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Mesoporous and hexagonally ordered CuAl-SBA-15-catalyzed tandem C–C and C–O bond formation between phenols and allylic alcohols

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ABSTRACT

A novel mesoporous catalyst, CuAl-SBA-15, with a hexagonally ordered porous structure prepared via a soft-templating approach in a highly acidic medium is used for tandem C–C and C–O bond formation between phenols and allylic alcohols to afford a variety of dihydrobenzopyrans in good yields. The catalyst is also found to be highly active for the synthesis of vitamin E and can be recycled several times without significant loss of its activity.

The dihydrobenzopyran (chroman) moiety is an important structural motif in both naturally occurring and biologically active products such as vitamin E (α-tocopherol) and its derivatives,[1] and flavonoids.[2] It is also found in pharmaceutical substrates such as clusifoliol (Fig. 1).[3] Dihydrobenzopyrans are generally prepared by the cycloaddition of phenol derivatives with 1,3-dienes. These reactions can be facilitated by either homogeneous or heterogeneous Brønsted and Lewis acid catalysts.[4] It has also been reported that dihydrobenzopyrans can be prepared from allylic alcohols using Brønsted or Lewis acid catalysts. However, in most cases, a stoichiometric amount of an acid catalyst is required,[5] and offers only a low to moderate yield of the required product with the formation of by-products such as dihydrobenzofurans.[5,6] Thus, there is a need for the development of novel catalysts, which should be stable, active, and environmentally friendly, for the straightforward synthesis of dihydrobenzopyrans.

Recently, mesoporous materials have emerged as efficient catalysts for selective organic transformations owing to their excellent physical characteristics including high surface areas, large pore volumes, and uniform pore size distribution.[7–10] They are not only highly efficient and stable, but are also eco-friendly. In addition, the associated simplicity in work-up and recyclability of these interesting catalysts make them attractive for various organic transformations.[7] Mesoporous catalysts such as faujasite zeolite HSZ-360 have also been used for the synthesis of dihydrobenzopyrans from phenols and isoprene through a simple cyclization. However this process requires a high temperature and most importantly, the pores of the zeolites are too small for the synthesis of bulky molecules.[8] To overcome these difficulties, we have used extensively mesoporous aluminosilicate catalysts with well-ordered porous structures and excellent physical characteristics as catalysts for several organic transformations involving bulky molecules, and found that they were highly efficient for the synthesis of alkylated nitrogen heterocycles, substituted quinolines, benzodiazepine and its derivatives, and triazolo indazolones.[9] The introduction of different metal species into the framework of the mesoporous silica matrix can tune the properties of the catalysts. It has been reported that the acidity and the catalytic activity of aluminosilicates can be enhanced or tuned by the simple addition of divalent metal ions such as Cu(II), Zn(II), or Fe(II) in the silica framework, as they generate highly acidic Lewis sites.[10]

Here we propose to introduce Cu and Al sites to the hexagonally ordered silica system as they can offer particular advantages in catalysis over mono metal catalysts due to their cooperative nature in tandem reactions.[11] In addition, it is expected that these catalysts

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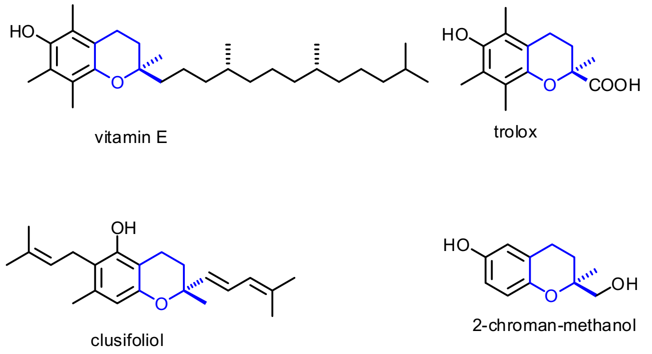
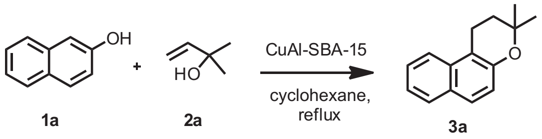


Figure 1. Biologically active compounds and pharmaceutical substrates of chromans.

can reduce the total mass of the solid support used for the reaction.[12] In our ongoing research on mesoporous catalyst mediated organic transformations,[9,13] we found that ordered mesoporous silica substituted with both Cu and Al in the silica framework catalyzed the formation of dihydrobenzopyrans from phenol derivatives.

