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9-Amino-(9-deoxy)cinchona alkaloid-derived new chiral phase-transfer catalysts†

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A new class of 9-amino-(9-deoxy)cinchona alkaloid-derived chiral phase-transfer catalysts bearing amino groups was developed by using known cinchona alkaloids as the starting materials. Due to the transformation of the 9-hydroxyl group into a 9-amino functional group, the catalytic performances were significantly improved in comparison with the corresponding first generation phase-transfer catalysts, and excellent yields (92–99%) and high enantioselectivities (87–96% ee) were achieved in the benchmark asymmetric α-alkylation of glycine Schiff base. Based on the special contribution of the amino group to the high yield and enantioselectivity, the possible catalytic mechanism was conjectured.

Introduction

Phase-transfer (PT) catalysis has long been recognized as a practical and versatile methodology for organic synthesis in both industry and academia, owing to its operational simplicity, mild reaction conditions, environmentally benign nature, and suitability for large-scale synthesis.[1] Recently, various natural and non-natural asymmetric phase-transfer catalysts with excellent catalytic performances, such as cinchona alkaloid-derived quaternary ammonium salts[2] and chiral *N*-spiro ammonium salts,[3] have been developed, particularly in the last 20 years. In particular, the numerous structural modifications of cinchona alkaloid-derived quaternary ammonium salts that concentrated on the quinuclidine nitrogen atom and 9-hydroxy group achieved excellent catalytic performances. Up to now, three successful generations of cinchona alkaloid-derived quaternary ammonium salts have been reported. The simple *N*-benzyl cinchona alkaloid ammonium salts, introduced by O'Donnell in 1989, were recognized as the first generation.[4] Later, the same group reported that the second generation of *N*-alkyl-*O*-alkyl cinchona alkaloid derivatives could lead to a remarkably higher enantiomeric excess.[5] Finally, the most efficient third generation of *N*-9-anthracenylmethyl-*O*-allyl quaternary ammonium salts was developed independently by Lygo and Corey.[6] These salts achieved a breakthrough in their high enantioselectivity in alkylation and conjugate addition, owing to the steric effects of the bulky 9-methylanthryl group.[7]

Despite all these successful results, there is always a need for new catalyst structures. Due to the available access to the first generation, the structural modification only at the quinuclidine nitrogen atom was expected to accomplish a high and satisfactory catalytic performance. Fortunately, two successful examples achieved considerably improved enantioselectivity in the asymmetric benzylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester, by using an aryl ketone and a benzotriazole moiety in substitution for the *N*-benzyl substituent.[8] Recently, Dixon reported bifunctional 9-amino-(9-deoxy)-*epi*-cinchona-derived PT catalysts bearing phase-transfer components (ammonium salts) and H-bond donor components (urea, amide and sulphonamide) through the structural modification of the 9-amino group.[9] In the enantioselective nitro-Mannich reaction of amidosulfones, good reactivity and high stereoselectivities (up to 24 : 1 dr and 95% ee) were obtained under optimal conditions. In this paper, we describe our efforts toward the design of a family of new 9-amino-(9-deoxy)cinchona alkaloid-derived PT catalysts bearing a primary amino group with different configurations at the 9-position and *N*-benzyl substituents (Scheme 1), which could achieve efficient catalytic performances (92–99% and 87–96% ee) similar to the third generation of *N*-9-anthracenylmethyl-*O*-allyl quaternary ammonium salts in the benchmark enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.

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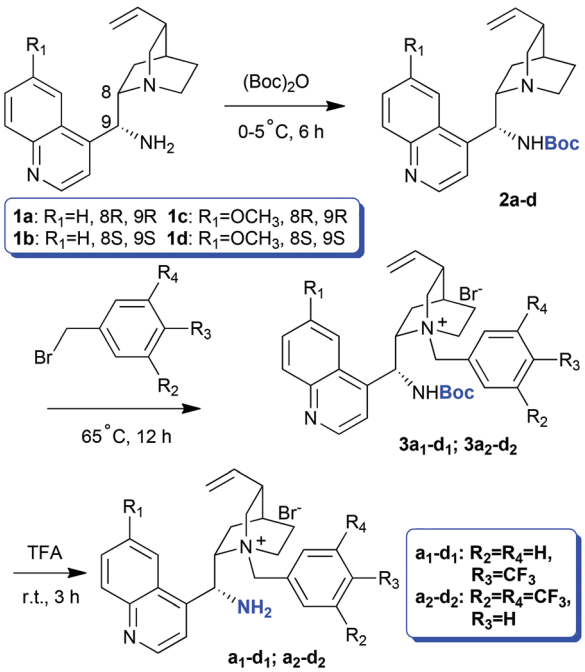
† Electronic supplementary information (ESI) available: ^{1}H and ^{13}C NMR spectra of various catalysts and products; HPLC spectra of products and the data of optimization procedure. See DOI: 10.1039/c4ob01648c



Scheme 1 The synthetic route to 9-amino-(9-deoxy)cinchona alkaloid-derived *N*-benzyl ammonium salts.

Results and discussion

Synthesis of the PT catalysts

Four 9-amino-(9-deoxy)cinchona alkaloids, **1a–d**, bearing different substituent groups (R_1, R_2, R_3 and R_4) and possessing (8*R*,9*R*), (8*S*,9*S*)-configurations were prepared in 75–81% yields by the Mitsunobu reaction, according to the references.[10] After the primary amino group at the 9-position was protected by using Boc_2O, the *N*-Boc-protected 9-amino-(9-deoxy)cinchona alkaloid-derived ammonium salts **3a$_1$–d$_1$** and **3a$_2$–d$_2$** could be precipitated out and filtered from the reaction mixture in 60–80% yields upon the quaternization of the quinuclidine nitrogen atom using 4-(trifluoromethyl) or 3,5-bis(trifluoromethyl)benzyl bromides, respectively, in toluene at 65 °C for 12 h. Finally, the target PT catalysts **a$_1$–d$_1$** and **a$_2$–d$_2$** bearing different substituents and (8*R*,9*R*), (8*S*,9*S*)-configurations were prepared in 90–95% yields by the deprotection of the *N*-Boc-amino group using TFA at room temperature for 3 h (Scheme 1).

The effect of an aromatic substituent and configuration on the catalytic performance

Using PT catalyst **b$_2$** as an example, the effects of the solvent, temperature, amount of the catalyst used and base species on the catalytic performances were investigated in detail and the following optimum conditions were established: 10 mol% **b$_2$**, −40 °C, 50% KOH and 12 h (ESI†). Thus, under these optimum conditions, the PT catalysts **a$_1$–d$_1$** and **a$_2$–d$_2$** with different structures, including substituent groups and configurations at 8,9-positions, were evaluated in the enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.

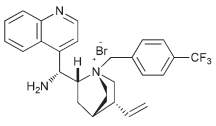
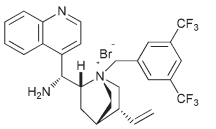
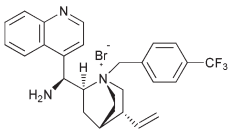
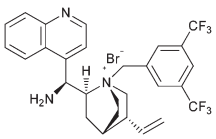
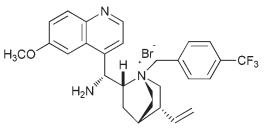
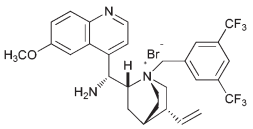
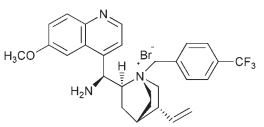
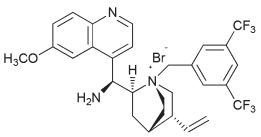
From Table 1, it was found that the PT catalysts **b$_1$**, **b$_2$**, **d$_1$** and **d$_2$** with (8*S*,9*S*)-configurations gave the better catalytic performances, including yields of 42–97% and enantioselectivities of 50–91% ee in an ether–water biphasic system, than the catalysts **a$_1$**, **a$_2$**, **c$_1$** and **c$_2$** with (8*R*,9*R*)-configurations. It was worth noting that the catalysts **c$_1$**, **c$_2$**, **d$_1$** and **d$_2$** (R_1 = OCH_3) produced lower yields and enantioselectivities owing to their poor organosolubilities in ether, compared with the catalysts **a$_1$**, **b$_1$**, **a$_2$** and **b$_2$** (R_1 = H). In addition, all the catalysts **a$_1$–d$_1$** and **a$_2$–d$_2$** afforded good to excellent yields in a toluene–water biphasic system (79–98%). In particular, the catalysts **c$_1$**, **c$_2$**, **d$_1$** and **d$_2$** (R_1 = OCH_3) afforded improved enantioselectivities (65–79% ee) in the toluene–water biphasic system owing to their good organosolubilities in toluene (entries 5–8). Unfortunately, it was found that the catalysts **a$_1$**, **a$_2$**, **b$_1$** and **b$_2$** (R_1 = H) gave relatively lower enantioselectivities in toluene, although good to excellent yields (80–98%) could be achieved. On the other hand, the modifications at the quinuclidine nitrogen atom were effective in improving the enantioselectivity. The PT catalysts **a$_2$–d$_2$** (R_1 = OCH_3) bearing 3,5-bis(trifluoromethyl)-benzyl moieties gave better yields and enantioselectivities than the PT catalysts **a$_1$–d$_1$** (R_1 = H) with a 4-(trifluoromethyl)benzyl group, both in toluene–water and ether–water biphasic systems.

