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Indium(III)-catalyzed Synthesis of Benzo[*b*]furans by Intramolecular Hydroalkoxylation of *ortho*-Alkynylphenols: Scope and Mechanistic Insights

Lorena Alonso-Marañón,[‡] M. Montserrat Martínez,[‡] Luis A. Sarandeses,[‡] Enrique Gómez-Bengoa,*[†] José Pérez Sestelo*[‡]

[‡] *Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química, Universidade da Coruña, E-15071 A Coruña, Spain*

[†]*Departamento de Química Orgánica I, Universidad del País Vasco UPV/EHU, 20009 Donostia-San Sebastián, Spain*

sestelo@udc.es, enrique.gomez@ehu.es

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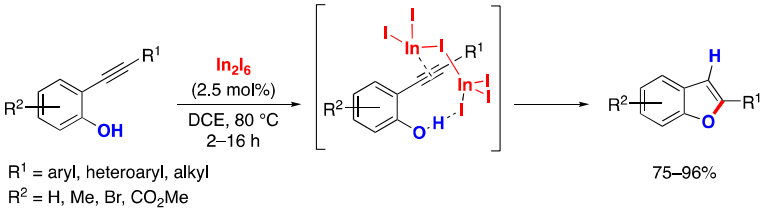


Abstract

Indium(III) halides catalyze the hydroalkoxylation reaction of *ortho*-alkynylphenols to afford benzo[*b*]furans in good yields. The reaction proceeds with 5-*endo-dig* regioselectivity with a variety of phenols functionalized at the arene and alkyne moieties in high yields using InI_3 (5 mol%) in DCE. Experimental and computational studies support a mechanism based on the indium(III) π-Lewis acid activation of the alkyne followed by nucleophilic addition of the phenol and final protodemetallation to afford the corresponding benzo[*b*]furan. DFT calculations suggest that dimer In_2I_6 is the catalytic species through a novel double coordination with the alkyne and the hydroxyl group.

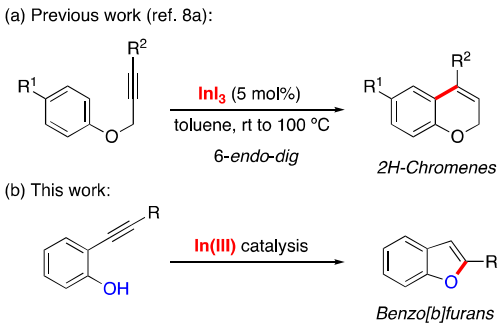
Introduction

Indium, in different oxidation states, has been widely recognized as a soft σ-Lewis acid for the activation of carbonyl groups in a variety of fundamental organic transformations.[1] In addition, indium is considered to be a green reagent based on its compatibility with aqueous media, low toxicity and excellent tolerance to oxygen- and nitrogen-containing substrates and functional groups.[2] In recent years, indium(III) has also proven to be an efficient π-Lewis acid for the activation of unsaturated systems, particularly alkynes.[3] The synthetic utility has been demonstrated in a variety of inter- and intramolecular indium-catalyzed carbon-carbon[4] and carbon-heteroatom transformations,[5] including polycyclization reactions using enynes.[6] This catalytic activity, which is often limited to transition metals, has been explained by Corey based on the hypothesis that the 5d orbitals of In(III) may be sufficiently lowered in energy to allow some hybridization with the vacant 5p orbital to facilitate a bidentate coordination mode with the two orthogonal π-bonding orbitals of the C–C triple bonds.[6] The dual Lewis acid activity of indium(III) has found interesting applications in the synthesis of complex organic compounds.[7]

In this context, we have disclosed the ability of indium(III) halides to catalyze a 6-*endo*-*dig* regioselective intramolecular hydroarylation (IMHA) of aryl propargyl ethers and amines for the synthesis of *2H*-chromenes and dihydroquinolines (Scheme 1a),[8a] a reaction that can be combined in one pot with a palladium-catalyzed cross-coupling reaction of triorganoindium reagents.[8b] Further computational studies,[9] support a mechanism based on the indium(III) π-Lewis activation of the alkyne. In connection with this work, we switched our attention to the formation of carbon-heteroatom bonds using indium catalysis, in particular to the indium(III)-catalyzed intramolecular hydroalkoxylation of *o*-alkynylphenols for the synthesis of benzo[*b*]furans (Scheme 1b). The benzofuran ring is a privileged structure that is present in a large number of biologically active compounds and natural products, and the development of

practical, green and economical methods for synthesis of this unit has been widely pursued.[10] One of the most straightforward approaches to benzofurans involves the hydroalkoxylation reaction of *o*-alkynylphenols using catalysis with precious transition metals such as palladium,[11] platinum,[12] rhodium,[13] or gold.[14] Although studies on the reactivity of *o*-alkynylanilines under indium(III) catalysis have been reported,[5b] to the best of our knowledge this is the first example of the synthesis of benzo[*b*]furans by indium catalysis.

Scheme 1. Indium(III)-catalyzed Hydroarylation and Hydroalkoxylation reactions

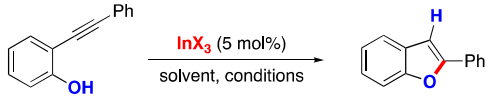


Results and discussion

Our investigation started with the reactivity of *o*-phenylethynylphenol (**1a**) with indium(III) halides. At the outset, treatment of **1a** with InI_3 (5 mol%) in DCE at room temperature only produced a small amount of 2-phenylbenzo[*b*]furan (**2a**) and most of the starting phenol **1a** was recovered (Table 1, entry 1). However, upon heating at 80 °C the yield increased to 95% yield in just 2 h (entry 2). Furthermore, it was found that on using $InBr_3$ (5 mol%) the cycloisomerization proceeded to give a high yield in a short reaction time (entry 3). In addition, it was observed that the hydroalkoxylation reaction also took place on using $InCl_3$ (5 mol%), although this reaction required 40 h at 80 °C to achieve full conversion (entry 4). Surprisingly, the use of $In(OTf)_3$ (5 mol%) only gave traces of the benzofuran **2a**, with unreacted starting *o*-alkynylphenol **1a** recovered (entry 5). These results show that InI_3 and $InBr_3$ are the most suitable indium(III) halides for this process. We reasoned that this result is based on the lower oxophilicity of these halides when compared with $InCl_3$ and $In(OTf)_3$,

which drives the preference for π-coordination with the alkyne over the σ-interaction with the hydroxyl group. This counteranion effect was previously observed in the indium-catalyzed hydroarylation reaction[8] and in the indium-promoted carboindiation of alkenes.[15] On the other hand, these results highlight the tolerance of indium(III) halides for the hydroxyl group. During the optimization process we observed that the reaction also proceeded in toluene, albeit with longer reaction times required (entry 6), and in CH_2Cl_2 at 40 °C – although this reaction required 48 h to afford 2-phenylbenzo[*b*]furan in excellent yield (entry 7). Evidence for reaction was not observed in MeOH or CH_3CN, probably due to coordination of the catalyst with the solvent (entries 8 and 9).

Table 1. Indium(III)-catalyzed Hydroalkoxylation of *o*-Phenylethynylphenol (**1a**).



1a **2a**

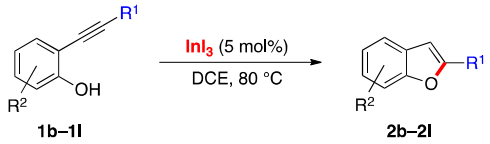
Entry	InX_3	Solvent	T (ºC)	t (h)	Yield (%)[a]
1	InI_3	DCE	25	16	15 (85)[b]
2	InI_3	DCE	80	2	95
3	$InBr_3$	DCE	80	2	85
4	$InCl_3$	DCE	80	40	82
5	$In(OTf)_3$	DCE	80	16	(99)[b]
6	InI_3	Toluene	80	7	93
7	InI_3	CH_2Cl_2	40	48	90
8	InI_3	MeOH	65	48	(99)[b]
9	InI_3	MeCN	80	16	(99)[b]

[a] Isolated yields. [b] Recovered starting material in parentheses.

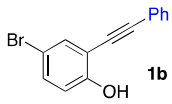
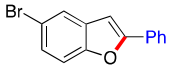
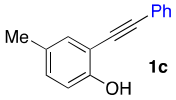
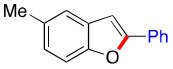
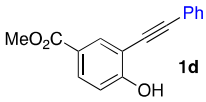
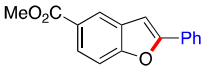
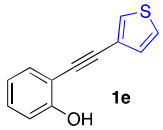
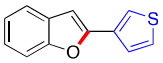
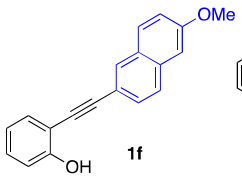
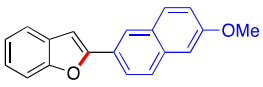
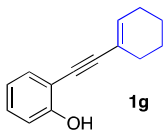
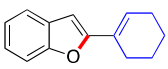
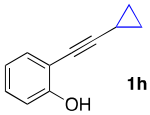
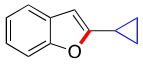
With the optimal reaction conditions in hand, we proceeded to examine the scope of the reaction using a variety of *o*-alkynylphenols functionalized at the arene and alkyne moieties. It was found that the presence of electron-donating or electron-withdrawing functional groups on the phenol ring, such as bromide, methyl or methyl ester (**1b**–**d**), did not have a significant effect on the reactivity and the corresponding 2-phenylbenzo[*b*]furans **2b**–**d** were obtained in high yield (Table 2, entries 1–3). The reactions of *o*-alkynylphenols with internal alkynes

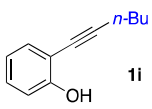
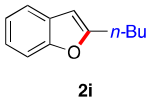
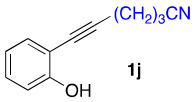
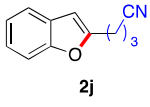
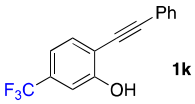
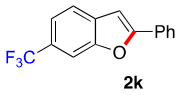
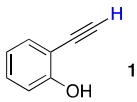
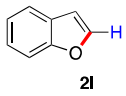
bearing heteroaryl groups, such as thienyl (**1e**), naphthyl (**1f**), alkenyl (**1g**), and alkyl groups (**1h**–**j**), also proceeded efficiently to provide a variety of 2-substituted benzo[*b*]furans (**2e**–**j**) under the same reaction conditions (Table 2, entries 4–9). In addition, the *m*-trifluoromethyl *o*-phenylethynyl phenol **1k** gave the corresponding benzo[*b*]furan **2k** in 96% yield (Table 2, entry 10). The hydroalkoxylation reaction with terminal alkynes proved to be more problematic both in terms of reactivity and side products. Only benzo[*b*]furan (**2l**) was obtained in toluene at 110 °C in 42% yield (Table 2, entry 11).

