JOURNAL OF combinatorial CHEMISTRY

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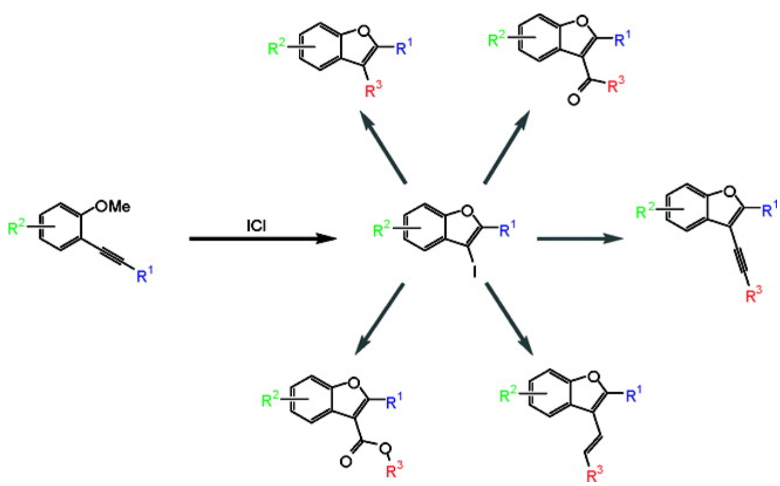
J. Comb. Chem., **2008**, 10 (6), 941-947• DOI: 10.1021/cc800120y • Publication Date (Web): 20 October 2008



Parallel Synthesis of a Multi-Substituted Benzo[*b*]furan Library

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Received July 14, 2008

The solution-phase parallel synthesis of a 121-member library of multi-substituted benzo[*b*]furans is described. 2,3,5-Trisubstituted benzo[*b*]furans have been prepared by the palladium-catalyzed substitution of 3-iodobenzofurans by Suzuki–Miyaura, carbonylative Suzuki, Sonogashira, Heck, and carboalkoxylation chemistry. The 3-iodobenzofurans are readily prepared in good to excellent yields by the palladium/copper-catalyzed cross-coupling of various *o*-iodoanisoles and terminal alkynes, followed by electrophilic cyclization with ICl.

Introduction

Benzo[*b*]furan derivatives are of considerable interest because of their widespread occurrence among natural products and their physiological properties.[1–6] For instance, 2,3-disubstituted benzo[*b*]furans and derivatives exhibit a broad range of biological activities. A small selection of biologically and pharmacologically active benzo[*b*]furan compounds is shown in Figure 1. Adenosine antagonist XH-14 (**1**) was isolated from the plant *Salvia miltiorrhiza*, which has been widely used in China for the treatment of coronary heart diseases, such as myocardial infarction and angina pectoris.[7–9] Obovaten (**2**) is known as a very important antitumor agent.[10,11] The methyl ester **3** was isolated from exudates released by the roots of iron-deficient alfalfa (*Medicago sativa*).[12,13] 2-Aryl-3-aroylbenzo[*b*]furans serve as core structures of many naturally occurring products and pharmaceutical drug candidates.[14,15] Recently, Flynn et al. prepared 2,3-disubstituted benzo[*b*]furan analogues (**4**) of some benzo[*b*]thiophenes identified as inhibitors of tubulin polymerization, and their biological activity was assessed.[16–18] Furopyridine derivatives are also highly biologically active.[19–22]

For these reasons, various routes to substituted benzo[*b*]furans have been the subject of extensive experimental studies. Major synthetic strategies for the construction of furan rings from various arene derivatives,[23,24] alkyne-based palladium-catalyzed reactions,[25–34] and C–O bond formation[35,36] have been reported. Recently, we developed a general synthesis of 2,3-disubstituted benzo[*b*]furans by the palladium/copper-catalyzed cross-coupling of various *o*-iodoanisoles and terminal alkynes, followed by electrophilic cyclization with I_2, PhSeCl, or p-$O_2NC_6H_4SCl$ under very mild reaction conditions (Scheme 1).[37]

In our continuing research efforts to adapt heterocyclization chemistry to a high-throughput synthesis format, we herein report the first solution-phase library synthesis of benzofurans by our electrophilic cyclization chemistry. We demonstrate the significance of this methodology by elaborating the resulting 3-iodobenzofurans via various palladium-catalyzed couplings, such as Suzuki–Miyaura, carbonylative Suzuki, Sonogashira, Heck, and carboalkoxylation chemistry, to a 121-member library of 2,3,5-trisubstituted benzo[*b*]furans **14** (see Scheme 4) in modest yields.

