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Synthesis of Chromans via [3 + 3] Cyclocoupling of Phenols with Allylic Alcohols Using a Mo/*o*-Chloranil Catalyst System

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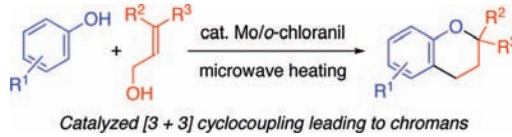
ABSTRACT



Catalyzed [3 + 3] cyclocoupling leading to chromans

The combination of a molybdenum complex ($CpMoCl(CO)_3$ or $[CpMo(CO)_3]_2$) and *o*-chloranil was used as a catalyst in the [3 + 3] cyclocoupling of phenols and allylic alcohols under microwave heating conditions. Substituted chromans were selectively obtained in moderate to good isolated yields.

Chroman (dihydrobenzopyran) is ubiquitously found in important biologically active compounds such as vitamin E and its derivatives[1] and flavonoids.[2] One of the most straightforward routes to the chroman framework is the cyclocoupling of phenol derivatives with 1,3-dienes mediated by homogeneous or heterogeneous acids.[3] Since it was first reported by Claisen,[3a] isoprene has been predominantly used as the 1,3-diene component in similar studies.[3] However, since the conventional methods used in these studies generally require (sub)stoichiometric amounts of acid promoters, large amounts of waste are generated; hence, more environmentally sound catalytic processes have been devised recently.[4] Bienaymé and co-workers used a rhodium catalyst system for the synthesis of vitamin E acetate via the coupling of trimethylhydroquinone (TMHQ) with β-springene.[4a] More recently, Youn and Eom successfully carried out efficient cyclocoupling of various linear and cyclic dienes using a carbophilic Lewis acid (AgOTf) as the catalyst under mild reaction conditions.[4b] Moreover, recyclable catalyst systems have been developed independently by Youn ($Sc(OTf)_3$/ionic liquid)[4c] and Hii and co-workers ($Cu(OTf)_2$/bipy).[4d] However, when these catalysts were employed in the cycloaddition, chromans and/or coumarans (dihydrobenzofurans) were obtained, depending on the structure of the 1,3-diene units used. Thus, a general method of cyclocoupling toward

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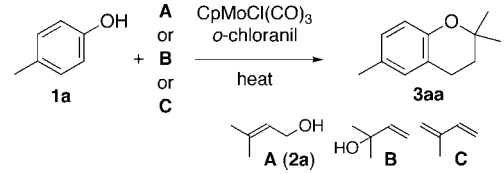
the selective synthesis of the chroman framework is yet to be developed.

The biosynthesis of natural chromans was assumed to occur through the assembly of a chroman skeleton via the Friedel−Crafts-type allylation of a phenolic core with an allylic pyrophosphate and the subsequent cyclization of the resulting *o*-allylated intermediate. On the basis of this biosynthetic mechanism, one can assume that the cyclocoupling of phenols with allylic alcohols or congeners is an alternative viable method of synthesizing chromans. Indeed, the very first syntheses of α-tocopherol were accomplished by the cyclocoupling of TMHQ with phytyl bromide or phytol,[5] and since then, this method has been widely used for the syntheses of α-tocopherol and its analogues.[6] Kočovský and co-workers also reported a few examples of the [3 + 3] cyclocoupling of phenol and *p*-cresol with some allylic compounds catalyzed by molybdenum Lewis acids under mild reaction conditions; however, the generality of this novel Mo-catalyzed method is yet to be established.[7]

We have previously reported that the combination of a molybdenum(II) complex, $CpMoCl(CO)_3$, with an organic oxidant, *o*-chloranil, efficiently catalyzes the Friedel−Crafts-type reactions of benzenes with alkenes or alcohols to yield alkylation products with ortho/para and Markovnikov selectivities.[8] As a continuation of our previous study, we herein report the application of our catalytic protocol to the cyclocoupling of phenols with allylic alcohols for the selective synthesis of various chromans.

At the outset, we examined the model reaction for the conversion of *p*-cresol (**1a**) to chroman **3aa** to identify the optimal reaction conditions (Table 1). Prenyl alcohol (**2a**, 1 mmol) and excess **1a** (3 mL) were stirred at 60 °C in the presence of 5 mol % $CpMoCl(CO)_3$ and 10 mol % *o*-chloranil for 3 h. Purification of the crude by silica gel chromatography afforded the desired product **3aa** in 69% isolated yield (based on **2a**, entry 1). A similar yield was obtained at a higher reaction temperature of 80 °C (entry 2). Subsequently, we carried out the abovementioned reactions under microwave (MW) irradiation conditions in a closed vessel. We found that the yield obtained with MW heating at 150 °C for 1 h was the highest (84%, entry 3), although the yield decreased with a decrease in the catalyst loading (entry 4). Further, we found that the use of 2-methylbut-3-en-2-ol or isoprene instead of **2a** brought about a decrease in the yield (entries 5 and 6). These results indicated that **2a** is an optimal substrate for the present cyclocoupling.

