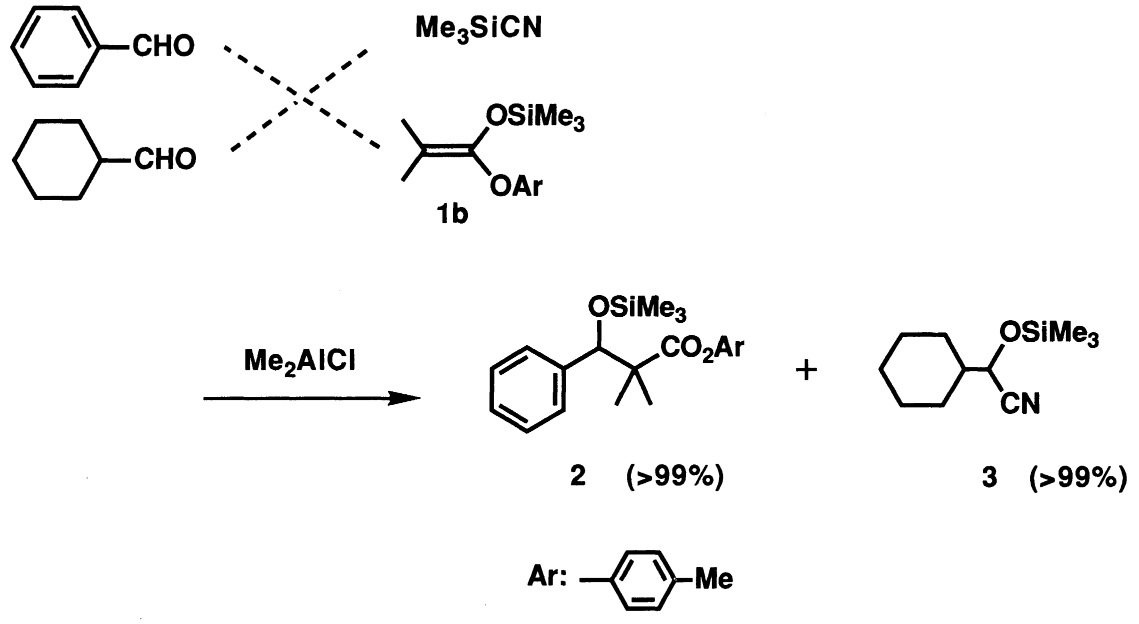


(2)

Indeed, the treatment of 1: 1: 1 mixture of benzaldehyde, cyclohexanecarbaldehyde and TMSCN at -78 °C with 20 mol% of Me_2AlCl, which was recognized as a strong Lewis acid, afforded the corresponding cyanohydrin of cyclohexanecarbaldehyde exclusively along with the recovery of benzaldehyde (Eq. 1).7) A similar competitive reaction by ketene trimethylsilyl acetal (**1a**) instead of TMSCN, in contrast, furnished the aldol adduct derived from benzaldehyde with unreacted cyclohexanecarbaldehyde (Eq. 2).

The remarkable differences shown above are highlighted by the following crossover reaction of the two different aldehydes with the mixture of the organosilicon reagents as depicted in Scheme 1. A 1: 1 mixture of benzaldehyde and cyclohexanecarbaldehyde was treated with a 1: 1 mixture of ketene trimethylsilyl acetal (**1b**)8) and TMSCN (excess to aldehydes) in the presence of a catalytic amount of Me_2AlCl. The reaction was completed within 1 h to yield the aldol product of benzaldehyde (**2**) and the cyanohydrin of cyclohexanecarbaldehyde (**3**), but neither the aldol adduct of cyclohexanecarbaldehyde (**4**) nor benzaldehyde cyanohydrin (mandelonitrile) (**5**) was obtained. Although both aldehydes are activated by the coordination of Me_2AlCl to carbonyl oxygen to allow nucleophilic attacks of the organosilicon reagents, benzaldehyde preferred the ketene silyl acetal (**1b**), to the contrary, cyclohexanecarbaldehyde reacted with TMSCN in excellent specificities respectively. Hence, Me_2AlCl is capable of discriminating the reaction pathway, aldol condensation or cyanosilylation, corresponding to the type of aldehydes to which Me_2AlCl coordinate.

