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Chiral Synthesis of McGeachin-type Bisaminals

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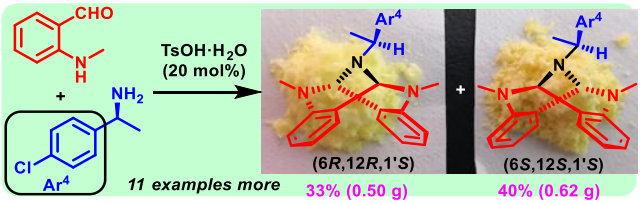
Supporting Information Placeholder



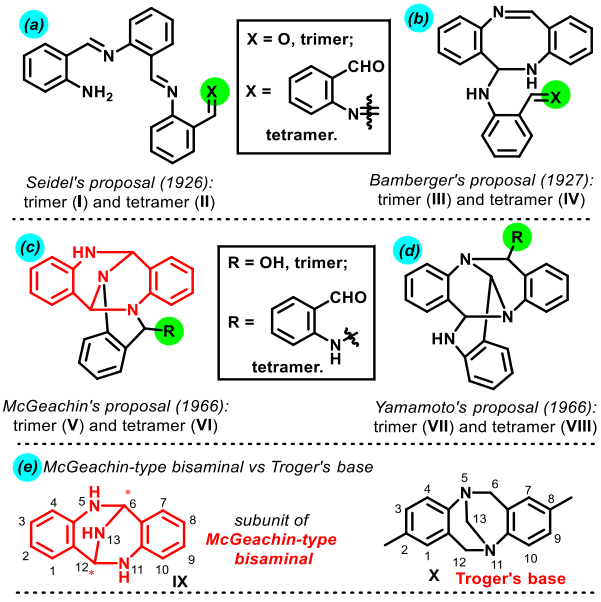
ABSTRACT: The bridged [3.3.1]-bisaminal structures, 6,12-epiminodibenzo[*b*,*f*][1,5]diazocines, are herein named as McGeachin-type bisaminals. A TsOH-catalyzed chiral synthesis of McGeachin-type bisaminals is first developed by condensation of two molecules of 2-(methylamino)benzaldehyde and one molecule of chiral amines. Two chiral diastereomers are generated simultaneously, and are isolated by column chromatography in up to total 99% yields. The absolute structure of one stereoisomer was determined by X-ray crystallography.

INTRODUCTION

In 1926, Seidel first claimed that a trimer and a tetramer of *o*-aminobenzaldehyde were obtained, and proposed linear structures for them (Figure 1a, **I** and **II**).[1] It must be noted that these compounds were not first observed by Seidel.[2] However, it was Seidel that first conceived the correct composition. An eight-membered structural proposal was subsequently proposed by Bamberger in 1927 (Figure 1b, **III** and **IV**).[3] In 1966, McGeachin proposed bridged cyclic structures with two bridged carbon atoms and one apical nitrogen atom (Figure 1c, **V** and **VI**).[4a] In the same year, Albert and Yamamoto independently proposed similar structures but with two bridged nitrogen atoms and one apical carbon atom (Figure 1d, **VII** and **VIII**).[4b] McGeachin's structural proposal was proved correct; thus, we herein name the aminals with the structural subunits of iminodibenzodiazocine **IX** (Figure 1e) to McGeachin-type bisaminals. In previous synthetic reports, these bases were classified into pseudo-Troger's bases [5a] or Troger's base analogues,[5b] although they contain different structural motifs (Figure 1e, **X**). McGeachin-type bisaminals have been used as ligand backbones in some transition metal complexes.[6] Additionally, their antibacterial bioactivity was also explored by Son and coworkers.[7]

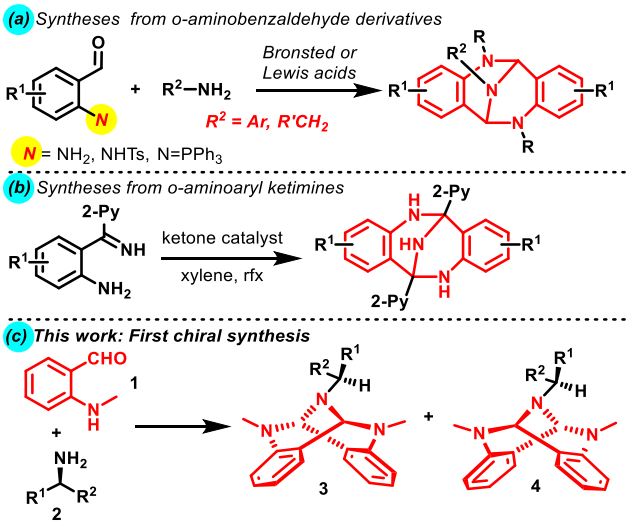
There exist limited methods to synthesize McGeachin-type bisaminals. The facile trimerization of *o*-aminobenzaldehyde implies that the condensation between two molecules of *o*-aminobenzaldehyde with one molecule of primary amines constitutes an efficient method. By using different surrogates of *o*-aminobenzaldehyde [8] or using different acid catalysts,[9] Molina's, Ukhin's, Yu and Wang's, and Sridharan's groups developed different synthetic routes to McGeachin-type bisaminals with functionalities at the apical nitrogen (Scheme 1a). In the above reports, primary aryl amines ($ArNH_2$) and α-substituted methylamines ($R'CH_2NH_2$) were used. Zonta and

Figure 1. Different structural proposals for McGeachin-type bisaminals in history.



coworkers achieved the synthesis by a metal-free cyclization of 2-aminophenyl ketimines with the corresponding 2-aminophenyl ketones as catalysts (Scheme 1b).[5b] In addition, occasional observations of McGeachin-type bisaminals were also reported by Aube,[10b,c] Loh,[10f] Menendez,[10g] our group,[11] and others.[10] However, the reported synthetic efforts all ignored the stereocenters (6- and 12-positions) of McGeachin-type bisaminals, and racemates were generated in all cases. It is of great importance to synthesize chiral McGeachin-type bisaminals, which may act as potential chiral catalysts or ligand backbones due to their unique structures.[11] Herein, we present the first chiral synthesis of McGeachin-type bisaminals from 2-(methylamino)benzaldehyde (**1**) and chiral amines (**2**), giving two diastereomeric chiral products **3** and **4**, which are isolated by column chromatography (Scheme 1c).

Scheme 1. Previous racemic syntheses and present chiral syntheses.



