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$Ga(OTf)_3$-catalyzed Three-component Mannich Reaction in Water Promoted by Ultrasound Irradiation

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$Ga(OTf)_3$-catalyzed three-component Mannich reaction of aromatic aldehydes, aromatic amines and cycloketones in water promoted by ultrasound gave the corresponding *β*-amino cycloketones in good to excellent yields and good *anti* selectivities.

Keywords $Ga(OTf)_3$, Mannich reaction, multi-component reaction (MCR), *β*-amino cycloketone

Introduction

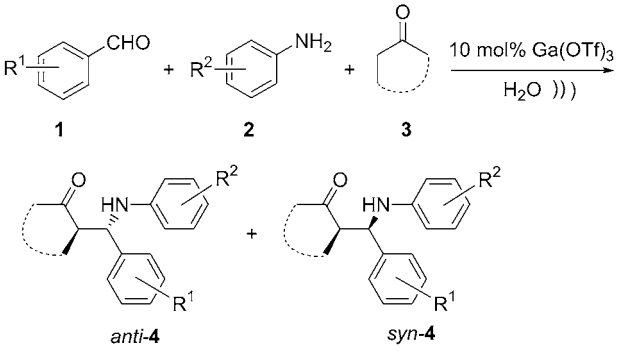
Using water as a solvent for the development of environmentaly friendly organic reactions is an important aspect of green chemistry.[1] Mannich reaction is one of the most important carbon-carbon bond forming reactions.[2] It produces *β*-amino carbonyl compounds, which are important intermediates for various pharmaceutical and natural product synthesis.[3] Numerous versions of the Mannich reaction have been developed to overcome the drawbacks associated with the classical Mannich reaction. One of the efficient routes is to conduct a one-pot three-component reaction of imines or ketones in aqueous media using catalysts such as $InCl_3$,[4] $H_3PM_{12}O_{40}$ (or $H_3PW_{12}O_{40}$),[5] HBF_4,[6a,6b] sodium tetrakis-(3,5-trifluoromethylphenyl)borate,[6c] $Bi(OTf)_3$[7] and sulfonated amino acids.[8]

$Ga(OTf)_3$ is a water-tolerant strong Lewis acid catalyst, which has been used in many organic reactions such as Beckmann rearrangement,[9] Friedel-Crafts reactions,[10,11] dehydration of aldoximes,[12] and highly regioselective rearrangement of 2-substituted vinylepoxides.[13] In continuation of our research on the catalytic properties of gallium(III) salts,[14-16] we report here a $Ga(OTf)_3$-catalyzed three-component Mannich reaction in water promoted by ultrasound irradiation (Scheme 1).

Experimental

^1H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ on an Inova-400MHz spectrometer and chemical shifts reported in ppm from internal TMS (*δ*). Melting points were determined on an XT-4 melting point apparatus and uncorrected. High resolution mass spectra were recorded on a Micromass OA-TOF (EI) mass spectrometer. All of the reagents were used directly as obtained commercially unless otherwise noted.

Scheme 1



General procedure for $Ga(OTf)_3$-catalyzed Mannich reaction in water promoted by ultrasound irradiation

To a mixture of arylamine (1 mmol), arylaldehyde (1 mmol) and cyclohexanone (or other carbonyl compounds) (2 mmol) were added successively $Ga(OTf)_3$ (10 mol%) and water (2 mL). The suspension was irradiated by ultrasonic wave until the reaction reached completion (monitored by TLC). The resultant was extracted with ethyl acetate (15 mL×3), the combined organic layers were dried over anhydrous Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (eluted with ethyl acetate/petroleum ether, V∶V=1∶4).

Compounds **4a**,[17] **4b**,[18] **4c**,[7] **4d**,[19] **4e**,[20] **4i**,[17] **4k**,[21] **4l**,[22] **4m**,[17] **4n**,[23] and **4o**[24] have been reported in the previous literatures.

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Selected spectral data for compounds 4

***Anti*/*syn*-2-(*α*-anilino-benzyl)cyclohexanone (4a)** Colorless solid, m.p. 142—143 ℃ (Lit.[17] m.p. 139—140 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.35 (s, 2H, ArH), 7.28 (s, 2H, ArH), 7.19 (d, *J*=6 Hz, 1H, ArH), 7.04 (s, 2H, ArH), 6.62 (d, *J*=6.8 Hz, 1H, ArH), 6.52 (d, *J*=6 Hz, 2H, ArH), 4.79 (s, 0.13H, CH, *syn* isomer), 4.68 (brs, 1H, NH), 4.61 (d, *J*=6 Hz, CH, 0.87H, *anti* isomer), 2.73 (d, *J*=4.8 Hz, 1H, CH), 2.39—2.29 (m, 2H, CH_2), 1.86—1.62 (m, 6H, 3×CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 23.9, 28.2, 31.6, 42.0, 57.7, 58.2, 113.9, 114.3, 117.8, 117.9, 127.2, 127.4, 127.5, 127.8, 128.6, 128.7, 129.3, 141.9, 147.5, 213.1; HRMS (EI) calcd for $C_{19}H_{21}NO$ [M^+] 279.1614, found 279.1623 (M^+, 17.78).

