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Enantioselective cyanosilylation of aldehydes catalyzed by a novel *N*,*N*′-dioxide-Ti(O^{i}Pr)$_4$ bifunctional catalyst

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Abstract—A novel bifunctional asymmetric catalyst containing *N*-oxide and titanium(IV) was developed and applied to the asymmetric cyanosilylation of aldehydes. Optically active trimethylsilyl cyanohydrin ethers were obtained up to 99% yield and 80% ee in the presence of 5 mol % catalyst loading at −78 °C. Based on the experimental results, the catalytic cycle was proposed as a pathway in which Lewis acid and Lewis base activated aldehyde and trimethylsilylcyanide (TMSCN), respectively.

1. Introduction

Optically active cyanohydrins are useful intermediates toward a wide variety of chiral compounds, such as α-amino acids,[1] α-hydroxy carboxylic acids,[2] β-amino alcohols,[3] α-hydroxy aldehydes,[3] α-hydroxy ketones,[3] etc. In view of their importance, asymmetric cyanosilylation of aldehydes has been studied intensively by employing chiral metal complexes and organocatalysts.[4] Titanium-based complexes have attracted the most interest, and the chiral ligands include sulfoximines,[5] phosphineoxide,[4g] BINOLs,[4b,c,6] TADDOL,[7] and others.[8] Shibasaki and co-workers reported asymmetric cyanosilylation of aldehydes by a Lewis acid–Lewis base bifunctional catalyst prepared from a BINOL derivative (Fig. 1).[6e,f] The concept of the double-activation method has been applied to perform asymmetric cyanosilylation of ketones.[9] As the subsequence of our previous work, a new bifunctional catalyst was designed (Fig. 2) and we expected that the catalyst containing Lewis acid and Lewis base could activate aldehydes and TMSCN, respectively.

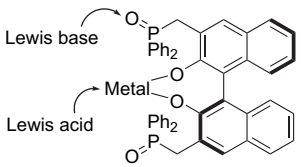

Figure 1. Shibasaki's bifunctional catalyst.[6e,f]

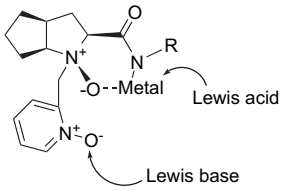

Figure 2. The designed bifunctional catalyst.

2. Results and discussion

2.1. Optimization of the catalysts

Based on the properties of bifunctional catalyst shown in Figure 2, several chiral ligands were synthesized (Fig. 3). The asymmetric addition of TMSCN to benzaldehyde was investigated in the presence of 5 mol % **1**-Ti(O^{i}Pr)$_4$ complexes in CH_2Cl_2 at −78 °C (Table 1, entries 1–12). The data listed in Table 1 showed that **1d**-Ti(O^{i}Pr)$_4$ gave the product with higher ee value (66% ee, Table 1, entry 4) than other amide *N*-oxide complexes derived from aromatic amines (Table 1, entries 1–3). Replacement of the cyclohexyl in the amide position with sterically more demanding adamantanyl decreased the enantiomeric excess from 55 to 50% (Table 1, entry 6 vs 5). Compound **1h** afforded the product with the highest ee value (Table 1, entry 8) among **1g–i** (Table 1, entries 7–9). Compound **1h** not only gave good enantioselectivity but also afforded the product in good yield. The poor results were obtained with mono *N*-oxide **2a** and **2b** (Table 1, entries 10 and 11), and no product was detected using **2c** without *N*-oxide (Table 1, entry 12). So it could be shown that complex **1h**-Ti(O^{i}Pr)$_4$ was the effective catalyst.

Keywords: Asymmetric catalysis; Cyanosilylation; Lewis acid; Lewis base; Bifunctional catalyst.
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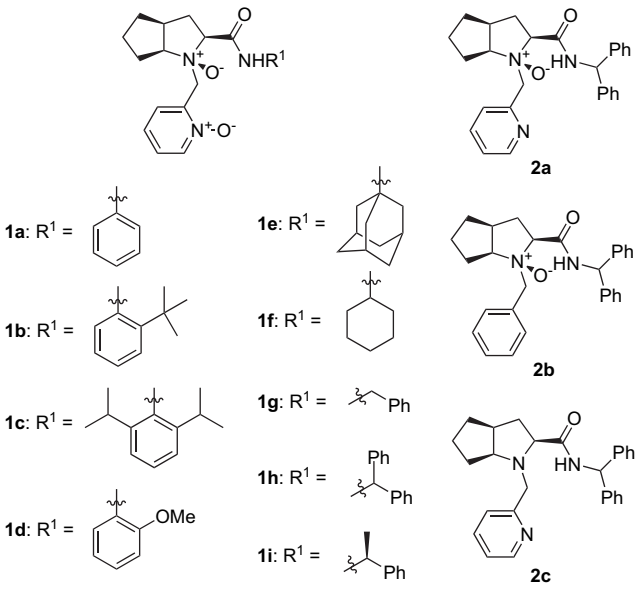


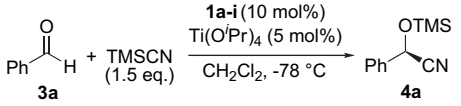
Figure 3. The evaluated ligands.

Inspired by our previous work,[11] several additives were examined in order to increase the yield (Table 2). The result revealed that 4-*tert*-butylphenol played a negative role in the enantioselectivity and reactivity (Table 2, entry 1). Excitingly, the reaction was found to improve significantly when organic amines or organic acids were used except 2-hydroxybenzoic acid and toluenesulfonic acid (Table 2, entries 2–14). By increasing the loading of 4-methylbenzoic acid from 10 to 20 mol %, the enantioselectivity could be improved up to 80% ee (Table 2, entry 15 vs 8). Further increasing amounts of additive did not increase ee value (Table 2, entry 16). Then, other reaction parameters were investigated using 4-methylbenzoic acid as an additive.

Subsequently, the reaction conditions were optimized in the presence of 20 mol % additive. When $Ti(O^iPr)_4$ was replaced by other metal reagents, such as $Al(O^iPr)_3$, Et_3Al, and $Zr(O^iPr)_4$, inferior results were obtained (Table 3, entries 1–3). Solvent screening revealed that CH_2Cl_2 was the best. Ether solvent (THF or Et_2O) gave moderate enantioselectivities (Table 3, entries 5 and 6), and toluene gave only 55% ee (Table 3, entry 7).