RESULTS AND DISCUSSION

We first tried the reaction of *o*-aminobenzaldehyde (**5**) with (*S*)-1-phenylethylamine (**2a**). (Scheme 2). After heating **5** and **2a** in toluene at 125 °C in a sealed tube for 12 h, desired product **6** and undesired trimer **7** were observed, together with an imine product (see Figures S1–S4 in the Supporting Information). However, products **6** and **7** could not be isolated. In Yu and Wang's work,[9a] the reactions of *o*-aminobenzaldehyde (**5**) with arylamines ($ArNH_2$) gave fused aminals that were formally derived from trimer **7** and arylamines, while the reactions with α-substituted methylamines ($R'CH_2NH_2$) gave McGeachin-type bisaminals. Based on their results, we postulated that the steric effect of the secondary alkyl group (1-phenylethyl) in amine **2a** disfavored the formation of **6**. To improve the chemoselectivity toward desired products, we must suppress the undesired trimerization. Pleasingly, Sridharan's work provided us a good solution by adding an alkyl group to the amino group of *o*-aminobenzaldehyde.[9b] So 2-(methylamino)benzaldehyde (**1**) was selected as the model substrate to perform the condition optimization (Table 1). Direct condensation of **1** and **2a** in the presence of $MgSO_4$ as desiccant did not give any product (entry 1). Initial screening of a number of Bronsted acids (entries 1-9) revealed that $TsOH{\cdot}H_2O$ was optimal. Without addition of $MgSO_4$, the yield was not affected (entry 10 vs entry 8). In contrast to Zonta's [5b] and Bergman's work,[10e] xylenes were not a suitable solvent, either under reflux conditions (entries 11-13) or in a sealed tube (entry 14). Tetrahydrofuran (THF) and acetonitrile were not effective (entries 15 and 16), although the latter was used as a very good solvent in Sridharan's work.[9b] Raising the temperature gave a higher 69% yield (entry 17). The Lewis acids explored all gave unsatisfactory yields (entries 18-24). Finally, heating in toluene at 150 °C for 48 h in a sealed tube with 20 mol % of $TsOH{\cdot}H_2O$ gave desired products in 99% total yield in 40:60 *d.r.* (entry 25). The absolute structure of **3a** was determined by XRD analysis.

Scheme 2. Reaction of *o*-aminobenzaldehyde with (*S*)-1-phenylethylamine.

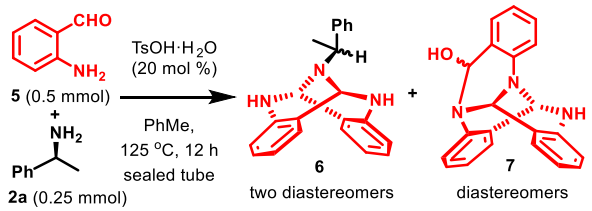
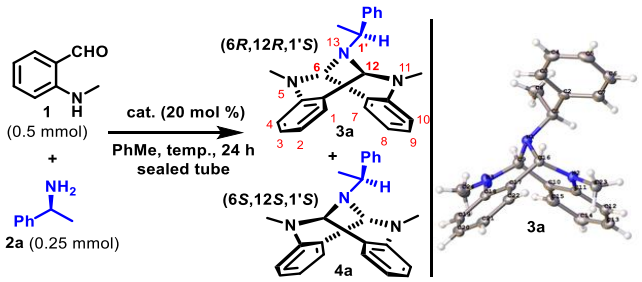


