Supplementary Material (ESI) for Green Chemistry

Supporting Information

Lipase-catalysed direct Mannich reaction in water: utilization of biocatalytic promiscuity for C-C bond formation in a "one-pot" synthesis

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Experimental Section

Materials and General Methods

Lipase from *Candida antarctica* (CAL-B), lipase from porcine pancreas (PPL), lipase from *Candida cylindracea* (CCL), lipase from *Candida rugosa* (CRL), lipase from *Mucor javanicus* (MJL) and lipase from *Rhizopus oryzae* (ROL) were purchased from Sigma. Lipase from *Mucor miehei* (MML) and lipase from *Penicillium camemberti* (PCL) were purchased from Fluka. Lipase from *Pseudomonas fluorescens* (PFL), Lipase from *Penicillium roqueforti* (PRL) and Lipase from *Burkholderia cepacia* (BCL) were a gift from Amano.

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker DMX 400. Chemical shifts are given in δ relative to tetramethylsilane (TMS). HPLC was carried out using a Shimadzu organizer consisting of a LC-2010A HT Integrator, a UV/VIS Detector. C18 column was used in the HPLC experiments with methanol/water = 70:30 (v/v), 0.8 ml/min and UV= 254 nm. Electrospray ionization (ESI) mass spectrometry experiments were performed on Bruker Daltonics Bio TOF mass spectrometer.

Time effect of the Mannich reaction catalyzed by MML

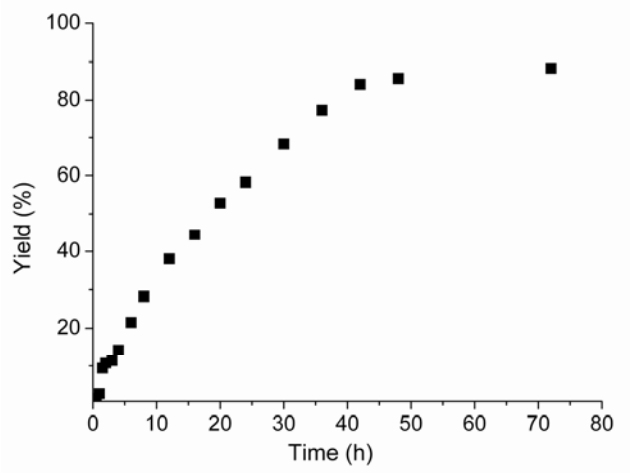


Fig. S1 Time course of the reaction catalysed by MML

Reaction conditions: a solution of 4-nitrobenzaldehyde (0.3 mmol), aniline (0.33 mmol), acetone (6 ml), 6 ml water and 30 mg MML was shaken at 200 rpm at 30 °C, and 40 μl reaction solvent was taken out at different time and yield was calculated by HPLC.

Catalyst recovery experiment

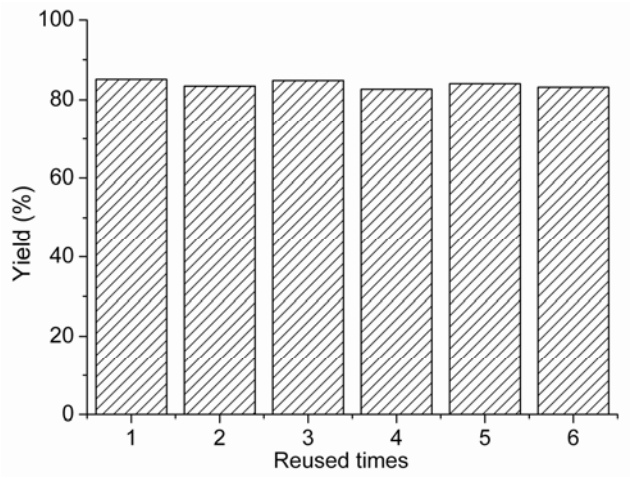
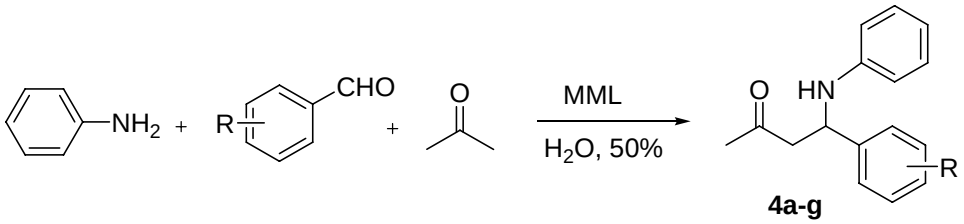


Fig. S2 The yield of Mannich Reaction by reused MML

Reaction conditions: a solution of 4-nitrobenzaldehyde (**2**, 0.1 mmol), aniline (**1**, 0.11 mmol), acetone (**3**, 1 ml), 2 ml solvent (the ratio of the mixture solvent is 1:1 in volme) and 10 mg MML was shaken at 200 rpm at 30 °C for 28 h. The catalyst can be easily recovered by washing with

water.