***Anti*/*syn*-2-(*α*-anilino-*p*-methylbenzyl)cyclohexanone (4b)** Colorless solid, m.p. 97—98 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.27—7.25 (m, 2H, ArH), 7.13—7.05 (m, 4H, ArH), 6.63 (t, *J*=7.2 Hz, 1H, ArH), 6.55 (d, *J*=7.6 Hz, 2H, ArH), 4.77 (d, *J*=4.4 Hz, 0.09H, CH, *syn* isomer), 4.69 (brs, 1H, NH), 4.60 (d, *J*=7.2 Hz, 0.91H, CH, *anti* isomer), 2.75—2.73 (m, 1H, CH), 2.44—2.31 (m, 5H, CH_2+CH_3), 1.92—1.69 (m, 6H, 3×CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 21.5, 23.9, 28.3, 31.6, 42.1, 57.9, 58.1, 114.0, 117.9, 127.6, 129.5, 129.6, 137.2, 139.0, 147.6, 213.5; HRMS (EI) calcd for $C_{20}H_{23}NO$ [M^+] 293.1768, found 293.1780 (M^+, 10.01).

***Anti*/*syn*-2-(*α*-anilino-*p*-nitrobenzyl)cyclohexanone (4c)** Colorless oil; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 8.09 (d, *J*=11.2 Hz, 2H, ArH), 7.55 (t, *J*=9.2 Hz, 2H, ArH), 7.06 (t, *J*=10 Hz, 2H, ArH), 6.63 (t, *J*=9.6 Hz, 1H, ArH), 6.50 (d, *J*=10.8 Hz, 2H, ArH), 4.96 (brs, 1H, NH), 4.88 (d, *J*=5.6 Hz, 0.20H, CH, *syn* isomer), 4.73 (d, *J*=6.8 Hz, 0.80H, CH, *anti* isomer), 2.86 (d, *J*=6.0 Hz, 1H, CH), 2.36—2.30 (m, 2H, CH_2), 1.98—1.59 (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 24.7, 28.1, 32.2, 42.6, 57.1, 57.8, 113.7, 114.2, 118.2, 123.8, 128.6, 128.8, 129.4, 129.5, 146.8, 147.1, 150.2, 212.1.

***Anti*/*syn*-2-(*α*-anilino-*α*-naphthylmethyl)cyclohexanone (4d)** Colorless solid, m.p. 168—169 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 8.08 (d, *J*=8.4 Hz, 1H, ArH), 7.88 (d, *J*=7.8 Hz, 1H, ArH), 7.75—7.69 (m, 2H, ArH), 7.61—7.50 (m, 2H, ArH), 7.39 (t, *J*=7.8 Hz, 1H, ArH), 7.00 (t, *J*=7.8 Hz, 2H, ArH), 6.60—6.49 (m, 3H, ArH), 5.88 (s, 0.10H, CH, *syn* isomer), 5.44 (brs, 1H, NH), 5.27 (d, *J*=4.8 Hz, 0.90H, CH, *anti* isomer), 3.03—2.99 (m, 1H, CH), 2.36—2.21 (m, 2H, CH_2), 2.11—1.89 (m, 6H, 3×CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) *δ*: 25.5, 28.6, 33.8, 43.6, 55.2, 56.8, 113.9, 114.7, 117.8, 122.4, 125.4, 125.7, 126.2, 126.7, 129.4, 129.5, 129.9, 131.6, 134.3, 137.4, 147.8, 213.7; HRMS (EI) calcd for $C_{23}H_{23}NO$ [M^+] 329.1753, found 329.1760 (M^+, 13.52).

***Anti*/*syn*-2-[*α*-(*p*-fluoroanilino)benzyl]cyclohexanone (4e)** Colorless solid, m.p. 93—94 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.41—7.23 (m, 5H, ArH), 6.80 (t, *J*=8.4 Hz, 2H, ArH), 6.53—6.50 (m, 2H, ArH), 4.80 (d, *J*=3.2 Hz, 0.12 H, CH, *syn* isomer), 4.69 (brs, 1H, NH), 4.60 (d, *J*=7.2 Hz, 0.88H, CH, *anti* isomer), 2.80—2.75 (m, 1H, CH), 2.47—2.32 (m, 2H, CH_2), 1.94—1.66 (m, 6H, 3×CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) *δ*: 24.2, 28.4, 31.9, 42.3, 57.9, 59.2, 115.1, 115.2, 115.8, 115.9, 127.7, 127.8, 128.9, 141.9, 144.1, 155.1, 157.4, 213.4; HRMS (EI) calcd for $C_{19}H_{20}FNO$ [M^+] 297.1522, found 297.1529 (M^+, 6.65).

