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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 In the case of mono-substituted electron-withdrawn electrophiles, excellent yield and selectivity for conjugate addition versus Heck–Mizoroki reaction can be achieved.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.

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

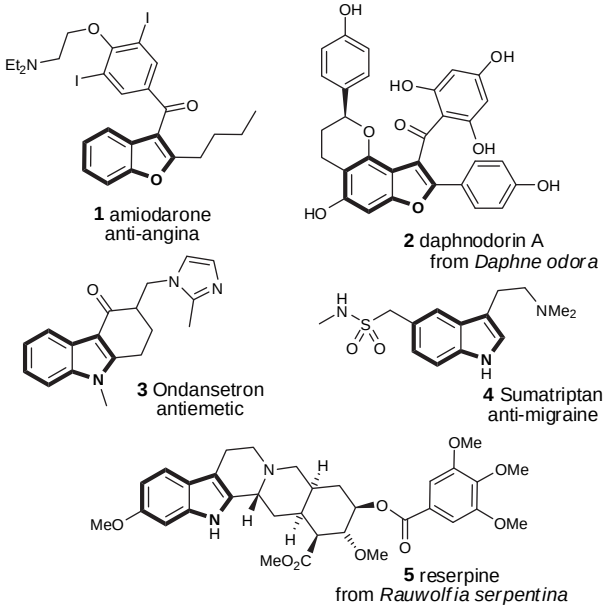

Figure 1. Benzofurans and indoles as motifs in natural products and drugs.

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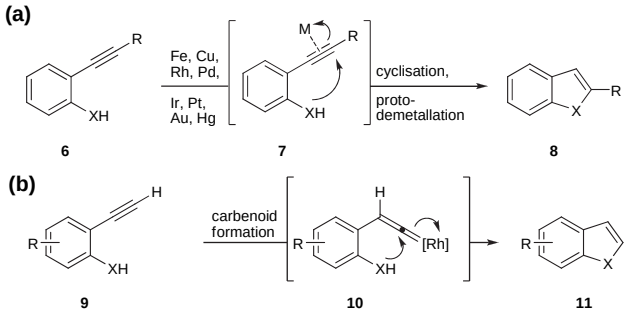
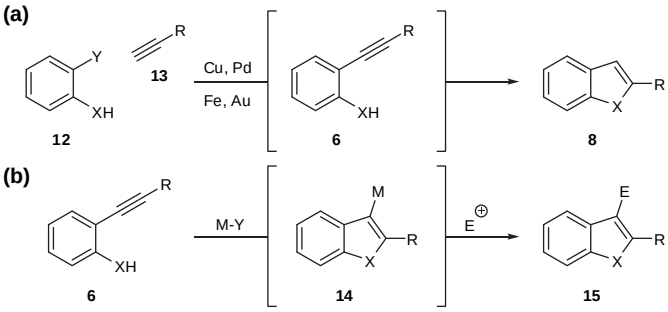


Scheme 1. Cycloisomerisation of *o*-alkynyl phenols and anilines.

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 protodemetallation 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] palladium[12] gold[13] and iron[14] to create a double domino reaction, forming benzofurans and indoles in a single operation from halophenols 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.

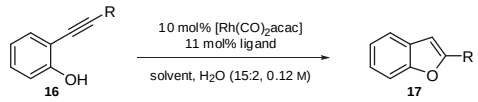
2. Results and discussion

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

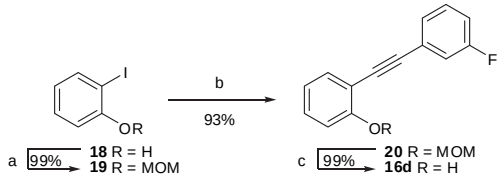
Table 1
Optimisation of the cycloisomerisation of *o*-alkynyl phenols to benzofurans



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.

