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Modular Construction of 2-Substituted Benzo[b]furans from 1,2-Dichlorovinyl Ethers

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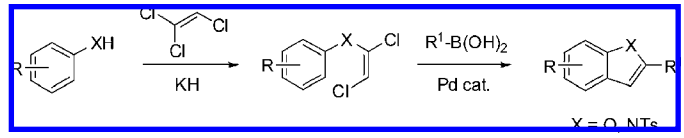
ABSTRACT



(*E*)-1,2-Dichlorovinyl ethers and amides are easily accessible from trichloroethylene via nucleophilic addition across in situ synthesized dichloroacetylene. A one-pot, sequential Suzuki−Miyaura coupling/intramolecular direct arylation between dichlorovinyl ethers and organoboronic acids provides easy access to a variety of benzofurans in only two steps from inexpensive commercially available compounds. The method is extendable to the preparation of indoles from the analogous dichlorovinyl amides.

Benzo[b]furans and indoles are common motifs in natural products, agrochemicals, and pharmaceuticals. The indole structure is widely regarded as "privileged" in drug development,[1] while the benzo[b]furan nucleus shows promise of attaining this status.[2] Methods for the synthesis of benzo[b]-furans and indoles have been reviewed,[3] but substantial activity continues because a broadly applicable strategy remains elusive.

Direct routes from simple phenols and anilines could minimize costs and reduce the number of manipulations prior to the key assembly of the heterocycle nucleus. Recent work by Glorius,[4] Jung,[5] and Zhao,[6] among others, points the way to a general strategy, but these methods suffer from either regioselectivity issues or restrictive functional group requirements.

1,1-Dichloroalkenes undergo stepwise Pd-catalyzed reactions with various organometallic reagents.[7] Organ[8] and others[9] have explored the use of a variety of 1,2-dihalo and 1,1,2-trihaloalkene derivatives including trichloroethylene (TCE) as synthetic "linchpins" for convergent synthesis. We thought that 1-aryloxy-1,2-dichloroethylenes (readily obtained by addition of phenols to TCE[10]) might be regioselectively functionalized by sequential cross-coupling and aryl

(1) de Sa Alves, F. R.; Barreiro, E. J.; Fraga, C. A. M. *Mini Rev. Med. Chem.* **2009**, *9*, 782.
(2) De Luca, L.; Nieddu, G.; Porcheddu, A.; Giacomelli, G. *Curr. Med. Chem.* **2009**, *16*, 1.
(3) (a) Cacchi, S.; Fabrizi, G.; Goggiomani, A. *Heterocycles* **2002**, *56*, 613. (b) Hou, X.-L.; Yang, Z.; Yeung, K.-S.; Wong, H. N. C. *Prog. Heterocycl. Chem.* **2007**, *18*, 187. (c) Cacchi, S.; Fabrizi, G.; Goggiamani, A. *Curr. Org. Chem.* **2006**, *10*, 1423. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (e) Krueger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (f) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2009**, *16*, 2531.
(4) Wuertz, S.; Rakshit, S.; Neumann, J. J.; Droege, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230.
(5) Jung, M. E.; Perez, F. *Org. Lett.* **2009**, *11*, 2165.
(6) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417.
(7) (a) Negishi, E.-i.; Huang, Z.; Wang, G.; Mohan, S.; Wang, C.; Hattori, H. *Acc. Chem. Res.* **2008**, *41*, 1474. (b) Tan, Z.; Negishi, E.-i. *Angew. Chem., Int. Ed.* **2006**, *45*, 762. (c) Liron, F.; Fosse, C.; Pernolet, A.; Roulland, E. *J. Org. Chem.* **2007**, *72*, 2220.
(8) (a) Organ, M. G.; Ghasemi, H.; Valente, C. *Tetrahedron* **2004**, *60*, 9453. (b) Ghasemi, H.; Antunes, L. M.; Organ, M. G. *Org. Lett.* **2004**, *6*, 2913. (c) Organ, M. G.; Cooper, J. T.; Rogers, L. R.; Soleymanzadeh, F.; Paul, T. *J. Org. Chem.* **2000**, *65*, 7959.
(9) (a) Pellegrini, S.; Castanet, Y.; Mortreux, A. *J. Mol. Catal. A: Chem.* **2007**, *277*, 21. (b) Anthony, J.; Boldi, A. M.; Rubin, Y.; Hobi, M.; Gramlich, V.; Knobler, C. B.; Seiler, P.; Diederich, F. *Helv. Chim. Acta* **1995**, *78*, 13. (c) Schmidt, B.; Ehlert, D. K.; Braun, H. A. *Tetrahedron Lett.* **2004**, *45*, 1751.
(10) (a) Darses, B.; Milet, A.; Philouze, C.; Greene, A. E.; Poisson, J.-F. *Org. Lett.* **2008**, *10*, 4445. (b) Kann, N.; Bernardes, V.; Greene, A. E. *Org. Synth.* **1997**, *74*, 13. (c) Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.

