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**PAPER**

# Asymmetric cyanation of nitroalkenes catalyzed by a salen–titanium catalyst†

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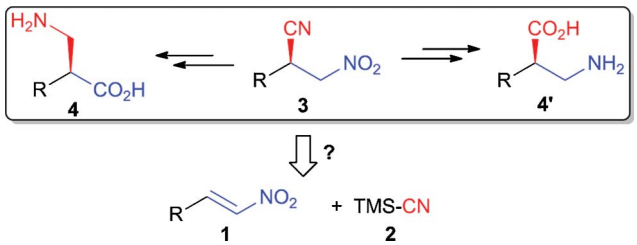
The salen–Ti complex catalyzed cyanation of nitroolefins was accomplished *via* the silyl nitronate intermediate for the synthesis of chiral β-nitronitriles with e.r. up to 92 : 8 and high yields (up to 90%). The catalyst also kept a high turnover frequency at room temperature. The yield and enantioselectivity of the protocol were slightly affected even in a 10 mmol scale.



## Introduction

The β-peptides, unlike α-peptides, display various advantages such as higher structural diversity, shorter residues to form helix, as well as more stable toward enzymatic degradation.[1–2] Thus, β-peptides have received growing attention for their potential pharmaceutical applications.[3] Although many methodologies have been developed for the synthesis of β-amino acids, the main shortcomings, also for other general asymmetric catalysis, are that different catalytic systems are necessary for obtaining the different enantioisomers.[4] As both nitro and nitrile groups are versatile functional frameworks, a single enantioisomer of chiral β-nitronitrile (**2**, Scheme 1) could be easily transformed to the two enantioisomers of the corresponding unnatural chiral β-amino acids (**3**, Scheme 1).[5] The simplest method to obtain this versatile synthon was the asymmetric Michael addition of cyanides to nitroolefins.[6] Although various methodologies for the Michael addition of nucleophiles to nitroolefins have been developed in recent years,[7] asymmetric protocols for conjugate cyanation of nitroolefins have rarely been reported. Only two Cinchona alkaloids derived tetralkylammoniums catalyzed cases have been reported.[8] However, these examples both lack high catalytic efficiencies. Reactions always proceeded over days to give ideal results. In addition, to date there is no conclusive study of the mechanism.

Organometallic catalysis occupies many advantages for the chiral ligands and metals are easily tunable. In terms of the organometallic catalyzed conjugate cyanations,[9] recent reports have just focused on exploiting unsaturated carbonyl substrates such as enones,[10] unsaturated imides,[11] unsaturated *N*-acylpyrroles,[6,7] and unsaturated diesters.[13] Feng and co-workers reported a cinchonidine–titanium complex catalyzed cyanation of activated olefins (**5**, Fig. 1) with a diphenol as an additive.[13] Unfortunately, their protocol was not compatible with using nitrostyrene (**1′**, Fig. 2) as the substrate. However, we have a different perspective on its structural property. We proposed that the more stable delocalized nature of **1′** and less polarization of its Michael receptor fragment lead to its poorer reactivity towards the conjugate cyanation. In contrast, nitroolefin **1** does not contain an aromatic ring to construct a huge delocalized system. It is much easier to break the conjugated system of alkyl nitroolefin **1** than that of aryl nitroolefin **1′**. From this point of view, alkyl nitroolefins (**1**), which are more polarized and lack aromatic delocalization, would be ideal Michael receptors for the conjugated cyanation.




**Scheme 1** Overview for the synthetic application of β-nitronitriles to β-amino acids.

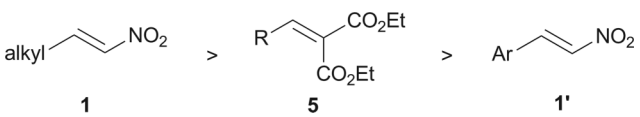



**Fig. 1** Relative polarization of different conjugated olefins.

Herein, we wish to report a salen–titanium catalyzed asymmetric conjugate cyanation of nitroalkenes. Unlike general reported catalytic systems for the conjugate cyanation, protonic additives were not essential in this work. *In situ* $^1$H NMR investigation was also accomplished to clarify the hypothesis of this interesting process.

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† Electronic supplementary information (ESI) available: NMR data and spectra of the starting materials **1**, HPLC and NMR spectra of the products. See DOI: 10.1039/c1ob05899a

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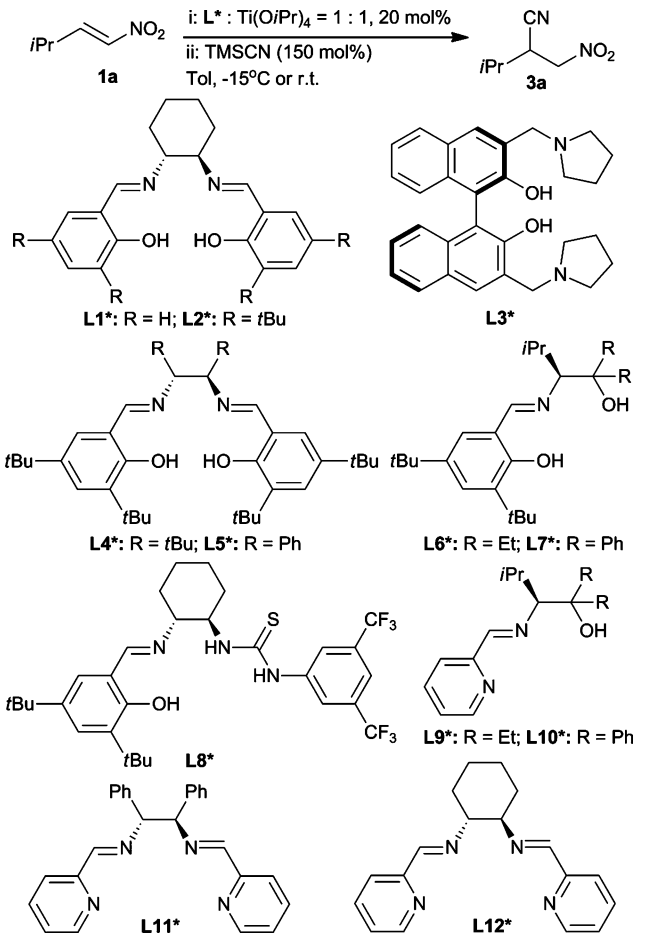
## Results and discussion