CuAl-SBA-15 was prepared using the polymeric triblock copolymer, P123 ($PEO_{20}PPO_{70}PEO_{20}$) as the structure-directing agent and inorganic substrates such as tetraethyl orthosilicate, copper nitrate, and aluminum isopropoxide were used as the sources of Si, Cu, and Al, respectively. The synthesis was carried out at a reaction temperature of 100 °C in a highly acidic medium.[14] The n_{Si}/n_{Cu} and n_{Si}/n_{Al} ratios of the samples were calculated to be 20 and 7, respectively. However, the $n_{Si}/(n_{Cu+}n_{Al})$ ratio of the final product after filtration and calcination was found to be 16.38. The prepared CuAl-SBA-15 catalyst was characterized by transmission electron microscopy (TEM), XRD, HRSEM, EDX, and nitrogen adsorption isotherm experiments. The results revealed that the prepared catalyst exhibited a well-defined hexagonally ordered porous structure with a rod-like morphology and excellent physical parameters such as high surface area ($546\ m^2g^{-1}$), large pore volume ($1.1\ cm^3g^{-1}$), and uniform pore size distribution (9.9 nm) (see Supplementary data Figs. 1S–4S). A highly intense peak together with several well-ordered peaks at lower angles revealed the hexagonally-ordered pore system in the catalyst, which was similar to that observed for pure SBA-15 (Fig. 1S). EDX and elemental mapping of the catalyst revealed a uniform distribution of Cu and Al in the mesoporous matrix along the silica walls (Fig. 2S).

As this catalyst exhibited excellent physical characteristics together with a well-ordered porous structure, we tried to synthesize dihydrobenzopyrans from phenols and allylic alcohols using this novel catalyst (Scheme 1). In a typical reaction, 2-naphthol (**1a**) was treated with methylbut-3-en-2-ol (**2a**) at reflux over CuAl-SBA-15. When a mixture of **1a** (2 mmol), **2a** (1 mmol), and CuAl-SBA-15 (30 mg) in cyclohexane (5 ml) was refluxed at 85 °C for 3 h, product **3a** was formed in 86% yield after column chromatographic purification. The effect of the solvent on the yield of the final product was also investigated and the results are shown in Table 1. Cyclohexane and 1,2-dichloroethane were good solvents leading to 86% and 76% yields of **3a**, respectively, whereas other solvents such as toluene and nitromethane were less suitable for the reaction. Interestingly, acetonitrile offered very low activity with the lowest yield of **3a** (16%) under similar reaction conditions.



Scheme 1. CuAl-SBA-15 catalyzed annulation of 2-naphthol with methylbut-3-en-2-ol.

Table 1
Optimization of the reaction of 2-naphthol (**1a**) with methylbut-3-en-2-ol (**2a**)[a]

Entry	Catalyst	Solvent	Yield (%)[b]
1	CuAl-SBA-15	cyclohexane	86
2	CuAl-SBA-15	1,2-DCE	76
3	CuAl-SBA-15	MeCN	16
4	CuAl-SBA-15	Toluene	74
5	CuAl-SBA-15	MeNO$_2$	61
6	AlSBA-15	Cyclohexane	72
7	CuAl-SBA-15[c]	Cyclohexane	88
8	None	Cyclohexane	—

[a] Reaction conditions: 2-naphthol (2 mmol), methylbut-3-en-2-ol (1 mmol), solvent (5 mL), catalyst (30 mg), 85 °C, 3 h.
[b] Isolated yield after column chromatographic purification.
[c] 40 mg of catalyst was used.

