Article

JOURNAL OF THE CHINESE CHEMICAL SOCIETY

Condensation-ring Expansion Reaction of Formyl[2.2.1]bicyclic Carbinols with *Para*-substituted Phenyl Amines: Application to the Preparation of [3.2.1]bicyclic *N*-aryl-1,2,3-oxathiazolidine-2-oxide Agents

Te-Fang Yang,[a,*] Li-Hsun Chen,[b] Li-Ta Kao,[b] Chih-Hsiang Chuang[a] and Yong-Yen Chen[a]
[a]*Department of Applied Chemistry, National Chi Nan University, Puli, 545, Nantou, Taiwan, R.O.C.*
[b]*Department of Applied Chemistry, Chaoyang University of Technology, Wufong, 413, Taichung, Taiwan, R.O.C.*

(Received: Aug. 26, 2011; Accepted: Dec. 12, 2011; Published Online: Jan. 12, 2012; DOI: 10.1002/jccs.201100517)

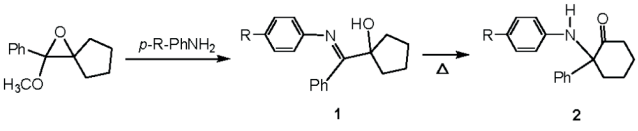
Individual reaction of camphene-derived *endo*-formyl[2.2.1]bicyclic carbinol and that of camphor-derived *exo*-formyl[2.2.1]bicyclic carbinol with parent and *para*-substituted phenyl amines gave regio- and stereospecific corresponding [3.2.1]bicyclic (*para*-substituted) phenyl amino ketones. Mechanism of each reaction was discussed. Some camphor-derived [3.2.1]bicyclic amino ketones were reduced to [3.2.1]bicyclic (*para*-substituted) phenyl amino alcohols, which were then treated with mesyl chloride to provide [3.2.1]bicyclic *N*-phenyl/aryl-1,2,3-oxathiazolidine-2-oxide agents. The mechanism of this final reaction was discussed as well.

Keywords: Formyl bicyclic carbinols; Ring expansion; Bicyclic aryl amino ketone; 1,2,3-Oxathiazolidine-2-oxide.

INTRODUCTION

It has been known for several decades that the reaction of cyclopentyl phenyl epoxyether with *para*-substituted aniline afforded *N*-*para*-substituted-phenyl-1-(α-phenyliminobenzyl)cyclopentol (**1**, Scheme I)[1], which could further undergo thermal rearrangement to give 2-phenyl-2-*para*-substituted-phenyl-aminocyclohexanone (**2**). The rearrangement was believed to proceed through a concerted transition state, which was unlikely stabilized by the resonance effect from the *para*-substituent. Nevertheless, the stereochemistry was not studied and discussed at that time. An application of this thermal reaction to the asymmetric synthesis of 2-chlorophenyl-2-methylamino cyclohexanone from 1-(2-chlorophenylmethyliminomethyl)-cyclopentanol, using metal complexes as the catalysts, was then reported by Brunner and co-workers.[2] Furthermore, conversion of α-hydroxy imines to α-amino ketones had been also carried out by utilizing thermal rearrangement, which involved a conventional alkyl 1,2-carbon migration rather than a ring expansion.[3] Recently, it has been reported by our lab that reaction of formyl[2.2.1]bicyclic carbinols with various C-nucleophiles provided corresponding regio- and stereospecific alkyl/aryl [3.2.1]bicyclic diols, whereas the solutions of the same substrate in methanol furnished various [3.2.1]bicyclic hydroxyl ketones.[4] On the other hand, [3.2.1]bicyclic alkyl amino ketone agents could be selectively obtained from the treatment of camphor-derived *exo*-formyl[2.2.1]bicyclic carbinol with alkyl primary amines.[5] Being encouraged by all the above interesting works, we have further studied the reaction of some formyl[2.2.1]bicyclic carbinols (**3** and **4**, Fig. 1) with various *para*-substituted analines, which are aryl amines and proved to be remarkable *N*-nucleophile donors as well. For the study on the title reaction, carbinols **3** and **4** were prepared using the known procedures.[4]

Scheme I Thermal rearrangement of phenyl-1-(α-phenyl iminobenzyl)cyclopentol



1 2

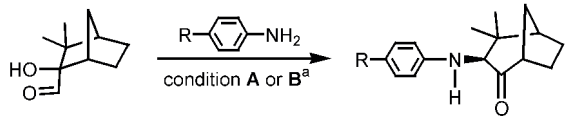
RESULTS AND DISCUSSION

As demonstrated in Table 1, the reaction of carbinol **3** with parent aniline (entry 1) as well as with various *para*-substituted phenyl amines (entries 2 ~ 10) correspondingly furnished products **5a**~**5j**. This reaction was individually carried out in dichloromethane at room temperature (condition A) and in toluene at reflux (condition B). On the proton NMR spectra of products **5**, it was found that the chemical

Dedicated to the memory of Professor Yung-Son Hon (1955–2011).

* Corresponding author. Tel: +886-49-2910960; Fax: +886-49-2917956; E-mail: tfyang@ncnu.edu.tw

Table 1. Results of the reaction of carbinol **3** with aryl amines

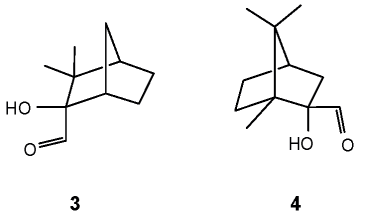


3 **5**

Entry	Aryl amine	Product	Yield (%)[c]	
			condition **A**	condition **B**
1	*p*-H-PhNH$_2$[b]	**5a** (R = H)	54	75
2	*p*-Me-PhNH$_2$	**5b** (R = Me)	42	88
3	*p*-HO-PhNH$_2$	**5c** (R = OH)	48	73
4	*p*-MeO-PhNH$_2$	**5d** (R = OMe)	64	83
5	*p*-*i*-Pr-PhNH$_2$	**5e** (R = *i*-Pr)	71	79
6	*p*-Cl-PhNH$_2$	**5f** (R = Cl)	58	95
7	*p*-Br-PhNH$_2$	**5g** (R = Br)	66	64
8	*p*-I-PhNH$_2$	**5h** (R = I)	63	61
9	*p*-NO$_2$-PhNH$_2$	**5i** (R = NO$_2$)	67	32
10	*p*-Ac-PhNH$_2$	**5j** (R = Ac)	82	65

[a]Condition **A**: CH_2Cl_2, r.t., 30 min. Condition **B**: toluene, reflux, 3h.
[b]Aniline.
[c]Yield of isolated product.

shifts of the signals of protons on the carbons which possess aryl amino groups ranged from 3.70 ppm to 4.04 ppm. Furthermore, the signal of each of those protons turned out to be either a singlet or a doublet, which was due to the coupling of that corresponding proton with the proton on nitrogen atom, demonstrating that the aryl amino group is bonded with *exo*-orientation to the ring-carbon atom which is farthest from both bridgehead carbons. The exact structures of products **5** were confirmed with X-ray crystallography. For each entry listed in Table 1, among all possible regio- and stereoisomers of [3.2.1]bicyclic amino ketone product, compound **5** was the only one observed and isolated. As expected, carbinol **3** reacted with most of the *para*-substituted phenylamines (entries 1~6) more efficiently under condition B compared to that in A. However,



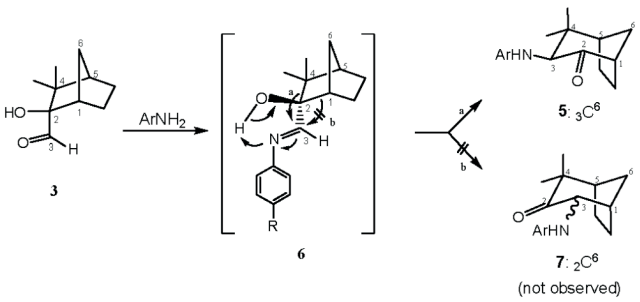
3 **4**

Fig. 1. Formyl[2.2.1]bicyclic carbinols that react with *para*-substituted analines.

para-bromo and *para*-iodo phenyl amines did not show significant difference in their nucleophilicities under both conditions (entries 7 and 8). Surprisingly, for the *N*-nucleophiles possessing nitro and acetyl groups at *para*-position, dichloromethane was a better solvent than toluene (entries 9 and 10).

