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Asymmetric cyanohydrin synthesis from aldehydes and ketones using chiral metal (salen) complex as catalyst*

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Abstract: Chiral Al(salen) is used as catalyst for enantioselective cyanosilylation of aldehydes and ketones.

Keywords: salen; aldehydes; ketones; cyanohydrin; asymmetric synthesis.

INTRODUCTION

Asymmetric addition of $(CH_3)_3SiCN$ to carbonyl compounds and subsequent hydrolysis produces chiral cyanohydrins [1–3]. Such chiral compounds are useful intermediates for synthesis of pharmaceutics. The two functional groups (–OH and –CN) can be easily transformed into various homochiral ones including α-hydroxy acids [4,5], α-hydroxy aldehydes [6], α-hydroxy ketones [6], β-hydroxy amines [5,6] and α-amino acid derivatives [7]. *N*-Methylmorphorin-*N*-oxide, cesium fluoride, potassium fluoride, and zirconium complex were, respectively, used as a catalyst for achiral silylcyanation [8–12] of aldehydes and ketones. Shibasaki has reported enantioselective catalytic additions of trimethylsilyl cyanide (TMSCN) to various ketones utilizing bifunctional ligand and $Ti(OiPr)_4$ or the lanthanide complexes [13]. The concept of dual activation was pioneered by Shibasaki's group. Deng first described the method of cyanosilylation of ketones employing chiral Lewis bases which are free of metal ions [14]. Snapper and Hoveyda described the addition of TMSCN to ketones catalyzed by peptidic chiral ligand and $Al(OiPr)_3$ [15]. Feng and Jiang employed chiral *N*-oxide/titanium(IV) complex for the cyanosilylation of ketones [16]. Feng utilized a catalytic double-activation method using chiral salen-Ti(IV) complex and various achiral *N*-oxides for the cyanosilylation of ketones [17]. Recently, Corey has shown that chiral oxazaborolidium salt is an excellent catalyst for the cyanosilylation of methyl ketones[18]. This method used TMSCN and diphenylmethyl phosphine oxide as co-reactants to generate $Ph_2MePOTMS(N{=}C{:})$ as a reactive intermediate.

We recently described our initial findings on the use of chiral Al(salen) for the enantioselective cyanosilylation of aldehydes[19] and ketones[20]. In this paper, we review our findings in the context of current developments in this important area of synthetic methodology.

RESULTS AND DISCUSSION

Chiral (salen)-metal complexes catalyze various asymmetric nucleophile–electrophile reactions including $TMSN_3$ [21] and carboxylic acid additions to meso epoxides [22], hetero Diels–Alder [23], and TMSCN addition to aldehydes [24]. Al(salen) complex is known to catalyze the enantioselective

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addition of hydrogen cyanide to imines [25]. The same Al(salen) complex coupled with triphenylphosphine oxide is used for the asymmetric cyanosilylation of benzaldehyde under various conditions (Table 1).

Table 1 Cyanosilylation of benzaldehyde catalyzed by Al(salen) under various conditions in CH_2Cl_2.

Entry	Al(salen) catalyst (mol %)	Additive $PO(Ph)_3$ (mol %)	Temp. (°C)	Time	% Yield[a]	% ee
1	5	10	25	30 min	95	61
2	1	20	25	20 min	95	70
3	1	10	25	30 min	94	69
4	1	5	25	2 h	91	60
5	0.5	10	25	1 h	94	69
6	0.1	10	25	3 h	94	69
7	1	–	25	1 h	–	–
8	–	10	25	1 h	–	–
9	1	10 (4 Å mol. sieves)	25	2 h	93	41
10	1	10 [$(t\text{Bu})_3PO$]	25	20 min	92	44
11	1	5	–40	24 h	32[b]	–
12	1	10	–40	18 h	95	78
13	1	10	–50	18 h	94	86
14	1	10	–70	3d	45[b]	–

[a]Yield of isolated product.
[b]Conversion.

A highly efficient double-activation catalysis has been developed for the enantioselective silylcyanation of various aldehydes. The Al atom of chiral Al(salen) activates the carbonyl oxygen for the formation of Si–O bond. Ph_3PO functions as a base for transfer of the N≡C group to the carbon atom of the carbonyl. The attack of cyanide should occur at the *si* face of the aldehyde carbonyl to afford an (*R*)-cyanohydrin because the *re* face is effectively blocked by bonding between the carbonyl oxygen and the Al atom of chiral Al(salen) (Fig. 1).

