Room-temperature synthesis of enantioenriched non-protected cyanohydrins using vanadium(salalen) catalyst†

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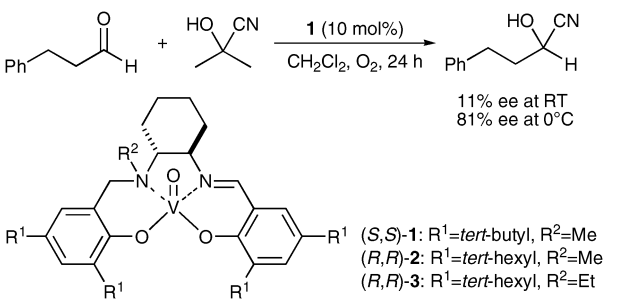
Room-temperature synthesis of enantioenriched non-protected cyanohydrins using acetone cyanohydrin as the cyanide source was achieved by V(salalen) catalyst. Aliphatic aldehydes underwent the cyanation with 89–95% ee in the presence of only 0.2–0.4 mol% catalyst. Aromatic cyanohydrins were also obtained in high enantiomeric excesses under modified conditions.

Optically active cyanohydrins are highly useful chiral building blocks that can be readily transformed into a wide variety of chiral molecules such as α-hydroxy carbonyl compounds and β-amino alcohol derivatives.[1] Asymmetric cyanation of carbonyl compounds is the most well-studied approach for the synthesis of enantioenriched cyanohydrins, and many efficient methods have been developed by using trimethylsilyl cyanide (TMSCN) as cyanating agent.[1,2] However, this cyanide source is volatile and relatively expensive. Thus, the development of asymmetric cyanation that employs other cyanide sources such as cyanoformate, cyanophosphate and potassium cyanide/acetic anhydride has attracted increasing attention.[3–5] The utilization of these cyanating agents including TMSCN provides protected cyanohydrins. On the other hand, Maruoka and co-workers reported asymmetric cyanation using an alternate cyanide source, acetone cyanohydrin, that provides non-protected cyanohydrins.[6,7] However, a relatively high catalyst loading and low reaction temperature were required for the asymmetric induction in Maruoka's methods. Nonetheless, the direct synthesis of non-protected cyanohydrins with inexpensive and easily manageable acetone cyanohydrin instead of the above-mentioned cyanide sources, providing protected cyanohydrins, is very attractive in terms of atom and step economies.[8] Although hydrogen cyanide also provides cyanohydrins with no protecting group, the extreme toxicity and high volatility cause handling difficulties, especially in the laboratory.[9] A major problem in the direct asymmetric synthesis of non-protected cyanohydrins is reverse cyanation which is a potential racemization pathway that renders the highly enantioselective cyanation difficult. In order to suppress the reverse cyanation, low reaction temperature is generally needed.[10] Thus, room-temperature synthesis of non-protected cyanohydrins with high optical purity is still a challenging theme in the field of asymmetric cyanation chemistry.[11,12] In this communication, we report room-temperature synthesis of non-protected cyanohydrins using acetone cyanohydrin, in which aliphatic aldehydes are transformed into the non-protected cyanohydrins with 89–95% ee in the presence of only 0.2–0.4 mol% catalyst. Aromatic aldehydes also undergo the cyanation with high enantioselectivity of more than 90% ee under a modified reaction conditions at room temperature.

To enhance the synthetic utility of acetone cyanohydrin as a cyanide source, we have reported on the vanadium(salalen)-catalyzed asymmetric cyanation using acetone cyanohydrin in an oxygen atmosphere, a process which produces non-protected cyanohydrins in high optical yields.[13,14] For example, complex **1** effectively promoted the reaction of 3-phenylpropanal for 24 h and furnished the cyanohydrin with the high enantioselectivity of 81% ee at 0 °C but in very low enantiomeric excess at room temperature (Scheme 1). In addition, we found that enantioenriched cyanohydrins gradually racemized under the reaction conditions, and that the racemization occurred more rapidly at room temperature. Thus, we had considered the possibility that the achievement of high enantioselectivity is difficult at room temperature. However, in the examination of the relationship between the aldehyde conversion and the enantiomeric excess of the cyanohydrin in the reaction of 3-phenylpropanal with 1 mol% of vanadium(salalen) **1** as catalyst at 25 °C, we found that the ee value remained at the high level of 80% ee until the aldehyde was exhausted (Fig. 1). After the completion of the aldehyde conversion, the enantiomeric excess was slowly depleted as time progressed. The racemization rate was dependent on the catalyst loading, and the ee value was rapidly decreased in the presence of 10 mol% of the catalyst. This finding encouraged us to reinvestigate the vanadium-catalyzed asymmetric cyanation at room temperature.