Taking into account the above mentioned considerations of the substituents attached to aromatic rings (R_1, R_2, R_3 and R_4) and the spatial configurations at the 8 and 9-positions, the (8*S*,9*S*)-9-amino-(9-deoxy)cinchonidine-derived ammonium salt (**b$_2$**) bearing 3,5-bis(trifluoromethyl)benzyl moieties produced the enantiomeric product *tert*-butyl 3-phenyl-2-(diphenylmethyleneamino)propanoate in an ether–water biphasic system with the highest enantioselectivity (91% ee) in 97% yield (entry 4).

The comparative kinetics of catalyst b$_2$ with the 3rd generation PT catalyst

To assess the comparative catalytic performances of the 9-amino-(9-deoxy)cinchona alkaloid-derived catalysts and the 3rd generation of *N*-9-anthracenylmethyl-*O*-allyl quaternary ammonium salts, the stereoselectivities and yields during the course of the catalytic reaction were monitored by using HPLC. The famous *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**1**) and the as-synthesized (8*S*,9*S*)-9-amino-(9-deoxy) cinchonidine-derived ammonium salt **b$_2$** were selected as representative samples. Under the same catalytic reaction conditions (−40 °C, ether, 50% aq. KOH, 10 mol% catalyst, 12 h), the yield and enantioselectivity profiles of *tert*-butyl 3-phenyl-2-(diphenylmethyleneamino)propanoate plotted *versus* time during the whole process are shown in Fig. 1. As shown in Fig. 1, the (8*S*,9*S*)-9-amino-(9-deoxy)cinchonidine-derived PT catalyst **b$_2$** gave better yields (up to 98%) and somewhat lower enantioselectivities (91% ee) than *O*-allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**1**) during the whole process.

Table 1 The benchmark enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester catalyzed by $\mathbf{a_1}$–$\mathbf{d_1}$ and $\mathbf{a_2}$–$\mathbf{d_2}$ [a]

Entry	Catalyst	Yield[b] (%)	% ee[c]
1	 $\mathbf{a_1}$ (8*R*, 9*R*)	76 80[d]	23 (*S*) 30 (*S*)
2	 $\mathbf{a_2}$ (8*R*, 9*R*)	85 88[d]	71 (*S*) 67 (*S*)
3	 $\mathbf{b_1}$ (8*S*, 9*S*)	94 91[d]	50 (*R*) 43 (*R*)
4	 $\mathbf{b_2}$ (8*S*, 9*S*)	97 98[d]	91 (*R*) 85 (*R*)
5	 $\mathbf{c_1}$ (8*R*, 9*R*)	37 79[d]	5 (*S*) 30 (*S*)
6	 $\mathbf{c_2}$ (8*R*, 9*R*)	43 87[d]	31 (*S*) 77 (*S*)
7	 $\mathbf{d_1}$ (8*S*, 9*S*)	42 83[d]	51 (*R*) 65 (*R*)
8	 $\mathbf{d_2}$ (8*S*, 9*S*)	48 89[d]	63 (*R*) 79 (*R*)

[a] Reaction conditions: *N*-(diphenylmethylene)glycine *tert*-butyl ester (0.1 mmol), −40 °C, 2 mL ether, 0.4 mL 50% aq. KOH, 10 mol% PT catalyst, 12 h. [b] Isolated yield. [c] Determined by chiral HPLC with Daicel Chiralpak OD-H column. [d] Toluene as the solvent.

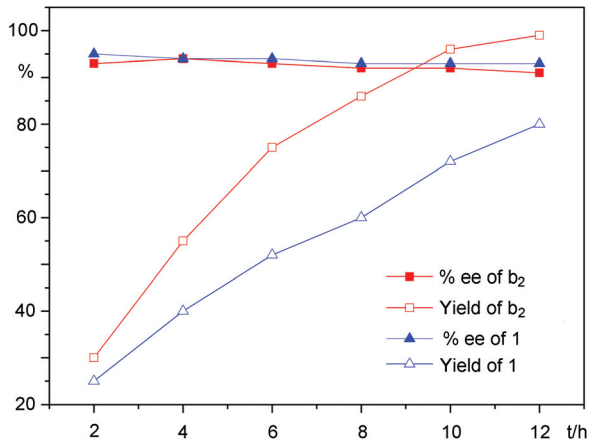


Fig. 1 The yield and enantioselectivity profiles of the catalysts $\mathbf{b_2}$ and **1** plotted *versus* time during the experiment.

Application in α-alkylation using different electrophiles

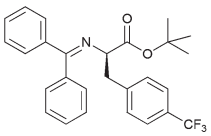
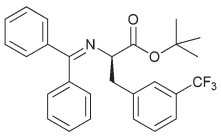
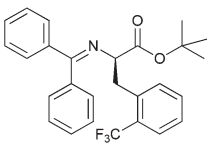
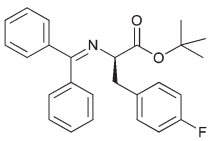
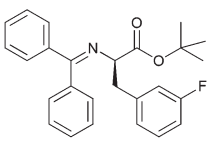
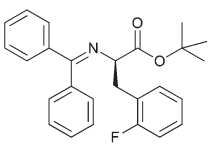
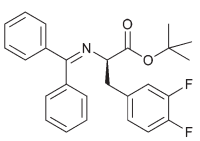
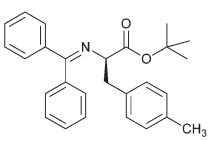
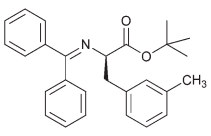
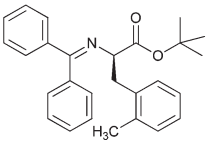
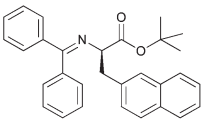
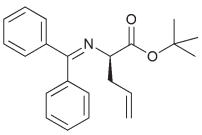
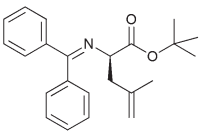
With the optimum conditions in hand, the scope of the catalyst $\mathbf{b_2}$ with respect to various electrophiles was surveyed in the enantioselective α-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.

As shown in Table 2, it was found that the various substituted aromatic aldehydes, both with electron-withdrawing (–CF_3 and –F) and electron-donating (–CH_3) substituents, could produce the corresponding α-alkylation products with high enantioselectivities (90–96% ee) in 92–99% yields (entries 1–11). In particular, when the aromatic aldehydes bearing *o*-CF_3, *o*-F and *o*-CH_3 were employed as electrophiles, slightly lower yields and higher enantioselectivities were observed owing to the sterically hindered and confined interactions between the *o*-substituents of the electrophiles and the catalyst (entries 3, 6 and 10).[8] Furthermore, good enantioselectivities in the enantioselective alkylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester with allyl bromides (89% ee and 87% ee) were also achieved in the presence of the catalyst $\mathbf{b_2}$ (entries 12 and 13).

Mechanism investigation

It is generally accepted that the enantioselective α-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester under basic conditions follows an interfacial mechanism.[1a] The first step is the interfacial deprotonation of the α-proton of *N*-(diphenylmethylene) glycine *tert*-butyl ester with bases such as KOH to give the corresponding metal enolate. Subsequently, the ion-exchange between the enolate anion and the PT catalyst ($Q^{*+}X^-$) generates a lipophilic chiral onium enolate. Finally, nucleophilic substitution with an alkyl halide affords the optically active monoalkylation product with the concomitant regeneration of the catalyst. Of particular importance to enantioselective α-alkylation is the generation of the highly reactive chiral onium enolate through sufficiently fast ion-exchange and the effective shielding of one of the two enantiotopic faces of the enolate anion.