The data in Table 4 indicated that low temperature was an essential factor to obtain high enantioselectivity. Increasing the temperature led to decrease in enantioselectivity (Table 4, entries 1–3). Increasing or decreasing the concentration of benzaldehyde from 0.2 M caused a slight decrease in enantiomeric excess (Table 4, entries 4–6). When the concentration of benzaldehyde was 0.1 M, the yield decreased sharply only to 41% (Table 4, entry 6). Changing the ratio of **1h** to $Ti(O^iPr)_4$ from 2:1 to 1:1 resulted in a drop in the enantiomeric excess of the product (Table 4, entry 7 vs 1). Unfortunately, more loading (10 mol %) of chiral titanium

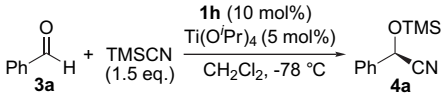
Table 1. Optimization of the chiral ligand



Entry[a]	Ligand	Time (h)	Yield[b] (%)	ee[c] (%)	Conf.[d]
1	**1a**	48	86	55	*R*
2	**1b**	48	78	40	*R*
3	**1c**	48	88	47	*R*
4	**1d**	48	40	66	*R*
5	**1e**	52	87	50	*R*
6	**1f**	52	85	55	*R*
7	**1g**	52	67	37	*R*
8	**1h**	52	83	65	*R*
9	**1i**	52	72	47	*R*
10	**2a**	48	62	48	*R*
11	**2b**	48	34	47	*R*
12	**2c**	48	0	—	—

[a] All reactions were carried out using 5 mol % catalyst in CH_2Cl_2 at −78 °C, concentration of benzaldehyde=0.2 M.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H column after derivation with acetic anhydride.
[d] Absolute configurations were determined by comparison of optical rotation with literature values.[10]

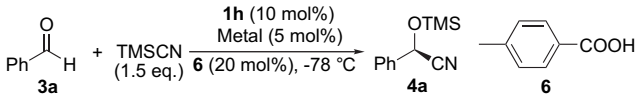
Table 2. The effect of additives



Entry[a]	Additive	Loading (mol %)	Time (h)	Yield[b] (%)	ee[c] (%)
1	4-*tert*-Butylphenol	10	48	41	43
2	*N*,*N*′-Diisopropylethylamine	10	28	90	59
3	Benzoic acid	10	25	90	69
4	3,5-Dinitrobenzoic acid	10	20	91	60
5	4-Nitrobenzoic acid	10	20	98	67
6	4-Bromobenzoic acid	10	20	85	75
7	4-*tert*-Butylbenzoic acid	10	20	89	67
8	4-Methylbenzoic acid	10	20	99	77
9	2-Methylbenzoic acid	10	20	95	65
10	3-Methylbenzoic acid	10	20	91	72
11	4-Aminobenzoic acid	10	20	86	56
12	4-Methoxybenzoic acid	10	20	71	66
13	2-Hydroxybenzoic acid	10	20	0	—
14	4-Toluenesulfonic acid	10	48	0	—
15	4-Methylbenzoic acid	20	20	99	80
16	4-Methylbenzoic acid	30	20	99	80

[a] All reactions were carried out using 5 mol % catalyst in CH_2Cl_2 at −78 °C, concentration of benzaldehyde=0.2 M.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H column after derivation with acetic anhydride.

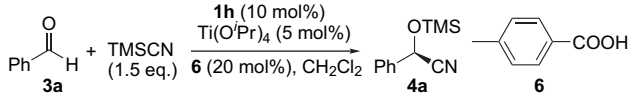
Table 3. Effect of metal reagents and solvents



Entry[a]	Metal	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	$Al(O^iPr)_3$	CH_2Cl_2	20	89	69
2	Et_3Al	CH_2Cl_2	48	54	36
3	$Zr(O^iPr)_4$	CH_2Cl_2	20	84	55
4	$Ti(O^iPr)_4$	CH_2Cl_2	20	99	80
5	$Ti(O^iPr)_4$	THF	20	98	60
6	$Ti(O^iPr)_4$	Et_2O	20	76	48
7	$Ti(O^iPr)_4$	Toluene	20	97	55

[a] All reactions were carried out in the presence of 20 mol % additive in CH_2Cl_2, concentration of benzaldehyde=0.2 M.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H column after derivation with acetic anhydride.

Table 4. Effect of temperature, concentration, and ratio of **1h**/Ti(O^iPr)$_4$



Entry[a]	Temp (°C)	Concentration (M)	Time (h)	Yield[b] (%)	ee[c] (%)
1	−78	0.2	20	99	80
2	−45	0.2	20	99	67
3	−20	0.2	15	99	54
4	−78	0.25	20	99	73
5	−78	0.4	20	99	74
6	−78	0.1	25	41	76
7[d]	−78	0.2	20	99	75
8[e]	−78	0.2	20	99	75

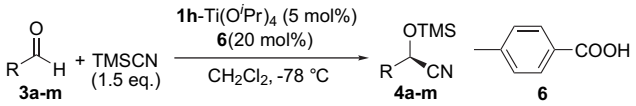
[a] All reactions were carried out in the presence of 20 mol % additive, **1h**/Ti(O^iPr)$_4$=2:1, and 5 mol % catalyst loading unless noted otherwise.
[b] Isolated yield.
[c] Determined by HPLC using Chiralcel OD-H column after derivation with acetic anhydride.
[d] **1h**/Ti(O^iPr)$_4$=1:1.
[e] Catalyst loading, 10 mol %.

complex caused a slight decrease in enantioselectivity (75% ee, Table 4, entry 8). Therefore the optimal reaction conditions were 5 mol % catalyst loading in the presence of 20 mol % of 4-methylbenzoic acid, and the concentration of aldehyde was 0.2 M in CH_2Cl_2 at −78 °C.

2.2. Scope of the substrates

Encouraged by the result of benzaldehyde, a range of aldehydes such as aromatic, aliphatic, heteroaromatic, and α,β-unsaturated aldehydes were investigated under the optimal conditions. The results are summarized in Table 5. In general, excellent yields and good enantiomeric excesses could be obtained with aromatic aldehydes. Methyl substituted aromatic aldehydes were found to be good substrates for this reaction (Table 5, entries 2 and 3), giving enantioselectivities of trimethylsilyl cyanohydrin ethers similar to those obtained with benzaldehyde (Table 5, entry 1), while the halogen substituted aromatic aldehydes led to slight decrease in enantioselectivity compared with benzaldehyde (Table 5, entries 4–7). 4-Methoxybenzaldehyde afforded the product with 70% ee and 91% yield (Table 5, entry 8). The result of 1-naphthaldehyde suggested that substrate with sterically bulky group had negative effect on enantioselectivity (Table 5, entry 9). Aliphatic aldehydes gave the corresponding trimethylsilyl cyanohydrin ethers with moderate enantiomeric excess (Table 5, entries 10 and 11). Heteroaromatic and α,β-unsaturated aldehydes also afforded similar results to aliphatic aldehydes (Table 5, entries 12 and 13). All the data showed that a wide range of aldehydes reacted smoothly with TMSCN to afford the corresponding products with moderate to good enantiomeric excesses.

