The Addition of Trimethylsilyl Cyanide to Carbonyl Compounds Using $Yb(OTf)_3$ as Lewis Acid Catalyst

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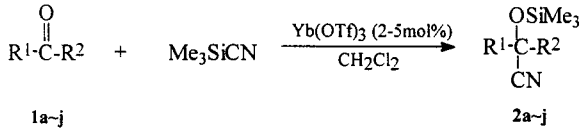
Abstract: $Yb(OTf)_3$ was found to be an effective catalyst in the addition of TMSCN to various carbonyl compounds. Highly chemoselective process was observed in the reactions of α-keto aldehyde acetals. Catalyst $Yb(OTf)_3$ is tolerant to the hydroxy group of glyoxylate hydrates used. Catalytic diastereoselective trimethylsilylcyanation of chiral aldehydes and cyanation of glyoxylate hydrates can be carried out under mild condition with moderate de.

Cyanohydrins, as well as their trimethylsilyl ethers are important building block in organic synthesis.[1] Use of trimethylsilyl cyanide (TMSCN) instead of HCN as a cyano anion source provides an efficient and safer routes to these compounds.[2] In general, the addition reactions of TMSCN to carbonyl compounds proceed in the presence Lewis acid (such as $TiCl_4$, ZnI_2, $AlCl_3$ and $(CH_3)_3SiOTf$), either in stoichiomeric or catalytic amounts. Lanthanide salts such as lanthanide chloride and ytterbium tricyanide have also been employed in these reactions as catalyst.[3] Recently, lanthanide trifluoromethane sulfonates [lanthanide triflates, $Ln(OTf)_3$] have attracted attention because of their catalytic ability in various Lewis acid promoted carbon-carbon bond forming reactions.[4] More recently, Kobayashi[5] reported that $Ln(OTf)_3$ also was an effective catalyst in the reaction of imines with TMSCN. Herein, we wish to report the addition reaction of TMSCN to various carbonyl compounds catalyzed by $Yb(OTf)_3$. The catalytic ability of $Yb(OTf)_3$ and the reactivity of TMSCN to different type of carbonyl groups and corresponding equivalents were examined. We also explored the extent of asymmetric induction in $Yb(OTf)_3$ catalyzed trimethylsilylcyanation reaction of chiral aldehyde and cyanation of chiral glyoxylate hydrate.

The trimethylsilylcyanation reactions (Scheme 1) were carried out following a standard procedure. To a solution of the aldehydes or ketones (0.5 mmol) and $Yb(OTf)_3$ (0.01-0.05mmol) in 2 mL of CH_2Cl_2, TMSCN (0.6 mmol) was added, followed by stirring for a given time (Table 1) at room temperature. The reaction mixture was worked up with saturated aqueous solution of Na_2CO_3 and extracted by Et_2O. The crude product was purified by flash chromatography. The experimental results are listed on Table 1.

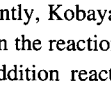


1a~j 2a~j

Scheme 1

It is shown on the Table 1 that in the presence of catalytic amount (2-5 mmol%) of $Yb(OTf)_3$ the addition reactions of TMSCN to aldehydes (**1a-f**) proceeded very well, giving trimethylsilyl ethers of cyanohydrins (**2a-f**) with excellent yields of 81-95%, except **1b** (yield of **2b**: 55%). Using aliphatic ketones (**1g-i**) as substrates exhibited similar results, producing trimethylsilyl ethers of cyanohydrins **2g-i** in yields of 85-90%, while for aromatic ketone **1k** no reaction was observed at all, even increasing the amount of the catalyst and prolonging the reaction time (entry 11). With the same trend, aromatic aldehydes have lower

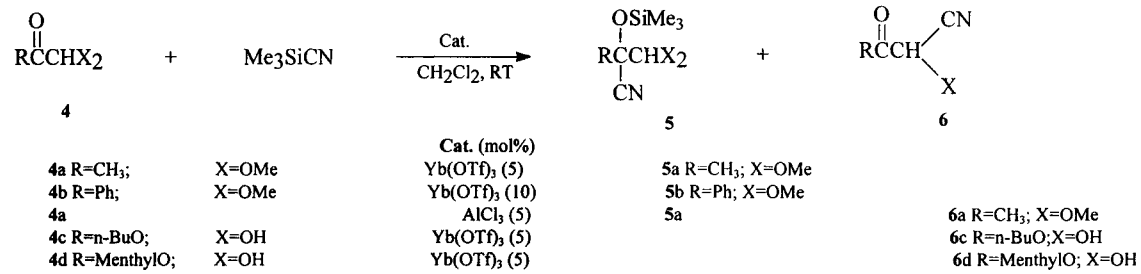
Table 1. $Yb(OTf)_3$ catalysed addition of TMSCN to aldehydes and ketones

