



Domino rhodium(I)-catalysed reactions for the efficient synthesis of substituted benzofurans and indoles

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Dedicated with congratulations and respect to Professor Steven V. Ley, the 2009 recipient of the Tetrahedron Prize

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ABSTRACT

Rhodium(I) catalysts promote the transformation of *o*-alkynyl phenols and anilines to the corresponding benzo[*b*]furans and indoles. The reaction is postulated to proceed via a transient 3-rhodium heterocycle intermediate, which can be trapped with suitable electrophiles to give poly-substituted heterocycles. In the case of mono-substituted electron-withdrawn electrophiles, excellent yield and selectivity for conjugate addition versus Heck–Mizoroki reaction can be achieved. In the case of 2-alkynyl pyridine electrophiles, novel 2-(benzofuran-3-yl)vinylpyridines are formed.

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1. Introduction

We have a long-standing interest in developing new routes to synthesise aromatic heterocyclic scaffolds. Herein, we report a novel rhodium-catalysed domino process to make poly-substituted benzo[*b*]furans and indoles.

Substituted benzofuran skeletons are found in a wide array of natural substances and are a recurring motif in active pharmaceutical ingredients (Fig. 1).¹ Indoles, their nitrogen analogue, are the key motif in tryptophan and as such have an even greater prevalence—they can be found in molecules ranging from natural products to blockbuster drugs.²

As a testament to their importance, there exist many diverse methods for the synthesis of benzofurans and indoles, which have been discussed at length in several comprehensive reviews.³ One of the most commonly employed syntheses of these important heterocycles is the cycloisomerisation of the corresponding *o*-alkynyl phenol or aniline compound.⁴

Indeed, this has been achieved using a diverse array of reagents, which are generally proposed to activate the alkyne to intramolecular nucleophilic attack (Scheme 1a). Rhodium has featured

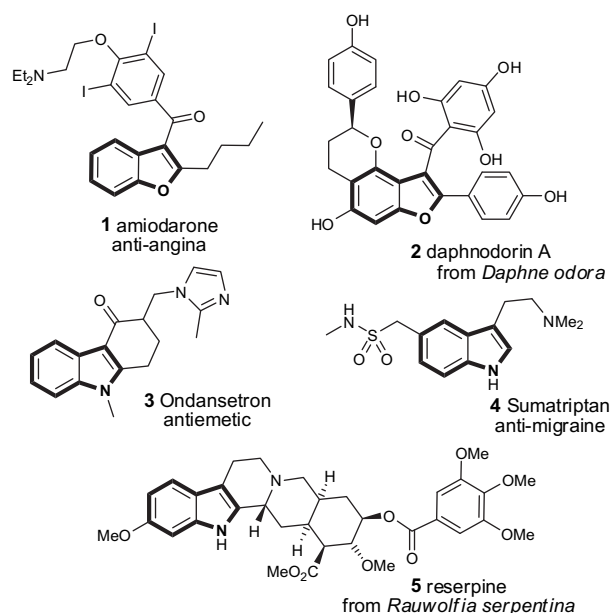
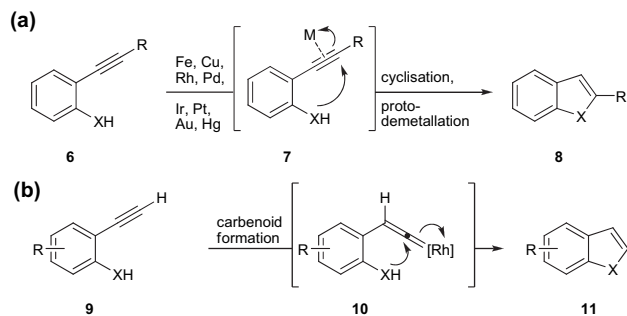


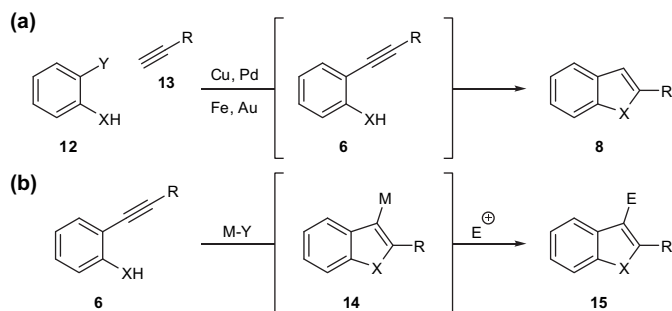
Figure 1. Benzofurans and indoles as motifs in natural products and drugs.

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Scheme 1. Cycloisomerisation of *o*-alkynyl phenols and anilines.

relatively few times as a catalyst for such transformations,^{5–7} but of these examples, Trost's catalytic is noteworthy (Scheme 1b).⁶ Under the reaction conditions the terminal alkyne substrate **9** is postulated to form a rhodium-carbenoid species **10**,⁸ which then undergoes nucleophilic attack from the nitrogen atom and protodemetalation to generate the 2,3-unsubstituted aniline product **11**. The principal advantages of using cycloisomerisation to synthesise benzofurans and indoles are that the starting materials are readily prepared and there are no by-products from the reaction.⁹ Further efficiency can be obtained by the design of processes in which several sequential transformations occur: a domino reaction.¹⁰ The ability of transition metal complexes both to promote cycloisomerisation and coupling between an alkyne and aryl halide has been exploited using copper,¹¹ palladium¹² gold¹³ and iron¹⁴ to create a double domino reaction, forming benzofurans and indoles in a single operation from haloanilines or haloanilines and alkynes (Scheme 2a).



Scheme 2. Domino sequences including cycloisomerisation.

Systems have also been developed in which cycloisomerisation is the first step in the domino sequence (Scheme 2b). In these instances, a metal catalyst promotes the cyclisation by activating the alkyne group and the result is a 3-metallo-benzofuran/indole **14**, which can be trapped using suitable electrophiles.^{15–18} Lu et al. have combined both of these strategies into a palladium-catalysed one-pot three-component coupling reaction.¹⁹ In this manuscript, we describe an approach based on the strategy outlined in Scheme 2b using alkynes and electron-poor alkenes as electrophiles under rhodium(I) catalysis.

2. Results and discussion

2.1. 2-Mono-substituted benzofurans and indoles

Our research in this area began with the observation that when *o*-alkynyl phenols **16** are treated with a rhodium(I) catalyst and BINAP ligand in a mixture of toluene and water (15:2) at 100 °C for 1 h, they are transformed to the corresponding 2-substituted benzofuran products **17** in good yield (Table 1).⁷

An initial screen of conditions demonstrated the transformation to be quite robust, although at temperatures lower than 90 °C or when dppp was used as ligand the yield diminished. Dioxane could

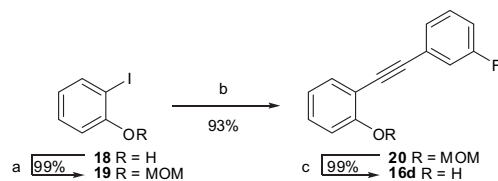
Table 1
Optimisation of the cycloisomerisation of *o*-alkynyl phenols to benzofurans

Entry	Phenol	Ligand	Solvent ^a	Temp (°C)	Time (h)	Yield ^b (%)
1	16a R= ⁿ Bu	BINAP	PhMe	100	1	88
2	16a R= ⁿ Bu	BINAP	PhMe	50	1	77
3	16a R= ⁿ Bu	BINAP	PhMe	rt	16	62
4	16a R= ⁿ Bu	dppp	PhMe	100	1	33
5	16b R=Ph	BINAP	PhMe	100	1	95
6	16b R=Ph	BINAP	Dioxane	100	1	92

^a Solvent used as a 15:2 mixture with water.

^b Isolated yield following chromatography.

be used in place of toluene to give similar yields. Further experiments were undertaken to explore the generality of this process. A range of *o*-alkynyl phenols was readily prepared by Sonogashira reaction²⁰ between MOM protected *o*-iodophenol **19**²¹ and the appropriate alkyne followed by acid-mediated deprotection (e.g., Scheme 3).



Scheme 3. Representative synthesis of *o*-alkynylphenol substrates. Reagents and conditions: (a) MOMCl, ^tPr₂NEt, CH₂Cl₂, rt, 99%; (b) 2 mol % PdCl₂(PPh₃)₂, 2 mol % CuI, NEt₃, 50 °C, 93%; (c) HCl, MeOH, rt, 99%.

The cycloisomerisation proved to be general and an array of benzofuran products were synthesised using this process (Table 2). Electron-rich and poor aromatic alkyne substituents were tolerated as well as alkyl groups. The presence of an ester group did not impede the process but for bulky groups, such as triisopropylsilane, the conversion was reduced. Using this method 2,5-disubstituted benzofurans could also be formed from the appropriate phenols, but in the case of a *tert*-butyl substituent harsher reaction conditions were required.

Table 2
Scope of the cycloisomerisation of *o*-alkynyl phenols to benzofurans

Entry	Phenol	R ¹	R ²	Product	Yield ^a (%)
1	16c	4-MeO-C ₆ H ₄	H	17c	92
2	16d	3-F-C ₆ H ₄	H	17d	90
3	16e	2-Br-C ₆ H ₄	H	17e	8
4	16f	3-Br-C ₆ H ₄	H	17f	72
5	16g	BzOCH ₂ CH ₂	H	17g	97
8	16h	Si(^t Pr) ₃	H	17h	30
9	16i	Ph	Cl	17i	84
10	16j	Ph	CO ₂ Me	17j	83
11	16k	Ph	^t Bu	No reaction	
12 ^b	16k	Ph	^t Bu	17k	44

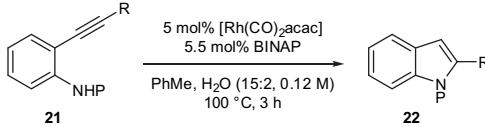
^a Isolated yield following chromatography.

^b Cs₂CO₃ (1.0 equiv) added; 4 h reaction time.

In many cases, the stoichiometric cyclisation of *o*-alkynyl phenols proceeds with the phenolic alcohol protected,²² however in this case when the phenol was protected as its methyl, methoxymethyl or *tert*-butyldimethylsilyl ether no reaction was observed.²³

When the reaction conditions were applied to *o*-alkynylanilines **21** the analogous transformation occurred to give 2-substituted indole products **22** (Table 3). Again, the reaction proceeded with both alkyl and phenyl alkynes (**21a/e**) but was somewhat more sensitive to the nitrogen substituent. The reaction did not occur in the case of unprotected or *N*-benzyl anilines (**21d/c**), but proceeded in excellent yield for *N*-mesyl anilines (**21a/e**). A *N*-tosyl substrate **21b** was tolerated by the catalytic system but the reaction was slower.

Table 3
Cycloisomerisation of *o*-alkynylanilines to indoles



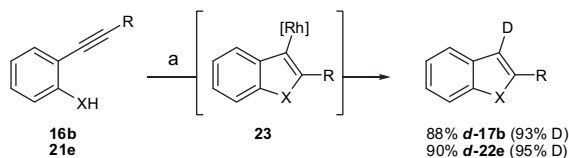
Entry	Aniline	Indole	Time (h)	Yield ^a (%)
1	21a P=Ms, R=Ph	22a	3	91
2	21b P=Ts, R=Ph	22b	3 ^b	75
3	21c P=Bn, R=Ph	22c	3	No reaction
4	21d P=H, R=Ph	22d	3	No reaction
5 ^c	21e P=Ms, R= ⁿ Bu	22e	1	93

^a Isolated yield following chromatography.

^b Incomplete conversion of starting material.

^c [Rh(CO)₂acac] (10%), 11% BINAP.

A key observation was that the use of deuterium oxide as reaction co-solvent led to complete deuterium incorporation at the 3-position of the benzofuran and indole products (Scheme 4). This suggested that the reaction proceeded by the protodemetalation of a 2-rhodium benzofuran/indole species **23** and we felt that this intermediate could be exploited.

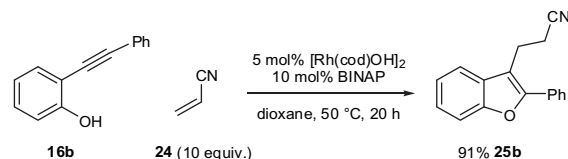


Scheme 4. Site of deuterium incorporation with D₂O solvent. Reagents and conditions: (a) 5 mol % [Rh(CO)₂acac], 5.5 mol % BINAP, PhMe, D₂O (15:2, 0.12 M), 100 °C, 1 h.

2.2. Extension to a domino process: 2,3-disubstituted benzofurans and indoles

The implication of the existence of an intermediate rhodium-heterocycle species **23** was that by judicious selection of reaction conditions, a domino process could be developed for the synthesis of 2,3-disubstituted benzofurans and indoles. Since the pioneering work of Miyaura et al.²⁴ and Hayashi et al.²⁵ there have been many examples of rhodium-catalysed conjugate addition.²⁶ We first investigated a domino reaction with mono-substituted electron-poor alkenes.

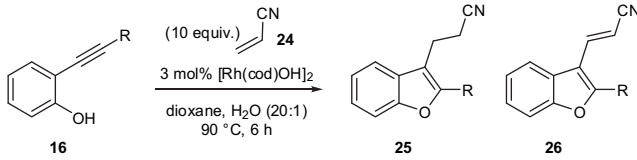
Initial studies employed 10 mol % Rh(CO)₂acac as catalyst with 10 equiv of acrylonitrile in dioxane at 50 °C for 20 h. These were selected as they had been shown to promote cycloisomerisation (cf. Table 1, entries 2 and 6) and were more in line with the published conditions for conjugate addition.²⁴ Quickly, it became apparent that Rh(CO)₂acac was unsuitable for this transformation (<2% desired product formed) and that [Rh(cod)OH]₂ was optimal, forming the product **25b** in excellent yield (Scheme 5). When [Rh(cod)Cl]₂ was used as rhodium-source, the desired product was isolated in only 40% yield.



Scheme 5. Domino cycloisomerisation conjugate-addition to **24**.

In order to study the scope of reaction the catalyst loading was lowered to 3 mol % (6 mol % Rh) and an interesting change in reaction outcome was observed. In all cases the expected product **25** was isolated as a mixture with the Heck–Mizoroki addition compound **26** (Table 4).²⁷ It has been demonstrated that the Heck–Mizoroki product **26** can be formed under palladium catalysis,¹⁷ so studies were focussed on maximising the amount of conjugate-addition product **25**. Indeed, the Miyaura-type addition product could be selectively obtained, simply by the addition of BINAP as ligand. The reaction proved successful with a variety of phenol substrates and the trend was conserved throughout the series.

Table 4
Substrate scope and effect of ligand in the conjugate addition to **24**

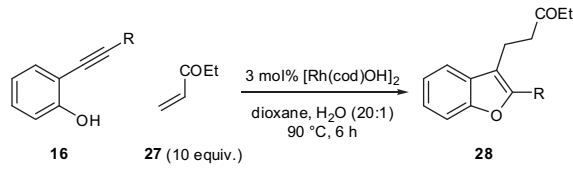


Entry	Phenol	Ligand	25 ^a (%)	26 ^a (%)	Ratio
1	16b R=Ph	None	67	19	3.5:1
2	16c R=4-OMe–C ₆ H ₄	None	66	26	2.5:1
3	16d R=3-F–C ₆ H ₄	None	83	10	8.3:1
4	16a R= ⁿ Bu	6.6 mol % BINAP	78	5	15:1
5	16b R=Ph	6.6 mol % BINAP	92	4	23:1
6	16c R=4-OMe–C ₆ H ₄	6.6 mol % BINAP	91	5	18:1
7	16d R=3-F–C ₆ H ₄	6.6 mol % BINAP	91	1	65:1

^a Isolated yield following chromatography.