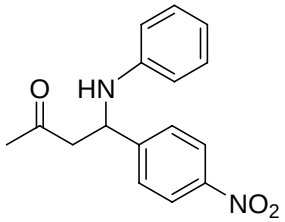
Subsrate expansion and characterization



4a-g

Entry	R	4	Yield (%)
1	4-NO_2	4a	83.5
2	3-NO_2	4b	82.4
3	H	4c	87.3
4	4-OMe	4d	89.1
5	4-OH	4e	43.6
6	4-CN	4f	65.3
7	4-Cl	4g	83.1

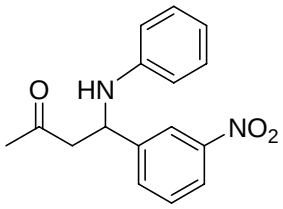
Reaction conditions: the reaction was initiated by adding 1 mmol aldehyde, 1.1 mmol amine and 50 mg MML to a mixture of 8 ml acetone and 8 ml water. The suspension was maintained at 30 °C and shaken at 200 rpm for 48 h. The residue was then filtered off and the solvent was evaporated. A single product was prepared by silica gel chromatography with an eluent consisting of petroleum/ethyl acetate (4 : 1, v/v).



4a

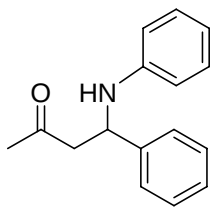
4-Phenylamino-4-(4-nitrophenyl)butan-2-one (4a): ^{1}H NMR ($CDCl_3$, 400 MHz),

δ (ppm): 8.23-8.18 (m, 2H, Ph-H), 7.57-7.54 (m, 2H, Ph-H), 7.15-7.10 (m, 2H, Ph-H), 6.71-6.68 (m, 1H, Ph-H), 6.50-6.48 (m, 2H, Ph-H), 4.94 (t, 1H, *J* = 6.4 Hz, Ph-CH-), 4.48 (s, 1H, NH), 2.97 (d, 2H, *J* = 6.4 Hz, -CH_2-), 2.15 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 205.9, 150.4, 147.2, 146.1, 128.8, 124.2, 124.1, 118.6, 113.8, 53.8, 50.6, 30.7. ESI-MS: 307.1 $[M+Na]^+$.



4b

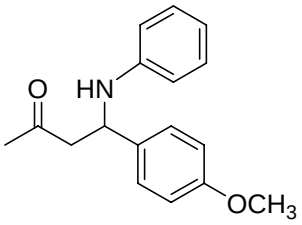
4-Phenylamino-4-(3-nitrophenyl)butan-2-one (4b): ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 8.26-8.22 (m, 1H, Ph-H), 8.09-8.07 (m, 1H, Ph-H), 7.76-7.74 (m, 1H, Ph-H), 7.50-7.46 (m, 1H, Ph-H), 7.10-7.08 (m, 2H, Ph-H), 6.71-6.68 (m, 1H, Ph-H), 6.53-6.51 (m, 2H, Ph-H), 4.95 (t, 1H, *J* = 6.4 Hz, Ph-CH-), 4.58 (s, 1H, NH), 2.98 (d, 2H, *J* = 6.4 Hz, -CH_2-), 2.15 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 206.1, 148.7, 146.3, 145.3, 140.3, 136.4, 133.9, 133.0, 130.1, 129.8, 129.5, 124.7, 122.7, 121.5, 118.5, 115.2, 113.9, 53.6, 50.8, 30.7. ESI-MS: 307.1 $[M+Na]^+$.