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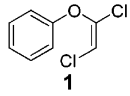
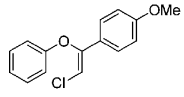
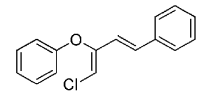
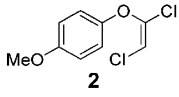
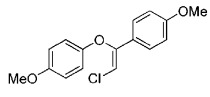
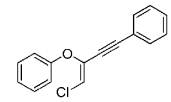
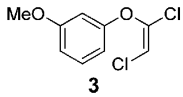
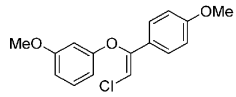
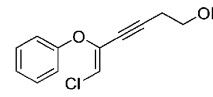
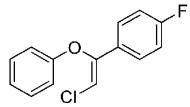
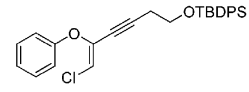
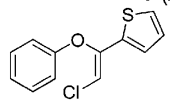
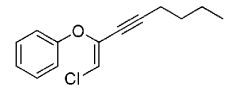
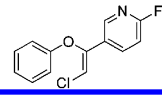
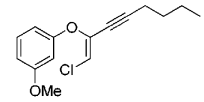
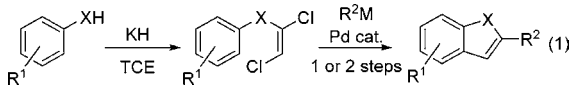
Table 1. Regioselective Cross-Coupling Reactions at C-1 in 1,2-Dichlorovinyl Ethers **1**−**3**

entry	vinyl ether[a]	product (conditions[b], yield[c])	entry	vinyl ether	product (conditions[b], yield[c])
1	 **1**	 **4** (A, 82%; B, 85%)	7	**1**	 **10** (B, 60%)
2	 **2**	 **5** (A, 57%; B, 72%)	8	**1**	 **11** (C, 71%)
3	 **3**	 **6** (B, 63%)	9	**1**	 **12** (C, 90%)
4	**1**	 **7** (A, 80%; B, 81%)	10	**1**	 **13** (C, 85%)[e]
5	**1**	 **8** (A, 73)[d]	11	**1**	 **14** (C, 77%)
6	**1**	 **9** (A, 54%)	12	**3**	 **15** (C, 64%)

[a] Preparation of **1**−**3** is described in the Supporting Information. [b] A: Aryl boronic acid (1.05 equiv), $Pd(PPh_3)_4$ (5 mol %), aq KOH, THF (0.4 M), 65 °C, 1−22 h. B: Arylboronic acid (1.05 equiv), Pd_2dba_3 (2.5 mol %), DPEphos (5 mol %), CsF (3 equiv), Cs_2CO_3 (3 equiv), THF (0.5 M), 65 °C, 6−24 h. C: Terminal alkyne (1.1 equiv), $Pd(PPh_3)_4$ (5 mol %), CuI (10 mol %), THF, rt, overnight. [c] Yields of pure compounds after chromatography on silica gel pretreated with triethylamine. See Supporting Information for details. [d] Gradually decomposed. [e] Based on recovered starting material (66% conversion). TBDPS = *tert*-butyldiphenylsilane.

