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A novel quaternary ammonium salts derived from α-amino acids with large steric hindrance group and its application in asymmetric Mannich reaction

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ABSTRACT

Quaternary ammonium salts derived from amino acids with large steric hindrance group have been designed and synthesized, which promoted the asymmetric Mannich reaction of glycine imines with *N*-Boc-aldimines in excellent yields with high enantio- and diastereo-control compared with known catalysts of this type reported by our group.

1. Introduction

The chiral ion pair catalysts have been one of the most important type of organocatalysts which were extensively applied in asymmetric synthesis featured by simple operations and mild reaction conditions [1]. In the past few decades, the development of chiral ammoniums have attracted intensive attention [2,3], especially those with H-bonding donors, such as ureas or thioureas. In 2010, Lassaletta and coworkers reported the first thiourea-containing ammonium salts derived from cinchona alkaloid [4]. Later, Dixon, Zhao and Waser independently reported different types of (thio)-urea ammonium salts based on different chiral backbones and their application in a range of asymmetric reactions (Scheme 1) [5–7].

Amino acids are dominant scaffolds for the synthesis of new chiral organocatalysts whose catalytic activity could be facilely regulated by structural modifications. In recent years, our group has focused on the development of novel bifunctional ion pair catalysts derived from amino acids (Scheme 2a). The carboxylic acid could be transformed to quaternary ammonium (phosphonium) salts, while the amine group provided the adjustable hydrogen bonding site. With these catalysts in hand, varieties of asymmetric reactions have been successfully realized [7,8].

As we know, Mannich reaction [9] is a typical asymmetric reaction to form C–C bond, and great progress have been made from organocatalysts to metal catalysts in the past few decades [10]. Among these transformations, the direct asymmetric Mannich reaction of glycine imines or α-amino acid derivatives with *N*-Boc-aldimines turned out to be a straightforward method to deliver α,β-diamino acid derivatives, which have been found frequently in natural products, peptides and pharmaceutical compounds [11].

In this text, a series of novel quaternary ammonium salts derived from amino acids with large steric hindrance group were synthesized and applied in the asymmetric Mannich reaction of glycine imines with *N*-Boc-aldimines. After systematic screening, these novel quaternary ammonium salts with large steric hindrance group proved to be better in both yields and enantioselectivities compared with known catalysts of this type reported by our group (Scheme 2b).

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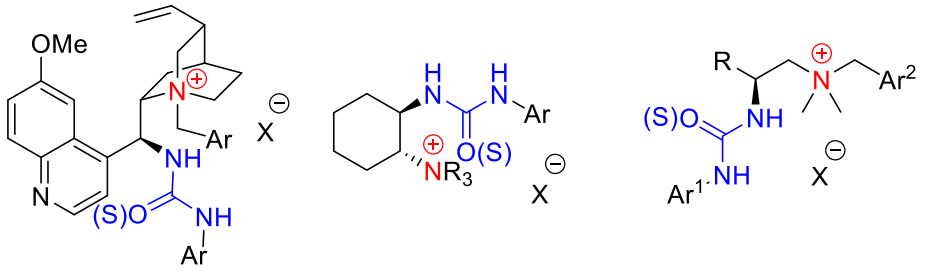
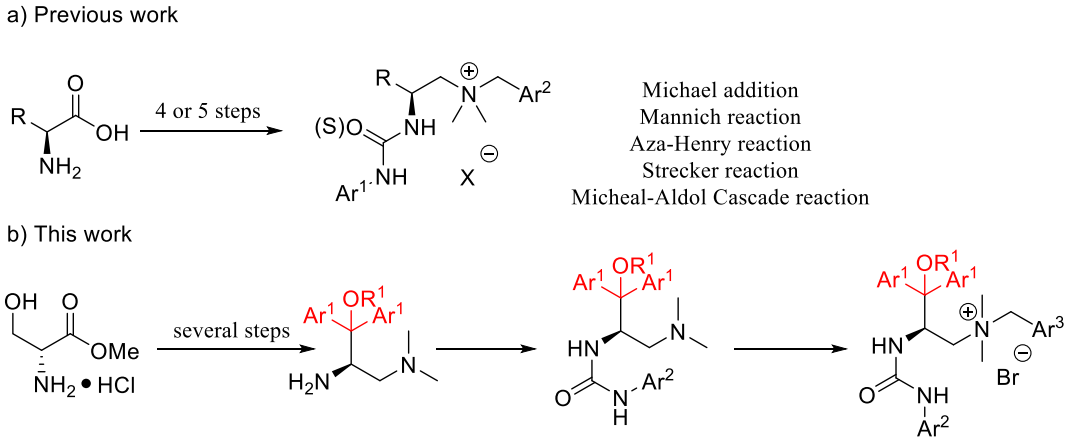


Scheme 1. Established (thio)-urea ammonium salts.



Scheme 2. The synthesis of quaternary ammonium salts derived from amino acids.

2. Results and discussion

Initially, catalysts **4a-4d** with different chiral backbones were evaluated in this reaction (Table 1, entries 1–4). Among these catalysts, **4a** derived from *L-tert*-leucine gave a better result. Later, a set of H-bonding type catalysts **4e-4g** were investigated (Table 1, entries 5–7). It turned out catalyst **4e** with urea as the double H-donor led to a higher enantioselectivity of the product (Table 1, entry 5). Then, more urea-ammonium catalysts **4h-4n** derived from *L-tert*-leucine with different cations were examined (Table 1, entries 8–14) and **4h** appeared to be the most suitable catalyst (Table 1, entry 8), which illustrated the stereoselectivity of product was greatly dependent on the steric hindrance of catalysts.

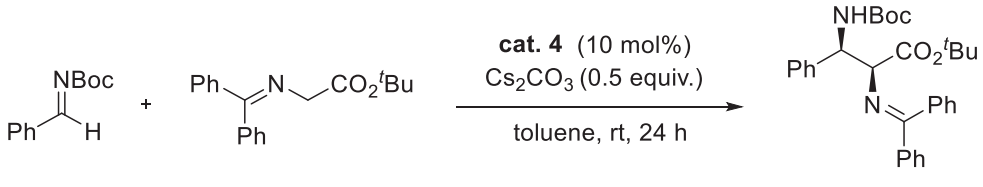
In the presence of the optimal catalyst **4h**, a variety of solvents were examined and toluene appeared to be the best media in terms of enantioselectivities of the products (Table 2, entries 1–9). The following screening of the bases indicated that Cs_2CO_3 was the best one (Table 2, entries 7, 10–14). Lowering the reaction temperature from room temperature to −20 °C did not bring an apparent difference in enantioselectivities of the products, but with a longer reaction time (Table 2, entries 7, 15–17). Changing the equivalent of additive of base, there were no obvious changes of experimental results (Table 2, entries 7, 18–20). However, among these conditions, only moderate enantioselectivities of products could be obtained.

Considering the steric effect of catalyst **4h** owning the *tert*-butyl afforded a better result relatively, we wondering that the enantioselectivities of the products could be enhanced by increasing the steric effect of catalyst further. Therefore, a series of novel quaternary ammonium salts catalysts with large steric hindrance group were deigned and synthesized based on D-serine. After systematic investigation (Table 3, entries 1–10), urea-ammonium **5i** turned out to be the best catalyst (Table 3, entry 9), affording the corresponding product **3a** in 90% ee with >20 : 1 dr in 24 h. There was no denying that the additional steric hindrance of catalysts contributed to enantioselectivities of the products. The relative configuration and absolute configuration of product **3a** was confirmed by comparing the reported ^{1}H NMR spectrum, HPLC spectrum and optical rotation [10], other products were assigned by analogy.

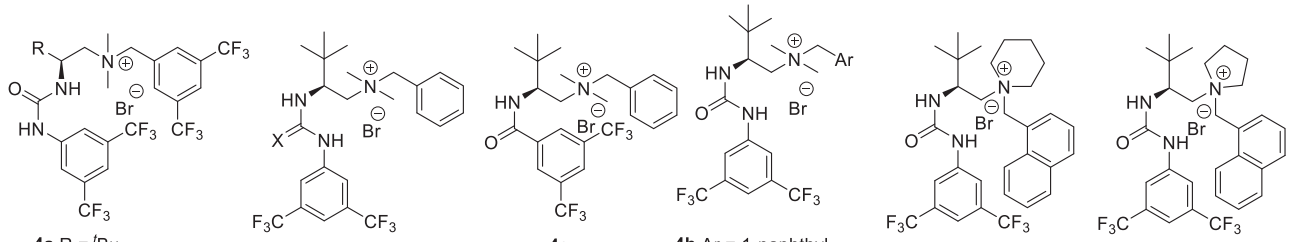
With the optimized condition in hand, the generality with a variety of *N*-Boc protected aldimines and glycine imines were examined. As shown in Table 4, all the reactions were completed in 24 h. The evaluation of different ester groups on glycine imines indicated *tert*-butyl group (Table 4 and **3a**) was superior to Ethyl and Benzyl (Table 4, **3b, 3c**), which indicated the large steric hindrance group of glycine imines availed to the enantioselectivity of the product. After the screening of *N*-Boc-imines with different aryl substituents, an obvious substituent effect of aryl group was found: poor diastereoselectivities and enantioselectivities of the products were obtained for *ortho*-substituted substrates (Table 4, **3f, 3k, 3n**). As for the *meta*-substituted or *para*-substituted *N*-Boc-imines, products **3** could be delivered with good diastereoselectivities and enantioselectivities. In addition, the presence of electronically withdrawing or neutral substituents basically provided higher enantioselectivities products than those bearing electron-donating substituents. Meanwhile, good yields and stereoselectivities of products **3** were also obtained for heteroaromatic substituted *N*-Boc-imines (Table 4, **3r, 3s, 3t**). However, poor enantioselectivity of the product **3u** was obtained for cyclohexyl substituted *N*-Boc-imine.

Based on experimental results and previous relevant studies [6], a possible transition state model was proposed as below (Scheme 3), which indicate that there existed H-bonding interactions between the carbonyl group of the *N*-Boc-imine and the urea moiety

Table 1
Optimization of conditions and evaluation of chiral catalysts **4**[a].