To confirm our hypothesis, we initially found that quinine in combination with $Ti(O^iPr)_4$ indeed can catalyze the conjugate addition of TMSCN to **1a** with very poor conversion and enantioselectivity at low temperature (–40 °C). No reaction was observed using only $Ti(O^iPr)_4$ to catalyze this conjugate cyanation. We considered that quinine–Ti could not construct a favorable chiral catalytic center. And most importantly, this result suggested that the quinine ligand was not able to affect titanium to display strong enough Lewis acidity to activate TMSCN. Then we intended to use a salen-type chiral ligand to improve the enantioselectivity.

Various chiral ligands were screened in the conjugated cyanation of **1a** (Scheme 2). As we expected, conjugate cyanation of **1a** with TMSCN was smoothly carried out at –15 °C with a moderate enantioselective ratio (e.r.; 82 : 18) and a high conversion catalyzed by a **L1***–Ti complex. Notably, it was critical that the structures of practical ligands (**L1***–**L5***) must contain two phenolic hydroxy groups which aided in forming strong Lewis acidic Ti-complex. Thus, **L6***–**L12*** in combination with $Ti(O^iPr)_4$ did not work to catalyze the model reaction even at room temperature for days. Salen–Ti complexes have been widely used in the cyanation of ketones,[14a,b] aldehydes,[14c] as well as epoxides.[14d] However, there was no report on the salen–Ti catalyzed conjugate cyanation of nitroolefins. Based on this encouraging result, a series of conditions, including different solvents and additives, as well as temperature, were then screened to improve the conversion and enantioselectivity of the reaction.




**Scheme 2** Chiral ligands used in the conjugate cyanation.

**Table 1** The ligands and solvent influences of TMSCN addition to **1a**[a]

| Entry | Ligand | Solvent | Time | e.r.[c] |
|---|---|---|---|---|
| 1 | **L1*** | Tol | overnight | 82 : 18 |
| 2 | **L2*** | Tol | overnight | 88 : 12 |
| 3 | **L3*** | Tol | 48 h[b] | 61 : 39 |
| 4 | **L4*** | Tol | 24 h[b] | Racemic |
| 5 | **L5*** | Tol | 24 h[b] | Racemic |
| 6 | **L1*** | THF | overnight | 76 : 24 |
| 7 | **L1*** | $Et_2O$ | overnight | 77 : 23 |
| 8 | **L1*** | DCM | overnight | 76 : 24 |
| 9 | **L2*** | THF | overnight | 87 : 13 |
| 10 | **L2*** | $Et_2O$ | overnight | 86 : 14 |
| 11 | **L2*** | DME | 8 h[b] | 87 : 13 |
| 12 | **L2*** | MTBE | 6.5h[b] | 88 : 12 |
| 13 | **L2*** | DCM | overnight | 80 : 20 |
| 14 | **L2*** | DCE | 6 h | 80 : 20 |
| 15 | **L2*** | $CHCl_3$ | 6.5 h[b] | 85 : 15 |
| 16 | **L2*** | $CH_3CN$ | 8 h[b] | 62 : 38 |

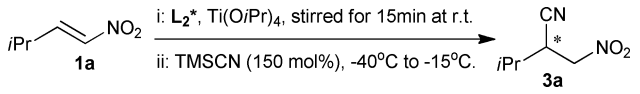
[a] The reactions were carried out in 2 ml toluene with 0.1 mmol of nitroolefin, and **L*** : $Ti(O^iPr)_4$ : **1a** : TMSCN = 0.2 : 0.2 : 1 : 1.5. [b] Not completed. [c] Determined by HPLC analysis.

Firstly, the reaction was carried out in toluene for the ligand screening. Using 20 mol% of **L1*** combined with 20 mol% $Ti(O^iPr)_4$ as the catalyst, conjugate cyanation of **1a** proceeded smoothly to afford **3a** with moderate enantioselectivity (82 : 18 e.r.) at –15 °C (Table 1, entry 1). An improved e.r. value of 88 : 12 was obtained using **L2***-Ti complex (entry 2, Table 1). While using 3,3′-substituted BINOL **L3*** as ligand, a very low enantioselectivity (61 : 39 e.r.) was observed (entry 3). For further improving the reaction enantioselectivity, 1,2-diphenyl as well as 1,2-di-*tert*-butylethylenediamine-derived salens (**L4*** and **L5***) were prepared and examined in the model reaction. Unfortunately, the reaction did not complete after two days at –15 °C catalyzed by neither **L4***–Ti nor **L5***–Ti. On the other hand, only racemic product was obtained (entry 4–5). Further solvent screening indicated that the enantioselectivity was to some extent affected by different solvents. Catalyzed by **L1***–Ti complex, some 10% decreases were observed when using ethers or DCM as the solvent (entry 6–8). Compared with using toluene as the solvent catalyzed by **L2***–Ti, similar enantioselectivities were obtained when the reaction proceeded in ethers (entry 9–12). Moderate e.r. values were obtained when the reactions were carried out in chloride hydrocarbon solvents (entry 13–15). A sharp decrease of e.r. value to only 62 : 38 was observed when the model reaction proceeded in $CH_3CN$ (entry 16). Therefore, subsequent studies were all carried out in toluene and catalyzed by **L2***–Ti complex.

