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Transition metals catalyzed C–C and C–O bonds formation: facile synthesis of flavans and benzoxepines

B. Venkat Ramulu, L. Mahendar, J. Krishna, A. Gopi Krishna Reddy, B. Suchand, G. Satyanarayana *

Department of Chemistry, Indian Institute of Technology (IIT) Hyderabad, Ordnance Factory Estate Campus, Yeddumailaram 502 205, Medak District, Andhra Pradesh, India

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ABSTRACT

A simple and practical method has been developed based on intermolecular [Pd]-catalyzed C–C and an intramolecular [Cu]-catalyzed C–O bond formations for the synthesis of flavans and benzoxepines. Interestingly, the method is amenable for the synthesis of a wide variety of flavans and benzoxepines with dense functionalities on aromatic moieties. Significantly, flavans and benzoxepines are present as core/part-structures in many biologically active natural products.

1. Introduction

Flavan (2-aryl-chroman) is a generic structural core present in a variety of flavonoid natural products. They are more abundant in the plant kingdom and show broad range of biological and pharmacological activities.[1] For example, 4′-hydroxy-7-methoxyflavan is known as one of the *anti*-feedant compounds in *Lycoris radiata*,[2] the compound 7-hydroxy-3′,4′-methylenedioxyflavan is traditionally used to cure diabetes, ear and chest disorders, and also for some sort of viral infections,[3] 4′,6-dichloroflavan (BW683C) hinders rhinovirus replication in vitro,[4] while, morusyunnansin E exhibits potent inhibitory activity on mushroom tyrosinase[5] (Fig. 1). Moreover, catechins (polyphenols) are the major constituents of green tea, also commonly known as flavanols, which exhibit excellent biological activities, such as antioxidative action, inhibit cell-growth of cancer, hypoglycemic action, and *anti*-hypertensive action.[6] Likewise, benzoxepines also form a main core in various natural products, as in, ponapensin[7,8] showed significant NF-κB inhibitory activity in an Elisa assay. The compound aglaxiflorin D[9] is most potent against PGE2 release.

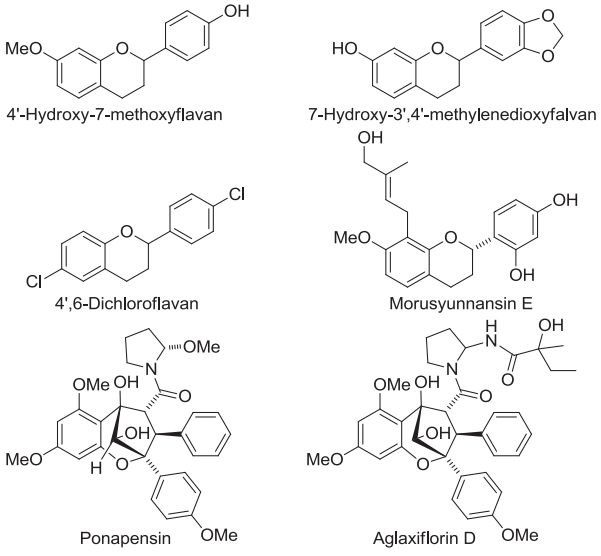

Fig. 1. Representative examples of naturally occurring flavonoid and benzoxepine natural products.

* Corresponding author. Tel.: +91 (40) 2301 6054; fax: +91 (40) 2301 6032; e-mail address: gvsatya@iith.ac.in (G. Satyanarayana).

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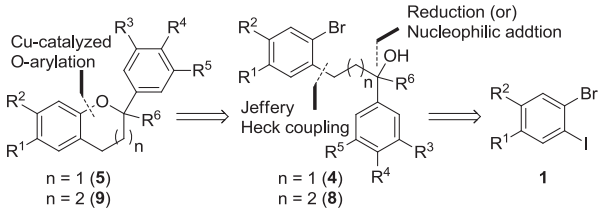
Owing to their unique structural features and interesting biological characteristics, flavans, and benzoxepines have attracted many synthetic chemists toward their synthesis. Consequently, there are reasonably good number of synthetic strategies reported, particularly, for the synthesis of flavan core structure (i.e., chromans).[10–13] Even recently, there have been a few reports on transition-metal [Pd][14] and [Cu][15]-catalyzed intramolecular C–O bond forming reactions between aryl halide moiety and alcohol tether, for the synthesis of various chromans.

As a continuation to our interest in transition metal-catalysis,[16] recently, we described an efficient and simple three-step strategy for the synthesis of functionalized flavans using transition metals, [Pd] and [Cu]-catalyzed individual reactions as the key transformations, for the construction of C–C and C–O bonds, respectively.[16e] Herein, we report an extensive application of this strategy for the synthesis of flavans as well as synthesis of good number of benzoxepines with dense functionalities on both aromatic moieties. Moreover, the present approach to arrive at the requisite precursor of cyclization is different (i.e., by using Pd-catalyzed Jeffery-Heck[17,18] conditions and reduction strategy) unlike the classical intramolecular Aldol condensation followed by reduction protocol. Most significantly, the strategy enables us for the synthesis of a wide variety of benzoxepines, unlike a closely related approach reported by the research group of Franzén.[15d] Though, there were reports on the synthesis of benzoxepines using transition metal-catalysis,[14] where simple alkyl group is connected to a carbon connected to the oxygen atom, however, to the best of our knowledge there are no reports for such compounds with different aryl substituent on oxygen attached carbon.

The study for the synthesis of substituted flavans **5** and benzoxepines **9** was envisioned based on a key [Cu]-catalyzed intramolecular C–O bond formation between aryl bromide moiety and alcohol tether of secondary and tertiary alcohols of **4** and **8**. The requisite secondary and tertiary alcohols of **4** and **8** were accomplished from 1-bromo-2-iodobenzenes **1**, using a key intermolecular [Pd]-catalyzed C–C bond formation under Jeffery-Heck conditions with allylic alcohol coupling partners followed by reduction or Grignard addition protocol, respectively (Scheme 1).



Scheme 1. Retrosynthetic plan for flavans **5** and benzoxepines **9** from 1-bromo-2-iodobenzenes **1**.

2. Results and discussion

The synthetic study has been initiated with the treatment of 1-bromo-2-iodobenzenes **1** with coupling allylic alcohol partners **2**, in the presence of a catalyst $Pd(OAc)_2$ (3 mol %) and Et_3N (2 equiv) in hot acetonitrile, under Jeffery-Heck conditions, led to the dihydrochalcones **3** in good to very good yields.[19,20] Reduction of ketones **3** with the reducing agent $NaBH_4$ in methanol gave the desired secondary alcohols **4aa**–**4ca** in near quantitative (97–99%) yields (Table 1). Also, the ketones were smoothly transformed into a variety of tertiary alcohols (**4aam**–**4bdv**) with addition of Grignard (methyl/ethyl/vinyl) reagents as well as with the treatment of allyl zinc bromide under Barbier reaction conditions (Table 1).

