Chiral phosphine-prolineamide as an organocatalyst in direct asymmetric aldol reactions Chiral phosphine-prolineamide 1a was employed as an organocatalyst in direct asymmetric aldol reactions of various aromatic aldehydes with ketones. Cyclohexanone led to the aldol products in up to 98% ee and	Chiral phosphine-prolineamide với vai trò là chất xúc tác hữu cơ trong các phản ứng aldol bất đối xứng trực tiếp Chiral phosphine-prolineamide 1a được sử dụng như một chất xúc tác hữu cơ trong các phản ứng aldol bất đối xứng trực tiếp của các aldehyde thơm khác nhau với ketones.

with good diastereoselectivity using 10 mol % of TFA and 30 mol % of prolineamide 1a in DMF at 0 °C.	Cyclohexanone cho ra các sản phẩm aldol với ee lên đến 98% và tính chọn lọc đồng phân dia dùng 10 mol% TFA và 30 mol % prolineamide 1a trong DMF ở 0 °C.
The aldol reaction is considered to be one of the most important C-C bond formations in organic synthesis. After the discovery of the direct intermolecular asymmetric aldol reaction using L-proline as an organocatalyst by List and Barbas in 2000,1 proline-derived organocatalysts were developed for aldol reactions and many other reactions. Many prolineamide-type organocatalysts from chiral amines, such as phenylethylamine,3 aminoalcohols,3b4 BINAM,5 and NOBIN,6 and also aniline-type compounds without chirality, such as aminophenol,7 and 8-aminoquinoline,8 have been reported in recent years.	Phản ứng aldol được xem là một trong những quá trình hình thành liên kết C-C quan trọng nhất trong quá trình tổng hợp hữu cơ. Sau phát hiện về phản ứng aldol bất đối xứng trực tiếp giữa các phân tử dùng L-proline là chất xúc tác hữu cơ của List và Barbas vào năm 2000,1 các chất xúc tác hữu cơ có nguồn gốc proline đã được điều chế phục vụ cho các phản ứng aldol và nhiều phản ứng khác. Nhiều loại chất xúc tác hữu cơ loại prolineamide từ các amin chiral chẳng hạn như phenylethylamine,3 aminoalcohols,3b4 BINAM,5 và NOBIN,6 cũng như các hợp chất loại aniline không có tính
On the other hand, phosphine atom containing pyrrolidine-type organocatalysts such as chiral phosphonates,9 phosamides,10 phosphinyl oxides,11 and MOP-type12 phosphine- prolineamides have also been reported. In continuation of our studies on the chiral P,N-type ligand design13 for transition metal catalysts, we designed chiral phosphine-prolineamide-type compound 1a as a chiral building block from 2-(diphenylphosphino)ani- line.	[redacted]

Herein we report chiral compound 1a as an organocatalyst for the direct asymmetric aldol reactions of aromatic aldehydes with ketones.

2.1. Preparation of organocatalyst 1

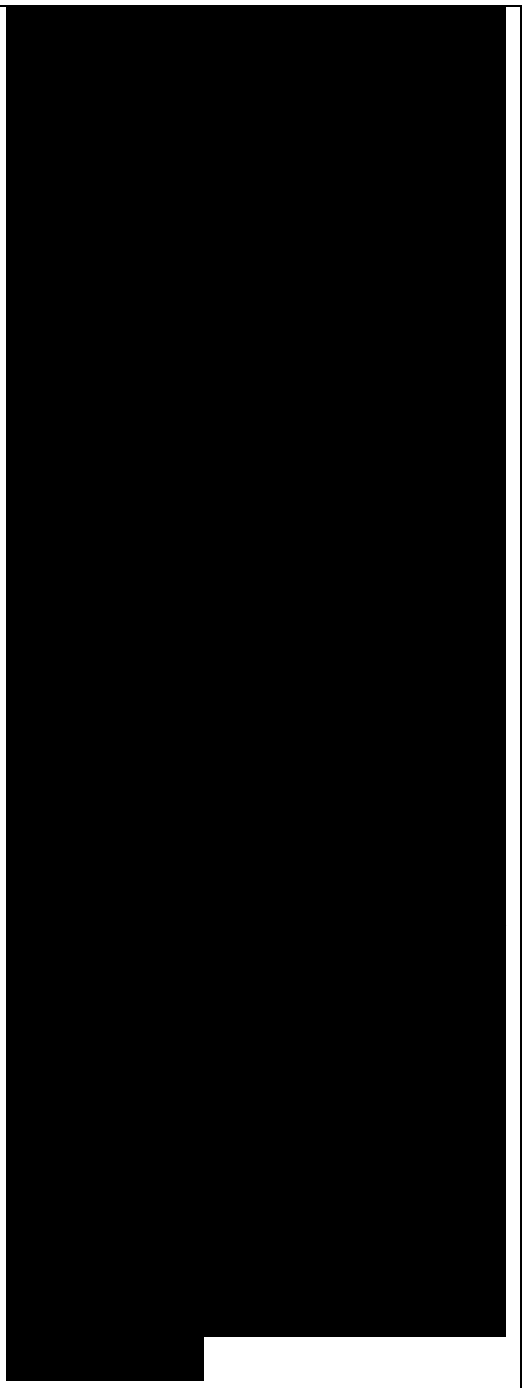
Organocatalyst 1a was easily prepared from N-Boc-proline (Scheme 1). The N-Boc-phosphineamide 2 was obtained by the reaction of ethyl chloroformate in the presence of N-methylmorpholine in THF, followed by amidation with 2-(diphenylphosphino)ani- line.14 This phosphineamide 2 was converted into the desired organocatalyst 1a using TFA in good yield. The phosphine-oxide- type organocatalyst 1b was prepared by the oxidation of 1a using H_2O_2 in $CHCl_3$.

