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

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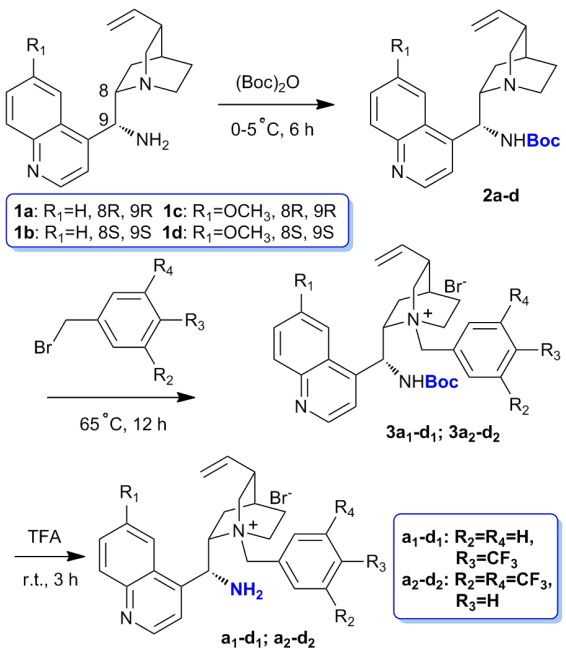
A new class of 9-amino-(9-deoxy) *cinchona* alkaloid-derived chiral phase-transfer catalysts bearing amino groups was developed by using the known cinchona alkaloids as starting materials. Due to the transformation of 9-hydroxyl group into 9-amino functional group, the catalytic performances were significantly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

Introduction

Phase-transfer catalysis (PTC) 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 condition, environmentally benign nature, and suitability for large-scale synthesis.[1] Nowadays, various natural and non-natural asymmetric phase-transfer catalysts with excelent catalytic performances, such as cinchona alkaloid-derived quarternary ammonium salts [2] and chiral *N*-spiro ammonium salts,[3] have been developed, particularly in the last 20 years. Especially, the numerous structural modifications of cinchona alkaloid-derived quarternary ammonium salts concentrated on quinuclidine nitrogen atom and 9-hydroxy group achieved excellent catalytic performance. Up to now, three successful generations of cinchona alkaloid-derived quarternary ammonium salts were 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 remarkably higher enantiomeric excess.[5] Finally, the most efficient third generation of *N*-9-anthracenylmethyl-*O*-allyl quarternary ammonium salts were developed independently by Lygo and Corey,[6] which achieved a breakthrough in the high enantioselectivity of alkylation and conjugate addition owing to the steric effect 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 high and satisfactory catalytic performance. Fortunately, two successful examples achieved the 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 *N*-benzyl substituent.[8] Recently, Dixon reported bifunctional 9-amino-(9-deoxy)-*epi*-cinchona-derived PTC catalysts bearing phase-transfer components (ammonium salts) and H-bond donor components (urea, amide and sulphonamide) through the structural modifications of 9-amino group.[9] In the enantioselective nitro-Mannich reaction of amidosulfones, the good reactivity and high stereoselectivities (up to 24:1 dr and 95% ee) were obtained under optimal conditions. In this paper, we described our efforts toward the design of a family of new 9-amino-(9-deoxy)cinchona alkaloid-derived PTC catalysts bearing primary amino group with different configurations at the 9-position and *N*-benzyl substituents (**Scheme 1**), which could achieve the similar efficient catalytic performances (92–99% and 87–96 %ee) as the third generation of *N*-9-anthracenylme-thyl-*O*-allyl quarternary ammonium salts in the benchmark enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.



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

Results and discussion

Synthesis of PTC catalyst

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 Mistunobu reaction according to the references. [10] After the primary amino group at the 9-position was protected by using Boc_2O, *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 quarternization of quinuclidine nitrogen atom using 4-(trifluoromethyl) or 3, 5-bis(trifluoromethyl)benzyl bromides, respectively in toluene at 65 ℃ for 12 h. Finally, the targeted PTC 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 *N*-Boc-amino group using TFA at room temperature for 3 h (**Scheme 1**).

