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# Regioselective synthesis of a series of bis-biaryl coupled heterocycles: The superiority of Heck protocol compared to $Bu_3SnH$ mediated radical cyclization

Pradipta Kumar Basu[1*], Amrita Ghosh[1]

1. Department of Chemistry, Durgapur Government College, Durgapur, Burdwan, West Bengal, 713214 (India).
*[Email: pkbasu74@gmail.com]

In this work two new effective methodologies involving Bu3SnH annulated radical cyclization and Heck protocol have been emphasized for the preparation of substituted dihydrobenzo-isochromeno[4,3-*h*] chromene derivatives**[4(a–f)]**. At first, 2,3-dihydroxy naphthalene**[1a]** or 1,5-dihydroxy naphthalene**[1b]** or 1,6-dihydroxy naphthalene**[1c]** was reacted with 2-bromobenzyl bromide**[2a]** or 2-bromo-5-methoxy benzyl bromide**[2b]** in presence of acetone and potassium carbonate under reflux and thus generated several bis (2-bromobenzyloxy)naphthalene derivatives**[3(a–f)]**. The superiority of the Heck protocol in comparison to the radical cyclization strategy has been highlighted for the regioselective synthesis of bis-biaryl coupled heterocycles[**4(a–f)]**. The Heck method is relatively simple, straightforward, and highly regioselective and high yielding too.

*Keyword:* Bis-biaryl, radical cyclization, Heck coupling, regioselective, azobisisobutyronitrile, tri-*n*-butyltin hydride, Palladium acetate.

## 1. Introduction

There are several efficacious methodologies for the formation of heterocyclic compounds involving radical cyclization pathway[1-13] and the result of which is the generation of a mixture of *5-exo*-trig and *6-endo*-trig ring products and the product ratio is dependent on the reagents, solvents, radical initiators and other reaction conditions[14-20].

Although radical cyclizations involving $Bu_3SnH$ are extremely useful, it is not effective in pharmaceutical industry due to the toxic nature of tin reagents and therefore substitutes such as $(Me_3Si)_3SiH$[21], $(Me_3Si)_3GeH$[22], $HGaCl_2$[23] and $HInCl_2$[24] are useful alternatives to $Bu_3SnH$.

Due to these difficulties scientists are actively engaged in finding an alternative of radical cyclization strategy and nowadays the well-established method is the palladium catalyzed intramolecular Heck reaction and the beauty of the reagent is that it is nontoxic and it involves very easy work up procedure and therefore is very much applicable for synthesizing various biologically active heterocycles and carbocycles.

Recently regioselective synthesis of naphthoxepine and naphthoxocine derivatives has been explored by palladium-catalyzed intramolecular Heck cyclization[25]. The synthesis of naphthoxocine derivatives based on the combined Claisen rearrangement and phosphine-free[26-30] palladium-catalyzed intramolecular Heck reaction was also studied. The highly strained medium-sized oxacyclic compounds and lactone derivatives have been emphasized by palladium-catalyzed intramolecular Heck protocol[31]. Regioselective synthesis of heterocyclic compounds has been carried out using palladium annulated ligand free bis- and tris-biaryl Heck coupling of unactivated phenyl aryl ethers[32]. Previously, Majumdar et al. synthesized various bis-benzofuran derivatives via Pd-mediated oxidative bis-cyclization[33].

Since there are only few reports of bis-biarylation of either activated or unactivated arenes, this prompted

us to undertake such studies and in this article, we report the regioselective synthesis of a number of substituted dihydrobenzo-isochromeno[4,3-*h*] chromene derivatives from several bis (2-bromobenzyloxy)naphthalene precursors by tri-*n*-butyltin hydride mediated radical cyclization as well as employing Heck strategy and a comparative study of both these methodologies have also been explored.

