Supporting Information

A Catalytic Enantioselective Conjugate Addition of Cyanide to Enones

Yuta Tanaka, Motomu Kanai,* and Masakatsu Shibasaki*

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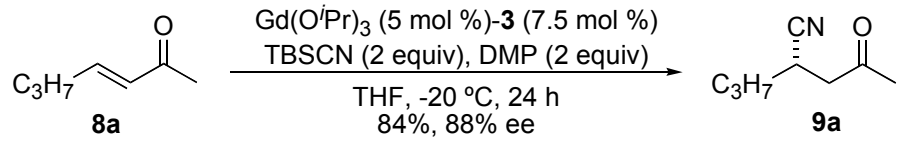
1. General Method: ^{1}H NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 500 MHz for ^{1}H NMR and 125.65 MHz for ^{13}C NMR. Chemical shifts were reported downfield from TMS (δ = 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. Optical rotations were measured on a JASCO P-1010 polarimeter. Column chromatographies were performed with silica gel Merck 60 (230-400 mesh ASTM). The enantiomeric excess (ee) was determined by HPLC or GC analysis. HPLC analysis was performed on JASCO HPLC systems consisting of the following: pump, 880-PU or PU-980; detector, 875-UV, UV-970, or RI930, measured at 254 nm, 220 nm, or RI; mobile phase, hexane–2-propanol. GC analysis was performed Shimazu GC-14A with Varian Chirasil DEX CB column (0.25 mm x 25 m). In general, reactions were carried out under an argon atmosphere. Gd(O^{i}Pr)$_3$ was purchased from Kojundo Chemical Laboratory Co., Ltd. (Fax: +81-492-84-1351, sales@kojundo.co.jp). Chiral ligand **1**~**3** were prepared by reported methods.[1] These ligands are also available from a commercially source (Junsei Chemical. Co., Ltd., Fax: +81-48-988-8719, shiyaku-t@junsei.co.jp).

2. General Procedure for the Catalytic Enantioselective Conjugate Addition of Cyanide to Enones (Table 2, entry 2):

[1] (a) For the synthesis of **1** and **2**, see: Kato, N.; Tomita, D.; Maki, K.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2004**, *69*, 6128. (b) For the synthesis of **3**, see: Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *Tetrahedron* **2007**, *63*, 5820.



To a solution of ligand **3** (6.7 mg, 0.015 mmol) in THF (0.3 mL), $Gd(O^iPr)_3$ (0.2 M in THF, 50 μL, 0.01 mmol) was added at room temperature. The mixture was stirred at 50 ºC for 1 h, and then the solvent was evaporated. After drying the resulting pre-catalyst under reduced pressure (<5 mmHg) for 3 h, THF (0.1 mL) was added. **8a** was added at room temperature, and immediately cooled to –78 ºC. A solution prepared by mixing a solution of TBSCN (56.5 mg, 0.40 mmol) in THF (0.2 mL) and a solution of 2,6-dimethylphenol (44.9 mg, 0.40 mmol) in THF (0.2 mL) at room temperature for 20 minutes,[2] was added to the reaction mixture at –78 ºC. Then, the temperature was elevated to –20 ºC. After 24 h, the reaction mixture was passed through short pad column chromatography (silica gel, AcOEt), and the solvent was removed under reduced pressure (*Caution! HCN generated in the reaction mixture is highly toxic. Those operations should be conducted in a well-ventilated hood*). The residue was purified by flash column chromatography (silica gel, Et_2O-hexane, 1:2) to afford the **9a** (23.4 mg, 0.168 mmol) in 84% yield as a colorless oil. The enantiometric excess of the product was determined bu GC analysis to be 88% ee.

3. Characterization of the Products and New Ligand 4

(*S*)-4-Oxo-2-propylpentanenitrile (9a): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.0 Hz, 3H), 1.4-1.57 (m, 4H), 2.17 (s, 3H), 2.64 (dd, J = 6.4, 18.3 Hz, 1H), 2.84 (dd, J = 7.0, 18.3 Hz, 1H), 3.03 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:13.40, 20.30, 25.70, 29.95, 33.73, 45.32, 121.58, 203.77; IR (neat, cm^{-1}): ν 1717, 2239; MS (ESI) m/z 162 $(M+Na)^+$; HRMS (ESI) calcd for $C_8H_{13}NONa$ $(M+Na)^+$ 162.0895. Found 162.0890; $[\alpha]_D^{20}$ = –3.8 (c = 0.65, $CHCl_3$) for 85% ee; GC condition: Chirasil DEX CB, injector temp. = 200 ºC, detector temp. = 250 ºC, column temp. = 100 ºC (isothermic), t = 9.6 min (*S*, major), 11.2 min (*R*, minor).

5-Methyl-4-oxo-2-propylhexanenitrile (9b): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.0 Hz, 3H), 1.09 (d, J = 6.7 Hz, 3H), 1.10 (d, J = 6.7 Hz, 3H), 1.4-1.6 (m, 4H), 2.57 (septet, J = 6.9 Hz, 1H), 2.65 (dd, J = 6.7, 18.0 Hz, 1H), 2.84 (dd, J = 6.7, 18.0 Hz, 1H), 3.07 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:13.41, 17.91, 17.96, 20.35, 25.77, 33.81, 40.89, 42.25, 121.77, 209.89; IR (neat, cm^{-1}): ν 1715, 2240; MS (ESI) m/z 190$(M+Na)^+$; HRMS (ESI) calcd for $C_{10}H_{17}NONa$ $(M+Na)^+$ 190.1208. Found 190.1212; $[\alpha]_D^{21}$ = –6.0 (c = 1.54, $CHCl_3$) for 94% ee; GC condition: Chirasil DEX CB, injector temp. = 200 ºC, detector temp. = 250 ºC, column temp. = 110 ºC (isothermic), t = 14.8 min (major), 16.2 min (minor).

