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# Zinc tetrafluoroborate catalyzed Mannich-type reaction of aldimines and silyl enol ethers in aqueous medium

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**Abstract**—The use of zinc tetrafluoroborate as a catalyst in Mannich-type addition of silyl enol ethers to aldimines in aqueous THF provides β-amino ketones or β-amino esters in high yields. A one-pot reaction of an aldehyde, amine and silyl enolate also works well. © 2002 Elsevier Science Ltd. All rights reserved.

## 1. Introduction

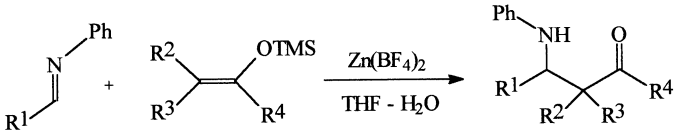
The Mannich reaction is one of the most important methods for the preparation of β-amino carbonyl compounds and has received wide applications in organic synthesis.[1] However, the classical procedure is associated with serious disadvantages involving drastic reaction conditions and long reaction periods. Thus, the Lewis acid promoted condensation of silyl enol ethers to imines, first reported by Ojima et al.[2] constitutes an excellent modification. Since then several methods using a variety of Lewis acids in anhydrous conditions have been reported.[3] However, many of these methods involve toxic and hazardous Lewis acids including $TiCl_4$ in chlorinated solvents which is not desirable from an environmental point of view. Thus, in recent times a number of procedures using less hazardous Lewis and Bronsted acids in aqueous media have been developed.[4] Being eco-friendly these methods are of much significance in the field of synthetic organic chemistry. As part of our program to study organic reactions in aqueous medium we have introduced a very cheap commercially available reagent, zinc tetrafluoroborate in water for the deprotection of TBDMS ethers[5] and we have discovered that this reagent is also very effective in catalyzing Mannich-type reactions of silyl enol ethers with aldimines (Scheme 1).

## 2. Results and discussion

In a typical experimental procedure, an imine in aqueous THF was stirred with a silyl enol ether in presence of a catalytic amount (30 mol%) of an aqueous solution (40%) of zinc tetrafluoroborate at room temperature for a few minutes (TLC). Extraction with ether and purification by column chromatography over silica gel furnished the pure product.

Several aldimines derived from aromatic aldehydes and aniline underwent clean additions to silyl enol ethers of a variety of acyclic ketones by this procedure to produce the corresponding β-amino ketones in high yields. The results are summarized in Table 1. However, the reaction with silyl enol ether from an aldehyde (entry 10) ended up with relatively lower yield. Aldimines from aliphatic aldehydes also did not give satisfactory results (poor yield).

Silyl enol ethers of cyclic ketones (5–8 membered) add readily to aldimines providing the corresponding β-amino ketones in very good yields. The diastereoselectivities are reasonably good, the *syn* isomers[6] being the major in cyclopentanone and cycloheptanone units while the *anti* isomers[6] dominate in six- and eight-membered ketones. The results




**Scheme 1.**

*Keywords*: Mannich reaction; β-amino carbonyl compounds; zinc tetrafluoroborate.
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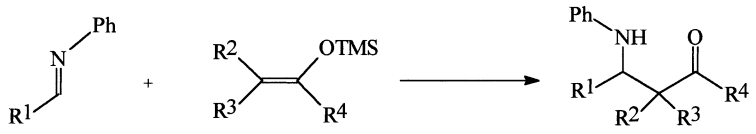
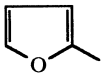
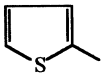
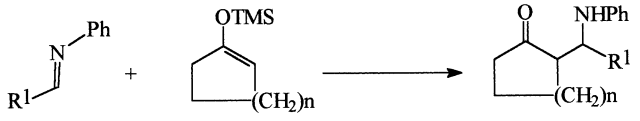
**Table 1.** Mannich-type addition of aldimines and silyl enol ethers of acyclic ketones



| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Time (min) | Yield (%)[a] | *syn/anti*[6] |
|---|---|---|---|---|---|---|---|
| 1 | Ph | H | H | Me | 10 | 80 | |
| 2 | Ph | H | H | Et | 20 | 71 | |
| 3 | Ph | Me | H | Et | 20 | 82 | 90:10 |
| 4 | Ph | H | H | Ph | 6 | 98 | |
| 5 | Ph | Me | Me | *p*-(Me)–$C_6H_4$ | 10 | 72 | |
| 6 | Ph | H | H | *p*-(Cl)–$C_6H_4$ | 10 | 95 | |
| 7 | Ph–CH=CH(t) | H | H | Ph | 12 | 81 | |
| 8 |  | H | H | Ph | 12 | 82 | |
| 9 |  | H | H | Ph | 12 | 84 | |
| 10 | Ph | Me | Me | H | 20 | 48 | |

[a] Yields refer to those of pure isolated products fully characterized by spectral data.