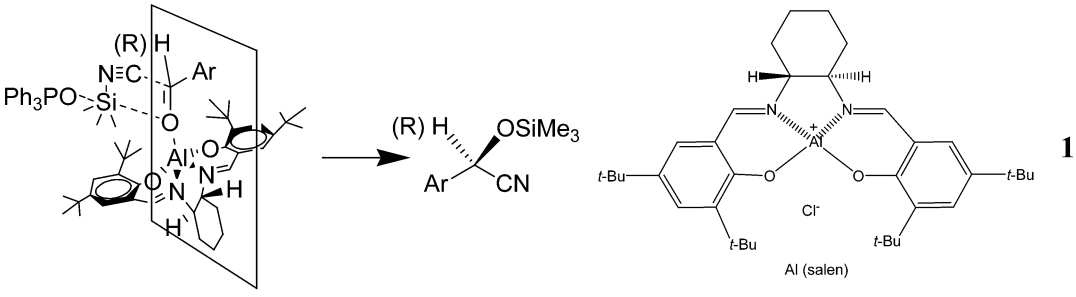
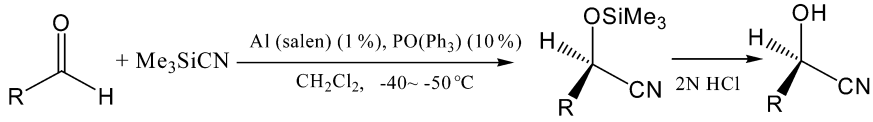


Fig. 1 Transition state involved in the enantioselective cyanosilylation of aldehydes by double-activation catalysis.

Accordingly, structurally different aldehydes were used as substrates in the reaction under the conditions of entry 13 of Table 1 (Table 2). Benzaldehydes with various electron-donating substituents were transformed into chiral cyanohydrins in over 90 % yield and 80 % ee (Table 3, entries 1–6). However, *p*-$NO_2C_6H_4CHO$ shows very poor reactivity toward the silylcyanation and was isolated in low yield (40 %) along with numerous other products. *trans*-Cinnamaldehyde underwent silylcyanation at relatively high temperature (–40 °C) with 91 % yield and 78 % ee (entry 7). Furaldehyde (entry 8) requires a shorter reaction time. 3-Phenylpropanal (entry 9) reacts smoothly with $(CH_3)_3SiCN$ to give the chiral cyanohydrin. The reaction of TMSCN with citral (entry 10) requires a longer reaction time and occurs with 72 % ee.

Table 2 Trimethylsilylcyanation of aldehydes catalyzed by 1/Ph_3PO



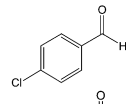
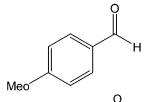
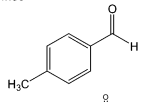
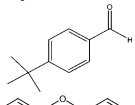
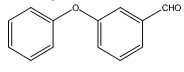
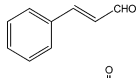
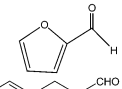
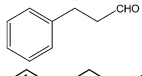
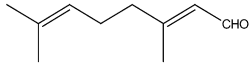
Entry	Substrate	Time (h)	Temp. (°C)	% Yield	% ee (*R* or *S*)
1		18	–50	95	83 (*R*)
2		18	–50	96	86 (*R*)
3		18	–50	92	82 (*R*)
4		22	–45	94	72 (*R*)
5		21	–45	93	73 (*R*)
6		20	–50	93	81 (*R*)
7		26	–40	91	78 (*R*)
8		18	–50	93	78 (*R*)
9		21	–50	93	79 (*R*)
10		24	–50	93	72 (*R*)

Table 3 Catalytic asymmetric cyanosilylation of methyl *p*-chlorophenyl ketone under various condition[a].

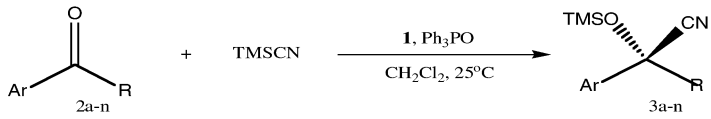
Entry	Solvent	Temp. (°C)	1 (mol %)	Time (h)	Yield (%)	ee (%)	M (mol/l)
1	CH_2Cl_2	25	1	11	98	77	1
2	$CHCl_3$	25	1	12	92	68	1
3	THF	25	1	16	97	72	1
4	Toluene	25	1	20	67	69	1
5	CH_2Cl_2	25	1	21	96	75	0.5
6	CH_2Cl_2	25	1	7	96	73	2
7	CH_2Cl_2	0	1	34	97	76	1
8	CH_2Cl_2	–10	1	72	93	77	1
9	CH_2Cl_2	–40	1	200	10	81	1
10	CH_2Cl_2	25	3	9	97	68	1
11	CH_2Cl_2	25	5	3	99	72	1
12	CH_2Cl_2	25	10	3	98	57	1

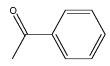
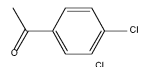
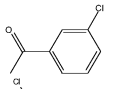
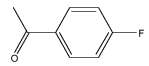
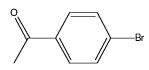
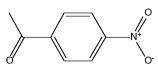
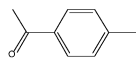
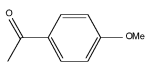
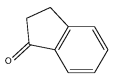
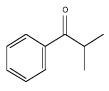
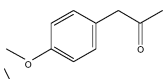
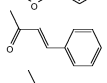
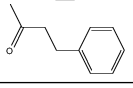
[a]10 mol % Ph_3PO has been used for the cyanosilylation.

