A Concise Route Towards Isoflavans

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Dedication ((optional))

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Abstract: Isoflavans have gained considerable interest owing to their potential health benefits. Herein, we have presented a straightforward strategy for isoflavans synthesis. The strategy features an intermolecular [Cu]-catalyzed arylation of malonates and an intramolecular [Pd]-catalyzed Buchwald coupling of hydroxy tethered bromoarenes as the key transformations. This protocol enabled the synthesis of a variety of isoflavan analogs.

Introduction

Through the work of a couple of decades, chemists have been able to develop broader transition-metal catalysts based applications that catalyze cross-coupling reactions.[1] Consequently, the implementation of these reactions in synthetic organic chemistry has led to successful results.[2] However, there have been concerns regarding target specific cross-coupling reactions, primarily involving C−heteroatom bond forming techniques.[3] Challenges in these sorts of transformations would be due to particular side reactions, particularly, dehalogenation.[4] In this context, isoflavans have gained much popularity with the synthetic chemists. Isoflavans are oxygen-containing fused bicyclic heterocycles featuring biological properties similar to isoflavones[5] and are C15 frameworks contemplated as derivatives of 3-phenylchroman.[6] Also, Isoflavans widely spread and constitute isoflavonoid natural products.[7] These compounds showcase prominent biological and pharmacological significance.[8] Interestingly, the first isoflavan was an accidental discovery, and it was named Equol. For the first time, Equol isolated during an attempt to isolate estrogen from equine urine.[9] After that, it was extracted from the urine of other animals and humans, as well.[10] Equol widely used as a dietary phytoestrogen to decrease the prostate weight of rats.[11] Apart from this, the compounds belonging to this family have also reportedly seen to possess anti-fungal, anticancer, and antioxidant properties.[12] Also, it revealed that these compounds help prevent osteoporosis, androgen, and inflammation and even slow down the process of ageing.[13] They also assist in brain mitochondrial activities and prohibit prostrate growth. The various other isoflavans isolated are sativan, vestitol, colutelol, lespedezol G1; lespecyrtin D1, etc.[14]

Because of their unique structure and significant biological activities, isoflavans have gained much recognition in synthetic chemistry. Various research groups have put in many efforts to develop numerous chemical routes to synthesize the isoflavan/chroman frameworks.[15] Most synthetic strategies utilized the process of catalytic hydrogenation of isoflavenes, under the action of a palladium catalyst in different solvents and at pH conditions.[16] A few of the approaches have mentioned. The synthesis of Equol achieved from the reaction of the racemic forms of formononetin and daidzein.[17] An enantioselective route to dimethoxy counterpart of (*S*)-Equol was established by Ferreira and co-workers.[18] Subsequently, Heemstra *et al*. demonstrated a total synthesis of (*S*)-Equol by employing enantioselective Evans' alkylation and intramolecular Buchwald-Hartwig etherification, as key steps.[19] Yang *et al*. shown enantioselective hydrogenation reaction of a-arylcinnamic acids under iridium-catalysis.[20] They have extended a similar strategy for the production of (*S*)-Equol.[21] Recently, the research group of Jingzhao Xia revealed asymmetric hydrogenation of 2*H*-chromenes *via* a catalytic action of Ir/In-BiphPHOX for the synthesis of (*S*)-Equol with >95% ee.[22] Gharpure *et al*. in his work employed hetero-Diels-Alder reaction between olefin and *ortho*-quinone methides.[23]

With this background, herein, we wish to disclose a new protocol towards the synthesis of isoflavans. Carrying forward our work on [TM]-catalysis,[24] we have recently reported effective synthetic strategies for flavans.[25] In continuation of our interests, we have demonstrated a protocol affording neoflavans.[26] Herein; we disclose a new strategy delivering functionalized isoflavans. The synthetic route shows two key transformations *via* transition-metal catalyzed reactions using [Pd] and [Cu] metal catalysts.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/jhet.4158

Results and Discussion

From the retrosynthetic analysis, it was conceived that isoflavans **8/9** could be accomplished utilizing an intramolecular [Pd]-catalyzed Buchwald–Hartwig coupling of hydroxy bromoarenes **6/7** (Figure 1). Required primary and tertiary alcohols **6/7** could be synthesized from aryl malonate esters **2** and *ortho*-bromobenzyl bromides **3**. A suitable synthetic path in achieving 6/7 would be benzylation, Krapcho decarboxylation, and reduction/nucleophilic addition.

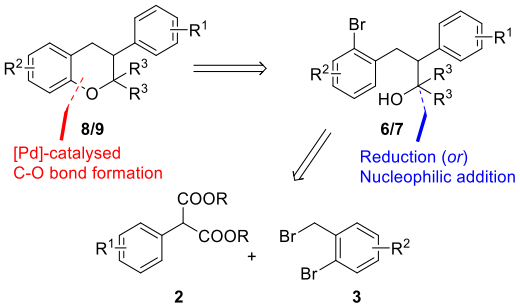
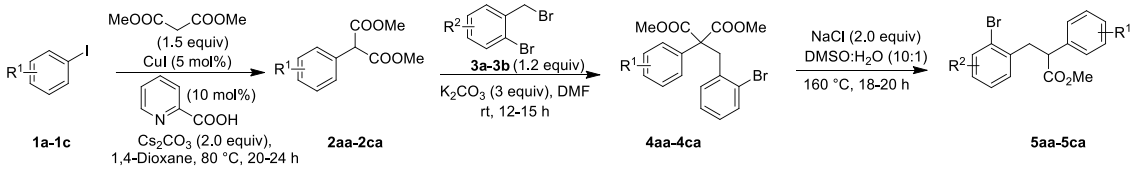


Figure 1: Retrosynthetic Analysis of Isoflavan **8/9**.

The synthetic route to achieve isoflavans was initiated with aryl malonate esters **2** and benzyl bromides **3**. Thus, we attempted the synthesis of aryl malonate esters **2** from iodoarenes **1** and dimethyl malonate. The reaction was carried out using CuI (5 mol%), picolinic acid (10 mol%), Cs_2CO_3 (1.5 equiv), in 1,4-dioxane as a solvent for 24 h at 100 °C. Consequently, aryl malonate esters **2** were isolated in high yields (Table 1).[27] Benzylation reaction of aryl malonate esters **2** was performed using *ortho*-bromobenzyl bromides **3** at ambient temperature, K_2CO_3, and in dry DMF. As a result, excellent yields of the tethered *ortho*-Bromo-bis-aryl malonate esters **4** were obtained (Table 1). Next, the Krapcho decarboxylation reaction was applied to the above-furnished compounds **4** using NaCl in DMSO and water mixture (10:1) at 160 °C for 20 h. So, *ortho*-Bromo-bis-aryl monoesters **5** were isolated in acceptable yields, as tabulated in Table 1.