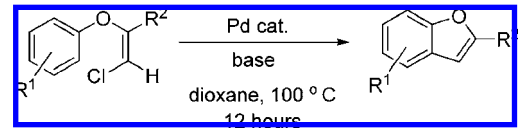
C−H functionalization steps to form benzo[b]furan derivatives (eq 1, X = O). Similar processes involving dichlorovinylaniline precursors might form indoles (eq 1, X = NR).[11]



This would allow modular construction of benzofurans or indoles from inexpensive phenols or anilines, trichloroethylene, and an organometallic R^2 donor in as few as two steps, with no need for specific functional groups or other structural modifications.

The 1,2-dichlorovinyl ethers **1**−**3** participated in representative Pd-catalyzed cross-coupling reactions specifically at the C-1 position. We found that Suzuki coupling in THF at 65 °C catalyzed by either $Pd(PPh_3)_4$ or Pd_2dba_3/DPEphos[12] could install aryl and heteroaryl groups (Table 1, entries 1−6) or styryl (entry 7) quite satisfactorily *using only 1.05 equiv of the boronic acid*. Many Suzuki reactions require excess boronic acid, combating uncertain stoichiometry.[13] In the Pd-DPEphos-catalyzed reactions, the presence of both CsF and Cs_2CO_3 afforded more consistent reaction times and higher conversions compared with processes employing either of these basic additives alone. Sonogashira alkynylation also took place at the C-1 position in good yields (Table 1, entries

Table 2. Cyclization of (*Z*)-1-Substituted-1′-aryloxy-2-chloroethylenes



entry		reactant R¹	reactant R²	product (yield)[b]
1	**7**	H	4-F-C_6H_4	**16** (72%)
2	**4**	H	4-MeO-$_6H_4$	**17** (86%)
3	**10**	H	(*E*)-C_6H_5−CH=CH−	**18** (32%)
4	**11**	H	−CC-C_6H_5	**19** (80%)
5	**5**	4-MeO	4-MeO-C_6H_4	**20** (82%)
6	**6**	3-MeO	4-MeO-C_6H_4−	**21** (74%)[c]

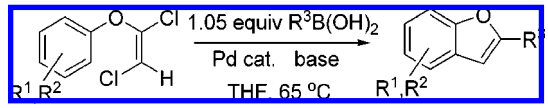
[a] Pd catalyst: Pd_2dba_3 (2.5 mol %), DPEphos (5 mol %). Base: 3 equiv of CsF and Cs_2CO_3. [b] Isolated yield. [c] A single regioisomer detected.

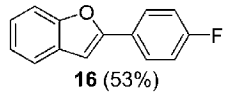
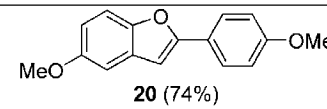
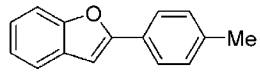
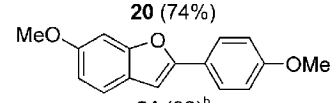
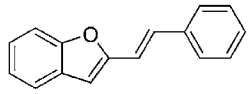
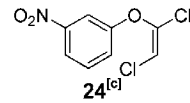
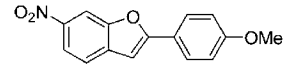
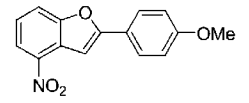
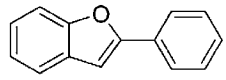
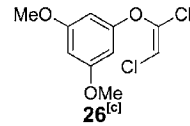
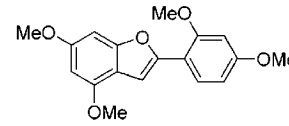
(11) Lautens has devised a related method for the synthesis of indoles and benzofurans. See: (a) Fang, Y.-Q.; Lautens, M. *J. Org. Chem.* **2008**, *73*, 538. (b) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (c) Isono, N.; Lautens, M. *Org. Lett.* **2009**, *11*, 1329. (d) Nagamochi, M.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2007**, *9*, 2955.

