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Regioselective synthesis of phthalans via $Cu(OTf)_2$-catalyzed 5-*exo*-*dig* intramolecular hydroalkoxylation of 2-(ethynyl)benzyl alcohols

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ABSTRACT

An efficient, regioselective $Cu(OTf)_2$-catalyzed 5-*exo*-*dig* intramolecular hydroalkoxylation of 2-(ethynyl)benzyl alcohol, which provides a concise access to functionalized phthalan in high yields has been developed. A wide range of substrates possessing terminal, internal, and heteroaromatic alkynes can be efficiently transformed into the targeted phthalans. Substrates with primary, secondary, and tertiary benzyl alcohols also proceed well to produce the corresponding phthalans in good yields. Irrespective of the nature of the substrates, the cyclization follows highly selective 5-*exo*-*dig* regiochemistry when regioselectivity is an issue.

Phthalans (1,3-dihydroisobenzofurans) have drawn considerable interest in organic chemistry, not only as useful building blocks[1] but also as key structural units in several natural products[2] and biologically active compounds.[3] For example, pestacin **1** (Fig. 1) isolated from the endophytic bacteria, *Pestalotiopsis microspora* exhibits potent antioxidant and antimycotic activities.[2e,f] Escitalopram **2** is an antidepressant of the selective serotonin reuptake inhibitor class.[3a] Molecule **3** (RPR 225,370) is a farnesyl transferase inhibitor with good cellular potency.[3c] Compound **4** is a representative of a group of molecules, possessing isobenzylidene ring system, proven to be a potential tyrosine kinase inhibitor.[3d]

While many synthetic routes for phthalans exist, they are still limited by the acidic/basic reaction conditions or narrow applicability to substrates.[4] On the other hand, cycloisomerization of 2-(ethynyl)benzyl alcohol offers opportunities for constructing oxygenated heterocycles and has attracted considerable attention in recent years.[5] This transformation relies on the catalytic activation of the C–C triple bond followed by the nucleophilic attack of the tethered hydroxyl function. Although these reactions have been extensively studied by a number of research groups,[5] the results in most cases offer no regioselectivity and lead to the formation of either isochromenes,[5a,h,j] or both isochromenes and phthalans.[5b,d,e] Moreover, most of these protocols suffer the limited use of pricey catalysts such as $CpRuCl(PPh_3)_2$,[5a] $La[N(SiMe_3)_2]_3$,[5i,o] Py-Pd-NHC,[5f] and hydridoiridium(III) complexes[5h] or the stoichiometric use of hazardous reagents such as NaH,[5m] NaOH,[5m] $^nBu_4NF$,[5d] $Hg(OAc)_2$,[5g] I_2,[5b] and metallic sodium.[5q] In the context of our ongoing studies on heterocyclic constructions,[6] the possibility of regioisomeric cyclization of 2-(ethynyl)benzyl alcohol leading to phthalan appeared attractive from the viewpoint of devising a regioselective synthetic route (phthalan vs isochromene). Herein, we describe $Cu(OTf)_2$-catalyzed 5-*exo*-*dig* cycloisomerization of 2-(ethynylbenzyl) alcohols, leading to phthalan derivatives. We started our investigation with 2-(phenylethynyl)benzyl alcohol **1a** which was prepared from the Sonogashira coupling of 2-iodobenzyl alcohol and phenyl acetylene (Scheme 1).[7]

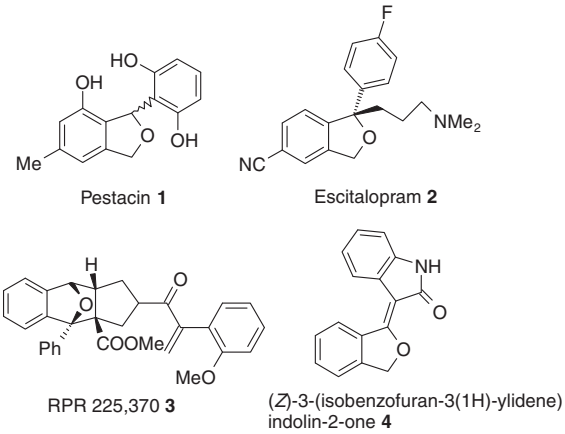

Figure 1. Biologically active compounds containing isobenzofuran scaffold.

