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Graphical Abstract:

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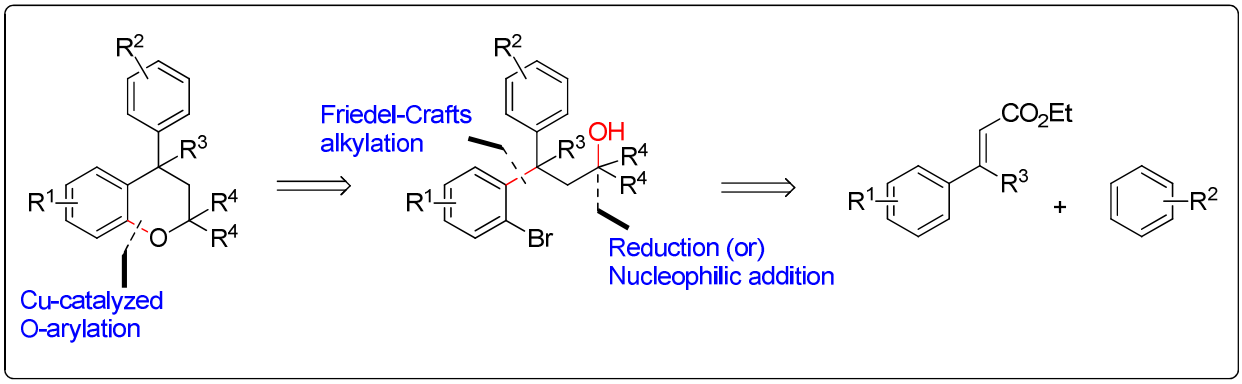
B. Suchand, J. Krishna, K. Mritunjoy and G. Satyanarayana*



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Lewis acid promoted C–C and Copper-catalyzed C–O bonds formation: Synthesis of neoflavans

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Abstract

An intramolecular [Cu]-catalyzed C□O bond formation for the synthesis of neoflavans is presented. Lewis acid promoted Friedel-Crafts Michael addition of electron rich aromatic systems onto the double bond of the cinnamate ester was employed to furnish β-diaryl ester. Electrophilic aromatic bromination of the β-diaryl ester and reduction/Grignard addition furnished the required precursor alcohols. The method is applicable to the synthesis of neoflavans containing tertiary as well as quaternary carbon center. Significantly, the neoflavan substructures are present in biologically active compounds.

Introduction

The neoflavans (4-aryl-3,4-dihydro-2*H*-chromenes) or substituted chromans are ubiquitous substructures present in biologically active natural compounds.[1-3] For example, the plant originated Dalbergia species are used as traditional Chinese medicine for curing inflammation, blood disorders and ischemia.[4] Similarly, the simple neoflavene dalbergichromene, isolated from the stembark of Dalbergia species [5,6] showed medicinal activity. Also, the chroman natural product centchroman exhibits antifertility properties as an estrogen antagonist, which was isolated from the methanolic extracts of A. indicum.[7] In addition, 3-hydroxy-4-arylchroman is also observed as a substructure in the 4-aryl-flavan-3-ol, isolated from the South African plant Nelia meyeri.[8] Further, the flavonoid myristinin A possessing the 4-arylchroman part structure is a potent polymerase beta inhibitor (Figure 1).[9]