(12) Xantphos was an equally effective ligand in these reactions, but we chose the less-expensive DPEphos for the bulk of our work.

(13) Molander, G. A.; Figueroa, R. *Aldrichimica Acta* **2005**, 49.

Table 3. One-Pot Suzuki Coupling/Direct Arylation Synthesis of 2-Substituted Benzofurans from 1,2-Dichlorovinyl Ethers



entry	reactants	product (yield)[a]	entry	reactants	product (yield)[a]
1	**1** 4-F-C_6H_4-$B(OH)_2$	 **16** (53%)	5	**2** 4-(MeO)-C_6H_4-$B(OH)_2$	 **20** (74%)
2	**1** 4-Me-C_6H_4-$B(OH)_2$	 **22** (51%)	6	**3** 4-(MeO)-C_6H_4-$B(OH)_2$	 **21** (92)[b]
3	**1** (*E*)-C_6H_5-CH=CH$B(OH)_2$	 **18** (71%)	7	 **24**[c] 4-(MeO)-C_6H_4-$B(OH)_2$	 **25** (71%)  **25′** (11%)
4	**1** C_6H_5-$B(OH)_2$	 **23** (75%)	8	 **26**[c] 2,4-$(MeO)_2$-C_6H_3-$B(OH)_2$	 **27** (80%)

[a] Isolated yields. [b] Only one isomer could be detected. [c] Preparation of **24** and **26** is described in the Supporting Information.

8−12).[14] In all cases, only one regio- and stereoisomer of the product could be detected.

However, when Suzuki arylation of vinyl ether **1** was allowed to proceed for extended periods of time, a byproduct was observed in addition to 1-aryl vinyl ether **7**. This was identified as a benzo[b]furan, and when **7** was treated with palladium, DPEphos, and the cesium bases, benzo[b]furan **16** became the sole product (72%). Benzo[b]furan formation under these conditions proved successful with a range of groups attached at C-1 (Table 2). The cyclization reactions probably proceed via oxidative insertion of Pd into the remaining vinylic C−Cl bond, followed by arylation and reductive elimination.

While Suzuki couplings of vinyl ethers **1**−**3** were successful in the presence of either CsF or Cs_2CO_3, the cyclizations shown in Table 2 are much more dependent on the bases. This reaction was moderately efficient with CsF as the sole base but hardly proceeded at all when attempted using only Cs_2CO_3, a notable difference from the Suzuki couplings. Replacing either CsF by KF or Cs_2CO_3 by K_2CO_3 caused the cyclization to fail.

Suzuki coupling and direct arylation could be combined in a one-pot procedure (Table 3). The benzofuran products were obtained in good to excellent yields after 12−24 h at 65 °C. The unsymmetrical derivatives **3** and **24** could react by two different cyclization pathways; we were surprised to find that the 3-methoxy compound **3** afforded only one regioisomeric benzofuran product (**21**), while 3-nitro **24** cyclized to give a 6:1 mixture of isomeric benzofurans **25** and **25′**.

We have not yet carried out detailed mechanistic studies on the cyclization. Electrophilic aromatic substitution or C−H activation are possible mechanisms consistent with our observed reactivity.[15] A concerted metalation−deprotonation (CMD, also referred to as "proton abstraction") mechanism for direct aryl coupling processes has been proposed,[16] most recently by Fagnou[17] and by Echavarren.[18] The similar reactivity of the 3- and 4-methoxy and 3-nitro enol ethers **2**, **3**, and **24** in our cyclizations might be consistent with a CMD

(14) Schmidt et al. (ref 9c) have reported an analogous Pd-catalyzed coupling to a 1,2-dichlorovinyl ether. Curiously, they obtained specific C-2 alkynylation.

