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Time and Temperature Dependent Palladium-Catalyzed Stereo- and Regioselective Alkoxy-arylation of Triple Bonds: Synthesis of (*E*)/(*Z*)-1,1-Disubstituted-3-(1-Phenylalkylidene)-1,3-dihydroisobenzofurans

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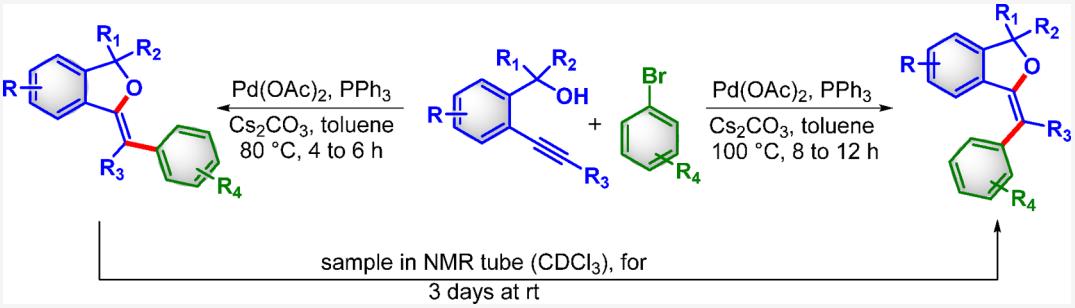

ABSTRACT: The development of synthetic strategies enabling the *stereo-* and *regio*-selective synthesis of organic molecules is indispensable in the pharmaceutical industry. This work describes a *stereo-* and *regio*selective synthesis of (*E*)/(*Z*)-1,1-disubstituted-3-(1-arylalkylidene)-1,3-dihydroisobenzofurans catalyzed by palladium. The DHIBFs are achieved from readily available aryl bromides and *ortho*-alkyne tertiary alcohols *via* intermolecular aryl Heck coupling and intramolecular *oxo*-cyclization of the suitably situated hydroxyl group. Significantly, it was demonstrated that a *Z*-isomer was formed as a substantial isomer at 80 °C for 6 h, whereas the stable *E*-isomer was the predominant one at slightly vigorous conditions (100 °C for 12 h). In addition, careful observation has also led to the realization that this double isomerization from *Z*- to *E*-isomer was triggered in the NMR tube itself in $CDCl_3$ at room temperature. Significantly, this protocol, for the first time, enabled the synthesis of heavily substituted dihydroisobenzofurans, especially, bearing a tetra-substituted double bond.

INTRODUCTION

The dihydroisobenzofurans are major building blocks in the natural product synthesis and are used as a core nucleus in many bioactive compounds.[1] Particularly, 1,3-dihydroisobenzofuran (phthalan) derivatives are known to exhibit a wide variety of drug-like properties,[2−5] such as potent antioxidant,[6] antidepressant, antihistaminic,[7] anti-inflammatories,[8,9] and antifungal properties, etc.[10,11] Therefore, the synthesis of dihydroisobenzofurans has drawn considerable attention from the synthetic community. Generally, the intramolecular cyclizations of 2-alkynyl phenyl ketones have been well explored to accomplish isobenzofurans,[12] isocoumarins,[13] isoindoline-1-ones,[14] cyclic imidates,[15] and dihydroisobenzofurans.[16−19] Jiang *et al.* reported the *β*-alkynyl ketones chemistry to synthesize *spiro-* and *dispiro*-1*H*-chromenes/chromenes.[20−23] Later on, the same group explored the synthesis of isobenzofurans from *β*-alkynyl ketones *via* Pd(II) catalysis,[12] concomitantly reporting the synthesis of sulfonated 1,3-dihydroisobenzofurans from *β*-alkynyl ketones *via* a radical MCR (Multi-Component Reactions) process.[24] At the same time, the intramolecular cyclization of 2-(1-alkynyl) tertiary benzylic alcohols was also well explored (Figure 1). Larock *et al.* demonstrated the synthesis of 1*H*-isochromenes and 1,3-dihydroisobenzofurans by iodocyclizations of 2-alkyne benzylic alcohols (Figure 1a).[25] Simultaneously, the research group of Costa presented the sequential nucleophilic ring-opening and heterocyclization, followed by oxidative carbonylation of alkynyloxiranes (Figure 1b).[26] Zhu and co-workers described the synthesis of 1,3-dihydroisobenzofurans using copper catalysis (Figure 1c).[11] In 2012, Perumal *et al.* reported the synthesis of 1,3-dihydroisobenzofurans and their antidepressant activity (Figure 1d).[11] In 2016, You *et al.* revealed the synthesis of dihydroisobenzofurans *via* alkyne/alkene directed

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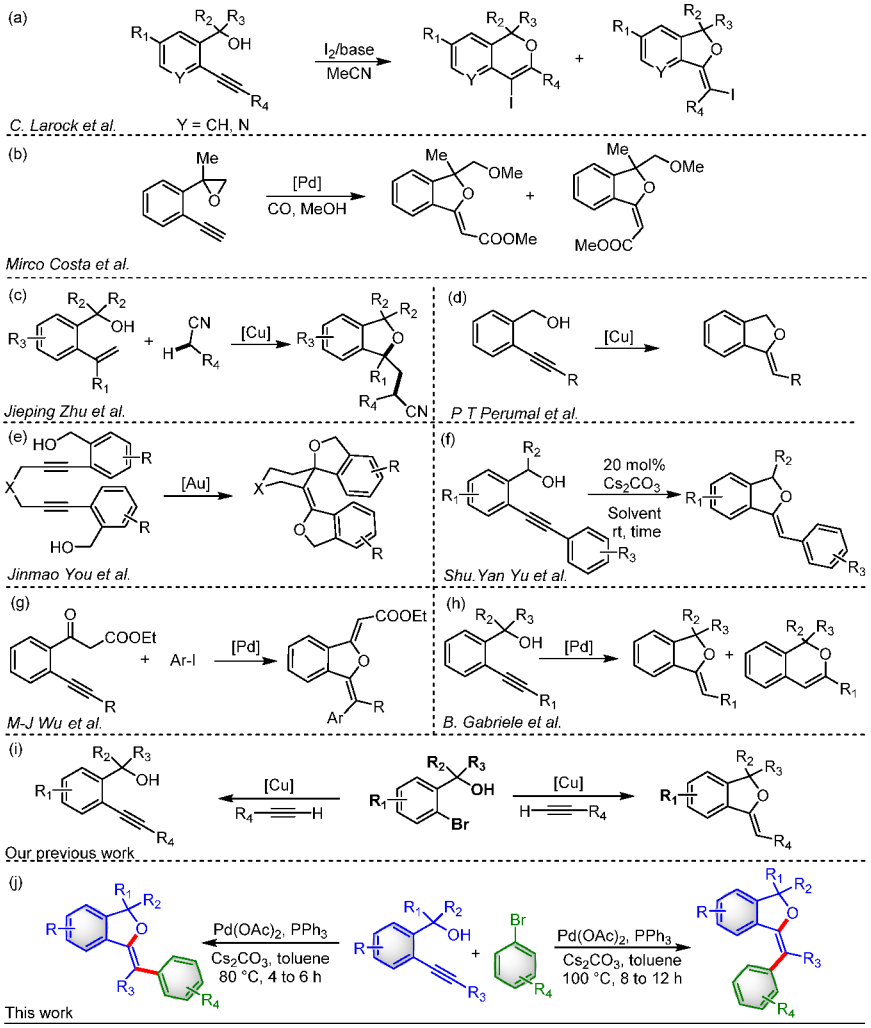

Figure 1. A comparison chart of earlier versus the present study to dihydroisobenzofurans.

5-*exo-dig* cyclization (Figure 1e).[27] Intramolecular hydroalkoxylation of 2-(1-alkynyl) tertiary benzylic alcohols was reported by Yu *et al.* (Figure 1f).[28] A palladium-catalyzed tandem oxocyclization/coupling process of ethyl 3-(2-alkynylphenyl)-3-oxopropanoates with aryl iodides to furnish dihydroisobenzofurans has been developed by Wu in 2015 (Figure 1g).[16] The research group of Gabriele has reported the synthesis of (*Z*)-1-alkylidene-1,3-dihydroisobenzofurans and 1*H*-isochromenes *via* cycloisomerization of 2-alkynylbenzyl alcohols by a palladium catalyst (Figure 1h).[18] In our earlier work, we described the dihydroisobenzofurans synthesis *via* Sonogashira coupling and subsequent intramolecular 5-*exo-dig* cyclization (Figure 1i).[29] To date, a reasonable number of reports were accomplished on the synthesis of dihydroisobenzofurans, majorly with a tri-substituted double bond moiety. In this respect, the synthesis of dihydroisobenzofurans with a tetra-substituted double bond has been scarcely explored.[17,30−33] Nevertheless, to the best of our knowledge, no report was developed on the synthesis of tetra-substituted exocyclic double bond containing 1,1-dialkyl/1,1-alkyl/1,1-diaryl-3-(1-arylalkylidene)-1,3-dihydroisobenzofurans. Herein, we present stereo- and regioselective synthesis of *E*- and *Z*-isomers of dihydroisobenzofurans from 2-(1-alkynyl) tertiary benzylic alcohols and aryl bromides *via* an intermolecular aryl Heck coupling and intramolecular *oxo*-cyclization path. Notably, it was observed that the process is time and temperature dependent to form the *Z*- or *E*-isomer of the product.

RESULTS AND DISCUSSION

The initial investigation began by choosing 2-(2-(oct-1-yn-1-yl)phenyl)propan-2-ol **1a** and bromobenzene **2a** as the model substrates. At first, the reaction was performed in the presence of $Pd(OAc)_2$, ligand PPh_3, and base Cs_2CO_3 at 110 °C in toluene (1.5 mL) for 24 h. The expected product dihydroisobenzofuran **3aa** was obtained in moderate (48%) yield (Table 1, entry 1). At the same time, the reaction with Na_2CO_3 and Ag_2CO_3 as mild bases furnished the product **3aa**, in 34% and 33% yields, respectively (Table 1, entries 2 and 3). When the reaction was conducted in the presence of base $CsCO_3$ and Ag_2O as an additive (1 equiv), the yield of **3aa** was further dropped to 20% yield (Table 1, entry 4). Also, the combination of Na_2CO_3 (2 equiv) and Ag_2O (0.2 mmol) was inferior and led to a complex mixture (Table 1, entry 5). When X-Phos was used as a ligand in place of PPh_3, trace amounts of **3aa** were observed (Table 1, entry 6). On the other hand, the reaction with reduced reaction times of 12 and 6 h afforded **3aa** with slightly increased yields of 51% and 55%, respectively (Table 1, entries 7 and 8). Further decreasing the reaction time to 2 h at 110 °C gave **3aa** in 61% yield (Table 1, entry 9).

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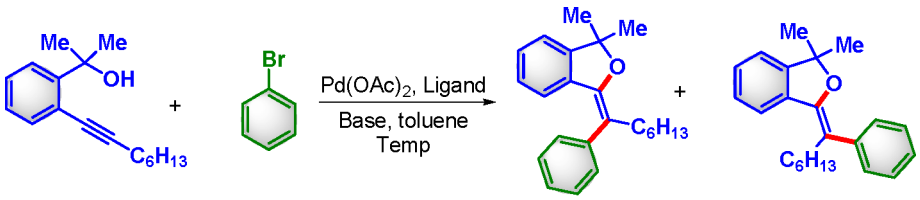
Table 1. Optimization of Reaction Conditions[a,b,c,d,e,f]



1a **2a** **3aa** **4aa**

S no.	ligand	base (2 equiv)	temp (°C)	time (h)	yield (%) **3aa** and **4aa**
1	PPh_3	Cs_2CO_3	110	24	48 and –
2	PPh_3	Na_2CO_3	110	24	34 and –
3	PPh_3	Ag_2CO_3	110	24	33 and –
4	PPh_3	Cs_2CO_3	110	24	20[c] and –
5	PPh_3	Na_2CO_3	110	24	TLC not clear[c]
6	X-Phos	Cs_2CO_3	110	24	trace
7	PPh_3	Cs_2CO_3	110	12	51 and –
8	PPh_3	Cs_2CO_3	110	6	55 and –
9	PPh_3	Cs_2CO_3	110	2	61 and –
10	PPh_3	Cs_2CO_3	110	2	62[d] and –
11	PPh_3	Cs_2CO_3	100	2	59 and –
12	**PPh_3**	**Cs_2CO_3**	**100**	**12**	**82 and –**
13	PPh_3	Cs_2CO_3	80	2	– and 45
14	**PPh_3**	**Cs_2CO_3**	**80**	**6**	**<5 and 80**
15	PPh_3	Cs_2CO_3	80	12	15 and 72
16	PPh_3	Cs_2CO_3	80	24	20 and 57
17	PPh_3	Cs_2CO_3	80	48	53 and 12
18		Cs_2CO_3	100	12	32 and –
19	PPh_3	Cs_2CO_3	100	12	– and –[e]
20	PPh_3	Cs_2CO_3	100	12	54 and –[f]

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.03 mmol), Cs_2CO_3 (0.4 mmol), toluene (1.5 mL) at 80 °C. [b]Isolated yields of the products by column chromatography. [c]Additive Ag_2O (0.2 mmol) used. [d]3 equiv of Cs_2CO_3 used. [e]The reaction has been carried out without $Pd(OAc)_2$. [f]Iodobenzene used as arylating agent (0.24 mmol).

Increasing the quantity of base Cs_2CO_3 to 3 equiv furnished **3aa** in 62% yield (Table 1, entry 10). In comparison, the reaction at 100 °C for 2 h led to **3aa** in 59% (Table 1, entry 11). Significantly, a prolonged reaction time (12 h) at 100 °C enhanced the yield to 82% of **3aa** (Table 1, entry 12). The further decrease of temperature to 80 °C for 2 h unpredictably resulted in a 45% yield of *Z*-isomeric product **4aa** (Table 1, entry 13). When the reaction was conducted at 80 °C for 6 h, surprisingly, the product **3aa** yield decreased to <5%, and the *Z*-isomeric product **4aa** yield was increased to 80% (Table 1, entry 14). Furthermore, increasing the reaction time to 12, 24, and 48 h at 80 °C resulted in "15% of **3aa** and 72% of **4aa**", "20% of **3aa** and 57% of **4aa**", and "53% of **3aa** and 12% of **4aa**", respectively (Table 1, entries 15, 16, and 17). The reaction without PPh_3 and with $Pd(OAc)_2$, at 100 °C for 12 h, delivered **3aa** in 32% (Table 1, entry 18). However, when the reaction was conducted without $Pd(OAc)_2$ and with PPh_3 at 100 °C for 12 h, it showed no progress at all (Table 1, entry 19). The reaction was also successful and furnished the product **3aa** in 54% yield when iodobenzene was used instead of bromobezene **2a** (Table 1, entry 20). Overall, this observation favors the geometrical interconversion from the thermodynamically less stable *Z*-isomer to the more stable *E*-isomer at the tetra-substituted double bond.