***Anti*/*syn*-2-[*α*-(*m*-chloroanilino)benzyl]cyclohexanone (4f)** Colorless solid, m.p. 120—121 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.34—7.26 (m, 4H, ArH), 7.21—7.18 (m, 1H, ArH), 6.95—6.90 (m, 1H, ArH), 6.58—6.49 (m, 2H, ArH), 6.39—6.37 (m, 1H, ArH), 4.83 (brs, 1H, NH), 4.74 (d, *J*=3.6 Hz, 0.23H, CH, *syn* isomer), 4.54 (d, *J*=6.4 Hz, 0.77H, CH, *anti* isomer), 2.77—2.70 (m, 1H, CH), 2.41—2.24 (m, 2H, CH_2), 2.00—1.54 (m, 6H, 3×CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 24.3, 28.4, 32.1, 42.5, 57.8, 58.4, 112.3, 113.7, 117.8, 127.6, 127.7, 127.8, 127.9, 128.9, 129.0, 130.5, 135.2, 141.6, 148.9, 213.3; IR (KBr) *v*: 3342, 1702, 1600, 1526, 1454, 831, 777, 704 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{20}ClNO$ [M^+] 313.1233, found 313.1233 (M^+, 8.73).

***Anti*/*syn*-2-[*α*-(*o*-chloro-*p*-fluoroanilino)(*p*-methyl)benzyl]cyclohexanone (4g)** Colorless solid, m.p. 126—128 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) *δ*: 7.23 (d, *J*=10.4 Hz, 2H, ArH), 7.11 (d, *J*=10.4 Hz, 1H, ArH), 6.95 (t, *J*=10.8 Hz, 1H, ArH), 6.59—6.51 (m, 2H, ArH), 6.42—6.39 (m, 1H, ArH), 4.87 (brs, 1H, NH), 4.71 (d, *J*=5.6 Hz, 0.11H, CH, *syn* isomer), 4.52 (d, *J*=9.2 Hz, 0.89H, CH, *anti* isomer), 2.74—2.73 (m, 1H, CH), 2.44—2.29 (m, 5H, CH_2+CH_3), 193—1.65 (m, 6H, 3×CH_2); ^{13}C NMR ($CDCl_3$, 100 MHz) *δ*: 21.5, 24.2, 28.4, 31.9, 42.4, 57.8, 58.3, 112.4, 113.8, 117.8, 117.9, 127.5, 129.7, 130.5, 135.2, 137.4, 138.4, 148.8, 213.5; IR (KBr) *v*: 3357, 2950, 1700, 1600, 1520, 1452, 833, 776, 685 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{21}ClFNO$ [M^+] 345.1296, found 327.1378 (M^+−F, 6.28).

***Anti*/*syn*-2-[*α*-(*o*-chloro-*p*-fluoroanilino)-*α*-naphthylmethyl]cyclohexanone (4h)** Colorless solid, m.p. 42—44 ℃; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 8.05—7.88 (m, 3H, ArH), 7.75—7.66 (m, 2H, ArH), 7.57—7.52 (m, 3H, ArH), 7.40 (t, *J*=7.8 Hz, 2H, ArH), 5.79 (s, 0.39H, CH, *syn* isomer), 5.51 (brs, 1H, NH), 5.14 (d, *J*=3.9 Hz, 0.61H, CH, *anti* isomer), 3.02—2.98 (m, 1H, CH), 2.32—2.16 (m, 2H, CH_2), 2.04—1.67 (m, 6H, 3×CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ*: 25.4, 26.9, 27.1, 28.5, 33.7, 42.4, 43.5, 52.2, 55.2, 55.7, 56.5, 112.7, 112.8, 113.4, 113.5, 115.0, 115.9, 116.6, 116.8, 116.9, 117.0, 122.1, 122.3, 124.7, 125.0, 125.7, 125.9, 126.7, 126.8, 128.1, 128.3, 129.7, 129.8, 131.4, 134.2, 134.5, 125.7, 136.5, 144.7, 144.8, 210.9, 213.5; IR (KBr) *v*: 3365, 1683, 1601, 1501, 1395, 780 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{21}ClFNO$ [M^+] 381.1296, found 284.0483 (M^+−C_6H_9O, 25.23).

***Anti*/*syn*-2-(*α*-anilino-benzyl)cycloheptanone (4i)** Colorless solid, m.p. 136—138 ℃ (Lit.[17] m.p. 145 ℃); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ*: 7.34—7.21 (m, 5H, ArH), 7.06 (t, *J*=8.1 Hz, 2H, ArH), 6.61 (t, *J*=7.2 Hz, 1H, ArH), 6.53 (d, *J*=7.5 Hz, 2H, ArH), 5.05 (brs, 1H, NH), 4.61 (d, *J*=4.5 Hz, 0.13H, CH, *syn* isomer), 4.47 (d, *J*=7.8 Hz, 0.87H, CH, *anti* isomer), 2.94—2.86 (m,

1H, CH), 2.49—2.45 (m, 1H, CH), 2.35—2.29 (m, 1H, CH), 1.87—1.27 (m, 8H, 4×CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.4, 25.9, 28.3, 29.5, 29.7, 43.0, 58.9, 60.8, 113.9, 117.9, 127.6, 127.7, 127.8, 128.9, 129.5, 141.7, 147.3, 216.4; HRMS (EI) calcd for $C_{20}H_{23}NO$ [M^+] 293.1780, found 293.1761 (M^+, 5.35).