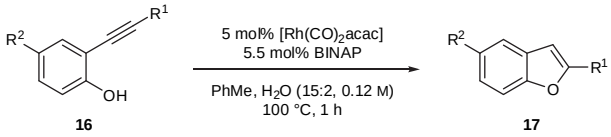
be used in place of toluene to give similar yields. Further experiments were undertaken to explore the generality of this process. A range of *o*-alkynyl phenols was readily prepared by Sonogashira reaction[20] between MOM protected *o*-iodophenol **19**[21] and the appropriate alkyne followed by acid-mediated deprotection (e.g., Scheme 3).



Scheme 3. Representative synthesis of *o*-alkynylphenol substrates. Reagents and conditions: (a) MOMCl, ^{i}Pr$_2$NEt, CH_2Cl_2, rt, 99%; (b) 2 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, NEt_3, 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



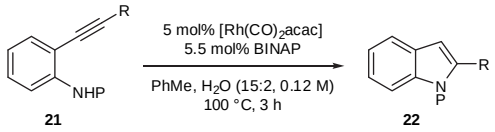
Entry	Phenol	R^1	R^2	Product	Yield[a] (%)
1	**16c**	4-MeO–C_6H_4	H	**17c**	92
2	**16d**	3-F–C_6H_4	H	**17d**	90
3	**16e**	2-Br–C_6H_4	H	**17e**	8
4	**16f**	3-Br–C_6H_4	H	**17f**	72
5	**16g**	$BzOCH_2CH_2$	H	**17g**	97
6	**16h**	Si(^{i}Pr)$_3$	H	**17h**	30
9	**16i**	Ph	Cl	**17i**	84
10	**16j**	Ph	CO_2Me	**17j**	83
11	**16k**	Ph	^{t}Bu	No reaction	
12[b]	**16k**	Ph	^{t}Bu	**17k**	44

[a] Isolated yield following chromatography.
[b] Cs_2CO_3 (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

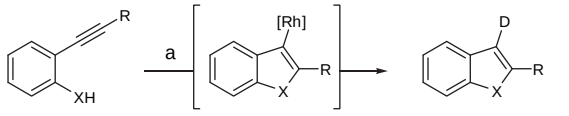


21 **22**

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)$_2$acac] (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 protodemetallation of a 2-rhodium benzofuran/indole species **23** and we felt that this intermediate could be exploited.



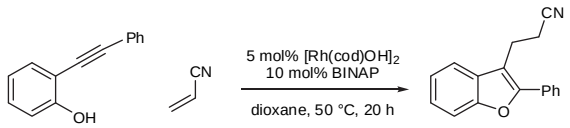
16b **21e** **23** 88% ***d*-17b** (93% D) 90% ***d*-22e** (95% D)

Scheme 4. Site of deuterium incorporation with D_2O solvent. Reagents and conditions: (a) 5 mol % [Rh(CO)$_2$acac], 5.5 mol % BINAP, PhMe, D_2O (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)$_2$acac 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)$_2$acac 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.

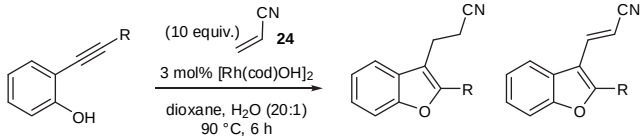


16b **24** (10 equiv.) 91% **25b**

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**



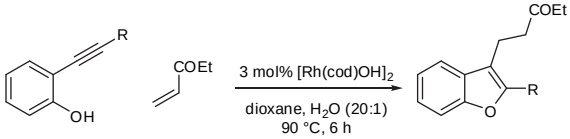
16 **25** **26**

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**



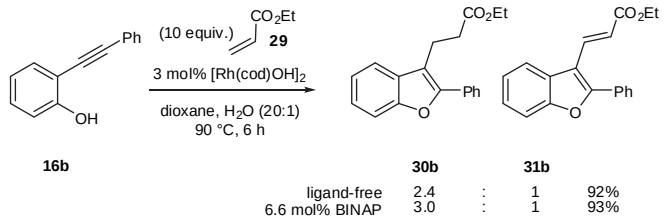
16 **27** (10 equiv.) **28**

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.