## 2. Experimental Details

All the reagents were obtained from commercial sources and used as received. Except methanol (which was HPLC-grade), the remaining solvents were dried and distilled before use. Elemental analyses and Mass spectra (ESI+) were performed at the Indian Institute of Chemical Biology, Kolkata. IR spectra were recorded on KBr discs on a Perkin Elmer L 120-000A apparatus ($\nu_{max}$ in $cm^{-1}$). Routine $^1H$ NMR (300, 400 and 500 MHz) and $^{13}C$ NMR (100 MHz) spectra were recorded on Bruker DPX-300, Bruker DPX-400 and Bruker DPX-500 instruments at 298 K. The chemical shifts (δ) are given in ppm and the coupling constants (*J*) in Hz. In all cases the solvent for the NMR experiments was $CDCl_3$ (99.9%) and the references were $SiMe_4$ [for $^1H$ and $^{13}C\{^1H\}$ NMR experiments]. Silica gel [(100-200, 230-400 mesh), SRL, India] was used for chromatographic separation. Silica gel G [E-Marck (India)] and Silica gel 60 F 254 [E-Marck (Germany)] were used for TLC. Petroleum ether refers to the fraction boiling between 60 and 80 ºC.

### 2.1. Typical Procedure for the preparation of bis(2-bromobenzyloxy)naphthalene derivatives [3(a–f)]

A mixture of 2,3-dihydroxy naphthalene **[1a]** or 1,5-dihydroxy naphthalene **[1b]** or 1,6-dihydroxy naphthalene **[1c]** (1 mmol), 2-bromobenzyl bromide **[2a]** (3.5 mmol) or 2-bromo-5-methoxybenzyl bromide **[2b]** (3.5 mmol), anhydrous $K_2CO_3$ (1.5 gm), and NaI (cat. amount) was refluxed in dry acetone (75 mL) under nitrogen for 12-16 h. The reaction mixture was cooled, filtered, and the solvent was evaporated. The residual mass was extracted with $CH_2Cl_2$ (3 x 25 mL), washed with water (2 x 10 mL) and dried ($Na_2SO_4$). The solvent was removed and the crude product was purified by column chromatography over silica gel (100 - 200 mesh) using petroleum ether–ethyl acetate (9:1) as eluent to afford bis(2-bromobenzyloxy) naphthalene derivatives **[3(a–f)]**.

#### 2.1.1. 2,3-bis(2-bromobenzyloxy) naphthalene [3a]

White solid, mp 144-146 ºC; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3045, 2887, 1590, 1521, 1432, 1387, 1245, 1187, 1065, 885, 745; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 5.37 (s, 4H, $-OCH_2$), 7.20-7.28 (m, 4H, ArH), 7.34-7.38 (m, 4H, ArH), 7.64 (d, *J* = 7.0 Hz, 2H, ArH), 7.70-7.75 (m, 4H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ (ppm) 70.18, 109.30, 122.14, 124.59, 126.6, 127.7, 128.86, 129.28, 129.56, 132.66, 136.42, 148.71; LRMS (70 eV, EI) *m/z*: 498 [$M^+$]; [Found: C, 57.72; H, 3.52. Calcd. for $C_{24}H_{18}Br_2O_2$: C, 57.86; H, 3.64].

#### 2.1.2: 2,3-bis(2-bromo-5 methoxybenzyloxy) naphthalene [3b]

White solid, mp 126-127 ºC; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3001, 2961, 2942, 2855, 1602, 1382, 1290, 1150, 1034, 887, 784; $^1H$ NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.72 (s, 6H, $OCH_3$), 5.30 (s, 4H, $-OCH_2$), 6.89 (d, *J* = 6.0 Hz, 2H, ArH), 7.28 (d, *J* = 6.0 Hz, 2H, ArH), 7.31 (d, *J* = 3.0 Hz, 2H, ArH), 7.39 (dd, *J* = 6.0, 3.0 Hz, 2H, ArH), 7.48 (s, 1H, ArH), 7.50 (s, 1H, ArH), 7.74 (dd, *J* = 6.0, 3.0 Hz, 2H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ (ppm) 55.50, 70.11, 109.11, 112.31, 114.19, 115.41, 124.61, 126.63, 129.58, 133.24, 137.35, 148.66, 159.40; LRMS (70 eV, EI) *m/z*: 558 [$M^+$]; [Found: C, 55.79; H, 4.09. Calcd. for $C_{26}H_{22}Br_2O_4$: C, 55.94; H, 3.97].

