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An efficient and facile synthesis of divergent C-3/C-5 bis-functionalized 2-oxindoles from 5-formyl-Morita-Baylis-Hillman adducts of oxindole

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Abstract. An efficient and facile synthesis of divergent C-3/C-5 bis-functionalized 2-oxindole derivatives has been achieved from 3,5-bis-Morita-Baylis-Hillman (MBH) adducts of oxindole *via* nucleophilic substitution reaction for the first time. Wider scope of substrate and rate acceleration has been observed in second MBH reaction under typical reaction condition. The synthetic usefulness of bi-functionalized bis-allyl derivative has been demonstrated by the synthesis of potent bis-pyrazole *via* [3+2]-annulation strategy.

Keywords. Bis-MBH adduct; Oxindole; Nucleophilic substitution; Tri-substituted olefins; bis-pyrazole.

1. Introduction

Oxindole and their derivatives continue to receive extensive attention in organic synthesis and also serve as potential synthons for the synthesis of alkaloids, drug intermediates and clinical pharmaceuticals.[1] Aimed at that purpose, oxindole has been functionalized in many ways, namely, nucleophilic substitution at C-3 carbonyl,[2] alkylation/acylation at oxindole nitrogen[3] and electrophilic substitution at aromatic nuclei.[4] In particular, bi-functionalization of isatin at C-2 carbonyl (amide carbonyl) with oxindole nitrogen provided the natural products such as ophiuroidine and hydroxytryptanthrins by Prey demethylation method.[5] In recent years, MBH adduct of oxindole has attracted attention due to its significance of multi-functionalized motifs, because they are also observed in a wide range of bioactive compounds and natural products.[6] Owing to the lack of inherent functional entity on the aryl core of MBH adduct of oxindole, the synthetic transformation has been carried out preferably at C-3/ N-position.[7] Interestingly, a mild and single electron oxidation strategy has been reported for the oxidation of 5-methyl MBH adduct of isatin into 5-formyl-mono MBH derivative (mMBH), which could enable various C–C, C–O and C–N bond-forming reactions.[8] Among the various carbon–carbon bond-forming reactions, MBH reaction plays an important role in synthetic chemistry, because they also serve as versatile synthons in the construction of complex molecular frameworks.[9]

In general, the MBH reaction of benzaldehyde exhibits a poor substrate scope and also requires prolonged reaction time under typical reaction conditions. To address these limitations, a number of strategies have been developed to pursue the MBH adduct either by increasing the concentration of reactive intermediates and/or by activating the electrophiles.[10] In addition, most of the reported strategies were applicable to a few activated alkenes and some catalysts showed substrate-associated rate acceleration.[11] We describe the synthesis of highly functionalized bis-allyl derivatives of oxindole from bis-MBH adducts *via* nucleophilic isomerization of C, O and Br nucleophiles. The second MBH reaction of 5-formyl MBH (mMBH) adduct has displayed a broad substrate scope with a variety of activated alkenes and shows substrate-allied rate acceleration under the common catalyst of 1,4-diazabicyclo [2.2.2]octane (DABCO). The successive synthetic transformations of bis-MBH adduct provide a multi-functionalized, tri-substituted olefins and bis-pyrazole derivatives.[12]

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2. Experimental

All chemicals and solvents were purchased from Sigma-Aldrich, Merck, and used without further purification. All reactions were carried out in oven-dried glassware. Progress of reactions was monitored by thin layer chromatography (TLC), while purification of crude compounds was done by column chromatography using silica gel (100–200 mesh). NMR spectra were recorded at 500 and 300 MHz (based on availability of the instruments), 125 and 75 MHz (for ^{13}C), respectively, on Bruker Avance DPX-500 MHz and Bruker Avance DPX-300 MHz. Chemical shifts are reported in δ (ppm) relative to TMS (^{1}H) or $CDCl_3$ (^{13}C) as internal standards. The multiplicities are shown as the abbreviations: s (singlet), brs (broad singlet), d (doublet), t (triplet), m (multiplet). Mass spectra were recorded using JEOL JMS 600H mass spectrometer. Infrared spectra were determined in 0.10 mm matched cells with a Bomem MB series FT-IR spectrometer using a scan time of 32 min in auto-suppression and were calibrated with polystyrene film. The infrared frequencies (cm^{-1}) of the observed hydroxyl bands are accurate to $\pm 0.5\ cm^{-1}$. Yield refers to quantities obtained after chromatography.

2.1 *General procedure for the synthesis of bis-MBH adducts (**3a-m**)*

A mixture of mMBH adducts of 5-formyl-*N*-alkyl-isatin **1a-g** (100 mg), activated alkenes **2a-g** (1.5 equiv.) and DABCO (20 mol%) was stirred under neat condition at for 8–32 h. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with ethyl acetate. The organic layer was washed successively with 0.2 N HCl, water and then brine solution. The organic layer was separated, dried over Na_2SO_4 and then concentrated *in vacuo*. The crude product was obtained and purified by silica gel column chromatography using EtOAc: hexane (40:60) as eluent. The desired bis-MBH adducts of oxindole (**3a-m**) was obtained in moderate to excellent yield (45–94%).