Table 2. Scope of the Indium(III)-catalyzed Hydroalkoxylation of *o*-Alkynylphenols.



1b–1l **2b–2l**

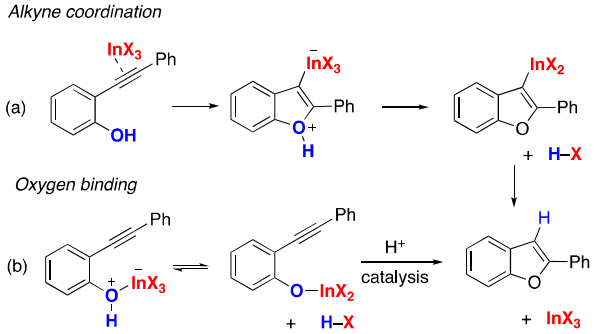
Entry	*o*-Alkynylphenol	Product	Yield (%)[a]
1	 **1b**	 **2b**	95
2	 **1c**	 **2c**	96
3	 **1d**	 **2d**	94
4	 **1e**	 **2e**	82
5	 **1f**	 **2f**	75
6	 **1g**	 **2g**	90[b]
7	 **1h**	 **2h**	86[b]

8	 **1i**	 **2i**	86
9	 **1j**	 **2j**	78
10	 **1k**	 **2k**	96
11	 **1l**	 **2l**	42[c]

[a] Isolated yields [b] Reaction at rt. [c] Reaction at 110 °C.

As the next step we focused our attention on the reaction mechanism. Our first proposal considered the π-coordination of InX_3 to the alkyne followed by nucleophilic attack of the hydroxyl group. The alkenylindium compound generated during this process should undergo a protodemetallation by the previously generated haloacid to give the corresponding benzo[*b*]furan with regeneration of the InX_3 (Scheme 2a). We also considered Brønsted acid catalysis promoted by the haloacid produced by reaction of the phenol with InI_3 (Scheme 2b).[16]

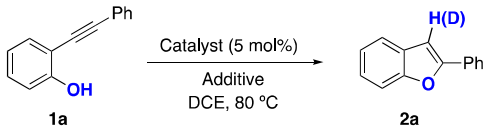
Scheme 2. Mechanistic Pathways for the Indium(III)-catalyzed Hydroalkoxylation Reaction of *o*-Alkynylphenols



With these proposals in mind, various experiments were carried out to obtain more information about the reaction mechanism. Firstly, the hydroalkoxylation reaction in the presence of deuterated water was explored. Treatment of *o*-alkynylphenol **1a** with InI_3 (5

mol%) and D_2O (300 mol%) in toluene at 100 °C gave the 2-phenylbenzofuran (**2a-*d***) in 93% yield with 75% deuterium incorporation at the C-3 position, a result that supports an intermolecular protonation step (Table 3, entry 1). Several experiments were also carried out using proton scavengers that could prevent Brønsted acid catalysis. Interestingly, the hydroalkoxylation reaction of **1a** using InI_3 (5 mol%) and K_2CO_3 (20 mol%) gave a similar yield, albeit with a longer reaction time (12 h) required, probably due to the slower rate for the protonation step (Table 3, entry 2). In contrast, evidence for reaction was not observed on using InI_3 (5 mol%) and *i*-Pr_2NEt (20 mol%) as the catalytic system. In this case, we reasoned that the Lewis acid-base interaction between the indium(III) halide and the amine inhibited the catalysis (Table 3, entry 3). Finally, proton catalysis using hydroiodic acid (HI, 57% aq sol.) was evaluated. The treatment of **1a** with 5 mol% of HI afforded the benzofuran **2a** in 5% yield (Table 3, entry 4) and higher amounts of HI produced the electrophilic addition to the alkyne (Equation 1).

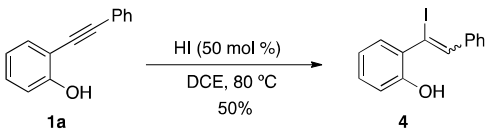
Table 3. Experimental Mechanistic Studies.



1a **2a**

Entry	Catalyst	Additive	Yield (%)[a]
1	InI_3	D_2O (300 mol%)	93 (75% D)[b]
2	InI_3	K_2CO_3 (20 mol%)	88
3	InI_3	*i*-Pr_2NEt (20 mol%)	–
4	HI (57% aq)	none	5

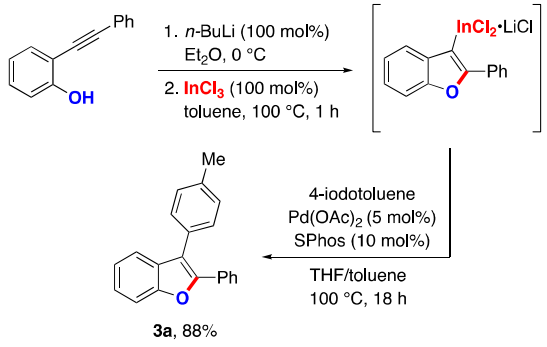
[a] Isolated yield. [b] Reaction in toluene at 100 °C



1a **4** (1)

The formation and reactivity of the alkenylindium species generated during the hydroalkoxylation was also investigated. Organoindium compounds are useful in metal-catalyzed organic reactions, especially in palladium-catalyzed cross-coupling reactions.[17] On applying a modified protocol described by Nakamura for the preparation of 3-metallobenzofuran intermediates,[18] the *o*-phenylethynylphenol (**1a**) was deprotonated using *n*-BuLi and the corresponding lithium phenoxide was heated under reflux in toluene in the presence of stoichiometric amounts of $InCl_3$. When the reaction was quenched with water the 2-phenylbenzo[*b*]furan (**2a**) was obtained in 88% yield. Alternatively, the addition of 4-iodotoluene, $Pd(OAc)_2$ (5 mol%), and SPhos (10 mol%) afforded the cross-coupling product **3a** in 88% yield (Scheme 3). This result provides evidence for the formation of the organoindium compound and represents the first example of a tandem indium(III)-promoted hydroalkoxylation/palladium-catalyzed cross-coupling for the synthesis of 2,3-disubstituted benzo[*b*]furans.

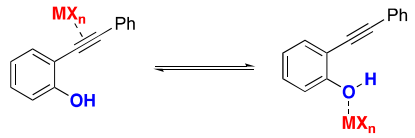
Scheme 3. Tandem Indium(III)-promoted Hydroalkoxylation/Palladium-catalyzed Cross-coupling.



Finally, the mechanism of the cycloisomerization reaction was investigated by performing density functional theory (DFT) calculations, with particular interest in ascertaining the coordination pattern of the indium(III) halides with the alkynyl substrate and the origin of the catalytic activity. According to our experimental results and the proposal of indium(III) as a soft Lewis acid, indium(III) should bind preferentially to soft basic functional groups such as

alkynes in preference to other harder groups (i.e., hydroxyl groups).[19] *o*-Phenylethynylphenol (**1a**) was used as a model and it was found that the preference of indium(III) halides for the triple bond is not total (Table 4) and equilibrium ratios close to 1:1 were computed for all InX_3 halides. Only InI_3 shows a low energy difference (0.7 kcal/mol, 3.3:1, entry 1) in favour of the alkynyl complex, whereas the chloride and bromide counterparts do not show any measurable preference. However, the alkynophilic character of In(III) is significant in relative terms when compared with the behavior of typical hard Lewis acids, such as $MgCl_2$ or $AlCl_3$. In these cases, the HO:MX_2 complex is 8 to 11 kcal/mol more stable than the alkyne:MX_n one, and these values correspond to equilibrium ratios of 10^7:1 (Al) and 10^5:1 (Mg) (entries 5 and 6), respectively. Thus, indium salts can be regarded as highly alkynophilic and this contrasts with the oxophilic character of magnesium or aluminium. Interestingly, $GaCl_3$ shows a relative preference that is intermediate between those of $AlCl_3$ and $InCl_3$, as corresponds to its hardness, which is between those of indium and aluminium (Table 4, entry 4).

Table 4. Computed Binding Enthalpies[a] and Equilibrium Ratios for Complexation to Oxygen *vs* Alkyne of *o*-Phenylethynylphenol (**1a**) and Lewis Acids of the Type MX_n.

