A highly efficient carbon-carbon bond formation reaction via nucleophilic addition to *N*-alkylaldimines without acids or metallic species

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Melting points were determined using Yanagimoto Micro Melting Point Apparatus and are uncorrected. IR spectra were recorded on JASCO FT-IR/420 Infrared Fourier Transfer Spectrometer indicating with cm^{-1} . ^1H and ^{13}C NMR spectra were measured with JEOL GSX400 Spectrometer at 400MHz and 100MHz, respectively, in chloroform-*d*, and chemical shifts are indicated as δ value in ppm from internal tetramethylsilane at 25°C unless otherwise noted. High Resolution Mass Spectra (HRMS) were measured with JEOL JMS-DX303.

A General Procedure for the synthesis of α -*N*-methylacetoamino acid methyl ester (3a~k)

To a solution of imine (0.5 mmol), imidazole (85.1 mg, 1.25 mmol) in anhydrous methanol (5 ml) at -40°C was added **2** (74.5 mg, 0.6 mmol), and the mixture was stirred at -40°C. The resulting solution was concentrated in vacuo, and the purification of the residue by silica gel column chromatography gave **3**.

Each NMR chart of **3** shows a mixture of inseparable rotational isomers caused by *N*-methylacetamide moiety at 25°C.

methyl 2-(*N*-methylacetyl-amino)-2-phenylacetate (**3a**)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, colorless oil, 97.4 mg, 0.44 mmol, 88% yield), FT-IR (neat): 3473, 2952, 1747, 1651, 1396, 1209, 1080, 1024, 920, 773, 741, 700 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.44-7.20 (m, 5H), 6.47 & 5.67 (s, 9:1, 1H), 3.85 & 3.78 (s, 1:9, 3H), 2.82 & 2.77 (s, 9:1, 3H), 2.25 & 2.17 (s, 1:9, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.4 (C), 170.9 (C), 134.3 (C), 128.8 (CH*2), 128.6 (CH*2), 128.3 (CH), 59.8 (CH), 52.1 (CH_3), 32.7 (CH_3), 21.9 (CH_3); EI-HRMS (m/z) [M]⁺ calcd for $\text{C}_{12}\text{H}_{15}\text{NO}_3$, 221.1040, found 221.1052

methyl 2-(*N*-methylacetyl-amino)-2-(4-methylphenyl)acetate (**3b**)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, yellow oil, 105.9 mg, 0.45 mmol, 90% yield); FT-IR (neat): 3471, 2952, 1747, 1651, 1516, 1394, 1134, 1024, 964, 917, 874, 833, 787, 758, 580 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.18 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 6.41 & 5.64 (s, 10:1, 1H), 3.84 & 3.76 (s, 1:10, 3H), 2.81 & 2.76 (s, 10:1, 3H), 2.35 & 2.06 (s, 10:1, 3H), 2.24 & 2.16 (s, 1:10, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.4 (C), 171.0 (C), 138.2 (C), 131.2 (C), 129.3 (CH*2), 128.8 (CH*2), 59.6 (CH), 52.1 (CH_3), 32.7 (CH_3), 21.9 (CH_3), 21.1 (CH_3); EI-HRMS (m/z) [M]⁺ calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_3$, 235.1208, found 235.1208

methyl 2-(4-methoxyphenyl)-2-(*N*-methylacetyl-amino)acetate (**3c**)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, yellow oil, 110.6 mg, 0.45 mmol, 90% yield); FT-IR (neat): 3471, 2954, 2841, 2048, 1747, 1651, 1516, 1030, 964, 918, 872, 841, 802, 762 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.16 (d, J = 8.8 Hz, 2H), 6.90 (d, J = 8.8 Hz, 2H), 6.39 & 5.62 (s, 10:1, 1H), 3.81 (s, 3H), 3.76

(s, 3H), 2.81 & 2.75 (s, 10:1, 3H), 2.23 & 2.16 (s, 10:1, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.3 (C), 171.1 (C), 159.4 (C), 130.2 (CH^*2), 126.3 (C), 114.1 (CH^*2), 59.4 (CH), 55.2 (CH_3), 52.1 (CH_3), 32.6 (CH_3), 22.0 (CH_3); EI-HRMS (m/z) $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_4$, 251.1165, found 251.1158

methyl 2-(4-cyanophenyl)-2-(N-methylacetylaminomethyl)acetate (3d)