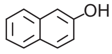
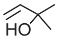
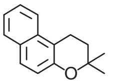
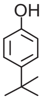
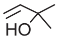
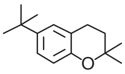
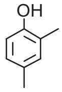
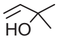
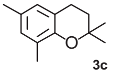
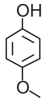
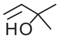
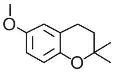
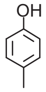
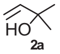
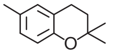
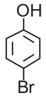
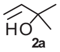
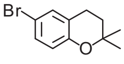
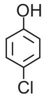
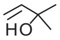
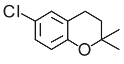
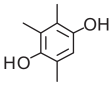
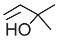
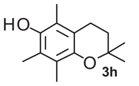
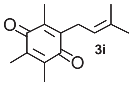
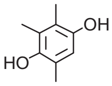
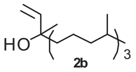
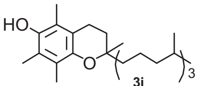
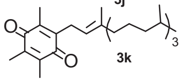
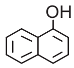
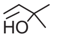
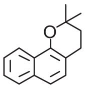
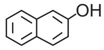
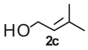
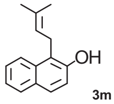
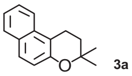
Without any catalyst the reaction did not proceed. The effect of the amount of catalyst on the synthesis of **3a** was also investigated. Increasing the catalyst loading did not make much difference to the final yield of the product **3a** (Table 1, entry 7). In order to check the influence of the Cu and Al sites in the catalyst, the reaction was carried out with pure AlSBA-15. To our delight, we found that the activity of CuAl-SBA-15 was much higher than that of pure AlSBA-15, revealing the influence of the copper species in the aluminosilicate framework of CuAl-SBA-15. Interestingly, the reaction did not occur when pure CuSBA-15 was used as the catalyst. These results reveal that the combination of both the acid and the redox sites was extremely important to obtain high yields in this particular reaction.

The scope of the reaction was extended using different phenols and the results are summarized in Table 2. The reactions were conducted under the optimized conditions.[15] Low yields were observed for 4-chlorophenol and 1-naphthol which are mainly due to the influence of steric effects and the electronic nature of these compounds. When, 2,3,5-trimethylhydroquinone (Table 2, entry 8) was subjected to the reaction with **2a**, both dihydrobenzopyran (**3h**) and prenylated 1,4-benzoquinone (**3i**) were formed in 52% and 28% yields, respectively. However, allylic alcohol **2b** (Table 2 entry 9) required a longer reaction time (16 h) for the formation of vitamin E (**3j**) in 61% yield. The by-product of this reaction, phytyl-trimethylbenzoquinone (**3k**) was also isolated and characterized. These results indicate that the methodology can be utilized for the straightforward synthesis of commercially important vitamin E and its analogues.

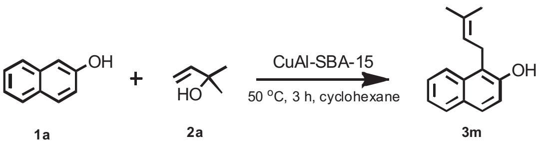
Interestingly, when the reaction was carried out at 50 °C with **1a** and **2a** for 3 h (Scheme 2), the Friedel–Crafts allylated intermediate, prenylated naphthol **3m** was formed in a yield of 61%. Subsequently, the intermediate **3m** was subjected to further reaction in the presence of the same catalyst at 85 °C and the product **3a** was formed within 30 min (Scheme 3), indicating that the reaction proceeds through Friedel–Crafts alkylation followed by cyclization.

The recyclability of CuAl-SBA-15 was tested in the annulation of **1a** and **2a**. The catalyst was recovered simply by filtration and reused after washing with dichloromethane and being calcined at 500 °C for 4 h under an O$_2$ atm. A yield of ca. 80% was achieved even after the third run, showing only a small change in the activity of the catalyst. These results revealed that the catalyst was highly robust in nature which is mainly due to the several layers of the metallosilicate framework which stabilizes the mesostructure of the catalyst. In addition, the structural order of the catalyst was completely retained even after the third cycle which should enable reuse of the catalyst several times. From the view point of stability, activity, and versatility, it can be envisaged that this novel catalyst could replace existing hazardous and homogenous toxic catalysts that are currently being used in industry for these types

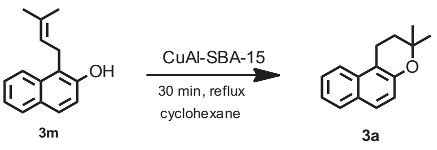
Table 2
CuAl-SBA-15-catalyzed annulations of phenols and naphthols with allylic alcohols[a]

Entry	ArOH	Alcohol	Product[a]	Time (h)	Yield (%)[b]
1		 2a	 3a	3	86
2		 2a	 3b	4.5	81
3		 2a	 3c	5	78
4		 2a	 3d	5	73
5		 2a	 3e	5	70
6		 2a	 3f	5.5	56
7		 2a	 3g	6	53
8		 2a	 3h	16	52
			 3i		28
9		 2b	 3j	16	61
			 3k		25
10		 2a	 3l	6	51
11		 2c	 3m	5	28
			 3a		47

[a] The products were characterized by ^{1}H, ^{13}C NMR and IR spectroscopy, and mass spectroscopy.
[b] Yield refers to pure products after chromatography.