Table 1. Synthesis of Chroman **3aa** from *p*-Cresol (**1a**)[a]



entry	substrates	conditions	**3aa** (%)[b]
1	**A**	5 mol % cat., 60 °C, 4 h	69
2	**A**	5 mol % cat., 80 °C, 4 h	68
3	**A**	5 mol % cat., MW 150 °C, 1 h	84
4	**A**	2 mol % cat., MW 150 °C, 1 h	68
5	**B**	5 mol % cat., MW 150 °C, 1 h	65
6	**C**	5 mol % cat., MW 150 °C, 1 h	72

[a] Substrates (1 mmol; **A**, prenyl alcohol; **B**, 2-methylbut-3-en-2-ol; **C**, isoprene), **1a** (3 mL), $CpMoCl(CO)_3$/*o*-chloranil (1:2). [b] Isolated yields based on the olefinic substrates.

We examined the cyclocoupling of various phenol derivatives with **2a** under the optimal reaction conditions (Table 2). Both *p*-chlorophenol **1b** and *p*-methoxyphenol **1c** were converted into the corresponding chromans **3ba** and **3ca** in 74% and 61% yields, respectively (entries 1 and 2). Chromans **3da** and **3ea** were selectively obtained in moderate yields from 2,4-dimethylphenol **1d** and 3,5-dimethylphenol **1e**, respectively (entries 3 and 4), although a small amount of *p*-prenylated side product was detected in the reaction involving **1e**. We also studied the cyclocouplings of naphthols **1f**−**h** with **2a**. The reaction of 2-naphthol **1f** afforded the desired tricyclic product **3fa** along with a known bis(2-naphthyl) ether.[9] This side reaction was suppressed when we carried out the coupling in chlorobenzene under conventional heating conditions at 60 °C to obtain **3fa** in 70% yield (entry 5). In contrast, the reaction of 1-naphthol **1g** afforded only a modest yield of **3ga** (entry 6). The more electron-rich 4-methoxy analogue **1h** underwent cyclocoupling more effectively to afford dihydrolapachenole **3ha** in a higher yield (entry 7).

The generality of this catalytic method with respect to the allylic alcohol components was explored (Table 3). Phytol **2b** was allowed to react with **1a** under optimal conditions to afford the corresponding chroman **3ab** in 85% yield (entry 1). The use of isophytol instead of phytol diminished the yield of **3ab** to 75%. 2-Cyclohexylideneethanol **2c** and 3,5,5-trimethylcyclohex-2-en-1-ol **2d** also underwent cyclocoupling uneventfully to afford spirotricyclic **3ac** and bridged tricyclic **3ad** in 73% and 66% yields, respectively (entries 2 and 3).

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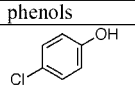
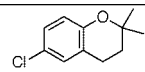
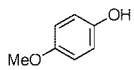
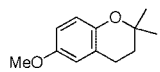
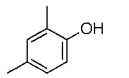
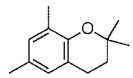
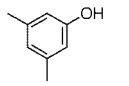
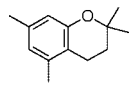
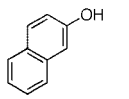
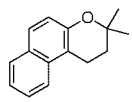
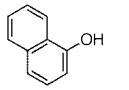
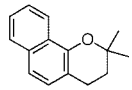
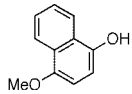
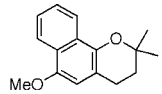
Table 2. Cyclocoupling of Phenols **1b**−**g** with Prenyl Alcohol **2a**[a]

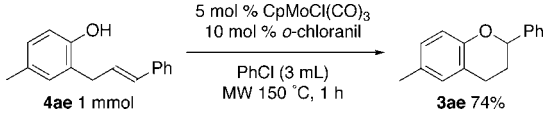
entry	phenols	chromans/%[b]
1	 **1b**	 **3ba**, 74
2[c]	 **1c**	 **3ca**, 61
3	 **1d**	 **3da**, 59
4[c]	 **1e**	 **3ea**, 60[d]
5[c]	 **1f**	 **3fa**, 67[e] (70)[f]
6[c]	 **1g**	 **3ga**, 40
7[c]	 **1h**	 **3ha**, 70

[a] Prenyl alcohol **2a** (1 mmol), phenols (3 mL), $CpMoCl(CO)_3$ (5 mol %), *o*-chloranil (10 mol %), MW 150 °C, 1 h. [b] Isolated yields based on prenyl alcohol **2a**. [c] Solid substrates (10 mmol) were heated in chlorobenzene (3 mL). [d] 3,5-Dimethyl-4-prenylphenol was detected as a side product. [e] Bis(2-naphthyl) ether was formed. [f] Conventional heating at 60 °C for 6 h.