Elution for column chromatography (Hexane:Ethyl acetate = 3 : 4, yellow oil, 86.2 mg, 0.35 mmol, 70% yield); FT-IR (neat): 3473, 2954, 2229, 1745, 1651, 1396, 1311, 1211, 1134, 1022, 841, 750 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.69 (d, $J = 8.0$ Hz, 2H), 7.40 (d, $J = 8.0$ Hz, 2H), 6.48 & 5.71 (s, 19:1, 1H), 3.88 & 3.81 (s, 1:19, 3H), 2.87 & 2.78 (s, 19:1, 3H), 2.25 & 2.20 (s, 1:19, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.4 (C), 169.6 (C), 139.8 (C), 132.3 (CH^*2), 129.5 (CH^*2), 118.1 (C), 112.2 (C), 59.5 (CH), 52.5 (CH_3), 33.2 (CH_3), 21.7 (CH_3); EI-HRMS (m/z) $[\text{M}]^+$ calcd for $\text{C}_{13}\text{H}_{14}\text{N}_2\text{O}_3$, 246.0992, found 246.1004

methyl 2-(N-methylacetylaminomethyl)-2-(4-nitrophenyl)acetate (3e)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, yellow oil, 109.2 mg, 0.41 mmol, 82% yield); FT-IR (neat): 3473, 2954, 1747, 1651, 1522, 1350, 1028, 858, 775, 741, 702 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 8.24 (d, $J = 8.4$ Hz, 2H), 7.46 (d, $J = 8.4$ Hz, 2H), 6.53 & 5.75 (s, 38:1, 1H), 3.90 & 3.83 (s, 1:38, 3H), 2.90 & 2.80 (s, 38:1, 3H), 2.26 & 2.21 (s, 1:38, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.5 (C), 169.6 (C), 147.6 (C), 141.8 (C), 129.8 (CH^*2), 123.8 (CH^*2), 59.3 (CH), 52.6 (CH_3), 32.3 (CH_3), 21.8 (CH_3); EI-HRMS (m/z) $[\text{M}]^+$ calcd for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}_5$, 266.0925, found 266.0903

methyl 2-(N-methylacetylaminomethyl)-2-(3-pyridyl)acetate (3f)

Elution for column chromatography (Hexane:Ethyl acetate : Triethylamine = 10 : 9 : 1, yellow oil, 88.9 mg, 0.40 mmol, 80% yield); FT-IR (neat): 3460, 2954, 1747, 1651, 1427, 1319, 1213, 1134, 1026, 766, 714 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 8.60 (brd, $J = 4.4$ Hz, 1H), 8.51 (brd, $J = 1.2$ Hz, 2H), 7.63 (d, $J = 8.0$ Hz, 1H), 7.34 (dd, $J = 4.4, 8.0$ Hz, 1H), 6.46 & 5.70 (s, 12:1, 1H), 3.90 & 3.80 (s, 1:12, 3H), 2.88 & 2.80 (s, 12:1, 3H), 2.27 & 2.19 (s, 1:12, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.4 (C), 169.8 (C), 149.9 (CH), 149.4 (CH), 136.6 (CH), 130.7 (C), 123.5 (CH), 58.0 (CH), 52.5 (CH_3), 33.1 (CH_3), 21.8 (CH_3); EI-HRMS (m/z) $[\text{M}]^+$ calcd for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_3$, 222.1012, found 222.1004

methyl 2-(2-furyl)-2-(N-methylacetylaminomethyl)acetate (3g)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, yellow oil, 79.9 mg, 0.38 mmol, 76% yield); FT-IR (neat): 3477, 3120, 2954, 1747, 1651, 1398, 1317, 1215, 1142, 1072, 1016, 937, 883, 758 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.42 (brt, $J = 1.2$ Hz, 1H), 6.47 & 5.65 (s, 12:1, 2H), 6.39 (d, $J = 1.2$ Hz, 2H), 3.83 & 3.78 (s, 1:12, 3H), 2.97 & 2.81 (s, 12:1, 3H), 2.23 & 2.17 (s, 1:12, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.2 (C), 168.8 (C), 147.7 (C), 143.0 (CH), 110.6 (CH), 110.5 (CH), 54.2 (CH), 52.6 (CH_3), 33.0 (CH_3), 21.7 (CH_3); EI-HRMS (m/z) $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_4$, 211.0858, found 211.0845

methyl 2-(N-methylacetylaminomethyl)-2-(2-thienyl)acetate (3h)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, colorless oil, 84.9 mg, 0.38 mmol, 75% yield); FT-IR (neat): 3473, 2952, 1747, 1651, 1435, 1396, 1313, 1211, 1134, 1022, 904, 850, 712 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.33 (dd, $J = 1.2, 4.8$ Hz, 1H), 7.05-6.98 (m, 2H), 6.60 & 5.81 (s, 11:1, 1H), 3.86 & 3.79 (s, 1:11, 3H), 2.93 & 2.85 (s, 11:1, 3H), 2.25 & 2.17 (s, 1:11, 3H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.1 (C), 169.9 (C), 136.4 (C), 127.9 (CH), 126.6 (CH), 126.5 (CH), 55.5 (CH), 52.5 (CH_3), 33.9 (CH_3), 21.9 (CH_3); EI-HRMS (m/z) $[\text{M}]^+$ calcd for $\text{C}_{10}\text{H}_{13}\text{NO}_3\text{S}$, 227.0616, found 227.0616