Results and Discussion

The strategy for library production is shown in Scheme 2. We hypothesized that our previously described iodocyclization process should readily afford 2,3,5-trisubstituted benzo[*b*]furans **14** as key intermediates to compounds of biological interest. Also, numerous analogues of **14** should be readily prepared through various coupling reactions and

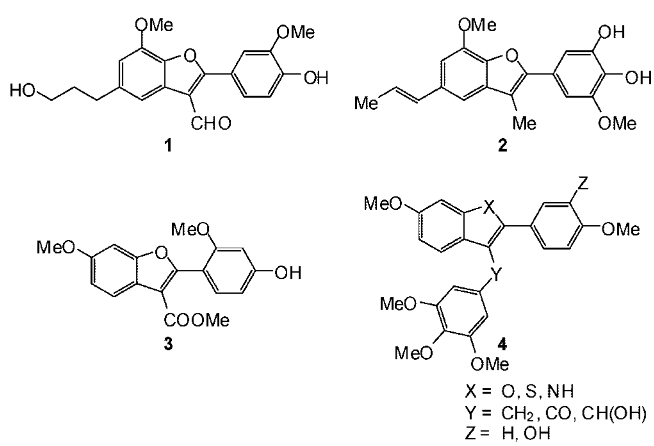
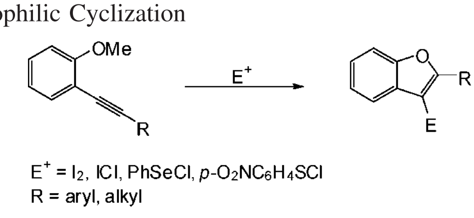


Figure 1. Some biologically active benzo[*b*]furans.

Scheme 1. Synthesis of 2,3-Disubstituted Benzo[*b*]furans by Electrophilic Cyclization



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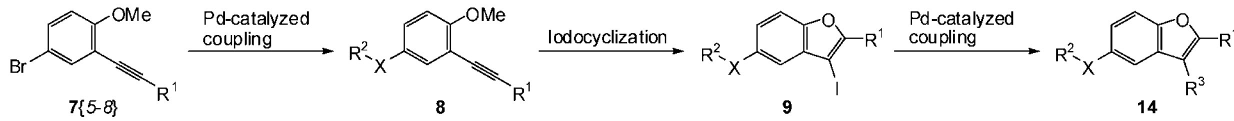
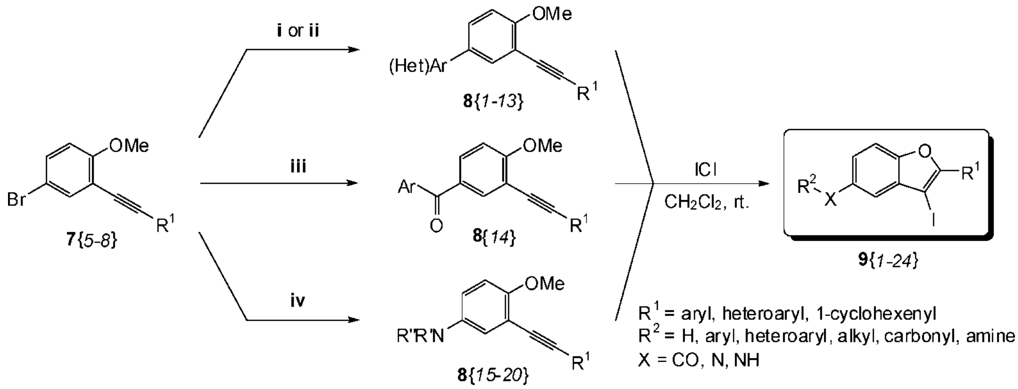
10.1021/cc800120y CCC: $40.75
Published on Web 10/21/2008

Scheme 2. Library Design for 2,3,5-Trisubstituted Benzo[*b*]furans **14**

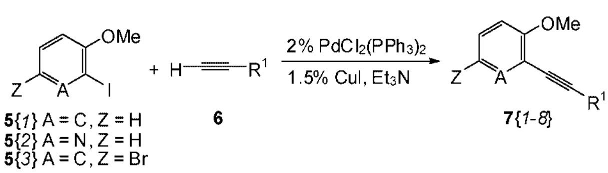


Scheme 3. Suzuki–Miyaura Coupling [**8**{*1–13*}], Carbonylative Suzuki Coupling [**8**{*14*}], Amination [**8**{*15–20*}], and Subsequent Iodocyclization [**9**{*1–24*}][a]