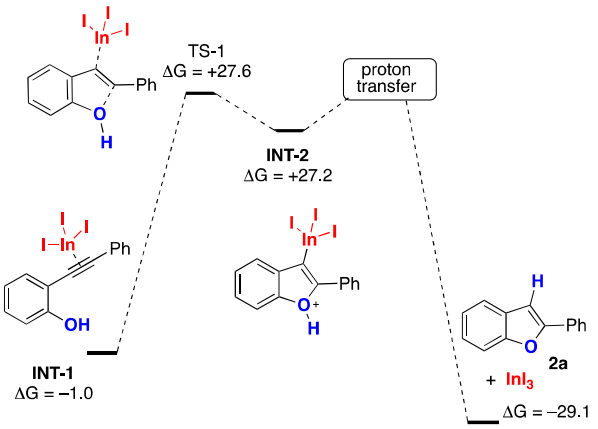


Entry	InX_3	ΔH_{f1} (kcal/mol)	ΔH_{f2} (kcal/mol)	Equilibrium ratio
1	InI_3	–13.8	–13.1	3.3 : 1
2	$InBr_3$	–16.2	–16.1	1.1 : 1
3	$InCl_3$	–17.8	–17.7	1.3 : 1
4	$GaCl_3$	–14.6	–19.4	$1 : 10^3$
5	$AlCl_3$	–15.6	–26.4	$1 : 10^7$
6	$MgCl_2$	–9.6	–17.5	$1 : 10^5$

[a] In the gas phase. ΔH_{f1} and ΔH_{f2} were calculated by subtraction of the absolute energies of the starting compounds from the absolute energy of the optimized complex between the substrate and the Lewis acid.

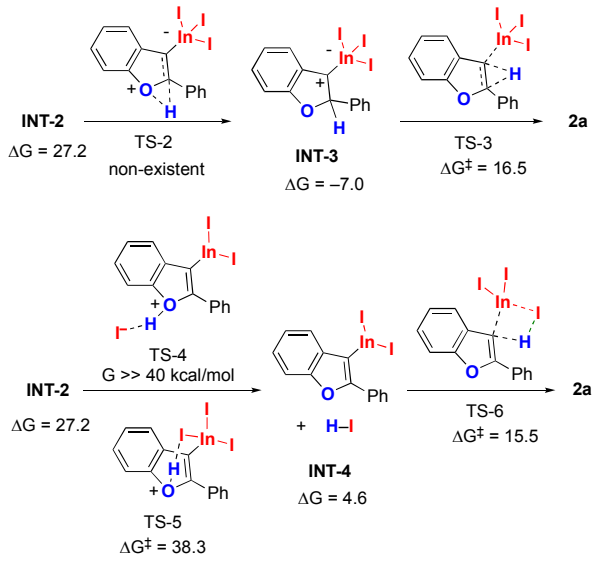
Next, computational studies to figure out the complete reaction mechanism were calculated using InI_3 as catalytic species.[20] It was found that the formation of the complex **INT-1** is exergonic, i.e., 1.0 kcal/mol lower in energy than the separate reactants, *o*-(phenylethynyl)phenol (**1a**) and InI_3, and this initiates the catalytic cycle (Figure 1, the sum of reactants is taken as G = 0). The results of previous computational studies[9] on the indium-catalyzed intramolecular hydroarylation showed that the coordination of the triple bond to indium activates it for the external nucleophilic attack, but this attack is not the rate-determining step of the reaction. We wanted to address this mechanistic proposal with our own system. After **INT-1**, the initial transition state (TS-1) for the ring closure was computed and this showed quite a high activation energy ($\Delta G^{\ddagger}$ = 28.6 kcal/mol). In this process, which is high in energy, an unstable zwitterionic intermediate containing the new C–O and C–In bonds is formed (**INT-2**, ΔG = 27.2 kcal/mol) and this lies 28.2 kcal/mol above the initial intermediate and only 0.4 kcal/mol below the transition state. These data indicate that the cyclization is a highly reversible process, and the reaction will not proceed to completion or become an exothermic process until the oxonium cation in **INT-2** is deprotonated or the hydrogen is transferred to its final position at the C-3 atom of the benzo[*b*]furan **2a** (ΔG = –29.1 kcal/mol). However, it became clear from the beginning that the proton transfer from **INT-2** to **2a** is not a straightforward process. Under the experimental conditions considered here, there is no external base that could promote it and, furthermore, the addition of bases shuts down the reaction, thus indicating the need for the OH proton to cleave the C–In bond and form the final adduct (**2a**).

Figure 1. Computed Energy Profile for the InI_3-catalyzed Hydroalkoxylation Reaction.



Under these circumstances, we envisioned several possible mechanistic alternatives for the H-transfer (Figure 2). For example, a double intramolecular [1,2]-proton shift would place the H first on the carbon adjacent to the oxygen (**INT-3**) and then in the benzofuran **2a**. Indeed, the second migration is energetically affordable (TS-3, $\Delta G^{\ddagger}$ = 23.5 kcal/mol). In contrast, TS-2 does not seem to exist, since the oxygen would have to adopt an extremely strained geometry to transfer the hydrogen. Alternatively, an iodide anion, detached from indium in **INT-2**, could be responsible for the abstraction of the proton to form the much more stable neutral intermediate **INT-4**. However, iodide is not basic enough to play this role, as demonstrated by the high activation energies of both the intermolecular (TS-4) and intramolecular (iodide still attached to indium, TS-5) variants of the process, which can be safely ruled out. It is noteworthy that the cleavage of the C–In bond by hydrogen iodide would be a straightforward step, as in TS-6 ($\Delta G^{\ddagger}$ = 10.9 kcal/mol), if **INT-4** or a similar intermediate is formed somehow.

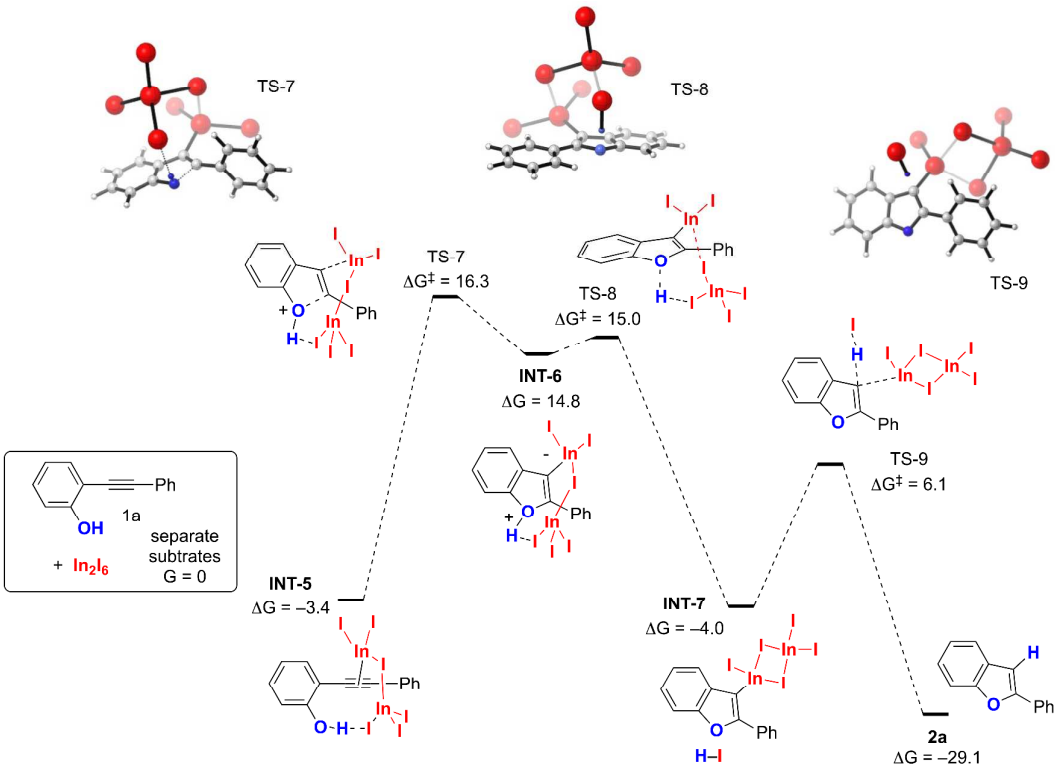
Figure 2. Computed Alternatives for the Hydrogen Transfer from the Oxygen atom to the Final Position in the 2-Phenylbenzo[*b*]furan (**2a**).



As there are no more good candidates for the deprotonation apart from iodide, we hypothesized that the dimeric nature of In_2I_6 could play a significant role in stabilizing and facilitating the different intermediates and transition states of the catalytic cycle. We therefore reconsidered the whole scheme in the presence of the indium iodide dimer. In fact, the complexation of the alkyne is stronger with In_2I_6 (**INT-5**, Figure 3) than with InI_3 (**INT-1**, Figure 2) due to the double coordination that the former is able to exert, i.e., between the indium center and the alkyne plus a new hydrogen bond between the hydroxyl group and one of the iodides in the second indium atom. In_2I_6 also has the advantage of a more flexible structure, which increases the binding free energy to 3.4 kcal/mol. The double interaction C–In and OH–I is even more important in the subsequent steps of the mechanism.[21] For example, the activation energy of TS-7 is only 19.7 kcal/mol (compared to 28.6 kcal/mol of TS-1 in Figure 2) due to the activation of the triple bond and the increased nucleophilicity of the hydroxyl group. The zwitterionic intermediate **INT-6** is still high in energy, but the reversibility of the process is now compensated by the ease of hydrogen abstraction in TS-8, which is only 0.2 kcal/mol higher that the energy of **INT-6**. The higher flexibility of the dimer In_2I_6 over the monomer InI_3 plays a crucial role. The formation of the neutral species **INT-7** becomes easy and irreversible, since the forward step, namely cleavage of C–InI_2 bond

(TS-9), is low in energy under these conditions. The indium dimer is recovered at the end of the cycle. We believe that this proposal explains the experimental observations for the reaction. Alternatively, the deprotonation step could also be seen as driven by the InI_4^- anion, which simultaneously interacts with the C–InI_2 moiety.