Table 5. Catalytic asymmetric cyanosilylation of various aldehydes under the optimized conditions



Entry[a]	Aldehydes	Time	Yield[b] (%)	ee[c] (%)	Conf.[d]
1	Benzaldehyde (**3a**)	20	99	80	*R*
2	4-Methylbenzaldehyde (**3b**)	20	99	77	*R*
3	3-Methylbenzaldehyde (**3c**)	20	99	79	*R*
4	4-Chlorobenzaldehyde (**3d**)	20	90	73	*R*
5	3-Chlorobenzaldehyde (**3e**)	20	99	71	*R*
6	2-Chlorobenzaldehyde (**3f**)	20	98	73	*R*
7	4-Fluorobenzaldehyde (**3g**)	20	95	71	—
8	4-Methoxybenzaldehyde (**3h**)	28	91	70	*R*
9	1-Naphthaldehyde (**3i**)	28	93	70	*R*
10	*n*-Hexaldehyde (**3j**)	25	90	59	*R*
11	Phenylacetaldehyde (**3k**)	25	93	46	*R*
12	2-Furaldehyde (**3l**)	28	80	55	*R*
13	Cinnamaldehyde (**3m**)	28	83	45	*R*

[a] All reactions were carried out using 5 mol % catalyst in CH_2Cl_2 at −78 °C, **1h**/Ti(O^iPr)$_4$=2:1, in the presence of 20 mol % additive, concentration of aldehyde=0.2 M.
[b] Isolated yield.
[c] Determined by HPLC or GC after derivation with acetic anhydride, see Section 4.
[d] Absolute configurations were determined by comparison of optical rotation with literature values.[10]

2.3. Preliminary mechanistic studies

Structure of **11** was proposed as shown in Figure 4, which contained a nine-membered ring. It was less stable compared to six-membered ring structure **12** (Fig. 5). Based on the results of the experiments and our early work,[9d,e,12] we thought that the pyrrolidine *N*-oxide and the nitrogen atom of amide might coordinate to titanium to activate the aldehyde, and the *N*-oxide of the pyridine acted as a Lewis base to activate TMSCN (Fig. 6, shown in intermediate **13**). Large steric hindrance between R group of the aldehyde and two phenyl groups of the amide might direct the CN to attack the

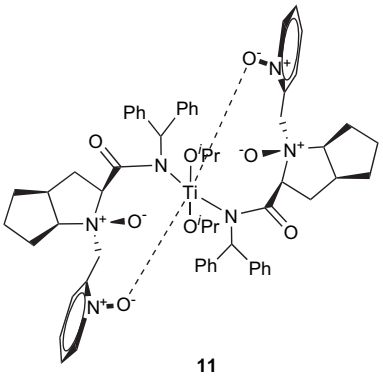


Figure 4. Proposed unfavorable nine-membered ring structure.

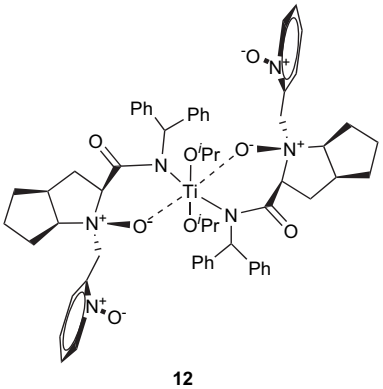


Figure 5. Favorable six-membered ring structure.