With the requisite secondary (**4aa**–**4ca**)/tertiary alcohols (**4aam**–**4bdv**), initially we explored different reaction conditions with the secondary alcohol **4ca**, for the key [Pd]-catalyzed C–O bond formation and the results are summarized in Table 2. It was noticed that the reaction, in presence of catalyst $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %), and the base Cs_2CO_3 (2 equiv) in hot DMF, was unsuccessful to yield **5ca**, rather, exclusively gave the ketone **5ca′** (entry 1, Table 2). The formation of the ketone **5ca′** can be justified because of the availability of β-hydrogen to Pd-species that may trigger *syn*-elimination in preference to the cyclization via C–O bond formation, which is in good agreement and reminiscent to that reported by Buchwald and co-workers.[13a–c] Similarly, use of different ligands (**L1** & **L2**) were also unsuccessful to give **5ca** (entries 2 and 4, Table 2). On the other hand, interestingly, the reaction with the biaryl ligand **L2**, which is known to produce cyclic ethers even with secondary alcohols, yielded the cyclic ether **5ca** in 62% yield (entry 3, Table 2) along with the minor amount of the ketone **5ca′** (9%). Since the [Pd]-catalyzed C–O bond formation was found to be inferior, we became interested to explore the reaction conditions using [Cu]-catalyzed C–O bond formations. Gratifyingly, the initial attempt was found efficient in the presence of catalytic system CuI (20 mol %)/2,2-bipyridyl (20 mol %), base KO^tBu (3 equiv) in hot DMF (120 °C) for 24 h with the secondary alcohol **4ca** and furnished exclusively the cyclized product flavan **5ca**, in good yield (68%, entry 6, Table 2). However, the trials in solvents dioxane and DMSO were totally ineffective to give the product **5ca** and led to the recovery of starting material **4ca**.

Among all screened reaction conditions, the entry 6, Table 2 turned to be the best; hence, these conditions were applied to various secondary alcohols (**4aa**–**4bd**). Gratifyingly, this method proved to be efficient and amenable for wide range of electron releasing substituents on either aromatic rings and gave the cyclized flavan products **5aa**–**5bd**, in very good yields (Table 3). After successful accomplishment of flavans **5aa**–**5ca**, we turned our interest to check the scope and applicability of the method. Therefore, [Cu]-catalyzed cyclization of tertiary alcohols **4aam**–**4bdv** was also investigated. Agreeably, the reaction was positive and gave the products **5aam**–**5bdv**, not only with simple to electron rich aromatic functionalities on either of aromatic moieties, but also with various groups (methyl/ethyl/vinyl/allyl) directly connected to the hydroxyl bearing carbon, in comparable yields to that obtained when secondary alcohols **4aa**–**4ca** were cyclized (Table 4).

After successful accomplishment of different flavans **5** with dense functionalities, to analyse the scope and limitations of the method, we turned our attention toward the synthesis of 2-aryl-2,3,4,5-tetrahydro-1-benzoxepine (seven-membered cyclic ether). In this regard, initially we were to check the feasibility of Jeffery-Heck coupling conditions in-order to produce the corresponding ketones **7** from the homoallylic alcohols **6**. The required homoallylic alcohol **6** coupling partners were synthesized by using standard Barbier reaction under sonochemical acceleration. Delightfully Jeffery-Heck conditions were successful on homoallylic alcohols **6** and gave us the ketones **7** albeit in fair yields in most of the cases along with the minor amount of corresponding coupled homoallylic alcohols (Table 4). Since it was well established, the ketones **7** were smoothly transformed to the corresponding secondary as well as tertiary alcohols (Table 4).

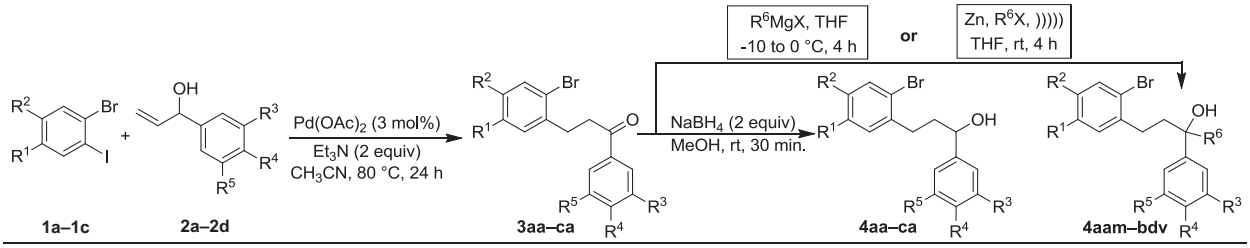
To conclude, [Cu]-mediated intermolecular C–O bond formation of secondary alcohols **8aa**–**8be** and tertiary alcohols **8aam**–**8afm**, was found to be amenable to the optimized reaction conditions and gave the benzoxepines **9** in very good yields (Table 5).

In addition to the NMR spectroscopic structural elucidation, the structure of flavan **5** as well as the benzoxepine **9** were further unambiguously confirmed by single crystal X-ray diffraction analysis of **5ac** and **9ad**, respectively (Fig. 2).[21]

3. Conclusion

In summary, we have developed an efficient three-step strategy for the synthesis of functionalized flavans and a benzoxepines.

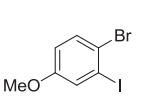
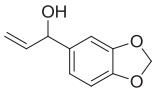
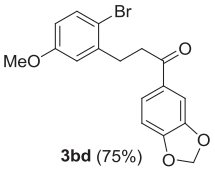
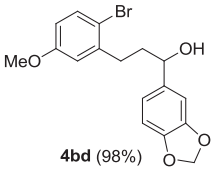
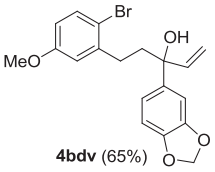
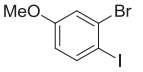
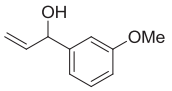
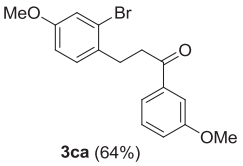
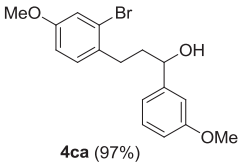
Table 1
Synthesis of secondary alcohols **4aa**–**4ca** and tertiary **4aam**–**4bdv** alcohols via ketones **3aa**–**3ca**[a,b,c,d,e,f]



1a	**2a**	**3aa** (78%)	**4aa** (99%)	**4aam** (88%)
1a	**2b**	**3ab** (70%)	**4ab** (98%)	R^6 = Me, **4abm** (70%) R^6 = Et, **4abe** (75%) R^6 = vinyl, **4abv** (85%) R^6 = allyl, **4aba** (86%)
1a	**2c**	**3ac** (69%)	**4ac** (98%)	R^6 = Me, **4acm** (82%) R^6 = Et, **4ace** (92%) R^6 = allyl, **4aca** (71%)
1a	**2d**	**3ad** (71%)	**4ad** (97%)	R^6 = Me, **4adm** (85%) R^6 = vinyl, **4adv** (89%) R^6 = allyl, **4ada** (77%)
1b	**2a**	**3ba** (72%)	**4ba** (97%)	(-----)[g]
1b	**2b**	**3bb** (74%)	**4bb** (99%)	**4bbe** (71%)
1b	**2c**	**3bc** (72%)	**4bc** (98%)	**4bcm** (67%)

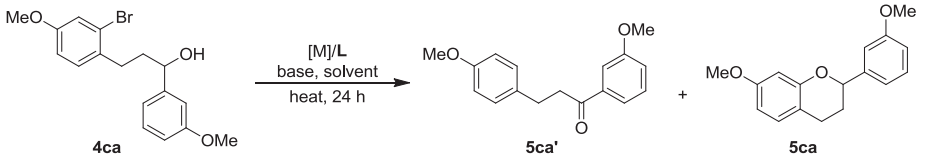
(*continued on next page*)

Table 1 (*continued*)

 **1b**	 **2d**	 **3bd** (75%)	 **4bd** (98%)	 **4bdv** (65%)
 **1c**	 **2a**	 **3ca** (64%)	 **4ca** (97%)	(---)[g]

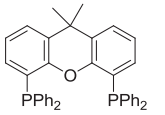
[a] Isolated yields of chromatographically pure products. [b] For compounds **3aa–ca**, **4aa–ca** the first letter refers to the 1-bromo-2-iodobenzenes part **1a–c** whereas the second letter indicates the aromatic ring coming from the allylic alcohol **2a–d**. [c] For compounds **4aam–bdv** the first letter refers to the 1-bromo-2-iodobenzenes part **1a–c**, the second letter indicates the aromatic ring coming from the allylic alcohol **2a–d** and the third letter comes from the organic part of either Grignard or allylzinc bromide reagents. [d] In case of Grignard reagents; methyl/ethyl/vinyl Grignard reagents were used (i.e. R^6 =methyl or ethyl or vinyl). [e] Allylzinc bromide was prepared under sonochemically accelerated Barbier conditions, used in-situ (i.e. R^6 = allyl). [f] Allylic alcohols (**2a–d**) were prepared by the addition of vinylmagnesium bromide reagent. [g] These compounds have not been prepared.

