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An efficient intermolecular [Pd]-catalyzed C–C and intramolecular [Cu]-catalyzed C–O bonds formation: synthesis of functionalized flavans and benzoxepine

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ABSTRACT

An efficient three-step strategy for the synthesis of functionalized flavans, starting from readily available 2-bromoiodobenzenes and aryl vinyl alcohols, is presented and successfully extended to benzoxepine. An intermolecular [Pd]-catalyzed C–C and an intramolecular [Cu]-catalyzed C–O bond formations have been employed as key transformations of the strategy.

Flavan is a ubiquitous 2-aryl-chroman structural unit present in a number of flavonoid natural products, which exhibit interesting biological and pharmacological activities.[1] Many members of this family show interesting biological activity; for example morusyunnansin E (**1**) showed potent inhibitory effects on mushroom tyrosinase,[2] 4′,6-dichloroflavan (BW683C; **2**) inhibits rhinovirus replication in vitro,[3] 7-hydroxy-3′,4′-methylenedioxyflavan (**3**) has been traditionally used for the treatment of diabetes, ear and chest ailments, and some viral infections,[4] whereas, 4′-hydroxy-7-methoxy flavan (**4**) is known as one of the anti-feedant compounds in *Lycoris raliata*[5] (Fig. 1).

Because of their unique structural features and interesting biological activities, flavans have drawn attention from many synthetic chemists. Therefore, reasonably a good number of synthetic strategies have been reported for the synthesis of flavan core structure (various chromans).[6–10] Recently, transition metal promoted intramolecular [Pd][11] as well as [Cu][12]-catalyzed C–O bond forming reactions between aryl halide and alcohol tether have also been developed for the synthesis of various chromans. In continuation of our interest on palladium-catalysis,[13] recently we disclosed an efficient and highly regio- and stereoselective [Pd]-catalyzed β-arylation method for the formation of β-arylallylic alcohols, which is unexpected under conventional Jeffery's conditions without the assistance of silver salt. It was believed that the size of the substituent present at the *ortho*-position of the aromatic ring of the allylic alcohol is crucial for controlled formation of the allylic alcohol product, rather producing the expected chalcone product.[13b] As a result of consecutive developments for the synthesis of chalocones and their extensions, herein, we report a new efficient synthetic route for functionalized flavans (2-aryl and 2-arylmethyl substituted chromans) and a benzoxepine using two transition metals

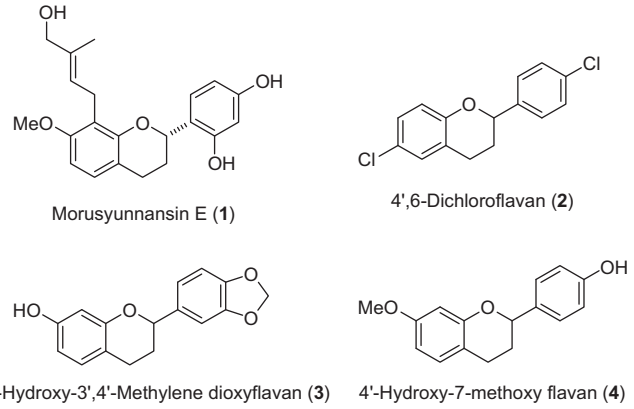

Figure 1. Representative examples of naturally occurring flavonoid natural products with flavan (2-aryl chroman) core structure.

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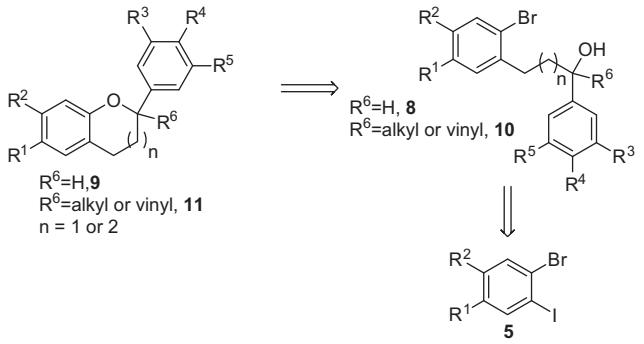
[Pd] and [Cu]-catalyzed individual reactions as the key transformations. During the preparation of our manuscript, a closely related approach was described by Wang and Franzén[12e] However, our strategic approach to the precursors for key cyclization, is different from Franzén approach and studied extensively with more number of examples (14 examples) bearing simple to electron rich functionalities on both aromatic moieties. Most significantly, the present strategy is amenable for the synthesis of benzoxepine.