From the optimization study, the standard reaction conditions are **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.03 mmol), Cs_2CO_3 (0.4 mmol), and toluene (1.5 mL) for 12 h at 100 °C, for the synthesis of thermodynamically stable (*E*)-3-(1-phenylalkylidene)-1,3-dihydroisobenzofuran **3aa** (Table 1, entry 12), and **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.03 mmol), Cs_2CO_3 (0.4 mmol), and toluene (1.5 mL) for 6 h at 80 °C, for the synthesis of (*Z*)-3-(1-phenylalkylidene)-1,3-dihydroisobenzofuran **4aa** (Table 1, entry 14). Next, we turned to evaluate the scope and generality of these conventions. This protocol has wide functional group tolerance; both electron-deficient (NO_2, COMe, CN) and electron-rich aryl bromides (Me, OMe) are compatible, resulting in a variety of substituted dihydroisobenzofuran derivatives.

Various 2-(1-alkynyl) tertiary benzylic alcohols **1a**–**l** are subjected to both electron-rich (3-Me = **2b**, 4-Me = **2c**, 4-OMe = **2e**, and α-naphthyl = **2d**) and electron-deficient (4-bromoacetophenone = **2i** and 4-bromobenzaldehyde = **2l**) aryl bromides under the optimal conditions (Table 1, entry 12), which resulted in 1,3-dihydroisobenzofurans derivatives **3aa**–**gh** (Table 2). Apart from the spectrometric evidence, for the structure determination of dihydroisobenzofuran products **3**, the skeletal structure including the stereo/regioselectivity around the double bond of **3gh** was confirmed from the single-crystal X-ray diffraction analysis (Figure 2, CCDC: 2071793). The ellipsoids are drawn at a 50% probability level (see in the Supporting Information for details).

Surprisingly, when independent coupling reactions were conducted between 2-(5-methoxy-2-(oct-1-yn-1-yl)phenyl)-

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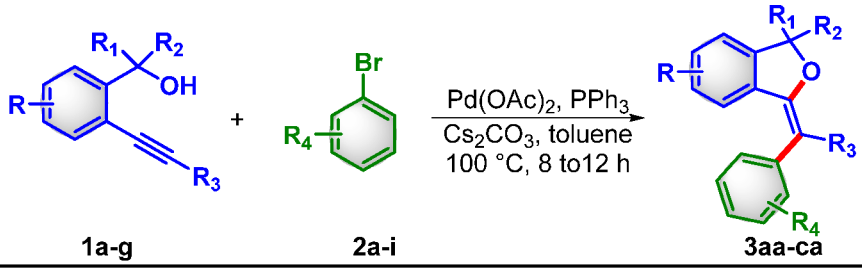
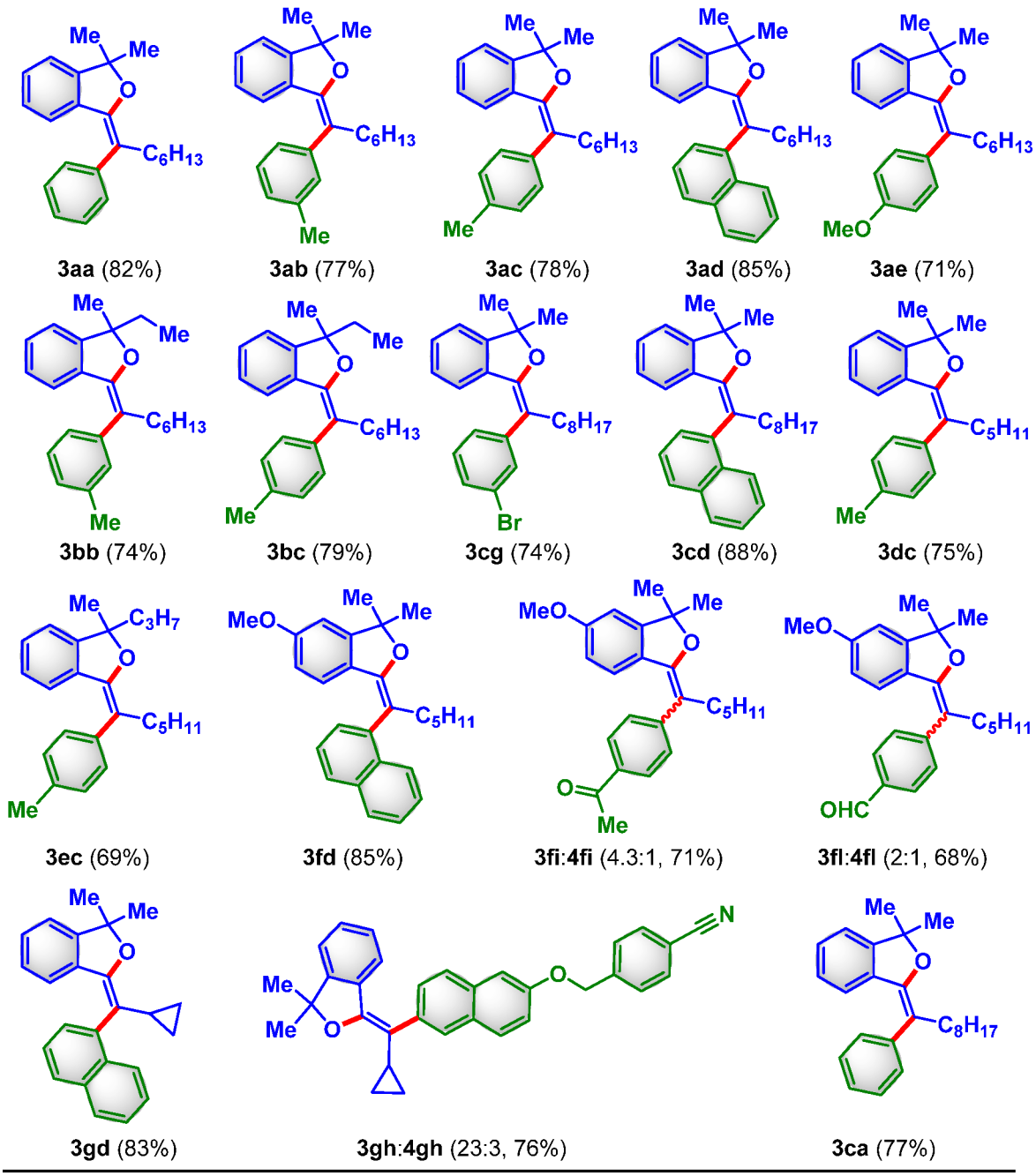
Table 2. Scope of (*E*)-1,1-Dialkyl-3-(1-arylalkylidene)-1,3-dihydroisobenzofurans 3aa−ca[a,b]



1a-g 2a-i 3aa-ca



3aa (82%) **3ab** (77%) **3ac** (78%) **3ad** (85%) **3ae** (71%)

3bb (74%) **3bc** (79%) **3cg** (74%) **3cd** (88%) **3dc** (75%)

3ec (69%) **3fd** (85%) **3fi**:**4fi** (4.3:1, 71%) **3fl**:**4fl** (2:1, 68%)

3gd (83%) **3gh**:**4gh** (23:3, 76%) **3ca** (77%)

[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.03 mmol), Cs_2CO_3 (0.4 mmol), toluene (1.5 mL) at 100 °C. [b]Isolated yields of the products by column chromatography.

propan-2-ol **1f** with electron-deficient haloarenes **2i** and **2l** as arylating agents, they afforded a diastereomeric mixture of products (**3fi**:**4fi** = 4.3:1 ratio, 71%, and **3fl**:**4fl** = 2:1 ratio, 68%). This may be ascribed to the fact that the functional group's electron-withdrawing effect derived from haloarene would make the tetra-substituted double bond of isobenzofur-

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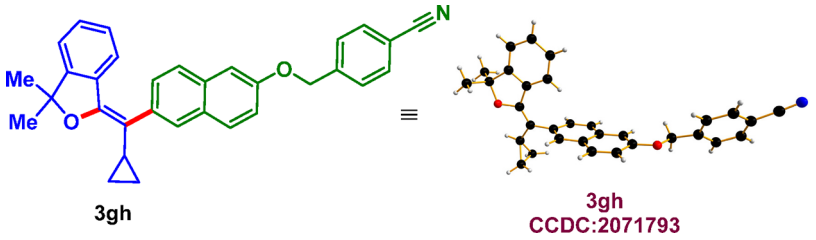

Figure 2. X-ray structure of the product **3gh** with the ellipsoids drawn at the 50% probability level.

an products less nucleophilic and therefore less likely to undergo geometrical isomerism.

As illustrated above (Table 1, entry 14), it would also be feasible to achieve the stereoselective synthesis of (*Z*)-3-(1-phenylalkylidene)-1,3-dihydroisobenzofurans **4**, under controlled conditions of the reaction time and the temperature. Thus, the coupling and cyclo-etherification reactions were performed on 2-(1-alkynyl) tertiary benzylic alcohols **1a**–**l** with different substituted haloarenes **2a**, **2c**, **2d**, **2e**, and **2h**, under standard conditions. The reaction was found compatible and afforded the requisite *Z*-isomeric products (**4dd**, **4ae**, **4ec**, **4gd**, **4cd**, and **4gh**) in good yields (Table 3). Delightfully, the reaction was smooth with bromoarenes connected to electron-deficient groups, such as 4-bromoacetophenone **2i**, 4-nitro-bromobenzene **2j**, 4-nitro-3-fluorobromobenzene **2k**, and methyl 4-bromobenzoate **2m**, at 80 °C for 6 h (Table 1, entry 14). As anticipated, it delivered (*Z*)-3-(1-phenyl-alkylidene)-1,3-dihydroisobenzofurans **4** (i.e., **4ai** in 79%; **4hj** in 76%, and **4gk** in 59% yields, respectively, Table 3). It is interesting to know that chloro substitution on 2-(1-alkynyl) tertiary benzylic alcohols **1k** also underwent smoothly with bromobenzene **2a** and resulted in **4ka** in 73% yield (Table 3). On the other hand, the reaction with 1,1-diphenyl substitution on the aromatic ring of 2-(1-alkynyl) tertiary benzylic alcohol **1l** with 3-bromotoluene **2b** provided the desired product **4lb** in 84% yield (Table 3). Also, the reaction with secondary benzylic alcohol **1i** was successful with an electron-withdrawing ester moiety on bromoarene **2m**, albeit the product **4im** was obtained in a moderate 49% yield. The reaction with primary benzylic alcohol was found to be sluggish and led to the formation of a complex mixture.

Nevertheless, the above optimization study (Table 1) noticed that the *Z*-isomer stereoselectivity seems sensitive to the reaction's time and temperature. On the other hand, it may also be presumed that such a geometrical isomerization would still be triggered by a nonmetal mediated pathway (i.e., the time and mild acidic conditions). Therefore, to further demonstrate this assumption, after confirming the *Z*-isomer's NMR (i.e., for **4ae**, **4ec**, **4gd**, **4cd**, **4ka**, and **4gh**), the compounds in their respective NMR tubes in $CDCl_3$ solution were intentionally kept aside for 3 days at room temperature and resubmitted for NMR spectra (Table 4). To our delight, as predicted, the NMR spectra analysis revealed the complete conversion to stable *E*-isomers of each (i.e., for **3ae**, **3ec**, **3gd**, **3cd**, **3ka**, and **3gh**), as depicted in Table 4. It also noted that there was no further change from the *E*-isomer even after a prolonged time. Whereas with the *Z*-isomer with more electron-withdrawing groups such as NO_2 and CO_2Me derived from aryl bromide, the rate at which isomerization from *Z* to *E* sluggishly took place [i.e., **4gk**:**3gk** = 83:17 (4-NO_2); **4im**:**3im** = 90:10 (4-CO_2Me)], as shown in Table 4.

The NMR spectra for converting *Z*-isomers to the corresponding stable *E*-ones are shown in Figure 3. Both (*E*/*Z*, **3**/**4**) isomeric product structures were unambiguously elucidated by spectroscopic analysis. It is pretty corroborative to note that the proton NMR analysis of bicyclic dihydrobenzofuran aromatic proton peaks of *E*-isomeric product **3** is more shielded than the *Z*-isomeric product **4**. This can be explained based on the diamagnetic anisotropy effect exerted by the other aromatic ring that originated from aryl bromide in *E*-isomer **3**. The aromatic ring derived from the haloarene would adopt a perpendicular orientation to the plane of the bicyclic dihydrobenzofuran ring to relieve the steric strain. As a result, particularly, the *ortho*-proton (highlighted with pink color) would face the diamagnetic ring current resulting from the other aromatic ring of haloarene (green one). Hence, the chemical shift of the pink proton shifted to upfield (i.e., *ortho* proton of **1** shifted from ~δ = 7.85 ppm to 5.73 ppm; also, the alkyl groups on the benzylic carbon and exocyclic double bond connected CH_2 proton peaks are slightly shielded), as shown in Figure 3. Even this sort of diamagnetic anisotropy is extended to the *meta*-proton of the dihydrobenzofuran to a little extent as it is a little farther from the diamagnetic ring current of the aromatic ring of haloarene.

Further, to estimate the synthetic utility of this strategy, it was thought to conduct the reaction on a 1.5 mmol scale. Thus, the reaction of **1c** (409 mg, 1.5 mmol) with **2a** (283 mg, 1.8 mmol), under the optimal conditions (Table 1, entry 12), resulted in the desired product **3ca** (345 mg, 66%) as shown in Scheme 1.