**Table 2.** Mannich-type addition of aldimines and silyl enol ethers of cyclic ketones



| Entry | $R^1$ | *n* | Time (min) | Yield (%)[a] | *syn/anti*[6] |
|---|---|---|---|---|---|
| 1 | Ph | 1 | 8 | 87 | 70:30 |
| 2 | Ph | 2 | 10 | 88 | 20:80 |
| 3 | *p*-(Cl)–$C_6H_4$ | 2 | 12 | 86 | 30:70 |
| 4 | Ph | 3 | 5 | 93 | 85:15 |
| 5 | *p*-(Cl)–$C_6H_4$ | 3 | 5 | 94 | 80:20 |
| 6 | Ph | 4 | 10 | 98 | 30:70 |
| 7 | *p*-(Cl)–$C_6H_4$ | 4 | 8 | 97 | 15:85 |
| 8 | *p*-(OMe)–$C_6H_4$ | 4 | 15 | 87 | 10:90 |

[a] Yields refer to pure isolated products fully characterized by spectral data.

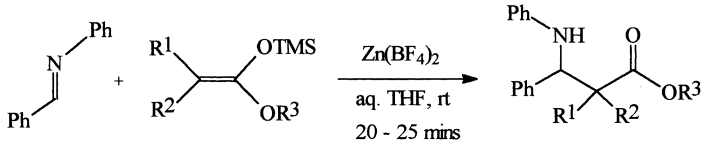
are presented in Table 2 Surprisingly, additions to silyl enol ethers of cyclic ketones are not adequately addressed in earlier methods,[4] except a recent one using indium(III) chloride which reports a few reactions with silyl enol ether of cyclopentanone in low yields (11–68%).[4d]

The addition of ketene silyl acetals is also carried out successfully by this procedure to give the corresponding β-amino esters (Scheme 2). The *syn* addition products are found to be major isomers in these reactions too.

Alternatively, a one-pot three-component condensation of aldehydes, amines and silyl enol ethers from acyclic as well as cyclic ketones was also found to proceed efficiently in the presence of zinc tetrafluoroborate. Some examples are presented in Schemes 3 and 4. The yields of products are reasonably good for a three-component condensation although lower than two-component one. The diastereoselectivities are found to remain more or less same as in the corresponding two-component reaction.

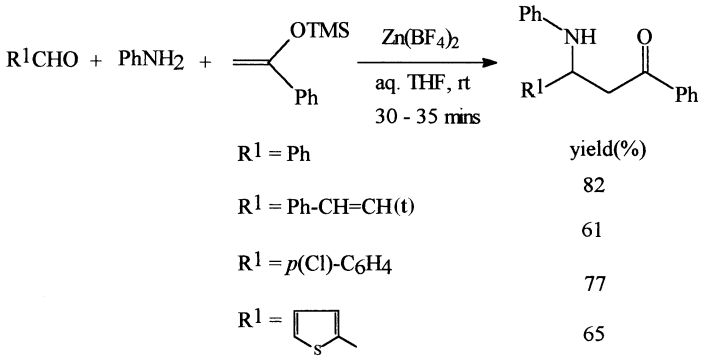
## 3. Conclusion

The present procedure using zinc tetrafluoroborate provides an efficient Mannich-type addition of aldehydes, amine and silyl enol ethers for the synthesis of β-amino carbonyl compounds which are useful intermediates for the synthesis of various biologically active units. The significant features

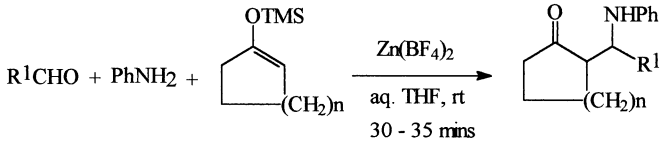


| | | yield(%) | *syn/anti*[6] |
|---|---|---|---|
| a, | $R^1 = PhCH_2$, $R^2 = H$, $R^3 = Me$ | 82 | 90:10 |
| b, | $R^1 = R^2 = Me$, $R^3 = Et$ | 83 | - |
| c, | $R^1 = Et$, $R^2 = H$, $R^3 = Et$ | 84 | 84:16 |