Our approach for the synthesis of substituted flavans **9** and **11** is based on a key intramolecular [Cu]-catalyzed C–O bond formation between aryl bromide and tethered alcohol moieties of secondary and tertiary alcohols **8** and **10**, respectively. The required precursors (secondary and tertiary alcohols) **8** and **10** can be obtained from 2-bromoiodbenzenes **5**, using a key intermolecular [Pd]-catalyzed C–C bond formation with allylic alcohol coupling partners **6** and followed by reduction and Grignard addition protocol, respectively (Scheme 1).

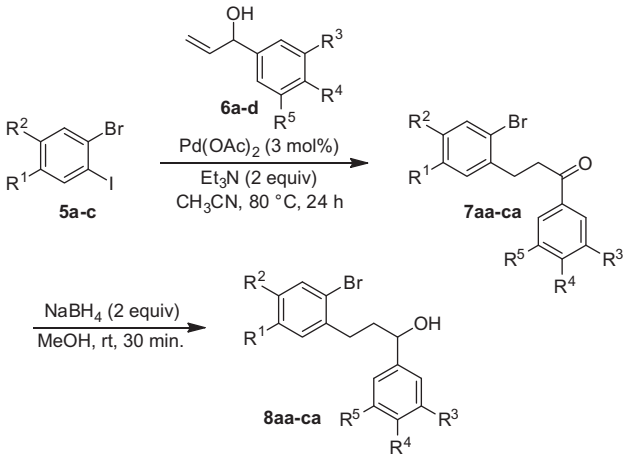
Accordingly, treatment of 2-bromoiodobenzenes **5** with coupling partners allylic alcohols **6** in the presence of a catalyst $Pd(OAc)_2$ (3 mol %) and Et_3N (2 equiv) in hot acetonitrile, led to the dihydrochalcones **7** in very good (64–78%) yields.[14,15] Reduction of dihydrochalcones **7** with $NaBH_4$ in methanol furnished the corresponding secondary alcohols **8** in near quantitative (97–99%) yields (Scheme 2, Table 1).

With the secondary alcohols **8** in hand, initially the key transition metal [Pd]-catalyzed C–O bond formation of the alcohol **8ca** was performed under various conditions and the results are summarized in Table 2. Reaction of the alcohol **8ca** with $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and Cs_2CO_3 (2 equiv) in hot DMF failed to furnish the product **9ca**, rather exclusively furnished ketone **9ca′** (entry 1, Table 2). The formation of ketone **9ca′** can be reasoned via syn-elimination of β-hydrogen-Pd-species due to the availability of β-hydrogen and is in good agreement with that of reported by Buchwald et al.[11a–c] Similarly, other catalytic variants also found to be inferior to produce the cyclic product **9ca** (entries 2 and 4, Table 2). On the other hand, the reaction with the biaryl ligand **L2**, which is known to produce cyclic ethers even with secondary alcohols, produced the product **9ca** in good yield 62% (entry 3, Table 2) along with the minor amount of ketone **9ca′** (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 itself was found to be very efficient in the presence of catalyst CuI (20 mol %)/2,2-bipyridyl (20 mol %), base KO^{t}Bu (3 equiv) in hot DMF (120 °C) for 24 h on secondary alcohol **8ca** and resulted exclusively the cyclized product flavan **9ca**, in good yield (68%). Interestingly, the above conditions proved to be amenable for various electron releasing substituents as well on aromatic ring bearing bromide and furnished the cyclized flavan products **9** in very good yields (Table 3).



Scheme 1. Retrosynthetic plan for flavans **9** and **10** starting from 2-bromoiodobenzenes **5**.