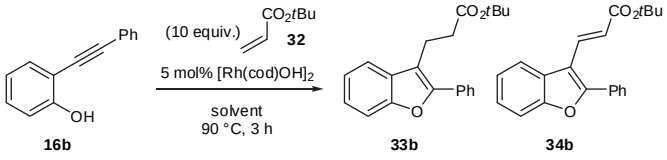
In the case of ethyl acrylate **29**, once again a mixture of products **30**/**31** was formed. However, the addition of BINAP in this case failed to influence the selectivity of the reaction (Scheme 6). It was



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**



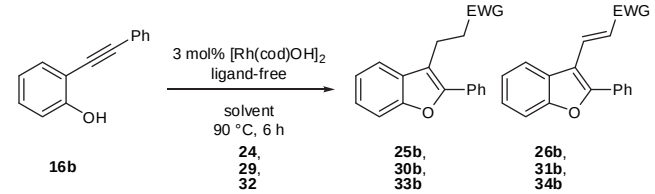
Entry	Equiv **32**	Solvent	(%)[a]	(%)[a]	Ratio
1	10.0	Dioxane	76	19	3.9:1
2[b]	10.0	DME	82	15	5.3:1
3	5.0	Dioxane	87	9	9.2:1
4	2.0	Dioxane	90	5.5	16:1
5[b]	2.0	DME	89	4.5	20:1

[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).

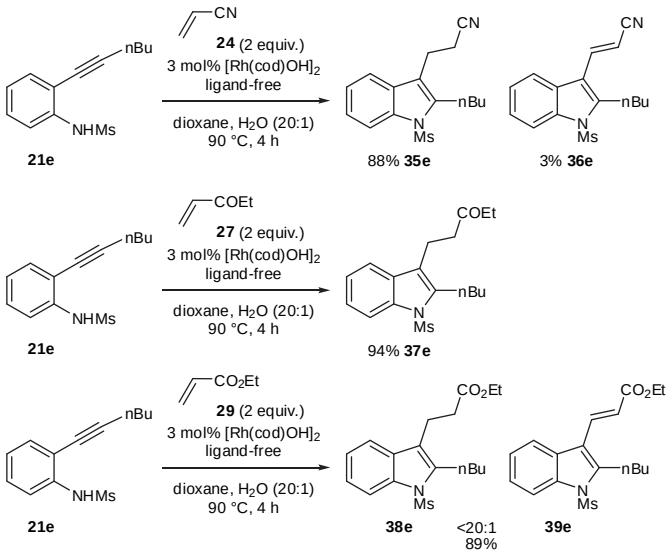
Using the knowledge gained from these studies, we turned our attention to the synthesis of indoles (Scheme 7).

Table 7
Effect of reaction stoichiometry



Entry	Electrophile	Solvent	*T* (°C)	Ratio	Yield[a] (%)
1	10 equiv **24**	Dioxane, H_2O (20:1)	90	3.5:1	86
2	2 equiv **24**	DME, H_2O (10:1)	85	20:1	86
3	10 equiv **29**	Dioxane, H_2O (20:1)	90	2.4:1	92
4	2 equiv **29**	DME, H_2O (10:1)	85	>20:1	85
5	10 equiv **32**	Dioxane, H_2O (20:1)	90	2.2:1	88
6	2 equiv **32**	DME, H_2O (10:1)	85	>20:1	77

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

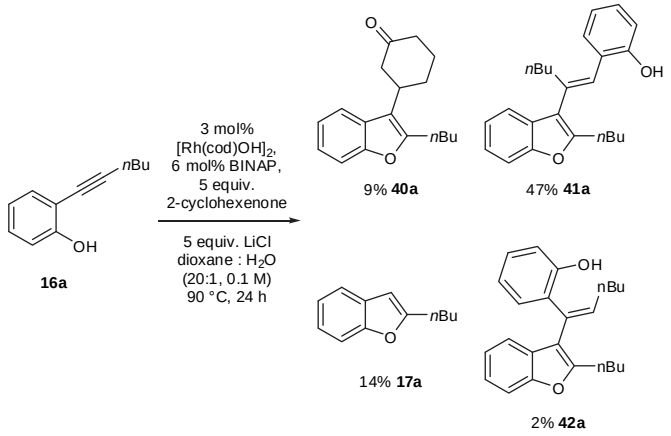


Scheme 7. Synthesis of 2,3-disubstituted indoles.

