High Stereoselective Mannich Reaction Catalyzed by Starch Sulfonic Acid in Water

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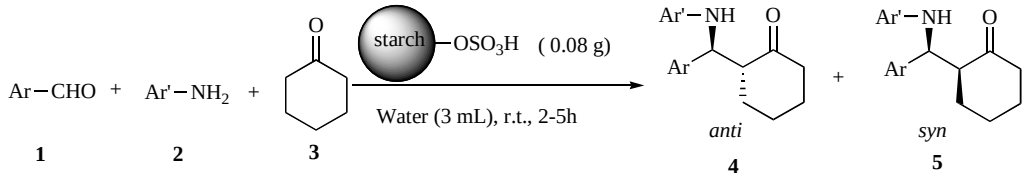
Abstract: Starch sulfonic acid was used as efficient and highly stereoselective catalyst for the three-component Mannich reaction of aldehydes, amines, and ketones in water at ambient temperature to afford the corresponding *β*-amino ketones in good to excellent stereoselectivity and yields.

Keywords: Highly stereoselective, Mannich reaction, Starch sulfonic acid.

Recently the emphasis of science and technology is shifting more towards sustainable resources and processes, in this regard biopolymers are attractive candidates to explore for supported catalysis. Starch is the cheapest and totally biodegradable natural biopolymer. To the best of our knowledge, starch has been widely used as surfactant in organic chemistry [1]. The reports about the combinations of starch and acid such as amino acid, fatty acid, sulfuric acid for organic synthesis were also studied recently [2-4]. In addition, sulfonic acid is often used as Brønsted acid to catalyze some important reactions [5]. These applications enlightened us to synthesize starch sulfuric acid (SSA) and use it as catalyst in organic synthesis. SSA has ever been used as catalyst for the preparation of quinidines *via* Fridedländer reaction [6]. In our previous work [7], it has also been synthesized and successfully used as catalyst to promote some interesting reaction.

β-Amino carbonyl compounds prepared from Mannich reaction are very important synthetic intermediates in the synthesis of pharmaceuticals and natural products [8]. Therefore, much attention has been drawn to the development of new synthetic methods to prepare these compounds. High stereoselective or asymmetric direct Mannich reaction using the unmodified aldehydes or ketones as reactant have been reported and a variety of stereo-selective or asymmetric catalysts such as (L)-proline [9], (S)-proline [10], sulfonated amino acids [11], (S)- proline [12], acyclic chiral amines and amino acids [13], and silica sulfuric acid [14], have been investigated. In recent years, Mannich reaction using water as media has received much attention [15-17].

As a part of our interest in Mannich reactions, herein we reported a SSA catalyzed highly stereoselective one-pot three-component Mannich reaction of aldehydes, amines and ketones using water as the reaction medium at ambient temperature to afford the corresponding β-amino ketones in good to excellent stereoselectivity and yields (Scheme **1**).



Scheme 1. Mannich reaction of aromatic aldehydes, arylamines and cyclohexanone.

At the beginning, SSA and some other Brønsted and Lewis acid was tested in the Mannich reaction of benzaldehyde (2.0 mmol), aniline (2.0 mmol) and cyclohexanone (2.1 mmol) (Table **1**). The reaction was carried out at room temperature in water for 2 h. No product was detected in the control reaction. Acids including silica sulfuric acid, TsOH and surfactant such as sodium dodecyl sulfate (SDS) (entries **1, 4, 5**, Table **1**) could not catalyze this reaction. Dodecylbenzenesulfonic acid (DBSA) (entry **2**, Table **1**) and SDS-HCl (entry **3**, Table **1**) could promote this reaction with good yield and stereoselectivity, but it is difficult to separate the product from mixture due to the formation of emulsions. SSA afforded the highest yield and excellent *anti* stereoselectivity because of its combination of high polarity and water solubility (entries **8-10,** Table **1**). These two important characters are necessary to form

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Table 1. One-Pot Mannich Reaction of Benzaldehyde (2.0 mmol), Aniline (2.0 mmol), and Cyclohexanone (2.1 mmol) in Water