1a **2a** **3a**



4a R = ^{t}Bu
4b R = 2-(*S*)-Bu
4c R = Ph
4d R = Bn

4e X = O
4f X = S

4g

4h Ar = 1-naphthyl
4i Ar = 2-naphthyl
4j Ar = 9-anthranyl
4k Ar = 3,5-$(OBn)_2C_6H_3$
4l Ar = 3,5-$(^tBu)_2C_6H_3$

4m

4n

Entry	cat. (10 mol%)	Yield (%)[b]	dr[c]	ee (%)[c]
1	**4a**	82	>20 : 1	36
2	**4b**	82	>20 : 1	27
3	**4c**	74	>20 : 1	30
4	**4d**	85	>20 : 1	7
5	**4e**	87	>20 : 1	62
6	**4f**	83	>20 : 1	8
7	**4g**	96	>20 : 1	26
8	**4h**	88	>20 : 1	74
9	**4i**	84	>20 : 1	57
10	**4j**	86	>20 : 1	73
11	**4k**	82	>20 : 1	65
12	**4l**	84	>20 : 1	72
13	**4m**	86	>20 : 1	67
14	**4n**	87	>20 : 1	69

[a] Reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), catalyst **4** (10 mol%) and additive of base Cs_2CO_3 (0.5 equiv.) in Toluene (1.0 mL) at room temperature in 24 h.
[b] Isolated yield.
[c] The dr and ee values were determined by chiral HPLC analysis.

within the catalyst, and the nucleophile glycine Schiff base would be directed by the quaternary ammonium centre due to the Coulomb force (electrostatic interaction) between them. Thus, a more favorable *Si*-face attack of the nucleophile could be rational the stereochemical results of the reaction.

3. Conclusion

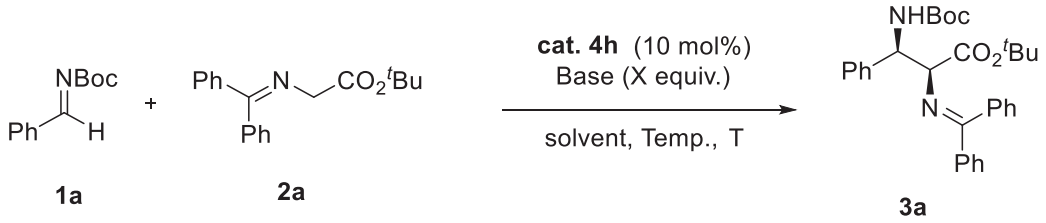
In summary, we have developed a novel strategy to obtain quaternary ammonium salts catalysts with large steric hindrance group from amino acids, which proved to process superior catalytic activity to known catalysts of this type in the asymmetric Mannich reaction of glycine imines with *N*-Boc-aldimines. It's no doubt that these novel catalysts were great complements, which enriched and developed ion pair catalysts derived from amino acids. A greater effort towards the application of these catalysts is needed. We believe these novel catalysts could be used in more asymmetric reactions due to the excellent catalytic activity.

4. Experimental

4.1. General information

The ^{1}H NMR spectra were recorded on a Bruker (400 MHz). All chemical shifts (d) were given in ppm. Data were reported as follows: chemical shift, integration, multiplicity (s = single, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constants (Hz). ^{13}C NMR spectra and ^{19}F NMR spectra were recorded on a DPX-400 (400 MHz). Flash column chromatography was performed using H silica gel. For thin-layer chromatography (TLC), silica gel plates (HSGF 254) were used and compounds were visualized by irradiation with UV light. Analytical high-performance liquid chromatography (HPLC) was carried out on SHIMADZU equipment using chiral columns. Melting point was determined on SGW X-4 melting point and was uncorrected. Optical rotation was measured on JASCO P-1010 Polarimeter at λ = 589 nm. IR spectra were recorded on Perkin-Elmer 983G instrument. Mass spectra analysis were performed on API 200 LC/MS system (Applied Biosystems Co. Ltd.). All simple quaternary ammonium salts catalysts **4**

Table 2
Optimization of conditions[a].



1a 2a 3a

Entry	Base	solvent	Temp./°C	t/h	Yield (%)[b]	dr[c]	ee (%)[c]
1	Cs_2CO_3 (0.5 equiv.)	Hexane	rt	24	85	>20 : 1	59
2	Cs_2CO_3 (0.5 equiv.)	CH_2Cl_2	rt	24	84	>20 : 1	61
3	Cs_2CO_3 (0.5 equiv.)	$CHCl_3$	rt	24	82	>20 : 1	60
4	Cs_2CO_3 (0.5 equiv.)	EtOAc	rt	24	82	>20 : 1	55
5	Cs_2CO_3 (0.5 equiv.)	THF	rt	24	86	>20 : 1	31
6	Cs_2CO_3 (0.5 equiv.)	TBME	rt	24	85	>20 : 1	69
7	Cs_2CO_3 (0.5 equiv.)	Toluene	rt	24	88	>20 : 1	74
8	Cs_2CO_3 (0.5 equiv.)	PhF	rt	24	84	>20 : 1	74
9	Cs_2CO_3 (0.5 equiv.)	$PhCF_3$	rt	24	82	>20 : 1	71
10	Na_2CO_3 (0.5 equiv.)	Toluene	rt	24	N.R.	/	/
11	K_2CO_3 (0.5 equiv.)	Toluene	rt	24	36	>20 : 1	9
12	K_3PO_4 (0.5 equiv.)	Toluene	rt	24	60	>20 : 1	69
13	KF (0.5 equiv.)	Toluene	rt	24	68	>20 : 1	70
14	CsF (0.5 equiv.)	Toluene	rt	24	90	>20 : 1	72
15	Cs_2CO_3 (0.5 equiv.)	Toluene	0	40	85	>20 : 1	74
16	Cs_2CO_3 (0.5 equiv.)	Toluene	−10	48	88	>20 : 1	74
17	Cs_2CO_3 (0.5 equiv.)	Toluene	−20	48	87	>20 : 1	74
18	Cs_2CO_3 (0.5 equiv.)	Toluene	rt	24	81	>20 : 1	73
19	Cs_2CO_3 (1.0 equiv.)	Toluene	rt	24	88	>20 : 1	73
20	Cs_2CO_3 (2.0 equiv.)	Toluene	rt	24	91	>20 : 1	72

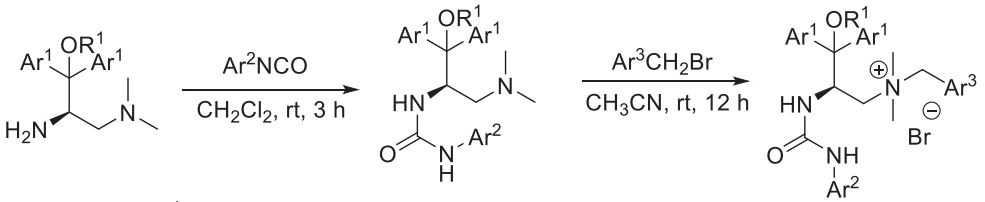
[a] Reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), catalyst **4h** (10 mol%) and additive of base in solvent (1.0 mL) at the special temperature.
[b] Isolated yield.
[c] The dr and ee values were determined by chiral HPLC analysis.

were synthesized according to procedures reported, and catalysts **4a, 4b, 4d, 4e, 4f** were synthesized [5]. As for quaternary ammonium salts **5** with large steric hindrance group, the precursors were synthesized as reported [11]. *N*-Boc-imines **1** and glycine Schiff bases **2** were synthesized according to known procedures [12–14].

4.2. Preparation of catalysts 4, 5

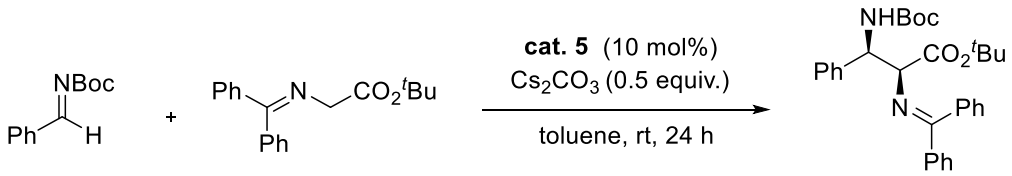
All simple quaternary ammonium salts **4c**, and **4g**-**4n** were synthesized according to procedures and reported previously. Quaternary ammonium salts **5** were synthesized as the scheme below.

To a solution of the precursor (1.0 equiv.) in CH_2Cl_2, adding the corresponding isocyanate (1.2 equiv.), and the resulting mixture was stirred at rt for 3 h. Then, the mixture was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to afford the solid product (V_{EA}/V_{MeOH} = 50 : 1–20 : 1). To a solution of the tertiary urea-amino product (1.0 equiv.) in CH_3CN, adding the corresponding bromide (1.2 equiv.), and the resulting mixture was stirred at room temperature for 12 h. Then, the mixture was concentrated under reduced pressure. The crude mixture was purified by flash column chromatography to afford the desired quaternary ammonium salt catalyst (V_{EA}/V_{MeOH} = 50 : 1–20 : 1).

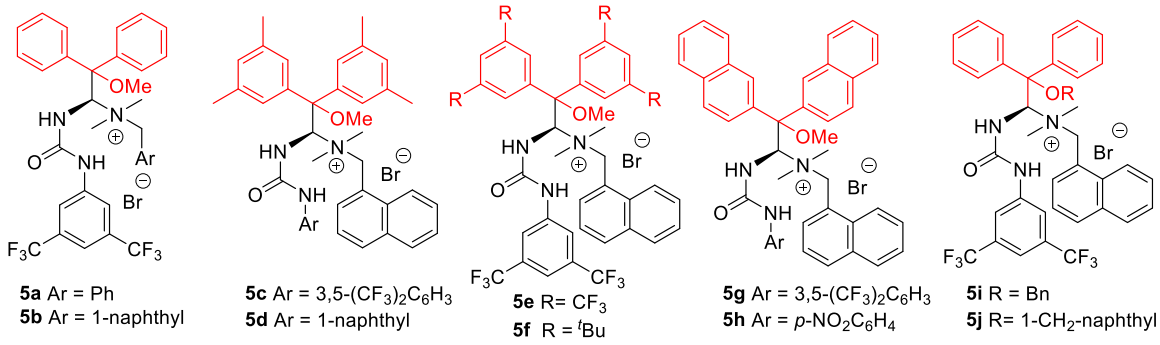


R^1 = Me, Bn, 1-CH_2-naphthyl
Ar^1 = Ph, 2-naphthly, 3,5-$(CF_3)_2C_6H_3$, 3,5-$(^tBu)_2C_6H_3$, 3,5-$(CH_3)_2C_6H_3$
Ar^2 = *p*-$NO_2C_6H_4$, 3,5-$(CF_3)_2C_6H_3$, 1-naphthyl
Ar^3 = Ph, 1-naphthyl

Table 3
Optimization of conditions and evaluation of chiral catalysts **5**[a].



1a **2a** **3a**



5a Ar = Ph
5b Ar = 1-naphthyl
5c Ar = 3,5-$(CF_3)_2C_6H_3$
5d Ar = 1-naphthyl
5e R= CF_3
5f R = ^{t}Bu
5g Ar = 3,5-$(CF_3)_2C_6H_3$
5h Ar = *p*-$NO_2C_6H_4$
5i R = Bn
5j R= 1-CH_2-naphthyl

Entry	cat. (10 mol%)	Yield (%)[b]	dr[c]	ee (%)[c]
1	**5a**	89	>20 : 1	79
2	**5b**	84	>20 : 1	87
3	**5c**	89	>20 : 1	79
4	**5d**	94	>20 : 1	43
5	**5e**	89	>20 : 1	87
6	**5f**	77	>20 : 1	76
7	**5g**	88	>20 : 1	83
8	**5h**	83	>20 : 1	59
9	**5i**	88	>20 : 1	90
10	**5j**	94	>20 : 1	89

[a] Reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol), catalysts **5** (10 mol%) and additive of base Cs_2CO_3 (0.5 equiv.) in toluene (1.0 mL) at room temperature in 24 h.
[b] Isolated yield.
[c] The dr and ee values were determined by chiral HPLC analysis.

