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2-Substituted Benzo[*b*]furans from (*E*)-1,2-Dichlorovinyl Ethers and Organoboron Reagents: Scope and Mechanistic Investigations into the One-Pot Suzuki Coupling/Direct Arylation

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Dedicated to the memory of Professor Keith Fagnou (1971–2009)

Keywords: Oxygen heterocycles / C-H activation / Cross-coupling / Palladium

2-Substituted benzo[*b*]furans can easily be assembled from simple phenols, boronic acids or other organoboron reagents, and trichloroethylene. The overall process requires only two synthetic steps, with the key step being a one-pot sequential Suzuki cross-coupling/direct arylation reaction. The method tolerates many useful functional groups and does not require the installation of any other activating functionality. The modular nature of the process permits the rapid synthesis of many analogues using essentially the same chemistry, of particular value in drug development. Results of kinetic isotope effect studies and investigations into the regioselectivity of the process indicate that the direct arylation step most likely does not involve an electrophilic palladation. The most likely mechanism lies somewhere on the continuum between a C–H bond metathesis and an assisted palladation or concerted metallation-deprotonation pathway.

Introduction

Heterocyclic structures play significant roles in the biological activities of pharmaceuticals. The benzo[*b*]furan ring system in particular is an important scaffold for drug development.[1] Several 2-substituted benzofurans have shown antifungal[2] and antiplasmodial[3] as well as antioxidant, anti-HIV, anticancer and estrogenic activities.[4]

Several retrosynthetic disconnections to commercially available starting materials for the synthesis of benzo[*b*]-furans are shown in Figure 1.[5] Common starting materials include 2-allylphenols,[6] α-bromocresols,[7] 1,2-dihaloarenes,[8] *o*-bromo benzylbromides,[9] and other 2-substituted phenols.[10] Benzo[*b*]furans bearing alkyl or aryl substituents at the R^2 and/or the R^3 positions have been accessed from 2-alkynylphenols, frequently obtained via Sonogashira couplings of 2-halophenol precursors.[11]

Cross-coupling approaches[12] require both components to be activated by the installation of halide or similar functionality (Figure 1). An efficient alternative route to the benzo[*b*]furan nucleus could employ *direct* metal-catalyzed cyclization[13] of an arene precursor, thus avoiding preliminary functionalization steps. To this end, Stoltz[14] and later Youn[15] have reported a useful palladium-catalyzed oxidative cyclization of *O*-allylphenols to give benzofurans. Liu has reported a zinc-catalyzed coupling and cyclization of phenol with a variety of propargylic alcohols.[16] Naito has demonstrated the sigmatropic rearrangement of aryl oxime ethers to give 2-substituted benzofurans.[17] Janin et al. used a [2+3] cycloaddition of in situ oxidized hydroquinone with an enol ether to give benzofurans.[18] Most recently Shibata used a directed, iridium-catalyzed cyclodehydration of α-aryloxyketones to make benzofurans,[19] and Li employed an iron-catalyzed sequential oxidative coupling and cyclization between phenols and β-keto esters.[20] While these results point in the direction of a broad and general route

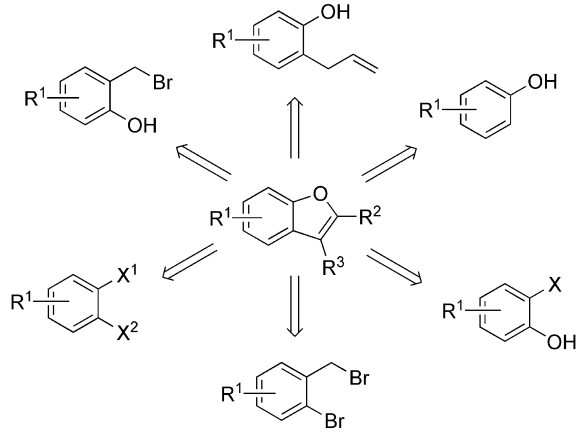

Figure 1. Simplified disconnections of benzo[*b*]furans to commercially available arene scaffolds.

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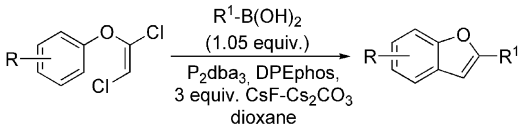
to benzofurans, all reported routes suffer from restrictive functional group requirements, limited scope, multistep synthesis or some combination thereof.

We have devised a simple strategy [Equation (1)] that generates 2-functionalized benzofurans in only two steps from minimally activated materials with no functional group manipulations prior to the two key C–C bond forming events. We recently reported preliminary results,[21] and now describe our detailed studies of the scope of the reaction as well as some mechanistic investigations.

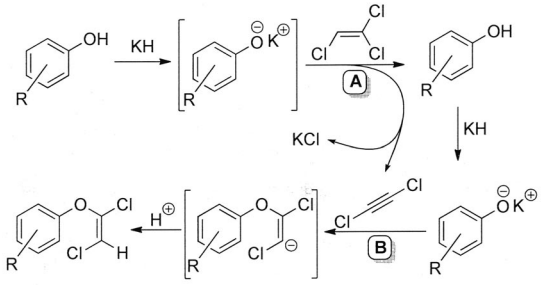


(1)

Results and Discussion

Synthesis of (*E*)-1,2-Dichlorovinyl Ethers

Our preparation of the 1,2-dichlorovinyl aryl ether precursors (Scheme 1) was based on Greene's method for the synthesis of aliphatic vinyl ethers.[22]

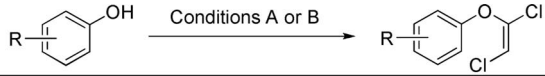


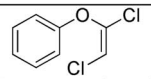
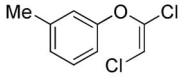
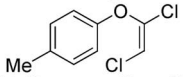
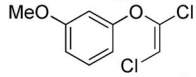
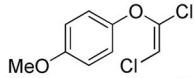
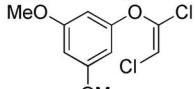
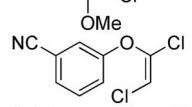
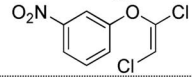
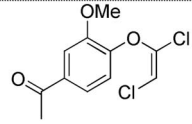
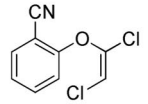
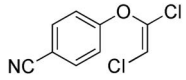
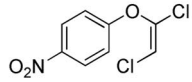
Scheme 1. Regio- and stereoselective substitution reactions of phenols with trichloroethylene.

