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Highly Selective Synthesis of *Ortho*-Prenylated Phenols and Chromans by using a New Bimetallic CuAl-KIT-5 with a 3D-Cage-type Mesoporous Structure

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Prenylated phenols are interesting compounds that form a group of marine natural products and are involved in many biological processes.[1] They exhibit a wide range of pharmacological activities, including anti-inflammatory-,[2] anti-tumor-,[3] anti-fungal-,[4] anti-HIV-,[5] and anti-Alzheimer's activity.[6] The derivatives of prenylated phenols also exhibit a broad range of biological activities. For instance, prenylated napthaquinones, such as shikonin, are claimed to be excellent anti-bacterial agents, whereas prenylated ubiquinones play an important role in cellular respiration.[7–9] On the other hand, chromans are interesting compounds that are constituents in several biologically important compounds, such as vitamin E, which is a natural inhibitor of the peroxidation of lipids and prevents the propagation of free radicals in tissues.[10] Some of the most-attractive compounds in the family of chromans are the derivatives of 2-methylchroman, which display excellent antidiabetic activity.[10] Because of these excellent biological activities, as well as their importance in the pharmaceutical industry, several efforts have been devoted to the synthesis of prenylated compounds, chromans, and prenylated 1,4-quinones.[11]

Typically, *ortho*-prenylated phenols are synthesized by Friedel–Crafts-like prenylation,[12] anionic alkylation,[13] Claisen rearrangement,[14] directed *ortho*-metalation,[15] and metal–halogen-exchange reactions.[16] However, although these reported methodologies are quite effective for their synthesis, unfortunately, they often require activating groups or additional protection- and deprotection steps,[17] because the formed intermediate would sometimes undergo cyclization to form the chroman. In addition, controlling the chemo- and regioselectivity by using these above-mentioned sophisticated catalytic systems is quite difficult, which has forced researchers to look for alternative methods.

Strong Lewis- and Brønsted acid catalysts are generally used for the synthesis of prenylated compounds and chromans.[12–17] However, these catalysts are mostly homogeneous in nature. From the view point of sustainable chemistry, most of these catalysts suffer from several disadvantages, such as a high cost, toxicity, long reaction times, the formation of side-products, and difficulty in the separation of the products or in reusing the catalysts. To overcome these disadvantages, researchers have used heterogeneous catalysts, which represent the best solution to both the stringent environmental legislation and the commercial requirements because they produce minimal amounts of pollution.[18]

One such type of emerging heterogeneous catalysts is 3D-cage-type mesoporous aluminosilicates with a tunable pore-size and large surface area and we have demonstrated their excellent catalytic activity for various organic transformations.[19] It has been found that the 3D porous structure can offer facile diffusion of the reactant molecules, which can avoid pore-blocking and provide better textural parameters than those of catalysts with 1D porous structures. Constructing this above catalytic system with multiple elements and multiple catalytic functions could expand its possible applications and would be expected to enhance the activity- and selectivity of the products. A similar system is quite common in many biochemical processes that involve enzymes with different active sites. However, the design of such a system in an inorganic matrix is quite challenging and fascinating.

Herein, we propose the creation of Brønsted- and Lewis- or redox acid catalytic sites in nanocages of mesoporous systems that are expected to operate concurrently to achieve an overall transformation. We demonstrate that the selectivity of the products can be controlled by simply adjusting the nature- and quantity of the active sites.

Shown in Figure 1 are the low-angle XRD patterns of CuAl-KIT-5-10 and CuAl-KIT-5-15. Both samples show a sharp peak at higher angle and several higher-order peaks that correspond to the (111), (200), and (220) reflections of the cubic space group *Fm*3*m*, thus revealing that the structural order of the samples is similar to that of the parent KIT-5 silica nanocage. The HRSEM and HRTEM images of CuAl-KIT-5-15 (Figure 1, inset) clearly show that the sample exhibits a 3D well-ordered mesoporous structure with a spherical morphology. The well-ordered cage-type pores in the samples were confirmed by nitrogen-adsorption measurements, which show a typical type-IV isotherm with a sharp capillary-condensation step and a H2 hysteresis loop (see the Supporting Information, Figure 1S).

