A recyclable copper(II) catalyst for the annulation of phenols with 1,3-dienes†

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Air- and moisture-stable Cu(OTf)$_2$–bipy catalyses the addition of phenols to 1,3-dienes under aerobic conditions in a tandem hydroalkoxylation–rearrangement–hydroalkylation sequence, furnishing O-heterocycles in moderate to good yields, and can be recycled without any loss in catalytic activity.

Benzofuran and pyran rings constitute common motifs in biologically-active natural products.[1] One of the most atom-economical ways of constructing these heterocycles is by the annulation of phenol derivatives with 1,3-dienes. These reactions can be facilitated by certain Brønsted[2] and Lewis[3] acids, but high reaction temperatures are often necessary. In most cases, only low to moderate yields of products were reported. Recently, two independent reports have described the use of $AuCl_3$–AgOTf[4] and AgOTf[5] as efficient catalysts for the annulation of phenol/naphthol with 1,3-dienes. In the latter paper, it was stated that Cu(OTf)$_2$ is catalytically-inactive for these reactions. This is in direct conflict with our preliminary work, carried out as part of a project on the application of copper(II) catalysts for O–H[6] and N–H[7] additions to C=C bonds. Herein, the development of an air-stable and recyclable copper(II) catalyst is described.

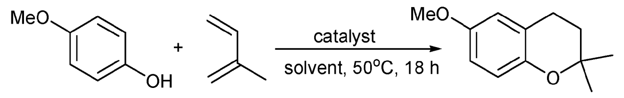
Initial studies were performed in 1,2-dichloroethane (DCE) using 4-methoxyphenol and isoprene as model substrates (Table 1). We began by comparing the catalytic activity of silver(I) and copper(II) triflate salts with their corresponding Brønsted acids (Table 1, entries 1–3). In all these reactions, a slightly elevated temperature (50 °C) was adopted to enable complete conversions within 18 h (unoptimised).[8] The use of triflic acid afforded a poor yield of benzopyran **1**, and the reaction was plagued by the formation of side products. In contrast, the metal triflates gave cleaner and *comparable yields* of the benzopyran under these conditions. In accordance with the earlier report,[5] addition of PPh_3 ligand (1 equivalent with respect to the metal) did not exert a significant effect (Table 1, entries 4 and 5). However, a significant increase in the product yield was observed in the Cu-catalysed reaction, where the M/L ratio was adjusted to 2 : 1 (Table 1, entry 6). The preliminary study concluded with a solvent screen, establishing DCE as the optimal reaction medium, with toluene as the second best (Table 1, entries 6–10).

A small ligand screening was then performed, where we found that 2,2′-bipyridine (bipy) was just as effective as PPh_3 in the Cu-catalysed reaction (Table 1, entries 6 and 11). As bipy is more resistant to oxidation, it allows these reactions to be performed in air without any degradation of the yield. It is also cheaper and has a lower molecular weight than phosphine, making it the preferred ligand for these reactions. Again, the catalyst was more effective when an M/L ratio of 2 : 1 was employed (Table 1, entries 11 and 12), which was not the case for the silver catalyst (Table 1, entries 2 and 13).

Next, the reaction scope was investigated using commercially available substrates, comparing the performance of PPh_3 and bipy ligands under optimised conditions (Table 2). The results were found to be largely comparable to those previously reported using AgOTf, which required 1–3 days to complete.[5]

The addition to acyclic isoprene and 2,5-dimethylhexa-2,4-diene afforded single regioisomers (Table 2, entries 1, 2, 6–9 and 11). In contrast, 2,3-dimethylbutadiene furnished a mixture of 5- and 6-membered heterocycles (Table 2, entries 3 and 11). The addition to cyclohexadiene was less efficient, but could be improved by using a higher catalytic loading (Table 2, entries 5 and 10); in these cases, the products were obtained exclusively as the *syn*-isomer. Reactions with myrcene were also notable for their production of spiro-cyclic ethers (Table 2, entries 4 and 12), in contrast to earlier reports of product mixtures.[3]

Table 1 Addition of 4-methoxyphenol to isoprene in the presence of different catalysts[a]



1

Entry	Catalyst (Loading/mol%)	Ligand (Loading/mol%)	Solvent[a]	Yield (%)[b]
1	TfOH (5)	—	DCE	23
2	AgOTf (5)	—	DCE	44
3	Cu(OTf)$_2$ (5)	—	DCE	45
4	AgOTf (5)	PPh_3 (5)	DCE	45
5	Cu(OTf)$_2$ (5)	PPh_3 (5)	DCE	49
6	Cu(OTf)$_2$ (5)	PPh_3 (2.5)	DCE	66
7	Cu(OTf)$_2$ (5)	PPh_3 (2.5)	Toluene	60
8	Cu(OTf)$_2$ (5)	PPh_3 (2.5)	CH_3CN	25
9	Cu(OTf)$_2$ (5)	PPh_3 (2.5)	Acetone	23
10	Cu(OTf)$_2$ (5)	PPh_3 (2.5)	THF	14
11	Cu(OTf)$_2$ (5)	bipy (2.5)	DCE	69
12	Cu(OTf)$_2$ (5)	bipy (1.25)	DCE	59
13	AgOTf (5)	bipy (2.5)	DCE	45

[a] General reaction conditions: 4-methoxyphenol (1 mmol), isoprene (1.5 mmol), solvent (1 mL), 50 °C, 18 h. [b] Isolated yield after column chromatography; average of two runs.