Table 2 The scope of the enantioselective α-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester using different electrophiles[a]

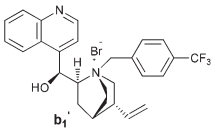
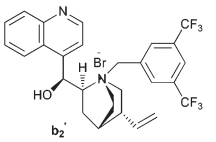
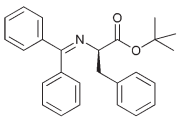
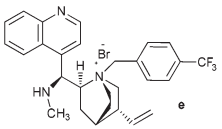
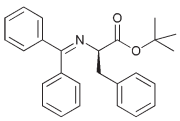
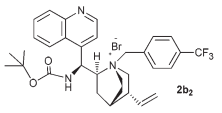
Entry	Product	Time (h)	Yield[b] (%)	% ee[c]
1	 **1**	5	99	90 (*R*)
2	 **2**	5	99	95 (*R*)
3	 **3**	5	93	96 (*R*)
4	 **4**	5	97	90 (*R*)
5	 **5**	5	94	90 (*R*)
6	 **6**	5	92	91 (*R*)
7	 **7**	4	99	90 (*R*)
8	 **8**	5	96	92 (*R*)
9	 **9**	8	95	91 (*R*)
10	 **10**	5	92	92 (*R*)
11	 **11**	8	99	96 (*R*)
12	 **12**	5	99	89 (*R*)
13	 **13**	10	93	87 (*R*)

[a] Reaction conditions: *N*-(diphenylmethylene)glycine *tert*-butyl ester (0.1 mmol), −40 °C, 2 mL ether, 0.4 mL 50% aq. KOH, 10 mol% catalyst $\mathbf{b_2}$. [b] Isolated yield. [c] Determined by chiral HPLC with Daicel Chiralpak OD-H column.

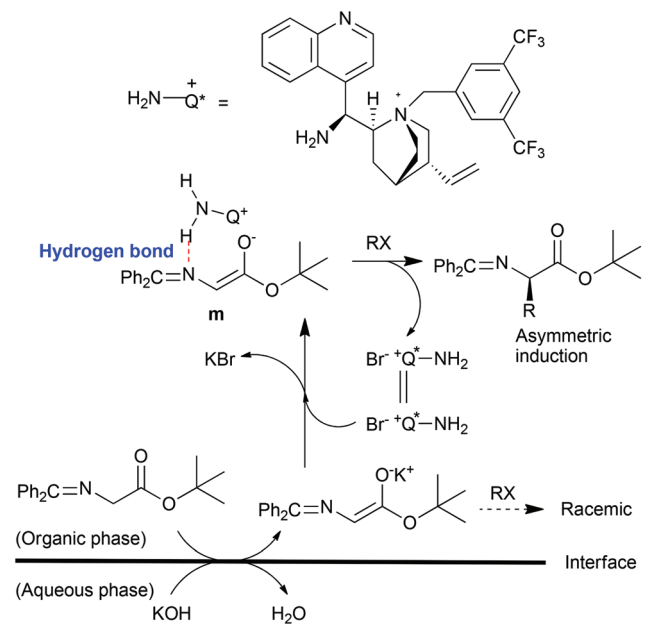
In order to elucidate the mechanism of the enantioselective α-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester catalyzed by the catalyst $\mathbf{b_2}$, the corresponding first generation PT catalysts $\mathbf{b_1}'$ and $\mathbf{b_2}'$, with the same (8*S*,9*S*)-configurations as $\mathbf{b_1}$ and $\mathbf{b_2}$ (Table 3), were synthesized and selected as a comparative trial (see ESI†). As shown in Table 3 (entries 1 and 2), it was found that the catalysts $\mathbf{b_1}'$ and $\mathbf{b_2}'$ afforded the various α-alkylation products with disappointing enantioselectivities (14–54% ee) in moderate to good yields (62–86%). Furthermore, when the amino functional group (–NH_2) in $\mathbf{b_2}$ was replaced by aminomethyl (–$NHCH_3$) and carbamate (–$NCO_2C(CH_3)_3$), the catalyst **e** bearing a secondary amine moiety only produced *tert*-butyl 3-phenyl-2-(diphenylmethyleneamino)propanoate with low enantioselectivity (56% ee) in 45% yield (entry 3), and $\mathbf{2b_2}$ with a carbamate moiety ($NHCO_2C(CH_3)_3$) exhibited no catalytic activity, owing to the acidity of the remaining hydrogen on the nitrogen atom (entry 4). Therefore, it was confirmed that the primary amino functional group (–NH_2) in $\mathbf{b_2}$ at the 9-position played a key role in controlling the stereochemical course and the yield of the reaction.

Based on the prominent role of the primary amino group in controlling the catalytic process and the mechanism never having been reported, a possible catalytic mechanism of the (8*S*,9*S*)-9-amino-(9-deoxy)cinchonidine-derived ammonium

Table 3 The enantioselective benzylation of *N*-(diphenylmethylene) glycine *tert*-butyl ester catalyzed by $\mathbf{b_1}'$, $\mathbf{b_2}'$, **e** and $\mathbf{2b_2}$ [a]

Entry	Product	Catalyst	Yield[b] (%)	% ee[c]
1	**3**		68	26
	4		69	14
	10		62	22
	11		65	20
2	**3**		86	54
	4		85	53
	10		83	45
	11		81	45
3			45	56.2
4			—	—

[a] Reaction conditions: *N*-(diphenylmethylene)glycine *tert*-butyl ester (0.1 mmol), −40 °C, 2 mL ether, 0.4 mL 50% aq. KOH, 10 mol% catalyst, 12 h. [b] Isolated yield. [c] Determined by chiral HPLC with Daicel Chiralpak OD-H column.



Scheme 2 The possible catalytic mechanism of the (8*S*,9*S*)-9-amino-(9-deoxy)cinchona alkaloid-derived *N*-benzyl ammonium salt $\mathbf{b_2}$.

salt $\mathbf{b_2}$ was conjectured, which is depicted in Scheme 2. The first step was the interfacial deprotonation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with base (KOH) to produce the corresponding metal enolate. Subsequently, a chiral lipophilic onium enolate **m** with an –N–H···N intramolecular hydrogen bond was generated through the fast ion-exchange of the enolate anion with the catalyst $\mathbf{b_2}$. The intermediate **m** could go deep into the organic phase and result in the improved yield for α-alkylation. Meanwhile, the intermediate **m** could shield one of the two enantiotopic faces of the enolate anion and thus achieve the aim of controlling the stereochemical course. With the hydroxyl (–OH), secondary amino ($-NHCH_3$) and carbamate ($-NCO_2C(CH_3)_3$) groups, instead of the primary amino group ($-NH_2$), the formation of an intramolecular hydrogen bond in the intermediate **m** could be retarded and result in a weakened enantioselectivity and yield. Finally, the nucleophilic substitution with an alkyl halide afforded the optically active α-alkylation product with the concomitant regeneration of the catalyst $\mathbf{b_2}$ (H_2N-Q*$^+X^-$).

Conclusion

In summary, we developed a family of novel 9-amino-(9-deoxy) cinchona alkaloid-derived *N*-benzyl ammonium salts with different substituents and configurations by the transformation of the 9-hydroxyl into a 9-amino functional group. Among them, (8*S*,9*S*)-9-amino-(9-deoxy)cinchonidine-derived ammonium salts with a (8*S*,9*S*)-configuration and *N*-[3,5-bis (trifluoromethyl)benzyl] group could achieve the same excellent yields and enantioselectivities as the third generation of cinchona alkaloid-derived phase-transfer catalysts in the enantioselective alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester. Furthermore, it was confirmed that the primary amino functional group ($-NH_2$) played a key role in controlling the stereochemistry of the catalytic reaction and the yield.

Experimental

General methods

All commercially available chemicals were used without further purification. Four 9-amino-(9-deoxy)-*epi*-cinchona alkaloids **1a–d** were synthesized according to the references and their identities were ascertained by ^{1}H and ^{13}C NMR.[10]

TLC, where applicable, was performed on pre-coated aluminium-backed plates and spots were made visible by using UV fluorescence (λ = 254 nm). The melting points were determined with an X-4 binocular microscope melting-point apparatus (Beijing Tech Instruments Co., Beijing, China) and the thermometer was not calibrated. Fourier transform infrared spectra were recorded on a Perkin-Elmer Model GX Spectrometer using a KBr pellet method with polystyrene as a standard. Low-resolution mass spectrometry (MS) was performed on a mass spectrometer (Brucker Daltonics, USA, Brucker Co.) with a HCT ultra ion trap. High resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS spectrometer using electrospray ionization (ESI). ^{1}H and ^{13}C NMR spectra

were obtained using a Bruker AV-300 NMR instrument at 300.1 and 75.0 MHz respectively, in which all of the chemical shifts were reported downfield in ppm relative to the hydrogen and carbon resonances of TMS and chloroform-d_1, respectively. Optical rotations were measured on a Perkin-Elmer 343plus polarimeter, concentrations (c) were given in g per 100 mL of solution. The enantioselectivities were determined by chiral HPLC analysis (Daicel Chiralpak OD-H or Phenomenex Lux 5u Amylose-2; hexane–dioxane = 95 : 5; flow rate: 0.5 mL min^{-1}; 25 °C; 254 nm). The absolute configuration was determined by the comparison of the HPLC retention time with the reported samples. C, H and N elemental analysis was performed using a FLASHEA1112 automatic elemental analyzer instrument (Italy).