When ethyl vinyl ketone **27** was used as electrophile, no such behaviour was observed and only the saturated compound **28** was formed (Table 5).

Table 5
Scope of the domino conjugate addition with ethyl vinyl ketone **27**

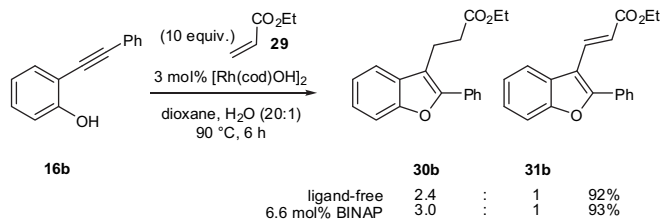


Entry	Phenol	Product	Yield ^a (%)
1	16a R= ⁿ Bu	28a	70
2	16b R=Ph	28b	94
3	16c R=4-OMe–C ₆ H ₄	28c	91
4	16d R=3-F–C ₆ H ₄	28d	86
5	16e R=2-Br–C ₆ H ₄	28e	—
6	16f R=3-Br–C ₆ H ₄	28f	80
7	16l R=CH=CH ₂	28l	75

^a Isolated yield following chromatography.

Again, the reaction proved to be general and good to excellent yields were achieved for a range of phenol substrates including electron-rich aromatic, electron-poor aromatic, vinyl and alkyl substituents. As before, the 2-bromo substituted substrate **16e** failed to react (cf. Table 2, entry 3), presumably as it does not complete the first of the domino steps.

In the case of ethyl acrylate **29**, once again a mixture of products **30/31** was formed. However, the addition of BINAP in this case failed to influence the selectivity of the reaction (Scheme 6). It was



Scheme 6. Effect of ligand in the conjugate addition to ethyl acrylate **29**.

postulated that the use of a bulkier group might improve the selectivity in the process so *tert*-butyl acrylate **32** was investigated. In the studies thus far a large excess (10.0 equiv) of electrophile was employed, and it was considered that this was unnecessary. Surprisingly, when the amount of electrophile was reduced by half (5.0 equiv) a dramatic effect in selectivity was observed (Table 6). This selectivity for the conjugate-addition product was even greater when the number of equivalents was lowered to 2.0 and 1,2-dimethoxyethane (DME) was used as solvent.

Table 6
Effect of solvent and stoichiometry in the conjugate addition to **32**

Entry	Equiv 32	Solvent	(%) ^a	(%) ^a	Ratio
1	10.0	Dioxane	76	19	3.9:1
2 ^b	10.0	DME	82	15	5.3:1
3	5.0	Dioxane	87	9	9.2:1
4	2.0	Dioxane	90	5.5	16:1
5 ^b	2.0	DME	89	4.5	20:1

^a Isolated yield following chromatography.

^b Reaction performed at 85 °C.

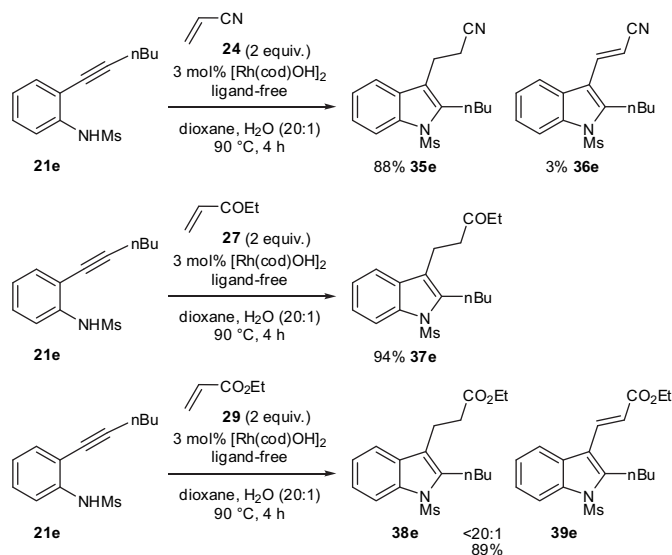
This effect proved general and also provided excellent selectivity for the domino reaction with ethyl acrylate and acrylonitrile under ligand-free conditions (Table 7).

Using the knowledge gained from these studies, we turned our attention to the synthesis of indoles (Scheme 7).

Table 7
Effect of reaction stoichiometry

Entry	Electrophile	Solvent	T (°C)	Ratio	Yield ^a (%)
1	10 equiv 24	Dioxane, H ₂ O (20:1)	90	3.5:1	86
2	2 equiv 24	DME, H ₂ O (10:1)	85	20:1	86
3	10 equiv 29	Dioxane, H ₂ O (20:1)	90	2.4:1	92
4	2 equiv 29	DME, H ₂ O (10:1)	85	>20:1	85
5	10 equiv 32	Dioxane, H ₂ O (20:1)	90	2.2:1	88
6	2 equiv 32	DME, H ₂ O (10:1)	85	>20:1	77

^a Isolated yield of mixture of conjugate-addition and Heck–Mizoroki products following chromatography.

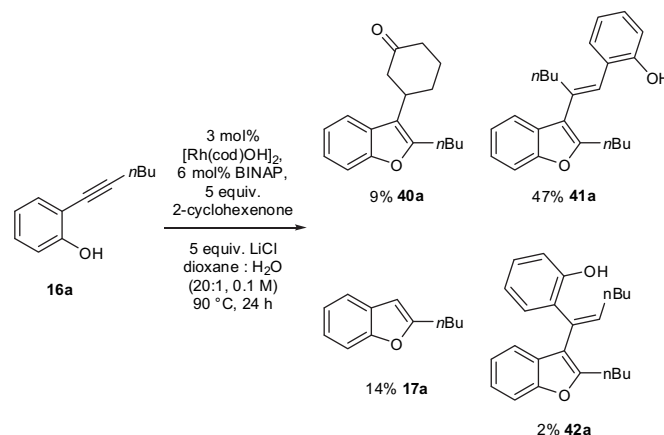


Scheme 7. Synthesis of 2,3-disubstituted indoles.

The same reaction conditions could be applied to generate 2,3-disubstituted indoles in excellent yields and selectivity for conjugate-addition versus Heck–Mizoroki product.

2.3. Disubstituted electrophiles

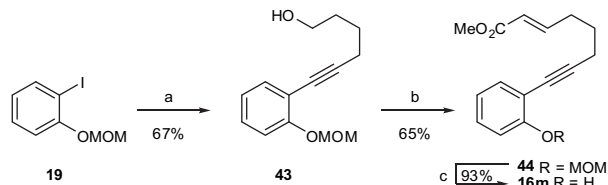
With an efficient process developed for the domino synthesis of 2,3-disubstituted benzofurans and indoles using mono-substituted electrophiles, attention was turned to the use of disubstituted electrophiles (i.e., 2-cyclohexenone). After a great deal of investigation, including studying the effect of varying conditions, ligand, metal catalyst and additive; it was found that the conjugate-addition product **40a** was formed typically in only 5–15% yield (Scheme 8).



Scheme 8. Typical product distribution for domino reaction with 2-cyclohexenone.

Despite the low selectivity for the desired conjugate-addition product, the mass balance of this process was quantitative, with the remainder comprising unsubstituted benzofuran **17a** and dimeric products **41a/42a**.^{28,29} From these results it was concluded that the increase in substitution meant that cyclohexenone was no longer a competitive electrophile as compared to the alkynylphenol starting material.³⁰ In order to favour the desired addition to an enone over dimerisation, a system was designed in which the second of the domino steps would be an intramolecular reaction. The starting material for this reaction was readily accessed by the Sonogashira

reaction²⁰ of aryl iodide **19** with 5-hexyn-1-ol, followed by a one-pot Ley oxidation—stabilised Wittig reaction (**43**→**44**)³¹ and finally deprotection to form the phenol **16m** (Scheme 9). Ley's one-pot sequence provided much improved access to the desired α,β -unsaturated compound **44** (65% over two steps) compared to isolation of the intermediate aldehyde, which was prone to decomposition.



Scheme 9. Synthesis of a substrate bearing a tethered electrophile. Reagents and conditions: (a) 5-hexyn-1-ol, 2 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, 4 mol % CuI , NEt_3 , THF, 50 °C, 67%; (b) 5 mol % Pr_4NRuO_4 , NMO, 4 Å sieves, CH_2Cl_2 , rt; then $\text{Ph}_3\text{PCHCO}_2\text{Me}$, rt, 65%; (c) HCl , MeOH, rt, 93%.

With the substrate in hand, optimisation studies revealed that the reaction resulted in a very good yield of conjugate-addition product **40m** when DME was used as a co-solvent with water (Table 8).

Table 8
Domino intramolecular cyclisation

Entry	Solvent	mol % Catalyst and additive	40m ^a (%)	17m ^a (%)	41m ^a (%)
1 ^b	Dioxane	3.5% catalyst	11	10	—
2	Dioxane, H_2O (20:1)	3.5% catalyst	66	9	—
3	Dioxane, H_2O (20:1)	3.0% catalyst	48	11	9
4 ^b	Dioxane, H_2O (20:1)	3.0% catalyst, 1.6 equiv LiCl	51	2	14
5 ^b	PhMe, H_2O (20:1)	3.0% catalyst	15	36	—
6	DME, H_2O (20:1)	3.0% catalyst	70	8	12

^a Isolated yield following chromatography.

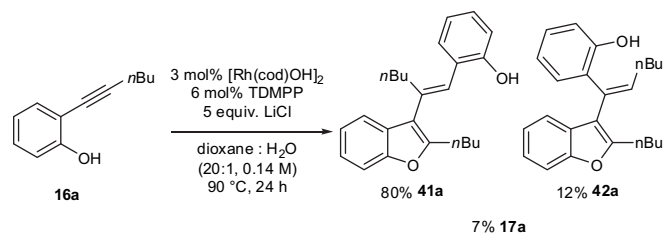
^b Incomplete conversion of **16m**.

It is important to note that the addition of lithium chloride^{18,32} to the reaction mixture generally shifted the distribution of products away from the 3-unsubstituted benzofuran **17m**.³³ Control experiments demonstrated that when the substrate **16a** is heated to 90 °C for 24 h in dioxane and water (10:1) there is a significant background reaction to form the 3-unsubstituted benzofuran **17a** (ca. 15% conversion by ^1H NMR). The addition of lithium chloride or bromide (5 equiv) completely inhibited this process.²³

2.4. Investigation of the side-reaction

The formation of the dimer species **41/42** represented a significant pathway within our domino process and warranted further investigation.

When the external electrophile was absent from the reaction mixture, the *o*-alkynyl phenol **16a** was transformed to the major dimer **41a** in 80% yield (Scheme 10). The conditions were selected for these experiments on the basis that they were those, which



Scheme 10. Dimerisation of the phenol **16a**. TDMPP=tris(2,6-dimethoxyphenyl) phosphine.

resulted in the greatest amount of dimer reaction in studies of the conjugate addition to cyclohexenone (see Section 2.3).

A series of experiments was performed in order to determine the characteristics of alkyne group, which would either promote or hinder the addition of the benzofuryl-rhodium species (Table 9). An

Table 9
Effect of coordinating groups for the dimerisation versus cross-addition ratio

Entry	Alkyne	Cross-addition product	Yield ^a (%)	Selectivity ^b
1	45	46a	75	>19:1
2	47	48a	34	1:1
3	49	50	43	1:1
4	51	52	24	1:1.3
5	53	54	n.d.	1:1.7
6	55	56	14	1:2.7

^a Isolated yield following chromatography.

^b Selectivity=relative integration of cross-addition product:**41a** in the crude ^1H NMR spectrum. n.d.=not determined.

equimolar mixture of *o*-1-hexynylphenol **16a** and alkyne partner was treated with a catalytic amount of rhodium(I) complex and TDMPP at 90 °C for 24 h.

When a pyridyl alkyne **45** was investigated, only a trace amount of the dimeric product **41/42** could be observed and the major product was the vinyl pyridine **46a** (Table 9, entry 1).

In the case of phenol-derived substrates, there was a general trend that the ratio of dimer **41** to cross-reaction product generally favoured the latter as the 'coordinating ability' of the substituent increased (Table 9, entries 2–5).^{29,34} In the case of unsubstituted 1-butylnylbenzene **55**, the cross-addition reaction still occurred but significantly less than dimerisation. For terminal alkynes (phenyl acetylene), or alkynes conjugated to ester groups (dimethyl but-2-ynedioate or ethyl but-2-ynoate) there was no cross-addition reaction and only compounds related to the phenol were observed (i.e., **17**, **41** and **42**).

2.5. Application to the synthesis of poly-heteroaromatics

The selective formation of the cross-addition product **46a** was encouraging and we were keen to further optimise this reaction. The rhodium-catalysed addition of boronic acids to alkynes with nitrogen containing heterocycles as directing groups has been reported previously by our group²⁹ and we investigated this in the context of a domino process. It was found that [Rh(cod)OH]₂ was an excellent catalyst for promoting this transformation and although at high loadings the analogous chloride catalyst performed comparably, at lower loading a significant drop in performance was seen (Table 10).

Table 10
Screening the domino reaction with pyridyl alkyne **45**

Entry	mol % Catalyst	Conversion ^a	46a/17a/41a	Yield ^b (%)
1	1.5 [Rh(cod)OH] ₂	93%	1:0.6:0.1	48
2 ^c	1.5 [Rh(cod)OH] ₂	>98%	1:0.2:—	62
3	3 [Rh(cod)OH] ₂	>98%	1:0.2:—	62
4 ^d	3 [Rh(cod)OH] ₂	—	No reaction	—
5	6 [Rh(cod)OH] ₂	>98%	1:0.1:0.2	80
6 ^c	6 [Rh(cod)OH] ₂	>98%	1:0.1:0.2	80
7 ^e	6 Rh(cod) ₂ OTf	>98%	1:0.1:—	67
8	1.5 [Rh(cod)Cl] ₂	72%	1:0.7:0.1	31
9	6 [Rh(cod)Cl] ₂	>98%	1:0.1:0.2	74
10	6 [Ir(cod)Cl] ₂	32%	1:25:—	Trace
11	12 PdCl ₂	55%	1:8.3:8.0	2

^a Consumption of **16a** by ¹H NMR.

^b Isolated yield.

^c Ligand-free conditions.

^d BINAP used in place of TDMPP.

^e No ligand, LiCl, or H₂O.

Electron-rich ligands, such as TDMPP and TFP gave the most amount of product, in the case of the bidentate BINAP ligand, there was no formation of the vinyl pyridine product (only **17**, **41** and **42** were observed). As before, the best results were obtained with a dioxane/water solvent system. Increasing the amount of pyridyl alkyne relative to phenol seemed to have little effect on the outcome and the reaction worked well using only 1.0 equiv.