#### 2.1.3: 1,5-bis (2-bromobenzyloxy) naphthalene [3c]

Yellow solid, mp 140-142 ºC; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3058, 2896, 1596, 1509, 1417, 1373, 1260, 1227, 1170, 1089, 1070, 1024, 895, 740; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ (ppm) 5.32 (s, 4H, $-OCH_2$), 6.65-6.73 (m, 3H, ArH), 6.86-7.12 (m, 4H, ArH), 7.18-7.31 (m, 2H, ArH), 7.33-7.40 (m, 3H, ArH), 7.43-7.49 (m, 1H, ArH), 7.52 (d, *J* = 6.6 Hz, 1H, ArH); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta_C$ (ppm) 69.59, 107.89, 115.40, 125.30, 126.72, 127.59, 128.74, 129.50, 129.57, 132.20, 136.44, 155.69; LRMS (70 eV, EI) *m/z*: 498 [$M^+$]; [Found: C, 58.01; H, 3.78. Calcd. for $C_{24}H_{18}Br_2O_2$: C, 57.86; H, 3.64].

#### 2.1.4: 1,5-bis(2-bromo-5-methoxybenzyloxy) naphthalene [3d]

Yellow solid, mp 210-212 ºC; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3006, 2958, 2935, 2835, 1597, 1512, 1471, 1365, 1296, 1272, 1160, 1052, 1013, 890, 755; $^1H$ NMR (300 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.79 (s, 6H, $OCH_3$), 5.27 (s, 4H, $-OCH_2$), 7.05-7.30 (m, 4H, ArH), 7.33-

7.42 (m, 2H, ArH), 7.43-7.50 (m, 4H, ArH), 8.12 (s, 1H, ArH), 8.15 (s, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta_C$ (ppm) 55.58, 70.35, 105.65, 113.38, 115.21, 116.82, 118.80, 125.42, 127.69, 129.39, 133.22, 155.62, 159.70; LRMS (70 eV, EI) *m/z*: 558 [$M^+$]; [Found: C, 56.08; H, 3.84. Calcd. for $C_{26}H_{22}Br_2O_4$: C, 55.94; H, 3.97].

### 2.1.5: 1,6-bis(2-bromobenzyloxy) naphthalene [3e]

White solid, mp 142-144 ºC; IR (KBr) ($\nu_{max}$/ cm$^{-1}$): 3050, 2890, 1578, 1504, 1487, 1261, 1180, 1089, 887, 778; $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 5.32 (s, 4H, -$OCH_2$), 6.79 (dd, *J* = 9.5, 4.3 Hz, 1H, ArH), 7.21-7.40 (m, 8H, ArH), 7.61-7.69 (m, 4H, ArH), 8.34 (d, *J* = 15.2 Hz, 1H, ArH); LRMS (70 eV, EI) *m/z*: 498 [$M^+$]; [Found: C, 57.98; H, 3.72. Calcd. for $C_{24}H_{18}Br_2O_2$: C, 57.86; H, 3.64].

### 2.1.6: 1,6-bis(2-bromo-5-methoxybenzyloxy) naphthalene [3f]

White solid, mp 116-118 ºC; IR (KBr) ($\nu_{max}$/ cm$^{-1}$): 3001, 2954, 2937, 2836, 1628, 1576, 1460, 1381, 1276, 1162, 1052, 1019, 866, 771; $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.71 (s, 6H, $OCH_3$), 5.18 (s, 4H, -$OCH_2$), 6.62-6.69 (m, 3H, ArH), 7.10-7.12 (m, 2H, ArH), 7.19 (d, *J* = 9.5 Hz, 2H, ArH), 7.27 (d, *J* = 6.5 Hz, 2H, ArH), 7.42 (dd, *J* = 8.5, 5.0 Hz, 2H, ArH), 8.24 (d, *J* = 9.5 Hz, 1H, ArH); LRMS (70 eV, EI) *m/z*: 558 [$M^+$]; [Found: C, 55.81; H, 4.14. Calcd. for $C_{26}H_{22}Br_2O_4$: C, 55.94; H, 3.97].