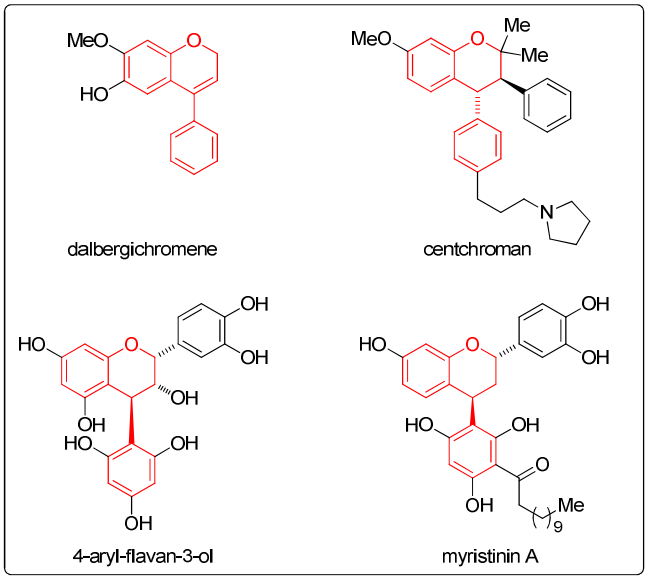

Figure 1. Representative examples of naturally occurring neoflavan natural products containing neoflavan scaffolds

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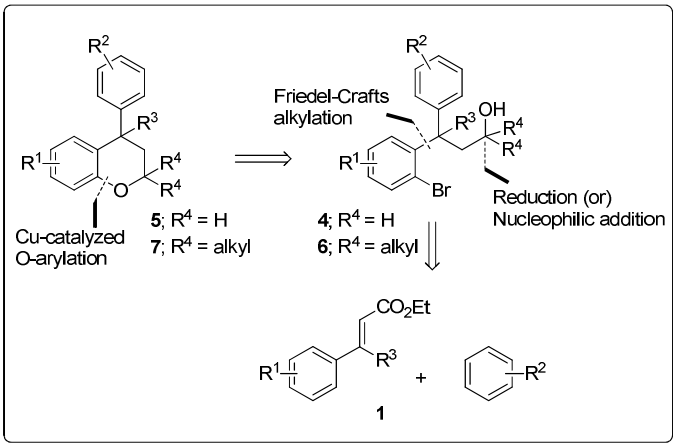
Owing to the interesting structural features and important biological properties of neoflavans/flavenes, there are a number of reports towards their synthesis.[10] Notably, Rui Wang et al., reported enantioselective synthesis of chromanes and dihydrobenzopyranes by employing Friedel-Crafts alkylation and cyclization of 1-naphthol and α,β-unsaturated aldehydes.[10c] Benzopyrans were accomplished by Pettus and co-workers using enantioselective [4 + 2] cycloaddition between *ortho*-quinone methides (*o*-QM) and enol ethers.[10f] The research group of Sames et al., developed new method for the construction of chromene core by means of Pt(IV)-catalyzed intramolecular hydroarylation of arene-alkyne substrates.[10g] The research group of Tunge disclosed a three-step stereoselective reduction as the key step for the synthesis of diarylchromans from phenols and cinnamic acid.[10h] To the best of our knowledge, thus far there is no report on the synthesis of neoflavans possessing quaternary C-4 carbon atom.

In continuation to our research interest on transition metal-catalysis,[11] recently, we have disclosed an efficient three-step strategy for the synthesis of flavans and benzoxepines by employing [Pd]-catalyzed C–C and [Cu]-catalyzed C–O bonds forming reactions as the key steps.[12] Herein, we present a practical method for the synthesis of neoflavans, wherein, Lewis acid ($FeCl_3$) promoted Friedel-Crafts Michael addition and an intramolecular [Cu]-catalyzed Buchwald-Hartwig coupling reactions are the key transformations involved in the strategy.

Results and Discussion

We envisioned that the substituted neoflavans **5** and **7** can be obtained by a key [Cu]-mediated intramolecular Buchwald-Hartwig C–O bond formation between aryl bromide and hydroxy (primary/tertiary) functionality of **4** & **6**. The required primary/tertiary alcohols **4** & **6** were accomplished from the corresponding esters, which were in turn accessed by employing Lewis acid ($FeCl_3$) induced controlled Friedel-Crafts alkylation (Michael addition type) of an electron rich external arene on ethyl cinnamates **1** followed by preferential electrophilic bromination of the electron rich aromatic ring particularly at *ortho*-position to the ester tether (Scheme 1). It is worth mentioning that the controlled Friedel-Crafts alkylation was observed, particularly, by the Lewis acid ($FeCl_3$) in our previous study, which formed the basic foundation for this work.[13]



Scheme 1 Retrosynthetic plan for flavans **5** and **7** from cinnamates **1**.