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

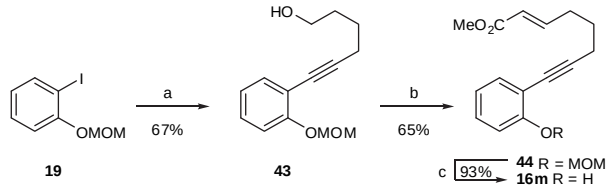
With an efficient process developed for the domino synthesis of 2,3-disubstituted benzofurans and indoles using mono-substituted electrophiles, attention was turned to the use of disubstituted electrophiles (i.e., 2-cyclohexenone). After a great deal of investigation, including studying the effect of 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

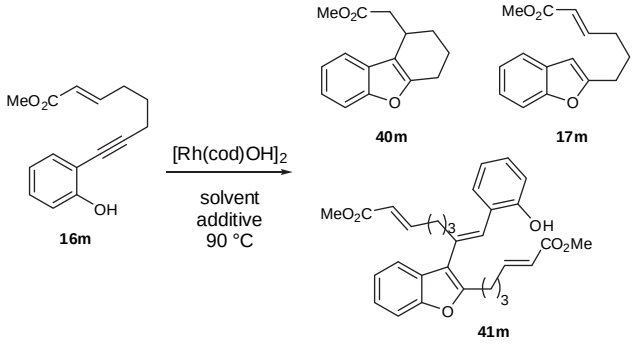
reaction[20] of aryl iodide **19** with 5-hexyn-1-ol, followed by a one-pot Ley oxidation—stabilised Wittig reaction (**43**→**44**)[31] and finally deprotection to form the phenol **16m** (Scheme 9). Ley's one-pot sequence provided much improved access to the desired α,β-unsaturated compound **44** (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 % $PdCl_2(PPh_3)_2$, 4 mol % CuI, NEt_3, THF, 50 °C, 67%; (b) 5 mol % $^nPr_4NRuO_4$, NMO, 4 Å sieves, CH_2Cl_2, rt; then Ph_3PCHCO_2Me, 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

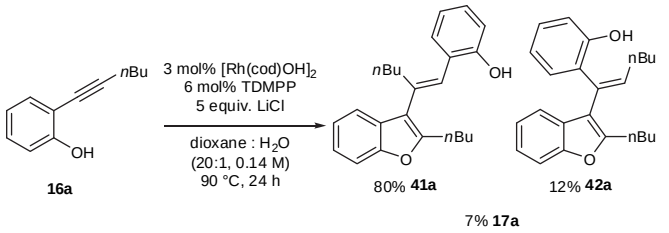
[a] Isolated yield following chromatography.
[b] Incomplete conversion of **16m**.

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

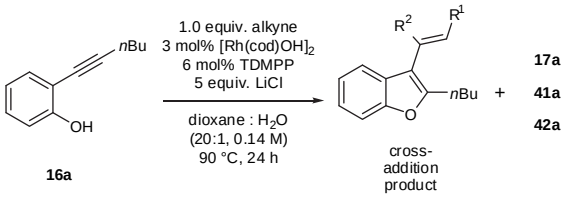


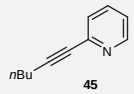
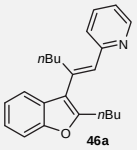
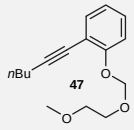
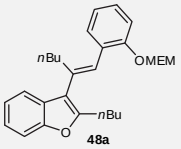
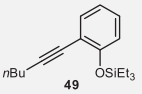
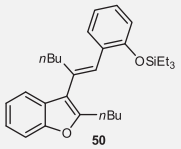
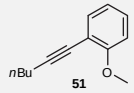
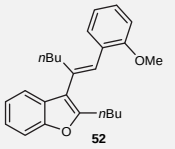
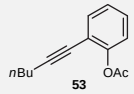
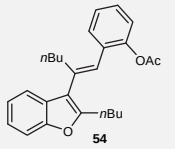
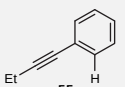
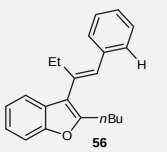
Scheme 10. Dimerisation of the phenol **16a**. TDMPP=tris(2,6-dimethoxyphenyl) phosphine.