[a] (i) Five mol % $Pd(PPh_3)_4$, K_2CO_3 (3.0 equiv), and $ArB(OH)_2$ **10**{*1,4,7–8*} (1.5 equiv) in toluene/EtOH, 80 °C; (ii) 5 mol % $Pd(dba)_2$, 8 mol % PPh_3, KOH (3.0 equiv), and (Het)$ArB(OH)_2$ **10**{*6*} (1.5 equiv) in toluene/EtOH, 80 °C; (iii) 5 mol % $PdCl_2$(dppf), K_2CO_3 (3.0 equiv), NaI (3.0 equiv), CO (1.0 atm), and $ArB(OH)_2$ **10**{*1*} (1.1 equiv) in toluene/EtOH, 80 °C; (iv) 5 mol % $Pd_2(dba)_3$, DavePhos (0.1 equiv), NaO^tBu (1.4 equiv), and amines **11** (1.5 equiv) in toluene, 60 °C.

Table 1. Library Data for Compounds **7**{*1–8*}



compd	A	Z	R^1	yield(%)
7{*1*}	C	H	4-MeOC_6H_4	93
7{*2*}	C	H	3-MeC_6H_4	95
7{*3*}	N	H	4-MeOC_6H_4	98
7{*4*}	N	H	$3,5\text{-(MeO)}_2C_6H_3$	93
7{*5*}	C	Br	1-cyclohexenyl	84
7{*6*}	C	Br	4-MeOC_6H_4	90
7{*7*}	C	Br	3-thiophenyl	94
7{*8*}	C	Br	3-MeC_6H_4	93

subsequent functionalization at the C-3 and C-5 positions. The starting material, 4-bromo-2-iodoanisole **5**{*3*} (see Table 1), can be easily prepared through regioselective iodination of 4-bromoanisole.[38] 2-Iodoanisole [**5**{*1*}] and 2-iodo-3-methoxypyridine [**5**{*2*}] were obtained commercially. The alkynes **7** required for cyclization are readily prepared by the palladium/copper-catalyzed Sonogashira cross-coupling[39] of the methoxy-substituted aryl or heteroaryl iodides **5** with terminal alkynes **6** at room temperature. The results are summarized in Table 1. As shown in the table, the requisite alkynes **7**{*1–8*} are readily obtained by this straightforward approach.

As outlined in Scheme 3, the bromoalkynes **7**{*5–8*} are readily elaborated to the more highly substituted alkynes **8** via standard palladium-based methodology. As summarized in Table 2, the palladium-catalyzed Suzuki–Miyaura coupling of bromoalkynes **7**{*5–8*} with boronic acids **10** proceeds in the presence of a base to provide alkynes **8**{*1–13*}.[40,41] Bromoalkyne **7**{*6*} readily reacts with 4-methoxyphenylboronic acid [**10**{*1*}] under one atmosphere of carbon monoxide in the presence of $PdCl_2$(dppf) as a catalyst to give the corresponding ketone **8**{*14*}.[42] Unfortunately, this process affords only a low yield of **8**{*14*} (38%) because of the formation of the direct coupling product **8**{*1*} (14%), as well as recovery of the starting material **7**{*6*}. Work is currently underway to improve this process. The corresponding amines **8**{*15–20*} were obtained by palladium-catalyzed amination of several bromoalkynes **7** with amines **11**.[43] The secondary amines morpholine [**11**{*1*}] and pyrrolidine [**11**{*2*}] gave the corresponding products **8**{*15–18*} in moderate yields after 12 h reaction time. As expected, compounds **8**{*19*} and **8**{*20*} were obtained in excellent yields within 3 h when employing *n*-butylamine [**11**{*3*}] and 4-methylaniline [**11**{*4*}] (see the Supporting Information for the experimental details).