2.2. Direct asymmetric aldol reactions of ketones using 1

We investigated the ability of chiral phosphine-prolineamide 1a as an organocatalyst for the direct asymmetric aldol reaction of aromatic aldehydes with ketones. p-Nitrobenzaldehyde 3a and cyclohexanone 4a were chosen as model substrates with 30 mol % of catalyst for 48 h under an argon atmosphere at 0 °C (Table 1). Using phosphine-prolineamide 1a as an organocatalyst under neat conditions, we observed that the aldol reaction gave the corresponding product 5aa

in an 80% yield and with good enantioselectivity (96% ee) and diastereoselectivity (anti/syn = 92:8) (entry 1). When the reaction was carried out by adding 10 mol % of TFA as a Bransted acid15 in DMF as a solvent, the yield improved to 93% also with high enantioselectivity (97% ee) and diastereoselectivity (anti/ syn = 98:2) (entry 2).16 When the reaction was carried out using 20 mol % of the catalyst, the enantioselectivity and diastereoselectivity were slightly decreased (95% ee; anti/syn = 97:3) (entry 3). We tested phosphine-oxide-type organocatalyst 1b and found that the reaction rate became slower with moderate diastereoselectivity (entry 4).

Using organocatalyst 1c315a17 without the 2-diphenyl- phosphino group led to a moderate yield (59%) with good diastere- oselectivity (entry 5). Under the optimized reaction conditions, we investigated the aldol reactions of various aromatic aldehydes with cyclohexanone 4a using 30 mol % of phosphine-prolineamide 1a and 10 mol %ofTFAin DMF at 0 °C (entries 6-13). The reaction with m-nitrobenzaldehyde 3b gave the corresponding product 5ba in moderate enantioselectivity (88% ee)



Scheme 1. Preparation of chiral phosphine-prolineamides 1.

and with high diastereoselec- tivity (anti/syn = 98:2) (entry 6). The reaction with o-nitrobenzalde- hyde 3c gave the corresponding product 5ca with high enantioselectivity (98% ee) and diastereoselectivity (anti/ syn = 98:2) in moderate yield (entry 7). When p-cyanobenzalde- hyde 3d was used, the reaction gave product 5da in moderate yield with good enantioselectivity (entry 8). However, the reactions with p-bromobenzaldehyde 3e, methyl 4-formylbenzoate 3f, and p-tri- fluoromethylbenzaldehyde 3g led to low-to-moderate yields with moderate enantioselectivities (entries 9-11). Using 2,4-dinitro- benzaldehyde 3h gave the product 5ha in high yield and with good enantioselectivity (entry 12). Conversely, the reaction with a heteroaryl containing aldehyde, such as 4-pyridinecarboxaldehyde 3i gave product 5ia in moderate yield with good enantioselectivity (entry 13). We also tested the reaction of p-nitrobenzaldehyde 3a with various ketones (entries 14-16).