2.2 *General procedure for the isomerization with oxygen and carbon nucleophiles*

A mixture of bis-MBH adduct of oxindole **3b** (50 mg, 0.152 mmol), trimethylorthoformate (2 mL) or propargyl alcohol (2 mL) or Ar-H (2 mL) and montmorillonite K-10 Clay (50% w/w) was subjected under solvolysis condition. After completion of the reaction (monitored by TLC), the reaction mixture was diluted with CH_2Cl_2 and passed through a pad of celite-545. On concentration under vacuum, the resulted crude mixture was purified by a silica gel column chromatography using EtOAc:hexane (15:85) as eluent. The isomerization afforded the corresponding isomerized products in combined moderate-to-good yield (54–75%).

2.3 *Procedure for the isomerization of Bromide nucleophile*

A mixture of bis-MBH adduct of oxindole **3b** (50 mg, 0.152 mmol), 46% aqua. HBr (2 equiv.) and silica gel (0.2 g) are made a slurry. The slurry was subjected to microwave irradiation (70% power level, 5 sec. pulse, SAMSUNG, Model: CE 118 KF) for 10 min. The crude mixture was cooled to room temperature and then extracted with CH_2Cl_2 and the organic phase washed with water. The organic layer was separated and dried (anhyd. Na_2SO_4) and concentrated *in vacuo*. The obtained crude mixture was purified by silica gel column chromatography using a gradient elution with EtOAc:hexane (20: 80) as eluent to afford allyl bromide of oxindole derivative (**4d** and **5d**) in combined good yield (67%).

2.4 *General procedure for the synthesis of bis-pyrazole from bis-allyl bromide of oxindole derivative*

A mixture bis-allyl bromide **5d** (100 mg, 0.221 mmol), dimethyl sulphide (1.2 equiv., 0.028 mmol), K_2CO_3 (2.1 equiv. 64 mg) in CH_3CN (2.0 mL) and diethyl azodicarboxylate **6** (2.2 equiv.) were added successively at RT. After completion of the reaction (monitored by TLC), the solvent was removed under vacuum. Water (5.0 mL) was added to the residue and extracted with ether (3 × 5.0 mL). Combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The obtained crude product was purified by silica gel column chromatography using EtOAc: hexane (25:75) eluent to afford bis-pyrazole **7** in good yield (82%).

2.4a *2-{[3-(1-Cyano-vinyl)-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl]-hydroxy-methyl}-acrylonitrile (**3a**)*: Gummy matter, yield 12%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 973, 1063, 1078, 1719, 2226, 2876, 3110, 3365. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.28 (3H, s), 3.84 (1H, bs), 4.44 (1H, bs), 5.33 (1H, s), 5.98–6.03 (2H, m), 7.26–7.38 (2H, m), 7.39–7.47 (3H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 27.2, 62.9, 73.4, 109.4, 122.0, 123.2, 123.4, 125.0, 125.1, 126.0, 126.2, 129.4, 129.6, 130.3, 130.5, 173.8. FAB mass: 296.43 (M+1). Anal. Calcd. for $C_{16}H_{13}N_3O_3$: C, 65.08; H, 4.44; N, 14.23; Found: C, 65.05; H, 4.42; N, 14.25.

2.4b *2-[5-(2-Cyano-1-hydroxy-allyl)-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-acrylic acid*

*methyl ester (**3b**)*: Gummy matter, yield 87%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1053, 1089, 1643, 1716, 2230, 3088, 3382. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.20(3H, s), 3.60(3H, s), 4.24–4.28(1H, bs), 5.18(1H, s), 5.98–5.99(1H, s), 6.06–6.10(1H, d, J = 8.0 Hz), 6.37–6.38(1H, s), 6.53(1H, s), 6.82–6.85(d, 1H, J = 8.0 Hz), 7.25(1H, s), 5.18(1H, s),7.34 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 26.5, 52.0, 60.4, 73.6, 108.7, 121.9, 122.2, 128.2, 128.6, 128.8, 129.8, 129.9, 130.0, 134.2, 134.2, 164.6, 176.3. FAB mass: 329.45 (M+1). Anal. Calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.21; H, 4.90; N, 8.54.

2.4c *2-{[3-(1-Cyano-vinyl)-3-hydroxy-2-oxo-1-prop-2-ynyl-2,3-dihydro-1H-indol-5-yl]-hydroxy-methyl}-acrylonitrile (**3c**)*: Gummy matter, yield 74%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1069, 1627, 1718, 2218, 3363. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31(1H, s), 3.02(1H, bs), 4.51(2H, s) 4.54(1H, bs), 5.33(1H, s), 6.06–6.35(4H, m), 7.14(1H, s), 7.46–7.51(2H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 29.9, 60.1, 73.3, 73.7, 75.5, 110.4, 113.4, 115.0, 116.4, 123.0, 123.2, 126.1, 127.7, 129.5, 129.8, 131.7, 142.1, 172.9. FAB mass: 320.13 (M+1). Anal. Calcd. for $C_{18}H_{13}N_3O_3$: C, 67.71; H, 4.10; N, 13.16. Found: C, 67.74; H, 4.09; N, 13.17.

2.4d *2-[5-(2-Cyano-1-hydroxy-allyl)-3-hydroxy-2-oxo-1-prop-2-ynyl-2,3-dihydro-1H-indol-3-yl]-acrylic acid methyl ester (**3d**)*: Gummy matter, yield 83%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1660, 1713, 1726, 2216, 2225, 3389. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.27–2.30 (1H, s), 3.51 (1H, bs), 3.57 (3H, s), 4.39–4.42 (1H, bs), 4.48 (2H, s), 5.20 (1H, s), 5.98–6.57 (4H, m), 7.06–7.09 (1H. d, J = 8.0 Hz), 7.18 (1H, s), 7.37–7.43 (1H, d, J = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 29.7, 52.1, 60.40, 72.8, 73.8, 76.1, 109.9, 122.5, 126.4, 128.2, 128.7, 128.9, 129.6, 129.8, 134.8, 138.8, 143.3, 165.1, 175.1. FAB mass: 352.37 (M^+). Anal. Calcd. for $C_{19}H_{16}N_2O_5$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.79; H, 4.57; N, 7.97.

