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Catalytic asymmetric synthesis of (*S*)-oxybutynin and a versatile intermediate for antimuscarinic agents

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Abstract—A practical synthesis of (*S*)-oxybutynin, a muscarinic receptor antagonist, using catalytic enantioselective cyanosilylation of cyclohexyl phenyl ketone (**9a**) as a key step is described. The key reaction proceeded with 94% ee using 1 mol% of Gd-**1** catalyst, and was performed on a 100 g-scale. In addition, a short catalytic enantioselective synthesis of the versatile intermediate for Scios Nova analogues of antimuscarinic agents (**7**) is described. Application of the catalytic enantioselective cyanosilylation to ketones containing two sterically similar substituents on the carbonyl group is also discussed.

1. Introduction

In 2000, we developed a general catalytic enantioselective cyanosilylation of ketones using a catalyst derived from ligand **1** and $Ti(O^iPr)_4$ in a 1:1 ratio (Scheme 1).[1,2] (*R*)-Ketone cyanohydrins are obtained with high enantioselectivity through a presumed dual activation[3] transition state depicted as **3**, which was suggested based on kinetic studies and results using a control catalyst lacking the Lewis base moiety. The efficiency (enantioselectivity and catalyst turnover number) of the Ti-catalyzed reaction was further improved by developing a tuned ligand **2** containing an electron-withdrawing benzoyl group at the catechol moiety.[4] For the synthesis of (*S*)-ketone cyanohydrins, we developed a catalyst prepared from **1** and $Gd(O^iPr)_3$ in a 1:2 ratio.[5] This (*S*)-selective Gd-catalyst is more reactive than the (*R*)-selective Ti-catalyst. Mechanistic studies suggested that the active catalyst is a 2:3 complex of gadolinium cyanide and **1**, and the reaction proceeds through an intramolecular cyanide transfer from the nucleophilic gadolinium cyanide activated by the phosphine oxide, to the ketone activated by the Lewis acidic gadolinium cyanide (**4**). These reactions are practical and of broad substrate scope, and the catalytic enantioselective syntheses of fostriecin[6] (a natural anticancer compound) and camptothecin[5] (an important anticancer drug) were achieved using these reactions as key steps.

Oxybutynin (Ditropan: **5**) is a widely utilized muscarinic receptor antagonist for the treatment of urinary urgency, frequency, and incontinence.[7] A number of derivatives have been synthesized mainly by modifying the ester (or the amide) and the cycloalkyl parts (for examples, see Fig. 1).[8] Some of these analogues have improved M_3-receptor subtype selectivity and thus the side effects caused by antagonizing other subtypes, such as M_1- and M_2-receptors, are minimized. A structurally common feature of oxybutynin and related compounds is the chiral tertiary α-hydroxy carbonyl moiety. Although oxybutynin is currently prescribed in racemic form, the (*S*)-enantiomer is proposed to have an improved therapeutic profile. Therefore, there is a high demand for the development of an efficient enantioselective synthetic route. Previously reported methods utilized diastereoselective reactions that require a stoichiometric amount of chiral auxiliary or a chiral starting material to construct the chiral stereocenter of **5**.[9] We reported the first practical catalytic enantioselective synthesis of the key synthetic intermediate **11**, utilizing catalytic cyanosilylation of the ketone as a key step.[10] Our synthesis produced high enantioselectivity (up to 94% ee) from cyclohexyl phenyl ketone (**9a**). Based on the high enantioselectivity obtained from a ketone containing two sterically similar substituents (phenyl and cyclohexyl), we investigated the applicability of the Gd-catalyst to other related ketones. Among the substrates studied, excellent enantioselectivity (97% ee) was obtained from cyclobutyl phenyl ketone (**9f**). This finding led us to apply the catalytic

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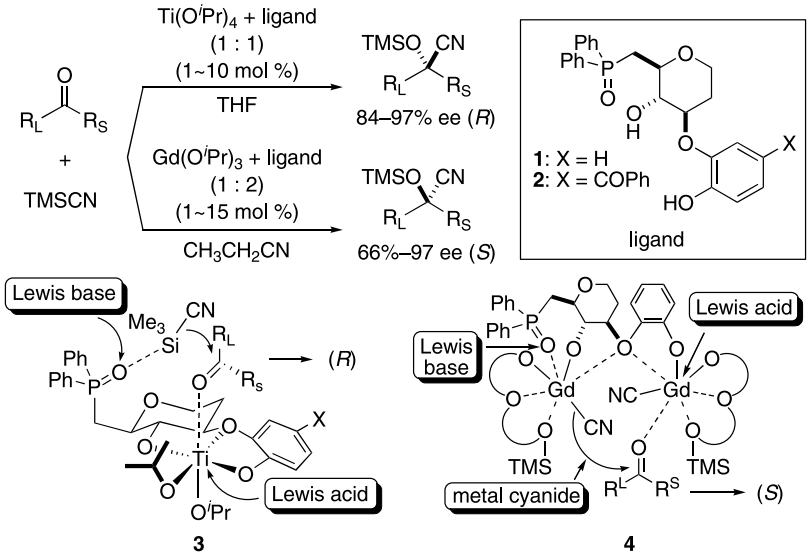


Scheme 1. Catalytic enantioselective cyanosilylation of ketones.