*4.2.1. (S)–N-(3,5-bis(trifluoromethyl)benzyl)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N,N-dimethyl-2-phenylethan-1-aminium bromide (**4c**)*

White solid, m.p.: 106–107 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.32 (s, 1H), 8.16–8.10 (m, 3H), 7.94 (s, 1H), 7.87 (s, 2H), 7.55–7.53 (d, J = 7.6 Hz, 2H), 7.32 (s, 1H), 7.19–7.15 (m, 2H), 7.08–7.04 (m, 1H), 5.73 (s, 1H), 5.21 (s, 2H), 3.88–3.84 (d, J = 8.8 Hz, 1H), 3.30 (s, 3H), 3.26 (s, 3H), 2.86 (s, 1H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 154.9, 140.6, 137.8, 132.9 (q, $^2J_{CF}$ = 34.0 Hz), 131.7 (q, $^2J_{CF}$ = 32.7 Hz), 129.4, 129.3, 128.8, 126.6, 125.0, 123.1 (q, $^1J_{CF}$ = 272.0 Hz), 122.4 (q, $^1J_{CF}$ = 271.3 Hz), 117.9, 115.5, 69.4, 66.5, 50.9, 49.9, 30.5; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −63.13 (s), −63.23 (s); **IR** (Neat): ν = 3218, 3051, 2955, 1693, 1624, 1574, 1475, 1443, 1388, 1278, 1181, 1134, 1045 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{28}H_{24}ON_3F_{12})^+$ requires 646.1722; found 646.1720; $[\alpha]_D^{25.0}$ = +23.8 (c = 1.0, MeOH).

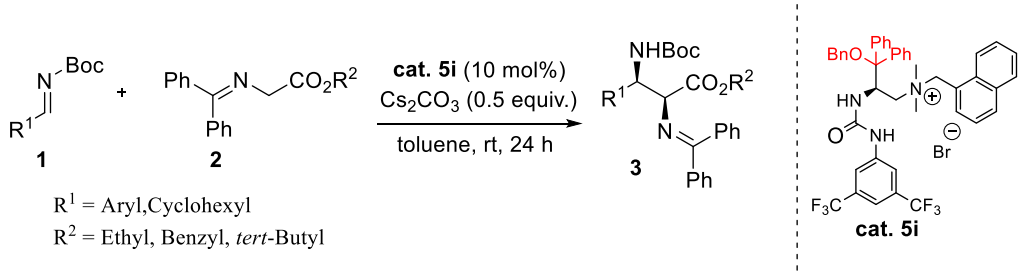
*4.2.2. (S)–N-benzyl-2-(3,5-bis(trifluoromethyl)benzamido)-N,N,3,3-tetramethylbutan-1-aminium bromide (**4g**)*

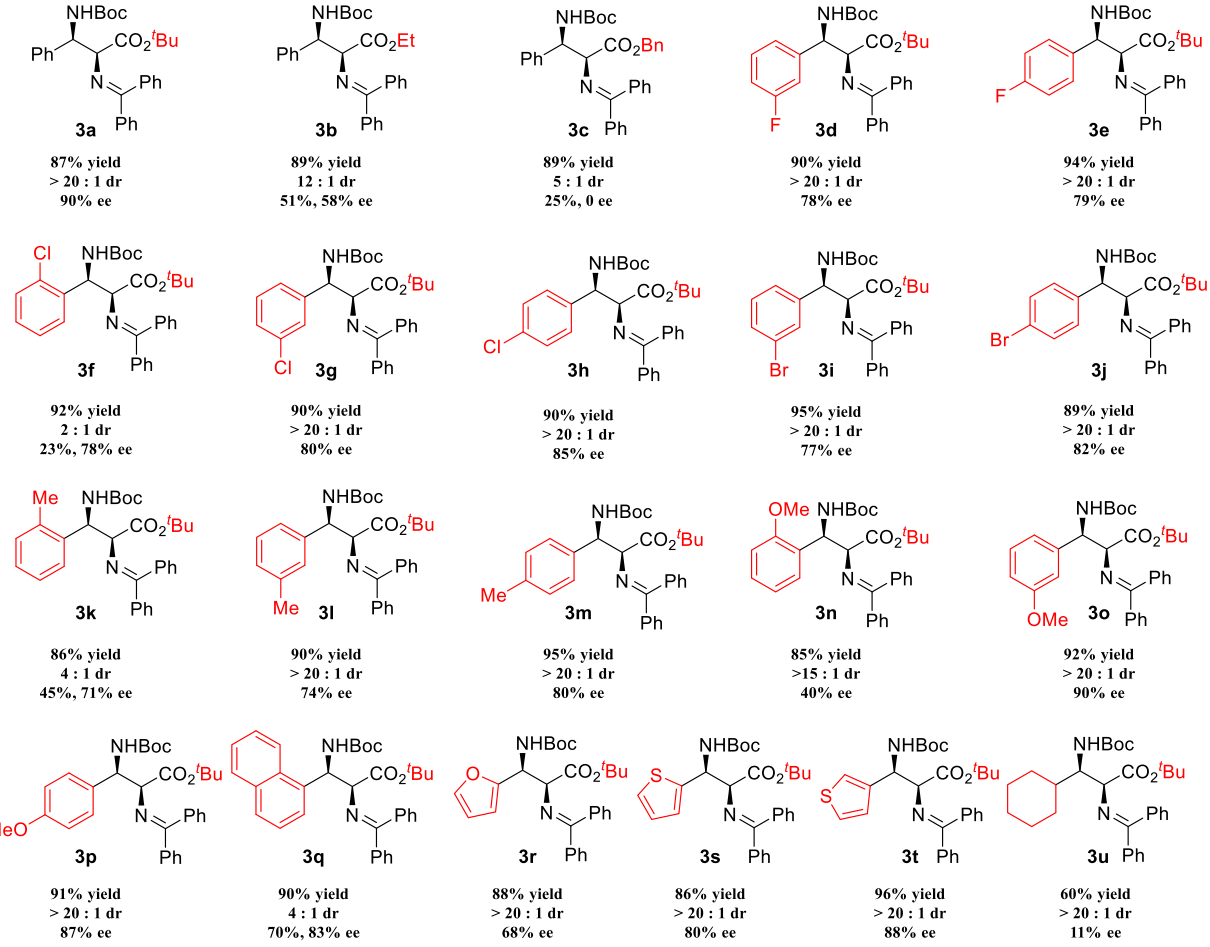
White solid, m.p.: 161–162 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.23–9.21 (d, J = 8.8 Hz, 1H), 8.75 (s, 2H), 7.91 (s, 1H), 7.59–7.57 (d, J = 6.8 Hz, 2H), 7.44–7.38 (m, 3H), 5.25–5.19 (m, 1H), 5.07–5.04 (d, J = 13.2 Hz, 1H), 4.87–4.84 (d, J = 13.2 Hz, 1H), 4.62–4.58 (t, J = 9.2 Hz, 1H), 4.08–4.05 (d, J = 13.2 Hz, 1H), 3.18 (s, 3H), 3.09 (s, 3H), 1.05 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 164.7, 134.9, 133.3, 131.7 (q, $^2J_{CF}$ = 33.7 Hz), 130.9, 129.2, 128.8, 126.8, 125.3, 122.8 (q, $^1J_{CF}$ = 271.3 Hz), 68.4, 65.9, 53.0, 49.3, 48.1, 36.8, 26.4; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.55 (s); **IR** (Neat): ν = 3229, 3051, 2967, 1661, 1620, 1541, 1480, 1380, 1280, 1182, 1136, 910, 728 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{24}H_{29}ON_2F_6)^+$ requires 475.2179; found 475.2178; $[\alpha]D^{25.0}$ = +5.3 (c = 1.0, MeOH).

*4.2.3. (S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N,N,3,3-tetramethyl-N-(naphthalen-1-ylmethyl)butan-1-aminium bromide (**4h**)*

White solid, m.p.: 112–113 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H), 8.35–8.30 (d, J = 8.4 Hz, 1H), 8.03 (s, 2H), 7.86–7.50 (m, 5H), 7.44–7.34 (m, 3H), 5.44–5.41 (d, J = 13.2 Hz, 1H), 5.20–5.17 (d, J = 13.2 Hz, 1H), 4.39–4.25 (m, 2H), 3.92–3.89 (d, J = 13.2 Hz, 1H), 3.15 (s, 3H), 3.06 (s, 3H), 1.06 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.7, 141.3, 134.0, 133.9, 132.8, 132.2, 131.7 (q, $^2J_{CF}$ = 33.0 Hz), 129.2, 128.2, 126.6, 125.3, 124.8, 123.3 (q, $^1J_{CF}$ = 272.0 Hz), 122.6, 118.0, 115.0, 68.3, 65.3, 53.1, 50.3, 50.1, 36.3, 26.3; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.95 (s); **IR** (Neat): ν = 3274, 3083, 2966, 1694, 1621, 1573, 1475, 1389, 1278, 1221, 1179, 1132, 1057, 880 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{28}H_{32}ON_3F_6)^+$ requires 540.2444; found 540.2443; $[\alpha]D^{25.0}$ = −41.9 (c = 1.0, MeOH).

Table 4
Scope of the Mannich Reaction Catalyzed by quaternary ammonium salt catalyst **5i**[a].