Entry	Catalyst	X (g)	Yield (%)[a]	*anti:syn*[c]
1	silica sulfuric acid	10	Nr[b]	-
2	DBSA	10	97	74:26
3	SDS-HCl	10	87	99:1
4	TsOH	10	Nr[b]	-
5	SDS	10	Nr[b]	-
6	$H_3PMo_{12}O_{40}$	10	84	63:37
7	starch sulfuric acid	0	Nr[b]	-
8	starch sulfuric acid	0.04	90	99:1
9	starch sulfuric acid	0.08	95	99:1
10	starch sulfuric acid	0.12	85	99:1

[a]Isolated yield. [b]No reaction. [c]Diastereomeric ratio is measured by HNMR spectroscopic analysis of the crude products.

colloidal dispersion, which can increase the water solubility of organic reactants in water. Although these organic reactants have low solubility in water, the Mannich reactions were successfully catalyzed by SSA at room temperature. We thought that SSA was used not only as a Brønsted acid but also a surfactant and the reactions took place at the interface of organic materials in water. Double catalytic loading of starch sulfonic acid from 0.04 g to 0.08 g improved the yield slightly from 90% to 95% (entries **8**-**9**, Table **1**). However, the yield decreased unexpectedly when the amount of catalyst was over 0.08 g (Table **1**, entries **10**), thus 0.08 g starch sulfonic acid is suitable choice for optimum yield of *β*-amino ketones (entry **9**, Table **1**).

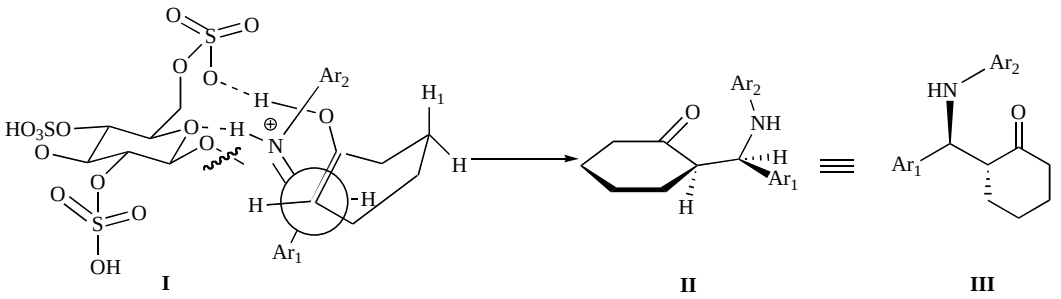
The *anti* and *syn* isomers were identified by the coupling constants (*J*) value between the vicinal protons adjacent to C=O and NH in ^{1}H NMR spectra [18]. The *anti*/*syn* ratio was determined by ^{1}H NMR.

Aromatic aldehydes **1**, anilines **2**, and cyclohexanone **3** in water were stirred in the presence of a catalytic amount (0.08 g) of starch sulfonic acid at room temperature for 2-5 h to give the corresponding β-Amino carbonyl compounds compounds (Table **2**) in good to high yield with good to excellent *anti* selectivity at room temperature, except the benzaldehyde bearing strong electron withdrawing group (entry **4h**, Table **2**).

Table 2. Direct Mannich-Type Reactions of Aromatic Aldehydes, Arylamines, and Cyclohexanone[a]

Comp.	Ar	Ar'	t (h)	*Anti/syn*[b]	Yield (%)[c]
4a	C_6H_5	C_6H_5	2	99:1	98
4b	2-$OCH_3C_6H_4$	C_6H_5	4	99:1	84
4c	3,4,5-$OCH_3C_6H_2$	C_6H_5	3	99:1	92
4d	4-$CH_3C_6H_4$	C_6H_5	5	99:1	85
4e	2,3-$OCH_3C_6H_3$	C_6H_5	4	95:5	78
4f	3,5-$OCH_3C_6H_3$	C_6H_5	3	99:1	81
4g	2,6-$OCH_3C_6H_3$	C_6H_5	3	99:1	87
4h	4-NO_2 C_6H_4	C_6H_5	12	-	Nr[d]
4i	C_6H_5	3-$CH_3C_6H_4$	2	88:12	78
4j	C_6H_5	3-ClC_6H_4	2	70:30	84
4k	C_6H_5	4-$CH_3C_6H_4$	3	88:12	78
4l	C_6H_5	3-Cl-4-FC_6H_3	4	97:3	87
4m	C_6H_5	4-ClC_6H_4	2	95:5	98
4n	C_6H_5	3-Cl-4-$CH_3C_6H_3$	3	99:1	89
4o	C_6H_5	4-FC_6H_4	4	84:16	82
4p	C_6H_5	3-Cl-2-$CH_3C_6H_3$	5	95:5	81