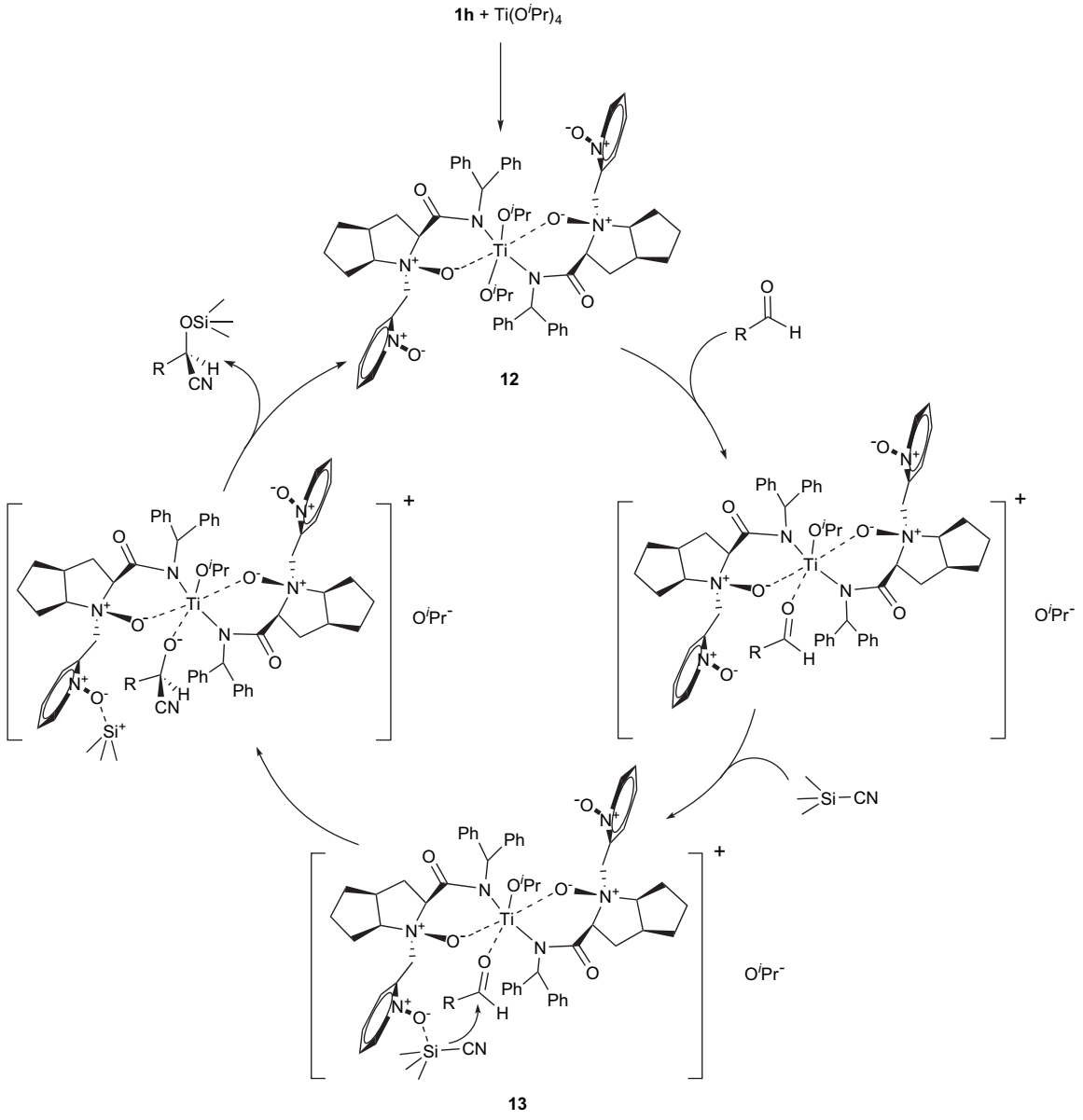


Figure 6. Proposed catalytic cycle.

aldehyde giving *R* configuration product. A proposed catalytic cycle (Fig. 6) and a possible transition state were illustrated based on the reactivity of the substrates and the configuration of the products.

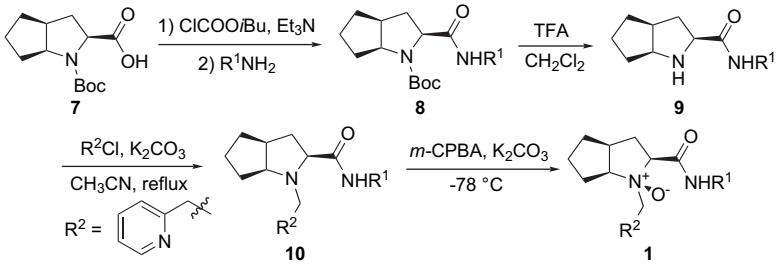
3. Conclusion

In conclusion, a novel bifunctional asymmetric catalyst was developed for the asymmetric cyanosilylation of aldehydes. A variety of aldehydes including aromatic, heteroaromatic, α,β-unsaturated, and aliphatic aldehydes reacted smoothly with TMSCN in the presence of 4-methylbenzoic acid to afford the corresponding trimethylsilyl cyanohydrin ethers in excellent yields with good enantiomeric excesses (up to 80% ee). Based on the experimental results, the catalytic cycle was proposed. Further efforts will be focused on the understanding of the reaction mechanism and search for more effective catalysts.

4. Experimental

4.1. General methods

All reactions were carried out using anhydrous solvents and under nitrogen in oven-dried tubes unless noted otherwise. Toluene, THF, and Et_2O were dried and distilled from sodium/benzophenone under nitrogen prior to use. CH_2Cl_2 was dried over powdered CaH_2 and distilled under nitrogen prior to use. $Ti(O^iPr)_4$ (from Acros) was distilled and diluted to 1 M in toluene, stored under nitrogen. HG/T2354-92 silica gel was used for flash chromatography (FC). Melting points (mp) were measured on electrothermal digital melting point apparatus and were uncorrected. Enantiomeric excesses (ee) were determined by HPLC using corresponding commercial chiral column as stated in the experimental procedures at 23 °C with UV detection at 254 nm or chiral GC with a Varian GC system: column Chirasil DEX CB. Optical rotations were measured on the Autopol V Automatic



Scheme 1. Synthesis of **1**.

Polarimeter. ^{1}H NMR spectra were recorded in $CDCl_3$ on Inova-400 (400 MHz) or Bruker Avance 600 (600 MHz) and were reported in parts per million using TMS (δ=0) or residual $CDCl_3$ (δ=7.26) as the reference. ^{13}C NMR spectra were recorded in $CDCl_3$ on Inova-400 (100 MHz) or Bruker Avance 600 (150 MHz) and were reported in parts per million relative to the central $CDCl_3$ resonance (δ=77.00).

4.2. Materials

It was noteworthy that oxidation was carried out at −78 °C with 3-chloroperbenzoic acid (*m*-CPBA) (Scheme 1).[13]

4.2.1. Typical procedure for the amino acid amide derivatives 10.

4.2.1.1. (2*S*,3a*S*,6a*S*)-*N*-Aryl/alkyl-1-(pyridin-2-ylmethyl)-octahydrocyclopenta[*b*]pyrrole-2-carboxamide 10. Anhydrous K_2CO_3 (276 mg, 2 mmol) was added at room temperature to a solution of (2*S*,3a*S*,6a*S*)-*N*-aryl/alkyl-octahydrocyclopenta[*b*]pyrrole-2-carboxamide **9** (2 mmol) in CH_3CN (10 mL). Then 2-(chloromethyl)pyridine hydrochloride (410 mg, 2.5 mmol) was added to the mixture. The resulting mixture was refluxed for 5 h, and the reaction was monitored by TLC. The mixture was then cooled to room temperature and filtered to give a red solution. Evaporation of the solvent under reduced pressure and purification by silica gel column chromatography (petroleum ether/ethyl acetate=1:1) afforded **10**, which was used for the next reaction without further purification.

4.2.1.2. (1*S*,2*S*,3a*S*,6a*S*)-1-((1-Oxidopyridin-2-yl)-methyl)-2-(arylcarbamoyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1a–i). *m*-CPBA (75%, 460 mg, 2 mmol) was added at −78 °C under nitrogen to a solution of amide **10** (1 mmol) and anhydrous K_2CO_3 (276 mg, 2 mmol) in CH_2Cl_2 (20 mL), the resulting mixture was stirred at the same temperature for 5 h, the mixture was then allowed to warm slowly to room temperature and filtered. The solvent was evaporated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/methanol=5:1, v/v).