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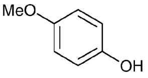
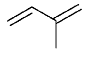
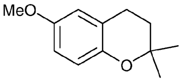
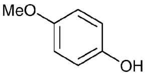
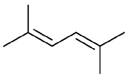
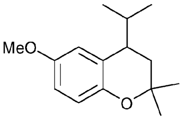
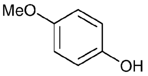
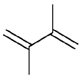
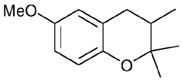
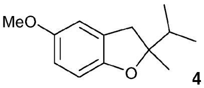
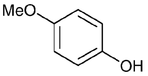
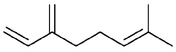
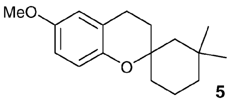
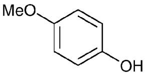
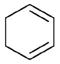
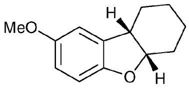
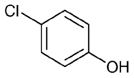
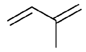
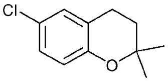
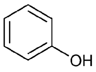
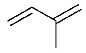
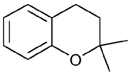
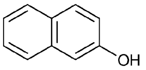
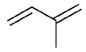
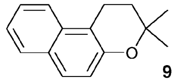
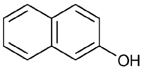
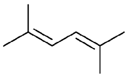
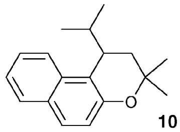
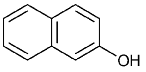
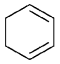
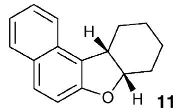
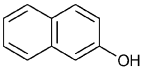
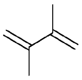
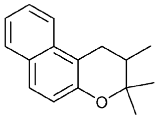
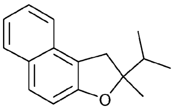
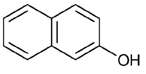
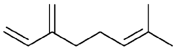
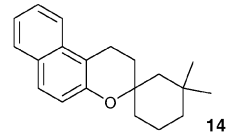
† Electronic supplementary information (ESI) available: Experimental procedure, characterisation data and NMR spectra of all compounds. See DOI: 10.1039/b719465j

Table 2 Copper-catalysed annulation of phenols and naphthol with 1,3-dienes[a]

Entry	Phenol	Diene	Product	Yield (bipy) (%)	Yield (PPh_3) (%)
1			 **1**	69	66
2			 **2**	68	64
3			 **3**  **4**	18[b]	42[b]
4			 **5**	50	—
5			 **6**	69[c]	65[c]
6			 **7**	49, 60[c]	41
7			 **8**	31	25
8			 **9**	87	74
9			 **10**	99	38
10			 **11**	67[c]	63[c]
11			 **12**  **13**	85[d]	86[d]
12			 **14**	93	88

[a] General reaction conditions: phenol/naphthol (1 equiv.), diene (1.5 equiv.), $Cu(OTf)_2$ (0.05 equiv.), ligand (0.025 equiv.), DCE, 50 °C, 18 h. Reported yields correspond to isolated products after column chromatography, averaged over two runs. [b] **3** : **4** = 68 : 32. [c] $Cu(OTf)_2$ (0.5 equiv.), ligand (0.25 equiv.). [d] **12** : **13** = 40 : 60.

Invariably, much better yields were obtained from reactions using 2-naphthol (Table 2, entries 1–5 *vs.* 8–12). The lower yield afforded by 4-chlorophenol was largely due to slow turnover. This could be improved by using a higher catalyst loading (Table 2, entry 6). In contrast, the low yield of product obtained from the reaction of phenol was due to a different reason; although the phenol substrate was completely consumed, very little of the expected product was obtained

Table 3 Performance of recycled Cu–bipy catalyst in the addition of 4-methoxyphenol and naphthol to isoprene[a]

		Yield (%)[b]			
ArOH	Product	Run 1	Run 2	Run 3	Run 4
4-Methoxyphenol	**1**	69	60	64	62
2-Naphthol	**9**	82	80	84	87

[a] General reaction conditions: ArOH (1 mmol), isoprene (1.5 mmol), solvent (1 mL), 50 °C, 18 h. [b] Isolated yield after column chromatography.