**Scheme 2.**




**Scheme 3.**




| | | yield(%) |
|---|---|---|
| $R^1$ = Ph | n = 1 | 72 |
| $R^1$ = Ph | n = 2 | 80 |
| $R^1$ = *p*(Cl)-$C_6H_4$ | n = 2 | 82 |
| $R^1$ = Ph | n = 3 | 75 |
| $R^1$ = *p*(Cl)-$C_6H_4$ | n = 3 | 72 |
| $R^1$ = Ph | n = 4 | 73 |
| $R^1$ = *p*(Cl)-$C_6H_4$ | n = 4 | 65 |
| $R^1$ = *p*(OMe)-$C_6H_4$ | n = 4 | 69 |

**Scheme 4.**

of this procedure are: (a) operational simplicity and fast reaction (10–40 min); (b) use of a very cheap commercially available reagent as catalyst; (c) general applicability to silyl enol ethers of both acyclic and cyclic ketones, aldehydes and esters; (d) high yields of products; (e) reasonably good diastereoselectivities; and (f) reaction in aqueous medium avoiding chlorinated solvents.

## 4. Experimental

### 4.1. General

Melting points were determined on a glass disk with an electrical bath and are uncorrected. $^1$H NMR (300 MHz) and $^{13}$C NMR (75 MHz) spectra were run in $CDCl_3$ solutions. IR spectra were taken as KBr plates. Elemental analyses were done by a Perkin Elmer autoanalyzer. Column chromatography was performed on silica gel (60–120 mesh, SRL, India) and alumina (neutral, SRL). The imines were prepared by keeping a mixture of aldehyde and amine at 0°C for half-an-hour followed by recrystallization from ethanol. Silyl enol ethers were prepared by standard procedures.[7] Chlorotrimethylsilane and the aldehydes, ketones and amines used are all commercially available and were distilled before use.

### 4.2. General procedure for the synthesis of β-amino carbonyl compounds

**4.2.1. General procedure for the addition of imine and silyl enol ethers (entry 4, Table 1).** A mixture of benzylideneaniline (181 mg, 1 mmol) and 1-phenyl-1-trimethylsilyloxy ethene (192 mg, 1 mmol) in aqueous (1:1) THF (2 mL) was stirred with an aqueous (40%) solution of zinc tetrafluoroborate (0.13 mL, 30 mol%, Aldrich) at room temperature (28–30°C) for 6 min (TLC). A solid separated out in the reaction media. The reaction mixture was then extracted with ether (3×15 mL) and the ether extract was washed with brine and dried over $Na_2SO_4$. Evaporation of solvent left the crude product which was purified by column chromatography over silica gel (eluted with petroleum ether/ether (9:1)) to provide a pure product, 3-amino-phenyl-1,3-diphenylpropan-1-one as a crystalline compound (295 mg, 98%), mp 168–170°C. The spectral (IR, $^1$H and $^{13}$C NMR) data of our compound is found to be identical with those reported.[4d]

This procedure is followed for the addition of all other imines and silyl enol ethers listed in Tables 1 and 2 and Scheme 2).

**4.2.2. General procedure for the one-pot addition of aldehyde, amine and silyl enol ethers.** To a stirred

(10 min) mixture of aniline (116 mg, 1.2 mmol) and benzaldehyde (106 mg, 1 mmol) in aqueous (1:1) THF (1 mL) was added 1-trimethylsilyloxycyclohexene (170 mg, 1 mmol) and aqueous solution (40%) of zinc tetrafluoroborate (0.13 mL, 30 mol%) and the reaction mixture was stirred for 25 min (TLC) at room temperature. Extraction with ether followed by work-up and purification as described in Section 4.2.1 provided the pure product, 2-[aminophenyl-(phenyl)methyl]cyclohexan-1-one, as a crystalline (cubes) compound (232 mg, 80%), mp 123–25°C; IR 3328, 1701, 1600 $cm^{-1}$; $^1H$ NMR (*syn*/*anti*=20:80) $\delta$ 7.18–7.37 (m, 5H), 7.02–7.07 (m, 2H), 6.51–6.63 (m, 3H), 4.79 (d, *J*=4.5 Hz, 0.2H), 4.61 (d, *J*=6.3 Hz, 0.8H), 2.69–2.74 (m, 1H), 2.27–2.41 (m, 2H), 1.77–1.89 (m, 4H), 1.59–1.71 (m, 2H); $^{13}C$ NMR (major isomer) $\delta$ 213.3, 147.7, 142.1, 129.5 (2C), 128.8 (2C), 127.7, 127.4 (2C), 117.9, 114.0 (2C), 58.3, 57.9, 42.2, 31.7, 28.3, 24.0; (minor isomer) $\delta$ 212.3, 147.9, 142.0, 129.4 (2C), 128.9 (2C), 127.9, 127.6 (2C), 118.1, 114.5 (2C), 57.6, 57.0, 42.8, 29.1, 27.4, 25.3. Anal. calcd for $C_{19}H_{21}NO$: C, 81.72; H, 7.52; N, 5.02. Found: C, 81.46; H, 7.49; N, 4.98.