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 verus 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.

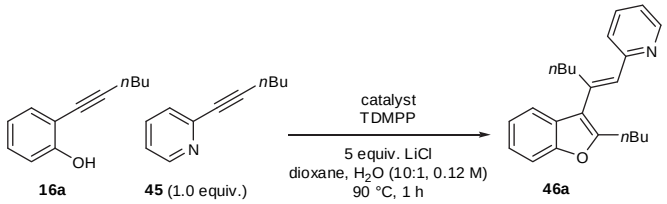
When a pyridyl alkyne **45** was investigated, only a trace amount of the dimeric product **41**/**42** could be observed and the major product was the vinyl pyridine **46a** (Table 9, entry 1).

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-butynylbenzene **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 group[29] 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**



16a **45** (1.0 equiv.) **46a**

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 $Rh(cod)_2OTf$	>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

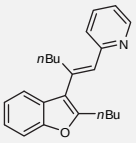
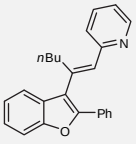
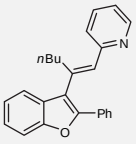
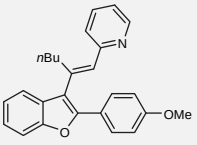
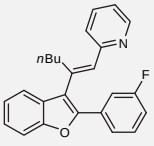
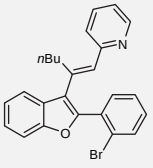
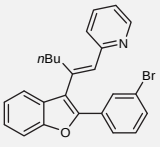
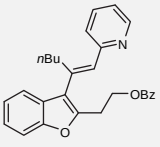
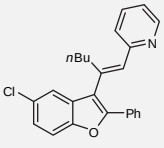
[a] Consumption of **16a** by ^1H NMR.
[b] Isolated yield.
[c] Ligand-free conditions.
[d] BINAP used in place of TDMPP.
[e] No ligand, LiCl, or H_2O.

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.

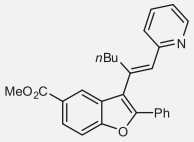
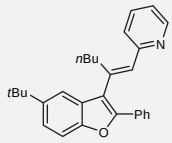
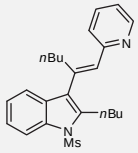
The reaction proved to be quite general and a range of *o*-alkynyl phenols, including both alkyl- and aryl-substituted alkynes underwent domino reaction in good to very good yield, even when the catalyst loading was reduced to half (Table 11). Surprisingly, the

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, H_2O (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, H_2O (10:1, 0.24 M), 90 °C, 24 h.

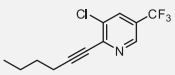
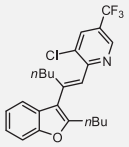
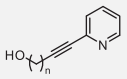
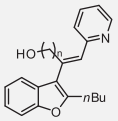
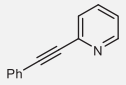
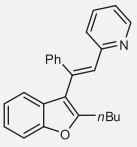
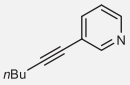
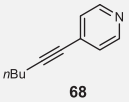
cross-addition product could be isolated even for the substrates, which displayed poor reactivity in the previous domino reactions (**16e**, **16k**). Unfortunately, when the reactions conditions were applied to the *o*-alkynyl aniline substrate **21a** the domino process did not occur and only the 3-unsubstituted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

Table 12
Scope of alkyne partner

Entry	Alkyne	Cross-addition product	Yield[a] (%)
			
1[b]	**58**	**59a**	42
2[c]	**58**	**59a**	52
3[d]	**58**	**59a**	68
			
4[b]	**60** (n=3)	**61a** (n=3)	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]	 **65**	 **66**	30
11[b]	 **67**	No reaction	
12[b]	 **68**	No reaction	

