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Convenient preparation of optically active cibenzoline and analogues from 3,3-diaryl-2-propen-1-ols

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ABSTRACT

(*R*)-(+)-Cibenzoline (95% ee) was synthesized in two steps from (+)-2,2-diphenylcyclopropylmethanol **3a** (98% ee), which was oxidized with IBX in DMSO, followed by treatment with ethylenediamine in the presence of I_2 and K_2CO_3 in *t*BuOH. Compound (*R*)-(+)-**3a** (98% ee) was prepared by cyclopropanation of 3,3-diphenyl-2-propen-1-ol **1** with Et_2Zn and CH_2I_2 in the presence of a catalytic amount of (*S*)-2-(methanesulfonyl)amino-1-(*p*-toluenesulfonyl)amino-3-phenylpropane **2**, followed by esterification with 3,5-dinitorobenzoyl chloride, recrystallization, and hydrolysis.

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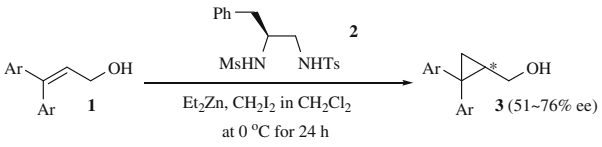
1. Introduction

Commercially available cibenzoline, which is a medicine as a class I antiarrhythmic agent,[1] consists of four rings: a cyclopropane containing a stereogenic carbon, two arene rings, and an imidazoline. A Simmons–Smith reaction is one of the most effective cyclopropane skeleton-forming procedures.[2] Since the first reports about the enantioselective Simmons–Smith cyclopropanation catalyzed by C_2-symmetrical disulfonamide-zinc or aluminum complex by Kobayashi,[3e,h–j] Denmark has optimized conditions for his method[3d,f,g] while Charette has developed another enantioselective catalytic cyclopropanation using 25 mol % of C_2-symmetrical titanium complex of (4*R*,5*R*)-2,2-diethyl-α,α,α',α'-tetraphenyl-1,3-dioxane-4,5-dimethanol (Ti-TADDOLate).[3c] Then, we have developed a catalytic enantioselective Simmons–Smith reaction[3a,b] using the simple disulfonamides derived from α-amino acid. Recently, Katsuki has found a catalytic asymmetric Simmons–Smith reaction using an Al Lewis acid/N Lewis base bifunctional Al Salalen complex.[4] We have also reported the convenient synthesis of optically active cibenzoline and the analogues.[5] Herein we report the catalytic enantioselective cyclopropanation of 3,3-diaryl-2-propen-1-ols **1**[6] with Et_2Zn and CH_2I_2 using a catalytic amount of (*S*)-2-(methanesulfonyl)amino-1-(*p*-toluenesulfonyl)amino-3-phenylpropane **2** and the synthesis of (*R*)-(+)-cibenzoline and analogues.

2. Results and discussion



The reaction of 3,3-diphenyl-2-propen-1-ol **1a** with Et_2Zn and CH_2I_2 in the presence of 10 mol % of **2** afforded the corresponding cyclopropane product **3a**[7] with 76% ee as indicated in entry 1 of Table 1. The cyclopropanation of 3,3-diaryl-2-propen-1-ols substituted on the aromatic ring by electron-donating or electron-withdrawing groups was then examined: the results from the cyclopropanation of various 3,3-diaryl-2-propen-1-ols **1b**–**1f** with Et_2Zn and CH_2I_2 in the presence of 10 mol % of **2** are collected in Table 1. We selected methoxy and methyl substituents as representative electron-donating groups (see entries 2 and 3), trifluoromethyl and chloro substituents as electron-withdrawing groups (see entries 4 and 5), and fluorenyl substituent for making the spiro-ring (see entry 6). The cyclopropanation of non-substituted allylic alcohol **1a** which can be converted to cibenzoline gave the highest ee among these 3,3-diaryl-2-propen-1-ols **1a**–**1f**. The reactions of the allylic alcohols **1b** and **1c** (entries 2 and 3, respectively) substituted with an electron-donating group afforded slightly lower enantioselectivities than those of the allylic alcohols **1d** and **1e** (entries 4 and 5, respectively) substituted with an electron-withdrawing group. The reactions of the allylic alcohol **1f** (entry 6) substituted with a tricyclic group also afforded slightly lower enantioselectivity than those of the allylic alcohol **1a** (entry 1) non-substituted on the aromatic ring.

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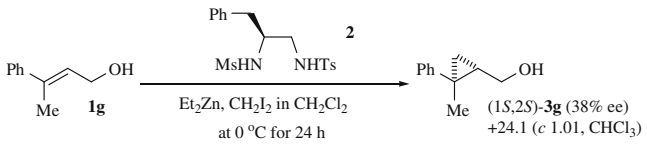
Table 1
Cyclopropanation of 3,3-diaryl-2-propen-1-ols **1a**–**1f** in the presence of **2**[a]

Entry	1	Ar	Yield (%)	ee[b] (%)	Eluent[c] (%)	$[\alpha]_D$
1	**1a**	Ph	82	76	5	+115.9 (*c* 1.07, $CHCl_3$)
2	**1b**	4-$MeOC_6H_4$	77	51	5	+74.2 (*c* 1.04, $CHCl_3$)
3	**1c**	4-MeC_6H_4	99	65	5	+101.7 (*c* 1.45, $CHCl_3$)
4	**1d**	4-$CF_3C_6H_4$	99	73	5	+80.0 (*c* 1.41, $CHCl_3$)
5	**1e**	4-ClC_6H_4	88	72	5	+100.4 (*c* 0.78, $CHCl_3$)
6	**1f**	Fluorenyl	97	60	5	+12.5 (*c* 1.12, $CHCl_3$)

[a] All reactions were carried out with 1 equiv of 3,3-diaryl-2-propen-1-ol **1**, 0.1 equiv of **2**, 2 equiv of Et_2Zn, and 3 equiv of CH_2I_2 in anhydrous CH_2Cl_2.
[b] Determined by HPLC analysis using Chiralcel OD.
[c] The number indicates the concentration of *i*PrOH in hexane as an eluent on HPLC analysis for the determination of enantiomeric excess of the product.