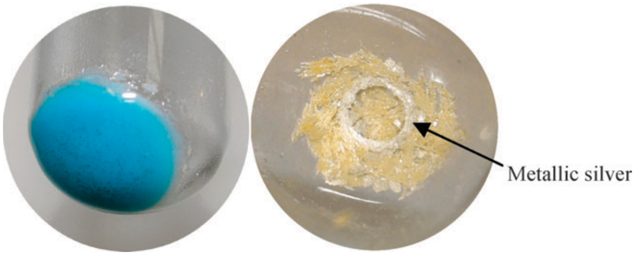


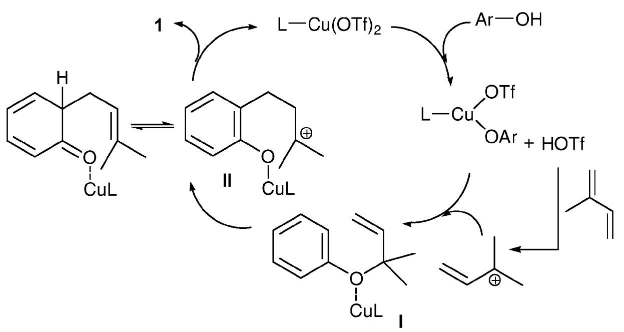
Fig. 1 Appearance of catalysts at the end of the reaction. Left: Cu(II)–bipy complex. Right: Decomposition of silver (separated from bipy).

(Table 2, entry 7). Instead, the reaction mixture contained an intractable mixture of highly-coloured products, which was attributed to the polymerisation of phenol, a process known to be catalysed by Cu(II)–bipy.[9]

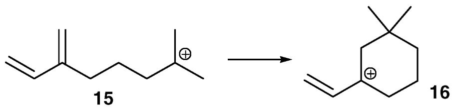
Use of the bipy ligand furnished a paramagnetic sky-blue precipitate at the end of the reaction, most likely to be a polymeric copper(II) complex. As the metal possesses a robust +2 oxidation state, it could be easily recovered and reused in at least four successive reactions in air without any detectable loss in activity (Table 3).[10] In contrast, AgOTf–bipy decomposed under these conditions, clearly depositing a silver mirror in the reaction vessel (Fig. 1).

A catalytic cycle involving Brønsted and Lewis acid catalysis has been evoked to explain the observed pattern of reactivity (Scheme 1). Ligand metathesis at copper generates TfOH, initiating the hydroalkoxylation reaction. The Lewis acidic copper(II) complex facilitates the aromatic Claisen rearrangment of intermediate **I** to **II**, which then undergoes a second hydroalkoxylation to furnish the heterocycle.[11]

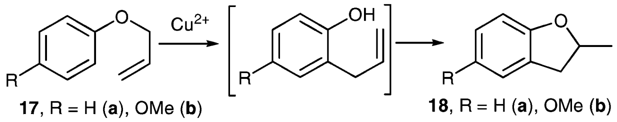
The proposed mechanism complements the following observations: (1) Product mixtures obtained from 2,3-dimethylbutadiene (Table 2, entries 3 and 11) can be explained by the competitive formation of tertiary carbocations in intermediate **II**; (2) lower efficiency for the addition to cyclohexadiene (Table 2, entries 5 and 10) is associated with the difficulty of generating secondary carbocations; and (3) myrcene is protonated initially at the trisubstituted alkene to form carbocation **15**, which cyclised to form **16** (Scheme 2), leading eventually to the formation of the spiro-product.



Scheme 1 Proposed catalytic cycle, illustrated for the reaction between phenol and 2,3-dimethyl butadiene.



Scheme 2 Formation of cyclic carbocations from myrcene.



Scheme 3 Cu-catalysed intramolecular cyclisation of an allyl aryl ether.

The Claisen rearrangement has previously been implicated in the intramolecular cyclisation of allyl aryl ethers (Scheme 3).[12] Reactions proceeded in the presence of 5 mol% Cu(OTf)$_2$, providing 2-methyl dihydrofuran **18a** from **17a** in 44% yield, under similar reaction conditions (DCE, 60 °C, 24 h). The result was duly replicated with **17b** using the Cu(OTf)$_2$–bipy catalyst, to furnish **18b** in 63% yield after 3 h.

In conclusion, this work demonstrates that Cu can have a comparable activity to Ag and Au catalysts in intermolecular annulation reactions of ArOH with 1,3-dienes. The Cu–bipy system has considerable advantages over other catalysts in terms of its cost, aerobic stability, ease of handling and recyclability.

We thank the Ministerio de Educación y Ciencia (project number CTQ2006-15621-C02-01/BQU) and Xunta Galicia for postdoctoral support (L. A. A.).

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