In general, conversion at 24 h was low (<20%) at temperatures below 80 °C. The optimum conversion and selectivity for the desired product were observed when the reaction was performed at 90 °C. As observed previously, the addition of lithium chloride seemed to favour the formation of the desired product, suppressing

the formation of the 3-unsubstituted benzofuran product, however in this case lithium bromide was found to be even better. The reaction also proceeded to give a higher yield of product at higher concentration. We settled upon the use of 5 equiv of lithium bromide with 12 mol % TDMPP ligand and 6 mol % [Rh(cod)OH]₂ in dioxane and water (10:1) at 90 °C for 24 h as optimal and proceeded to test the scope of the reaction.

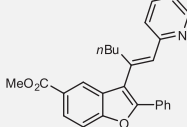
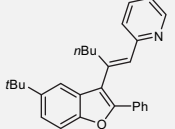
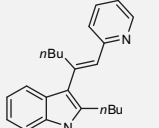
The reaction proved to be quite general and a range of *o*-alkynyl phenols, including both alkyl- and aryl-substituted alkynes underwent domino reaction in good to very good yield, even when the catalyst loading was reduced to half (Table 11). Surprisingly, the

Table 11
Scope of the domino reaction with pyridyl alkyne **45**

Entry	Substrate	Product	Yield ^a (%)
1 ^c	16a		46a 83 ^c
2 ^b	16b		46b 77
3 ^c	16b		46b 83
4 ^c	16c		46c 85
5 ^c	16d		46d 76
6 ^b	16e		46e 37 (51% 17e)
7 ^b	16f		46f 55
8 ^b	16g		46g 87
9 ^c	16i		46i 75

(continued on next page)

Table 11 (continued)

Entry	Substrate	Product	Yield ^a (%)
10 ^b	16j		46j 71
11 ^b	16k		46k 41
12 ^c	21e		57e Only 22e formed

^a Isolated yield following column chromatography.

^b Compound **16** (1.0 equiv), **45** (1.0 equiv), 3 mol % [Rh(cod)OH]₂, 6 mol % TDMPP, 5 equiv LiBr, dioxane, H₂O (10:1, 0.24 M), 90 °C, 24 h.

^c Compound **16** or **21** (1.0 equiv), **45** (1.0 equiv), 6 mol % [Rh(cod)OH]₂, 12 mol %, TDMPP, 5 equiv LiBr, dioxane, H₂O (10:1, 0.24 M), 90 °C, 24 h.

cross-addition product could be isolated even for the substrates, which displayed poor reactivity in the previous domino reactions (**16e**, **16k**). Unfortunately, when the reactions conditions were applied to the *o*-alkynyl aniline substrate **21a** the domino process did not occur and only the 3-unsubstituted indole **22e** was formed.

A range of alkynes was also considered (Table 12). It was found that, although in many cases 2-hexynylpyridine gave good yields at 3 mol % catalyst loading, in general 6 mol % was required to obtain an acceptable yield. Further improvement could be achieved by using a 1.5 times excess of phenol, compared to the alkynyl pyridine substrate.

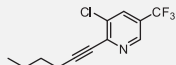
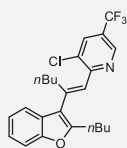
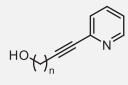
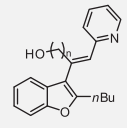
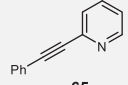
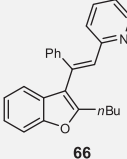
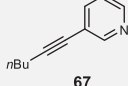
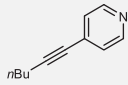
We were particularly pleased to find that the 2-alkynyl-3-chloro-5-(trifluoromethyl)-2-pyridine (**58**) was a competent partner in the reaction, owing to its prevalence in bioactive compounds.³⁵

In accordance with the findings for the rhodium-catalysed addition of boronic acids to alkynylpyridines,²⁹ there was no cross-addition reaction in the case of a substrate bearing a propargylic alcohol (**64**) or for 3- or 4-alkynylpyridines (**67**, **68**). However, we were able to generate 30% of the addition product **66** with 2-phenylethynyl-pyridine (**65**) despite this being unsuccessful previously.

2.6. Mechanism

A series of deuterium labelling and control experiments were performed in order to gain insight to the mechanism of this process (Scheme 11). First of all, it is important to note that the substrates used in these studies contain an internal alkyne. Thus we propose that initial step in the mechanism is the activation of the alkyne to intramolecular nucleophilic attack (**II**), forming a 3-rhodium heterocycle (**III**). This is complimentary to the report of Trost, whose catalyst did not promote reaction with internal alkynes and was postulated to proceed through a rhodium carbenoid species.⁶ When Rh(CO)₂acac is used as the catalyst, the major pathway is protodemetalation to generate the corresponding heterocyclic product (**17**). When [Rh(cod)OH]₂ is used as the catalyst, a domino reaction is more likely to occur; either addition to an external electrophile component (**29** or **45**) or to another molecule of starting material (**16**). Control experiments demonstrated that Friedel–Crafts type reaction of the 3-unsubstituted benzofuran was not in operation.³⁶

Table 12
Scope of alkyne partner

Entry	Alkyne	Cross-addition product	Yield ^a (%)
1 ^b			42
2 ^c	58	59a	52
3 ^d	58	59a	68
4 ^b			49
5 ^c	60 (n=3)	61a (n=3)	73
6 ^b	62 (n=2)	63a (n=2)	27
7 ^c	62 (n=2)	63a (n=2)	46
8 ^d	62 (n=2)	63a (n=2)	57
9 ^b	64 (n=1)	No reaction	
10 ^b			30
11 ^b		No reaction	
12 ^b		No reaction	

^a Isolated yield following column chromatography.

^b Compound **16a** (1.0 equiv), alkyne (1.0 equiv), 3 mol % [Rh(cod)OH]₂, 6 mol % TDMPP, LiBr (5.0 equiv), dioxane, H₂O (10:1, 0.24 M), 90 °C, 24 h.

^c Compound **16a** (1.0 equiv), alkyne (1.0 equiv), 6 mol % [Rh(cod)OH]₂, 12 mol % TDMPP, LiBr (5.0 equiv), dioxane, H₂O (10:1, 0.24 M), 90 °C, 24 h.

^d Compound **16a** (1.5 equiv), alkyne (1.0 equiv), 9 mol % [Rh(cod)OH]₂, 18 mol % TDMPP, LiBr (5.0 equiv), dioxane, H₂O (10:1, 0.24 M), 90 °C, 24 h.

In the case of mono-substituted electron-poor alkenes (**29**) the 3-rhodium heterocycles adds in a conjugate fashion to form a rhodium π -oxo allyl species (**V**).³⁷ Depending on the nature of the electrophile and the exact reaction conditions, this intermediate can undergo protodemetalation to give the saturated product (i.e., **30**) and regenerate the rhodium catalyst; or β -hydride elimination to give the unsaturated product **31** and a rhodium/hydride species (**VI**).^{27,38} When hexyl acrylate was used as electrophile (10 equiv, 1 equiv **16a**, 3 mol % [Rh(cod)OH]₂, ligand-free, 90 °C, 6 h) we were able to detect hexyl propionate (¹H NMR δ =2.32, q, *J*=7.6 Hz) in the crude reaction mixture suggesting that the active rhodium catalyst is regenerated from the hydride following reduction of the electrophile.

The increase in steric crowding in the case of more substituted electron-poor alkenes, such as 2-cyclohexene means that the alkyne motif within the starting material (**16**) presents a reactive site and the dimer (**41**) is formed at a competitive rate. The judicious choice of alkyne can lead to the generation of interesting cross-addition products, following addition of the 3-rhodium-heterocycle



3. Conclusions

4. Experimental procedures

4.1. General

4.2. Cycloisomerisation (general procedure A)

4.2.1. 2-*n*-Butyl-1-benzofuran (17a). Subjecting phenol **16a** (43 mg, 0.25 mmol) to general procedure A (with 10 mol % catalyst loading) followed by purification (gradient from 5 to 9% Et₂O in hexane) gave the title compound as a colourless oil (38 mg, 88%). The analytical data were in agreement with literature values.⁴² δ_{H} (400 MHz; CDCl₃): 7.49–7.45 (m, 1H), 7.42–7.39 (m, 1H), 7.22–7.14 (m, 2H), 6.37 (s, 1H), 2.77 (t, *J*=7.5 Hz, 2H), 1.73 (app. quintet, *J*=7.5 Hz, 2H), 1.43 (app. sextet, *J*=7.5 Hz, 2H), 0.96 (t, *J*=7.5 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 159.7, 154.6, 129.0, 123.0, 122.3, 120.1, 110.7, 101.7, 29.8, 28.1, 22.3, 13.8.

4.2.2. 2-Phenyl-1-benzofuran (17b). Subjecting phenol **16b** (50 mg, 0.26 mmol) to general procedure A (with 10 mol % catalyst loading) followed by purification (gradient from 5 to 9% Et₂O in hexane) gave the title compound as a white solid (47 mg, 95%). The analytical data were in agreement with literature values.⁴³ Mp=118–119 °C; δ_{H} (400 MHz; CDCl₃): 7.87 (d, J =8.4 Hz, 2H), 7.59 (d, J =7.6 Hz, 1H), 7.53 (d, J =8.0 Hz, 1H), 7.45 (dd, J =8.4, 7.4 Hz, 2H), 7.36 (t, J =7.4 Hz, 1H), 7.29 (dd, J =8.0, 7.3 Hz, 1H), 7.23 (dd, J =7.6, 7.3 Hz, 1H), 7.03 (s, 1H); δ_{C} (100 MHz; CDCl₃): 155.9, 154.9, 130.5, 129.2, 128.8, 128.5, 124.9, 124.2, 122.9, 120.9, 111.1, 101.3.

4.2.3. 3-Duetero-2-phenyl-1-benzofuran (*d*-**17b**). Subjecting phenol **16b** (50 mg, 0.26 mmol) to general procedure A (using D₂O in

place of H₂O) followed by purification (gradient from 5 to 9% Et₂O in hexane) gave the title compound as a white solid (44 mg, 88%, 93% D by ¹H NMR). Mp=118–119 °C; δ_{H} (400 MHz; CDCl₃): 7.87 (d, $J=7.4$ Hz, 2H), 7.58 (d, $J=7.6$ Hz, 1H), 7.53 (d, $J=8.2$ Hz, 1H), 7.45 (dd, $J=7.7$, 7.4 Hz, 2H), 7.35 (t, $J=7.7$ Hz, 1H), 7.28 (dd, $J=7.8$, 7.4 Hz, 1H), 7.23 (dd, $J=7.6$, 7.4 Hz, 1H); δ_{C} (100 MHz; CDCl₃): 155.8, 154.9, 130.4, 129.1, 128.7, 128.5, 124.9, 124.2, 122.9, 120.8, 111.1, 101.1 ($J=26.7$ Hz); ν_{max} 3066, 1553, 1470, 1454, 1269, 1207, 1069 cm⁻¹; m/z (EI) 195.0785 (M^+ : C₁₄H₉DO requires 195.0794).

4.2.4. 2-(4-Methoxyphenyl)-1-benzofuran (17c). Subjecting phenol **16c** (45 mg, 0.20 mmol) to general procedure A followed by purification (10:1:1 hexane/CH₂Cl₂/Et₂O in hexane) gave the title compound as a white solid (41 mg, 92%). The analytical data were in agreement with literature values.⁴³ Mp=148–150 °C; δ_{H} (400 MHz; CDCl₃): 7.80 (d, $J=8.9$ Hz, 2H), 7.56 (dd, $J=7.2$, 1.0 Hz, 1H), 7.50 (dd, $J=7.0$, 1.2 Hz, 1H), 7.28–7.18 (m, 2H), 6.98 (d, $J=8.9$ Hz, 2H), 6.89 (s, 1H), 3.87 (s, 3H); δ_{C} (100 MHz; CDCl₃): 160.0, 156.0, 154.7, 129.5, 126.4, 123.7, 133.3, 122.8, 120.5, 114.2, 111.0, 99.6, 55.3.

4.2.5. 2-(3-Fluorophenyl)-1-benzofuran (17d). Subjecting phenol **16d** (46 mg, 0.22 mmol) to general procedure A followed by purification (9% Et₂O in hexane) gave the title compound as a white solid (41 mg, 90%). The analytical data were in agreement with literature values.^{12c} Mp=77–78 °C; δ_{H} (400 MHz; CDCl₃): 7.64 (ddd, $J=7.8$, 1.8, 1.0 Hz, 1H), 7.60 (dd, $J=7.8$, 1.3 Hz, 1H), 7.56 (ddd, $J=10.0$, 2.3, 1.8 Hz, 1H), 7.53 (dd, $J=8.2$, 1.0 Hz, 1H), 7.41 (ddd, $J=7.8$, 7.8, 6.0 Hz, 1H), 7.31 (ddd, $J=8.2$, 7.3, 1.3 Hz, 1H), 7.23 (ddd, $J=7.8$, 7.3, 1.0 Hz, 1H), 7.08–7.02 (m, 1H), 7.05 (s, 1H); δ_{C} (100 MHz; CDCl₃): 163.1 (d, $J=245.8$ Hz), 154.9, 154.5 (d, $J=3.2$ Hz), 132.5 (d, $J=8.6$ Hz), 130.4 (d, $J=8.6$ Hz), 128.9, 124.7, 123.1, 121.1, 120.5 (d, $J=3.0$ Hz), 115.3 (d, $J=21.4$ Hz), 111.8 (d, $J=23.7$ Hz), 111.2, 102.3.

4.2.6. 2-(2-Bromophenyl)benzofuran (17e). Subjecting phenol **16e** (40 mg, 0.15 mmol) to general procedure A followed by purification (gradient from 5 to 15% Et₂O in hexane) gave the title compound as a yellow oil (3 mg, 8%). The analytical data were in agreement with literature values.⁴³ δ_{H} (400 MHz; CDCl₃): 7.97 (dd, $J=7.9$, 1.7 Hz, 1H), 7.71 (dd, $J=8.0$, 1.2 Hz, 1H), 7.65 (dd, $J=7.7$, 1.3 Hz, 1H), 7.54 (s, 1H), 7.53 (dd, $J=8.3$, 1.0 Hz, 1H), 7.43 (ddd, $J=7.9$, 7.4, 1.2 Hz, 1H), 7.33 (ddd, $J=8.3$, 7.3, 1.3 Hz, 1H), 7.26 (ddd, $J=7.7$, 7.3, 1.0 Hz, 1H), 7.21 (ddd, $J=8.0$, 7.4, 1.7 Hz, 1H); δ_{C} (100 MHz; CDCl₃): 154.3, 153.1, 134.3, 131.0, 129.8, 129.4, 128.8, 127.5, 124.8, 123.0, 121.5, 120.8, 111.1, 107.0.

4.2.7. 2-(3-Bromophenyl)benzofuran (17f). Subjecting phenol **16f** (55 mg, 0.20 mmol) to general procedure A followed by chromatography (gradient from 5 to 15% Et₂O in hexane) gave the title compound as a white solid (40 mg, 72%). The analytical data were in agreement with literature values.⁴⁴ Mp=84–85 °C; δ_{H} (400 MHz; CDCl₃): 8.02 (dd, $J=2.0$, 1.6 Hz, 1H), 7.78 (ddd, $J=7.8$, 1.6, 1.0 Hz, 1H), 7.59 (dd, $J=7.6$, 1.4 Hz, 1H), 7.52 (dd, $J=8.1$, 1.0 Hz, 1H), 7.47 (ddd, $J=8.0$, 2.0, 1.0 Hz, 1H), 7.31 (dd, $J=8.0$, 7.8 Hz, 1H), 7.31 (ddd, $J=8.1$, 7.3, 1.4 Hz, 1H), 7.24 (ddd, $J=7.6$, 7.3, 1.0 Hz, 1H), 7.03 (s, 1H); δ_{C} (100 MHz; CDCl₃): 154.9, 154.2, 132.4, 131.3, 130.3, 128.9, 127.8, 124.8, 123.4, 123.1, 123.0, 121.1, 111.2, 102.4.