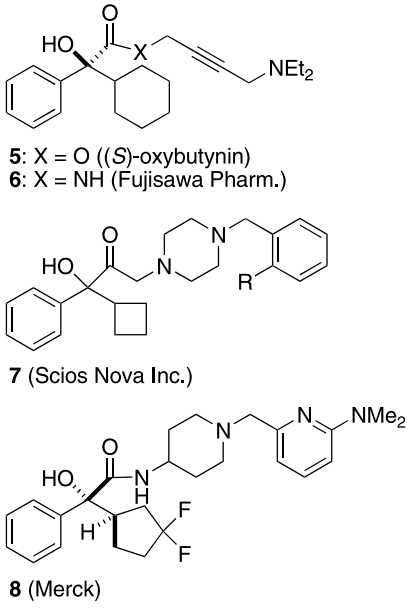


Figure 1.

enantioselective cyanosilylation to a short synthesis of the versatile synthetic intermediate for Scios Nova analogues (for example, see **7**)[8b] of subtype-selective antimuscarinic agents. This paper describes the details of these syntheses.

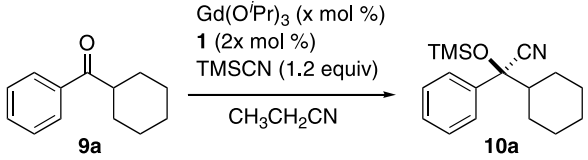
2. Results and discussion

2.1. Catalytic enantioselective synthesis of (*S*)-oxybutynin

Substrate **9a** for the oxybutynin synthesis is an extremely challenging ketone with respect to the induction of enantioselectivity. In general, to achieve high enantioselectivity of a nucleophilic addition to carbonyl compounds, the chiral catalyst needs to differentiate two lone pairs of the carbonyl oxygen atom for the coordination to the Lewis acid metal of the chiral catalyst. In the case of ketone **9a**, however, the difference in the steric demand of these lone pairs is not sufficient because these lone pairs are *cis* to sterically similar phenyl or cyclohexyl groups.[11]

Despite the expected difficulties, the catalytic enantioselective cyanosilylation of ketone **9a** proceeded at −60 °C

Table 1. Catalytic enantioselective cyanosilylation of ketone **9a**



Entry	Cat. (×mol%)	Temperature (°C)	Time (h)	Yield (%)[a]	ee (%)[b]
1	5	−60	21	96	95
2	5	−40	1.5	99	91
3	1	−40	50	99	85
4[c]	1	−40	40	100	94

[a] Isolated yield.
[b] Determined by chiral HPLC analysis.
[c] The ketone was added prior to TMSCN (see Section 4 for details). In other entries, ketones were added at the last stage.

for 21 h in the presence of 5 mol % of Gd-catalyst, affording the desired (*S*)-**10a** in 96% yield with 95% ee (Table 1, entry 1, catalyst concentration = 0.075 M, ketone concentration = 1.5 M). The absolute configuration of **10a** was determined after conversion to carboxylic acid **11**, and by comparing the optical rotation with the reported value.[9a] This is the same enantioselectivity as obtained with other previously studied simple ketones such as acetophenone,[5] suggesting that the catalyst recognizes the cyclohexyl group as being smaller than the phenyl group. For comparison of the reactivity, we investigated the reaction using the (*R*)-selective Ti-catalyst; however the Ti-complex did not promote the reaction of **9a** at low temperature. The reaction proceeded at room temperature with the Ti-catalyst, and (*R*)-**10a** was obtained in 96% yield with only 7% ee (36 h).