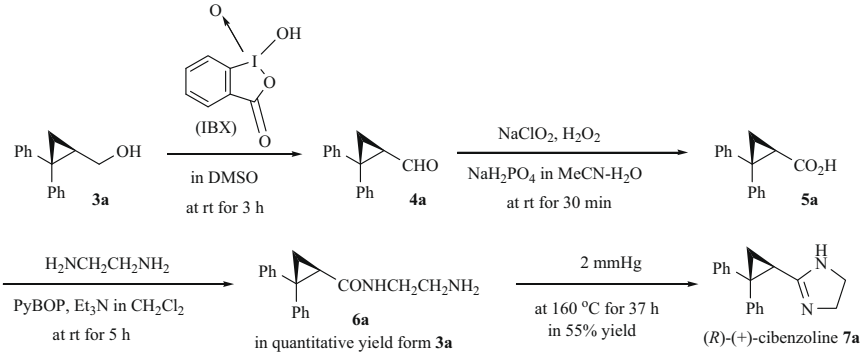


trans-3-Phenylbut-2-enol **1g**, which possesses different substituents on the 3-position, was converted to the corresponding cyclopropylmethanol **3g**[3c] in 85% yield with a low enantiomeric excess, unfortunately.

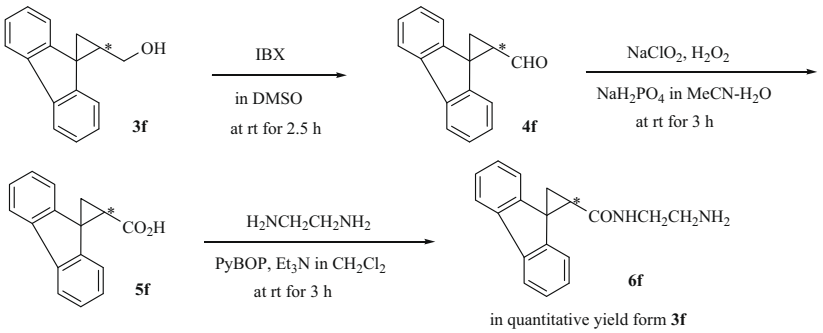
(*R*)-(+)-Cibenzoline **7a**, the absolute configuration and specific rotation of which were already known in the literature,[1a] was synthesized from (+)-2,2-diphenylcyclopropylmethanol **3a** as follows; alcohol **3a** was oxidized with 2-iodoxybenzoic acid (IBX) in dimethylsulfoxide (DMSO) at rt for 3 h to afford the corresponding aldehyde **4a**, which was treated with $NaClO_2$, H_2O_2, and NaH_2PO_4 in MeCN–H_2O at rt for 30 min to give acid **5a**. Acid **5a** was condensed with ethylenediamine in the presence of benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP) and Et_3N in CH_2Cl_2 at rt for 5 h to give the corresponding amide **6a** in quantitative overall yield from **3a**. Then, the amide **6a** was converted under reduced pressure (2 mmHg) at 160 °C for 37 h to (*R*)-(+)-cibenzoline **7a** in 55% yield as shown in Scheme 1. These results suggest that the absolute configurations of the compounds **3a**, **4a**, **5a**, and **6a** are *R*. The fluorenyl alcohol **3f**, which is connected at the *ortho*-position of each benzene ring in **3a**, was converted to the corresponding amide **6f** in quantitative overall yield in a similar manner to that described for the preparation of **6a** as indicated in Scheme 2. Amide **6f** was not cyclized under reduced pressure (2 mmHg) at 160 °C for 26 h and recovered in 52% yield after silica gel column chromatograpy. It was found that the fluorenyl group of the amide **6f** hinders the stereochemical formation of the 2-imidazoline ring because the two benzene rings of **6f** are fixed at the same plane.

Cyclopropylmethanols **3c**, **3d,** and **3e**[8] which are oriented with methyl, trifluoromethyl, chloro groups at the *para*-position on the benzene rings, were converted to the corresponding cibenzoline analogues in a similar manner to that described for the preparation of cibenzoline. All specific rotations of the amides **6a**–**6f**, cibenzoline **7a**, and analogues **7c**–**7e** are summarized in Table 2.

The enantiomeric excess of (*R*)-(+)-cibenzoline **7a** was checked by HPLC analysis with a 80:15:5:0.1 mixture of hexane–ethanol–

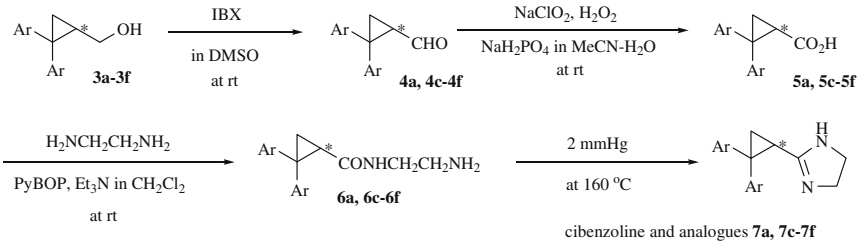


Scheme 1. Synthesis of (*R*)-(+)-cibenzoline **7a** from (+)-2,2-diphenylcyclopropylmethanol **3a**.



Scheme 2. Trial for the preparation of a cibenzoline analog **7f** from (+)-cyclopropylmethanol **3f**.