Table 2
Attempts of [M]-catalyzed intramolecular C–O bond formation for the synthesis of **5ca** starting from **4ca**

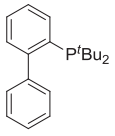


Entry	Catalyst (mol %)	Ligand (mol %)	Base (equiv)	Solvent	Temp (°C)	Recovery of **4ca** (%)[a]	Yield of **5ca** (%)[a]	Yield of **5ca'** (%)[a]
1	$Pd(OAc)_2$ (5)	PPh_3 (10)	Cs_2CO_3 (2)	toluene	80	—	—	69
2	$Pd(OAc)_2$ (3)	**L1** (6)	Cs_2CO_3 (2)	toluene	80	—	—	65
3	$Pd(OAc)_2$ (3)	**L2** (6)	Cs_2CO_3 (2)	toluene	80	—	62	9
4	$Pd_2(dba)_3$ (3)	**L3** (3)	KO^tBu (3)	toluene	80	—	9	17
5	CuI (20)	**L4** (20)	KO^tBu (3)	toluene	80	82	—	—
6	CuI (20)	**L4** (20)	KO^tBu (3)	DMF	120	—	—	68
7	CuI (20)	**L4** (20)	KO^tBu (3)	dioxane	80	89	—	—
8	CuI (20)	**L4** (20)	KO^tBu (3)	DMSO	150	85	—	—

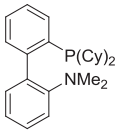
[a] Isolated yields of chromatographically pure products.



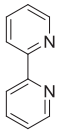
L1



L2



L3



L4

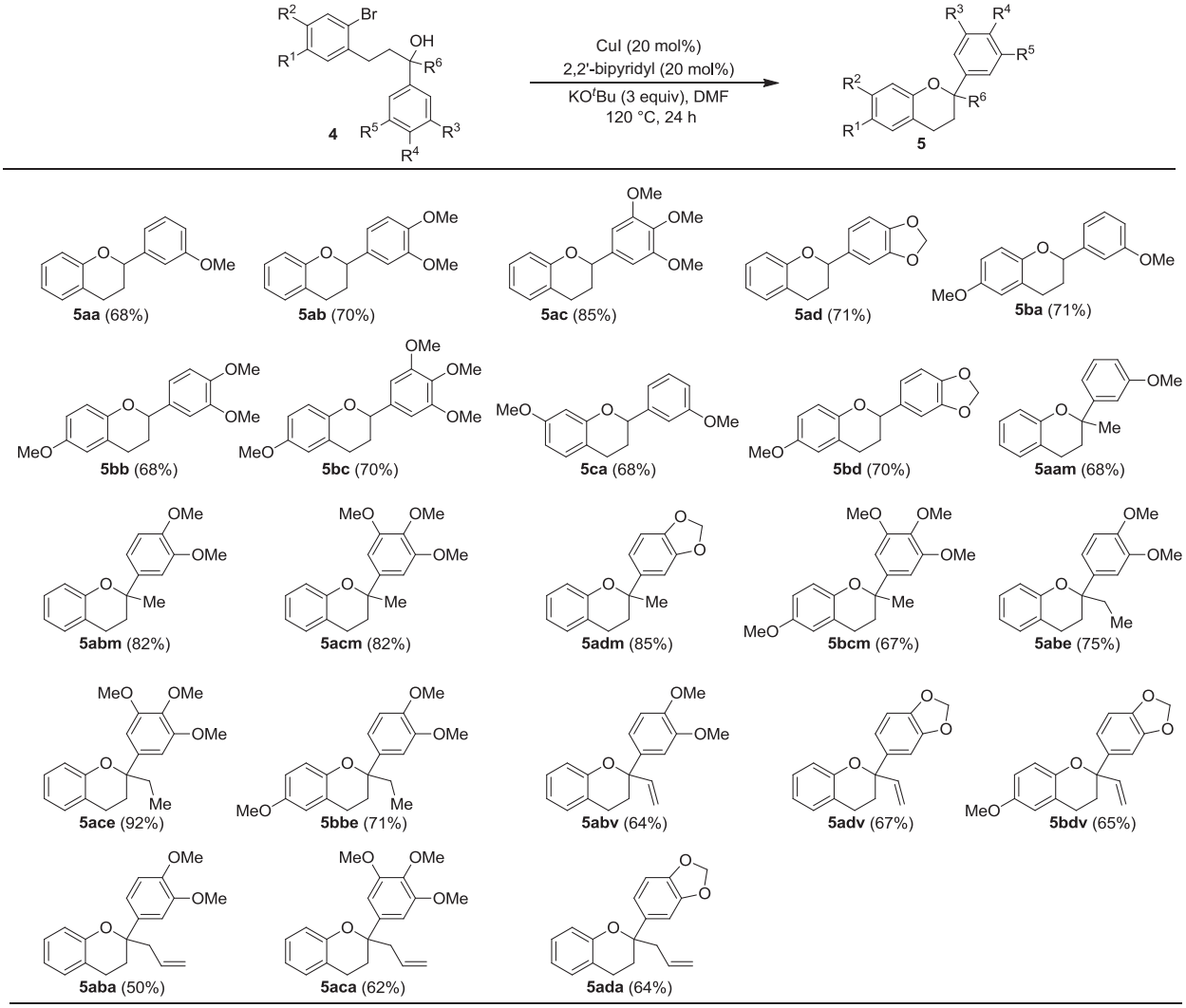
Intermolecular [Pd]-catalyzed C–C and intramolecular [Cu]-catalyzed C–O bonds formation as key steps of the strategy. The strategy is proved to be efficient and amenable for the synthesis of a number of analogues and successfully applied to the synthesis of various benzoxepines.

4. Experimental section

4.1. General

IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^1H NMR spectra were recorded on Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ in parts per million) and coupling constants (J in Hertz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H=0.00 ppm) or $CHCl_3$ (δ_H=7.25 ppm). ^{13}C NMR spectra were recorded on Bruker Avance 400 (100 MHz) spectrometer at room temperature in $CDCl_3$; chemical shifts (δ in ppm) are reported relative to $CHCl_3$ [δ_C=77.00 ppm (central line of triplet)]. In the ^{13}C NMR, the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT-135 spectra, and is given in parentheses and noted as s=singlet (for C), d=doublet (for CH), t=triplet (for CH_2), and q=quartet (for CH_3). In the ^1H NMR, the following abbreviations were used throughout: s=singlet, d=doublet, t=triplet, q=quartet, qui=quintet, m=multiplet, and br s=broad singlet. The assignment of signals was confirmed by ^1H, ^{13}C CPD, and DEPT spectra. High-resolution mass spectra (HRMS) were recorded on an Agilent 6538 UHD Q-TOF using multimode source. All small scale dry reactions were carried out using Schlenk tube technique. Reactions were monitored by TLC on silica gel using a mixture of petroleum ether and ethyl acetate as eluents. Reactions were generally run under an argon or nitrogen atmosphere. Solvents, petroleum ether, ethyl acetate, and dichloromethane were distilled prior use. Petroleum ether with a boiling range of

Table 3
Synthesis of different flavans **5** from alcohols **4**



[a] Isolated yields of chromatographically pure products.