4c

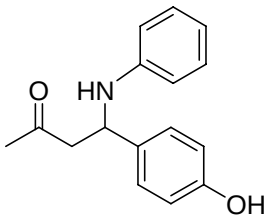
4-Phenylamino-4-phenyl-butan-2-one (4c): ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.31-7.24 (m, 4H, Ph-H), 7.11-7.09 (m, 2H, Ph-H), 6.68-6.65 (m, 1H, Ph-H),

6.55-6.54 (m, 2H, Ph-H), 4.86 (t, 1H, *J* = 6.4 Hz, Ph-CH-), 4.43 (s, 1H, NH), 2.93 (d, 2H, *J* = 6.4 Hz, -CH_2-), 2.10 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 207.2, 146.8, 142.5, 129.1, 128.8, 127.4, 126.3, 117.9, 113.8, 54.4, 51.2, 30.7. ESI-MS: 262.1 $[M+Na]^+$.



4d

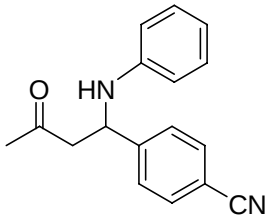
4-Phenylamino-4-(4-methoxy-phenyl)butan-2-one (4d): ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.28-7.25 (m, 2H, Ph-H), 7.11-7.07 (m, 2H, Ph-H), 6.86-6.83 (m, 2H, Ph-H), 6.68-6.64 (m, 1H, Ph-H), 6.55-6.53 (m, 2H, Ph-H), 4.80 (t, 1H, *J* = 6.4 Hz, Ph-CH-), 3.77 (s, 3H, -OCH_3), 2.89 (d, 2H, *J* = 6.4 Hz, -CH_2-), 2.09 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 207.4, 158.8, 146.8, 134.5, 130.0, 129.1, 127.4, 117.8, 114.2, 113.8, 55.3, 53.8, 51.3, 30.8. ESI-MS: 292.1 $[M+Na]^+$.



4e

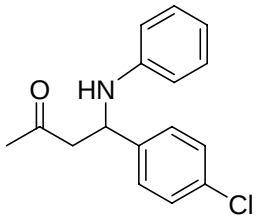
4-Phenylamino-4-(4-hydroxy-phenyl)butan-2-one (4e): ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.42-7.40 (m, 1H, Ph-H), 7.20-7.17 (m, 2H, Ph-H), 7.10-7.06 (m, 2H, Ph-H), 6.87-6.78 (m, 1H, Ph-H), 6.77-6.67 (m, 1H, Ph-H), 6.56-6.54 (m, 2H, Ph-H), 4.78 (t, 1H, *J* = 6.4 Hz, Ph-CH-), 2.89 (d, 2H, *J* = 6.4 Hz, -CH_2-), 2.08 (s, 3H, -CH_3).

^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 208.5, 159.3, 146.8, 144.8, 130.4, 129.2, 127.5, 116.1, 115.7, 113.8, 53.9, 51.3, 30.8. ESI-MS: 278.1 $[M+Na]^+$.



4f

4-Phenylamino-4-(4-Cyanophenyl)butan-2-one (4f): ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.31-7.26 (m, 4H, Ph-H), 7.11-7.07 (m, 2H, Ph-H), 6.70-6.66 (m, 1H, Ph-H), 6.52-6.50 (m, 2H, Ph-H), 4.81 (t, 1H, *J* = 6.4 Hz, Ph-CH-), 4.45 (s, 1H, NH), 2.89 (d, 2H, *J* = 6.4 Hz, -CH_2-), 2.10 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 206.8, 146.6, 141.3, 133.1, 129.4, 129.1, 127.9, 118.3, 115.3, 113.9, 53.9, 51.1, 30.9. ESI-MS: 287.1 $[M+Na]^+$.



4g

4-Phenylamino-4-(4-chlorophenyl)butan-2-one (4g): ^{1}H NMR ($CDCl_3$, 400 MHz), δ (ppm): 7.60-7.58 (m, 2H, Ph-H), 7.50-7.48 (m, 2H, Ph-H), 7.11-7.07 (m, 2H, Ph-H), 6.71-6.67 (m, 1H, Ph-H), 6.50-6.47 (m, 2H, Ph-H), 4.88 (t, 1H, *J* = 6.4 Hz, Ph-CH-), 4.56 (s, 1H, NH), 2.93 (d, 2H, *J* = 6.4 Hz, -CH_2-), 2.12 (s, 3H, -CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz), δ (ppm): 206.1, 148.4, 146.3, 135.6, 129.3, 127.3, 118.8, 113.8, 111.2, 53.9, 50.7, 30.7. ESI-MS: 296.1 $[M+Na]^+$.