We found that this procedure was quite general for phenols bearing electron-donating groups (Table 1, entries 1–6). However, when we used phenols with electron-withdrawing groups, we found that the success of the reaction was highly dependent on the position of the group. Both 3-nitro- and 3-cyanophenol reacted smoothly under these conditions (Table 1, entries 7 and 8), but 4′-hydroxy-3′-methoxyacetophenone (acetovanillone), 2- and 4-cyano-, and 4-nitrophenol failed to react at all under these conditions (Table 1, entries 9, 11, 13, 15).

This result can be rationalized by considering the pK_as of the phenols; while electron-poor phenols are in general more acidic and less nucleophilic, those with electron-withdrawing groups in the 3-position are not quite as influenced as those with electron-withdrawing groups in the 2- or 4-positions. The potassium salts of those phenols are either not basic enough to deprotonate trichloroethylene (step A in Scheme 1) or not nucleophilic enough to add to dichloroacetylene (step B in Scheme 1) under our standard conditions (Table 1, entries 9, 11, 13, 15). Sales and Mani recently

Table 1. Synthesis of 1,2-dichlorovinyl ethers from phenols and trichloroethylene.



Entry	Conditions[b]	Product		Yield[d]
1[a]	A		**1**	85%
2	A		**2**	98%
3	A		**3**	97%
4[a]	A		**4**	98%
5[a]	A		**5**	93%
6[a]	A		**6**	58%
7	A		**7**	90%
8[a]	A		**8**	97%
9	A		**9**	n.r.
10	B			80%
11	A		**10**	trace
12	B			68%
13	A		**11**	n.r.
14	B			94%
15	A		**12**	n.r.
16	B[c]			88%

[a] Previously published results.[21] [b] *Conditions A:* 2.05 equiv. KH, 1.5 equiv. TCE, –50 °C to room temp.; *Conditions B:* 3 equiv. K_2CO_3, 3 equiv. TCE, DMF, 70 °C. [c] Required the addition of catalytic amounts of methanol. [d] Isolated yields.

reported that the reactions of salicylaldehydes with TCE promoted by K_2CO_3 in DMF at 70 °C gave good yields of the corresponding dichlorovinyl ethers.[10i] When we applied their conditions to the reactions of electron-poor phenols, adducts **9**, **10** and **11** were isolated in excellent yields (Table 1, entries 10, 12 and 14). However, adduct **12** from *p*-nitrophenol was not detected at all. Sales and Mani likewise had noted that 5-nitrosalicylaldehyde failed to add to trichloroethylene.[10i] When we added catalytic amounts of methanol to the reaction of *p*-nitrophenol with TCE (based on an observation by Greene et al.[23]) smooth substitution occurred giving adduct **12** in excellent isolated yields (Table 1, entry 16). This suggests that potassium *p*-nitro-

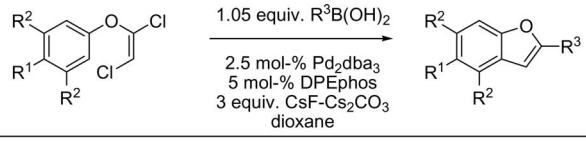
phenolate is nucleophilic enough to add across dichloroacetylene, but not sufficiently basic to deprotonate trichloroethylene.

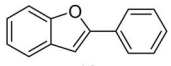
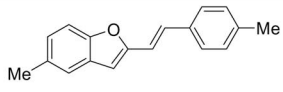
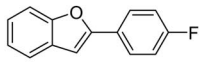
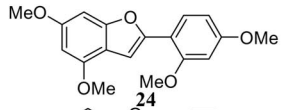
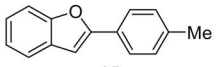
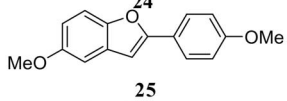
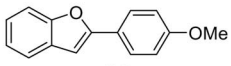
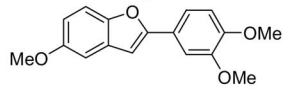
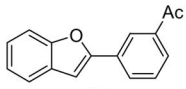
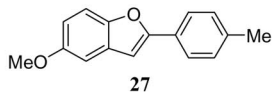
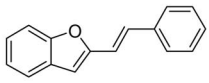
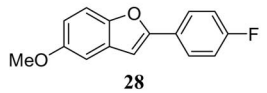
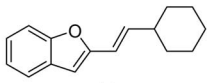
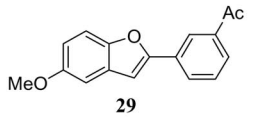
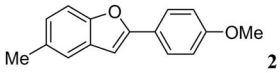
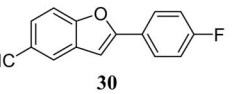
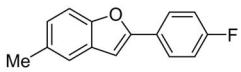
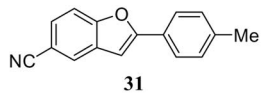
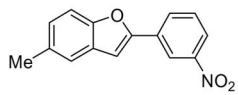
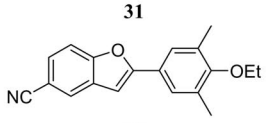
One-Pot Preparation of 2-Aryl Benzo[*b*]furans from Dichlorovinylaryl Ethers and Boronic Acids

We next explored the reactivity of dichlorovinylaryl ethers **1**–**12** as electrophiles in Suzuki couplings.[21,24] Suzuki cross-coupling always occurred at C^1–Cl and the adducts were always isolated as single regio- and stereoisomers, consistent with other observations that oxidative addition of palladium occurs at the most electrophilic carbon position.[25] A variety of conditions were found to be appropriate for selective C^1–Cl functionalization. Prolonged heating after completion of the Suzuki coupling led to subsequent cyclization to produce the benzo[*b*]furan. Reactions performed at high concentration proceeded at 65 °C, while those carried out at lower concentrations required heating at 100 °C to occur at an acceptable rate.