A plausible mechanism for the reaction of **3** is illustrated in Figure 2. In order to demonstrate how amino ketone **5** was exclusively furnished from the reaction, the structure of **3** is partially numbered. Based on the molecular model study,[4c] it is deduced that imino alcohol **6**, the condensation product, was formed at the beginning of reaction. Then, the nitrogen atom captured the proton of hydroxyl group on C2, such that C2-C4 bond was forced to break. Immediately, thus, C4 attacked C3 smoothly from the *si*-face (route a), resulting in the formation of **5** (a $_3C^6$ conformation), in which the aryl amino group on C3 is equatorial.[6] Alternatively, if the formation of **7** (a $_2C^6$ conformation) occurred, then C1-C2 bond would have to break. Thus, C2-C4 bond would rotate somewhat such that C3 swung up and C2 flopped down, then, C1 could attack C3 (route b). Accordingly, it is concluded that the process for the formation of **7** was kinetically unfavorable due to higher energy barrier, comparing with the process for the formation of **5**.

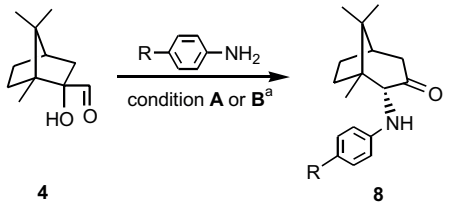
In order to assure that *para*-substituted phenyl amines are indeed good *N*-nucleophiles for the title reaction, carbinol **4** was adopted as the second substrate, and reaction conditions A and B listed in Table 1 were employed. As shown in Table 2, the outcome of reaction of **4** was analogical to that of reaction of **3**. Obviously, compound **4** showed higher reactivity under reaction condition B than under condition A. Generally, under each condition, the *para*-halogen-containing phenyl amines (entreis 6 ~ 8) are better *N*-nucleophiles than parent and other *para*-substituted anilines. That product **8i** (entry 9) was obtained in low yield



3 **6** **5**: $_3C^6$ **7**: $_2C^6$ (not observed)

Fig. 2. Mechanism for the reaction of **3** with aryl amines.

Table 2. Results of the reaction of carbinol **4** with aryl amines



4 **8**

Entry	Aryl amine	Product	Yield (%)[c]	
			condition **A**	condition **B**
1	*p*-H-PhNH$_2$[b]	**8a** (R = H)	58	89
2	*p*-Me-PhNH$_2$	**8b** (R = Me)	54	87
3	*p*-HO-PhNH$_2$	**8c** (R = OH)	38	65
4	*p*-MeO-PhNH$_2$	**8d** (R = OMe)	42	90
5	*p*-*i*-Pr-PhNH$_2$	**8e** (R = *i*-Pr)	45	95
6	*p*-Cl-PhNH$_2$	**8f** (R = Cl)	68	92
7	*p*-Br-PhNH$_2$	**8g** (R = Br)	74	93
8	*p*-I-PhNH$_2$	**8h** (R = I)	83	95
9	*p*-NO$_2$-PhNH$_2$	**8i** (R = NO$_2$)	36	40
10	*p*-Ac-PhNH$_2$	**8j** (R = Ac)	86	86

[a]Condition **A**: CH_2Cl_2, r.t., 30 min. Condition **B**: toluene, reflux, 3h.
[b]Aniline.
[c]Yield of isolated product.

was probably due to poor solubility of *para*-nitro-aniline. Furthermore, it is noteworthy that the reaction under condition A provided bicyclic imino carbinol **9** (Fig. 3) as the intermediate, which could not be isolated with silica gel column chromatography. However, the existence of **9** was proved with ^{1}H-NMR spectroscopy (*vide infra*). On the proton NMR spectra of products **8**, it was found that the chemical shifts of the signals of protons on the carbons which possess aryl amino groups ranged from 3.88 ppm to 4.21 ppm. Furthermore, the signal of each of those protons turned out to be a singlet, indicating that the aryl amino

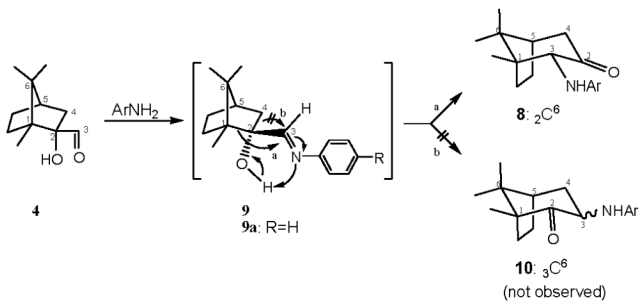


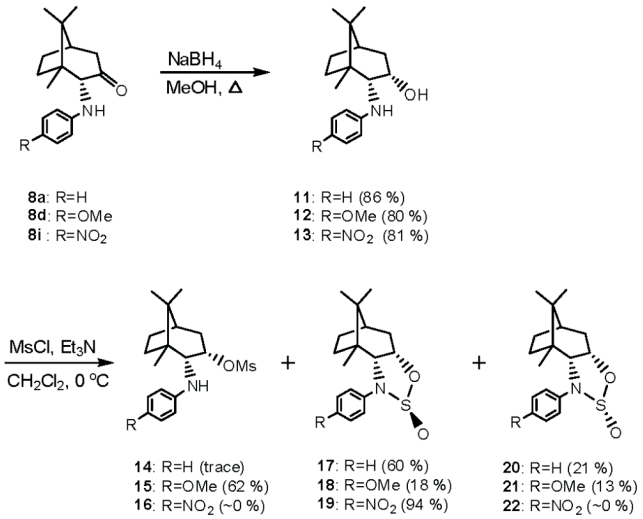
Fig. 3. Mechanism for the reaction of **4** with aryl amines.

group is bonded with *endo*-orientation to the ring-carbon atom which is located between the bridgehead quaternary carbon and the carbonyl group. On the other hand, the ring-carbonyl group is located at the farthest position from the bridgehead carbon atoms. The exact structures of products **8** were confirmed with X-ray crystallography. For each entry, among all possible regio- and stereoisomers of [3.2.1]bicyclic amino ketone product, compound **8** was the only one observed and isolated. On the other hand, it was found that there was no significant difference between the reactivity of parent aniline (entry 1) and that of any aniline possessing electron-donating group at *para*-position (entries 2~5).