60–80 °C was used. Diethyl ether and THF were dried over benzophenone/sodium. DMF was dried over calcium hydride. CuI and 2,2′-bipyridine were purchased from Sigma–Aldrich and used as received. KO^{t}Bu was dried under vacuum at 100 °C for 2 h prior to use. Acme's silica gel (60–120 mesh) was used for column chromatography (approximately 20 g per one gram of crude material).

4.2. General procedure 1 (GP-1): for the preparation of ketones (7) by Jeffery-Heck reaction

In an oven dried Schlenk tube under nitrogen atmosphere, were added allylic alcohol **6** (500.0 mg, 1.76–3.38 mmol), aryl halide **1** (2.11–4.06 mmol), $Pd(OAc)_2$ (11.8–22.7 mg, 3 mol %), triethylamine (356.2–684.1 mg, 3.52–6.76 mmol), followed by dry acetonitrile (4 mL), at room temperature. The resulted reaction mixture was stirred for 24 h at 80 °C. Progress of the reaction was monitored by TLC. The reaction mixture was quenched with the aqueous NH_4Cl solution and extracted with ethyl acetate (3×20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as eluent furnished the ketone 7 (46–58%).

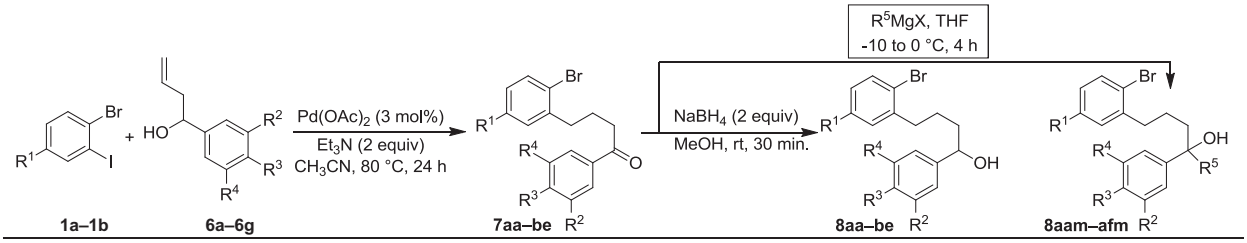
4.3. General procedure 2 (GP-2): for reduction of ketones to alcohols (8)

To an ice cold, magnetically stirred solution of a ketone **7** (300 mg, 0.68–0.99 mmol) in methanol (10 mL), was added sodium borohydride in 10–15 portions (51.4–74.0 mg, 1.36–1.98 mmol). Then the reaction mixture was allowed to attain room temperature and stirred for 2 h. Progress of the reaction was monitored by TLC. Solvent was removed under reduced pressure, treated with aqueous NH_4Cl solution, and extracted with ethyl acetate (3×15 mL). The organic layer was washed with saturated NaCl solution, dried (Na_2SO_4), and filtered. Evaporation of the filtrate under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol **8** (80–94%).

4.4. General procedure 3 (GP-3): preparation of tertiary alcohols (8)

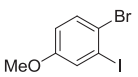
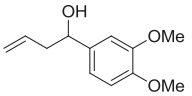
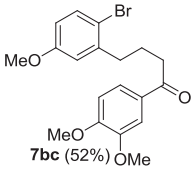
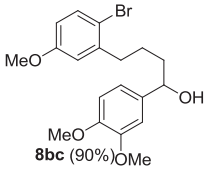
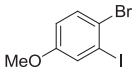
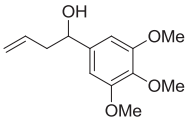
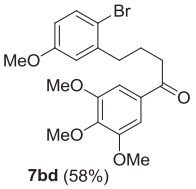
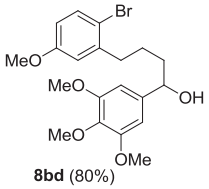
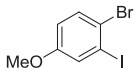
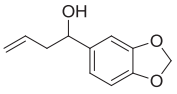
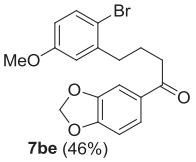
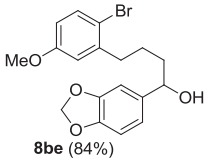
To a cold (−10 °C) magnetically stirred solution of a ketone **7** (300 mg, 0.68–0.86 mmol) in dry diethyl ether or dry THF (10 mL), was added vinylmagnesium bromide or

Table 4
Synthesis of secondary alcohols **8aa**–**8be** and tertiary **8aam**–**8afm** alcohols via ketones **7aa**–**7be**[a,b,c,d,e]



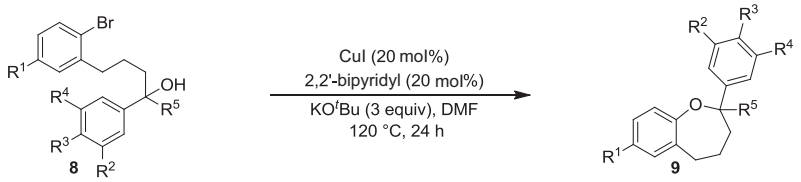
1a–1b	6a–6g	7aa–be	8aa–be	8aam–afm
1a	**6a**	**7aa** (53%)	**8aa** (84%)	(-----)[f]
1a	**6c**	**7ac** (56%)	**8ac** (92%)	R^5 = Me, **8acm** (92%) R^5 = vinyl, **8acv** (85%)
1a	**6d**	**7ad** (53%)	**8ad** (83%)	(-----)[f]
1a	**6e**	**7ae** (58%)	**8ae** (94%)	R^5 = Me, **8aem** (85%) R^5 = vinyl, **8aev** (89%)
1a	**6f**	**7af** (52%)	**8af** (92%)	**8afm** (90%)
1a	**6g**	**7ag** (50%)	**8ag** (90%)	(-----)[f]
1b	**6b**	**7bb** (54%)	**8bb** (91%)	(-----)[f]

Table 4 (*continued*)

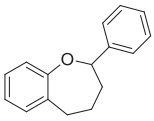
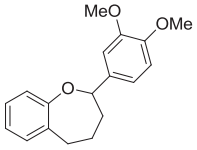
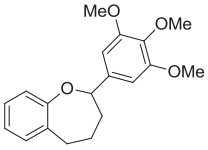
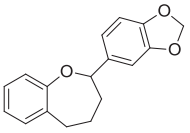
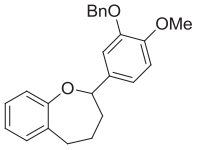
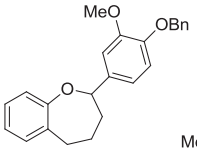
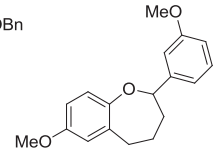
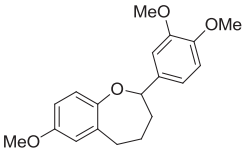
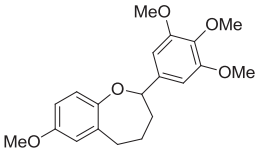
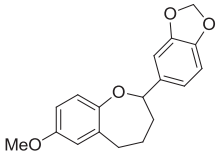
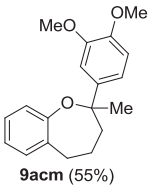
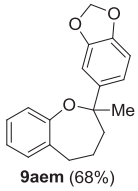
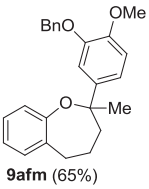
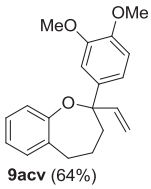
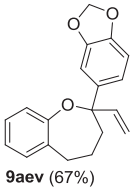
 **1b**	 **6c**	 **7bc** (52%)	 **8bc** (90%)	(-----)[f]
 **1b**	 **6d**	 **7bd** (58%)	 **8bd** (80%)	(-----)[f]
 **1b**	 **6e**	 **7be** (46%)	 **8be** (84%)	(-----)[f]