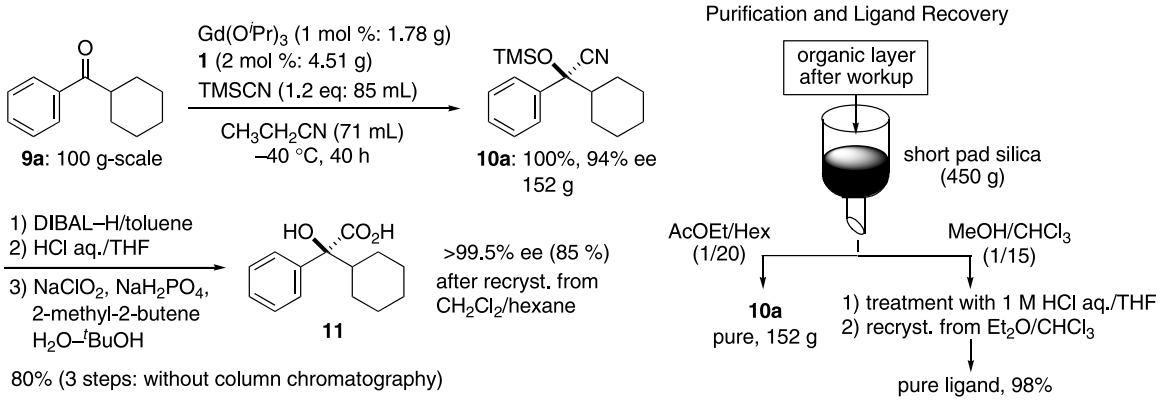
To improve the practicality of the Gd-catalyzed ketone cyanosilylation for (*S*)-oxybutynin synthesis, we decreased the catalyst loading. Using 1 mol% Gd-catalyst, however, resulted in a sluggish reaction at −60 °C, giving the product in 39% yield with 64% ee (9 days, catalyst concentration = 0.015 M, ketone concentration = 1.5 M). Increasing the reaction temperature to −40 °C and using a higher concentration, the reaction proceeded to completion to give the product in 99% yield with 85% ee (entry 3, catalyst concentration = 0.075 M, ketone concentration = 7.5 M). We hypothesized that the decrease in enantioselectivity with the lower amount of catalyst was due in part to the initial heat generation when a large amount of substrate ketone was added in one portion to a mixture of the catalyst and TMSCN, following the previous general procedure. Therefore, we first added the substrate ketone to the catalyst, then cooled the reaction temperature to −40 °C, added the solvent, and slowly added the TMSCN (over 15 min). This procedure improved the results and the product was obtained with 94% ee (entry 4). The reaction and purification procedures are practical and we performed the reaction on a 100 g-scale. After the usual aqueous workup, the crude oil was purified through short-pad silica gel column chromatography (Scheme 2). Pure **10a** was obtained with EtOAc/hexane (1:20) elution, followed by MeOH/$CHCl_3$ (1:15) elution to obtain the ligand-containing fraction (a mixture of ligand **1** and the silylated ligand). The pure ligand **1** was recovered in 98% yield after acidic desilylation (1 M HCl aq in THF) and recrystallization. The recovered ligand can be reused many times without any loss of efficiency.

Having established a practical method for the catalytic enantioselective cyanosilylation of the ketone, the next task was to convert the cyanide to the carboxylic acid. The conversion was initially problematic, however, probably due to steric hindrance. Acidic hydrolysis or alcoholysis gave predominantly ketone **9a** through the elimination of HCN. Basic hydrolysis after conversion to the THP-protected cyanohydrin resulted in no reaction. Therefore, we investigated the reduction–oxidation procedure (Scheme 2). Careful reduction of **10a** with DIBAL-H in toluene, desilylation with 4 M HCl aq in THF, followed by oxidation with $NaClO_2$ gave the known α-hydroxy carboxylic acid **11** in 80% overall yield (3 steps). Chemically pure **11** was obtained through a base/acid aqueous workup without silica gel column chromatography. Recrystallization from CH_2Cl_2/hexane gave an enantiomerically pure intermediate for oxybutynin synthesis.[12]

2.2. Catalytic enantioselective cyanosilylation of ketones containing two sterically similar substituents on the carbonyl carbon

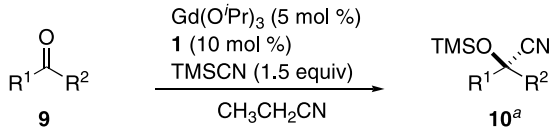
The unusually high enantio-differentiation ability of the catalyst on the apparently difficult substrate **9a** led us to study the applicability of the Gd-catalyzed enantioselective cyanosilylation to other ketones containing two sterically similar substituents on the carbonyl carbon. High to excellent enantioselectivity was obtained except in the cases of cyclopentyl phenyl ketone (**9e–H**: entry 4) and isopropyl phenyl ketone (**9l–H**: entry 14: Table 2). Even simple linear ketone **9n** gave the product with 85% ee (entry 17). Therefore, differentiation of the two carbonyl oxygen lone pair by the Gd-**1** catalyst might be due mainly to the electronic characteristics of the two substituents on the carbonyl group.[11] Some of the products obtained with high enantioselectivity should be very useful for synthesizing new chiral oxybutynin analogues (for example, see Section 4).

The sharp contrast in the enantiomeric excess of **10e–H** and **10l–H**, and products from other ketones is intriguing from a mechanistic point of view. The results cannot be explained from the ground state structure difference, based on the

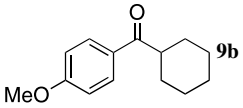
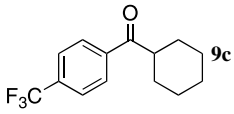
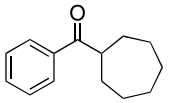
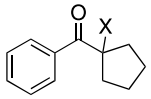
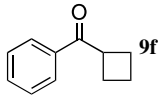
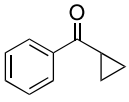
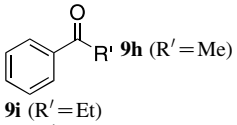
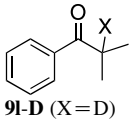
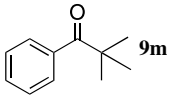
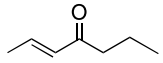


Scheme 2. Practical catalytic enantioselective synthesis of (*S*)-oxybutynin key intermediate.