A plausible mechanism for the reaction shown in Table 2 is illustrated in Figure 3, and is similar to that of reaction of **4** with alkyl primary amines.[5] In order to demonstrate how amino ketone **8** was exclusively furnished from the reaction, the structure of **4** is partially numbered. Based on the molecular model study,[4c] it is deduced that *N*-aryl imino carbinol **9**, the condensation product, was provided first. Then, the nitrogen atom abstracted the proton of the hydroxyl group on C2, such that C1-C2 bond was forced to break. Immediately, thus, C1 attacked C3 from the *re*-face (route a), resulting in the formation of **8** (a $_2C^6$ conformation), in which the aryl amino group is equatorial. Alternatively, if the formation of **10** (a $_3C^6$ conformation) occurred, then C2-C4 bond would have to break. Thus, C1-C2 bond would rotate ~180^o such that C3 swung down and C2 relatively flopped up, then C4 could attack C3 (route b). Accordingly, it is speculated that the process for the formation of **10** was kinetically unfavorable comparing with that for the formation of **8**. For the verification of existence of **9**, the reaction of **4** with aniline had also been carried out in dichloromethane, and the reaction mixture was worked up in 30 minutes. Then, the mixture of the crude products was subject to the experiment for ^{1}H-NMR spectroscopy. Evidently, on the spectrum of the mixture, it was found that a singlet signal appeared at 8.10 ppm, corresponding to the proton of imino moiety on structure **9a**. Presumably, the structure of **9** was instantaneously stabilized by the conjugated double bond system, which was composed of the imino group and aryl moiety. Such stabilization might be the reason why the yields of products given from the reaction of **4** with anilines are higher than those given from the reaction with alkyl primary amines under the same conditions.[5]

For application of the title reaction, products **8a**, **8d** and **8i** shown in Table 2, were then reduced with sodium borohydride to give [3.2.1]bicyclic aryl amino alcohols **11**, **12** and **13**, respectively (Scheme II). Our original plan involved the utilization of **11** ~ **13** as the intermediates for the preparation of some [3.2.1]bicyclic allyl aryl amines for synthetic purposes. Therefore, compounds **11** ~ **13** were then individually treated with mesyl chloride in order to activate the hydroxyl group. This activation reaction was expected to efficiently provide compounds **14** ~ **16**, which perhaps further undergo an elimination reaction in the presence of appropriate basic agent. Surprisingly, however, corresponding bicyclic 1,2,3-oxathiazolidine-2-oxide **17** was primarily obtained from the reaction of **11** with MsCl. Furthermore, the reaction of aryl amino alcohol **13**, which possesses nitro group at *para*-position in the aryl moiety, gave exclusively **19** in a good yield (94%). As shown in Figure 4, the absolute structure of **19**, a stereo-specific compound, was confirmed with X-ray analysis.[7]

Scheme II Reaction of [3.2.1]bicyclic aryl amino alcohol with mesyl chloride



It is known that chiral 1,2,3-oxathiazolidine-2-oxide agents are useful intermediates for the syntheses of enantiopure sulfoxides, sulfinamides and sulfimines.[8-12] Usually, this heterocyclic 2-oxide system can be smoothly obtained from the treatment of *N*-alkyl/aryl amino alcohol with thionyl chloride.[8-18] Thus, what has to be specially noted is that the reaction of **11** ~ **13** shown in Scheme II demonstrates, to the best of our knowledge, the first example of using mesyl chloride instead of thionyl chloride as the resource of sulfoxide (S=O) moiety for 1,2,3-ozathiazolidine-2-oxide system. The mechanism for this reaction, which afforded the originally unexpected new product(s), is illustrated in Figure 5. At the beginning of reaction, intermediates **14** ~ **16** might be furnished, releasing triethyl ammonium chloride. Structure **26** was then formed by abstraction of proton to sulfonate moiety from the aryl amino group on **14** ~ **16** followed by cyclization *via* species **23**, **24** or **25**. Presumably, on species **25**, the *para*-nitro group on aryl moiety participated in through-resonance with nitrogen anion, such that compound **16** was completely con-

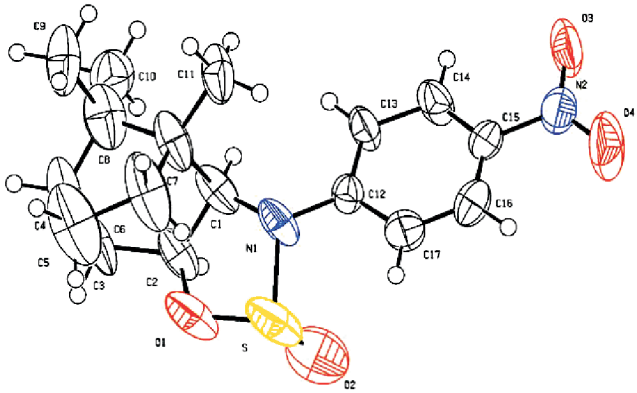


Fig. 4. ORTEP drawing of [3.2.1]bicyclic 1,2,3-oxathiazolidine-2-oxide **19**.

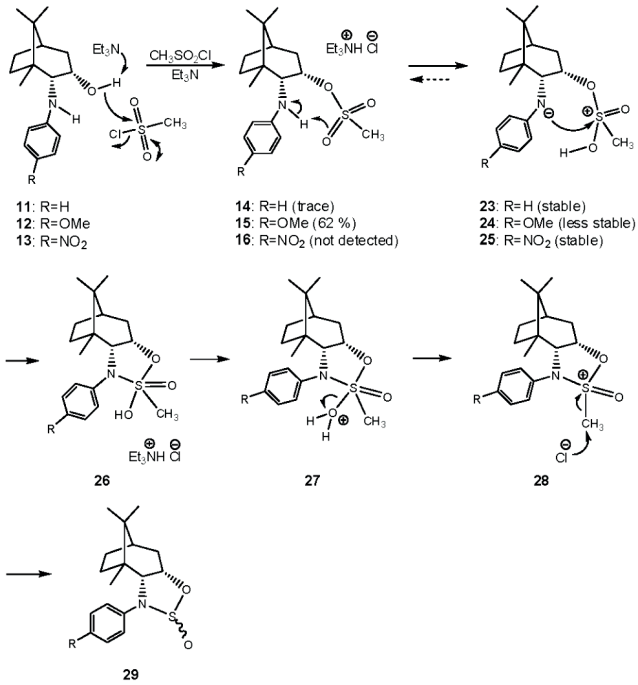
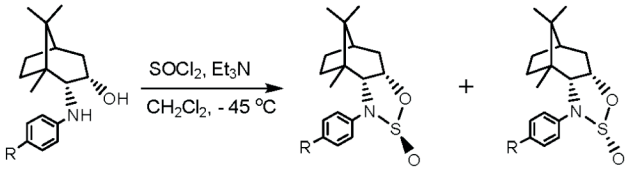


Fig. 5. Proposed mechanism for the reaction of **11**, **12** and **13** with MsCl.

sumed and not detected at all upon work-up. On the contrary, the *para*-methoxy group on aryl moiety might make species **24** unstable, such that compound **15** was obtained in a relatively significant yield (62%). The oxygen atom of hydroxyl group bonded to sulfur on **26** was then protonated in the presence of triethyl ammonium chloride to give species **27**. Finally, [3.2.1]bicyclic product **29**, a new class of *N*-aryl-1,2,3-oxathiazolidine-2-oxide agent, was produced by release of water molecule from sulfur atom on **27** and subsequent attack of the chloride ion to methyl group on **28**.