Table 1: Scope for the formation of diaryl-monoesters **5aa-5ca**.[a]



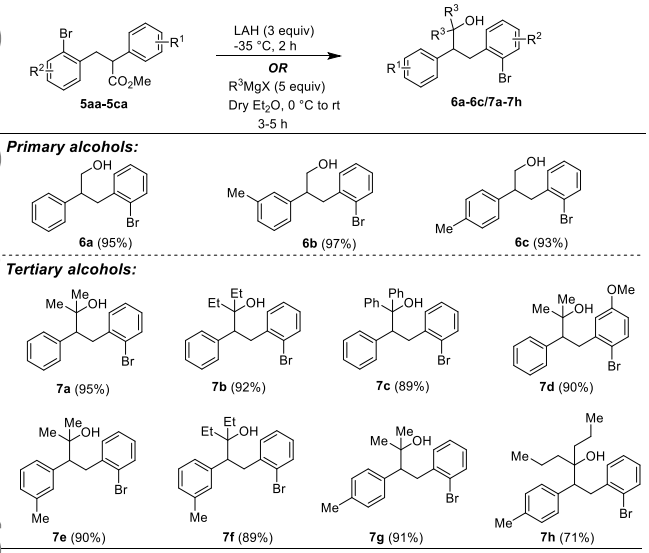
1a	**2a** (89%)	**4aa** (95%)	**5aa** (75%)
1a	**2a** (89%)	**4ab** (87%)	**5ab** (71%)
1b	**2b** (92%)	**4ba** (91%)	**5ba** (79%)
1c	**2c** (90%)	**4ca** (89%)	**5ca** (69%)

[a]Isolated yields of chromatographically pure products **2a-2c**, **4aa-4ca** and **5aa-5ca**.

After achieving aryl benzyl esters **5**, reduction of the ester group was employed to furnish the corresponding alcohol, which is a synthetic precursor for the metal-mediated cyclizations. Consequently, the reduction reaction of the esters **5**

mediated by $LiAlH_4$, afforded the corresponding primary alcohols **6a-6c** in nearly quantitative yields without affecting the bromo-substitution (Table 2). Furthermore, the reduction of the ester by a Grignard reagent furnished the corresponding tertiary alcohols **7a-7h** in very good to excellent yields (Table 2).

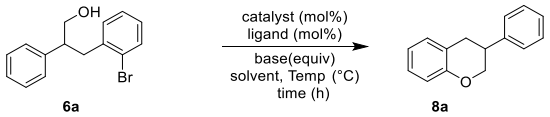
Table 2: Scope for the formation of alcohols **6a-6c**/**7a-7h**.[a,b,c,d]



[a]Isolated yields of chromatographically pure products **6a-6c** and **7a-7h**. Tertiary alcohols **7a-7h** were prepared from bromo-esters **5aa-5ca** using alkyl/aryl Grignard reaction. [c]For Lithium Aluminium Hydride (LAH) reduction and methyl Grignard reaction, dry diethyl ether (Et_2O) was used as solvent. [d]For ethyl/propyl/phenyl Grignard reaction dry tetrahydrofuran (THF) was used as a solvent.

After obtaining bromo alcohols **6a-6c**/**7a-7h**, we went ahead with the key transformation step. It was an intramolecular reaction leading to the construction of a C-O bond facilitated by a transition metal catalyst to generate the corresponding isoflavan. In this context, initially, we tested with our previously established conditions in the synthesis of flavans and neo-flavans [i.e. CuI (20 mol%)/2,2-bipyridyl (20 mol%), base KO^{t}Bu (3 equiv.) in dry DMF (120 °C) for 24 h].[25] However, unfortunately, these conditions were not favorable in delivering the expected isoflavan **8a** (entries 1, Table 3). At this stage, we reckoned that the use of excess base (KO^{t}Bu) might have hampered the reaction. Thus we thought less amount of base (KO^{t}Bu) would be more effective. Hence, the reaction was conducted using 2 and 1 equiv of KO^{t}Bu (entries 2 & 3, Table 3). However, the attempts were futile in obtaining the isoflavan product **8a**. Since copper alone was not an optimum and general catalyst for the C–O bond formation, we turned our focus towards utilizing [Pd]-catalyst, which might also serve as more effective. Interestingly, the commencing attempt alone showed effective results [$Pd(OAc)_2$ (10 mol%), JohnPhos (10 mol%), Cs_2CO_3 (2.0 equiv), in dry toluene, at 90 °C for 24 h (entry 4, Table 3)].[28] The final product was predominantly the cyclized compound isoflavan **8a**, which isolated in a good yield of 80%. Additionally, to find the most efficient operational conditions, the conditions were modified by altering the temperature (entries 5 & 6, Table 3). The attempt has not found to be effective in increasing the yield. Moving ahead, we increased the base to 3 equiv and observed the undesired products at the expense of the desired product **8a** (entry 7, Table 3). While running the reaction in solvent DMF at 90 °C for 14 h, we afforded isoflavan **8a** in 60% yield (entry 8, Table 3). Ultimately, by increasing the catalyst loading and decreasing the reaction times to 12 h, we managed to improve the yield to 85% (entry 9, Table 3). Delightfully, the same results obtained by using 3 mol% of a palladium catalyst and 5 mol% of ligand (entry 10, Table 3).

Table 3: Screening studies for the formation of isoflavan **8a**.[a,b,c]

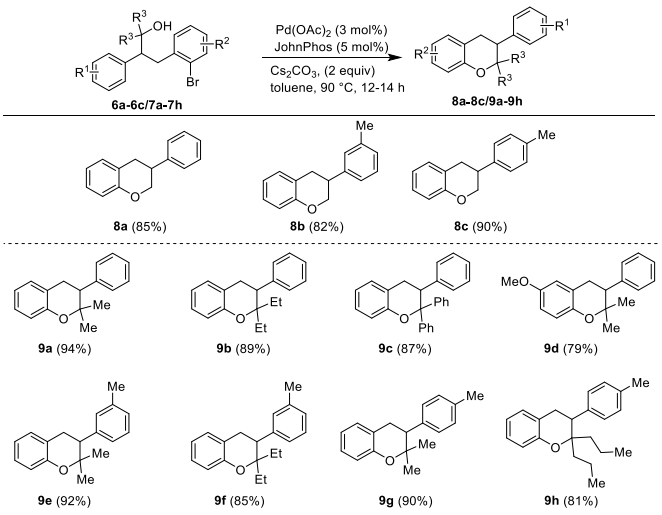


Entry	Catalyst (mol%)	Ligand (mol%)	Base (equiv)	Solvent (mL)	Temp (°C)	Time (h)	% of Yield (**8a**)[b]
1	CuI (20)	2,2'-bipyridyl (20)	KO^{t}Bu (3)	DMF	120	24	–[c]
2	CuI (20)	2,2'-bipyridyl (20)	KO^{t}Bu (2)	DMF	120	24	SM
3	CuI (20)	2,2'-bipyridyl (20)	KO^{t}Bu (1)	DMF	120	24	SM
4	$Pd(OAc)_2$ (10)	JohnPhos (20)	Cs_2CO_3 (2)	Toluene	90	24	79
5	$Pd(OAc)_2$ (10)	JohnPhos (20)	Cs_2CO_3 (2)	Toluene	110	12	80
6	$Pd(OAc)_2$ (10)	JohnPhos (20)	Cs_2CO_3 (2)	toluene	70	20	73
7	$Pd(OAc)_2$ (10)	JohnPhos (10)	Cs_2CO_3 (3)	toluene	90	12	64
8	$Pd(OAc)_2$ (10)	JohnPhos (20)	Cs_2CO_3 (2)	DMF	90	14	60
9	$Pd(OAc)_2$ (20)	JohnPhos (20)	Cs_2CO_3 (2)	toluene	90	12	85
10	$Pd(OAc)_2$ (3)	JohnPhos (5)	Cs_2CO_3 (2)	toluene	90	12	85

[a]Unless then stated, all reactions were conducted by using 58.0 mg (0.20 mmol) of **6a**, in 2 mL dry solvent. [b]Yields of isolated product **8a**. [c]No significant spot was observed on TLC.