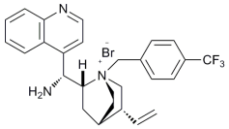
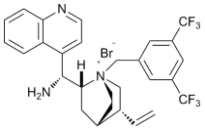
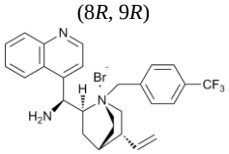
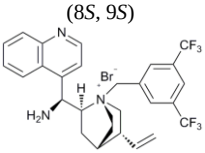
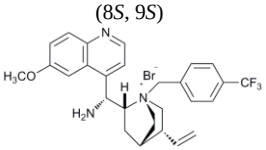
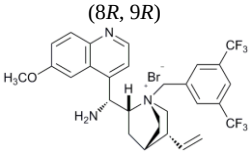
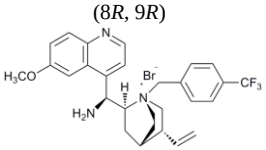
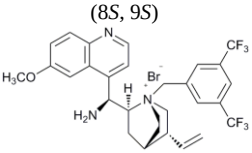
The effect of aromatic substituent and configuration on catalytic performance

Using PTC catalyst **b$_2$** as an example, the effect of solvent, temperature, used amount of catalyst and species of base on catalytic performances were investigated in detail and offered the optimum conditions: 10 mol% **b$_2$**, -40 ℃, 50% KOH and 12 h (ESI†). Thus, under these optimum conditions, the PTC 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 PTC catalysts **b$_1$**, **b$_2$**, **d$_1$** and **d$_2$** with (8*S*, 9*S*)-configurations gave the better catalytic performances including the yields (42–97%) and enantioselectivities (50–91 %ee) in ether/water biphasic system than the catalysts **a$_1$**, **a$_2$**, **c$_1$** and **c$_2$** with (8*R*, 9*R*)-configurations. It was worthy noting that the catalysts **c$_1$**, **c$_2$**, **d$_1$** and **d$_2$** (R_1 = OCH_3) produced the 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 catalysts **a$_1$–d$_1$** and **a$_2$–d$_2$** afforded good to excellent yields in toluene/water biphasic system (79–98%). Especially, the catalysts **c$_1$**, **c$_2$**, **d$_1$** and **d$_2$** (R_1 = OCH_3) afforded the improved enantioselectivities (65–79 %ee) in toluene/water biphasic system owing to their good organosolubilities in toluene (**entries 5–8**). Unfortunately, it was found the catalysts **a$_1$**, **a$_2$**, **b$_1$** and **b$_2$** (R_1 = H) gave the relatively lower enantioselectivities in toluene, although the good to excellent yields (80–98%) could be achieved. On the other hand, the modifications at the quinuclidine nitrogen atom would be effective in improving the enantioselectivity. The PTC catalysts **a$_2$–d$_2$** (R_1 = OCH_3) bearing 3, 5-bis(trifluoromethyl)benzyl moieties gave the better yields and enantioselectivities than the PTC catalysts **a$_1$-d$_1$** (R_1= H) with a 4-(trifluoromethyl)benzyl group, both in toluene/water and ether/water biphasic systems.

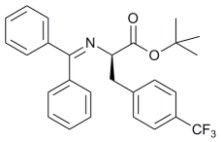
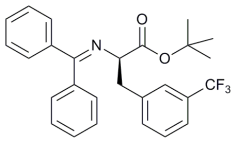
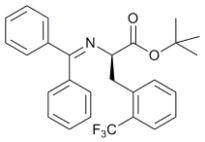
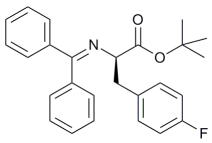
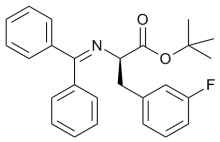
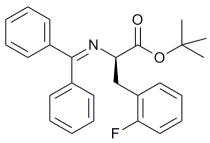
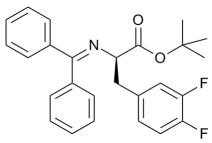
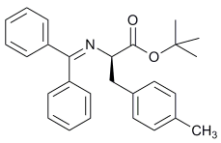
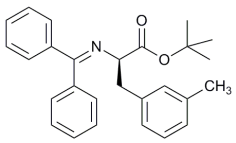
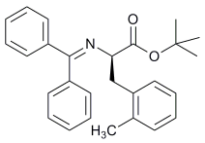
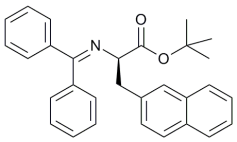
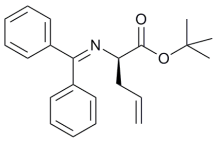
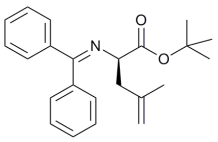
Taking into account the above mentioned considerations of the substituents attached to aromatic rings (R_1, R_2, R_3 and R_4) and the spatial configurations at 8 and 9-positions, (8*S*, 9*S*)-9-amino-(9-deoxy)cinchonidine-derived ammonium salt (**b$_2$**) bearing 3, 5-bis (trifluoromethyl) benzyl moieties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