## 3. Method A: Typical Procedure for the preparation of dihydrobenzo-isochromeno[4,3-*h*] chromene derivatives [4(a–f)] by Radical Cyclization Reaction

*n*-$Bu_3SnH$ (0.89 mL, 0.33 mmol) was added slowly in one portion to a magnetically stirred suspension of **[3a]** (100 mg, 0.20 mmol) and AIBN (24.9 mg, 0.15 mmol) in anhydrous degassed toluene (10 mL) under argon atmosphere. The mixture was heated at 110 °C for 16 hr. Then the solvent was removed under reduced pressure. The liquid mass thus obtained was dissolved in $CH_2Cl_2$ (5 mL) and stirred with 10% aq KF (10 mL) for 5 h. The white precipitate was separated by filtration and the aqueous phase was extracted with $CH_2Cl_2$ (3 x 25 mL). The combined extract was washed with brine (3 x 25 mL) and dried ($Na_2SO_4$). $CH_2Cl_2$ was removed by rotary evaporator and the residual mass was subjected to column chromatography using silica gel (100-200 mesh) and pet ether- EtOAc– 9:1) as eluent to furnish product **[4a]** in 18% yield. Other substrates **[3(b–f)]** were subjected to the same reaction conditions to afford the corresponding products **[4(b–f)]** in 8–20% yield.

## 3.1 Method B: Typical Procedure for the preparation of dihydrobenzo-isochromeno[4,3-*h*]chromene derivatives [4(a–f)] by Heck Reaction

A mixture of the compound [**3a]** (100 mg, 0.20 mmol), TBAB (1.5 equiv), dry KOAc (3.0 equiv) was mixed well in anhydrous DMF (8 mL) under argon atmosphere. Then, the catalyst $Pd(OAc)_2$ (12 mmol%, 5.39 mg) was added and the resulting mixture was magnetically stirred in an oil bath at 140 °C for 12 hr. The reaction mixture was cooled, and $H_2O$ (4 mL) was added. It was extracted with EtOAc (3 x 10 mL), washed with $H_2O$ (2 x 10 ml), and then by brine (10 mL). The organic layer was dried ($Na_2SO_4$), evaporation of EtOAc furnished the crude mass, which was purified by column chromatography over silica gel (100 – 200 mesh) using petroleum ether–ethyl acetate (9:1) as eluent to furnish the product **[4a]**. Similarly, the other substrates **[3(b–f)]** were subjected to the same reaction conditions to give products **[4(b–f)]**.

### 3.1.1: 5,8-dihydrodibenzo[*c,f*] isochrome[4,3-*h*]chromene [4a]

Light yellow solid, mp 184-186 ºC; IR (KBr) ($\nu_{max}$/ cm$^{-1}$): 3076, 2965, 2919, 1589, 1447, 1418, 1398, 1210, 1099, 1006, 994, 727; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ (ppm) 5.16 (s, 4H, -$OCH_2$), 7.31-7.38 (m, 4H, ArH), 7.42-7.49 (m, 4H, ArH), 7.99 (d, *J* = 7.8 Hz, 2H, ArH), 8.49-8.53 (dd, *J* = 6.6, 3.6 Hz, 2H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta_C$ (ppm) 69.73, 119.73, 125.0, 125.31, 125.56, 126.37, 126.81, 127.36, 128.19, 129.98, 132.55, 144.96; LRMS (70 eV, EI) *m/z*: 336 [$M^+$]; [Found: C, 85.82; H, 4.92. Calcd. for $C_{24}H_{16}O_2$: C, 85.69; H, 4.79].