methyl 2-(N-methylacetylaminomethyl)-4-phenylbutanoate (3i)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, colorless oil, 103.5 mg, 0.42 mmol, 83% yield); FT-IR (neat): 3465, 3026, 3952, 1739, 1651, 1402, 1213, 1090, 1014, 750, 702 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.15 - 7.36 (m, 5H), 5.26 & 4.23 (s, 3:1, 1H), 3.73 & 3.70 (s, 1:3, 3H), 2.90 & 2.86 (s, 3:1, 3H), 2.79 - 2.52 (m, 2H), 2.44 - 2.27 (m, 1H), 2.12 & 1.86 (s, 3:1, 3H), 2.06 - 1.95 (m, 1H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.7 & 171.3 (3:1) (C), 171.5 & 171.0 (3:1) (C), 140.7 & 139.6 (3:1) (C), 128.6 & 128.2 (1:3) (CH^*2), 128.3 & 128.2 (3:1) (CH^*2), 126.4 & 126.0 (3:1) (CH), 59.1 & 55.8 (1:3) (CH), 52.5 & 52.2 (1:3) (CH_3), 32.6 & 31.6 (3:1) (CH_2), 32.3 & 28.4 (3:1) (CH_2), 30.3 & 30.2 (3:1) (CH_3), 22.0 & 21.5 (3:1) (CH_3); FAB-HRMS (m/z) $[\text{MH}]^+$ calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_3$, 250.1420, found 250.1443

methyl 3-ethyl-2-(N-methylacetylaminopentanoate (3j)

Elution for column chromatography (Hexane:Ethyl acetate = 1 : 1, colorless oil, 87.2 mg, 0.41 mmol, 81% yield); FT-IR (neat): 3464, 2964, 1739, 1651, 1435, 1400, 1319, 1267, 1198, 1018, 904, 748 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 5.21 & 4.10 (d, J = 10.4, 2.3:1, 1H), 3.72 & 3.69 (s, 1:2.3, 3H), 2.97 & 2.86 (s, 2.3:1, 3H), 2.15 & 2.10 (s, 1:2.3, 3H), 2.06 - 1.85 (m, 1H), 1.46 - 1.15 (m, 4H), 0.91 & 0.85 (t, J = 7.6, 2.3:1, 6H); ^{13}C -NMR (CDCl_3 , 100MHz): 172.0 (C), 171.3 (C), 63.1 & 57.1 (1:2.3) (CH), 52.1 & 51.8 (1:2.3) (CH_3), 39.0 & 38.5 (2.3:1) (CH), 32.0 & 28.4 (2.3:1) (CH_3), 22.1 & 21.9 (2.3:1) (CH_3), 21.5 & 21.1 (2.3:1) (CH_2), 20.8 & 20.0 (2.3:1) (CH_2), 10.6 & 9.98 (2.3:1) (CH_3), 9.93 & 9.86 (2.3:1) (CH_3); FAB-HRMS (m/z) $[\text{MH}]^+$ calcd for $\text{C}_{11}\text{H}_{22}\text{NO}_3$, 216.1594, found 216.1600

methyl 2-[4-(diethoxymethyl)phenyl]-2-(N-methylacetylaminopentanoate (3k)

Elution for column chromatography (Hexane:Ethyl acetate : Triethylamine = 10 : 9 : 1, colorless oil, 132.6 mg, 0.41 mmol, 82% yield); FT-IR (neat): 3477, 2976, 1747, 1651, 1437, 1396, 1335, 1211, 1178, 1113, 1055, 1022, 920, 877, 793, 766 cm^{-1} ; ^1H -NMR (CDCl_3 , 400MHz): 7.49 (d, J = 8.0, 2H), 7.23 (d, J = 8.0, 2H), 6.47 & 5.67 (s, 11:1, 1H), 5.50 (s, 1H), 3.85 & 3.78 (s, 1:11, 3H), 3.67 - 3.51 & 3.61 - 3.45 (m, 11:1, 4H), 2.81 & 2.76 (s, 11:1, 3H), 2.24 & 2.17 (s, 1:11, 3H), 1.25 & 1.21 (t, J = 7.2, 11:1, 6H); ^{13}C -NMR (CDCl_3 , 100MHz): 171.4 (C), 170.9 (C), 139.3 (C), 134.4 (C), 128.8 (CH^*2), 127.0 (CH^*2), 101.1 (CH), 61.23 (CH_2), 61.20 (CH_2), 59.6 (CH), 52.2 (CH_3), 32.8 (CH_3), 22.0 (CH_3), 15.2 (CH_3^*2); EI-HRMS (m/z) $[\text{M}]^+$ calcd for $\text{C}_{17}\text{H}_{25}\text{NO}_5$, 323.1738, found 323.1733