Figure 3. Reaction Profile of the Mechanistic Proposal for the In_2I_6-promoted Hydroxyalkoxylation, and 3D Representation of the Main Transition States.[22]



Conclusions

Indium(III) halides catalyze the intramolecular 5-*endo-dig* hydroalkoxylation of *o*-alkynylphenols to give benzo[*b*]furans. The reaction proceeds efficiently with 5 mol% of InI_3 or $InBr_3$ at 80 °C in DCE and non-coordinating solvents such as toluene or dichloromethane. The cycloisomerization takes place with *o*-alkynylphenols substituted at the arene and internal alkynes to provide a variety of 2-substituted benzo[*b*]furans. Experimental studies support indium(III) catalysis over Brønsted acid catalysis. The reaction of the phenoxide with stoichiometric amounts of $InCl_3$ followed by addition of an aryl halide under palladium

catalysis allows the tandem cycloisomerization/cross-coupling process to give the 2,3-disubstituted benzo[*b*]furans in one pot. DFT calculations support a mechanism in which In_2I_6 acts as a catalytic species through a double coordination with the alkyne and the hydroxyl group of the *o*-alkynylphenol. In this proposal the rate-limiting step is the cyclization to give a zwitterionic intermediate that, after losing H–I, affords a new indium organometallic that undergoes fast protodemetallation to give the corresponding benzo[*b*]furan.

Experimental section

General experimental methods.

All reactions were carried out in flame-dried glassware, under argon atmosphere, using standard gastight syringes, cannulae and septa. Toluene and THF were distilled from sodium/benzophenone. Dichloromethane was distilled from calcium hydride. Dry DCE, MeOH, Et_3N, iPr_2NH and other commercially available reagents were used as received. Reaction temperatures refer to external bath temperatures. Butyllithium was titrated prior to use. Indium(III) iodide (99.998%), indium(III) bromide (99%), indium(III) chloride (99.99%) and indium(III) trifluoromethanesulfonate were purchased from Aldrich and used as received under argon. Reactions were monitored by TLC using pre-coated silica gel plates (Alugram® Xtra SIL G/UV_{254}, 0.20 mm thick), UV light as the visualizing agent and ethanolic phosphomolybdic acid as the developing agent. Flash column chromatography was performed with 230–400 mesh silica gel packed in glass columns. Melting points were measured in a Stuart Scientific melting point apparatus SMP3 and are uncorrected.

General Procedure for the Preparation of *ortho*-Alkynylphenols.[23]

To a rt solution of 2-iodophenol (4.54 mmol) in THF/Et_3N (4:1), CuI (0.182 mmol, 4 mol%), $Pd(PPh_3)_2Cl_2$ (0.091 mmol, 2 mol%) and the alkyne (9.09 mmol, 200 mol%) were added and stirred overnight. The reaction mixture was poured into a separatory funnel with saturated aqueous NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layer

was washed with H_2O (20 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography with silica gel (EtOAc/hexane) to afford, after concentration and high vacuum-drying, the corresponding 2-alkynylphenols.

2-Phenylethynylphenol (1a).[11c]

Following the General Procedure, the reaction of 2-iodophenol (2.00 g, 9.09 mmol) with phenylacetylene (2.00 mL, 18.18 mmol), $Pd(PPh_3)_2Cl_2$ (128 mg, 0.182 mmol) and CuI (70.0 mg, 0.364 mmol) in Et_3N (20 mL) and THF (80 mL) afforded, after purification by flash chromatography (10% EtOAc/hexane), **1a** (1.52 g, 86%) as a brown solid. TLC: R_f = 0.20 (10% EtOAc/hexane). Mp = 73–75 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58–7.55 (m, 2H), 7.45 (dd, J = 7.7, 1.6 Hz, 1H), 7.40–7.38 (m, 3H), 7.32–7.26 (m, 1H), 7.0 (dd, J = 8.2, 0.8 Hz, 1H), 6.93 (td, J = 7.5, 1.0 Hz, 1H), 5.85 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 156.5 (C), 131.7 (CH), 131.6 (2 × CH), 130.5 (CH), 128.8 (CH), 128.5 (2 × CH), 122.4 (C), 120.4 (CH), 114.7 (CH), 109.6 (C), 96.4 (C), 83.0 (C). MS (EI, 70 ev): *m/z* (%): 194 (98) $[M]^+$, 165 (100), 77 (62). HRMS (EI): *m/z* calcd for $C_{14}H_{10}O$: 194.0726 $[M]^+$, found: 194.0726.

4-Bromo-2-(phenylethynyl)phenol (1b).[24]

To a rt solution of 4-bromo-2-iodophenylacetate (460 mg, 1.35 mmol) in THF (5 mL) and Et_3N (0.750 mL, 5.40 mmol), $Pd(PPh_3)_2Cl_2$ (19 mg, 0.027 mmol), CuI (12.8 mg, 0.067 mmol) and phenylacetylene (0.440 mL, 4.05 mmol) were added. After 16 h the reaction was diluted with CH_2Cl_2 (15 mL) and poured into a separatory funnel with saturated aqueous NH_4Cl (15 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layer was washed with H_2O (10 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (10% EtOAc/hexane) to afford 4-bromo-2-(phenylethynyl)phenylacetate (**1b-OAc**, 355 mg, 84%) as a light brown solid. TLC: R_f = 0.20 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ

7.72 (d, J = 2.4 Hz, 1H), 7.52–7.46 (m, 3H), 7.39–7.36 (m, 3H), 7.02 (d, J = 8.6 Hz, 1H), 2.37 (s, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 168.5 (C), 150.6 (C), 135.4 (CH), 132.4 (CH), 131.6 (2 × CH), 128.9 (CH), 128.4 (2 × CH), 123.8 (CH), 122.4 (C), 119.5 (C), 118.7 (C), 95.4 (C), 82.9 (C), 20.8 (CH_3). MS (EI, 70 ev): *m/z* (%): 316 (8) [M (^{81}Br)]$^+$, 314 (8) [M (^{79}Br)]$^+$, 274 (98) [$C_{14}H_8BrO$ (^{81}Br)]$^+$, 272 (100) [$C_{14}H_8BrO$ (^{79}Br)]$^+$. HRMS (EI): *m/z* calcd for $C_{16}H_{11}BrO_2$: 313.9937 [M^+]; found: 313. 9927.

A solution of **1b-OAc** (350 mg, 1.11 mmol) in THF (2 mL) at 0 °C was added dropwise to a solution of K_2CO_3 (307 mg, 2.22 mmol, 200 mol%) in MeOH (8 mL) and THF (6 mL). The resulting mixture was stirred for 2 h. After completion, the reaction mixture was poured into a separating funnel over saturated aqueous NH_4Cl (10 mL) and extracted with EtOAc (3 × 10 mL), dried ($MgSO_4$), filtered and concentrated *in vacuo*, to afford, after purification by flash chromatography (10% EtOAc/hexane) **1b** (270 mg, 0.987 mmol, 89%) as an orange solid. TLC: R_f = 0.75 (10% EtOAc/hexane). Mp = 105–107 °C (lit.:[24] mp = 82–83 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56–7.53 (m, 3H), 7.41–7.35 (m, 4H), 6.89 (d, J = 8.7 Hz, 1H), 5.82 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 155.1 (C), 133.8 (CH), 133.3 (CH), 131.7 (2 × CH), 129.2 (CH), 128.6 (2 × CH), 121.8 (C), 116.5 (CH), 112.0 (C), 111.7 (C), 97.5 (C), 81.7 (C). MS (EI, 70 ev): *m/z* (%): 274 (98) [M (^{81}Br)]$^+$, 272 (100) [M (^{79}Br)]$^+$. HRMS (EI): *m/z* calcd for $C_{14}H_9BrO$: 271.9831 [$M]^+$; found: 271.9841.

4-Methyl-2-(phenylethynyl)phenol (1c).[11c]

To a rt solution of 2-iodo-4-methylphenol (600 mg, 2.56 mmol) in THF (16 mL) $Pd(PPh_3)_2Cl_2$ (18 mg, 0.026 mmol), CuI (9.8 mg, 0.051 mmol) and phenylacetylene (0.340 mL, 3.08 mmol) followed by addition of aqueous solution of NH_3 (~0.5 M, 200 mol%) were added. After 16 h, the reaction mixture was poured into a separating funnel over saturated aqueous NH_4Cl (10 mL) The aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL) and the combined organic layer dried ($MgSO_4$), filtered, and the solvent evaporated under reduced

pressure. The crude was purified by flash chromatography using (10% EtOAc/hexane) to afford **1c** (420 mg, 2.02 mmol, 79% yield) as an orange solid. TLC: R_f = 0.26 (10% EtOAc/hexane). Mp = 71–73 °C (lit.:[11c] mp = 59–60 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.54 (m, 2H), 7.40–7.38 (m, 3H), 7.26 (d, J = 1.5 Hz, 1H), 7.10 (dd, J = 8.4, 1.7 Hz, 1H), 6.91 (d, J = 8.4 Hz, 1H), 5.71 (s, 1H), 2.30 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.4 (C), 131.7 (CH), 131.6 (2 × CH), 131.3 (CH), 129.6 (C), 128.7 (CH), 128.5 (2 × CH), 122.5 (C), 114.5 (CH), 109.2 (C), 96.0 (C), 83.3 (C), 20.3 (CH_3. MS (EI, 70 ev): *m/z* (%): 208 (100) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{15}H_{12}O$: 208.0883 $[M]^+$; found: 208.0880.