General procedure for synthesizing the *N*-Boc-9-amino-(9-deoxy)-*epi*-cinchona alkaloids 2a–d

A THF solution (20 mL) containing the 9-amino-(9-deoxy)-*epi*-cinchona alkaloid **1a** (1.47 g, 5.0 mmol) was added to a 100 mL round-bottom flask and cooled to 0–5 °C. Subsequently, the THF solution (20 mL) containing Boc_2O (1.31 g, 6.0 mmol) was added dropwise and stirred at 0–5 °C for 6 h. After the solvent was evaporated under reduced pressure, the residue was subjected to flash column chromatography by gradient elution with $CHCl_3$–CH_3OH (v/v = 60/1→30/1→15/1→5/1) to obtain the pale yellow and oily liquid **2a**.

2a: 1.7 g, 86%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.88 (d, ^3J = 4.5 Hz, 1H), 8.33 (s, 1H), 8.12 (d, ^3J = 8.4 Hz, 1H), 7.71 (t, ^3J = 7.1 Hz, 1H), 7.58 (t, ^3J = 7.1 Hz, 1H), 7.51 (s, 1H), 6.18 (s, 1H), 5.97–5.86 (m, 1H), 5.19–5.10 (m, 3H), 3.18–2.87 (m, 5H), 2.36–2.28 (m, 1H), 1.64 (s, 1H), 1.56–1.47 (m, 2H), 1.34–1.11 (m, 9H), 0.93–0.84 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 155.2, 149.7, 148.2, 147.2, 139.9, 130.0, 128.6, 127.1, 126.0, 123.0, 118.9, 114.5, 79.2, 60.1, 55.2, 48.8, 46.8, 38.9, 27.8, 27.1, 26.2, 24.7.

2b: 1.8 g, 91%, mp 181–183 °C; ^{1} H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.88 (d, ^3J = 4.1 Hz, 1H), 8.37 (d, ^3J = 6.8 Hz, 1H), 8.12 (d, ^3J = 8.3 Hz, 1H), 7.70 (t, ^3J = 7.0 Hz, 1H), 7.58 (t, ^3J = 7.6 Hz, 1H), 7.48 (d, ^3J = 3.6 Hz, 1H), 6.09 (s, 1H), 5.72–5.60 (m, 1H), 5.12–4.88 (m, 3H), 3.28–2.64 (m, 5H), 2.27 (s, 1H), 1.63 (s, 3H), 1.40–1.27 (m, 9H), 0.97–0.91 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 155.5, 150.0, 148.4, 141.6, 141.2, 130.3, 128.9, 127.4, 126.4, 123.2, 118.3, 114.4, 79.5, 59.7, 55.8, 42.5, 40.7, 39.5, 28.1, 27.8, 27.3, 25.6; FT-IR (KBr) cm^{-1}: 3447, 2975, 1717, 1630, 1172.

2c: 1.6 g, 83%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.60 (d, ^3J = 4.3 Hz, 1H), 7.90 (d, ^3J = 7.1 Hz, 1H), 7.44 (s, 1H), 7.33 (d, ^3J = 3.5, 1H), 7.26–7.22 (m, 2H), 5.95 (s, 1H), 5.86–5.75 (m, 1H), 5.04–4.85 (m, 3H), 3.84 (s, 3H), 2.99–2.76 (m, 5H), 2.33–2.28 (m, 1H), 1.53 (s, 1H), 1.41–1.30 (m, 2H), 1.24–1.14 (m, 9H), 0.94–0.78 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 157.5, 155.4, 147.5, 144.5, 140.3, 131.6, 128.2, 121.7, 119.0, 114.7, 111.4, 101.1, 79.5, 77.2, 60.3, 55.4, 49.1, 46.9, 39.0, 28.1, 27.2, 26.4, 25.1.

2d: 1.8 g, 87%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.72 (d, ^3J = 4.5 Hz, 1H), 8.02 (d, ^3J = 9.2 Hz, 1H), 7.63 (s, 1H), 7.38 (d, ^3J = 2.4, 1H), 7.35 (d, ^3J = 2.6 Hz, 1H), 5.94 (s, 1H), 5.74–5.63 (m, 1H), 4.98–4.90 (m, 3H), 3.96 (s, 3H), 3.29–2.52 (m, 7H), 2.28 (s, 1 H), 1.64–1.60 (m, 2 H), 1.34–1.26 (m, 9H), 0.98–0.91 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 157.5, 155.4, 147.5, 147.2, 144.6, 141.2, 131.7, 131.3, 121.3, 120.4, 114.5, 101.8, 79.5, 77.2, 55.9, 55.5, 49.4, 40.8, 39.5, 28.1, 27.9, 27.3, 25.9.

General procedure for synthesizing the *N*-Boc-9-amino-(9-deoxy)-*epi*-cinchona alkaloid-derived ammonium salts $3a_1$–d_1 and $3a_2$–d_2

A toluene solution (4 mL) containing the *N*-Boc-9-amino-(9-deoxy)-*epi*-cinchona alkaloid **2a** (0.20 g, 0.51 mmol) and 4-trifluoromethyl benzyl bromide (0.12 g, 0.51 mmol) or 3,5-bis(trifluoromethyl)benzyl bromide (0.16 g, 0.51 mmol) was added to a 50 mL round-bottom flask and stirred at 65 °C for 12 h. During this process, a white solid gradually separated out. The white precipitate was filtered, washed with toluene (3 mL × 2) and dried under reduced pressure to afford the pure *N*-Boc-9-amino-(9-deoxy)-*epi*-cinchona alkaloid-derived ammonium salt $\mathbf{3a_1}$ or $\mathbf{3a_2}$.

$\mathbf{3a_1}$: 0.19 g, 58%, mp 154–156 °C; ^{1}H NMR (300.1 MHz, CD_3OD, TMS) δ 8.82 (d, ^3J = 4.0 Hz, 1H), 8.48 (d, ^3J = 6.7 Hz, 1H), 8.10 (d, ^3J = 8.1 Hz, 1H), 7.84–7.67 (m, 7H), 6.24 (d, ^3J = 8.5 Hz, 1H), 5.63–5.48 (m, 1H), 5.19–4.96 (m, 3H), 4.78–4.64 (m, 2H), 3.93–3.72 (m, 2H), 3.72–3.55 (m, 1H), 3.42–3.15 (m, 2H), 2.67 (s, 1H), 2.04–1.71 (m, 3H), 1.48 (s, 1H), 1.17 (s, 10H); ^{13}C NMR (75.0 MHz, CD_3OD, TMS) δ 153.7, 148.3, 146.1, 144.6, 134.1, 132.5, 130.6 (q, $^1J_{C-F}$ = 32.9 Hz, CF_3), 130.0, 128.5, 127.5, 126.2, 124.0, 124.3 (q, $^2J_{C-F}$ = 3.7 Hz), 124.0, 121.6, 120.4, 118.1, 115.1, 78.9, 76.4, 67.9, 61.8, 55.0, 50.7, 35.0, 27.7, 25.4, 24.5, 21.3; FT-IR (cm^{-1}): 3446 (N–H), 2929 (C–H), 1707 (C═O), 1570 (C═C).

$\mathbf{3a_2}$: 0.16 g, 46%, mp 202–204 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.94 (d, ^3J = 4.4 Hz, 1H), 8.48 (d, ^3J = 7.7 Hz, 1H), 8.22 (s, 2H), 8.12 (d, ^3J = 4.6 Hz, 1H), 8.03 (s, 1 H), 7.79–7.67 (m, 3H), 6.47–6.18 (m, 3H), 5.69–5.57 (m, 1H), 5.35–5.18 (m, 2H), 4.96–4.86 (m, 2H), 4.09–4.03 (m, 1H), 3.51–3.43 (m, 1H), 3.06–2.99 (m, 2H), 2.60–2.55 (m, 1H), 2.24–2.14 (m, 1H), 1.86 (s, 2H), 1.52–1.43 (m, 1H), 1.28 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 155.4, 150.9, 148.2, 144.9, 134.5, 133.6, 132.8 (q, ^1J = 33.9 Hz, CF_3), 130.6, 130.3, 129.5, 127.5, 126.6, 126.2, 124.7 (q, ^2J = 2.1 Hz), 124.3, 122.6, 120.3, 118.8, 81.0, 67.5, 62.5, 55.4, 52.5, 48.6, 37.4, 28.0, 27.3, 26.3, 23.6; FT-IR (cm^{-1}): 3452 (N–H), 1711 (C═O), 1628 (C═C).