[a]Reaction conditions: aldehydes (2.0 mmol), arylamines (2.0 mmol), cyclohexanone (2.1 mmol), and starch sulfonic acid (0.08 g). [b]Diastereomeric ratio measured by ^{1}H NMR spectroscopy analysis of the crude reaction mixture. [c]Isolated yield. [d]No reaction.



Scheme 2. The proposed Mechanism for SSA catalyzed Mannich reaction.

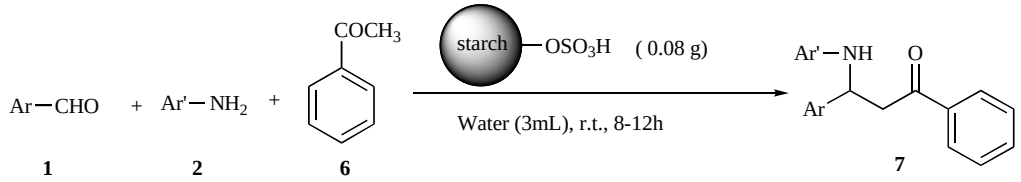
It should be mentioned that all methods reported required excess cyclohexanone (1.7-6.0 equiv.), for example, when $H_3PW_{12}O_{40}$ [19], $ZrOCl_2 \cdot 8H_2O$ [20], DBSA[21] , SDS-HCl [22], (Gn[Me])-Cu$(OTf)_2$ [23] etc. were used as catalyst. However, only stoichiometric cyclohexanone was used in our protocol. Moreover, no organic solvent was involved. Therefore, the workup was easy. As the products were solid and insoluble in water, the pure products were obtained directly by filtration and then recrystallization from ethanol or DMF.

A possible reaction mechanism is outlined in Scheme **3**. We propose that the high steroselectivity of products come from the characteristic of SSA. If hydrogen bonds are formed between SSA and the enol form of cyclohexanone, the aryl groups of aldimine would be *anti* to each other and there should be less steric repulsion in **I**, between the methylene groups of cyclohexanone and aryl group on the carbon atom, as well as SSA and H_1. So the most stable transition state **I** would produce the *anti* isomer **III** (Scheme **2**).

This encouraging result prompted us to test ketones such as acetophenone (Scheme **3**, Table **3**). As acetophenone was less reactive than cyclohexanone, longer reaction time was necessary to afford the desired products. When 0.08 g of starch sulfonic acid was used, β-amino ketones were obtained with yields ranging from 58% to 78 %. We found that the electronic effect of substituents had no influence on the yields.

We also tried to recycle the catalyst. After completion of the reaction, product was extracted by ethyl acetate and the water was used for the reaction. As shown in Scheme **4**, when the same reaction was carried out in this solution, slightly lower yields (85%) of the product were obtained compared with the first one, but the solution was still effective for the reaction.

In summary, one-pot Mannich reaction in aqueous media catalyzed by SSA with good *anti*-selectivity has been developed. This method has several advantages including mild reaction conditions, low catalyst loading, and no formation of by-products such as aldol or deamination

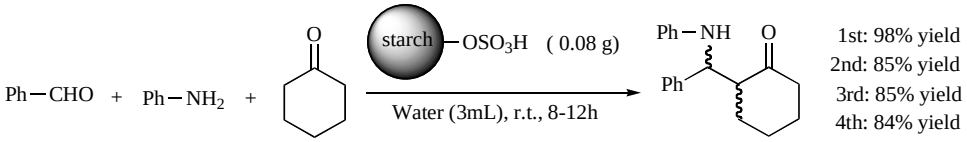


Scheme 3. Mannich reaction of aromatic aldehydes, arylamines and acetophenone.