This procedure is followed for all one-pot condensation of aldehydes, amines and silyl enol ethers listed in Schemes 3 and 4.

The known compounds (entries 4 and 7 in Table 1 and entry 1 in Table 2) have been identified by comparison of spectral data and mp with those reported.[4b,d] The unknown compounds have been characterized by their spectral (IR, $^1H$ and $^{13}C$ NMR) data and elemental analysis. These data are presented below in order of their entries.

**4.2.3. 4-Aminophenyl-4-phenylbutan-2-one (entry 1, Table 1).** Yield: 80%, colorless needles, mp 79–81°C; IR 3369, 1707, 1604 $cm^{-1}$; $^1H$ NMR $\delta$ 7.22–7.37 (m, 5H), 7.06–7.11 (m, 2H), 6.52–6.68 (m, 3H), 4.84 (t, *J*=6.5 Hz, 1H), 4.34 (br s, 1H), 2.91 (d, *J*=6.5 Hz, 2H), 2.09 (s, 3H); $^{13}C$ NMR $\delta$ 206.9, 146.7, 142.5, 129.0 (2C), 128.7 (2C), 127.2, 126.2 (2C), 117.7, 113.7 (2C), 54.3, 51.1, 30.6. Anal. calcd for $C_{16}H_{17}NO$: C, 80.33; H, 7.11; N, 5.85. Found: C, 79.98; H, 7.21; N, 5.61.

**4.2.4. 5-Aminophenyl-5-phenylpentan-3-one (entry 2, Table 1).** Waxy solid; IR 3398, 1706, 1602 $cm^{-1}$; $^1H$ NMR $\delta$ 7.20–7.34 (m, 5H), 7.04–7.09 (m, 2H), 6.50–6.66 (m, 3H), 4.81 (t, *J*=6.4 Hz, 1H), 2.87 (d, *J*=6.4 Hz, 2H), 2.27–2.34 (m, 2H), 0.95 (t, *J*=7.2 Hz, 3H); $^{13}C$ NMR $\delta$ 210.2, 147.2, 143.0, 129.5 (2C), 129.0 (2C), 127.7, 126.7 (2C), 118.2, 114.1 (2C), 59.3, 50.3, 37.3, 7.9. Anal. calcd for $C_{17}H_{19}NO$: C, 80.63; H, 7.50; N, 5.53. Found: C, 80.41; H, 7.44; N, 5.29.

**4.2.5. 5-Aminophenyl-4-methyl-5-phenylpentan-3-one (entry 3, Table 1).** Colorless needles (*syn*/*anti*=90:10), mp 114–116°C; IR 3381, 1701, 1602 $cm^{-1}$; $^1H$ NMR (*syn*+*anti*) $\delta$ 7.19–7.30 (m, 5H), 7.01–7.06 (m, 2H), 6.62 (t, *J*=7.3 Hz, 1H), 6.44–6.49 (m, 2H), 4.64 (d, *J*=5.6, 0.9 H), 4.52 (d, *J*=6.8 Hz, 0.1H), 2.96–3.03 (m, 1H), 2.25–2.38 (m, 2H), 1.18 (d, *J*=7.1 Hz, 0.3H), 1.09 (d, *J*=7.0 Hz, 2.7H), 0.85–0.97 (m, 3H); $^{13}C$ NMR (major isomer) $\delta$ 213.1, 147.3, 141.5, 129.4 (2C), 128.9 (2C), 127.7, 127.2 (2C), 118.1, 114.0 (2C), 59.6, 52.62, 35.9, 11.9, 10.0. Anal. calcd for $C_{18}H_{21}NO$: C, 80.89; H, 7.86; N, 5.24. Found: C, 80.56; H, 7.76; N, 5.19.