Table 1. Optimization of reaction conditions

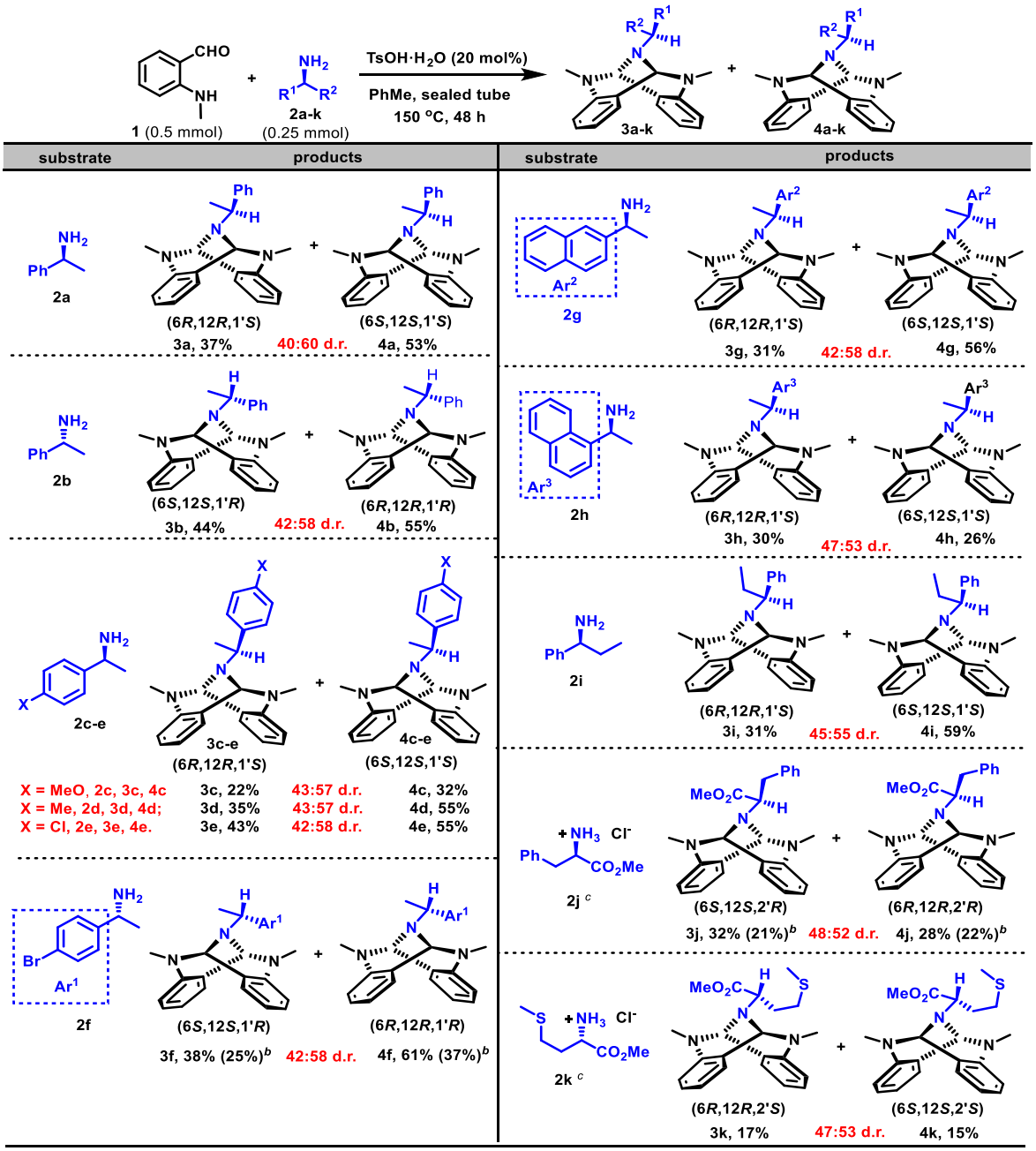


Entry	Cat.	Temp. (°C)	Yield (%)[a]	Ratio[b]
1[c]	-	125	0	-
2[c]	PPTS	125	0	-
3[c]	$PhCO_2H$	125	0	-
4[c]	CSA	125	0	-
5[c]	$Et_3N{\cdot}HCl$	125	0	-
6[c]	$4\text{-}ClC_5H_4N{\cdot}HCl$	125	0	-
7[c]	CF_3CO_2H	125	0	-
8[c]	$TsOH{\cdot}H_2O$	125	52	41:59
9[c]	$4\text{-}O_2NC_6H_4CO_2H$	125	21	42:58
10	$TsOH{\cdot}H_2O$	125	51	41:59
11[d]	$TsOH{\cdot}H_2O$	rfx	17	41:59
12[d]	$4\text{-}O_2NC_6H_4CO_2H$	rfx	2	50:50
13[d]	$2,4\text{-}(O_2N)_2C_6H_3CO_2H$	rfx	13	46:54
14[e]	$TsOH{\cdot}H_2O$	150	23	43:57
15[f]	$TsOH{\cdot}H_2O$	100	0	-
16[g]	$TsOH{\cdot}H_2O$	100	0	-
17	$TsOH{\cdot}H_2O$	150	69	40:60
18	$Sc(OTf)_3$	150	21	43:57
19	$Yb(OTf)_3$	150	21	43:57
20	$ZnCl_2$	150	9	44:56
21	$FeCl_3$	150	24	42:58
22	$AlCl_3$	150	9	45:55

23	$Cu(OTf)_2$	150	17	47:53
24	$PhB(OH)_2$	150	0	-
25 [h]	**$TsOH·H_2O$**	**150**	**99**	**40:60**

[a]Determined by ^1H NMR of the crude reaction mixtures with 4-nitroiodobenzene as an internal standard. [b]Ratio of **3a**:**4a** determined by ^1H NMR of the crude reaction mixtures. [c]In these cases, 1.5 equiv of $MgSO_4$ was added, while in the rest cases, no $MgSO_4$ was added. [d]Xylenes as solvent, and reaction refluxed in open air for 10 h. [e]Xylenes as solvent in a sealed tube. [f]THF as solvent. [g]MeCN as solvent. [h]Reaction time 48 h. PPTS = Pyridinium *p*-toluenesulfonate; CSA = Camphorsulfonic acid; rfx = reflux.

Table 2. Preparation of various chiral McGeachin-type bisaminals[a]



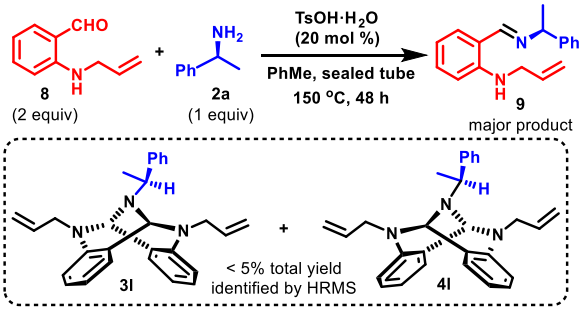
[a]Isolated yields after column chromatography, and the *d.r.* values were determined by the ^1H NMR of the crude reaction mixtures. [b]Yields in the parentheses were obtained from 1-mmol scale reactions. [c]1 equiv of triethylamine to chiral amine was added.

Various McGeachin-type bisaminals were prepared under the optimal conditions from chiral amines **2** and 2-(methylamino)benzaldehyde (**1**) (Table 2). The reaction of *S*-1-phenylethylamine (**2a**) gave (6*R*,12*R*,1'*S*)-**3a** and its diastereomer (6*S*,12*S*,1'*S*)-**4a** in 37 and 53% yields, respectively. By using (*R*)-1-phenylethylamine (**2b**) as chiral source,

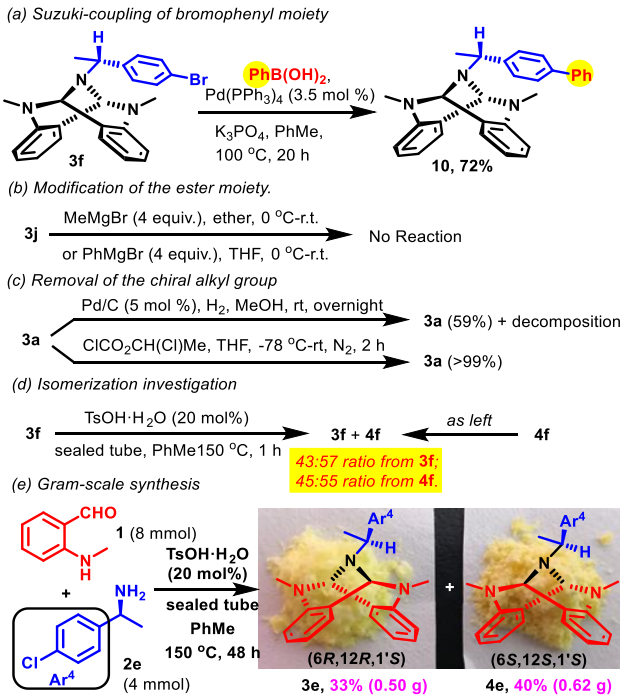
(6*S*,12*S*,1'*R*)-**3b** and its diastereomer (6*R*,12*R*,1'*R*)-**4b** were synthesized in 44 and 55% yields, respectively. Notably, **3a** and **3b**, and **4a** and **4b** are two pairs of enantiomers. Similar results were also obtained from the reactions of chiral amines **2c-h**, with desired products isolated in 54-99% total yields and around 45:55 *d.r.* values. The lower total yields of **3c** and **4c** (54%), and **3h** and **4h** (56%) were attributed to the very close polarity of the diastereomeric products during the purification by column chromatography. Sterically larger (*S*)-1-phenylpropan-1-amine (**2i**) also readily underwent the cascade reaction to deliver (6*R*,12*R*,1'*S*)-**3i** and (6*S*,12*S*,1'*S*)-**4i** in total 90% yields. Methyl *L*-phenylalaninate (**2j**) and methyl *L*-methioninate (**2k**) were also suitable substrates to prepare the corresponding McGeachin-type bisaminals, although the desired products were obtained in moderate yields.