[a] Isolated yields of chromatographically pure products. [b] For compounds **7aa–be**, **8aa–be** the first letter refers to the 1-bromo-2-iodobenzenes part **1a–b** whereas the second letter indicates the aromatic ring coming from the homo allylic alcohol **6a–g**. [c] For compounds **8aam– afm** the first letter refers to the 1-bromo-2-iodobenzenes part **1a–b**, the second letter indicates the aromatic ring coming from the homo allylic alcohol **6a– g** and the third letter comes from the organic part of either Grignard or allylzinc bromide reagents. [d] In case of Grignard reagents; methyl/ethyl/vinyl Grignard reagents were used (i.e. R^5 = methyl or vinyl). [e] Homoallylic alcohols (**6a–g**) were prepared using sonochemically accelerated Barbier reaction conditions with in-situ generated allylzinc bromide. [f] These compounds have not been prepared.

Table 5
Synthesis of various benzoxepines **9** from alcohols **8**



8 **9**

 **9aa** (92%)	 **9ac** (57%)	 **9ad** (72%)	 **9ae** (71%)	 **9af** (68%)
 **9ag** (62%)	 **9bb** (72%)	 **9bc** (74%)	 **9bd** (80%)	 **9be** (62%)
 **9acm** (55%)	 **9aem** (68%)	 **9afm** (65%)	 **9acv** (64%)	 **9aev** (67%)

[a] Isolated yields of chromatographically pure products.

alkylmagnesium halide (2.72–3.44 mmol) [alkylmagnesium halide was prepared from magnesium (65.3–82.6 mg, 2.72–3.44 mmol), alkylhalide (5.44–6.88 mmol), and a catalytic amount of iodine in 8 mL of dry ether]. The reaction mixture was stirred at −10 °C for 4 h. Progress of the reaction was monitored by TLC. It was then quenched with saturated aqueous NH_4Cl solution and extracted with ethyl acetate (3×15 mL). The ethyl acetate extract was washed with saturated NaCl solution, dried over Na_2SO_4, and filtered. Evaporation of the solvent and purification of the residue over a silica gel column using petroleum ether/ethyl acetate as eluent furnished the tertiary alcohol **8** (70–92%).

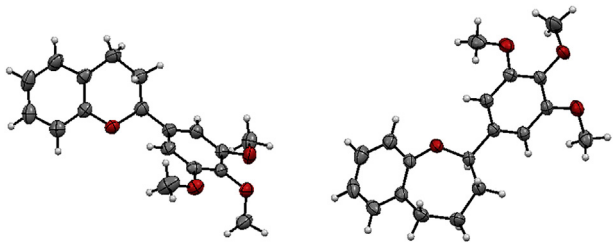


Fig. 2. X-ray crystal structures of **5ac** and **9ad**. Thermal ellipsoids are drawn at 50% probability level.

4.5. General procedure 4 (GP-4): for Barbier reaction on ketones (3)

The allyl bromide (653–574 mg/0.5–0.4 mL, 5.4–4.7 mmol) in THF (1 mL) was added drop wise to a sonicated suspension of zinc dust (235.6–206.7 mg, 3.60–3.16 mmol) in THF (2 mL) at room temperature and the mixture was further sonicated for 30 min, then ketone **3** (300 mg, 0.90–0.79 mmol) in THF (3 mL) was added and continued sonication at room temperature for 3 h. Progress of the reaction was monitored by TLC. The reaction mixture was quenched by addition of aqueous NH_4Cl solution and extracted with ethyl acetate (3×15 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography (petroleum ether/ethyl acetate) as furnished homoallylic alcohol **8** (71–86%).

4.6. General procedure 5 (GP-5): synthesis of flavans (5) and benzoxepines (9)

In an oven dried Schlenk tube under nitrogen atmosphere, were added alcohol **8** (100 mg, 0.22–0.33 mmol), CuI (8.3–12.5 mg, 20 mol %), 2,2′-bipyridine (9.9–6.6 mg, 20 mol %), KO^{t}Bu (111.08–74.06 mg, 0.99–0.66 mmol), and followed by the addition of dry DMF (3 mL). The resulted reaction mixture was stirred at 120 °C for 24 h. Progress of the reaction was monitored by TLC until the reaction is completed. The reaction mixture was quenched by addition of aqueous NH_4Cl solution and extracted with ethyl acetate (3×10 mL). The collected organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue on a silica gel column chromatography using petroleum ether/ethyl acetate as eluent furnished the flavan **5** (50–85%)/benzoxepine **9** (55–92%).

The success of the reaction was achieved by pre-drying the alcohol over silica gel and subjected to high vacuo at 40 °C for 1 h. The required amount of KO^{t}Bu was taken in a round bottom flask and was heated to 100 °C under vacuum for 2 h. The Schlenk was brought to room temperature and immediately weighed. Under nitrogen atmosphere, CuI, 2,2′-bipyridine and KO^{t}Bu were added in succession followed by the addition of dry DMF.

4.7. 4-(2-Bromophenyl)-1-phenylbutan-1-one (7aa)

GP-1 was carried out with allylic alcohol **6a** (500.0 mg, 3.37 mmol), aryl halide **1a** (4.05 mmol), $Pd(OAc)_2$ (22.7 mg, 3 mol %), triethylamine (682.79 mg, 6.75 mmol), and dry acetonitrile (4 mL) at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5–92:8) furnished the ketone **7aa** (541 mg, 53%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate, 90:10), R_f(**6a**)=0.35, R_f(**7aa**)=0.60, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=2923, 2852, 1683, 1597, 1470, 1448, 1367, 1224, 1022, 748, 689 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.94 (d, 2H, J=7.3 Hz, ArH), 7.60–7.50 (m, 2H, ArH), 7.45 (dd, 2H, J=7.8 and 7.3 Hz, ArH), 7.30–7.17 (m, 2H, ArH), 7.05 (ddd, 1H, J=8.3, 8.3, and 2.4 Hz, ArH), 3.03 (t, 2H, J=7.3 Hz, $ArCOCH_2$), 2.85 (t, 2H, J=7.8 Hz, $ArCOCH_2CH_2CH_2$), 2.20–1.95 (m, 2H, $ArCOCH_2CH_2CH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=199.9 (s, ArCO), 141.0 (s, ArC), 137.0 (s, ArC), 132.9 (d, ArCH), 132.8 (d, ArCH), 130.4 (d, ArCH), 128.6 (d, 2C, ArCH), 128.0 (d, 2C, ArCH), 127.7 (d, ArCH), 127.5 (d, ArCH), 124.5 (s, ArC), 37.7 (t, $ArCOCH_2$), 35.3 (t, $ArCOCH_2CH_2CH_2$), 24.3 (t, $ArCOCH_2CH_2CH_2$) ppm. HRMS (APCI+) m/z calculated for $[C_{16}H_{16}BrO]^+$=$[M+H]^+$: 303.0379; found: 303.0375.