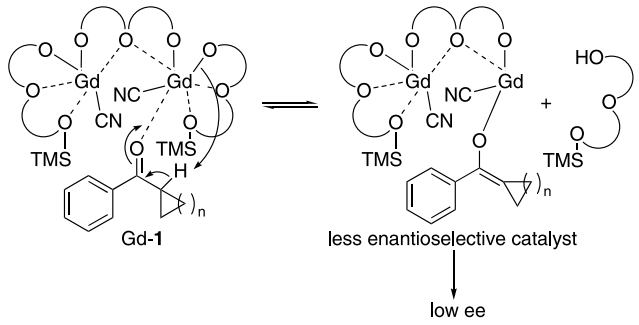
Table 2. Catalytic enantioselective cyanosilylation of ketones containing sterically similar substituents



9 **10**[a]

Entry	Ketone	Temperature (°C)	Time (h)	Yield[b] (%)	ee[c] (%)
1	 **9b**	−40	22	99	94
2	 **9c**	−40	1	96	83
3	 **9d**	−40	5	99	94
4	 **9e-H** (X=H)	−40	64	87	22
5[d]	**9e-D**	−40	1	99	95
6[e]	**9e-D**	−40	1	99	95
7[f]	**9e-D** (X=D)	−40	18	99	78
8	 **9f**	−40	2	99	97
9	 **9g**	−40	48	97	82
10	 **9h** (R′=Me)	−40	1	89	95
11	**9i** (R′=Et)	−60	14	93	97
12	**9j** (R′-Pr)	−60	2.5	94	97
13	**9k** (R′=Bu)	−60	14	91	87
14	 **9l-H** (X=H)	−40	20	99	38
15[g]	**9l-D** (X=D)	−40	1	81	96
16	 **9m**	−60	2.5	90	80
17	 **9n**	−40	1	87	85

[a] The absolute configuration of the product was temporarily assigned based on the analogy to **10a**.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis.
[d] 85%-D.
[e] 65%-D.
[f] 21%-D.
[g] 80%-D.



Scheme 3.

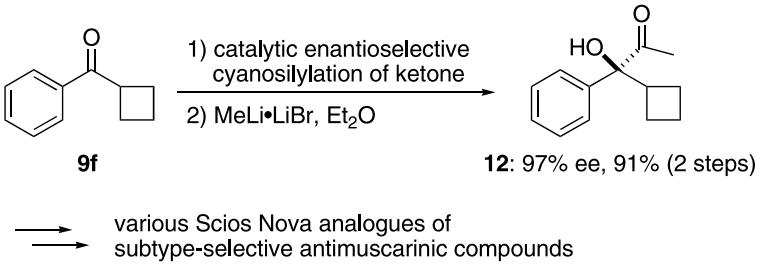
comparison of the most stable conformation of these substrates; molecular modeling studies indicated that **9e–H** and **9l–H** contain similar conformation and electronic characteristics to other ketones. The reactivity-enantioselectivity relation indicated a general trend in that high enantioselectivity was obtained when the reactions proceeded smoothly (Table 2). To explain this trend, we hypothesized that the asymmetric catalyst might act as a Brönsted base to deprotonate the starting ketones. Based on the analogy from the fact that the equilibrium acidity of nitrocyclopentane is significantly higher (pK_a units of ca. 2) than nitrocyclobutane or nitrocyclohexane due to the difference in the released strain energy in the nitronate formation,[13] it might be reasonable to assume that the α-proton of **9e–H** is more acidic than that of **9a** or **9f**. Thus, **9e–H** (and maybe **9l–H**) might be more prone to deprotonation. This competitive deprotonation pathway might cause a ligand exchange to produce a less enantioselective catalyst (Scheme 3). Based on this hypothesis, we planned to utilize a deuterium kinetic isotope effect to prevent the undesired deprotonation.[14] As we expected, the reactions using **9e–D** and **9l–D** proceeded rapidly and the products were obtained with up to 95 and 96% ee, respectively (Table 2, entry 5 vs entry 4 and entry 15 vs entry 14). Even using the starting ketone with 21% deuterium incorporation at the α-position, the enantioselectivity was significantly higher than the non-deuterated one (entry 7 vs entry 4). Thus, the enantioselectivity of the product should be determined by the population ratio of the highly enantioselective Gd-**1** and ligand-exchanged catalyt(s) with reduced enantioselectivity (see Scheme 3), as well as the reaction kinetics promoted by these complexes. To our knowledge, this is the first example of a dramatic advantage using an isotope effect in catalytic enantioselective reactions. The results provide very important insight for a new use of the Gd-catalyst as a Brönsted base.