***Anti*/*syn*-2-(*α*-anilino-*p*-methylbenzyl)cycloheptanone (4j)** Colorless oil; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.24—7.19 (m, 2H, ArH), 7.15—7.02 (m, 4H, ArH), 6.59—6.51 (m, 3H, ArH), 4.82 (brs, 1H, NH), 4.56 (d, J=4.5 Hz, CH, 0.22H, *syn* isomer), 4.44 (d, J=7.5 Hz, CH, 0.78H, *anti* isomer), 2.89—2.82 (m, 1H, CH), 2.49—2.44 (m, 2H, CH_2), 2.22 (s, 3H, CH_3), 1.99—1.10 (m, 8H, 4×CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 21.6, 24.8, 25.5, 28.3, 29.5, 29.8, 30.9, 42.9, 44.4, 59.1, 60.3, 60.4, 113.8, 113.9, 117.7, 127.5, 127.6, 129.5, 129.6, 129.7, 129.8, 137.3, 138.7, 147.4, 216.5; IR (KBr) ν: 3353, 2945, 1696, 1600, 1517, 1446, 778, 696 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{25}NO$ [M^+] 307.1936, found 307.1930 (M^+, 7.25).

***Anti*/*syn*-2-(*α*-anilino-*p*-chlorobenzyl)cycloheptanone (4k)** Colorless solid, m.p. 108—110 ℃ (Lit.[21] m.p. 113—114 ℃); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.30—7.21 (m, 4H, ArH), 7.06 (t, J=7.8 Hz, 2H, ArH), 6.63 (t, J=7.2 Hz, 1H, ArH), 6.49 (d, J=7.8 Hz, 2H, ArH), 5.05 (brs, 1H, NH), 4.57 (d, J=2.7 Hz, 0.24H, CH, *syn* isomer), 4.46 (d, J=6.9 Hz, 0.76 H, CH, *anti* isomer), 2.91—2.84 (m, 1H, CH), 2.51—2.28 (m, 2H, CH_2), 2.01—1.27 (m, 8H, 4×CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 25.2, 28.5, 29.6, 29.7, 43.3, 44.7, 58.6, 60.1, 113.8, 113.9, 118.0, 128.9, 129.0, 129.1, 129.2, 129.6, 133.3, 140.5, 147.1, 216.1; HRMS (EI) calcd for $C_{20}H_{22}ClNO$ [M^+] 327.1320, found 327.1321 (M^+, 8.73).

***Anti*/*syn*-1-anilino-1-phenyl-2-methylpentan-3-one (4l)** Mucilage; ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.31—7.22 (m, 5H, ArH), 7.06 (t, J=7.5 Hz, 2H, ArH), 6.65 (t, J=7.2 Hz, 1H, ArH), 6.52 (t, J=8.4 Hz, 2H, ArH), 4.91 (brs, 1H, NH), 4.66 (d, J=5.7 Hz, 0.65H, CH, *syn* isomer), 4.49 (d, J=6.3 Hz, 0.35H, CH, *anti* isomer), 3.11—3.00 (m, 1H, CH), 2.41—2.27 (m, 2H, CH_2), 1.18—1.10 (m, 3H, CH_3), 0.95—0.86 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 7.7, 7.9, 12.1, 16.1, 25.9, 36.0, 36.7, 52.4, 52.6, 59.8, 59.9, 114.1, 114.2, 114.3, 118.3, 127.1, 127.3, 127.8, 127.9, 129.0, 129.1, 129.5, 129.6, 141.4, 147.1, 213.9, 215.9.

1-Anilino-1-phenylpentan-3-one (4m) Colorless solid, m.p. 102—104 ℃ (Lit.[17] m.p. 118—119 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.36—7.22 (m, 6H, ArH), 7.09—7.07 (m, 2H, ArH), 6.68—6.64 (m, 1H, ArH), 6.55—6.54 (m, 2H, ArH), 4.84—4.81 (m, 1H, CH), 4.69 (brs, 1H, NH), 2.91—2.89 (m, 2H, CH_2), 2.36—2.32 (m, 2H, CH_2), 0.99—0.95 (m, 2H, CH_3).