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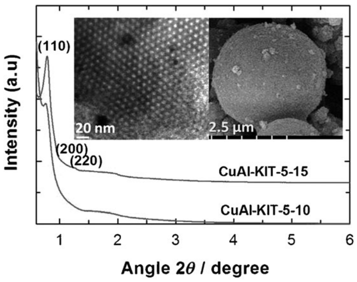
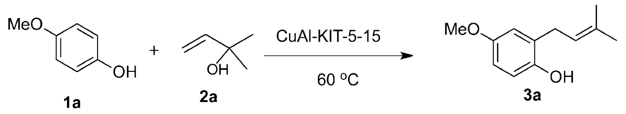


Figure 1. Powder XRD patterns of CuAl-KIT-5 (inset: HRSEM and HRTEM images of CuAl-KIT-5-15).

The specific surface area, specific pore volume, and the pore diameter of CuAl-KIT-5-15 are 928 $m^2 g^{-1}$, 0.70 $cm^3 g^{-1}$, and 6.13 nm, respectively. However, the specific surface area and specific pore volume of CuAl-KIT-5-10 decreased to 831 $m^2 g^{-1}$ and 0.67 $cm^3 g^{-1}$, respectively. In addition, the acidity of the sample increased with increasing amount of Al in the sample. Interestingly, the textural parameters of these catalysts are much better than those of pure mesoporous KIT-5 silica.[20] The UV results reveal that the samples show a sharp peak at 215 nm with a high intensity that increases with increasing Cu content (see the Supporting Information, Figure 2S). This result is mainly attributed to the charge-transfer transitions between O^{2-}- and Cu^{2+} ions and is indicative of the isomorphous substitution of Cu into the aluminosilicate framework of CuAl-KIT-5; these Cu species offer either redox- or Lewis acid active sites, which are required for the catalytic transformation to occur. These dual catalytic functions, together with their excellent textural characteristics, should make a significant difference in various catalytic reactions.

Initially, the activity of the CuAl-KIT-5-15 catalyst (50 mg) was checked at 60 °C in the reaction between 4-methoxyphenol (**1 a**, 2 mmol) and allylic alcohol (**2 a**, 1 mmol) to generate chromans in a tandem allylation/cyclization process. To our surprise, *o*-prenylated phenol was formed instead of the chroman (Scheme 1). This result encouraged us to investigate the activity of this catalyst for the synthesis of biologically important prenylated phenols under different experimental conditions. Thus, we first investigated the effect of temperature on the activity of the catalyst. No reaction was observed at 25 °C, whereas only a mixture of *o*-prenylated phenol (65 %) and chroman (15 %) was formed at 85 °C. At 60 °C, the catalyst exclusively afforded *o*-prenylated phenol (see the Supporting Information, Table 1S) and, thus, we concluded that a reaction temperature of 60 °C was the optimal temperature for the formation of prenylated phenols.

A screen of various solvents revealed that the highest yield was obtained when the model reaction between 4-methoxyphenol (**1 a**) and *o*-prenylated phenol (**3 a**) was conducted in 1,2-dichloroethane. However, nitromethane and toluene afforded low yields of the product, whereas MeCN was found not to be suitable for the reaction. The yield of the reaction also increased with higher loading of the catalyst (see the Supporting Information, Table 1S, entries 1 and 2). A control experiment showed that no product was obtained when the reaction was performed without CuAl-KIT-5 (see the Supporting Information, Table 1S, entry 7). To study the combined synergistic effect of Cu and Al in KIT-5, the reaction was also performed with the pure CuKIT-5 and AlKIT-5 catalysts, which afforded no product and the prenylated phenol in only 43 % yield, respectively. These results confirmed the role of the synergistic effect that was generated by the combination of Cu and Al in the silica framework of KIT-5 for the formation of *o*-prenylated phenols.



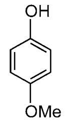
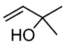
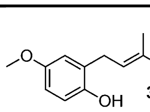
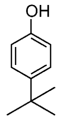
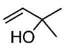
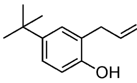
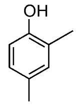
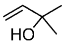
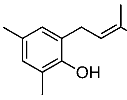
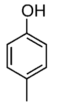
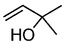
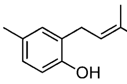
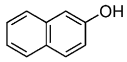
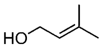
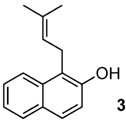
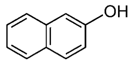
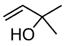
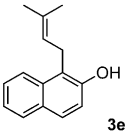
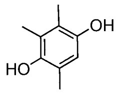
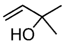
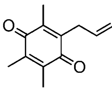
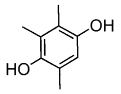
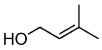
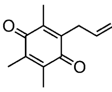
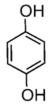
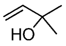
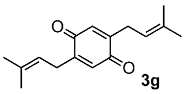
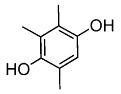
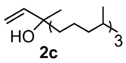
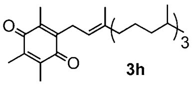
Scheme 1. Synthesis of a prenylated phenol catalyzed by CuAl-KIT-5-15.