Using tetrahydro-4H-pyran- 4- one 4b led to good yield (85%) and diastereoselectivity with moderate enantioselectivity (entry 14). The reaction of cyclopentanone 4c gave the corresponding product 5ac with a moderate enantiose- lectivity in moderate yield (entry 7). When acetone 4d was used, the reaction gave product 5ad in a 48% yield with moderate enanti- oselectivity (entry

16).

The mechanism of this reaction using organocatalyst 1a is believed to be similar to that of the previously reported prolineamide via an enamine intermediate.63,8,153

Organocatalyst 1a showed a much better ability at controlling the enantioselectivity and diaste-reoselectivity of the direct aldol reaction than N-phenylprolinea-mide 1c. At this stage, we propose that not only does the hydrogen bonding between the aryl aldehyde and the amide NH group play an important role in the selectivity but also the steric hindrance of the 2-diphenylphosphino group or p-p interactions613 between the aryl aldehyde and the aromatic ring at 2-diphenylphosphino group plays an important role.

3. Conclusion

In conclusion, we found that a chiral phosphine-prolineamide with a 2-(diphenylphosphino)aniline backbone can be employed as an organocatalyst in the direct asymmetric aldol reactions of various aromatic aldehydes with ketones giving up to 98% ee with good diastereoselectivity using 10 mol % of TFA and 30 mol % of catalyst 1a in DMF at 0 °C. Further studies focusing on the

Table 1
Direct asymmetric aldol reaction of ketones using 1a

The reactions were carried out on a 0.25 mmol scale of 3 in DMF (0.375 mL) at 0 ”C with 27 equiv of 4 in the presence of 1 (30 mol %) and TFA (10 mol %). Isolated yields (anti/syn).

Determined by 'H NMR of the crude mixture.
Determined for the anti-isomer by HPLC analysis using a chiral column.
This reaction was carried out without using TFA and DMF.

This reaction was carried out using 20 mol % of 1.

generality of other substrates and the application of 1a and 1b in other reactions are currently in progress in our laboratory and will be reported in due course.

4. Experimental

4.1. Preparation of 2

To a solution of N-Boc-proline (0.65 g, 3.0 mmol) in THF (4.0 mL), were added ClCOOEt (0.32 mL, 3.3 mmol) and N-methyl- morpholine (0.36 mL, 3.3 mmol). After 3 h at -15 °C, 2-(diphenyl-phosphino)aniline13 (0.83 g, 3.0 mmol) in THF (6.0 mL) was added and the stirring was continued for 17 h at room temperature. The reaction mixture was filtered and evaporated under reduced pressure. The residue was purified by silica gel

chromatography (hex- ane/EtOAc = 8:1): 1.16 g, 2.44 mmol, 81% as a white solid; mp 109-110 °C; [a]D5 = -103.9 (c 0.30, CHCl3); 1H NMR (CDCl3) d 1.25-2.04 (m, 1D3H), 3.24 and 3.36 (br s and br s, 2H, rotamer), 4.21 and 4.39 (br s and br s, 1H, rotamer), 6.80 (s, 1H), 7.04, (t, J = 7.2 Hz, 1H), 7.22-7.42 (m, 11H), 8.22 (dd, J =4.7 and 7.9 Hz, 1H), 8.61 (s, 1H, major rotamer), 8.99 (s, 1H, minor rotamer), 13C NMR (CDCl3, major rotamer) 5 23.6, 28.4, 31.0, 46.9, 62.2, 80.6, 121.5 (JCP = 10.0 Hz), 124.9, 126.6 (JCP = 10.5 Hz), 128.7, 128.8, 128.9, 129.2, 130.1, 133.4, 133.5 (JCP = 10.6 Hz), 133.9 (Jcp = 19.6 Hz), 140.4, 154.4, 171.1; 31P NMR (CDCl3) d -20.5; HRMS (ESI-MS) m/z calcd for C28H31N2O3P + Na 497.1965, found 497.1953.