CONTROL EXPERIMENTS

To understand the reaction mechanism of whether the reaction sequence is proceeding through the initial aryl Heck coupling across the triple bond, followed by intramolecular oxo-cyclization, or through an initial intramolecular oxo-cyclization, followed by intermolecular aryl Heck coupling, it was some sort to conduct a few control experiments. Thus, initially, the isobenzofuran **7** was prepared by using the established copper catalysis process developed by us (Scheme 2a).[29] Now, with the compound **7** in hand, next, we explored the reaction to check the feasibility to undergo intermolecular Heck reaction across the tri-substituted double bond of **7** under standard conditions of entry 12 of Table 1 (Scheme 2b). However, the expected Heck product **8** has not been observed and it led to the isolation of the starting material **7**. On the basis of this observation, the possibility of initial oxo-cyclization *via* the formation of an isobenzofuran intermediate and subsequent Heck coupling path may be precluded. At the same time, it may be predicted that the reaction proceeds *via* a sequence of intermolecular aryl Heck coupling, followed by intramolecular oxo-cyclization. Further, to rationalize whether the *E*-isomeric product is formed directly or initially generating

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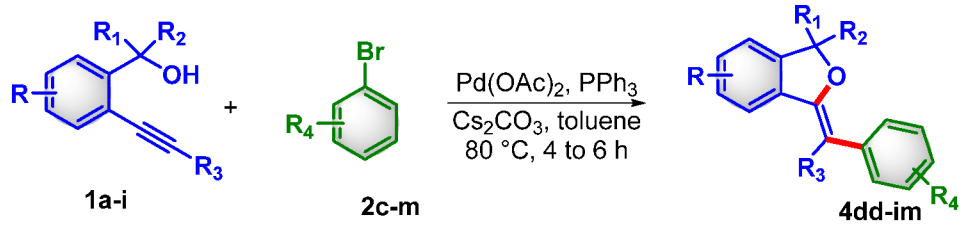
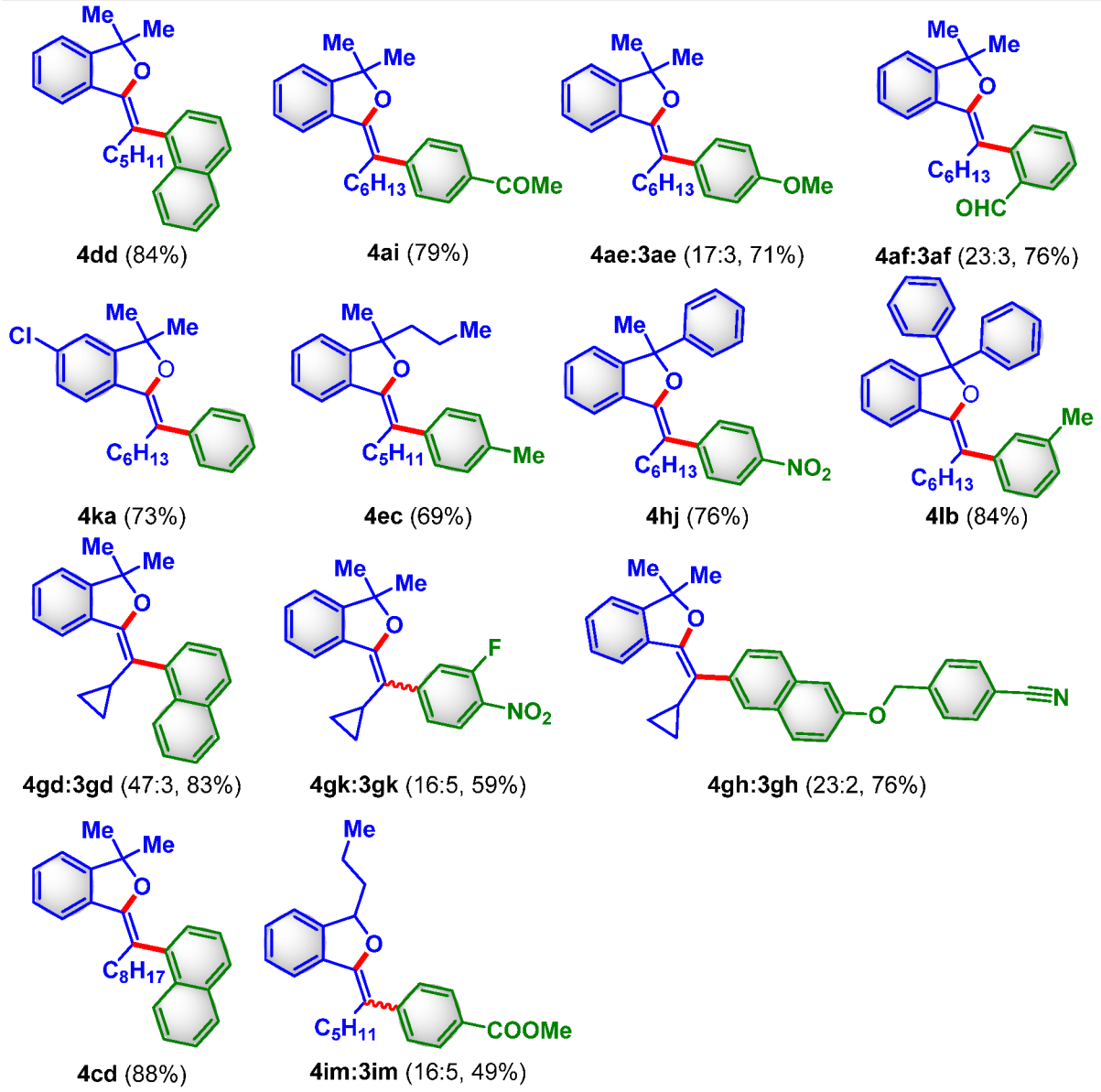
Table 3. Synthetic Scope of (*Z*)-Dihydroisobenzofurans 4dd–im[a,b]





[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Pd(OAc)_2$ (0.01 mmol), PPh_3 (0.03 mmol), Cs_2CO_3 (0.4 mmol), toluene (1.5 mL) at 80 °C. [b]Isolated yields of the products by column chromatography.

the *Z*-isomeric product and then converting into the *E*-isomer in situ in the reaction flask from the *Z*-isomer, we performed a reaction between **1c** and **2a** by using the standard optimal conditions for the formation of the *Z*-isomer (Table 1, entry 14; 80 °C, 6 h). After confirming the formation of the *Z*-isomer **4ca** [by TLC, confirmed that product **4ca** (R_f (**4ca**) = 0.3; using 2% ethyl acetate/hexane) and starting materials **1c** and **2a** got consumed], further, the same reaction was continued at 100 °C for an additional 6 h time, anticipating the conversion of the *Z*-isomer **4ca** to the *E*-isomer **3ca** *via* double bond isomerization. As predicted, at the end of the reaction, the stable *E*-isomer **3ca** was isolated in 69% yield [by TLC, confirmed the formation of **3ca** (R_f (**3ca**) = 0.8; using 2% ethyl acetate/hexane) at the expense of **4ca**], as depicted in Scheme 2 d, based on which it was understood that the reaction would prefer the initial Heck reaction on the triple bond and oxo-cyclization.

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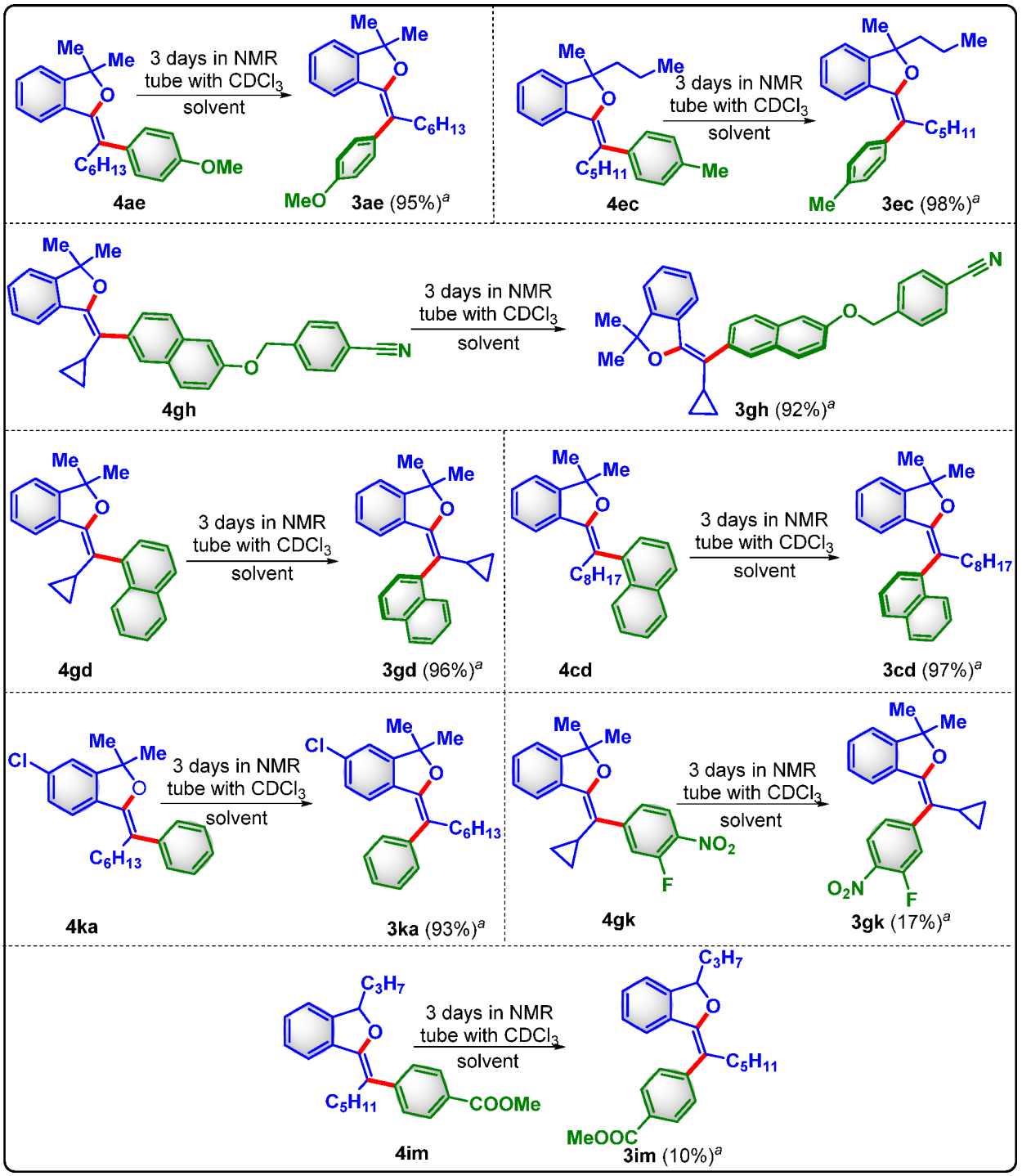
Table 4. Conversion of *Z*-Isomeric Products 4 to *E*-Isomeric Products 3[a,b]



[a]The percentage of conversion from *Z*-isomer to *E*-isomer is as mentioned in the parentheses. [b]The isomeric ratio of *Z*-/*E*-isomers is determined from the ^{1}H NMR spectra.

PLAUSIBLE REACTION MECHANISM

On the basis of the above control experimental observations (Scheme 2), a plausible mechanism is proposed as depicted in Scheme 3. Thus, initially, oxidative addition of Pd(0) catalyst **A** to aryl bromide generates aryl-Pd(II) species **B**. Subsequently, syn-addition of the aryl and palladium of **B** to the alkyne bond in the anti-direction to the *tert*-hydroxyl moiety of **1** furnishes **C**. Then a 180° rotation around the C−C bond of aryl and alkenyl palladium species gives **D** *via* **path a**, which, upon HBr elimination, would yield palladacycle **E**. The intermediate **D** may also be formed directly *via* a syn-addition of the aryl and palladium of **B** across the triple bond in the syn-direction to the *tert*-hydroxyl moiety of **1** *via* **path b**. Through reductive elimination of the palladacycle, **E** forms *Z*-isomeric product **4** and regenerates Pd(0) species **A**. With the experimental observations, thermodynamically unstable *Z*-isomeric product **4** is converting into stable *E*-isomeric product **3** in two pathways. One way is in the presence of

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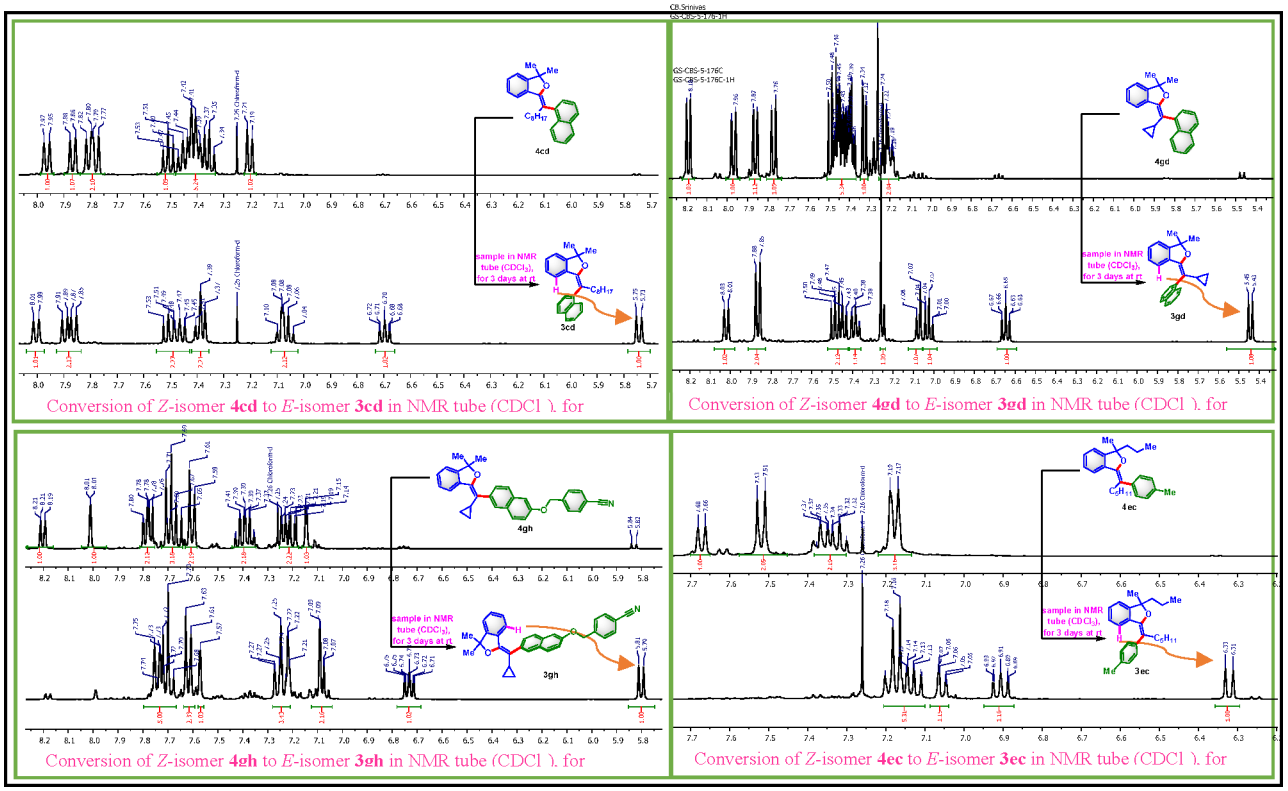
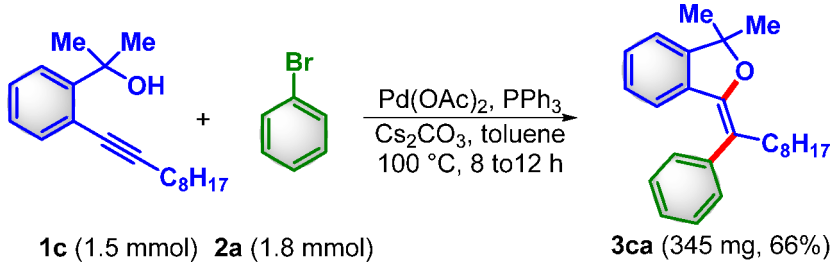


Figure 3. ^{1}H NMR spectra of *Z*-isomeric product **4** converted into *E*-isomeric product **3**.