2-(2-Cyclohexyl-2-oxo-ethyl)pentanenitrile (9c): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.0 Hz, 3H), 1.4-1.55 (m, 4H), 2.55 (dd, J = 6.7, 18.0 Hz, 1H), 2.7-2.8 (m, 3H), 2.90 (t, J = 7.6 Hz, 2H), 3.05 (m, 1H), 7.1-7.2 (m, 3H), 7.27 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:13.41, 20.29, 25.67, 29.59, 33.75, 44.34, 44.78, 121.58, 126.32, 128.26, 128.58, 140.35, 205.27; IR (neat, cm^{-1}): ν 1710, 2239; MS (ESI) m/z 230 $(M+Na)^+$; HRMS (FAB) calcd for $C_{13}H_{22}NO$ $(M+H)^+$ 208.1701. Found 208.1706; $[\alpha]_D^{22}$ = –7.9 (c = 2.40, $CHCl_3$) for 94% ee; HPLC condition: Chiralpak AS-H column, flow rate: 1.0 mL / min, *n*-hexane / *i*-PrOH =

[2] Using TBSCN, silylation of DMP (therefore, HCN generation) proceeded in ~5% yield during this operation. Silylation of DMP was, however, markedly accelerated by the Gd-catalyst, and DMP silylation was completed in ca. 20 min in the reaction mixture at –20 ºC. Using TMSCN, treatment by DMP at rt for 20 min in the absence of the catalyst resulted in almost complete silylation of DMP. Therefore, the stoichiometric cyanation reagent is HCN, irrespective of the cyanide source (either TBSCN or TMSCN).

9 / 1, t = 8.1 min (major), 9.2 min (minor). RI detection.

4-Oxo-6-phenyl-2-propylhexanenitrile (9d): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.0 Hz, 3H), 1.15-1.35 (m, 5H), 1.4-1.55 (m, 4H), 1.65 (m, 1H), 1.73-1.85 (m, 4H), 2.30 (m, 1H), 2.64 (dd, J = 6.4, 18.0 Hz, 1H), 2.82 (dd, J = 7.0, 18.0 Hz, 1H), 3.05 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 13.40, 20.33, 25.40, 25.43, 25.63, 25.68, 28.13, 28.21, 33.81, 42.48, 50.67, 121.81, 209.21; IR (neat, cm^{-1}): ν 1717, 2239; MS (ESI) m/z 252 $(M+Na)^+$; HRMS (FAB) calcd for $C_{15}H_{20}NO$ $(M+H)^+$ 230.1545. Found 230.1553; $[\alpha]_D^{21}$ = –2.1 (c = 0.54, $CHCl_3$) for 90% ee; HPLC condition: Chiralcel OD-H column, flow rate: 1.0 mL / min, *n*-hexane / *i*-PrOH = 9 / 1, t = 20.9 min (major), 23.1 min (minor). λ = 254 nm.

2-Methyl-4-oxo-4-phenylbutyronitrile (9e): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.41 (d, J = 7.0 Hz, 3H), 3.20 (dd, J = 6.7, 17.2 Hz, 1H), 3.33 (sextet, 7.0 Hz, 1H), 3.40 (dd, J = 6.1, 17.2 Hz, 1H), 7.47 (m, 2H), 7.58 (m, 1H), 7.93 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 17.88, 20.49, 42.22, 122.61, 128.00, 128.03, 128.82, 133.82, 135.85, 195.13; IR (neat, cm^{-1}): ν 1685, 2241; MS (ESI) m/z 196 $(M+Na)^+$; HRMS (ESI) calcd for $C_{11}H_{11}NONa$ $(M+Na)^+$ 196.0738. Found 196.0731; $[\alpha]_D^{20}$ = –6.2 (c = 0.6, $CHCl_3$) for 88% ee; HPLC condition: Chiralpak AS-H column, flow rate: 1.0 mL / min, *n*-hexane / *i*-PrOH = 4 / 1, t = 10.8 min (minor), 11.9 min (major). λ = 254nm.

2-(2-Oxo-propyl)heptanenitrile (9f): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.87 (t, J = 7.0 Hz, 3H), 1.29 (m, 4H), 1.47 (m, 1H), 1.53 (m, 3H), 2.18 (s, 3H), 2.65 (dd, J = 6.4, 18.0 Hz, 1H), 2.84 (dd, J = 7.0, 18.0 Hz, 1H), 3.02 (quintet, J = 6.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:13.89, 22.32, 25.94, 26.72, 29.97, 31.08, 31.72, 45.36, 121.63, 203.72; IR (neat, cm^{-1}): ν 1719, 2240; MS (ESI) m/z 190 $(M+Na)^+$; HRMS (ESI) calcd for $C_{10}H_{17}NONa$ $(M+Na)^+$ 190.1208. Found 190.1203; $[\alpha]_D^{22}$ = –10.1 (c = 0.48, $CHCl_3$) for 90% ee; GC condition: Chirasil DEX CB, injector temp. = 200 °C, detector temp. = 250 °C, column temp. = 115 °C (isothermic), t = 14.0 min (major), 15.4 min (minor).

4-Oxo-2-phenethylpentanenitrile (9g): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.87 (m, 2H), 2.16 (s, 3H), 2.65 (dd, J = 6.7, 18.3 Hz, 1H), 2.74 (m, 1H), 2.84-2.90 (m, 2H), 3.01 (m, 1H), 7.17 (m, 3H), 7.29 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:25.50, 29.86, 33.16, 33.28, 45.19, 121.25, 126.44, 128.34, 128.62, 139.75, 203.57; IR (neat, cm^{-1}): ν 1718, 2240; MS (ESI) m/z 224 $(M+Na)^+$; HRMS (FAB) calcd for $C_{13}H_{16}NO$ $(M+H)^+$ 202.1232. Found 202.1226; $[\alpha]_D^{26}$ = –40.5 (c = 1.81, $CHCl_3$) for 87% ee; GC condition: Chirasil DEX CB, injector temp. = 200 °C, detector temp. = 250 °C, column temp. = 130 °C (isothermic), t = 60.5 min (major), 65.2 min (minor).

2-Acetylcyclopentanecarbonitrile (*trans*-9h)[3]: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.67 (m, 2H), 1.81 (m, 1H), 1.93 (m, 1H), 2.08 (m, 1H), 2.18 (m, 1H), 2.22 (s, 3H), 3.23 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:25.22, 28.64, 28.92, 29.70, 31.36, 56.45, 122.42, 206.22; IR (neat, cm^{-1}): ν 1711, 2237; MS (ESI) m/z 160 $(M+Na)^+$; HRMS (ESI) calcd for $C_8H_{11}NONa$ $(M+Na)^+$ 160.0738. Found 160.0744. Less polar and minor isomer (AcOEt/Hex = 1/5, R_f ~ 0.2).