### 3.1.2: 3,10-dimethoxy-5,8-dihydrodibenzo[*c,f*] isochrome [4,3-*h*] chromene [4b]

White solid, mp 116-117 ºC; IR (KBr) ($\nu_{max}$/ cm$^{-1}$): 3070, 2981, 2906, 1622, 1571, 1444, 1299, 1250, 1172, 1002, 853, 739; $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.88 (s, 6H, $OCH_3$), 5.11 (s, 4H, -$OCH_2$), 6.74 (dd, *J* = 8.5, 2.0 Hz, 1H, ArH), 6.89 (s, 1H, ArH), 7.00 (d, *J* = 8.5 Hz, 1H, ArH), 7.11 (s, 1H, ArH), 7.20 (s, 1H, ArH), 7.38-7.42 (m, 1H, ArH), 7.47 (d, *J* = 8.5 Hz, 1H, ArH), 7.72 (d, *J* = 8.5 Hz,

1H, ArH), 7.95 (d, $J$ = 8.5 Hz, 1H, ArH), 8.42 (d, $J$ = 8.5 Hz, 1H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta_C$ (ppm) 55.58, 69.86, 111.0, 113.65, 119.49, 124.58, 124.73, 125.65, 127.90, 130.52, 137.17, 147.63, 159.40; LRMS (70 eV, EI) *m/z*: 396 [$M^+$]; [Found: C, 78.61; H, 5.22. Calcd. for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09].

### 3.1.3: 1,5-dihydrodibenzo[*c,f*] isochrome[4,3-*h*] chromene [4c]

White solid, mp 132-134 °C; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3065, 2962, 2912, 1570, 1432, 1375, 1202, 1104, 976, 712; $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 5.21 (s, 4H, -$OCH_2$), 7.37-7.42 (m, 4H, ArH), 7.62-7.72 (m, 4H, ArH), 7.91 (d, $J$ = 8.2 Hz, 2H, ArH), 8.36 (d, $J$ = 8.2 Hz, 2H, ArH); LRMS (70 eV, EI) *m/z*: 336 [$M^+$]; [Found: C, 85.57; H, 4.62. Calcd. for $C_{24}H_{16}O_2$: C, 85.69; H, 4.79].

### 3.1.4: 2,9-dimethoxy-1,5-dihydrodibenzo[*c,f*] isochrome[4,3-*h*] chromene [4d]

White solid, mp 144-146 °C; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3061, 2972, 2900, 1604, 1582, 1432, 1282, 1189, 986, 732; $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.80 (s, 6H, $OCH_3$), 5.18 (s, 4H, -$OCH_2$), 6.91 (d, $J$ = 8.4 Hz, 2H, ArH), 7.29 (d, $J$ = 8.4 Hz, 2H, ArH), 7.54-7.63 (m, 2H, ArH), 7.77-7.91 (m, 2H, ArH), 8.31 (d, $J$ = 8.4 Hz, 2H, ArH); LRMS (70 eV, EI) *m/z*: 396 [$M^+$]; [Found: C, 78.89; H, 4.92. Calcd. for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09].

### 3.1.5: 2,7-dihydrodibenzo[*c,f*] isochrome[4,3-*h*] chromene [4e]

Yellow solid, mp 90-92 °C; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3393, 2849, 1586, 1487, 1437, 1395, 1240, 1100, 997, 747; $^1$H NMR (300 MHz, $CDCl_3$): $\delta_H$ (ppm) 5.18 (s, 2H, -$OCH_2$), 5.29 (s, 2H, -$OCH_2$), 7.15-7.46 (m, 2H, ArH), 7.67-7.78 (m, 2H, ArH), 7.87 (d, $J$ = 9.0 Hz, 2H, ArH), 7.98 (d, $J$ = 9.0 Hz, 2H, ArH), 8.03 (d, $J$ = 7.8 Hz, 2H, ArH), 8.17-8.22 (dd, $J$ = 9.0, 6.6 Hz, 2H, ArH); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta_C$ (ppm) 68.59, 68.99, 112.55, 115.70, 118.51, 124.37, 125.23, 127.07, 127.09, 127.22, 127.95, 128.17, 128.56, 131.45, 132.95, 135.64, 150.77, 153.77; LRMS (70 eV, EI) *m/z*: 336 [$M^+$]; [Found: C, 85.76; H, 4.84. Calcd. for $C_{24}H_{16}O_2$: C, 85.69; H, 4.79].