Scheme 1. Scale-Up Experiment to Give 3ca



1c (1.5 mmol) **2a** (1.8 mmol) **3ca** (345 mg, 66%)

palladium catalyst at an elevated temperature like 100 °C and a prolonged reaction time *via* intermediate **F**, as observed in Scheme 2d. In another way, mild acidic solvent $CDCl_3$ triggers the isomerization *via* intermediate **G** (as noted from Table 4).

In conclusion, this paper dealt with a palladium-catalyzed intermolecular Heck coupling and intramolecular oxo-cyclization enabling the access to (*E*)/(*Z*-)-(3-(alkyl(aryl)-methylene)-1,1-dialkyl-1,3-dihydroisobenzofurans, in a highly stereoselective manner. For the first time, this protocol allows the synthesis of dihydroisobenzofuran derivatives with a tetra-substituted double bond. Apart from simple to electron-donating functional groups, this methodology exhibited a broad functional group tolerance such as −CHO, −CN, −COMe, and $-NO_2$ substituents on the haloarene component. Moreover, a careful study of the conversion of the unstable *Z*-isomer to the relatively more stable *E*-isomer of 1,3-dihydroisobenzofurans had revealed interesting insights on the stereoselective geometrical isomerization of the double bond.

GENERAL

IR spectra were recorded on a Bruker Tensor 37 (FTIR) spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker Avance 400 (400 MHz) spectrometer at 295 K in $CDCl_3$; chemical shifts (δ ppm) and coupling constants (Hz) are reported in standard fashion with reference to either internal standard tetramethylsilane (TMS) (δ_H = 0.00 ppm) or $CHCl_3$ (δ_H = 7.25 ppm). $^{13}C\{^{1}H\}$ NMR spectra were recorded on a Bruker Avance 400 (100 MHz) spectrometer at RT in $CDCl_3$; chemical shifts (δ ppm) are reported relative to $CHCl_3$ [δ_C = 77.00 ppm (central line of triplet)]. In the $^{13}C\{^{1}H\}$ NMR, the nature of carbons (C, CH, CH_2, and CH_3) was determined by recording the DEPT-135 spectra and is given in parentheses and noted as s = singlet (for C), d = doublet (for CH), t = triplet (for CH_2), and q = quartet (for CH_3). In the ^{1}H NMR, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, sept = septet, dd = doublet of doublet, m = multiplet, and brs = broad singlet. The assignment of signals was confirmed by ^{1}H, $^{13}C\{^{1}H\}$ CPD, and DEPT spectra. High-resolution mass spectra (HR-MS) were recorded on an Agilent 6538 UHD Q-TOF electron spray ionization (ESI) mode and atmospheric pressure chemical ionization (APCI) modes. Melting points are recorded using Tempo and Mettler FP1 melting point apparatus in capillary tubes and are uncorrected. A single

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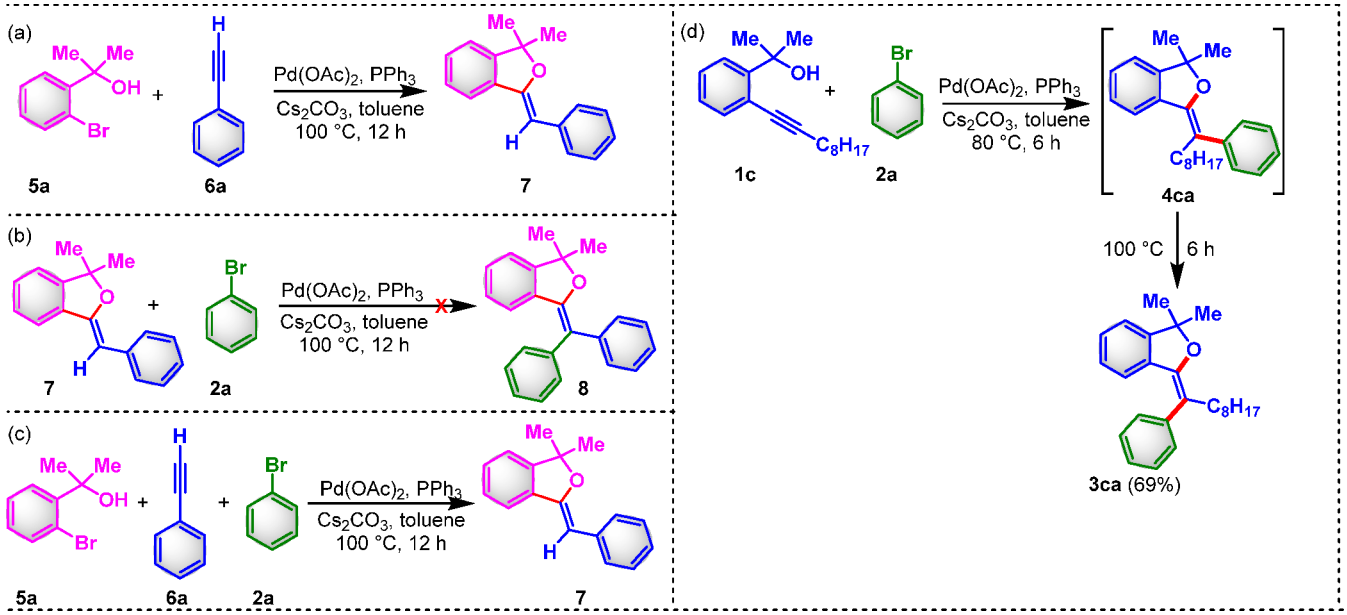
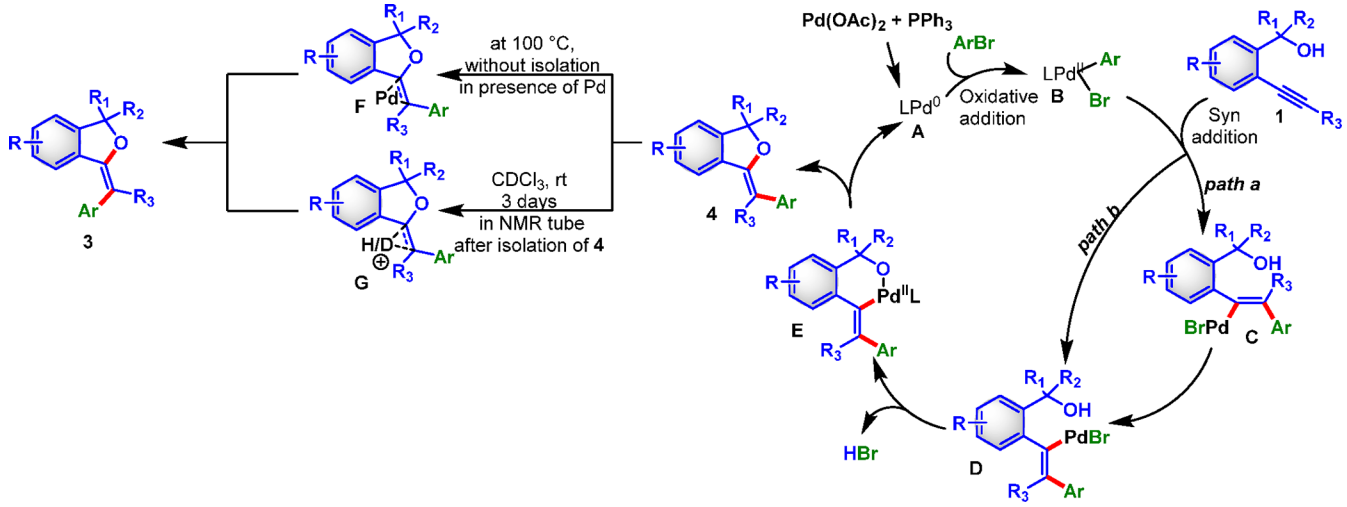
Scheme 2. Control Experiments



Scheme 3. Plausible Reaction Mechanism for the Formation of 3/4



crystal of **3gh** was selected and mounted on an Oxford SuperNova, Dual, Cu at zero, Eos diffractometer. The crystal was kept at 298 K during data collection. Using Olex2, the structure was solved with the olex2.solve structure solution program using direct methods, and refined with the olex2. refinement package using Gauss−Newton minimization. All small-scale dry reactions were carried out using Schlenk tubes under an inert atmosphere. Reactions were monitored by TLC on silica gel using a combination of hexane and ethyl acetate as eluents. Reactions were generally run under argon or a nitrogen atmosphere. Solvents were distilled before use; petroleum ether with a boiling range of 60−80 °C was used. Bromination of aromatics has been carried out in dry methanol. All Grignard reactions were performed in dry ether solvent. Palladium-catalyzed reactions were done in dry toluene. Methanol was distilled under a nitrogen atmosphere using $LiAlH_4$ and toluene solvent deoxygenated by distillation over sodium benzophenone under argon and then distilled and stored in a nitrogen atmosphere. Acme's silica gel (60−120 mesh) was used for column chromatography (approximately 20 g per 1 g of crude material). $Pd(OAc)_2$, cesium carbonate, triphenylphosphine (TPP), 4-bromotoluene, 4-bromoanisole, 3-bromotoluene, and 1-nitro-4-bromobenzene were purchased from Sigma-Aldrich and used as received. Substituted benzaldehydes, alkyl iodide/bromide, 1-alkynes, and bromobenzene, 1-bromonaphthalene, 4-bromoacetophenone, 4-bromobenzaldehyde, 2-bromobenzaldehyde, 4-bromomethyl benzoate, and 4-bromo-2-fluoro-1-nitrobenzene were purchased from TCI/local.

EXPERIMENTAL SECTION

General Procedure for the Preparation of *E*-Isomer (1,3-Dihydroisobenzofurans 3): GP 1. To a solution of 2-(2-(alkyl-1-yn-1-yl)phenyl)alkyl/phenyl-2-ol **1a−k** (46−59 mg, 0.2 mmol) in dry toluene (2 mL) were added aryl bromide **2a−l** (38−81 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) under a nitrogen atmosphere. The resultant reaction mixture was stirred at 100 °C (oil bath), for 8−12 h. Completion of the reaction was monitored by TLC (5:95 ethyl

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acetate and hexane). The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine solution, dried (Na_2SO_4), and filtered. Evaporation under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol **3aa**−**3gh** (68−88%).

General Procedure for the Preparation of *Z*-Isomer (1,3-Dihydroisobenzofurans 4): GP 2. To a solution of 2-(2-(alkyl-1-yn-1-yl)phenyl)alkyl/phenyl-2-ol **1a**−**g** (46−59 mg, 0.2 mmol) in dry toluene (2 mL) were added arylbromide **2c**−**k** (41−81 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol) under a nitrogen atmosphere. The resultant reaction mixture was stirred at 80 °C (oil bath), for 4−6 h. Completion of the reaction was monitored by TLC (5:95 ethyl acetate and hexane). The reaction mixture was cooled to room temperature and extracted with ethyl acetate (3 × 15 mL). The combined organic layers were washed with brine solution, dried (Na_2SO_4), and filtered. Evaporation under reduced pressure and purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate) furnished the alcohol **4dd**−**4im** (49−88%).

General Procedure for the Preparation of *E*-Isomer 3 from Z-Isomer 4: GP 3. After recording the NMR spectra of *Z*-isomer **4** in $CDCl_3$, the same compound was kept aside in the NMR tube for 72 h. During this period, conversion (geometrical isomerization) of *Z*-isomer **4** into *E*-isomer **3** took place. This isomerization to *E*-isomeric product **3** has been confirmed by measuring ^1H NMR analysis.

X-ray Crystallographic Studies. A single crystal of compound **3gh** was grown from hexane and CH_2Cl_2 at room temperature. For compound **3gh**, a crystal of suitable dimensions was mounted on a CryoLoop (Hampton Research Corp.) with a layer of light mineral oil. A single crystal of **3gh** was selected and mounted on a Bruker APEX-II CCD diffractometer. The crystal was kept at 298 K during data collection. Using Olex2, the structure was solved with the olex2.solve structure solution program using direct methods and refined with the olex2. refinement package using Gauss−Newton minimization. Absorption corrections were performed based on multiple scans. Non-hydrogen atoms were anisotropically refined. Hydrogen atoms were included in the refinement in the calculated positions riding on their carrier atoms.