For the comparison of mesyl chloride with thionyl chloride in their functions, reaction of the latter with **11** ~ **13** has also been carried out, as shown in Scheme III, under the conditions reported by Senanayake and coworkers.[9,10] As expected, for the reaction of **11** and **12**, products **17** and **18** were predominantly obtained over **20** and **21**, respectively. Furthermore, the reaction of **13** with thionyl chloride was similar to that with mesyl chloride, giving exclusive product **19** in good yield.

Scheme III Reaction of [3.2.1]bicyclic aryl amino alcohol with thionyl chloride



11: R=H
12: R=OMe
13: R=NO_2

17: R=H (60 %)
18: R=OMe (60 %)
19: R=NO_2 (90 %)

20: R=H (2 %)
21: R=OMe (4 %)
22: R=NO_2 (~0 %)

CONCLUSION

In conclusion, both the reaction of camphene-derived *exo*-formyl[2.2.1]bicyclic carbinol and that of camphor-derived *endo*-formyl[2.2.1]bicyclic carbinol with phenyl/aryl amines proved to be regio- and stereoselective, furnishing the corresponding [3.2.1]bicyclic *N*-phenyl/aryl amino ketones. These reactions were individually composed of consecutive condensation and ring-expansion. Some of the camphor-derived products obtained from the reaction were converted to [3.2.1]bicyclic *N*-phenyl/aryl 1,2,3-oxathiazolidine-2-oxide agents, which are new compounds and expected to be used as chiral synthons for the synthesis of enantiopure sulfinamides. One of the new findings in this work is that mesyl chloride can be the resource of sulfoxide (S=O) moiety for 1,2,3-ozathiazolidine-2-oxide system.

EXPERIMENTAL

General information

Moisture-sensitive solvents were dried with standard methods and, when necessary, transferred via a syringe. Round bottom flasks were employed for carrying out all the reactions. Solutions of crude product were dried on Na_2SO_4 or $MgSO_4$. The dried solutions were then filtered and concentrated with a rotary evaporator below 40 ^oC at ~30 Torr. Silica gel (230-400 mesh) was employed for flash column chromatography. R_f values were obtained from thin layer chromatography (TLC). TLC was performed on silica gel sheets with organic binder and detected by 0.5% phosphor-molybdic acid solution in 95% ethanol. Melting points were measured on a Fargo MP-1D apparatus and were uncorrected. An FT/IR spectrophotometer (Perkin Elmer-paragon 500) was used for obtaining the infrared spectra, in which data were expressed as wave number of absorption (cm^{-1}). ^1H NMR and ^{13}C NMR spectra were obtained using a 200 MHz (Varian) or 300 MHz (Bruker) spectrometer. Chemical shifts (δ scale) were expressed in parts per million downfield from tetramethylsilane (TMS, δ = 0.00). ^1H NMR data were presented as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet and/or multiple resonances), coupling constant (*J*) in Hz (Hertz), integration. Optical rotation ([α]) values were recorded at room temperature on a JASCO (P-1010), or JASCO (P-2000) digital polarimeter.

General procedure for the reaction of carbinol 3 with parent or *para*-substituted phenyl amines under condition A

To a solution of carbinol **3** (0.5 g, 2.98 mmol) in CH_2Cl_2 (20 mL) was added parent or p-substituted phenyl amine (1.30 eq. 3.57 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min under argon, then washed with water (30 mL × 3). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography (n-hexanes:EtOAc = 3:1) to give the corresponding camphene-derived [3.2.1]-bicyclic α-amino ketone (**5**).

General procedure for the reaction of carbinol 3 with parent or *para*-substituted phenyl amines under condition B

To a solution of carbinol **3** (0.5 g, 2.98 mmol) in toluene (20 mL) was added parent or various p-substituted phenyl amine (1.30 eq. 3.57 mmol) at room temperature.

The reaction mixture was heated at reflux for 3 hours under argon, then cooled to room temperature, and washed with water (30 mL× 3). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes:EtOAc = 3:1) to give the corresponding camphene-derived [3.2.1]bicyclic α-amino ketone (**5**).

Data of camphene-derived [3.2.1]bicyclic (*para*-substituted) phenyl amino ketones

Compound 5a

White solid, R_f = 0.74 (3:1, hexanes/EtOAc); 75% yield, mp 93-94 °C; $[\alpha]_D^{27}$ = +26.3 (0.2, CH_2Cl_2); IR (KBr): 3365, 3048, 2964, 2913, 1720, 1602, 1499 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25-6.66 (m, 5H), 4.20 (br s, 1H), 3.87 (s, 1H), 2.83 (m, 1H), 2.17-1.61 (m, 7H), 1.20 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.1, 149.0, 129.2, 118.2, 114.0, 65.9, 49.6, 46.7, 45.3, 35.51, 26.7, 26.1, 25.0, 21.4. HRMS calcd. for $C_{16}H_{21}NO$: 243.1623; found: 243.1620.

Compound 5b

White solid, R_f = 0.77 (3:1, hexanes/EtOAc); 88% yield; mp 104-105 °C; $[\alpha]_D^{27}$ = +58.1 (0.2, CH_2Cl_2); IR (KBr): 3356, 3014, 2964, 2913, 1715, 1608, 1522 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.98-6.57 (m, 4H), 4.20 (br s, 1H), 3.81 (s, 1H), 2.81 (s, 1H), 2.22 (s, 3H), 2.18-1.60 (m, 7H), 1.19 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.4, 147.1, 129.6, 127.2, 114.1, 66.2, 49.6, 46.6, 45.2, 35.5, 26.7, 26.0, 25.0, 21.4, 20.3. HRMS calcd. for $C_{17}H_{23}NO$: 257.1780; found: 257.1784.

Compound 5c

Yellowish solid, R_f = 0.28 (3:1, hexanes/EtOAc); 73% yield; mp 129-130 °C; $[\alpha]_D^{27}$ = +26.1 (0.2, CH_2Cl_2); IR (KBr): 3378, 3227, 3020, 2958, 2874, 1710, 1614, 1519 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.68-6.54 (m, 4H), 4.43 (br s, 1H), 3.70 (s, 1H), 2.81 (s, 1H), 2.12-1.62 (m, 8H), 1.20 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 213.7, 148.4, 143.1, 116.1, 115.9, 67.6, 49.6, 46.7, 45.1, 35.6, 26.7, 25.9, 25.0, 21.3. HRMS calcd. for $C_{16}H_{21}NO_2$: 259.1572; found: 259.1579.

Compound 5d

White solid, R_f = 0.63 (3:1, hexanes/EtOAc); 83% yield; mp 103-104 °C; $[\alpha]_D^{27}$ = +22.0 (0.2, CH_2Cl_2); IR (KBr): 3367, 3059, 3008, 2964, 2874, 1709, 1510, 1245 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.78-6.60 (m, 4H), 4.08 (br s, 1H), 3.73 (s, 3H), 3.72 (s, 1H), 2.81 (m, 1H), 2.20-1.60 (m, 7H), 1.20 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.8, 152.5, 143.6, 115.6, 114.8, 67.4, 55.8, 49.6, 46.7, 45.1, 35.5, 26.7, 26.0, 25.0, 21.4. HRMS calcd. for $C_{17}H_{23}NO_2$: 273.1729; found: 273.1721.