Methyl 4-hydroxy-3-(phenylethynyl)benzoate (1d).[25]

Following the General Procedure, the reaction of methyl 4-hydroxy-3-iodobenzoate (500 mg, 1.80 mmol) with phenylacetylene (0.400 mL, 3.57 mmol), $Pd(PPh_3)_2Cl_2$ (25.2 mg, 0.036 mmol) and CuI (13.7 mg, 0.072 mmol) in Et_3N (4 mL) and THF (18 mL) afforded, after purification by flash chromatography (20–30% EtOAc/hexane), **1d** (189 mg, 0.756 mmol, 42%) as a yellow solid. TLC: R_f= 0.35 (30% EtOAc/hexane). Mp = 116–118 °C (lit.:[25] mp = 114–116 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (d, J = 2.1 Hz, 1H) 7.97 (dd, J = 8.6, 2.1 Hz, 1H), 7.57–7.53 (m, 2H), 7.40–7.38 (m, 3H), 7.02 (d, J = 8.6 Hz, 1H), 6.25 (s, 1H), 3.90 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.2 (C), 160.0 (C), 133.8 (CH), 132.1 (CH), 131.7 (2 × CH), 129.1 (CH), 128.6 (2 × CH), 122.7 (C), 121.9 (C), 114.8 (CH), 109.9 (C), 97.0 (C), 81.9 (C), 52.1 (CH_3). MS (EI, 70 ev): *m/z* (%): 252 (100) $[M]^+$, 221 (98), 193 (80) $[C_{14}H_9O]^+$. HRMS (EI): *m/z* calcd for $C_{16}H_{12}O_3$: 252.0781 $[M]^+$; found: 252.0787.

2-(Thien-3-ylethynyl)phenol (1e).[26]

Following the General Procedure, the reaction of 2-iodophenol (250 mg, 1.14 mmol) with 3-ethynylthiophene (0.220 mL, 2.27 mmol), $Pd(PPh_3)_2Cl_2$ (16.3 mg, 0.023 mmol) and CuI (9.2 mg, 0.045 mmol) in Et_3N (3 mL) and THF (12 mL) afforded, after purification by flash chromatography (10% EtOAc/hexane), **1e** (746 mg, 82%) as a brown solid. TLC: R_f= 0.21

(10% EtOAc/hexane). Mp = 103–105 °C (lit.:[26] mp = 113–115 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.58 (dd, J = 3.0, 1.1 Hz, 1H), 7.43 (dd, J = 7.7, 1.6 Hz, 1H), 7.35 (dd, J = 5.0, 3.0 Hz, 1H), 7.31–7.21 (m, 2H), 6.99 (d, J = 8.3 Hz, 1H), 6.92 (td, J = 7.5, 1.0 Hz, 1H), 5.83 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 156.5 (C), 131.6 (CH), 130.4 (CH), 129.8 (CH), 129.3 (CH), 125.7 (CH), 121.4 (C), 120.4 (CH), 114.7 (CH), 109.5 (C), 91.4 (C), 82.6 (C). MS (EI, 70 ev): *m/z* (%): 200 (100) $[M]^+$, 171 (95). HRMS (EI): *m/z* calcd for $C_{12}H_8OS$: 200.0290 $[M]^+$; found: 200.0294.

2-[(6-Methoxynaphthalen-2-yl)ethynyl]phenol (1f).[27]

To a room temperature solution of $Pd(PPh_3)_4$ (39.4 mg, 0.134 mmol) and CuI (12.9 mg, 0.068 mmol) in THF (5 mL), *i*-Pr_2NH (3.5 mL, 23.2 mmol), 2-iodophenol (300 mg, 1.36 mmol) and 6-methoxy-2-ethynylnaphthalene (298 mg, 1.64 mmol) were added and stirred overnight. The reaction was diluted with CH_2Cl_2 (15 mL) and saturated aqueous NH_4Cl (15 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL) and the combined organic layer were washed with H_2O (10 mL), dried ($MgSO_4$), filtered, and the solvent evaporated under reduced pressure. The crude was purified by flash chromatography (5–10% EtOAc/hexane) to afford **1f** (252 mg, 67%) as a light yellow solid. TLC: R_f = 0.15 (10% EtOAc/hexane). Mp = 114–116 °C (lit.:[27] mp = 115–117 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.99 (s, 1H), 7.72 (d, J = 8.7 Hz, 2H), 7.55 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 7.7 Hz, 1H), 7.29 (t, J = 7.5 Hz, 1H), 7.20 (dd, J = 9.0, 2.4 Hz, 1H), 7.13 (d, J = 2.2 Hz, 1H), 7.04 (d, J = 8.3 Hz, 1H), 6.94 (t, J = 7.5 Hz, 1H), 5.98 (s, 1H), 3.93 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.6 (C), 156.5 (C), 134.4 (C), 131.7 (CH), 131.5 (CH), 130.4 (CH), 129.4 (CH), 128.7 (CH), 128.4 (C), 127.0 (CH), 120.5 (CH), 119.6 (CH), 117.2 (C), 114.8 (CH), 109.9 (C), 105.9 (CH), 97.1 (C), 82.7 (C), 55.4 (CH_3). MS (EI, 70 ev): *m/z* (%): 274 (100) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{19}H_{14}O_2$: 274.0988 $[M]^+$; found: 274.0986.

2-(Cyclohex-1-en-1-ylethynyl)phenol (1g).

Following the General Procedure, the reaction of 2-iodophenol (500 mg, 2.27 mmol) with 1-ethynylcyclohexene (0.540 mL, 4.55 mmol), $Pd(PPh_3)_2Cl_2$ (32.0 mg, 0.045 mmol) and CuI (17.3 mg, 0.091 mmol) in Et_3N (6 mL) and THF (20 mL) afforded, after purification by flash chromatography in neutral alumina (5% EtOAc/hexane), **1g** (336 mg, 75%) as an orange solid. TLC: R_f = 0.25 (2% EtOAc/hexane). Mp = 62–64 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33 (dd, J = 7.7, 1.7 Hz, 1H), 7.23 (td, J = 7.5, 1.6 Hz, 1H), 6.95 (dd, J = 8.2, 0.7 Hz, 1H), 6.87 (td, J = 7.5, 1.1 Hz, 1H), 6.29–6.25 (m, 1H), 5.77 (s, 1H), 2.28–2.15 (m, 4H), 1.74–1.63 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 156.2 (C), 136.2 (CH), 131.3 (CH), 129.9 (CH), 120.2 (CH), 120.1 (C), 114.4 (CH), 110.1 (C), 98.5 (C), 80.2 (C), 29.3 (CH_2), 25.8 (CH_2), 22.2 (CH_2), 21.4 (CH_2). MS (EI, 70 ev): *m/z* (%): 198 (100) $[M]^+$, 170 (80). HRMS (EI): *m/z* calcd for $C_{14}H_{14}O$: 198.1039 $[M]^+$; found: 198.1037.

2-(Cyclopropylethynyl)phenol (1h).[28]

Following the General Procedure, the reaction of 2-iodophenol (500 mg, 2.27 mmol) with ethynylcyclopropane (0.385 mL, 4.55 mmol), $Pd(PPh_3)_2Cl_2$ (32.0 mg, 0.045 mmol) and CuI (17.3 mg, 0.091 mmol) in Et_3N (6 mL) and THF (20 mL), afforded, after purification by flash chromatography (5% Et_2O/hexane), **1h** (238 mg, 66%) as a yellow oil. TLC: R_f = 0.18 (5% Et_2O/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29 (dd, J = 7.8, 1.5 Hz, 1H), 7.20 (td, J = 7.8, 1.6 Hz, 1H), 6.93 (dd, J = 8.2, 0.9 Hz, 1H), 6.84 (td, J = 7.5, 1.1 Hz, 1H), 5.80 (s, 1H), 1.55–1.48 (m, 1H), 0.98–0.90 (m, 2H), 0.88–0.82 (m, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 156.8 (C), 131.6 (CH), 129.6 (CH), 120.1 (CH), 114.3 (CH), 110.1 (C), 101.0 (C), 69.5 (C), 9.0 (2 × CH_2), 0.2 (CH). MS (EI, 70 ev): *m/z* (%): 158 (100) $[M]^+$, 131 (71). HRMS (EI): *m/z* calcd for $C_{11}H_{10}O$: 158.0726 $[M]^+$; found: 158.0724.

2-(Hex-1-ynyl)-phenol (1i).[29]

Following the General Procedure, the reaction of 2-iodophenol (500 mg, 2.27 mmol) with hexyne (0.522 mL, 4.55 mmol), $Pd(PPh_3)_2Cl_2$ (32.0 mg, 0.045 mmol) and CuI (17.3 mg, 0.091 mmol) in Et_3N (6 mL) and THF (20 mL) afforded, after purification by flash chromatography (10% EtOAc/hexane), compound **1i** (274 mg, 66%) as an orange oil. TLC: R_f= 0.41 (20% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (dd, J = 7.7, 1.6 Hz, 1H), 7.20 (td, J = 7.8, 1.6 Hz, 1H), 6.93 (dd, J = 8.2, 1.0 Hz, 1H), 6.84 (td, J = 7.5, 1.1 Hz, 1H), 5.79 (s, 1H), 2.72 (t, J = 7.0 Hz, 2H), 1.68–1.58 (m, 2H), 1.55–1.43 (m, 2H), 0.96 (t, J = 7.2 Hz, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 156.5 (C), 131.4 (CH), 129.5 (CH), 120.1 (CH), 114.3 (CH), 110.2 (C), 98.0 (C), 74.5 (C), 30.8 (CH_2), 22.0 (CH_2), 19.3 (CH_2), 13.6 (CH_3). MS (EI, 70 ev): *m/z* (%): 174 (42) $[M]^+$, 131 (100) $[C_9H_7O]^+$. HRMS (EI): *m/z* calcd for $C_{12}H_{14}O$: 174.1039 $[M]^+$; found: 174.1039.