*(E)-1,1-Dimethyl-3-(1-phenylheptylidene)-1,3-dihydroisobenzofuran (**3aa**).* **GP-1** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)-propan-2-ol **1a** (49 mg, 0.2 mmol), bromobenzene **2a** (38 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 10 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3aa** (52 mg, 82%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1a**) = 0.3, R_f (**3aa**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2896, 2829, 2252, 1441, 1376, 1039, 918, 748 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.42−7.35 (m, 2H), 7.33 (dt, J = 5.2, 2.1 Hz, 1H), 7.30−7.26 (m, 2H), 7.18−7.07 (m, 2H), 6.95−6.84 (m, 1H), 6.24 (d, J = 7.9 Hz, 1H), 2.55 (t, J = 7.1 Hz, 2H), 1.57 (s, 6H), 1.41−1.25 (m, 8H), 0.86 (t, J = 7.0 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.0, 140.8, 132.7, 130.1, 128.6, 127.5, 127.1, 126.6, 122.7, 120.2, 113.5, 85.1, 32.8, 31.8, 28.9, 28.5, 27.5, 22.7, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{29}O$ 321.2213; Found 321.2209.

*(E)-1,1-Dimethyl-3-(1-(m-tolyl)heptylidene)-1,3-dihydroisobenzofuran (**3ab**).* **GP-1** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)propan-2-ol **1a** (49 mg, 0.2 mmol), 3-bromotoluene **2b** (41 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 10 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3ab** (51 mg, 77%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1a**) = 0.3, R_f (**3ab**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3434, 3003, 2926, 2893, 2827, 1747, 1444, 1359, 1081, 1018, 752, 704 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.29−7.25 (m, 1H), 7.16−7.03 (m, 5H), 6.90 (ddd, J = 8.3, 7.0, 1.5 Hz, 1H), 6.27 (d, J = 7.9 Hz, 1H), 2.54 (t, J = 7.1 Hz, 2H), 2.36 (s, 3H), 1.57 (s, 6H), 1.42−1.33 (m, 4H), 1.27 (dd, J = 7.5, 3.6 Hz, 4H), 0.86 (t, J = 9.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.1, 149.0, 140.7, 138.1, 132.9, 130.6, 128.4, 127.4, 127.4, 127.1, 122.8, 120.1, 113.7, 85.0, 32.8, 31.8, 28.9, 28.5, 27.6, 22.7, 21.4, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}O$ 335.2369; Found 335.2371.

*(E)-1,1-Dimethyl-3-(1-(p-tolyl)heptylidene)-1,3-dihydroisobenzofuran (**3ac**).* **GP-1** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)-propan-2-ol **1a** (49 mg, 0.2 mmol), 4-bromotoluene **2c** (41 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 10 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3ac** (52 mg, 78%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1a**) = 0.3, R_f (**3ac**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2892, 2824, 1708, 1444, 1251, 723 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.23−7.07 (m, 6H), 6.94−6.88 (m, 1H), 6.31 (d, J = 7.9 Hz, 1H), 2.53 (t, J = 7.1 Hz, 2H), 2.41 (s, 3H), 1.57 (s, 6H), 1.36 (d, J = 1.9 Hz, 4H), 1.30−1.23 (m, 4H), 0.86 (t, J = 6.9 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.0, 149.0, 137.7, 136.1, 132.9, 129.9, 129.3, 127.4, 127.0, 122.8, 120.1, 113.4, 85.0, 32.9, 31.8, 28.9, 28.5, 27.5, 22.7, 21.3, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}O$ 335.2369; Found 335.2380.

*(E)-1,1-Dimethyl-3-(1-(naphthalen-1-yl)heptylidene)-1,3-dihydroisobenzofuran (**3ad**).* **GP-1** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)propan-2-ol **1a** (49 mg, 0.2 mmol), 1-bromonaphthalene **2d** (50 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 8 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3ad** (63 mg, 85%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1a**) = 0.3, R_f (**3ad**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3424, 3022, 2898, 2830, 1735, 1590, 1475, 1293, 1220,1077, 1027, 777, 725, 695 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 13.4, 8.2 Hz, 2H), 7.54−7.44 (m, 2H), 7.38 (td, J = 7.0, 3.4 Hz, 2H), 7.11−7.03 (m, 2H), 6.70 (ddd, J = 8.2, 6.8, 1.6 Hz, 1H), 5.74 (d, J = 7.9 Hz, 1H), 2.88 (dt, J = 13.2, 7.6 Hz, 1H), 2.44 (dt, J = 13.8, 6.9 Hz, 1H), 1.63 (d, J = 5.4 Hz, 6H), 1.44−1.34 (m, 4H), 1.29−1.24 (m, 4H), 0.86 (dd, J = 9.2, 4.9 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.0, 149.0, 138.3, 134.0, 132.7, 132.6, 128.2, 127.7, 127.4, 127.2, 125.9, 125.9, 125.7, 122.8, 120.0, 110.5, 85.3, 33.0, 31.8, 29.2, 28.6, 28.5, 27.9, 22.7, 14.1 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{27}H_{30}NaO$ 393.2189; Found 393.2155.

*(E)-3-(1-(4-Methoxyphenyl)heptylidene)-1,1-dimethyl-1,3-dihydroisobenzofuran (**3ae**).* **GP-3** was followed for the conversion of *Z*-isomer **4ae** to *E*-isomer **3ae** (63 mg, 71%) as a colorless oil, in an NMR tube in $CDCl_3$ for 3 days.

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3409, 3023, 2896, 2829, 1733, 1589, 1474, 1444, 1291, 1218, 1076, 1024, 776 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.16 (m, 2H), 7.15−7.07 (m, 2H), 6.95−6.90 (m, 3H), 6.30 (d, J = 7.9 Hz, 1H), 3.87 (s, 3H), 2.52 (t, J = 7.1 Hz, 2H), 1.56 (s, 6H), 1.36 (d, J = 3.4 Hz, 2H), 1.29−1.26 (m, 4H), 0.90−0.84 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.4, 149.1, 149.0, 133.1, 132.9, 131.1, 127.4, 127.1, 122.7, 120.2, 114.0, 113.0, 85.0, 55.2, 32.9, 31.8, 28.9, 28.5, 27.5, 22.7, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{31}O_2$ 351.2319; Found 351.2314.

*(E)-1-Ethyl-1-methyl-3-(1-(m-tolyl)heptylidene)-1,3-dihydroisobenzofuran (**3bb**).* **GP-1** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)butan-2-ol **1b** (52 mg, 0.2 mmol), 3-bromotoluene **2b** (41 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3bb** (52 mg, 74%) as a colorless oil.

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[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1b**) = 0.3, R_f (**3bb**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3032, 2892, 2825, 1747, 1573, 1497, 1443, 1322, 1076, 1047, 845, 747, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.5 Hz, 1H), 7.13 (ddd, J = 24.3, 15.5, 7.4 Hz, 5H), 6.98−6.90 (m, 1H), 6.34 (d, J = 7.9 Hz, 1H), 2.65 (dd, J = 13.8, 6.9 Hz, 1H), 2.53 (dt, J = 13.7, 6.9 Hz, 1H), 2.40 (s, 3H), 1.97 (dt, J = 14.7, 7.3 Hz, 1H), 1.91−1.82 (m, 1H), 1.57 (s, 3H), 1.47−1.39 (m, 4H), 1.34−1.30 (m, 4H), 0.91 (t, J = 6.9 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 147.6, 140.8, 138.1, 133.8, 130.6, 128.4, 127.3, 127.2, 127.1, 122.7, 120.4, 113.1, 87.5, 34.4, 32.9, 31.8, 29.0, 27.6, 26.8, 22.7, 21.4, 14.1, 8.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{33}O$ 349.2526; Found 349.2526.

*(E)-1-Ethyl-1-methyl-3-(1-(p-tolyl)heptylidene)-1,3-dihydroisobenzofuran (**3bc**).* **GP-1** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)butan-2-ol **1b** (52 mg, 0.2 mmol), 4-bromotoluene **2c** (41 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3bc** (55 mg, 79%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1b**) = 0.3, R_f (**3bc**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3428, 2896, 2833, 1740, 1663, 1441, 1357, 1010, 800, 753, 711 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22−7.12 (m, 5H), 7.06 (d, J = 7.4 Hz, 1H), 6.95−6.89 (m, 1H), 6.34 (d, J = 7.9 Hz, 1H), 2.62 (dt, J = 14.3, 7.1 Hz, 1H), 2.50 (dd, J = 13.2, 7.0 Hz, 1H), 2.42 (s, 3H), 1.95 (dd, J = 14.1, 7.3 Hz, 1H), 1.83 (dd, J = 14.1, 7.3 Hz, 1H), 1.55 (s, 3H), 1.44−1.35 (m, 4H), 1.32−1.26 (m, 4H), 0.88 (t, J = 6.8 Hz, 3H), 0.82 (t, J = 7.4 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.7, 147.6, 137.8, 136.1, 133.8, 129.9, 129.3, 127.3, 127.0, 122.6, 120.4, 112.8, 87.5, 34.4, 33.0, 31.8, 29.0, 27.6, 26.8, 22.7, 21.3, 14.1, 8.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{33}O$ 349.2526; Found 349.2521.

*(E)-1,1-Dimethyl-3-(1-phenylnonylidene)-1,3-dihydroisobenzofuran (**3ca**).* **GP-1** was carried out with 2-(2-(dec-1-yn-1-yl)phenyl)-propan-2-ol **1c** (54 mg, 0.2 mmol), bromobenzene **2a** (38 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3ca** (54 mg, 77%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1c**) = 0.3, R_f (**3ca**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2993, 2892, 2824, 1640, 1446, 1228, 1133, 1083, 896, 747, 697, 647 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.39 (ddd, J = 7.4, 4.4, 1.3 Hz, 2H), 7.35−7.30 (m, 1H), 7.30−7.25 (m, 2H), 7.18−7.07 (m, 2H), 6.89 (ddd, J = 8.3, 6.9, 1.5 Hz, 1H), 6.24 (d, J = 7.9 Hz, 1H), 2.55 (t, J = 7.1 Hz, 2H), 1.57 (s, 6H), 1.38 (dd, J = 6.6, 5.0 Hz, 4H), 1.26 (d, J = 13.6 Hz, 8H), 0.86 (t, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.1, 140.8, 132.8, 130.1, 128.6, 127.5, 127.1, 126.6, 122.7, 120.2, 113.5, 85.1, 32.8, 31.9, 29.5, 29.4, 29.2, 28.5, 27.5, 22.7, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{33}O$ 349.2526; Found 349.2511.

*(E)-3-(1-(3-Bromophenyl)nonylidene)-1,1-dimethyl-1,3-dihydroisobenzofuran (**3cg**).* **GP-1** was carried out with 2-(2-(dec-1-yn-1-yl)phenyl)propan-2-ol **1c** (54 mg, 0.2 mmol), 1,3-dibromobenzene **2g** (57 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3cg** (63 mg, 74%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1c**) = 0.3, R_f (**3cg**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2893, 2825, 1639, 1449, 1259, 1131, 1083, 745, 698 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.49−7.43 (m, 2H), 7.26−7.19 (m, 2H), 7.16 (d, J = 7.3 Hz, 1H), 7.14−7.09 (m, 1H), 6.95 (dd, J = 11.1, 4.0 Hz, 1H), 6.33 (d, J = 7.9 Hz, 1H), 2.52 (t, J = 6.7 Hz, 2H), 1.57 (s, 6H), 1.36−1.24 (m, 12H), 0.87 (t, J = 6.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.6, 149.2, 143.1, 133.0, 132.3, 130.1, 129.7, 128.9, 127.8, 127.2, 122.7, 122.5, 120.3, 112.0, 85.4, 32.7, 31.9, 29.5, 29.3, 29.2, 28.4, 27.5, 22.7, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{32}Br^{79}O$ 427.1631; Found 427.1624. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{32}Br^{81}O$ 429.1611; Found: 429.1606.

*(E)-1,1-Dimethyl-3-(1-(naphthalen-1-yl)nonylidene)-1,3-dihydroisobenzofuran (**3cd**).* **GP-1** was carried out with 2-(2-(dec-1-yn-1-yl)phenyl)propan-2-ol **1c** (54 mg, 0.2 mmol), 1-bromonaphthalene **2d** (50 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3cd** (70 mg, 88%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1c**) = 0.3, R_f (**3cd**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2892, 2823, 1642, 1446, 1320, 1132, 1079, 770, 749 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, J = 8.4 Hz, 1H), 7.88 (dd, J = 13.3, 8.1 Hz, 2H), 7.56−7.43 (m, 2H), 7.39 (t, J = 6.9 Hz, 2H), 7.13−7.02 (m, 2H), 6.74−6.65 (m, 1H), 5.74 (d, J = 7.9 Hz, 1H), 2.94−2.83 (m, 1H), 2.44 (dt, J = 13.7, 6.7 Hz, 1H), 1.63 (d, J = 5.2 Hz, 6H), 1.39 (dd, J = 13.0, 6.6 Hz, 4H), 1.26 (d, J = 14.5 Hz, 8H), 0.86 (t, J = 6.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.0, 149.0, 138.3, 134.0, 132.6, 132.6, 128.2, 127.7, 127.4, 127.2, 125.9, 125.9, 125.7, 122.8, 120.0, 110.5, 85.3, 32.9, 31.9, 29.5, 29.5, 29.4, 28.6, 28.5, 27.9, 22.7, 14.12 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{35}O$ 399.2682; Found: 399.2673.

*(E)-1,1-Dimethyl-3-(1-(p-tolyl)hexylidene)-1,3-dihydroisobenzofuran (**3dc**).* **GP-1** was carried out with 2-(2-(hept-1-yn-1-yl)phenyl)-propan-2-ol **1d** (46 mg, 0.2 mmol), 4-bromotoluene **2c** (41 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **3dc** (48 mg, 75%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1d**) = 0.3, R_f (**3dc**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2995, 2893, 2833, 1585, 1477, 1447, 1165, 1067, 1023, 759, 718, 683 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22−7.08 (m, 6H), 6.92 (ddd, J = 8.3, 7.0, 1.5 Hz, 1H), 6.32 (d, J = 7.9 Hz, 1H), 2.58−2.52 (m, 2H), 2.42 (s, 3H), 1.58 (s, 6H), 1.42−1.31 (m, 6H), 0.87 (t, J = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.0, 149.0, 137.7, 136.1, 132.9, 129.9, 129.3, 127.4, 127.0, 122.8, 120.1, 113.4, 85.0, 32.8, 31.4, 28.5, 27.2, 22.6, 21.3, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{29}O$ 321.2213; Found: 321.2198.