Compound 5e

White solid, R_f = 0.86 (3:1, hexanes/EtOAc); 79% yield; mp 69-70 °C; $[\alpha]_D^{27}$ = +28.9 (0.2, CH_2Cl_2); IR (KBr): 3360, 3022, 2953, 2873, 1713, 1614, 1513 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.06-6.60 (m, 4H), 4.26 (br s, 1H), 3.81 (s, 1H), 2.86-2.72 (m, 2H), 2.23-1.59 (m, 7H), 1.19 (s, 3H), 1.18 (d, *J* = 6.8 Hz, 6H), 0.82 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 212.4, 147.3, 138.5, 127.0, 113.9, 66.1, 49.5, 46.6, 45.2, 35.5, 33.1, 26.7, 26.0, 25.0, 24.2, 21.4. HRMS calcd. for $C_{19}H_{27}NO$: 285.2093; found: 285.2097.

Compound 5f

White solid, R_f = 0.69 (3:1, hexanes/EtOAc); 95% yield; mp 124-125 °C; $[\alpha]_D^{27}$ = +19.1 (0.2, CH_2Cl_2); IR (KBr): 3361, 3031, 2958, 2924, 2874, 1715, 1591, 1504, 1491 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.09 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.8 Hz, 2H), 3.89 (br s, 1H), 3.80 (s, 1H), 2.83 (m, 1H), 2.20-1.62 (m, 7H), 1.18 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.8, 147.5, 129.0, 122.7, 115.2, 66.0, 49.5, 46.6, 45.3, 35.5, 26.7, 26.0, 25.0, 21.4. HRMS calcd. for $C_{16}H_{20}ClNO$: 277.1233; found: 277.1232.

Compound 5g

White solid, R_f = 0.69 (3:1, hexanes/EtOAc); 66% yield; mp 131-132 °C; $[\alpha]_D^{27}$ = +47.3 (0.2, CH_2Cl_2); IR (KBr): 3378, 3070, 2958, 2908, 2880, 1720, 1589, 1488, 1311 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.26-7.18 (m, 2H), 6.58-6.51 (m, 2H), 3.90 (br s, 1H), 3.80 (s, 1H), 2.83 (m, 1H), 2.15-1.62 (m, 7H), 1.16 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.8, 148.1, 131.8, 115.5, 109.6, 65.7, 49.5, 46.6, 45.3, 35.5, 26.7, 26.1, 25.0, 21.4. HRMS calcd. for: $C_{16}H_{20}BrNO$: 321.0728; found: 321.0725.

Compound 5h

White solid, R_f = 0.69 (3:1, hexanes/EtOAc); 63% yield; mp 172-173 °C; $[\alpha]_D^{27}$ = +27.3 (0.2, CH_2Cl_2); IR (KBr): 3384, 3014, 2964, 2908, 1717, 1617, 1586, 1508, 1483, 1315 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.39 (d, *J* = 9.0 Hz, 2H), 6.45 (d, *J* = 9.0 Hz, 2H), 4.32 (br s, 1H), 3.81 (d, *J* = 6.4 Hz, 1H), 2.83 (m, 1H), 2.16-1.62 (m, 7H), 1.16 (s, 3H), 0.83 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.7, 148.8, 137.7, 116.0, 78.5, 65.4, 49.5, 46.7, 45.4, 35.5, 26.8, 26.1, 25.0, 21.4. HRMS calcd. for: $C_{16}H_{20}INO$: 369.0590; found: 369.0587.

Compound 5i

Yellowish solid, R_f = 0.34 (3:1, hexanes/EtOAc); 67% yield; mp 173-174 °C; $[\alpha]_D^{27}$ = +12.7 (0.2, CH_2Cl_2);

IR (KBr): 3373, 3087, 2952, 2913, 1717, 1600, 1314 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.50 (d, *J* = 9.2 Hz, 2H), 6.60 (d, *J* = 9.2 Hz, 2H), 5.03 (d, *J* = 8.2 Hz, 1H), 4.04 (d, *J* = 8.2 Hz, 1H), 2.89 (m, 1H), 2.20-1.68 (m, 7H), 1.17 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.3, 154.0, 138.5, 126.2, 112.0, 64.0, 49.5, 46.7, 45.7, 35.4, 26.6, 26.2, 25.0, 21.3. HRMS calcd. for $C_{16}H_{20}N_2O_3$: 288.1474; found: 288.1465.

Compound 5j

Yellowish solid, R_f = 0.34 (3:1, hexanes/EtOAc); 82% yield; mp 123-125 °C; $[\alpha]_D^{27}$ = +16.0 (0.2, CH_2Cl_2); IR (KBr): 3361, 3053, 2964, 2930, 1715, 1664, 1600, 1533 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80 (d, *J* = 9.0 Hz, 2H), 6.62 (d, *J* = 9.0 Hz, 2H), 4.77 (br s, 1H), 4.02 (s, 1H), 2.86 (m, 1H), 2.47 (s, 3H), 2.24-1.65 (m, 7H), 1.17 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 211.0, 196.2, 152.9, 130.7, 127.3, 112.3, 64.1, 49.5, 46.7, 45.6, 35.5, 26.7, 26.1, 26.0, 25.0, 21.3. HRMS calcd. for $C_{18}H_{23}NO_2$: 285.1729; found: 285.1736.

General procedure for the reaction of carbinol 4 with parent or *para*-substituted phenyl amines under condition A

To a solution of carbinol **4** (0.5 g, 2.75 mmol) in CH_2Cl_2 (20 mL) was added parent or *p*-substituted phenyl amine (1.30 eq., 3.57 mmol) at room temperature. The reaction mixture was stirred at room temperature for 30 min under argon, then washed with water (30 mL × 3). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes: EtOAc = 3:1) to give the corresponding camphor-derived [3.2.1]bicyclic α-amino ketone (**8**).

General procedure for the reaction of carbinol 4 with parent or *para*-substituted phenyl amines under condition B

To a solution of carbinol **4** (0.5 g, 2.75 mmol) in toluene (20 mL) was added parent or *p*-substituted phenyl amine (1.30 eq., 3.57 mmol) at room temperature. The reaction mixture was heated at reflux for 3 hours under argon, then cooled to room temperature, and washed with water (30 mL × 3). The organic layers were combined, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes:EtOAc = 3:1) to give the corresponding camphor-derived [3.2.1]bicyclic α-amino ketone (**8**).

Data of camphor-derived [3.2.1]bicyclic (*para*-substituted) phenyl amino ketones

Compound 8a

White solid: R_f = 0.70 (3:1, hexanes/EtOAc); mp 76-78 °C; $[\alpha]_D^{28}$ = -14.9 (0.2, CH_2Cl_2); IR (KBr): 3367 (br), 3060, 2960, 1710, 1602, 1498 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.19-7.11 (m, 2H), 6.74-6.63 (m, 3H), 4,68 (br s, 1H), 4.04 (s, 1H), 2.79 (d, *J* = 14.9 Hz, 1H), 2.31 (dd, *J* = 3.2 Hz, *J* = 14.9 Hz, 1H), 2.06-1.89 (m, 2H), 1.64-1.23 (m, 3H), 1.37 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.3, 149.2, 129.1, 117.9, 113.8, 67.1, 53.0, 46.5, 45.6, 44.9, 30.9, 27.1, 24.5, 18,5, 18,2. HRMS calcd. for $C_{17}H_{23}NO$: 257.1780; found: 257.1782.