4.2. Preparation of 1a

To a solution of N-Boc-phosphineamide 2 (0.47 g, 1.0 mmol) in CHCl3 (5.0 mL) was added TFA (1.49 mL, 20.0 mmol). The reaction mixture was stirred for 3 h at 50 °C. Next, the reaction mixture was evaporated under reduced pressure, the residue was diluted with CHCl3, and quenched with sat. NaHCO3 aq. The organic layer was washed with water, dried over MgSO4, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (CHCl3/MeOH = 60:1): 0.37 g, 0.98 mmol, 98% as a white solid; mp 94-95 °C; [a]D5 = -

39.3 (c 0.30, CHCl3); 1H NMR (CDCl3) d 1.27-1.41 (m, 1H), 1.46-1.59 (m, 1H), 1.71-1.81 (m, 1H), 1.92-2.09 (m, 2H), 2.66 (dt, J =6.4 and 9.3 Hz, 1H), 2.88 (dt, J = 7.0 and 9.9 Hz, 1H), 3.72 (dd, J = 4.7 and 9.3 Hz, 1H), 6.75 (ddd, J =1.4, 2.8, and 6.3 Hz, 1H), 7.00 (t, J = 7.3 Hz, 1H), 7.257.40 (m, 11H), 8.28 (ddd, J = 0.9, 4.4, and 5.4 Hz, 1H), 10.43 (d, J= 4.6 Hz, 1H); 13C NMR (CDCl3) d 25.8, 30.7, 47.1, 61.1, 121.1 (d, Jcp = 2.2 Hz), 124.3 (d, Jcp =1.2 Hz), 126.6 (d, Jcp =11.4 Hz), 128.6 (d, JCP = 2.7 Hz), 128.7 (d, JCP = 3.0 Hz), 129.1, 129.2, 129.9, 133.1 (d, JCP =1.2 Hz), 133.7 (d, JCP=19.6Hz), 134.1 (d, JCP=19.8Hz), 134.7 (d, Jcp =7.9 Hz), 134.8 (d, Jcp = 7.9 Hz), 140.6 (d, JCP = 18.1 Hz), 173.6 (d, JCP = 2.0 Hz), 31P NMR (CDCl3) d -17.2; HRMS (ESI-MS) m/z calcd for C23H23ON2P+H 375.1621, found 375.1616.

4.3. Preparation of 1b

To a solution of phosphineamide 1a (0.11 g, 0.3 mmol) in CHCl3 (2.0 mL) was added hydrogen peroxide (30%) (2.0 mL) at room temperature. The reaction mixture was stirred for 3 h at room tem-perature. The reaction mixture was diluted with CHCl3 and 2 M NaOH aq. The organic layer was washed with water, dried over MgSO4, and concentrated under reduced pressure: 0.11 g, 0.29 mmol, 97%; as a white solid; mp 129-131 °C; [a]D5 = +36.8 (c 0.30, CHCl3); 1H NMR (CDCl3)

d 1.26-1.38 (m, 1H), 1.46-1.66 (m, 2H), 1.95-2.07 (m, 2H), 2.87-2.98 (m, 2H), 3.70 (dd, J =4.6 and 9.0 Hz, 1H), 6.92 (ddd, J =1.5, 7.6, and 14.0 Hz, 1H), 6.99
7.5 (m, 1H), 7.43-7.67 (m, 11H), 8.46 (dd, J = 4.4 and 8.3 Hz, 1H), 11.4 (s, 1H); 13C NMR (CDCl3) 5 25.6, 30.9, 47.1, 61.1, 120.0 (d, JCP = 101.8 Hz), 122.6 (d, JCP = 7.4 Hz), 122.9 (d, JCP = 13.1 Hz),
128.5 (d, JCP =12.4 Hz), 128.6 (d, JCP = 12.4 Hz), 131.0, 131.7 (d, JCP = 104.9 Hz), 131.8 (d, JCP = 9.5 Hz), 132.1 (d, JCP = 9.5Hz),
132.1.132.2 (d, Jcp = 2.9 Hz), 132.7 (d, Jcp = 10.5 Hz), 133.2 (d, JCP = 2.9 Hz), 142.9 (d, JCP = 3.8Hz), 174.9; 31P NMR (121MHz, CDCl3) 5 34.5; HRMS (FAB-MS) m/z calcd for C23H23N2O2P + H 391.1575, found 391.1576.

4.4. General procedure for the direct asymmetric aldol reaction of ketones using 1

To a mixture of aryl aldehyde 3 (0.25 mmol), and chiral phos-phineamide 1 (0.075 mmol) in DMF (0.275 mL) were added TFA (0.025 mmol) in DMF (0.25 M, 0.1 mL) and ketone 4 (6.75 mmol) at 0 °C under an argon atmosphere. After 48 h, the reaction mixture was quenched with satd NH4Cl (aq) and diluted with EtOAc. The organic layer was washed with water and brine, and dried over MgSO4. The filtrate was concentrated with a rotary

evaporator and the residue was purified by column chromatography.