2.4e *2-{[1-Benzyl-3-(1-cyano-vinyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-5-yl]-hydroxy-methyl}-acrylonitrile (**3e**)*: Gummy matter, yield 79%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1079, 1717, 2236, 3108, 3371. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.55 (1H, bs), 4.01 (1H, bs), 4.65–4.70 (1H, d, J = 15.7 Hz), 4.91–4.97 (d, 1H, J = 5.7 Hz,), 5.22 (1H, s), 5.88–6.26 (4H, m), 6.68–6.71 (1H, d, J = 8.1Hz), 7.24–7.27 (6H, m), 7.36–7.40 (1H, d, J = 8.1Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 42.6, 62.1, 73.5, 115.6, 116.6, 116.87, 125.6, 125.6, 126.1, 126.7, 127.3, 127.7, 127.9, 128.6, 128.8, 129.8, 129.9, 130.5, 134.3, 135.2, 135.39, 174.3. FAB mass: 372.41 (M+1). Anal. Calcd. for $C_{22}H_{17}N_3O_3$: C, 71.15; H, 4.61; N, 11.31. Found: C, 71.12; H, 4.60; N, 11.32.

2.4f *2-[1-Benzyl-5-(2-cyano-1-hydroxy-allyl)-3-hydroxy-2-oxo-2,3-dihydro-1H-indol-3-yl]-acrylic acid methyl ester (**3f**)*: Gummy matter, yield 88%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}) 1181, 1610, 1721, 2211, 2990, 3295. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.11 (1H, bs), 3.62 (3H, s), 3.64 (1H, bs), 4.79–4.84 (1H, d, J = 17.5 Hz), 4.90–4.95 (1H, d, J = 17.5 Hz), 5.1 (1H, s), 5.94–6.61 (4H, m), 6.67–6.70 (1H, d, J = 8.2 Hz), 7.17 (1H, s), 7.27–7.36 (6H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 44.1, 52.0, 73.7, 76.0, 109.8, 121.2, 122.2, 125.8, 125.9, 127.3, 127.7, 128.5, 128.6, 128.73, 128.8, 129.8, 129.9, 130.1, 134.2, 135.1, 138.5, 165.0, 176.4. FAB mass: 405.76 (M+1). Anal. Calcd. for $C_{23}H_{20}N_2O_5$: C, 68.31; H, 4.98; N, 6.93. Found: C, 68.34; H, 4.97; N, 6.95.

2.4g *2-{Hydroxy-[3-hydroxy-3-(1-methoxycarbonyl-vinyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl]-methyl}-acrylic acid methyl ester (**3h**)*: Gummy matter, yield 94%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1254, 1631, 1713, 1718, 3215, 3391. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.20 (s, 3H), 3.40 (1H, bs), 3.58 (3H, s), 3.66 (3H, s), 4.46 (1H, bs), 5.46 (1H, s), 5.79–5.84 (1H, m), 6.28–6.29 (1H, d, J = 6 Hz), 6.43 (1H, s), 6.54 (1H, s), 6.78–6.81 (1H, m), 7.18 (1H, s), 7.26–7.27 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 26.4, 51.9, 52.0, 72.6, 76.0, 108.4, 122.4, 125.9, 128.0, 128.6, 128.7, 129.6, 136.1, 138.9, 141.8, 165.0, 166.6, 176.4. FAB mass: 362.16 (M+1). Anal. Calcd. for $C_{18}H_{19}NO_7$: C, 59.83; H, 5.30; N, 3.88; Found: C, 59.84; H, 5.31; N, 3.87.

2.4h *2-{Hydroxy-[3-hydroxy-3-(1-methoxycarbonyl-vinyl)-1-methyl-2-oxo-2,3-dihydro-1H-indol-5-yl]-methyl}-acrylic acid butyl ester (**3i**)*: Gummy matter, yield 54%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1184, 1589, 1720, 3020, 3296. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 0.89–0.92 (3H, m), 1.33–1.34 (2H, m), 3.24 (3H, s), 3.25 (1H, bs), 3.34 (2H, m), 3.65 (3H, s), 4.10–4.11 (2H, m), 4.87 (1H, bs), 5.50 (1H, s), 5.75–5.79 (1H, d, J = 17.5 Hz), 6.30–6.36 (1H, m), 6.40 (1H, s), 6.56 (1H, s), 6.82–6.85 (1H, m), 7.18 (1H, s), 7.31–7.39 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.6, 19.1, 26.5, 30.5, 52.0, 69.0, 73.0, 108.5, 122.6, 125.9, 126.0, 127.8, 127.8, 128.6, 128.8, 129.3, 139.0, 165.1, 170.5, 176.2. FAB mass: 404.47 (M+1). Anal. Calcd. for $C_{21}H_{25}NO_7$: C, 62.52; H, 6.25; N, 3.47. Found: C, 62.50; H, 6.26; N, 3.48.