It should be noted that while previously used coinage-metal Lewis acids and $Sc(OTf)_3$ catalyzed the reactions of cyclohexadiene with phenol derivatives to produce fused benzofurans instead of the corresponding bridged compounds,[4b−d,f] our method selectively affords the bridged products. A similar selectivity was observed when using Kočovský's Mo Lewis acid catalyst, which afforded bridged products from cyclohex-2-enyl acetates.[7a]

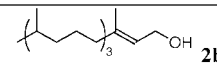
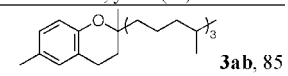
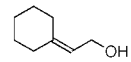
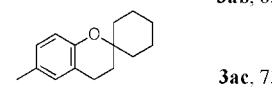
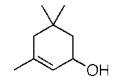
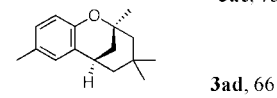
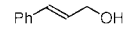
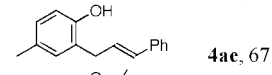
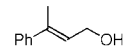
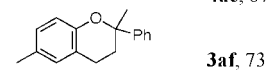
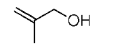
In contrast to the above examples, the reaction of cinnamyl alcohol **2e** with **1a** resulted in a complex mixture under the same reaction conditions. However, when this reaction was carried out under conventional heating at 60 °C for 4 h, the uncyclized product **4ae** was isolated in 67% yield (entry 4). The desired cyclization product **3ae** was then obtained in 74% yield when **4ae** and the catalyst were further subjected to MW heating in chlorobenzene (Scheme 1).

Scheme 1

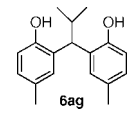


Cyclocoupling of the 3-methyl analogue **2f** with **1a** proceeded effectively under the standard conditions to give **3af** in a good yield (entry 5). We expected that the use of methallyl alcohol **2g** would lead to the formation of a dihydrobenzofuran; unfortunately, we isolated the desired product **5ag** in a low yield of 13% due to the unexpected formation of a 2:1 adduct **6ag** (entry 6).

Table 3. Cyclocoupling of *p*-Cresol **1a** with Alcohols **2b**−**g**[a]

entry	alcohols	chromans, yield (%)[b]
1	 **2b**	 **3ab**, 85
2	 **2c**	 **3ac**, 73
3	 **2d**	 **3ad**, 66
4[c]	 **2e**	 **4ae**, 67
5	 **2f**	 **3af**, 73
6	 **2g**	 **5ag**, 13[d]

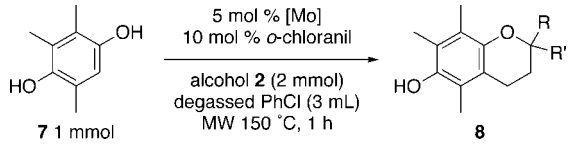
[a] Allylic alcohols (1 mmol), *p*-cresol (3 mL), $CpMoCl(CO)_3$ (5 mol %), *o*-chloranil (10 mol %), MW 150 °C, 1 h. [b] Isolated yields based on allylic alcohols. [c] Conventional heating at 60 °C for 3 h. [d] 2:1 adduct **6ag** was obtained in 27% yield.

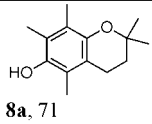
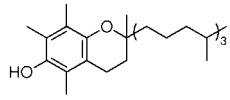
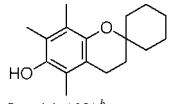
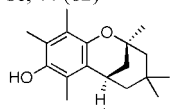