Different ratios of Ligand to titanium and additives were studied for the enantioselectivity improvement (results in Table 2). No reaction occurred neither in the absence of **L2*** nor titanium (entry 1–2). The yield and enantioselectivity of the reaction were critically affected by the temperature. An excellent e.r. of 96 : 4 was observed when the reaction was carried out under –78 °C (entry 3). However, only trace of **3a** was obtained after 24 h. Then, it was found that conjugate cyanation of **1a** was finished after 19 h with 91 : 9 e.r. value under –40 °C (entry 4). Reducing the loadings of **L2*** and $Ti(O^iPr)_4$ to 10 mol%, no decrease was observed for the reaction enantioselectivity but with much longer time (34 h)

**Table 2** Optimal condition screening for the conjugate cyanation of **1a**[a]



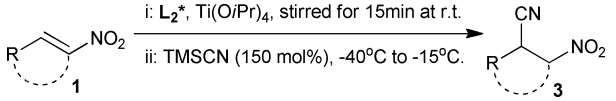

| Entry | **L2*** (mol%) | $Ti(O^iPr)_4$ (mol%) | Additive[b] | Temperature | Time (h) | e.r.[c] |
|---|---|---|---|---|---|---|
| 1 | 20% | 0 | None | R.T. | N.R.[e] | N.D.[f] |
| 2 | 0 | 20% | — | R.T. | N.R.[e] | N.D.[f] |
| 3 | 20% | 20% | — | –78 °C | Trace | 96 : 4 |
| 4 | 20% | 20% | — | –40 °C | 19h | 91 : 9 |
| 5 | 10% | 10% | — | –40 °C | 34h | 91 : 9 |
| 6 | 20% | 20% | — | –15 °C | 8 h | 90 : 10 |
| 7 | 10% | 10% | — | –15 °C | 13 h | 90 : 10 |
| 8 | 5% | 5% | — | –15 °C | 18 h | 90 : 10 |
| 9 | 2% | 2% | — | –15 °C | Trace | N.D.[f] |
| 10 | 20% | 40% | — | –15 °C | 8 h | 90 : 10 |
| 11 | 20% | 10% | — | –15 °C | 24 h | 90 : 10 |
| 12 | 20% | 20% | Py | –15 °C | [g] | 89 : 11 |
| 13 | 20% | 20% | DIPEA | –15 °C | [g] | 88 : 12 |
| 14 | 20% | 20% | TEA | –15 °C | [g] | 87 : 13 |
| 15 | 20% | 20% | *i*-PrOH | –15 °C | [g] | 87 : 13 |
| 16 | 20% | 20% | *t*-BuOH | –15 °C | [g] | 88 : 12 |
| 17 | 20% | 20% | *p*-cresol | –15 °C | [g] | 90 : 10 |
| 18 | 20% | 20% | BHT | –15 °C | [g] | 90 : 10 |
| 19 | 20% | 20% | *t*-BuOK | –15 °C | 16h | 58 : 42 |
| 20 | 20% | 20% | 4 Å MS[d] | –15 °C | 48 h | 91 : 9 |

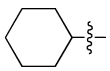
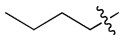
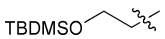
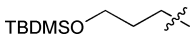
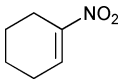
[a] The reactions were carried out in 2 ml toluene with 0.1 mmol of **1a** and 0.15 mmol of TMSCN. [b] All of the additive loading was 100 mol% according to nitroolefin **1a** except otherwise noted. [c] Determined by HPLC analysis. [d] 100 mg of 4 Å MS was added. [e] No reaction. [f] Not determined. [g] Overnight.

(entry 5). It was pleasing to find that similar enantioselectivity was obtained when the reaction was carried out between –40 °C and –15 °C (entry 6). During the subsequent study, the reaction mixture was precooled to –40 °C before adding TMSCN, and then warmed to –15 °C and stirred until the reaction was complete. The e.r. value of **3a** was not affected by either reducing the catalyst loadings (entry 7–8) or changing the ratios of **L2*** and $Ti(O^iPr)_4$ (entry 10–11). But the reaction rate was markedly influenced with the loading of $Ti(O^iPr)_4$. Longer reaction time was necessary for the completion of the cyanation when using less $Ti(O^iPr)_4$. Unfortunately, 2 mol% of the catalyst failed to promote the conjugate cyanation of **1a** (entry 9). Considering the shorter reaction time, 20 mol% of **L2*** and $Ti(O^iPr)_4$ was exploited in the additive screening process. Although it was found that a Lewis base could enhance the turnover frequency of the titanium-catalyst (unpublished results), Lewis bases did not work in improving the reaction enantioselectivity (entry 12–14). In addition, the e.r. value of **3a** was also not improved by adding protonic additives which were always explored as promising additives in various cyanations (entry 15–18). The model reaction was restrained by *t*-BuOK and with very poor enantioselectivity (entry 19). Using molecular sieves led to a slight improvement of the reaction enantioselectivity but with much longer reaction time (entry 20).