As the key step in our library synthesis, variously substituted iodobenzofuran derivatives **9** were efficiently prepared within 1–2 h by electrophile cyclization of the corresponding methoxy-containing alkynes **7**{*1–4*} and **8**{*1–20*} using ICl in CH_2Cl_2 at ambient temperature (Table 2 and Figure 2). All of the reactions were monitored by thin layer chromatography, and the products were purified by column chromatography. We did not systematically investigate the effects of various substituents in the C-5 position of the aromatic ring system. However, it is noteworthy that pyridine derivatives were treated with ICl under our standard electrophilic cyclization conditions, affording the desired furopyridines **9**{*3–4*} in moderate yields. The presence of an electron-donating OMe group in the para position of the phenyl ring of the R^1 group gave excellent yields of the desired iodobenzofuran products **9**{*5–9*} and **9**{*19*}. It is also noteworthy that substitution of the alkynyl unit with a thiophene heterocycle gave 3-iodobenzofurans **9**{*10–13*} in good to excellent yields. Alkynes **8**{*10–12*}, having a 1-cyclohexenyl group, also reacted by electrophilic cycliza-

Table 2. Library Data for Compounds **8**{*1−20*} and **9**{*1−24*}

alkyne **7/8**	R^1	R^2	*t* (h)	yield (%)[b]	3-iodobenzofuran[a] **9**	yield (%)[b]
7{*1*}	4-$MeOC_6H_4$				**9**{*1*}	97
7{*2*}	3-MeC_6H_4				**9**{*2*}	92
7{*3*}	4-$MeOC_6H_4$				**9**{*3*}	76
7{*4*}	3,5-$(MeO)_2C_6H_3$				**9**{*4*}	58
8{*1*}	4-$MeOC_6H_4$	**10**{*1*}	8	69	**9**{*5*}	93
8{*2*}	4-$MeOC_6H_4$	**10**{*4*}	8	63	**9**{*6*}	89
8{*3*}	4-$MeOC_6H_4$	**10**{*6*}	8	57	**9**{*7*}	87
8{*4*}	4-$MeOC_6H_4$	**10**{*7*}	8	63	**9**{*8*}	90
8{*5*}	4-$MeOC_6H_4$	**10**{*8*}	8	72	**9**{*9*}	83
8{*6*}	3-thiophenyl	**10**{*1*}	8	78	**9**{*10*}	91
8{*7*}	3-thiophenyl	**10**{*4*}	8	81	**9**{*11*}	83
8{*8*}	3-thiophenyl	**10**{*6*}	8	62	**9**{*12*}	78
8{*9*}	3-thiophenyl	**10**{*7*}	8	83	**9**{*13*}	88
8{*10*}	1-cyclohexenyl	**10**{*4*}	8	71	**9**{*14*}	91
8{*11*}	1-cyclohexenyl	**10**{*6*}	8	68	**9**{*15*}	88
8{*12*}	1-cyclohexenyl	**10**{*7*}	8	68	**9**{*16*}	92
8{*13*}	3-MeC_6H_4	**10**{*4*}	8	67	**9**{*17*}	87
8{*14*}	4-$MeOC_6H_4$	**10**{*1*}	24	38(14)[c]	**9**{*18*}	82
8{*15*}	4-$MeOC_6H_4$	**11**{*1*}	12	78	**9**{*19*}	84
8{*16*}	3-MeC_6H_4	**11**{*1*}	12	73	**9**{*20*}	82
8{*17*}	3-thiophenyl	**11**{*1*}	12	71	**9**{*21*}	81
8{*18*}	3-MeC_6H_4	**11**{*2*}	12	59	**9**{*22*}	77
8{*19*}	4-$MeOC_6H_4$	**11**{*3*}	3	87	**9**{*23*}	51[d]
8{*20*}	4-$MeOC_6H_4$	**11**{*4*}	3	93	**9**{*24*}	28[d,e]

[a] All reactions were carried out using alkynes **7**{*1−4*} or **8**{*1−20*} and 1.5 equiv of ICl in CH_2Cl_2 at room temperature within 2−3 h, unless otherwise indicated. [b] Isolated yields after column chromatography. [c] Some starting material remained. The yield of the Suzuki−Miyaura direct coupling product is in parentheses. [d] ICl (2.0 + 1.0 equiv) was used. [e] An inseparable mixture was obtained.