6-(2-Hydroxyphenyl)hex-5-ynenitrile (1j).

Following the General Procedure, the reaction of 2-iodophenol (300 mg, 1.36 mmol) with 5-hexynenitrile (0.285 mL, 2.73 mmol), $Pd(PPh_3)_2Cl_2$ (19.1 mg, 0.027 mmol) and CuI (10.4 mg, 0.054 mmol) in Et_3N (5 mL) and THF (15 mL) afforded, after purification by flash chromatography (20% EtOAc/hexane), **1j** (262 mg, 99%) as a yellow solid. TLC: R_f= 0.16 (20% EtOAc/hexane). Mp = 50–52 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (dd, J = 7.7, 1.6 Hz, 1H), 7.23 (t, J = 7.0 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H), 6.86 (td, J = 7.5, 1.0 Hz, 1H), 5.75 (s, 1H), 2.69 (t, J = 6.8 Hz, 2H), 2.56 (t, J = 7.0 Hz, 2H), 2.00 (t, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 156.6 (C), 131.8 (CH), 130.1 (CH), 120.3 (CH), 119.0 (C), 114.7 (CH), 109.4 (C), 100.0 (C), 94.1 (C), 24.5 (CH_2), 18.8 (CH_2), 16.4 (CH_2). MS (EI, 70 ev): *m/z* (%): 174 (46) $[M]^+$, 131 (100) $[C_9H_7O]^+$. HRMS (EI): *m/z* calcd for $C_{12}H_{11}NO$: 185.0835 $[M]^+$; found: 185.0837.

2-(Phenylethynyl)-5-(trifluoromethyl)phenol (1k).

To a cold solution of 2-bromo-5-(trifluoromethyl)phenol (300 mg, 1.25 mmol) and K_2CO_3 (0.69 g, 5.0 mmol, 400 mol%) in DMF (3 mL) MOMCl (0.14 mL, 1.88 mmol, 150 mol%) was added the reaction stirred overnight at rt. The reaction mixture was quenched with H_2O (4 mL), extracted with Et_2O (2 x 10 mL), and the combined organic layers washed with H_2O (10 mL), dried, filtered, and the solvent evaporated under reduced pressure. Concentration and high vacuum-drying afforded crude of 1-bromo-2(methoxymethoxy)-4-(trifluoromethyl)benzene. This product was transferred to a Schlenk tube under argon and Et_3N (2.5 mL, 17.8 mmol), ethynylbenzene (0.30 mL, 2.74 mmol, 200 mol%), $Pd(PPh_3)_2Cl_2$ (17 mg, 0.025 mmol, 2 mol%) and CuI (12 mg, 0.063 mmol, 5 mol%) were added and the mixture stirred for 20 h at 50 ºC. Then the reaction was filtered through a pad of Celite® and the solvent evaporated under reduced pressure and the crude purified by flash chromatography (5% EtOAc/hexane) to afford 2-(methoxymethoxy)-1-(phenylethynyl)-4-(trifluoromethyl)benzene (**1k-MOM**, 106 mg). The **1k-MOM** (106 mg, 0.35 mmol) was dissolved in methanol (5 mL) and HCl (37%, 70 μL) was slowly added. The resulting mixture was stirred at rt for 12 h. After completion, the reaction was neutralized with saturated $NaHCO_3$ aq., extracted with EtOAc (3 × 10 mL), dried, filtered and concentrated *in vacuo*, to afford, after purification by flash chromatography (5% EtOAc/hexane) compound **1k** (82 mg, 0.088 mmol, 25% yield over three steps) as an orange solid. TLC: R_f =0.27 (5% EtOAc/hexane). Mp = 73–75 °C. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.60–7.52 (m, 4H), 7.44–7.39 (m, 3H), 7.19 (dd, J = 8.1, 1.9 Hz, 1H), 6.05 (s, 1H). ^{13}C{1H}NMR (75 MHz, $CDCl_3$): δ 156.5 (C), 132.3 (C, q, J = 32 Hz), 132.1 (CH), 131.7 (2 × CH), 129.4 (CH), 128.6 (2 × CH), 125.4 (C), 121.4 (C, q, J = 272 Hz), 121.7 (C), 117.1 (CH, q, J = 4.1 Hz), 112.0 (CH, q, J = 4.1 Hz), 98.3 (C), 81.7 (C). MS (EI, 70 ev): *m/z* (%): 262 (68) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{15}H_9F_3O$: 262.0600 $[M]^+$; found: 262.0606.

Methyl 3-ethynyl-4-hydroxybenzoate (1l).

Following the General Procedure, the reaction of methyl 4-hydroxy-3-iodobenzoate (800 mg, 2.88 mmol) with ethynyltrimethylsilane (0.815 mL, 5.76 mmol), $Pd(PPh_3)_2Cl_2$ (40.0 mg, 0.058 mmol) and CuI (22.0 mg, 0.115 mmol) in Et_3N (4 mL) and THF (16 mL) afforded, after purification by flash chromatography (20% EtOAc/hexane), methyl 4-hydroxy-3-((trimethylsilyl)-ethynyl)benzoate (**1l-TMS**, 0.694 g, 97%) as a light yellow solid. TLC: R_f= 0.28 (20% EtOAc/hexane). Mp = 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (d, J = 2.1 Hz, 1H) 7.94 (dd, J = 8.6, 2.1 Hz, 1H), 6.98 (d, J = 8.6 Hz, 1H), 6.19 (s, 1H), 3.88 (s, 3H), 0.29 (s, 9H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.1 (C), 160.5 (C), 133.7 (CH), 132.3 (CH), 122.5 (C), 114.5 (CH), 109.8 (C), 103.5 (C), 97.6 (C), 52.0 (CH_3), -0.14 (3 × CH_3). MS (EI, 70 ev): *m/z* (%): 248 (15) $[M]^+$, 233 (100) $[C_{12}H_{13}O_3Si]^+$. HRMS (EI): *m/z* calcd for $C_{13}H_{16}O_3Si$: 248.0863 $[M]^+$; found: 248.0864.

To a rt solution of **1l-TMS** (440 mg, 1.77 mmol) in THF (15 mL), TBAF (2.22 mL, 1.0 M in THF) was added and the resulting mixture was stirred for 2 h under argon. The reaction was diluted with Et_2O (20 mL) and saturated aqueous NaCl (20 mL). The aqueous layer was extracted with Et_2O (2 × 20 mL) and the combined organic layer were dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to afford, after purification by flash chromatography (20% EtOAc/hexane), **1l** (0.306 g, 98%) as a brown oil. TLC: R_f = 0.25 (40% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (d, J = 2.1 Hz, 1H) 7.98 (dd, J = 8.7, 2.1 Hz, 1H), 7.01 (d, J = 8.7 Hz, 1H), 6.24 (s, 1H), 3.90 (s, 3H), 3.51 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 166.0 (C), 160.9 (C), 134.2 (CH), 132.6 (CH), 122.7 (C), 114.9 (CH), 108.5 (C), 85.0 (CH), 77.2 (C), 52.1 (CH_3). MS (EI, 70 ev): *m/z* (%): 176 (63) $[M]^+$, 145 (100) $C_9H_5O_2]^+$. HRMS (EI): *m/z* calcd for $C_{10}H_8O_3$: 176.0468 $[M]^+$; found: 176.0466.

General Procedure for the Indium(III)-catalyzed Hydroalkoxylation Reaction of *ortho*-Alkynylphenols.

In an oven-dried Schlenk tube filled with argon, the *ortho*-alkynylphenol (100 mg scale) was dissolved in DCE (5–7 mL) and InI_3 (5 mol%) was added. The resulting mixture was heated at 80 °C and monitored by TLC. The mixture was cooled to rt and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexane) to afford, after concentration and high-vacuum drying, the corresponding 2-substituted benzo[*b*]furan.

2-Phenylbenzo[*b*]furan (2a).[30]

Following the General Procedure, the reaction of 2-phenylethynylphenol (**1a**, 100 mg, 0.515 mmol) with InI_3 (12.7 mg, 0.026 mmol) in DCE (6 mL) at 80 ºC overnight afforded, after purification by flash chromatography (10% EtOAc/hexane), **2a** (94 mg, 94% yield) as a white solid. TLC: R_f= 0.53 (10% AcOEt/hexane). Mp = 122–124 °C (lit.:[30] mp = 118–120 ºC); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (dd, J = 8.4, 1.2 Hz, 2H), 7.60 (dd, J = 7.2, 1.7 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 7.46 (t, J = 7.4 Hz, 2H), 7.39–7.21 (m, 3H), 7.04 (d, J = 0.8 Hz, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 155.9 (C), 154.9 (C), 130.5 (C), 129.2 (C), 128.8 (2 × CH), 128.5 (CH), 124.9 (2 × CH), 124.2 (CH), 122.9 (CH) 120.9 (CH), 116.2 (CH), 101.3 (CH). MS (EI, 70 ev): *m/z* (%): 194 (100) $[M]^+$, 165 (40). HRMS (EI): *m/z* calcd for $C_{14}H_{10}O$: 194.0726 $[M]^+$; found: 194.0726.