Moving forward, we examined the generality of the scheme by implementing it on other substrates and applying the above optimal conditions (entry 10, Table 3). The various precursor alcohols **6a-6c** subjected to the C–O bond formation intramolecularly. To our delight, the experimental conditions verified to be practical in furnishing cyclized isoflavans **8a-8c** efficiently (Table 4). Furthermore, to test the scope and limitations of the strategy, we employed the same protocol for the production of tertiary alcohols. Thus, concluding the scheme, we investigated the critical step constructing C–O bond intramolecularly from bromo tertiary alcohols **7a-7h** catalyzed using palladium. As expected, the synthetic strategy worked well on tertiary alcohols **7a-7h** and afforded functionalized isoflavans **9a-9h** in good to excellent yields (Table 4).

Table 4: Scope for the formation of isoflavans **8a-8c/9a-9h**.[a,b]



[a]Chromatographically isolated yields of pure compounds **8a-8c** & **9a-9h**. [b]Reaction carried out on alcohols **6a-7h** (0.20 mmol) in dry toluene (2 mL).

Conclusion

In conclusion, a straightforward synthetic route about the synthesis of functionalized isoflavans devised. An intermolecular C–C and intramolecular C–O bonds formation were facilitated by [Cu] and [Pd], as the key transformations of the strategy, respectively. This method is practical and flexible in enabling the synthesis of different isoflavan derivatives.

Experimental Section

General procedure:

A Bruker Tensor 37 (FT-IR) spectrophotometer was used to record the IR spectra. Bruker Avance 400 (400 MHz) spectrometer was used to record ^{1}H-NMR spectra at 295 K in $CDCl_3$; chemical shifts (δ in ppm) and coupling constants (J in Hz) are reported in standard manner with reference to either internal standard tetramethylsilane (TMS) (δH = 0.00 ppm) or $CHCl_3$ (δH = 7.25 ppm). Bruker Avance 400 (100 MHz) spectrometer was used to record ^{13}C-NMR spectra at RT in $CDCl_3$; chemical shifts (δ in ppm) are reported relative to $CDCl_3$ [δC = 77.00 ppm (central line of triplet)]. The various initials notations used in the ^{1}H-NMR are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. ^{1}H, ^{13}C CPD and DEPT spectra were useful to validate the assignment of signals. For accurate mass measurements, Agilent 6538 UHD Q-TOF was used to record High-resolution mass spectra (HR-MS) through the multimode source. TLC monitored the progress of reactions on silica gel coated on alumina plate or glass plate. The eluents employed were a mixture of petroleum ether and ethyl acetate. Reactions were conducted under nitrogen atmosphere in order to maintain the inert condition.

Materials: Solvents were distilled/dried before use. Petroleum ether, dichloromethane (DCM), ethyl acetate and dry DMSO were employed as solvents. Petroleum ether has a boiling range of 60 to 80 °C and dry DMSO has a boiling range of 160 to 170 °C with purity 99%. They were bought from Sigma Aldrich as well as local commercial sources. For chromatography, Acme's silica gel (100-200 mesh) was used.

General Procedure-1 for the synthesis of aryl malonate esters (**2a**-**2c**): To an oven-dried round-bottomed flask charged with a Teflon-coated magnetic stirrer bar, were added aryl iodides **1** (5.0 mmol), CuI (5.0 mol%), 2-picolinic acid (10.0 mol%), Cs_2CO_3 (10.0 mmol), and distilled diethyl malonate (7.5 mmol) and purged with nitrogen gas (3 cycles). Anhydrous 1,4-dioxane (10 mL) was added to the reaction mixture heated in a preheated oil bath at 80 °C. After the designated time, the completed reaction (judged by TLC analysis) was allowed to reach room temperature. The mixture was separated using ethyl acetate (3 × 20 mL) and saturated aqueous NH_4Cl (40 mL). The separated organic layers were dried using Na_2SO_4, filtered and concentrated by rotary evaporator under reduced pressure. Purification of the crude mixture using silica gel column chromatography, furnished α-aryl malonate products **2a-2c** (89-92%).

General Procedure-2 for the synthesis of alkylated malonate esters (4aa-4ca): Potassium carbonate (1.14 gm, 8.18 mmol, 3.0 equiv) was suspended in dry DMF (10 mL) at room temperature. A solution containing aryl malonates **2** (2.72 mmol, 1.0 equiv) in 5 mL dry DMF was added to it dropwise. After 30 min stirring at room temperature, a solution of *ortho*-bromobenzyl bromides **3** (3.27 mmol, 1.2 equiv) in dry DMF (5 mL) was added, and stirring was continued for further 12-15 h. The reaction mixture was quenched with saturated aqueous NH_4Cl solution (40 mL), and extracted with EtOAc (3 × 20 mL). Then the organic layers were washed with brine solution (30 mL) and dried using anhydrous Na_2SO_4, filtered and the organic layer was concentrated in rotary evaporator under reduced pressure. Silica gel column chromatography of the residue, generated the products, *ortho*-bromobenzyl malonates **4aa**-**4ca** (87-95%).

General Procedure-3 for the synthesis of aryl mono esters (5aa-5ca): A mixture of the alkylated malonate esters **4** (1.53 mmol), sodium chloride (178.0 mg, 3.07 mmol, 2.0 equiv) in DMSO:H_2O (10:1) (12 mL) was placed in a sealed tube. The reaction mixture was heated at a temperature of 160 ^{o}C for 18-20 h. The mixture was cooled to room temperature and poured into EtOAc (60 mL), washed using brine solution (2 × 30 mL), dried by Na_2SO_4 and concentrated using rotary evaporator under reduced pressure. The crude reaction mixture was purified by silica gel column chromatography to afford the products (**5aa**-**5ca**) as an oil (69-75%).

General Procedure-4 for reduction of malonate esters (5aa-5ca): Under N_2 atmosphere, in a dry round-bottomed flask bromo malonate esters **5** (0.50 mmol) in dry Et_2O (25 mL) was taken, to which $LiAlH_4$ (1.50 mmol) was slowly added in portion wise at 0 ˚C. Then the reaction mixture was allowed to stirrer for 2 h at 0 ˚C. Then quenched with ethyl acetate (30 mL), and the resultant mixture was separated using ethyl acetate (2 × 30 mL) and brine solution (60 mL). The separated organic layers were dried by Na_2SO_4 and concentrated using rotary evaporator under reduced pressure. Then the reaction mixture was purified by silica gel column chromatography to furnish the primary alcohols **6a-6c** (93-97%).

General Procedure-5 for the synthesis of tertiary alcohol (7a-7h): In a round-bottomed flask magnetically stirred esters **5** (0.50 mmol) in 5 mL of dry ether/THF was taken, to which methylmagnesium iodide (2.5 mmol) or ethyl/ propyl/ phenyl magnesium bromide (2.5 mmol) [prepared from magnesium (2.5 mmol) and methyl iodide (4.00 mmol) in dry ether or ethyl/propyl/phenyl bromide (4.00 mmol) in dry THF and a catalytic amount of iodine] was added at −10 °C. The reaction mixture was stirred for 3-5 h −10 °C to rt. Then quenched by aqueous NH_4Cl (50 mL) and extracted using ethyl acetate (2 × 30 mL). The organic layers were dried by Na_2SO_4 and concentrated in rotary evaporator. The crude products were purified by using silica gel column chromatography to furnish the tertiary alcohols **7a**-**7h** (71–95%).

General Procedure-6 for the Synthesis of Isoflavans (8a-8c/9a-9h): Alcohol **6** or **7** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol) were added to a dried Schlenk tube under N_2 atmosphere. Then 2 mL dry toluene was added to the mixture and stirred at 90 °C for 12-14 h. After completion of the reaction, the reaction mixture was quenched by aq. NH_4Cl (30 mL) and extracted with ethyl acetate (3 × 20 mL). The organic layers were dried by Na_2SO_4 and concentrated in rotary evaporator under reduced pressure. The purification of crude mixture using silica gel column chromatography, furnished the isoflavan products **8a-8c**/**9a**-**9h** (79-94%).