**4.2.6. 3-Aminophenyl-2,2-dimethyl-1-(4′-methylphenyl)-3-phenylpropan-1-one (entry 5, Table 1).** Colorless needles, mp 136–138°C; IR 3419, 1681, 1600 $cm^{-1}$; $^1H$ NMR $\delta$ 7.19–7.28 (m, 7H), 7.09 (d, *J*=7.8 Hz, 2H), 7.00 (d, *J*=7.5 Hz, 1H), 6.97 (d, *J*=7.5 Hz, 1H), 6.54–6.58 (m, 1H), 6.40 (d, *J*=7.5 Hz, 2H), 4.76 (s, 1H), 4.65 (s, 1H), 2.33 (s, 3H), 1.33 (s, 3H), 1.20 (s, 3H); $^{13}C$ NMR $\delta$ 209.9, 146.7, 141.0, 139.2, 137.2, 129.4 (2C), 129.1 (2C), 129.0 (2C), 128.5 (2C), 127.9, 127.5 (2C), 117.9, 113.9 (2C), 63.8, 52.4, 25.9, 21.8. Anal. calcd for $C_{24}H_{25}NO$: C, 83.96; H, 7.28; N, 4.08. Found: C, 83.57; H, 6.98; N, 3.97.

**4.2.7. 3-Aminophenyl-1-(4′-chlorophenyl)-3-phenylpropan-1-one (entry 6, Table 1).** Colorless round crystal, mp 116–118°C; IR 3377, 1672, 1602 $cm^{-1}$; $^1H$ NMR $\delta$ 7.78 (d, *J*=8.4 Hz, 2H), 7.18–7.49 (m, 7H), 7.04–7.09 (m, 2H), 6.62–6.67 (m, 1H), 6.54 (d, *J*=8.1 Hz, 2H), 4.98 (t, *J*=6.3 Hz, 1H), 4.49 (br s, 1H), 3.32–3.46 (m, 2H); $^{13}C$ NMR $\delta$ 197.5, 147.3, 143.2, 140.3, 135.4, 130.0 (2C), 129.6 (2C), 129.4 (2C), 129.3 (2C), 127.9, 126.8 (2C), 118.3, 114.3 (2C), 55.1, 46.6. Anal. calcd for $C_{21}H_{18}NOCl$: C, 75.12; H, 5.36; N, 4.17. Found: C, 74.77; H, 5.12; N, 4.01.

**4.2.8. 3-Aminophenyl-3-(2′-furyl)-1-phenylpropan-1-one (entry 8, Table 1).** Brownish needles, mp 101–103°C; IR 3369, 1674 $cm^{-1}$; $^1H$ NMR $\delta$ 7.90–7.92 (m, 2H), 7.40–7.57 (m, 3H), 7.12–7.30 (m, 3H), 6.66–6.74 (m, 3H), 6.19–6.25 (m, 2H), 5.22 (t, *J*=6.0 Hz, 1H), 4.38 (br s, 1H), 3.55 (d, *J*=6.1 Hz, 2H); $^{13}C$ NMR $\delta$ 198.3, 155.3, 147.0, 142.0, 137.1, 133.8, 129.7 (2C), 129.0 (2C), 128.5 (2C), 118.7, 114.4 (2C), 110.8, 106.9, 49.0, 42.8. Anal. calcd for $C_{19}H_{17}NO_2$: C, 78.35; H, 5.84; N, 4.81. Found: C, 77.98; H, 5.89; N, 4.68.

**4.2.9. 3-Aminophenyl-1-phenyl-3-(2′-thiophenyl)propan-1-one (entry 9, Table 1).** Brownish needles, mp 115–117°C; IR 3375, 1672, 1600 $cm^{-1}$; $^1H$ NMR $\delta$ 7.94–7.97 (m, 2H), 7.45–7.59 (m, 3H), 7.16–7.19 (m, 3H), 7.04–7.05 (m, 1H), 6.93–6.96 (m, 1H), 6.71–6.77 (m, 3H); 5.43 (t, *J*=6.1 Hz, 1H), 3.61 (d, *J*=6.1 Hz, 2H) $^{13}C$ NMR $\delta$ 198.3, 148.1, 147.1, 137.2, 133.9, 129.7 (2C), 129.1 (2C), 128.6 (2C), 127.4, 124.6, 124.4, 118.8, 114.5 (2C), 51.1, 46.4. Anal. calcd for $C_{19}H_{17}NOS$: C, 74.26; H, 5.54; N, 4.56. Found: C, 73.97; H, 5.50; N, 4.32.