4.8. 1-(1,3-Benzodioxol-5-yl)-4-(2-bromophenyl)butan-1-one (7ae)

GP-1 was carried out with allylic alcohol **6e** (500.0 mg, 2.60 mmol), aryl halide **1a** (3.12 mmol), $Pd(OAc)_2$ (19.1 mg, 3 mol %), triethylamine (525.8 mg, 5.20 mmol), and dry acetonitrile (4 mL) at 80 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 94:06–92:08) furnished the ketone **7ae** (525 mg, 58%) as yellow color semi-solid. [TLC control (petroleum ether/ethyl acetate, 85:15), R_f(**6e**)=0.30, R_f(**7ae**)=0.60, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=2899, 1674, 1604, 1502, 1486, 1438, 1357, 1245, 1106, 1035, 933, 806, 749 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.53 (dd, 1H, J=8.2 and 1.6 Hz, ArH), 7.52 (d, 1H, J=7.8 Hz, ArH), 7.41 (d, 1H, J=1.5 Hz, ArH), 7.23 (s, 1H, ArH), 7.22 (d, 1H, J=2.4 Hz, ArH), 7.10–7.00 (m, 1H, Ar–H), 6.82 (d, 1H, J=8.2 Hz, ArH), 6.02 (s, 2H, OCH_2O), 2.94 (t, 2H, J=7.3 Hz, $ArCOCH_2$), 2.82 (t, 2H, J=7.5 Hz, $ArCOCH_2CH_2CH_2$), 2.13–1.98 (m, 2H, $ArCOCH_2CH_2CH_2$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=197.9 (s, ArCO), 151.6 (s, ArC), 148.1 (s, ArC), 141.0 (s, ArC), 132.8 (d, ArCH), 131.8 (s, ArC), 130.4 (d, ArCH), 127.7 (d, ArCH), 127.4 (d, ArCH), 124.5 (s, ArC), 124.2 (d, ArCH), 107.9 (d, ArCH), 107.8 (d, ArCH), 101.8 (t, OCH_2O), 37.5 (t, $ArCOCH_2$), 35.3 (t, $ArCOCH_2CH_2CH_2$), 24.5 (t, $ArCOCH_2CH_2CH_2$) ppm. HRMS (APCI+) m/z calculated for $[C_{17}H_{16}BrO_3]^+$=$[M+H]^+$: 347.0277; found: 347.0273.

4.9. 4-(2-Bromophenyl)-2-(3,4-dimethoxyphenyl)butan-2-ol (4abm)

GP-3 was carried out with ketone **3ab** (300.0 mg, 0.86 mmol), methylmagnesium iodide (3.44 mmol), and diethyl ether (10 mL) for Grignard reaction at −10 °C for 4 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10–80:20) furnished the alcohol **4abm** (219 mg, 70%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate, 85:15), R_f(**3ab**)=0.50, R_f(**4abm**)=0.35, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=3507, 2962, 2934, 2835, 1591, 1510, 1463, 1440, 1409, 1372, 1325, 1255, 1167, 1138, 1023, 967, 922, 869, 853, 751, 733, 673, 611 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.47 (dd, 1H, J=7.8 and 1.0 Hz, ArH), 7.18 (ddd, 1H, J=7.3, 7.3, and 1.0 Hz, ArH), 7.13 (dd, 1H, J=7.3 and 2.0 Hz, ArH), 7.07 (d, 1H, J=2.0 Hz, ArH), 7.05–6.95 (m, 2H, ArH), 6.85 (d, 1H, J=8.3 Hz, ArH), 3.91 (s, 3H, $ArOCH_3$), 3.88 (s, 3H, $ArOCH_3$), 2.80–2.65 (m, 1H, $ArCH_aH_b$), 2.64–2.48 (m, 1H, $ArCH_aH_b$), 2.20–1.95 [m, 2H, ArC(OH)CH_2], 1.78 (br s, 1H, OH), 1.62 [s, 3H, ArC(OH)CH_3] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=148.7 (s, ArC), 147.7 (s, ArC), 141.6 (s, ArC), 140.1 (s, ArC), 132.7 (d, ArCH), 130.3 (d, ArCH), 127.5 (d, ArCH), 127.4 (d, ArCH), 124.3 (s, ArC), 116.9 (d, ArCH), 110.7 (d, ArCH), 108.6 (d, ArCH), 74.4 [s, ArC(OH)CH_3], 56.0 (q, $ArOCH_3$), 55.9 (q, $ArOCH_3$), 44.3 (t, $ArCH_2$), 31.2 [t, ArC(OH)CH_2], 30.4 [q, ArC(OH)CH_3] ppm. HRMS (APCI+) m/z calculated for $[C_{18}H_{20}BrO_2]^+$=$[(M+H)-H_2O]^+$: 347.0641; found: 347.0638.

4.10. 1-(2-Bromophenyl)-3-(3,4-dimethoxyphenyl)pentan-3-ol (4abe)

GP-3 was carried out with ketone **3ab** (300.0 mg, 0.86 mmol), ethylmagnesium bromide (3.44 mmol), and diethyl ether (10 mL)

for Grignard reaction at −10 °C for 4 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10–85:15) furnished the alcohol **4abe** (243 mg, 75%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate, 85:15), R_f(**3ab**)=0.50, R_f(**4abe**)=0.40, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=3518, 2962, 2933, 2834, 1590, 1510, 1463, 1440, 1254, 1235, 1135, 1025, 752 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.47 (dd, 1H, J=7.8 and 1.0 Hz, ArH), 7.17 (ddd, 1H, J=7.8, 7.3, and 1.0 Hz, ArH), 7.12 (dd, 1H, J=7.8 and 2.0 Hz, ArH), 7.02 (ddd, 1H, J=7.8, 7.3, and 2.0 Hz, ArH), 7.01 (d, 1H, J=2.0 Hz, ArH), 6.94 (dd, 1H, J=8.3 and 2.0 Hz, ArH), 6.85 (d, 1H, J=8.3 Hz, ArH), 3.90 (s, 3H, $ArOCH_3$), 3.88 (s, 3H, $ArOCH_3$), 2.74 [dt, 1H, J=12.7 and 4.9 Hz, ArC(OH)CH_aH$_b$(Et)CH_2], 2.49 [dt, 1H, J=11.7 and 4.9 Hz, ArC(OH)CH_2(Et)CH_aH$_b$], 2.20–1.96 [m, 2H, ArC(OH)C$H_a$$H_b$(-C$H_aH_b$$CH_3$)$CH_2$], 1.95–1.78 [m, 2H, ArC(OH)CH_2($CH_a$$H_b$$CH_3$)C$H_a$$H_b$], 1.73 (br s, 1H, OH), 0.79 [t, 3H, J=7.3 Hz, ArC(OH)(CH_2CH_3)CH_2] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=148.6 (s, ArC), 147.5 (s, ArC), 141.8 (s, ArC), 138.0 (s, ArC), 132.7 (d, ArCH), 130.4 (d, ArCH), 127.5 (d, 2C, ArCH), 124.3 (s, ArC), 117.6 (d, ArCH), 110.7 (d, ArCH), 109.1 (d, ArCH), 76.9 [s, ArC(OH)], 55.9 (q, $ArOCH_3$), 55.8 (q, $ArOCH_3$), 42.8 (t, $ArCH_2$), 35.7 (t, $ArCH_2CH_2$), 30.8 [t, ArC(C$H_2$$CH_3$)OH], 7.8 [q, ArC($CH_2CH_3$)OH] ppm. HRMS (APCI+) m/z calculated for $[C_{19}H_{22}BrO_2]^+$=[(M+H)−H_2O]$^+$: 361.0803; found: 361.0809.