When *N*-allyl aldehyde (**8**) was used, imine **9** was observed predominantly (Scheme 3). Desired McGeachin-type products (**3l** and **4l**) were only isolated in a trace amount, and were identified by HRMS analysis. This reaction indicated the strong steric effect of the *N*-alkyl group on the chiral synthesis.

Scheme 3. Reaction of *o*-(allylamino)benzaldehyde



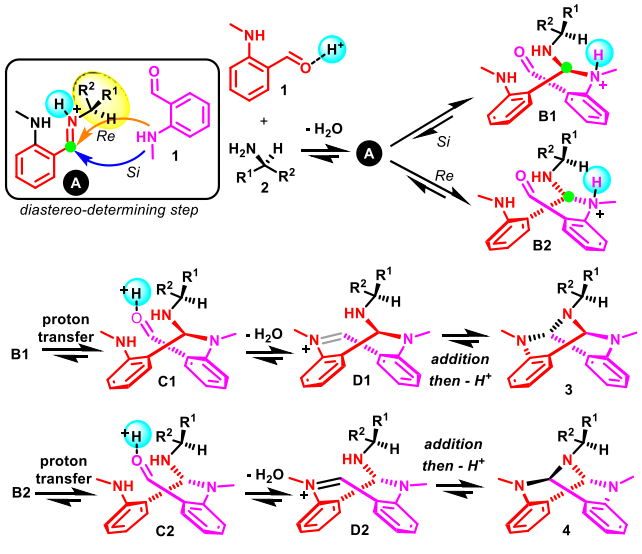
Scheme 4. Further manipulations and Gram-scale Synthesis



Further modification of the synthesized McGeachin-type bisaminals were performed. The Suzuki coupling of **3f** gave desired product **10** in 72% yield (Scheme 4a). However, modification of the ester group of **3j** with Grignard reagents (PhMgBr or MeMgBr) failed (Scheme 4b). We also tried to remove the chiral (*S*)-1-phenylethyl auxiliary with Pd/C-H_2 or 1-chloroethyl chloroformate,[12] but the results were not so satisfactory (Scheme 4c). The thermal equilibrium between the two chiral diastereomers were investigated (Scheme 4d). Treating **3f** under optimal conditions gave a mixture of **3f** and **4f** in 43:57 ratio, while the same treatment of **4f** gave a mixture in 45:55 ratio. Similar diastereomeric ratios were also observed in Table 1 and Table 2. Thus, the diastereoselectivity in the chiral synthesis of McGeachin-type bisaminals is probably thermodynamically controlled. The results in Scheme 1d also implied that once the chiral auxiliary was removed, racemization might occur under acidic conditions. Molina and coworkers first observed the racemization of a chiral McGeachin-type bisaminal.[5a] In a gram-scale synthesis, desired products **3e** and **4e** were isolated in 33% (0.50 g) and 40% (0.62 g) yields, respectively (Scheme 4e).

A tentative mechanism for the chiral synthesis of McGeachin-type bisaminals is proposed (Scheme 5). Proton-catalyzed condensation between 2-(methylamino)benzaldehyde (**1**) and chiral amine **2** gives an iminium intermediate **A**. Subsequent addition of a second molecular of **1** to **A** might occur from either *Re* or *Si* face of the iminium moiety. The *Re* addition delivers ammonium **B1**, while the *Si* addition gives **B2**. Through the same sequence of intramolecular proton transfer (**C1** and **C2**), amine-aldehyde condensation (**D1** and **D2**), amine-iminium addition and deprotonation, **B1** and **B2** finally evolve to **3** and **4**, respectively. We suggest that the *Si* or *Re* addition of **1** to **A** is the diastereo-determining step, although the *d.r.* values are ultimately regulated by a thermodynamical control. The thermal equilibrium investigation in Scheme 4d indicated that the reaction might be reversible. According to the mechanism, pure **3f** or **4f** go reversely through the sequence (from **D1** or **D2** to **A**) to regenerate intermediate **A**, which then go through the sequence (from **A** to **3** and **4**) a second time to reproduce a mixture of **3f** and **4f** in almost identical ratios (substrate **2f** in Table 2 vs Scheme 4d).

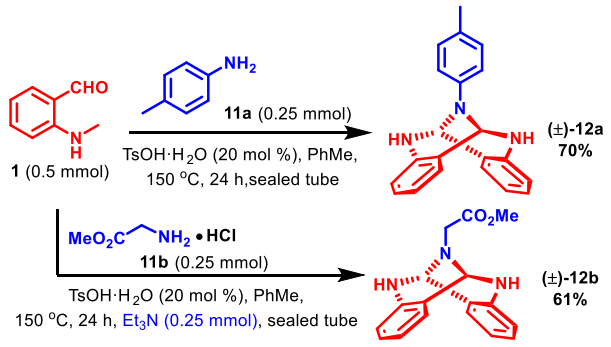
Scheme 5. Proposed mechanism



The current protocol is also applicable to the synthesis of racemic McGeachin-type bisaminals from aryl and alkyl amines. For example, under the optimal conditions, the reactions of *p*-tolylamine (**11a**) and methyl glycinate hydrochlo-

ride (**11b**) delivered desired products **12a** and **12b** in 70% and 61% isolated yields, respectively (Scheme 6).

Scheme 6. TsOH-catalyzed synthesis of racemic McGeachin-type bisaminals from aryl and alkyl amines



CONCLUSION

In summary, we have developed a TsOH-catalyzed chiral synthesis of McGeachin-type bisaminals from 2-(methylamino)benzaldehyde and chiral amines. A pair of chiral diastereomers are generated simultaneously in about 40:60 *d.r.*. The two diastereomers are isolated by column chromatography in up to 99% yields. The steric hindrance between the secondary *N*-alkyl of chiral amine and the *N*-alkyl of 2-(alkylamino)benzaldehyde is crucial to the occurrence of the chiral condensation. Preliminary results show that the McGeachin-type bisaminals show very weak nucleophilicity and basicity. We hope the unique bridged cyclic structures of our synthesized chiral McGeachin-type bisaminals will enable their applications as chiral catalyst or ligand backbones in the future.

EXPERIMENTAL SECTION

General Information

All the reactions were performed in dry toluene under nitrogen atmosphere, and the reaction tubes were flame-dried prior to use. Column chromatography was performed on silica gel (200–300 mesh) from Anhui Liangchen silicon source material Co., Ltd, and petroleum ether (PE, b.p. 60–90 °C) and ethyl acetate (EA, commercially received) were used as eluents. Reactions were monitored by thin-layer chromatography on silica gel from Anhui Liangchen silicon source material Co., Ltd. The plates were visualized under UV light. Melting points were obtained on a melting point apparatus and were uncorrected. The specific rotation analysis was measured by Anton Paar MCP200 Pa polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer in $CDCl_3$ with TMS as an internal standard, and the chemical shifts (δ) were reported in part(s) per million (ppm). The high-resolution mass analyses were performed under ESI ionization using a Thermoscientific Q Exactive spectrometer (only for **12a** and **12b**) and an Agilent LC/MSD TOF mass spectrometer. The GC-MS analyses were performed on a Thermo Sscientific tandem equipment.

