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A Remarkable Titanium-Catalyzed Asymmetric Strecker Reaction using Hydrogen Cyanide at Room Temperature

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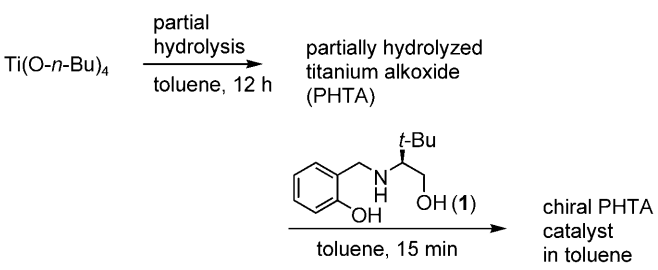
Abstract: Close to perfect enantioselectivity (up to 98% *ee*) is obtained for the formation of amino nitriles using hydrogen cyanide (HCN) as the cyanide source at room temperature for the first time. In an operationally simple process, the catalyst generated from a partially hydrolyzed titanium alkoxide (PHTA) and (*S*)-*N*-salicyl-β-amino alcohol ligand, catalyzes the cyanation of imines in a short reaction time.

Keywords: enantioselective cyanation; hydrogen cyanide; imines; *in-situ* IR studies; Strecker reaction; titanium catalyst

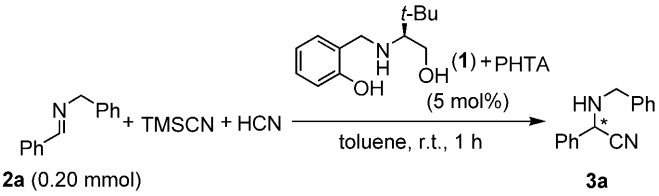
The enantioselective addition of carboxyl group or its equivalent onto imines constitutes an elegant method for the synthesis of α-amino acids.[1] The most important example of this strategy is the Strecker reaction[2] or the cyanation of preformed imines followed by hydrolysis. After the first catalytic enantioselective cyanation of imines in 1996 by Lipton and co-workers using a chiral diketopiperazine as an organo catalyst,[3] significant progress has been made[4] in the design of both organic[5–7] and metal[8–11] catalysts achieving very high enantioselectivities. The main drawbacks of most of these methodologies are the requirement of very low temperatures (−75 to −40 °C) and the use of expensive TMSCN as the cyanide source which may preclude the use of Strecker reaction on the large-scale synthesis of chiral amino acids. Although high enantioselectivities (up to 98% *ee*) were recently reported at temperatures 0–23 °C using TMSCN as the cyanide source,[11] achieving higher enantioselectivities using cheaper cyanide sources such as HCN at these temperatures remains a challenge. To the best of our knowledge, higher enantioselectivities (>90% *ee*) have not been reported at temperatures higher than −75 °C using HCN[12] as the cyanide source with organic[5] or metal catalysts.[8] This may be mainly due to the competing non-catalytic racemic reaction pathway with HCN at these temperatures. *Herein, we report the first enantioselective cyanation of imines at room temperature using HCN as a primary cyanide source.*

In a recent report,[11d] we disclosed the use of a partially hydrolyzed titanium alkoxide (PHTA)[13] together with the chiral ligand (*S*)-2-[(1-hydroxy-3,3-dimethylbutan-2-ylamino)methyl]phenol (**1**) as an efficient catalyst system (Scheme 1) for the enantioselective cyanation of imines using TMSCN as the cyanide source and *n*-BuOH as the proton donor giving up to 98% *ee* at room temperature. Attempts to use HCN[14,15] as the cyanide source instead of TMSCN at room temperature resulted only in the formation of racemic product **3a** (Table 1, entry 1). Gratifyingly, when 1 equivalent of HCN was used in combination with 1.5 equivalents of TMSCN, 78% *ee* was observed with complete conversion in 1 h (Table 1, entry 2).



Scheme 1. Preparation of chiral catalyst for cyanation reactions.

Table 1. Initial cyanation of *N*-benzylidene-1-phenylmethanamine (**2a**) using HCN.



Entry	TMSCN [mmol]	HCN [mmol]	Conversion [%][a]	*ee* [%][b]
1	0.00	0.30	95	*rac*
2	0.30	0.20	99	78
3	0.18	0.06	97	83
4	0.12	0.12	99	83
5	0.06	0.18	95	44

[a] Determined by ^{1}H NMR spectroscopy.
[b] Analyzed by HPLC.