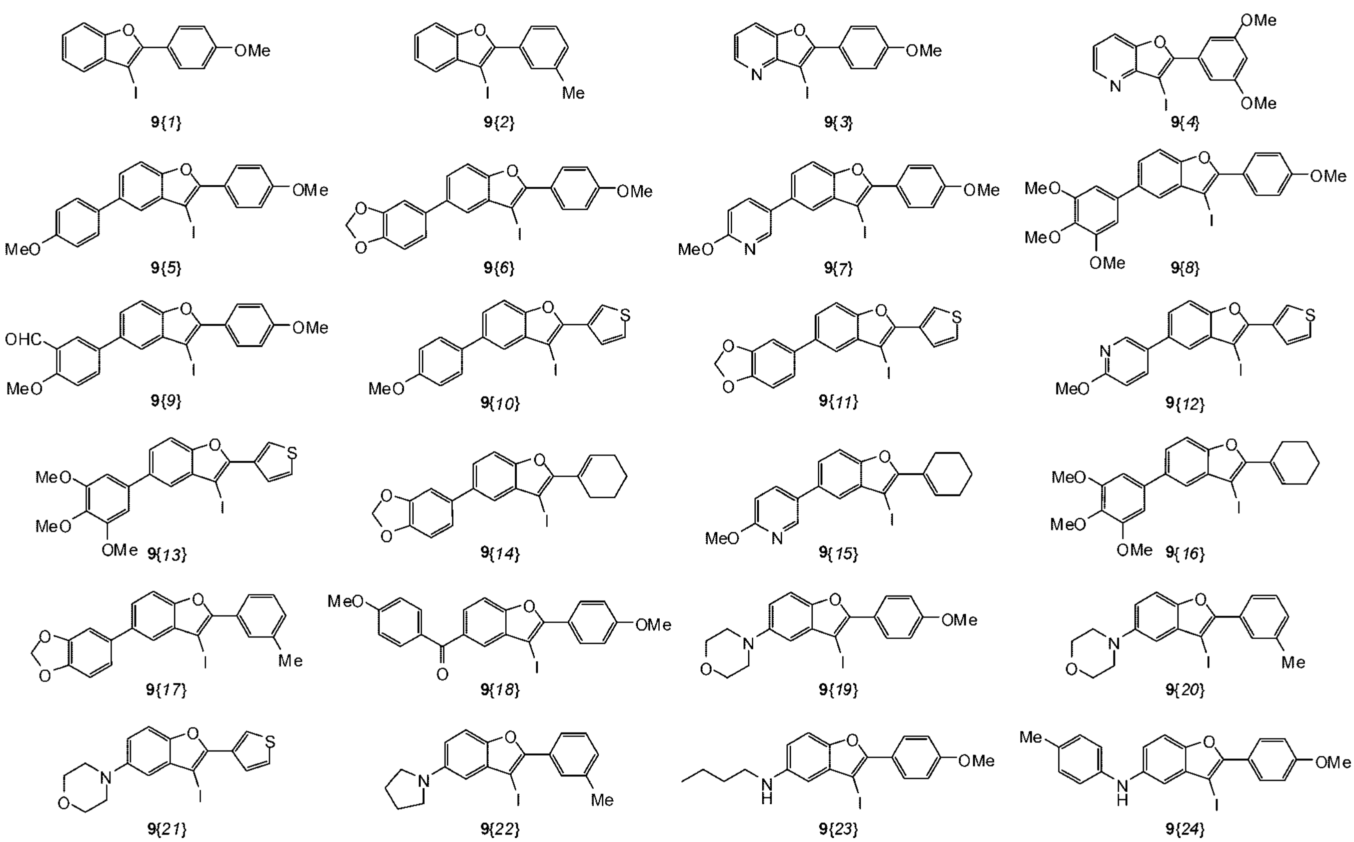


Figure 2. Synthesis of 3-iodobenzofurans **9**{*1−24*}.

tion to give the desired products **9**{*14−16*}. Alkynes with an *m*-tolyl substituent gave the desired products **9**{*17*}, **9**{*20*}, and **9**{*22*}. The iodobenzofuran **9**{*18*}, having a carbonyl group in the C-5 position, was produced in a good yield. The reaction of C-5 amine-substituted aryl alkynes generally afforded the desired benzofuran products in good yields under ordinary reaction conditions. However, the secondary amine-substituted alkyne **8**{*19*} produced the desired product **9**{*23*} in a slightly lower yield. As expected, an aniline-substituted alkyne **8**{*20*} also generated the desired product **9**{*24*}, but in a lower yield. The low yield here is probably caused by electrophilic substitution of the aniline ring of the product **9**{*24*}. This iodobenzofuran synthesis tolerates a wide variety of substituents, including halides, ethers, acetals, aldehydes, ketones, amines, aryl, heteroaryl, and alkyl groups, and proceeds under mild reaction condi-