2.4i *2-(5-Formyl-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl)-4-methylene-5-oxo-hexanoic acid methyl*

*ester (**3j**)*: Gummy matter, yield 54%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1056, 1574, 1681, 1716, 1715, 1726, 3315. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.31 (3H, s), 2.67–2.72 (1H, dd, J = 2.5, 10.5 Hz), 2.98–3.01 (1H, dd, J = 1.5, 10.5 Hz), 3.23 (3H, 2), 3.57 (3H, s), 3.65 (1H, m), 4.86 (1H, bs), 5.82-6.07 (2H, m), 6.96 (1H, s), 7.88–8.02 (2H, m), 9.91 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.6, 26.5, 27.5, 50.3, 52.0, 75.5, 108.7, 126.3, 127.9, 128.6, 129.2, 132.0, 134.0, 145.65, 171.9, 176.5, 190.6, 199.8. FAB mass: 345.51 (M+1). Anal. Calcd. for $C_{18}H_{19}NO$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.62; H, 5.54; N, 4.05.

2.4j *2-{3-Hydroxy-5-[hydroxy-(5-oxo-cyclopent-1-enyl)-methyl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-acrylic acid methyl ester (**3k**)*: Gummy matter, yield 89%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1289, 1615, 1714, 1723, 3009, 3289. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.36–2.38(2H, m), 2.41–2.44(2H, m), 3.23(3H, s), 3.47(1H, bs), 3.53(3H, s), 3.90(1H, bs), 5.49(1H, s), 6.41(1H, d, J = 6.5 Hz), 6.55(1H, s), 6.66–6.68(1H, m), 6.80–6.6.85(1H, m), 7.25(1H, s), 7.35–7.37(1H, t, J = 6.5 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.4, 25.7, 38.5, 52.0, 72.1, 76.2, 108.4, 122.5, 127.9, 128.3, 128.7, 129.2, 136.4, 136.6, 139.0, 140.9, 165.1, 176.2, 199.5. FAB mass: 358.46 (M+1). Anal. Calcd. for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92. Found: C, 63.89; H, 5.35; N, 3.93.

2.4k *2-{3-Hydroxy-5-[hydroxy-(6-oxo-cyclohex-1-enyl)-methyl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-acrylic acid methyl ester (**3l**)*: Gummy matter, yield 75%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1258, 1659, 1711, 1725, 1986, 3310. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.96–1.99(2H, m), 2.36–2.38(2H, m), 2.41–2.44(2H, m), 3.24(3H, s), 3.41(1H, bs), 3.62(3H, s), 3.91(1H, bs), 5.49(1H, s), 6.41(1H, s), 6.55(1H, s), 6.68–6.72(1H, m), 6.81–6.84(1H, m), 7.25–7.27(1H, m), 7.35–7.37(1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.4, 25.7, 26.5, 38.5, 52.0, 72.1, 76.2, 108.4, 122.5, 127.9, 128.3, 128.7, 129.2, 136.4, 136.6, 138.9, 140.9, 165.1, 176.2, 200.5. FAB mass: 372.12 (M+1). Anal. Calcd. for $C_{20}H_{21}NO_6$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.66; H, 5.71; N, 3.78.

2.4l *2-{3-Hydroxy-5-[hydroxy-(7-oxo-cyclohept-1-enyl)-methyl]-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl}-acrylic acid methyl ester (**3m**)*: Gummy matter, yield 67%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1053, 1435, 1713, 1720, 2995, 3269. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.74–1.75(4H, m), 2.42(2H, m), 2.50–2.51(2H, m), 3.23(1H, bs), 3.61(3H, s), 3.68(1H, bs), 4.02(1H, bs), 5.30(1H, s), 6.41(1H, s), 6.54–6.60(2H, m), 6.79–6.81(2H, m), 7.12(1H, m), 7.22–7.25(1H, m), 7.26–7.27(1H m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.4, 24.9, 26.5, 27.6, 43.1, 52.0, 75.05, 76.1, 108.4, 121.9, 122.2, 127.8, 128.1, 129.3, 129.3, 137.2, 143.7, 143.8, 165.1, 176.3, 206.4. FAB mass: 386.52 (M+1). Anal. Calcd. for $C_{21}H_{23}NO_6C$, 65.44; H, 6.02; N, 3.63;. Found: C, 65.41; H, 6.01; N, 3.64.

2.5a *2-[5-(2-Cyano-3-methoxy-propenyl)-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-acrylic acid methyl ester (**4a**)*: Gummy matter, yield 46%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1097, 1216, 1353, 1634, 1717, 1736, 2231, 3056, 3364. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.26(3H, s), 3.56(3H, s), 3.95(3H, s) 4.10(1H, bs), 4.22(2H, s), 6.28(1H, s), 6.62(1H, s), 6.85-6.88(1H, d, J = 8.3 Hz), 7.02(1H, s), 7.79–7.82 (1H, d, J = 8.3 Hz), 8.05(1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 29.7, 35.6, 42.0, 52.2, 73.0, 124.4, 124.9, 127.3, 128.2, 128.3, 128.5, 128.9, 128.9, 129.0, 129.75, 131.25, 164.9, 175.1. FAB mass: 343.67 (M+1). Anal. Calcd. for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.30; N, 8.18; Found: C, 63.17; H, 5.31; N, 8.17.