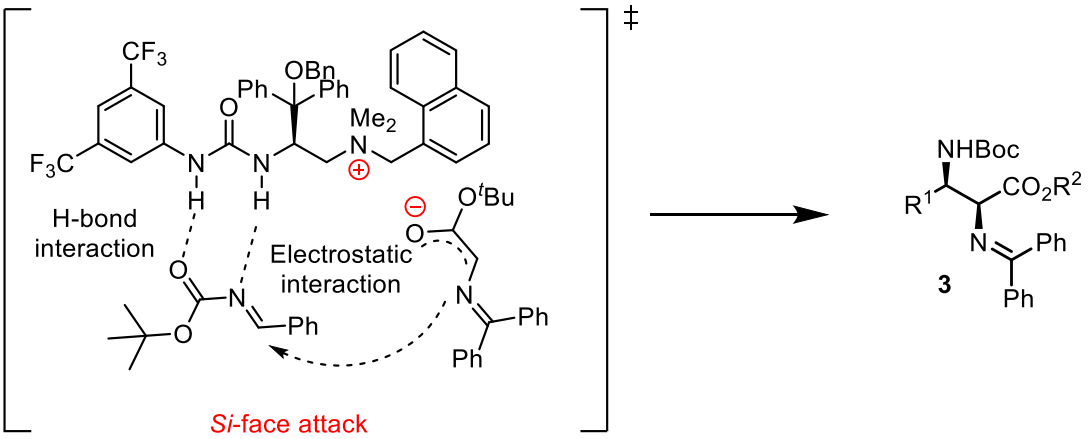


*4.2.4. (S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N,N,3,3-tetramethyl-N-(naphthalen-2-ylmethyl)butan-1-aminium bromide (**4i**)*

White solid, m.p.: 116–117 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.42 (s, 1H), 8.01 (s, 2H), 7.98 (s, 1H), 7.77–7.75 (d, J = 12.0 Hz, 3H), 7.57–7.45 (m, 4H), 7.35 (s, 1H), 5.09–5.06 (d, J = 13.2 Hz, 1H), 4.84–4.81 (d, J = 13.2 Hz, 1H), 4.23–4.12 (m, 2H), 3.86–3.82 (d, J = 13.2 Hz, 1H), 3.21 (s, 3H), 3.12 (s, 3H), 1.06 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.5, 141.2, 138.8, 138.7, 132.7, 131.6 (q, $^2J_{CF}$ = 33.0 Hz), 129.2, 128.7, 128.3, 128.1, 127.8, 127.3, 123.6, 123.3 (q, $^1J_{CF}$ = 271.7 Hz), 118.0, 115.1, 69.5, 67.7, 53.0, 50.0, 49.4, 36.3, 26.3; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.94 (s); **IR** (Neat): ν = 3276, 2966, 1696, 1570, 1474, 1389, 1279, 1179, 1132, 1059, 882 cm^{-1}; **HRMS** (ESI): calcd. for $[M-Br]^+$ $(C_{28}H_{32}ON_3F_6)^+$ requires 540.2444; found 540.2442; $[\alpha]D^{25.0}$ = −40.6 (c = 1.0, MeOH).

*4.2.5. (S)–N-(anthracen-9-ylmethyl)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N,N,3,3-tetramethylbutan-1-aminium bromide (**4j**)*

Light yellow solid, m.p.: 133–134 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 8.60–8.58 (d, J = 8.8 Hz, 1H), 8.37 (s, 2H), 8.18 (s, 1H), 7.92–7.72 (m, 3H), 7.51–7.36 (m, 5H), 7.18–7.14 (t, J = 7.2 Hz, 1H), 6.00–5.97 (d, J = 13.2 Hz, 1H), 5.86–5.83 (d, J = 13.2 Hz, 1H), 4.40–4.35 (t, J = 10.0 Hz, 1H), 3.93–3.90 (d, J = 13.2 Hz, 1H), 3.00 (s, 3H), 2.89 (s, 3H), 1.13 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.9, 141.4, 132.9, 132.3, 131.6 (q, $^2J_{CF}$ = 34.0 Hz), 129.6, 129.2, 128.4, 128.2, 125.4, 125.3, 124.0, 123.6, 123.3 (q, $^1J_{CF}$ = 271.7 Hz), 118.0, 116.9, 115.0, 68.6, 53.4, 51.7, 50.3, 36.4, 31.2, 26.4; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.96 (s); **IR** (Neat): ν = 3272, 3054, 2966, 1694, 1624, 1569, 1474, 1388, 1278, 1179, 1132, 1057, 733 cm^{-1}; **HRMS** (ESI): calcd. for $[M-Br]^+$ $(C_{32}H_{34}ON_3F_6)^+$ requires 590.2601; found



Scheme 3. A possible transition state.

590.2599; $[\alpha]_D^{25.0} = -48.6$ ($c = 1.0$, MeOH).

*4.2.6. (S)−N-(3,5-bis(benzyloxy)benzyl)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N,N,3,3-tetramethylbutan-1-aminium bromide (**4k**)*

White solid, m.p.: 106−107 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.32 (s, 1H), 8.00 (s, 2H), 7.34−7.23 (m, 12H), 6.66−6,64 (m, 3H), 4.96−4.91 (m, 4H), 4.71−4.67 (d, J = 13.2 Hz, 1H), 4.48−4.45 (d, J = 13.2 Hz, 1H), 4.11−4.08 (m, 2H), 3.64−3.61 (d, J = 13.2 Hz, 1H), 2.99 (s, 3H), 2.86 (s, 3H), 0.99 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 160.1, 155.4, 141.2, 136.0, 131.6 (q, $^2J_{CF}$ = 33.3 Hz), 128.6, 128.2, 127.6, 123.3 (q, $^1J_{CF}$ = 271.3 Hz), 122.7, 118.0, 115.0, 112.2, 70.3, 52.8, 49.9, 49.2, 36.2, 27.2, 26.6, 26.2; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.90 (s); **IR** (Neat): ν = 3048, 2965, 1694, 1596, 1572, 1474, 1389, 1279, 1172, 1133, 1059, 738 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{38}H_{42}O_3N_3F_6)^+$ requires 702.3125; found 702.3123; $[\alpha]_D^{25.0} = -32.0$ ($c = 1.0$, MeOH).

*4.2.7. (S)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N-(3,5-di-tert-butylbenzyl)-N,N,3,3-tetramethylbutan-1-aminium bromide (**4l**)*

White solid, m.p.: 110−111 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.37 (s, 1H), 8.00 (s, 2H), 7.49 (s, 2H), 7.32−7.29 (m, 3H), 4.81−4.78 (d, J = 13.2 Hz, 1H), 4.56−4.53 (d, J = 13.2 Hz, 1H), 4.22−4.16 (m, 2H), 3.68−3.65 (d, J = 13.2 Hz, 1H), 3.20 (s, 3H), 3.04 (s, 3H), 1.24 (s, 18H), 1.02 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.5, 152.2, 141.3, 131.6 (q, $^2J_{CF}$ = 32.7 Hz), 127.3, 125.7, 124.9, 123.3 (q, $^1J_{CF}$ = 271.7 Hz), 118.0, 114.9, 70.3, 68.6, 52.8, 50.4, 49.1, 36.2, 34.9, 31.2, 26.3; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.96 (s); **IR** (Neat): ν = 3276, 3086, 2967, 2871, 1697, 1572, 1475, 1389, 1279, 1178, 1135, 882 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{32}H_{46}ON_3F_6)^+$ requires 602.3540; found 602.3537; $[\alpha]_D^{25.0} = -31.5$ ($c = 1.0$, MeOH).

*4.2.8. (S)-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3-dimethylbutyl)-1-(naphthalen-1-ylmethyl)piperidin-1-ium bromide (**4m**)*

White solid, m.p.: 122−124 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 10.07 (s, 1H), 8.23−8.18 (m, 3H), 8.03−8.00 (m, 1H), 7.71−7.60 (m, 3H), 7.40−7.37 (m, 3H), 7.14−7.10 (t, J = 8.0 Hz, 1H), 5.43−5.31 (m, 2H), 4.40−3.97 (m, 6H), 3.45−3.39 (m, 1H), 1.83−1.65 (m, 6H), 1.14 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 156.1, 141.5, 134.7, 133.7, 133.2, 132.3, 131.8, 131.6 (q, $^2J_{CF}$ = 33.0 Hz), 129.1, 128.0, 126.5, 124.6, 123.4 (q, $^1J_{CF}$ = 271.5 Hz), 122.5, 118.0, 115.0, 65.0, 59.4, 58.2, 56.0, 52.6, 36.8, 26.6, 20.5, 20.3, 20.2; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.92 (s); **IR** (Neat): ν = 3267, 3050, 2964, 1694, 1573, 1474, 1389, 1278, 1179, 1132, 1056, 881, 806 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{31}H_{36}ON_3F_6)^+$ requires 580.2757; found 580.2755; $[\alpha]_D^{25.0} = -47.1$ ($c = 1.0$, MeOH).

*4.2.9. (S)-1-(2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3-dimethylbutyl)-1-(naphthalen-1-ylmethyl)pyrrolidin-1-ium bromide (**4n**)*

White solid, m.p.: 122−124 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.92 (s, 1H), 8.19−8.14 (m, 3H), 8.00−7.98 (d, J = 9.6 Hz, 1H), 7.71−7.67 (m, 2H), 7.58−7.56 (m, 1H), 7.43−7.35 (m, 3H), 7.13−7.10 (t, J = 7.6 Hz, 1H), 5.42 (s, 2H), 4.39−4.06 (m, 4H), 3,73−3.69 (d, J = 13.2 Hz, 1H), 3.27−3.20 (m, 1H), 3.03−2.95 (m, 1H), 2.23−1.95 (m, 3H), 1.14 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 156.0, 141.5, 134.2, 133.6, 133.0, 132.3, 131.8, 131.7 (q, $^2J_{CF}$ = 33.0 Hz), 129.1, 128.0, 126.6, 124.6, 123.3 (q, $^1J_{CF}$ = 271.3 Hz), 123.0, 122.7, 118.0, 115.0, 62.3, 59.9, 57.8, 53.5, 36.4, 31.8, 26.5, 26.3, 20.7; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.91 (s); **IR** (Neat): ν = 3272, 3050, 2967, 1694, 1571, 1474, 1389, 1279, 1179, 1132, 1056, 881 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{30}H_{34}ON_3F_6)^+$ requires 566.2601; found 566.2598; $[\alpha]_D^{25.0} = -34.6$ ($c = 1.0$, MeOH).

*4.2.10. (R)-N-benzyl-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3-methoxy-N,N-dimethyl-3,3-diphenylpropan-1-aminium bromide (**5a**)*

White solid, m.p.: 106−107 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.50 (s, 1H), 7.92 (s, 2H), 7.52−7.40 (m, 10H), 7.36−7.28 (m, 6H), 7.24−7.23 (m, 1H), 5.38−5.33 (t, J = 9.2 Hz, 1H), 4.57−4.54 (d, J = 13.2 Hz, 1H), 4.44−4.40 (d, J = 13.2 Hz, 1H), 3.66−3.63 (d, J = 13.2 Hz, 1H), 3.53−3.48 (m, 1H), 3.10 (s, 3H), 3.03 (s, 3H), 2.93 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.0, 140.9, 138.1, 136.0, 132.9, 131.6 (q, $^2J_{CF}$ = 33.0 Hz), 131.3, 129.4, 129.1, 128.8, 128.4, 128.3 (2C), 128.2, 126.0, 123.3 (q, $^1J_{CF}$ = 271.7 Hz), 118.2, 115.2, 86.5, 70.3, 67.8, 53.4, 51.3, 50.7, 49.3; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.92 (s); **IR** (Neat): ν = 3267, 3067, 2992, 2831, 1692, 1574, 1475, 1388, 1279, 1179, 1132, 1076, 882, 738 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{34}H_{34}O_2N_3F_6)^+$ requires 630.2550; found 630.2548; $[\alpha]_D^{25.0} = +73.5$ ($c = 1.0$, MeOH).