Dimethyl 2-(2-bromobenzyl)-2-phenylmalonate (4aa): **GP-2** was followed with potassium carbonate (1.14 gm, 8.18 mmol, 3.0 equiv) in dry DMF (10 mL), aryl malonate **2a** (566 mg, 2.72 mmol, 1.0 equiv), *ortho*-bromobenzyl bromides **3a** (814 mg, 3.27 mmol, 1.2 equiv) in 5 mL dry DMF (5 mL), and stirred for 12 h. The column chromatography purification (PE/EA, 95:05 to 90:10), furnished the isolflavan **4aa** (975 mg, 95%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**2a**)= 0.30, R_f(**3a**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.44 (dd, J = 7.9, 1.4 Hz, 1H), 7.29 – 7.19 (m, 5H), 7.09 (td, J = 7.5, 1.4 Hz, 1H), 7.01 (ddd, J = 16.9, 7.6, 1.8 Hz, 2H), 3.87 (s, 2H), 3.76 (s, 6H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.5, 136.0, 135.8, 132.6, 131.0, 128.3, 128.3, 128.0, 127.6, 127.0, 126.6, 63.4, 52.9, 41.2 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{18}BrO_4^+$: 377.0383, found: 377.0378.

Dimethyl2-(2-bromo-5-methoxybenzyl)-2-phenylmalonate (4ab): GP-2 was followed with potassium carbonate (1.14 gm, 8.18 mmol, 3.0 equiv) in dry DMF (10 mL), aryl malonate **2a** (566 mg, 2.72 mmol, 1.0 equiv), *ortho*-bromobenzyl bromides **3b** (915 mg, 3.27 mmol, 1.2 equiv) in 5 mL dry DMF, and stirred for 15 h. The column chromatography purification (PE/EA, 90:10 to 85:15), furnished **4ab** (964 mg, 87%) as colourless viscus liquid. [TLC monitor (PE/EA 90:10), R_f(**2a**) = 0.30, R_f(**3b**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.34 – 7.21 (m, 6H), 6.60 (dd, J = 8.8, 3.1 Hz, 1H), 6.48 (d, J = 3.1 Hz, 1H), 3.82 (s, 2H), 3.77 (s, 6H), 3.57 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.4, 158.2, 136.6, 136.1, 132.9, 128.3, 128.0, 127.6, 117.0, 116.2, 114.7, 63.4, 55.1, 52.9, 41.5 ppm. HRMS (ESI) calculated $[M+Na]^+$ for $C_{19}H_{19}BrNaO_5^+$: 429.0308, found: 429.0305.

Dimethyl 2-(2-bromobenzyl)-2-(*m*-tolyl)malonate (4ba): **GP-2** was followed with potassium carbonate (1.14 gm, 8.18 mmol, 3.0 equiv) in dry DMF (10 mL), aryl malonate **2b** (604 mg, 2.72 mmol, 1.0 equiv) was added with *ortho*-bromobenzyl bromides **3a** (814 mg, 3.27 mmol, 1.2 equiv) in 5 mL dry DMF, and stirred for 14 h. The column chromatography purification (PE/EA, 95:05 to 90:10), furnished **4ba** (968 mg, 91%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**2b**) = 0.30, R_f(**3a**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (dd, J = 7.8, 1.3 Hz, 1H), 7.15 – 7.11 (m, 2H), 7.11 – 7.04 (m, 3H), 7.00 (ddd, J = 14.3, 7.6, 1.8 Hz, 2H), 3.85 (s, 2H), 3.73 (s, 6H), 2.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 137.5, 136.0, 135.9, 132.6, 131.0, 129.0, 128.4, 128.2, 127.9, 126.9, 126.6, 125.2, 63.4, 52.9, 41.2, 21.6 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{20}BrO_4^+$: 391.0539, found: 391.0535

Dimethyl 2-(2-bromobenzyl)-2-(*p*-tolyl)malonate (4ca): **GP-2** was followed with potassium carbonate (1.14 gm, 8.18 mmol, 3.0 equiv) in dry DMF (10 mL), aryl malonate **2c** (604 mg, 2.72 mmol, 1.0 equiv) was added with *ortho*-bromobenzyl bromides **3a** (814 mg, 3.27 mmol, 1.2 equiv) in 5 mL dry DMF, and stirred for 14 h. The column chromatography purification (PE/EA, 95:05 to 90:10), furnished **4ca** (947 mg, 89%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**2c**) = 0.30, R_f(**3a**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 (dd, J = 7.8, 1.3 Hz, 1H), 7.16 – 7.11 (m, 2H), 7.11 – 7.05 (m, 3H), 7.01 (ddd, J = 13.1, 7.5, 1.8 Hz, 2H), 3.86 (s, 2H), 3.73 (s, 6H), 2.32 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 170.6, 137.4, 136.0, 133.1, 132.6, 131.0, 128.7, 128.2, 128.1, 126.9, 126.5, 63.0, 52.8, 41.0, 21.0 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{20}BrO_4^+$: 391.0539, found: 391.0533

Methyl 3-(2-bromophenyl)-2-phenylpropanoate (5aa): **GP-3** was followed with alkylated malonate esters **4aa** (1.53 mmol), sodium chloride (178.0 mg, 3.07 mmol, 2.0 equiv) in DMSO:H_2O (10:1) (12 mL) in sealed tube and stirred at 160 ^{o}C for 18 h. The column chromatography purification (PE/EA, 97:03 to 95:05), afforded **5aa** (366 mg, 75%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**4aa**) = 0.30, R_f(**5aa**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (dd, J = 7.8, 1.2

Hz, 1H), 7.34 – 7.22 (m, 5H), 7.13 – 7.01 (m, 3H), 4.04 (dd, *J* = 13.0, 10.3 Hz, 1H), 3.60 (s, 3H), 3.50 (dd, *J* = 13.6, 9.0 Hz, 1H), 3.13 (dd, *J* = 13.6, 6.3 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.6, 138.5, 138.1, 132.8, 131.5, 128.7, 128.2, 127.8, 127.4, 127.2, 124.6, 52.0, 51.0, 40.2 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{16}Br^{79}O_2^+$: 319.0328, found: 319.0324 and $[M+H]^+$ for $C_{16}H_{16}Br^{81}O_2^+$: 321.0308, found: 321.0305.

Methyl-3-(2-bromo-5-methoxyphenyl)-2-phenylpropanoate (5ab): **GP-3** was followed with alkylated malonate esters **4ab** (1.53 mmol), sodium chloride (178.0 mg, 3.07 mmol, 2.0 equiv) in DMSO:H_2O (10:1) (12 mL) in sealed tube and stirred at 160 °C for 20 h. The column chromatography purification (PE/EA, 97:03 to 93:07), afforded **5ab** (379 mg, 71%) as colourless viscus liquid. [TLC monitor (PE/EA 93:07), R_f(**4ab**) = 0.30, R_f(**5ab**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.39 (d, *J* = 8.5 Hz, 1H), 7.34 – 7.22 (m, 5H), 6.64 – 6.58 (m, 2H), 4.00 (dd, *J* = 8.7, 6.5 Hz, 1H), 3.65 (s, 3H), 3.62 (s, 3H), 3.47 (dd, *J* = 13.6, 8.8 Hz, 1H), 3.08 (dd, *J* = 13.6, 6.5 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.5, 158.5, 139.0, 138.4, 133.2, 128.7, 127.8, 127.4, 116.7, 115.0, 114.3, 55.3, 52.0, 51.0, 40.3 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{18}Br^{79}O_3^+$: 349.0434, found: 349.0421 and $[M+H]^+$ for $C_{17}H_{18}Br^{81}O_3^+$: 351.0413, found: 351.0408.