2.5b *2-[5-(2-Cyano-3-phenyl-propenyl)-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-acrylic acid methyl ester (**4b**)*: Gummy matter, yield 53%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1056, 1333, 1654, 1718, 2229, 3012, 3098, 3352. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.35(3H, s), 3.64(4H, bs), 3.66(2H, s), 6.45(1H, s), 6.58(1H, s), 6.85–6.90(3H, m), 7.26–7.35(4H, m), 7.78(1H, s), 7.80–7.97 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.4, 36.5, 54.7, 73.5, 125.4, 126.9, 126.9, 127.1, 127.8, 128.0, 128.15, 128.5, 128.9, 129.0, 129.1, 129.6, 132.0, 132.1, 134.0, 143.5, 144.4, 166.9, 174.3. FAB mass: 388.49 (M+1). Anal. Calcd. for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.14; H, 5.18; N, 7.20.

2.5c *2-[5-(2-Cyano-3-prop-2-ynyloxy-propenyl)-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-acrylic acid methyl ester (**4c**)*: Gummy matter, yield 54%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1045, 1098,1337, 1624, 1716, 1735, 2185, 2236, 3362. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.46(1H, s), 3.28(3H, s), 3.65(3H, s) 3.76(1H, bs), 4.23–4.28(4H, m), 6.48(1H, s), 6.58(1H, s), 6.90–6.93(1H, d, J = 8.1 Hz), 7.08(1H, s), 7.58(1H, s), 7.83–7.86(1H, d, J = 8.1 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 22.6, 33.4, 33.5, 54.4, 65.0, 73.0, 76.0, 104.9, 112.6, 125.2, 128.2, 128.3, 130.0, 130.0, 131.7, 132.5, 138.4, 138.7, 164.0, 175.1. FAB mass: 367.65 (M+1). Anal. Calcd. for $C_{20}H_{18}N_2O_5$: C, 65.57; H, 4.95; N, 7.65. Found: C, 65.55; H, 4.96; N, 7.645.

2.5d *2-[5-(3-Bromo-2-cyano-propenyl)-3-hydroxy-1-methyl-2-oxo-2,3-dihydro-1H-indol-3-yl]-acrylic acid methyl ester (**4d**)*: Gummy matter, yield 43%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1223, 1623, 1664, 1716, 2258, 3361. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.31(3H, s), 3.41 (1H, bs), 3.85(3H, s), 4.75(2H, s), 6.01–6.05(2H, m), 6.98–7.00(2H, m), 7.38–7.40(1H, d, J = 6 Hz), 7.46–7.48(1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 23.0, 43.4, 51.0, 75.0, 108.6, 122.3, 122.4, 127.0, 128.6, 129.0, 129.1, 131.5, 137.9, 138.2, 164.0, 175.4. FAB mass: 390.57 (M+1). Anal. Calcd. for $C_{17}H_{15}BrN_2O_4$: C, 52.19; H, 3.86; N, 7.16. Found: C, 52.18; H, 3.87; N, 7.15.

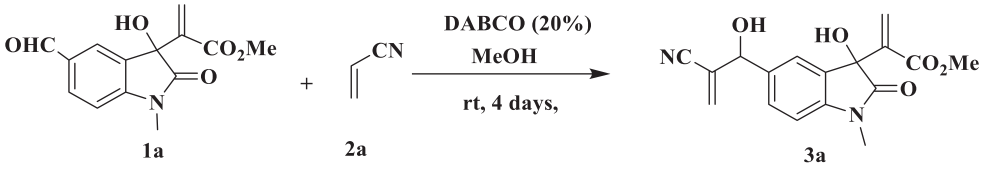
2.5e *2-[5-(2-Cyano-3-methoxy-propenyl)-1-methyl-2-oxo-1,2-dihydro-indol-3-ylidene]-3-methoxy-propionic acid methyl ester (**5a**)*: Gummy matter, yield 23%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1094, 1303, 1609, 1654, 1716, 1728, 2238, 3076, 3106. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.33(3H, s), 3.38(3H, s), 4.17(3H, s) 4.19(2H, s), 4.60(3H, s) 5.09(2H, s), 6.62–6.64(1H, d, J = 7.3 Hz), 6.87–6.90(1H, d, J = 8.2 Hz), 7.73(1H, s), 7.80–7.83 (1H, d, J = 8.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 26.1, 45.3, 51.6, 51.9, 55.0, 59.1, 126.6, 127.2, 127.6, 128.1, 128.3, 128.5, 128.9, 129.8, 131.4, 133.8, 135.8, 158.3, 166.3. FAB mass: 356.60 (M+1). Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.06; H, 5.65; N, 7.85.

2.5f *2-[5-(2-Cyano-3-phenyl-propenyl)-1-methyl-2-oxo-1,2-dihydro-indol-3-ylidene]-3-phenyl-propionic acid methyl ester (**5b**)*: Gummy matter, yield 22%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1053, 1123, 1523, 1664, 1713, 1732, 2238, 3021, 3087. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.28(3H, s), 3.67(2H, s), 3.78(3H, s) 4.58(2H, s), 6.82–6.85(1H, d, J = 8.9 Hz), 7.28–7.37(12H, m), 7.68–7.71(1H, d, J = 8.9 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 23.3, 44.7, 44.7, 53.5, 107.2, 110.6, 110.7, 115.4, 117.6, 122.4, 125.4, 126.9, 126.9, 127.1, 127.8, 128.0, 128.1, 128.5, 128.9, 129.0, 129.1, 129.64, 132.0, 132.1, 134.0, 143.5, 144.4, 165.4, 174.3. FAB mass: 448.64 (M+1). Anal. Calcd. for $C_{29}H_{24}N_2O_3$: C, 77.66; H, 5.39; N, 6.25. Found: C, 77.68; H, 5.38; N, 6.26.