To improve the enantioselectivity at room temperature, an array of vanadium(salalen) complexes were prepared and tested. Bulky substituents at the C3- and C3′-positions are essential, and the use of the more sterically demanding *tert*-hexyl group was more effective than *tert*-butyl group.



Scheme 1 V(salalen)-catalyzed cyanation under the previous conditions.[13]

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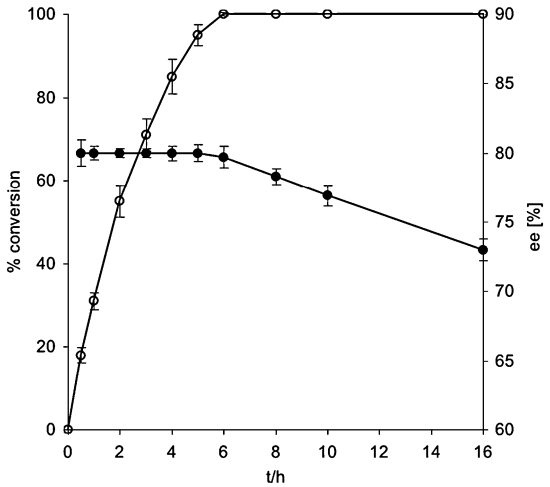


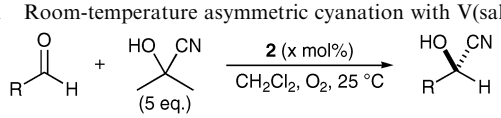
Fig. 1 A plot of conversion (○) and enantiomeric excess (●) *vs.* time in asymmetric cyanation of 3-phenylpropanal with 5 equivalents of acetone cyanohydrin in the presence of 1 mol% of V(salalen) complex **1**. Each data point is an average of at least four runs.

Although *N*-ethyl **3** gave higher enantiomeric excess than *N*-methyl **2** in the previous study at 0 °C for 24 h, this study disclosed that both complexes display comparable asymmetric induction at the initial stage. Thus, we chose more simple complex **2** as the optimum catalyst.

In the presence of catalyst **2**, various aldehydes underwent the cyanation with high enantioselectivity at room temperature (Table 1). In the reaction of aliphatic aldehydes with no branch at α-position, the cyanohydrins were obtained with 89–91% ee (entries 1–4). α-Branched aldehydes were also good substrates for the cyanation, and higher enantioselectivity of 92–95% ee was observed (entries 5–8). It is noteworthy that the cyanation completed within several hours in the presence of only 0.2–0.4 mol% of catalyst. Unfortunately, however, the reaction of an aromatic aldehyde, benzaldehyde, was diminished (entry 9).

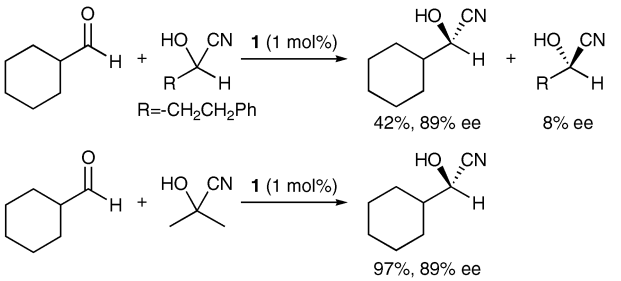
In this cyanation reaction, the produced cyanohydrins can also work as cyanating agent. Thus, we examined the asymmetric cyanation of cyclohexanecarbaldehyde with 5 equivalent of racemic cyanohydrin derived from

Table 1 Room-temperature asymmetric cyanation with V(salalen) **2**



Entry	R	*x* (mol%)	*t*/h	Yield[a] (%)	ee[b,c] (%)
1	$PhCH_2CH_2$	0.2	6.5	95	89 (*S*)
2	n-C_7H_{15}	0.2	7	92	91
3	Me_2CHCH_2	0.2	3	87	89 (*S*)
4	$BnO(CH_2)_3$	0.4	7	87	89
5	Me_2CH	0.4	4	85	94 (*S*)
6	c-C_5H_9	0.4	3	92	92 (*S*)
7	c-C_6H_{11}	0.4	2	92	95 (*S*)
8	Me_3C	0.4	2	89	93 (*S*)
9	Ph	1.5	6	66[d]	29 (*S*)

[a] Isolated yield. [b] Determined by GC or HPLC analysis after conversion to the corresponding acetate or benzoate. [c] Determined by comparison of the optical rotation with literature value. [d] Determined by ^{1}H NMR analysis (400 MHz).