6ag

To demonstrate the synthetic utility of the proposed catalytic method, we further explored the cyclocoupling of TMHQ **7** toward the synthesis of vitamin E and its analogues. We realized that the use of excessive amounts of an expensive phenol precursor for this reaction is impractical. Hence, we attempted to identify alternative cyclocoupling conditions for carrying out the prototypical reaction of **7** with the prenyl derivatives to synthesize chroman **8a** (Table 4). A mixture of **7** and **2a** (2 equiv) in degassed chlorobenzene was subjected to MW irradiation at 150 °C for 1 h in the presence of 5 mol % $CpMoCl(CO)_3$ and 10 mol % *o*-chloranil. The resultant mixture was rather complex, probably due to the oligomerization of **2a**, although the desired product **8a** was obtained in 71% yield (entry 1). Encouraged by this result, we attempted the reaction of **7** with other molybdenum precatalysts, which were expected to diminish the oligomerization of the alcohol substrate. In our previous study, chloride-free precatalyst $[CpMo(CO)_3]_2$ proved to be effective in reducing the oligomerization of an acid-labile aromatic substrate.[8] The reaction carryied out using $[CpMo(CO)_3]_2$ was found to be clean, and the yield of **8a** improved to 80% (entry 2). To examine the influence of leaving groups, the corresponding acetate and chloride were subjected to the cyclocoupling, and similar yields were obtained (78% and 79%, respectively).

Table 4. Cyclocoupling of TMHQ **7** with Alcohols **2**



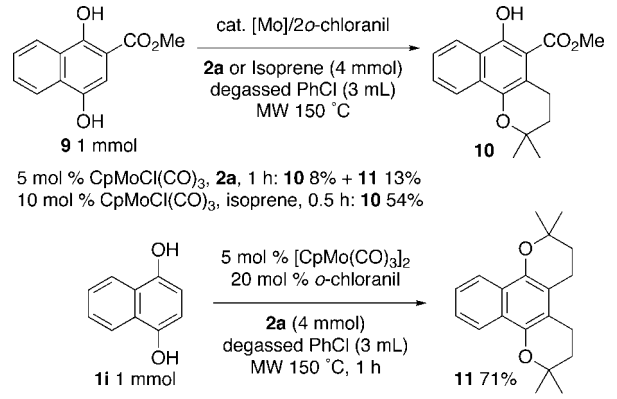
entry	2	[Mo]	8, yield (%)
1	**2a**	$CpMoCl(CO)_3$	 **8a**, 71
2	**2a**	$[CpMo(CO)_3]_2$	**8a**, 80
3	**2b**	$[CpMo(CO)_3]_2$	 **8b**, 75[a]
4	**2c**	$[CpMo(CO)_3]_2$	 **8c**, 44 (62)[b]
5	**2d**	$[CpMo(CO)_3]_2$	 **8d**, 33 (54)[b]

[a] **2**, 4 mmol. [b] Alcohols (4 mmol) were added in two portions (for details, see Supporting Information).

Under similar reaction conditions, 4 equiv of phytol **2b** was required for the complete consumption of **7**, and (all-rac)-α-tocopherol **8b** was obtained in 75% yield (entry 3). Cyclocoupling with less reactive alcohols **2c** and **2d** was also carried out under modified conditions to obtain corresponding adducts **8c** and **8d** in 62% and 54% yields, respectively (entries 4 and 5).

One limitation of molybdenum-catalyzed cyclocoupling using allylic alcohols was the acid-catalyzed decarboxylation of the aromatic ester substrate. It has been reported that the BF_3-mediated cyclocoupling of naphthohydroquinone ester **9** with 2-methyl-3-buten-2-ol or 3-methyl-3-buten-1-ol furnished a natural product 3,4-dihydromollugin **10**[10] in 40−75% yield.[11] Our first attempt to synthesize **10** from **9** and **2a** (4 equiv) in the presence of 5 mol % $CpMoCl(CO)_3$ and 10 mol % *o*-chloranil at 150 °C (MW) for 1 h resulted in a low yield formation of **10** and **11** (Scheme 2). The use of a milder

Scheme 2



precatalyst $[CpMo(CO)_3]_2$ did not improve the yield of **10**. It is reasonable to assume that the decarboxylation of **9** or **10** was caused by the alcohol nucleophile under acidic conditions and that the subsequent cyclocoupling produced **11**. In fact, the 2-fold cyclocoupling of **1i** with **2a** and $[CpMo(CO)_3]_2$ afforded **11** in 71% yield. To avoid decarboxylation, we introduced isoprene as a non-nucleophilic C_3 unit. In addition, we also found that an increased catalyst loading was beneficial in terms of the yield. Ultimately, the reaction was carried out with 4 equiv of isoprene and 10 mol % $CpMoCl(CO)_3$ at 150 °C (MW) for 0.5 h to obtain **10** in 54% yield.

In conclusion, we have developed the molybdenum complex/*o*-chloranil-catalyzed formal [3 + 3] cyclocoupling of phenol derivatives with allylic alcohols. This method employs MW irradiation and allows the rapid and selective synthesis of various chromans in moderate to good yields. The synthetic utility of this molybdenum-catalyzed protocol was demonstrated by the synthesis of α-tocopherol derivatives and 3,4-dihydromollugin.

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Supporting Information Available: Experimental procedures and analytical data for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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