(15) (a) Campo, M. A.; Huang, Q.; Yao, T.; Tian, Q.; Larock, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 11506. (b) Hennessy, E. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 12084.

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(17) (a) Lafrance, M.; Lapointe, D.; Fagnou, K. *Tetrahedron* **2008**, *64*, 6015. (b) Liegault, B.; Lee, D.; Huestis, M. P.; Stuart, D. R.; Fagnou, K. *J. Org. Chem.* **2008**, *73*, 5022. (c) Caron, L.; Campeau, L.-C.; Fagnou, K. *Org. Lett.* **2008**, *10*, 4533. (d) Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Am. Chem. Soc.* **2008**, *130*, 10848.

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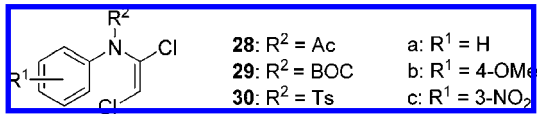
mechanism. On the other hand, it may simply indicate that oxidative insertion into the vinyl C−Cl bond is rate determining.

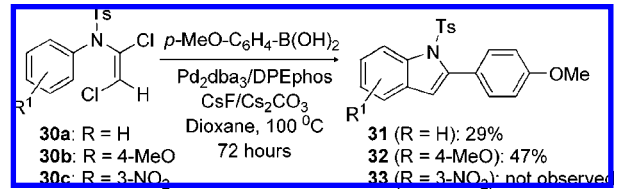
To extend our method to the synthesis of indoles, the dichlorovinyl enamides **28**−**30** were prepared from the corresponding anilines and TCE.[19] The outcome of one-pot Suzuki coupling/direct intramolecular cyclization of **28**−**30** to form 2-substituted indoles was dependent on the nitrogen protecting group. *N*-Acetyl enamide **28** did not survive any cross-coupling conditions, and the *N*-BOC derivatives **29a**−**c** were difficult to cyclize.[20]



Finally, *N*-tosyl enamides **30a**,**b** underwent one-pot arylation and cyclization to afford moderate yields of 2-arylindoles **31**−**32**, after extended reaction times (Scheme 4). The 3-nitro enamide **30c** underwent Suzuki coupling smoothly, but even after 72 h of heating no evidence of the desired nitroindole **33** could be detected either by TLC or ^{1}H NMR analysis of the crude reaction residue. The significance of this poor reactivity is unclear but could support a mechanism in which arylation is now rate determining.

In conclusion, we have developed an efficient modular route to 2-substituted benzofurans from inexpensive phenols, trichloroethylene, and a single equivalent of boronic acid in only two steps. To our knowledge, this is only the second report of sequential Suzuki cross coupling and direct arylation

Scheme 4. One-Pot Access to 2-Aryl-*N*-tosyl Indoles from 1,2-Dichlorovinyl Amides



in one pot.[21] Among the benzofurans we have prepared are the natural product Corsifuran C (**20**)[22] and the core structure (**27**) of the Ebenfuran family of estrogen receptor modulators.[23] We have also obtained promising initial results toward extending this method to the synthesis of indoles. Further studies to define the scope of this process, enhance its efficiency, and understand its mechanism are ongoing.

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Supporting Information Available: Experimental procedures and full characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) The preparation and characterization of **28**−**30** are described in the Supporting Information.

(20) The *N*-BOC enamides underwent Suzuki coupling but failed to cyclize under the one-pot conditions. When monoarylated *N*-BOC enamides were separately subjected to Pd-catalyzed cyclization conditions, cyclization did occur, but substantial loss of the BOC group was observed. See the Supporting Information for experimental details.

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