*(E)-1-Methyl-1-propyl-3-(1-(p-tolyl)hexylidene)-1,3-dihydroisobenzofuran (**3ec**).* **GP-3** was followed for the conversion of *Z*-isomer **4ec** to *E*-isomer **3ec** (48 mg, 69%) as a colorless oil, in an NMR tube in $CDCl_3$ for 3 days.

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2927, 2897, 2839, 1744, 1444, 1358, 1253, 1090, 1010, 727, 694 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.11 (m, 5H), 7.08−7.04 (m, 1H), 6.94−6.88 (m, 1H), 6.32 (d, J = 7.9 Hz, 1H), 2.58 (dd, J = 14.0, 6.9 Hz, 1H), 2.52−2.43 (m, 1H), 2.41 (s, 3H), 1.89 (ddd, J = 13.8, 11.7, 4.8 Hz, 1H), 1.76 (ddd, J = 13.8, 11.7, 4.7 Hz, 1H), 1.53 (s, 3H), 1.43−1.30 (m, 7H), 1.16−1.02 (m, 1H), 0.87 (dd, J = 9.9, 4.8 Hz, 6H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.6, 148.0, 137.8, 136.1, 133.6, 129.9, 129.3, 127.3, 127.0, 122.7, 120.4, 112.9, 87.3, 43.9, 32.9, 31.5, 27.3, 27.1, 22.6, 21.3, 17.0, 14.3, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{33}O$ 349.2526; Found: 349.2494.

*(E)-6-Methoxy-1,1-dimethyl-3-(1-(naphthalen-1-yl)hexylidene)-1,3-dihydroisobenzofuran (**3fd**).* **GP-1** was carried out with 2-(2-(hept-1-yn-1-yl)-5-methoxyphenyl)propan-2-ol **1f** (52 mg, 0.2 mmol), 1-bromonaphthalene **2d** (50 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **3fd** (66 mg, 85%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1f**) = 0.5, R_f (**3fd**) = 0.4, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3021, 2897, 2830, 1732, 1590, 1473, 1291, 1218, 1076, 1022, 777, 688

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cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.3 Hz, 1H), 7.87 (dd, J = 16.1, 8.1 Hz, 2H), 7.53−7.44 (m, 2H), 7.41−7.36 (m, 2H), 6.59 (d, J = 2.3 Hz, 1H), 6.26 (dd, J = 8.7, 2.4 Hz, 1H), 5.63 (d, J = 8.6 Hz, 1H), 3.68 (s, 3H), 2.84 (dt, J = 13.4, 7.6 Hz, 1H), 2.43 (dt, J = 13.8, 6.8 Hz, 1H), 1.62 (d, J = 5.5 Hz, 6H), 1.37−1.27 (m, 6H), 0.86 (d, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.5, 150.9, 149.8, 138.6, 134.1, 132.8, 128.2, 127.9, 127.0, 126.0, 125.9, 125.8, 125.7, 125.4, 123.9, 113.3, 108.2, 105.4, 85.0, 55.3, 32.7, 31.7, 28.5, 28.4, 27.6, 22.6, 14.1 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{27}H_{31}O_2$ 387.2319; Found 387.2316.

*(E)-1-(4-(1-(5-Methoxy-3,3-dimethylisobenzofuran-1(3H)-ylidene)hexyl)phenyl)ethan-1-one (**3fi**).* **GP-1** was carried out with 2-(2-(hept-1-yn-1-yl)-5-methoxyphenyl)propan-2-ol **1f** (52 mg, 0.2 mmol), 4-bromoacetophenone **2i** (48 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 90:10) furnished the product **3fi** (54 mg, 71%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1f**) = 0.5, R_f (**3fi**) = 0.3, UV detection]. Major isomer NMR data (**3fi**:**4fi** = 4.3:1): IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2894, 2829, 1660, 1390, 1345, 1250, 948, 827, 722 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.95 (m, 2H), 7.44−7.35 (m, 2H), 6.62 (d, J = 2.3 Hz, 1H), 6.48 (dd, J = 8.7, 2.4 Hz, 1H), 6.34 (d, J = 8.7 Hz, 1H), 3.76 (s, 3H), 2.65 (s, 3H), 2.55 (t, J = 7.2 Hz, 2H), 1.57 (s, 6H), 1.38−1.30 (m, 6H), 0.85 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.0, 159.9, 151.4, 149.5, 146.9, 135.3, 130.4, 128.7, 125.0, 123.7, 113.4, 110.3, 105.5, 85.1, 55.4, 32.3, 31.3, 28.3, 27.5, 26.6, 22.5, 14.1 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{25}H_{31}O_3$ 379.2268; Found: 379.2267.

*(E)-4-(1-(5-Methoxy-3,3-dimethylisobenzofuran-1(3H)-ylidene)-hexyl)benzaldehyde (**3fl**).* **GP-1** was carried out with 2-(2-(hept-1-yn-1-yl)-5-methoxyphenyl)propan-2-ol **1f** (52 mg, 0.2 mmol), 4-bromobenzaldehyde **2l** (44 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 100 °C, for 12 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 90:10) furnished the product **3fl** (50 mg, 68%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1f**) = 0.5, R_f (**3fl**) = 0.3, UV detection]. Major isomer NMR data (**3fl**:**4fl** = 2:1): IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3426, 2894, 2828, 1745, 1663, 1584, 1445, 1345, 1252, 1079, 1026, 945, 751, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.92−7.86 (m, 2H), 7.53−7.44 (m, 2H), 6.63 (d, J = 2.3 Hz, 1H), 6.49 (dd, J = 8.7, 2.4 Hz, 1H), 6.36 (d, J = 8.7 Hz, 1H), 3.76 (s, 3H), 2.61−2.53 (m, 2H), 1.57 (s, 6H), 1.38−1.31 (m, 6H), 0.85 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 192.0, 160.0, 151.5, 149.8, 148.5, 134.7, 130.9, 130.0, 125.0, 123.7, 113.5, 110.2, 105.5, 85.3, 55.4, 32.3, 31.3, 28.3, 27.5, 22.5, 14.1 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{24}H_{29}O_3$ 365.2111; Found 365.2115.

*(E)-3-(Cyclopropyl(naphthalen-1-yl)methylene)-1,1-dimethyl-1,3-dihydroisobenzofuran (**3gd**).* **GP-3** was followed for the conversion of *Z*-isomer **4gd** to *E*-isomer **3gd** (54 mg, 83%) as a colorless oil, in an NMR tube in $CDCl_3$ for 3 days.

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2896, 2829, 1733, 1664, 1589, 1474, 1291, 1218, 1075, 1021, 777, 688 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 8.2 Hz, 2H), 7.46 (ddd, J = 9.3, 8.1, 4.1 Hz, 2H), 7.42−7.36 (m, 1H), 7.26 (s, 1H), 7.08 (d, J = 7.4 Hz, 1H), 7.06−6.98 (m, 1H), 6.69−6.59 (m, 1H), 5.44 (d, J = 7.9 Hz, 1H), 2.49 (ddd, J = 10.6, 6.8, 4.2 Hz, 1H), 1.66 (s, 6H), 0.77−0.64 (m, 1H), 0.62−0.50 (m, 1H), 0.35 (td, J = 9.4, 5.3 Hz, 1H), −0.08 (td, J = 9.9, 5.5 Hz, 1H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.5, 148.4, 133.8, 133.7, 133.6, 132.6, 128.9, 128.0, 127.7, 127.3, 127.2, 126.1, 126.0, 125.8, 125.6, 122.4, 120.0, 110.6, 85.5, 28.9, 28.5, 12.8, 4.4, 4.0 ppm. HRMS (ESI) m/z: [M + K]$^+$ Calcd for $C_{24}H_{22}KO$ 365.1302; Found 365.1294.

*(E)-4-(((6-(Cyclopropyl(3,3-dimethylisobenzofuran-1(3H)-ylidene)methyl)naphthalen-2-yl)oxy)methyl)benzonitrile (**3gh**).* **GP-3** was followed for the conversion of *Z*-isomer **4gh** to *E*-isomer **3gh** (69 mg, 76%) as a colorless solid, in an NMR tube in $CDCl_3$ for 3 days.

Mp: 129−131 °C; IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3030, 2940, 2893, 2827, 2205, 1741, 1609, 1579, 1484, 1446, 1371, 1245, 1191, 1153, 1047, 1012, 843, 806, 749 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80−7.67 (m, 5H), 7.62 (d, J = 8.3 Hz, 2H), 7.57 (s, 1H), 7.28−7.21 (m, 2H), 7.08 (dd, J = 6.4, 0.9 Hz, 2H), 6.73 (ddd, J = 8.3, 6.4, 2.1 Hz, 1H), 5.80 (d, J = 7.9 Hz, 1H), 5.26 (s, 2H), 2.36 (tt, J = 8.4, 5.3 Hz, 1H), 1.63 (s, 6H), 0.67 (d, J = 8.4 Hz, 2H), 0.29 (d, J = 8.4 Hz 2H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.2, 149.9, 148.5, 142.4, 133.4, 132.8, 132.4, 131.9, 130.5, 129.9, 129.8, 129.4, 127.6, 127.6, 127.3, 127.2, 127.0, 122.4, 120.2, 118.7, 113.2, 111.7, 107.0, 85.5, 68.9, 28.6, 12.5, 3.8 ppm. HRMS (ESI) m/z: [M + K]$^+$ Calcd for $C_{32}H_{27}KNO_2$ 496.1673; Found 496.1647.

*(E)-6-Chloro-1,1-dimethyl-3-(1-phenylheptylidene)-1,3-dihydroisobenzofuran (**3ka**).* **GP-3** was followed for the conversion of *Z*-isomer **4ka** to *E*-isomer **3ka** (52 mg, 73%) as a colorless liquid, in an NMR tube in $CDCl_3$ for 3 days.

IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2894, 2827, 1641, 1444, 1272, 1136, 1094, 1001, 816, 763 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.35 (m, 2H), 7.34−7.31 (m, 1H), 7.25−7.21 (m, 2H), 7.05 (d, J = 1.6 Hz, 1H), 6.84 (dd, J = 8.4, 1.9 Hz, 1H), 6.11 (d, J = 8.4 Hz, 1H), 2.52 (t, J = 7.1 Hz, 2H), 1.55 (s, 6H), 1.35 (dd, J = 4.2, 2.9 Hz, 4H), 1.27−1.23 (m, 4H), 0.85 (t, J = 5.3 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 150.8, 148.2, 140.5, 133.2, 131.4, 129.9, 128.7, 127.5, 126.8, 123.8, 120.6, 114.3, 84.8, 32.8, 31.8, 28.9, 28.4, 27.4, 22.7, 14.1 ppm. HRMS (ESI) m/z: [M + K]$^+$ Calcd for $C_{23}H_{27}ClKO$ 393.1382; Found 393.1405.

*(Z)-1,1-Dimethyl-3-(1-(naphthalen-1-yl)hexylidene)-1,3-dihydroisobenzofuran (**4dd**).* **GP-2** was carried out with 2-(2-(hept-1-yn-1-yl)phenyl)propan-2-ol **1d** (46 mg, 0.2 mmol), 1-bromonaphthalene **2d** (50 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 5 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:02) furnished the product **4dd** (60 mg, 84%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1d**) = 0.3, R_f (**4dd**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3435, 2896, 2833, 1741, 1644, 1442, 1357, 1262, 1174, 1081, 1009, 912, 799, 750 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.80 (dd, J = 10.4, 8.0 Hz, 2H), 7.55−7.49 (m, 1H), 7.48−7.33 (m, 5H), 7.21 (d, J = 7.3 Hz, 1H), 2.91−2.73 (m, 2H), 1.57 (dd, J = 13.4, 9.9 Hz, 2H), 1.37 (d, J = 11.8 Hz, 6H), 1.35−1.22 (m, 4H), 0.85 (t, J = 7.1 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.1, 149.5, 140.5, 133.7, 132.8, 131.7, 128.1, 128.0, 127.8, 126.8, 126.5, 126.2, 125.5, 125.3, 125.0, 123.2, 120.7, 110.7, 85.1, 33.2, 32.0, 28.7, 28.5, 28.0, 22.6, 14.1 ppm. HRMS (ESI) m/z: [M + K]$^+$ Calcd for $C_{26}H_{28}KO$ 395.1772; Found 395.1774.

*(Z)-1-(4-(1-(3,3-Dimethylisobenzofuran-1(3H)-ylidene)heptyl)-phenyl)ethan-1-one (**4ai**).* **GP-2** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)propan-2-ol **1a** (52 mg, 0.2 mmol), 4-bromoacetophenone **2i** (48 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4ai** (57 mg, 79%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1a**) = 0.6, R_f (**4ai**) = 0.4, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3429, 2894, 2829, 1744, 1663, 1585, 1445, 1346, 1252, 1022, 945, 897, 837, 751, 692 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.92 (m, 2H), 7.74−7.70 (m, 2H), 7.69−7.66 (m, 1H), 7.37 (ddd, J = 6.9, 5.2, 1.3 Hz, 2H), 7.23 (dd, J = 6.5, 2.0 Hz, 1H), 2.83−2.76 (m, 2H), 2.61 (s, 3H), 1.59−1.52 (m, 8H), 1.46−1.38 (m, 2H), 1.30 (td, J = 7.0, 3.6 Hz, 4H), 0.88 (t, J = 7.0 Hz, 3H) ppm. ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 197.8, 151.2, 149.9, 146.8, 134.0, 132.9, 128.6, 128.5, 128.0, 128.0, 123.7, 120.7, 111.4, 86.0, 31.7, 30.7, 29.4, 29.2, 28.3, 26.5, 22.6, 14.0 ppm. HRMS (ESI) m/z: [M + H]$^+$ Calcd for $C_{25}H_{31}O_2$ 363.2319; Found 363.2324.