All the chiral amines were commercially available. 2-(Methylamino)benzaldehyde (**2**)[13] and 2-(allylamino)benzaldehyde (**8**)[14] were prepared according to published procedures, and their ^{1}H NMR spectra were identical with those reported.

General Procedure for Synthesis of McGeachin-type bisaminals

To a heavy-wall reaction tube charged with a magnetic stirring bar was sequentially added 2-(methylamino)benzaldehyde (**1**) (68 mg, 0.5 mmol), amine **2** (0.25 mmol), triethylamine (0.25 mmol, only for **2j**, **2k**, and **11b**), TsOH·H_2O (9.5 mg, 0.1 mmol), and dry toluene (2.5 ml). Then the tube was sealed by a polytetrafluoroethylene screw cap, and was immersed into a preheated 150 °C heating-mantle for 48 h. The solvent was removed under reduced pressure. The crude residue was purified by silica gel column chromatography to give a pair of diastereomers **3** and **4**.

(6*R*,12*R*)-5,11-Dimethyl-13-((*S*)-1-phenylethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3a**)

Yield: 32.9 mg (37%); white solid, m.p.: 166–168 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 79.1 (*c*, 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43–7.30 (m, 5H), 7.12 (ddd, *J* = 8.5, 7.4, 1.6 Hz, 2H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.66–6.57 (m, 4H), 4.75 (s, 2H), 3.67 (q, *J* = 6.5 Hz, 1H), 2.90 (s, 6H), 1.49 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 143.6, 143.5, 128.7, 128.4, 127.8, 127.5, 127.3, 71.6, 56.8, 36.2, 21.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}N_3^+$, 356.2121; found, 356.2115.

(6*S*,12*S*)-5,11-Dimethyl-13-((*S*)-1-phenylethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4a**)

Yield: 47.0 mg (53%); white solid, m.p.: 148–150 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -145.7 (*c*, 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.41–7.29 (m, 5H), 7.16–7.09 (m, 2H), 7.01 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.66 (t, *J* = 7.3 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 2H), 4.81 (s, 2H), 3.64 (q, *J* = 6.5 Hz, 1H), 2.95 (s, 6H), 1.52 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 143.9, 128.6, 128.5, 127.7, 127.5, 127.2, 120.7, 116.4, 111.8, 71.6, 57.1, 36.4, 21.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}N_3^+$, 356.2121; found, 356.2128.

(6*S*,12*S*)-5,11-Dimethyl-13-((*R*)-1-phenylethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3b**)

Yield: 39.0 mg (44%); white solid; m.p.: 97–100 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -71.8 (*c*, 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.43–7.28 (m, 5H), 7.16–7.09 (m, 2H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.67–6.56 (m, 2H), 4.75 (s, 2H), 3.67 (q, *J* = 6.5 Hz, 1H), 2.91 (s, 6H), 1.49 (d, J = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 143.5, 128.7, 128.4, 127.9, 127.5, 127.3, 120.2, 116.2, 111.5, 71.6, 56.7, 36.2, 21.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}N_3^+$, 356.2121; found, 356.2122.

(6*R*,12*R*)-5,11-dimethyl-13-((*R*)-1-phenylethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4b**)

Yield: 48.8 mg (55%); white solid; m.p.: 134–136 °C; R_f = 0.50 (PE:EA = 3:1, *v/v*); $[\alpha]_D^{25}$ = 137.5 (*c*, 1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$, δ): 7.38–7.23 (m, 5H), 7.09 (td, *J* = 7.6, 1.6 Hz, 2H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.62 (td, *J* = 7.4, 1.1 Hz, 2H), 6.56 (dd, *J* = 8.2, 1.1 Hz, 2H), 4.78 (s, 2H), 3.61 (q, *J* = 6.5 Hz, 1H), 2.91 (s, 6H), 1.48 (d, *J* = 6.5 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$, δ): 143.9, 128.6, 128.45, 127.7, 127.5, 127.2, 120.7, 116.4, 111.8, 71.56, 57.1, 36.4, 21.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{26}N_3^+$, 356.2121; found, 356.2130.

(6*R*,12*R*)-13-((*S*)-1-(4-methoxyphenyl)ethyl)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3c**)

Yield: 21.2 mg (22%); white solid; m.p.: 138–140 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 23.5 (*c*, 0.8, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.33–7.27 (m, 2H), 7.13–7.06 (m, 2H), 6.95 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.90–6.84 (m, 2H), 6.64 – 6.53 (m, 4H), 4.72 (s, 2H), 3.83 (s, 3H), 3.60 (q, *J* = 6.5 Hz, 1H), 2.89 (s,6H), 1.45 (d, *J* = 6.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 158.8, 143.5, 135.7, 129.0, 128.7, 127.5, 120.2, 116.2, 113.7, 111.5, 71.6, 56.0, 55.3, 36.2, 21.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}N_3O^+$, 386.2227; found, 386.2221.

(6*S*,12*S*)-13-((*S*)-1-(4-Methoxyphenyl)ethyl)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo [*b*,*f*][1,5]diazocine (**4c**)

Yield: 30.8 mg (32%); white solid; m.p.: 138–140 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -80.2 (*c*, 0.48, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.26–7.22 (m, 2H), 7.09 (td, *J* = 8.0, 1.5 Hz, 2H), 6.97 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.88–6.82 (m, 2H), 6.62 (td, *J* = 7.4, 1.1 Hz, 2H), 6.56 (d, *J* = 8.2 Hz, 2H), 4.77 (s, 2H), 3.81 (s, 3H), 3.55 (t, *J* = 6.5 Hz, 1H), 2.92 (s, 6H), 1.47 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 158.7, 143.9, 136.5, 128.6, 128.5, 127.7, 120.7, 116.4, 113.8, 111.8, 71.5, 56.3, 55.2, 36.4, 21.7. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}N_3O^+$, 386.2227; found, 386.2235.