The synthetic study began with the controlled Friedel-Crafts alkylation (i.e. the reaction impeded after Friedel-Crafts Michael addition without allowing it for subsequent intramolecular acylation) of ethyl cinnamates **1** with electron rich aromatic systems such as 1,2-dimethoxybenzene or 1,2,3-trimethoxybenzene. Thus, treatment of simple as well as *β*-alkyl substituted ethyl cinnamates **1** with the external arene in the presence of Lewis acid ($FeCl_3$ 3 equiv.), at ambient temperature, furnished the *β*-arylated esters **2a**-**2f,** containing tertiary/quaternary carbon atom, in fair to very good yields (Table 1).[13] It is worth mentioning that

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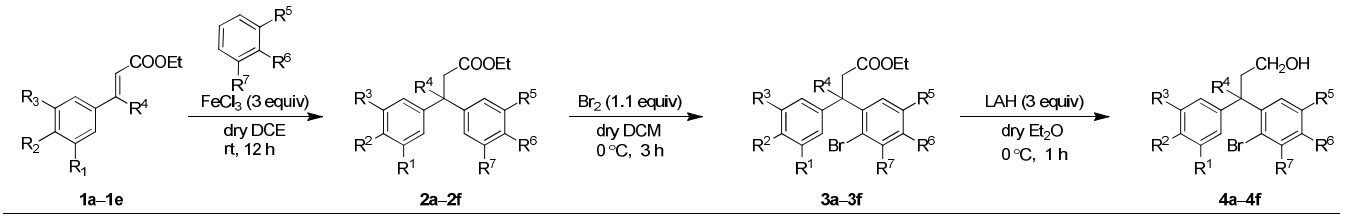
the use of DCE as a medium was found to be more general than that of CH_2Cl_2 in order to give good yields of the products **2**. However, the same Friedel-Crafts Michael addition with external arene either on 2-bromocinnamate or with external bromoarene on simple cinnamate was failed to furnish the corresponding product.[14] Now, preferential bromination of the electron rich aromatic ring under the standard electrophilic bromination conditions, providing the esters **3a-3f** in excellent yields as shown in Table 1. It is worth mentioning that when both the aromatic rings are electron rich, the bromination was not selective and gave a mixture of brominated products. Next, reduction of the ester function was required to provide the corresponding alcohols for the planned metal mediated cyclization. The esters **3a-3f** were reduced with $LiAlH_4$, and the precursor primary alcohols **4a-4f** yielded in near quantitative yields, in a controlled manner without affecting the bromo-substituent (Table 1).

Table 1. Synthesis of primary alcohols **4a-4f** starting from cinnamates**1a-1e** *via* β-diaryl esters **2a-2f** and bromo-esters **3a-3f**.[a]



1a–1e	2a–2f	3a–3f	4a–4f
1a	**2a** (67%)	**3a** (97%)	**4a** (90%)
1b	**2b** (87%)	**3b** (93%)	**4b** (89%)
1c	**2c** (71%)	**3c** (94%)	**4c** (92%)
1c	**2d** (47%)	**3d** (95%)	**4d** (94%)
1d	**2e** (62%)	**3e** (90%)	**4e** (94%)
1e	**2f** (80%)	**3f** (92%)	**4f** (92%)

[a] Isolated yields of chromatographically pure products.