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E-mail address: ptperumal@gmail.com (P.T. Perumal).

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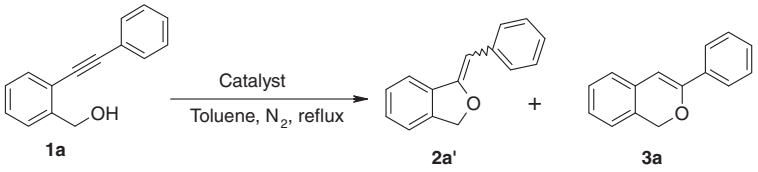
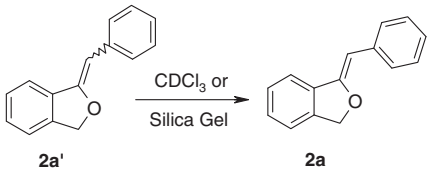


Scheme 1. Screening of different Lewis acids for the cyclization of model substrate **1a**.

Table 1
Screening of carbophilic Lewis acids for the cyclization of **1a**[a]

Entry	Catalyst (5 mol %)	Regioisomeric ratio (%)		Yield[b] (%)
		Phthalan (**2a′**)	Isochromene (**3a**)	
1	$AuBr_3$	35	65	70
2	$In(OTf)_3$	55	45	75
3	$PtCl_2$	100	—	20
4	$Zn(OTf)_2$	51	49	70
5	$NiBr_2$	44	66	25
6	$Cu(OTf)_2$	100	–	95

[a] Crude ^1H NMR yield obtained in $CDCl_3$ solvent.
[b] All reactions were carried out in 20 min.



Scheme 2. Isomerization of **2a′**–**2a**.

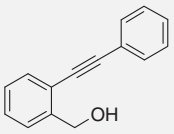
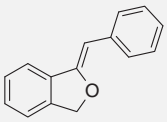
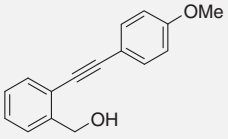
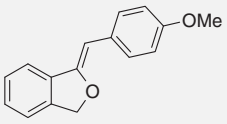
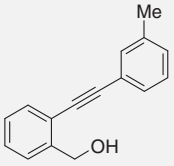
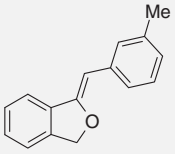
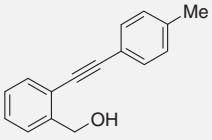
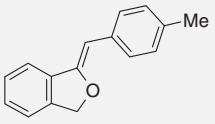
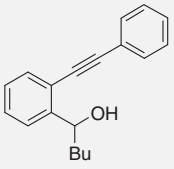
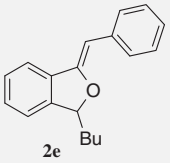
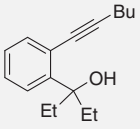
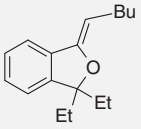
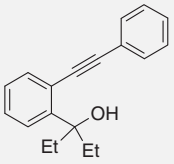
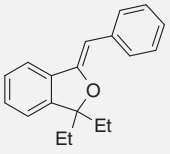
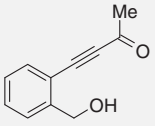
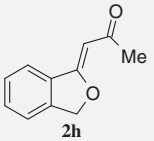
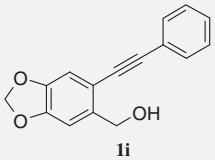
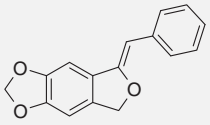
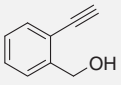
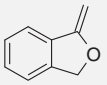
Treatment of **1a** with 5 mol % of $AuBr_3$ in toluene[8] at reflux temperature for 20 min resulted in the formation of the expected isochromene **3a** and phthalan **2a′** in 35:65 ratio and with 20% of the starting material remains unconsumed, as evidenced by crude ^1H NMR analysis (Table 1, entry 1). In order to improve the formation of the targeted phthalan exclusively, we screened different carbophilic Lewis acids. The results revealed that the use of $In(OTf)_3$ led to the product formation in 75% yield, with equal amount of phthalan **2a′** and isochromene **3a** (entry 2). In contrast, the use of $PtCl_2$[9] resulted in slower reactions and decreased yields of **2a′** because of the incomplete conversion and partial decomposition of the substrate (entry 3). The conversion of **1a** was also catalyzed by $Zn(OTf)_2$, although a mixture of both regioisomers was obtained (entry 4). The use of $NiBr_2$ resulted in a poor yield of products (entry 5). Finally, treatment of **1a** with 5 mol % of $Cu(OTf)_2$[10] in toluene at reflux temperature led to the regioselective 5-*exo*-*dig* cyclization within 1 h to give the corresponding phthalan **2a′** in a quantitative yield (entry 6). Although, the reaction yielded the desired phthalan **2a′** in an excellent yield, the stereochemistry of the product was not fixed. Crude ^1H NMR analysis indicated the formation of both the *Z* (=C*H*, δ_H = 5.95 ppm) and the *E* (=C*H*, δ_H = 6.49 ppm) isomers in 88:12 ratios. However, when the NMR spectrum of the same mixture was recorded after 6 h it revealed the formation of only the *Z*-isomer. Our attempts at separating the two isomers on a silica gel column led to the *Z*-isomer exclusively. These observations confirmed the isomerization of the minor *E*-isomer to the thermodynamically more stable *Z*-isomer **2a**, under $CDCl_3$ or silica gel condition (Scheme 2).