4.2.1.3. (1*S*,2*S*,3a*S*,6a*S*)-1-((1-Oxidopyridin-2-yl)-methyl)-2-(phenylcarbamoyl)-octahydrocyclopenta[*b*]-pyrrole 1-oxide (1a). The title compound **1a** was obtained by silica gel column chromatography (ethyl acetate/methanol=8:1, v/v) as a white solid in 89% yield. Mp 142–143 °C. $[\alpha]_D^{25}$ +63.5 (*c* 0.24, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=13.54 (s, 1H), 8.23 (d, *J*=6.0 Hz, 1H), 7.83–7.81 (m, 1H), 7.60 (d, *J*=7.6 Hz, 2H), 7.32–7.23 (m, 4H), 7.07 (t, *J*=7.4 Hz, 1H), 5.01 (d, *J*=12 Hz, 1H), 4.65–4.55 (m, 2H), 4.18 (dd, *J*=5.6, 6 Hz, 1H), 2.80–2.74 (m, 1H), 2.66–2.59 (m, 1H), 2.29–2.20 (m, 1H), 2.08–2.01 (m, 1H), 1.92–1.88 (m, 1H), 1.76–1.70 (m, 1H), 1.59–1.50 (m, 2H), 1.38–1.30 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.1, 141.5, 139.4, 137.9, 132.0, 126.8, 128.9, 125.2, 123.9, 84.3, 79.9, 63.6, 42.2, 34.7, 32.8, 27.9, 24.8 ppm. HRMS (ESI) calcd for $C_{20}H_{23}N_3O_3$ $[M+H]^+$: 354.1812, found 354.1815.

4.2.1.4. (1*S*,2*S*,3a*S*,6a*S*)-2-(2-*tert*-Butylphenylcarbamoyl)-1-((1-oxidopyridin-2-yl)methyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1b). The title compound **1b** was obtained by silica gel column chromatography (ethyl acetate/methanol=8:1, v/v) as a white solid in 80% yield. Mp 80–82 °C. $[\alpha]_D^{25}$ +121.1 (*c* 0.36, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=13.01 (s, 1H), 8.29 (d, *J*=6.4 Hz, 1H), 7.85–7.82 (m, 1H), 7.48–7.40 (m, 2H), 7.30–7.16 (m, 4H), 5.24 (d, *J*=12 Hz, 1H), 4.70–4.66 (m, 1H), 4.53 (d, *J*=11.6 Hz, 1H), 4.26 (dd, *J*=5.6, 5.6 Hz, 1H), 2.80–2.74 (m, 1H), 2.66–2.59 (m, 1H), 2.38–2.30 (m, 1H), 1.90–1.84 (m, 1H), 1.74–1.68 (m, 1H), 1.59–1.45 (m, 11H), 1.28–1.21 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ= 165.8, 141.6, 139.4, 134.8, 131.9, 128.9, 128.1, 126.6, 83.8, 80.1, 63.4, 42.1, 34.7, 34.1, 32.8, 27.9, 24.8, 21.1 ppm. HRMS (ESI) calcd for $C_{24}H_{31}N_3O_3$ $[M+H]^+$: 410.2438, found 410.2444.

4.2.1.5. (1*S*,2*S*,3a*S*,6a*S*)-2-(2,6-Diisopropylphenylcarbamoyl)-1-((1-oxidopyridin-2-yl)methyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1c). The title compound **1c** was obtained by silica gel column chromatography (ethyl acetate/methanol=8:1, v/v) as a white solid in 79% yield. Mp 94–96 °C. $[\alpha]_D^{25}$ +153.0 (*c* 0.73, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ=12.66 (s, 1H), 8.32 (d, *J*=6.0 Hz, 1H), 7.88 (d, *J*=7.2 Hz, 1H), 7.36–7.26 (m, 3H), 7.19 (d, *J*=7.6 Hz, 2H), 5.43 (d, *J*=11.6 Hz, 1H), 4.75 (t, *J*= 7.6 Hz, 1H), 4.48 (d, *J*=11.6 Hz, 1H), 4.25–4.21 (m, 1H), 2.82–2.67 (m, 2H), 2.40–2.32 (m, 1H), 1.84–1.83 (m, 2H), 1.73–1.70 (m, 1H), 1.57–1.49 (m, 2H), 1.38–1.15 (m, 15H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 141.7, 139.4, 131.8, 127.8, 126.8, 125.3, 83.3, 80.7, 63.2, 42.4, 34.6, 34.5, 32.8, 27.9, 24.8 ppm. HRMS (ESI) calcd for $C_{26}H_{35}N_3O_3$ $[M+H]^+$: 438.2751, found 438.2757.

4.2.1.6. (1*S*,2*S*,3a*S*,6a*S*)-2-(2-Methoxyphenylcarbamoyl)-1-((1-oxidopyridin-2-yl)methyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1d). The title compound **1d** was obtained by silica gel column chromatography (ethyl acetate/methanol=8:1, v/v) as a white solid in 85% yield.

Mp 128–130 °C. $[\alpha]_D^{25}$ +109.1 (*c* 0.21, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=13.46 (s, 1H), 8.26 (d, *J*=7.2 Hz, 2H), 7.94–7.92 (m, 1H), 7.30–7.27 (m, 2H), 7.10–7.06 (m, 1H), 6.97–6.89 (m, 2H), 5.13 (d, *J*=11.6 Hz, 1H), 4.63–4.56 (m, 2H), 4.18–4.14 (m, 1H), 3.94 (s, 3H), 2.75–2.71 (m, 1H), 2.66–2.59 (m, 1H), 2.36–2.29 (m, 1H), 1.97–1.86 (m, 2H), 1.73–1.69 (m, 1H), 1.55–1.47 (m, 2H), 1.28–1.25 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.3, 149.8, 141.8, 139.2, 132.3, 127.3, 126.6, 125.0, 124.4, 121.8, 120.7, 110.2, 83.9, 80.4, 62.9, 55.9, 42.3, 34.4, 32.8, 28.2, 24.5 ppm. HRMS (ESI) calcd for $C_{21}H_{25}N_3O_4$ $[M+H]^+$: 384.1918, found 384.4488.

4.2.1.7. (1*S*,2*S*,3a*S*,6a*S*)-2-Adancarbamoyl-1-((1-oxidopyridin-2-yl)methyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1e). The title compound **1e** was obtained by silica gel column chromatography (ethyl acetate/methanol=5:1, v/v) as a white solid in 87% yield. Mp 67–69 °C. $[\alpha]_D^{25}$ +72.7 (*c* 0.44, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=10.55 (s, 1H), 8.32 (d, *J*=5.2 Hz, 1H), 7.85–7.83 (m, 1H), 7.37–7.33 (m, 2H), 5.12 (d, *J*=12.0 Hz, 1H), 4.60–4.54 (m, 2H), 4.20–4.15 (m, 1H), 2.69–2.65 (m, 1H), 2.55–2.50 (m, 1H), 2.15–2.01 (m, 10H), 1.88–1.84 (m, 1H), 1.68 (s, 7H), 1.54–1.45 (m, 2H), 1.35–1.26 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.8, 141.6, 139.5, 129.4, 126.9, 125.7, 83.8, 80.1, 62.8, 41.8, 41.6, 36.3, 34.3, 32.8, 27.9, 24.8 ppm. HRMS (ESI) calcd for $C_{24}H_{33}N_3O_3$ $[M+H]^+$: 412.2595, found 412.2600.