### 3.1.6: 1,8-dimethoxy-2,7-dihydrodibenzo [*c,f*] isochrome [4,3-*h*] chromene [4f]

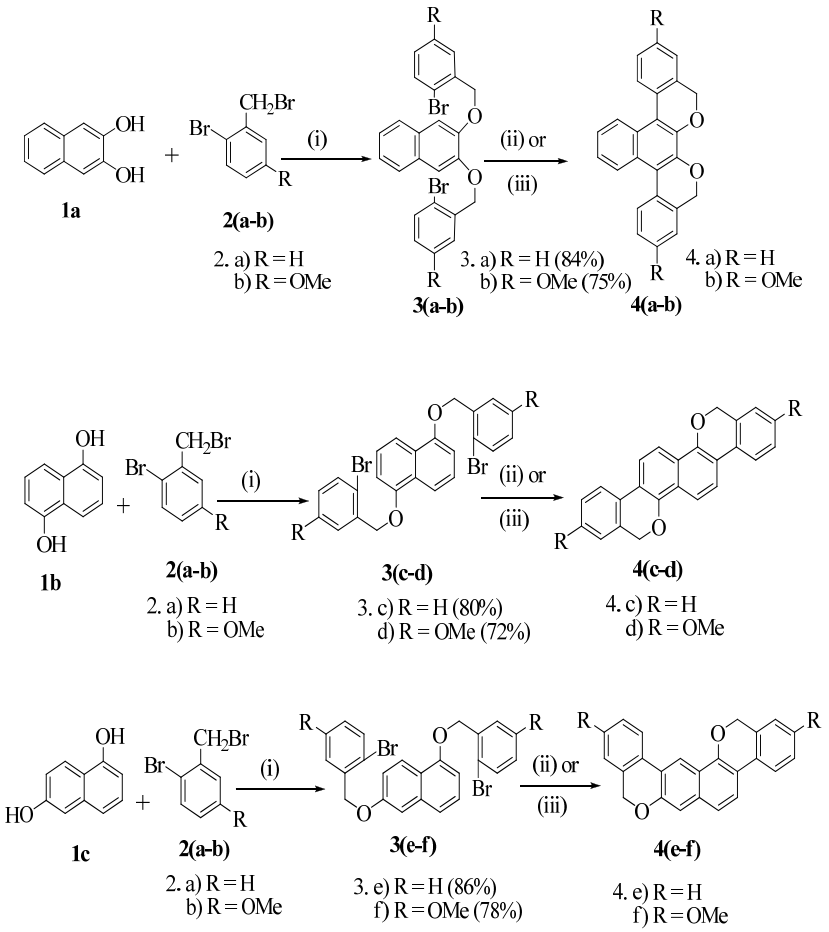
White solid, mp 166-168 °C; IR (KBr) ($\nu_{max}$/ $cm^{-1}$): 3081, 2972, 2911, 1645, 1582, 1440, 1276, 1189, 1022, 876, 756; $^1$H NMR (500 MHz, $CDCl_3$): $\delta_H$ (ppm) 3.81 (s, 6H, $OCH_3$), 5.19 (s, 2H, -$OCH_2$), 5.21 (s, 2H, -$OCH_2$), 6.63-6.69 (m, 1H, ArH), 6.85-6.93 (m, 1H, ArH), 7.12-7.31 (m, 2H, ArH), 7.55-7.63 (m, 3H, ArH), 7.84-7.90 (dd, $J$ = 20.5, 8.5 Hz, 1H, ArH), 8.07-8.09 (dd, $J$ = 8.5, 3.5 Hz, 1H, ArH), 8.44 (s, 1H, ArH); LRMS (70 eV, EI) *m/z*: 396 [$M^+$]; [Found: C, 78.93; H, 5.24. Calcd. for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09].

## 4. Results and Discussion

The required precursors **[3(a–f)]** for our present study were synthesized in moderate to good yields by refluxing 2,3-dihydroxy naphthalene **[1a]** or 1,5-dihydroxy naphthalene **[1b]** or 1,6-dihydroxy naphthalene **[1c]** with either 2-bromobenzyl bromide **[2a]** or 2-bromo-5-methoxybenzyl bromide **[2b]** in anhydrous acetone in the presence of anhydrous potassium carbonate and a small amount of sodium iodide (Finkelstein conditions) (Scheme 1).