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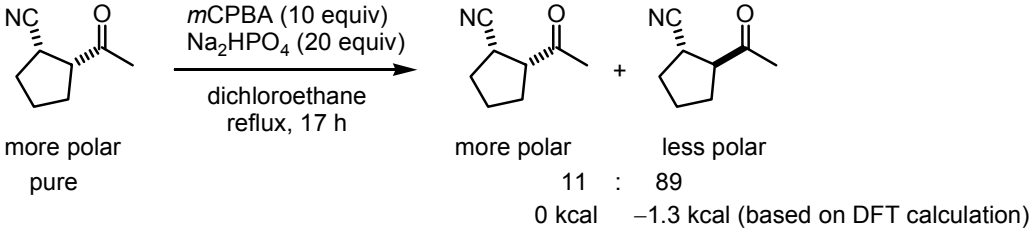
[3] The relative configuration was determined based on the following experiments and calculation.



2-Acetylcyclopentanecarbonitrile (*cis*-9h)[3]: ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.72 (m, 1H), 1.9-2.1 (m, 5H), 2.24 (s, 3H), 3.00 (dd, J = 7.4, 13.4 Hz, 1H), 3.08 (dd, J = 7.4, 15.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:23.26, 26.91, 29.48, 30.44, 31.21, 54.60, 120.42, 206.14; IR (neat, cm^{-1}): ν 1712, 2237; MS (ESI) m/z 160 $(M+Na)^+$; HRMS (ESI) calcd for $C_8H_{11}NONa$ $(M+Na)^+$ 160.0738. Found 160.0746; $[\alpha]_D^{25}$ = +34.0 (c = 0.41, $CHCl_3$) for 92% ee; GC condition: Chirasil DEX CB, injector temp. = 200 ^{o}C, detector temp. = 250 ^{o}C, column temp. = 95 ^{o}C (isothermic), t = 34.6 min (minor), 35.7 min (major). More polar and major isomer (AcOEt/Hex = 1/5, $R_f \sim 0.09$).

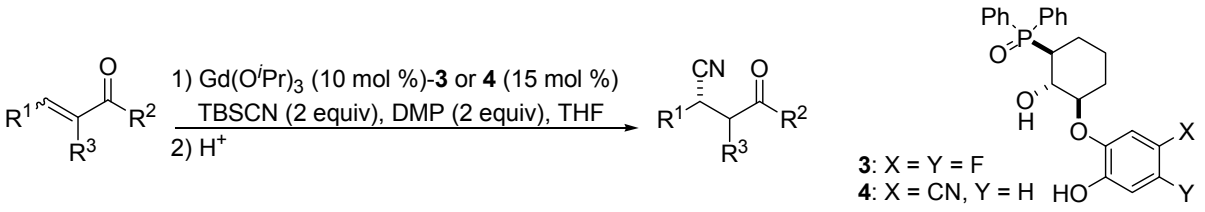
(*S*)-3-Oxo-cyclohexanecarbonitrile (9i): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.82 (m, 1H), 2.01 (m, 1H), 2.15 (m, 2H), 2.38 (m, 2H), 2.58 (dd, J = 9.5, 15.5 Hz, 1H), 2.65 (dd, J = 5.2, 15.5 Hz, 1H), 3.01 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:23.76, 28.13, 28.66, 40.68, 43.20, 120.15, 205.37; IR (neat, cm^{-1}): ν 1716, 2241; MS (ESI) m/z 146 $(M+Na)^+$; HRMS (ESI) calcd for C_7H_9NONa $(M+Na)^+$ 146.0582. Found 146.0586; $[\alpha]_D^{22}$ = +16.6 (c = 0.17, $CHCl_3$) for 79% ee; HPLC condition: Chiralpak AS-H column, flow rate: 1.0 mL / min, *n*-hexane / *i*-PrOH = 4 / 1, t = 17.1 min (*S*, major), 23.4 min (*R*, minor). RI detection. In this specific case, 1,4-product was further converted to the corresponding cyanohydrin in the reaction mixture. This over-cyanated compound was reconverted **9i** by the treatment with K_2CO_3 in MeOH at rt for 15 min.

3-Oxo-cycloheptanecarbonitrile (9j): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.72 (m, 3H), 1.92-2.01 (m, 3H), 2.52 (ddd, J = 3.7, 9.2, 15.9 Hz, 1H), 2.63 (ddd, J = 3.4, 8.5, 15.9 Hz, 1H), 2.73 (dd, J = 3.7, 15.9 Hz, 1H), 2.82 (dd, J = 8.3, 15.9 Hz, 1H), 2.98 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:23.43, 26.62, 27.38, 33.36, 43.66, 45.38, 120.73, 209.01; IR (neat, cm^{-1}): ν 1703, 2239; MS (ESI) m/z 160 $(M+Na)^+$; HRMS (ESI) calcd for $C_8H_{11}NONa$ $(M+Na)^+$ 160.0738. Found 160.0745; $[\alpha]_D^{26}$ = +3.8 (c = 0.72, $CHCl_3$) for 55% ee; HPLC condition: Chiralpak AS-H column, flow rate: 1.0 mL / min, *n*-hexane / *i*-PrOH = 4 / 1, t = 18.5 min (major), 29.9 min (minor). RI detection.

3-Oxo-cyclooctanecarbonitrile (9k): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.38 (m, 1H), 1.46 (m, 1H), 1.55 (m, 1H), 1.67-1.8 (m, 2H), 1.86-2.2 (m, 3H), 2.4 (m, 2H), 2.62 (dd, J = 3.4, 12.8 Hz, 1H), 2.86 (tlike, J = 12.8 Hz, 1H), 3.05 (dddd, J = 3.7, 3.7, 11.3, 11.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:22.94, 23.85, 27.23, 29.03, 30.30, 41.91, 43.10, 121.28, 211.69; IR (neat, cm^{-1}): ν 1685, 2234; MS (ESI) m/z 174 $(M+Na)^+$; HRMS (ESI) calcd for $C_9H_{13}NONa$ $(M+Na)^+$ 174.0895. Found 174.0893; $[\alpha]_D^{23}$ = +6.2 (c = 0.34, $CHCl_3$) for 81% ee; HPLC condition: Chiralpak AS-H column, flow rate: 1.0 mL / min, *n*-hexane / *i*-PrOH = 4 / 1, t = 21.2 min (major), 22.3 min (minor). RI detection.