$\mathbf{3b_1}$: 0.20 g, 62%, mp 168–170 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.89 (d, ^3J = 4.5 Hz, 1H), 8.17 (d, ^3J = 8.3 Hz, 1H), 8.09–8.05 (m, 2H), 7.69–7.58 (m, 6H), 6.88 (d, ^3J = 9.4 Hz, 1H), 6.23–5.99 (m, 3H), 5.82–5.71 (m, 1H), 5.21–5.10 (m, 2H), 4.89 (d, ^3J = 12.9 Hz, 1H), 4.35–4.25 (m, 2H), 3.35–3.16 (m, 2H), 2.48–2.42 (m, 1H), 2.18 (s, 2H), 2.02–1.87 (m, 3H), 1.23 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 155.4, 151.1, 148.6, 143.9, 134.8, 134.0, 132.7 (q, $^1J_{C-F}$ = 33.1 Hz, CF_3), 131.5, 130.9, 129.7, 127.9, 126.2 (q, $^2J_{C-F}$ = 3.5 Hz), 125.7, 125.1, 122.2, 120.1, 119.1, 81.4, 67.5, 64.5, 59.1, 50.3, 49.1, 37.6, 28.1, 27.4, 26.7, 24.8; FT-IR (cm^{-1}): 3447 (N–H), 1713 (C═O), 1567 (C═C).

3b$_2$: 0.19 g, 52%, mp 168–170 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.98 (d, ^3J = 4.5 Hz, 1H), 8.31 (d, ^3J = 8.2 Hz, 1H), 8.21 (d, ^3J = 4.5 Hz, 1H), 8.15 (d, ^3J = 8.5 Hz, 1H), 8.10 (s, 2H), 8.03 (s, 1H), 7.79–7.67 (m, 2H), 7.08 (d, ^3J = 8.7 Hz, 1H), 6.45–6.40 (m, 1H), 6.32–6.18 (m, 2H), 5.94–5.83 (m, 1H), 5.34–5.23 (m, 3H), 4.54–4.43 (m, 1H), 3.45 (t, ^3J = 10.5 Hz, 1H), 3.19–3.09 (m, 1H), 2.63–2.58 (m, 1H), 2.27 (s, 2H), 2.15–2.02 (m, 1H), 1.35 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 155.5, 151.1, 148.5, 143.9, 134.6, 133.6, 132.9 (q, $^1J_{C-F}$ = 33.8 Hz, CF_3), 130.9, 130.3, 129.6, 127.8, 125.7, 124.5 (q, $^2J_{C-F}$ = 3.4 Hz), 122.2, 120.7, 120.1, 119.3, 81.6, 67.6, 63.5, 59.4, 50.6, 49.1, 37.6, 28.0, 27.1, 26.8, 24.7; FT-IR (cm^{-1}): 3445 (N–H), 1712 (C═O), 1628 (C═C).

3c$_1$: 0.17 g, 53%, mp 172–174 °C; ^{1}H NMR (300.1 MHz, CD_3OD, TMS) δ 8.66 (d, ^3J = 4.3 Hz, 1H), 7.91 (d, ^3J = 9.2 Hz, 1H), 7.81 (s, 4H), 7.63 (s, 1H), 7.59 (d, ^3J = 4.5 Hz, 1H), 7.42 (d, ^3J = 9.2 Hz, 1H), 6.12 (d, ^3J = 9.6 Hz, 1H), 5.72–5.63 (m, 1H), 5.27–5.12 (m, 2H), 4.98–4.94 (m, 1H), 4.80–4.71 (m, 2H), 4.00 (s, 4H), 3.84–3.69 (m, 2H), 3.31–3.27 (m, 1H), 2.63 (s, 1H), 2.00–1.94 (m, 1H), 1.82 (s, 2H), 1.67–1.60 (m, 1H), 1.24 (s, 9H), 1.18 (s, 1H); ^{13}C NMR (75.0 MHz, CD_3OD, TMS) δ 159.1, 155.7, 147.0, 144.3, 143.8, 136.2, 134.1, 132.1 (q, $^1J_{C-F}$ = 32.7 Hz, CF_3), 131.6, 130.4, 127.5, 125.8 (q, $^2J_{C-F}$ = 3.8 Hz), 122.7, 121.9, 119.6, 116.5, 101.1, 80.6, 69.0, 63.8, 56.6, 55.1, 52.5, 48.9, 36.5, 27.5, 27.0, 25.7, 23.1; FT-IR (cm^{-1}): 3453 (N–H), 1710 (C═O), 1621 (C═C).

3c$_2$: 0.15 g, 43%, mp 175–177 °C; ^{1}H NMR (300.1 MHz, CD_3OD, TMS) δ 8.66 (d, ^3J = 4.5 Hz, 1H), 8.31 (s, 2H), 8.15 (s, 1H), 7.91 (d, ^3J = 9.2 Hz, 1H), 7.65 (d, ^3J = 4.8 Hz, 2H), 7.42 (d, ^3J = 7.8 Hz, 1 H), 6.12 (d, ^3J = 9.4 Hz, 1H), 5.70–5.60 (m, 1H), 5.25–5.10 (m, 3H), 4.92–4.87 (m, 1H), 4.00 (s, 5H), 3.70–3.61 (m, 1H), 3.35–3.29 (m, 1H), 2.63 (s, 1H), 2.07–1.63 (m, 4H), 1.22 (s, 10H); ^{13}C NMR (75.0 MHz, CD_3OD, TMS) δ 159.0, 155.7, 147.1, 144.2, 143.8, 136.0, 133.8, 132.3 (q, $^1J_{C-F}$ = 33.7 Hz, CF_3), 130.5, 128.4, 127.4, 124.8, 124.3 (q, $^2J_{C-F}$ = 4.1 Hz), 122.6, 121.2, 119.9, 116.6, 101.0, 80.6, 69.4, 62.8, 56.3, 55.1, 52.5, 48.7, 36.5, 27.4, 27.0, 25.7, 23.0; FT-IR (cm^{-1}): 3449 (N–H), 1715 (C═O), 1622 (C═C).

3d$_1$: 0.19 g, 60%, mp 182–184 °C; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.72 (d, ^3J = 4.4 Hz, 1H), 7.99–7.96 (m, 2H), 7.72 (s, 4H), 7.51 (s, 1H), 7.36 (d, ^3J = 7.1 Hz, 1H), 6.95 (d, ^3J = 8.3 Hz, 1H), 6.20–6.18 (m, 1H), 6.12–6.02 (m, 1H), 5.30–5.18 (m, 2H), 4.39–4.19 (m, 3H), 3.99 (s, 3H, OCH_3), 3.49–3.09 (m, 3H), 2.84 (s, 1H), 2.58–2.51 (m, 1H), 2.21–1.88 (m, 5H), 1.33 (s, 9H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 158.6, 155.3, 147.9, 144.5, 141.8, 134.5, 133.7, 132.4 (q, $^1J_{C-F}$ = 32.3 Hz, CF_3), 131.8, 131.3, 126.7, 126.0 (q, $^2J_{C-F}$ = 3.7 Hz), 122.1, 121.3, 119.7, 118.8, 100.2, 81.1, 67.3, 64.5, 59.0, 55.5, 50.8, 49.0, 37.3, 27.9, 27.3, 26.5, 24.5; FT-IR (cm^{-1}): 3442 (N–H), 1692 (C═O), 1590 (C═C).

3d$_2$: 0.17 g, 49%, mp 215–217 °C; ^{1} H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.82 (d, ^3J = 4.3 Hz, 1H), 8.08–8.04 (m, 5H), 7.49 (s, 1H), 7.41 (d, ^3J = 7.0 Hz, 1H), 6.73 (d, ^3J = 9.1 Hz, 1H), 6.50 (s, 1H), 6.16–6.09 (m, 1H), 5.94–5.82 (m, 1H), 5.36–5.25 (m, 3H), 4.51 (s, 2H), 4.01 (s, 3H, OCH_3), 3.50–3.43 (m, 1H), 3.20–3.10 (m, 1H), 2.65–2.57 (m, 1H), 2.28–1.94 (m, 5H), 1.38 (s, 9H); ^{13} C NMR (75.0 MHz, $CDCl_3$, TMS) δ 158.7, 155.4, 148.2, 144.6, 141.6, 134.1, 133.3, 132.8 (q, $^1J_{C-F}$ = 33.9 Hz, CF_3), 132.0, 130.1, 126.5, 124.4 (q, $^2J_{C-F}$ = 3.0 Hz), 124.1, 122.1, 120.4, 119.7, 119.2, 100.0, 81.6, 67.2, 63.3, 59.1, 55.5, 50.9, 49.0, 37.3, 29.4, 27.8, 26.6, 24.5; FT-IR (cm^{-1}): 3447 (N–H), 1719 (C═O), 1589 (C═C).