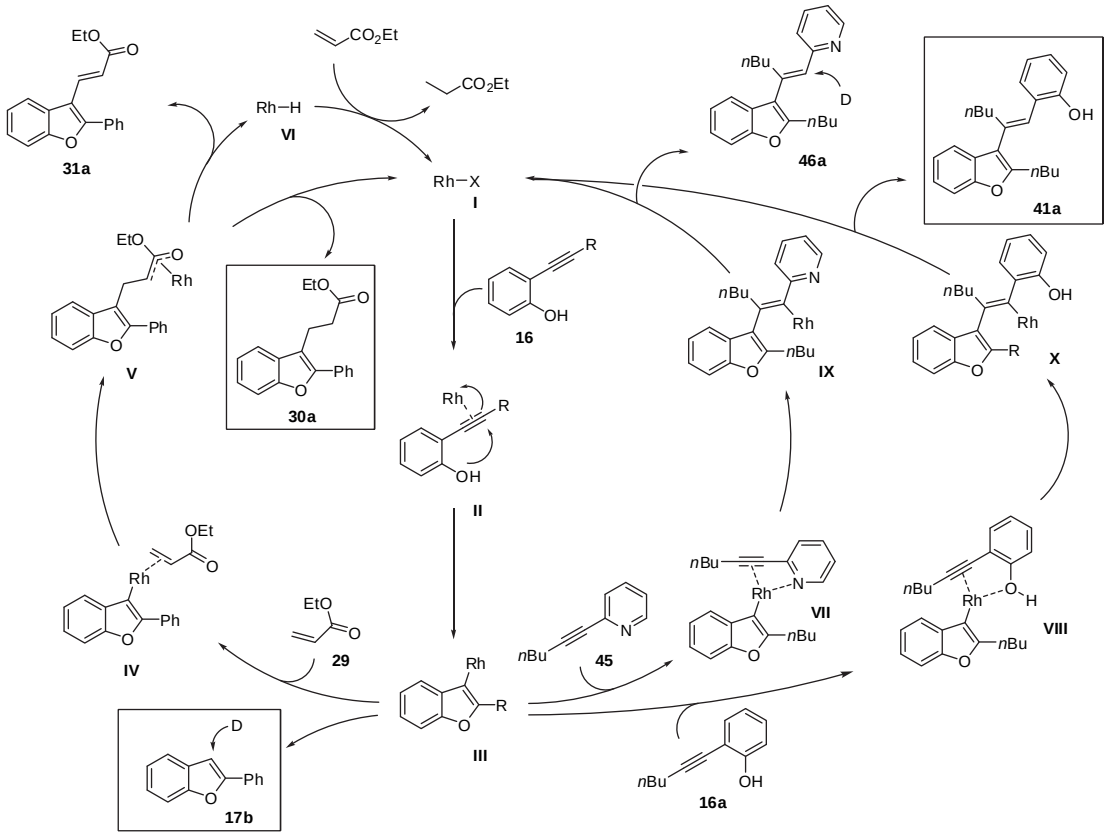
[a] Isolated yield following column chromatography.
[b] Compound **16a** (1.0 equiv), alkyne (1.0 equiv), 3 mol % $[Rh(cod)OH]_2$, 6 mol % TDMPP, LiBr (5.0 equiv), dioxane, H_2O (10:1, 0.24 M), 90 °C, 24 h.
[c] Compound **16a** (1.0 equiv), alkyne (1.0 equiv), 6 mol % $[Rh(cod)OH]_2$, 12 mol % TDMPP, LiBr (5.0 equiv),dioxane, H_2O (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, H_2O (10:1, 0.24 M), 90 °C, 24 h.

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 protodemetallation 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]

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 protodemetallation 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 (^{1}H 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



Scheme 11. Mechanistic hypothesis for domino reaction of *o*-alkynyl phenols and anilines. D indicates the site of deuterium incorporation when the reaction is performed in D_2O.

to the alkyne and protodemetallation. Under the conditions used, the reaction fails with electron-poor alkynes with no coordinating groups (e.g., dimethyl but-2-ynedioate, ethyl but-2-ynoate, **67** or **68**), supporting our belief that it is coordination of the alkyne substrate to rhodium and not the inherent electronics of the system, which controls the process.