4-CN-Fuji-CAPO (chiral ligand 4): ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.13 (m, 1H), 1.35 (m, 1H), 1.50 (m, 1H), 1.70 (m, 1H), 1.82 (m, 1H), 2.21 (dlike, J = 10.9 Hz, 1H), 2.67 (m, 1H), 3.70 (m, 1H), 4.07 (qlike, J = 9.2 Hz, 1H), 6.84 (br, 1H), 6.97 (d, J = 8.3 Hz, 1H), 7.16 (m, 1H), 7.28 (m, 1H), 7.44 (m, 2H), 7.53 (m, 3H), 7.60 (m, 1H), 7.71 (m, 4H), 9.88 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ:23.39, 23.51, 24.87, 29.33, 40.59, 41.17, 72.11, 84.73, 101.89, 117.57, 119.63, 127.95, 128.47, 128.56, 128.63, 128.72, 129.91, 130.21, 130.29, 130.68, 131.40, 131.48, 131.61, 131.96, 132.49; IR (neat, cm^{-1}): ν 2220, 3313; MS (ESI) m/z 456 $(M+Na)^+$; HRMS (FAB) calcd for $C_{25}H_{25}NO_4P$ $(M+H)^+$ 434.1521. Found 434.1510; $[\alpha]_D^{28}$ = +95.9 (c = 1.24, $CHCl_3$) for>99% ee; HPLC condition: Chiralpak OD-H column, flow rate: 1.0 mL / min, *n*-hexane / *i*-PrOH = 9 / 1, t = 10.1 min (minor), 13.1 min (major). λ = 254 nm.

4. Advantage of 4 to 3 in Reactions of Cyclic and α,β-Disubstituted Enones:

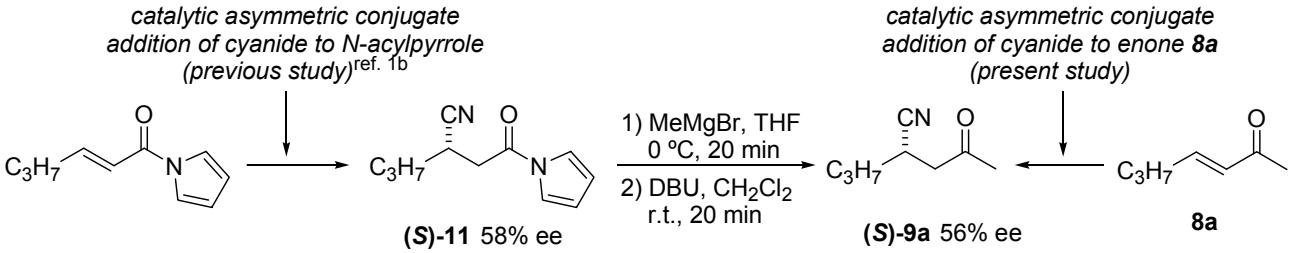


entry	substrate	ligand	temp (ºC)	time (h)	yield	ee (%)
1	**8h**	**3**	0	24 h	37[a] (dr = 1.6:1)	94[a]
2		**4**	0	24 h	67[a] (dr = 3.6:1)	95[a]
3[b]	**8i**: n = 1	**3**	r.t.	24 h	95	53
4		**4**	r.t.	4 h	90	81
5	**8j**: n = 2	**3**	r.t.	12 h	53	13
6		**4**	r.t.	24 h	73	52
7	**8k**: n = 3	**3**	r.t.	18 h	79	61
8		**4**	r.t.	18 h	74	81

[a] Combined yield of diastereomers and enantiomeric excess of the major isomer.
[b] 2.5 equiv of TBSCN and 2.5 equiv of DMP were used.

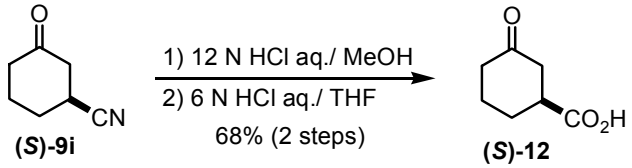
5. Determination of the Absolute Configuration of the Products and Conversion to Synthetically Useful Keto Carboxylic Acid Derivatives

(*S*)-4-Oxo-2-propylpentanenitrile (9a)



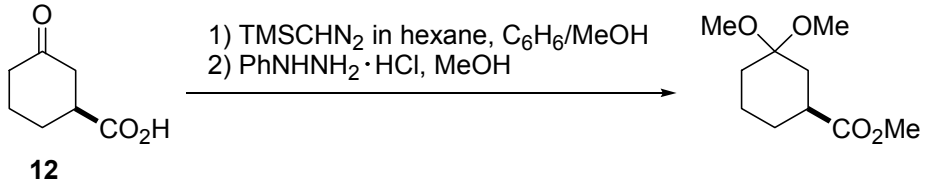
(*S*)-11 was synthesized using the catalytic asymmetric conjugate addition of cyanide to the corresponding α,β-unsaturated *N*-acylpyrrole.[1b] To a solution of **(*S*)-11** (58 % ee) (19.0 mg, 0.10 mmol) in THF (0.7 mL), MeMgBr (0.96 M THF solution, 105 μL, 0.10 mmol) was added at –78 ºC. After 5 minutes, the temperature was gradually elevated to 0 ºC, and the mixture was stired for 20 minutes. Saturated NH_4Cl was added and the organic layer was extracted with AcOEt 3 times. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dissolved with CH_2Cl_2 (1 mL), and DBU (0.75 μL, 0.005 mmol) was added at 0 ºC. After stirring for 20 minutes at 0 ºC, saturated NH_4Cl was added. The organic layer was extracted with AcOEt, washed with saturated NH_4Cl, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified with preparative TLC (hexane-AcOEt, 2:1) to afford **(*S*)-9a** with 56% ee (~60% yield for 2 steps). By comparing chiral GC profile, absolute configuration of the conjugate addition product **9a** was determined to be (*S*).