Table 1 The benchmark enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester catalyzed by **a$_1$-d$_1$** and **a$_2$-d$_2$**[a]

Entry	Cat.	Yield (%)[b]	%ee[c]
1	 **a$_1$** (8*R*, 9*R*)	76 80[d]	23 (S) 30 (S)
2	 **a$_2$** (8*R*, 9*R*)	85 88[d]	71 (S) 67 (S)
3	 **b$_1$** (8*S*, 9*S*)	94 91[d]	50 (R) 43 (R)
4	 **b$_2$** (8*S*, 9*S*)	97 98[d]	91 (R) 85 (R)
5	 **c$_1$** (8*R*, 9*R*)	37 79[d]	5 (S) 30 (S)
6	 **c$_2$** (8*R*, 9*R*)	43 87[d]	31 (S) 77 (S)
7	 **d$_1$** (8*S*, 9*S*)	42 83[d]	51 (R) 65 (R)
8	 **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 ℃, 2 mL ether, 0.4 mL 50% aq. KOH, 10 mol% PTC Cat., 12 h. [b] Isolated yield. [c] Determined by chiral HPLC with Daicel Chiralpak OD-H column. [d] Toluene as solvent.

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 ℃, 2 mL ether, 0.4 mL 50% aq. KOH, 10 mol% cat. **b₂**. [b] Isolated yield. [c] Determined by chiral HPLC with Daicel Chiralpak OD-H column.

The comparative kinetics of catalyst b_2 with the 3rd generation PTC catalyst

To assess the comparative catalytic performances of 9-amino-(9-deoxy)cinchona alkaloid-derived catalysts and the 3rd generation of *N*-9-anthracenylmethyl-*O*-allyl quarterary ammonium salts, the stereoselectivities and yields during the course of catalytic reaction were monitored by using HPLC. The famous *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**1**) and as-synthesized (8*S*, 9*S*)-9-amino-(9-deoxy)cinchonidine-derived ammonium salt **b₂** were selected as representative samples. Under the same catalytic reaction conditions (-40 ℃, ether, 50% aq. KOH, 10 mol% Cat., 12 h), the yield and enantioselectivity profiles of *tert*-butyl 3-phenyl-2-(diphenylmethyleneamino)propanoate plotted versus time during the whole process were shown in **Fig. 1**. From **Fig. 1**, (8*S*, 9*S*)-9-amino-(9-deoxy)cinchonidine-derived PTC catalyst **b₂** gave the better yields (up to 98%) and somewhat lower enantioselectivities (91 %ee) than *O*-Allyl-*N*-(9-anthracenylmethyl)cinchonidinium bromide (**1**) during the whole process.

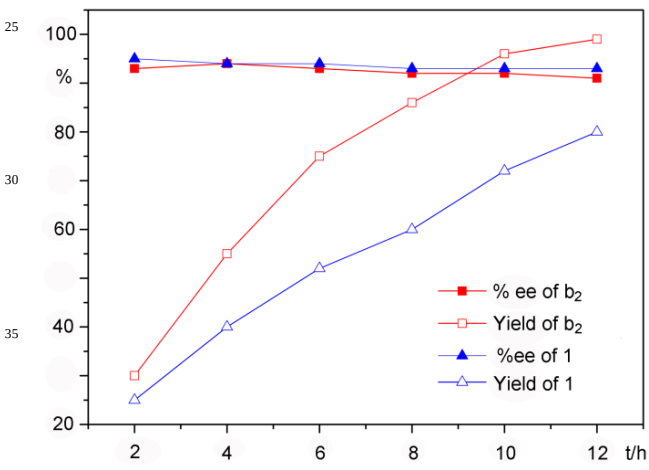


Fig.1 The yield and enantioselectivity profiles of the catalysts **b₂** and **1** plotted versus time during the experiment