The sequential cross-coupling/direct arylation was first examined for unsubstituted (Table 2, entries 1–7) and symmetrically substituted phenols (Table 2, entries 8–20). The majority of our experiments employed arylboronic acids to

Table 2. One-pot preparation of 2-substituted benzo[*b*]furans from symmetrical phenols.



Entry	Reactants	*t* (h)	Product	Yield[a]	Entry	Reactants	*t* (h)	Product	Yield[a]
1[b]	**1** C_6H_5-$B(OH)_2$	12[c]	 **13**	75%	11	**3** (*E*)-4-Me-$C_6H_4CH{=}CH$-$B(OH)_2$	24	 **23**	71%
2[b]	**1** 4-F-C_6H_4-$B(OH)_2$	12[c]	 **14**	53%	12[b]	**6** 4-MeO-C_6H_4-$B(OH)_2$	12	 **24**	80%
3[b]	**1** 4-Me-C_6H_4-$B(OH)_2$	12[c]	 **15**	51%	13[b]	**5** 4-MeO-C_6H_4-$B(OH)_2$	12	 **25**	82%
4[b]	**1** 4-OMe-C_6H_4-$B(OH)_2$	12[c]	 **16**	74%	14	**5** 3,4-$(MeO)_2$-C_6H_3-$B(OH)_2$	12	 **26**	90%
5	**1** 3-Ac-C_6H_4-$B(OH)_2$	65	 **17**	50%	15	**5** 4-Me-C_6H_4-$B(OH)_2$	12	 **27**	69%
6[b]	**1** (*E*)-$C_6H_5CH{=}CH$-$B(OH)_2$	12[c]	 **18**	71%	16	**5** 4-F-C_6H_4-$B(OH)_2$	12	 **28**	68%
7	**1** (*E*)-$C_6H_{11}CH{=}CH$-$B(OH)_2$	24	 **19**	59%	17	**5** 3-Ac-C_6H_4-$B(OH)_2$	30	 **29**	36%
8	**3** 4-OMe-C_6H_4-$B(OH)_2$	24	 **20**	87%	18	**11** 4-F-C_6H_4-$B(OH)_2$	30	 **30**	81%
9	**3** 4-F-C_6H_4-$B(OH)_2$	24	 **21**	76%	19	**11** 4-Me-C_6H_4-$B(OH)_2$	30	 **31**	85%
10	**3** 3-NO_2-C_6H_4-$B(OH)_2$	24	 **22**	13%	20	**11** 3,5-Me_2-4-EtO-C_6H_2-$B(OH)_2$	30	 **32**	87%

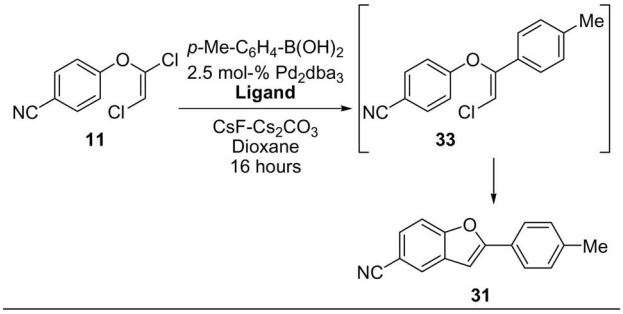
[a] Isolated yield. [b] Previously published results.[21] [c] Reactions could be run as 0.4 M (with respect to dichlorovinyl ether, see Experimental) solutions in dioxane at 100 °C or 1.0 M solutions in THF at 65 °C with comparable results.

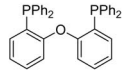
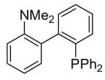
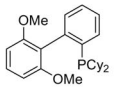
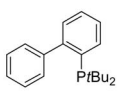
form 2-aryl benzofurans, but a few examples of 2-alkenyl benzofurans were also prepared (entries 6, 7 and 11). This method proved particularly successful for highly oxygenated benzofurans (entries 12–15), including the core structure (**24**) of the Ebenfuran family of estrogen receptor modulators[1c,4] and the natural product Corsifuran C (**25**).[26]

There have not been many reported syntheses of benzofurans bearing electron-withdrawing groups such as nitro, cyano or carbonyl.[8c,8f,11l,27] We therefore examined the coupling and cyclization of dichlorovinylaryl ethers **7**–**12**. The behaviour of these compounds was not as straightforward as that of their more electron-rich analogues.

Several ligands were tested in the cross-coupling/direct arylation between *p*-cyanophenol derivative **11** and *p*-tolylboronic acid (Table 3). The amounts of remaining starting material and the product ratios were determined after 16 hours of reaction, using ^{1}H NMR spectroscopy. Under these conditions DPEphos appeared to be the best ligand (Table 3, entry 1); while the cyclization was not complete during this time, the starting material was completely consumed and converted to intermediate **33**. $PCy_3{\cdot}HBF_4$ also led to clean conversion from **11** to **33**, but cyclization from **33** to **31** was slower (only 67% conversion compared to 84% conversion from the DPEphos system).[28] In contrast, the complexes formed from Pd_2dba_3 and PhDavePhos, S-Phos or JohnPhos were less efficient catalysts in Suzuki couplings between **11** and *p*-tolylboronic acid under these conditions; incomplete conversion to **33** was observed by crude ^{1}H NMR, and no benzofuran could be detected (Table 3, entries 3, 4 and 5). These observations, combined with our previously-published results[21] led us to select the reaction conditions shown in Table 2 as our "standard conditions" for all subsequent experiments.