Table 2
Synthesis of (*R*)-(+)-cibenzoline and analogues **7a** and **7c–7f** from (+)-2,2-diarylcyclopropylmethanols **3a–3f**



Entry	3	Ar	6		Cibenzoline and analogues 7		
			Yield[a] (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$	ee[b] (%)
1	**3a**	Ph	quant.	+102.8 (*c* 1.03, MeOH)	55	+30.1 (*c* 1.12, MeOH)	15
2	**3b**	4-$MeOC_6H_4$	0	—	—	—	—
3	**3c**	4-MeC_6H_4	quant.	+23.9 (*c* 1.38, MeOH)	43	+25.6 (*c* 0.64, MeOH)	17
4	**3d**	4-$CF_3C_6H_4$	89	+19.2 (*c* 1.27, MeOH)	46	+21.6 (*c* 0.75, MeOH)	20
5	**3e**	4-ClC_6H_4	55	+38.7 (*c* 1.39, MeOH)	50	+3.3 (*c* 0.67, MeOH)	1.2
6	**3f**	Fluorenyl	quant.	+97.4 (*c* 1.63, MeOH)	0	—	—

[a] Overall yields from the cyclopropylmethanols **3a–3f**.
[b] The enantiomeric excesses were determined by HPLC analysis with a 80:15:5:0.1 mixture of hexane–ethanol–isopropanol–diethylamine as an eluent using Chiralcel OD.[1a]

isopropanol–diethylamine as an eluent using Chiralcel OD and found to be 15% ee, which is lower than that (76% ee) of the starting alcohol **3a**. It is supposed that racemization proceeds under cyclization of the amide **6a** at the high reaction temperature. In order to avoid racemization, an alternative route reported by Togo[9] was examined. The aldehydes **4a** and **4c–4e** were reacted with ethylenediamine in the presence of K_2CO_3 and I_2 in *t*BuOH to afford the corresponding 2-imidazoline derivatives **7a, 7c–7e** in quantitative yields as indicated in Table 3. No racemization was observed in entries 1 and 3–6.

Even when using the fluorenyl type's aldehyde **4f**, which hinders steric hinderance, the reaction proceeded to give the cibenzoline analogue **7f** in 48% yield. The specific rotation (+186.4) is completely different from that (+75.7) of cibenzoline, hence the biological activity is very interesting.

Next, we tried to improve the enantiomeric purity of the alcohol **3a** (76% ee) by recrystallization after the formation of the 3,5-dinitrobenzoyl ester, followed by hydrolysis under basic conditions to afford 98% ee of **3a**.[3a] The alcohol **3a** with 98% ee was converted to the aldehyde **4a**, which was then cyclized by Togo's method with ethylenediamine, (1*R*,2*R*)-1,2-diphenylethylenediamine, or (1*R*,2*R*)-cyclohexanediamine to obtain the corresponding 2-imidazolines **7a, 7h,** and **7i**, respectively, as described in Scheme 3 and Table 4.

3. Conclusion

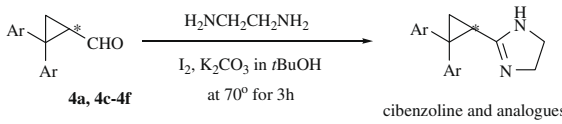
In conclusion, (*S*)-2-(methanesulfonyl)amino-1-(4-toluenesulfonyl)amino-3-phenylpropane **2** efficiently works as a catalyst in the Simmons–Smith cyclopropanation of steric hindered allylic alcohols such as 3,3-diaryl-2-propen-1-ols **1**. In our procedure, it is possible to prepare various chiral 3,3-disubstituted 2,3-methano-1-propanols **3** conveniently and to synthesize the corresponding chiral cibenzoline analogues **7** including the imidazoline derivatives. We are still working on the optimization of α-amino acid-derived chiral disulfonamides for the catalytic enantioselective cyclopropanation of 3,3-diphenyl-2-propen-1-ol **1a**.

4. Experimental

4.1. General

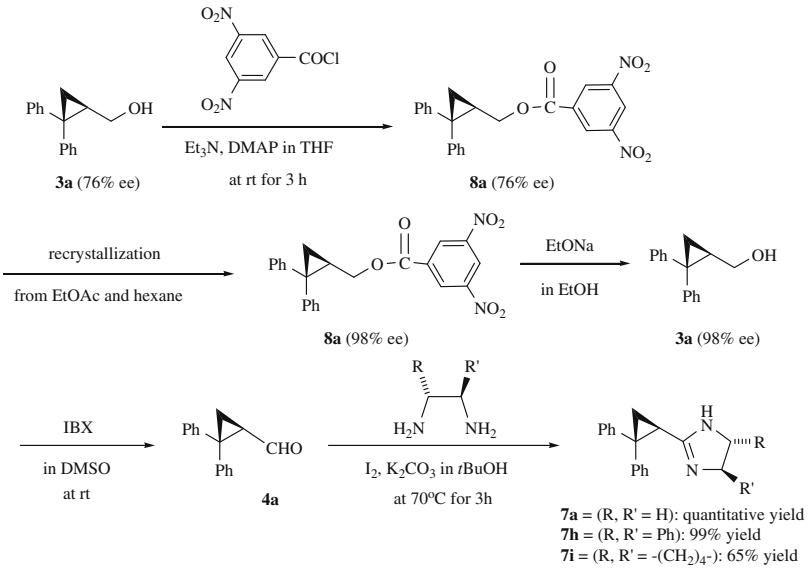
The ^1H NMR spectra were measured with a Bruker Ultrashield™ 400 Plus (400 MHz) spectrometer. The chemical shifts are expressed in ppm downfield from tetramethylsilane ($\delta = 0.00$) as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad signal. The high-resolution Mass spectra (HRMS) of the compounds

Table 3
Alternative synthesis of (+)-cibenzoline and analogues **7a** and **7c–7f** from the aldehydes **4a** and **4c–4f**