(*S*)-3-Oxo-cyclohexanecarbonitrile (9i)



To the conjugate addition product **9i** (24.6 mg, 0.20 mmol, 70% ee), 12 N HCl aq.–MeOH (1:1, 2 mL) was added at room temperature. The mixture was heated to 70 ºC. After stirring for 4 h at 70 ºC, H_2O was added, and the organic compounds were extracted with AcOEt 3 times. The combined organic layer was dried over Na_2SO_4, and the solvent was removed under reduced pressure. The residue was dissolved in THF (2 mL), and 6 N HCl aq. was added at room temperature. The mixture was heated to 70 ºC for 1 h. H_2O was added, and the organic compounds were extracted with CH_2Cl_2 5 times. The combined organic layer was dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (hexane-AcOEt-formic acid, 200:100:3) to afford **12** (19.3 mg, 68% yield). The absolute configuration of **12** was determined to be (*S*) by comparing the optical rotation to the reported value.[4] Accordingly, the absolute configuration of the conjugate addition product **9i** was determined to be (*S*).

Racemization during the hydrolysis process was checked as follows (scheme below). Carboxylic acid **12** was reconverted to the corresponding methyl ester through the treatment with trimethylsilyldiazomethane. The methyl ester was dissolved in MeOH, and phenylhydrazinium chloride (1 equiv) was added. After stirring the mixture for 1 h at rt, solvent was evaporated. The resulting crude mixture was purified by PTLC (SiO_2: AcOEt/hexane = 1/3). The obtained product was dimethylacetal (>80% yield). The enantiomeric excess of the acetal was checked by chiral GC to be 66% ee [Chirasil DEX CB, injector temp. = 200 °C, detector temp. = 250 °C, column temp. = 110 °C (isothermic), t = 15.5 min (minor), 16.0 min (major)]. Therefore, decrease in enantiomeric excess during the acid hydrolysis was very small to within error range.



[4] Numata, A.; Suzuki, T.; Ohno, K.; Uyeo, S. *Yakugaku Zasshi* **1968**, *88*, 1298.

6. ESI-MS Information of the Catalyst[5]

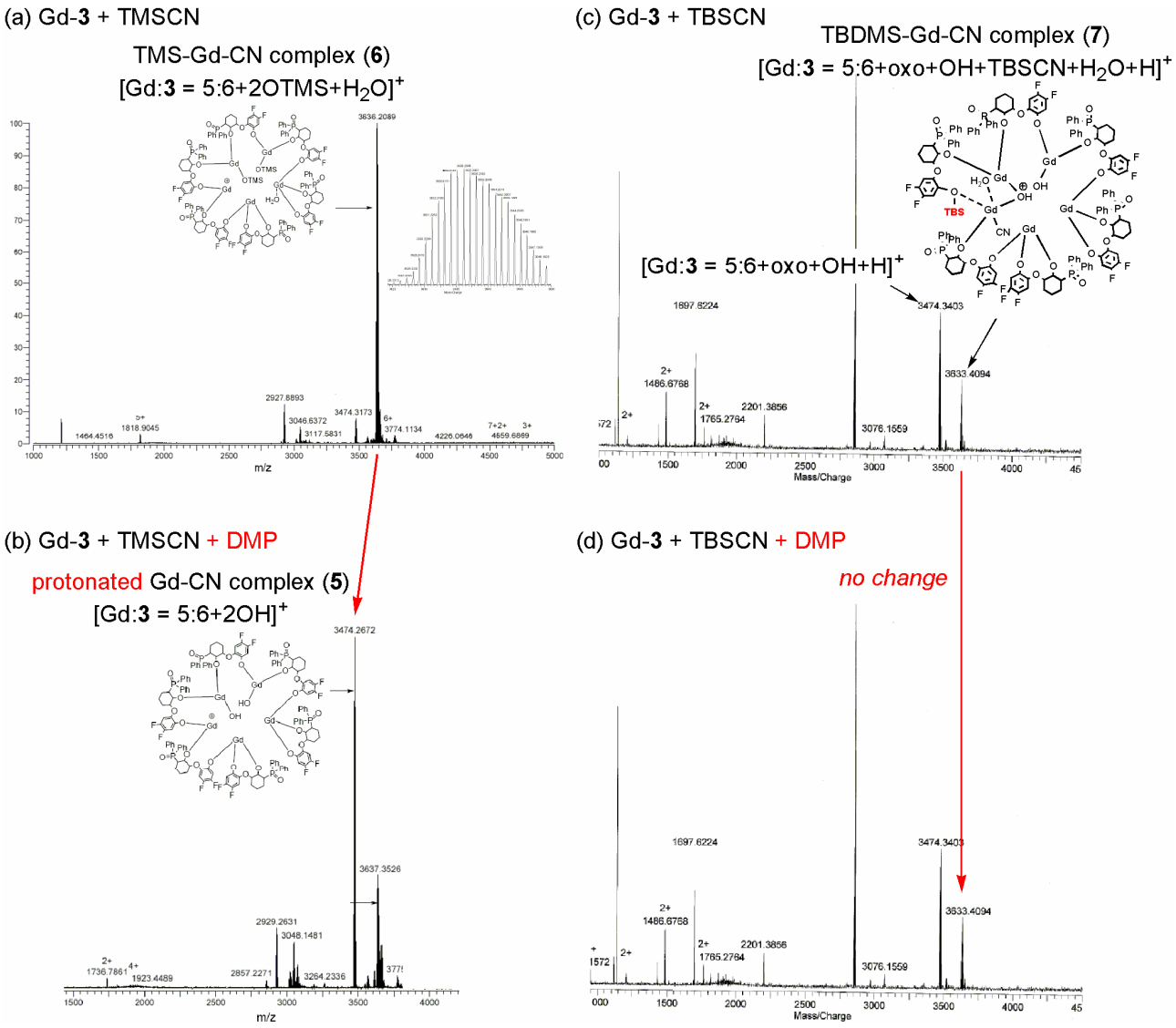


Figure S-1. Spectrum of Gd-**3** complex (analyzed by ESI-QFT-MS: QFT-7)

(a) Gd-**3** catalyst + TMSCN: The peak corresponding to ligand-*O*-trimethylsilylated 5:6 complex was observed as a sole peak (complete transmetalation to generate Gd-CN complex).[6] (b) Gd-**3** catalyst + TMSCN + DMP: Protonolysis of TMS–ligand oxygen atom bond occurred, and protonated 5:6 complex was generated.[4] (c) Gd-**3** catalyst + TBSCN (5 equiv to Gd): Although transmetalation was not complete, ligand-*O*-*t*-butyldimethylsilylated 5:6 complex was generated. (c) Gd-**3** catalyst + TMSCN (5 equiv to Gd) + DMP (5 equiv to Gd): Protonolysis of TBS–ligand oxygen atom bond did not proceed. Therefore, the TBS-containing catalyst was maintained.