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*(Z)-3-(1-(4-Methoxyphenyl)heptylidene)-1,1-dimethyl-1,3-dihydroisobenzofuran (**4ae**).* **GP-2** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)propan-2-ol **1a** (52 mg, 0.2 mmol), 4-bromoanisole **2e** (45 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 4 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4ae** (50 mg, 71%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1a**) = 0.6, R_f (**4ae**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2928, 2860, 1762, 1677, 1603, 1507, 1460, 1288, 1246, 1174, 1036, 831, 762 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 1H), 7.62−7.56 (m, 2H), 7.40−7.31 (m, 2H), 7.24−7.21 (m, 1H), 6.96−6.91 (m, 2H), 3.86 (s, 3H), 2.79 (dd, J = 8.8, 7.5 Hz, 2H), 1.57 (s, 6H), 1.39 (ddd, J = 11.1, 10.5, 5.5 Hz, 8H), 0.93−0.90 (m, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.3, 149.5, 148.9, 133.7, 133.4, 129.7, 127.8, 127.7, 123.2, 120.6, 113.1, 112.1, 85.1, 55.1, 31.7, 31.3, 29.4, 29.1, 28.4, 22.6, 14.1 ppm. HRMS (ESI) m/z: $[M + Na]^+$ Calcd for $C_{25}H_{31}O_2$ 363.2138; Found 363.2102.

*(Z)-2-(1-(3,3-Dimethylisobenzofuran-1(3H)-ylidene)heptyl)benzaldehyde (**4af**).* **GP-2** was carried out with 2-(2-(oct-1-yn-1-yl)phenyl)propan-2-ol **1a** (52 mg, 0.2 mmol), 2-bromobenzaldehyde **2f** (44 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4af** (53 mg, 76%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1a**) = 0.6, R_f (**4af**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2892, 2797, 2705, 1673, 1587, 1288, 1197, 1155, 836, 798, 747, 722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.07 (s, 1H), 7.94 (dd, J = 7.7, 1.3 Hz, 1H), 7.74 (d, J = 7.1 Hz, 1H), 7.60 (td, J = 7.6, 1.5 Hz, 1H), 7.41−7.33 (m, 4H), 7.22−7.17 (m, 1H), 2.71 (dd, J = 13.8, 6.9 Hz, 2H), 1.64−1.49 (m, 4H), 1.41 (s, 6H), 1.29−1.25 (m, 4H), 0.86 (d, J = 6.8 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 193.5, 150.4, 150.1, 145.8, 133.9, 133.6, 131.7, 129.3, 128.7, 128.0, 126.5, 126.4, 123.4, 120.8, 107.5, 85.9, 32.5, 31.6, 29.4, 29.2, 28.9, 22.6, 14.0 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{29}O_2$ 349.2162; Found 349.2144.

*(Z)-6-Chloro-1,1-dimethyl-3-(1-phenylheptylidene)-1,3-dihydroisobenzofuran (**4ka**).* **GP-2** was carried out with 2-(5-chloro-2-(oct-1-yn-1-yl)phenyl)propan-2-ol **1k** (52 mg, 0.2 mmol), bromobenzene **2a** (38 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4ka** (52 mg, 73%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1k**) = 0.6, R_f (**4ka**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2892, 2797, 2705, 1673, 1587, 1288, 1197, 1155, 836, 798, 747, 722 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (dd, J = 8.3, 1.4 Hz, 3H), 7.36−7.29 (m, 3H), 7.21−7.16 (m, 1H), 7.15 (d, J = 1.9 Hz, 1H), 2.76−2.64 (m, 2H), 1.54−1.47 (m, 8H), 1.36 (dd, J = 14.1, 7.5 Hz, 2H), 1.30−1.25 (m, 4H), 0.86 (t, J = 6.7 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 151.5, 148.6, 141.1, 133.6, 131.9, 128.7, 128.1, 127.7, 125.8, 124.4, 121.1, 113.2, 85.0, 31.7, 31.4, 29.4, 29.0, 28.2, 22.6, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{23}H_{28}ClO$ 355.1823; Found 355.1794.

*(Z)-1-Methyl-1-propyl-3-(1-(p-tolyl)hexylidene)-1,3-dihydroisobenzofuran (**4ec**).* **GP-2** was carried out with 2-(2-(hept-1-yn-1-yl)phenyl)pentan-2-ol **1e** (52 mg, 0.2 mmol), 4-bromotoluene **2c** (41 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (195 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4ec** (48 mg, 69%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1e**) = 0.3, R_f (**4ec**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2926, 2896, 2838, 1746, 1496, 1443, 1267, 1209, 1126, 1090, 913, 802, 750, 692 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 8.1 Hz, 2H), 7.38−7.31 (m, 2H), 7.18 (d, J = 8.4 Hz, 3H), 2.80−2.73 (m, 2H), 2.38 (s, 3H), 1.88 (ddd, J = 13.8, 11.8, 4.8 Hz, 1H), 1.79−1.70 (m, 1H), 1.63−1.56 (m, 2H), 1.50 (s, 3H), 1.39 (tdd, J = 11.2, 8.7, 3.5 Hz, 6H), 0.92 (t, J = 7.0 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 149.9, 148.6, 138.6, 134.9, 134.2, 128.5, 128.4, 127.7, 127.7, 123.2, 120.8, 111.9, 87.5, 43.7, 32.0, 31.2, 28.9, 27.1, 22.6, 21.2, 17.1, 14.3, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{33}O$ 349.2526; Found 349.2505.

*(Z)-1-Methyl-3-(1-(4-nitrophenyl)heptylidene)-1-phenyl-1,3-dihydroisobenzofuran (**4hj**).* **GP-2** was carried out with 1-(2-(oct-1-yn-1-yl)phenyl)-1-phenylethan-1-ol **1h** (61 mg, 0.2 mmol), 1-bromo-4-nitrobenzene **2j** (48 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 90:10) furnished the product **4hj** (65 mg, 76%) as a pale-yellow oil.

[TLC (petroleum ether/ethyl acetate 85:15, R_f (**1h**) = 0.7, R_f (**4hj**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2891, 2824, 1748, 1573, 1498, 1444, 1323, 1257, 1178, 1125, 1076, 1047, 1016, 846, 748, 689 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26−8.12 (m, 2H), 7.82−7.75 (m, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.43−7.35 (m, 4H), 7.32−7.27 (m, 3H), 7.25 (t, J = 3.6 Hz, 1H), 2.89−2.79 (m, 2H), 1.93 (s, 3H), 1.60 (dd, J = 11.0, 5.1 Hz, 2H), 1.43 (dd, J = 9.4, 5.4 Hz, 2H), 1.35−1.27 (m, 4H), 0.89 (t, J = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.3, 149.1, 148.4, 145.2, 143.9, 132.4, 129.1, 129.1, 128.5, 128.4, 127.6, 125.0, 123.9, 123.2, 122.2, 111.2, 89.0, 31.6, 30.6, 29.3, 29.2, 27.6, 22.6, 14.0 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{28}H_{30}NO_3$ 428.2220; Found 428.2227.

*(Z)-1,1-Diphenyl-3-(1-(m-tolyl)heptylidene)-1,3-dihydroisobenzofuran (**4lb**).* **GP-2** was carried out with (2-(oct-1-yn-1-yl)phenyl)-diphenylmethanol **1l** (74 mg, 0.2 mmol), 1-bromo-3-methylbenzene **2b** (41 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 90:10) furnished the product **4lb** (77 mg, 84%) as a pale-yellow oil.

[TLC (petroleum ether/ethyl acetate 85:15, R_f (**1l**) = 0.7, R_f (**4lb**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2892, 2824, 2705, 1640, 1446, 1268, 1131, 1083, 1000, 749, 695, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ = 7.71 (d, J = 7.8 Hz, 1H), 7.42−7.31 (m, 5H), 7.31−7.20 (m, 11H), 7.00 (d, J = 7.5 Hz, 1H), 2.84−2.71 (m, 2H), 2.33 (s, 3H), 1.59−1.52 (m, 2H), 1.40 (dt, J = 14.2, 7.1 Hz, 2H), 1.33−1.26 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 149.1, 146.0, 144.0, 141.0, 136.8, 133.9, 129.7, 128.2, 128.0, 127.7, 127.5, 127.4, 127.2, 126.5, 125.8, 124.3, 123.4, 114.3, 92.0, 31.7, 31.5, 29.4, 29.1, 22.6, 21.6, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{34}H_{35}O$ 459.2682; Found 459.2719.

*(Z)-3-(Cyclopropyl(naphthalen-1-yl)methylene)-1,1-dimethyl-1,3-dihydroisobenzofuran (**4gd**).* **GP-2** was carried out with 2-(2-(cyclopropylethynyl)phenyl)propan-2-ol **1g** (40 mg, 0.2 mmol), 1-bromonaphathalene **2d** (50 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4gd** (54 mg, 83%) as a pale yellow liquid.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1g**) = 0.3, R_f (**4gd**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2895, 2830, 1656, 1581, 1440, 1362, 1251, 1163, 1102, 994, 960, 797, 726 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, J = 7.7 Hz, 1H), 8.00−7.93 (m, 1H), 7.89−7.84 (m, 1H), 7.77 (d, J = 8.2 Hz, 1H), 7.51−7.39 (m, 4H), 7.33 (dd, J = 7.0, 1.2 Hz, 1H), 7.25−7.16 (m, 2H), 2.24 (tt, J = 8.3, 5.2 Hz, 1H), 1.40 (d, J = 18.1 Hz, 6H), 0.89−0.82 (m, 1H), 0.81−0.71 (m, 1H), 0.32 (td, J = 9.6, 5.4 Hz, 1H), 0.20 (td, J = 9.6, 5.3 Hz, 1H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.3, 150.1, 137.8, 133.6, 133.0, 132.2, 128.1, 128.0, 127.6, 127.1, 126.8, 126.5, 125.3, 125.2, 125.0, 124.1, 120.5, 110.0, 85.7, 28.6, 28.0, 13.4,

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7.6, 7.6 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{24}H_{23}O$ 327.1743; Found 327.1730.

*(Z)-3-(Cyclopropyl(3-fluoro-4-nitrophenyl)methylene)-1,1-dimethyl-1,3-dihydroisobenzofuran (**4gk**).* **GP-2** was carried out with 2-(2-(cyclopropylethynyl)phenyl)propan-2-ol **1g** (40 mg, 0.2 mmol), 4-bromo-2-fluoro-1-nitrobenzene **2k** (53 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4gk** (40 mg, 59%) as a pale yellow liquid.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1g**) = 0.5, R_f (**4gk**) = 0.4, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2892, 2826, 1644, 1576, 1510, 1452, 1328, 1250, 1172, 1085, 1047, 881, 708 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.26−8.18 (m, 1H), 8.03 (t, J = 8.5 Hz, 1H), 7.74−7.60 (m, 2H), 7.47−7.40 (m, 2H), 7.29−7.26 (m, 1H), 1.93 (tt, J = 8.0, 5.2 Hz, 1H), 1.60 (s, 6H, 2 × CH_3), 1.23−1.06 (m, 2H), 0.50−0.33 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5, 155.3 (d, $J_{c\text{-}f}$ = 259 Hz), 150.1, 132.2, 129.6, 128.9, 127.9, 125.8, 124.9 (d, $J_{c\text{-}f}$ = 2 Hz), 124.7 (d, $J_{c\text{-}f}$ = 3 Hz), 120.4, 117.8 (d, $J_{c\text{-}f}$ = 21 Hz), 109.1, 88.0, 28.3, 11.5, 11.4 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{20}H_{19}FNO_3$ 340.1343; Found 340.1328.

*(Z)-1,1-Dimethyl-3-(1-(naphthalen-1-yl)nonylidene)-1,3-dihydroisobenzofuran (**4cd**).* **GP-2** was carried out with 2-(2-(dec-1-yn-1-yl)phenyl)propan-2-ol **1c** (54 mg, 0.2 mmol), 1-bromonaphthalene **2d** (50 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 98:2) furnished the product **4cd** (70 mg, 88%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 95:05, R_f (**1c**) = 0.3, R_f (**4cd**) = 0.5, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2893, 2823, 1643, 1447, 1255, 1132, 1080, 897,770, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.0 Hz, 1H), 7.79 (dd, J = 10.6, 8.2 Hz, 2H), 7.51 (t, J = 7.6 Hz, 1H), 7.40 (tt, J = 21.0, 7.0 Hz, 5H), 7.20 (d, J = 7.4 Hz, 1H), 2.81 (t, J = 8.1 Hz, 2H), 1.58−1.48 (m, 2H), 1.37 (d, J = 11.5 Hz, 6H), 1.33−1.15 (m, 10H), 0.86 (t, J = 6.7 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.1, 149.4, 140.6, 133.7, 132.8, 131.7, 128.1, 128.0, 127.8, 126.8, 126.5, 126.2, 125.5, 125.3, 125.0, 123.2, 120.7, 110.7, 85.1, 33.3, 31.8, 29.8, 29.5, 29.3, 28.8, 28.8, 28.0, 22.6, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{29}H_{35}O$ 399.2682; Found 399.2877.

*(Z)-4-(((6-(Cyclopropyl(3,3-dimethylisobenzofuran-1(3H)-ylidene)methyl)naphthalen-2-yl)oxy)methyl)benzonitrile (**4gh**).* **GP-2** was carried out with 2-(2-(cyclopropylethynyl)phenyl)propan-2-ol **1g** (40 mg, 0.2 mmol), 4-(((6-bromonaphthalen-2-yl)oxy)-methyl)benzonitrile **2h** (81 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4gh**:**3gh** (16:5, 69 mg, 76%) as a pale yellow liquid.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1g**) = 0.5, R_f (**4gh**) = 0.6, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 3028, 2893, 2827, 2206, 1715, 1609, 1579, 1484, 1447, 1372, 1247, 1192, 1155, 1082, 1047, 944, 897, 844, 807, 747 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.22−8.14 (m, 1H), 7.99 (d, J = 1.0 Hz, 1H), 7.78−7.72 (m, 2H), 7.70−7.62 (m, 3H), 7.58 (d, J = 8.4 Hz, 2H), 7.42−7.31 (m, 2H), 7.19 (ddd, J = 11.4, 7.8, 2.1 Hz, 2H), 7.12 (d, J = 2.5 Hz, 1H), 5.22 (s, 2H), 2.05 (tt, J = 8.1, 5.2 Hz, 1H), 1.55 (s, 6H), 1.08−1.00 (m, 2H), 0.45−0.37 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.6, 153.2, 149.6, 142.6, 136.5, 133.2, 132.4, 132.3, 129.8, 129.2, 129.0, 128.2, 127.6, 127.5, 125.3, 124.8, 120.3, 118.7, 118.1, 111.6, 111.6, 107.1, 86.1, 68.8, 28.4, 12.5, 10.3 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{32}H_{28}NO_2$ 458.2115; Found 458.2099.