Entry	4	Ar	4		Cibenzoline and analogues 7		
			Yield (%)	$[\alpha]_D$	Yield (%)	$[\alpha]_D$	ee[a] (%)
1	**4a**	Ph	86	+112.4 (*c* 1.47, $CHCl_3$)	quant.	+110.0 (*c* 1.12, MeOH)	72
2	**4b**	4-$MeOC_6H_4$	0	—	—	—	—
3	**4c**	4-MeC_6H_4	90	+77.9 (*c* 1.37, $CHCl_3$)	quant.	+66.0 (*c* 0.90, MeOH)	65
4	**4d**	4-$CF_3C_6H_4$	89	+86.4 (*c* 1.43, $CHCl_3$)	quant.	+68.6 (*c* 1.18, MeOH)	74
5	**4e**	4-ClC_6H_4	98	+95.0 (*c* 0.65, $CHCl_3$)	quant.	+86.0 (*c* 0.97, MeOH)	71
6	**4f**	Fluorenyl	94	+125.5 (*c* 0.99, $CHCl_3$)	48	+186.4 (*c* 0.34, $CHCl_3$)	58

[a] The enantiomeric excesses were determined by HPLC analysis with a 80:15:5:0.1 mixture of hexane–ethanol–isopropanol–diethylamine as an eluent using Chiralcel OD.[1a]



Scheme 3. Synthesis of the enantiopure (*R*)-(+)-cibenzoline and analogues **7a, 7h**, and 7i via recrystallization of the ester **8a**.

Table 4
The 2-imidazoline derivatives **7a, 7h,** and **7i** from the aldehyde **4a**

Entry	7	Yield (%)	$[\alpha]_D$
1	**7a**[a]	quant.	+154.4 (*c* 1.40, MeOH)
2	**7h**	99	+152.5 (*c* 1.00, MeOH)
3	**7i**	65	+177.1 (*c* 0.71, MeOH)

[a] The enantiomeric excess (95% ee) was determined by HPLC analysis with a 80:15:5:0.1 mixture of hexane–ethanol–isopropanol–diethylamine as an eluent using Chiralcel OD.[1a]

with a high molecular weight were recorded using a Waters LCT Premier (ESI-TOF-MS) spectrometer. Unless otherwise noted, all experiments were carried out under an argon atmosphere. For thin layer chromatographic (TLC) analyses, Merck precoated TLC plates (Silica Gel 60 F_{254}, Art 5715) were used.

4.2. Typical procedure for Simmons–Smith cyclopropanations

To a colorless clear solution of the sulfonamide **2** (38 mg, 0.5 mmol, 0.1 equiv) and **1** (1 mmol, 1 equiv) in anhydrous CH_2Cl_2 (7.5 mL) was added dropwise at −40 °C a solution of Et_2Zn in hexane (1.05 M, 0.95 mL, 1 mmol, 2 equiv) and CH_2I_2 (121 μL, 1.5 mmol, 3 equiv). After stirring for 3 h at 0 °C, the colorless suspension was quenched at the temperature with Et_3N (0.3 mL), diluted with Et_2O (70 mL), washed with brine (20 mL), and dried over $MgSO_4$. The crude product was chromatographed on silica gel with a 1:10 mixture of EtOAc and hexane to afford **3**.

4.2.1. 2,2-Bis(4-methoxyphenyl)cyclopropylmethanol, 3b

Pale yellow oil; 77% yield; $[\alpha]^{24}_D$ = +74.2 (*c* 1.04, $CHCl_3$); 51% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18 (1H, dd, *J* = 4.8, 8.8 Hz), 1.26 (1H, t, *J* = 4.8 Hz), 1.89 (1H, m), 3.33 (1H, dd, *J* = 7.9, 11.5 Hz), 3.47 (1H, dd, *J* = 6.3, 11.5 Hz), 3.73 (3H, s), 3.76 (3H, s), 6.77 (2H, d, *J* = 8.8 Hz), 6.82 (2H, d, *J* = 8.8 Hz), 7.15 (2H, d, *J* = 8.8 Hz), 7.27 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 27.5, 34.2, 55.1, 55.2, 63.8, 113.6, 113.8, 128.8, 130.8, 133.5, 138.9, 157.7, 158.1; HRMS (ESI-TOF): Calcd for $C_{18}H_{20}O_3Na$ (M+Na)$^+$: 307.1305, Found: 307.1338.

4.2.2. 2,2-Bis(4-methylphenyl)cyclopropylmethanol, 3c

Colorless oil; 99% yield; $[\alpha]^{24}_D = +101.7$ (*c* 1.45, $CHCl_3$); 65% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (1H, dd, *J* = 4.8, 8.8 Hz), 1.30 (1H, br s), 1.33 (1H, t, *J* = 4.8 Hz), 1.95 (1H, m), 2.28 (3H, s), 2.30 (3H, s), 3.35 (1H, t, *J* = 10.9 Hz), 3.48 (1H, t, *J* = 10.9 Hz), 7.04 (2H, d, *J* = 8.2 Hz), 7.10 (2H, d, *J* = 7.9 Hz), 7.12 (2H, d, *J* = 8.2 Hz), 7.25 (2H, d, *J* = 7.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.7, 20.9, 21.0, 27.5, 34.9, 63.9, 127.8, 129.0, 129.3, 129.8, 135.5, 136.2, 138.3, 143.6; HRMS (ESI-TOF): Calcd for $C_{18}H_{20}ONa$ (M+Na)$^+$: 275.1406, Found: 275.1389.

4.2.3. 2,2-Bis(4-trifluoromethylphenyl)cyclopropyl-methanol, 3d

Colorless oil; 99% yield; $[\alpha]^{24}_D = +80.0$ (*c* 1.41, $CHCl_3$); 73% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (1H, dd, *J* = 5.2, 9.0 Hz), 1.43 (1H, t, *J* = 5.2 Hz), 1.44 (1H, br s), 2.04 (1H, m), 3.29 (1H, dd, *J* = 8.2, 11.4 Hz), 3.57 (1H, dd, *J* = 6.0, 11.4 Hz), 7.31 (2H, d, *J* = 8.1 Hz), 7.52 (4H, s), 7.59 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.2, 28.2, 35.5, 63.3, 124.08 (q, $^1J_{C-F}$ = 272 Hz), 124.11 (q, $^1J_{C-F}$ = 272 Hz), 125.5 (q, $^3J_{C-F}$ = 3.6 Hz), 125.7 (q, $^3J_{C-F}$ = 3.8 Hz), 128.1, 128.7(q, $^2J_{C-F}$ = 32.4 Hz), 129.4 (q, $^2J_{C-F}$ = 32.6 Hz), 130.8, 144.4, 149.3; HRMS (ESI-TOF): Calcd for $C_{18}H_{14}F_6ONa$ (M+Na)$^+$: 383.0841, Found: 383.0871.