2.3. Short-step synthesis of a versatile intermediate for subtype-selective muscarinic receptor antagonists

The research group of Scios Nova Inc., reported a series of compounds with M_3-subtype-selective antimuscarinic activity.[8b] These compounds contain a tertiary alcohol with phenyl and cyclobutyl groups as substituents on the tetrasubstituted carbon (for example, see **7**) as the common structure. These compounds were readily synthesized using the methyl ketone **12** as a versatile synthetic intermediate; α-bromination followed by the substitution with amines. Although the Scios Nova group reported promising biological activities using racemic compounds, it is highly probable that the (*S*)-enantiomer possesses higher potency than the (*R*)-enantiomer, based on the analogy to oxybutynin. Thus, we developed a short synthetic route to (*S*)-**12**, using the catalytic enantioselective cyanosilylation of ketone **9f**. As described in the above section, the corresponding precursor cyanohydrin **10f** was obtained with excellent enantioselectivity (97% ee: Table 2, entry 6). The addition of MeLi to **10f**[15] followed by hydrolysis with silica gel gave the methyl ketone **12** with no decrease in enantioselectivity (91% yield over 2 steps). Thus, a two-step catalytic enantioselective synthesis of the versatile intermediate for subtype-selective antimuscarinic lead compounds from commercially available ketone **9f** was achieved (Scheme 4).

3. Conclusions

We developed a practical synthetic route for an important pharmaceutical, (*S*)-oxybutynin. The chiral center of the core tertiary α-hydroxy carboxylic acid was constructed by the catalytic enantioselective cyanosilylation of ketones using 1 mol% of Gd-**1** complex. These procedures are suitable for large-scale synthesis with minimal silica gel column chromatography purification. In addition, a two-step catalytic enantioselective synthesis of the versatile intermediate for subtype-selective antimuscarinic compounds (Scios Nova analogues) was developed. Furthermore, the excellent enantioselectivity obtained in the reaction of ketones containing two sterically similar substituents indicated that the Gd-**1** catalyst differentiates the electronic characteristics of the substituents. There was a dramatic deuterium isotope effect on the reaction kinetics and enantioselectivity in the case of ketones **9e** and **9l**, which suggested that ketone deprotonation might be a possible competitive pathway for some ketones. Based on these new findings, studies to develop a new chiral Brönsted base catalyst are currently ongoing.



Scheme 4. Short-step synthesis of versatile intermediate for subtype-selective antimuscarinic compounds.

4. Experimental

4.1. 100 g-Scale cyanosilylation of 9a

$Gd(O^iPr)_3$ (5.31 mmol, 0.2 M stock solution in THF, purchased from Kojundo Chemical Laboratory Co., Ltd. Fax: +81-492-84-1351) in THF (26.6 ml) was added to a suspension of chiral ligand **1** (4.51 g, 10.6 mmol) in THF (106 ml) in an ice bath and the mixture was stirred for 30 min at 45 °C. After cooling to room temperature, THF was evaporated and the residue was dried for 6 h under vacuum (5 mmHg). To this catalyst powder, ketone **9a** (100 g, 0.531 mol) was added. Propionitrile (71 ml) and TMSCN (85 ml, 0.637 mol) were successively added at −40 °C, and the mixture was stirred for 40 h at −40 °C. H_2O was added to quench the reaction (caution: HCN is generated), and the product and the ligand were extracted with EtOAc. The combined organic layers was washed with brine and dried over Na_2SO_4. Evaporation of the solvent gave a crude oil, which was purified through short pad SiO_2 column chromatography (450 g; EtOAc/hexane=1:20) to give pure **10a** as a colorless oil (152 g, 100% yield). The ligand and the silylated ligand were eluted from the column with $CHCl_3$/MeOH=15:1, treated with HCl aq in THF, extracted, and purified by recrystallization to recover pure ligand **1** in 98% yield.

4.2. General procedure for the conversion to benzoyl amide for ee determination

To a solution of **10a** (16.7 mg, 0.0581 mmol) in THF (0.2 ml) was added $LiAlH_4$ (6.3 mg, 0.166 mmol) at room temperature, and the resulting mixture was stirred at 40 °C for 1 h H_2O (1 drop), 15% NaOH (1 drop) and H_2O (3 drops) were successively added to the reaction mixture in an ice bath and ether (2 ml) was added to the resulting mixture. After stirring at room temperature for 30 min, Et_3N (2 drops) and benzoyl chloride (14 μl, 0.121 mmol) were added to the reaction mixture in an ice bath. After stirring for 20 min, water was added and the mixture was extracted with EtOAc. The organic layer was washed with satd $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated to give a crude product, which was purified by preparative TLC (EtOAc/hexane, 1:3) to give the corresponding benzoyl amide.