This observation encouraged us to use a mixture of TMSCN and HCN while keeping the total concentration of cyanide as 1.2 equivalents with respect to the imine **2a**. The *ee* increased up to 83% (Table 1, entry 4) when a 1:1 mixture of TMSCN and HCN was used. No appreciable change in enantioselectivity was observed with a higher ratio of TMSCN (Table 1, entry 3). However, the enantioselectivity dropped to 44% at a TMSCN:HCN ratio of 1:3 (Table 1, entry 5). This loss in the selectivity could be due to competing non-catalyzed cyanation reaction in the presence of large amounts of HCN.

In order to limit the amount of HCN present at any one time in the reaction mixture, the HCN was added as a solution in toluene slowly over a period of 1 h after the addition of TMSCN. Using this protocol, up to 91% *ee* with quantitative conversion of **2a** to **3a** was obtained when equal amounts of TMSCN and HCN were used (Figure 1). To improve on the cost effectiveness of the reaction, it is desirable to reduce the quantity of the expensive TMSCN while maintaining the best conversions and enantioselectivities. In this regard, the TMSCN:HCN ratio was varied while the total amount of cyanide was maintained as 1.2 equivalents with respect to the imine. Interestingly, both the selectivity and the conversion of the reaction were not affected much when the TMSCN:HCN ratio was varied from 50:50 to 5:95. As a comparison, in the absence of TMSCN, only 11% *ee* was obtained with the slow addition of HCN. These results show that a small amount of TMSCN is necessary to achieve high enantioselectivities. Further optimization revealed that 1.2 equivalents of HCN with respect to the imine in the presence of 0.10 equivalent (10 mol% with respect to imine) of TMSCN can be used to achieve high enantioselectivities. The catalyst loading can be reduced to 2.5 mol% without any significant drop in enantioselectivity and catalytic activity.[16]

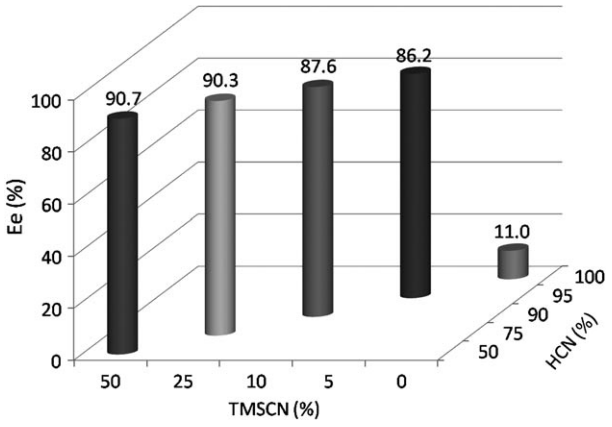
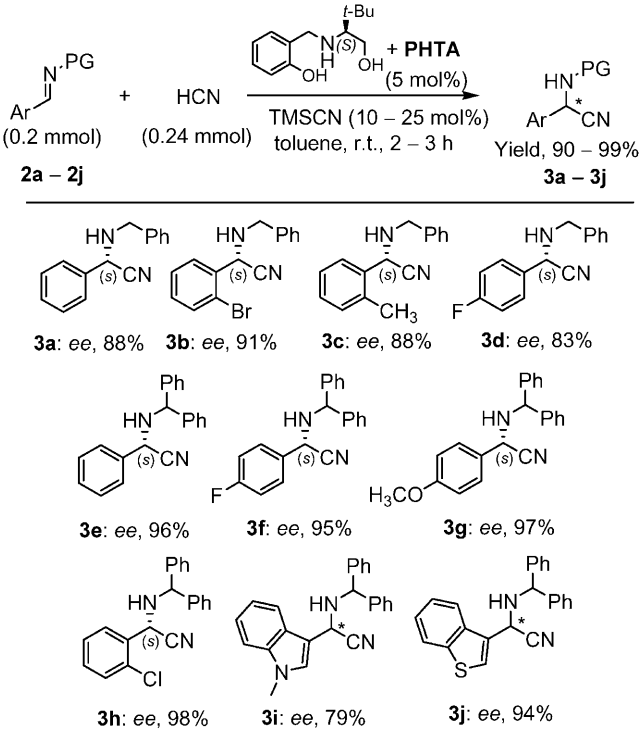


Figure 1. Enantioselectivities obtained for the cyanation of **2a** using variable ratios of TMSCN and HCN.