4.4.1. Compound 5aa6a (Table 1, entry 2)
93% yield [mixture of anti- and syn-products (anti/syn = 98:2)]; 97% ee; [a]D° = +10.0 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.25-1.86 (m, 5H), 2.08-2.18 (m, 1H), 2.31-2.64 (m, 3H), 4.09 (d, J =3.1 Hz, 1H), 4.90 (dd, J = 2.9 and 8.4 Hz, 1H), 7.51 (d, J = 8.7 Hz, 2H), 8.22 (d, J = 8.7 Hz, 2H); 13C NMR (CDCl3) d 24.6, 27.6, 30.7, 42.7, 57.2,
74.0, 123.6, 127.8, 147.5, 148.3, 214.7; HRMS(ESI-MS) m/z calcd for C13H15O4N + Na 272.0893, found 272.0891; HPLC (Daicel CHIR- ALPAK® AD-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 33.3 min, tR (minor) = 25.9 min (hexane/2-propanol = 80:20, 0.5 mL/min).

4.4.2. Compound 5ba18 (Table 1, entry 6)
71% yield [mixture of anti- and syn-products (anti/syn = 98:2)]; 88% ee; [a]D0 = +26.9 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.32-1.86 (m, 5H), 2.09-2.18 (m, 1H), 2.32-2.43 (m, 1H), 2.47-2.55 (m, 1H), 2.58-2.67 (m, 1H), 4.14 (d, J = 3.0 Hz, 1H), 4.90 (dd, J = 2.9, 8.5 Hz, 1H), 7.53 (t, J = 7.9 Hz, 1H), 7.68 (d, J = 7.7 Hz, 1H), 8.15-8.22 (m, 2H), 13C NMR (CDCl3) d 24.6, 27.6, 30.7, 42.6, 57.1, 74.0, 122.0,
122.9,129.3, 133.2, 143.2, 148.2, 214.9; HRMS (ESI-MS) m/z calcd

for C13H15O4N+Na 272.0893, found 272.0892; HPLC (Daicel CHIR- ALPAK® AD-H, 0. 46 ux25 cm, UV 220 nm) tR (major) = 37.1 min, tR (minor) = 47.5 min (hexane/2-propanol = 92:8, 0.8 mL/min).

4.4.3. Compound 5ca6a (Table 1, entry 7)
64% yield [mixture of anti- and syn-products (anti/syn = 98:2)]; 98% ee; [a]D0 = +10.0 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.52-1.88 (m, 5H), 2.D05-2.18 (m, 1H), 2.28-2.50 (m, 2H) 2.72-2.80 (m, 1H) 4.20 (s, 1H), 5.45 (d, J = 7.0 Hz, 1H), 7.41-7.46 (m, 1H), 7.64 (td, J =1.2, 7.6 Hz, 1H), 7.77 (dd, J =1.4 and 7.9 Hz, 1H), 7.85 (dd, J =1.2 and 8.2 Hz, 1H); 13C NMR (CDCl3) d 25.0, 27.7, 31.1, 42.8,
57.3. 69.8, 124.1, 128.4, 129.0, 133.1, 136.6, 214.9; HRMS(ESI-MS) m/z calcd for C13H15O4N + Na 272.0893, found 272.0892; HPLC (Daicel CHIRALPAK® AD-H, 0.46 / x 25 cm, UV 220 nm) tR (major) = 29.4 min, tR (minor) = 31.5 min (hexane/2-propanol = 92:8, 0. 8 mL/min).

4.4.4. Compound 5da6a (Table 1, entry 8)
77% yield [mixture of anti- and syn-products (anti/syn = 95:5)]; 92% ee; [a]D0 = +24.4 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.25-1.43 (m, 1H), 1.48-1.85 (m, 4H), 2.08-2.14 (m, 1H), 2.31-2.41 (m, 1H) 2.47-2.62 (m, 2H), 4.06 (d, J = 3.0 Hz, 1H), 4.84 (dd, J = 2.5 and

8.4 Hz, 1H), 7.43-7.46 (m, 2H), 7.63-7.66 (m, 2H); 13C NMR (CDCl3) d 24.7, 27.6, 30.7, 42.6, 57.1, 74.2, 111.7,118.7, 127.7,132.2, 146.3, 214.8; HRMS(ESI-MS) m/z calcd for C14H15O2N + Na 252.0995, found 252.0995; HPLC (Daicel CHIRALPAK® AD-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 33.9 min, tR (minor) = 26.8 min (hexane/2-propanol = 90:10, 1.0 mL/min).