4.2.1. Cyclohexyl(phenyl)[(trimethylsilyl)oxy]acetonitrile (10a). Colorless oil; ^1H NMR ($CDCl_3$) δ 7.47–7.45 (m, 2H), 7.39–7.32 (m, 3H), 2.03–1.99 (m, 1H), 1.82–1.79 (m, 1H), 1.75–1.68 (m, 2H), 1.65–1.62 (m, 1H), 1.39–1.35 (m, 1H), 1.21–1.02 (m, 5H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.33, 128.60, 128.35, 125.96, 120.35, 79.71, 50.84, 27.49, 27.40, 26.13, 26.09, 26.07, 0.97; EI-MS *m/z* 287 (M^+); EI-HRMS calcd for $C_{17}H_{25}NOSi$ (M^+): 287.1705, Found: 287.1705; $[\alpha]_D^{27}=-19.4$ ($c=1.41$, $CHCl_3$) (94% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 18.9 min (major), 20.8 min (minor).

4.2.2. (2*S*)-Cyclohexyl(hydroxy)phenylacetic acid (11). DIBAL-H (1.0 M in toluene, 34.8 ml, 34.8 mmol) was added dropwise to a solution of cyanohydrin **10a** (5.00 g, 17.4 mmol) in toluene (50 ml) at −78 °C for 75 min. Then, the bath temperature was increased to −40 °C and the solution was stirred for 11 h. After the reaction was completed, satd NH_4Cl aq was added, followed by the addition of 1 M HCl. After stirring for 30 min, the product was extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was dissolved in THF (30 ml) and 4 M HCl aq (30 ml) was added at room temperature for desilylation (2 h). Extraction with EtOAc, successive wash with satd $NaHCO_3$ aq and brine, and evaporation of the organic solvent gave the corresponding hydroxy aldehyde, which was subjected to the following oxidation. $NaClO_2$ (79%, 2.99 g, 26.1 mmol) was added portionwise to a solution of the residue, 2-methyl-2-butene (8.1 ml), and NaH_2PO_4 (2.09 g, 17.4 mmol) in ^{t}BuOH (50 ml) and H_2O (12.5 ml) for 15 min in an ice bath, and the mixture was stirred for 1 h at room temperature. After cooling in an ice bath, 2 M NaOH aq was added until pH was greater than 10, and the solution was slowly added to Na_2SO_3 (4.84 g, 38.4 mmol) in H_2O (80 ml). ^{t}BuOH was evaporated under reduced pressure and the water layer (pH >10) was washed with Et_2O (×3). The water layer was acidified with conc. HCl to pH=1 and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Filtration and evaporation of the solvent gave a white powder of **11** (3.28 g, 80%). The enantiomeric excess of **11** was determined by chiral HPLC [DAICEL CHIRALPAK AS, hexane/2-propanol/TFA=95:5:0.1, 1.0 ml/min, t_R 7.3 (minor) and 10.6 min (major)]. Enantiomerically pure (>99% ee) **11** was obtained by recrystallization from CH_2Cl_2/hexane (1:30) in 85% yield. ^1H NMR ($CDCl_3$) δ 7.64 (d, 2H, $J=7.6$ Hz), 7.36–7.33 (m, 2H), 7.29–7.26 (m, 1H), 2.29–2.23 (m, 1H), 1.83–1.81 (m, 1H), 1.67–1.61 (m, 3H), 1.49–1.41 (m, 1H), 1.38–1.29 (m, 1H), 1.21–1.02 (m, 4H); ^{13}C NMR (C_6D_6) δ 180.71, 140.04, 128.36, 127.88, 126.09, 81.21, 45.88, 27.55, 26.43 (overlap), 26.29, 25.60; mp 142–143 °C; EI-MS *m/z* 234 (M^+); EI-HRMS calcd for $C_{14}H_{18}O_3$ (M^+): 234.1256, Found: 234.1257; $[\alpha]_D^{27}=+21.8$ ($c=1.00$, EtOH) (>99% ee) (lit.[9c] $[\alpha]^{22}{}_D=+22.6$ (EtOH)).

4.3. General procedure for the catalytic asymmetric cyanosilylation of ketones

$Gd(O^iPr)_3$ (0.015 mmol, 0.2 M stock solution in THF) in THF (75 μl) was added to a suspension of chiral ligand **1** (12.7 mg, 0.030 mmol) in THF (0.3 ml) in an ice bath and the mixture was stirred for 30 min at 45 °C. After cooling to room temperature, THF was evaporated and the residue was dried for 1 h under vacuum (5 mmHg). Propionitrile (0.2 ml) was added to this catalyst powder, and TMSCN (60 μl, 0.45 mmol) and a ketone (0.300 mmol) were added at −40 or −60 °C, and the mixture was stirred at the temperature shown in Table 2 until the starting ketone disappeared on TLC. Workup and purification procedures are the same as for the large-scale reaction (vide supra). ee was determined after conversion to the corresponding benzoyl amide (1. LAH, THF, 2. benzoyl chloride, Et_3N).