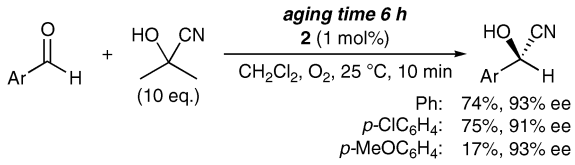


Scheme 2 Independence of enantioselectivity on cyanide source.

3-phenylpropanal in the presence of complex **1** (Scheme 2). As the result, the cyanohydrin of cyclohexanecarbaldehyde was obtained in 42% with 89% ee after 6 h. The ee value was comparable with that observed in the reaction with acetone cyanohydrin. It is of note that the 3-phenylpropanal-derived cyanohydrin was recovered with 8% ee in the (*R*)-enriched form indicating preferential consumption of the (*S*)-enantiomer. Since the (*S*)-cyanohydrin was selectively produced in the reaction of 3-phenylpropanal with acetone cyanohydrin, this enantiomer-differentiating decomposition of cyanohydrins accounts for the time-dependent erosion of the enantioselectivity. Still, in the presence of 5 equivalents of acetone cyanohydrin, the decomposition process was effectively suppressed and the high enantioselectivity can be maintained to a significant extent.

When acetone cyanohydrin was treated with complex **1** in dichloromethane in an oxygen atmosphere, acetone cyanohydrin gradually decomposed to generate acetone, which was observed by ^{1}H NMR and GC analyses. Moreover, the production of hydrogen cyanide was directly detected by ^{13}C NMR analysis.[15–17] Thus, we conducted the cyanation of 3-phenylpropanal after aging for 2 h and 6 h. A jump in the aldehyde conversion in accordance with the aging time was observed (Fig. 2). With 6 h aging, the cyanation completed within 1 h. In these cases, the enantioselectivities were identical with those observed in the reaction without aging. On the basis of this finding, we conducted the asymmetric cyanation of benzaldehyde under the reaction conditions with 6 h aging (Scheme 3). As we expected, the cyanohydrin was obtained in high enantiomeric excess of 93% ee just after 10 min in the presence of 10 equivalent of acetone cyanohydrin. Chloro- and methoxybenzaldehydes also underwent the cyanation with high enantioselectivity, but the reaction of *p*-methoxybenzaldehyde was sluggish. Prolongation of the reaction time led to the improvement of the yield, but the enantioselectivity was significantly deteriorated. This aging condition is also applicable to aliphatic aldehydes, and the cyanohydrins with high enantioselectivity comparable to that observed under the reaction conditions without aging were obtained with much shorter reaction time.

Considering all the results together, we propose a plausible mechanism of this vanadium-catalyzed cyanation using acetone cyanohydrin. The vanadium(salalen) complexes play two roles: (a) the generation of hydrogen cyanide and (b) cyanation of aldehydes. The complexes decompose acetone cyanohydrin to generate hydrogen cyanide, which serves as a real cyanating agent. Then, aldehyde is activated by a Lewis acidic vanadium complex and reacts with hydrogen cyanide intermolecularly or



Scheme 3 Asymmetric cyanation of aromatic aldehydes under aging conditions.

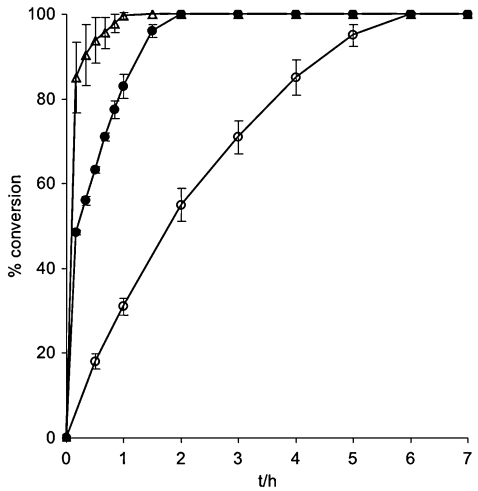


Fig. 2 Time dependence of conversion in the presence of 1 mol% of complex **1** after aging for 0 h (○), 2 h (●) and 6 h (△). Each data point is an average of at least four runs.

with vanadium cyanide intramolecularly to produce enantio-enriched cyanohydrin.

In summary, we achieved the highly enantioselective synthesis of non-protected cyanohydrins at room temperature, which was realized by the vanadium(salalen) catalysis with acetone cyanohydrin as a cyanide source. Various aliphatic cyanohydrins were obtained in high yield with high enantioselectivity ranging from 89 to 95% ee in the presence of only 0.2–0.4 mol% of the catalyst. While aromatic aldehydes showed poor enantioselectivity under the conditions, high enantioselectivity could be obtained under the reaction conditions with aging. Further studies to clarify the reaction mechanism and other applications of the vanadium catalysis are ongoing.

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