*4.2.11. (R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3-methoxy-N,N-dimethyl-N-(naphthalen-1-ylmethyl)-3,3-diphenylpropan-1-aminium bromide (**5b**)*

White solid, m.p.: 117−118 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.58 (s, 1H), 8.20−8.18 (d, J = 8.4 Hz, 1H), 7.97 (s, 2H), 7.92−7.84 (m, 2H), 7.60−7.27 (m, 15H), 7.24−7.20 (m, 1H), 5.46−5.42 (t, J = 8.8 Hz, 1H), 5.13−5.10 (d, J = 13.2 Hz, 1H), 4.95−4.92 (d, J = 13.2 Hz, 1H), 3.78−3.70 (m, 2H), 3.10 (s, 3H), 3.04 (s, 3H), 2.92 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.2, 141.0, 138.4, 136.7, 132.7, 132.4, 131.6 (q,

$^{2}J_{CF}$ = 33.0 Hz), 129.4, 128.9, 128.8, 128.4, 128.3 (2C), 128.2, 126.8, 124.7, 123.3 (q, $^{1}J_{CF}$ = 270.7 Hz), 123.1, 122.3, 118.1, 115.1, 86.4, 68.5, 65.9, 53.4, 51.5, 51.0, 50.1; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.91 (s); **IR** (Neat): ν = 3271, 3049, 2990, 1690, 1574, 1475, 1387, 1278, 1179, 1132, 1076, 941, 880 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{38}H_{36}O_2N_3F_6)^+$ requires 680.2706; found 680.2703; $[\alpha]_D^{25.0}$ = +51.9 (*c* = 1.0, MeOH).

4.2.12. (R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3-bis(3,5-dimethylphenyl)-3-methoxy-N,N-dimethyl-N-(naphthalen-1-ylmethyl)propan-1-aminium bromide (**5c**)

White solid, m.p.: 135−136 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.55 (s, 1H), 8.18−8.16 (d, *J* = 8.4 Hz, 1H), 7.97−7.85 (m, 4H), 7.69−7.50 (m, 4H), 7.41−7.37 (m, 2H), 7.08 (s, 4H), 6.95 (s, 1H), 6.85 (s, 1H), 5.42−5.37 (t, *J* = 9.2 Hz, 1H), 5.11−5.08 (d, *J* = 13.2 Hz, 1H), 4.91−4.87 (d, *J* = 13.2 Hz, 1H), 3.91−3.85 (m, 1H), 3.68−3.65 (d, *J* = 13.2 Hz, 1H), 3.13 (s, 3H), 3.10 (s, 3H), 2.87 (s, 3H), 2.35 (s, 6H), 2.23 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.3, 141.0, 138.9, 138.1, 137.5, 137.3, 134.0, 133.5, 132.7, 132.4, 131.7 (q, $^{2}J_{CF}$ = 33.0 Hz), 129.9, 129.7, 129.4, 128.4, 127.4, 126.8, 126.5, 125.6, 124.7, 123.3 (q, $^{1}J_{CF}$ = 271.0 Hz), 123.1, 122.3, 118.2, 115.0, 86.6, 68.7, 66.0, 53.6, 51.7, 51.0, 50.2, 21.8, 21.4; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.99 (s); **IR** (Neat): ν = 3271, 3046, 2983, 1693, 1574, 1474, 1388, 1278, 1180, 1134, 1081, 880, 852 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{42}H_{44}O_2N_3F_6)^+$ requires 736.3332; found 736.3330; $[\alpha]_D^{25.0}$ = +81.6 (*c* = 1.0, MeOH).

4.2.13. (R)-3,3-bis(3,5-dimethylphenyl)-3-methoxy-N,N-dimethyl-2-(3-(naphthalen-1-yl)ureido)-N(naphthalen-1-ylmethyl)propan-1-aminium bromide (**5d**)

White solid, m.p.: 127−128 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 8.58 (s, 1H), 8.36−8.34 (d, *J* = 8.0 Hz, 1H), 8.22−8.20 (d, *J* = 8.4 Hz, 1H), 7.93−7.85 (m, 3H), 7.74−7.71 (m, 2H), 7.61−7.34 (m, 8H), 7.13−7.09 (m, 4H), 6.93 (s, 1H), 6.84 (s, 1H), 5.44−5.39 (t, *J* = 9.2 Hz, 1H), 5.12−5.09 (d, *J* = 13.2 Hz, 1H), 4.84−4.80 (d, *J* = 13.2 Hz, 1H), 4.22−4.14 (m, 1H), 3.59−3.55 (d, *J* = 13.2 Hz, 1H), 3.21 (s, 3H), 3.12 (s, 3H), 2.75 (s, 3H), 2.34 (s, 6H), 2.23 (s, 6H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 156.6, 140.3, 138.0, 137.9, 137.5, 134.2, 134.0, 133.9, 133.5, 132.7, 132.3, 129.6, 129.4, 129.3, 128.3, 127.9, 127.4, 126.7, 126.2, 126.0, 125.7, 125.5, 124.8, 124.1, 123.4, 123.0, 122.6, 119.1, 86.6, 68.2, 66.1, 53.7, 52.2, 50.9, 49.7, 21.8, 21.5; **IR** (Neat): ν = 3257, 3047, 2960, 1682, 1598, 1545, 1405, 1343, 1227, 1091, 854, 735 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{44}H_{48}O_2N_3)^+$ requires 650.3741; found 650.3738; $[\alpha]_D^{25.0}$ = 43.1 (*c* = 1.0, MeOH).

4.2.14. (R)-3,3-bis(3,5-bis(trifluoromethyl)phenyl)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3-methoxy-N,N-dimethyl-N-(naphthalen-1-ylmethyl)propan-1-aminium bromide (**5e**)

White solid, m.p.: 128−129 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.46 (s, 1H), 8.33−8.30 (d, *J* = 9.6 Hz, 1H), 8.22−8.20 (d, *J* = 8.4 Hz, 1H), 7.99−7.81 (m, 10H), 7.61−7.31 (m, 5H), 5.63−5.58 (t, *J* = 9.2 Hz, 1H), 5.30−5.27 (d, *J* = 13.2 Hz, 1H), 4.94−4.90 (d, *J* = 13.2 Hz, 1H), 4.54−4.49 (m, 1H), 3.47−3.44 (d, *J* = 13.2 Hz, 1H), 3.36 (s, 3H), 3.23 (s, 3H), 2.87 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.5, 140.1, 139.7, 134.0, 133.5, 132.8, 132.5, 132.3 (q, $^{2}J_{CF}$ = 33.7 Hz), 132.2 (q, $^{2}J_{CF}$ = 33.7 Hz), 131.4, 129.6, 128.5, 128.0, 127.8, 127.0, 124.6, 124.3, 123.2, 123.1 (q, $^{1}J_{CF}$ = 271.7 Hz), 122.8, 122.7 (q, $^{1}J_{CF}$ = 271.7 Hz), 121.6 (2C), 118.4, 115.9, 85.7, 66.7, 66.1, 54.4, 50.8, 50.1; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.71 (s), −62.92 (s), −63.20 (s); **IR** (Neat): ν = 3223, 3050, 1699, 1623, 1574, 1475, 1388, 1279, 1175, 1135, 904 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{42}H_{32}O_2N_3F_{18})^+$ requires 952.2202; found 952.2220; $[\alpha]_D^{25.1}$ = +67.4 (*c* = 1.0, MeOH).

4.2.15. (R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3,3-bis(3,5-di-tert-butylphenyl)-3-methoxy-N,N-dimethyl- N-(naphthalen-1-ylmethyl)propan-1-aminium bromide (**5f**)

White solid, m.p.: 140−141 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.45 (s, 1H), 8.09−8.07 (d, *J* = 8.8 Hz, 1H), 8.02 (s, 2H), 7.94−7.86 (m, 2H), 7.69−7.60 (m, 2H), 7.55−7.51 (m, 2H), 7.44−7.35 (m, 7H), 7.27 (s, 1H), 5.58−5.54 (t, *J* = 8.8 Hz, 1H), 5.04−5.00 (d, *J* = 13.2 Hz, 1H), 4.71−4.67 (d, *J* = 13.2 Hz, 1H), 4.31−4.26 (m, 1H), 3.82−3.78 (d, *J* = 13.2 Hz, 1H), 3.37 (s, 3H), 2.91 (s, 3H), 2.79 (s, 3H), 1.31 (s, 18H), 1.25 (s, 18H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.4, 150.6 (2C), 141.0, 136.9, 134.0, 133.4, 132.6, 132.5, 131.6 (q, $^{2}J_{CF}$ = 32.7 Hz), 129.5, 128.4, 126.9, 124.8, 123.3 (q, $^{1}J_{CF}$ = 271.3 Hz), 122.9, 122.4, 122.1 (2C), 121.8, 121.3, 118.1, 115.0, 87.5, 69.7, 65.2, 54.0, 52.1, 50.1, 50.0, 35.0 (2C), 31.5, 31.4; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.97 (s); **IR** (Neat): ν = 3273, 2963, 1696, 1574, 1475, 1388, 1278, 1180, 1136, 880 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{54}H_{68}O_2N_3F_6)^+$ requires 904.5210; found 904.5208; $[\alpha]_D^{25.0}$ = +71.3 (*c* = 1.0, MeOH).

4.2.16. (R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-3-methoxy-N,N-dimethyl-N-(naphthalen-1-ylmethyl)-3,3-di(naphthalen-2-yl)propan-1-aminium bromide (**5g**)

White solid, m.p.: 162−163 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.56 (s, 1H), 8.14−8.09 (m, 2H), 8.01 (s, 1H), 7.96 (s, 2H), 7.88−7.72 (m, 9H), 7.60−7.36 (m, 10H), 7.28−7.24 (m, 1H), 5.67−5.63 (t, *J* = 8.4 Hz, 1H), 5.07−5.04 (d, *J* = 13.2 Hz, 1H), 4.90−4.87 (d, *J* = 13.2 Hz, 1H), 3.87−3.78 (m, 2H), 3.22 (s, 3H), 3.11 (s, 3H), 2.89 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.4, 140.8, 136.4, 134.9, 133.9, 133.5, 132.9, 132.8, 132.7, 132.6 (2C), 132.4, 131.7 (q, $^{2}J_{CF}$ = 33.0 Hz), 129.3, 128.7, 128.6 (2C), 128.4, 128.3, 128.0, 127.6, 127.2, 126.7, 126.6, 126.4, 126.3, 126.0, 125.9, 123.3 (q, $^{1}J_{CF}$ = 271.3 Hz), 123.0, 122.1, 118.2, 115.2, 86.9, 68.4, 66.2, 54.0, 51.7, 51.1, 49.9; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.90 (s); **IR** (Neat): ν = 3266, 3054, 1689, 1574, 1474, 1387, 1278, 1180, 1132, 1082, 880, 803 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{46}H_{40}O_2N_3F_6)^+$ requires 780.3019; found 780.3018; $[\alpha]_D^{25.0}$ = +90.5 (*c* = 1.0, MeOH).