Methyl 3-(2-bromophenyl)-2-(*m*-tolyl)propanoate (5ba): **GP-3** was followed with alkylated malonate esters **4ba** (1.53 mmol), sodium chloride (178.0 mg, 3.07 mmol, 2.0 equiv) in DMSO:H_2O (10:1) (12 mL) in sealed tube and stirred at 160 °C for 19 h. The column chromatography purification (PE/EA, 97:03 to 95:05), afforded **5ba** (403 mg, 79%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**4ba**) = 0.30, R_f(**5ba**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.17 – 7.02 (m, 6H), 4.00 (dd, *J* = 9.2, 5.9 Hz, 1H), 3.60 (s, 3H), 3.49 (dd, *J* = 13.6, 9.2 Hz, 1H), 3.12 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.6, 138.4, 138.3, 138.3, 132.8, 131.5, 128.5, 128.4, 128.2, 128.2, 127.2, 124.8, 124.7, 52.0, 51.0, 40.1, 21.4 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{18}Br^{79}O_2^+$: 333.0485, found: 333.0484 and $[M+H]^+$ for $C_{17}H_{18}Br^{81}O_2^+$: 335.0464, found: 335.0463.

Methyl 3-(2-bromophenyl)-2-(*p*-tolyl)propanoate (5ca): **GP-3** was followed with alkylated malonate esters **4ca** (1.53 mmol), sodium chloride (178.0 mg, 3.07 mmol, 2.0 equiv) in DMSO:H_2O (10:1) (12 mL) in sealed tube and stirred at 160 °C for 18 h. The column chromatography purification (PE/EA, 97:03 to 95:05), afforded **5ca** (352 mg, 69%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**4ca**) = 0.30, R_f(**5ca**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.53 (dd, *J* = 7.9, 1.1, 1H), 7.22 (d, *J* = 8.1, 2H), 7.18 – 7.08 (m, 4H), 7.05 (ddd, *J* = 7.9, 3.0, 2.3 Hz, 1H), 4.01 (dd, *J* = 13.0, 6.2 Hz, 1H), 3.60 (s, 3H), 3.50 (dd, *J* = 13.6, 9.0 Hz, 1H), 3.12 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.33 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 173.7, 138.3, 137.1, 135.5, 132.8, 131.5, 129.3, 128.1, 127.6, 127.2, 124.7, 51.9, 50.7, 40.1, 21.0 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{18}Br^{79}O_2^+$: 333.0485, found: 333.0482 and $[M+H]^+$ for $C_{17}H_{18}Br^{81}O_2^+$: 335.0464, found: 335.0460.

3-(2-Bromophenyl)-2-phenylpropan-1-ol (6a): **GP-4** was followed with bromo malonateester **5aa** (0.50 mmol) in dry ether (25 mL), was added slowly $LiAlH_4$ (1.50 mmol) in portion wise 0 °C and the resultant reaction mixture was stirred for at 0 °C for 2 h to get compound **6a**. The column chromatography purification (PE/EA, 93:07 to 90:10), gave **6a** (138 mg, 95%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**5aa**) = 0.70, R_f(**6a**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.50 (d, *J*=8.4 Hz, 1H), 7.31 – 7.25 (m, 2H), 7.20 (t, *J* = 6.6 Hz, 3H), 7.10 – 7.05 (m, 1H), 6.98 (ddd, *J* = 14.6, 7.5, 1.8 Hz, 2H), 3.77 (dd, *J* = 5.9, 2.9 Hz, 2H), 3.21 – 3.14 (m, 2H), 2.93 (ddd, *J* = 16.5, 9.1, 4.3 Hz, 1H), 1.63 (br.s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.6, 139.1, 132.7, 131.3, 128.5, 128.0, 127.7, 127.0, 126.8, 124.6, 65.9, 48.1, 38.8 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{15}H_{14}Br^{79+}$: 273.0273, found: 273.0271 and $[(M+H)+(-H_2O)]^+$ for $C_{15}H_{14}Br^{81+}$: 275.0254, found: 275.0251.

3-(2-Bromophenyl)-2-(*m*-tolyl)propan-1-ol (6b): GP-4 was followed with bromo malonateester **5ba** (0.50 mmol) in dry ether (25 mL), was added slowly $LiAlH_4$ (1.50 mmol) in portion wise 0 °C and the resultant reaction mixture was stirred for at 0 °C for 2 h. The column chromatography purification (PE/EA, 93:07 to 90:10), gave **6b** (148 mg, 97%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**5ba**) = 0.70, R_f(**6b**) = 0.30, UV detection]. ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 8.4, 1.2 Hz, 1H), 7.24 – 7.17 (m, 1H), 7.12 (td, *J* = 7.4, 1.3 Hz, 1H), 7.08 – 6.99 (m, 5H), 3.86 – 3.74 (m, 2H), 3.23 – 3.13 (m, 2H), 3.03 – 2.92 (m, 1H), 2.33 (s, 3H), 1.39 (br.s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.5, 139.3, 138.2, 132.8, 131.3, 128.8, 128.5, 127.8, 127.7, 127.1, 125.0, 124.7, 66.0, 48.1, 38.8, 21.5 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{16}H_{21}Br^{79}NO^+$: 322.0801, found: 322.0799 and $[M+NH_4]^+$ for $C_{16}H_{21}Br^{81}NO^+$: 324.0781, found: 324.0780.

3-(2-Bromophenyl)-2-(*p*-tolyl)propan-1-ol (6c): **GP-4** was followed with bromo malonate ester **5ca** (0.50 mmol) in dry ether (25 mL), was added slowly $LiAlH_4$ (1.50 mmol) in portion wise 0 °C and the resultant reaction mixture was stirred for at 0 °C for 2 h. The column chromatography purification (PE/EA, 93:07 to 90:10), gave **6c** (142 mg, 93%) as colourless viscus liquid. [TLC control PE/EA 95:05), R_f(**5ba**) = 0.70, R_f(**6c**) = 0.30, UV

detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.52 (d, J = 8.0 Hz, 1H), 7.15 – 7.09 (m, 5H), 7.03 (dd, J = 12.1, 4.7 Hz, 2H), 3.79 (s, 2H), 3.18 (dt, J = 11.1, 6.2 Hz, 2H), 3.02 – 2.90 (m, 1H), 2.32 (s, 3H), 1.42 (br. s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 139.3, 138.4, 136.4, 132.8, 131.3, 129.3, 127.9, 127.7, 127.1, 124.7, 66.1, 47.7, 38.9, 21.0 ppm. HRMS (ESI) calculated $[M+NH_4]^+$ for $C_{16}H_{21}Br^{79}NO^+$: 322.0801, found: 322.0797 and $[M+NH_4]^+$ for $C_{16}H_{21}Br^{81}NO^+$: 324.0782, found: 324.0777.