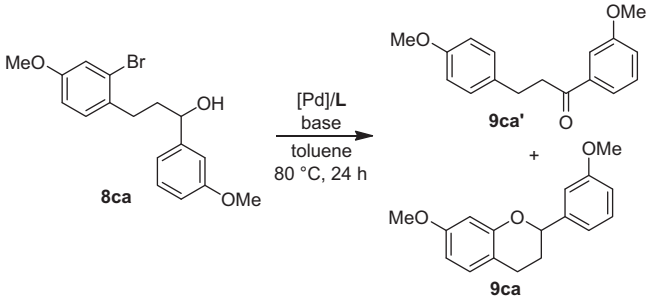
Scheme 2. Synthesis of secondary alcohols **8aa–ca** via ketones **7aa–ca** using 2-bromoiodobenzenes **5a–c**.

Table 1
Synthesis of secondary alcohols **8aa–ca** via ketones **7aa–ca**

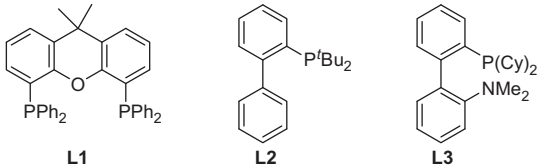
Entry	R^1	R^2	R^3	R^4	R^5	Yield of **7**[a] (%)	Yield of **8**[a] (%)
1	H	H	OMe	H	H	**7aa** 78	**8aa** 99
2	H	H	OMe	OMe	H	***7ab*** *70*	**8ab** 98
3	H	H	OMe	OMe	OMe	**7ac** 69	**8ac** 98
4	H	H	OCH_2–	OCH_2–	H	**7ad** 71	**8ad** 97
5	OMe	H	OMe	H	H	**7ba** 72	**8ba** 97
6	OMe	H	OMe	OMe	H	**7bb** 74	**8bb** 99
7	OMe	H	OMe	OMe	OMe	**7bc** 72	**8bc** 98
8	OMe	H	OCH_2–	OCH_2–	H	**7bd** 75	**8bd** 98
9	H	OMe	OMe	H	H	**7ca** 64	**8ca** 97

[a] Isolated yields of chromatographically pure products; for compounds **7** and **8** the first letter refers to the 2-bromoiodobenzenes part **5a–5c** whereas the second letter indicates the aromatic ring coming from the allylic alcohol **6a–6d**.

Table 2
Attempts of [Pd]-catalyzed intramolecular C–O bond formation on **8ca**

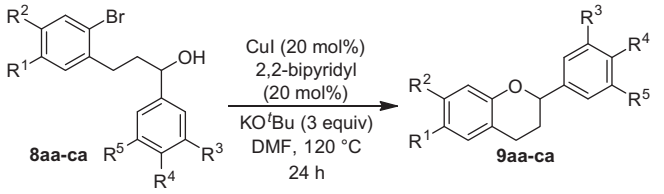


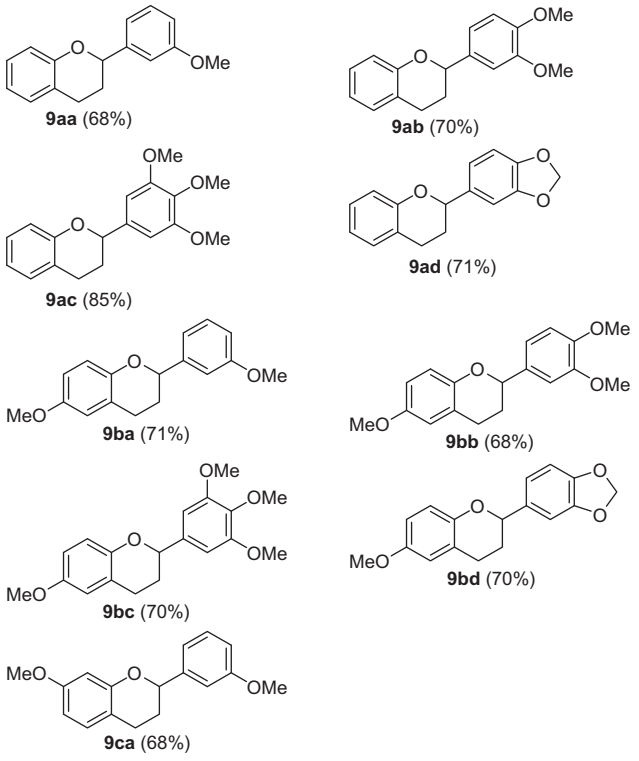
Entry	Catalyst (mol %)	Ligand (mol %)	Base (equiv)	Yield of **9ca**[a] (%)	Yield of **9ca′**[a] (%)
1	$Pd(OAc)_2$ (5)	PPh_3 (10)	Cs_2CO_3 (2)	–	69
2	$Pd(OAc)_2$ (3)	**L1** (6)	Cs_2CO_3 (2)	–	65
3	$Pd(OAc)_2$ (3)	**L2** (6)	Cs_2CO_3 (2)	62	9
4	$Pd_2(dba)_3$ (3)	**L3** (3)	KO^{t}Bu (3)	9	17



[a] Isolated yields of chromatographically pure products.