4.2.17. (R)-3-methoxy-N,N-dimethyl-N-(naphthalen-1-ylmethyl)-3,3-di(naphthalen-2-yl)-2-(3-(4-nitrophenyl)ureido)propan-1-aminium bromide (**5h**)

Yellow solid, m.p.: 155−156 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.70 (s, 1H), 8.13−8.11 (d, *J* = 8.4 Hz, 1H), 8.06 (s, 1H), 7.99−7.97 (m, 3H), 7.91−7.88 (m, 3H), 7.85−7.72 (m, 6H), 7.60−7.40 (m, 11H), 7.31−7.27 (m, 1H), 5.65−5.61 (t, *J* = 8.0 Hz, 1H), 5.04−5.00 (d, *J* = 13.2 Hz, 1H), 4.90−4.87 (d, *J* = 13.2 Hz, 1H), 3.83−3.75 (m, 2H), 3.18 (s, 3H), 3.10 (s, 3H), 2.89 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.1, 145.6, 141.8, 136.1, 134.7, 133.9, 133.5, 132.9 (2C), 132.7, 132.6, 132.5, 129.4, 128.8, 128.7, 128.6, 128.4, 128.3, 128.0, 127.6, 127.4, 127.2, 126.8, 126.7, 126.4, 126.1, 125.9, 124.9, 124.7, 123.0, 122.1, 117.7, 115.2, 86.9, 68.4, 66.2, 53.9, 51.7, 51.2, 50.0; **IR** (Neat): ν = 3260, 3049, 2830, 1693, 1597, 1558, 1505, 1329, 1221, 1176, 1111, 1081, 854 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ $(C_{44}H_{41}O_4N_4)^+$ requires 689.3122; found 689.3119; $[\alpha]_D^{25.0}$ = +152.3 (*c* = 1.0, MeOH).

4.2.18. (R)-3-(benzyloxy)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N,N-dimethyl-N-(naphthalen-1-ylmethyl)-3,3-diphenylpropan-1-aminium bromide (**5i**)

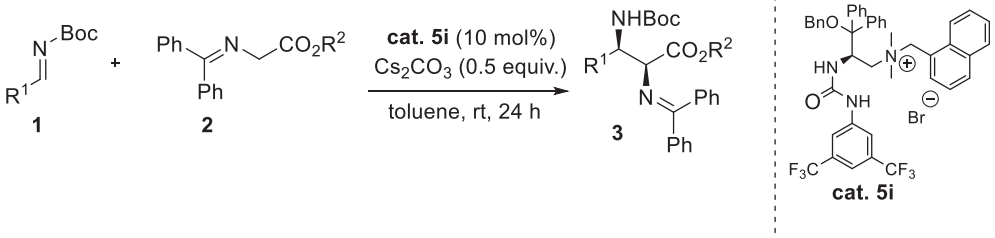
White solid, m.p.: 100−101 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.61 (s, 1H), 8.12−8.10 (d, *J* = 8.8 Hz, 1H), 7.91−7.86 (m, 4H), 7.54−7.28 (m, 14H), 7.24−7.18 (m, 5H), 7.06−7.05 (m, 2H), 5.50−5.46 (t, *J* = 8.8 Hz, 1H), 5.09−5.06 (d, *J* = 13.2 Hz, 1H), 4.93−4.90 (d, *J* = 13.2 Hz, 1H), 4.37−4.34 (d, *J* = 11.6 Hz, 1H), 3.93−3.90 (d, *J* = 11.6 Hz, 1H), 3.80−3.69 (m, 2H), 3.20 (s, 3H), 2.88 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.2, 141.0, 138.6, 137.9, 136.8, 133.9, 133.5, 132.6, 132.4, 131.6 (q, $^{2}J_{CF}$ = 33.0 Hz), 129.3, 128.9 (2C), 128.5, 128.4 (2C), 128.3, 128.0, 127.5, 126.9, 126.8, 124.7, 123.3 (q,

$^{1}J_{CF}$ = 271.3 Hz), 123.1, 122.3, 118.1, 115.1, 86.4, 67.8, 66.7, 66.6, 51.4, 51.3, 49.6; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.89 (s); **IR** (Neat): ν = 3273, 3061, 1692, 1575, 1475, 1388, 1278, 1179, 1132, 1066, 880 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ ($C_{44}H_{40}O_2N_3F_6$)$^+$ requires 756.3019; found 756.3017; $[\alpha]_D^{25.0}$ = +41.8 (*c* = 1.0, MeOH).

*4.2.19. (R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)ureido)-N,N-dimethyl-3-(naphthalen-1-ylmethoxy)-N-(naphthalen-1-ylmethyl)-3,3-diphenylpropan-1-aminium bromide (**5j**)*

White solid, m.p.: 132−133 °C; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 9.64 (s, 1H), 7.97 (s, 2H), 7.84−7.79 (m, 4H), 7.76−7.73 (m, 2H), 7.67−7.65 (d, *J* = 7.6 Hz, 2H), 7.56−7.53 (d, *J* = 10.0 Hz, 1H), 7.49−7.28 (m, 15H), 7.22−7.18 (m, 2H), 5.58−5.34 (t, *J* = 9.2 Hz, 1H), 4.91−4.87 (d, *J* = 13.2 Hz, 1H), 4.71−4.86 (d, *J* = 13.2 Hz, 1H), 4.51−4.83 (d, *J* = 13.2 Hz, 1H), 4.28−4.25 (d, *J* = 13.2 Hz, 1H), 3.68−3.65 (d, *J* = 13.2 Hz, 1H), 3.58−3.53 (m, 1H), 2.99 (s, 3H), 2.92 (s, 1H), 2.84 (s, 1H), 2.75 (s, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 155.1, 141.0, 137.6, 136.3, 133.7, 133.6, 133.5, 133.2, 132.5, 132.3, 131.6 (q, $^{2}J_{CF}$ = 33.0 Hz), 131.3, 129.5, 129.3, 129.0, 128.9, 128.6, 128.5, 128.4 (2C), 128.3, 126.6, 126.1, 125.8 (2C), 125.3, 124.5, 123.9, 123.3 (q, $^{1}J_{CF}$ = 271.3 Hz), 122.8, 122.0, 118.2, 115.1, 86.8, 68.3, 66.1, 65.7, 51.3, 49.7; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −62.89 (s); **IR** (Neat): ν = 3048, 1689, 1575, 1475, 1388, 1278, 1179, 1131, 804 cm^{-1}; **HRMS** (ESI): calcd. for $[M - Br]^+$ ($C_{48}H_{42}O_2N_3F_6$)$^+$ requires 806.3176; found 806.3174; $[\alpha]_D^{25.0}$ = −0.9 (*c* = 1.0, MeOH).

4.3. Quaternary ammonium salt catalyzed the reaction of glycine imines with N-Boc-aldimines



A mixture of *N*-Boc-aldimines (0.12 mmol, 1.2 equiv.), Cs_2CO_3 (0.05 mmol, 0.5 equiv.), catalyst **5i** (0.01 mmol, 10 mol%) and glycine imines (0.10 mmol, 1.0 equiv.) dissolved in toluene (1.0 mL). The resulting mixture was stirred for 24 h at room temperature until the reaction finished (monitored by TLC). The resultant solution was purified through flash column chromatography on silica gel (V_{PE}/V_{EA} = 8 : 1) to yield pure products **3a-3t**. The diastereomeric ratio and enantiomeric excess of the product was determined by HPLC.

*4.3.1. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-phenylpropanoate (**3a**) [10]*

Colorless amorphous, 87% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56−7.55 (d, *J* = 7.6 Hz, 2H), 7.38−7.29 (m, 4H), 7.25−7.15 (m, 7H), 6.50−6.49 (d, *J* = 6.4 Hz, 2H), 6.37−6.35 (d, *J* = 8.8 Hz, 1H), 5.44−5.41 (d, *J* = 8.4 Hz, 1H), 4.13 (s, 1H), 1.47 (s, 9H), 1.45 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.1, 169.1, 155.1, 140.7, 138.9, 136.0, 130.4, 128.8, 128.4, 128.2, 128.1, 127.9, 127.1, 126.9, 126.6, 81.9, 79.2, 56.7, 28.4, 27.9; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 9.6 min, t_{major} = 18.7 min, 90% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −93.6 (*c* = 1.0, $CHCl_3$).

*4.3.2. Ethyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-phenylpropanoate (**3b**)*

Colorless amorphous, 89% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56−7.54 (d, *J* = 11.2 Hz, 2H), 7.38−7.29 (m, 4H), 7.23−7.12 (m, 7H), 6.42−6.34 (m, 3H), 5.46−5.44 (d, *J* = 8.0 Hz, 1H), 4.30−4.12 (m, 3H), 1.44 (s, 9H), 1.29−1.25 (t, *J* = 7.2 Hz, 3H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.6, 169.9, 155.2, 140.4, 138.8, 135.8, 130.6, 128.9, 128.5, 128.0, 127.1 (2C), 126.6, 79.4, 69.7, 61.4, 56.6, 28.4, 14.2; **IR** (Neat): ν = 3437, 2978, 1719, 1488, 1367, 1169, 1027, 698 cm^{-1}; **HRMS** (ESI): calcd. for $[M+H]^+$ ($C_{29}H_{32}N_2O_4$+H^+)$^+$ requires 473.2362; found 473.2360; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 98/2, flow rate 1.0 mL/min, 254 nm, t_{minor} = 26.1 min, t_{major} = 28.6 min; t_{minor} = 31.2, t_{major} = 39.2, 51% ee; 58% ee, dr = 12 : 1; $[\alpha]_D^{25.0}$ = −75.3 (*c* = 1.0, $CHCl_3$).

*4.3.3. Benzyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-phenylpropanoate (**3c**) [10]*

Colorless amorphous, 89% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56−7.54 (d, *J* = 7.6 Hz, 2H), 7.39−7.29 (m, 9H), 7.21−7.12 (m, 7H), 6.38−6.36 (m, 3H), 5.50−5.48 (d, *J* = 8.4 Hz, 1H), 5.19 (s, 2H), 4.27 (s, 1H), 1.44 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.8, 169.9, 155.2, 140.3, 138.7, 135.7, 135.6, 130.7, 129.0, 128.9, 128.6, 128.4, 128.3, 128.1, 127.6 (2C), 127.1 (2C), 126.6, 79.5, 69.7, 67.0, 56.6, 28.4; HPLC analysis: Chiralpak Phenomenex Cellulose-2, Hexane/i-PrOH = 98/2, flow rate 1.0 mL/min, 254 nm, t_{majorr} = 15.3 min, t_{minor} = 40.7 min; t_{major} = 23.6, t_{major} = 31.9, 0 ee; 25% ee, dr = 5 : 1; $[\alpha]_D^{25.0}$ = −38.5 (*c* = 1.0, $CHCl_3$).