Encouraged by the high regioselectivity and excellent yield, we next set out to examine the scope of the reaction, by treating various substituted 2-(ethynyl)benzyl alcohols with $Cu(OTf)_2$ and obtained the corresponding phthalans **2a**–**2o** in high yields (Table 2).[11] The reaction appears to be general and works well regardless of the nature of the substituents on the triple bond terminus. However, alkynes possessing electron-rich groups enhance the cyclization and generally higher yields are obtained at a shorter reaction time (entries 2–4). The presence of substituent at the benzylic position did have deleterious effects on the cyclization; primary alcohols underwent cyclization significantly (entries 1–4, 8–10, and 13–15) in terms of shorter reaction times and higher yields, than the secondary alcohols (entries 5, 11, and 12), which in turn react efficiently than their tertiary counterparts (entries 6 and 7). The copper-catalyzed cyclization of substrate **1l** is particularly noteworthy of these functionalities, only the hydroxyl group reacts to afford phthalan **2l** in a good yield, leaving the amine group intact. Our method also finds application in a more complex heteroaromatic synthesis as well. For example, the piperanol-derived substrate **1i** gave an excellent yield of the product **2i** under the same reaction conditions.[11] It is noteworthy to mention that substrates possessing heteroaromatic motif like pyridine **1n** and pyrazine **1o** tolerated well under our reaction conditions (entries 14 and 15). A preparative scale-catalytic reaction was performed for the reaction of **2j**–**2m** in benzene-d_6, since these compounds readily underwent decomposition in $CDCl_3$ solvent.[12] The *Z*-configuration of phthalan was assigned from the comparison of the chemical shifts of the vinylic protons with those reported for similar compounds.[5d] The (*Z*)-stereochemistry of phthalan **2i** has been assigned using a 1-D NOE experiment. Selective irradiation of the vinylic proton effected the enhancement of the signals of C_4–H (9.1%) and *ortho*-phenyl proton (16.7%), respectively. Irradiation of C_4–H effected the enhancement of vinylic proton (7.5%) and no enhancement of *ortho*-phenyl proton. This observation confirmed that the vinylic proton is *cis* to C_4–H, thus the compound **2i** is *Z*-configured. Similarly, for compound **2c**, irradiation of vinylic proton effected the enhancement of both C_4–H (11.5%) and *ortho*-phenyl proton (22.4%). Irradiation of C_4–H proton however effected the enhancement of vinylic proton (8.7%) and no enhancement of the *ortho*-phenyl proton. These facts confirmed the *cis* relationship of the vinylic proton and C_4–H, thus favoring the *Z*-configuration (Fig. 2). The stereochemistry of the other phthalan is assigned by analogy to **2i** and **2c**.