Table 3
Synthesis of flavans **9aa–ca** from secondary alcohols **8aa–ca**[a]





[a] Isolated yields of chromatographically pure products; for compounds **9** the first letter refers to the 2-bromoiodobenzenes part **5a–5c** whereas the second letter indicates the aromatic ring coming from the allylic alcohol **6a–6d**.

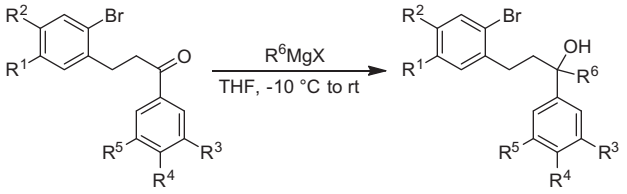
After successful accomplishment of flavans **9aa–ca**, we turned our attention to determine the scope and limitation of the method. Hence, [Cu]-catalysis of tertiary alcohols **10** was also investigated. The required tertiary alcohols **10** were synthesized by the addition of alkyl/alkenyl Grignard reagents to dihydrochalcones **7**, in very good yields (Scheme 3).

In general, the results were fairly comparable to those observed for secondary alcohols **8aa–ca**, and furnished the products **11aam–bdm** possessing simple as well as electron rich aromatic functionality on either of aromatic rings, in good yields (Table 4).

In addition to the NMR spectroscopic confirmation, the structure of one flavan was unambiguously further confirmed by single crystal X-ray diffraction analysis on **9ac** (Fig. 2).

Finally to the check the scope and applicability of the method, we explored the synthesis of 2-aryl-2,3,4,5-tetrahydro-1-benzoxepine (seven-membered cyclic ether). Interestingly, compounds featuring bezoxepines core are also found to be pharmaceutically important as they exhibit interesting biological activities. The requisite coupling partner, homoallylic alcohol **12a** was synthesized by using Barbier reaction under sonochemical acceleration. Unlike the case of allylic alcohols, the Jeffery–Heck coupling on homoallylic alcohol **12a** with 2-bromoidobenzene **5a**, resulted in ketone **13aa** in moderate yield (51%) along with a mixture of other unidentified products. Finally, [Cu]-catalyzed intramolecular C–O bond formation on the secondary alcohol **14aa**, proved to be amenable to the standard conditions and gave the cyclic ether **15aa** in very good yield 78% (Scheme 4).

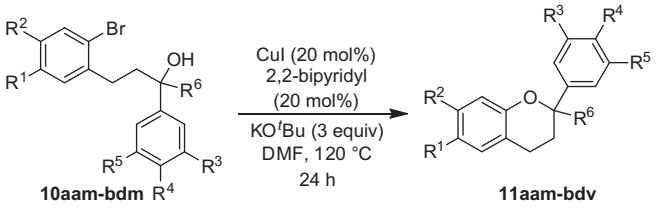
In summary, we have developed an efficient three-step strategy for the synthesis of functionalized flavans and a benzoxepine,