3. Conclusions

We have demonstrated that rhodium can catalyse the cycloisomerisation of *o*-alkynyl phenols and anilines to the corresponding benzofurans and indoles. The process, which we have developed is complimentary to the previous example of Trost and proceeds via a transient 3-rhodium-heterocycle species. This intermediate has been exploited in the development of a domino carbon–carbon bond-forming process. The conjugate addition to alkenes can be performed with excellent selectivity for the conjugate-addition product versus the Heck–Mizoroki product in the case of mono-substituted electron-poor alkenes, however more substituted systems represent a current limitation of the method. We have also applied this to a chelation-controlled domino addition to alkynes, resulting in the rapid synthesis of several novel poly-heteroaromatic molecules.

4. Experimental procedures

4.1. General

The preparation of compounds **16a**,[15a] **16b**,[38] **16c**,[4c] **16h**,[39] **16i**,[15b] **16k**,[40] **19**,[21] **21**,[15e] **51**[41] and (**45**, **60**, **62**, **64**, **65**, **67**, **68**)[29b] have been reported previously. The synthesis of other starting materials and general experimental information is listed in the Supplementary data, which is available free of charge from the Tetrahedron website.

4.2. Cycloisomerisation (general procedure A)

A solution of $[Rh(CO)_2acac]$ (5 mol %) and *rac*-BINAP (5.5 mol %) in toluene (0.7 cm^3) and water (0.15 cm^3) was stirred at room temperature for 15 min. The substrate (1 equiv) was added as a solution in toluene (0.8 cm^3) and the reaction mixture was stirred at 100 °C for the stated time. The reaction was cooled to room temperature and filtered through a short pad of silica gel, washing with Et_2O (5×5 cm^3). The filtrate was concentrated under reduced pressure and purified by flash column chromatography to yield the product.

*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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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 D_2O in

place of H_2O) followed by purification (gradient from 5 to 9% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{14}H_9DO$ 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/CH_2Cl_2/Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{17}H_{14}O_3$ 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{17}H_{26}OSi$ 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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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: CH_2Cl_2/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; $CDCl_3$): 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; $CDCl_3$): 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 Cs_2CO_3 for 4 h followed by purification (hexane/CH_2Cl_2/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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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 D_2O in place of H_2O (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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{13}H_{16}DNO_2S$ 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 cm^3) and water (0.1 cm^3) 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 cm^3) and the reaction mixture was stirred at 90 °C for 6 h. Et_2O (5 cm^3) was added to the reaction mixture and it was filtered (short silica pad) washing with Et_2O (4×5 cm^3). 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 cm^3, 2.4 mmol) to general procedure B followed by purification (gradient from 5 to 11% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{15}H_{17}NO$ requires 227.1310). Compound **26a**: δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{15}H_{15}NO$ 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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{17}H_{13}NO$ requires 247.0997). **26b**: mp=126–128 °C; δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{17}H_{11}NO$ 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{18}H_{15}NO_2$ requires 277.1103). **35ca**: mp=122–124 °C; δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{18}H_{13}NO_2$ 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{17}H_{12}FNO$ requires 265.0903). Compound **26d**: δ_H (400 MHz; $CDCl_3$): 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 cm^3) and water (0.1 cm^3) was flushed with argon. The electrophile was added followed by a solution of the phenol/aniline in dioxane (1.0 cm^3) and the reaction mixture was stirred at 90 °C for 6 h. Et_2O (5 cm^3) was added to the reaction mixture and it was filtered (short silica pad) washing with Et_2O (4×5 cm^3). 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% Et_2O in hexane) gave the title compound (46 mg, 70%) as a colourless oil. δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{17}H_{22}O_2$ 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% Et_2O in hexane) gave the title compound (56 mg, 94%) as a white solid. mp=52–53 °C; δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{19}H_{18}O_2$ 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% Et_2O in hexane) gave compound the title compound (54 mg, 91%) as a white solid. mp=67–68 °C; δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{20}H_{20}O_3$ 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% Et_2O in hexane) gave the title compound (54 mg, 86%) as a white solid. mp=72–73 °C; δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{19}H_{17}FO_2$ 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 cm^3, 1.6 mmol) to general procedure C followed by chromatography (gradient from 5 to 11% Et_2O in hexane) gave the title compound (45 mg, 80%) as a white solid. mp=72–73 °C; δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{19}H_{17}BrO_2$ 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% Et_2O in hexane) gave the title compound (53 mg, 75%) as a colourless oil. δ_H (400 MHz; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{15}H_{16}O_2$ 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 cm^3) and water (0.2 cm^3). 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, Et_2O (5 cm^3) was added and it was filtered through a short silica pad, washing with Et_2O (4×5 cm^3). The filtrate was concentrated under reduced pressure, then purified by column chromatography (gradient from 5 to 11% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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; $CDCl_3$): 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% Et_2O 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{21}H_{22}O_3$ requires 322.1569). Compound **34b**: δ_H (400 MHz; $CDCl_3$): 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^+: $C_{16}H_{20}N_2O_2S$ 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: $C_{16}H_{19}N_2O_2S$ 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: $C_{18}H_{26}NO_3S$ 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% Et_2O 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: $C_{18}H_{26}NO_4S$ 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: $C_{18}H_{23}NO_4SNa$ requires 372.1240).