Under the optimal conditions, the substrate scope of this approach was examined and the results are shown in Table 3. Asymmetric cyanation of either linear nitroolefins or cyclic nitroolefin proceeded favorably with moderate to high enantioselectivities. The reaction was not markedly affected by simple alkyl substitution of the nitroolefins. Asymmetric synthesis of β-nitronitriles

**Table 3** Salen–Ti catalyzed asymmetric conjugated cyanation of alkyl nitroolefins[a]



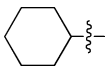
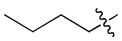
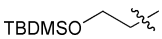
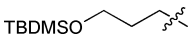
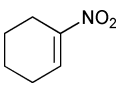

| Entry | R | Product | Time (h) | Yield (%)[b] | e.r.[c] |
|---|---|---|---|---|---|
| 1 |  | **3a**[d] | 8 | 73% | 91 : 9 |
| 2 |  | **3b** | 8 | 81% | 92 : 8 |
| 3 |  | **3c** | 8 | 90% | 91 : 9 |
| 4 |  | **3d** | 10 | 74% | 86 : 14 |
| 5 |  | **3e** | 8 | 83% | 80 : 20 |
| 6 |  | **3f** | 12 | 44% | 85 : 15 |
| 7 |  | **3g** | 15 | 60%[e] | 74 : 26 (*anti*)<br>73 : 27 (*syn*) |

[a] The reactions were carried out in 2 ml toluene with 0.1 mmol of nitroolefin, and **L2*** : $Ti(O^iPr)_4$ : **1** : TMSCN = 0.2 : 0.2 : 1 : 1.5. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The *S*-configuration of **3a** was confirmed by comparing with literature optical rotation (ref. 8a). [e] The yield referred to both *anti*-**3g** and *syn*-**3g**. The ratio of *anti*-**3g** : *syn*-**3g** was 16 : 84 and determined by $^1$H NMR of the crude product.

**3a–c** was achieved with high yields and similar enantioselectivities (e.r of 91 : 9, 92 : 8 and 91 : 9, respectively) (entry 1–3). Cyanation of **1d** gave **3d** with moderate enantioselectivity (86 : 14 e.r.) due to the negative chelating effect of the methoxy group to the titanium (entry 4). The sterically bulky TBDMS hydroxy-protecting group in **1e–f** led to moderate enantioselectivities (e.r. of 80 : 20 and 85 : 15 respectively) (entry 5–6). Cyclic nitroolefin **1g** was also a suitable substrate for this approach. A relatively longer reaction time (15 h) was needed for the cyanation of **1g**. Cyclic β-nitronitrile **3g** was obtained with high diastereoselectivity (*anti*-**3g** : *syn*-**3g** = 16 : 84) and moderate enantioselectivity (e.r. of 74 : 26 and 73 : 27 for *anti*-**3g** and *syn*-**3g**, respectively) (entry 7).

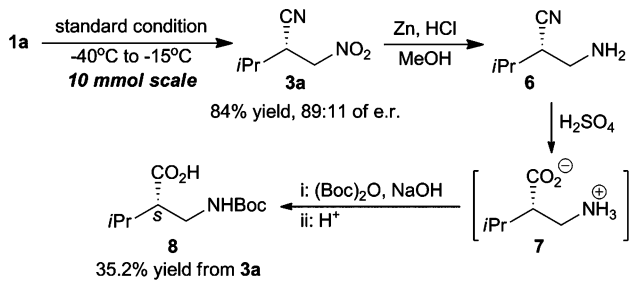
In order to synthesize racemic β-nitronitriles for HPLC analysis, cyanation of nitroolefins using racemic salen–Ti complex was carried out at room temperature. It was pleasing to find that the cyanation proceeded very rapidly and completed in minutes. Then enantioselective cyanation of nitroolefins at room temperature was examined with results in Table 4. The asymmetric cyanations was generally completed within ten minutes. The cyanation of **1g** needed a longer reaction time (60 min). However, the enantioselectivities and yields did not vary much. The enantioselectivities of **3a–3c** were less decreased with e.r. of 84 : 16, 85 : 15 and 81 : 18, respectively (entry 1–3). Much lower yield (26%) of **3f** was obtained while the cyanation was carried out at room temperature (entry 6). A similar result was obtained for the cyanation of cyclic nitroolefin **1g** (entry 7).

**Table 4** Salen-Ti catalyzed asymmetric conjugated cyanation of alkyl nitroolefins at room temperature[a]

| Entry | R | Product | Time (min) | Yield (%)[b] | e.r.[c] |
|---|---|---|---|---|---|
| 1 |  | **3a** | 10 | 77% | 84 : 16 |
| 2 |  | **3b** | 10 | 71% | 85 : 15 |
| 3 |  | **3c** | 10 | 75% | 81 : 18 |
| 4 |  | **3d** | 15 | 76% | 77::23 |
| 5 |  | **3e** | 10 | 78% | 77 : 23 |
| 6 |  | **3f** | 15 | 26% | 81 : 19 |
| 7 |  | **3g** | 60 | 63%[d] | 71 : 29 (*anti*)<br>72 : 28(*syn*) |

[a] The reactions were carried out in 2 ml toluene with 0.1 mmol of nitroolefin, and **L2***:Ti($O^iPr$)$_4$:**1**:TMSCN = 0.2:0.2:1:1.5. [b] Isolated yield. [c] Determined by HPLC analysis. [d] The yield referred to both *anti*-**3g** and *syn*-**3g**. The ratio of *anti*-**3g**:*syn*-**3g** was 62:38 and determined by $^1$H NMR of the crude product.