Entry		Substrate R^1	R^2	Catalyst (mol%)	Time (hr.)	Yield (%)
1	1a	Ph	H	5	15	86
2	1b		H	5	15	55
3	1c	$n\text{-}C_5H_{11}$	H	2	2	95
4	1d	$(CH_3)_2CH$	H	2	2	91
5	1e	BuOOC	H	5	2	94
6	1f	PhCH=CH	H	5	2	81
7	1g	$-C_5H_{10}-$		5	2	85
8	1h	$Ph(CH_2)_2$	CH_3	5	2	85
9	1i	Et	CH_3	5	2	90
10	1j	 (2R)-	H	5	2	86
11	1k	Ph	CH_3	20	20	0

reactivity than that of aliphatic aldehydes (*cf.* entry 1 and 2 *vs.* entry 3 and 4). The steric effect of the substituents on carbonyl group, for example in the case of cyclohexanone **1g**, does not interrupt the trimethylsilylcyanation reaction (*cf.* entry 7). No conjugation addition was found when cinnamaldehyde **1f** was used (entry 6), but cinnamic cyanohydrin **3** instead of trimethylsilyl ether (**2f**) was obtained after purification by silica column.

It was reported that acetals, as an equivalent of aldehyde, could be activated by the use of $TiCl_4$,[6] $BF_3{\cdot}Et_2O$[7] and transition metal salts[8] in the cyanation reactions with TMSCN. If there were both acetal and carbonyl groups in identical molecule, it is possible to get a mixture of trimethylsilyl ether of cyanohydrin and cyanation product of acetal. In contrast, when hexaldehyde dimethyl acetal was employed under $Yb(OTf)_3$ catalyzed trimethylsilylcyanation reaction condition, it did not work at all, even using 10 mol% catalyst. We chose α-keto aldehyde dimethyl acetals (**4a-b**) to examine the chemoselectivity of $Yb(OTf)_3$ catalyzed trimethylsilylcyanation reactions (Scheme 2). The results from the investigations indicated that the reaction exclusively occurred on the carbonyl group, giving trimethylsilyl ethers of cyanohydrins (**5a-b**) in yields of 87 and 83% respectively with excellent chemoselectivity. However, for catalyst $AlCl_3$, both ketone carbonyl and acetal group could react with TMSCN, forming a mixture of **5a** and **6a** in the yield of 92%. The chemoselectivity of the reaction is 1.7 : 1 (**5a** : **6a**=63 : 37 determined by ^{1}HNMR).

The addition reaction of TMSCN to (4R)-2,2,-dimethyl-1,3,-dioxolane-4-carboxaldehyde (**1j**) catalyzed by $Yb(OTf)_3$ also showed to be highly



4

		Cat. (mol%)
4a R=CH_3;	X=OMe	$Yb(OTf)_3$ (5)
4b R=Ph;	X=OMe	$Yb(OTf)_3$ (10)
4a		$AlCl_3$ (5)
4c R=n-BuO;	X=OH	$Yb(OTf)_3$ (5)
4d R=MenthylO;	X=OH	$Yb(OTf)_3$ (5)

5

5a R=CH_3; X=OMe
5b R=Ph; X=OMe
5a

6

6a R=CH_3; X=OMe
6c R=n-BuO;X=OH
6d R=MenthylO; X=OH

Scheme 2

chemoselective. The aldehyde carbonyl group exclusively reacted and ketal group remained entirely in the product **2j**. The diastereomeric excess (de) of the **2j** was 21%, determined by the ratio of absorptions of diastereomeric protons and carbons in ^1H and ^{13}C NMR spectra of **2j**.

It is interesting to note that if glyoxylate hydrate **4c** was used instead of aldehyde acetal, the $Yb(OTf)_3$ catalyzed cyanation reaction could proceed under the same condition (2hr, at room temperature) to give cyanohydrin **6c** in yield of 91% (Scheme 2). The catalytic ability of $Yb(OTf)_3$ appears not to be affected by hydroxy group on the substrate.[9] Although, in general, both acetal group and aldehyde hydrate can be treated as the equivalents of aldehyde group, they possess very different reactivity in this catalytic cyanation. Obviously, the $Yb(OTf)_3$ catalyzed cyanation reactions of glyoxylate hydrates provide a convenient synthetic method to α-ester cyanohydrins. When chiral glyoxylate hydrate **4d** was employed, catalytic diastereoselective cyanation occurred, producing chiral α-ester cyanohydrin **6d** in yield of 82%. The diastereoselectivity of the reaction was 30% de, determined by the same method as above.

In summary, $Yb(OTf)_3$ was found to be an effective catalyst for the addition of TMSCN to various carbonyl compounds, which showed the reactions were highly chemoselective. Aromatic ketones, acetals and ketals are unreactable, and aromatic aldehydes exhibit relatively low reactivity in the $Yb(OTf)_3$ catalyzed trimethylsilylcyanation. Catalyst $Yb(OTf)_3$ is also tolerant to the hydroxy group of glyoxylate hydrates used. It is possible to perform catalytic diastereoselective trimethylsilylcyanation of aldehydes and cyanation of glyoxylate hydrates by using $Yb(OTf)_3$ as catalyst. Although the de of the catalytic diastereoselective reactions is moderate, further improvement and potential application in the synthesis of chiral cyanohydrin are expected.

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