4.4.5. Compound 5ea19 (Table 1, entry 9)

37% yield [mixture of anti- and syn-products (anti/syn = 84:16)]; 60% ee; [a]D° = +6.1 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.21-1.37 (m, 1H), 1.46-1.83 (m, 4H), 2.06-2.15 (m, 1H), 2.30-2.60 (m, 3H), 3.99 (s, 1H), 4.75 (d, J = 8.7 Hz, 1H), 7.18-7.22 (m, 2H), 7.457.50 (m, 2H); 13C NMR (CDCl3) d 24.7, 27.7, 30.7, 42.7, 57.3, 74.2,
121.7.128.7, 131.5, 140.0, 215.3; HRMS(ESI-MS) m/z calcd for C13H15O2Br+ Na 305.0148, found 305.0146; HPLC (Daicel CHIR-ALPAK® AD-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 19.6 min, tR (minor) = 16.8 min (hexane/2-propanol = 90:10, 1.0 mL/min).

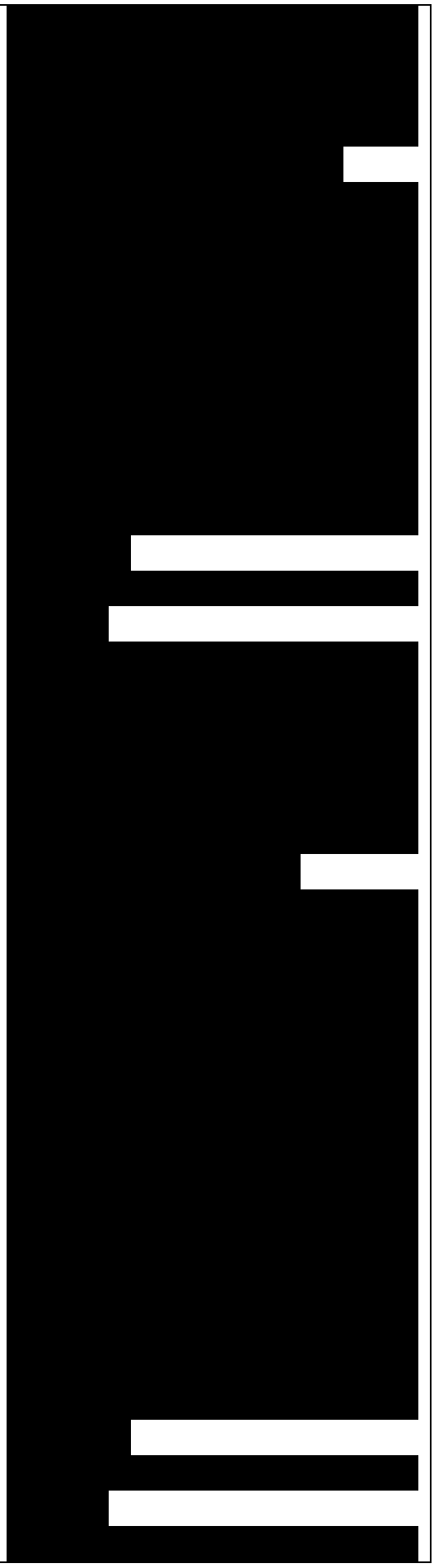
4.4.6. Compound 5fa19 (Table 1, entry 10)

67% yield [mixture of anti- and syn-products (anti/syn = 88:12)]; 73% ee; [a]D0 = +12.5 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.25-1.38 (m, 1H), 1.47-1.82 (m, 4H), 2.06-2.14 (m, 1H), 2.31-2.65 (m, 3H) 3.92 (s, 3H),

4.03 (s, 1H), 4.85 (d, J = 8.6 Hz, 1H), 7.40 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 8.1 Hz, 2H); 13C NMR (CDCl3) d 24.7,
27.7. 30.7, 42.7, 52.1, 57.3, 74.4, 127.0, 129.65, 129.68, 146.0, 166.8, 215.1; HRMS(ESI-MS) m/z calcd for C15H18O4 + Na 285.1097, found 285.1092; HPLC (Daicel CHIRALPAK® AS-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 28.4 min, tR (minor) = 44.9 min (hexane/2-propanol = 80:20, 0.8 mL/min).