2.5g *3-Bromo-2-[5-(3-bromo-2-cyano-propenyl)-1-methyl-2-oxo-1,2-dihydro-indol-3-ylidene]-propionic acid methyl ester (**5d**)*: Gummy matter, yield 24%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1609, 1654, 1720, 2260, 3061. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.30 (3H, s), 4.10 (3H, s), 4.22 (2H, s) 5.23 (2H, s), 6.85–6.88 (1H, d, J = 8.4 Hz), 7.12 (1H, s), 7.79–7.82 (1H, d, J = 8.4 Hz), 8.05 (1H, s). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 25.1, 26.2, 32.9, 53.5, 106.2, 108.6, 117.1, 117.1, 120.2, 125.7, 127.0, 133.2, 138.9, 145.9, 146.1, 166.9, 173.1. FAB mass: 452.83 (M+1). Anal. Calcd. for $C_{17}H_{14}Br_2N_2O_3$: C, 44.96; H, 3.11; N, 6.17. Found: C, 44.97; H, 3.10; N, 6.187.

2.6a *1',2'-diethyl 5-(4-cyano-1,2-bis(ethoxycarbonyl)-2,3-dihydro-1H-pyrazol-3-yl)-1 -methyl-2-oxospiro[indo-*

Table 1. Synthesis of bis-MBH adduct **3a** from mMBH adduct **1a**.[a]

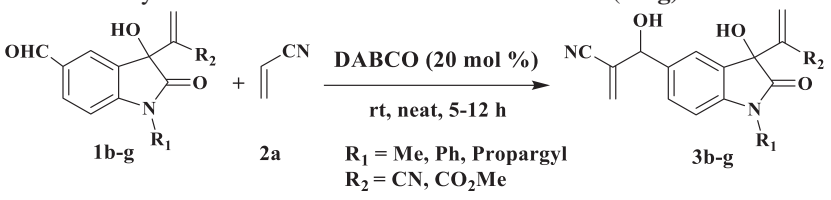


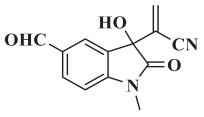
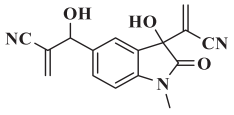
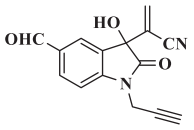
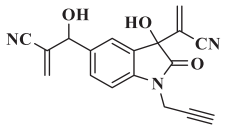
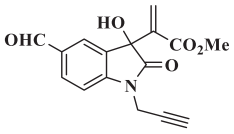
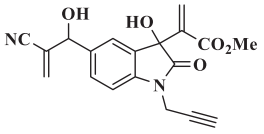
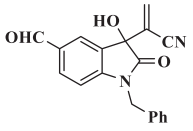
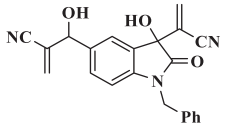
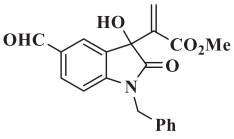
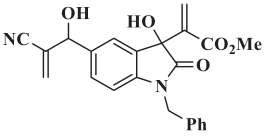
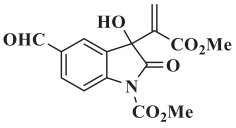
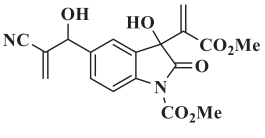
Entry	Solvents	Time (d)	Yield **3a** (%)[b]
1	MeOH	4	12
2	CH_3CN	4	NR
3	1,4-Dioxane	4	NR
4	THF	4	trace
5	DMF	4	NR
6	CH_2Cl_2	4	NR
7	$CHCl_3$	4	NR
8	CCl_4	4	NR
9	H_2O	4	NR
10	MeOH-H_2O (1:1)	4	NR
11	CH_3CN-H_2O (1:1)	4	NR
12	1,4-Dioxane-H_2O (1:1)	4	13
13	**Neat**	**8h**	**87**

[a]General condition: mMBH adduct **1a** (100 mg, 0.413 mmol), acrylonitrile **2a** (1.5 equiv.) and DABCO (20 mol%) at rt; [b]Isolated yield; NR-No reaction; d-days.

*line-3,3'-pyrazole]-1',2',4'-tricarboxylate-methyl-2-oxo-spiro[indoline-3,3'-pyrazole]-1',2',4'-tricarboxylate (**7**)*: Gummy matter, yield 82%. IR (CH_2Cl_2) (ν_{max}, cm^{-1}): 1609, 1654, 1711, 1720, 2260, 3150. ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.25–1.39 (12H, m), 3.28 (3H, s), 3.59 (3H, s), 4.12–4.36 (8H, m), 5.96–5.96 (1H, d, $J = 2.5$ Hz), 6.87–6.89 (1H, m), 7.14–7.15 (1H, m), 7.32–7.33 (1H, m), 7.34–7.35 (1H, m), 7.40–7.50 (1H, m). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 13.9, 14.2 (2C), 14.9, 26.9, 29.6, 51.8, 64.0, 64.2, 64.2, 64.3, 67.3, 73.7, 108.7, 113.2, 113.5, 121.3, 121.9, 127.8, 131.90, 138.7, 139.2, 144.2, 150.9, 154.0, 157.2, 164.0,