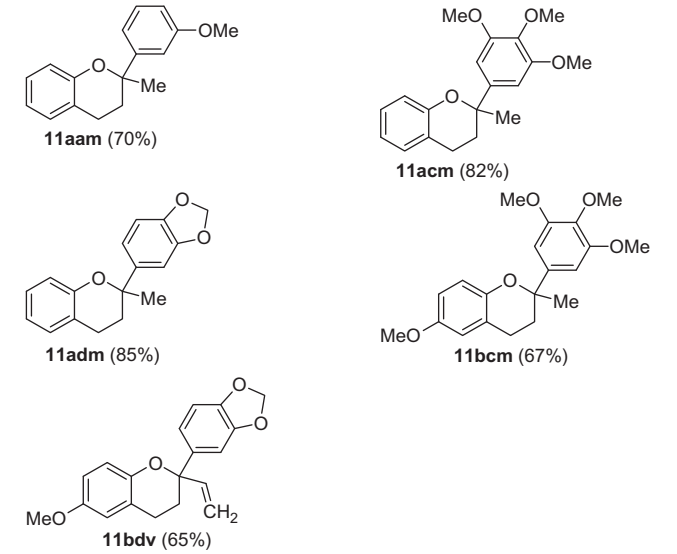


7aa R^1=R^2=R^4=R^5=H, R^3=OMe, R^6=Me, **10aam** (88%)
7ac R^1=R^2=H, R^3=R^4=R^5=OMe, R^6=Me, **10acm** (97%)
7ad R^1=R^2= R^3=H, R^4=R^5=OCH$_2$-, R^6=Me, **10adm** (93%)
7bc R^1=R^3=R^4=R^5=OMe, R^2=H, R^6=Me, **10bcm** (93%)
7bd R^1=OMe, R^2=R^3=H, R^4=R^5=OCH$_2$-, R^6=CH=CH$_2$, **10bdv** (93%)

Scheme 3. Synthesis of tertiary alcohols **10aam–bdv** from dihydrochalcones **7aa–bd**. Isolated yields of chromatographically pure products. Grignard reagents prepared in anhydrous diethyl ether and added to the substrates (ketones) dissolved in anhydrous THF. For compounds **10** the first letter refers to the 2-bromoiodobenzenes part **5a–5c**, second letter indicates the aromatic ring coming from the allylic alcohol **6a–6d**, whereas the third letter indicates sixth substituent that connected to the quaternary center (**m** for R^6 = Me and **v** for R^6 = vinyl).

Table 4
Synthesis of flavans **11aam–bdv** from tertiary alcohols **10aam–bdv**[a]





[a] Isolated yields of chromatographically pure products; For compounds **11** the first letter refers to the 2-bromoiodobenzenes part **5a–5c**, second letter indicates the aromatic ring coming from the allylic alcohol **6a–6d**, whereas the third letter indicates sixth substituent that connected to the quaternary center (**m** for R^6 = Me and **v** for R^6 = vinyl).

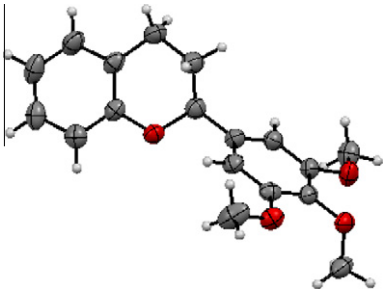
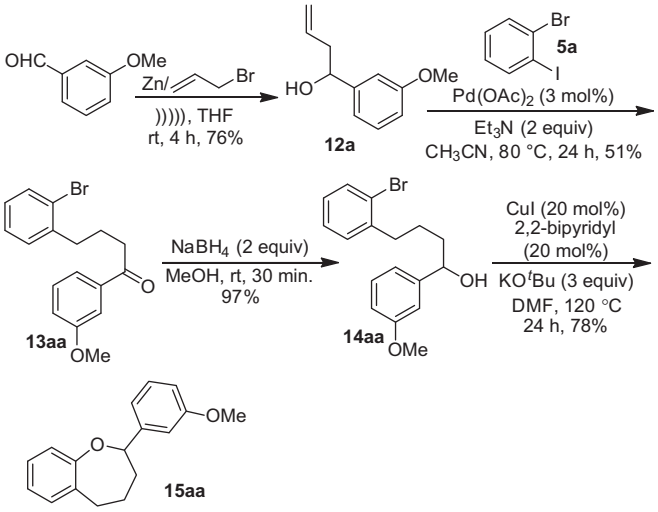


Figure 2. X-ray crystal structure of **9ac**. Thermal ellipsoids are drawn at 50% probability level.



Scheme 4. Synthesis of benzoxepine **15aa** starting from *meta*-anisaldehyde.

employing an intermolecular [Pd]-catalyzed C–C and intramolecular [Cu]-catalyzed C–O bond formations as the key steps. The strategy is efficient and amenable for the synthesis of a number of analogs. Further investigations on the application of the current strategy for other benzoxepine analogs and for the total synthesis of flavonoid natural products are under progress.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.05.050.

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