In IR spectra, a peak observed at 1620–1650 cm^{-1} for all compounds revealed the presence of an ether linkage. In ^1H NMR spectra, all products exhibited a sharp singlet between δ_H 4.75 (for unsubstituted olefins) and 6.43 ppm (for substituted olefins) and indicated the presence of vinylic proton. In ^{13}C NMR spectra, a peak at δ_c 120–125 ppm ascertained the presence of olefinic carbon, characteristic of the exocyclic alkylidene carbon of isobenzofuran. All these findings confirmed the formation of phthalans.

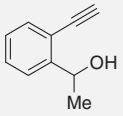
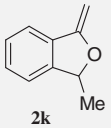
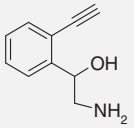
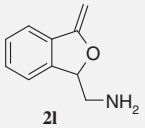
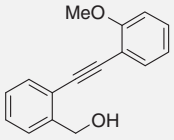
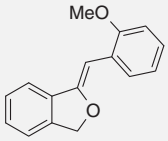
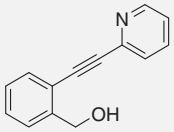
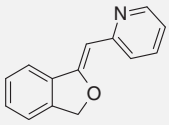
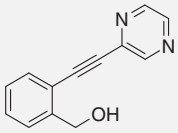
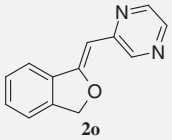
The reason for the exclusive formation of the five-membered ring over their six-member counter part was not clear. However, a tentative mechanism, on the basis of the obtained results is proposed (Scheme 3), according to which a six-membered transition state **4** was formed via a bidentate complexation of [Cu] with the hydroxyl group and α-carbon of the alkyne of **1**. As a consequence, a partial depletion of electron density at the β-carbon of the acetylene function drives the nucleophilic attack of the pendant hydroxyl group toward the β-carbon leading to the five-membered

Table 2
Copper(II)-catalyzed synthesis of phthalans via cycloisomerisation of 2-(ethynyl)benzyl alcohols[a]

Entry	2-(Ethynyl)benzyl alcohol (**1**)	Phthalan (**2**)[b]	Time (min)	Yield (%)[c]
1	 **1a**	 **2a**	20	92
2	 **1b**	 **2b**	20	95
3	 **1c**	 **2c**	45	94
4	 **1d**	 **2d**	45	95
5	 **1e**	 **2e**	30	88
6	 **1f**	 **2f**	3.5	76
7	 **1g**	 **2g**	40	79
8	 **1h**	 **2h**	25	86
9	 **1i**	 **2i**	30	85
10	 **1j**	 **2j**	25	85[d]

(*continued on next page*)

Table 2 (*continued*)

Entry	2-(Ethynyl)benzyl alcohol (**1**)	Phthalan (**2**)[b]	Time (min)	Yield (%)[c]
11	 **1k**	 **2k**	40	75[d]
12	 **1l**	 **2l**	30	77[d]
13	 **1m**	 **2m**	40	87[d]
14	 **1n**	 **2n**	35	75
15	 **1o**	 **2o**	55	78

[d] The reaction was carried out in benzene-d_6 solvent at 65 °C.
[a] All reactions were carried out at 110 °C in toluene using 5 mol % of $Cu(OTf)_2$ under nitrogen atmosphere.
[b] All products were characterized by IR, ^1H NMR, ^{13}C NMR, and mass spectroscopy.
[c] Isolated yield.

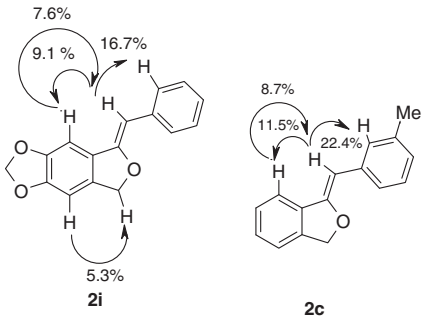


Figure 2. 1-D NOE enhancement of compounds **2i** and **2c**.

intermediate **5**. Subsequent protodecupration of **5** results in the formation of phthalan **2**.