Cyanation of **1a** under standard conditions at low temperature was carried out on a 10 mmol scale affording a high yield of 84% (Scheme 3). It was pleasing to find that the reaction enantioselectivity decreased slightly to e.r. 89:11. Reduction of the nitro group of **3a** with Zn/HCl afforded amine **6** favorably.[6] Enantioenriched N-Boc protected β-amino acids **8** was obtained by hydrolyzing **6** with $H_2SO_4$ (75%) and subsequently protecting **7** with $(Boc)_2O$ under basic conditions.[6] The total yield of **8** was 35.2% from **3a**. The absolute configuration of **8** was confirmed to be *S* after comparison with the literature optical rotation.[15] Thus, the *S*-configuration of **3a** was further confirmed by this result. Based on the configurational relation between **L2*** and **3a**, the *enantio*-discrimination role of the present **L2***–Ti complex could be explained similarly with Feng's report.[14c]




**Scheme 3** Synthesis of β-amino acids from **3a**.

The reported studies on conjugate cyanation indicated that protonic additives such as IPA and phenols were always necessary for the *in situ* formation of HCN and maintaining high turnovers of the conjugate cyanation catalysts.[10–12] However, these protonic additives were not critical in this example. Most importantly, the present salen–Ti complex displayed high turnover frequency even without protonic additives. Based on these observations, we proposed that the asymmetric cyanation of nitroolefin proceeds *via* an unusual pathway. *In situ* $^1$H NMR investigation of the asymmetric nitroolefin cyanation was carried out to examine the whole process (Fig. 2). The model cyanation of **1a** was carried out in $CDCl_3$ at room temperature. A series of $^1$H NMR spectra were acquired:

1) **S1** referred to the mixture of **L2***–Ti complex and **1a**. Chemical shifts of the $\mathbf{H_a}$, $\mathbf{H_b}$, and $\mathbf{H_c}$ could be easily identified as shown in Fig. 2.

2) **S2**, **S3**, and **S4** were acquired after adding TMSCN to the above reaction mixture for 2 min, 5 min and 20 min, respectively. Peaks, referring to $\mathbf{H_a}'$, $\mathbf{H_b}'$ as well as $\mathbf{H_c}'$, appeared immediately after addition of TMSCN and disappeared immediately after addition of $H_2O$ to quench the reaction. The relative abundances between $\mathbf{H_a}'$ to $\mathbf{H_a}$, $\mathbf{H_b}'$ to $\mathbf{H_b}$, **and** $\mathbf{H_c}'$ to $\mathbf{H_c}$ increased during the reaction.

3) **S5** was acquired after quenching the reaction with water. Related $\mathbf{H_a}''$, $\mathbf{H_b}''$ and $\mathbf{H_c}''$ matched well with the spectra of purified **3a**.

According to the literature,[16] the chemical shift of the silyl nitronate proton was generally between 6.0–6.5 ppm. Thus, $\mathbf{H_b}'$ refers to the silyl nitronate proton (6.23 ppm). For $\mathbf{H_a}'$ was no longer a olefinic proton, its chemical shift was close to that of **Ha**'' but at lower field. Chemical shifts of $\mathbf{H_c}$, $\mathbf{H_c}'$ and $\mathbf{H_c}''$ varied in little, gradually shifting to higher field. Hereby, $\mathbf{H_a}'$, $\mathbf{H_b}'$ and $\mathbf{H_c}'$ were identified as the corresponding protons of the silyl nitronate intermediate. As the phenolic hydroxyl hydrogen of **L2*** could act as the proton source, the silyl nitronate intermediate was partly protonated and transformed to **3a**. The observation of the silyl nitronate intermediate indicated that *in situ* generated HCN is not needed. In addition, the silyl nitronate intermediate was stable enough under the reaction conditions for a long period of time to be captured by other electrophiles.

## Conclusions

In conclusion, the enantioselective cyanation of nitroolefins *via* silyl nitronate intermediate has been achieved by using a salen–Ti complex. The present protocol was used to prepare a series of alkyl nitroolefins with moderate to high enantioselectivities and yields. Although the enantioselectivities of this approach still need to be further improved, the salen–Ti complex maintains a significantly high turnover frequency in the field of conjugate cyanation, especially at room temperature. The present protocol was also successfully applied on a 10 mmol scale. The product could be readily transformed to the corresponding β-amino acids. The silyl nitronate intermediate pathway was confirmed through an *in situ* $^1$H NMR investigation. Studies on refining the enantioselectivities and applying the silyl nitronate intermediate to useful tandem reactions are underway.