Table 3. Library Data for Compounds **14**{*1*−*121*}

product	9	R3	method	yield (%)[b]	purity (%)[e]	product	9	R3	method	yield (%)[b]	purity (%)[e]
14{*1*}	**9**{*1*}	**10**{*5*}	A	39	84	**14**{*65*}	**9**{*8*}	**6**{*10*}	C	77	>99
14{*2*}	**9**{*2*}	**10**{*9*}	A[a]	47	>99	**14**{*66*}	**9**{*12*}	**6**{*9*}	C	76	>99
14{*3*}	**9**{*3*}	**10**{*1*}	A	51	>99	**14**{*67*}	**9**{*13*}	**6**{*5*}	C	82[c]	99
14{*4*}	**9**{*3*}	**10**{*6*}	A	38	99	**14**{*68*}	**9**{*13*}	**6**{*9*}	C	67	>99
14{*5*}	**9**{*3*}	**10**{*7*}	A	55	99	**14**{*69*}	**9**{*17*}	**6**{*6*}	C	52	98
14{*6*}	**9**{*5*}	**10**{*1*}	A	88[c]	>99	**14**{*70*}	**9**{*18*}	**6**{*2*}	C	85	>99
14{*7*}	**9**{*5*}	**10**{*6*}	A	78	>99	**14**{*71*}	**9**{*19*}	**6**{*1*}	C	78	>99
14{*8*}	**9**{*5*}	**10**{*7*}	A	83	>99	**14**{*72*}	**9**{*19*}	**6**{*7*}	C	57	>99
14{*9*}	**9**{*8*}	**10**{*10*}	A	71[c]	99	**14**{*73*}	**9**{*19*}	**6**{*9*}	C	78	>99
14{*10*}	**9**{*9*}	**10**{*1*}	A	57	>99	**14**{*74*}	**9**{*19*}	**6**{*12*}	C	34	99
14{*11*}	**9**{*10*}	**10**{*10*}	A	73[c]	98	**14**{*75*}	**9**{*21*}	**6**{*5*}	C	83[c]	>99
14{*12*}	**9**{*11*}	**10**{*1*}	A	62	>99	**14**{*76*}	**9**{*21*}	**6**{*7*}	C	61	>99
14{*13*}	**9**{*11*}	**10**{*6*}	A	53	99	**14**{*77*}	**9**{*21*}	**6**{*9*}	C	86[c]	>99
14{*14*}	**9**{*14*}	**10**{*1*}	A	47	>99	**14**{*78*}	**9**{*1*}	**12**{*1*}	D	66[c]	96
14{*15*}	**9**{*14*}	**10**{*2*}	A	28	>99	**14**{*79*}	**9**{*1*}	**12**{*3*}	D	61[c]	99
14{*16*}	**9**{*14*}	**10**{*6*}	A	51	>99	**14**{*80*}	**9**{*3*}	**12**{*1*}	D	47[c]	95
14{*17*}	**9**{*14*}	**10**{*7*}	A	69	>99	**14**{*81*}	**9**{*3*}	**12**{*2*}	D	72[c]	98
14{*18*}	**9**{*14*}	**10**{*9*}	A	53	99	**14**{*82*}	**9**{*3*}	**12**{*3*}	D	58	97
14{*19*}	**9**{*15*}	**10**{*3*}	A	32	98	**14**{*83*}	**9**{*5*}	**12**{*1*}	D	69[c]	99
14{*20*}	**9**{*17*}	**10**{*1*}	A	72[c]	>99	**14**{*84*}	**9**{*5*}	**12**{*3*}	D	71[c]	>99
14{*21*}	**9**{*17*}	**10**{*6*}	A	67	>99	**14**{*85*}	**9**{*6*}	**12**{*1*}	D	76[c]	98
14{*22*}	**9**{*17*}	**10**{*7*}	A	73[c]	>99	**14**{*86*}	**9**{*9*}	**12**{*3*}	D	71	99
14{*23*}	**9**{*17*}	**10**{*9*}	A	85[c]	>99	**14**{*87*}	**9**{*11*}	**12**{*2*}	D	71	>99
14{*24*}	**9**{*18*}	**10**{*9*}	A[a]	69[c]	>99	**14**{*88*}	**9**{*12*}	**12**{*1*}	D	78	99