Table 3. Mannich-Type Reactions of Aromatic Aldehydes, Arylamines, and Acetophenone[a]

Comp.	Ar	Ar'	t (h)	Yield (%)[b]
7a	C_6H_5	C_6H_5	12	78
7b	C_6H_5	3-$CH_3C_6H_4$	10	65
7c	C_6H_5	4-$OCH_3C_6H_4$	10	58
7d	C_6H_5	4-$CH_3C_6H_4$	8	62
7e	C_6H_5	3-ClC_6H_4	9	67
7f	4-$OCH_3C_6H_4$	C_6H_5	9	60
7g	4-$CH_3C_6H_4$	C_6H_5	12	76
7h	4-ClC_6H_4	C_6H_5	10	62
7i	4-BrC_6H_4	C_6H_5	12	61

[a]Reaction conditions: aldehydes (2.0 mmol), arylamines (2.0 mmol), acetophenone (2.1 mmol), and starch sulfonic acid (0.08 g). [b]Isolated yield.



Scheme 4. Recovered catalyst for Mannich reaction.

products. In addition, our process involves an environmentally benign, cheap and easy to handle catalyst. To the best of our knowledge, this is the first report of a starch sulfonic acid-catalyzed direct-type Mannich reaction. Because of its numerous benefits, the protocol should be very useful in the synthesis of β-aminocarbonyl compounds that might have biological activities.

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General procedure: All reagents were purchased from commercial sources and used without further purification. TLC analysis was performed with glass backed plates precoated with silica gel and examined under UV (254 nm). NMR spectra were measured in $CDCl_3$ with Me_4Si as the internal standards on a Bruker Advance DPX- 400 at room temperature. IR spectra were recorded on Bruker FT-IR spectrometer, absorbencies were reported in cm^{-1}. Elemental analyses were performed on a Perkin Elmer-2400 elemental analyzer. The high-resolution electrospray ionization (ESI) mass spectra were obtained on Bruker MSTOFQII mass spectrometer.

General procedure for the synthesis of β-Amino carbonyl compounds compounds 4: A mixture of aromatic aldehyde (2.0 mmol), arylamine (2.0 mmol), cyclohexanone (2.1 mmol), and SSA (0.08 g) was stirred in H_2O (3 mL) at room temperature for 2-5 h. The reaction was monitored by TLC. Ethanol was added upon completion and catalyst was removed by filtration. The product was purified by recrystallization with EtOH. The analytical data for represent compounds are shown below.

General procedure for the synthesis of β-Amino carbonyl compounds compounds 7: A mixture of benzaldehyde (2.0 mmol), aniline (2.0 mmol), acetophenone (2.1 mmol), and SSA (0.08 g) was stirred in H_2O (3 mL) at room temperature for 8-12 h. The reaction was monitored by TLC. Ethanol was added upon completion and catalyst was removed by filtration. The product was purified by recrystallization with EtOH. The analytical data for represent compounds are shown below.

SSA was synthesized following the same procedure reported by us [7].

The known compounds (**4a**, **4b**, **4d**, **7a**, **7c**, **7f**, **7g**, **7h**, **7i**) have been identified by comparison of spectral date with those reported [7c, 17d, 18, 19].

Data

2-((3,4,5-trimethoxyphenyl)(phenylamino)methyl)cyclohexanone 4c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.11 (t, *J*=7.6 Hz, 2H), 6.67 (t, *J*=7.6 Hz, 1H), 6.62 (s, 1H), 6.57 (d, *J*=8.0 Hz, 2H), 4.68 (br. s, 1H), 4.53 (d, *J*=6.8 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.83 (s, 3H), 2.70-2.75 (m, 1H), 2.34-2.47 (m, 2H), 1.84-1.96 (m, 4H), 1.70-1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 222.57, 152.95, 147.05, 137.62, 128.78, 117.39, 113.41, 103.92, 60.53, 58.25, 57.28, 55.86, 41.59, 31.01, 27.60, 23.45; IR (KBr, ν, cm^{-1}): 3336.80, 1703.03, 1592.72, 1497.75, 839.55; HRMS (ESI) calcd for $C_{22}H_{27}NO_4$ $[MH]^+$, 370.2018; Found: 370.2035; Anal. Calcd for $C_{22}H_{27}NO_4$: C, 71.52; H, 7.37; N, 3.79 Found: C, 71.50; H, 7.38; N, 3.76%.