Table 3. Ligand screen for the conversion of **11** to benzofuran **31**.



Entry	Ligand (Name, mol-%)	**11**: **33**: **31**[a]
1	 (DPEphos, 5)	0: 1.0: 5.4 (84% conv.)
2	$PCy_3{\cdot}HBF_4$ (10)	0: 1.0: 2.0 (67% conv.)
3	 (PhDavePhos, 10)	1.0: 4.6: 0
4	 (S-Phos, 10)	1.0: 3.3: 0
5	 (JohnPhos, 10)	1.0: 1.4: 0

[a] A similar trend was observed when the reaction was performed in toluene rather than dioxane.

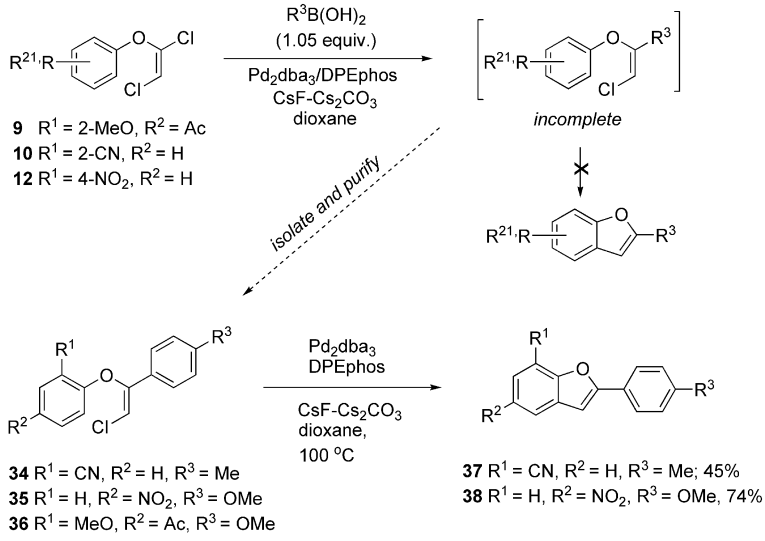
Using the Pd/DPEphos catalyst under our standard conditions, the *p*-cyanophenyl ether **11** reacted very smoothly with *p*-fluorophenyl, *p*-tolyl and 3,5-dimethyl-4-ethoxyphenylboronic acids, leading to benzofurans **30**, **31**, and **32** in good yields (Table 2, entries 18–20). However, the Suzuki cross-coupling reactions of **11** with several other boronic acids [2-fluoro-3-formylphenyl, 3,5-bis(trifluoromethyl)-phenyl, *m*-nitrophenyl, *o*-(methylthio)phenyl] were sluggish and incomplete even after prolonged reaction times. Moreover, no evidence of benzofuran formation could be observed in these stalled reactions.

Dichlorovinyl ethers **9**, **10** and **12** proved challenging as well and the one pot protocol did not afford benzofurans from these compounds (Scheme 2). Again, the initial Suzuki couplings were sluggish and there was substantial competing homocoupling and/or protiodeboration[29] of the boronic acids used.

To determine whether the intermediates were intrinsically unreactive in the cyclization step, they were isolated and resubjected to the cyclization conditions (Scheme 2). 5-Nitrobenzofuran **38** was isolated in excellent yield after a 12 hour reaction time but the *o*-cyano compound afforded the 7-cyanobenzofuran **37** in only 45% yield with 38% recovered starting material after 40 hours. Curiously, the acetophenone compound **36** did not cyclize and was isolated unchanged.

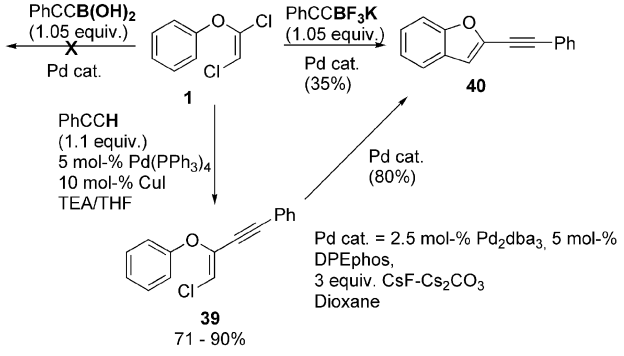
The results in Table 3 and Scheme 2 above suggest that the major restriction on the one pot protocol for benzofuran formation is the efficiency of the initial cross-coupling reaction. In our experience, if the cross-coupling step was incomplete, then subsequent cyclization did not occur under these conditions. We did not observe degradation of the unreacted starting material by ^{1}H NMR analysis of the crude products. The absence of protonolysis by-products suggests that oxidative insertion of palladium into the C^1–Cl bond may be reversible. Increasing the number of equivalents of boronic acid in problem cases might improve the efficiency of the Suzuki coupling step, and permit one pot conversion to the benzofurans.[30]

Enynes can easily be formed by Sonogashira cross-coupling between the dichlorovinyl ethers and terminal alkynes.[21] Thus, for example, phenylacetylene derivative **39** could be prepared in good yields from **1**. Unfortunately, palladium(0) tetrakis(triphenylphosphane), the catalyst used in the Sonogashira reaction, failed to mediate cyclization to **40**. Therefore a two-pot procedure was necessary to obtain 2-alkynyl benzofurans. Desiring a direct, one-pot synthesis, we turned to alkynyl boronic acids or alkynyl tri-



Scheme 2. One-pot Suzuki-coupling/cyclizations of **9**, **10** and **12** failed when cross-coupling was incomplete, but cyclization of purified intermediates is successful.