4-(2-Bromophenyl)-2-methyl-3-phenylbutan-2-ol (7a): **GP-5** was followed to obtain title compound **7a** from ester **5aa** (0.50 mmol). The column chromatography purification (PE/EA, 93:07 to 90:10), delivered **7a** (152 mg, 95%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**5aa**) = 0.70, R_f(**7a**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.48 – 7.37 (m, 1H), 7.24 – 7.12 (m, 5H), 6.96 – 6.84 (m, 2H), 6.78 – 6.70 (m, 1H), 3.46 (dd, J = 12.8, 2.2 Hz, 1H), 3.17 – 3.00 (m, 2H), 1.49 (br. s, 1H), 1.36 (s, 3H), 1.24 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.3, 139.9, 132.6, 131.4, 129.7, 127.9, 127.3, 126.7, 126.6, 124.5, 73.1, 56.6, 36.4, 28.4, 28.2 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{17}H_{18}Br^{79+}$: 301.0586, found: 301.0582 and $[(M+H)+(-H_2O)]^+$ for $C_{17}H_{18}Br^{81+}$: 303.0567, found: 303.0562.

1-(2-Bromophenyl)-3-ethyl-2-phenylpentan-3-ol (7b): **GP-5** was followed to obtain title compound **7b** from ester **5aa** (0.50 mmol). The column chromatography purification (PE/EA, 93:07 to 90:10), delivered **7b** (160 mg, 92%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**5aa**) = 0.70, R_f(**7b**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.45 – 7.36 (m, 1H), 7.23 – 7.10 (m, 5H), 6.94 – 6.81 (m, 2H), 6.72 – 6.62 (m, 1H), 3.40 (dd, J = 11.8, 1.5 Hz, 1H), 3.17 – 3.07 (m, 2H), 1.89 – 1.73 (m, 2H), 1.33 – 1.27 (m, 2H), 1.05 – 0.94 (m, 3H), 0.87 – 0.75 (m, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.7, 140.0, 132.4, 131.7, 129.9, 127.8, 127.2, 126.5, 126.3, 124.5, 51.6, 36.2, 29.5, 28.2, 8.2, 7.7 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{19}H_{22}Br^{79+}$: 329.0899, found: 329.0889 and $[(M+H)+(-H_2O)]^+$ for $C_{19}H_{22}Br^{81+}$: 331.0881, found: 331.0875.

3-(2-Bromophenyl)-1,1,2-triphenylpropan-1-ol (7c): **GP-5** was followed to obtain title compound **7c** from ester **5aa** (0.50 mmol). The column chromatography purification (PE/EA, 93:07 to 90:10), delivered **7c** (197 mg, 89%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**5aa**) = 0.70, R_f(**7c**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.77 (dd, J = 8.4 and 1.0 Hz, 2H), 7.51 – 7.46 (m, 1H), 7.39 – 7.33 (m, 4H), 7.25 – 7.21 (m, 2H), 7.18 – 7.06 (m, 4H), 7.03 – 6.98 (m, 3H), 6.84 (dddd, J = 26.7, 17.2, 7.4 and 1.6 Hz, 3H), 4.32 (dd, J = 11.6 and 3.8 Hz, 1H), 3.26 (dd, J = 14.2 and 11.7 Hz, 1H), 3.15 (dd, J = 14.3 and 3.7 Hz, 1H), 2.67 (s, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 146.2, 145.4, 139.5, 139.1, 132.5, 131.5, 130.3, 130.0, 128.2, 127.7, 127.6, 127.2, 126.8, 126.6, 126.4, 126.3, 126.1, 125.7, 124.6, 80.9, 53.2, 36.7 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{27}H_{22}Br^{79+}$: 425.0899, found: 425.0896 and $[(M+H)+(-H_2O)]^+$ for $C_{27}H_{22}Br^{81+}$: 427.0883, found: 427.0879.

4-(2-Bromo-5-methoxyphenyl)-2-methyl-3-phenylbutan-2-ol (7d): **GP-5** was followed to obtain title compound **7d** from ester **5ab** (0.50 mmol). The column chromatography purification (PE/EA, 90:10 to 85:15), delivered **7d** (157 mg, 90%) as colourless viscus liquid. [TLC monitor PE/EA 90:10), R_f(**5ab**) = 0.70, R_f(**7d**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.29 (d, J = 8.7 Hz, 1H), 7.25 – 7.13 (m, 5H), 6.47 (dd, J = 8.7 and 3.1 Hz, 1H), 6.23 (d, J = 3.1 Hz, 1H), 3.45 (s, 3H), 3.42 (d, J = 1.9 Hz, 1H), 3.12 – 2.87 (m, 2H), 1.46 (s, 1H), 1.36 (s, 3H), 1.24 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 158.1, 140.8, 140.4, 132.9, 129.7, 128.0, 126.7, 116.4, 114.9, 113.8, 73.2, 56.7, 55.1, 36.7, 28.5, 28.2 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{18}H_{20}Br^{79}O^+$: 331.0692, found: 331.0688 and $[(M+H)+(-H_2O)]^+$ for $C_{18}H_{20}Br^{81}O^+$: 333.0673, found: 333.0668.

4-(2-Bromophenyl)-2-methyl-3-(*m*-tolyl)butan-2-ol (7e): **GP-5** was followed to obtain compound **7e** from ester **5ba** (0.50 mmol). The column chromatography purification (PE/EA, 93:07 to 90:10), delivered **7e** (150 mg, 90%) as colourless viscus liquid. [TLC monitor PE/EA 93:07), R_f(**5ba**) = 0.70, R_f(**7e**) = 0.30, UV detection]. ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.43 (dd, J = 7.6 and 1.7 Hz, 1H), 7.11 (t, J = 7.7 Hz, 1H), 7.02 – 6.86 (m, 5H), 6.77 (dd, J = 7.2 and 2.1 Hz, 1H), 3.44 (dd, J = 13.4 and 2.8 Hz, 1H), 3.15 – 3.05 (m, 1H), 3.00 (dd, J = 11.8 and 2.8 Hz, 1H), 2.27 (s, 3H), 1.47 (s, 1H), 1.34 (s, 3H), 1.26 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.1, 134.0, 137.4, 132.6, 131.3, 130.5, 127.8, 127.4, 127.3, 126.7, 126.7, 124.6, 73.2, 56.5, 36.3, 28.2, 21.5 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{18}H_{20}Br^{79+}$: 315.0743, found: 315.0738 and $[(M+H)+(-H_2O)]^+$ for $C_{18}H_{20}Br^{81+}$: 317.0724, found: 317.0719.

1-(2-Bromophenyl)-3-ethyl-2-(*m*-tolyl)pentan-3-ol (7f): **GP-5** was followed to obtain title compound **7f** from ester **5ba** (0.50 mmol). The column chromatography purification (PE/EA, 93:07 to 90:10), delivered **7f** (161 mg, 89%) as colourless viscus liquid. [TLC monitor PE/EA 93:07), R_f(**5ba**) = 0.70, R_f(**7f**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (dd, J = 7.4 and 1.7 Hz, 1H), 7.18 – 6.80 (m, 7H), 6.75 – 6.66 (m, 1H), 3.47 – 3.29 (m, 1H), 3.18 – 3.07 (m, 2H), 2.26 (s, 3H), 1.81 (dt, J = 13.9 and 7.1 Hz, 2H), 1.31 (dd, J = 15.1 and 7.3 Hz, 2H), 0.98 (t, J = 7.5 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.4, 140.1, 137.2, 132.4, 131.6, 130.6, 127.6,

127.1, 127.1, 126.9, 126.5, 124.5, 76.9, 51.5, 36.0, 29.4, 28.1, 21.5, 8.2, 7.8 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{20}H_{24}Br^{79+}$: 343.1056, found: 343.1048 and $[(M+H)+(-H_2O)]^+$ for $C_{20}H_{24}Br^{81+}$: 345.1034, found: 345.1030.