2-((2,3-dimethoxyphenyl)(phenylamino)methyl)cyclohexanone 4e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (t, *J*=7.6 Hz, 2H), 7.01 (q, 2H), 6.79 (dd, *J*=8.0, 2.0 Hz, 1H), 6.64 (d, *J*=7.6 Hz, 1H), 6.60 (d, *J*=8.0Hz, 2H), 4.94 (d, *J*=6.8 Hz, 1H), 4.90 (br. s, 1H), 4.0 (s, 3H), 3.87 (s, 3H), 2.89-2.94 (m, 1H), 2.39-2.43 (m, 1H), 2.28-2.34 (m,

1H), 1.70-1.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.24, 151.97, 147.11, 146.53, 134.68, 128.10, 128.74, 123.53, 119.76, 117.07, 113.72, 113.26, 110.79, 60.24, 56.29, 55.34, 53.00, 41.88, 31.95, 27.97, 23.78; IR (KBr, ν, cm^{-1}): 3334.72, 1703.50, 1601.57, 1528.75, 813.21. HRMS (ESI) calcd for $C_{21}H_{25}NO_3$ $[MH]^+$, 340.1913; Found: 340.1903; Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.35; H, 7.40; N, 4.10%.

2-((3,5-dimethoxyphenyl)(phenylamino)methyl)cyclohexanone 4f. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, *J*=8.4 Hz, 1H), 7.07 (t, *J*=7.6 Hz, 2H), 6.61 (t, *J*=6.8 Hz, 1H), 6.55 (d, *J*=8.0 Hz, 2H), 6.44 (t, *J*=8.0 Hz, 2H), 4.93 (d, *J*=6.8 Hz, 1H), 4.85 (br. s, 1H), 3.91 (s, 3H), 3.77 (s, 3H), 2.83 (m, 1H), 2.41-1.45 (m, 1H), 2.31- 2.35 (m, 1H), 1.94-1.99 (m, 4H), 1.67-1.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.70, 159.47, 157.90, 147.11, 128.74, 128.47, 121.50, 116.89, 113.17, 104.05, 98.04, 55.97, 55.13, 54.99, 51.88, 41.49, 31.35, 27.98, 23.27; IR (KBr, ν, cm^{-1}): 3338.59, 1702.14, 1603.20, 1502.23, 808.22. HRMS (ESI) calcd for $C_{21}H_{25}NO_3$ $[MH]^+$, 340.1913; Found: 340.1901; Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.31; H, 7.42; N, 4.13. Found: C, 74.38; H, 7.38; N, 4.07%.

2-((2,6-dimethoxyphenyl)(phenylamino)methyl)cyclohexanone 4g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 (t, *J*=8.0 Hz, 2H), 6.95 (d, *J*=3.2 Hz, 1H), 6.80 (d, *J*=8.8 Hz, 1H), 6.70 (dd, *J*=9.2, 3.2 Hz, 1H), 6.62 (t, *J*=7.2 Hz, 1H), 6.56 (d, *J*=8.0 Hz, 2H), 5.00 (d, *J*=4.4 Hz, 1H), 4.84 (br. s, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 2.84 (q, 1 H), 2.41 (m, 1H), 2.30-2.35 (m, 1H), 1.86-1.99 (m, 4H), 1.67-1.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 213.38, 153.44, 151.26, 147.03, 130.50, 128.76, 117.02, 114.07, 113.18, 112.00, 110.78, 55.90, 55.58, 55.28, 52.15, 41.48, 31.32, 27.95, 23.28; IR (KBr, ν, cm^{-1}): 3352.33, 1702.17, 1603.05, 1498. 68, 813.02. HRMS (ESI) calcd for $C_{21}H_{25}NO_3$ $[MH]^+$, 340.1913; Found: 340.1915; Anal. Calcd for $C_{21}H_{25}NO_3$: C, 74.45; H, 7.40; N, 4.10. Found: C, 74.38; H, 7.38; N, 4.07%.