We initially attempted the radical cyclization of the substrate **[3a]** involving the well established

procedure using tri-*n*-butyltin chloride, sodium cyanoborohydride and 2,2′-azobis (isobutyronitrile) as radical initiator and dry degassed benzene under argon atmosphere for 6 h. But there was no appreciable change in TLC and even after increasing the concentration of the reagents and by increasing the reaction time up to 12 hr, there was no sharp change in the reaction mixture (Table 1, entry 1 and 2). We therefore decided to use tri-*n*-butyltin hydride in place of tri-*n*-butyltin chloride, sodium cyanoborohydride and the high boiling solvent such as dry degassed toluene in place of dry degassed benzene. The desired radical cyclized product **[4a]** was obtained in 18% yield after refluxing for 16 h (Table 1, entry 3).




**Scheme 1:** (i) $K_2CO_3$, $Me_2CO$, NaI, reflux; (ii) [**3**(**a-e**)] (0.20 mmol), $Bu_3SnH$ (0.20 mmol), AIBN (0.15 mmol), PhMe, argon atmosphere, reflux; (iii) $Pd(OAc)_2$ (12 mol%), KOAc (3.0 equiv), TBAB (1.5 equiv), argon atmosphere, heat.

In order to increase the yield of the cyclized product **[4a]** we have utilized various reaction conditions by changing the concentration of the reagents and reaction time. But the reaction failed to increase the reaction yield in any case and the optimisation of the reaction condition is depicted in Table 1.

The radical cyclization strategy was effected with other precursors **[3(b-f)]** under the above optimized condition to produce **[4(b-f)]** in very low yield.

**Table 1:** Optimization condition of Radical cyclization strategy of **[3a]**

| Entry | Substrate [3a] (mmol) | $Na(CN)BH_3$ (mmol) | $Bu_3SnCl$ (mmol) | $Bu_3SnH$ (mmol) | AIBN (mmol) | PhH (ml.) | PhMe (ml.) | Time (h) | Yield [4a] (%) |
|---|---|---|---|---|---|---|---|---|---|
| 1. | 0.20 | 0.20 | 0.20 | -- | 0.10 | 5 | -- | 6 | -- |
| 2. | 0.20 | 0.30 | 0.30 | -- | 0.15 | 5 | -- | 12 | -- |
| 3. | 0.20 | -- | -- | 0.20 | 0.15 | -- | 5 | 16 | 18 |
| 4. | 0.20 | -- | -- | 0.30 | 0.20 | -- | 5 | 18 | 18 |

Since radical cyclization strategy was not successful from the consideration of product yield, we turned our attention to the intramolecular Heck reaction. The precursor **[3a]** when subjected to intramolecular Heck reaction condition in presence of 12 mol% palladium (II) acetate as catalyst, 3.0 equivalent of potassium acetate as base and 1.5 equivalent of tetrabutylammonium bromide as additive in dry *N*,*N*-Dimethylformamide as solvent at 140 oC for 12 h afforded the bis-cyclized product **[4a]** in 90% yield (Table 2, entry 1).

When the catalyst was changed to palladium (II) chloride and then to dichlorobis (phosphine) palladium (II) the yield was decreased (54% to 5%) (Table 2, entry 2 and 3). By changing the solvent from DMF to acetonitrile or dioxane there was almost no reaction (Table 2, entry 4-6 and 10-12). Again it is worth mentioning to note that by changing the base from potassium acetate to triethylamine, the bis cyclized product **[4a]** was obtained in fairly good yield using palladium (II) acetate (Table 2, entry 7), but there was almost no reaction with $PdCl_2$ and $PdCl_2(PPh_3)_2$ (Table 2, entry 8, and 9).