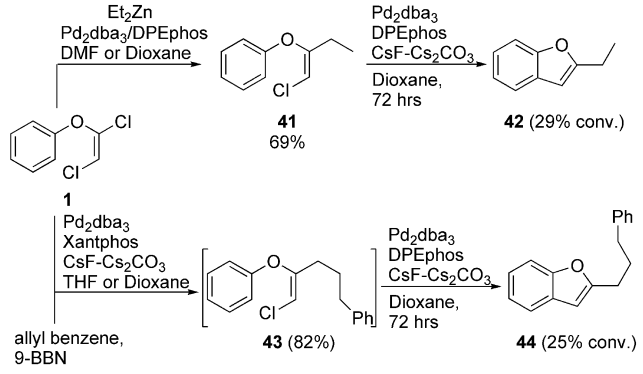
fluoroborate salts.[31] Unfortunately, in our hands attempts to cross-couple alkynyl boronic acids with **1** were unsuccessful. Several attempts to couple alkynyl trifluoroborates with **1** only produced **40** in low yields (Scheme 3), accompanied by substantial amounts of a black, gummy material that hampered both stirring and product isolation.



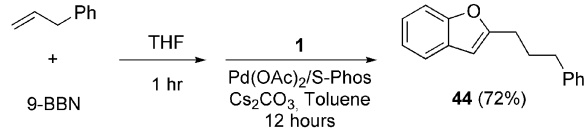
Scheme 3. Preparation of 2-alkynylbenzo[*b*]furan **40**.

Alkyl compounds also proved not as straightforward. Any attempt at cross-coupling 2-cyclohexylboronic acid with **1** proved unsuccessful,[32] so we turned our attention to other aliphatic organometallic donors.

Alkyl groups could be installed via Negishi coupling[33] or using Suzuki coupling of an alkyl borane[34] but the one-pot conversion to benzofurans **42** and **44** was incomplete even after days of reflux (Scheme 4). Subjecting the isolated intermediates **41** or **43** to these conditions did not improve the result. However, $Pd(OAc)_2$/S-Phos[33] afforded complete cyclization of **43** to **44** in under 8 hours. Moreover the one pot cross-coupling/direct arylation in the presence of this catalyst produced the 2-alkyl benzofuran in excellent isolated yield (Scheme 5). It is interesting to contrast this result with that obtained using the Pd_2dba_3/S-Phos catalyst in hot dioxane, which did not appear to be a promising system for coupling and cyclization (Table 3, entry 4).



Scheme 4. Initial studies on the preparation of 2-alkylbenzofurans.

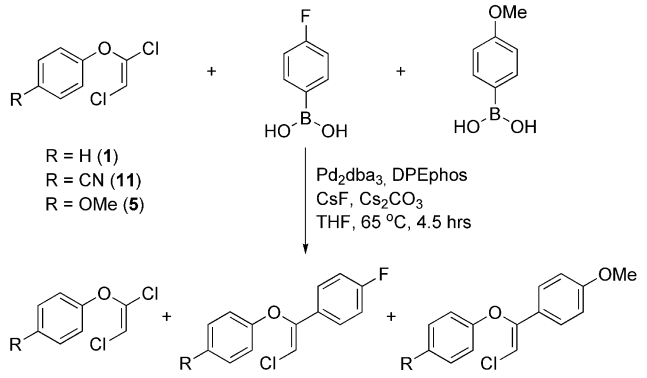


Scheme 5. One pot preparation of 2-alkylbenzofuran **44**.

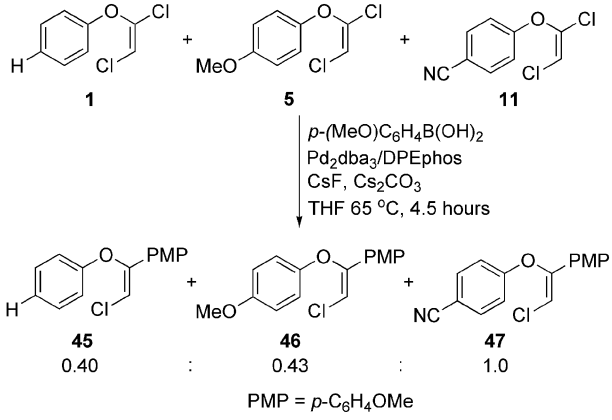
Mechanistic Investigations

We started our mechanistic studies by taking a brief look at the C^1–Cl functionalization step in the one pot procedure (Table 4 and Scheme 6). Intermolecular competition experiments were carried out using the Pd_2dba_3/DPEphos catalyst in hot THF. Equimolar mixtures consisting of a dichlorovinyl ether (one of **1**, the electron-rich **5** or the electron-poor **11**), *p*-fluorophenylboronic acid and *p*-methoxyphenylboronic acid were allowed to react in the presence of the catalyst and stopped after 4.5 hours, before any significant conversion to the benzofuran could be observed by tlc. In all three cases (Table 4), the *p*-methoxyphenyl derivative was produced faster than was the *p*-fluorophenyl derivative, consistent with a faster rate of transmetallation with the electron-rich boronic acid.

Table 4. Initial Suzuki coupling step: Intermolecular competition experiments with electron-rich and electron-poor boronic acids.



Entry		S.M.	Fluoro	Methoxy
1	R = H	0.26	0.66	1.0
2	R = CN	0.062	0.53	1.0
3	R = OMe	0.00	0.61	1.0



Scheme 6. Initial Suzuki coupling step: Intermolecular competition experiments between electron-rich and electron-poor dichlorovinyl phenyl ethers.