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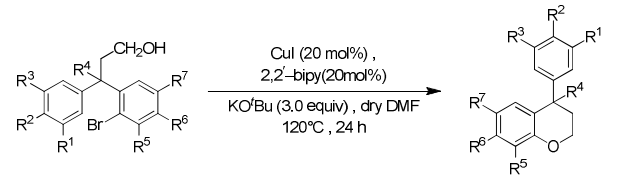
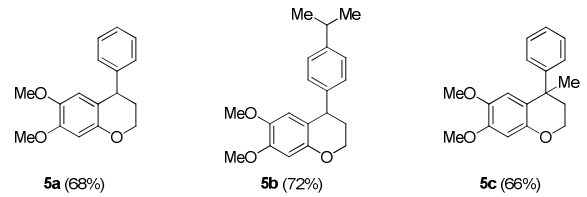
With the precursor alcohols **4** in hand, the key transition metal catalyzed intramolecular C–O bond formation was explored. In this regard, we employed the same reaction conditions [CuI (20 mol%)/2,2-bipyridyl (20 mol%), base KO^{t}Bu (3 equiv) in hot DMF (120 °C) for 24 h] which were successful in our previous reports for the synthesis of flavans.[12] As expected, the reaction was quite successful and furnished the neoflavan **5a** in very good yield.

Since the above [Cu]-catalyzed C–O bond forming reaction conditions were successful for the construction of neoflavan **5a** (Table 2), hence, these conditions were applied to other alcohols **4b-4f** as well. Agreeably, these conditions were found to be versatile and gave the cyclized neoflavans **5b-5f (**Table 2) possessing tertiary and quaternary C-4 carbon center, in very good yields.

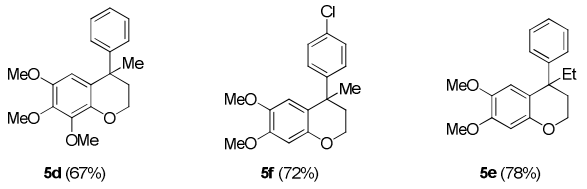
Table 2. [Cu]-catalyzed synthesis of neoflavans **5a-5f** from primary alcohols **4a-4f**.[a,b]



4a–4f **5a–5f**



5a (68%) **5b** (72%) **5c** (66%)

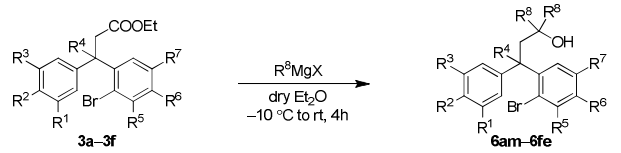


5d (67%) **5f** (72%) **5e** (78%)

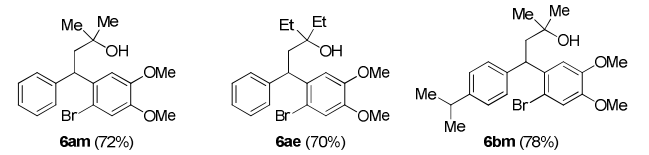
[a] Isolated yields of chromatographically pure products. [b] Reaction has been carried-out on alcohol **4a-4f** (0.30 mmol) in DMF (3 mL).

After successful synthesis of various neoflavan derivatives **5a-5f** with varied functionalities on either aromatic rings starting from primary alcohol precursors **4a-4f**, to check the scope and limitations of the method, we turned our attention for the synthesis of tertiary alcohols. Thus, the reaction of β-diaryl esters **3** with Grignard reagents furnished the corresponding tertiary alcohols **6** as described in Table 3.

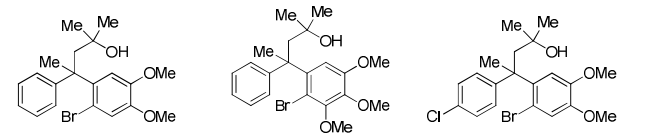
Table 3. Synthesis of tertiary alcohols **6am-6fe** from bromo-esters **3a-3f** using alkyl Grignard reaction.[a,b,c]



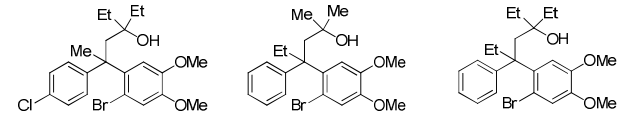
3a–3f **6am–6fe**



6am (72%) **6ae** (70%) **6bm** (78%)