**Table 2:** Optimization condition of Heck cyclization strategy of [**3a**]:

| Entry | Catalyst | Base | Solvent | Temp (°C) | Yield (%) |
|---|---|---|---|---|---|
| 1. | $Pd(OAc)_2$ | KOAc | DMF | 140 | 90 |
| 2. | $PdCl_2$ | KOAc | DMF | 140 | 54 |
| 3. | $PdCl_2(PPh_3)_2$ | KOAc | DMF | 140 | 5 |
| 4. | $Pd(OAc)_2$ | KOAc | MeCN | 80 | <2 |
| 5. | $PdCl_2$ | KOAc | MeCN | 80 | 0 |
| 6. | $PdCl_2(PPh_3)_2$ | KOAc | MeCN | 80 | 0 |
| 7. | $Pd(OAc)_2$ | $Et_3N$ | DMF | 140 | 68 |
| 8. | $PdCl_2$ | $Et_3N$ | DMF | 140 | 10 |
| 9. | $PdCl_2(PPh_3)_2$ | $Et_3N$ | DMF | 140 | <2 |
| 10. | $Pd(OAc)_2$ | KOAc | Dioxane | 90 | <5 |
| 11. | $PdCl_2$ | KOAc | Dioxane | 90 | 0 |
| 12. | $PdCl_2(PPh_3)_2$ | KOAc | Dioxane | 90 | 0 |

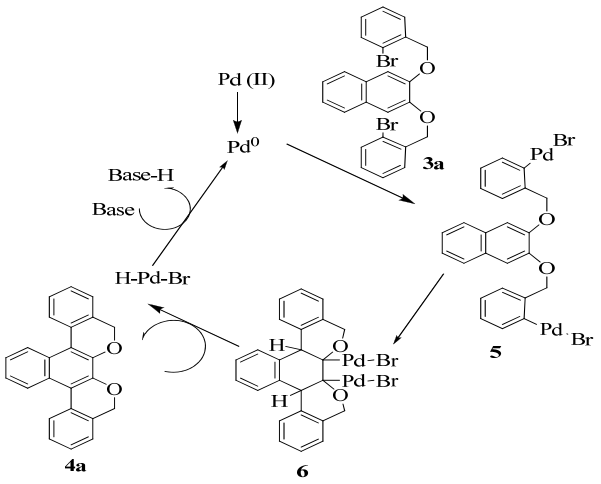
**Reagents and conditions:** Catalyst (12 mol%), base (3.0 equiv), TBAB (1.5 equiv), argon atmosphere, heat, 12 hr.

In **Table 3**, a comparative yield of the cyclization products **[4(a-f)]** in radical cyclization and Heck cyclization strategy have been explored.

**Table 3:** Comparative yield of **[(4a-f)]** in Radical and Heck cyclization strategy

| Entry | Reactant | Product | % Yield in Radical cyclization strategy | % Yield in Heck cyclization strategy |
|---|---|---|---|---|
| 1. | **3a** | **4a** | 18 | 90 |
| 2. | **3b** | **4b** | 12 | 86 |
| 3. | **3c** | **4c** | 16 | 82 |
| 4. | **3d** | **4d** | 8 | 80 |
| 5. | **3e** | **4e** | 14 | 88 |
| 6. | **3f** | **4f** | 20 | 85 |

From the study of the literature the mechanistic pathway for the bis-cyclization by Heck protocol may be proposed as follows. At first, the bis-aryl-palladium intermediate **[5]** may be formed via the oxidative addition of the Heck precursor **[3a]**, and this intermediate upon addition of the double bond may generate the σ-alkyl palladium intermediate **[6]** and this is followed by the β-hydrogen elimination may afford the bis-cyclized product **[4a]**.




**Scheme 2:** Mechanistic pathway for the formation of[4a] by Heck cyclization protocol

## 5. Conclusion

A number of substituted dihydrobenzo-isochromeno[4,3-*h*]chromene derivatives **[4(a–f)]** has been synthesized regioselectivily from several bis(2-bromobenzyloxy) naphthalene derivatives **[3(a–f)]** using $Bu_3SnH$ annulated radical cyclization and intramolecular Heck cyclization strategy and in this work the superiority of the Heck protocol in comparison to the radical cyclization strategy has been well established from the consideration of high product yield and simplicity of the reaction methodology.

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