3-Anilino-1,3-diphenylpropan-1-one (4n) Colorless solid, m.p. 168—169 ℃ (Lit.[23] m.p. 171—172 ℃); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.91 (t, J=7.2 Hz, 2H, ArH), 7.55 (d, J=7.2 Hz, 1H, ArH), 7.45 (t, J=1.2 Hz, 4H, ArH), 7.44 (t, J=5.6 Hz, 2H, ArH), 7.34—7.30 (m, 1H, ArH), 7.09—7.07 (m, 2H, ArH), 6.69—6.65 (m, 1H, ArH), 6.56 (d, J=7.6 Hz, 2H, ArH), 5.02—4.99 (dd, $J_{1,2}$=5.6, 7.4 Hz, 1H, CH), 3.55—3.40 (m, 2H, CH_2); HRMS (EI) calcd for $C_{21}H_{19}NO$ [M^+] 301.1451, found 301.1460 (M^+, 8.45).

2,6-Bis(4-methoxybenzylidene)cyclohexanone (4o) Colorless solid, m.p. 154—156 ℃ (Lit.[24] m.p. 160 ℃); ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 7.77 (s, 2H, ArH), 7.47—7.44 (d, J=8.7 Hz, 4H, ArH), 6.95—6.92 (d, J=8.7 Hz, 4H, ArH), 3.84 (s, 6H, 2×CH_3), 2.92 (t, J=5.4 Hz, 4H, 2×CH_2), 1.79 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 23.5, 28.9, 55.8, 114.3, 129.1, 132.7, 134.7, 136.9, 160.3, 160.7; HRMS (EI) calcd for $C_{22}H_{22}O$ [M^+] 334.1569, found 334.1567 (M^+, 100).

Results and discussion

The initial three-component reaction of benzaldehyde (1 mmol), aniline (1 mmol) and cyclohexanone (2 mmol) in THF in the presence of 10 mol% $Ga(OTf)_3$ gave no desired product (Table 1, Entry 1). So we screened solvents such as CH_3CN, CH_2Cl_2 and Et_2O, and found that the reaction could proceed in CH_3CN and CH_2Cl_2 to give the 2-(*α*-anilino-benzyl)-cyclohexanone (**4a**) in good yields and *anti*/*syn* selectivity (Scheme 2, Table 1, Entries 2, 3). This result encour

Scheme 2

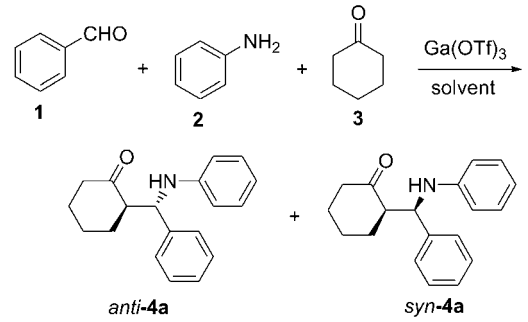


Table 1 $Ga(OTf)_3$-catalyzed Mannich reaction of benzaldehyde, aniline and cyclohexanone

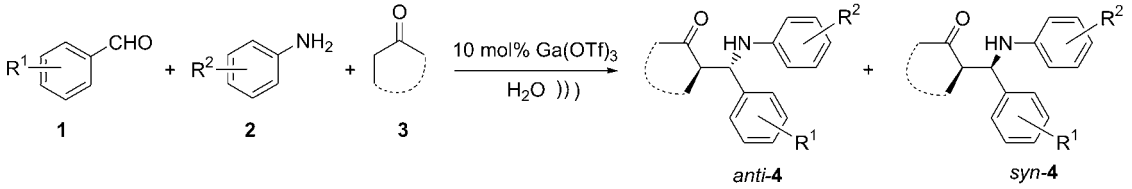
Entry	Solvent	$Ga(OTf)_3$/mol%	Time/h	*anti*/*syn*[a]	Yield[b]/%
1[c]	THF	10	24	—	Trace
2[c]	CH_3CN	10	2	76∶24	89
3[c]	CH_2Cl_2	10	5	65∶35	72
4[c]	Et_2O	10	24	—	Trace
5[c]	Water	10	12	80∶20	89
6[d]	Water	0	5	—	—[e]
7[d]	Water	5	2	86∶14	64
8[d]	Water	10	0.5	87∶13	96
9[d]	Water	15	0.5	88∶12	96