4.2.4. 2,2-Bis(4-chlorophenyl)cyclopropylmethanol, 3e[8]

Yellow oil; 88% yield; $[\alpha]^{24}_D = +100.4$ (*c* 0.78, $CHCl_3$); 72% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (1H, dd, *J* = 5.1, 9.0 Hz), 1.28 (1H, br s), 1.32 (1H, t, *J* = 5.1 Hz), 1.95 (1H, m), 3.29 (1H, m), 3.54 (1H, m), 7.13 (2H, d, *J* = 8.6 Hz), 7.21 (2H, d, *J* = 8.6 Hz), 7.29 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0, 27.8, 34.6, 63.4, 128.5, 128.8, 129.1, 131.5, 132.0, 132.7, 139.2, 144.3.

4.2.5. 2,2-Fluorenylcyclopropylmethanol, 3f

Pale brown oil; 97% yield; $[\alpha]^{24}_D = +12.5$ (*c* 1.12, $CHCl_3$); 60% ee; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (1H, br s), 1.73 (1H, dd, *J* = 5.2, 7.4 Hz), 1.95 (1H, dd, *J* = 5.2, 9.0 Hz), 2.26 (1H, m), 3.91 (1H, dd, *J* = 8.7, 12.1 Hz), 4.10 (1H, dd, *J* = 6.2, 12.1 Hz), 7.02 (1H, d, *J* = 7.0 Hz), 7.22–7.39 (5H, m), 7.80 (1H, d, *J* = 7.0 Hz), 7.84 (1H, d, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 33.5, 61.9, 118.5, 119.7, 120.3, 121.1, 126.1, 126.4, 126.6, 127.1, 139.0, 141.1, 144.1, 148.1; HRMS (ESI-TOF): Calcd for $C_{16}H_{14}ONa$ (M+Na)$^+$: 245.0937, Found: 245.0891.

4.2.6. (1*S*,2*S*)-(+)-2-Methyl-2-phenylcyclopropyl-methanol, 3g[3c]

Colorless oil; 85% yield; $[\alpha]_D^{27} = +24.1$ (*c* 1.01, $CHCl_3$); 38% ee; ^1H NMR (400 MHz, $CDCl_3$) δ 0.60 (1H, dd, *J* = 5.0, 5.5 Hz), 1.14 (1H, dd, *J* = 5.0, 9.0 Hz), 1.39–1.45 (1H, m), 1.45 (3H, s), 1.65 (1H, br s), 3.70 (1H, dd, *J* = 8.6, 11.5 Hz), 3.90 (1H, dd, *J* = 6.4, 11.5 Hz), 7.15–7.31 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 20.5, 24.8, 27.8, 63.6, 125.8, 127.2, 128.3, 147.6; HRMS (ESI-TOF): Calcd for $C_{11}H_{14}ONa$ $(M+Na)^+$: 185.0937, Found: 185.0917.

4.3. Typical procedure for oxidation of alcohols 3 into the aldehydes 4

To a solution of alcohol **3** in dimethylsulfoxide (DMSO, 2 mL) was added 2-iodoxybenzoic acid (IBX, 4 equiv) at room temperature. After stirring for 3 h at room temperature, EtOAc (10 mL) was added to the reaction mixture. The suspension was filtered. To the filtrate was added half brine, extracted three times with AcOEt. The combined AcOEt layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel with a 5:1 mixture of EtOAc and hexane to afford the aldehyde **4.**

4.3.1. 2,2-Bis(4-methylphenyl)cyclopropanecarbox-aldehyde, 4c

Colorless oil; 90% yield; $[\alpha]_D^{27} = -77.9$ (*c* 1.37, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.83 (1H, dd, *J* = 5.2, 8.4 Hz), 2.21 (1H, t, *J* = 5.2 Hz), 2.28 (3H, s), 2.30 (3H, s), 2.49 (1H, ddd, *J* = 5.2, 6.8, 8.4 Hz), 7.05–7.13 (6H, m), 7.27 (2H, m), 8.67 (1H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 20.9, 21.1, 36.8, 40.4, 127.2, 129.3, 129.6, 129.8, 136.6, 136.7, 137.1, 141.3, 200.8; HRMS (ESI-TOF): Calcd for $C_{18}H_{18}ONa$ $(M+Na)^+$: 273.1250, Found: 273.1258.

4.3.2. 2,2-Bis(4-trifluoromethylphenyl)cyclopropane-carboxaldehyde, 4d

Colorless oil; 89% yield; $[\alpha]_D^{27} = -86.4$ (*c* 1.43, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.93 (1H, dd, *J* = 5.5, 8.5 Hz), 2.34 (1H, t, *J* = 5.5 Hz), 2.65–2.70 (1H, m), 7.34 (2H, d, *J* = 8.2 Hz), 7.52 (2H, d, *J* = 8.2 Hz) 7.55 (2H, d, *J* = 8.2 Hz) 7.62 (2H, d, *J* = 8.2 Hz), 8.80 (1H, d, *J* = 6.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 36.4, 40.3, 123.80 (q, $^1J_{C-F}$ = 272 Hz), 123.84 (q, $^1J_{C-F}$ = 272 Hz), 125.9 (q, $^3J_{C-F}$ = 3.7 Hz), 126.1 (q, $^3J_{C-F}$ = 3.7 Hz), 127.8, 129.6 (q, $^2J_{C-F}$ = 32.8 Hz), 130.2 (q, $^2J_{C-F}$ = 32.7 Hz), 130.5, 142.4, 146.7, 198.7; HRMS (ESI-TOF): Calcd for $C_{18}H_{12}F_6ONa$ $(M+Na)^+$: 381.0685, Found: 381.0703.