4.2.1.8. (1*S*,2*S*,3a*S*,6a*S*)-2-(Cyclohexylcarbamoyl)-1-((1-oxidopyridin-2-yl)methyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1f). The title compound **1f** was obtained by silica gel column chromatography (ethyl acetate/methanol=5:1, v/v) as a white solid in 77% yield. Mp 124–126 °C. $[\alpha]_D^{25}$ +100.5 (*c* 0.21, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=10.87 (s, 1H), 8.23 (d, *J*=6.0 Hz, 1H), 7.75–7.73 (m, 1H), 7.29–7.24 (m, 2H), 5.01 (d, *J*=12.0 Hz, 1H), 4.53–4.48 (m, 1H), 4.34 (d, *J*=12 Hz, 1H), 3.98 (dd, *J*=4.8, 5.2 Hz, 1H), 3.76 (s, 1H), 2.61 (d, *J*=7.2 Hz, 1H), 2.46 (s, 1H), 2.08–2.05 (m, 1H), 1.80 (d, *J*=12 Hz, 4H), 1.62–1.18 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=165.2, 140.6, 138.4, 128.8, 125.8, 124.5, 82.7, 78.9, 62.0, 46.4, 41.0, 33.5, 31.9, 31.7, 31.5, 27.0, 24.5, 23.6, 23.5 ppm. HRMS (ESI) calcd for $C_{20}H_{29}N_3O_3$ $[M+H]^+$: 360.2282, found 360.2285.

4.2.1.9. (1*S*,2*S*,3a*S*,6a*S*)-2-(Benzylcarbamoyl)-1-((1-oxidopyridin-2-yl)methyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1g). The title compound **1g** was obtained by silica gel column chromatography (ethyl acetate/methanol=5:1, v/v) as a white solid in 87% yield. Mp 122–123 °C. $[\alpha]_D^{25}$ +120.1 (*c* 0.24, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=11.58 (d, *J*=5.2 Hz, 1H), 8.24 (d, *J*=6.4 Hz, 1H), 7.60–7.58 (m, 1H), 7.33–7.21 (m, 7H), 5.05 (d, *J*=12.0 Hz, 1H), 4.62–4.55 (m, 2H), 4.41 (dd, *J*=5.2, 5.2 Hz, 1H), 4.25 (d, *J*=11.6 Hz, 1H), 4.08 (dd, *J*=5.6, 5.6 Hz, 1H), 2.75–2.66 (m, 1H), 2.59–2.53 (m, 1H), 2.21–2.13 (m, 1H), 1.87–1.78 (m, 2H), 1.67–1.64 (m, 1H), 1.50–1.44 (m, 2H), 1.22–1.19 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=167.3, 141.6, 139.3, 138.6, 132.1, 128.7, 127.7, 127.3, 126.7, 125.0, 83.7, 80.1, 63.1, 42.8, 42.2, 34.5, 32.8, 27.9, 24.7 ppm. HRMS (ESI) calcd for $C_{21}H_{25}N_3O_3$ $[M+Na]^+$: 390.1788, found 390.4390.

4.2.1.10. (1*S*,2*S*,3a*S*,6a*S*)-2-(Benzhydrylcarbamoyl)-1-((1-oxidopyridin-2-yl)methyl)-octahydrocyclopenta[*b*]-pyrrole 1-oxide (1h). The title compound **1h** was obtained by silica gel column chromatography (ethyl acetate/methanol=5:1, v/v) as a white solid in 86% yield. Mp 80–83 °C. $[\alpha]_D^{25}$ +88.4 (*c* 0.22, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=12.32 (d, *J*=8.2 Hz, 1H), 8.24 (d, *J*=6.4 Hz, 1H), 7.46–7.15 (m, 13H), 6.34 (d, *J*=8.8 Hz, 1H), 5.02 (d, *J*=11.6 Hz, 1H), 4.65–4.61 (m, 1H), 4.16–4.09 (m, 2H), 2.75–2.68 (m, 1H), 2.61–2.54 (m, 1H), 2.32–2.19 (m, 1H), 1.85–1.83 (m, 2H), 1.73–1.66 (m, 1H), 1.56–1.43 (m, 2H), 1.29–1.23 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.4, 142.6, 141.6, 141.5, 139.3, 132.0, 128.8, 128.6, 127.6, 127.4, 127.1, 126.9, 126.8, 125.5, 84.0, 80.1, 63.0, 56.2, 42.3, 34.4, 32.8, 28.0, 24.7 ppm. HRMS (ESI) calcd for $C_{27}H_{29}N_3O_3$ $[M+H]^+$: 444.2282, found 444.4870.

4.2.1.11. (1*S*,2*S*,3a*S*,6a*S*)-1-((1-Oxidopyridin-2-yl)-methyl)-2-((*S*)-1-phenylethylcarbamoyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (1i). The title compound **1i** was obtained by silica gel column chromatography (ethyl acetate/methanol=5:1, v/v) as a white solid in 81% yield. Mp 47–49 °C. $[\alpha]_D^{25}$ +109.1 (*c* 0.23, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=11.64 (d, *J*=8.4 Hz, 1H), 8.21 (d, *J*=6.4 Hz, 1H), 7.46–7.42 (m, 3H), 7.34 (t, *J*=7.6 Hz, 2H), 7.26–7.22 (m, 2H), 7.17 (t, *J*=7.6 Hz, 1H), 5.21–5.16 (m, 1H), 4.94 (d, *J*=12 Hz, 1H), 4.61–4.55 (m, 1H), 4.13–4.08 (m, 1H), 4.00 (dd, *J*=5.6, 5.2 Hz, 1H), 2.72–2.66 (m, 1H), 2.66–2.53 (m, 1H), 2.26–2.15 (m, 1H), 1.88–1.81 (m, 2H), 1.73–1.67 (m, 1H), 1.56–1.43 (m, 5H), 1.28–1.21 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.3, 144.0, 141.5, 139.2, 132.0, 128.7, 127.2, 126.7, 126.3, 125.2, 83.7, 80.0, 62.9, 48.5, 42.2, 34.4, 32.8, 28.0, 24.6, 22.6 ppm. HRMS (ESI) calcd for $C_{22}H_{27}N_3O_3$ $[M+H]^+$: 382.2125, found 382.4760.