4.2.8. Benzoic acid 2-benzo[b]furan-2-ylethyl ester (17g). Subjecting phenol **16g** (44 mg, 0.16 mmol) to general procedure A followed by purification (gradient from 5 to 12% EtOAc in hexane) gave the title compound as a white solid (42 mg, 97%). Mp=43–44 °C; δ_{H} (400 MHz; CDCl₃): 8.03 (d, $J=7.8$ Hz, 2H), 7.58–7.53 (m, 1H), 7.50 (dd, $J=7.4$, 1.5 Hz, 1H), 7.44 (dd, $J=7.8$, 1.4 Hz, 1H), 7.43 (dd, $J=7.8$, 7.4 Hz, 2H), 7.24 (ddd, $J=7.8$, 7.2, 1.5 Hz, 1H), 7.19 (ddd, $J=7.4$, 7.2, 1.4 Hz, 1H), 6.54 (s, 1H), 4.68 (t, $J=6.6$ Hz, 2H), 3.27 (t, $J=6.6$ Hz, 2H); δ_{C} (100 MHz; CDCl₃): 166.4, 155.0, 154.8, 133.0, 130.0, 129.6, 128.7, 128.3, 123.6, 122.6, 120.5, 110.8, 103.5, 62.3, 28.3; ν_{max} 3061, 2962,

1722, 1601, 1586, 1454, 1316, 1275, 1175, 1115, 1071, 1026 cm⁻¹; m/z (EI) 266.0930 (M^+ : C₁₇H₁₄O₃ requires 266.0943).

4.2.9. 2-Tri-iso-propylsilylbenzofuran (17h). Subjecting phenol **16h** (50 mg, 0.18 mmol) to general procedure A followed by purification (hexane) gave the title compound as a colourless oil (15 mg, 30%). δ_{H} (400 MHz; CDCl₃): 7.59 (ddd, $J=7.6$, 1.4, 0.7 Hz, 1H), 7.51 (ddd, $J=8.2$, 1.7, 0.9 Hz, 1H), 7.27 (ddd, $J=8.2$, 7.1, 1.4 Hz, 1H), 7.20 (ddd, $J=8.2$, 7.1, 1.0 Hz, 1H), 7.01 (d, $J=1.0$ Hz, 1H), 1.44–1.34 (m, 3H), 1.15 (d, $J=7.6$ Hz, 18H); δ_{C} (100 MHz; CDCl₃): 160.52, 157.94, 127.92, 123.99, 122.12, 120.77, 118.03, 111.25, 18.57, 11.04; ν_{max} 2944, 2890, 2866, 1467, 1441, 1253, 1223, 1111, 1057 cm⁻¹; m/z (EI) 274.1759 (M^+ : C₁₇H₂₆OSi requires 274.1753).

4.2.10. 5-Chloro-2-phenylbenzofuran (17i). Subjecting phenol **16i** (46 mg, 0.20 mmol) to general procedure A followed by purification (gradient from 5 to 10% Et₂O in hexane) gave the title compound as a white solid (38 mg, 84%). The analytical data were in agreement with literature values.^{11b} Mp=146–148 °C (sublimed); δ_{H} (400 MHz; CDCl₃): 7.85–7.81 (m, 2H), 7.52 (d, $J=2.2$ Hz, 1H), 7.47–7.34 (m, 4H), 7.22 (dd, $J=8.7$, 2.2 Hz, 1H), 6.93 (s, 1H); δ_{C} (100 MHz; CDCl₃): 157.4, 153.2, 130.5, 129.9, 129.0, 128.8, 128.5, 125.0, 124.4, 120.4, 112.1, 100.8.

4.2.11. Methyl 2-phenylbenzofuran-5-carboxylate (17j). Subjecting phenol **16j** (50 mg, 0.20 mmol) to general procedure A followed by purification (hexane: CH₂Cl₂/EtOAc, 10:1:1) gave the title compound as a white solid (41 mg, 83%). The analytical data were in agreement with literature values.⁴⁶ Mp=155–157 °C; δ_{H} (400 MHz; CDCl₃): 8.30 (d, $J=1.8$ Hz, 1H), 8.00 (dd, $J=8.6$, 1.8 Hz, 1H), 7.85 (dd, $J=8.2$, 1.3 Hz, 2H), 7.52 (d, $J=8.6$ Hz, 1H), 7.45 (dd, $J=8.2$, 7.4 Hz, 2H), 7.37 (tt, $J=7.4$, 1.3 Hz, 1H), 7.04 (s, 1H), 3.93 (s, 3H); δ_{C} (100 MHz; CDCl₃): 167.2, 157.4, 157.3, 129.8, 129.2, 129.0, 128.8, 126.0, 125.3, 125.0, 123.2, 110.9, 101.4, 52.1.

4.2.12. 5-tert-Butyl-2-phenylbenzofuran (17k). Subjecting phenol **16k** (41 mg, 0.16 mmol) to general procedure A with the addition of Cs₂CO₃ for 4 h followed by purification (hexane/CH₂Cl₂/EtOAc, 10:1:1) gave the title compound as a white solid (18 mg, 44%). The analytical data were in agreement with literature values.^{11b} Mp=100–102 °C; δ_{H} (400 MHz; CDCl₃): 7.85 (dd, $J=8.5$, 1.3 Hz, 2H), 7.58 (d, $J=2.0$ Hz, 1H), 7.46–7.41 (m, 2H), 7.44 (d, $J=8.6$ Hz, 1H), 7.35 (dd, $J=8.6$, 2.0 Hz, 1H), 7.35–7.31 (m, 1H), 6.97 (s, 1H), 1.39 (s, 9H); δ_{C} (100 MHz; CDCl₃): 156.0, 153.1, 146.0, 130.7, 128.9, 128.7, 128.3, 124.8, 122.2, 117.1, 110.4, 101.5, 34.7, 31.8.

4.2.13. 1-Methanesulfonyl-2-phenylindole (22a). Subjecting aniline **21a** (58 mg, 0.22 mmol) to general procedure A followed by purification (gradient from 5 to 10% EtOAc in hexane) gave the title compound as a white solid (53 mg, 91%). The analytical data were in agreement with literature values.^{15e} Mp=103–105 °C; δ_{H} (400 MHz; CDCl₃): 8.14 (d, $J=8.0$ Hz, 1H), 7.64–7.55 (m, 3H), 7.47–7.32 (m, 5H), 6.73 (s, 1H), 2.74 (s, 3H); δ_{C} (100 MHz; CDCl₃): 141.93, 137.95, 131.93, 130.26, 130.08, 128.83, 127.67, 125.07, 124.50, 120.98, 115.78, 113.01, 39.42.

4.2.14. 1-(4-Toluene)-sulfonyl-2-phenylindole (22b). Subjecting aniline **21b** (80 mg, 0.22 mmol) to general procedure A followed by purification (gradient from 5 to 10% EtOAc in hexane) gave the title compound as a white solid (60 mg, 75%). The analytical data were in agreement with literature values.^{15e} Mp=145–147 °C; δ_{H} (400 MHz; CDCl₃): 8.31 (d, $J=8.4$ Hz, 1H), 7.53–7.46 (m, 2H), 7.46–7.38 (m, 4H), 7.34 (t, $J=7.6$ Hz, 1H), 7.29–7.21 (m, 3H), 7.02 (d, $J=8.1$ Hz, 2H), 6.53 (s, 1H), 2.26 (s, 3H); δ_{C} (100 MHz; CDCl₃): 144.47, 142.08, 138.23, 134.60, 132.37, 130.50, 130.28, 129.14, 128.59, 127.44, 126.73, 124.72, 124.26, 120.64, 116.60, 113.57, 21.47.

4.2.15. 2-n-Butyl-1-methanesulfonylindole (22e). Subjecting aniline **21e** (54 mg, 0.22 mmol) to general procedure A followed by

purification (gradient from 10 to 17% EtOAc in hexane) gave the title compound as a white solid (50 mg, 93%). The analytical data were in agreement with literature values.^{15d} Mp=79–80 °C; δ_{H} (400 MHz; CDCl₃): 8.02–7.98 (m, 1H), 7.51–7.47 (m, 1H), 7.30–7.23 (m, 2H), 6.46 (s, 1H), 3.00 (s, 3H), 2.96 (t, $J=7.6$ Hz, 2H), 1.75 (app. quintet, $J=7.6$ Hz, 2H), 1.46 (app. sextet, $J=7.6$ Hz, 2H), 0.98 (t, $J=7.6$ Hz, 3H); δ_{C} (100 MHz; CDCl₃): 142.5, 136.8, 129.8, 123.9, 123.6, 120.2, 114.1, 108.4, 40.3, 31.0, 28.6, 22.4, 13.9.

4.2.16. 2-*n*-Butyl-3-deutero-1-methanesulfonylindole (d-22e). Subjecting aniline **21e** (55 mg, 0.22 mmol) to general procedure A with D₂O in place of H₂O (purification using gradient from 10 to 17% EtOAc in hexane) gave the title compound as a white solid (50 mg, 90%, 95% D by ¹H NMR). Mp=80–81 °C; δ_{H} (300 MHz; CDCl₃): 8.02–7.97 (m, 1H), 7.52–7.46 (m, 1H), 7.30–7.22 (m, 2H), 3.00 (s, 3H), 2.95 (t, $J=7.6$ Hz, 2H), 1.75 (app. quintet, $J=7.6$ Hz, 2H), 1.46 (app. sextet, $J=7.6$ Hz, 2H), 0.98 (t, $J=7.6$ Hz, 3H); δ_{C} (100 MHz; CDCl₃): 142.4, 136.8, 129.8, 123.9, 123.6, 120.2, 114.1, 108.2 ($J=26.4$ Hz), 40.3, 31.0, 28.5, 22.4, 13.9; ν_{max} 2959, 2932, 2872, 1559, 1452, 1366, 1327, 1223, 1169, 1150, 1047, 1024 cm⁻¹; m/z (EI) 252.1037 (M^+ : C₁₃H₁₆DNO₂S requires 252.1043).

4.3. Domino reaction with mono-substituted electron-withdrawn electrophiles using *rac*-BINAP (general procedure B)

A solution of [Rh(cod)OH]₂ (3 mol %), *rac*-BINAP (6.6 mol %) in dioxane (1.0 cm³) and water (0.1 cm³) was flushed with argon and stirred at room temperature for 15 min. The electrophile was added followed by a solution of the phenol in dioxane (1.0 cm³) and the reaction mixture was stirred at 90 °C for 6 h. Et₂O (5 cm³) was added to the reaction mixture and it was filtered (short silica pad) washing with Et₂O (4×5 cm³). The filtrate was concentrated under reduced pressure then purified by flash column chromatography to yield the product.

4.3.1. 3-(2-*n*-Butylbenzofuran-3-yl)propionitrile (25a) and 3-(2-*n*-butylbenzofuran-3-yl)acrylonitrile (26a). Subjecting phenol **16a** (42 mg, 0.24 mmol) and acrylonitrile (0.16 cm³, 2.4 mmol) to general procedure B followed by purification (gradient from 5 to 11% Et₂O in hexane) gave **25a** (43 mg, 78%) as a colourless oil and **26a** (3 mg, 5%) as a yellow oil. **25a**: δ_{H} (400 MHz; CDCl₃): 7.43–7.40 (m, 2H), 7.25–7.20 (m, 2H), 3.01 (t, $J=7.3$ Hz, 2H), 2.78 (t, $J=7.5$ Hz, 2H), 2.64 (t, $J=7.5$ Hz, 2H), 1.74 (app. quintet, $J=7.5$ Hz, 2H), 1.40 (app. sextet, $J=7.5$ Hz, 2H), 0.96 (t, $J=7.5$ Hz, 3H); δ_{C} (100 MHz; CDCl₃): 156.1, 154.0, 128.2, 123.6, 122.4, 119.1, 118.1, 111.0, 110.7, 30.4, 26.1, 22.4, 20.2, 17.9, 13.8; IR (neat): 2957, 2932, 2862, 2247, 1626, 1456, 1424, 1379, 1325, 1279, 1256, 1211, 1171, 1103, 1065, 1030 cm⁻¹; m/z (EI) 227.1309 (M^+ : C₁₅H₁₇NO requires 227.1310). Compound **26a**: δ_{H} (400 MHz; CDCl₃): 7.66–7.62 (m, 1H), 7.49–7.46 (m, 1H), 7.47 (d, $J=16.5$ Hz, 1H), 7.36–7.31 (m, 2H), 5.90 (d, $J=16.5$ Hz, 1H), 2.87 (t, $J=7.5$ Hz, 2H), 1.75 (app. quintet, $J=7.5$ Hz, 2H), 1.41 (app. sextet, $J=7.5$ Hz, 2H), 0.96 (t, $J=7.5$ Hz, 3H); δ_{C} (100 MHz; CDCl₃): 163.1, 154.3, 141.0, 125.2, 124.8, 123.8, 119.9, 118.9, 112.3, 111.5, 94.3, 30.3, 26.6, 22.3, 13.7; IR (neat): 2959, 2932, 2872, 2216, 1626, 1564, 1478, 1454, 1389, 1209, 1182, 1103, 957 cm⁻¹; m/z (EI) 225.1162 (M^+ : C₁₅H₁₅NO requires 225.1154).

4.3.2. 3-(2-Phenylbenzofuran-3-yl)propionitrile (25b) and 3-(2-phenylbenzofuran-3-yl)acrylonitrile (26b). Subjecting phenol **16b** (43 mg, 0.22 mmol) with acrylonitrile (0.15 ml, 2.2 mmol) to general procedure B followed by chromatography (gradient from 5 to 25% Et₂O in hexane) gave **25b** (51 mg, 92%) as a white solid and **26b** (2 mg, 4%) as a white solid. Compound **25b**: Mp=59–60 °C; δ_{H} (400 MHz; CDCl₃): 7.75 (d, $J=7.3$ Hz, 2H), 7.58–7.41 (m, 5H), 7.34 (ddd, $J=8.2, 7.2, 1.4$ Hz, 1H), 7.29 (ddd, $J=7.6, 7.2, 1.4$ Hz, 1H), 3.33 (t, $J=7.8$ Hz, 2H), 2.75 (t, $J=7.8$ Hz, 2H); δ_{C} (100 MHz; CDCl₃): 153.9,

152.1, 130.3, 129.0, 128.9, 128.9, 127.1, 124.9, 122.9, 119.0, 118.9, 112.1, 111.4, 20.8, 17.3; ν_{max} cm⁻¹; 3061, 2930, 2247, 1456, 1443, 1260, 1215, 1177, 1119, 1065, 1007 cm⁻¹; m/z (EI) 247.0991 (M^+ : C₁₇H₁₃NO requires 247.0997). **26b**: mp=126–128 °C; δ_{H} (400 MHz; CDCl₃): 7.76–7.71 (m, 3H), 7.69 (d, $J=16.6$ Hz, 1H), 7.60–7.52 (m, 4H), 7.42 (ddd, $J=7.7, 7.3, 1.5$ Hz, 1H), 7.37 (ddd, $J=7.7, 7.3, 1.3$ Hz, 1H), 6.08 (d, $J=16.6$ Hz, 1H); δ_{C} (100 MHz; CDCl₃): 158.0, 154.5, 142.0, 130.3, 129.1, 129.1, 128.6, 125.9, 125.8, 124.2, 120.4, 118.7, 112.3, 111.9, 96.7; ν_{max} 3067, 2216, 1620, 1555, 1456, 1441, 1252, 1206, 1136, 1072, 961 cm⁻¹; m/z (EI) 245.0830 (M^+ : C₁₇H₁₁NO requires 245.0841).