4.3.3. 2,2-Bis(4-chlorophenyl)cyclopropanecarbox-aldehyde, 4e

Yellow solid; 98% yield; Mp 88–89 °C; $[\alpha]_D^{27} = -95.0$ (*c* 0.65, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 1.84 (1H, dd, *J* = 5.4, 8.4 Hz), 2.24 (1H, t, *J* = 5.4 Hz), 2.52–2.57 (1H, m), 7.14 (2H, d, *J* = 8.6 Hz), 7.25 (2H, d, *J* = 8.6 Hz), 7.30 (4H, s), 8.73 (1H, d, *J* = 6.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.3, 36.5, 39.7, 128.7, 128.9, 129.3, 131.3, 133.1, 133.7, 137.4, 141.9, 199.5; HRMS (ESI-TOF): Calcd for $C_{16}H_{12}Cl_2ONa$ $(M+Na)^+$: 313.0157, Found: 313.0202.

4.3.4. 2,2-Fluorenylcyclopropanecarboxaldehyde, 4f

Yellow oil; 94% yield; $[\alpha]_D^{27} = -125.2$ (*c* 0.99, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.30 (1H, dd, *J* = 5.5, 8.3 Hz), 2.66 (1H, dd, *J* = 5.5, 7.4 Hz), 2.90 (1H, ddd, *J* = 4.1, 7.4, 8.3 Hz), 7.09 (1H, d, *J* = 7.5 Hz), 7.27–7.43 (5H, m), 7.81 (1H, d, *J* = 6.5 Hz), 7.82 (1H, d, *J* = 7.6 Hz), 9.70 (1H, d, *J* = 4.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6, 39.7, 40.4, 118.8, 120.0, 120.2, 122.7, 127.0, 127.3, 127.4, 139.8, 141.0, 141.9, 145.6, 197.0; HRMS (ESI-TOF): Calcd for $C_{16}H_{12}ONa$ $(M+Na)^+$: 243.0780, Found: 243.0762.

4.4. Typical procedure for oxidation of the aldehydes 4 into the carboxylic acids 5

To a colorless clear solution of aldehyde **4** and NaH_2PO_4 (0.3 equiv) in MeCN (4 mL) and H_2O (0.4 mL) were added 35% H_2O_2 (1.1 equiv) and a solution of $NaClO_2$ (1.5 equiv) in H_2O (2 mL) at 0 °C. After stirring for 30 min at room temperature, saturated Na_2SO_3 aq (1 mL) was added to the reaction mixture. Next, 1 M HCl was added, and the reaction mixture was adjusted to pH 3. The reaction mixture was extracted three times with AcOEt. The combined AcOEt layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The obtained the crude carboxylic acid **5** was used in the next step without further purification.

4.5. Typical procedure of the carboxylic acids 5 into the amides 6

To a colorless clear solution of carboxylic acid **5** in anhydrous CH_2Cl_2 (2 mL) were added ethylenediamine (20 equiv), triethylamine (3 equiv), and benzotriazol-1-yloxytripyrrolidinophosphonium hexafluorophosphate (PyBOP; 1.2 equiv) at room temperature. After stirring for 5 h at room temperature, water (2 mL) was added to reaction mixture. Then, 1 M NaOH was added, and the reaction mixture was adjusted to pH 10. The reaction mixture was extracted three times with AcOEt. The combined AcOEt layers were washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The crude product was chromatographed on silica gel with a 7:3:0.5 mixture of $CHCl_3$, MeOH, and H_2O to afford the amine **6**.

4.5.1. *N*-(2-Aminoethyl)-2,2-diphenylcyclopropane-carboxamide, 6a

Pale yellow oil; quantitative yield; $[\alpha]_D^{21} = +102.8$ (*c* 1.03, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.50 (1H, dd, *J* = 5.0, 8.2 Hz), 2.16 (1H, dd, *J* = 5.0, 5.9 Hz), 2.53 (1H, dd, *J* = 5.9, 8.2 Hz), 2.73 (2H, m), 3.23 (2H, t, *J* = 6.2 Hz), 7.12–7.36 (10H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 19.4, 31.0, 38.6, 40.2, 41.1, 127.5, 127.9, 128.7, 129.3, 129.4, 130.9, 142.0, 146.6, 173.6; HRMS (ESI-TOF): Calcd for $C_{18}H_{21}N_2O$ $(M+H)^+$: 281.1648, Found: 281.1654.

4.5.2. *N*-(2-Aminoethyl)-2,2-bis(4-methylphenyl)-cyclopropane-carboxamide, 6c

Colorless oil; quantitative yield; $[\alpha]_D^{21} = +23.9$ (*c* 1.38, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.42 (1H, dd, *J* = 4.8, 8.2 Hz), 2.08 (1H, dd, *J* = 4.8, 5.9 Hz), 2.23 (3H, s), 2.25 (3H, s), 2.46 (1H, dd, *J* = 5.9, 8.2 Hz), 2.74 (2H, m), 3.21 (2H, t, *J* = 6.2 Hz), 7.02 (2H, d, *J* = 8.0 Hz), 7.05 (2H, d, *J* = 8.2 Hz), 7.15 (2H, d, *J* = 8.2 Hz), 7.20 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 19.3, 20.9, 21.1, 31.2, 39.4, 40.3, 41.4, 128.5, 129.8, 129.9, 130.7, 137.0, 137.4, 139.1, 143.9, 173.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{25}N_2O$ $(M+H)^+$: 309.1961, Found: 309.2000.