## Experimental

### General methods

All reactions were monitored by thin layer chromatography (TLC), column chromatography purifications were carried out using silica

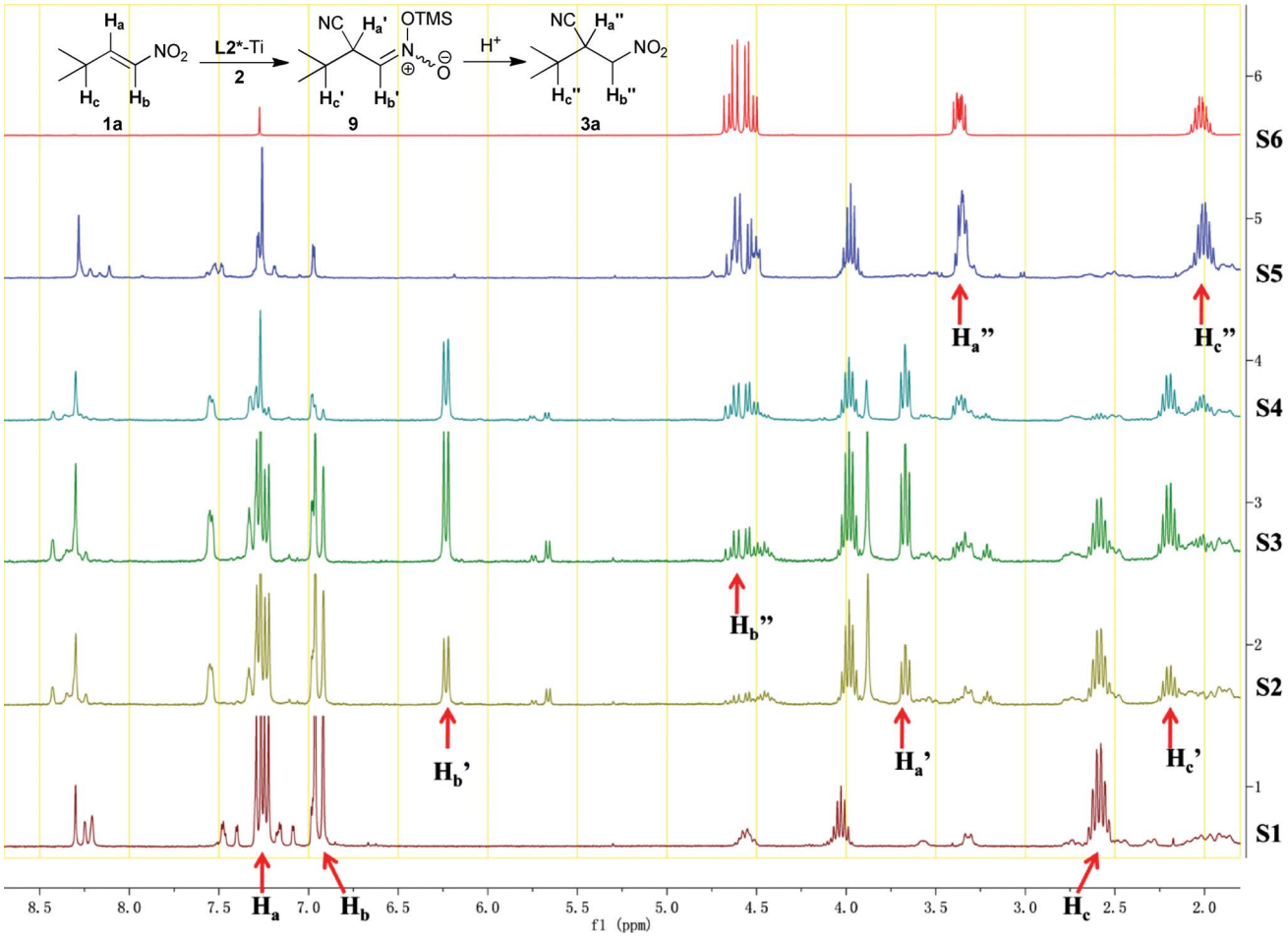



**Fig. 2** *In situ* $^1$H NMR investigation of the asymmetric nitroolefin cyanation. To a NMR tube was added **L2***:Ti(O$^i$Pr)$_4$:**1a** = 20 mol%:20 mol%:100mol% in 1 mL $CDCl_3$. **S1** was obtained after the reaction mixture standing for 15 min at r.t.. After adding 150 mol% of TMSCN to the above mixture, **S2**, **S3** and **S4** were obtained after 2 min, 5 min and 20 min, respectively. **S5** was obtained after quenching the reaction by adding 0.5 mL $H_2O$. **S6** referred to the $^1$H NMR of purified **3a**.

gel. All of the alkyl nitroolefins were prepared according to the literature. $^1$H NMR and $^{13}$C NMR spectra were recorded on a 300 M Bruker® instrument (300 MHz and 75 MHz, respectively) using tetramethylsilane as internal reference. Data for $^1$H NMR are recorded as follows: chemical shift ($\delta$, ppm), multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet, q = quartet or unresolved, coupling constant(s) in Hz, integration). Data for $^{13}$C NMR are reported in terms of chemical shift ($\delta$, ppm). Optical rotations were reported as follows: $[\alpha]_D^{20}$ (*c*: g/100 mL, in solvent). HR-MS was measured with an APEX II 47e mass spectrometer. The e.r. value determination was carried out using chiral HPLC with Daicel Chiracel AD-H/OD-H/OJ column on Waters® with a 996 UV-detector, flow rate = 1.0 mL min$^{-1}$.

### General procedure for the asymmetric cyanation of nitroolefins at low temperature

Freshly distilled Ti(O$^i$Pr)$_4$ (5.8 μL, 0.02 mmol, 20 mol%) was added to the solution of **L2*** (10.9 mg, 0.02 mmol, 20 mol%) in toluene (2 mL) under Ar. After stirring for 15 min at room temperature, nitroolefin **1** (0.1 mmol) was added to the above solution which was then cooled to –40 °C. TMSCN (20.0 μL, 0.15 mmol, 150 mol%) in 0.5 mL THF was added to the reaction mixture in dropwise. The reaction was slowly warmed to –15 °C and kept stirring until the reaction was completed (monitored by TLC). Saturated $NaHCO_3$ solution was added to quench the reaction and the mixture was extracted with methylene chloride. The extract was dried with sodium sulfate and concentrated under reduced pressure. After column chromatography on silica gel eluting with 10% ethyl acetate in petroleum, the β-nitronitrile was obtained.