(6*R*,12*R*)-5,11-Dimethyl-13-((*S*)-1-(*p*-tolyl)ethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3d**)

Yield: 32.3 mg (35%); yellow solid; m.p.: 130–132 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 55.8 (*c*, 0.4, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.29 (d, *J* = 8.0 Hz, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 7.11 (td, *J* = 8.8, 1.6 Hz, 2H), 6.62 (td, *J* = 7.4, 1.1 Hz, 2H), 6.58 (dd, *J* = 8.2, 1.0 Hz, 4H), 4.75 (s, 2H), 3.63 (q, *J* = 6.5 Hz, 1H), 2.90 (s, 6H), 2.38 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.5, 140.6, 136.9, 129.1, 128.7, 127.8, 127.5, 120.2, 116.2, 111.5, 71.6, 56.4, 36.2, 21.2. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}N_3^+$, 370.2278; found, 370.2277.

(6*S*,12*S*)-5,11-Dimethyl-13-((*S*)-1-(*p*-tolyl)ethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4d**)

Yield: 50.7 mg (55%); yellow solid; m.p.: 54–56 °C; R_f = 0.50 (PE:EA = 3:1, *v/v*); $[\alpha]_D^{25}$ = -151.3 (*c*, 0.6, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.24–7.20 (m, 2H), 7.14–7.06 (m, 4H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.62 (td, *J* = 7.4, 1.1 Hz, 2H), 6.56 (dd, *J* = 8.2, 1.1 Hz, 2H), 4.78 (s, 2H), 3.57 (q, *J* = 6.5 Hz, 1H), 2.92 (s, 6H), 2.35 (s, 3H), 1.47 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.9, 141.5, 136.7, 129.1, 128.6, 127.7, 127.4, 120.7, 116.4, 111.7, 71.5, 56.7, 36.4, 21.8, 21.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}N_3^+$, 370.2278; found, 370.2283.

(6*R*,12*R*)-13-((*S*)-1-(4-Chlorophenyl)ethyl)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3e**)

Yield: 41.8 mg (43%); yellow solid; m.p.: 191–193 °C; R_f = 0.60 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 36.1 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.38–7.30 (m, 4H), 7.16–7.08 (m, 2H), 6.97 (dd, *J* = 7.5, 1.5 Hz, 2H), 6.64 (td, *J* = 7.4, 1.1 Hz, 2H), 6.59 (d, *J* = 8.2 Hz, 2H), 4.72 (s, 2H), 3.67 (q, *J* = 6.5 Hz, 1H), 2.91 (s, 6H), 1.45 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.4, 142.3, 132.9, 129.2, 128.2, 1286, 127.5, 120.0, 116.4, 111.6, 71.5, 56.1, 36.2, 21.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{25}ClN_3^+$, 390.1732 found, 390.1735.

(6*S*,12*S*)-13-((*S*)-1-(4-Chlorophenyl)ethyl)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4e**)

Yield: 53.4 mg (55%); white solid; m.p.: 129–132 °C; R_f = 0.70 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -158.7 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.31 (s, 4H), 7.13 (td, *J* = 8.6, 1.5 Hz, 2H), 7.00 (d, *J* = 7.6 Hz, 2H), 6.66 (t, *J* = 7.6 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 2H), 4.77 (d, *J* = 1.7 Hz, 2H), 3.62 (qd, *J* = 6.5, 1.6 Hz, 1H), 2.94 (s, 6H), 1.48 (d, *J* = 6.5, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.8, 143.2, 132.7, 128.8, 128.7, 128.7, 127.7, 120.5, 116.5, 111.8, 71.6, 56.6, 36.3, 21.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{25}ClN_3^+$, 390.1732; found, 390.1730.

(6*S*,12*S*)-13-((*R*)-1-(4-Bromophenyl)ethyl)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine(**3f**)

Yield: 41.1 mg (38%); white solid; m.p.: 203–205 °C; R_f = 0.55 (PE:EA = 3:1, *v/v*); $[\alpha]_D^{25}$ = -24.5 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.53–7.44 (m, 2H), 7.31–7.26 (m, 2H), 7.15–7.09 (m, 2H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.63 (td, *J* = 7.4, 1.1 Hz, 2H), 6.58 (d, *J* = 8.3 Hz, 2H), 4.72 (s, 2H), 3.65 (q, *J* = 6.5 Hz, 1H), 2.90 (s, 6H), 1.44 (d, J = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.4, 142.8, 131.6 , 129.6, 128.8, 127.5, 121.0, 120.0, 116.4, 111.6, 71.5, 56.2, 36.2, 21.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{25}BrN_3^+$, 434.1226; found, 434.1221.

(6*R*,12*R*)-13-((*R*)-1-(4-Bromophenyl)ethyl)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4f**)

Yield: 66.0 mg (61%); yellow solid; m.p.: 165–167 °C; R_f = 0.75 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 165.0 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.48–7.42 (m, 2H), 7.29–7.22 (m, 2H), 7.15–7.09 (m, 2H), 7.00 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.65 (td, *J* = 7.4, 1.1 Hz, 2H), 6.59 (d, *J* = 8.2 Hz, 2H), 4.76 (s, 2H), 3.60 (d, *J* = 6.5 Hz, 1H), 2.94 (s, 6H), 1.47 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.9, 143.8, 131.7, 129.3, 128.8, 127.8, 120.9, 120.5, 116.6, 111.9, 71.6, 56.7, 36.4, 21.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{25}BrN_3^+$, 434.1226; found, 434.1226.

(6*R*,12*R*)-5,11-Dimethyl-13-((*S*)-1-(naphthalen-2-yl)ethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3g**)

Yield: 31.4 mg (31%); white solid; m.p.: 68–70 °C; R_f = 0.65 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 23.3 (*c*, 0.54, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.87–7.79 (m, 4H), 7.59 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.48 (dd, *J* = 6.2, 3.2 Hz, 2H), 7.11 (td, *J* =

8.4, 1.6 Hz, 2H), 6.92 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.64–6.57 (m, 4H), 4.77 (s, 2H), 3.83 (q, *J* = 6.5 Hz, 1H), 2.89 (s, 6H), 1.54 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.5, 141.3, 133.5, 133.1, 128.8, 128.31 , 127.9, 127.7, 127.5, 126.7, 126.0, 125.9, 125.8, 120.2, 116.4, 111.6, 71.7, 56.9, 36.6, 21.2. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{28}N_3^+$, 406.2278; found, 406.2279.

(6*S*,12*S*)-5,11-dimethyl-13-((*S*)-1-(naphthalen-2-yl)ethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4g**)

Yield: 56.7 mg (56%); yellow solid; m.p.: 66–68 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -106.1 (*c*, 0.28, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.87–7.77 (m, 3H), 7.73 (s, 1H), 7.61 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.48 (dd, *J* = 6.2, 3.3 Hz, 2H), 7.13 (td, *J* = 8.0, 1.6 Hz, 2H), 6.99 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.65 (td, *J* = 7.4, 1.1 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 4.85 (s, 2H), 3.81 (q, *J* = 6.5 Hz, 1H), 2.93 (s, 6H), 1.58 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.9, 142.1, 133.5, 133.0, 128.7, 128.3, 127.8, 127.8, 1276, 126.1, 125.9, 125.7, 125.6, 120.7, 116.5, 111.8, 71.6, 57.3, 36.4, 21.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{28}N_3^+$, 406.2278; found, 406.2281.