When we subjected an equimolar mixture of **1**, **5**, **11** and *p*-methoxyphenylboronic acid to the cross-coupling conditions, the *p*-cyanophenol derivative **11** was both consumed fastest and converted into the monoaryl intermediate fastest (Scheme 6). The cyano group in **11**, while remote from the reacting C^1 site, presumably renders the C^1–Cl bond less electron-rich and hence better able to act as an oxidant towards Pd^0. The results of the experiments shown in Table 4 and Scheme 6 are consistent with the standard palladium-catalyzed cross-coupling mechanism.[29]

The mechanism of aryl C–H functionalization[35] during the cyclization step was less obvious. We deemed an oxidative pathway via Pd^{IV} intermediates unlikely, especially since our reactions were performed without obvious oxidants, under argon in degassed solvents. We also discarded the possibility of a Heck-type carbopalladation on geometric grounds. Other mechanisms for C–H activation which have been proposed are summarized in Figure 2.[13a,35]

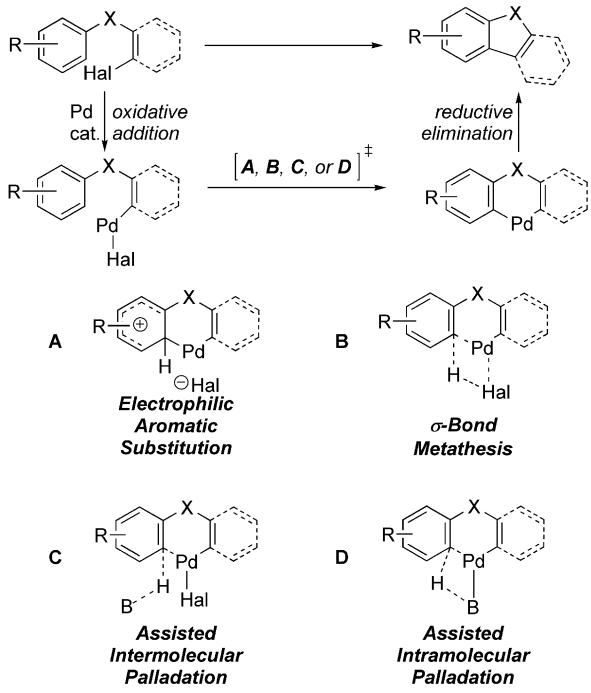


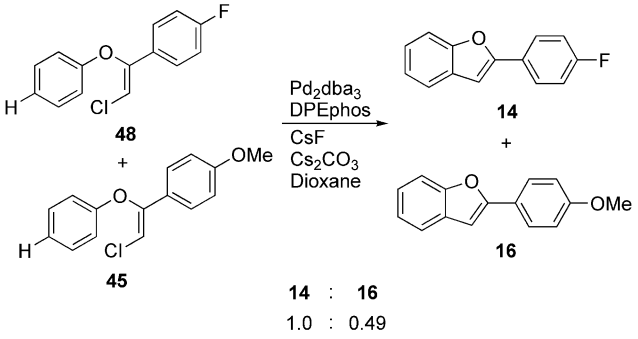
Figure 2. Mechanistic possibilities proposed for Pd-catalyzed intramolecular aryl C–H functionalization processes.

Based on these alternative proposals, we devised a series of intramolecular competition experiments to probe the influence of electronic effects on the rate of cyclization. We also examined the regioselectivity in cyclization reactions of unsymmetrically-substituted dichlorovinyl aryl ethers. Finally, we measured deuterium-hydrogen primary kinetic isotope effects (KIEs) in selected reactions.

Intermolecular Competition Experiments

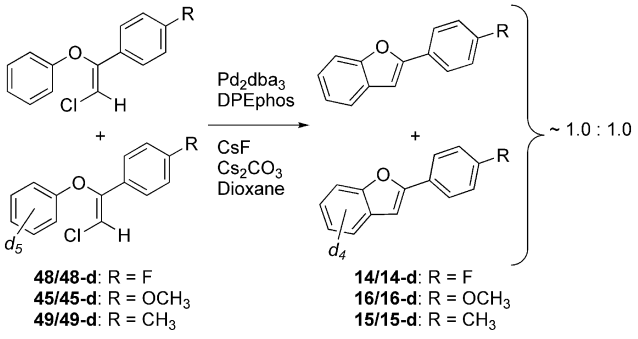
Three intermolecular competition experiments were carried out using 1-aryl-2-chlorovinyl aryl ethers **45**–**48**.[21] The reactions were carried out under our standard Pd_2dba_3/DPEphos conditions in hot dioxane. The reactions were stopped when tlc clearly indicated the presence of both benzofuran products as well as unreacted starting materials. ^1H NMR spectra of the crude materials obtained after workup allowed the product ratios to be determined. The cyclizations of the unsubstituted precursors **48** or **45** to form benzofurans **14** or **16** were taken as standards for comparison.

Competition between **45** and **48** probed the long-range influence of *para* substitution in the C^1 aryl component (Scheme 7). We observed that *p*-fluoro-substituted **14** was formed substantially faster than was *p*-methoxy substituted **16**. This may indicate faster oxidative addition of Pd into the C^2–Cl bond of **48**, paralleling results from Table 4 related to the C^1–Cl arylation. The striking difference in the reaction rates suggests that the rate-determining step in the direct arylation may be oxidative insertion of palladium into the C^2–Cl bond.



Scheme 7. Competition in cyclization of **48** and **45** favours the less electron-rich compound **48**.

A set of intermolecular kinetic isotope effect experiments (Scheme 8) revealed no detectable KIE in three different cases. This is consistent with previous observations by Hennessy and Buchwald in a related situation, which they interpreted as indicating rate-limiting oxidative insertion of Pd into the C–X bond.[36] Taken together with the competition results from Scheme 7, these KIE data strongly support a similar conclusion in our reactions: oxidative insertion is likely the overall rate-determining step in the cyclization.