4-(2-Bromophenyl)-2-methyl-3-(*p*-tolyl)butan-2-ol (7g): **GP-5** was followed to obtain title compound **7g** from ester **5ca** (0.50 mmol). The column chromatography purification (PE/EA, 93:07 to 90:10), delivered **7g** (152 mg, 91%) as colourless viscus liquid. [TLC monitor PE/EA 93:07), R_f(**5ca**) = 0.70, R_f(**7g**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.43 (dd, J = 7.5 and 1.7 Hz, 1H), 7.05 (dd, J = 23.6 and 7.9 Hz, 4H), 6.95 – 6.87 (m, 2H), 6.78 (dd, J = 7.2 and 2.0 Hz, 1H), 3.43 (dd, J = 13.1 and 2.3 Hz, 1H), 3.16 – 2.93 (m, 2H), 2.27 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.0, 137.0, 136.1, 132.5, 131.3, 129.5, 128.7, 127.3, 126.7, 124.5, 73.2, 56.2, 36.3, 28.2, 28.1, 21.0 ppm. HRMS (ESI) calculated $[(M+H)+(-H_2O)]^+$ for $C_{18}H_{20}Br^{79+}$: 315.0743, found: 315.0738 and $[(M+H)+(-H_2O)]^+$ for $C_{18}H_{20}Br^{81+}$: 317.0724, found: 317.0719.

4-(2-(2-Bromophenyl)-1-(*p*-tolyl)ethyl)heptan-4-ol (7h): **GP-5** was followed to obtain title compound **7h** from ester **5ca** (0.50 mmol). The column chromatography purification (PE/EA, 93:07 to 90:10), delivered **7h** (138 mg, 71%) as colourless viscus liquid. [TLC monitor PE/EA 93:07), R_f(**5ca**) = 0.70, R_f(**7h**) = 0.30, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.41 (d, J = 7.4 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.98 (d, J = 7.6 Hz, 2H), 6.89 (q, J = 7.2 Hz, 2H), 6.72 (d, J = 7.1 Hz, 1H), 3.37 (d, J = 8.7 Hz, 1H), 3.17 – 3.03 (m, 2H), 2.26 (s, 3H), 1.83 – 1.60 (m, 2H), 1.39 – 1.18 (m, 6H), 0.96 (t, J = 7.2 Hz, 3H), 0.78 (t, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 140.2, 137.3, 135.7, 132.4, 131.6, 128.6, 127.1, 126.6, 124.5, 76.6, 51.9, 39.9, 38.8, 35.9, 21.0, 17.1, 16.7, 14.7, 14.5 ppm.

3-(*m*-Tolyl)chromane (8b): **GP-6** was followed with alcohol **6b** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 12 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **8b** (37 mg, 82%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**6b**) = 0.20, R_f(**8b**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.28 (t, J = 7.5 Hz, 1H), 7.22 – 7.04 (m, 5H), 6.96 – 6.87 (m, 2H), 4.39 (ddd, J = 10.6, 3.6 and 2.2 Hz, 1H), 4.05 (t, J = 10.6 Hz, 1H), 3.34 – 3.19 (m, 1H), 3.18 – 2.93 (m, 2H), 2.40 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.3, 141.2, 138.4, 129.7, 128.6, 128.1, 127.8, 127.4, 124.3, 122.0, 120.3, 116.5, 70.9, 38.5, 32.4, 21.4 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{16}H_{17}O^+$: 225.1274, found: 225.1272.

2,2-Dimethyl-3-phenylchromane (9a): **GP-6** was carried out with alcohol **7a** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 12 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **9a** (45 mg, 94%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**7a**) = 0.20, R_f(**9a**) = 0.70, UV detection]. ^{1}H NMR(400 MHz, $CDCl_3$) δ = 7.33 – 7.24 (m, 5H), 7.17 – 7.07 (m, 2H), 6.91 – 6.80 (m, 2H), 3.20 (dd, J = 16.2 and 10.5 Hz, 1H), 3.06 (dd, J = 10.5 and 5.3 Hz, 1H), 2.96 (dd, J = 16.2 and 5.3 Hz, 1H), 1.30 (s, 3H), 1.22 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5, 141.5, 129.3, 128.8, 128.2, 127.4, 126.9, 121.6, 120.0, 117.2, 77.2, 47.8, 29.1, 28.1, 21.3 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{17}H_{19}O^+$: 239.1430, found: 239.1426.

2,2-Diethyl-3-phenylchromane (9b): **GP-6** was carried out with alcohol **7b** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 13 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **9b** (47 mg, 89%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**7b**) = 0.20, R_f(**9b**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.27 – 7.10 (m, 6H), 7.08 – 7.01 (m, 1H), 6.95 – 6.78 (m, 2H), 3.25 – 3.06 (m, 2H), 2.96 (dd, J = 16.9 and 6.1 Hz, 1H), 1.77 – 1.67 (m, 2H), 1.58 (dq, J = 14.6 and 7.4 Hz, 1H), 1.38 (dq, J = 14.6 and 7.4 Hz, 1H), 0.92 (t, J = 7.4 Hz, 3H), 0.84 (t, J = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.8, 142.5, 129.4, 128.7, 128.3, 127.3, 126.6, 121.5, 120.0, 117.3, 80.3, 43.1, 29.4, 26.6, 25.6, 7.5, 7.3 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{19}H_{23}O^+$: 267.1743, found: 267.1742.

2,2,3-Triphenylchromane (9c): **GP-6** was followed with alcohol **7c** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 14 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **9c** (63 mg, 87%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**7c**) = 0.20, R_f(**9c**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.66 (dd, J = 8.4 and 1.1 Hz, 2H), 7.37 – 7.25 (m, 4H), 7.24 – 7.14 (m, 3H), 7.14 – 7.05 (m, 2H), 7.07 – 6.90 (m, 7H), 6.90 – 6.81 (m, 1H), 4.24 (dd, J = 7.0 and 1.3 Hz, 1H), 3.32 (dd, J = 17.0 and 7.1 Hz, 1H), 2.90 (d, J = 16.2 Hz, 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 154.1, 144.8, 144.0, 141.5, 129.5, 129.2, 128.5, 127.7, 127.5, 127.3, 127.0, 126.3, 126.3, 126.1, 125.8, 121.4, 121.0, 117.4, 83.4, 44.4, 30.1 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{27}H_{23}O^+$: 363.1743, found: 363.1737.

6-Methoxy-2,2-dimethyl-3-phenylchromane (9d): **GP-6** was followed with alcohol **7d** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 14 h. The column chromatography purification (PE/EA,, 98:02 to 93:07), furnished

9d (42 mg, 79%) as colourless viscus liquid. [TLC monitor PE/EA 93:07), R_f(**7d**) = 0.20, R_f(**9d**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.26 – 7.12 (m, 5H), 6.71 (d, *J* = 8.8 Hz, 1H), 6.65 (dd, *J* = 8.9 and 3.0 Hz, 1H), 6.56 (d, *J* = 2.9 Hz, 1H), 3.67 (s, 3H), 3.07 (dd, *J* = 16.1 and 9.9 Hz, 1H), 2.95 (dd, *J* = 9.9 and 5.4 Hz, 1H), 2.86 (dd, *J* = 16.1 and 5.4 Hz, 1H), 1.20 (s, 3H), 1.11 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.1, 147.5, 141.5, 128.7, 128.2, 126.9, 122.1, 117.7, 113.7, 113.5, 76.8, 55.6, 47.7, 29.5, 27.9, 21.4 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{21}O_2^+$: 269.1536, found: 269.1539.