4.3.3. 3-[2-(4-Methoxyphenyl)benzofuran-3-yl]propionitrile (25c) and 3-[2-(4-methoxyphenyl)benzofuran-3-yl]acrylonitrile (26c). Subjecting phenol **16c** (42 mg, 0.19 mmol) with acrylonitrile (0.13 ml, 1.9 mmol) to general procedure B followed by chromatography (gradient from 10 to 25% EtOAc in hexane) gave **25c** (48 mg, 91%) as a white solid and **26c** (3 mg, 5%) as a white solid. **25c**: mp=96–97 °C; δ_{H} (400 MHz; CDCl₃): 7.68 (d, $J=9.0$ Hz, 2H), 7.53 (dd, $J=7.5, 1.5$ Hz, 1H), 7.50 (dd, $J=7.6, 1.3$ Hz, 1H), 7.32 (ddd, $J=7.6, 7.2, 1.5$ Hz, 1H), 7.27 (ddd, $J=7.5, 7.2, 1.3$ Hz, 1H), 7.04 (d, $J=9.0$ Hz, 2H), 3.88 (s, 3H), 3.29 (t, $J=7.7$ Hz, 2H), 2.73 ($J=7.7$ Hz, 2H); δ_{C} (100 MHz; CDCl₃): 160.1, 153.8, 152.3, 129.2, 128.5, 124.4, 122.9, 122.8, 119.1, 118.6, 114.4, 111.2, 110.8, 55.4, 20.8, 17.3; ν_{max} 2957, 2934, 2837, 2247, 1611, 1508, 1454, 1298, 1252, 1177, 1098, 1032, 833 cm⁻¹; m/z (EI) 277.1105 (M^+ : C₁₈H₁₅NO₂ requires 277.1103). **35ca**: mp=122–124 °C; δ_{H} (400 MHz; CDCl₃): 7.72 (dd, $J=7.0, 1.6$ Hz, 1H), 7.67 (d, $J=8.9$ Hz, 2H), 7.66 (d, $J=16.6$ Hz, 1H), 7.55 (dd, $J=7.8, 1.4$ Hz, 1H), 7.39 (ddd, $J=7.8, 7.3, 1.6$ Hz, 1H), 7.36 (ddd, $J=7.3, 7.0, 1.4$ Hz, 1H), 7.07 (d, $J=8.9$ Hz, 2H), 6.04 (d, $J=16.6$ Hz, 1H), 3.91 (s, 3H); δ_{C} (100 MHz; CDCl₃): 161.3, 158.4, 154.3, 142.2, 130.2, 126.1, 125.4, 124.1, 121.5, 120.2, 119.0, 114.6, 111.7, 111.3, 95.8, 55.5; ν_{max} 2934, 2839, 2214, 1607, 1505, 1452, 1422, 1387, 1346, 1304, 1261, 1209, 1179, 1078, 1028 cm⁻¹; m/z (EI) 275.0942 (M^+ : C₁₈H₁₃NO₂ requires 275.0946).

4.4. 3-[2-(3-Fluorophenyl)benzofuran-3-yl]propionitrile (25d) and 3-[2-(3-fluorophenyl)benzofuran-3-yl]acrylonitrile (26d)

Subjecting phenol **16d** (48 mg, 0.22 mmol) with acrylonitrile (0.15 ml, 2.2 mmol) to general procedure B followed by chromatography (gradient from 10 to 17% EtOAc in hexane) gave **25d** (54 mg, 91%) as a white solid and **26d** (1 mg, 1%) as a yellow solid. **25d**: mp=80–81 °C; δ_{H} (400 MHz; CDCl₃): 7.57–7.49 (m, 3H), 7.49–7.42 (m, 2H), 7.35 (ddd, $J=8.2, 7.6, 1.4$ Hz, 1H), 7.29 (ddd, $J=7.6, 7.2, 1.0$ Hz, 1H), 7.10 (dddd, $J=8.4, 8.2, 2.5, 1.0$ Hz, 1H), 3.29 (t, $J=7.6$ Hz, 2H), 2.73 (t, $J=7.6$ Hz, 2H); δ_{C} (100 MHz; CDCl₃): 162.9 (d, $J=246.7$ Hz), 153.9, 150.6 (d, $J=2.7$ Hz), 132.3 (d, $J=8.4$ Hz), 130.5 (d, $J=8.4$ Hz), 128.8, 125.3, 123.0, 122.5 (d, $J=3.2$ Hz), 119.1, 118.8, 115.7 (d, $J=21.2$ Hz), 114.0 (d, $J=23.3$ Hz), 113.0, 111.5, 20.7, 17.3; ν_{max} 3073, 2924, 2249, 1614, 1582, 1489, 1456, 1424, 1223, 878 cm⁻¹; m/z (EI) 265.0910 (M^+ : C₁₇H₁₂FNO requires 265.0903). Compound **26d**: δ_{H} (400 MHz; CDCl₃): 7.75 (dd, $J=7.4, 1.1$ Hz, 1H), 7.67 (d, $J=16.6$ Hz, 1H), 7.59 (dd, $J=7.3, 1.2$ Hz, 1H), 7.54 (ddd, $J=8.0, 7.6, 5.5$ Hz, 1H), 7.51–7.42 (m, 3H), 7.39 (ddd, $J=7.6, 7.4, 1.2$ Hz, 1H), 7.23 (dddd, $J=8.4, 8.1, 2.6, 1.3$ Hz, 1H), 6.11 (d, $J=16.6$ Hz, 1H).

4.5. Ligand-free domino reaction with mono-substituted electron-withdrawn electrophiles (general procedure C)

A solution of [Rh(cod)OH]₂ (3 mol %), in dioxane (1.0 cm³) and water (0.1 cm³) was flushed with argon. The electrophile was added followed by a solution of the phenol/aniline in dioxane (1.0 cm³) and the reaction mixture was stirred at 90 °C for 6 h. Et₂O (5 cm³) was added to the reaction mixture and it was filtered (short silica pad) washing with Et₂O (4×5 cm³). The filtrate was concentrated under reduced pressure then purified by flash column chromatography to yield the product.

4.5.1. 1-(2-*n*-Butylbenzofuran-3-yl)pentan-3-one (28a). Subjecting phenol **16a** (45 mg, 0.26 mmol) with ethyl vinyl ketone (0.25 ml, 2.5 mmol) to general procedure C followed by chromatography (gradient from 5 to 10% Et₂O in hexane) gave the title compound (46 mg, 70%) as a colourless oil. δ_{H} (400 MHz; CDCl₃): 7.44–7.36 (m, 2H), 7.23–7.15 (m, 2H), 2.90 (t, *J*=7.6 Hz, 2H), 2.76–2.71 (m, 4H), 2.34 (q, *J*=7.3 Hz, 2H), 1.68 (app. quintet, *J*=7.5 Hz, 2H), 1.38 (app. sextet, *J*=7.5 Hz, 2H), 1.04 (t, *J*=7.5 Hz, 3H), 0.94 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 210.6, 155.0, 153.9, 129.2, 123.1, 122.0, 118.6, 112.9, 110.7, 42.0, 36.2, 30.5, 26.0, 22.4, 17.7, 13.8, 7.7; ν_{max} 2957, 2934, 2872, 1717, 1628, 1456, 1377, 1360, 1256, 1211, 1169, 1113, 1055, 1013 cm⁻¹; *m/z* (EI) 258.1623 (*M*⁺: C₁₇H₂₂O₂ requires 258.1620).

4.5.2. 1-(2-Phenylbenzofuran-3-yl)pentan-3-one (28b). Subjecting phenol **16b** (42 mg, 0.22 mmol) with ethyl vinyl ketone (0.21 ml, 2.1 mmol) to general procedure C followed by chromatography (gradient from 5 to 15% Et₂O in hexane) gave the title compound (56 mg, 94%) as a white solid. mp=52–53 °C; δ_{H} (400 MHz; CDCl₃): 7.78 (d, *J*=7.2 Hz, 2H), 7.55 (dd, *J*=7.9, 1.2 Hz, 1H), 7.52–7.46 (m, 3H), 7.40–7.35 (m, 1H), 7.31 (ddd, *J*=7.9, 7.2, 1.4 Hz, 1H), 7.25 (ddd, *J*=7.4, 7.2, 1.2 Hz, 1H), 3.23 (t, *J*=8.0 Hz, 2H), 2.84 (t, *J*=8.0 Hz, 2H), 2.43 (q, *J*=7.3 Hz, 2H), 1.06 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 210.4, 153.9, 150.8, 131.0, 130.0, 128.7, 128.2, 126.7, 124.4, 122.5, 119.3, 114.8, 111.1, 41.6, 36.1, 18.3, 7.7; ν_{max} 2976, 2937, 1713, 1456, 1443, 1358, 1260, 1213, 1113, 1069, 1026 cm⁻¹; *m/z* (EI) 278.1307 (*M*⁺: C₁₉H₁₈O₂ requires 278.1307).

4.5.3. 1-[2-(4-Methoxyphenyl)benzofuran-3-yl]pentan-3-one (28c). Subjecting phenol **16c** (43 mg, 0.19 mmol) with ethyl vinyl ketone (0.19 ml, 1.9 mmol) to general procedure C followed by chromatography (gradient from 5 to 15% Et₂O in hexane) gave compound the title compound (54 mg, 91%) as a white solid. mp=67–68 °C; δ_{H} (400 MHz; CDCl₃): 7.71 (d, *J*=8.9 Hz, 2H), 7.52 (dd, *J*=7.2, 1.5 Hz, 1H), 7.47 (dd, *J*=7.4, 1.3 Hz, 1H), 7.28 (ddd, *J*=7.4, 7.3, 1.5 Hz, 1H), 7.24 (ddd, *J*=7.3, 7.2, 1.3 Hz, 1H), 7.01 (d, *J*=8.9 Hz, 2H), 3.87 (s, 3H), 3.19 (t, *J*=7.9 Hz, 2H), 2.82 (t, *J*=7.9 Hz, 2H), 2.43 (q, *J*=7.4 Hz, 2H), 1.05 (t, *J*=7.4 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 210.5, 159.6, 153.7, 151.0, 130.1, 128.2, 124.0, 123.6, 122.4, 119.1, 114.2, 113.2, 110.9, 55.3, 41.6, 36.1, 18.3, 7.7; ν_{max} 2974, 2935, 2837, 1715, 1613, 1510, 1456, 1298, 1252, 1179, 1113, 1094, 1030, 833 cm⁻¹; *m/z* (EI) 308.1417 (*M*⁺: C₂₀H₂₀O₃ requires 308.1412).

4.5.4. 1-[2-(3-Fluorophenyl)benzofuran-3-yl]pentan-3-one (28d). Subjecting phenol **16d** (45 mg, 0.22 mmol) with ethyl vinyl ketone (0.21 ml, 2.1 mmol) to general procedure C followed by chromatography (gradient from 5 to 11% Et₂O in hexane) gave the title compound (54 mg, 86%) as a white solid. mp=72–73 °C; δ_{H} (400 MHz; CDCl₃): 7.58–7.54 (m, 2H), 7.51 (ddd, *J*=9.9, 2.5, 1.8 Hz, 1H), 7.49 (dd, *J*=8.0, 1.2 Hz, 1H), 7.44 (ddd, *J*=8.2, 7.8, 6.0 Hz, 1H), 7.33 (ddd, *J*=8.0, 7.4, 1.4 Hz, 1H), 7.26 (ddd, *J*=7.4, 7.0, 1.2 Hz, 1H), 7.07 (dddd, *J*=8.4, 8.2, 2.5, 1.0 Hz, 1H), 3.23 (t, *J*=7.8 Hz, 2H), 2.84 (t, *J*=7.8 Hz, 2H), 2.43 (q, *J*=7.3 Hz, 2H), 1.06 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 210.1, 162.9 (d, *J*=246.1 Hz), 153.8, 149.4 (d, *J*=2.6 Hz), 133.0 (d, *J*=8.5 Hz), 130.3 (d, *J*=8.5 Hz), 129.8, 124.9, 122.7, 122.2 (d, *J*=3.0 Hz), 119.6, 115.8, 115.1 (d, *J*=21.3 Hz), 113.6 (d, *J*=23.4 Hz), 111.2, 41.4, 36.1, 18.3, 7.7; ν_{max} 2976, 2938, 1715, 1614, 1582, 1491, 1456, 1360, 1229, 1223, 1184, 1115, 880 cm⁻¹; *m/z* (EI) 296.1213 (*M*⁺: C₁₉H₁₇FO₂ requires 296.1213).

4.5.5. 1-(2-(3-Bromophenyl)benzofuran-3-yl)pentan-3-one (28f). Subjecting phenol **16f** (43 mg, 0.16 mmol) with ethyl vinyl ketone (0.16 ml, 1.6 mmol) to general procedure C followed by chromatography (gradient from 5 to 11% Et₂O in hexane) gave the title compound (45 mg, 80%) as a white solid. mp=72–73 °C; δ_{H} (400 MHz; CDCl₃): 7.95 (dd, *J*=2.0, 1.6 Hz, 1H), 7.70 (ddd, *J*=7.8, 1.6,

1.0 Hz, 1H), 7.56 (dd, *J*=7.7, 1.4 Hz, 1H), 7.49 (ddd, *J*=8.0, 2.0, 1.0 Hz, 1H), 7.49 (dd, *J*=8.1, 1.0 Hz, 1H), 7.34 (dd, *J*=8.0, 7.8 Hz, 1H), 7.32 (ddd, *J*=8.1, 7.3, 1.4 Hz, 1H), 7.26 (ddd, *J*=7.7, 7.3, 1.0 Hz, 1H), 3.22 (t, *J*=7.8 Hz, 2H), 2.83 (t, *J*=7.8 Hz, 2H), 2.43 (q, *J*=7.3 Hz, 2H), 1.06 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 210.2, 153.9, 149.1, 133.0, 131.1, 130.3, 129.7, 129.6, 125.1, 125.0, 122.9, 122.7, 119.6, 116.0, 111.2, 41.5, 36.2, 18.3, 7.8; ν_{max} 2974, 2938, 1717, 1586, 1476, 1452, 1408, 1358, 1273, 1211, 1111, 1074, 1051 cm⁻¹; *m/z* (EI) 356.0407 (*M*⁺: C₁₉H₁₇BrO₂ requires 356.0412).