**4.2.10. 3-Aminophenyl-2,2-dimethyl-3-phenylpropan-1-al (entry 10, Table 1).** Gummy mass; IR 3382, 1705, 1602 $cm^{-1}$; $^1H$ NMR $\delta$ 9.95 (s, 1H), 7.18–7.36 (m, 7H), 6.45–6.68 (m, 3H), 4.63 (s, 1H), 1.23 (s, 3H), 1.18 (s, 3H); $^{13}C$ NMR $\delta$ 192.9, 147.5, 141.2, 129.7 (2C), 129.3 (2C), 127.3, 127.1 (2C), 117.7, 113.8 (2C), 61.6, 42.3, 23.3, 21.9. Anal. calcd for $C_{17}H_{19}NO$: C, 80.63; H, 7.50; N, 5.53. Found: C, 80.42; H, 7.19; N, 5.21.

**4.2.11. 2-[Aminophenyl(4′-chlorophenyl)methyl]cyclohexan-1-one (entry 3, Table 2).** Gummy solid (*syn*/*anti*=30:70); IR 3388, 1705, 1600 $cm^{-1}$; $^1H$ NMR (*syn*+*anti*) $\delta$ 7.19–7.33 (m, 4H), 7.01–7.07 (m, 2H), 6.48–6.49 (m, 3H), 4.72 (d, *J*=4.5 Hz, 0.3 H), 4.59 (d, *J*=6.3 Hz, 0.7H), 2.47–2.74 (m, 1H), 2.25–2.38 (m, 2H),

1.57–1.84 (m, 6H); $^{13}$C NMR (major isomer) $\delta$ 212.8, 147.7, 140.9, 133.1, 129.6 (2C), 129.3 (2C), 129.0 (2C), 118.1, 114.0 (2C), 57.8, 57.7, 42.5, 31.9, 28.3, 24.4; $^{13}$C NMR (minor isomer) $\delta$ 211.6, 147.7, 140.7, 133.0, 129.5 (2C), 129.3 (2C), 129.2 (2C), 118.3, 114.5 (2C), 57.2, 56.8, 42.8, 29.4, 27.5, 24.2. Anal. calcd for $C_{19}H_{20}NOCl$: C, 72.74; H, 6.38; N, 4.46. Found: C, 72.63; H, 6.21; N, 4.19.

**4.2.12. 2-[Aminophenyl(phenyl)methyl]cycloheptan-1-one (entry 4, Table 2).** Colorless cubes (*syn*/*anti*=85:15), mp 124–126°C; IR 3390, 1689, 1602 cm$^{-1}$; $^1$H NMR (*syn*+*anti*) $\delta$ 7.16–7.33 (m, 5H), 7.01–7.06 (m, 2H), 6.59 (t, *J*=7.2 Hz, 1H), 6.50 (d, *J*=7.8 Hz, 2H), 4.91 (br s, 1H), 4.61 (d, *J*=4.8 Hz, 0.85H), 4.48 (d, *J*=7.5 Hz, 0.15H), 2.80–2.87 (m, 1H), 2.18–2.24 (m, 2H), 1.15–2.03 (m, 8H); $^{13}$C NMR (major isomer) $\delta$ 216.8, 147.2, 140.9, 129.5 (2C), 128.9 (2C), 127.7 (2C), 127.6, 117.7, 113.9 (2C), 60.6, 58.8, 44.6, 30.2, 28.9, 27.9, 25.6; $^{13}$C NMR (minor isomer) $\delta$ 215.5, 147.5, 142.1, 128.8 (2C), 128.5 (2C), 127.8 (2C), 127.7, 117.8, 113.8 (2C), 60.7, 58.9, 43.1, 29.7, 29.5, 28.3, 25.4. Anal. calcd for $C_{20}H_{23}NO$: C, 81.91; H, 7.85; N, 4.78. Found: C, 81.63; H, 7.76; N, 4.56.