4.2.1.12. (1*S*,2*S*,3a*S*,6a*S*)-2-(Benzhydrylcarbamoyl)-1-(pyridin-2-ylmethyl)-octahydrocyclopenta[*b*]pyrrole 1-oxide (2a). The title compound **2a** was obtained by silica gel column chromatography (ethyl acetate) as a white solid in 53% yield. Mp 45–47 °C. $[\alpha]_D^{25}$ +21.1 (*c* 0.26, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=12.50 (d, *J*=8.9 Hz, 1H), 8.57 (d, *J*=5.0 Hz, 1H), 7.66–7.61 (m, 1H), 7.45–7.43 (m, 2H), 7.39–7.20 (m, 10H), 6.36 (d, *J*=8.3 Hz, 1H), 4.44–4.38 (m, 2H), 4.28–4.25 (m, 1H), 3.86–3.82 (m, 1H), 2.69–2.60 (m, 1H), 2.55–2.46 (m, 1H), 2.30–2.21 (m, 1H), 1.95–1.86 (m, 2H), 1.70–1.44 (m, 3H), 1.28–1.18 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 150.6, 149.4, 141.7, 136.6, 129.5, 128.8, 128.6, 128.0, 127.6, 127.3, 127.1, 127.0, 124.1, 82.0, 78.4, 62.9, 71.9, 56.3, 41.8, 34.3, 32.6, 27.7, 25.4 ppm. HRMS (ESI) calcd for $C_{27}H_{29}N_3O_2$ $[M+H]^+$: 428.2333, found 428.5461.

4.2.1.13. (1*S*,2*S*,3a*S*,6a*S*)-2-(Benzhydrylcarbamoyl)-1-benzyl-octahydrocyclopenta[*b*]pyrrole 1-oxide (2b). The title compound **2b** was obtained by silica gel column chromatography (ethyl acetate/petroleum ether=2:1, v/v) as a white solid in 87% yield. Mp 55–58 °C. $[\alpha]_D^{25}$ −15.1 (*c* 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ=12.01 (d, *J*=7.2 Hz, 1H), 7.45–7.20 (m, 15H), 6.33 (d, *J*=6.8 Hz, 1H), 4.47–4.37 (m, 2H), 4.18–3.92 (m, 1H), 2.65–2.45 (m, 2H), 2.45–2.31 (m, 1H), 2.30–2.18 (m, 1H), 2.12–2.00 (m, 1H), 1.78–1.41 (m, 4H), 1.37–1.31 (m, 1H) ppm;

^{13}C NMR (100 MHz, $CDCl_3$): δ=166.5, 132.3, 131.9, 128.9, 128.8, 128.6, 127.5, 127.1, 126.9, 125.5, 69.9, 63.8, 56.7, 41.6, 34.0, 32.8, 28.1, 24.7 ppm. HRMS (ESI) calcd for $C_{28}H_{30}N_2O_2$ $[M+H]^+$: 427.2386, found 427.5579.

4.2.2. General procedure for the catalytic asymmetric trimethylsilylcyanation of aldehydes. To a solution of **1h** (8.8 mg, 0.02 mmol) and 4-methylbenzoic acid (5.4 mg, 0.04 mmol) in CH_2Cl_2 (0.6 mL) was added $Ti(O^iPr)_4$ (1 M in toluene, 10 μL, 0.01 mmol) at room temperature under nitrogen atmosphere, and the resulting mixture was stirred for 0.5 h. The solvent was evaporated under reduced pressure. The residue was dissolved in CH_2Cl_2 (1 mL). To this solution aldehyde (0.2 mmol) was added at room temperature. After 0.5 h the solution was cooled to −78 °C and TMSCN (40 μL, 0.3 mmol) [caution!] was added. The reaction mixture was allowed to stir for the indicated time in Table 5 at −78 °C. Purification of the trimethylsilyl cyanohydrin ether was performed by silica gel column chromatography (petroleum ether/ethyl acetate=10:1, v/v) to give the product as colorless oil. To the product was added a mixture of 1 M HCl (5 mL) and CH_3OH (10 mL) and stirred for 4 h at room temperature. Then it was extracted with CH_2Cl_2 (3×10 mL) and the organic layer was washed with brine and dried over anhydrous Na_2SO_4. The cyanohydrin was converted into the corresponding acetate by reaction with Ac_2O (100 μL) and pyridine (50 μL) in CH_2Cl_2 (5 mL) at room temperature for 1 h. The reaction was quenched with 5 mL water. The organic layer was separated, washed with H_2O, dried over anhydrous Na_2SO_4, and concentrated. The crude product was purified by flash chromatography on silica gel (petroleum/EtOAc=10:1, v/v) to yield the corresponding acetylated cyanohydrin for further analysis.

4.2.2.1. (*R*)-(+)-2-Hydroxy-2-phenylacetonitrile (5a). $[\alpha]_D^{20}$ +5.0 (*c* 0.11, $CHCl_3$) (80% ee) [lit.[10a] $[\alpha]_D^{20}$ −7.24 (*c* 0.23, $CHCl_3$) for *S* enantiomer in 99% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.60–7.40 (m, 5H), 5.55 (s, 1H), 2.91 (s, 1H). The product was determined as 80% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=99:1, 1 mL/min) analysis of its acetate, t_R (major)=10.54 min and t_R (minor)=12.52 min.

4.2.2.2. (*R*)-(−)-2-Hydroxy-2-(4-methylphenyl) acetonitrile (5b). $[\alpha]_D^{25}$ −26.5 (*c* 0.10, benzene) (77% ee) [lit.[10b] $[\alpha]_D^{25}$ +30.4 (*c* 1.41, benzene) for *S* enantiomer in 91% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.42–7.25 (m, 4H), 5.50 (s, 1H), 3.10 (s, 1H), 1.98 (s, 3H). The product was determined as 77% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=10.17 min and t_R (minor)=11.07 min.