The experimental procedure is as follows: To a mixture of **1b** (1.5 mmol) and TMSCN (1.5 mmol) in toluene (2 mL) was added dropwise Me_2AlCl (1.0 mmol) at -78 °C followed by a mixed solution of benzaldehyde (1.0 mmol) and cyclohexanecarbaldehyde (1.0 mmol) in 2 mL of toluene. The reaction mixture was allowed to stand for 1 h at -78 °C and quenched by $NaHCO_3$ to yield, after evaporation of the solvent, the crude product as a mixture of the corresponding silyl ethers and the desilylated compounds by ^{1}H NMR analysis.



Scheme 1.

It should also be pointed out that this specificity was observed, as far as we had examined, only when Me_2AlCl was employed as a Lewis acid catalyst.[9)] The crossover reactions in the presence of a catalytic or a stoichiometric amount of other Lewis acids, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf),[6b)] BF_3 etherate and peptide (α-amino acid amide)-aluminum complex,[4, 10)] as shown in Table 1, did not give similar specificity observed in Me_2AlCl.

Table 1. Crossover reactions of PhCHO and $C_6H_{11}CHO$ with organosilicon reagents, TMSCN and **1b** promoted by several Lewis acids[a)]

Lewis acid (mol%)[b)]	Conv. of PhCHO / %	Aldol (**2**) / Cyanohydrin (**5**)	Conv. of $C_6H_{11}CHO$ / %	Aldol (**4**) / Cyanohydrin (**3**)
Me_2AlCl (50)	quant	100 : 0	quant	0 : 100
Me_3SiOTf (10)	81	59 : 41	85	0 : 100
$BF_3 \cdot OEt_2$ (100)	quant	100 : 0	quant	69 : 31
Nap-Val-NHCy -Me_3Al[c)] (20)	15	0 : 100	73	0 : 100

a) Unless noted, the crossover reactions were carried out as described in the text.
b) [Lewis acid] / [PhCHO + $C_6H_{11}CHO$] c) At -40 °C for 2 h.

A simple organoaluminum compound, Me_2AlCl as a catalyst exhibited a notably high substrate specificity in the crossover reaction of aromatic and aliphatic aldehydes with two organosilicon reagents, ketene silyl acetal and TMSCN, to give the corresponding products of aldol condensation and cyanosilylation although the specificity was quite limited.[11)] Thus, the crossover reaction constitutes a molecular recognition system in the reaction pathways.[12)]

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7) We consider that Me$_2$AlCl acts as Lewis acid catalyst in this reaction. Although Utimoto reported that TMSCN reacted with diethylaluminum chloride to form diethylaluminum cyanide at 25 °C for 3 h, the reaction condition in the addition of TMSCN to aldehyde was completely different (-78 °C within 10 min); K. Imai, N. Yanagihara, and K. Utimoto, *J. Org. Chem.*, **52**, 1013 (1987).

8) The use of **1a** caused confusion in ^{1}H NMR analysis due to the signals of CH$_2$ protons of ethyl ester overlapped with those of methyne proton of **3** (around 4.1 ppm). The use of ketene acetals of acetic acid esters was less effective since the reactivity was lower than that of **1b**.

9) Other alkylaluminum halides such as Et$_2$AlCl and EtAlCl$_2$ were shown to be less reactive as a catalyst for aldol and cyanasilylation reactions: Unpublished results in our group; see also Ref 6a.

10) Attempted asymmetric aldol type reaction catalyzed by peptide-aluminum complex were found to result in no reaction; A. Mori, H. Ohno, and S. Inoue, unpublished results.

11) The discrimination was also observed in the reactions of heptanal and 3-methoxybenzaldehyde as aliphatic and aromatic aldehydes, however, the attempted crossover reaction between aromatic aldehydes with electoron withdrawing *vs* donating groups, for example, did not show the considerable discrimination.

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