**(*S*)-3-Methyl-2-(nitromethyl)butanenitrile (3a)[8a].** 73% yield, 91:9 e.r. was determined by HPLC analysis (OD-H column, hexane/iPrOH = 90/10); retention times: $t_{major}$ = 16.8, $t_{minor}$ = 19.8. $[\alpha]_D^{21}$ +3.8 (*c* 1.05, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.59 (ddd, *J* = 20.0, 14.0, 7.2 Hz, 2H), 3.37 (ddd, *J* = 8.4, 6.0, 5.1 Hz, 1H), 2.02 (dtd, *J* = 13.5, 6.7, 5.1 Hz, 1H), 1.15 (dd, *J* = 10.1, 6.8 Hz, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 116. 9, 73.6, 36.8, 28.5, 20.7, 18.3. Anal. Calcd. for $C_6H_{10}N_2O_2$: C 50.69%, H 7.09%, N 19.63%. Found C 51.83%, H 7.22%, N 19.69%.

**(*S*)-2-Cyclohexyl-3-nitropropanenitrile (3b)[8c,17].** 81% yield, 92:8 e.r. was determined by HPLC analysis (OD-H column, hexane/iPrOH = 90/10); retention times: $t_{major}$ = 17.9, $t_{minor}$ = 21.9. $[\alpha]_D^{21}$ –8.9 (*c* 1.01, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.60

(qd, $J$ = 14.0, 7.2 Hz, 2H), 3.33 (dt, $J$ = 8.4, 5.6 Hz, 1H), 1.97–1.55 (m, 6H), 1.40–1.08 (m, 5H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 117.3, 73.2, 37.4, 36.0, 30.9, 29.0, 25.6, 25.4, 25.3. Anal. Calcd. for $C_9H_{14}N_2O_2$: C 59.32%, H 7.74%, N 15.37%. Found C 58.93%, H 6.99%, N 14.89%.

**(*S*)-2-(Nitromethyl)hexanenitrile (3c).** 90% yield, 91 : 9 e.r. was determined by HPLC analysis (OD-H column, hexane/iPrOH = 95/5); retention times: $t_{major}$ = 23.8, $t_{minor}$ = 27.3. $[\alpha]_D^{21}$ −19.8 ($c$ 1.01, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.57 (ddd, $J$ = 20.2, 13.9, 7.0 Hz, 2H), 3.40 (ddd, $J$ = 16.5, 7.8, 6.2 Hz, 1H).1.80–1.65 (m, 2H), 1.65–1.47 (m, 2H), 1.46–1.32 (m, 2H), 0.95 (t, $J$ = 7.2 Hz, 3H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 118.0, 74.6, 29.8, 29.1, 28.6, 21.9, 13.6. Anal. Calcd. for $C_7H_{12}N_2O_2$: C 53.83%, H 7.74%, N 17.94%. Found C 54.00%, H 7.67%, N 16.62%.

**3,3-Dimethoxy-2-(nitromethyl)propanenitrile (3d).** 74% yield, 86 : 14 e.r. was determined by HPLC analysis (AD-H column, hexane/iPrOH = 97/3); retention times: $t_{minor}$ = 36.3, $t_{major}$ = 38.9. $[\alpha]_D^{21}$ +2.9 ($c$ 0.68, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.77–4.61 (m, 3H), 3.70–3.62 (m, 1H), 3.51 (d, $J$ = 1.3 Hz, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 115.7, 101.8, 70.8, 56.7, 56.3, 34.5. Anal. Calcd. for $C_6H_{10}N_2O_4$: C 41.38%, H 5.79%, N 14.35%. Found C 43.83%, H 6.12%, N 14.24%.

**4-((*tert*-Butyldimethylsilyl)oxy)-2-(nitromethyl)butanenitrile (3e).** 83% yield, 80 : 20 e.r. was determined by HPLC analysis (OD-H column, hexane/iPrOH = 95/5); retention times: $t_{major}$ = 14.0, $t_{minor}$ = 15.9. $[\alpha]_D^{21}$ −13.1 ($c$ 0.61, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.79–4.57 (m, 2H), 3.91–3.77 (m, 2H), 3.73–3.61 (m, 1H), 0.91 (s, 9H), 0.09 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 117.9, 74.5, 59.2, 32.1, 27.1, 25.8, 18.1, −5.6. HRMS (ESI): $C_{11}H_{22}N_2O_3Si$ +$NH^4$, Calc: 276.1738, Found: 276.1733.

**5-((Tert-butyldimethylsilyl)oxy)-2-(nitromethyl)pentanenitrile (3f).** 44% yield, 85 : 15 e.r. was determined by HPLC analysis (OJ column, hexane/iPrOH = 98/2); retention times: $t_{minor}$ = 17.4, $t_{major}$ = 19.5. $[\alpha]_D^{21}$ −9.7 ($c$ 0.72, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.64 (dd, $J$ = 14.0, 7.8 Hz, 1H), 4.52 (dd, $J$ = 14.0, 6.1 Hz, 1H), 3.75–3.63 (m, 2H), 3.61–3.47 (m, 1H), 1.88–1.67 (m, 4H), 0.89 (s, 9H), 0.06 (s, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 118.0, 74.7, 61.8, 29.6, 29.3, 26.6, 25.8, 18.2, −5.5. HRMS (ESI): $C_{12}H_{24}N_2O_3Si$ +H, Calc: 273.1629, Found: 273.1631.