4.5.6. 1-(2-Vinylbenzofuran-3-yl)pentan-3-one (28l). Subjecting phenol **16g** (45 mg, 0.31 mmol) with ethyl vinyl ketone (0.31 ml, 3.1 mmol) to general procedure C followed by chromatography (gradient from 5 to 11% Et₂O in hexane) gave the title compound (53 mg, 75%) as a colourless oil. δ_{H} (400 MHz; CDCl₃): 7.47 (dd, *J*=7.6, 1.3 Hz, 1H), 7.41 (dd, *J*=8.2, 1.0 Hz, 1H), 7.26 (ddd, *J*=8.2, 7.2, 1.3 Hz, 1H), 7.19 (ddd, *J*=7.6, 7.2, 1.0 Hz, 1H), 6.75 (dd, *J*=17.3, 11.2 Hz, 1H), 5.92 (dd, *J*=17.3, 1.5 Hz, 1H), 5.37 (dd, *J*=11.2, 1.5 Hz, 1H), 2.99 (t, *J*=7.7 Hz, 2H), 2.74 (t, *J*=7.7 Hz, 2H), 2.37 (q, *J*=7.3 Hz, 2H), 1.02 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 210.2, 154.1, 150.4, 129.1, 124.8, 123.1, 122.4, 119.3, 116.4, 114.9, 111.0, 41.8, 36.2, 17.4, 7.7; ν_{max} 2974, 2938, 1715, 1614, 1456, 1414, 1360, 1258, 1115, 1013, 878 cm⁻¹; *m/z* (EI) 228.1151 (*M*⁺: C₁₅H₁₆O₂ requires 228.1150).

4.5.7. 3-(2-Phenylbenzofuran-3-yl)propionic acid ethyl ester (30b) and 3-(2-phenylbenzofuran-3-yl)acrylic acid ethyl ester (31b). Ethyl acrylate (0.04 ml, 0.41 mmol) was added to a solution of phenol **16b** (39 mg, 0.20 mmol) in DME (2.0 cm³) and water (0.2 cm³). The mixture was flushed with argon then [Rh(cod)OH]₂ (3 mol %) was added and the resulting mixture was stirred at 90 °C for 6 h. The reaction mixture was cooled, Et₂O (5 cm³) was added and it was filtered through a short silica pad, washing with Et₂O (4×5 cm³). The filtrate was concentrated under reduced pressure, then purified by column chromatography (gradient from 5 to 11% Et₂O in hexane) to give a mixture of **30b** and **31b** (51 mg, 85%, >20:1 **30b/31b** by ¹H NMR) as a colourless oil. Compound **30b**: δ_{H} (400 MHz; CDCl₃): 7.79 (d, *J*=7.2 Hz, 2H), 7.58 (dd, *J*=7.6, 1.3 Hz, 1H), 7.51–7.46 (m, 3H), 7.41–7.35 (m, 1H), 7.30 (ddd, *J*=7.8, 7.4, 1.3 Hz, 1H), 7.25 (ddd, *J*=7.6, 7.4, 1.2 Hz, 1H), 4.12 (q, *J*=7.2 Hz, 2H), 3.28 (t, *J*=8.2 Hz, 2H), 2.73 (t, *J*=8.2 Hz, 2H), 1.21 (t, *J*=7.2 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 172.7, 153.9, 151.1, 131.0, 129.9, 128.8, 128.3, 126.9, 124.5, 122.5, 119.4, 114.3, 111.1, 60.6, 34.1, 19.8, 14.1. Compound **31b**: δ_{H} (400 MHz; CDCl₃): 8.02 (d, *J*=16.0 Hz, 1H), 7.87 (dd, *J*=7.1, 1.7 Hz, 1H), 7.76 (dd, *J*=8.1, 1.3 Hz, 2H), 7.54–7.46 (m, 4H), 7.38–7.31 (m, 2H), 6.67 (d, *J*=16.0 Hz, 1H), 4.30 (q, *J*=7.1 Hz, 2H), 1.36 (t, *J*=7.1 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 167.2, 157.5, 154.4, 135.8, 129.7, 129.7, 128.9, 128.5, 126.7, 125.2, 123.7, 121.0, 119.2, 112.6, 111.5, 60.4, 14.3.

4.5.8. tert-Butyl 3-(2-phenylbenzofuran-3-yl)propanoate (33b) and (E)-tert-butyl 3-(2-phenylbenzofuran-3-yl)acrylate (34b). Subjecting phenol **16b** (40 mg, 0.20 mmol) with tert-butyl acrylate (0.06 ml, 0.41 mmol) to general procedure C followed by chromatography (gradient from 5 to 11% Et₂O in hexane) gave a mixture of **33b** and **34b** (51 mg, 77%, >20:1 **33b/34b** by ¹H NMR) as a colourless oil. Compound **33b**: δ_{H} (400 MHz; CDCl₃): 7.80 (dd, *J*=8.4, 1.3 Hz, 2H), 7.60 (dd, *J*=7.4, 1.6 Hz, 1H), 7.52–7.46 (m, 3H), 7.38 (tt, *J*=7.4, 1.3 Hz, 1H), 7.30 (ddd, *J*=7.9, 7.2, 1.6 Hz, 1H), 7.25 (ddd, *J*=7.4, 7.2, 1.1 Hz, 1H), 3.24 (t, *J*=8.2 Hz, 2H), 2.65 (t, *J*=8.2 Hz, 2H), 1.42 (s, 9H); δ_{C} (100 MHz; CDCl₃): 172.1, 153.1, 151.0, 131.0, 130.0, 128.7, 128.3, 126.9, 124.4, 122.5, 119.6, 114.5, 111.1, 80.6, 35.3, 28.1, 20.0; ν_{max} 2978, 1732, 1589, 1476, 1456, 1443, 1393, 1368, 1258, 1211, 1146, 1065, 1009 cm⁻¹; *m/z* (EI) 322.1568 (*M*⁺: C₂₁H₂₂O₃ requires 322.1569). Compound **34b**: δ_{H} (400 MHz; CDCl₃): 7.97 (d, *J*=16.0 Hz, 1H), 7.90 (dd, *J*=6.9, 1.7 Hz, 1H), 7.79

(dd, $J=7.0$, 1.5 Hz, 2H), 7.57–7.44 (m, 4H), 7.38 (ddd, $J=7.8$, 7.3, 1.7 Hz, 1H), 7.34 (d, $J=7.3$, 6.9, 1.4 Hz, 1H), 6.62 (d, $J=16.0$ Hz, 1H), 1.56 (s, 9H); δ_{C} (100 MHz; CDCl_3): 166.6, 157.3, 154.5, 134.8, 129.8, 129.6, 128.9, 128.5, 126.9, 125.2, 123.6, 121.1, 121.1, 112.7, 111.5, 80.5, 28.3.

4.5.9. 3-(2-*n*-Butyl-1-methanesulfonylindol-3-yl)propionitrile (35e) and 3-(2-*n*-butyl-1-methanesulfonylindol-3-yl)acrylonitrile (36e). Subjecting aniline **67** (50 mg, 0.20 mmol) with acrylonitrile (0.13 ml, 2.0 mmol) to general procedure B followed by chromatography (gradient from 9 to 25% EtOAc in hexane) gave **35e** (53 mg, 88%) as a white solid and **36e** (2 mg, 3%) as a white solid. Compound **35e**: mp=100–101 °C; δ_{H} (400 MHz; CDCl_3): 8.08–8.03 (m, 1H), 7.46–7.41 (m, 1H), 7.36–7.29 (m, 2H), 3.07 (t, $J=7.3$ Hz, 2H), 2.99 (t, $J=7.6$ Hz, 2H), 2.96 (s, 3H), 2.67 (t, $J=7.3$ Hz, 2H), 1.72–1.63 (m, 2H), 1.42 (app. sextet, $J=7.4$ Hz, 2H), 0.96 (t, $J=7.4$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 139.6, 136.4, 129.3, 124.7, 123.9, 118.8, 117.9, 116.7, 114.9, 40.0, 33.1, 26.0, 22.7, 20.4, 17.9, 13.8; ν_{max} 2959, 2932, 2872, 2247, 1607, 1454, 1362, 1329, 1242, 1171, 1082 cm^{-1} ; m/z (EI) 304.1251 (M^+ : $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$ requires 304.1245). **36e**: mp=116–118 °C; δ_{H} (400 MHz; CDCl_3): 8.11–8.06 (m, 1H), 7.74–7.69 (m, 1H), 7.54 (d, $J=16.7$ Hz, 1H), 7.427.37 (m, 2H), 5.98 (d, $J=16.7$ Hz, 1H), 3.12 (s, 3H), 3.08 (t, $J=7.4$ Hz, 2H), 1.72–1.64 (m, 2H), 1.50–1.41 (m, 2H), 0.97 (t, $J=7.4$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 145.1, 141.4, 136.2, 126.6, 125.4, 124.8, 119.6, 118.8, 115.2, 114.6, 96.4, 41.4, 33.3, 26.0, 22.7, 13.7; ν_{max} 2959, 2932, 2872, 2214, 1616, 1452, 1368, 1329, 1175, 1090 cm^{-1} ; m/z (ESI) 303.1165 (M^++H : $\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ requires 303.1161).

4.5.10. 1-(2-*n*-Butyl-1-methanesulfonylindol-3-yl)pentan-3-one (37e). Subjecting aniline **21e** (47 mg, 0.19 mmol) with ethyl vinyl ketone (0.19 ml, 1.9 mmol) to general procedure C followed by chromatography (gradient from 10 to 17% EtOAc in hexane) gave the title compound (60 mg, 94%) as a white solid. mp=58–59 °C; δ_{H} (400 MHz; CDCl_3): 8.04–7.99 (m, 1H), 7.47–7.43 (m, 1H), 7.32–7.27 (m, 2H), 2.98–2.93 (m, 4H), 2.92 (s, 3H), 2.71 (t, $J=7.7$ Hz, 2H), 2.42 (q, $J=7.3$ Hz, 2H), 1.63 (app. quintet, $J=7.5$ Hz, 2H), 1.41 (app. sextet, $J=7.5$ Hz, 2H), 1.06 (t, $J=7.3$ Hz, 3H), 0.94 (t, $J=7.5$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 210.3, 138.1, 136.3, 130.2, 124.2, 123.6, 119.4, 118.4, 114.6, 42.0, 39.8, 36.1, 33.0, 25.8, 22.7, 18.3, 13.8, 7.7; ν_{max} 2959, 2934, 2872, 1713, 1607, 1454, 1412, 1362, 1240, 1171, 1153, 1113, 1067, 964 cm^{-1} ; m/z (ESI) 336.1645 (M^++H : $\text{C}_{18}\text{H}_{26}\text{NO}_3\text{S}$ requires 336.1627).

4.5.11. 3-(2-*n*-Butyl-1-methanesulfonylindol-3-yl)propionic acid ethyl ester (38e) and 3-(2-*n*-butyl-1-methane sulfonylindol-3-yl) acrylic acid ethyl ester (39e). Subjecting aniline **21e** (48 mg, 0.19 mmol) and ethyl acrylate (0.042 cm^3 , 0.39 mmol) to general procedure C followed chromatography (gradient from 9 to 17% Et₂O in hexane) to give **38e** and **39e** (59.9 mg, 89%, >40:1 **37e/39e** by ¹H NMR). Compound **38e**: colourless oil. δ_{H} (400 MHz; CDCl_3): 8.04–7.99 (m, 1H), 7.52–7.47 (m, 1H), 7.32–7.27 (m, 2H), 4.13 (q, $J=7.2$ Hz, 2H), 3.01 (t, $J=8.0$ Hz, 2H), 2.95 (t, $J=7.8$ Hz, 2H), 2.92 (s, 3H), 2.60 (t, $J=8.0$ Hz, 2H), 1.67–1.61 (m, 2H), 1.41 (app. sextet, $J=7.4$ Hz, 2H), 1.24 (t, $J=7.2$ Hz, 3H), 0.95 (t, $J=7.4$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 172.7, 138.4, 136.4, 130.2, 124.3, 123.6, 119.1, 118.5, 114.6, 60.6, 39.8, 34.4, 33.0, 25.9, 22.7, 19.7, 14.2, 13.8; ν_{max} 2959, 2932, 2872, 1732, 1607, 1454, 1362, 1242, 1171, 1119, 1080, 1047, 1020 cm^{-1} ; m/z (ESI) 352.1586 (M^++H : $\text{C}_{18}\text{H}_{26}\text{NO}_4\text{S}$ requires 352.1577). **39e**: white solid. Mp=132–133 °C; δ_{H} (400 MHz; CDCl_3): 8.10–8.05 (m, 1H), 7.90–7.84 (m, 1H), 7.88 (d, $J=16.2$ Hz, 1H), 7.39–7.34 (m, 2H), 6.58 (d, $J=16.2$ Hz, 1H), 4.30 (q, $J=7.2$ Hz, 2H), 3.15 (t, $J=7.8$ Hz, 2H), 3.09 (s, 3H), 1.74–1.62 (m, 2H), 1.50–1.39 (m, 2H), 1.37 (t, $J=7.2$ Hz, 3H), 0.96 (t, $J=7.4$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 167.4, 144.8, 136.3, 135.3, 127.5, 125.0, 124.5, 120.2, 118.7, 115.9, 114.4, 60.5, 41.0, 33.2, 25.9, 22.6, 14.4, 13.7; ν_{max} 2959, 2932, 2874, 1705, 1628, 1452, 1366, 1306, 1277, 1169,

1088, 1034, 1011 cm^{-1} ; m/z (ESI) 372.1233 (M^++Na : $\text{C}_{18}\text{H}_{23}\text{NO}_4\text{SNa}$ requires 372.1240).

4.6. Typical domino reaction with 2-cyclohexene

A solution of $[\text{Rh}(\text{cod})\text{OH}]_2$ (4 mg, 3 mol%, 6 mol% Rh) and Tol-BINAP (12 mg, 6 mol%) in dioxane–water (1 cm^3 , 10:1) was stirred at room temperature for 0.5 h. A solution of phenol **16a** (50 mg, 0.29 mmol) and 2-cyclohexenone (0.14 cm^3 , 1.4 mmol) in dioxane (1 cm^3) was added and the mixture was heated to 90 °C for 6 h. The reaction was cooled to room temperature, diluted with Et₂O (5 cm^3) and filtered through a short pad of silica, washing with Et₂O (4 $\times$ 5 cm^3). The filtrate was concentrated under reduced pressure and purified by column chromatography (gradient from 0 to 3% Et₂O in pentane) to give **17a** (7 mg, 14%) followed by **42a** (1 mg, 2%), then **41a** (24 mg, 47%) and **40a** (3 mg, 9%) all as pale yellow oils.

4.6.1. 3-(2-Butylbenzofuran-3-yl)cyclohexanone (40a). The analytical data were in agreement with literature values.¹⁶ δ_{H} (400 MHz; CDCl_3): 7.62–7.59 (m, 1H), 7.44–7.40 (m, 1H), 7.26–7.17 (m, 2H), 3.14 (dddd, $J=12.9$, 12.9, 3.8, 3.8 Hz, 1H), 2.93 (t, $J=13.7$ Hz, 1H), 2.73 (t, $J=7.5$ Hz, 2H), 2.57–2.42 (m, 3H), 2.35–2.19 (m, 2H), 2.04–1.97 (m, 1H), 1.88–1.74 (m, 1H), 1.72–1.64 (m, 2H), 1.42–1.32 (m, 2H), 0.94 (t, $J=7.4$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 210.60, 154.14, 154.12, 127.63, 123.10, 121.94, 119.55, 116.12, 111.15, 47.40, 41.29, 36.44, 31.03, 30.65, 26.26, 25.85, 22.30, 13.78.

