Stereoselective Synthesis of 3-Alkylideneoxindoles Using Tandem In-mediated Carbometallation and Pd-catalyzed Coupling Reaction

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General. All reactions were carried out under a positive pressure of argon or nitrogen. ^1H NMR spectra were recorded on a JEOL JNM-LA-500 spectrometer using tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on a JEOL JNM-LA-500 (125.0 MHz) spectrometer. Nominal (LRMS) and exact mass (HRMS) spectra were recorded on a JEOL JMS-HX/HX-110A instrument. Metallic indium was purchased from Kojundo Chemical Laboratory Co., Ltd. For flash chromatography, silica gel FL60D (Fuji Silysia Chemical Ltd.) and silica gel 60N (Kanto Chemical Co. Inc.) were employed.

All new compounds gave satisfactory ^1H -NMR, ^{13}C -NMR, LRMS, HRMS, IR, and/or Elemental Analysis.

General procedure (Reductive radical cyclization reaction for synthesis of (*E*)-alkenes)

To a solution of compound **1e** (50 mg, 0.12 mmol) in dry dimethylformamide (0.5 ml) was added indium (0) (27 mg, 0.24 mmol) and pyridinium tribromide (38 mg, 0.12 mmol). The mixture was stirred for 12 h at room temperature under argon atmosphere. The mixture was filtered through a plug of celite, and concentrated in vacuo. Chromatography over silica gel using 9% AcOEt in hexane afforded the desired 3-alkylideneoxindole **3e** (30 mg, 80%) as a yellow oil.

(*E*)-1-Benzyl-3-benzylidene-1,3-dihydro-indol-2-one (3e)

^1H -NMR (500 MHz, CDCl_3) δ 7.93 (s, 1H), 7.67–7.62 (m, 2H), 7.49–7.44 (m, 2H), 7.34–7.31 (m, 4H), 7.15 (t, J = 7.0 Hz, 1H), 6.84 (t, J = 7.6 Hz, 1H), 6.72 (d, J = 7.9 Hz, 1H), 5.00 (s, 1H); ^{13}C -NMR (126 MHz, CDCl_3) δ 143.4, 137.7, 136.1, 135.1, 132.0, 129.8, 129.3, 128.7, 127.4, 122.9, 127.9, 121.4, 109.2, 43.8; LRMS (CI) m/z , 312 (MH^+), HRMS (CI) Calcd for $\text{C}_{22}\text{H}_{18}\text{NO}$ (MH^+) 312.1394, found 312.1388; IR (CHCl_3 , cm^{-1}) 2932, 2361, 1692.

(*Z*)-1-Benzyl-3-benzylidene-1,3-dihydro-indol-2-one (3e)

^1H -NMR (500 MHz, CDCl_3) δ 8.31 (d, J = 4.0 Hz, 1H), 7.60 (s, 1H), 7.54 (d, J = 4.0 Hz, 1H), 7.46–7.44 (m, 2H), 7.33–7.24 (m, 8H), 7.20–7.18 (M, 1H), 7.03(t, J = 7.4Hz, 1H), 6.73 (d, J = 8.6

Hz, 1H), 5.00 (s, 2H); ^{13}C -NMR (126 MHz, CDCl_3) δ 137.5, 136.3, 130.0, 128.9, 128.8, 128.3, 127.4, 125.9, 124.5, 121.9, 119.0, 108.8, 43.6; LRMS (CI) m/z , 312 (MH^+), HRMS (CI) Calcd for $\text{C}_{22}\text{H}_{18}\text{NO}$ (MH^+) 312.1388, found 312.1396; IR (CHCl_3 , cm^{-1}) 3014, 2361, 1675.