4.4.7. Compound 5ga6a (Table 1, entry 11)
57% yield [mixture of anti- and syn-products (anti/syn = 90:10)]; 78% ee; [a]D0 = +16.3 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.26-1.41 (m, 1H), 1.48-1.84 (m, 4H), 2.07-2.16 (m, 1H), 2.31-2.64 (m, 3H),
4.5 (s, 1H), 4.85 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 8.2 Hz, 2H), 7.61 (d, J = 8.1 Hz, 2H); 13C NMR (CDCl3) d 24.7, 27.7, 30.7, 42.7, 57.2, 74.3, 121.3 (q, JCF = 271.8 Hz), 125.3 (q, JCF = 3.85Hz), 127.4, 130.1 (q, JCF= 32.4Hz), 145.0, 215.1; HRMS(ESI-MS) m/z calcd for C14H15O2F3+Na 295.0916, found 295.0914; HPLC (Daicel CHIR-ALPAK® AD-H, 0.46 / x 25 cm, UV 220 nm) tR (major) = 16.3 min, tR (minor) = 12.8 min (hexane/2-propanol = 90:10, 1.0 mL/min).

4.4.8. Compound 5ha20 (Table 1, entry 12)
100% yield [mixture of anti- and

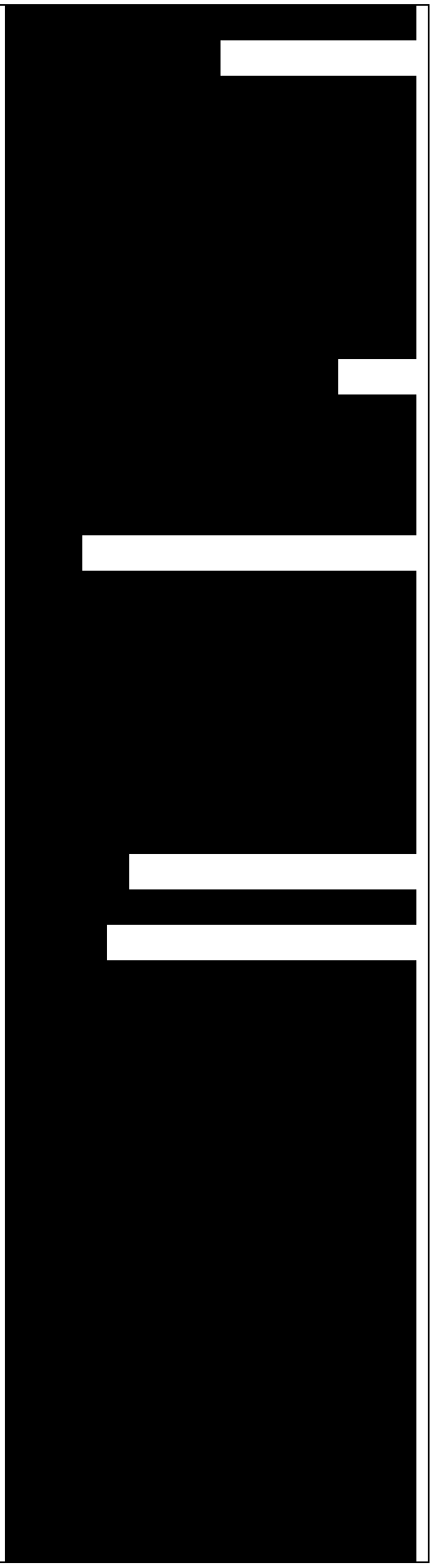


syn-products (anti/syn = 98:2)]; 90% ee; [a]D0 = +11.5 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.55-1.93 (m, 5H), 2.05-2.18 (m, 1H), 2.28-2.50 (m, 2H) 2.71-2.89 (m, 1H), 4.32 (d, J =5.8 Hz, 1H), 5.52 (t, J = 5.9 Hz, 1h), 8.08 (d, J = 8.7 Hz, 1H), 8.48 (dd, J = 2.3 and 8.7 Hz, 1H), 8.75 (d, J = 2.3 Hz, 1H); 13C NMR (CDCl3) d 24.9, 27.7, 31.4, 42.8, 56.9, 70.1, 119.8, 127.1,
131.0,143.8, 147.0, 148.1, 214.5; HRMS(ESI-MS) m/z calcd for C13H14O6N2+Na 317.0744, found 317.0741; HPLC (Daicel CHIR-ALPAK® AD-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 37.3 min, tR (minor) = 33.2 min (hexane/2-propanol = 85:15, 0.7 mL/min).