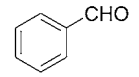
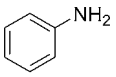
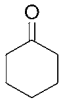
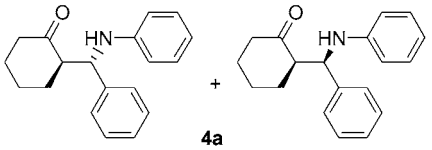
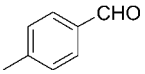
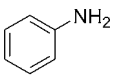
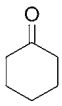
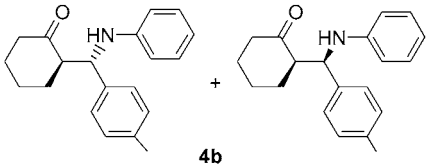
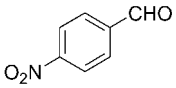
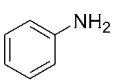
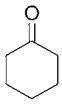
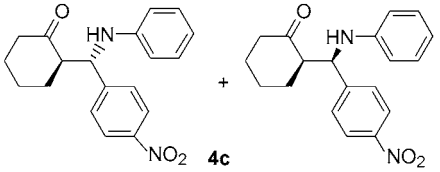
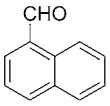
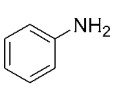
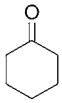
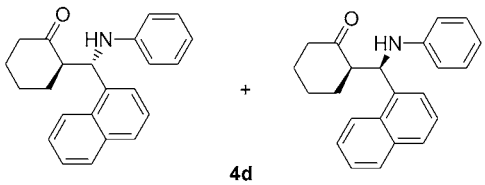
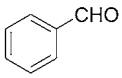
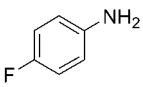
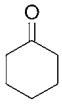
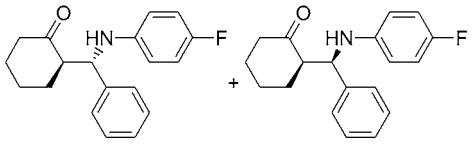
[a] *anti*/*syn* ratio was determined by ^{1}H NMR. [b] Isolated yield. [c] Stirred at room temperature. [d] Under ultrasound irradiation. [e] Imine was obtained as the main product.

aged us to conduct the reaction in water, fortunately, **4a** was obtained in an 89% yield with 8/20 *anti*/*syn* ratio (Table 1, Entriy 5). However, the reaction time was much longer than that in organic solvents, therefore, the ultrasound technology was applied. As expected, when a mixture of benzaldehyde, aniline, cyclohexanone and water was irradiated by ultrasound, the reaction was completed in 30 min in a 96% yield with an 87/13 ratio of *anti*/*syn* (Table 1, Entry 6). To optimize the reaction conditions, the reaction was performed in the presence of 0, 5, 10 and 15 mol% of $Ga(OTf)_3$, respectively, founding that $Ga(OTf)_3$ is neccessary for the reaction (Table 1, Entry 6). As the mol amount of catalyst increased from 5% to 10%, the yields were increased (Table 1, Entries 7, 8), however, 15 mol% of catalyst could not improve the yield further (Table 1, Entry 9), so 10 mol% $Ga(OTf)_3$ was the best choice. Thus, the optimized reaction condition was determined as: benzaldehyde 1 mmol, aniline 1 mmol, cyclohexanone 2 mmol, water 2 mL, the mixture being irradiated by ultrasound using 10 mol% of $Ga(OTf)_3$ as catalyst.

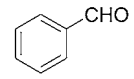
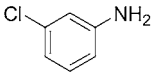
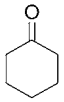
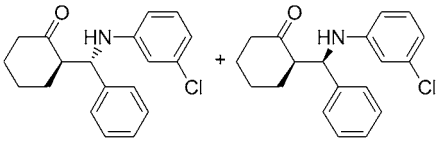
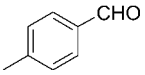
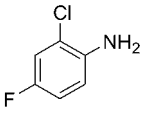
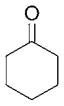
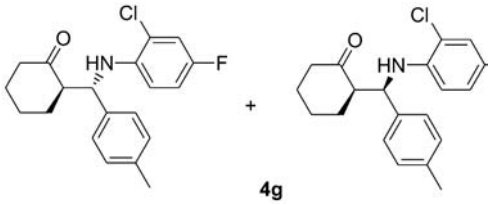
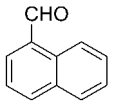
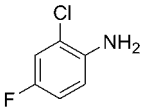
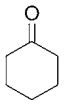
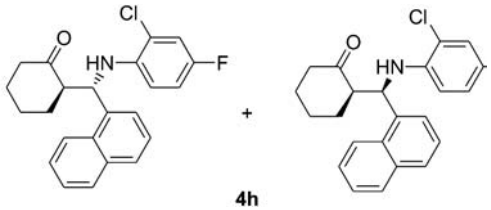
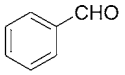
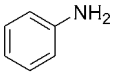
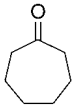
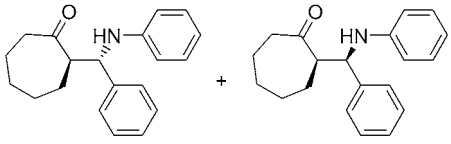
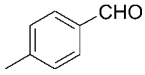
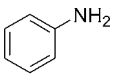
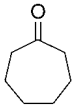
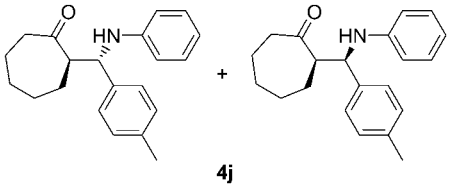
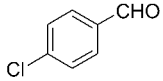
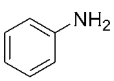
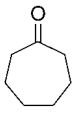
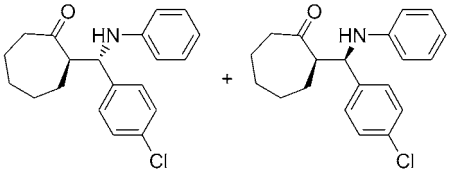
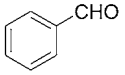
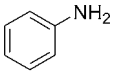
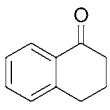
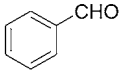
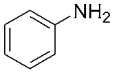
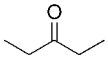
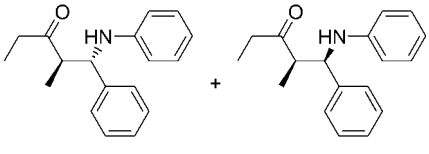
It is noteworthy that there are two competition reactions of cross-aldol condensation and Mannich reaction. In fact, only Mannich reaction product was obtained in