Compound 8b

White solid: R_f = 0.70 (3:1, hexanes/EtOAc); mp 129-130 °C; $[\alpha]_D^{28}$ = -117.7 (0.2, CH_2Cl_2); IR (KBr): 3383, 3037, 2955, 2850, 1708, 1607, 1456 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.96 (d, *J* = 8.2 Hz, 2H), 6.57 (d, *J* = 8.2 Hz, 2H), 4.60 (br s, 1H), 3.98 (s, 1H), 2.78 (m, 1H), 2.30 (dd, *J* = 3.4 Hz, 15.0 Hz, 1H), 2.22 (s, 3H), 2.06-1.23 (m, 5H), 1.36 (s, 3H), 1.04 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.4, 146.9, 129.5, 127.0, 113.9, 67.5, 52.9, 46.4, 45.5, 44.8, 30.9, 27.0, 24.5, 20.2, 18.4, 18.1. HRMS calcd. for $C_{18}H_{25}NO$: 271.1936; found: 271.1939.

Compound 8c

White solid: R_f = 0.56 (3:1, hexanes/EtOAc); mp 73-74 °C; $[\alpha]_D^{28}$ = -18.1 (0.2, CH_2Cl_2); IR (KBr): 3487 (br), 3054, 2972, 1708, 1601, 1455 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.69-6.53 (m, 4H), 4.63 (br s, 2H), 3.88 (s, 1H), 2.78 (d, *J* = 15.0 Hz, 1H), 2.30 (dd, *J* = 3.2 Hz, 15.0 Hz, 1H), 2.06-1.26 (m, 5H), 1.33 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 210.3, 148.0, 143.5, 116.0, 115.3, 68.6, 53.0, 46.5, 45.7, 44.9, 30.9, 27.1, 24.6, 18.5, 18.3. HRMS calcd. for $C_{17}H_{23}NO_2$: 273.1729; found: 273.1734.

Compound 8d

White solid: R_f = 0.70 (3:1, hexanes/EtOAc); mp 118-119 °C; $[\alpha]_D^{28}$ = -65.8 (0.2, CH_2Cl_2); IR (KBr): 3330 (br), 3028, 2960, 2918, 2854, 1707, 1644, 1452 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 6.79-6.58 (m, 4H), 4.49 (br s, 1H), 3.90 (s, 1H), 3.73 (s, 3H), 2.76 (d, *J* = 15.0 Hz, 1H), 2.29 (dd, *J* = 3.2 Hz, 15.0 Hz, 1H), 2.05-1.24 (m, 5H), 1.34 (s, 3H), 1.05 (s, 3H), 1.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.8, 152.3, 143.6, 115.1, 114.7, 68.5, 55.7, 52.9, 46.5, 45.6, 44.9, 30.9, 27.0, 24.5, 18.5, 18.2. HRMS calcd. for $C_{18}H_{25}NO_2$: 287.1885; found: 287.1880.

Compound 8e

White solid: R_f = 0.70 (3:1, hexanes/EtOAc); mp 129-130 °C; $[\alpha]_D^{28}$ = -67.8 (0.2, CH_2Cl_2); IR (KBr): 3376 (br), 3073, 2963, 2915, 2854, 1708, 1644, 1453 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.05 (d, *J* = 8.4 Hz, 2H), 6.65 (d, *J* = 8.4 Hz, 2H), 4.60 (br s, 1H), 4.00 (s, 1H), 2.85-2.75 (m, 2H), 2.32 (dd, *J* = 3.2, 14.8 Hz, 1H), 2.08-1.90 (m, 2H), 1.66 (m, 1H), 1.42-1.26 (m, 2H), 1.37 (s, 3H), 1.21 (d, *J* = 7.0 Hz, 6H), 1.08 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.4, 147.2, 138.5, 126.9, 114.0, 67.9, 52.9, 46.5, 45.5, 44.9, 33.0, 30.9, 27.1, 24.5, 24.1, 18.5, 18.2. HRMS calcd. for $C_{20}H_{29}NO$: 299.2249; found: 299.2251.

Compound 8f

White solid: R_f = 0.62 (3:1, hexanes/EtOAc); mp 143-145 °C; $[\alpha]_D^{28}$ = -61.5 (0.2, CH_2Cl_2); IR (KBr): 3383, 3077, 2964, 1708, 1590, 1499 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.8 Hz, 2H), 6.56 (d, *J* = 8.8 Hz, 2H), 4.20 (br s, 1H), 3.97 (s, 1H), 2.79 (m, 1H), 2.32 (dd, *J* = 3.4 Hz, 15 Hz, 1H), 2.36-1.23 (m, 5H), 1.36 (s, 3H), 1.03 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.1, 147.7, 128.9, 122.4, 114.9, 67.2, 53.1, 46.5, 45.6, 44.9, 30.9, 27.1, 24.5, 18.5, 18.2. HRMS calcd. for $C_{17}H_{22}ClNO$: 291.1390; found: 291.1383.

Compound 8g

White solid: R_f = 0.60 (3:1, hexanes/EtOAc); mp 147-148 °C; $[\alpha]_D^{28}$ = -69.9 (0.2, CH_2Cl_2); IR (KBr): 3379, 3075, 2956, 1708, 1591, 1504 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.21 (d, *J* = 9.0 Hz, 2H), 6.52 (d, *J* = 9.0 Hz, 2H), 4.67 (br s, 1H), 3.98 (s, 1H), 2.56 (d, *J* = 15 Hz, 1H), 2.32 (dd, *J* = 3.4 Hz, 15 Hz, 1H), 2.08-1.32 (m, 5H), 1.36 (s, 3H), 1.23 (s, 3H), 1.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 209.0, 148.2, 131.8, 115.3, 109.4, 66.9, 53.1, 46.5, 45.6, 44.9, 30.9, 27.1, 24.5, 18.5, 18.2. HRMS calcd. for $C_{17}H_{22}BrNO$: 335.0885; found: 335.0877.

Compound 8h

White solid: R_f = 0.60 (3:1, hexanes/EtOAc); mp 155-157 °C; $[\alpha]_D^{28}$ = -75.5 (0.2, CH_2Cl_2); IR (KBr): 3370, 3077, 2961, 1710, 1602, 1508 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.37 (d, *J* = 9.0 Hz, 2H), 6.42 (d, *J* = 9.0 Hz, 2H), 4.66 (br s, 1H), 3.96 (s, 1H), 2.77 (d, *J* = 15 Hz, 1H), 2.30 (dd, *J* = 3.2 Hz, 15 Hz, 1H), 2.04-1.21 (m, 5H), 1.34 (s, 3H), 1.01 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 208.9, 148.7, 137.7, 137.5, 117.2, 115.8, 66.6, 53.0, 46.4, 45.5, 44.8, 30.8, 27.0, 24.4, 18.5, 18.1. HRMS calcd. for $C_{17}H_{22}INO$: 383.0746; found: 383.0741.

Compound 8i

White solid: R_f = 0.62 (3:1, hexanes/EtOAc); mp 150-151 °C; $[\alpha]_D^{28}$ = -49.3 (0.2, CH_2Cl_2); IR (KBr): 3554, 3076, 2987, 1700, 1611, 1455 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 8.06 (d, *J* = 9.4 Hz, 2H), 6.58 (d, *J* = 9.4 Hz, 2H), 4.21 (s, 1H), 2.84 (d, *J* = 15.0 Hz, 1H), 2.37 (dd, *J* = 3.2 Hz, 15.0 Hz, 1H), 2.13-1.22 (m, 6H), 1.40 (s, 3H), 1.05 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.7, 154.1, 138.6, 126.2, 112.1, 65.7, 53.4, 46.5, 45.6, 45.1, 30.8, 27.1, 24.5, 18.6, 18.1. HRMS calcd.for $C_{17}H_{22}N_2O_3$: 302.1630; found: 302.1632.