4.3.1. Cyclohexyl(4-methoxyphenyl)[(trimethylsilyl)oxy]acetonitrile (10b). Colorless oil; ^1H NMR ($CDCl_3$) δ 7.39–7.36 (m, 2H), 6.90–6.87 (m, 2H), 3.82 (s, 3H), 2.04–2.01 (m, 1H), 1.82–1.80 (m, 1H), 1.73–1.68 (m, 2H), 1.65–1.63

(m, 1H), 1.38–1.35 (m, 1H), 1.22–1.00 (m, 5H), 0.09 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 159.79, 132.40, 127.24, 120.50, 113.67, 79.43, 55.41, 50.90, 27.52 (overlap), 26.17, 26.12, 26.10, 1.02; EI-MS *m/z* 317 (M^+); EI-HRMS calcd for $C_{18}H_{27}NO_2Si$ (M^+): 317.1811, found: 317.1807; $[\alpha]_D^{27} = -20.8$ ($c=1.16$, $CHCl_3$) (94% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALCEL OD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 13.2 min (minor), 17.4 min (major).

4.3.2. Cyclohexyl[4-(trifluoromethyl)phenyl] [(trimethylsilyl)oxy]acetonitrile (10c). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.65 (d, 2H, $J=8.4$ Hz), 7.60 (d, 2H, $J=8.4$ Hz), 1.97–1.95 (m, 1H), 1.83–1.80 (m, 1H), 1.72 (m, 2H), 1.66–1.64 (m, 1H), 1.40–1.38 (m, 1H), 1.22–1.05 (m, 5H), 0.13 (s, 9H); EI-MS *m/z* 355 (M^+); EI-HRMS calcd for $C_{18}H_{24}F_3NOSi$ (M^+): 355.1579, Found: 355.1577; $[\alpha]_D^{26} = -14.2$ ($c=1.98$, $CHCl_3$) (83% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 14.4 min (major), 22.6 min (minor).

4.3.3. Cycloheptyl(phenyl)[(trimethylsilyl)oxy] acetonitrile (10d). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.50–7.48 (m, 2H), 7.39–7.32 (m, 3H), 2.08–2.04 (m, 1H), 1.97–1.92 (m, 1H), 1.82–1.75 (m, 1H), 1.65–1.40 (m, 8H), 1.33–1.22 (m, 2H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.64, 128.64, 128.42, 126.15, 120.65, 80.02, 52.34, 29.34, 28.75, 28.28, 27.92, 26.69, 26.68, 1.02; EI-MS *m/z* 301 (M^+); EI-HRMS calcd for $C_{18}H_{27}NOSi$ (M^+): 301.1862, found: 301.1862; $[\alpha]_D^{26} = -27.9$ ($c=0.31$, $CHCl_3$) (94% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 18.1 min (major), 23.3 min (minor).

4.3.4. Cyclopentyl(phenyl)[(trimethylsilyl)oxy] acetonitrile (10e). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.49 (m, 2H), 7.39–7.31 (m, 3H), 2.43–2.36 (m, 1H), 1.77–1.62 (m, 4H), 1.58–1.46 (m, 2H), 1.44–1.39 (m, 2H), 0.10 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 141.28, 128.60, 128.49, 125.55, 120.72, 79.10, 53.72, 28.28 (overlap), 25.68, 25.62, 1.04; EI-MS *m/z* 273 (M^+); EI-HRMS calcd for $C_{16}H_{23}NOSi$ (M^+): 273.1549, found: 273.1553; $[\alpha]_D^{26} = -5.8$ ($c=0.48$, $CHCl_3$) (22% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 15.9 min (major), 18.1 min (minor).

4.3.5. Cyclobutyl(phenyl)[(trimethylsilyl)oxy]acetonitrile (10f). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.46 (m, 2H), 7.37–7.3 (m, 3H), 2.71 (m, 1H), 2.18 (m, 1H), 2.03 (m, 1H), 1.87–1.73 (m, 4H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 140.04, 128.63, 128.54, 125.18, 120.34, 77.76, 47.79, 23.32, 23.13, 16.51, 1.06; EI-MS *m/z* 259 (M^+); EI-HRMS calcd for $C_{15}H_{21}NOSi$ (M^+): 259.1392, found: 259.1401; $[\alpha]_D^{25} = -7.0$ ($c=0.60$, $CHCl_3$) (97% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALCEL OJ-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 8.5 min (major), 10.3 min (minor).

4.3.6. Cyclopropyl(phenyl)[(trimethylsilyl)oxy] acetonitrile (10g). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.57–7.55 (m, 2H), 7.41–7.34 (m, 3H), 1.41–1.35 (m, 1H), 0.86–0.81 (m, 1H), 0.70–0.57 (m, 3H), 0.14 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 141.53, 128.83, 128.64, 125.41, 120.35, 75.64, 24.17, 3.02, 2.74, 1.14; EI-MS *m/z* 245 (M^+); EI-HRMS calcd for $C_{14}H_{19}NOSi$ (M^+): 245.1236, found: 245.1233; $[\alpha]_D^{24} = -12.2$ ($c=1.23$, $CHCl_3$) (82% ee). HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AD-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 16.3 min (minor), 37.1 min (major).

4.3.7. Phenyl-2-[(trimethylsilyl)oxy]pentanenitrile (10i).[16] HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AS, hexane/2-propanol=9:1, 1.5 ml/min) t_R 15.3 min (major), 21.0 min (minor).