4.6.2. (E)-2-(2-*n*-Butyl-2-(2-*n*-butylbenzofuran-3-yl)vinyl)phenol (41a). δ_{H} (400 MHz; CDCl_3): 7.54–7.51 (m, 1H), 7.45–7.42 (m, 1H), 7.27–7.19 (m, 4H), 6.99–6.93 (m, 2H), 6.45 (s, 1H), 5.00 (s, 1H), 2.87 (dd, $J=7.5$, 7.8 Hz, 2H), 2.54 (dd, $J=7.8$, 7.2 Hz, 2H), 1.82–1.74 (m, 2H), 1.44 (ddt, $J=14.7$, 7.3, 7.4 Hz, 2H), 1.33–1.16 (m, 4H), 0.96 (t, $J=7.4$ Hz, 3H), 0.74 (t, $J=7.2$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 155.50, 153.79, 152.96, 139.39, 129.74, 128.78, 128.69, 124.02, 124.00, 123.37, 122.41, 120.33, 119.58, 117.56, 115.18, 110.83, 31.28, 30.63, 30.58, 26.83, 22.56, 22.49, 13.84, 13.72; m/z (EI) 348.2094 (M^+ : $\text{C}_{24}\text{H}_{28}\text{O}_2$ requires 348.2089).

4.6.3. (E)-2-(1-(2-*n*-Butyl-benzofuran-3-yl)hex-1-enyl)phenol (42a). δ_{H} (400 MHz; CDCl_3): 7.38 (d, $J=8.1$ Hz, 1H), 7.28–7.16 (m, 3H), 7.12 (td, $J=7.8$, 1.0 Hz, 1H), 7.04 (dd, $J=7.6$, 1.7 Hz, 1H), 6.97 (dd, $J=8.2$, 1.1 Hz, 1H), 6.88 (ddd, $J=7.5$, 7.5, 1.2 Hz, 1H), 6.18 (t, $J=7.5$ Hz, 1H), 5.28 (s, 1H), 2.58 (t, $J=7.6$ Hz, 2H), 2.22–2.16 (m, 2H), 1.62–1.24 (m, 8H), 0.91–0.83 (m, 6H).

4.6.4. (1,2,3,4-Tetrahydridibenzofuran-1-yl)acetic acid methyl ester (40m) and 6-benzofuran-2-ylhex-2-enoic acid methyl ester (17m). Subjecting phenol **16m** (42 mg, 0.17 mmol) to general procedure C (with DME in place of dioxane) followed by chromatography (gradient from 5 to 20% Et₂O in hexane) gave **40m** (30 mg, 70%) as a colourless oil, followed by **17m** (3 mg, 8%) as a colourless oil. **40m**: δ_{H} (400 MHz; CDCl_3): 7.45, (dd, $J=7.2$, 1.7 Hz, 1H), 7.40, (dd, $J=7.6$, 1.6 Hz, 1H), 7.21 (ddd, $J=7.6$, 7.4, 1.7 Hz, 1H), 7.18 (ddd, $J=7.4$, 7.2, 1.6 Hz, 1H), 3.72 (s, 3H), 3.50–3.42 (m, 1H), 2.94 (dd, $J=15.4$, 4.3 Hz, 1H), 2.78–2.68 (m, 2H), 2.42 (dd, $J=15.4$, 10.1 Hz, 1H), 2.02–1.85 (m, 3H), 1.76–1.67 (m, 1H); δ_{C} (100 MHz; CDCl_3): 173.1, 154.4, 154.4, 127.6, 123.1, 122.2, 118.8, 114.9, 111.0, 51.6, 38.9, 29.0, 28.3, 23.4, 19.5; ν_{max} 2945, 1738, 1634, 1476, 1454, 1435, 1360, 1269, 1192, 1167, 1071, 1013 cm^{-1} ; m/z (ESI) 267.1004 (M^++Na): $\text{C}_{15}\text{H}_{16}\text{O}_3\text{Na}$ requires 267.0991. Compound **17m**: δ_{H} (400 MHz; CDCl_3): 7.48 (dd, 7.5, 1.6 Hz, 1H), 7.41 (dd, 7.8, 1.2 Hz, 1H), 7.21 (ddd, $J=7.8$, 7.2, 1.6 Hz, 1H), 7.18 (ddd, $J=7.5$, 7.2, 1.2 Hz, 1H), 6.98 (dt, $J=15.6$, 7.0 Hz, 1H), 6.39 (s, 1H), 5.86 (dt, $J=15.6$, 1.5 Hz, 1H), 3.73 (s, 3H), 2.80 (t, $J=7.2$ Hz, 2H), 2.31 (ddt, $J=7.6$, 7.0, 1.5 Hz, 2H), 1.93 (tt, $J=7.6$, 7.2 Hz, 2H); δ_{C} (100 MHz; CDCl_3): 167.0, 158.3, 154.7, 148.4, 128.8, 123.2, 122.5, 121.6, 120.2, 110.7, 102.4, 51.4, 31.4, 27.7, 26.0; ν_{max} 2949, 1728, 1659,

1603, 1587, 1456, 1435, 1275, 1198, 1175, 1148, 1084, 1042 cm^{-1} ; m/z (EI) 244.1096 (M^+ : $\text{C}_{15}\text{H}_{16}\text{O}_3$ requires 244.1099).

4.7. Domino reaction with pyridyl alkynes: general procedure D

A solution of $[\text{Rh}(\text{cod})\text{OH}]_2$ (3 or 6 mol%) and tris(2,5-dimethylphenyl)phosphine (1.0 equiv per atom of Rh) in a mixture of dioxane and water (0.24 M) was stirred at ambient temperature for 30 min. The catalyst solution was added to the phenol/indole and alkyne. Lithium bromide (5.0 equiv) was added, the reaction vessel was flushed with argon and the mixture was stirred at 90 °C for 24 h. The reaction mixture was cooled to ambient temperature and filtered through a short silica pad, washing with ethyl acetate (5 $\times$). The filtrate was concentrated under vacuum and purified by flash column chromatography.

4.7.1. (E)-2-(2-(2-*n*-Butylbenzofuran-3-yl)hex-1-enyl)pyridine (46a). Subjecting phenol **16a** (50 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (6 mol% $[\text{Rh}(\text{cod})\text{OH}]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (85 mg, 83%) as a yellow oil. δ_{H} (400 MHz; CDCl_3): 8.66 (ddd, $J=4.8, 1.8, 0.8$ Hz, 1H), 7.67 (ddd, $J=7.8, 7.7, 1.8$ Hz, 1H), 7.57–7.54 (m, 1H), 7.45–7.42 (m, 1H), 7.28 (br d, $J=7.8$ Hz, 1H), 7.26–7.18 (m, 2H), 7.14 (ddd, $J=7.7, 4.8, 1.1$ Hz, 1H), 6.56 (s, 1H), 3.05 (t, $J=7.3$ Hz, 2H), 2.87 (t, $J=7.5$ Hz, 2H), 1.82–1.73 (m, 2H), 1.48–1.36 (m, 4H), 1.36–1.26 (m, 2H), 0.95 (t, $J=7.4$ Hz, 3H), 0.82 (t, $J=7.2$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 156.77, 155.31, 153.84, 149.31, 139.89, 135.96, 129.42, 128.99, 124.15, 123.23, 122.31, 121.07, 119.83, 118.84, 110.73, 31.29, 30.68, 30.59, 26.81, 22.72, 22.57, 13.88, 13.84; ν_{max} 2957, 2929, 2871, 2860, 1632, 1584, 1559, 1471, 1455, 1427, 1379, 1255, 1175, 1013 cm^{-1} ; m/z (EI) 333.2099 (M^+ : $\text{C}_{23}\text{H}_{27}\text{NO}$ requires 333.2093).

4.7.2. (E)-2-(2-(2-Phenylbenzofuran-3-yl)hex-1-enyl)pyridine (46b). Subjecting phenol **16b** (56 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (6 mol% $[\text{Rh}(\text{cod})\text{OH}]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (85 mg, 83%) as colourless plates. $\text{Mp}=64\text{--}66$ °C, δ_{H} (400 MHz; CDCl_3): 8.69 (dd, $J=4.8, 0.8$ Hz, 1H), 7.94 (d, $J=7.6$ Hz, 2H), 7.68 (td, $J=7.6, 2.0$ Hz, 1H), 7.63 (dd, $J=7.6, 0.4$ Hz, 1H), 7.53 (d, $J=8.0$ Hz, 1H), 7.42 (t, $J=7.6$ Hz, 2H), 7.35–7.30 (m, 2H), 7.29–7.23 (m, 2H), 7.16 (ddd, $J=7.6, 4.8, 0.8$ Hz, 1H), 6.75 (s, 1H), 3.03 (dd, $J=9.6, 6.4$ Hz, 2H), 1.48–1.37 (m, 2H), 1.25 (app. sextet, $J=7.6$ Hz, 2H), 0.75 (t, $J=7.6$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 156.7, 153.9, 150.1, 149.4, 139.9, 136.1, 131.0, 130.6, 130.5, 128.5, 128.3, 126.9, 124.5, 124.3, 122.8, 121.3, 120.3, 119.9, 111.0, 31.8, 30.9, 22.9, 13.8; ν_{max} 3006, 3005, 2956, 2928, 2870, 2858, 1635, 1584, 1559, 1472, 1454, 1443, 1427, 1257, 1092, 1064 cm^{-1} ; m/z (EI) 353.1775 (M^+ : $\text{C}_{25}\text{H}_{23}\text{NO}$ requires 353.1780).

4.7.3. (E)-2-(2-(2-(4-Methoxyphenyl)benzofuran-3-yl)hex-1-enyl)pyridine (46c). Subjecting phenol **16c** (65 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (6 mol% $[\text{Rh}(\text{cod})\text{OH}]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (94 mg, 85%) as a yellow oil. δ_{H} (400 MHz; CDCl_3): 8.69 (d, $J=4.4$ Hz, 1H), 7.87 (d, $J=8.8$ Hz, 2H), 7.68 (td, $J=7.7, 1.7$ Hz, 1H), 7.60 (d, $J=7.7$ Hz, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.31–7.21 (m, 3H), 7.15 (dd, $J=7.7, 4.8$ Hz, 1H), 6.95 (d, $J=8.8$ Hz, 2H), 6.74 (s, 1H), 3.84 (s, 3H), 3.04–2.98 (m, 2H), 1.48–1.38 (m, 2H), 1.24 (app. sextet, $J=7.3$ Hz, 2H), 0.75 (t, $J=7.3$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 159.8, 156.8, 153.7, 150.3, 149.9, 140.1, 136.0, 130.7, 130.5, 128.4, 124.3, 124.1, 123.7, 122.7, 121.2, 120.0, 118.3, 114.0, 110.9, 55.3, 31.8, 30.9, 22.9, 13.8; ν_{max} 3057, 3003, 2956, 2931, 2870, 2837, 1612, 1583, 1559, 1505, 1454, 1427, 1303, 1249,

1178, 1092, 1031 cm^{-1} ; m/z (EI) 383.1892 (M^+ : $\text{C}_{26}\text{H}_{25}\text{NO}_2$ requires 383.1885).

4.7.4. (E)-2-(2-(2-(3-Fluorophenyl)benzofuran-3-yl)hex-1-enyl)pyridine (46d). Subjecting phenol **16d** (61 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (6 mol% $[\text{Rh}(\text{cod})\text{OH}]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (81 mg, 76%) as a pale yellow solid. $\text{mp}=73\text{--}75$ °C, δ_{H} (400 MHz; CDCl_3): 8.70 (d, $J=4.6$ Hz, 1H), 7.74 (d, $J=7.9$ Hz, 1H), 7.72–7.64 (m, 2H), 7.63 (d, $J=7.8$ Hz, 1H), 7.53 (d, $J=8.2$ Hz, 1H), 7.40–7.31 (m, 2H), 7.30–7.24 (m, 2H), 7.17 (dd, $J=7.4, 4.5$ Hz, 1H), 7.02 (td, $J=8.3, 2.5$ Hz, 1H), 6.73 (s, 1H), 3.06–3.00 (m, 2H), 1.49–1.39 (m, 2H), 1.26 (app. sextet, $J=7.4$ Hz, 2H), 0.76 (t, $J=7.2$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 162.9 (d, $J=251.3$ Hz), 156.4, 153.9, 149.5, 148.6, 139.4, 136.1, 132.9 (d, $J=8.5$ Hz), 130.9, 130.4, 130.1 (d, $J=8.4$ Hz), 125.0, 124.3, 123.0, 122.45 (d, $J=3.1$ Hz), 121.4, 121.0, 120.5, 115.1 (d, $J=21.4$ Hz), 113.5 (d, $J=23.7$ Hz), 111.1, 32.0, 30.8, 22.9, 13.8; ν_{max} 2957, 2926, 2855, 1613, 1585, 1454, 1428, 1222, 1180, 1157, 1095 cm^{-1} ; m/z (EI) 371.1691 (M^+ : $\text{C}_{25}\text{H}_{22}\text{FNO}$ requires 371.1685).

4.7.5. (E)-2-(2-(2-(2-Bromophenyl)benzofuran-3-yl)hex-1-enyl)pyridine (46e). Subjecting phenol **16e** (79 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (3 mol% $[\text{Rh}(\text{cod})\text{OH}]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave **17e** (40 mg, 51%) followed by the title compound **46e** (46 mg, 37%) as a white solid. **46e**: $\text{mp}=48\text{--}50$ °C, δ_{H} (400 MHz; CDCl_3): 8.64 (d, $J=4.6$ Hz, 1H), 7.81 (dd, $J=7.7, 1.3$ Hz, 1H), 7.71 (dd, $J=7.9, 1.3$ Hz, 1H), 7.64 (td, $J=7.7, 2.0$ Hz, 1H), 7.58–7.52 (m, 2H), 7.37 (tt, $J=7.9, 1.4$ Hz, 2H), 7.34–7.27 (m, 2H), 7.22 (d, $J=7.9$ Hz, 1H), 7.11 (ddd, $J=7.5, 4.9, 1.0$ Hz, 1H), 6.81 (s, 1H), 2.77–2.71 (m, 2H), 1.42–1.33 (m, 2H), 1.21–1.12 (m, 2H), 0.73 (t, $J=7.2$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 156.7, 154.5, 150.5, 149.3, 138.9, 135.9, 133.2, 132.8, 132.6, 130.8, 130.1, 128.7, 127.1, 124.7, 124.3, 124.2, 122.9, 121.3, 121.1, 120.8, 111.4, 30.8, 30.6, 22.7, 13.7; ν_{max} 3056, 3004, 2956, 2928, 2870, 1738, 1629, 1585, 1472, 1448, 1428, 1246, 1200, 1093, 1027 cm^{-1} ; m/z (EI) 431.0892 (M^+ : $\text{C}_{25}\text{H}_{22}\text{BrNO}$ requires 431.0885).