2-((m-toluidino)(phenyl)methyl)cyclohexanone 4i. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, *J*=8.0 Hz, 2H), 7.32 (t, *J*=7.6 Hz, 2H), 7.23 (t, *J*=7.6 Hz, 1H), 6.97 (t, *J*=8.0 Hz, 1H), 6.47 (d, *J*=7.6 Hz, 1H), 6.41 (s, 1H), 6.35 (d, *J*=8.0 Hz, 1H), 4.82 (d, *J*=4.4 Hz, 0.12 H), 4.68 (br. s, 1H), 4.64 (d, *J*=7.2 Hz, 0.88 H), 2.74-2.77 (m, 1H), 2.42-2.47 (m, 1H), 2.32-2.38 (m, 1H), 2.20 (s, 3H), 1.87-1.94 (m, 4H), 1.68-1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 211.06, 147.21, 141.42, 138.42, 128.67, 128.62, 128.18, 128.08, 127.21, 126.95, 126.84, 126.67, 118.39, 118.23, 114.71, 110.71, 110.22, 57.24, 56.91, 56.39, 42.14, 41.46, 30.98, 28.45, 27.63, 26.77, 24.58, 23.33, 21.32; IR (KBr, ν, cm^{-1}): 3386.31, 1695.13, 1602.90, 1524.73, 802.64. HRMS (ESI) calcd for $C_{20}H_{23}NO$ $[MH]^+$, 294.1858; Found: 294.1849; Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.95; H, 7.78; N, 4.68%.

2-((3-chlorophenylamino)(phenyl)methyl)cyclohexanone 4j. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32-7.38 (m, 3H),7.23-7.26 (m, 2H), 6.96-7.26 (m, 1H), 6.61 (t, *J*=7.2 Hz, 1H), 6.54 (d, *J*=8.0 Hz, 1H), 6.42 (d, *J*=8.0 Hz,1H), 4.90 (br, s, 1H), 4.67 (d, *J*=6.4 Hz, 0.3H), 4.57 (d, *J*=6.4 Hz, 0.7H), 2.75-2.81 (m, 1H), 2.32-2.46 (m, 2H), 1.91-2.00 (m, 4H), 1.69-1.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.46, 148.21, 140.91, 134.49, 129.76, 128.29, 127.07, 126.86, 117.11, 113.01, 111.55, 57.79, 57.07, 41.73, 31.36, 27.68, 23.60; IR (KBr, ν, cm^{-1}): 3342.02, 1701.50, 1599.60, 1525.80, 829.73. HRMS (ESI) calcd for $C_{19}H_{20}ClNO$ $[MH]^+$, 314.1301, Found: 314.1312; Anal. Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.68; H, 6.48; N, 4.52%.

2-((p-toluidino)(phenyl)methyl)cyclohexanone 4k. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (d, *J*=7.2 Hz, 2H), 7.32 (t, *J*=7.6 Hz, 2H), 7.24 (d, *J*=7.2 Hz, 1H), 6.89 (d, *J*=8.0Hz, 2H), 6.47 (d, *J*=8.0 Hz, 2H), 4.79 (d, *J*=3.6 Hz, 0.12H), 4.61 (d, *J*=7.2 Hz, 0.88H), 4.62 (br, s, 1H), 2.72-2.75 (m, 1H), 2.43-2.49 (m, 1H), 2.31-2.38 (m, 1H), 2.19 (s, 3H), 1.86-1.94 (m, 4H), 1.70-1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.65, 144.61, 141.56, 129.27, 128.17, 126.99, 126.84, 126.40, 113.48, 57.91, 57.26, 41.41, 30.91, 27.61, 23.31, 20.05; IR (KBr, ν, cm^{-1}): 3406.42, 1702.39, 1620.45, 1524.27, 805.21. HRMS (ESI) calcd for $C_{20}H_{23}NO$ $[MH]^+$, 294.1858; Found: 294.1839; Anal. Calcd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.80; H, 7.98; N, 4.81 %.

2-((3-chloro-4-fluorophenylamino)(phenyl)methyl)cyclohexanone 4l. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26-7.35 (m, 5H), 6.82-6.87 (m, 1H), 6.53-6.58 (m, 1H), 6.36-6.38 (m, 1H), 4.74 (d, *J*=6.4 Hz, 0.97H), 2.67-2.73 (m, 1H), 2.31-2.51 (m, 2H), 1.69-1.85 (m, 4H), 1.48-1.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.81, 144.25, 141.02, 128.64, 128.55, 127.47, 127.44, 127.31, 127.20, 116.73, 116.52, 114.85, 112.96, 112.90, 58.81, 57.37, 42.12, 31.73, 28.00, 23.99; IR (KBr, ν, cm^{-1}): 3389.29, 1699.09, 1608.22, 1520.74, 813.10. HRMS (ESI) calcd for $C_{19}H_{19}ClFNO$ $[MH]^+$, 332.1217; Found: 332.1208; Anal. Calcd for $C_{19}H_{19}ClFNO$: C, 68.77; H, 5.77; N, 4.22. Found: C, 68.70; H, 5.80; N, 4.28%.