4.3.8. Phenyl-2-[(trimethylsilyl)oxy]hexanenitrile (10k). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.52–7.50 (m, 2H), 7.40–7.33 (m, 3H), 2.04–1.99 (m, 1H), 1.93–1.87 (m, 1H), 1.52–1.43 (m, 1H), 1.35–1.24 (m, 3H), 0.87 (t, 3H, $J=7.2$ Hz), 0.13 (s, 9H); HPLC (the corresponding benzoyl amide; DAICEL CHIRALPAK AS-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 22.9 min (major), 27.5 min (minor).

4.3.9. 3-Methyl-2-phenyl-2-[(trimethylsilyl)oxy] butanenitrile (10l).[17] GC (Varian Chirasil DEX CB (0.25 mm×25 m), column temperature=100 °C (isothermal), injector temperature=250 °C, detector temperature=280 °C, inlet pressure=1.3 kg/cm^2): t_R 25.9 min (major), 27.7 min (minor).

4.3.10. 3,3-Dimethyl-2-phenyl-2-[(trimethylsilyl)oxy] butanenitrile (10m).[18] GC (Varian Chirasil DEX CB (0.25 mm×25 m), column temperature=100 °C (isothermal), injector temperature=250 °C, detector temperature=280 °C, inlet pressure=1.3 kg/cm^2): t_R 31.7 min (major), 33.5 min (minor).

4.3.11. 2-Propyl-2-[(trimethylsilyl)oxy]-3-pentenenitrile (10n). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 6.05–5.98 (m, 1H), 5.39 (dq, $J=1.7$, 15.5 Hz, 1H), 1.81–1.75 (m, 4H), 1.69–1.61 (m, 1H), 1.56–1.47 (m, 1H), 1.46–1.36 (m, 1H), 0.94 (t, $J=7.5$ Hz, 3H), 0.18 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 131.27, 128.25, 120.33, 73.65, 45.23, 17.29, 13.70, 1.31; IR (neat, cm^{-1}) 2963; ESI-MS *m/z* 234 ($M+Na^+$); EI-HRMS calcd for $C_{11}H_{21}NOSi$ (M^+): 211.1392, Found: 211.1396; $[\alpha]_D^{22} = +3.6$ ($c=2.87$, $CHCl_3$) (80% ee). HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol=9:1, 1.0 ml/min) t_R 14.4 min (minor), 16.8 min (major).

4.4. General procedure for preparation of α-D ketones (9e-D and 9l-D)

To a solution of KHMDS (0.5 M solution in toluene, 1.2 ml, 0.60 mmol), a ketone (0.50 mmol) was added at room temperature, and the mixture was stirred for 3.5 h in the case of **9e** and 10 h in the case of **9l**. After cooling in an ice bath, CD_3OD (0.2 ml, 5.0 mmol) was added, and the mixture was stirred for 10 min. Satd NH_4Cl was added, and the product was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4. Filtration, evaporation of the solvent, and purification through silica gel column chromatography (EtOAc/hexane=1:19) gave the deuterated ketone. The D-incorporation ratio was determined to be 87% for **9e-D** and 80% for **9l-D**, respectively, based on ^{1}H NMR analysis.

4.4.1. Synthesis of methyl ketone 12. To a solution of the cyanohydrin **10f** (100 mg, 0.386 mmol) in ether (0.5 ml), MeLi·LiBr (1.5 M in ether, 0.39 ml, 0.578 mmol) was added in an ice bath. The reaction temperature was allowed to increase to room temperature for 3 h, and the reaction was continued at room temperature for 1 h. Silica gel was added, and the resulting suspension was stirred for 15 min. Filtration, evaporation, and purification through silica gel column chromatography gave the product methyl ketone in 91% yield as a colorless oil.

4.4.2. 1-Cyclobutyl-1-hydroxy-1-phenyl-propan-2-one (12). Colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.39–7.41 (m, 2H), 7.34 (m, 2H), 7.28 (m, 1H), 4.70 (s, 1H), 3.47 (quintet, J=8.3 Hz, 1H), 2.16 (m, 1H), 2.04 (m, 1H), 2.03 (s, 3H), 1.94 (m, 2H), 1.75–1.83 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 208.67, 139.85, 128.59, 127.78, 126.59, 83.09, 38.75, 23.50, 22.59, 20.56, 17.64; IR (neat, cm^{-1}) 3460, 1705; EI-MS *m/z* 204 (M^+), 186 (M+1-OH), 161 (M−$COCH_3$); EI-HRMS calcd for $C_{11}H_{13}O$ (M−$COCH_3$): 161.0961, found: 161.0322; $[\alpha]^{22}_D$=+149.0 (c=1.76, $CHCl_3$) (97% ee). HPLC (DAICEL CHIRALPAK AS-H, hexane/2-propanol=99:1, 1.0 ml/min) t_R 6.9 min (minor), 7.4 min (major).

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