*4.3.4. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(3-fluorophenyl)propanoate (**3d**) [10]*

Colorless amorphous, 90% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.54−7.52 (d, *J* = 7.2 Hz, 2H), 7.37−7.26 (m, 6H), 7.18−7.17 (m, 1H), 6.94−6.86 (m, 3H), 6.57−6.56 (d, *J* = 6.8 Hz, 2H), 6.35−6.33 (d, *J* = 8.8 Hz, 1H), 5.40−5.38 (d, *J* = 7.6 Hz, 1H), 1.46 (s, 9H), 1.45 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.5, 168.8, 162.8 (d, $^{1}J_{CF}$ = 245.0 Hz), 155.2, 143.6, 138.7, 136.0, 130.6, 129.7 (d, $^{3}J_{CF}$ = 8.0 Hz), 128.8, 128.6, 128.3, 128.0, 127.1, 122.2 (d, $^{4}J_{CF}$ = 2.0 Hz), 113.8 (d, $^{2}J_{CF}$ = 19.0 Hz), 113.6 (d, $^{2}J_{CF}$ = 20.0 Hz), 82.1, 79.5, 69.8, 56.3, 28.4, 27.9; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −113.50, −113.2, −113.53, −113.54, −113.55, −113.57 (m); HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 98/2, flow rate 1.0 mL/min, 254 nm, t_{minor} = 11.1 min, t_{major} = 17.9 min, 78% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −55.6 (*c* = 1.0, $CHCl_3$).

*4.3.5. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(4-fluorophenyl)propanoate (**3e**) [10]*

Colorless amorphous, 94% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz)

δ 7.56–7.54 (d, J = 8.0 Hz, 2H), 7.38–7.22 (m, 6H), 7.14–7.10 (m, 2H), 6.93–6.89 (t, J = 8.4 Hz, 2H), 6.56–6.54 (d, J = 6.8 Hz, 2H), 6.36–6.33 (d, J = 8.8 Hz, 1H), 5.39–5.37 (d, J = 8.4 Hz, 1H), 4.09 (s, 1H), 1.46 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.3, 168.9, 161.8 (d, $^1J_{CF}$ = 243.0 Hz), 155.1, 138.7, 136.6, 136.0, 130.6, 128.8, 128.6, 128.3, 128.2 (d, $^3J_{CF}$ = 8.0 Hz), 128.0, 127.1, 114.9 (d, $^2J_{CF}$ = 22.0 Hz), 82.0, 79.5, 70.1, 56.2, 28.4, 27.9; **^{19}F NMR** ($CDCl_3$, 376 MHz) δ −116.05 (s); HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 98/2, flow rate 1.0 mL/min, 254 nm, t_{minor} = 12.4 min, t_{major} = 26.7 min, 79% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −82.8 (c = 1.0, $CHCl_3$).

4.3.6. *tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-3-(2-chlorophenyl)-2-((diphenylmethylene)amino)propanoate (**3f**)*

Colorless amorphous, 92% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.57–7.55 (d, J = 7.2 Hz, 2H), 7.44–7.31 (m, 8H), 7.15–7.14 (m, 3H), 6.43–6.39 (m, 2H), 5.82–5.80 (d, J = 8.4 Hz, 1H), 4.32 (s, 1H), 1.48 (s, 9H), 1.46 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.6, 172.0, 169.0, 155.0, 138.7, 137.9, 137.6, 136.0, 135.8, 133.2, 132.5, 132.4, 130.5, 130.0, 129.4, 129.3, 129.0, 128.7, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 126.9, 126.6, 126.4, 81.9, 79.5, 66.8, 54.2, 28.4, 27.9, 27.7; **IR** (Neat): ν = 3430, 2972, 1721, 1488, 1361, 1158, 1025, 702 cm^{-1}; **HRMS** (ESI): calcd. for $[M+H]^+$ $(C_{31}H_{35}ClN_2O_4+H^+)^+$ requires 535.2285; found 535.2282; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 98/2, flow rate 0.7 mL/min, 254 nm, t_{minor} = 8.3 min, t_{major} = 28.8 min; t_{minor} = 13.9, t_{major} = 20.4, 23% ee; 78% ee, dr = 2 : 1; $[\alpha]_D^{25.0}$ = −96.3 (c = 1.0, $CHCl_3$).

4.3.7. *tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-3-(3-chlorophenyl)-2-((diphenylmethylene)amino)Propanoate (**3g**)*

Colorless amorphous, 90% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55–7.53 (d, J = 11.2 Hz, 2H), 7.38–7.29 (m, 6H), 7.17–7.06 (m, 4H), 6.58–6.57 (d, J = 6.8 Hz, 2H), 6.34–6.32 (d, J = 8.8 Hz, 1H), 4.13 (s, 1H), 1.47 (s, 9H), 1.46 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.5, 168.8, 155.1, 142.9, 138.7, 135.9, 134.1, 132.4, 130.6, 130.0, 129.4, 128.8, 128.6, 128.3, 128.0, 127.1, 124.7, 82.1, 79.6, 69.8, 56.3, 28.4, 27.9; **IR** (Neat): ν = 3435, 2977, 1726, 1487, 1364, 1162, 1035, 703 cm^{-1}; **HRMS** (ESI): calcd. for $[M+H]^+$ $(C_{31}H_{35}ClN_2O_4+H^+)^+$ requires 535.2285; found 535.2283; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 99/1, flow rate 1.0 mL/min, 254 nm, t_{minor} = 18.1 min, t_{major} = 29.5 min, 80% ee, dr > 20 : 1; $[\alpha]_D^{25.0}$ = −99.9 (c = 1.0, $CHCl_3$).

4.3.8. *tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-3-(4-chlorophenyl)-2-((diphenylmethylene)amino)propanoate (**3h**) [10]*

Colorless amorphous, 90% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55–7.53 (d, J = 7.2 Hz, 2H), 7.38–7.25 (m, 6H), 7.20–7.08 (m, 4H), 6.57–6.55 (d, J = 7.2 Hz, 2H), 6.35–6.33 (d, J = 8.8 Hz, 1H), 4.07 (s, 1H), 1.45 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.4, 168.9, 155.1, 139.4, 138.7, 135.9, 132.7, 130.7, 128.8, 128.6, 128.3 (2C), 128.1, 128.0, 127.1, 82.1, 79.5, 69.9, 56.4, 28.4, 27.9; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 10.1 min, t_{major} = 25.2 min, 85% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −57.7 (c = 1.0, $CHCl_3$).

4.3.9. *tert-Butyl (2S,3R)-3-(3-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)propanoate (**3i**)*

Colorless amorphous, 95% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.53–7.52 (d, J = 7.2 Hz, 2H), 7.37–7.26 (m, 8H), 7.10–7.08 (m, 2H), 6.56–6.54 (d, J = 6.8 Hz, 2H), 6.33–6.31 (d, J = 8.8 Hz, 1H), 5.38–5.36 (d, J = 8.8 Hz, 1H), 4.11 (s, 1H), 1.46 (s, 9H), 1.45 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.6, 168.8, 155.1, 143.1, 138.7, 135.9, 130.6, 130.0, 129.9, 129.8, 128.8, 128.7, 128.4, 128.0, 127.1, 125.1, 122.4, 82.2, 79.6, 69.9, 56.3, 28.4, 27.9; **IR** (Neat): ν = 3427, 2970, 1714, 1477, 1364, 1161, 1031, 696 cm^{-1}; **HRMS** (ESI): calcd. for $[M+H]^+$ $(C_{31}H_{35}BrN_2O_4+H^+)^+$ requires 579.1780; found 579.1778; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 99/1, flow rate 1.0 mL/min, 254 nm, t_{minor} = 17.6 min, t_{major} = 31.3 min, 77% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −79.2 (c = 1.0, $CHCl_3$).

4.3.10. *(2S,3R)-tert-Butyl 3-(4-bromophenyl)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)propanoate (**3j**) [10]*

Colorless amorphous, 89% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56–7.56 (d, J = 7.2 Hz, 2H), 7.40–7.29 (m, 8H), 7.06–7.04 (d, J = 8.0 Hz, 2H), 6.58–6.57 (d, J = 7.2 Hz, 2H), 6.35–6.33 (d, J = 8.4 Hz, 1H), 5.37–5.35 (d, J = 8.4 Hz, 1H), 4.11 (s, 1H), 1.47 (s, 9H), 1.45 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.4, 168.8, 155.1, 139.9, 138.7, 135.9, 132.4, 131.2, 130.6, 130.0, 128.8, 128.6, 128.4, 128.3, 128.2, 128.0, 127.1, 120.8, 82.1, 79.5, 69.8, 56.3, 28.4, 27.9; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 10.6 min, t_{major} = 29.2 min, 82% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −42.9 (c = 1.0, $CHCl_3$).

4.3.11. *tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(o-tolyl)propanoate (**3k**) [10]*

Colorless amorphous, 86% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.59–7.57 (d, J = 7.2 Hz, 2H), 7.41–7.27 (m, 5H), 7.21–7.01 (m, 5H), 6.43–6.29 (m, 3H), 5.64–5.62 (d, J = 9.2 Hz, 1H), 4.01 (s, 1H), 2.07 (s, 3H), 1.47 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.2, 169.3, 155.1, 138.8, 138.6, 136.0, 134.7, 130.5, 130.2, 129.0, 128.8, 128.7, 128.4, 128.3, 128.1, 128.0, 127.9, 127.2, 127.0, 126.9, 126.4, 126.0, 125.6, 81.8, 79.2, 67.6, 53.7, 31.6, 28.4, 27.9, 27.3; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 0.8 mL/min, 254 nm, t_{minor} = 5.9 min, t_{major} = 16.1 min; t_{minor} = 8.6 min, t_{major} = 10.0 min, 45% ee; 71% ee, dr = 4 : 1; $[\alpha]_D^{25.0}$ = −60.7 (c = 1.0, $CHCl_3$).

4.3.12. *tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(m-tolyl)propanoate (**3l**) [10]*

Colorless amorphous, 90% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.55–7.53 (d, J = 7.2 Hz, 2H), 7.38–7.23 (m, 6H), 7.11–7.04 (t, J = 7.6 Hz, 1H), 6.98–6.91 (m, 3H), 6.48–6.46 (d, J = 10.4 Hz, 2H), 6.34–6.32 (d, J = 8.8 Hz, 1H), 5.39–5.37 (d, J = 8.0 Hz, 1H), 4.11 (s, 1H), 1.46 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.0, 169.2, 155.2, 140.5, 139.0, 137.6, 136.1, 130.4, 128.8, 128.4, 128.1, 128.0, 127.9, 127.6, 127.5, 123.6, 81.9, 79.2, 70.2, 56.7, 28.4, 28.0, 21.3; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 8.5 min, t_{major} = 15.3 min, 74% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −76.2 (c = 1.0, $CHCl_3$).