General procedure of 9-amino-(9-deoxy)-*epi*-cinchona alkaloid-derived ammonium salts a_1–d_1 and a_2–d_2

The CH_2Cl_2 solution (4 mL) containing *N*-Boc-9-amino-(9-deoxy)-*epi*-cinchona alkaloid **3a$_1$** (98.0 mg, 0.16 mmol) and TFA (0.36 g, 3.2 mmol) was added to a 50 mL round-bottom flask and stirred at room temperature for 3 h. The organic solvents were removed under reduced pressure. The residues were adjusted to pH = 8–9 by aqueous ammonia and extracted by CH_2Cl_2 (2 mL × 3). After the combined organic phases were evaporated under reduced pressure, the residue was subjected to flash silica column chromatography with $CHCl_3$–CH_3OH (v/v = 60/1→30/1→15/1→5/1) mixtures as the eluents to afford the pale yellow solid **a$_1$** (75 mg, 93%).

a$_1$: 75.1 mg, 93%, mp 153–155 °C; $[\alpha]_D^{20}$ = +16.2 (*c* = 1.16, $CHCl_3$); ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.80 (d, ^3J = 4.6 Hz, 1H), 8.48 (d, ^3J = 8.1 Hz, 1H), 8.00 (d, ^3J = 8.0 Hz, 1H), 7.87–7.67 (m, 7H), 5.63–5.49 (m, 2H), 5.28–5.03 (m, 3H), 4.81 (s, 2H), 4.52–4.49 (m, 1H), 3.95–3.76 (m, 3H), 3.66–3.58 (m, 1H), 3.16–3.13 (m, 2H), 2.57–2.50 (m, 1H), 1.95–1.76 (m, 2H), 1.68 (s, 1H), 1.51–1.42 (m, 1H), 1.22–1.11 (m, 1H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 150.3, 148.2, 147.6, 134.8, 134.1, 132.7, 131.7 (q, $^1J_{C-F}$ = 33.1 Hz, CF_3), 130.5, 129.5, 127.5, 125.3, 124.7, 124.0, 121.1, 119.3, 118.3, 71.9, 64.4, 55.4, 51.7, 49.0, 37.5, 27.5, 26.8, 23.6; FT-IR (cm^{-1}): 3444, 3384 (N–H), 1571 (C═C); Mass (MS): *m*/*z* 532.4 $[M + H]^+$; Anal. calcd for $C_{27}H_{29}BrF_3N_3$: C 60.91, H 5.49, N 7.89; Found: C 60.89, H 5.42, N 7.82%.

a$_2$: 72.0 mg, 86%, mp 132–134 °C; $[\alpha]_D^{20}$ = +9.2 (*c* = 0.84, $CHCl_3$); ^{1}H NMR (300.1 MHz, CD_3OD, TMS) δ 8.81 (d, ^3J = 4.7 Hz, 1H), δ 8.42 (d, ^3J = 8.2 Hz, 1H), 8.30 (s, 2H), 8.10 (s, 1H), 8.02 (d, ^3J = 7.7 Hz, 3H), 7.79–7.65 (m, 3H), 5.64–5.53 (m, 1H), 5.47–5.33 (m, 2H), 5.21–5.04 (m, 2H), 4.46–4.41 (m, 1H), 3.93–3.79 (m, 2H), 3.58–3.50 (m, 1H), 3.29–3.19 (m, 2H), 2.58–2.54 (m, 1H), 1.97–1.83 (m, 2H), 1.68 (s, 1H), 1.55–1.45 (m, 1H), 1.25–1.17 (m, 1H); ^{13}C NMR (75.0 MHz, CD_3OD, TMS) δ 148.4, 147.8, 146.2, 134.2, 132.3, 130.5 (q, $^1J_{C-F}$ = 33.5 Hz, CF_3), 129.9, 128.3, 127.5, 126.9, 126.0, 124.3, 123.3, 122.3 (q, $^2J_{C-F}$ = 3.6 Hz), 121.6, 119.7, 114.9, 71.0, 63.2, 59.4, 54.7, 50.4, 35.2, 25.7, 24.8, 21.4; FT-IR (cm^{-1}): 3444, 3358 (N–H), 1571 (C═C); Mass (MS): *m*/*z* 602.1 $[M + H]^+$; Anal. calcd for $C_{28}H_{28}BrF_6N_3$: C 56.01, H 4.70, N 7.00; Found: C 55.89, H 4.54, N 6.92%.

b$_1$: 73.8 mg, 92%, mp 142–144 °C; $[\alpha]_D^{20}$ = +37.4 (*c* = 0.92, $CHCl_3$); ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.81 (d, ^3J = 4.5 Hz, 1H), 8.74 (s, 1H), 8.11 (d, ^3J = 9.5 Hz, 1H), 8.01 (d, ^3J = 6.9 Hz, 2H), 7.73 (d, ^3J = 4.4 Hz, 2H), 7.57 (s, 1H), 7.41 (d, ^3J = 8.0 Hz, 2H), 5.97–5.86 (m, 1H), 5.82–5.66 (m, 3H), 5.20–5.12 (m, 2H), 5.00 (s, 1H), 4.77 (s, 1H), 3.75–3.45 (m, 3H), 2.61 (s, 3H), 1.06 (s, 1H), 1.89–1.77 (m, 3H); ^{13}C NMR (75.0 MHz,

$CDCl_3$, TMS) δ 150.5, 149.7, 148.6, 135.6, 134.2, 132.6, 131.9 (q, $^1J_{C-F}$ = 32.6 Hz, CF_3), 130.6, 129.7, 128.7, 127.8, 125.5 (q, $^2J_{C-F}$ = 3.7 Hz), 125.1, 123.6, 121.5, 118.3, 68.9, 64.5, 60.3, 51.5, 49.7, 37.5, 28.1, 27.0, 26.8, 24.9; FT-IR (cm^{-1}): 3447, 3387 (N–H), 1571 (C═C); HRMS: *m*/*z* calcd for $C_{27}H_{29}F_3N_3^+$ 452.2308; found: 452.2308; Anal. calcd for $C_{27}H_{29}BrF_3N_3$: C 60.91, H 5.49, N 7.89; Found: C 60.88, H 5.46, N 7.86%.

b_2: 74.9 mg, 89%, mp 144–146 °C; $[\alpha]_D^{20}$ = +79.1 (*c* = 0.54, $CHCl_3$); ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.80 (d, ^3J = 4.3 Hz, 1H), 8.66 (s, 1H), 8.56 (s, 1H), 8.06 (d, ^3J = 8.2 Hz, 1H), 7.86 (s, 1H), 7.71–7.66 (m, 2H), 7.35 (s, 1H), 6.13 (s, 1H), 5.91 (d, ^3J = 11.2 Hz, 1H), 5.69 (s, 1H), 5.57–5.46 (m, 1H), 5.16 (s, 1H), 5.03–4.97 (m, 2H), 4.23–4.05 (m, 3H), 2.93–2.73 (m, 5H), 2.18–1.84 (m, 3H), 1.77–1.66 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 150.5, 148.8, 148.3, 135.1, 134.1, 132.2 (q, $^1J_{C-F}$ = 33.6 Hz, CF_3), 131.6, 131.5, 130.5, 129.9, 128.0, 125.6, 124.5, 123.9 (q, $^2J_{C-F}$ = 3.5 Hz), 123.1, 120.9, 118.3, 117.7, 67.3, 63.0, 61.3, 51.9, 51.3, 37.1, 26.7, 26.3, 25.0; FT-IR (cm^{-1}): 3446, 3369 (N–H), 1571 (C═C); HRMS: *m*/*z* calcd for $C_{28}H_{28}F_6N_3^+$ 520.2200; found: 520.2182; Anal. calcd for $C_{28}H_{28}BrF_6N_3$: C 56.01, H 4.70, N 7.00; Found: C 55.87, H 4.64, N 6.90%.

c_1: 79.3 mg, 95%, mp 155–157 °C; $[\alpha]_D^{20}$ = +4.5 (*c* = 0.92, $CHCl_3$); ^{1}H NMR (300.1 MHz, CD_3OD, TMS) δ 8.64 (d, ^3J = 4.7 Hz, 1H), 7.90–7.76 (m, 5H), 7.63 (d, ^3J = 4.7 Hz, 1H), 7.42 (d, ^3J = 9.2 Hz, 1H) 5.68–5.57 (m, 1H), 5.47 (d, ^3J = 8.7 Hz, 1H), 5.33 (d, ^3J = 13.3 Hz, 1H), 5.18–5.06 (m, 3H), 4.45–4.37 (m, 1H), 4.01 (s, 3H, OCH_3), 3.96–3.61 (m, 3H), 3.16–3.13 (m, 3H), 2.58–2.51 (m, 1H), 1.98–1.76 (m, 2H), 1.71 (s, 1H), 1.52–1.43 (m, 1H), 1.25–1.18 (m, 1H); ^{13}C NMR (75.0 MHz, CD_3OD, TMS) δ 157.4, 147.7, 145.7, 142.3, 134.6, 132.7, 131.1, 130.2 (q, $^1J_{C-F}$ = 32.4 Hz, CF_3), 128.9, 125.6, 124.0 (q, $^2J_{C-F}$ = 3.7 Hz), 120.9, 120.5, 118.4, 114.9, 99.8, 70.9, 64.1, 54.9, 54.0, 50.5, 48.9, 35.2, 25.8, 24.7, 21.5; FT-IR (cm^{-1}): 3444, 3354 (N–H), 1540 (C═C); Mass (MS): *m*/*z* 561.2 $[M + H]^+$; Anal. calcd for $C_{28}H_{31}BrF_3N_3O$: C 59.79, H 5.56, N 7.47; Found: C 59.67, H 4.51, N 7.36%.