4.11. 4-(2-Bromophenyl)-1-phenylbutan-1-ol (8aa)

GP-2 was carried out with ketone **7aa** (300.0 mg, 0.99 mmol), $NaBH_4$ (73.3 mg, 1.98 mmol), and methanol (10 mL) for reduction at 0 °C to room temperature for 2 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5–90:10) furnished the alcohol **8aa** (253 mg, 84%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate, 95:5), R_f(**7aa**)=0.65, R_f(**8aa**)=0.35, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=3358, 3061, 3029, 2924, 2855, 1493, 1470, 1454, 1439, 1286, 1061, 1021, 981, 749 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.50 (d, 1H, J=7.8 Hz, ArH), 7.40–7.10 (m, 7H, ArH), 7.03 (ddd, 1H, J=8.8, 8.3, and 2.4 Hz, ArH), 4.70 [dd, 1H, J=6.4 and 5.9 Hz, ArCH(OH)], 2.75 (t, 2H, J=7.3 Hz, $ArCH_2$), 2.05–1.45 [m, 5H, ArCH(OH)CH_2CH_2] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=144.6 (s, ArC), 141.5 (s, ArC), 132.7 (d, ArCH), 130.3 (d, ArCH), 128.5 (d, 2C, ArCH), 127.6 (d, ArCH), 127.5 (d, ArCH), 127.3 (d, ArCH), 125.9 (d, 2C, ArCH), 124.4 (s, ArC), 74.4 [d, ArCH(OH)], 38.5 (t, $ArCH_2$), 35.9 [t, ArCH(OH)C$H_2$$CH_2$], 26.1 [t, ArCH(OH)$CH_2CH_2$] ppm. HRMS (APCI+) m/z calculated for $[C_{16}H_{19}BrN]^+$=[(M+NH_4)−H_2O]$^+$: 304.0695; found: 304.0681.

4.12. 2-(1,3-Benzodioxol-5-yl)-5-(2-bromophenyl)pentan-2-ol (8aem)

GP-3 was carried out with ketone **7ae** (300.0 mg, 0.86 mmol), methylmagnesium iodide (3.44 mmol), and diethyl ether (10 mL) for Grignard reaction at −10 °C for 4 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 85:15–75:25) furnished the alcohol **8aem** (266 mg, 85%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate, 80:20), R_f(**7ae**)=0.60, R_f(**8aem**)=0.45, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=3428, 2923, 1502, 1487, 1236, 1095, 1038, 937, 921, 813, 751, 728, 670 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.48 (dd, 1H, J=7.8 and 1.0 Hz, ArH), 7.18 (ddd, 1H, J=7.8, 7.8, and 1.0 Hz, ArH), 7.14 (dd, 1H, J=7.8 and 2.0 Hz, ArH), 7.01 (ddd, 1H, J=7.8, 7.8, and 2.0 Hz, ArH), 6.92 (d, 1H, J=2.0 Hz, ArH), 6.85 (dd, 1H, J=8.3 and 2.0 Hz, ArH), 6.74 (d, 1H, J=8.3 Hz, ArH), 5.93 (s, 2H, OCH_2O), 2.67 (t, 2H, J=7.8 Hz, $ArCH_2$), 2.00–1.53 [m, 5H, ArC(OH)CH_2CH_2], 1.51 [s, 3H, ArCCH_3(OH)] ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=147.5 (s, ArC), 146.0 (s, ArC), 142.0 (s, ArC), 141.4 (s, ArC), 132.7 (d, ArCH), 130.2 (d, ArCH), 127.5 (d, ArCH), 127.3 (d, ArCH), 124.4 (s, ArC), 117.8 (d, ArCH), 107.7 (d, ArCH), 105.9 (d, ArCH), 100.9 (t, OCH_2O), 74.5 [s, ArC(CH_3)OH], 43.7 (t, $ArCH_2$), 36.2 [t, $ArCCH_3$(OH)C$H_2$$CH_2$], 30.3 [q, ArC(C$H_3$)OH], 24.3 [t, $ArCCH_3$(OH)CH_2CH_2] ppm. HRMS (APCI+) m/z calculated for $[C_{18}H_{18}BrO_2]^+$=[(M+H)−H_2O]$^+$: 345.0485; found: 345.0484.

4.13. 2-(3,4-Dimethoxyphenyl)-2-methylchromane (5abm)

GP-5 was carried out with alcohol **4abm** (100 mg, 0.27 mmol), CuI (10.4 mg, 20 mol %), 2,2′-bipyridine (8.4 mg, 20 mol %), KO^{t}Bu (90.8 mg, 0.81 mmol), and DMF (3 mL) at 120 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 90:10–85:15) furnished the flavan **5abm** (63 mg, 82%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate, 85:15), R_f(**4abm**)=0.30, R_f(**5abm**)=0.70, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=2929, 2834, 1607, 1582, 1512, 1488, 1454, 1372, 1265, 1225, 1179, 1115, 1081, 976, 946, 811, 754 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.12 (ddd, 1H, J=8.8, 8.3, and 1.5 Hz, ArH), 6.97 (dd, 1H, J=8.3 and 1.5 Hz, ArH), 7.00–6.90 (m, 1H, ArH), 6.93 (d, 1H, J=1.9 Hz, ArH), 6.89 (dd, 1H, J=8.8 and 1.9 Hz, ArH), 6.81 (ddd, 1H, J=7.3, 7.3, and 1.5 Hz, ArH), 6.79 (d, 1H, J=8.8 Hz, ArH), 3.83 (s, 3H, $ArOCH_3$), 3.81 (s, 3H, $ArOCH_3$), 2.67 (td, 1H, J=16.1 and 5.4 Hz, $ArCH_a$$H_b$$CH_2$), 2.56–2.44 (m, 1H, $ArCH_a$$H_b$$CH_2$), 2.34 (td, 1H, J=16.1 and 5.4 Hz, $ArCH_a$$H_b$$CH_2$), 2.13–2.01 (m, 1H, $ArCH_2CH_2$), 1.64 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=154.1 (s, ArC), 148.6 (s, ArC), 147.6 (s, ArC), 138.2 (s, ArC), 129.3 (d, ArCH), 127.3 (d, ArCH), 121.6 (s, ArC), 119.9 (d, ArCH), 117.0 (d, ArCH), 116.8 (d, ArCH), 110.9 (d, ArCH), 108.6 (d, ArCH), 78.0 (s, ArOCMe), 55.8 (q, $ArOCH_3$), 55.7 (q, $ArOCH_3$), 32.9 (t, $ArOCH_2CH_2$), 30.0 (q, CH_3), 22.6 (t, $ArOCH_2CH_2$) ppm. HRMS (APCI+) m/z calculated for $[C_{18}H_{21}O_3]^+$=[M+H]$^+$: 285.1485; found: 285.1480.