**4.2.13. 2-[Aminophenyl(4′-chlorophenyl)methyl]cycloheptan-1-one (entry 5, Table 2).** Colorless cylindrical crystal (*syn*/*anti*=80:20), mp 143–145°C; IR 3388, 1689, 1602 cm$^{-1}$; $^1$H NMR (*syn*+*anti*) $\delta$ 7.17–7.25 (m, 4H), 7.06 (d, *J*=8.4 Hz, 1H), 7.04 (d, *J*=8.4 Hz, 1H), 6.62 (t, *J*=7.3 Hz, 1H), 6.47 (d, *J*=7.5 Hz, 2H), 4.58 (d, *J*=4.8 Hz, 0.8H), 4.47 (d, *J*=7.2 Hz, 0.2H), 2.79–2.91 (m, 1H), 1.18–2.28 (m, 10H); $^{13}$C NMR (major isomer) $\delta$ 216.3, 146.9, 139.7, 133.4, 129.5 (2C), 129.1 (2C), 128.9 (2C), 118.0, 113.9 (2C), 59.9, 58.6, 44.6, 30.1, 28.9, 27.9, 25.4; $^{13}$C NMR (minor isomer) $\delta$ 215.1, 147.2, 141.3, 129.5 (2C), 129.2 (2C), 129.1 (2C), 118.0, 113.8 (2C), 60.1, 58.5, 43.3, 29.6, 29.5, 28.4, 25.1. Anal. calcd for $C_{20}H_{22}NOCl$: C, 73.29; H, 6.72; N, 4.27. Found: C, 73.01; H, 6.47; N, 4.13.

**4.2.14. 2-[Aminophenyl(phenyl)methyl]cyclooctan-1-one (entry 6, Table 2).** Colorless needles (*syn*/*anti*=30:70), mp 138–140°C; IR 3388, 1693, 1602 cm$^{-1}$; $^1$H NMR (*syn*+*anti*) $\delta$ 7.13–7.25 (m, 5H), 7.00–7.06 (m, 2H), 6.57–6.62 (m, 1H), 6.49–6.53 (m, 2H), 4.78 (br s, 1H), 4.54 (d, *J*=7.2 Hz, 0.7H), 4.50 (d, *J*=6.6 Hz, 0.3H), 2.98–3.12 (m, 1H), 1.19–2.03 (m, 12H); $^{13}$C NMR (major isomer) $\delta$ 219.5, 147.6, 141.7, 129.5 (2C), 129.0 (2C), 127.6 (2C), 127.2, 117.8, 113.9 (2C), 60.8, 57.3, 44.0, 30.7, 28.1, 26.8, 25.4, 25.3; $^{13}$C NMR (minor isomer) $\delta$ 220.6, 147.5, 142.3, 129.5 (2C), 128.9 (2C), 127.7 (2C), 127.5, 117.5, 113.7 (2C), 60.9, 55.8, 44.7, 32.8, 28.3, 25.8, 25.6, 24.4. Anal. calcd for $C_{21}H_{25}NO$: C, 82.08; H, 8.14; N, 4.56. Found: C, 81.91; H, 7.87; N, 4.43.

**4.2.15. 2-[Aminophenyl(4′-chlorophenyl)methyl]cyclooctan-1-one (entry 7, Table 2).** Colorless needles (*syn*/*anti*=15:85), mp 176–178°C; IR 3400, 1687, 1602 cm$^{-1}$; $^1$H NMR (*syn*+*anti*) $\delta$ 7.19–7.26 (m, 4H), 7.04–7.09 (m, 2H), 6.61–6.66 (m, 1H), 6.46–6.50 (m, 2H), 4.51 (d, *J*=7.2 Hz, 0.85H), 4.47 (d, *J*=6.3 Hz, 0.15H), 2.95–3.18 (m, 1H), 1.22–2.04 (m, 12H); $^{13}$C NMR (major isomer) $\delta$ 219.1, 147.1, 140.2, 133.4, 129.2 (2C), 129.1 (2C), 128.9 (2C), 118.1, 113.9 (2C), 60.3, 57.0, 44.1, 30.6, 28.0, 26.6, 25.6, 25.5; $^{13}$C NMR (minor isomer) $\delta$ 220.5, 147.2, 140.8, 133.2, 129.5 (2C), 129.1 (2C), 128.5 (2C), 117.7, 113.6 (2C), 60.3, 55.5, 44.9, 33.0, 28.3, 25.4, 25.3, 24.2. Anal. calcd for $C_{21}H_{24}NOCl$: C, 73.80; H, 7.02; N, 4.10. Found: C, 73.63; H, 6.73; N, 3.87.