Compound 8j

White solid: R_f = 0.65 (3:1, hexanes/EtOAc); mp 158-159 °C; $[\alpha]_D^{28}$ = -55.2 (0.2, CH_2Cl_2); IR (KBr): 3324, 3063, 2958, 1722, 1705, 1698, 1615, 1450 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.80-7.74 (m, 2H), 6.61-6.55 (m, 2H), 5.06 (br s, 1H), 4.19 (s, 1H), 2.66 (m, 1H), 2.37 (s, 3H), 2.32 (dd, *J* = 3.2 Hz, 15.0 Hz, 1H), 2.07-1.21 (m, 5H), 1.37 (s, 3H), 1.02 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 208.3, 196.2, 153.0, 130.6, 127.2, 112.4, 65.7, 53.2, 46.5, 45.6, 45.0, 30.8, 27.0, 26.0, 24.4, 18.5, 18.0. HRMS calcd. for $C_{19}H_{25}NO_2$: 299.1885; found: 299.1894.

General procedure for the preparation of 11, 12 and 13

To a solution of **8a**, **8d** or **8i** (1.39 mmol) in methanol (30 mL) was added sodium borohydride (0.21 g, 5.56 mmol). The reaction mixture was heated at reflux for 1 hour, then quenched with water (5 mL) and extracted with ethyl acetate (20 mL × 3). The organic layers were combined, dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes : EtOAc = 3:1) to give the corresponding [3.2.1]bicyclic α-amino alcohol **11** (syrup, 86%), **12** (solid, 80%) or **13** (solid, 81%).

Data of camphor-derived [3.2.1]bicyclic (*para*-substituted) phenyl amino alcohols

Compound 11

Syrup: R_f = 0.62 (5:1, hexanes/EtOAc); $[\alpha]_D^{28}$ = -56.9 (0.2, CH_2Cl_2); IR (film): 3348, 3050, 2955, 1602, 1507, 1318, 1057 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22-7.10 (m, 2H), 6.75-6.62 (m, 3H), 4.05 (t, *J* = 5.5 Hz, 1H), 3.86 (br s, 1H), 3.40 (d, *J* = 5.0 Hz, 1H), 2.59 (s, 1H), 2.16-1.62 (m, 6H), 1.46-1.26 (m, 1H), 0.96 (s, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.8, 129.3, 117.8, 113.5, 66.1, 60.2, 47.1, 44.5, 43.8, 34.5, 29,8, 26.5, 24,9, 18.7, 17.4. HRMS calcd. for $C_{17}H_{25}NO$: 259.1936; found: 259.1934.

Compound 12

White solid: R_f = 0.46 (5:1, hexanes/EtOAc); mp

55-56 °C; $[\alpha]_D^{19}$ = +24.9 (0.2, CH_2Cl_2); IR (KBr): 3344, 3063, 2948, 2892, 1511, 1243, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.77-6.60 (m, 4H), 4.02 (t, *J* = 5.7 Hz, 1H), 3.72 (s, 3H), 3.59 (br s, 1H), 3.26 (d, *J* = 5.1 Hz, 1H), 3.01 (br s, 1H), 2.10-1.78 (m, 5H), 1.63 (m, 1H), 1.37 (m, 1H), 0.94 (s, 3H), 0.88 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 152.2, 143.2, 115.2, 115.0, 66.1, 62.0, 55.8, 47.2, 44.6, 43.9, 34.5, 29.8, 26.6, 25.0, 18.9, 17.6. HRMS calcd. for $C_{18}H_{27}NO_2$: 289.2042; found: 289.2034.

Compound 13

Yellow solid: R_f = 0.22 (5:1, hexanes/EtOAc); mp 201-203 °C; $[\alpha]_D^{21}$ = +52.1 (0.2, CH_2Cl_2); IR (KBr): 3486, 3403, 3105, 2954, 2928, 2886, 1603, 1524, 1333, 1121, 833 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02 (d, *J* = 9.2 Hz, 2H), 6.54 (d, *J* = 9.2 Hz, 2H), 5.29 (d, *J* = 9.0 Hz, 1H), 4.06 (s, 1H), 3.64 (m, 1H), 2.20 (m, 1H), 2.08 (m, 1H), 1.97-1.69 (m, 5H), 1.41 (m, 1H), 1.03 (s, 3H), 0.92 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.2, 137.5, 126.7, 111.6, 67.0, 57.6, 47.9, 44.7, 43.8, 36.1, 30.0, 26.7, 25.1, 18.7, 17.5. HRMS calcd. for $C_{17}H_{24}N_2O_3$: 304.1787; found: 304.1797.

General procedure for the reaction of 11, 12 and 13 with MsCl

To a solution of **11**, **12** or **13** (0.35 mmol) in dichloromethane (7 mL) was added triethyl amine (1.75 mmol) at 0 °C. After the reaction mixture was stirred for 30 min, methanesulfonyl chloride (MsCl, 1.75 mmol) was added. The new reaction mixture was stirred at 0 °C for 5 min, then, quenched with water (3 mL). The organic layer was washed with more water (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes : EtOAc = 5:1) to give compounds **14**, **15**, **17** ~ **21**.

Data of compound 14

White solid: R_f = 0.48 (5:1, hexanes/EtOAc); mp 99-100 °C; $[\alpha]_D^{19}$ = +63.3 (0.2, CH_2Cl_2); IR (KBr): 3404, 3043, 2928, 2897, 1604, 1513, 1347, 1173, 909 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.16-7.11 (m, 2H), 6.68-6.56 (m, 3H), 4.94 (t, *J* = 5.1 Hz, 1H), 3.96 (br s, 1H), 3.75 (d, *J* = 4.5 Hz, 1H), 2.73 (s, 3H), 2.24 (m, 1H), 2.08 (ddd, *J* = 0.6, 3.3, 15.9 Hz, 1H), 2.03-1.41 (m, 5H), 1.02 (s, 3H), 0.94 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.6, 129.7, 117.5, 112.8, 79.8, 55.7, 47.8, 44.7, 43.4, 38.2, 34.4, 29.8, 26.4, 25.0, 18.7, 17.2. HRMS calcd. for $C_{18}H_{27}NSO_3$: 337.1712; found: 337.1708.

Data of compound 15

Syrup: R_f = 0.28 (5:1, hexanes/EtOAc); $[\alpha]_D^{22}$ = +55.7 (0.2, CH_2Cl_2); IR (KBr): 065, 2919, 2890, 1515, 1337, 1233, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.75 (d, *J* = 9 Hz, 2H), 6.56 (d, *J* = 9 Hz, 2H), 4.93 (t, 1H), 3.78 (m, 1H), 3.72 (s, 3H), 3.63 (d, *J* = 5.1 Hz, 1H), 2.76 (s, 3H), 2.30-1.67 (m, 6H), 1.45 (m, 1H), 1.00 (s, 3H), 0.93 (s, 3H), 0.90 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.9, 141,9, 115.2, 113.9, 79.8, 56.8, 55.8, 47.8, 44.6, 43.3, 38.2, 34.2, 29.7, 26.3, 25.0, 18.6, 17.3. HRMS calcd. for $C_{19}H_{29}NSO_4$: 367.1817; found: 367.1810.