The cyanosilylations of ketones employing 1/Ph_3PO have been developed. *p*-Chlorophenyl methyl ketone was chosen as a test substrate to find out the best conditions for the cyanosilylations. Various solvents were used for the cyanosilylations, and CH_2Cl_2 proved to be the proper medium for the reactions (entries 1~4). The substrate concentration of 1 M appears adequate (entries 1, 5, and 6). The reactions were run at four different temperatures and room temperature (r.t.) offers the best outcome (entries 1, 7–9). The amount of **1** for the reactions should be 1 mol % that gives highest % yield and % ee (entries 1, 10–12) (Table 3). The reaction appears to be catalyzed by double-activation process occurring through the catalysis of both chiral Lewis acid and achiral Lewis base. Al(salen) complex functions as a Lewis acid to activate the aldehydic oxygen and Ph_3PO acts as a Lewis base for activation of TMSCN. Entry 1 of Table 3 can be the optimal condition for the cyanosilylation of numerous ketones (Table 4).

o-Chlorophenyl methyl ketone appears susceptible to steric effect compared to *p*-chloro- and *m*-chlorophenyl methyl ketone so as to give the much longer reaction time (23, 11, and 6 h) and lower % ee (62, 77, and 91 %) although the % yields are nearly unaffected (entries 1–4). *p*-Chloro- and *m*-chloro group shorten the reaction time from 19 to 11 and 6 h (entries 1–3). Electron-withdrawing substituents (entries 2, 4–7) exert favorable influence for the cyanosilylation in terms of reaction time (11, 6, 7, 5, and 2 h) to give excellent % yield and good % ee. On the other hand, electron-donating substituents indicate much longer reaction time (~20 h) and give a little sluggish effect on reactions (entries 8 and 9). The negative influence of longer reaction time is also shown in entry 10 (25 h) and entry 11 (40 h). However, cyanosilylation of isobutyl phenyl ketone (entry 11) produces excellent ee (92 %). *p*-Methoxyphenylacetone (entry 12), 4-phenylbutan-2-one (entry 14), and 4-phenylbut-3-en-2-one (entry 13) take relatively short reaction time (3~4 h).

Table 4 Catalytic asymmetric cyanosilylation of ketones catalyzed by **1**/$POPh_3$[a].



Entry	Substrate[b]	Time (h)	Yield (%)	ee (%)	Config.[c]
1		19	93	78	*S*
2		11	97	77	–
3		6	98	91	–
4		23	98	62	–
5		7	95	73	*S*
6		5	96	73	–
7		2	95	72	–
8		21	90	66	*S*
9		20	87	71	–
10		25	87	68	–
11		40	80	92	–
12		3	85	65	–
13		3	90	75	–
14		4	75	60	–

[a]The reactions were run at r.t. 1 mol % **1** was used for all the cyanosilylations. 30 mol % of Ph_3PO has been used except for entry 2. 10 mol % Ph_3PO was employed for the reaction of entry 2.
[b]Substrate concentration is 1M.
[c]Determined by HPLC (see refs. [13,15])

The % ee is quite good, and % yield appears excellent, which could be compared with other works [13–18]. The reaction temperature is milder (r.t.) than the previous cyanosilylations (below –20 °C) [13–15]. Cyanosilylations by others [13–18] usually report quite longer reaction time. On the other hand, *p*-nitrophenyl methyl ketone underwent cyanosilylation for only 2 h in our hand. The oxazaboro-

lidium-catalyzed cyanosilylation of ketones [18] takes place at temperature of 25~40 °C, which is higher than 0 °C at which similar reactions of the aldehydes [26] occur. Similar increase of reaction temperature from aldehydes (–40 ~ –50 °C) [19] to ketones (r.t.) (present reactions) were also observed for our reactions. Compared to aldehydes, ketonic structure maintains steric hindrance so that TMSCN could add to the carbonyl at elevated temperature. However, the steric effects render reaction time much longer for ketones [18] than aldehydes [23]. Such difference of reaction time between aldehydes [19] and ketones (present work) appears not significant in our reactions.

A highly efficient double-activation catalysis by **1**/Ph_3PO has been developed for the enantioselective cyanosilylations of various ketones. The cyanosilylations take place under comparatively mild conditions in terms of temperature and reaction time. Several ketones with electron-withdrawing groups in phenyl ring (entries 2, 3, 5~7) exhibit quite short reaction time that may indicate nucleophilic addition of CN^- group to carboxyl carbon as rate-determining process. Some other ketones without methyl group (entries 12–14) undergo cyanosilylation also for quite short reaction time.

CONCLUSION

An efficient double-activation catalysis by Al(salen)/Ph_3PO has been developed for enantioselective cyanosilylations of various ketones and aldehydes. The cyanosilylations take place under comparatively mild conditions in terms of temperature and reaction time. Particularly, several ketones with electron-withdrawing groups in phenyl ring and other ketones without methyl group undergo cyanosilylation for quite short reaction time (3~7 h), at 25 °C. The similar cyanosilylation of ketones by other workers [13–15] usually requires much reduced temperature (below –20 °C) and longer reaction time (18 h ~ several days) for the improved yield.

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