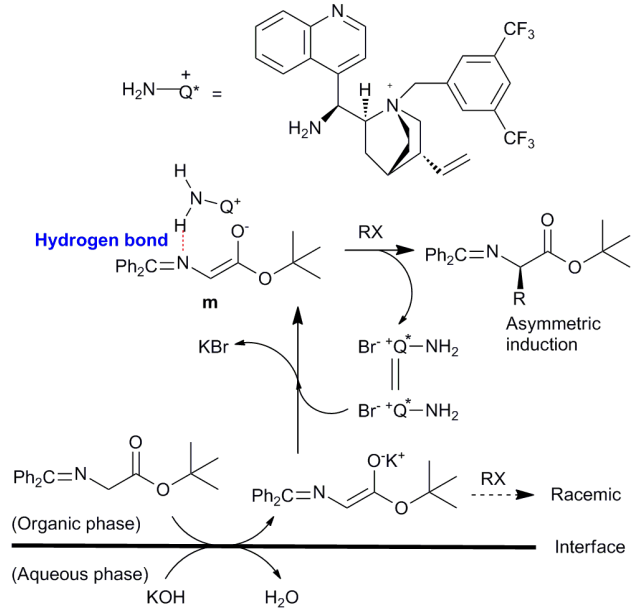
Application in *α*-alkylation using different electrophiles

With the optimum conditions in hand, the scope of the catalyst **b$_2$** with respect to various electrophiles was surveyed in the enantioselective α-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester.

From **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 the high enantioselectivities (90–96 %ee) in 92–99% yields (**entries 1-11**). Especially, when the aromatic aldehydes bearing *o*-CF_3, *o*-F and *o*-CH_3 were employed as electrophiles, the slightly lower yields and higher enantioselectivities were observed owing to the sterically hindered and confined interaction between the *o*-substituents of electrophiles and the catalyst (**entries 3, 6 and 10**).[8] Furthermore, the 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 catalyst **b$_2$** (**entries 12 and 13**).

Mechanism investigation

It is generally admitted 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 the bases such as KOH to give the corresponding metal enolate. Subsequently, the ion-exchange between of enolate anion and the PTC catalyst ($Q^{*+}X^-$) generates a lipophilic chiral onium enolate. Finally, the 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 highly reactive chiral onium enolate through sufficiently fast ion-exchange and effective shielding of one of two enantiotopic faces of enolate anion.



Scheme 2 The possible catalytic mechanism of (8*S*, 9*S*)-9-amino-(9-deoxy)cinchona alkaloid-derived *N*-benzyl ammonium salts **b$_2$**

In order to elucidate the mechanism of the enantioselective α-alkylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester catalyzed by the catalyst **b$_2$**, the corresponding first generation of PTC catalysts **b$_1$**' and **b$_2$**' with the same (8*S*, 9*S*)-configurations as **b$_1$** and **b$_2$** (**Table 3**), was synthesized and selected as a comparative trial (see ESI†). From **Table 3 (entries 1 and 2)**, it was found that the catalysts **b$_1$**' and **b$_2$**' afforded the various α-alkylation products with the disappointed enantioselectivities (14–54 %ee) in moderate to good yields (62–86%). Furthermore, when the amino functional group (-NH_2) in **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 the low enantioselectivity (56 %ee) in 45% yield (**entries 3**), and **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 (**entries 4**). Therefore, it was confirmed that the primary amino functional group (-NH_2) in **b$_2$** at the 9-position played a key role in controlling the stereochemical course and the yield of the reaction.

Table 3 The enantioselective benzylation of *N*-(diphenylmethylene)glycine *tert*-butyl ester catalyzed by **b$_1$**', **b$_2$**', **e** and **2b$_2$**[a]

Entry	Product	Cat.	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 ℃, 2 mL ether, 0.4 mL 50% aq. KOH, 10 mol% Cat., 12 h. [b] Isolated yield. [c] Determined by chiral HPLC with Daicel Chiralpak OD-H column.