4.7.6. (E)-2-(2-(2-(3-Bromophenyl)benzofuran-3-yl)hex-1-enyl)pyridine (46f). Subjecting phenol **16f** (20 mg, 0.07 mmol) with 2-(1-hexynyl)-pyridine (12 mg, 0.07 mmol) to general procedure D (3 mol% $[\text{Rh}(\text{cod})\text{OH}]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (21 mg, 55%) as a yellow oil. δ_{H} (400 MHz; CDCl_3): 8.70 (d, $J=4.4$ Hz, 1H), 8.13 (br s, 1H), 7.87 (d, $J=7.9$ Hz, 1H), 7.69 (dt, $J=7.6, 1.6$ Hz, 1H), 7.63 (d, $J=7.7$ Hz, 1H), 7.53 (d, $J=8.1$ Hz, 1H), 7.45 (d, $J=7.7$ Hz, 1H), 7.34 (t, $J=7.3$ Hz, 1H), 7.30–7.24 (m, 3H), 7.17 (dd, $J=7.1, 5.1$ Hz, 1H), 6.74 (s, 1H), 3.05–2.97 (m, 2H), 1.49–1.37 (m, 2H), 1.31–1.21 (m, 2H), 0.76 (t, $J=7.3$ Hz, 3H); m/z (EI) 431.0896 (M^+ : $\text{C}_{25}\text{H}_{22}\text{BrNO}$ requires 431.0885).

4.7.7. (E)-2-(3-(1-(Pyridin-2-yl)hex-1-en-2-yl)benzofuran-2-yl)ethyl benzoate (46g). Subjecting phenol **16g** (77 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (3 mol% $[\text{Rh}(\text{cod})\text{OH}]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (107 mg, 87%) as a yellow oil. δ_{H} (400 MHz; CDCl_3): 8.65 (d, $J=5.5$ Hz, 1H), 8.01 (d, $J=8.3$ Hz, 2H), 7.64 (t, $J=7.6$ Hz, 1H), 7.57 (d, $J=7.6$ Hz, 1H), 7.52 (t, $J=7.1$ Hz, 1H), 7.45 (d, $J=8.3$ Hz, 1H), 7.38 (t, $J=8.3$ Hz, 2H), 7.30–7.16 (m, 3H), 7.13 (dd, $J=7.3, 5.1$ Hz, 1H), 6.58 (s, 1H), 4.73 (t, $J=6.8$ Hz, 2H), 3.36 (t, $J=5.5$ Hz, 2H), 3.10–3.03 (m, 2H), 1.45–1.34 (m, 2H), 1.33–1.21 (m, 2H), 0.78 (t, $J=7.8$ Hz, 3H); δ_{C} (100 MHz; CDCl_3): 166.4, 156.5, 154.1, 150.5, 149.3, 139.3, 136.0, 132.9, 130.1, 129.8, 129.7, 128.6, 128.3, 124.3, 123.9, 122.6, 121.2, 121.0, 120.1, 111.0, 62.7, 31.3, 30.7, 27.0, 22.7, 13.8; ν_{max} 3425, 3062, 3005, 2956, 2930, 2871, 1725, 1715, 1634, 1603, 1583, 1559, 1472, 1454, 1428, 1385,

1267, 1176, 1111, 1071, 1027 cm⁻¹; *m/z* (ESI) 426.2056 (M⁺+H: C₂₈H₂₈NO₃ requires 426.2063).

4.7.8. (*E*)-2-(2-(5-Chloro-2-phenylbenzofuran-3-yl)hex-1-en-1-yl)pyridine (**46i**). Subjecting phenol **16i** (66 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (6 mol % [Rh(cod)OH]₂) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (84 mg, 75%) as a white solid. mp 110–112 °C. δ_{H} (400 MHz; CDCl₃): 8.70 (d, *J*=4.5 Hz, 1H), 7.92 (d, *J*=7.9 Hz, 2H), 7.69 (td, *J*=7.5, 1.3 Hz, 1H), 7.57 (d, *J*=1.6 Hz, 1H), 7.46–7.40 (m, 3H), 7.35 (t, *J*=7.2 Hz, 1H), 7.30–7.25 (m, 2H), 7.17 (dd, *J*=7.5, 4.9 Hz, 1H), 6.72 (s, 1H), 3.03–2.97 (m, 2H), 1.47–1.37 (m, 2H), 1.30–1.19 (m, 2H), 0.76 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 156.4, 152.2, 151.5, 149.4, 139.2, 136.1, 132.0, 130.9, 130.4, 128.7, 128.6, 128.5, 126.9, 124.7, 124.4, 121.4, 119.8, 119.4, 112.1, 31.8, 30.9, 22.9, 13.8; ν_{max} 2956, 2926, 2855, 1727, 1631, 1583, 1462, 1452, 1440, 1260, 1204, 1093, 1068, 1027 cm⁻¹; *m/z* (EI) 387.1391 (M⁺: C₂₅H₂₂NOCl requires 387.1390).

4.7.9. (*E*)-Methyl 2-phenyl-3-(1-(pyridin-2-yl)hex-1-en-2-yl)benzofuran-5-carboxylate (**46j**). Subjecting phenol **16j** (73 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (3 mol % [Rh(cod)OH]₂) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (84 mg, 71%) as a pale yellow solid. mp=100–101 °C. δ_{H} (400 MHz; CDCl₃): 8.79 (d, *J*=4.8 Hz, 1H), 8.32 (s, 1H), 8.05 (dd, *J*=8.5, 1.0 Hz, 1H), 7.95 (d, *J*=7.8 Hz, 2H), 7.70 (td, *J*=7.5, 1.4 Hz, 1H), 7.55 (d, *J*=8.5 Hz, 1H), 7.43 (t, *J*=7.6 Hz, 2H), 7.35 (t, *J*=7.4 Hz, 1H), 7.29 (d, *J*=7.8 Hz, 1H), 7.18 (dd, *J*=7.2, 5.0, 1H), 6.74 (s, 1H), 3.93 (s, 3H), 3.05 (dd, *J*=9.5, 6.0 Hz, 2H), 1.49–1.40 (m, 2H), 1.32–1.21 (m, 2H), 0.76 (t, *J*=7.6 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 167.3, 156.5, 156.4, 151.4, 149.4, 139.2, 136.1, 130.9, 130.6, 130.4, 128.7, 128.6, 126.9, 126.4, 125.3, 124.5, 122.6, 121.4, 120.2, 111.0, 52.1, 31.9, 30.9, 22.9, 13.8; ν_{max} 3059, 2955, 2929, 2871, 1724, 1584, 1469, 1443, 1435, 1283, 1266, 1238, 1207, 1100, 1058 cm⁻¹; *m/z* (EI) 411.1840 (M⁺: C₂₇H₂₅NO₃ requires 411.1834).

4.7.10. (*E*)-2-(2-(5-*tert*-Butyl-2-phenylbenzofuran-3-yl)hex-1-en-1-yl)pyridine (**46k**). Subjecting phenol **16k** (72 mg, 0.29 mmol) with 2-(1-hexynyl)-pyridine (46 mg, 0.29 mmol) to general procedure D (3 mol % [Rh(cod)OH]₂) followed by chromatography (gradient from 0 to 10% EtOAc in hexane) gave the title compound (49 mg, 41%) as a yellow oil. δ_{H} (0 MHz): 8.70 (dd, *J*=4.8, 0.9 Hz, 1H), 7.96–7.92 (m, 2H), 7.67 (td, *J*=7.7, 1.9 Hz, 1H), 7.58 (d, *J*=1.6 Hz, 1H), 7.44 (d, *J*=9.6 Hz, 2H), 7.40–7.37 (m, 3H), 7.33–7.23 (m, 1H), 7.15 (ddd, *J*=7.5, 4.9, 1.0 Hz, 1H), 6.73 (s, 1H), 3.08 (dd, *J*=8.0, 7.8 Hz, 2H), 1.55–1.21 (m, 4H), 1.38 (s, 9H), 0.78 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 156.73, 152.09, 150.22, 149.35, 145.88, 140.18, 136.05, 131.12, 130.44, 130.06, 128.45, 128.06, 126.74, 124.33, 122.47, 121.19, 120.15, 116.31, 110.29, 34.79, 31.88, 31.39, 30.80, 22.90, 13.79; ν_{max} 2957, 2930, 2870, 1584, 1473, 1427, 1266, 1062 cm⁻¹; *m/z* (EI) 409.2403 (M⁺: C₂₉H₃₁NO requires 409.2406).

4.7.11. (*E*)-2-(2-(2-*n*-Butylbenzofuran-3-yl)hex-1-en-1-yl)-3-chloro-5-(trifluoromethyl)pyridine (**59a**). Subjecting phenol **16a** (50 mg, 0.29 mmol) with alkyne **58** (50 mg, 0.19 mmol) to general procedure D (9 mol % [Rh(cod)OH]₂) followed by chromatography (pentane) gave the title compound (57 mg, 68%) as a pale orange oil. δ_{H} (400 MHz; CDCl₃): 8.81 (d, *J*=1.0 Hz, 1H), 7.93 (dd, *J*=2.1, 0.6 Hz, 1H), 7.61–7.57 (m, 1H), 7.46–7.43 (m, 1H), 7.28–7.20 (m, 2H), 6.85 (s, 1H), 3.09 (dd, *J*=7.8, 7.5 Hz, 2H), 2.90 (dd, *J*=7.8, 7.5 Hz, 2H), 1.83–1.74 (m, 2H), 1.49–1.22 (m, 6H), 0.95 (t, *J*=7.4 Hz, 3H), 0.80 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 157.23 (q, *J*=1.4 Hz, 1H), 155.95, 153.86, 145.85, 143.57 (q, *J*=4.0 Hz), 133.94 (q, *J*=3.7 Hz), 130.95, 128.56, 124.69 (q, *J*=33.5 Hz), 123.65, 123.51, 122.89 (q, *J*=272.6 Hz),

122.56, 119.83, 118.78, 110.88, 31.38, 30.74, 30.57, 26.94, 22.65, 22.61, 13.89, 13.80; ν_{max} 2959, 2932, 2873, 2863, 1594, 1455, 1320, 1165, 1137, 1090, 1054 cm⁻¹; *m/z* (EI) 435.1577 (M⁺: C₂₄H₂₅ClF₃NO requires 435.1577).

4.7.12. (*E*)-4-(2-butylbenzofuran-3-yl)-5-(pyridin-2-yl)pent-4-en-1-ol (**61a**). Subjecting phenol **16a** (50 mg, 0.29 mmol) with **60** (46 mg, 0.29 mmol) to general procedure D (6 mol % [Rh(cod)OH]₂) followed by chromatography (gradient from 30 to 50% EtOAc in pentane) gave the title compound (70 mg, 73%) as a yellow oil. δ_{H} (400 MHz; CDCl₃): 8.59 (d, *J*=4.5 Hz, 1H), 7.72 (td, *J*=7.7, 1.9, 1H), 7.54 (d, *J*=7.3 Hz, 1H), 7.44 (d, *J*=8.0 Hz, 1H), 7.27–7.24 (m, 1H), 7.23–7.17 (m, 3H), 6.63 (s, 1H), 6.61 (br s, 1H), 3.65 (br d, *J*=4.6 Hz, 2H), 3.28–3.22 (m, 2H), 2.84 (t, *J*=8.4 Hz, 2H), 1.79–1.70 (m, 2H), 1.69–1.62 (m, 2H), 1.46–1.36 (m, 2H), 0.94 (t, *J*=7.3 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 156.0, 155.6, 154.0, 148.3, 139.4, 137.2, 129.6, 128.4, 125.5, 123.5, 122.5, 121.8, 119.8, 117.8, 110.9, 59.4, 30.6, 29.8, 27.0, 26.5, 22.6, 13.9; ν_{max} 3287, 3057, 2930, 2860, 1725, 1634, 1588, 1560, 1473, 1454, 1428, 1377, 1255, 1234, 1176, 1155, 1077, 1014 cm⁻¹; *m/z* (EI) 335.1894 (M⁺: C₂₂H₂₅NO₂ requires 335.1885).

4.7.13. (*E*)-3-(2-Butylbenzofuran-3-yl)-4-(pyridin-2-yl)but-3-en-1-ol (**63a**). Subjecting phenol **16a** (50 mg, 0.29 mmol) with **62** (28 mg, 0.19 mmol) to general procedure D (9 mol % [Rh(cod)OH]₂) followed by chromatography (30% EtOAc in pentane) gave the title compound (36 mg, 57%) as a yellow oil. δ_{H} (400 MHz; CDCl₃): 8.57 (d, *J*=4.7 Hz, 1H), 7.73 (td, *J*=7.7, 1.6 Hz, 1H), 7.48 (d, *J*=7.4 Hz, 1H), 7.27–7.21 (m, 3H), 7.19 (t, *J*=7.1 Hz, 1H), 6.88 (br s, 1H), 6.73 (s, 1H), 3.81–3.76 (m, 2H), 3.15–3.09 (m, 2H), 2.88 (t, *J*=8.1 Hz, 2H), 1.81–1.71 (m, 2H), 1.47–1.36 (m, 2H), 0.93 (t, *J*=7.4 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 156.5, 154.7, 153.9, 147.9, 138.2, 137.2, 130.7, 128.6, 124.7, 123.5, 122.5, 122.2, 119.5, 118.1, 110.9, 61.0, 34.3, 30.7, 26.5, 22.5, 13.9; ν_{max} 3233, 3057, 2956, 2929, 2859, 2684, 1725, 1635, 1588, 1560, 1473, 1454, 1428, 1378, 1281, 1237, 1175, 1151, 1044, 1005 cm⁻¹; *m/z* (EI) 321.1724 (M⁺: C₂₁H₂₃NO₂ requires 321.1729).

4.7.14. (*E*)-2-(2-(2-Butylbenzofuran-3-yl)-2-phenylvinyl)pyridine (**66a**). Subjecting phenol **16a** (50 mg, 0.29 mmol) with **65** (52 mg, 0.29 mmol) to general procedure D (3 mol % [Rh(cod)OH]₂) followed by chromatography (gradient from 0 to 20% EtOAc in pentane) gave the title compound (31 mg, 30%) as a yellow oil. δ_{H} (400 MHz; CDCl₃): 8.56 (ddd, *J*=4.9, 1.7, 0.9 Hz, 1H), 7.41 (dt, *J*=8.3, 0.7, 1H), 7.35 (dd, *J*=7.7, 1.9 Hz, 1H), 7.31 (dd, *J*=5.0, 1.5 Hz, 1H), 7.30–7.25 (m, 4H), 7.19 (ddd, *J*=8.5, 7.0, 1.5 Hz, 1H), 7.11 (ddd, *J*=7.8, 1.5, 0.7 Hz, 1H), 7.08–7.05 (m, 1H), 7.04–7.00 (m, 1H), 6.98 (s, 1H), 6.89 (d, *J*=8.1, 1H), 2.65–2.59 (m, 2H), 1.69–1.60 (m, 2H), 1.34–1.23 (m, 2H), 0.85 (t, *J*=7.6 Hz, 3H); δ_{C} (100 MHz; CDCl₃): 157.6, 156.6, 153.9, 149.5, 139.5, 137.6, 135.2, 130.1, 129.9, 128.6, 128.5, 128.0, 124.2, 123.4, 122.4, 121.2, 120.4, 118.4, 110.7, 30.3, 27.0, 22.4, 13.8; ν_{max} 3055, 2957, 2928, 2871, 2859, 1612, 1597, 1583, 1563, 1493, 1455, 1431, 1256, 1174, 1069 cm⁻¹; *m/z* (EI) 353.1779 (M⁺: C₂₅H₂₃NO requires 353.1780).

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.05.106. These data include MOL files and InChIKeys of the most important compounds described in this article.

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