*(Z)-1-(4-(1-(3-Propylisobenzofuran-1(3H)-ylidene)hexyl)phenyl)-ethan-1-one (**4im**).* **GP-2** was carried out with 1-(2-(hept-1-yn-1-yl)phenyl)butan-1-ol **1i** (49 mg, 0.2 mmol), methyl 4-bromobenzoate **2m** (52 mg, 0.24 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol), Cs_2CO_3 (130 mg, 0.4 mmol), and toluene (2 mL) at 80 °C, for 6 h. Purification of the crude material by silica gel column chromatography (petroleum ether/ethyl acetate, 100:0 to 95:05) furnished the product **4im**:**3im** (16:5, 47 mg, 49%) as a colorless oil.

[TLC (petroleum ether/ethyl acetate 90:10, R_f (**1i**) = 0.5, R_f (**4im**) = 0.4, UV detection]. IR (MIR-ATR, 4000−600 cm^{-1}): ν_{max} = 2924, 2895, 2827, 1750, 1703, 1446, 1264, 1088, 899, 751, 721 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−7.97 (m, 2H), 7.70 (d, J = 7.4 Hz, 1H), 7.69−7.63 (m, 2H), 7.37 (ddt, J = 8.3, 7.3, 3.8 Hz, 2H), 7.27 (d, J = 4.4 Hz, 1H), 5.42 (dd, J = 7.7, 3.8 Hz, 1H), 3.92 (s, 3H), 2.89−2.68 (m, 2H), 1.88 (dddd, J = 14.0, 9.9, 6.0, 3.9 Hz, 1H), 1.76−1.64 (m, 1H), 1.54−1.24 (m, 8H), 0.95 (t, J = 7.4 Hz, 3H), 0.88 (t, J = 7.1 Hz, 3H) ppm. $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 167.3, 152.2, 146.4, 145.2, 133.8, 129.1, 128.5, 128.3, 128.1, 126.9, 123.6, 121.3, 111.4, 83.3, 51.9, 38.2, 31.9, 30.7, 28.9, 22.6, 18.4, 14.1, 14.1 ppm. HRMS (ESI) m/z: $[M + H]^+$ Calcd for $C_{25}H_{31}O_3$ 379.2268; Found 379.2259.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00666.

Spectral data for all new compounds and crystallographic data (PDF)

Accession Codes

CCDC 2071793 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Sekine, K.; Takayanagi, A.; Kikuchi, S.; Yamada, T. Silver-Catalyzed C-C Bond Formation with Carbon Dioxide: Significant Synthesis of Dihydroisobenzofurans. *Chem. Commun.* **2013**, *49* (96), 11320−11322.

(2) Kwon, Y.-J.; Sohn, M.-J.; Kim, C.-J.; Koshino, H.; Kim, W.-G. Flavimycins A and B, Dimeric 1,3-Dihydroisobenzofurans with

Peptide Deformylase Inhibitory Activity from Aspergillus Flavipes. *J. Nat. Prod.* **2012**, *75* (2), 271−274.
(3) Abdelfattah, M. S.; Arai, M. A.; Ishibashi, M. Bioactive Secondary Metabolites with Unique Aromatic and Heterocyclic Structures Obtained from Terrestrial Actinomycetes Species. *Chem. Pharm. Bull.* **2016**, *64* (7), 668−675.
(4) Harper, J. K.; Arif, A. M.; Ford, E. J.; Strobel, G. A.; Porco, J. A.; Tomer, D. P.; Oneill, K. L.; Heider, E. M.; Grant, D. M. Pestacin: A 1,3-Dihydro Isobenzofuran from Pestalotiopsis Microspora Possessing Antioxidant and Antimycotic Activities. *Tetrahedron* **2003**, *59* (14), 2471−2476.
(5) Yang, J.; Huang, R.; Qiu, S. X.; She, Z.; Lin, Y. A New Isobenzofuranone from the Mangrove Endophytic Fungus Penicillium Sp. (ZH58). *Nat. Prod. Res.* **2013**, *27* (20), 1902−1905.
(6) Mousavi, S. H.; Mohammadizadeh, M. R.; Roshan, Z.; Jamaleddini, A.; Arimitsu, S. One-Pot Synthesis of Spiro-Isobenzofuran Compounds via the Sequential Condensation/Oxidation Reaction of Ninhydrin with 4-Amino-1,2-Naphthoquinones/2-Amino-1,4-Naphthoquinones under Mild Conditions. *ACS Omega* **2020**, *5* (29), 18273−18288.
(7) Coote, S. J.; Davies, S. G.; Middlemiss, D.; Naylor, A. Stereoselective Synthesis of Cis-1,3-Disubstituted 1,3-Dihydroisobenzofurans via Arenechromium Tricarbonyl Methodology. *J. Organomet. Chem.* **1989**, *379* (1), 81−88.
(8) Gözler, B.; Gözler, T.; Shamma, M. Egenine: A Possible Intermediate in Phthalideisoquinoline Biogenesis. *Tetrahedron* **1983**, *39* (4), 577−580.
(9) Jing, L.; Wenzao, L.; Guoshi, T. Two Phthalideisoquinoline Hemiacetal Alkaloids from Corydalis Decumbens. *Planta Med.* **1994**, *60* (5), 486−487.
(10) Sekine, K.; Takayanagi, A.; Kikuchi, S.; Yamada, T. Silver-Catalyzed C-C Bond Formation with Carbon Dioxide: Significant Synthesis of Dihydroisobenzofurans. *Chem. Commun.* **2013**, *49* (96), 11320−11322.
(11) Praveen, C.; Iyyappan, C.; Girija, K.; Kumar, K. S.; Perumal, P. T. Regioselective Synthesis and Evaluation of 3-Alkylidene-1,3-Dihydroisobenzofurans as Potential Antidepressant Agents. *J. Chem. Sci.* **2012**, *124* (2), 451−462.
(12) Liu, S.; Chen, K.; Hao, W.-J.; Tu, X.-C.; Tu, S.-J.; Jiang, B. Generation of 1,3-Dimethylene-Substituted Isobenzofurans via Pd-(II)-Catalyzed Selective Oxo-Cyclization/SO2 Insertion Cascade of *β*-Alkynyl Ketones. *J. Org. Chem.* **2019**, *84* (4), 1964−1971.
(13) Peuchmaur, M.; Lisowski, V.; Gandreuil, C.; Maillard, L. T.; Martinez, J.; Hernandez, J.-F. Solid-Phase Synthesis of Isocoumarins: A Traceless Halocyclization Approach. *J. Org. Chem.* **2009**, *74* (11), 4158−4165.
(14) Yao, T.; Larock, R. C. Regio- and Stereoselective Synthesis of Isoindolin-1-Ones via Electrophilic Cyclization. *J. Org. Chem.* **2005**, *70* (4), 1432−1437.
(15) Mehta, S.; Yao, T.; Larock, R. C. Regio- and Stereoselective Synthesis of Cyclic Imidates via Electrophilic Cyclization of 2-(1-Alkynyl)benzamides. A Correction. *J. Org. Chem.* **2012**, *77* (23), 10938−10944.
(16) Wei, L.-L.; Wei, L.-M.; Lin, P.-Y.; Chen, C.-C.; Pan, W.-B.; Wu, M.-J. Palladium(0)-Catalyzed 5-Exo-Dig O-Cyclization/Coupling of Ethyl 3-(2-Alkynylphenyl)-3-Oxopropanoates with Aryl Iodides to 1,3-Dihydroisobenzofurans. *Tetrahedron Lett.* **2015**, *56* (47), 6629−6632.
(17) Bacchi, A.; Costa, M.; Della Ca, N.; Fabbricatore, M.; Fazio, A.; Gabriele, B.; Nasi, C.; Salerno, G. Synthesis of 1-(Alkoxycarbonyl)-Methylene-1,3-Dihydroisobenzofurans and 4-(Alkoxycarbonyl)Benzo-[c]Pyrans by Palladium-Catalysed Oxidative Carbonylation of 2-Alkynylbenzyl Alcohols, 2-Alkynylbenzaldehydes and 2-Alkynylphenyl Ketones. *Eur. J. Org. Chem.* **2004**, *2004* (3), 574−585.
(18) Gabriele, B.; Salerno, G.; Fazio, A.; Pittelli, R. Versatile Synthesis of (Z)-1-Alkylidene-1,3-Dihydroisobenzofurans and 1H-Isochromenes by Palladium-Catalyzed Cycloisomerization of 2-Alkynylbenzyl Alcohols. *Tetrahedron* **2003**, *59* (33), 6251−6259.
(19) Zhao, X.; Miao, Z.; Chen, R. Efficient Syntheses of 1H-Isochromen-1-Ylmethylphosphonates via Regioselective 6-Endo-Dig Addition to Carbon—Carbon Triple Bond Catalyzed by Pd(OAc)2. *Phosphorus, Sulfur Silicon Relat. Elem.* **2011**, *186* (12), 2357−2367.
(20) Sun, J.; Qiu, J.-K.; Wu, Y.-N.; Hao, W.-J.; Guo, C.; Li, G.; Tu, S.-J.; Jiang, B. Silver-Mediated Radical C(Sp3)-H Biphosphinylation and Nitration of *β*-Alkynyl Ketones for Accessing Functional Isochromenes. *Org. Lett.* **2017**, *19* (4), 754−757.
(21) Wang, D.; Liu, S.; Lan, X.-C.; Paniagua, A.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Tunable Dimerization and Trimerization of *β*-Alkynyl Ketones via Silver Catalysis for Accessing Spiro and Dispiro Compounds Containing 1H-Isochromene. *Adv. Synth. Catal.* **2017**, *359* (18), 3186−3193.
(22) Liu, S.; Chen, K.; Lan, X.-C.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Synergistic Silver/Scandium Catalysis for Divergent Synthesis of Skeletally Diverse Chromene Derivatives. *Chem. Commun.* **2017**, *53* (77), 10692−10695.
(23) Liu, S.; Lan, X.-C.; Chen, K.; Hao, W.-J.; Li, G.; Tu, S.-J.; Jiang, B. Ag/Brønsted Acid Co-Catalyzed Spiroketalization of *β*-Alkynyl Ketones toward Spiro[Chromane-2,1′-Isochromene] Derivatives. *Org. Lett.* **2017**, *19* (14), 3831−3834.
(24) Shi, H.-N.; Huang, M.-H.; He, C.-L.; Lu, H.-P.; Hao, W.-J.; Tu, X.-C.; Tu, S.-J.; Jiang, B. Completely Stereoselective Synthesis of Sulfonated 1,3-Dihydroisobenzofurans via Radical Multicomponent Reactions. *J. Org. Chem.* **2019**, *84* (21), 13686−13695.
(25) Mancuso, R.; Mehta, S.; Gabriele, B.; Salerno, G.; Jenks, W. S.; Larock, R. C. A Simple and Mild Synthesis of 1H-Isochromenes and (Z)-1-Alkylidene-1,3-Dihydroisobenzofurans by the Iodocyclization of 2-(1-Alkynyl)Benzylic Alcohols. *J. Org. Chem.* **2010**, *75* (3), 897−901.
(26) Della Ca, N.; Campanini, F.; Gabriele, B.; Salerno, G.; Massera, C.; Costa, M. Cascade Reactions: Catalytic Synthesis of Functionalized 1,3-Dihydroisobenzofuran and Tetrahydrofuran Derivatives by Sequential Nucleophilic Ring Opening-Heterocyclization- Oxidative Carbonylation of Alkynyloxiranes. *Adv. Synth. Catal.* **2009**, *351* (14−15), 2423−2432.
(27) Cao, Z.; Li, S.; Li, J.; Meng, X.; Zhang, H.; Sun, X.; You, J. Gold-Catalyzed *π*-Directed Regioselective Cyclization of Bis(o-Alkynyl Benzyl Alcohols): Rapid Access to Dihydroisobenzofuran Derivatives. *New J. Chem.* **2016**, *40* (10), 8211−8215.
(28) Yu, S.-Y.; Gao, L.-H.; Wu, J.-X.; Lan, H.-B.; Ma, Y.; Yin, Z.-G. Regio- and Stereoselective Intramolecular Hydroalkoxylation of Aromatic Alkynols: An Access to Dihydroisobenzofurans under Transition-Metal-Free Conditions. *Chem. Pap.* **2020**, *74* (10), 3303−3310.
(29) Mahendar, L.; Gopi Krishna Reddy, A.; Krishna, J.; Satyanarayana, G. [Cu]-Catalyzed Domino Sonogashira Coupling Followed by Intramolecular 5-Exo-Dig Cyclization: Synthesis of 1,3-Dihydro-2-Benzofurans. *J. Org. Chem.* **2014**, *79* (18), 8566−8576.
(30) Nandakumar, A.; Kiruthika, S. E.; Naveen, K.; Perumal, P. T. Pd(0)-Catalyzed Regio- and Stereoselective Cyclization of Alkynes: Selective Synthesis of (E)-4-(Isobenzofuran-1(3H)-Ylidene)-1,2,3,4-Tetrahydroisoquinolines and Aze/Oxepinoindoles. *Org. Biomol. Chem.* **2014**, *12* (6), 876−880.
(31) Peng, P.; Tang, B.-X.; Pi, S.-F.; Liang, Y.; Li, J.-H. Synthesis of (E)-3-(Isobenzofuran-3(1H)-Ylidene)Indolin-2-Ones by the Palladium-Catalyzed Intramolecular C-H Functionalization Process. *J. Org. Chem.* **2009**, *74* (9), 3569−3572.
(32) Madich, Y.; Álvarez, R.; Aurrecoechea, J. M. Palladium-Catalyzed Regioselective 5-Exo-O-Cyclization/Oxidative Heck Cascades from o-Alkynylbenzamides and Electron-Deficient Alkenes. *Eur. J. Org. Chem.* **2014**, *2014* (28), 6263−6271.
(33) Kołodziejczyk, A.; Domański, S.; Chaładaj, W. Tandem Palladium-Catalyzed 6-Exo-Dig Oxocyclization Coupling of *δ*-Acetylenic *β*-Ketoesters with Aryl Bromides and Chlorides: Route to Substituted Dihydropyrans. *J. Org. Chem.* **2018**, *83* (20), 12887−12896.

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