Data of compound 17

White sloid: R_f = 0.57 (5:1, hexanes/EtOAc); mp 128-129 °C; $[\alpha]_D^{28}$ = -168.1 (0.2, CH_2Cl_2); IR (KBr): 3050, 2958, 2945, 2930, 2885, 1593, 1495, 1266, 1168, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.08 (m, 5H), 5.33 (t, *J* = 6.3 Hz, 1H), 4.23 (dd, *J* = 1.2 Hz, 6.3 Hz, 1H), 2.37 (m, 1H), 2.06 (dd, *J* = 2.7 Hz, 16.2 Hz, 1H), 1.94-1.55 (m, 4H), 1.32 (m, 1H), 0.96 (s, 3H), 0.87 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.1. 129.7, 125.0, 124.6, 78.5, 65.1, 48.0, 43.4, 42.8, 31.8, 30.3, 26.4, 24.6, 18.6, 18.5. HRMS calcd. for $C_{17}H_{23}NSO_2$: 305.1449; found: 305.1444. Anal Calcd. for $C_{17}H_{23}NSO_2$: C, 66.85; H, 7.59; N, 4.59; S, 10.50. Found: C, 66.78; H, 7.27; N, 4.47; S, 10.68.

Data of compound 18

White solid: R_f = 0.46 (5:1, hexanes/EtOAc); mp 143-145 °C; $[\alpha]_D^{21}$ = -135.7 (0.2, CH_2Cl_2); IR (KBr): 3066, 2928, 2911, 2872, 1509, 1246, 1151 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.33 (t, *J* = 6.3 Hz, 1H), 4.00 (d, *J* = 5.7 Hz, 1H), 3.79 (s, 3H), 2.35 (m, 1H), 2.04 (dd, *J* = 2.1, 15.9 Hz, 1H), 1.93-1.54 (m, 4H), 1.36 (m, 1H), 0.92 (s, 3H), 0.87 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 157.9, 133.5, 128.2, 114.9, 78,2, 68.4, 55.6, 47.9, 43.4, 42.9, 31.9, 30.2, 26.5, 24,6, 18.6, 18.3. HRMS calcd. for $C_{18}H_{25}NSO_3$: 335.1555; found: 335.1550.

Data of compound 19

Yellow solid: R_f = 0.28 (5:1, hexanes/EtOAc); mp 230-232 °C; $[\alpha]_D^{19}$ = -172.7 (0.2, CH_2Cl_2); IR (KBr): 3116, 2956, 2916, 1594, 1505, 1339, 1288, 1177, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.18 (d, *J* = 9.0 Hz, 2H), 7.22 (d, *J* = 9.0 Hz, 2H), 5.33 (t, *J* = 6.0 Hz, 1H), 4.42 (d, *J* = 5.4 Hz, 1H), 2.40 (m, 1H), 2.11 (dd, *J* = 1.8, 16.2 Hz, 1H), 1.97-1.78 (m, 2H), 1.67-1.56 (m, 2H), 1.37 (m, 1H), 1.04 (s, 3H), 0.91 (s, 3H), 0.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.1, 142.5, 125.5, 120.2, 80.0, 63.3, 48.3, 43.7, 42.6, 31.5, 30.9, 26.3, 24.7, 19.1, 18.5. HRMS calcd. for $C_{17}H_{22}N_2SO_4$: 350.1300; found: 350.1303.

Data of compound 20

White solid: R_f = 0.70 (5:1, hexanes/EtOAc); mp 185-187 °C; $[\alpha]_D^{19}$ = +263.3 (0.2, CH_2Cl_2); IR (KBr): 3040, 2980, 2947, 2929, 2890, 1599, 1500, 1267, 1173, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.35-7.08 (m, 5H), 4.75 (t, *J* = 6.3 Hz, 1H), 4.18 (d, *J* = 6.3 Hz, 1H), 2.75 (m, 1H), 2.21 (m, 1H), 2.03 (dd, *J* = 2.4, 15.9 Hz, 1H), 1.91 (m, 1H), 1.82-1.73 (m, 2H), 1.46 (m, 1H), 0.98 (s, 3H), 0.94 (s, 3H), 0.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.2, 129.8, 124.3, 119.9, 80.7, 64.8, 47.3, 44.1, 43.3, 32.5, 30.3, 26.5, 24.8, 18.7, 18.6. HRMS calcd. for $C_{17}H_{23}NSO_2$: 305.1449; found: 305.1446. Anal Calcd. for $C_{17}H_{23}NSO_2$: C, 66.85; H, 7.59; N, 4.59; S, 10.50. Found: C, 66.71; H, 7.60; N, 4.47; S, 10.35.

Data of compound 21

White solid: R_f = 0.59 (5:1, hexanes/EtOAc); mp 172-174 °C; $[\alpha]_D^{19}$ = +256.5 (0.2, CH_2Cl_2); IR (KBr): 3065, 2951, 2900, 1509, 1461, 12490, 1157. 1037 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.80 (t, *J* = 6.3 Hz, 1H), 3.95 (dd, *J* = 1.5, 6.3 Hz, 1H), 3.79 (s, 3H), 2.75 (m, 1H), 2.20 (m, 1H), 2.03-1.87 (m, 2H), 1.81-1.71 (m, 2H), 1.46 (m, 1H), 0.92 (s, 6H), 0.72 (s, 3H); ^{13}C-NMR (75 MHz, $CDCl_3$): δ 157.5, 153.0, 124.6, 115.0, 80.8, 67.8, 55.6, 47.2, 44.0, 43.2, 32.6, 30.2, 26.4, 24.7, 18.6, 18.4. HRMS calcd. for $C_{18}H_{25}NSO_3$: 335.1555; found: 335.1554.

General procedure for the reaction of 11, 12 and 13 with $SOCl_2$

To a solution of **11**, **12** or **13** (0.35 mmol) in dichloromethane (7 mL) was added triethyl amine (0.53 mmol) at -45 °C. Thionyl chloride ($SOCl_2$, 0.88 mmol) was then dropwise added. The new reaction mixture was stirred at -45 °C for 5 min, then, quenched with sodium bicarbonate (pH = 7~8). The mixture was diluted with dichloromethane (10 mL). Then, the organic layer was washed with water (3 × 5 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified with flash column chromatography (*n*-hexanes : EtOAc = 5:1) to give compounds **17** ~ **21**.

ACKNOWLEDGEMENTS

This work was supported by the National Science Council (Grants NSC 96-2113-M-324-001 and NSC 98-2119-M-260-001), which is gratefully acknowledged. The authors thank Regional Instruments Center at National Chung-Hsing University and the Instrumental Center at National Taiwan University for elemental analysis, high resolution mass spectra and X-ray crystallography.

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6. $_nC^m$ is an abbreviation for a chair conformation, in which carbon-n is located at the lower-left corner, and carbon-m at the upper-right corner. For example, $_3C^6$ is an abbreviation for a chair conformation, in which carbon-3 is located at the lower-left corner, and catbon-6 at the upper-right corner.
7. Crystallographic data for structures **5a**, **5b**, **5i**, **8a**, **8b**, **8j**, **13**, **19** and **21** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 817964, CCDC 817965, CCDC 817966, CCDC 817967, CCDC 817968, CCDC 817969, CCDC 817970, CCDC 817971, and CCDC 817972, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.com.ac.uk).
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