4.6. Typical domino reaction with 2-cyclohexene

A solution of $[Rh(cod)OH]_2$ (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 Et_2O (5 cm^3) and filtered through a short pad of silica, washing with Et_2O (4×5 cm^3). The filtrate was concentrated under reduced pressure and purified by column chromatography (gradient from 0 to 3% Et_2O 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^+: $C_{24}H_{28}O_2$ 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-Tetrahydrodibenzofuran-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% Et_2O 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): $C_{15}H_{16}O_3Na$ 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^+: $C_{15}H_{16}O_3$ requires 244.1099).

4.7. Domino reaction with pyridyl alkynes: general procedure D

A solution of $[Rh(cod)OH]_2$ (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×). 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 % $[Rh(cod)OH]_2$) 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^+: $C_{23}H_{27}NO$ 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 % $[Rh(cod)OH]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (85 mg, 83%) as colourless plates. Mp=64–66 °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^+: $C_{25}H_{23}NO$ 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 % $[Rh(cod)OH]_2$) 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^+: $C_{26}H_{25}NO_2$ 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 % $[Rh(cod)OH]_2$) followed by chromatography (gradient from 0 to 20% EtOAc in hexane) gave the title compound (81 mg, 76%) as a pale yellow solid. mp=73–75 °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^+: $C_{25}H_{22}FNO$ 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 % $[Rh(cod)OH]_2$) 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**: mp=48–50 °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^+: $C_{25}H_{22}BrNO$ 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 % $[Rh(cod)OH]_2$) 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^+: $C_{25}H_{22}BrNO$ 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 % $[Rh(cod)OH]_2$) 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: $C_{28}H_{28}NO_3$ requires 426.2063).

*4.7.8. (E)-2-(2-(5-Chloro-2-phenylbenzofuran-3-yl)hex-1-enyl)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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{25}H_{22}NOCl$ 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{27}H_{25}NO_3$ requires 411.1834).

*4.7.10. (E)-2-(2-(5-tert-Butyl-2-phenylbenzofuran-3-yl)hex-1-enyl) 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; $CDCl_3$): 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^+: $C_{29}H_{31}NO$ requires 409.2406).

*4.7.11. (E)-2-(2-(2-n-Butylbenzofuran-3-yl)hex-1-enyl)-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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{24}H_{25}ClF_3NO$ 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{22}H_{25}NO_2$ 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{21}H_{23}NO_2$ 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; $CDCl_3$): 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; $CDCl_3$): 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^+: $C_{25}H_{23}NO$ 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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