(6*R*,12*R*)-5,11-Dimethyl-13-((*S*)-1-(naphthalen-1-yl)ethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3h**)

Yield: 30.4 mg (30%); yellow solid; m.p.: 138–140 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 69.0 (*c*, 0.4, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.21 (s, 1H), 7.92 (dd, *J* = 8.0, 1.5 Hz, 3H), 7.83 (d, *J* = 8.2 Hz, 3H), 7.52–7.43 (m, 3H), 7.16 (td, *J* = 8.4, 1.6 Hz, 2H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.65 (td, *J* = 7.3, 1.1 Hz, 2H), 6.62 (dd, *J* = 8.3, 1.0 Hz, 2H), 4.86 (s, 2H), 4.56 (s, 1H), 2.81 (s, 6H), 1.61 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.5, 139.7, 133.9, 131.5, 128.8, 127.6 (d, *J* = 2.4 Hz), 125.7, 125.7, 125.4, 120.4, 116.3, 111.6, 71.7, 36.3, 21.0. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{28}N_3^+$, 406.2278; found, 406.2279.

(6*S*,12*S*)-5,11-dimethyl-13-((*S*)-1-(naphthalen-1-yl)ethyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4h**)

Yield: 26.3 mg (26%); white solid; m.p.: °C; R_f = 0.65 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -85.3 (*c*, 0.6, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 8.15-7.65 (m, 4H), 7.56–7.44 (m, 2H), 7.37 (td, *J* = 8.4, 1.5 Hz, 1H), 7.16 (td, *J* = 7.7, 1.5 Hz, 2H), 6.98 (dt, *J* = 7.8, 1.5 Hz, 2H), 6.69–6.61 (m, 4H), 4.92 (d, *J* = 1.5 Hz, 2H), 4.53 (s, 1H), 2.97 (s, 6H), 1.65 (d, *J* = 6.6 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 144.0, 140.4, 133.9, 131.5, 128.7, 128.6, 127.9, 127.4, 125.9, 125.6, 125.3, 120.9, 116.4, 111.7, 71.7, 36.4, 21.2. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{28}H_{28}N_3^+$, 406.2278; found, 406.2278.

(6*R*,12*R*)-5,11-Dimethyl-13-((*S*)-1-phenylpropyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**3i**)

Yield: 28.6 mg (31%); yellow solid; m.p.: 52–54 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 4.3 (*c*, 0.32, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.39–7.28 (m, 5H), 7.12 (td, *J* = 8.8 Hz, 1.6 Hz, 2H), 6.96 (dd, *J* = 7.4, 1.6 Hz,2H), 6.63 (td, *J* = 7.4, 1.1 Hz,2H), 6.58 (d, *J* = 8.2 Hz, 2H), 4.77 (s, 2H), 3.41 (dd, *J* = 10.3, 3.7 Hz, 2H), 2.88 (s, 6H), 2.09 (ddq, *J* = 18.4, 11.2, 3.6 Hz, 1H), 1.84 (ddq, *J* = 13.2, 10.1, 7.5 Hz, 1H), 0.62 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.6, 141.1, 128.9, 128.7, 128.2, 127.5, 127.3, 120.4, 116.2, 111.5, 71.8, 63.5, 36.2, 26.4, 10.6. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}N_3^+$, 370.2278; found, 370.2278.

(6*S*,12*S*)-5,11-Dimethyl-13-((*S*)-1-phenylpropyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**4i**)

Yield: 54.5 mg (59%); yellow solid; m.p.: 98–100 °C; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -71.8 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.34–7.27 (m, 5H), 7.09 (td, *J* = 8.2, 7.8, 1.6 Hz, 2H), 6.97 (dd, *J* = 7.4, 1.6 Hz, 2H), 6.63 (t, *J* = 7.4, 2H), 6.57 (d, *J* = 8.2 Hz, 2H), 4.79 (s, 2H), 3.42 (dd, *J* = 9.5, 3.8 Hz, 1H), 2.92 (s, 6H), 2.09 (ddq, *J* = 19.2, 11.6, 4.0 Hz, 1H), 1.86–1.72 (m, 1H), 0.64 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 144.0, 141.8, 128.6, 128.2, 127.7, 127.2, 120.8, 116.4, 111.8, 71.7, 63.1, 36.5, 26.4, 10.2. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{25}H_{28}N_3^+$, 370.2278; found, 370.2283.

(*R*)-2-((6*S*,12*S*)-5,11-Dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocin-13-yl)-3-phenylpropanoate (**3j**)

Yield: 33.0 mg (32%); yellow solid; m.p.: 144–146 °C; R_f = 0.55 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -2.4 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.25–7.14 (m, 5H), 7.09 (td, *J* = 8.2, 1.6 Hz, 2H), 7.04 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.66 (td, *J* = 7.4, 1.1 Hz, 2H), 6.57 (d, *J* = 8.2 Hz, 2H), 4.93 (s, 2H), 3.72 (dd, *J* = 9.8, 5.4 Hz, 1H), 3.34 (s, 3H), 3.29 (dd, *J* = 13.0, 5.4 Hz, 1H), 3.14 (dd, *J* = 13.0, 9.8 Hz, 1H), 2.98 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 172.5, 143.6, 137.0, 129.1, 128.8, 128.4, 127.4, 126.7, 120.8, 117.0, 112.4, 72.5, 64.7, 51.5, 37.4, 36.6. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_2^+$, 414.2176; found, 414.2182.

(*R*)-2-((6*R*,12*R*)-5,11-Dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocin-13-yl)-3-phenylpropanoate (**4j**)

Yield: 28.8 mg (28%); yellow solid; m.p.: 115–117 °C; R_f = 0.75 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 0.6 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.24–7.17 (m, 3H), 7.14–7.07 (m, 4H), 7.02 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.65 (td, *J* = 7.4, 1.1 Hz, 2H), 6.56 (d, *J* = 8.3 Hz, 2H), 4.96 (s, 2H), 3.65 (t, *J* = 7.5 Hz, 1H), 3.35 (s, 3H), 3.16 (d, *J* = 7.5 Hz, 2H), 2.97 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 172.1, 143.3, 137.3, 129.2, 128.8, 128.3, 127.2, 126.6, 120.8, 116.7, 112.1, 72.6, 64.2, 51.3, 37.5, 36.6. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{26}H_{28}N_3O_2^+$, 414.2176; found, 414.2177.