General procedure (Tandem carboidation and cross-coupling reaction for disubstituted 3-alkylideneoxindoles)

3-Phenyl-propynoic acid benzyl-(2-iodo-phenyl)-amide **1e** (50 mg, 0.12 mmol), indium (0) (27 mg, 0.24 mmol) and bromine (19 mg, 0.12 mmol) in dry dimethylformamide (0.5ml) was stirred for 8 h at room temperature under argon atmosphere. Then $\text{Pd}(\text{acac})_2$ (1.8 mg, 0.006 mmol), lithium bromide (31 mg, 0.36 mmol) and 4-iodotoluene (52 mg, 0.24 mmol) was added to the reaction mixture. Then the solution was stirred at 100 °C for 6 h. The mixture was filtered through a plug of celite, and concentrated in vacuo. Chromatography over silica gel using 9% AcOEt in hexane afforded the oxindole **4a** (Z) (30 mg, 80%) as a yellow oil.

1-Benzyl-3-(phenyl-p-tolyl-methylene)-1,3-dihydro-indol-2-one (4a-(Z))

^1H -NMR (500 MHz, CDCl_3) δ 7.44–7.43 (m, 1H), 7.37–7.18 (m, 13H), 7.14 (t, $J = 7.7$ Hz, 1H), 6.67–6.65 (m, 2H), 6.55 (d, $J = 8.0$ Hz, 1H), 4.91 (s, 2H), 2.42 (s, 3H); ^{13}C -NMR (126 MHz, CDCl_3) δ 166.9, 155.4, 142.3, 140.0, 139.5, 138.0, 136.5, 130.5, 130.3, 129.6, 128.7, 127.8, 127.5, 123.6, 123.1, 121.4, 108.6, 43.4, 21.4; LRMS (FAB) m/z , 402 (MH^+), HRMS (FAB) Calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$ (MH^+) 402.1858, found 402.1850; IR (CHCl_3 , cm^{-1}) 3157, 2361, 1602.

1-Benzyl-3-(phenyl-p-tolyl-methylene)-1,3-dihydro-indol-2-one (4a-(E))

^1H -NMR (500 MHz, CDCl_3) δ 7.45–7.42 (m, 2H), 7.36–7.17 (m, 11H), 7.03 (t, $J = 7.6$ Hz, 1H), 6.67–6.61 (m, 2H), 6.38 (d, $J = 8.0$ Hz, 1H), 4.93 (s, 3H), 2.38 (s, 3H); ^{13}C -NMR (126 MHz, CDCl_3) δ 166.9, 155.4, 142.3, 141.5, 139.6, 136.9, 136.5, 130.5, 129.5, 128.7, 127.5, 123.6, 123.1, 121.4, 108.6, 43.4, 21.4; LRMS (FAB) m/z , 402 (MH^+), HRMS (FAB) Calcd for $\text{C}_{29}\text{H}_{24}\text{NO}$ (MH^+) 402.1858, found 402.1859; IR (CHCl_3 , cm^{-1}) 2944, 2361, 1602.

27 May 2004
noe

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No.	(ppm)	Height	(Hz)	Value	Absolute Value
1	7.33	0.2711	3662.8	2.000	2.05811e+8
2	7.26	0.1471	1933.5	1.001	1.02911e+8
3	7.15	0.1471	1933.5	1.015	1.04325e+8
4	7.08	0.1028	1371.2	1.030	1.10222e+8
5	6.86	0.1064	1418.4	0.769	7.90152e+7
6	6.78	0.1091	1454.4	3.961	4.09270e+8
7	6.72	0.1572	2096.6	2.972	3.05496e+8
8	6.66	0.1482	1972.8	7.739	7.96475e+8
9	6.58	0.1755	2339.7	0.823	8.46401e+7

No.	(ppm)	Height	(Hz)	Value	Absolute Value
10	6.52	0.1139	1518.4	0.1139	0.1139
11	6.46	0.1126	1500.0	0.1126	0.1126
12	6.40	0.1670	2211.2	0.1670	0.1670
13	6.34	0.1452	1922.4	0.1452	0.1452
14	6.28	0.1452	1922.4	0.1452	0.1452
15	6.22	0.1766	2344.8	0.1766	0.1766

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27 May 2004
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		Temperature (degree C)		