Table 2. Synthesis of *N*-substituted bis-MBH adducts (**3b-g**).[a]



Entry	substrates (**1b-g**)	Time (h)	Yield (%)[b]	Products (**3b-g**)
1	 1b	5	87	 3b
2	 1c	6	74	 3c
3	 1d	12	83	 3d
4	 1e	5	79	 3e
5	 1f	11	88	 3f
6	 1g	-	-	 3g[c]

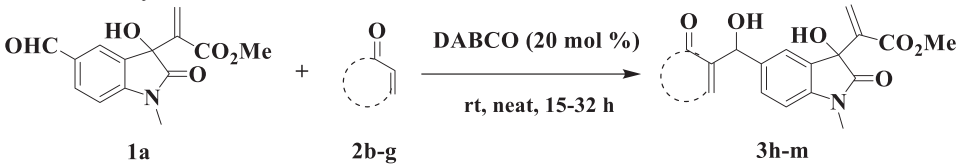
[a]General condition: mMBH adduct **1b-g** (100 mg), acrylonitrile (1.5 equiv.), DABCO (20 mol %), rt; [b]Isolated yield; [c]Reaction was monitored in 4 days.

164.2, 164.2, 172.6. FAB mass: 641.54 (M+1). Anal. Calcd. for $C_{29}H_{32}N_6O_{11}$: C, 54.37; H, 5.03; N, 13.12. Found: C, 54.39; H, 5.02; N, 13.11.

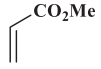
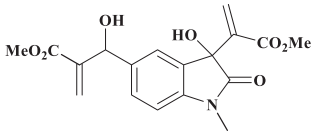
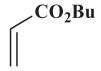
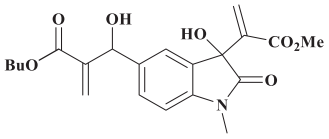
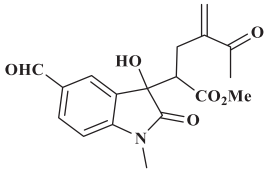
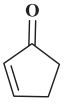
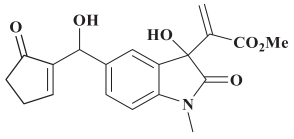
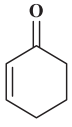
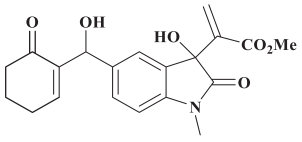
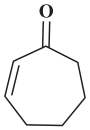
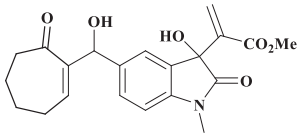
3. Results and Discussion

At the outset, the preliminary reaction was carried out between mMBH adduct **1a**, acrylonitrile **2a** (1.5 equiv.) and DABCO (20 mol%) in methanol at room temperature. The reaction mixture afforded a bis-MBH adduct **3a** in 12% yield after 4 days. The compound **3a** was completely characterized by general spectroscopic methods (IR, ^{1}H, ^{13}C NMR and mass) (In the ^{1}H NMR spectrum of **3a**, the characteristic methine proton of second MBH adduct appeared at 5.33 ppm). Encouraged by the preliminary result obtained, the conditions were then optimized for the second MBH reaction. In view of this, we turned our attention to study the effect of various solvents, solvent-free condition and catalyst load for the

Table 3. Synthesis of bis-functionalized oxindole derivatives (**3h-m**).[a]



1a **2b-g** **3h-m**

Entry	Substrates(**2b-g**)	Time(h)	Yield (%)[b]	Products(**3h-m**)
1	 2b	18	94	 3h
2	 2c	32	54	 3i
3	 2d	18	54	 3j
4	 2e	15	89	 3k
5	 2f	28	75	 3l
6	 2g	20	67	 3m

[a]General condition: mMBH adduct **1a** (100 mg, 0.363 mmol), activated olefins **2b-g** (1.5 equiv.), DABCO (20 mol%), rt; [b]Isolated yield.

second MBH reaction. The results are summarized in table 1 (entries 1–13).

The catalyst lode was increased more than 20 mol% because it did not improve the yield of the product.[13] To establish a suitable solvent system for the reaction of **1a** with **2a**, we screened a number of solvents such as methanol, acetonitrile, 1,4-dioxane, tetrahydrofuran, dimethylformamide, dicholoromethane, chloroform, tetrachloromethane and water, etc. (table 1, entries 1–9). Of these, methanol provided bis-MBH adduct in 12% yield (table 1, entry 1). Binary solvents were reluctant for bis-MBH reaction (entries 9–11). Remarkably, the mixture of 1,4-dioxane:water gave the desired product **3a** in low yield (table 1, entry 12). Among them, the neat reaction showed promise for the second MBH reaction up to 87% yield (table 1, entry 13).

Next, we examined the substrate scope and viability of the second MBH reaction with a broad range of nitrogen substituted mMBH adducts **1b-f** with acrylonitrile under the optimized reaction condition. The results are summarized in table 2.

More interestingly, the reaction progressed well in oxindole nitrogen-bearing electron-donating substituents such as methyl, propargyl and benzyl mMBH adducts and offered the corresponding bis-MBH adducts **3b-f** in good yields. The reaction was found to be more compatible with the nitrile appended mMBH adduct than the ester appended mMBH adduct. However, the reaction did not work with *N*-ester mMBH adduct derivative **1g**, presumably due to poor solubility of **1g** in acrylonitrile.