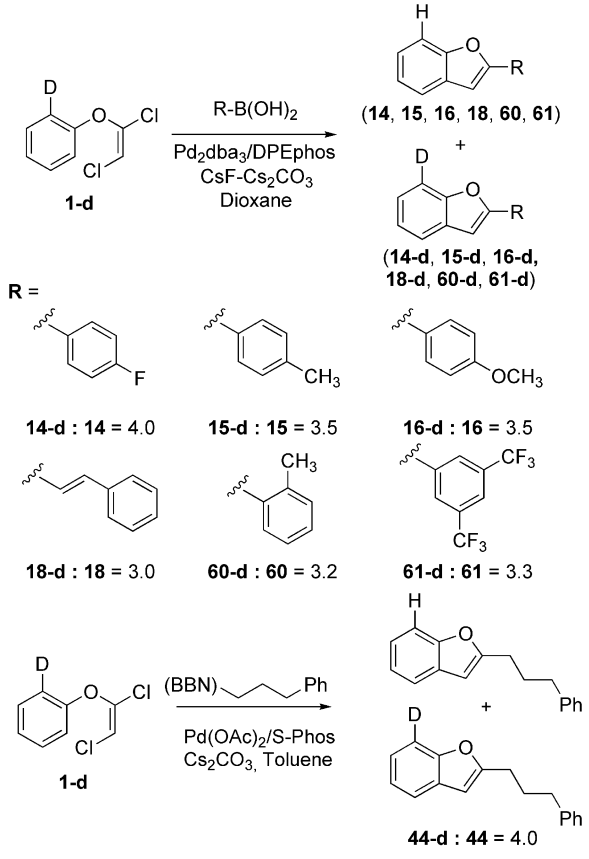
Scheme 8. $^1H/^2H$ intermolecular kinetic isotope effect experiments reveal no effect of deuteration on overall cyclization rates.

Regioselectivity of the Cyclization

To get a better understanding of the influence of electronic factors on the cyclization, we explored the regioselectivity of cyclization of unsymmetrical derivatives. We previously reported one-pot preparations of benzofurans from dichlorovinyl ethers from *m*-methoxyphenol or *m*-nitrophenol and *p*-methoxyphenylboronic acid and found that these reactions afforded a single regioisomer for the electron-rich methoxy substituted, but 6.0:1.0 regioselectivity for the electron-deficient nitro-substituted compounds[21] (reproduced in Table 5, entries 4 and 7). The high regioselectivity in the cyclization step was also observed with other electron-rich arenes: reaction of either *m*-methylphenol derivative **2** or *m*-methoxyphenol derivative **4** with all boronic acids explored always led exclusively to the 6-substituted benzofuran in high yields (Table 5, entries 1–6). In all cases, only a single benzofuran isomer could be identified in ^1H NMR spectra of the crude products.

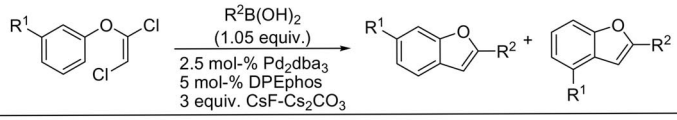
In contrast, reaction between *m*-nitrophenol-based **8** and boronic acids afforded mixtures of regioisomeric products (Table 5, entries 7–9), favouring the formation of 6-nitrobenzofurans in 3.3–5.9:1.0 ratios. We were therefore surprised to find that reaction of *m*-cyanophenol **7** and *p*-methoxyphenylboronic acid (Table 5, entry 10) formed the *4-substituted benzofuran* predominantly (i.e. C–C bond formation *ortho* to the cyano group rather than *para*). Fagnou reported a similar switch in regioselectivity between nitro- or chloro-substituted aryl substrates on the one hand and similar fluoro-substituted compounds on the other.[37] In these studies, C–C bond formation occurred preferentially *para* to a nitro group, but *ortho* to a fluorine. It is evident that the regioselectivity of the cyclization is not simply dependent on the electron-donating or withdrawing character of the aryl substituent.

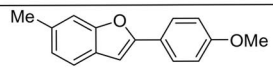
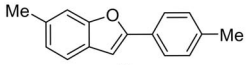
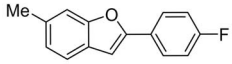
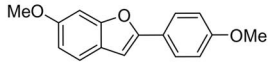
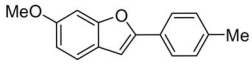
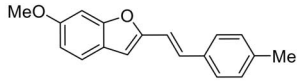
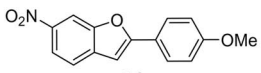
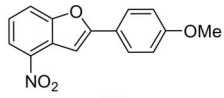
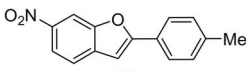
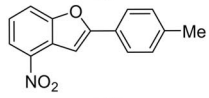
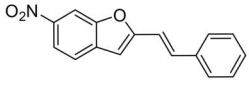
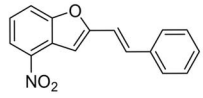
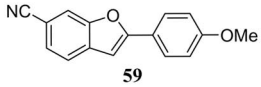
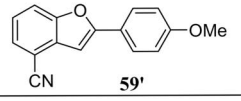
The cyclization mechanism was further probed in a set of *intramolecular* kinetic isotope effect studies (Scheme 9). The dichlorovinyl ether derived from 6-deuteriophenol was prepared and subjected to the one-pot coupling/cyclization protocol with several boronic acids using the Pd_2dba_3/DPEphos catalyst in hot dioxane. In all cases the KIE was approximately 3. We also observed a KIE of 4.0 using the $Pd(OAc)_2$/S-Phos catalyst in hot toluene to obtain **48**–**d** and **48**. This KIE is not consistent with an electrophilic palladation mechanism[38] but rather suggests a mechanism in



Scheme 9. Intramolecular $^1H/^2H$ kinetic isotope effects in the Pd-catalyzed cyclization reaction indicate that C–H bond scission is rate-determining in the palladation of the aryl ring.

Table 5. Regioselectivity in the synthesis of benzofurans from unsymmetrical monosubstituted precursors.