Based on the prominent role of primary amino group in controlling the catalytic process and the mechanism which ever reported, a possible catalytic mechanism of (8*S*, 9*S*)-9-amino-(9-deoxy)cinchonidine-derived ammonium salt **b$_2$**, was conjectured and depicted in **Scheme 2**. The first step was the interfacial deprotonation of *N*-(diphenylmethylene)glycine *tert*-butyl ester with base (KOH) to produce corresponding metal enolate. Subsequently, a chiral lipophilic onium enolate **m** with -N–H...N intramolecular hydrogen bond was generated through the fast ion-exchange of enolate anion with the catalyst **b$_2$**. The intermediate **m** could go deep into the organic phase and resulted in the improved yield of α-alkylation. Meanwhile, the intermediate **m** could shield one of two ena-

ntiotopic faces of enolate anion and thus achieved the aim to control the stereochemical course. Instead of primary amino group (-NH_2) with hydroxyl (-OH), secondary amino (-$NHCH_3$) and carbamate -$NCO_2C(CH_3)_3$ groups, the formation of intramolecular hydrogen bond in the intermediate **m** could be retarded and resulted in the weakened enantioselectivity and yield. Finally, the nucleophilic substitution with an alkyl halide afforded the optically active *α*-alkylation product with the concomitant regeneration of 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 9-hydroxyl into 9-amino functional group. Among them, (8*S*, 9*S*)-9-amino-(9-deoxy)cinchonidine-derived ammonium salts with (8 S, 9S)-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 reference and 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 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 spectra (MS) performed on mass spectrometer (Brucker Daltonics, USA, Brucker Co.) with HCT ultra ion trap. High resolution mass spectra (ESI) were recorded on a Bruker Apex IV FTMS spectrometer. ^{1}H and ^{13}C NMR spectra were performed on a Bruker AV-300 NMR instrument at 300.1 and 75.0 MHz respectively, in which all 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; 25 ℃; 254 nm). The absolute configuration was determined by comparison of the HPLC retention time with the reported samples. C, H, N elemental analysis was obtained from a FLASHEA1112 automatic elemental analyzer instrument (Italy).

General procedure of N-Boc-9-amino-(9-deoxy)-*epi*-cinchona alkaloids 2a-d

The THF solution (20 mL) containing 9-amino-(9-deoxy)-epi-cinchona alkaloid **1a** (1.47 g, 5.0mmol) was added to a 100 mL round-bottom flask and cooled to 0-5 ℃. Subsequently, the THF solution (20 mL) containing Boc_2O (1.31 g, 6.0 mmol) was added dropwise and stirred at 0-5 ℃ 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 ℃; ^{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 of N-Boc-9-amino-(9-deoxy)-*epi-cinchona* alkaloid-derived ammonium salts $\mathbf{3a_1}$-$\mathbf{d_1}$ and $\mathbf{3a_2}$-$\mathbf{d_2}$

The toluene solution (4 mL) containing 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 ℃ for 12 h. During this process, white solid gradually separated out. The white precipitate was filtered, washed with toluene (3 mL×2) and dried under reduced pressure to afford 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 ℃; ^{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, $^1J_{C\text{-}F}$ = 32.9 Hz, CF_3), 130.0, 128.5, 127.5, 126.2, 124.0, 124.3 (q, $^2J_{C\text{-}F}$ = 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).

3a$_2$: 0.16 g, 46%, mp 202−204 ℃; ^{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).

3b$_1$: 0.20 g, 62%, mp 168−170 ℃; ^{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, $^1J_{C\text{-}F}$ = 33.1 Hz, CF_3), 131.5, 130.9, 129.7, 127.9, 126.2 (q, $^2J_{C\text{-}F}$= 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 ℃; ^{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, $^1J_{C\text{-}F}$ = 33.8 Hz, CF_3), 130.9, 130.3, 129.6, 127.8, 125.7, 124.5 (q, $^2J_{C\text{-}F}$ = 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 ℃; ^{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, $^1J_{C\text{-}F}$ = 32.7 Hz, CF_3), 131.6, 130.4, 127.5, 125.8 (q, $^2J_{C\text{-}F}$ = 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 ℃; ^{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, $^1J_{C\text{-}F}$ = 33.7 Hz, CF_3), 130.5, 128.4, 127.4, 124.8, 124.3 (q, $^2J_{C\text{-}F}$ = 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 ℃; ^{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, $^1J_{C\text{-}F}$ = 32.3 Hz, CF_3), 131.8, 131.3, 126.7, 126.0 (q, $^2J_{C\text{-}F}$ = 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 ℃; ^{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, $^1J_{C\text{-}F}$= 33.9 Hz, CF_3), 132.0, 130.1, 126.5, 124.4 (q, $^2J_{C\text{-}F}$= 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) as eluents to afford pale yellow solid **a$_1$** (75 mg, 93%).