2,2-Dimethyl-3-(*m*-tolyl)chromane (9e): **GP-6** was followed with alcohol **7e** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 14 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **9e** (46 mg, 92%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**7e**) = 0.20, R_f(**9e**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.24 – 7.16 (m, 1H), 7.17 – 7.11 (m, 1H), 7.11 – 7.01 (m, 4H), 6.87 (dd, *J* = 11.8, 4.5 Hz, 2H), 3.20 (dd, *J* = 16.3, 10.9 Hz, 1H), 3.03 (dd, *J* = 10.9, 5.3 Hz, 1H), 2.92 (dd, *J* = 16.3, 5.3 Hz, 1H), 2.35 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5, 141.4, 137.7, 129.6, 129.3, 128.1, 127.6, 127.3, 125.8, 121.7, 119.9, 117.1, 77.3, 47.8, 29.1, 28.2, 21.5, 21.1 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{21}O^+$: 253.1587, found: 253.1584.

2,2-Diethyl-3-(*m*-tolyl)chromane (9f): **GP-6** was followed with alcohol **7f** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 14 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **9f** (48 mg, 85%) as colourless viscus liquid. [TLC monitor PE/EA 95:05), R_f(**7f**) = 0.20, R_f(**9f**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.20 – 7.10 (m, 2H), 7.08 – 6.96 (m, 4H), 6.93 – 6.81 (m, 2H), 3.17 (t, *J* = 6.7 Hz, 1H), 3.09 (dd, *J* = 17.0 and 6.5 Hz, 1H), 2.98 (dd, *J* = 17.0 and 6.9 Hz, 1H), 2.30 (s, 3H), 1.74 (dqd, *J* = 14.8, 7.5 and 2.4 Hz, 2H), 1.65 – 1.50 (m, 2H), 1.41 (dq, *J* = 14.6 and 7.4 Hz, 1H), 0.93 (t, *J* = 7.4 Hz, 3H), 0.85 (t, *J* = 7.5 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.8, 142.3, 137.6, 129.5, 129.4, 128.2, 127.3, 127.3, 125.6, 121.6, 119.9, 117.3, 80.3, 43.1, 29.4, 26.7, 25.4, 21.5, 7.5, 7.3 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{20}H_{25}O^+$: 281.1900, found: 281.1899.

2,2-Dimethyl-3-(*p*-tolyl)chromane (9g): **GP-6** was followed with alcohol **7g** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 14 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **9g** (45 mg, 90%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**7g**) = 0.20, R_f(**9g**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.18 – 7.08 (m, 6H), 6.88 (dd, *J* = 11.6, 4.4 Hz, 2H), 3.19 (dd, *J* = 16.2 and 10.8 Hz, 1H), 3.04 (dd, *J* = 10.7 and 5.3 Hz, 1H), 2.93 (dd, *J* = 16.3 and 5.3 Hz, 1H), 2.35 (s, 3H), 1.31 (s, 3H), 1.22 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.5, 138.4, 136.5, 129.3, 128.9, 128.6, 127.3, 121.7, 119.9, 117.1, 77.3, 47.4, 29.2, 28.1, 21.1, 21.0 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{18}H_{21}O^+$: 253.1587, found: 253.1585.

2,2-Dipropyl-3-(*p*-tolyl)chromane (9h): **GP-6** was carried out with alcohol **7h** (0.20 mmol), $Pd(OAc)_2$ (3 mol%), JohnPhos (5 mol%), Cs_2CO_3 (0.40 mmol), 2 mL toluene(dry) was added and allowed to stirrer at 90 °C for 14 h. The column chromatography purification (PE/EA, 98:02 to 95:05), furnished **9h** (50 mg, 81%) as colourless viscus liquid. [TLC monitor (PE/EA 95:05), R_f(**7h**) = 0.20, R_f(**9h**) = 0.70, UV detection]. ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.19 – 7.11 (m, 1H), 7.12 – 7.00 (m, 5H), 6.94 – 6.79 (m, 2H), 3.15 (t, *J* = 6.6 Hz, 1H), 3.03 (ddd, *J* = 41.2, 16.7, 6.5 Hz, 2H), 2.32 (s, 3H), 1.73 – 1.59 (m, 2H), 1.54 – 1.28 (m, 6H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.80 (t, *J* = 7.1 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 153.8, 139.3, 136.1, 129.4, 128.9, 128.5, 127.2, 121.5, 119.9, 117.2, 80.2, 43.3, 37.3, 35.7, 29.5, 21.0, 16.5, 16.3, 14.5 ppm. HRMS (ESI) calculated $[M+H]^+$ for $C_{22}H_{29}O^+$: 309.2213, found: 309.2205.

Acknowledgments

We thankful to DST-SERB [No.EMR/2017/005312], New Delhi, for financial support. S.B. thankful to MHRD and C.B.S thankful to UGC for the research fellowship.

Keywords: Isoflavans 1 • Intramolecular arylation 2 • Iodobenzene 3 • malonates 4 • *ortho*-bromobenzylbromide 5

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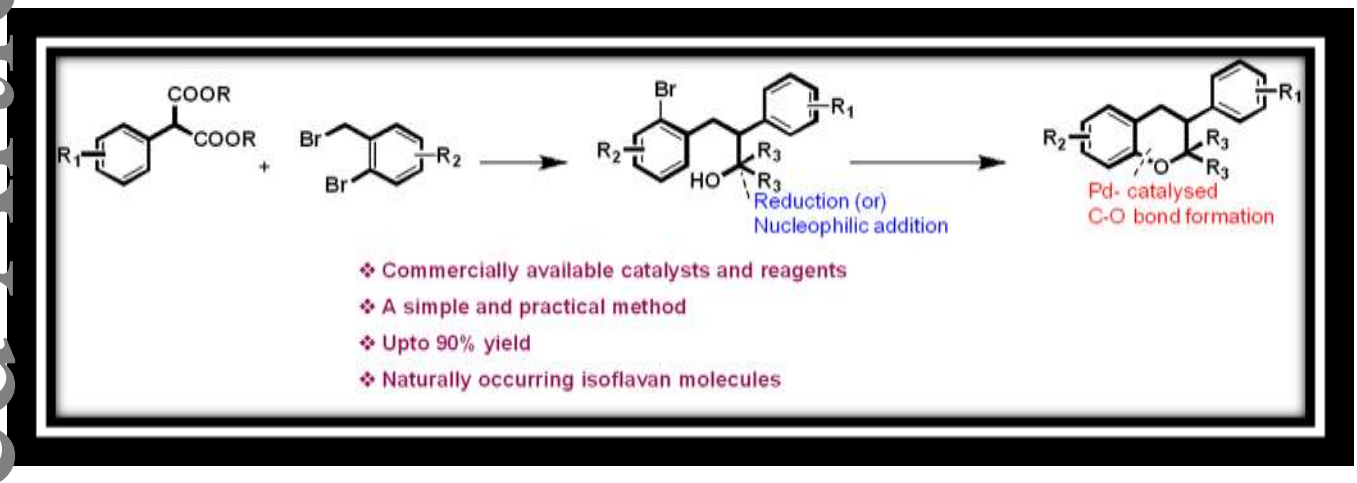

Insert text for Table of Contents here. We have presented a straightforward strategy for isoflavans synthesis. The strategy features an intermolecular [Cu]-catalyzed arylation of malonates and an intramolecular [Pd]-catalyzed Buchwald coupling of hydroxyl tethered bromoarenes, as the key transformations. This method is practical and flexible in enabling the synthesis of different isoflavan derivatives.

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