2-((4-chlorophenylamino)(phenyl)methyl)cyclohexanone 4m. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.37 (m, 5H), 7.01 (d, *J*=8.8 Hz, 2H), 6. 46 (d, *J*=8.4 Hz, 2H), 4.79 (br, s, 1H), 4.56 (d, *J*=6.8 Hz, 1H), 2.76-2.78 (m, 1H), 2.35-2.46 (m, 2H), 1.84-1.97 (m, 4H), 1.69-1.74 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.82, 145.87, 141.27, 128.90, 128.55, 128.57, 128.48, 127.48, 127.35, 127.22, 122.13, 115.23, 114.77, 58.34, 57.41, 41.99, 31.57, 27.97, 23.87; IR (KBr, ν, cm^{-1}): 3412.29, 1699.12, 1600.26, 1500.75, 803.99. HRMS (ESI) calcd for $C_{19}H_{20}ClNO$ $[MH]^+$, 314.1312; Found: 314.1295; Anal Calcd for $C_{19}H_{20}ClNO$: C, 72.72; H, 6.42; N, 4.46. Found: C, 72.70; H, 6.45; N, 4.40%.

2-((3-chloro-4-methylphenylamino)(phenyl)methyl)cyclohexanone 4n. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.38 (m, 5H), 6.90 (d, *J*=8.0 Hz, 1H), 6.57 (s, 1H), 6.37 (d, *J*=8.4 Hz, 1H), 4.73 (br. s, 1H), 4.56 (d, *J*=6.8 Hz 1H), 2.76-2.78 (m, 1H), 2.35-4.46 (m, 2H), 2.19 (s, 3H), 1.83-1.94 (m, 4H), 1.70-1.75 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.48, 146.12, 141.09, 134.31, 130.83, 128.26, 127.00, 126.90, 124.08, 113.68, 112.05, 57.96, 57.13, 41.65, 31.25, 27.68, 23.54, 18.56, IR (KBr, ν, cm^{-1}): 3363.19, 1705.91, 1612.66, 1513.34, 815.14. HRMS (ESI) calcd for $C_{20}H_{22}ClNO$ $[MH]^+$, 328.1468; Found: 328.1458; Anal. Calcd for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.17; H, 6.70; N, 4.29 %.

2-((4-fluorophenylamino)(phenyl)methyl)cyclohexanone 4o. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.38 (s, 5H), 6.76-6.81 (m, 2H), 6.46-6.51 (m, 2H), 6.42 (br, s, 1H), 4.54 (d, *J*=7.2 Hz, 1H), 2.74-2.77 (m, 1H), 2.33-2.48 (m, 2H), 1.83-1.98 (m, 4H), 1.67-1.72 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.58, 156.74, 154.40, 143.30, 141.21, 128.24, 128.14, 127.20, 127.01, 115.28, 115.24, 115.06, 114.41, 114.34, 58.59, 57.21, 41.64, 31.16, 27.66, 23.53; IR (KBr, ν, cm^{-1}): 3403.80, 1699.75, 1612.08, 1512.24, 825.47. HRMS (ESI) calcd for $C_{19}H_{20}FNO$ [$MH]^+$, 298.1607; Found: 298.1594; Anal. Calcd for $C_{19}H_{20}FNO$: C, 76.74; H, 6.78; N, 4.71. Found: C, 76.65; H, 6.96; N, 4.70%.