5-Bromo-2-phenylbenzo[*b*]furan (2b).[31]

Following the General Procedure, the reaction of 4-bromo-2-(phenylethynyl)phenol (**1b**, 100 mg, 0.366 mmol) with InI_3 (9.1 mg, 0.018 mmol) in DCE (5 mL) at 80 °C for 16 h afforded, after purification by flash chromatography (10% EtOAc/hexane), **2b** (135 mg, 95%) as a white solid. TLC: R_f= 0.40 (10% EtOAc/hexane). Mp = 157–159 °C (lit.:[32] mp = 158–159 ºC); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (dd, J = 8.4, 1.3 Hz, 2H), 7.72–7.71 (m, 1H), 7.50–7.45 (m, 2H), 7.43–7.36 (m, 3H), 6.97 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 157.2 (C),

153.6 (C), 131.2 (C), 129.9 (C), 129.0 (CH), 128.8 (2 × CH), 127.1 (CH), 125.0 (2 × CH), 123.5 (CH), 116.0 (C), 112.6 (CH), 100.6 (CH). MS (EI, 70 ev): *m/z* (%): 274 (98) [M (^{81}Br)]$^+$, 272 (100) [M (^{79}Br)]$^+$. HRMS (EI): *m/z* calcd for $C_{14}H_9BrO$: 271.9831 [M]$^+$; found: 271.9832.

5-Methyl-2-phenylbenzo[*b*]furan (**2c**).[33]

Following the General Procedure, the reaction of 4-methyl-2-(phenylethynyl)phenol (**1c**, 100 mg, 0.480 mmol) with InI_3 (11.9 mg, 0.024 mmol) in DCE (6 mL) at 80 °C for 16 h afforded, after purification by flash chromatography (10% EtOAc/hexane), **2c** (96 mg, 96%) as a white solid. TLC: R_f = 0.48 (10% EtOAc/hexane). Mp = 132–134 °C (lit.:[33] mp = 131–133 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.88 (d, J = 7.3 Hz, 2H), 7.49–7.36 (m, 5H), 7.11 (dd, J = 8.3, 1.2 Hz, 1H), 6.97 (s, 1H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 156.0 (C), 153.3 (C), 132.3 (C), 130.6 (C), 129.3 (C), 128.7 (2 × CH), 128.4 (CH), 125.5 (CH), 124.8 (2 × CH), 120.7 (CH), 110.6 (CH), 101.1 (CH), 21.3 (CH_3). MS (EI, 70 ev): *m/z* (%): 208 (100) [M]$^+$. HRMS (EI): *m/z* calcd for $C_{15}H_{12}O$: 208.0883 [M]$^+$; found: 208.0878.

Methyl 2-phenylbenzo[*b*]furan-5-carboxylate (**2d**).

Following the General Procedure, the reaction of methyl 4-hydroxy-3-(phenylethynyl)benzoate (**1d**, 100 mg, 0.396 mmol) with InI_3 (9.8 mg, 0.020 mmol) in DCE (5 mL) at 80 °C for 16 h afforded, after purification by flash chromatography (20% EtOAc/hexane), **2d** (92.3 mg, 92%) as a light brown solid. TLC: R_f = 0.38 (20% EtOAc/hexane). Mp = 160–162 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ.32 (d, J = 1.3 Hz, 1H), 8.02 (dd, J = 8.6, 1.8 Hz, 1H), 7.87 (dd, J = 8.3, 1.2 Hz, 2H), 7.55 (d, J = 8.7 Hz, 1H), 7.49 – 7.44 (m, 2H), 7.41–7.35 (m, 1H), 7.07 (d, J = 0.7 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.3 (C), 157.4 (C), 157.3 (C), 129.9 (C), 129.2 (C), 129.0 (CH), 128.9 (2 × CH), 126.0 (CH), 125.3 (C), 125.1 (2 × CH), 123.3 (CH), 111.0 (CH), 101.5 (CH), 52.1

(CH_3). MS (EI, 70 ev): *m/z* (%): 252 (100) $[M]^+$, 221 (60), 193 (27). HRMS (EI): *m/z* calcd for $C_{16}H_{12}O_3$: 252.0781 $[M]^+$; found: 252.0769.

2-(Thien-3-yl)benzo[*b*]furan (2e).[34]

Following the General Procedure, the reaction of 2-(thien-3-ylethynyl)phenol (**1e**, 100 mg, 0.500 mmol) with InI_3 (12.3 mg, 0.025 mmol) in DCE (6 mL) at 80 °C overnight afforded, after purification by flash chromatography (10% EtOAc/hexane), **2e** (81.8 mg, 82%) as a white solid. TLC: R_f = 0.46 (10% AcOEt/hexane). Mp = 134–136 °C (lit.:[34] mp = 133–135 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73 (dd, J = 2.9, 1.2 Hz, 1H), 7.58–7.56 (m, 1H), 7.51–7.46 (m, 2H), 7.41–7.39 (m, 1H), 7.31–7.20 (m, 2H), 6.84 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.5 (C), 152.7 (C), 134.2 (C), 129.1 (C), 126.5 (CH), 125.1 (CH), 124.1 (CH), 122.9 (CH), 121.4 (CH), 120.8 (CH), 111.0 (CH), 101.0 (CH). MS (EI, 70 ev): *m/z* (%): 200 (100) $[M]^+$, 171 (30). HRMS (EI): *m/z* calcd for $C_{12}H_8OS$: 200.0290 $[M]^+$; found: 200.0290.

2-(6-Methoxynaphthalen-2-yl)benzo[*b*]furan (2f).[35]

Following the General Procedure, the reaction of 2-[(6-methoxynaphthalen-2-yl)ethynyl]phenol (**1f**, 100 mg, 0.364 mmol) with InI_3 (9.1 mg, 0.018 mmol) in DCE (4 mL) at 80 °C for 16 h afforded, after purification by flash chromatography (20% EtOAc/hexane), **2f** (75.4 mg, 75%) as a beige solid. TLC: R_f = 0.45 (20% EtOAc/hexane). Mp = 193–195 °C (lit.:[36] mp = 193–195 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.31 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.82 (t, J = 9.6 Hz, 2H), 7.61 (d, J = 7.6 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.31–7.17 (m, 4H), 7.10 (s, 1H), 3.96 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 158.2 (C), 156.2 (C), 154.9 (C), 134.6 (C), 129.9 (CH), 129.4 (CH), 128.9 (CH), 127.3 (CH), 125.7 (C) 124.1 (CH), 123.8 (CH), 123.4 (CH), 122.9 (CH), 120.8 (CH), 119.4 (CH), 111.1 (CH), 105.9 (CH), 101.1 (CH), 55.4 (CH_3). MS (EI, 70 ev): *m/z* (%): 274 (100) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{19}H_{14}O_2$: 274.0988 $[M]^+$; found: 274.0986.

2-(Cyclohex-1-en-1-yl)benzo[*b*]furan (2g).[37]

Following the General Procedure, the reaction of 2-(cyclohex-1-en-1-ylethynyl)phenol (**1g**, 100 mg, 0.504 mmol) with InI_3 (12.5 mg, 0.025 mol) in DCE (6 mL) at 80 °C overnight afforded, after purification by flash chromatography (5% EtOAc/hexane), **2g** (90.2 mg, 90%) as a white solid. TLC: R_f= 0.62 (5% EtOAc/hexane). Mp = 92–94 °C (lit.:[37] mp = 55–57 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, J = 7.6 Hz, 1H), 7.44 (d, J = 7.9 Hz, 1H), 7.27–7.16 (m, 2H), 6.64 (t, J = 4.2 Hz 1H), 6.52 (s, 1H), 2.42–2.29 (m, 4H), 1.82–1.72 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 157.5 (C), 154.4 (C), 129.2 (C), 127.2 (C), 126.1 (CH), 123.8 (CH), 122.5 (CH), 120.5 (CH), 110.7 (CH) 100.0 (CH), 25.4 (CH_2), 25.0 (CH_2), 22.4 (CH_2), 22.1 (CH_2). MS (EI, 70 ev): *m/z* (%): 198 (100) $[M]^+$, 170 (71) $[C_{12}H_{10}O]^+$. HRMS (EI): *m/z* calcd for $C_{14}H_{14}O$: 198.1039 $[M]^+$; found: 198.1027.

2-Cyclopropylbenzo[*b*]furan (**2h**).

Following the General Procedure, the reaction of 2-(cyclopropylethynyl)phenol (**1h**, 100 mg, 0.632 mmol) with InI_3 (15.7 mg, 0.032 mmol) in DCE (8 mL) at 80 °C overnight afforded, after purification by flash chromatography (2% EtOAc/hexane), **2h** (86.3 mg, 86%) as a colorless oil. TLC: R_f= 0.57 (2% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47–7.44 (m, 1H), 7.40–7.37 (m, 1H), 7.20–7.16 (m, 2H), 6.36 (s, 1H), 2.07– 2.02 (m 1H), 1.02–0.98 (m, 4H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 160.5 (C), 154.3 (C), 129.1 (C), 122.9 (CH), 122.4 (CH), 119.9 (CH), 110.6 (CH), 100.3 (CH), 9.3 (CH), 7.2 (2 × CH_2). MS (EI, 70 ev): *m/z* (%): 158 (98) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{11}H_{10}O$: 158.0726 $[M]^+$; found: 158.0728.

2-Butylbenzo[*b*]furan (2i).[38]

Following the General Procedure, the reaction of 2-(hex-1-ynyl)phenol (**1i**, 100 mg, 0.574 mmol) with InI_3 (14.2 mg, 0.029 mmol) in DCE (7 mL) at 80 °C overnight afforded, after purification by flash chromatography (5% EtOAc/hexane), **2i** (86.1 mg, 86%) as a yellow oil. TLC: R_f= 0.68 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.47 (m, 1H),

7.43–7.40 (m, 1H), 7.24–7.14 (m, 2H), 6.38 (d, J = 0.9 Hz, 1H), 2.78 (t, J = 7.6 Hz, 2H), 1.74 (quint, J = 7.5 Hz, 2H), 1.43 (sext, J = 7.4 Hz, 2H), 0.96 (t, J = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 159.7 (C), 154.6 (C), 129.0 (C), 123.0 (CH), 122.3 (CH), 120.1 (CH), 110.7 (CH) 101.7 (CH), 29.8 (CH_2), 28.1 (CH_2), 22.3 (CH_2), 13.8 (CH_3). MS (EI, 70 ev): *m/z* (%): 174 (25) $[M]^+$, 131 (100) $[C_9H_7O]^+$. HRMS (EI): *m/z* calcd for $C_{12}H_{14}O$: 174.1039 $[M]^+$; found: 174.1040.