Table 2 $Ga(OTf)_3$-catalyzed one-pot Mannich reaction in water under ultrasound irradiation



Entry	Arylaldehyde	Amine	Ketone	Time/h	Yield[a]/%	Product	*anti* : *syn*[b]
1				0.5	95	 **4a**	87 : 13
2				0.5	90	 **4b**	91 : 9
3				0.5	94	 **4c**	80 : 20
4				0.75	86	 **4d**	90 : 10
5				0.5	87	 **4e**	88 : 12

Continued

Entry	Arylaldehyde	Amine	Ketone	Time/h	Yield[a]/%	Product	*anti* : *syn*[b]
6				1	75	 **4f**	77 : 23
7				0.75	93	 **4g**	89 : 11
8				1	88	 **4h**	61 : 39
9				0.5	90	 **4i**	87 : 13
10				0.75	85	 **4j**	78 : 22
11				0.75	87	 **4k**	76 : 24
12				5		N.R.[c]	—
13				2	78	 **4l**	35 : 65

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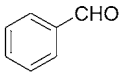
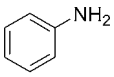
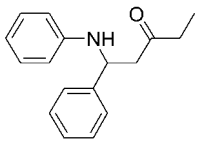
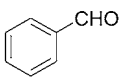
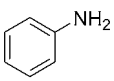
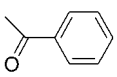
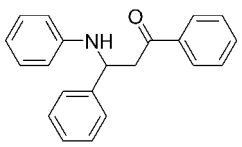
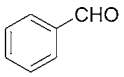
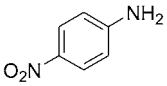
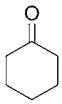
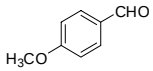
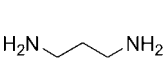
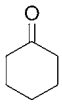
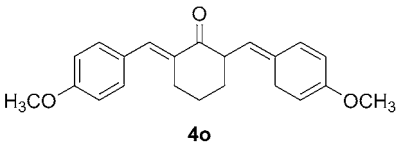
Entry	Arylaldehyde	Amine	Ketone	Time/h	Yield[a]/%	Product	*anti* : *syn*[b]
14				2	80	 **4m**	—
15				5	84	 **4n**	—
16				5	—	N.R.[d]	
17[d]				1	79	 **4o**	—

[a] Isolated yield. [b] *anti/syn* ratio was determined by ^{1}H NMR of the product. [c] Only the unreacted starting materials was observed. [d] Only cross-aldol condensation product was isolated.

our work (except Table 2, Entry 17), which demonstrated that the reaction catalyzed by $Ga(OTf)_3$ mentioned above had a good chemoselectivity.