To extend the scope of this catalytic system, we examined the prenylation of mono-, dialkyl-, and *tert*-butyl-substituted phenols with allyl alcohol (Table 1). The reaction proceeds smoothly with a variety of phenols and offered good-to-excellent yields (69–73 %), irrespective of the nature of the substituents on the phenolic ring. However, the highest yield was obtained for the reaction with 2-naphthol (Table 1, entry 6), whereas a relatively lower yield (65 %) was obtained when the reaction was performed with prenyl alcohol (**2 b**; Table 1, entry 5).

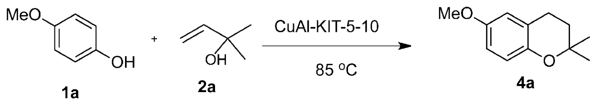
The prenylation reactions of 2,3,5-trimethylhydroquinone with 2-methylbut-3-en-2-ol (**2 a**) and prenyl alcohol (**2 b**; Table 1, entries 7 and 8) were examined and the catalyst was found to work well, thereby affording the important compound 3,5,6-trimethyl-2-(3-methylbut-2-enyl)-1,4-benzoquinone (**3 f**) in 91 % and 85 %, respectively. Furthermore, 2,3,5-trimethylhydroquinone underwent smooth prenylation with 3,7-dimethyloct-1-en-3-ol (**2 c**) and the catalyst afforded the commercially important phytyl-trimethylbenzoquinone (Tocoquinone, **3 h**) in high yield (79 %). Notably, other mono-metal-substituted catalysts afforded a relatively lower yield of compound **3 h**. This result confirms the important feature of this new bimetallic catalyst, which would replace the existing environmentally harmful acidic catalysts and make a significant breakthrough in the pharmaceutical industry.

One of the interesting parts of this work is the tuning of the selectivity of the product with a simple adjustment of the amount of Al in the bimetallic catalyst. The reaction of 4-methoxyphenol with 2-methylbut-3-en-2-ol (**2 a**) was performed with CuAl-KIT-5-10, which has the highest acidity of the synthesized catalysts owing to the presence of more Al atoms. Surprisingly, the catalyst afforded chroman **4 a** as the main product in 75 % yield (Scheme 2). The catalyst also afforded an excellent yield of different-substituted phenols (Table 2). However, the catalyst gave a mixture of compounds **3 a** (38 %) and **4 a** (21 %) when the reaction was performed at 60 °C for 16 h. To obtain the chroman as the major product at a low temperature, we tried to further increase the Al content in CuAl-KIT-5-10. However, the mesoporous structure of the catalyst collapsed when the n_{Si}/n_{Al} ratio in the synthetic mixture fell below 10 (see the Supporting Information, Figure 3S).

Table 1. Synthesis of *o*-prenylated phenols and quinines.

Entry	Reactants		Product[a]	*t* [h]	Yield[b] [%]
1		 **2a**	 **3a**	16	75
2			 **3b**	16	73
3			 **3c**	14	71
4			 **3d**	15	69
5		 **2b**	 **3e**	15	65
6			 **3e**	12	86
7			 **3f**	6	91
8			 **3f**	8	85
9			 **3g**	6	76
10		 **2c**	 **3h**	6	79

[a] The products were characterized by using ^{1}H NMR, ^{13}C NMR, and IR spectroscopies, as well as by MS. [b] Yield of the pure product after column chromatography on silica gel.



Scheme 2. Synthesis of chromans catalyzed by CuAl-KIT-5-10.

Furthermore, the efficiency of heterogeneous catalyst CuAl-KIT-5 was analyzed in terms of its recyclability in the prenylation of compound **1a** with compound **2a** because it is an important parameter for industrial applications. The catalyst was recovered by simple filtration and reused after calcination at 500 °C for 4 h under an oxygen atmosphere. The yield of prenylated phenol **3a** was, in turn, 75%, 71%, and 67% over three cycles. Although a slight decrease in activity was observed after three cycles, the activity remained constant for a further three cycles. The structure of the catalyst after the third cycle was also investigated by powder X-ray diffraction and nitrogen-adsorption analysis (see the Supporting Information, Figure S4). However, no difference in the structure was observed, even after the third cycle. The reason for the slight drop in activity of the catalyst after three cycles might be due to a slight variation in the nature of the active sites on the surface of the catalysts.