Methyl (*S*)-2-((6*R*,12*R*)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocin-13-yl)-4-(methylthio)butanoate (**3k**)

Yield: 16.8 mg (17%); yellow liquid; R_f = 0.50 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = -2.7 (*c*, 0.62, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.13–7.04 (m, 2H), 7.04 (dd, *J* = 7.5, 1.5 Hz, 2H), 6.65 (td, *J* = 7.4, 1.1 Hz, 2H), 6.56 (d, *J* = 8.1 Hz, 2H), 4.85 (s, 2H), 3.59 (dd, *J* = 7.4, 5.6 Hz, 1H), 3.49 (s, 3H), 3.01 (s, 6H), 2.59–2.45 (m, 2H), 2.26–2.13 (m, 2H), 2.09 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 172.7, 143.6, 128.7, 127.4, 120.9,

116.9, 112.4, 72.5, 61.7, 51.7, 36.7, 30.0, 29.9, 15.5. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_2S^+$, 398.1897; found, 398.1900.

Methyl (*S*)-2-((6*S*,12*S*)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocin-13-yl)-4-(methylthio)butanoate (**4k**)

Yield: 14.9 mg (15%); yellow liquid; R_f = 0.75 (PE:EA = 5:1, *v/v*); $[\alpha]_D^{25}$ = 1.4 (*c*, 0.22, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.14–7.08 (m, 2H), 7.07 (dd, *J* = 7.5, 1.6 Hz, 2H), 6.68 (td, *J* = 7.4, 1.1 Hz, 2H), 6.58 (dd, *J* = 8.2, 1.0 Hz, 2H), 4.93 (s, 2H), 3.60 (dd, *J* = 8.0, 5.7 Hz, 1H), 3.47 (s, 3H), 3.00 (s, 6H), 2.58 (ddd, *J* = 13.1, 7.1, 4.4 Hz, 1H), 2.49 (ddd, *J* = 13.2, 8.5, 6.4 Hz, 1H), 2.23–2.11 (m, 2H), 2.09 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 172.5, 143.4, 128.7, 127.1, 121.1, 116.8, 112.2, 72.5, 60.9, 51.4, 36.7, 30.3, 29.8, 15.4. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{28}N_3O_2S^+$, 398.1897; found, 398.1892.

5,11-Dimethyl-13-(*p*-tolyl)-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocine (**12a**)

Yield: 60.1 mg (70%); white solid, m.p.:65–67 °C; R_f = 0.60 (PE:EA = 5:1, *v/v*). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.23–7.13 (m, 4H), 7.11–6.98 (m, 4H), 6.73 (td, *J* = 7.4, 1.0 Hz, 2H), 6.64 (d, *J* = 8.2 Hz, 2H), 5.55 (s, 2H), 3.09 (s, 6H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 144.7, 143.6, 130.8, 129.6, 128.8, 127.1, 121.1, 118.5, 116.7, 112.4, 73.2, 36.7, 20.5. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{24}N_3^+$, 342.1965; found, 342.1956.

Methyl 2-(5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo[*b*,*f*][1,5]diazocin-13-yl)acetate (**12b**)

Yield: 49.3 mg (61%); white solid, m.p.:45–47 °C; R_f = 0.40 (PE:EA = 2:1, *v/v*). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.14 (td, *J* = 8.0, 1.6 Hz, 2H), 7.09 (dd, *J* = 7.5, 1.5 Hz, 2H), 6.68 (t, *J* = 7.4 Hz, 2H), 6.61 (d, *J* = 8.2 Hz, 2H), 4.91 (s, 2H), 3.76 (s, 3H), 3.64 (d, *J* = 16.9 Hz, 1H), 3.36 (d, *J* = 16.9 Hz, 1H), 3.04 (s, 6H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 170.8, 143.1, 128.9, 127.7, 119.9, 116.7, 112.0, 74.2, 51.9, 51.6, 36.5. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{22}N_3O_2^+$, 324.1707; found, 324.1696.

Procedure for the Suzuki-Coupling of 3f

To a dry reaction tube charged with a magnetic stirring bar was added **3f** (43.3 mg, 0.1 mmol), $PhB(OH)_2$ (18.3 mg, 0.15 mmol), K_3PO_4 (42.5 mg, 0.2 mmol), $Pd(PPh_3)_4$ (4 mg, 3.25 μmol, 3.5 mol %), and dry toluene (1.5 ml) under a nitrogen atmosphere. The tube was sealed and the mixture was stirred for 20 h at 100 °C in a heating-mantle. The solvent was removed by distillation under reduced pressure. The crude residue was purified by silica gel column chromatography to give desired product **10**.

(6*S*,12*S*)-13-((*R*)-1-([1,1'-Biphenyl]-4-yl)ethyl)-5,11-dimethyl-5,6,11,12-tetrahydro-6,12-epiminodibenzo [*b*,*f*][1,5]diazocine (**10**)

Yield: 31.0 mg (72%); yellow solid, m.p.: 144–146 °C; R_f = 0.55 (PE:EA = 10:1, *v/v*); $[\alpha]_D^{25}$ = -30 (*c*, 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$, δ): 7.66 (d, *J* = 8.0 Hz, 2H), 7.61 (d, *J* = 8.2 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 4H), 7.40–7.32 (m, 1H), 7.13 (t, *J* = 7.7 Hz, 2H), 6.99 (d, *J* = 7.4 Hz, 2H), 6.64 (t, *J* = 7.4 Hz, 2H), 6.60 (d, *J* = 8.2 Hz, 2H), 4.80 (s, 2H), 3.73 (q, *J* = 6.4 Hz, 1H), 2.93 (s, 6H), 1.52 (d, *J* = 6.5 Hz, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$, δ): 143.5, 142.7, 140.8, 140.1, 128.7, 128.3, 127.5, 127.2, 127.1, 127.0, 120.1, 116.3, 111.5, 71.6, 56.4, 36.2, 21.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{30}H_{30}N_3^+$, 432.2434; found, 432.2437.

Procedure for the isomerization investigation of 3f and 4f

To a dry reaction tube charged with a magnetic stirring bar was added **3f** or **4f** (21.7 mg, 0.05 mmol), $TsOH\cdot H_2O$ (2 mg, 0.01 mmol, 20 mol %), and dry toluene (1 ml). The tube was sealed and was heated for 1 h at 150 °C in a heating-mantle. The solvent was removed under reduced pressure. The crude residue was submitted to ^1H NMR to measure the diastereometic ratio.

ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR, MS, and HRMS spectra, and CIF file of **3a**. These material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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