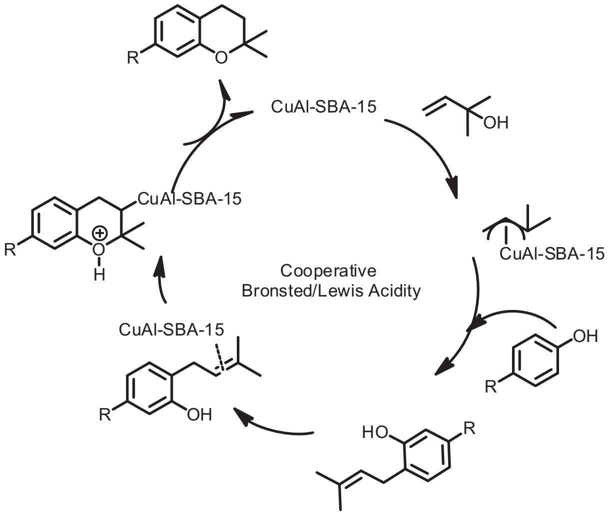


Scheme 2. CuAl-SBA-15-catalyzed prenylation of 2-naphthol.



Scheme 3. CuAl-SBA-15-catalyzed cyclization of prenylated naphthol.

of reactions. It is also expected that the linear arrays of mesopores, as shown in the TEM images, help the diffusion of even bulky reactants along the one-dimensional pore channels and allow access to sites deep inside the pores and may further enhance the accessibility. These excellent features of this catalyst create scope for the synthesis of fine chemicals.



Scheme 4. Plausible mechanism for the CuAl-SBA-15-catalyzed reactions.

Scheme 4 shows the probable pathway for this process. The proposed mechanism is consistent with our experimental observations. The mechanism involves several steps: at first activation of the allylic alcohol is induced by CuAl-SBA-15 which leads to the formation of a π-allyl type complex followed by the Friedel–Crafts reaction, preferably at the *ortho* position of the phenol. The high *ortho* regioselectivity of the product arises from the close spatial arrangement and the coordination of the metallosilicate framework between the hydroxy and allyl groups, which leads to the formation of an *ortho*-allylated intermediate (prenylated phenol). Further co-ordination and intramolecular cyclization of this intermediate lead to formation of the product dihydrobenzopyrans. It should be mentioned that the cyclization step follows Markovnikov's rule with the attack of oxygen at the most substituted allylic carbon.[16]

In summary, we have demonstrated the preparation of a novel mesoporous catalyst incorporating Cu and Al with a hexagonally-ordered porous structure for the synthesis of dihydrobenzopyrans through simple tandem C–C and C–O bond formation between various phenols and allylic alcohols. The catalyst was found to be highly active, stable, and recyclable. Moreover, this catalyst afforded commercially important vitamin E in good yield, and showed much better activity than mono metal substituted mesoporous catalysts and zeolites. We believe that this novel catalytic system should create an excellent platform for the synthesis of a variety of fine chemicals.

Acknowledgments

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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.2012.08.043.

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14. *Synthesis of the catalyst:* 4 g of amphiphilic triblock copolymer, poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) was dispersed in 30 ml of H_2O, and 120 g of 2 M HCl solution was added while stirring. 8 g of TEOS was then added to the homogeneous solution with stirring. The required quantities of aluminum isopropoxide (1.26 g) and copper nitrate (0.52 g) were added. The resulting gel mixture was stirred continuously at 40 °C for 24 h and finally crystallized in a Teflon-lined autoclave at100 °C over 2 d. After crystallization, the solid product was filtered, washed with distilled H_2O, and dried in air at room temperature. The material was calcined in static air at 550 °C for 24 h to decompose the triblock copolymer and afford sky-blue colored CuAl-SBA-15.
15. *General procedure for the synthesis of dihydrobenzopyrans:* A mixture of the phenol (2 mmol), allylic alcohol (1 mmol), and CuAl-SBA-15 (30 mg) in cyclohexane (5 ml) was refluxed for 3–4 h and the progress of the reaction was monitored by TLC. The crude mixture was filtered and concentrated, and the residue was purified by silica gel column chromatography to afford the pure dihydrobenzopyran.
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