4.14. 2-(3,4-Dimethoxyphenyl)-2-ethylchromane (5abe)

GP-5 was carried out with alcohol **4abe** (100 mg, 0.26 mmol), CuI (10.1 mg, 20 mol %), 2,2′-bipyridine (8.1 mg, 20 mol %), KO^{t}Bu (87.5 mg, 0.78 mmol), and DMF (3 mL) at 120 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5–90:10) furnished the flavan **5abe** (58 mg, 75%) as pale yellow viscous liquid. [TLC control (petroleum ether/ethyl acetate, 85:15), R_f(**4abe**)=0.35, R_f(**5abe**)=0.70, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=2933, 2834, 1606, 1582, 1511, 1488, 1454, 1346, 1258, 1216, 1179, 1166, 1096, 983, 888, 807, 751, 666 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.11 (ddd, 1H, J=8.8, 7.8, and 1.5 Hz, ArH), 6.96 (d, 1H, J=8.8 Hz, ArH), 6.92 (d, 1H, J=7.8 Hz, ArH), 6.86 (d, 1H, J=2.0 Hz, ArH), 6.83 (dd, 1H, J=8.3 and 2.4 Hz, ArH), 6.79 (d, 1H, J=7.8 and 1.5 Hz, ArH), 6.77 (d, 1H, J=8.3 Hz, ArH), 3.83 (s, 3H, $ArOCH_3$), 3.78 (s, 3H, $ArOCH_3$), 2.61 (td, 1H, J=15.6 and 4.9 Hz, $ArCH_a$$H_b$$CH_2$), 2.55–2.40 (m, 1H, $ArCH_a$$H_b$$CH_2$), 2.36–2.25 (m, 1H, $ArCH_2CH_2$), 2.15–2.03 (m, 1H, $ArCH_2CH_2$), 2.01–1.82 (m, 2H, CH_2CH_3), 0.86 (t, 3H, J=7.3 Hz, CH_2CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=154.2 (s, ArC), 148.6 (s, ArC), 147.5 (s, ArC), 136.4 (s, ArC), 129.3 (d, ArCH), 127.2 (d, ArCH), 122.1 (s, ArC), 119.8 (d, ArCH), 117.8 (d, ArCH), 116.8 (d, ArCH), 110.9 (d, ArCH), 109.4 (d, ArCH), 80.5 (s, ArOCEt), 55.8 (q, 2C, 2×$ArOCH_3$), 35.7 (t, $ArCH_2CH_2$), 30.9 (t, $ArCH_2CH_2$), 22.4 (t, CH_2CH_3), 7.7 (q, CH_2CH_3) ppm. HRMS (APCI+) m/z calculated for $[C_{19}H_{23}O_3]^+$=[M+H]$^+$: 299.1642; found: 299.1643.

4.15. 2-Phenyl-2,3,4,5-tetrahydro-1-benzoxepine (9aa)

GP-5 was carried out with alcohol **8aa** (100 mg, 0.32 mmol), CuI (12.5 mg, 20 mol %), 2,2′-bipyridine (9.9 mg, 20 mol %), KO^{t}Bu (107.7 mg, 0.96 mmol), and DMF (3 mL) at 120 °C for 24 h. Purification of the crude material by silica gel column chromatography

(petroleum ether/ethyl acetate, 95:5–90:10) furnished the benzoxepine **9aa** (68 mg, 92%) as colorless viscous liquid. [TLC control (petroleum ether/ethyl acetate, 90:10), R_f(**8aa**)=0.35, R_f(**9aa**)=0.80, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=2924, 2852, 1602, 1579, 1487, 1452, 1352, 1288, 1230, 1076, 1023, 953, 932, 888, 827, 757, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.47 (d, 2H, J=7.3 Hz, ArH), 7.40 (dd, 2H, J=7.8 and 7.3 Hz, ArH), 7.32 (t, 1H, J=7.8 Hz, ArH), 7.18 (d, 1H, J=7.8 Hz, ArH), 7.14 (dd, 1H, J=8.3 and 2.0 Hz, ArH), 7.04 (d, 1H, J=8.3 Hz, ArH), 7.01 (dd, 1H, J=7.3 and 1.5 Hz, ArH), 4.61 (dd, 1H, J=9.8 and 3.4 Hz, ArC*H*CH_2CH_2), 3.04 (t, 1H, J=12.7 Hz, ArC$H_aH_bCH_2$), 2.80 (dd, 1H, J=14.2 and 6.3 Hz, Ar$CH_aH_bCH_2$), 2.30–2.02 (m, 3H, Ar$CH_2CH_2CH_aH_b$), 1.77–1.58 (m, 1H, Ar$CH_2CH_2CH_aH_b$) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=159.5 (s, ArC), 143.5 (s, ArC), 136.0 (s, ArC), 130.1 (d, ArCH), 128.3 (d, 2C, ArCH), 127.4 (d, ArCH), 127.3 (d, ArCH), 125.8 (d, 2C, ArCH), 123.7 (d, ArCH), 121.7 (d, ArCH), 85.0 (d, Ar*C*HCH_2CH_2), 39.6 (t, Ar$CH_2CH_2CH_2$), 33.8 (t, Ar$CH_2CH_2CH_2$), 26.3 (t, Ar$CHCH_2CH_2CH_2$) ppm. HRMS (APCI+) m/z calculated for $[C_{16}H_{17}O]^+$=$[M+H]^+$: 225.1274; found: 225.1274.

4.16. 2-(1,3-Benzodioxol-5-yl)-2-methyl-2,3,4,5-tetrahydro-1-benzoxepine (9aem)

GP-5 was carried out with alcohol **8aem** (100 mg, 0.27 mmol), CuI (10.5 mg, 20 mol %), 2,2′-bipyridine (8.4 mg, 20 mol %), KO^{t}Bu (91 mg, 0.81 mmol), and DMF (3 mL) at 120 °C for 24 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 95:5–90:10) furnished the benzoxepine **9aem** (52 mg, 68%) as pale yellow solid, recrystallized the solid with dichloromethane/hexane, mp 50–54 °C. [TLC control (petroleum ether/ethyl acetate, 90:10), R_f(**8aem**)=0.30, R_f(**9aem**)=0.75, UV detection]. IR (MIR–ATR, 4000–600 cm^{-1}): ν_{max}=2923, 2853, 1503, 1487, 1434, 1373, 1284, 1250, 1230, 1105, 1083, 1039, 940, 888, 767, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz): δ=7.18 (s, 1H, ArH), 7.13 (dd, 2H, J=8.8 and 7.3 Hz, ArH), 7.05 (dd, 1H, J=8.3 and 2.0 Hz, ArH), 7.02 (d, 1H, J=7.3 Hz, ArH), 6.98 (d, 1H, J=7.8 Hz, ArH), 6.82 (d, 1H, J=8.3 Hz, ArH), 5.96 (s, 2H, OCH_2O), 3.02–2.87 (m, 1H, ArCHC*H*$_2CH_2$), 2.64 (td, 1H, J=14.2 and 4.9 Hz, ArCHC*H*$_2CH_2$), 2.03 (t, 2H, J=6.4 Hz, Ar$CH_2CH_2CH_2$), 1.93–1.55 (m, 2H, Ar$CH_2CH_2CH_2$), 1.39 (s, 3H, CH_3) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ=154.8 (s, ArC), 147.4 (s, ArC), 146.0 (s, ArC), 142.1 (s, ArC), 135.7 (s, ArC), 129.3 (d, ArCH), 127.1 (d, ArCH), 123.7 (d, ArCH), 123.4 (d, ArCH), 118.0 (d, ArCH), 107.8 (d, ArCH), 106.3 (d, ArCH), 100.9 (t, OCH_2O), 80.8 (d, Ar*O*CCH_3), 40.7 (t, Ar$CHCH_2CH_2CH_2$), 32.0 (t, Ar$CH_2CH_2CH_2$), 27.0 (q, CH_3), 21.4 (t, Ar$CH_2CH_2CH_2$) ppm. HRMS (APCI+) m/z calculated for $[C_{18}H_{18}NaO_3]^+$=$[M+Na]^+$: 305.1148; found: 305.1143.

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Supplementary data

Copies of ^1H and ^{13}C NMR spectra related to this article can be found. Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2013.05.046.

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