4.5.3. *N*-(2-Aminoethyl)-2,2-bis(4-trifluoromethyl-phenyl)cyclopropanecarboxamide, 6d

Colorless oil; 89% yield; $[\alpha]_D^{21} = +19.2$ (*c* 1.27, MeOH); ^1H NMR (400 MHz, CD_3OD) δ 1.63 (1H, dd, *J* = 5.5, 8.3 Hz), 2.22 (1H, t, *J* = 5.5 Hz), 2.65 (1H, dd, *J* = 5.5, 8.3 Hz), 2.81(2H, t, *J* = 6.3 Hz), 3.26 (2H, t, *J* = 6.3 Hz), 7.54 (8H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 19.8, 31.1, 39.5, 40.4, 41.2, 125.6 (q, $^1J_{C-F}$ = 271 Hz), 125.7 (q, $^1J_{C-F}$ = 271 Hz), 126.3 (q, $^3J_{C-F}$ = 3.7 Hz), 126.5 (q, $^3J_{C-F}$ = 3.7 Hz), 129.6, 129.9 (q, $^2J_{C-F}$ = 32.0 Hz), 130.2 (q, $^2J_{C-F}$ = 32.0 Hz), 131.7, 145.8, 150.1, 172.1; HRMS (ESI-TOF): Calcd for $C_{20}H_{19}F_6N_2O$ $(M+H)^+$: 417.1396, Found: 417.1385.

4.5.4. *N*-(2-Aminoethyl)-2,2-bis(4-chlorophenyl)-cyclopropanecarboxamide, 6e

Pale yellow oil; 55% yield; $[\alpha]_D^{23} = +38.7$ (*c* 1.39, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 1.49 (1H, dd, *J* = 5.0, 8.3 Hz), 2.12 (1H, dd, *J* = 5.0, 6.0 Hz), 2.51 (1H, dd, *J* = 6.0, 8.3 Hz), 2.62 (2H, t, *J* = 6.4 Hz), 3.14 (2H, m), 7.28 (8H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 19.5, 31.3, 38.5, 42.0, 42.8, 129.4, 129.5, 130.4, 132.5, 133.4, 133.7, 140.4, 145.1, 171.8; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}Cl_2N_2O$ $(M+H)^+$: 349.0869, Found: 349.0869.

4.5.5. *N*-(2-Aminoethyl)-2,2-fluorenylcyclopropane-carboxamide, 6f

Colorless oil; quantitative yield; $[\alpha]_D^{23} = +97.4$ (*c* 1.63, MeOH); ^{1}H NMR (400 MHz, CD_3OD) δ 2.07 (1H, dd, *J* = 5.0, 8.1 Hz), 2.38 (1H, dd, *J* = 5.0, 8.1 Hz), 2.73 (2H, m), 2.79 (1H, t, *J* = 8.1 Hz), 3.25 (2H, m), 7.14 (1H, d, *J* = 7.3 Hz), 7.21 (1H, t, *J* = 7.5 Hz), 7.31 (3H, m), 7.46 (1H, d, *J* = 7.8 Hz), 7.80 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 20.1, 35.4, 37.3, 40.3, 41.2, 120.1, 120.7, 120.9, 123.3, 127.6, 127.8, 127.9, 128.3, 140.8, 142.2, 144.3, 148.2, 171.2; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}N_2O$ $(M+H)^+$: 279.1492, Found: 279.1488.

4.6. Typical procedure for cyclization of the amides 6 into (*R*)-(+)-cibenzoline and analogs 7

Amide **6** was heated at 160 °C under vacuum (2 mmHg) for 37 h. The crude product was chromatographed on silica gel with a 8:2:0.2 mixture of $CHCl_3$, MeOH, and Et_3N to afford (*R*)-(+)-cibenzoline and analogues.

4.7. Typical procedure for cyclization of the aldehydes 4 into (*R*)-(+)-cibenzoline and analogues 7

To a solution of the aldehyde **4** (1 equiv) in *t*BuOH (5 mL) was added a diamine (1.1 equiv). After stirring for 30 min at rt, K_2CO_3 (3 equiv) and I_2 (1.25 equiv) were added to the mixture. The suspension was stirred for 3 h at 70 °C under an argon atmosphere, quenched at the temperature with satd Na_2SO_3 (4 mL), extracted with AcOEt (3 × 200 mL), washed with sat. $NaHSO_3$ (20 mL) and brine (20 mL), and dried over Na_2SO_4. The crude product was pure enough without purification.

4.7.1. (*R*)-(+)-Cibenzoline 7a[1]

Colorless oil; quantitative yield; $[\alpha]_D^{24} = +110.0$ (*c* 1.12, MeOH); 72% ee; ^{1}H NMR (400 MHz, CD_3OD) δ 1.58 (1H, dd, *J* = 5.4, 8.6 Hz), 2.09 (1H, dd, *J* = 5.4, 6.3 Hz), 2.43 (1H, dd, *J* = 6.3, 8.6 Hz), 3.20 (2H, m), 3.37 (2H, m), 7.11–7.38 (10H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 19.5, 25.2, 30.8, 39.9, 48.9, 127.6, 128.1, 128.8, 129.3, 129.5, 131.0, 141.4, 146.4, 168.9; HRMS (ESI-TOF): Calcd for $C_{18}H_{19}N_2$ $(M+H)^+$: 263.1543, Found: 263.1540.

4.7.2. 2-(2,2-Bis(4-methylphenyl)cyclopropyl)-imidazoline 7c

Colorless oil; quantitative yield; $[\alpha]_D^{23} = +66.0$ (*c* 0.90, MeOH); 65% ee; ^{1}H NMR (400 MHz, CD_3OD) δ 1.61 (1H, dd, *J* = 5.9, 8.6 Hz), 2.08 (1H, t, *J* = 5.9 Hz), 2.25 (3H, s), 2.28 (3H, s), 2.46 (1H, dd, *J* = 5.9, 8.6 Hz), 3.29 (2H, m), 3.46 (2H, m), 7.04 (2H, d, *J* = 8.1 Hz), 7.09 (2H, d, *J* = 8.0 Hz), 7.15 (2H, d, *J* = 8.1 Hz), 7.23 (2H, d, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 19.7, 21.0, 21.1, 25.1, 39.6, 48.5, 128.5, 129.9, 130.0, 130.8, 137.3, 137.9, 138.3, 143.4, 169.3; HRMS (ESI-TOF): Calcd for $C_{20}H_{23}N_2$ $(M+H)^+$: 291.1856, Found: 291.1863.