In conclusion, we have strikingly demonstrated the synthesis of a new bimetallic catalyst with excellent structural characteristics, that is, a well-ordered 3D porous structure, which showed remarkable performance in the synthesis of *o*-prenylated phenols and chromans. We also demonstrated the synergistic effect of the bimetals (Cu and Al) in the mesoporous catalysts that controls the formation and the selectivity of the final products. The selectivity of the product could also be controlled with a simple adjustment of the amount of Al content in the catalyst. The catalyst also afforded a high yield of Tocoquinone and was highly stable and could be reused several times. We strongly believe that this new catalytic bimetallic catalyst can open the possibility for the synthesis of various pharmaceutical products for commercial applications.

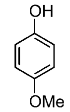
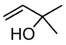
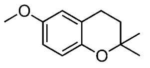
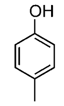
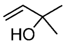
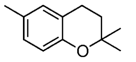
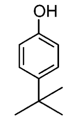
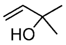
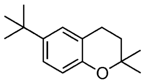
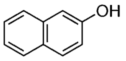
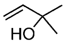
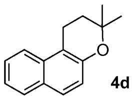
Experimental Section

Mesoporous CuAl-KIT-5 was prepared by using a soft-templating method under acidic conditions. In a typical synthesis, a mixture of pluronic F127 (5.0 g), aqueous HCl (3.0 g of a 35 wt.% solution), and distilled water (240 g) was stirred for 2–3 h at 45 °C. Tetraethyl orthosilicate (TEOS, 24.0 g) and the required amounts of aluminum isopropoxide and copper nitrate were added and the reaction mixture was stirred at 45 °C for 24 h and then hydrothermally treated under static conditions at 100 °C for 24 h. The resulting solid was filtered without washing with water, dried at 100 °C, and finally calcined at 540 °C for 10 h. The Cu content in the samples is kept constant ($n_{Si}/n_{Cu}=15$) but the n_{Si}/n_{Al} ratio of the samples is varied. The prepared material is labeled as CuAl-KIT-5-*X* where *X* denotes the n_{Si}/n_{Al}.

Synthesis of *o*-prenylated phenols and quinones

A mixture of the allylic alcohol (1 mmol), phenol (2 mmol), catalyst CuAl-KIT-5-15 (50 mg), and 1,2-dichloroethane (5 mL) was heated at 60 °C for 6–16 h and the progress of the reaction was monitored by TLC. The crude reaction mixture was filtered, concentrated under vacuum, and purified by column chromatography on silica gel to afford the desired product.

Table 2. Synthesis of 2,2-dimethylchroman and its derivatives.

Entry	Reactants[a]	Product[b]	*t* [h]	Yield [%]
1	 	 **4a**	11	83
2	 	 **4b**	10	78
3	 	 **4c**	10	81
4	 	 **4d**	7	88

[a] The products were characterized by using ^{1}H NMR, ^{13}C NMR, and IR spectroscopies, as well as by MS. [b] Yield of the pure product after column chromatography on silica gel.

Synthesis of chromans

A mixture of the allylic alcohol (1 mmol), phenol (2 mmol), catalyst CuAl-KIT-5-10 (50 mg), and 1,2-dichloroethane (5 mL) was heated at 60–85 °C for 10 h and the progress of the reaction was monitored by TLC. The crude reaction mixture was filtered, concentrated under vacuum, and purified by column chromatography on silica gel to afford the desired product.

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Keywords: cage compounds · chromans · heterogeneous catalysis · mesoporous materials · prenylated phenols

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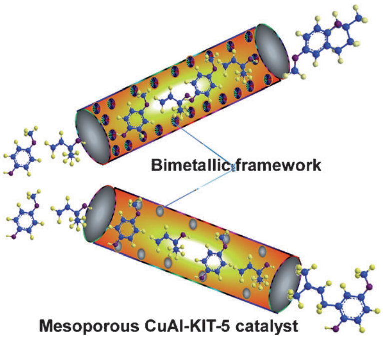
A nice piece of KIT: The first synthesis of a new bimetallic 3D-cage-type mesoporous catalyst CuAl-KIT-5 and its remarkable performance for the highly selective synthesis of *ortho*-prenylated phenols and chromans is reported.



*S. Varghese, C. Anand, D. Dhawale, G. P. Mane, M. A. Wahab, A. Mano, G. A. G. Raj, S. Nagarajan, A. Vinu**

■■–■■

Highly Selective Synthesis of *Ortho*-Prenylated Phenols and Chromans by using a New Bimetallic CuAl-KIT-5 with a 3D-Cage-type Mesoporous Structure