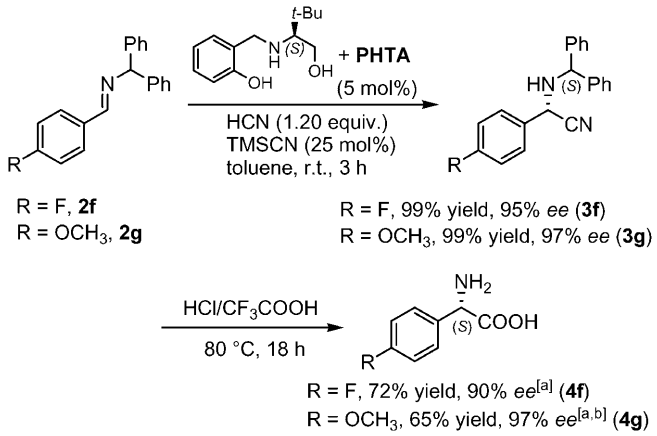
A variety of *N*-benzyl- and *N*-benzhydryl-substituted imines was examined as substrates under the optimized conditions at room temperature (Scheme 2). Benzyl-protected imines **2a**–**d** gave high enantioselectivities (80–91% *ee*), while up to 98% *ee* was obtained with benzhydryl-protected imines **2e**–**j**. When *N*-benzhydrylimines were used as substrates, we found that the reaction was slower with 10 mol% of TMSCN.



Scheme 2. Substrate scope for the cyanation of imines using HCN in presence of 10–25 mol% of TMSCN. The toluene solution of HCN was added slowly over the period of 1 h using a syringe pump.

Further optimization studies revealed that 25 mol% of TMSCN and 1.2 equivalents of HCN were necessary to obtain high enantioselectivities and quantitative conversion of **2e–j**. Substitution at *o*-positions as in **3b**, **3c** and **3h**, has a beneficial effect on the enantioselectivity of cyanation. Cyanation of *p*-OMe (**2g**) and *o*-Cl (**2h**) substituted imines gave very high enantioselectivities. The amino nitriles **3a–g** were hydrolyzed to the corresponding amino acids **4a–g** and the configurations were assigned in comparison with their reported specific rotation values.[16]

To illustrate the applicability and reproducibility of the present methodology, the cyanation of one gram each of imines **2f** and **2g** was carried out and further converted[17] to the corresponding amino acids **4f** and **4g** (Scheme 3). The amino acids **4f** and **4g** are chiral intermediates that can be potentially used for the synthesis of (3*S*)-4-benzyl-3-(4-fluorophenyl)morpholin-2-one[18] and amoxicillin,[19] respectively.



Scheme 3. Cyanation of gram quantity of **2f** and **2g** and hydrolysis to amino acids. [a] Calculated from the specific rotation values. [b] Yield and *ee* of the corresponding Boc-protected **4g**.

The possible role of TMSCN in the catalytic reaction remains ambiguous. One possibility may be that the real active nucleophile is derived from TMSCN while the HCN present is simply a proton donor which serves to eliminate the product from the catalyst as proposed by Shibasaki et al.[9b] During this elimination process, TMSCN is regenerated *in situ* and may be utilized for further reaction. In order to understand the catalytic cycle and the role of the small amounts of TMSCN, the reactivity difference between TMSCN and HCN was studied. The progress of the reactions was monitored by *in situ* infrared (IR) spectroscopy and a typical cyanation reaction of **2a** is depicted in Figure 2. In each cyanation reaction, the respective cyanide source was added in one portion. The initial cyanation of **2a** with either HCN or TMSCN took place at similar rates (Figure 3). As the reaction proceeds, it is clear that the overall cyanation of **2a** with HCN gave better conversion than TMSCN. Interestingly, in the presence of 10 mol% of TMSCN, addition of HCN to imine **2a** is significantly rapid and $>50\%$ of the reaction was completed within 8 min (Table 2, entry 3). To gain more insight on the initial progress of the reaction, the relative rates of the reactions were analyzed based on the time taken for 50% conversion ($t_{1/2}$) of **2a** to aminonitrile **3a**.

In the presence of 10 mol% of TMSCN, the cyanation of **2a** was 2.5 and 3.0 times faster than (Table 2, entries 3 *vs.* 1 and 2) that with HCN and TMSCN alone, respectively. The enhanced reactivity in the presence of 10 mol% TMSCN may be attributed to the initial addition of TMSCN to imine followed by the product elimination by HCN, that is, HCN was used as a proton source to regenerate TMSCN. This could be rationalized by evaluating the reactivity of TMSCN with imine in the presence of other proton sources. Our observations show that the reaction of TMSCN with imine **2a** in the presence of protic addi-