4-(Benzo[*b*]furan-2-yl)butanonitrile (2j).

Following the General Procedure, the reaction of 6-(2-hydroxyphenyl)hex-5-ynenitrile (**1j**, 100 mg, 0.540 mmol) with InI_3 (13.4 mg, 0.027 mmol) in DCE (7 mL) at 80 °C overnight afforded, after purification by flash chromatography (20% EtOAc/hexane), **2j** (77.9 mg, 78%) as a yellow oil. TLC: R_f= 0.30 (20% EtOAc/hexane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 7.9 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.29–7.21 (m, 2H), 6.49 (s, 1H), 2.96 (t, J = 7.1 Hz, 2H), 2.41 (t, J = 7.1 Hz, 2H), 2.12 (quint, J = 7.1 Hz, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 156.3 (C), 154.8 (C), 128.6 (C), 123.7 (CH), 122.7 (CH), 120.5 (CH), 119.2 (C), 110.9 (CH) 103.4 (CH), 27.1 (CH_2), 23.7 (CH_2), 16.5 (CH_2). MS (EI, 70 ev): *m/z* (%): 185 (33) $[M]^+$, 131 (100). HRMS (EI): *m/z* calcd for $C_{12}H_{11}NO$: 185.0835 $[M]^+$; found: 185.0836.

2-Phenyl-6-(trifluoromethyl)benzofuran (2k). Following the General Procedure, the reaction of 2-(phenylethynyl)-5-(trifluoromethyl)phenol (**1k**, 77 mg, 0.294 mmol) with InI_3 (7.3 mg, 0.015 mmol) in DCE (4 mL) at 80 ºC overnight afforded, after purification by flash chromatography (5% EtOAc/hexane), **2k** (74 mg, 96% yield) as a white solid. TLC: R_f=0.48 (5% EtOAc/hexane). Mp = 121–123°C (lit.:[39] mp = 120–121°C). ^1H-NMR (300 MHz, $CDCl_3$): δ 7.89 (dd, J = 8.1, 2.0 Hz, 2H), 7.81 (s, 1H), 7.67 (dd, J = 8.1, 1.0 Hz, 1H), 7.51 (dd, J = 8.1, 1.0 Hz, 1H), 7.49–7.42 (m, 3H), 7.08 (s, 1H). $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$): δ 158.6 (C), 153.9 (C), 132.3 (C, q, J = 1.2 Hz), 129.7 (C), 129.3 (CH), 129.0 (2 × CH), 126.2 (C, q, J = 32.4 Hz), 125.2 (2 × CH), 122.8 (C, q, J = 283 Hz), 121.2 (CH), 119.9 (CH, q, J =

4.1 Hz), 108.7 (CH, q, J = 4.1 Hz), 101.0 (CH). MS (EI, 70 ev): *m/z* (%): 262 (100) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{15}H_9F_3O$: 262.0600 $[M]^+$; found: 262.0602.

Methyl benzo[*b*]furan-5-carboxylate (2l).[40]

Following the General Procedure, the reaction of methyl 3-ethynyl-4-hydroxybenzoate (**1l**) (100 mg, 0.568 mmol) with InI_3 (14.1 mg, 0.028 mmol) at 80 °C overnight afforded, after purification by flash chromatography using (30–40% EtOAc/hexane), **2l** (42.3 mg, 42%) as a white solid. TLC: R_f = 0.56 (40% EtOAc/hexane). Mp = 79–81 °C (lit.:[40] mp = 69–70 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.36 (d, J = 1.2 H, 1H), 8.04 (dd, J = 8.7, 1.8 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.54 (d, J = 8.7 Hz, 1H), 6.85 (dd, J = 2.3, 1.0 Hz, 1H), 3.95 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 167.2 (C), 157.5 (C), 146.2 (CH), 127.4 (C), 126.0 (CH), 125.2 (C), 123.7 (CH), 111.2 (CH), 107.1 (CH), 52.1 (CH_3). MS (EI, 70 ev): *m/z* (%): 176 (44) $[M]^+$, 145 (100) $[C_9H_5O_2]^+$. HRMS (EI): *m/z* calcd for $C_{10}H_8O_3$: 176.0468 $[M]^+$; found: 176.0467.

2-Phenylbenzo[*b*]furan-3*d* (2a-3*d*).[13b]

According to the General Procedure, the reaction of 2-phenylethynylphenol (**1a**, 100 mg, 0.515 mmol) with InI_3 (12.7 mg, 0.026 mmol) at 100 °C in toluene (6 mL) with D_2O (30 μL, 1.54 mmol, 300 mol%) overnight afforded, after purification by flash chromatography (20% EtOAc/hexane), **2a-3*d*** (93.4 mg, 93%, 75%-D) as a white solid. TLC: R_f = 0.53 (10% EtOAc/hexane). Mp = 120–122 °C (lit.,[13b] mp = 118–119 ºC). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.90 (d, J = 7.2 Hz, 2H), 7.60 (dd, J = 6.9, 1.5 Hz, 1H), 7.55 (d, J = 7.6 Hz, 1H), 7.47 (t, J =7.4 Hz, 2H), 7.39 (d, J = 7.4 Hz, 1H), 7.35–7.23 (m, 3H), 7.05 (s, 0.10H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 155.9 (C), 154.9 (C), 130.5 (C), 129.2 (C), 128.8 (2 × CH), 128.5 (CH), 124.9 (2 × CH), 124.2 (CH), 122.9 (CH) 120.9 (CH), 111.2 (CH), 101.3 (CH). MS (EI, 70 ev): *m/z* (%): 195 (100) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{14}H_9OD$: 195.0785 $[M]^+$; found: 195.0786.

2-(1-Iodo-2-phenylvinyl)phenol (4).

To a solution of **1a** (95 mg, 0.489 mmol) in DCE (6 mL), HI (32 μL, 0.245 mmol, 57% aqueous solution) was added dropwise at rt and the resulting mixture was stirred for 4 h at 80 ºC. The reaction was diluted with CH_2Cl_2 (10 mL) and saturated aqueous NH_4Cl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL) and the combined organic layer were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford, after purification by flash chromatography (5% EtOAc/hexane), 2-(1-iodo-2-phenylvinyl)phenol (**4**) (79 mg, 50%) as a yellow oil. TLC: R_f= 0.17 (10% EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.62 (s, 1H) 7.42–7.14 (m, 5H), 7.00–6.90 (m, 4H), 5.19 (s, 1H). $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ 151.1 (C), 144.9 (CH), 136.2 (CH), 130.7 (CH), 129.3 (C), 128.5 (2 x CH), 128.2 (2 x CH), 121.2 (CH), 116.5 (CH), 91.6 (C). MS (EI, 70 ev): *m/z* (%): 323 (3) [M (^{128}I)]$^+$, 322 (18) [M (^{127}I)]$^+$, 195 (71) [$C_{14}H_{11}O$ (^{128}I)]$^+$, 194 (100) [$C_{14}H_{11}O$ (^{127}I)]$^+$. HRMS (EI): *m/z* calcd for $C_{14}H_{11}OI$: 321.9849 [M]$^+$; found: 321.9849.

2-Phenyl-3-(*p*-tolyl)benzo[*b*]furan (3a).[41]

To a 0 ºC solution of **1a** (100 mg, 0.515 mmol) in Et_2O (1.0 mL) a solution of *n*-BuLi (0.220 mL, 2.40 M in hexane, 100 mol%) was added dropwise and stirred for 10 min. The resulted yellow solution was left to reach rt and stirred for additional 30 min. Then, a solution of $InCl_3$ (1.15 mL, 0.45 M in THF) was added, the solvents were removed in *vacuo*, and the residue dried under high-vacuum. Toluene (2 mL) was then added and the resulting solution heated to 120 ºC for 1 h (TLC monitoring). A mixture $Pd(OAc)_2$ (5.8 mg, 0.026 mmol), SPhos (21.1 mg, 0.052 mmol), and 4-iodotoluene (94.5 mg, 0.432 mmol) in THF (2 mL) were added and heated to 95 ºC overnight. The reaction mixture was quenched with a saturated aqueous solution of NH_4Cl (10 mL), poured into a separatory funnel and extracted with AcOEt (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo* to afford, after purification by flash chromatography using hexane, compound **3a** (88.8 mg,

88%) as a colorless oil. TLC: R_f = 0.38 (hexane). Mp = 72–74 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (d, J = 7.7 Hz, 2H), 7.59 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.43 (d, J = 7.9 Hz, 2H), 7.35–7.26 (m 7H), 2.47 (s, 3H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 154.0 (C), 150.4 (C), 137.4 (C), 130.8 (C), 130.4 (C), 129.7 (2 × CH), 129.6 (2 × CH), 129.0 (C), 128.4 (CH), 128.3 (2 × CH), 127.0 (2 × CH), 124.6 (CH), 122.9 (CH), 120.1 (CH), 117.5 (C), 110.0 (CH), 21.4 (CH_3). MS (EI, 70 ev): *m/z* (%): 284 (100) $[M]^+$. HRMS (EI): *m/z* calcd for $C_{21}H_{16}O$: 284.1196 $[M]^+$; found: 284.1191.

Supporting Information

Computational Methods and NMR copies for all of the compounds prepared are supplied.

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