**4.2.16. 2-[Aminophenyl(4′-methoxyphenyl)methyl]cyclooctan-1-one (entry 8, Table 2).** Gummy solid (*syn*/*anti*=10:90); IR 3391, 1687, 1602 cm$^{-1}$; $^1$H NMR (*syn*+*anti*) $\delta$ 6.89–7.39 (m, 5H), 6.50–6.81 (m, 4H), 4.49 (d, *J*=7.2 Hz, 0.9H), 4.45 (d, *J*=6.7 Hz, 0.1H), 3.81 (s, 0.3H), 3.74 (s, 2.7H), 2.96–3.15 (m, 1H), 1.25–2.07 (m, 12H); $^{13}$C NMR (major isomer) $\delta$ 219.6, 159.1, 147.5, 133.5, 129.5 (2C), 128.5 (2C), 117.7, 113.9 (2C), 60.3, 57.5, 55.6, 44.5, 30.6, 28.0, 26.9, 26.0, 25.4. Anal. calcd for $C_{22}H_{27}O_2N$: C, 78.34; H, 8.01; N, 4.15. Found: C, 78.12; H, 7.97; N, 3.77.

**4.2.17. Ethyl 3-aminophenyl-2-benzyl-3-phenylpropanoate (entry a, Scheme 2).** Colorless powder (*syn*/*anti*=90:10), mp 106–108°C; IR 3400, 1697, 1604 cm$^{-1}$; $^1$H NMR (*syn*+*anti*) $\delta$ 7.05–7.37 (m, 12H), 6.50–6.67 (m, 3H), 4.59–4.71 (m, 1H), 3.86–4.15 (m, 2H), 2.84–3.15 (m, 3H), 1.14 (t, *J*=7.1 Hz, 0.3H), 0.96 (t, *J*=7.2 Hz, 0.7H); $^{13}$C NMR (major isomer) $\delta$ 173.4, 147.4, 140.9, 139.6, 129.5 (2C), 129.4 (2C), 128.8 (2C), 128.7 (2C), 127.9, 127.7 (2C), 127.0, 118.2, 114.1 (2C), 61.1, 60.1, 55.0, 34.2, 14.3. Anal. calcd for $C_{24}H_{25}O_2N$: C, 80.22; H, 6.96; N, 3.90. Found: C, 80.56; H, 6.49; N, 3.68.

**4.2.18. Ethyl 3-aminophenyl-2,2-dimethyl-3-phenylpropanoate (entry b, Scheme 2).** Waxy solid; IR 3398, 1712, 1602 cm$^{-1}$; $^1$H NMR $\delta$ 7.20–7.30 (m, 5H), 7.00–7.05 (m, 2H), 6.47–6.60 (m, 3H), 4.80 (d, *J*=7.0 Hz, 1H), 4.49 (d, *J*=7.4 Hz, 1H), 4.07–4.16 (m, 2H), 1.26 (s, 3H), 1.16 (t, *J*=7.1 Hz, 3H), 1.14 (s, 3H); $^{13}$C NMR $\delta$ 176.9, 147.4, 139.7, 129.4 (2C), 128.9 (2C), 128.4 (2C), 127.8, 117.6, 113.7 (2C), 64.7, 61.3, 47.3, 25.0, 20.1, 14.5. Anal. calcd for $C_{19}H_{23}NO_2$: C, 76.76; H, 7.74; N, 4.71. Found: C, 76.62; H, 7.82; N, 4.43.

**4.2.19. Ethyl 3-aminophenyl-2-ethyl-3-phenylpropanoate (entry c, Scheme 2).** Colorless powder (*syn*/*anti*=84:16), mp 113–115°C; IR 3390, 1708, 1602 cm$^{-1}$; $^1$H NMR (*syn*+*anti*) $\delta$ 7.02–7.33 (m, 7H), 6.48–6.65 (m, 3H), 4.61 (d, *J*=6.0 Hz, 0.84H), 4.54 (d, *J*=6.8 Hz, 0.16H), 4.49 (br s, 1H), 3.92–4.12 (m, 2H), 2.66–2.74 (m, 1H), 1.56–1.85 (m, 2H), 1.07–1.12 (m, 3H), 0.86–0.92 (m, 3H); $^{13}$C NMR (major isomer) $\delta$ 174.0, 147.3, 129.5 (2C), 128.8 (2C), 127.7, 127.4 (2C), 117.9, 113.9 (2C), 60.9, 59.9, 54.9, 21.2, 14.5, 12.7. Anal. calcd for $C_{19}H_{23}NO_2$: C, 76.76; H, 7.74; N, 4.71. Found: C, 76.41; H, 7.52; N, 4.46.

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