In summary, we have developed an effective Cu-catalyzed intramolecular hydroalkoxylation of various 2-(ethynyl) benzyl alcohols leading to the regioselective synthesis of substituted phthalans. Substrates possessing tertiary, secondary, and primary benzyl alcohols and alkynes having hydrogen, alkyl, aromatic, and heteroaromatic groups can be used in this procedure. For reasons that are not clear, this Cu(II)-catalyzed protocol affords only the five-membered oxygenated heterocycle. We are in the process of examining the relationship between the regioselectivity and the Lewis acidity of $Cu(OTf)_2$. DFT computational studies are now being evaluated to reason out the predominant formation of phthalans over isochromenes. Biological activity of the synthesized compounds is underway in our laboratory and will be reported in due course.

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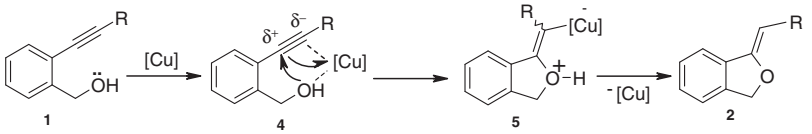
Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.07.030.



Scheme 3. Plausible mechanism for the formation of isobenzofuran **2**.

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11. Representative procedure for the synthesis of (*Z*)-5-benzylidene-5,7-dihydrofuro[3′,4′:4,5]benzo[1,2-*d*][1,3]dioxole (**2i**): To a degassed solution of (5-(2-phenylethynyl)benzo[*d*][1,3]dioxol-6-yl)methanol (**1i**, 252 mg, 1.0 mmol) in dry toluene (1 mL) under N_2 was added $Cu(OTf)_2$ (18.08 mg, 0.018 mmol) and the reaction mixture was stirred at 110 °C for 30 min. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated under reduced pressure and was purified by column chromatography over silica gel (100–200 mesh) to afford the pure product of **2i** in 85% (214 mg) yield as a pale yellow solid; mp 132–134 °C; IR (KBr) 2898, 1733, 1632, 1481, 1367, 1291, 1152, 1035, 860, 757 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ_H 5.11 (s, 2H, –O*CH*$_2$Ar); 5.93 (s, 2H, –O*CH*$_2$O–); 6.36 (s, 1H, =*CH*); 6.60 (s, 1H, C_8–*H*); 6.62 (s, 1H, C_4–*H*); 7.32–7.38 (m, 3H, Ar-*H*); 7.69 (d, 2H, *J* = 6.8 Hz, Ar-*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ_C 69.0, 101.0, 101.4, 104.6, 105.2, 121.5, 124.8, 126.3, 128.4, 128.7, 134.2, 146.1, 147.5, 152.7. MS (EI): *m*/*z* = 253 $[M+H]^+$. Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.79. Found: C, 75.99; H, 4.85.
12. Representative procedure for the intramolecular hydroalkoxylation of **2m** in C_6D_6: To an NMR tube equipped with a screw cap containing benzene-d_6 (0.50 mL) under argon, 2-(2-(2-methoxyphenyl)ethynyl)phenylmethanol (**1m**, 50.0 mg, 0.21 mmol) and $Cu(OTf)_2$ (3.79 mg, 0.0105 mmol) were added. The resulting mixture was heated at 65 °C and monitored by NMR until the starting material had been consumed. At completion of the reaction, this reaction mixture was filtered through a small plug of silica gel to remove the catalyst. The crude product was purified by silica gel column chromatography (petroleum ether/AcOEt 9.5:0.5) to afford the pure product of (*Z*)-1-(2-methoxy-benzylidene)-1,3-dihydro-isobenzofuran **2m** in 87% (43 mg) yield as a brown oil. IR (neat): 3308, 2938, 2189, 1635, 1427, 1327, 1200, 1076, 878 cm^{-1}. ^1H NMR (500 MHz, benzene-d_6): δ_H 3.25 (s, 3H, –O*CH*$_3$); 4.92 (s, 2H, –O*CH*$_2$Ar); 6.48–7.05 (m, 8H, Ar-*H*); 7.92–7.93 (m, 1H, Ar-*H*). ^{13}C NMR (125 MHz, benzene-d_6): 54.8, 68.5, 107.0, 111.2, 120.4, 123.7, 123.8, 126.2, 128.3, 128.5, 128.8, 129.4, 129.6, 132.6, 151.4, 157.6. MS (EI): *m*/*z* = 239 $[M+H]^+$. Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.92. Found: C, 80.85; H, 5.86.