a$_1$: 75.1 mg, 93 %, mp 153−155 ℃; $[\alpha]_D^{20}$ = + 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, $^1J_{C\text{-}F}$ = 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 ℃; $[\alpha]_D^{20}$ = + 9.2 (c = 0.84, $CHCl_3$); ^1H 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, $^1J_{C\text{-}F}$ = 33.5 Hz, CF_3), 129.9, 128.3, 127.5, 126.9, 126.0, 124.3, 123.3, 122.3 (q, $^2J_{C\text{-}F}$ = 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 ℃; $[\alpha]_D^{20}$ = +37.4 (c = 0.92, $CHCl_3$); ^1H 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, $^1J_{C\text{-}F}$ = 32.6 Hz, CF_3), 130.6, 129.7, 128.7, 127.8, 125.5 (q, $^2J_{C\text{-}F}$ = 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 ℃; $[\alpha]_D^{20}$ = +79.1 (c = 0.54, $CHCl_3$); ^1H 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, $^1J_{C\text{-}F}$ = 33.6 Hz, CF_3), 131.6, 131.5, 130.5, 129.9, 128.0, 125.6, 124.5, 123.9 (q, $^2J_{C\text{-}F}$ = 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 ℃; $[\alpha]_D^{20}$ = +4.5 (c = 0.92, $CHCl_3$); ^1H 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, $^1J_{C\text{-}F}$= 32.4 Hz, CF_3), 128.9, 125.6, 124.0 (q, $^2J_{C\text{-}F}$= 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 ℃; $[\alpha]_D^{20}$ = +4.1 (c = 1.12, CH_3OH); ^1H 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, $^1J_{C\text{-}F}$ = 33.5 Hz, CF_3), 131.4, 130.5, 127.0, 124.9, 123.8 (q, $^2J_{C\text{-}F}$ = 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 ℃; $[\alpha]_D^{20}$ = +48.5 (c = 0.74, $CHCl_3$); ^1H 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, $^1J_{C\text{-}F}$ = 29.2 Hz), 131.8, 126.8, 125.6 (q, $^2J_{C\text{-}F}$ = 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 ℃; $[\alpha]_D^{20}$ = +82.0 (c = 0.40, $CHCl_3$); ^1H 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, $^1J_{C\text{-}F}$ = 33.6 Hz, CF_3), 131.8, 131.6, 126.9, 124.5, 123.9 (q, $^2J_{C\text{-}F}$ = 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 catalyst **b_2** (6 mg, 0.01mmol) in ether (2 mL) was cooled to -40 ℃ and then added 50% aqueous KOH (0.4 mL, 3.6mmol) and benzyl bromide (20 mg, 0.12 mmol). The reaction mixture was stirred at -40 ℃ for 12 h, extracted by ethyl acetate (10 mL×3) and evaporated under reduced pressure. The crude product was purified by column chromatography using hexanes/EtOAc (*v/v* = 50:1) as eluents to afford pure *α*-alkylation product which was identified by NMR spectra. The data of new *α*-alkyla-

tion products was shown as follows and the others were listed in 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, $^2J_{C\text{-}F}$ = 3.7 Hz, CF_3), 125.9 (Ph), 123.0 (q, $^1J_{C\text{-}F}$ = 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, 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, $^2J_{C\text{-}F}$ = 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, $^1J_{C\text{-}F}$ = 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, 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, $^3J_{C\text{-}F}$ = 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, $^2J_{C\text{-}F}$ = 20.9 Hz), 112.9 (d, $^1J_{C\text{-}F}$ = 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, 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, $^3J_{C\text{-}F}$ = 15.5 Hz), 123.5 (d, $^2J_{C\text{-}F}$ = 3.5 Hz), 114.9 (d, $^1J_{C\text{-}F}$ = 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, 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, $^3J_{C\text{-}F}$ = 12.5 Hz), 147.3 (d, $^3J_{C\text{-}F}$ = 12.5 Hz), 139.2, 136.1, 135.3 (dd, $^1J_{C\text{-}F}$ = 5.7 Hz, F, $^2J_{C\text{-}F}$ = 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, $^1J_{C\text{-}F}$ = 6.0 Hz, F, $^2J_{C\text{-}F}$ = 3.6 Hz, F), 118.4 (d, $^2J_{C\text{-}F}$ = 16.8 Hz), 116.6 (d, $^2J_{C\text{-}F}$ = 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, 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, 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, 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) δ7.60 (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, retention time: 10.1 min (R), 12.3 min (S).

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Notes and references

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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/b000000x/

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