The MS information can be summarized as Scheme S-1.

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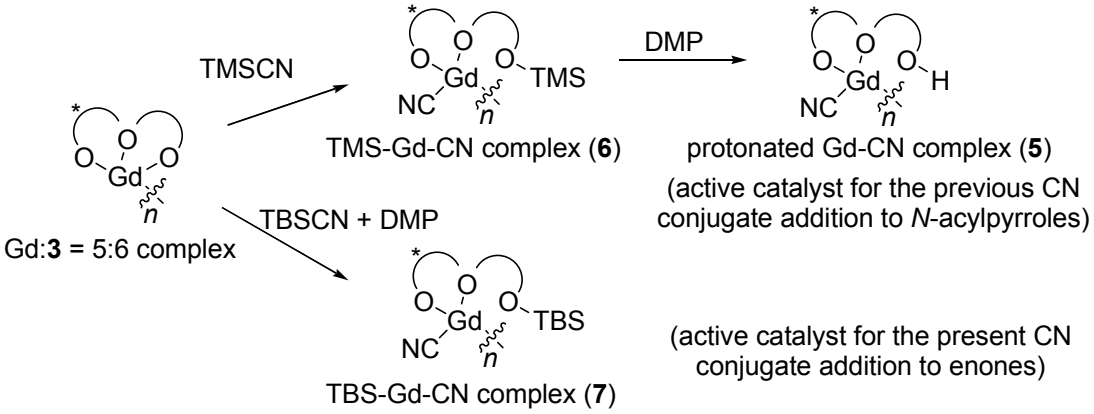
[5] We acknowledge Drs. Akihiro Sato and Sanae Furusho in JASCO International Co., LTD., for measuring the ESI-QFT-MS of the catalysts.

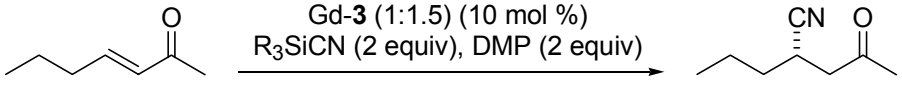
[6] Fujimori, I.; Mita, T.; Maki, K.; Shiro, M.; Sato, A.; Furusho, S.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 16438.



Scheme S-1. Active catalyst detected by mass analysis.

7. Experimental Supports for the Hypothesis of Silylated Complex as More Effective 1,4-Selective Catalyst than the Protonated Complex

Results shown in Table 1, entries 5, 7, 8 (text) and ESI-MS studies of the catalyst led us to propose the hypothesis that the silylated complex is a more effective 1,4-selective asymmetric catalyst. To get further support for this hypothesis, we performed additional experiments, and results are summarized in the following two tables. First, three different experimental procedures were applied to substrate **8a**. Entries 1 and 2 are the same as entries 5 and 8 in Table 1 of the text. Concentration of the silylated Gd-complex should be higher in entry 2 than in entry 1 due to the higher stability of TBS group compared to TMS group against hydrolysis. Accordingly, 1,4-selectivity and catalyst activity were higher in entry 2. In entry 3, the catalyst was *tert*-butyldimethylsilylated by *pre*-incubating the Gd-complex with 10 mol % of TBSCN at 50 °C for 15 min. Then cyantion was performed using HCN produced by mixing TMSCN and DMP. Thus, the cyanating reagent is the same as entry 1, but the catalyst is stably silylated with TBS. As a result, both 1,4-selectivity and catalyst activity markedly improved in entry 3 compared to entry 1.

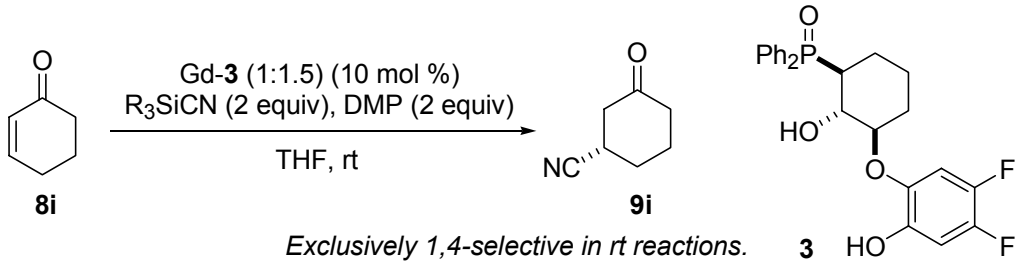


entry	procedure	1,4-/1,2-	**9a**
1	Gd-**3** + premixed (TMSCN + DMP)	72/28	29%, 90% ee
2	Gd-**3** + premixed (TBSCN + DMP)	100/ 0	77%, 92% ee
3	Gd-**3** *pre*-incubated with TBSCN (10 mol %)[a]; then + (TMSCN + DMP)	93/ 7	58%, 89% ee

[a] 50 °C for 15 min.

Effects of the silyl group on enantioselectivity were more obvious when using **8i** as substrate, as shown in the following table. Using the premixed TMSCN and DMP as the cyanating reagent, product **9i** was obtained with 33% ee (entry 1). The enantioselectivity improved to 48% ee when Gd-**3** complex was *pre*-incubated with a stoichiometeric (3 equiv to **8i**) amount of TMSCN, and the cyanation was performed in the presence of 3 equiv of DMP (entry 2). Enantioselectivity was further improved to 53% ee when Gd-**3** was

pre-incubated with a catalytic amount of TBSCN at 50 °C for 15 min (entry 3). Because the concentration of the silylayed complex should be higher according to entry 1 < 2 < 3, those results again support the hypothesis proposing the silylated complex as an effective asymmetric catalyst. When TBSCN was used as a cyanide source, enantioselectivity was almost constant irrespective of the reaction procedure (entries 3, 4, and 5). Because those reactions were performed at rt, the reactions were completely 1,4-selective.



entry	procedure	**9i**
1	Gd-**3** + premixed (TMSCN + DMP)	94%, 33% ee
2	Gd-**3** *pre*-incubated with TMSCN[a]; then DMP	74%, 48% ee
3	Gd-**3** *pre*-incubated with TBSCN (10 mol %)[a]; then + (TMSCN + DMP)	89%, 53% ee
4	Gd-**3** + premixed (TBSCN + DMP)	95%, 53% ee
5	Gd-**3** *pre*-incubated with TBSCN[a]; then DMP	97%, 55% ee

[a] 50 °C for 15 min.