4.7.3. 2-(2,2-Bis(4-trifluoromethylphenyl)cyclopropyl)-imidazoline 7d

Colorless oil; quantitative yield; $[\alpha]_D^{23} = +68.6$ (*c* 1.18, MeOH); 74% ee; ^{1}H NMR (400 MHz, CD_3OD) δ 1.82 (1H, dd, *J* = 6.2, 8.7 Hz), 2.29 (1H, t, *J* = 6.2 Hz), 2.69 (1H, dd, *J* = 6.2, 8.7 Hz), 3.35 (2H, m), 3.51 (2H, m), 7.57 (8H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 19.7, 25.1, 39.6, 125.6 (q, $^1J_{C-F}$ = 271 Hz), 126.5 (q, $^3J_{C-F}$ = 3.7 Hz), 126.6 (q, $^3J_{C-F}$ = 3.7 Hz), 129.5, 130.2 (q, $^2J_{C-F}$ = 32.7 Hz), 130.7 (q, $^2J_{C-F}$ = 32.7 Hz), 131.9, 144.7, 149.4, 168.2; HRMS (ESI-TOF): Calcd for $C_{20}H_{17}F_6N_2$ $(M+H)^+$: 399.1290, Found: 399.1302.

4.7.4. 2-(2,2-Bis(4-chlorophenyl)cyclopropyl)imidazoline 7e

Colorless oil; quantitative yield; $[\alpha]_D^{24} = +86.0$ (*c* 0.97, MeOH); 71% ee; ^{1}H NMR (400 MHz, CD_3OD) δ 1.88 (1H, dd, *J* = 6.3, 8.6 Hz), 2.28 (1H, t, *J* = 6.3 Hz), 2.76 (1H, dd, *J* = 6.3, 8.6 Hz), 3.53 (2H, m), 3.71 (2H, m), 7.30 (2H, d, *J* = 8.9 Hz), 7.34 (2H, d, *J* = 8.9 Hz), 7.37 (4H, s); ^{13}C NMR (100 MHz, CD_3OD) δ 20.0, 23.7, 40.7, 46.2, 129.9, 130.1, 130.4, 132.4, 134.2, 135.0, 138.5, 143.3, 170.0; HRMS (ESI-TOF): Calcd for $C_{18}H_{17}Cl_2N_2$ $(M+H)^+$: 331.0763, Found: 331.0769.

4.7.5. 2-(2,2-Fluorenylcyclopropyl)imidazoline 7f

Colorless solid; 48% yield; Mp 151–166 °C; $[\alpha]_D^{27} = +186.4$ (*c* 0.34, $CHCl_3$); 58% ee; ^{1}H NMR (400 MHz, CD_3OD) δ 2.11 (1H, dd, *J* = 5.1, 8.6 Hz), 2.50 (1H, dd, *J* = 5.1 *J* = 7.4 Hz), 2.57 (1H, t, *J* = 8.0 Hz), 3.46–3.57 (2H, m), 3.59–3.74 (2H, m), 4.76 (1H, br s), 7.07 (2H, d, *J* = 7.5 Hz), 7.23–7.46 (5H, m), 7.82 (2H, d, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 20.3, 27.9, 29.7, 35.1, 49.1, 118.6, 119.9, 120.0, 121.3, 126.8, 126.9, 127.1, 139.8, 140.6, 143.3, 146.7, 164.2; HRMS (ESI-TOF): Calcd for $C_{18}H_{17}N_2$ $(M+H)^+$: 261.1386, Found: 261.1376.

4.7.6. (4*R*,5*R*,1'*R*)-2-(2,2-Diphenylcyclopropyl)-4,5-diphenyl-2-imidazoline 7h

Yellow oil; 99% yield; $[\alpha]_D^{27} = -152.5$ (*c* 1.00, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.63 (1H, dd, *J* = 5.2, 8.7 Hz), 2.34 (1H, dd, *J* = 5.2, 6.2 Hz), 2.69 (1H, dd, *J* = 6.2, 8.7 Hz), 4.30 (1H, br s), 4.68 (1H, br s), 6.60 (1H, br s), 7.17–7.52 (20H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.8, 25.0, 38.3, 77.2, 126.5, 126.6, 127.0, 127.8, 128.4, 128.5, 128.8, 130.2, 140.3, 143.1, 145.3, 163.7; HRMS (ESI-TOF): Calcd for $C_{30}H_{27}N_2$ $(M+H)^+$: 415.2169, Found: 415.2203.

4.7.7. (4*R*,5*R*,1'*R*)-2-(2,2-Diphenylcyclopropyl)-4,5-cyclohexanimidazoline 7i

Yellow solid; 65% yield; Mp 155–165 °C; $[\alpha]_D^{27} = -177.1$ (*c* 0.71, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07–1.35 (4H, m), 1.53 (1H, dd, *J* = 5.3, 8.8 Hz), 1.58–1.73 (2H, m), 1.94–2.07 (2H, m), 2.19 (1H, t, *J* = 5.7 Hz), 2.53 (1H, dd, *J* = 6.3, 8.8 Hz), 2.49–2.63 (4H, m), 3.12 (1H, br s), 7.16–7.30 (10H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.6, 24.8, 25.8, 30.5, 37.5, 69.1, 126.5, 126.7, 128.07, 128.11, 128.5, 129.5, 140.1, 145.0, 166.2; HRMS (ESI-TOF): Calcd for $C_{22}H_{25}N_2$ $(M+H)^+$: 317.2012, Found: 317.1969.

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