c_2: 76.0 mg, 89%, mp 161–163 °C; $[\alpha]_D^{20}$ = +4.1 (*c* = 1.12, CH_3OH); ^{1}H NMR (300.1 MHz, CD_3OD, TMS) δ 8.71 (d, ^3J = 4.7 Hz, 1H), 8.38 (s, 2H), 8.18 (s, 1H), 7.90 (d, ^3J = 9.2 Hz, 1H), 7.63 (d, ^3J = 4.8 Hz, 2H), 7.42 (d, ^3J = 6.8 Hz, 1H), 5.69–5.57 (m, 1H), 5.49–5.44 (m, 2H), 5.22–5.07 (m, 3H), 4.46–4.37 (m, 1H), 4.08 (s, 3H, OCH_3), 3.88–3.81 (m, 1H), 3.61–3.49 (m, 1H), 3.29–3.27 (m, 3H), 2.62–2.56 (m, 1H), 1.97–1.78 (m, 2H), 1.55 (s, 1H), 1.50–1.46 (m, 1H), 1.25–1.19 (m, 1H); ^{13}C NMR (75.0 MHz, CD_3OD, TMS) δ 158.9, 149.0, 147.2, 143.9, 136.0, 133.9, 132.1 (q, $^1J_{C-F}$ = 33.5 Hz, CF_3), 131.4, 130.5, 127.0, 124.9, 123.8 (q, $^2J_{C-F}$ = 3.7 Hz), 122.4, 121.2, 119.8, 116.4, 101.2, 72.6, 64.8, 56.8, 56.2, 55.4, 52.1, 36.7, 27.3, 26.2, 23.0; FT-IR (cm^{-1}): 3446, 3381 (N–H), 1540 (C═C); Mass (MS): *m*/*z* 631.2 $[M + H]^+$; Anal. calcd for $C_{29}H_{30}BrF_6N_3O$: C 55.25, H 4.80, N 6.66; Found: C 55.17, H 4.75, N 6.60%.

d_1: 73.4 mg, 88%, mp 146–148 °C; $[\alpha]_D^{20}$ = +48.5 (*c* = 0.74, $CHCl_3$); ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.62 (d, ^3J = 4.1 Hz, 1H), 8.04 (d, ^3J = 7.1 Hz, 2H), 7.97 (d, ^3J = 8.8, 2H), 7.44 (d, ^3J = 6.4 Hz, 2H), 7.38 (d, ^3J = 9.2, 2H), 5.91 (s, 2H), 5.82–5.77 (m, 1H), 5.69–5.65 (m, 1H), 5.18–5.11 (m, 3H), 4.53 (s, 1H), 4.18 (s, 3H, OCH_3), 3.85 (s, 1H), 3.70 (s, 1H), 3.33 (s, 1H), 2.84 (s, 3H), 2.68 (s, 1H), 2.11 (s, 1H), 1.92 (s, 1H), 1.81–1.74 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 159.0, 147.6, 144.8, 135.5, 134.1, 132.6, 132.2, 132.0 (q, $^1J_{C-F}$ = 29.2 Hz), 131.8, 126.8, 125.6 (q, $^2J_{C-F}$ = 3.5 Hz), 125.1, 122.8, 121.5, 118.2, 118.1, 101.4, 68.3, 64.2, 60.6, 57.0, 51.6, 50.3, 37.4, 29.6, 26.8, 25.0; FT-IR (cm^{-1}): 3445, 3386 (N–H), 1559 (C═C); HRMS: *m*/*z* calcd for $C_{28}H_{31}F_3N_3O^+$ 482.2414; found: 482.2414; Anal. calcd for $C_{28}H_{31}BrF_3N_3O$: C 59.79, H 5.56, N 7.47; Found: C 59.77, H 5.54, N 7.44%.

d_2: 74.1 mg, 87%, mp 158–160 °C; $[\alpha]_D^{20}$ = +82.0 (*c* = 0.40, $CHCl_3$); ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 8.71 (d, ^3J = 4.1 Hz, 1H), 8.99 (d, ^3J = 9.0 Hz, 1H), 7.91 (d, ^3J = 10.4 Hz, 2H), 7.38 (d, ^3J = 9.0 Hz, 1H), 7.29 (s, 1H), 6.18 (d, ^3J = 12.5 Hz, 1H), 5.95 (d, ^3J = 12.7 Hz, 1H), 5.77 (d, ^3J = 10.2 Hz, 1H), 5.66–5.52 (m, 1H), 5.41–5.32 (m, 1H), 5.11–5.04 (m, 2H), 4.24–4.21 (m, 2H), 4.10 (m, 4H), 3.18 (s, 3H), 2.98–2.86 (m, 2H), 2.20–2.10 (m, 2H), 1.86–1.72 (m, 2H); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 159.1, 147.5, 146.7, 144.9, 135.1, 133.9, 132.2 (q, $^1J_{C-F}$ = 33.6 Hz, CF_3), 131.8, 131.6, 126.9, 124.5, 123.9 (q, $^2J_{C-F}$ = 3.5 Hz), 122.8, 120.9, 118.3, 117.6, 101.3, 67.1, 62.7, 61.4, 56.7, 51.9, 51.6, 37.1, 26.8, 26.4, 25.1; FT-IR (cm^{-1}): 3450, 3369 (N–H), 1540 (C═C); HRMS: *m*/*z* calcd for $C_{29}H_{30}F_6N_3O^+$ 550.2288; found: 550.2288; Anal. calcd for $C_{29}H_{30}BrF_6N_3O$: C 55.25, H 4.80, N 6.66; Found: C 55.19, H 4.72, N 6.59%.

Enantioselective phase-transfer alkylation

A mixture of *N*-(diphenylmethylene)glycine-*tert*-butyl ester (30 mg, 0.1 mmol) and the catalyst **b_2** (6 mg, 0.01 mmol) in ether (2 mL) was cooled to −40 °C and then 50% aqueous KOH (0.4 mL, 3.6 mmol) and benzyl bromide (20 mg, 0.12 mmol) were added. The reaction mixture was stirred at −40 °C for 12 h, extracted by ethyl acetate (10 mL × 3) and evaporated under reduced pressure. The crude product was purified by column chromatography using hexane–EtOAc (v/v = 50 : 1) as the eluent to afford the pure α-alkylation product, which was identified using NMR spectra. The data of the new α-alkylation products are shown as follows and the others are listed in the ESI.†

***tert*-Butyl 3-(3-trifluoromethylphenyl)-2-(diphenylmethyleneamino)propanoate (2).** 45.1 mg, 99%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.52 (d, ^3J = 7.0 Hz, 2H, Ph–H), 7.40–7.21 (m, 10H, Ph–H), 6.57 (d, ^3J = 6.6 Hz, 2H, Ph–H), 4.09 (dd, ^3J = 5.6 Hz, 5.6 Hz, 1H, NCH), 3.23–3.21 (m, 2H, CH_2), 1.41 (s, 9 H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 170.8, 170.3 (C═N, C═O), 139.3, 139.2, 136.1, 133.4, 133.4, 132.4, 130.5, 130.2, 130.1, 130.0, 128.6, 128.4, 128.3, 128.2, 128.1, 127.9, 127.4, 126.4 (q, $^2J_{C-F}$ = 3.7 Hz, CF_3), 125.9 (Ph), 123.0 (q, $^1J_{C-F}$ = 3.8 Hz, CF_3), 81.4 (O–C), 67.3 (NCH), 39.2 (CH_2), 27.9 (CH_3); Mass (MS): *m*/*z* 454.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 9.4 min (*R*), 10.9 min (*S*).