6cm (90%) **6dm** (76%) **6em** (77%)



6ee (79%) **6fm** (92%) **6fe** (71%)

[a] Isolated yields of chromatographically pure products. [b] The first letter (**a-f**) for compounds (**6**) indicates that it is coming from starting material, where second letters (**m** or **e**) referred to methyl or ethyl groups, respectively. [c] 8 equiv. of alkyl Grignard reagent was used.

Finally, the key intramolecular C–O bond formation catalyzed by copper metal complex was explored. As expected, the method was found to be quite successful on the tertiary alcohols as well and generated the cyclized neoflavans, **7am-7fe**, in very good yields (Table 4).

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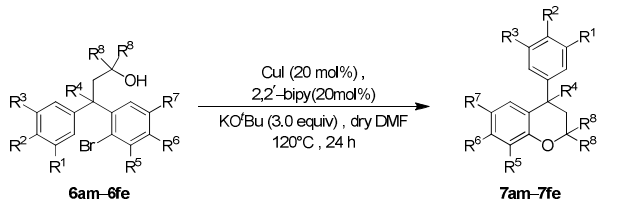
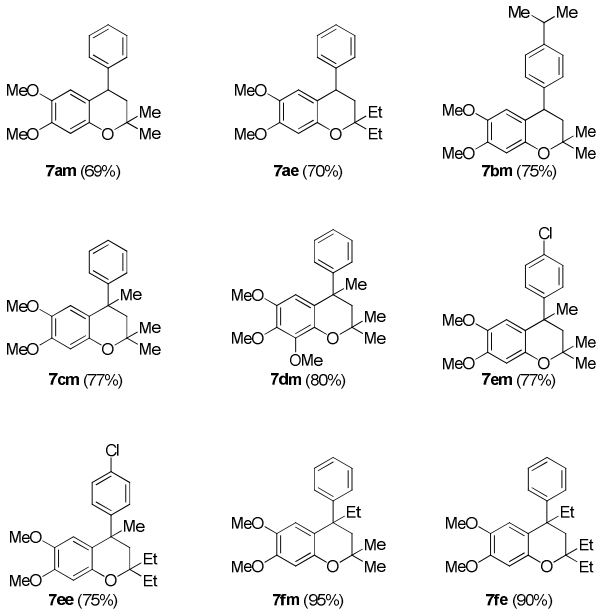
Table 4. [Cu]-catalyzed synthesis of neoflavans **7am-7fe** from tertiary alcohols **6am-6fe**.[a,b]



6am–6fe **7am–7fe**



7am (69%) **7ae** (70%) **7bm** (75%)

7cm (77%) **7dm** (80%) **7em** (77%)

7ee (75%) **7fm** (95%) **7fe** (90%)

[a] Isolated yields of chromatographically pure products.
[b] Reaction has been carried-out on alcohol **6am-6fe** (0.30 mmol) in DMF(3 mL).

Conclusions

In summary, we have developed a simple and practically applicable four-step strategy for the synthesis of functionalized neoflavans. Intermolecular Friedel-Crafts alkylation (C–C bond formation) and intramolecular [Cu]-catalyzed C–O bonds formation were applied as key steps of the strategy. The strategy is efficient and amenable for the synthesis of neoflavans containing tertiary as well quaternary carbon center.

Acknowledgments

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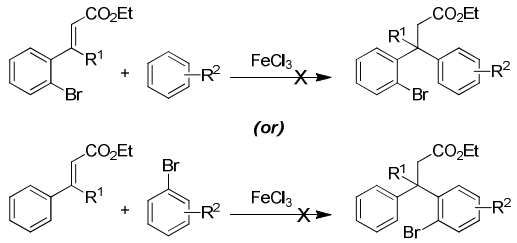

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