2-((3-chloro-2-methylphenylamino)(phenyl)methyl)cyclohexanone 4p. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24-7.38 (m, 5H), 6.93 (d, *J*=8.0 Hz, 1H), 6.55 (d, *J*=8.0 Hz, 1H), 6.36 (m, 1H), 4.90 (d, *J*=6.4 Hz, 0.95 H), 4.58 (t, *J*=4.8 Hz, 1H), 2.82 (br, s, 1H), 2.33-2.46 (m, 2H), 2.18 (s, 3H), 1.72-1.97 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 212.97, 145.95, 140.91, 132.03, 130.44, 128.35, 127.12, 126.76, 120.57, 116.33, 110.23, 57.91, 57.23, 41.70, 31.43, 27.70, 23.44, 16.89; IR (KBr, ν, cm^{-1}): 3380.93, 1698.42, 1597.24, 1516.59, 802.16. HRMS (ESI) calcd for $C_{20}H_{22}ClNO$ $[MH]^+$, 328.1468; Found: 328.1473; Anal. Calcd for $C_{20}H_{22}ClNO$: C, 73.27; H, 6.76; N, 4.27. Found: C, 73.17; H, 6.79; N, 4.37%.

3-(m-tolylamino)-1,3-diphenylpropan-1-one 7b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*=7.6 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 7.56-7.60 (m, 4H), 7.47 (t, *J*=6.4 Hz, 2H), 7.25-7.28 (m, 2H), 6.99 (t, *J*=8.0 Hz, 1H), 6.36-6.52 (m, 3H), 5.02 (t, *J*=6.0 Hz, 1H), 4.50 (br. s, 1H), 3.40-3.56 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.30, 147.02, 143.09, 138.87, 136.72, 133.41, 129.01, 128.82, 128.71, 128.23, 127.32, 126.37, 118.77, 114.70, 110.78, 100.01, 54.77, 46.30, 21.60; IR (KBr, ν, cm^{-1}): 3388.35, 1667.62, 1602.38, 1520.80, 843.72. HRMS (ESI) calcd for $C_{22}H_{21}NO$ $[MH]^+$, 316.1701; Found: 316.1668; Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.85; H, 6.70; N, 4.50 %.

3-(p-tolylamino)-1,3-diphenylpropan-1-one 7d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, *J*=7.6 Hz, 2H), 7.58 (t, *J*=7.6 Hz, 1H), 7.47 (t, *J*=6.4 Hz, 2H), 7.35 d, *J*=8.0 Hz, 2H), 7.09-7.16 (m, 4H), 7.68 (t, *J*=6.0 Hz, 1H), 6.58 (d, *J*=8.0 Hz, 2H), 5.00 (t, *J*=6.4 Hz, 1H), 4.53 (br. s, 1H), 3.39-3.55 (m, 2H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.06, 144.39, 142.85, 136.42, 133.11, 129.32, 128.52, 128.41, 127.93, 127.02, 126.72, 126.10, 113.71, 54.79, 46.10, 20.09; IR (KBr, ν, cm^{-1}): 3406.42, 1702.39, 1620.45,

1524.27, 805.21. HRMS (ESI) calcd for $C_{22}H_{21}NO$ $[MH]^+$, 316.1701; Found: 316.1688; Anal. Calcd for $C_{22}H_{21}NO$: C, 83.78; H, 6.71; N, 4.44. Found: C, 83.85; H, 6.74; N, 4.40 %.

3-(3-chlorophenylamino)-1,3-diphenylpropan-1-one 7e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J*=8.0 Hz, 2H), 7.60 (t, *J*=6.4 Hz, 1H), 7.03-7.50 (m, 4H), 7.45-7.48 (m, 4H), 6.97-7.28 (m, 3H), 6.99 (t, *J*=8.0 Hz, 1H), 6.51 (d, *J*=7.8 Hz, 1H), 6.44 (s, 1H), 6.37 (d, *J*=8.0 Hz, 1H), 5.02 (t, *J*=6.0Hz, 1H), 4.50 (br. s, 1H), 3.40-3.56 (m, 2H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.81, 147.87, 142.05, 136.28, 134.51, 133.29, 129.81, 128.66, 128.48, 127.93, 127.28, 125.99, 117.41, 113.31, 111.66, 54.35, 45.85; IR (KBr, ν, cm^{-1}): 3342.02, 1701.50, 1599.60, 1525.80, 829.73. HRMS (ESI) calcd for $C_{21}H_{18}ClNO$ $[MH]^+$, 336.1155; Found: 336.1147; Anal. Calcd for $C_{21}H_{18}ClNO$: C, 75.11; H, 5.40; N, 4.17. Found: C, 75.21; H, 5.45; N, 4.10 %.