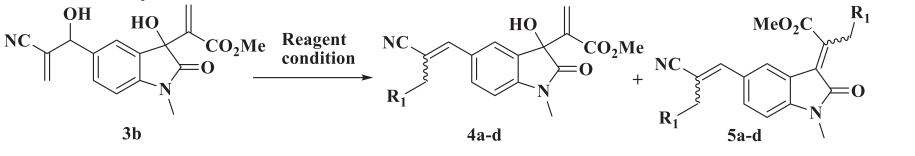
We then probed the reaction with other activated alkenes to generalize the scope of the second MBH reaction. It was observed that the activated alkenes had a great influence on the rate of the second MBH reaction. Under the optimized condition, the bis-MBH adducts (**3h-m**) were obtained in good-to-excellent yields (54–94%). The results are shown in table 3.

Activated alkenes such as methyl acrylate and butyl acrylate were worked well with mMBH adduct **1a** and afforded bis-MBH adducts (**3h** and **3i**) in 94 and 54% yields, respectively (table 3, entries 1–2). Similarly, with cyclic enones such as cyclopentenone, cyclohexenone and cycloheptenone, the corresponding bis-MBH adducts were obtained (**3k**, **3l** and **3m**) in good-to-excellent yields (table 3, entries 4–6). When methyl vinyl ketone was employed as activated olefin, Rauhut-Currier adduct **3j** was observed predominantly along with a trace of uncharacterized product.[14] It should be noted that the present work discloses the cyclic enone appended bis-MBH adducts exclusively without prerequisite of any promoters and/or Lewis acids.[15]

The successful accomplishment of bis-MBH adducts prompted us to explore further the functionalization *via* isomerization with various nucleophilic reagents such as Ar-H, $CH(OMe)_3$, propargyl alcohol and HBr.[16] The results are summarized in table 4.

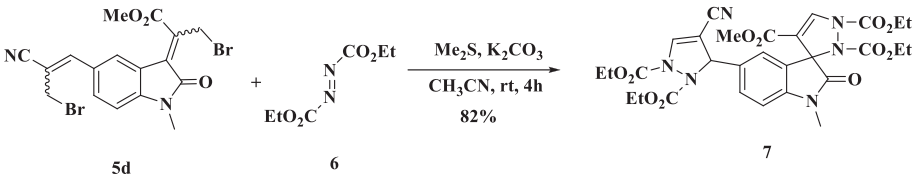
Accordingly, bis-MBH adduct **3b**, K-10 clay with benzene or trimethoxymethane underwent isomerization smoothly and afforded the corresponding highly functionalized mono- and bis-allyl derivative in good yields (table 3, entries 1–2). However, with propargyl alcohol, mono-isomerized compound **4c** was exclusively obtained from bis-MBH adduct **3b** under solvolysis condition (table 3, entry 3). Under the microwave irradiation, mono- and bis-bromo allyl derivatives were obtained in good yield from mMBH adduct **3b** with aqua. HBr (table 3, entry 4). A notable trend was observed that isomerization preferentially takes place at the C-5 position (2°-alcohol) rather than at the C-3 position (3°-alcohol) (table 3, entries 1–4). The novel mono- and

Table 4. Synthesis of mono- and bis-functionalized oxindole derivatives (**4**&**5**).[a]



Entry	Adduct	Reagent (R_1H) / Condition	Yield (%)[b] (Products) (**4a-d**)	(**5a-d**)
1	**3b**	$CH(OMe)_3$/ 3h, 110°C	46 (**4a**)	23 (**5a**)
2	**3b**	Benzene/ 12h, 90°C[a]	53 (**4b**)	22 (**5b**)
3	**3b**	Propargyl alcohol/ 6h, 110°C	54 (**4c**)	– (**5c**)
4	**3b**	46%aqua.HBr, silica gel/ MW, 5 min	43 (**4d**)	24 (**5d**)

[a]50% w/w Mont. K-10 clay was used as catalyst; [b]Isolated yield.



Scheme 1. Synthesis of bis-pyrazole derivative **7** from bis-allyl bromides of oxindole.

bis-isomerized compounds were unambiguously characterized by various spectroscopic techniques.

Furthermore, synthetic utility was demonstrated by the synthesis of medicinally important bis-pyrazole derivative (**7**) and was prepared from **5d**, diethyl diazenedicarboxylate **6**, Me_2S and K_2CO_3 exploiting [3+2]-annulation reaction (scheme 1).[17,18]

All the new compounds were thoroughly characterized by spectroscopic methods (IR, ^1H, ^{13}C NMR and FAB mass spectra).

4. Conclusions

An efficient synthesis of bis-functionalized oxindole derivatives from 3, 5-bis-MBH adducts of isatin via isomerization is disclosed for the first time. The 5-formyl MBH adduct of oxindole has displayed a wide substrate scope, rate acceleration and selective formation of bis-MBH adduct with cyclic enones with DABCO as catalyst. The synthetic utility of bis-allyl derivative was demonstrated by the synthesis of potent bis-pyrazole derivative *via* [3+2]-annulation strategy.

Supplementary Information

The electronic supplementary information consists of the general procedure for the synthesis of target molecules and their analytical data/spectral proof in detail. Supplementary Information is available at www.ias.ac.in/chemsci.

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