***tert*-Butyl 3-(2-trifluoromethylphenyl)-2-(diphenylmethyleneamino)propanoate (3).** 42.0 mg, 93%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.76 (d, ^3J = 7.1 Hz, 1H, Ph–H), 7.57–7.41

(m, 4H, Ph–H), 7.35–7.15 (m, 7H, Ph–H), 6.43 (d, ^3J = 6.4 Hz, 2H, Ph–H), 4.13 (dd, ^3J = 3.5 Hz, 1H, 3.5 Hz, NCH), 3.50–3.22 (m, 2H, CH_2), 1.39 (s, 9H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 170.7, 170.5 (C═N, C═O), 139.2, 136.8 (q, $^2J_{C–F}$ = 1.6 Hz), 136.0, 133.3, 132.4, 131.1, 130.2, 131.0, 129.6, 128.7, 128.2, 128.1, 127.9, 127.9, 127.3, 126.3, 126.0 (Ph), 125.7 (q, $^1J_{C–F}$ = 5.7 Hz, CF_3), 81.2 (O–C), 66.5 (NCH), 36.0 (CH_2), 27.9 (CH_3); Mass (MS): *m*/*z* 454.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 10.8 min (*R*), 13.5 min (*S*).

***tert*-Butyl 3-(3-fluorophenyl)-2-(diphenylmethyleneamino)-propanoate (5).** 37.9 mg, 94%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.49 (d, ^3J = 6.7 Hz, 2H, Ph–H), 7.26–7.19 (m, 7H, Ph–H), 7.08 (q, ^3J = 6.6 Hz, 1H, Ph–H), 6.79–6.62 (m, 4H, Ph–H), 6.66 (d, ^3J = 6.6 Hz, 2H, Ph–H), 4.04 (dd, ^3J = 3.8 Hz, 3.8 Hz, 1H, NCH), 3.17–3.04 (m, 2H, CH_2), 1.37 (s, 9H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 170.5, 170.4 (C═N, C═O), 164.2, 160.9, 140.8 (d, $^3J_{C–F}$ = 7.4 Hz), 139.3, 136.2, 132.3, 130.1, 130.0, 128.6, 128.3, 128.2, 128.1, 127.9, 127.5, 125.5, 125.4 (Ar and Ph), 116.4 (d, $^2J_{C–F}$ = 20.9 Hz), 112.9 (d, $^1J_{C–F}$ = 20.9 Hz), 81.2 (O–C), 67.4 (NCH), 39.2 (CH_2), 27.9 (CH_3); Mass (MS): *m*/*z* 404.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 9.8 min (*R*), 12.1 min (*S*).

***tert*-Butyl 3-(2-fluorophenyl)-2-(diphenylmethyleneamino)-propanoate (6).** 37.1 mg, 92%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.56 (d, ^3J = 7.1 Hz, 2H, Ph–H), 7.37–7.25 (m, 6H, Ph–H), 7.16–7.11 (m, 2H, Ph–H), 6.98–6.87 (m, 2H, Ph–H), 6.66 (d, ^3J = 6.6 Hz, 2H, Ph–H), 4.19 (dd, ^3J = 4.4 Hz, 4.4 Hz, 1H, NCH), 3.36–3.12 (m, 2H, CH_2), 1.44 (s, 9H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS): δ 170.6, 170.5 (C═N, C═O), 162.9, 159.7, 139.4, 136.1, 132.3, 130.1, 130.0, 128.7, 128.2, 128.2, 128.0, 128.0, 127.9, 127.9, 127.6 (C–Ph), 125.2 (d, $^3J_{C–F}$ = 15.5 Hz), 123.5 (d, $^2J_{C–F}$ = 3.5 Hz), 114.9 (d, $^1J_{C–F}$ = 21.9 Hz), 81.2 (O–C), 66.0 (NCH), 32.6 (CH_2), 27.9 (CH_3); Mass (MS): *m*/*z* 404.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 11.0 min (*R*), 13.7 min (*S*).

***tert*-Butyl 3-(3, 4-difluorophenyl)-2-(diphenylmethyleneamino)propanoate (7).** 41.7 mg, 99%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.57 (d, ^3J = 7.0 Hz, 2H, Ph–H), 7.40–7.25 (m, 6H, Ph–H), 7.02–6.73 (m, 5H, Ph–H), 4.10 (dd, ^3J = 4.7 Hz, 4.7 Hz, 1H, NCH), 3.21–3.07 (m, 2H, CH_2), 1.44 (s, 9H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 170.7, 170.3 (C═N, C═O), 148.1 (d, $^3J_{C–F}$ = 12.5 Hz), 147.3 (d, $^3J_{C–F}$ = 12.5 Hz), 139.2, 136.1, 135.3 (dd, $^1J_{C–F}$ = 5.7 Hz, F, $^2J_{C–F}$ = 3.9 Hz, F), 132.3, 130.3, 130.0, 128.6, 128.4, 128.2, 128.1, 127.9, 127.5, 125.6 (dd, $^1J_{C–F}$ = 6.0 Hz, F, $^2J_{C–F}$ = 3.6 Hz, F), 118.4 (d, $^2J_{C–F}$ = 16.8 Hz), 116.6 (d, $^2J_{C–F}$ = 16.8 Hz), 114.4 (Ar and Ph), 81.4 (O–C), 67.3 (NCH), 38.7 (CH_2), 27.9 (CH_3); Mass (MS): *m*/*z* 422.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 10.3 min (*R*), 12.3 min (*S*).

***tert*-Butyl 3-(4-methylphenyl)-2-(diphenylmethyleneamino)-propanoate (8).** 37.8 mg, 95%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.81 (d, ^3J = 7.2 Hz, 1H, Ph–H), 7.58 (d, ^3J = 7.1 Hz, 2H, Ph–H), 7.39–7.25 (m, 6H, Ph–H), 6.96 (q, ^3J = 7.9 Hz, 4H, Ph–H), 6.62 (d, ^3J = 6.6 Hz, 2H, Ph–H), 4.09 (dd, ^3J = 4.4 Hz, 4.4 Hz, 1 H, NCH), 3.23–3.07 (m, 2H, CH_2), 2.28 (s, 3H, CH_3), 1.44 (s, 9H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 170.9, 170.1 (C═N, C═O), 139.5, 137.5, 136.3, 135.5, 135.1, 132.4, 130.0, 129.6, 128.7, 128.2, 128.1, 128.0, 127.9, 127.6 (Ar and Ph), 81.0 (O–C), 68.0 (NCH), 39.1 (CH_2), 28.0 (CH_3), 21.0 (CH_3); Mass (MS): *m*/*z* 400.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 10.7 min (*R*), 13.1 min (*S*).

***tert*-Butyl 3-(3-methylphenyl)-2-(diphenylmethyleneamino)-propanoate (9).** 37.9 mg, 95%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.81 (d, ^3J = 7.2 Hz, 1H, Ph–H), 7.62–7.46 (m, 4H, Ph–H), 7.38–7.26 (m, 7H, Ph–H), 6.59 (d, ^3J = 6.5 Hz, 2H, Ph–H), 4.09 (dd, ^3J = 4.5 Hz, 4.3 Hz, 1H, NCH), 3.23–3.08 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 1.45 (s, 9H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS) δ 170.8, 170.2 (C═N, C═O), 139.5, 138.1, 137.4, 136.3, 132.4, 132.3, 130.6, 130.0, 130.0, 128.6, 128.2, 128.2, 128.1, 127.9, 127.8, 127.7, 126.8, 126.7 (Ar and Ph), 81.0 (O–C), 67.8 (NCH), 39.4 (CH_3), 28.0 (CH_2), 21.1 (CH_3); Mass (MS): *m*/*z* 400.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 10.0 min (*R*), 12.3 min (*S*).

***tert*-Butyl 3-(2-methylphenyl)-2-(diphenylmethyleneamino)-propanoate (10).** 36.7 mg, 92%; ^{1}H NMR (300.1 MHz, $CDCl_3$, TMS) δ 7.60 (d, ^3J = 7.2 Hz, 2H, Ph–H), 7.35–7.23 (m, 6H, Ph–H), 7.09–7.04 (m, 4H, Ph–H), 6.52 (d, ^3J = 4.1 Hz, 2H, Ph–H), 4.15 (dd, ^3J = 3.9 Hz, 3.9 Hz, 1 H, NCH), 3.33–3.15 (m, 2H, CH_2), 2.06 (s, 3H, CH_3), 1.39 (s, 9H, CH_3); ^{13}C NMR (75.0 MHz, $CDCl_3$, TMS): δ 171.0, 170.1 (C═N, C═O), 139.3, 136.9, 136.3, 136.2, 132.4, 131.0, 130.0, 130.0, 129.9, 128.7, 128.2, 128.1, 127.9, 127.8, 127.6, 126.3, 125.9, 125.5 (Ar and Ph), 81.0 (O–C), 66.4 (NCH), 36.7 (CH_3), 28.0 (CH_2), 19.2 (CH_3); Mass (MS): *m*/*z* 400.2 $[M + H]^+$; HPLC analysis: Daicel Chiralpak OD-H, hexane–dioxane = 95 : 5, 254 nm, flow rate = 0.5 ml min^{-1}, retention time: 10.1 min (*R*), 12.3 min (*S*).

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