Date	Thu May 27 18:58:44 2004
Number of Transients	4
Original Points Count	32768

No.	(ppm)	Value	Absolute Value
1	4.91..5.06	2.092	1.83284e+8
2	6.66..6.79	1.000	8.76107e+7
3	6.97..7.08	1.105	9.67703e+7
4	7.09..7.21	1.469	1.28721e+8
5	7.27..7.38	4.983	4.35568e+8
6	7.36..7.50	3.300	2.89119e+8
7	7.50..7.57	1.467	1.28513e+8
8	7.58..7.64	0.965	8.45344e+7
9	8.22..8.39	1.723	1.50991e+8

No.	(ppm)	Height	No.	(ppm)	Height
1	-0.00	0.0000	19	7.29	3645.1
2	1.25	627.2	20	7.31	3652.8
3	1.55	776.7	21	7.32	3660.1
4	2.17	1085.2	22	7.33	3665.3
5	2.85	1425.5	23	7.43	3714.7
6	5.00	2488.6	24	7.43	3717.2
7	5.11	2553.2	25	7.44	3720.2
8	6.72	3361.6	26	7.44	3721.7
9	6.74	3369.2	27	7.45	3723.3
10	7.02	3510.8	28	7.45	3726.3
11	7.04	3518.2	29	7.47	3733.6
12	7.05	3525.8	30	7.48	3740.3
13	7.17	3584.4	31	7.55	3773.0
14	7.18	3592.0	32	7.56	3780.3
15	7.20	3599.7	33	7.60	3801.4
16	7.23	3616.7	34	8.31	4157.2
17	7.25	3623.8	35	8.33	4164.9
18	7.26	3630.2

C:\Documents and Settings\Owner\My Documents\N@um.la600-614r15.27.2r1.nm1d

25 Mar 2004
n06

Acquisition Time (sec)	3.2768	Comment	n06	Date	Wed Mar 24 22:21:08 2004	File Name	C:\Documents and Settings\Owner\My Documents\1_N06.m\q601-956h3.24f1.nm.fid
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No.	(ppm)	Value	Absolute Value
1	[2.40 - 2.48]	2.378	4.00297e+8
2	[4.85 - 4.85]	0.000	4.09359e+4
3	[4.85 - 5.00]	2.059	3.46638e+8
4	[6.50 - 6.50]	0.912	1.36562e+8
5	[6.60 - 6.72]	2.048	3.44789e+8
6	[6.97 - 7.10]	1.122	1.88817e+8
7	[7.14 - 7.39]	14.840	2.49773e+9
8	[7.39 - 7.50]	0.960	1.61533e+8

No.	(ppm)	Height	(Hz)
1	-0.00	0.2766	7.19
2	1.26	629.3	0.0862
3	1.56	778.2	0.3217
4	2.04	1022.4	0.1250
5	2.38	1188.7	0.1353
6	2.43	1214.9	0.4431
7	4.92	2459.5	0.3616
8	6.55	3274.6	0.0841
9	6.57	3282.6	0.0976
10	6.65	3325.6	0.0882
11	6.87	3326.8	0.0860
12	6.86	3330.8	0.1519
13	6.97	3333.2	0.1341
14	6.98	3338.4	0.1379
15	7.03	3516.6	0.0823
16	7.05	3524.3	0.1048

Comment	Date	File Name
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frequency (MHz)	Original Points Count 32768	Solvent CHLOROFORM-D

No.	(ppm)	(Hz)	Height
1	-0.00	0.00	0.1972
2	1.24	621.4	0.0551
3	1.25	622.6	0.0529
4	1.26	628.7	0.1508
5	1.27	633.7	0.0836
6	1.56	779.1	0.0631
7	2.04	1021.8	0.1950
8	2.38	1189.0	0.1000
9	2.43	1214.9	0.0964
10	6.37	2463.8	0.0658
11	6.37	3186.1	0.1572
12	6.39	3194.1	0.1766
13	6.39	3197.3	0.0984
14	6.83	3315.2	0.1837
15	6.85	3322.9	0.0949
16	6.66	3331.7	0.1793
17	6.68	3339.3	0.1939
18	7.02	3509.3	0.1024
19	7.03	3517.3	0.1842
20	7.05	3524.9	0.0960