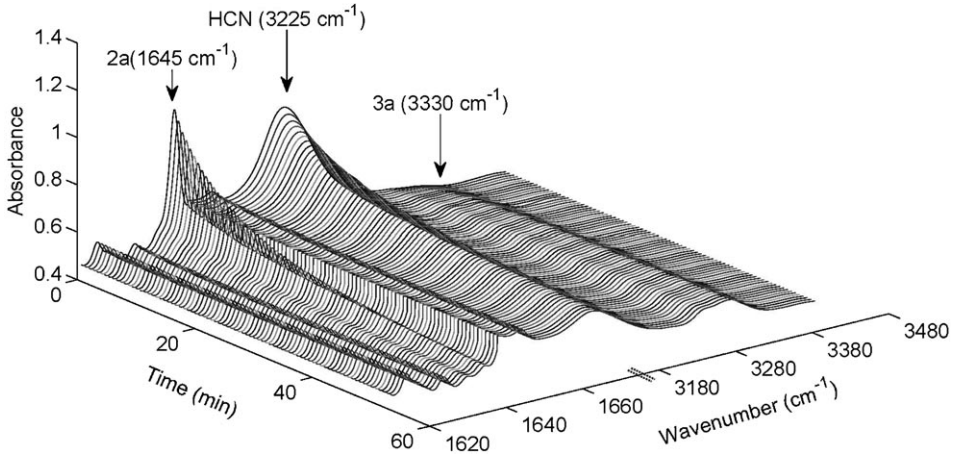


Figure 2. Reaction progress for the cyanation of **2a** using HCN and 10 mol% of TMSCN. Disappearance of **2a** and HCN and subsequent formation of **3a** are shown.

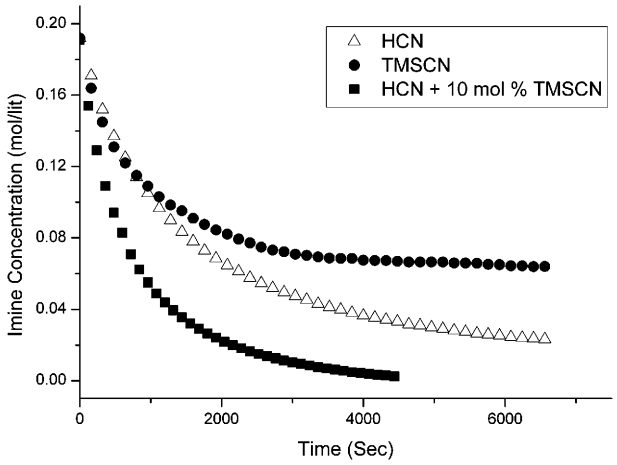


Figure 3. Reaction profile for the cyanation of **2a** using (i) HCN (△), (ii) TMSCN (●) and (iii) HCN + 10 mol% TMSCN (■). Disappearance of **2a** was monitored by *in situ* IR.

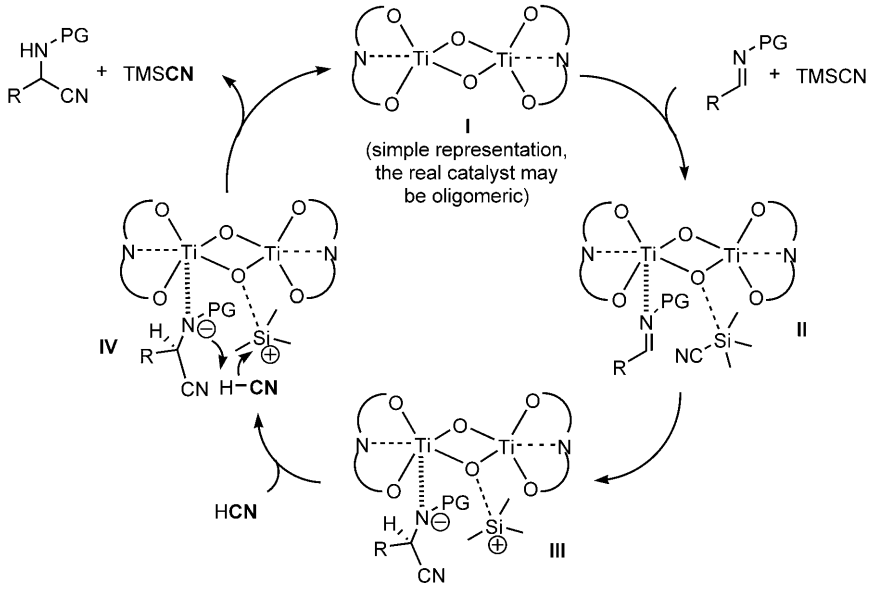
Table 2. Reaction time needed for 50% conversion of imine **2a** to **3a**.