4.3.13. *tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(p-tolyl)propanoate (**3 m**) [10]*

Colorless amorphous, 95% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.57–7.55 (d, J = 7.2 Hz, 2H), 7.37–7.22 (m, 6H), 7.05–7.02 (m, 4H), 6.53–6.51 (d, J = 6.4 Hz, 2H), 6.34–6.31 (d, J = 8.4 Hz, 1H), 5.39–5.37 (d, J = 8.4 Hz, 1H), 4.11 (s, 1H), 2.27 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.0, 169.2, 155.1, 139.0, 137.7, 136.4, 128.8, 128.4, 128.2, 128.0, 127.2, 126.5, 81.8, 79.2, 70.2, 56.5, 28.4, 27.9, 21.0; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 10.0 min, t_{major} = 19.0 min, 80% ee, dr > 20 : 1; $[\alpha]_D^{25.0}$ = −73.6 (c = 1.0, $CHCl_3$).

4.3.14. *tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(2-methoxyphenyl)propanoate (**3n**)*

Colorless amorphous, 85% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.52–7.50 (d, J = 7.2 Hz, 2H), 7.34–7.27 (m, 5H), 7.23–7.12 (m, 3H), 6.84–6.80 (t, J = 8.0 Hz, 1H), 6.67–6.65 (m, 1H), 6.46–6.44 (d, J = 6.4 Hz, 2H), 6.23–6.20 (d, J = 8.8 Hz, 1H), 5.70–5.67 (m, 1H), 4.31–4.30 (d, J = 2.8 Hz, 1H), 3.47 (s, 3H), 1.45 (s, 9H), 1.42 (s, 9H);

^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.7, 169.7, 155.0, 139.1, 136.3, 130.2, 130.1, 129.0, 128.8, 128.2, 128.0 (2C), 127.9, 127.8, 127.4, 120.0, 109.8, 81.4, 79.1, 67.4, 54.8, 52.3, 28.4, 28.0; **IR** (Neat): ν = 3436, 2970, 1714, 1485, 1364, 1315, 1149, 1050, 696 cm^{-1}; **HRMS** (ESI): calcd. for $[M+H]^+$ $(C_{32}H_{38}N_2O_5+H^+)^+$ requires 531.2781; found 531.2779; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 0.8 mL/min, 254 nm, t_{major} = 19.5 min, t_{minor} = 26.9 min, 40% ee, dr > 15 : 1; $[\alpha]_D^{25.1}$ = −84.0 (c = 1.0, $CHCl_3$).

*4.3.15. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(3-methoxyphenyl)propanoate (**3o**) [10]*

Colorless amorphous, 92% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56−7.54 (d, J = 7.2 Hz, 2H), 7.38−7.24 (m, 6H), 7.14−7.10 (t, J = 8.0 Hz, 1H), 6.75−6.70 (m, 2H), 6.66 (s, 1H), 6.52−6.51 (d, J = 6.8 Hz, 2H), 6.34−6.32 (d, J = 8.4 Hz, 1H), 5.39−5.37 (d, J = 8.8 Hz, 1H), 4.13 (d, J = 2.0 Hz, 1H), 3.64 (s, 3H), 1.46 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.0, 169.1, 159.5, 155.2, 142.3, 138.9, 136.0, 130.5, 129.1, 128.8, 128.5, 128.2, 128.0, 127.2, 118.9, 113.1, 111.7, 81.9, 79.3, 70.1, 56.7, 55.1, 28.4, 27.9; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97/3, flow rate 0.8 mL/min, 254 nm, t_{minor} = 11.1 min, t_{major} = 21.3 min, 90% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −92.9 (c = 1.0, $CHCl_3$).

*4.3.16. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(4-methoxyphenyl)propanoate (**3p**) [10]*

Colorless amorphous, 91% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56−7.55 (d, J = 7.2 Hz, 2H), 7.37−7.23 (m, 6H), 7.08−7.06 (d, J = 8.4 Hz, 2H), 6.76−6.73 (d, J = 8.8 Hz, 2H), 6.55−6.54 (d, J = 6.8 Hz, 2H), 6.32−6.30 (d, J = 8.8 Hz, 1H), 5.36−5.34 (d, J = 8.4 Hz, 1H), 4.08 (s, 1H), 3.74 (s, 3H), 1.45 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.0, 169.2, 158.5, 155.1, 138.9, 136.1, 133.0, 130.5, 128.8, 128.4, 128.2, 128.0, 127.7, 127.2, 113.5, 81.8, 79.2, 70.2, 56.2, 55.3, 28.4, 27.9; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 16.0 min, t_{major} = 57.2 min, 87% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −65.6 (c = 1.0, $CHCl_3$).

*4.3.17. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(naphthalen-1-yl)propanoate (**3q**) [10]*

Colorless amorphous, 90% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.81−7.71 (m, 3H), 7.53−7.51 (d, J = 7.2 Hz, 2H), 7.44−7.27 (m, 7H), 7.04−7.00 (t, J = 7.6 Hz, 1H), 6.81−6.77 (t, J = 7.6 Hz, 2H), 6.55−6.53 (d, J = 8.4 Hz, 1H), 6.26−6.24 (d, J = 8.4 Hz, 1H), 5.93 (m, 2H), 4.29 (s, 1H), 1.54 (s, 9H), 1.47 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.2, 169.4, 155.1, 138.8, 135.8, 135.4, 133.7, 130.4, 133.0, 128.7, 127.9, 127.7, 126.4, 126.1, 123.5, 122.1, 82.0, 79.4, 67.9, 53.6, 28.4, 27.0; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 98/2, flow rate 0.5 mL/min, 254 nm, t_{minor} = 12.9 min, t_{major} = 34.2 min; t_{minor} = 22.1 min, t_{major} = 28.9 min, 70% ee; 83% ee, dr = 4 : 1; $[\alpha]_D^{25.0}$ = −56.8 (c = 1.0, $CHCl_3$).

*4.3.18. tert-Butyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(furan-2-yl)propanoate (**3r**) [10]*

Colorless amorphous, 88% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.56−7.54 (d, J = 8.0 Hz, 2H), 7.37−7.27 (m, 6H), 7.22 (s, 1H), 6.89−6.87 (d, J = 6.4 Hz, 2H), 6.22 (m, 1H), 6.12−6.09 (m, 2H), 5.49−5.47 (d, J = 9.2 Hz, 1H), 4.34 (s, 1H), 1.45 (s, 9H), 1.44 (s, 9H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.6, 168.7, 155.1, 153.8, 141.5, 139.2, 136.2, 130.5, 128.9, 128.7, 128.3, 127.9, 127.4, 110.3, 106.3, 82.0, 79.5, 67.8, 51.8, 28.4, 27.9; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 11.5 min, t_{major} = 17.4 min, 68% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −58.0 (c = 1.0, $CHCl_3$).

*4.3.19. tert-Butyl (2S,3S)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(thiophen-2-yl)propanoate (**3s**) [10]*

Colorless amorphous, 86% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.64−7.62 (d, J = 7.6 Hz, 2H), 7.41−7.31 (m, 6H), 7.11−7.10 (m, 1H), 6.87−6.86 (m, 4H), 6.27−6.25 (d, J = 9.2 Hz, 1H), 5.69−5.66 (d, J = 9.2 Hz, 1H), 4.19 (s, 1H), 1.44 (s, 18H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.9, 168.1, 154.9, 144.8, 139.0, 136.2, 130.6, 129.1, 128.7, 128.3, 128.0, 127.3, 126.4, 124.6, 124.4, 82.1, 79.4, 70.0, 53.1, 28.4, 27.9; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 98/2, flow rate 1.0 mL/min, 254 nm, t_{minor} = 10.6 min, t_{major} = 26.8 min, 80% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −105.7 (c = 1.0, $CHCl_3$).

*4.3.20. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-2-((diphenylmethylene)amino)-3-(thiophen-3-yl)propanoate (**3t**)*

Colorless amorphous, 96% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.57−7.56 (d, J = 7.2 Hz, 2H), 7.38−7.29 (m, 6H), 7.17−7.15 (m, 1H), 7.02 (s, 1H), 6.85−6.84 (d, J = 4.8 Hz, 1H), 6.74−6.73 (d, J = 6.8 Hz, 2H), 5.49−5.47 (d, J = 8.8 Hz, 1H), 4.16 (s, 1H), 1.44 (s, 18H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 172.2, 169.0, 155.1, 142.3, 139.0, 136.2, 130.5, 130.1, 128.8, 128.6, 128.4, 128.3, 128.0, 127.3, 126.5, 125.4, 121.1, 81.9, 79.3, 69.6, 53.3, 28.4, 27.9; **IR** (Neat): ν = 3438, 2972, 1717, 1486, 1364, 1315, 1161, 1050, 703 cm^{-1}; **HRMS** (ESI): calcd. for $[M+H]^+$ $(C_{29}H_{34}N_2O_4S + H^+)^+$ requires 507.2239; found 507.2238; HPLC analysis: Chiralpak AD-H, Hexane/i-PrOH = 97.5/2.5, flow rate 1.0 mL/min, 254 nm, t_{minor} = 12.9 min, t_{major} = 30.6 min, 88% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −68.6 (c = 1.0, $CHCl_3$).

*4.3.21. tert-Butyl (2S,3R)-3-((tert-butoxycarbonyl)amino)-3-cyclohexyl-2-((diphenylmethylene)amino)propanoate (**3u**)*

Colorless amorphous, 60% yield; **^{1}H NMR** ($CDCl_3$, 400 MHz) δ 7.66−7.64 (d, J = 7.6 Hz, 2H), 7.43−7.39 (m, 4H), 7.36−7.33 (m, 2H), 7.14−7.13 (m, 2H), 5.66−5.64 (d, J = 10.0 Hz, 1H), 4.66−4.65 (d, J = 2.4 Hz, 1H), 3.95−3.90 (m, 1H), 1.84−1.73 (m, 6H), 1.44 (s, 9H), 1.41 (s, 9H), 1.30−1.19 (m, 5H); **^{13}C NMR** ($CDCl_3$, 100 MHz) δ 171.6, 170.5, 155.7, 139.2, 136.6, 130.5, 128.9, 128.8, 128.4, 128.0, 127.4, 81.4, 78.6, 77.3, 77.0, 76.7, 65.8, 57.7, 40.6, 29.5, 29.3, 28.4, 27.8, 26.2, 26.1, 26.0; **IR** (Neat): ν = 3448, 2929, 2855, 2360, 1737, 1721, 1493, 1367, 1172, 1024, 801, 705 cm^{-1}; **HRMS** (ESI): calcd. for $[M+H]^+$ $(C_{31}H_{42}N_2O_4+H^+)^+$ requires 507.3145; found 507.3142; HPLC analysis: Chiralpak IC, Hexane/i-PrOH = 98/2, flow rate 0.7 mL/min, 214 nm, t_{minor} = 9.7 min, t_{major} = 14.0 min, 11% ee, dr > 20 : 1; $[\alpha]_D^{25.1}$ = −15.6 (c = 1.0, $CHCl_3$).

Declaration of competing interest

We (Authors) herein declare no competing financial interest or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131484.

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