Entry	Reactants	Product(s)		Yield	Selectivity
1	**2** 4-OMe-C_6H_4-B(OH)$_2$	 **50**		78%	[c]
2	**2** 4-Me-C_6H_4-B(OH)$_2$	 **51**		86%	[c]
3	**2** 4-F-C_6H_4-B(OH)$_2$	 **52**		66%	[c]
4[b]	**2** 4-OMe-C_6H_4-B(OH)$_2$	 **53**		92%	[c]
5	**4** 4-Me-C_6H_4-B(OH)$_2$	 **54**		64%	[c]
6	**4** (*E*)-4-Me-C_6H_4CH=CH-B(OH)$_2$	 **55**		61%	[c]
7[b]	**8** 4-OMe-C_6H_4-B(OH)$_2$	 **56**	 **56'**	82%[d]	5.9:1.0[e] (**56**:**56'**)
8	**8** 4-Me-C_6H_4-B(OH)$_2$	 **57**	 **57'**	72%[d]	4.5:1.0[e] (**57**:**57'**)
9	**8** (*E*)-C_6H_5CH=CH-B(OH)$_2$	 **58**	 **58'**	73%[d]	3.3:1.0[e] (**58**:**58'**)
10	**7** 4-OMe-C_6H_4-B(OH)$_2$	 **59**	 **59'**	88%[d]	1.0:3.1[e] (**59**:**59'**)

[a] Isolated yield. [b] Previously published results.[21] [c] Only one isomer was detected by crude ^{1}H NMR spectroscopy. [d] Combined yield of both isomers. Isomers were isolated, purified and independently characterized. [e] Estimated from ^{1}H NMR of the crude material.

which C–H bond scission may be product-determining (although not necessarily rate-limiting overall).[37a,39] Base-assisted palladation of the aryl ring (via either **C** or **D** in Figure 2) might be facilitated by increased aryl C–H acidity,[40] although theoretical work by Gorelsky, Lapointe and Fagnou[41] did not support a simple correlation. Transition states **B** – **D** in Figure 2 are plausible in light of our KIE observations.

Conclusions

We have developed a very general and efficient route to 2-alkyl, alkenyl and alkynyl benzofurans by combining a cross-coupling reaction with a direct arylation process. The overall one-pot reaction employs one set of catalytic conditions for unsaturated compounds, and another set of conditions for saturated compounds. The method is modular in that different components are assembled around the central core derived from trichloroethylene. This method provides rapid access to substituted benzofurans, compounds with potential for the development of therapeutic agents against a number of diseases.

The reaction mechanism of the direct arylation process involves a rate-determining oxidative insertion of palladium into a vinyl C–Cl bond. The mechanism of the second step, palladation of the aryl ring, proved more challenging to elucidate. The observed KIEs and the regioselectivity of cyclization in unsymmetrical cases argue against an electrophilic palladation mechanism in the C–H functionalization event. Our data are consistent with a C–H metathesis or assisted palladation pathway, although we cannot as yet determine where on this mechanistic continuum our reaction lies.

Experimental Section

General Comments: Full details of materials, experimental protocols and the spectroscopic characterization of products are available in the Supporting Information. All glassware was oven dried at 140 °C overnight and cooled in a desiccator before use. All reactions were carried out under argon using standard syringe techniques. All materials were purchased from standard commercial sources and were generally used as received, with the following exceptions: THF was dried by passage through activated alumina under argon pressure (PureSolv system); both THF and anhydrous dioxane were degassed by sparging with argon before use; K_2CO_3 was stored in an oven at 140 °C and cooled in a desiccator prior to use; phenylacetylene was passed through a short column of activated alumina immediately before use.

General Procedure for the Substitution Reactions of Phenols with Trichloroethylene (Conditions A): KH (2.05 equiv.) was weighed into a round-bottom flask and washed with 3 portions of pentane or petroleum ether. The KH was then suspended in THF (ca. 2.4 mL per mmol of KH). A solution of the phenol (1.0 equiv.) in THF (ca. 1.25 mL per mmol of phenol) was added drop wise (vigorous gas evolution was noted) and the reaction was allowed to stir for 30 to 120 min. The suspension was cooled to –50 °C [$CHCl_3$/CO_2(*s*) bath]. Trichloroethylene (1.5 equiv.) was then added drop wise, after which the reaction was warmed to room temperature overnight.

The reaction was diluted with petroleum ether and quenched with ice-cold water. The phases were separated and the aqueous phase was extracted once more with petroleum ether. The organic layers were combined, dried with sodium sulfate, filtered and concentrated to give a yellow to dark brown oil. The crude oil was applied to a silica column pre-treated with triethylamine (ca. 2.5 vol.-% with respect to the volume of dry silica) and eluted with an appropriate solvent to give a colourless oil or solid.

General Procedure for the Substitution Reactions of Phenols with Trichloroethylene (Conditions B): Powdered K_2CO_3 (3 equiv.) and a phenol (1.0 equiv.) were weighed into an oven-dried round-bottomed flask. Anhydrous DMF (0.75 mL/mmol phenol) was added and the suspension was heated to 60 °C while stirring. Trichloroethylene (3 equiv.) was added drop wise and the reaction was heated at 70 °C overnight. The reaction was then cooled to room temperature, transferred to a separatory funnel and partitioned between ethyl acetate and water (75:25 mL). The phases were separated and the organic layer was dried with magnesium sulfate, filtered and concentrated to give a viscous oil. The crude oil was applied to a silica column pre-treated with triethylamine (ca. 2.5 vol.-% with respect to the volume of dry silica) and eluted with an appropriate solvent to give a colourless oil or solid.

General Procedure for the One-Pot Suzuki Coupling/Direct Arylation: The boronic acid, Pd_2dba_3, DPEphos, CsF and Cs_2CO_3 bases were placed into a one piece round-bottomed flask/condenser, sealed with a septum and purged with argon for 20–30 min. A 0.4 M solution of the 1,2-dichlorovinyl ether in dioxane was added. The solution was vigorously stirred and brought to reflux until judged complete by tlc. The cooled reaction mixture was partitioned between water and dichloromethane. The layers were separated and the aqueous layer was extracted with dichloromethane once more. The combined organic layers were dried with magnesium sulfate, filtered and concentrated onto silica gel, applied to a column and the benzofuran product was eluted with the appropriate solvent.

Supporting Information (see footnote on the first page of this article): Full experimental procedures and characterization data for all new compounds, including original ^1H and ^{13}C NMR spectra, as well as details of the competition and kinetic isotope effect experiments.

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