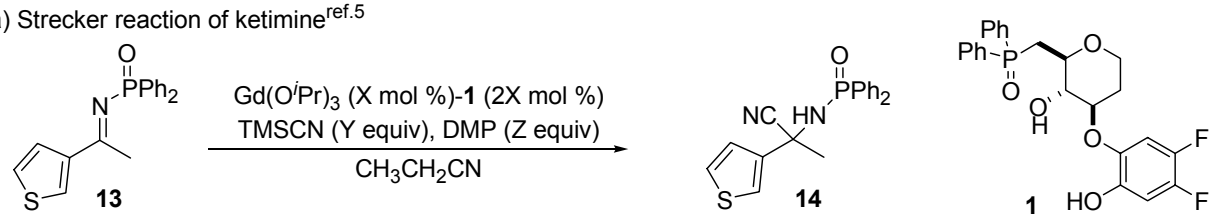
All of the above results support that the silylated complex is more effective 1,4-selective asymmetric catalyst than protonated complex.

8. Comparison between the Previous Conditions (slight excess TMSCN to DMP) and the Present Conditions (TMSCN:DMP = 1:1) in Various Reactions

Previously, we found that a protic additive facilitated the catalytic asymmetric Strecker reaction[7] and CN conjugate addition to *N*-acylpyrroles.[1b] Enantioselectivity also improved in the presence of the additive. In those reactions, however, slight excess TMSCN compared to the protic additive (DMP) was always required. To demonstrate the novelty of the present conditions using TMSCN:DMP = 1:1, we compared the previous and present conditions in the Strecker reaction and the CN conjugate addition to *N*-acylpyrroles (see table below). In both cases, the reactivity and enantiselectivity markedly decreased under the current optimized conditions for the CN conjugate addition to enones.

[7] Kato, N.; Suzuki, M. Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2004**, *45*, 3147.

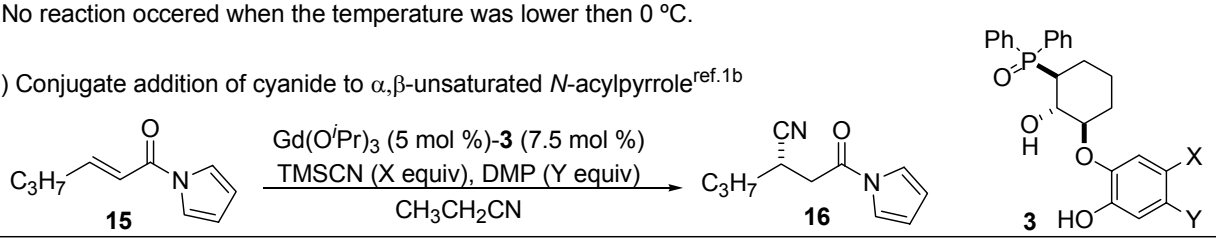
(a) Strecker reaction of ketimine[ref.5]



entry	catalyst loading (X mol %)	TMSCN (Y equiv)	DMP (Z equiv)	temp (ºC)	time (h)	yield (%)	ee (%)
1	2.5	1.5	1	-40	1.3	98	99
2	5	2	2	rt [a]	33	quant	-46

[a] No reaction occered when the temperature was lower then 0 ºC.

(b) Conjugate addition of cyanide to α,β-unsaturated *N*-acylpyrrole[ref.1b]



entry	TMSCN (X equiv)	DMP (Y equiv)	temp (ºC)	time (h)	yield (%)	ee (%)
1	1.5	1	-20	2.5	93	93
2	2	2	0 [a]	11	53	29

[a] No reaction occered at -20 ºC.

These results might be explained from the proposed catalytic cycle (Figure S-2 and 3). In the Strecker reaction and CN conjugate addition to *N*-acylpyrroles, protonated polymetallic complex **18**, generated through transmetalation from **21** and TMSCN (**17**) followed by protonolysis,[6] works as the active catalyst.