**2-Nitrocyclohexanecarbonitrile (*anti*-3g)[8].** 60% yield, 74 : 26 e.r. was determined by HPLC analysis (OJ column, hexane/iPrOH = 85/15); retention times: $t_{major}$ = 27.0, $t_{minor}$ = 32.1. $[\alpha]_D^{28}$ +28.2 ($c$ 0.78, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.55 (td, $J$ = 10.3, 4.2 Hz, 1H), 3.23 (ddd, $J$ = 11.1, 9.9, 4.1 Hz, 1H), 2.53–2.35 (m, 1H), 2.33–2.19 (m, 1H), 1.95–1.77 (m, 3H), 1.76–1.62 (m, 1H), 1.54–1.30 (m, 2H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 118.4, 84.6, 31.8, 30.5, 27.9, 23.2, 23.1.

**2-Nitrocyclohexanecarbonitrile (*syn*-3g)[8].** 60% yield, 73 : 27 e.r. was determined by HPLC analysis (AD-H column, hexane/iPrOH = 95/5); retention times: $t_{major}$ = 21.7, $t_{minor}$ = 23.3. $[\alpha]_D^{28}$ +37.5 ($c$ 0.64, $CHCl_3$). $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 4.36 (dt, $J$ = 11.7, 4.0 Hz, 1H), 3.76–3.63 (m, 1H), 2.44 (m, 1H), 2.32–2.17 (m, 1H), 2.17–2.09 (m, 1H), 2.01 (m, 1H), 1.80–1.61 (m, 3H), 1.51–1.32 (m, 1H). $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 117.3, 82.4, 32.0, 28.1, 26.9, 23.6, 20.9.

### General procedure for the asymmetric cyanation of nitroolefins at room temperature

After stirring a solution of freshly distilled $Ti(O^iPr)_4$ (5.8 μL, 0.02 mmol, 20 mol%) and **L2*** (10.9 mg, 0.02 mmol, 20 mol%) in toluene (2 mL) under Ar for 15 min at room temperature, nitroolefin **1** (0.1 mmol) was added. TMSCN (20.0 μL, 0.15 mmol, 150 mol%) was added to the reaction mixture in one-pot. When the reaction was completed (monitored by TLC), the product was obtained following a general work-up procedure.

**(*S*)-2-(((*tert*-Butoxycarbonyl)amino)methyl)-3-methylbutanoic acid 8.** To a stirred solution of **3a** (142 mg, 1 mmol) in EtOH (10 mL) was added zinc powder (0.98 g, 15 equ.) and 5 mL of 6 M HCl (aq.). The reaction was stirred for 1h. Excess zinc powder was removed by filtration, the EtOH was removed *in vacuo*. NaOH (15%) was added to the above mixture until pH 10. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), the combined organic layer was washed with brine, dried, and concentrated to give the crude amine **6**, which was used for the next step without purification.

To the above residue was added 5 mL $H_2SO_4$ (75%) and heated at reflux for 2 h. The solution was then cooled to 0 °C and carefully adjusted to pH 10 with 40% NaOH. Dioxane (5 mL) was added to the above aqueous solution followed by $(Boc)_2O$ (240 mg, 1.1 eq. according to the starting loading of **3a**). The solution was warmed to room temperature and stirred for 1 h. The dioxane was removed *in vacuo*, the aqueous layer was acidified to pH 2 with 1 M $NaHSO_4$ and extracted with ethyl acetate (2 × 15 mL). The organic phase was dried and concentrated *in vacuo*. The residue was purified by flash column chromatography on $SiO_2$ (33% ethyl acetate/hexane) to afford **8** as a white solid (81.3 mg, 35.2% from **3a**). $[\alpha]_D^{rt}$ +3° ($c$ 1.0, $CHCl_3$). $^1$H NMR (300 MHz, CDCl3) $\delta$ 10.6 (br,1H), 6.70 & 5.03 (br, 1H), 3.44–3.40 (m, 1H), 3.28–3.09 (m, 1H), 2.52–2.38 (m, 1H), 2.05–1.90 (m, 1H), 1.48–1.44 (m, 9H), 1.02–0.96 (m, 6H). $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ 179.8 & 178.3, 158.1 & 155.9, 81.0&79.6, 52.8 & 52.1, 40.7&39.5, 28.7, 28.3, 28.2, 20.4, 20.3, 19.8. ESI-MS $(M+H)^+$: 232.1.[15]

### Procedure for the *in situ* $^1$H NMR investigation

To an NMR tube was added **L2*** (5.5 mg, 0.01 mmol, 20 mol%), $Ti(O^iPr)_4$ (2.9 μL, 0.01 mmol, 20 mol%), and **1a** (0.05 mmol) in 1 mL $CDCl_3$. $^1$H NMR **S1** was obtained after the reaction mixture had been left for 15 min at room temperature. After addition of 150 mol% of TMSCN to the above mixture, **S2**, **S3** and **S4** were obtained after standing for 2 min, 5 min and 20 min, respectively. **S5** was obtained after quenching the reaction with 0.5 mL $H_2O$.

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17 HPLC spectra indicate that opposite enantiomer of **3b** was obtained in this work compared with the one obtained in ref. 8c (see ESI†). After further HPLC experimentation and carefully re-checking the product rotation values, we became aware some erroneous data in ref. 8c. The optical rotation value of **3b** obtained in ref. 8c should be positive but not negative. Similar instance was also found for compound **3c**.