Entry	Catalyst [mol%]	HCN [mmol]	TMSCN [mmol]	$t_{1/2}$ [min][a]
1	5	0.30	–	18.8
2	5	–	0.30	22.5
3	5	0.30	0.02	7.7
4	5	–	0.30	3.0[b]
5	5	–	0.30	6.7[c]
6	–	–	0.30	108.3
7	–	0.30	–	48.3

[a] Time required for 50% conversion of **2a**.
[b] 1.0 equiv. of *n*-butanol was added as proton source, 85% *ee*.
[c] 1.0 equiv. of water was added as proton source, 78% *ee*.

tives such as *n*-butanol and water[16] proceeds with similar reactivity (Table 2, entries 4 and 5) to that of HCN/TMSCN system (Table 2, entry 3). The reactivity of TMSCN and HCN with imine **2a** in the presence and absence of chiral PHTA catalyst system was also studied by *in-situ* IR.[16] The cyanation of imine **2a** with TMSCN in the presence of the catalyst was found to be 4.8 times faster than the non-catalyzed reaction (Table 2, entry 2 *vs.* 6). On the other hand, the catalyst has very little influence on the reactivity of HCN addition (Table 2, entry 1 *vs.* 7). The results indicate that TMSCN may be more readily activated by PHTA catalyst than that of HCN.

Based on the following observations, the proposed catalytic cycle (Scheme 4) would explain the possible role of TMSCN in the reaction. The key observations are, (i) the IR absorptions[16] in the range of 420–700 cm^{-1} suggest the possible presence of Ti–O–Ti bridged complex (**I**, Scheme 4) in solution.[20,21] (ii) Under the reaction conditions we did not observe any IR absorptions around 2100 cm^{-1} as expected[20a] for Ti–CN vibrations. The cyanide group is either weakly bonded to titanium or the intermediate with Ti–CN bond may be extremely short-lived. (iii) The reactivity of TMSCN is 4.8 times faster in the presence of catalyst and this indicates the possible activation of TMSCN prior to reaction with the imine (**II**, Scheme 4). (iv) In the presence of 10 mol% of TMSCN, the cyanation with HCN (Table 2, entry 3) was significantly faster than that of either TMSCN or HCN alone (Table 2, entries 1 and 2). Finally (v), the overall cyanation with TMSCN/protic additive and HCN/TMSCN system proceeds with comparable reactivity and this suggests the possibility of initial addition by TMSCN. HCN presumably acts as proton source and thus accelerates the formation of amino



Scheme 4. Proposed catalytic cycle for cyanide addition.

nitriles (**IV**, Scheme 4) and regenerates the TMSCN for further addition to imines. A similar catalytic cycle was proposed by Shibasaki et al.[9b] for the cyanation of *N*-fluorenylimines using the mixture of TMSCN and HCN. Our proposed mechanistic cycle does not provide a rationale for the observed enantioselectivities and further investigation on the reaction intermediates and the structure of the catalyst is needed.

In summary, a highly enantioselective cyanation of imines using HCN is described at room temperature. In view of the importance of natural and unnatural α-amino acids in the fine chemicals and pharmaceutical industries, the current methodology offers the possibility of utilizing the Strecker reaction economically for large-scale synthesis. The mild reaction conditions and the operational simplicity render this atom-economic cyanation process extremely attractive. *To the best of our knowledge, this is the first report on the enantioselective Strecker reaction at room temperature using HCN as the cyanide source that gives a very high level of enantioselectivity up to 98% ee.*

Experimental Section

General Procedure for the Asymmetric Cyanation of Imines

Caution: *HCN is an extremely poisonous liquid and boils at 26 °C. Proper safety precautions will need to be adhered to and appropriate safety equipment for example, cyanide detector and personal protection equipment MUST be used. Reactions must be carried out in a well ventilated fume hood.*

To the chiral ligand (0.02 mmol) in toluene (0.10 mL), PHTA precatalyst[13] (0.20 mL, 0.02 mmol) was added and stirred for 15 min. Imine (0.20 mmol) and trimethylsilyl cyanide (0.02 or 0.05 mmol) were added to the catalyst solution in order. HCN[14] (0.24 mmol, 0.48 mL of 0.50 M solution in toluene) was added slowly over the period of 1 h using a syringe pump. After the addition was complete, the reaction mixture was stirred at room temperature (23 °C) for 1–2 h. The reaction mixture was filtered through celite, washed with dichloromethane and the solvent evaporated to dryness. In many cases no further purification was necessary. HPLC analysis of the amino nitriles was performed to determine the enantiomeric excess (*ee*).

Acknowledgements

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