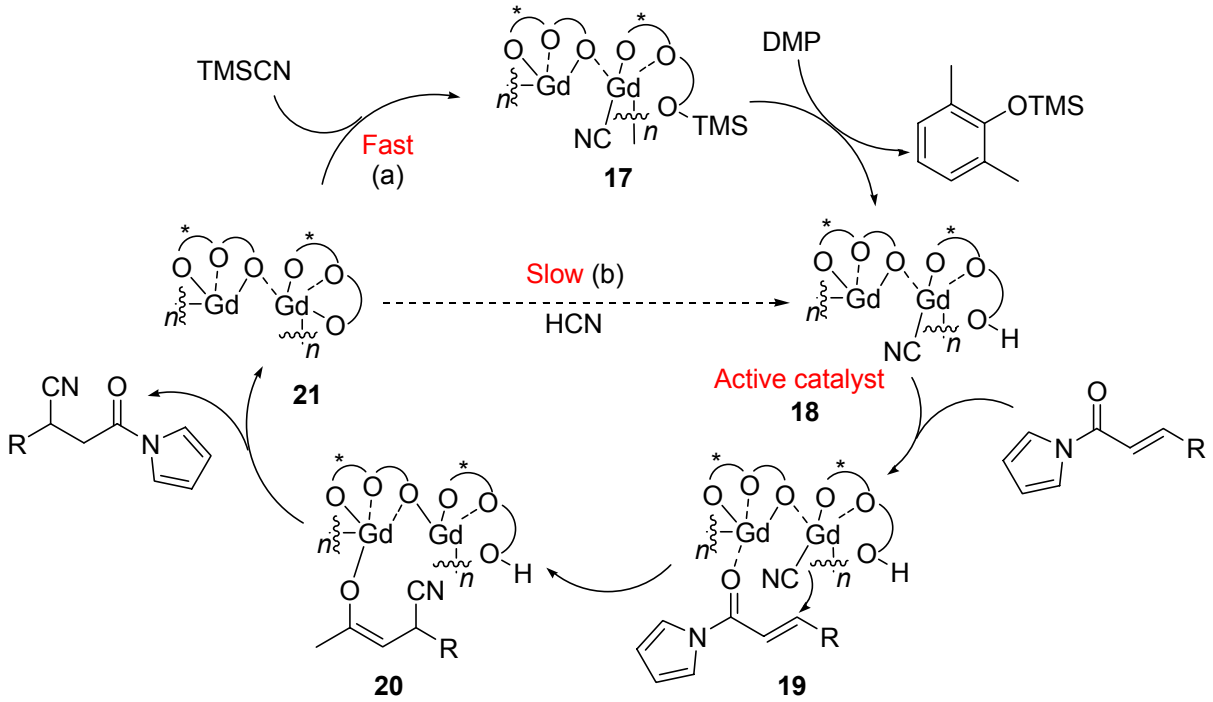


Figure S-2. Proposed catalyst cycle for the conjugate addition of cyanide to α,β-unsaturated *N*-acylpyrrroles (and the Strecker reaction of ketimines) (Previous conditions with slight excess of TMSCN to DMP).

After enantioselective cyanation (**19**), intramolecular proton transfer (**20**) should produce Gd-alkoxide complex **21**. There are two pathways for regeneration of the active catalyst **18** from **21**: (a) transmetalation to **17** followed by protonolysis, and (b) direct protonolysis with in situ generated HCN. The fact that an excess amount of TMSCN is required for the facile catalyst turnover indicates that pathway (a) is the more favorable (faster) pathway than (b). Retarding the desired catalyst regeneration pathway (a) by completely consuming TMSCN (present conditions) might have detrimental effects on the reaction rate, as well as the enantioselectivity through intervention by undesired catalytic species.

On the other hand, a catalytic cycle for the CN conjugate addition of enones under the present conditions is proposed in Figure S-3. The active catalyst is a silylated polymetallic complex **22**. After the conjugate addition (**23**) producing **24**, the intermediate Gd-enolate should be protonated by external HCN with regenerating the active catalyst **22**. Because there is no Gd-alkoxide intermediate (such as **21** in Figure S-2) in this catalytic cycle, the direct protonolysis pathway by HCN in the active catalyst regeneration should be reasonably fast. Therefore, excess TBSCN is not required in the present studies. Moreover, the absence of excess TBSCN (or TMSCN) is advantageous for the high 1,4-selectivity, because the 1,2-product is less possible to be trapped by the silicon and thus the proofreading of the asymmetric catalyst functions efficiently.

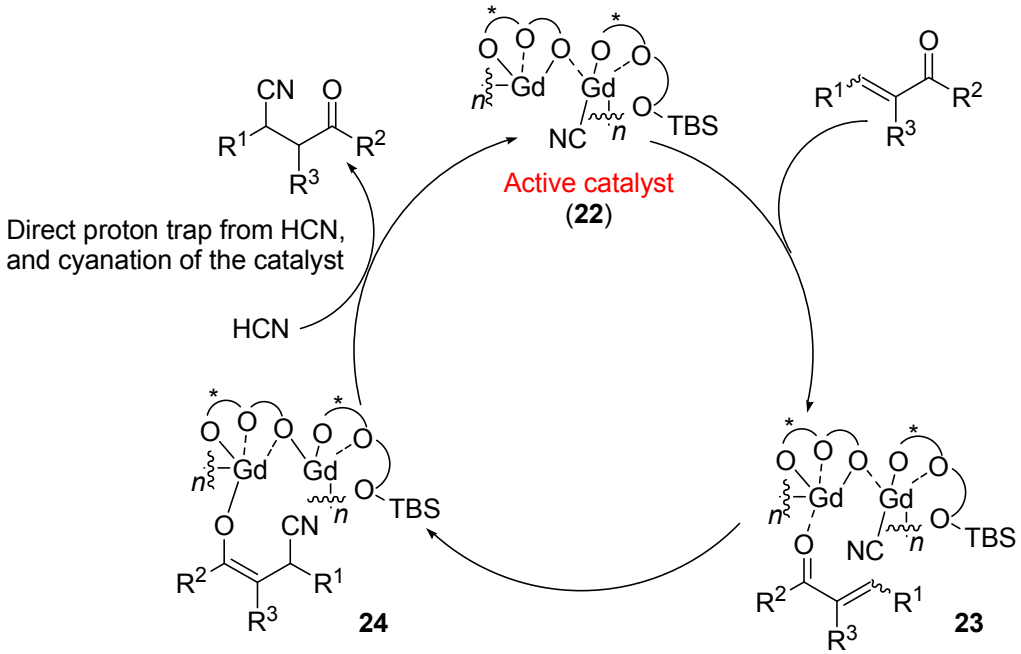
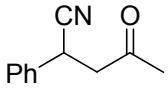


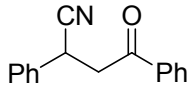
Figure S-3. Proposed catalyst cycle for conjugate addition of cyanide to enones (TBSCN:DMP = 1:1).

9. Unsuccessful Substrates

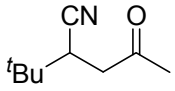
Although significant substrate scope was demonstrated in this preliminary communication (Table 2 in the text), there still exist unsuccessful substrates beyond the current limitation. Unsuccessful results are summarized here (10 mol % catalyst). In addition, an enal (2-nonenal) produced TBS-protected cyanohydrin as the sole product under the current optimized conditions.



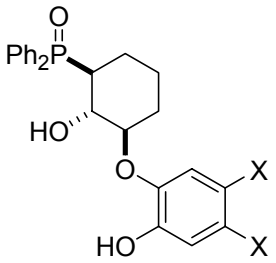
27%, 2% ee
(**3**, rt, 20 h)



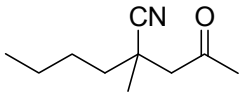
8%, 29% ee
(**3**, -20 ^{o}C, 65 h)



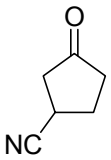
32%, 25% ee
(**4**, -20 ^{o}C, 24 h)



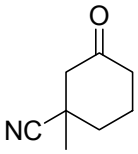
3: X, Y = F
4: X = CN, Y = H
25: X, Y = H



26%, 33% ee
(**25**, rt, 18 h)



38%, 5% ee
(**4**, rt, 1 h)



70%, 25% ee
(**3**, 50 ^{o}C, 22 h)