4.4.9. Compound 5ia18 (Table 1, entry 13)
58% yield [mixture of anti- and syn-products (anti/syn = 96:4)]; 93% ee; [a]D0 = +13.9 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.25-1.87 (m, 5H), 2.06-2.18 (m, 1H), 2.30-2.63 (m, 3H), 4.03 (br s, 1H), 4.78 (d, J = 8.2 Hz, 1H), 7.25-7.26 (m, 2H), 8.59 (d, J = 4.9 Hz, 2H); 13C NMR (CDCl3) d 24.7, 27.7, 30.8, 42.7, 56.8, 73.7, 122.0, 149.8,
149.9.214.8; HRMS(ESI-MS) m/z calcd for C12H15O2N + Na 228.0995, found 228.0993; HPLC (Daicel CHIRALPAK® AD-H, 0.46 / x 25 cm, UV 220 nm) tR (major) = 44.3 min, tR (minor) = 39.6 min (hexane/2-propanol = 98:2, 0.8 mL/min).

4.4.10. Compound 5ab6a (Table 1, entry 14)
85% yield [mixture of anti- and syn-products (anti/syn = 91:9)]; 83% ee; [a]D0 = -6.9 (c 0.50, CHCl3); 1H NMR (CDCl3) d 2.51-2.57 (m, 1H), 2.64-2.70 (m, 1H), 2.88-2.92 (m, 1H), 3.46 (dd, J =10.0 and 11.3 Hz, 1H), 3.70-4.22 (m, 3H), 4.97-5.00 (m, 1H), 7.52 (d,
J = 8.7 Hz, 2H), 8.24 (dt, J = 2.0 and 6.8 Hz, 2H); 13C NMR (CDCl3) d 42.8, 57.6, 68.3, 69.8, 71.3, 123.7, 123.8, 126.3, 127.4, 147.3,
147.7,209.3; HRMS (Negative ESI-MS) m/z calcd for C12H13NO5-H 250.0721, found 250.0723; HPLC (Daicel CHIRALPAK® AD-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 76.1 min, tR (minor) = 66.7 min (hexane/2-propanol = 90:10, 0.8 mL/min).

4.4.11. Compound 5ac6a (Table 1, entry 15)
54% yield [mixture of anti- and syn-products (anti/syn = 34:66)]; 84% ee; [a]D0 = -29.9 (c 0.50, CHCl3); 1H NMR (CDCl3) d 1.47-1.84 (m, 3H), 1.95-2.02 (m, 1H), 2.10-2.53 (m, 3H), 4.77 (s, 1H), 4.85 (d, J =9.2 Hz, 1H), 7.51-7.56 (m, 2H), 8.20-8.24 (m, 2H); 13C NMR (CDCl3) d 20.3, 26.8, 38.6, 55.1, 74.4, 123.7, 127.3, 147.6, 148.6, 222.2; HRMS(ESI-MS) m/z calcd for C12H13O4N + Na 258.0737, found 258.0735; HPLC (Daicel CHIRALPAK® AD-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 108.2 min, tR (minor) = 102.1 - min (hexane/2-propanol = 95:5, 0.5 mL/min).



4.4.12. Compound 5ad6a (Table 1, entry 16) 48% yield; 62% ee; [a]D0 = +27.4(c 0.50, CHCl3); 1H NMR(CDCl3) d 2.22 (s, 3H), 2.85 (d, J = 8.1 Hz, 1H), 2.86 (d, J = 4.1 Hz, 1H), 3.61 (s, 1H), 5.26 (dd, J = 4.6, 7.5 Hz, 1H), 7.52-7.55 (m, 2H), 8.19-8.23 (m, 2H); 13C NMR (CDCl3) d 30.7, 51.5, 68.9, 123.8, 126.4, 147.3, 149.9, 208.5; HRMS(ESI-MS) m/z calcd for C10H11O4N+Na 232.0580, found 232.0584; HPLC (Daicel CHIRALPAK® AS-H, 0.46 / x 25 cm, UV 254 nm) tR (major) = 32.1 min, tR (minor) = 39.1 min (hexane/2- propanol = 70:30, 0.5 mL/min).