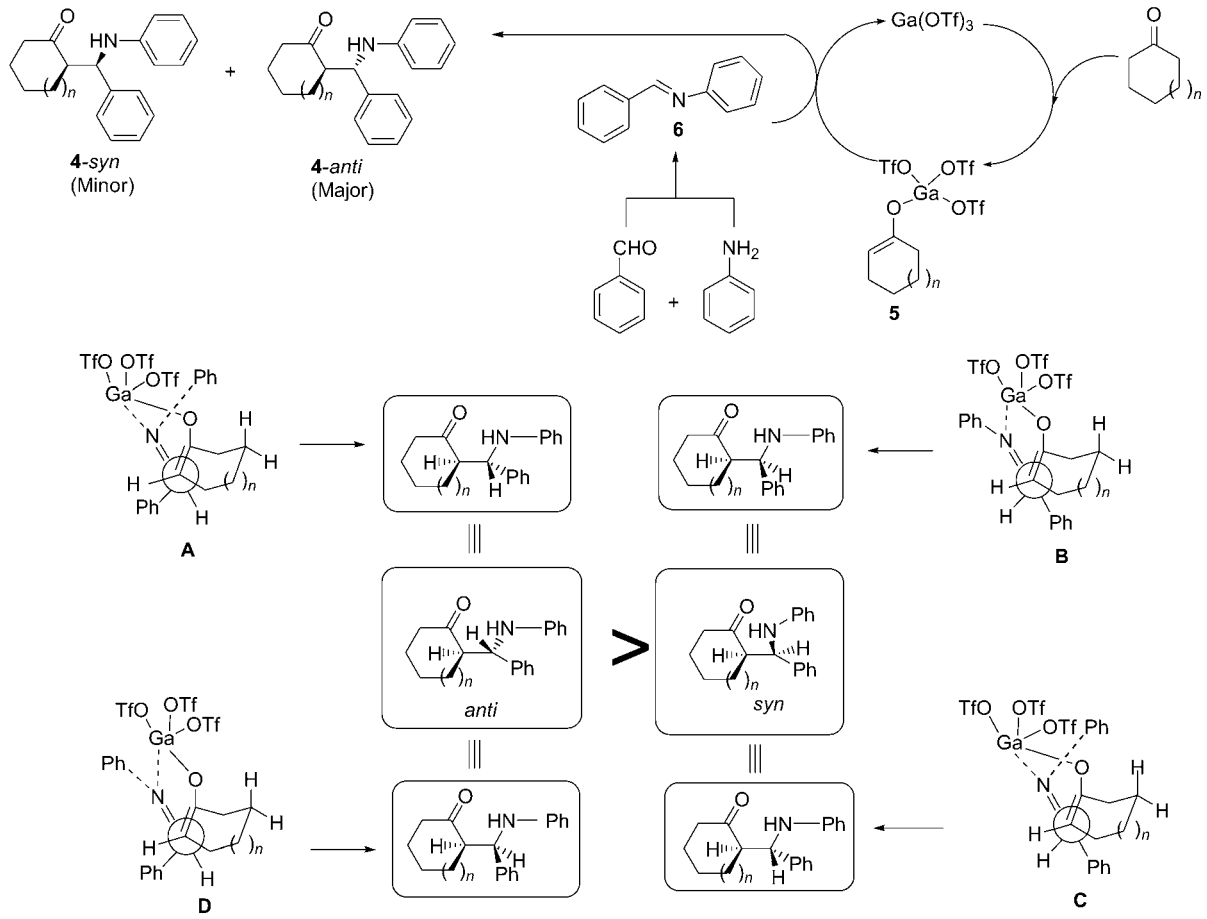
With the experiences above in hand, we further studied this reaction in detail using different arylaldehydes, amines and ketones. To know the scope of arylaldehydes, and the reaction of arylaldehydes, aniline and cyclohexanone was used as a model, and the results showed that arylaldehydes bearing either electron-donating or electron-withdrawing groups all gave excellent yields (90%—95%) (Table 2, Entries 1—3). When *α*-naphthaldehyde was brought in this reaction instead of benzaldehyde, the yields were slightly decreased (Table 2, Entries 4, 8), which might be attributed to the hindrance of the aldehyde. Secondly, the effect of amines on yield was investigated, in the case of arylamines, F and Cl on the phenyl ring gave no obvious effect on the yields (Table 2, Entries 5, 7) except 3-chloroaniline (yield 75%, Table 2, Entry 6), but nitroaniline yielded no expected product (Table 2, Entry 16), which showed that a strong electron-withdrawing group in aniline retarded the reaction. On the other hand, when alkylamine, such as 1,3-propyldiamine was used, the cross-aldol condensation product became major (Table 2, Entry 17), which might be due to the less stability of the imine formed by alkylamine. Thirdly, the effect of ketones was evaluated. Cycloheptanone, whose cycle is larger than that of cyclohexanone, afforded the Mannich product in similar yields (85%—90%, Table 2, Entries 9—11). However, the reaction did not work for benzocyclohexenone, which might be attributed to the rigidity of benzocyclohexenone. Moreover, to compare the difference between cyclic ketones and acyclic ketones, 3-pentanone, 2-butanone and acetophenone were selected as substrates, and the Mannich reaction products were isolated in slightly low yields (78%—84%, Table 2, Entries 13—15).

Based on the experimental results described above, a possible mechanism for the Mannich reaction was proposed in Scheme 3. Enolate **5** *in situ* generated attacks imine **6** *in situ* formed to afford a mixture of *syn* and *anti* of *β*-amino carbonyl compound **4**, accompanied by release of $Ga(OTf)_3$, which takes part in the next catalytic cycle. In this process the *anti*-form is the major one, which may be explained by the relative stability of transition states of **A**, **B**, **C** and **D**. As seen in Scheme 3, **A** and **D** leading to the *anti*-form are more stable than **B** and **C** leading to the *syn*-form, therefore, the formation of the *anti*-form is more favorable than that of the *syn*-form.

Conclusion

In conclusion, 10 mol% $Ga(OTf)_3$ can efficiently catalyze the three-component Mannich reaction of arylaldehydes, arylamines and ketones in water under ultrasonic irradiation to afford *β*-amino carbonyl compounds in good to excellent yields. This new method has good *chemo*- and *stereo*-selectivities. The solvent of water makes it an attractive green chemistry process.

Scheme 3



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