4.2.2.3. (*R*)-(+)-2-Hydroxy-2-(3-methlyphenyl) acetonitrile (5c). $[\alpha]_D^{25}$ +36.8 (*c* 0.13, $CDCl_3$) (79% ee) [lit.[10d] $[\alpha]_D^{25}$ +41.2 (*c* 2.286, $CDCl_3$) for *R* enantiomer in 91% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.69–7.22 (m, 4H), 5.48 (s, 1H), 2.43 (s, 1H), 2.39 (s, 3H). The product was determined as 79% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=9.41 min and t_R (minor)=10.00 min.

4.2.2.4. (*R*)-(−)-2-Hydroxy-2-(4-chlorophenyl) acetonitrile (5d). $[\alpha]_D^{25}$ −24.2 (*c* 0.12, benzene) (73% ee) [lit.[10b] $[\alpha]_D^{25}$ +31.5 (*c* 1.17, benzene) for *S* enantiomer in 84% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.82–7.39 (m, 4H), 5.52 (s, 1H), 4.28 (s, 1H). The product was determined as 73% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=14.43 min and t_R (minor)=16.26 min.

4.2.2.5. (*R*)-(+)-2-Hydroxy-2-(3-chlorophenyl) acetonitrile (5e). $[\alpha]_D^{25}$ +37.5 (*c* 0.12, $CDCl_3$) (71% ee) [lit.[10d] $[\alpha]_D^{25}$ +32.0 (*c* 1.338, $CDCl_3$) for *R* enantiomer in 57% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.86–7.27 (m, 4H), 5.54 (s, 1H), 3.94 (s, 1H). The product was determined as 71% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=12.66 min and t_R (minor)=13.99 min.

4.2.2.6. (*R*)-(−)-2-Hydroxy-2-(2-chlorophenyl) acetonitrile (5f). $[\alpha]_D^{25}$ −5.5 (*c* 0.186, $CDCl_3$) (73% ee) [lit.[10d] $[\alpha]_D^{25}$ −2.5 (*c* 0.924, $CDCl_3$) for *R* enantiomer in 67% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.93–7.27 (m, 4H), 5.89 (s, 1H), 3.41 (s, 1H). The product was determined as 73% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=31.20 min and t_R (minor)=31.93 min.

4.2.2.7. (+)-2-Hydroxy-2-(4-fluorophenyl) acetonitrile (5g). $[\alpha]_D^{25}$ +23.5 (*c* 0.26, $CHCl_3$) (71% ee). ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.92–7.18 (m, 4H), 5.52 (s, 1H), 4.48 (s, 1H). The product was determined as 71% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=7.22 min and t_R (minor)=7.87 min.

4.2.2.8. (*R*)-(−)-2-Hydroxy-2-(4-methoxyphenyl) acetonitrile (5h). $[\alpha]_D^{20}$ −13.5 (*c* 0.11, $CHCl_3$) (70% ee) [lit.[10a] $[\alpha]_D^{20}$ +19.0 (*c* 1.55, $CHCl_3$) for *S* enantiomer in 95% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.46–6.96 (m, 4H), 5.49 (s, 1H), 3.84 (s, 3H), 2.7 (s, 1H). The product was determined as 70% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=99:1, 1 mL/min) analysis of its acetate, t_R (major)=16.49 min and t_R (minor)=20.14 min.

4.2.2.9. (*R*)-(+)-2-Hydroxy-2-(1′-naphthyl) acetonitrile (5i). $[\alpha]_D^{25}$ +25.9 (*c* 0.11, $CHCl_3$) (70% ee) [lit.[10b] $[\alpha]_D^{25}$ −25.6 (*c* 1.04, $CHCl_3$) for *S* enantiomer in 70% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=8.16–7.50 (m, 7H), 6.18 (s, 1H), 3.20 (br s, 1H). The product was determined as 70% ee by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol=99:1, 1 mL/min) analysis of its acetate, t_R (minor)=23.09 min and t_R (major)=27.46 min.

4.2.2.10. (*R*)-(+)-2-Hydroxyheptanenitrile (5j). $[\alpha]_D^{25}$ +33.7 (*c* 0.10, benzene) (59% ee) [lit.[10b] $[\alpha]_D^{25}$ −8.4 (*c* 2.13, benzene) for *S* enantiomer in 15% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=4.48 (m, 1H), 2.83 (br s, 1H), 1.87–1.23 (m, 11H). The product was determined as 59% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=4.48 min and t_R (minor)=4.65 min.

4.2.2.11. (*R*)-(+)-2-Hydroxy-3-phenylpropionenitrile (5k). $[\alpha]_D^{20}$ +20.6 (*c* 0.15, $CHCl_3$) (46% ee), [lit.[10a] $[\alpha]_D^{20}$ −61.5 (*c* 1.5, $CHCl_3$) for *S* enantiomer in 99% ee]. ^{1}H NMR (600 MHz, $CDCl_3$): δ=7.46–7.19 (m, 5H), 4.68 (s, 1H), 3.14 (m, 2H), 2.28 (br s, 1H). The product was determined as 46% ee by GC (Varian, CP-Chirasil DEX CB), t_R (major)=10.20 min and t_R (minor)=10.66 min.

4.2.2.12. (*R*)-(+)-2-Hydroxy-2-(2′-furyl) acetonitrile (5l). $[\alpha]_D^{25}$ +14.2 (*c* 0.13, $CHCl_3$) (55% ee) [lit.[10a] $[\alpha]_D^{20}$ +24.3 (*c* 1.6, $CHCl_3$) for *R* enantiomer in 98% ee]. ^1H NMR (600 MHz, $CDCl_3$): δ=7.71–7.27 (m, 3H), 5.57 (s, 1H), 4.31 (br s, 1H). The product was determined as 55% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=5.63 min and t_R (minor)=5.92 min.

4.2.2.13. (*R*)-(−)-(*E*)-2-Hydroxy-4-phenyl-3-butenenitrile (5m). $[\alpha]_D^{25}$ −28.1 (*c* 0.10, $CHCl_3$) (45% ee) [lit.[10c] $[\alpha]_D^{25}$ +14.4 (*c* 1.1, $CHCl_3$) for *S* enantiomer in 45% ee]. ^1H NMR (600 MHz, $CDCl_3$): δ=7.49–7.32 (m, 5H), 6.75 (d, *J*=16 Hz, 1H), 6.28 (d, *J*=16 Hz, 1H), 5.19 (d, *J*=6.0 Hz, 1H), 2.71 (br s, 1H). The product was determined as 45% ee by GC (Varian, CP-Chirasil DEX CB) analysis of its acetate, t_R (major)=15.77 min and t_R (minor)=16.90 min.

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