14{*25*}	**9**{*19*}	**10**{*1*}	A	81[c]	>99	**14**{*89*}	**9**{*13*}	**12**{*1*}	D	69	93
14{*26*}	**9**{*19*}	**10**{*6*}	A	73	>99	**14**{*90*}	**9**{*14*}	**12**{*1*}	D	61	98
14{*27*}	**9**{*21*}	**10**{*1*}	A	83[c]	>99	**14**{*91*}	**9**{*14*}	**12**{*4*}	D	57	98
14{*28*}	**9**{*21*}	**10**{*6*}	A	71[c]	>99	**14**{*92*}	**9**{*17*}	**12**{*1*}	D	76[c]	99
14{*29*}	**9**{*22*}	**10**{*1*}	A	67	>99	**14**{*93*}	**9**{*17*}	**12**{*4*}	D	68	96
14{*30*}	**9**{*23*}	**10**{*3*}	A	57[c]	98	**14**{*94*}	**9**{*19*}	**12**{*2*}	D	58	99
14{*31*}	**9**{*23*}	**10**{*9*}	A	68[c]	99	**14**{*95*}	**9**{*19*}	**12**{*3*}	D	64[c]	>99
14{*32,(33)*}	**9**{*5*}	**10**{*4*}	B	34(29)[c,d]	>99	**14**{*96*}	**9**{*20*}	**12**{*1*}	D	81[c]	>99
14{*34,(35)*}	**9**{*6*}	**10**{*6*}	B	44(33)[c,d]	>99	**14**{*97*}	**9**{*21*}	**12**{*3*}	D	53[c]	>99
14{*36,(37)*}	**9**{*7*}	**10**{*1*}	B	46(27)[c,d]	>99	**14**{*98*}	**9**{*22*}	**12**{*3*}	D	57	>99
14{*38,(39)*}	**9**{*8*}	**10**{*1*}	B	41(31)[c,d]	>99	**14**{*99*}	**9**{*1*}	**13**{*1*}	E	58[c]	98
14{*40,(41)*}	**9**{*8*}	**10**{*6*}	B	43(35)[c,d]	>99	**14**{*100*}	**9**{*1*}	**13**{*3*}	E	29	>99
14{*42,(43)*}	**9**{*10*}	**10**{*1*}	B	49(32)[c,d]	>99	**14**{*101*}	**9**{*1*}	**13**{*5*}	E	56[c]	>99
14{*44,(45)*}	**9**{*20*}	**10**{*6*}	B	37(28)[c,d]	>99	**14**{*102*}	**9**{*1*}	**13**{*6*}	E	26	>99
14{*46*}	**9**{*1*}	**6**{*6*}	C	43	96	**14**{*103*}	**9**{*1*}	**13**{*7*}	E	27	96
14{*47*}	**9**{*2*}	**6**{*2*}	C	81[c]	99	**14**{*104*}	**9**{*3*}	**13**{*1*}	E	59	98
14{*48*}	**9**{*2*}	**6**{*4*}	C	82[c]	99	**14**{*105*}	**9**{*3*}	**13**{*5*}	E	37	97
14{*49*}	**9**{*3*}	**6**{*1*}	C	77[c]	>99	**14**{*106*}	**9**{*5*}	**13**{*1*}	E	71[c]	99
14{*50*}	**9**{*3*}	**6**{*8*}	C	41	96	**14**{*107*}	**9**{*5*}	**13**{*5*}	E	73	>99
14{*51*}	**9**{*3*}	**6**{*9*}	C	48	98	**14**{*108*}	**9**{*6*}	**13**{*6*}	E	37	>99
14{*52*}	**9**{*4*}	**6**{*2*}	C	21	97	**14**{*109*}	**9**{*7*}	**13**{*1*}	E	76[c]	>99
14{*53*}	**9**{*4*}	**6**{*3*}	C	18	98	**14**{*110*}	**9**{*7*}	**13**{*2*}	E	69[c]	>99
14{*54*}	**9**{*5*}	**6**{*1*}	C	83	>99	**14**{*111*}	**9**{*7*}	**13**{*4*}	E	48	>99
14{*55*}	**9**{*5*}	**6**{*2*}	C	84	>99	**14**{*112*}	**9**{*7*}	**13**{*5*}	E	55	>99
14{*56*}	**9**{*5*}	**6**{*5*}	C	73	98	**14**{*113*}	**9**{*8*}	**13**{*1*}	E	76[c]	>99
14{*57*}	**9**{*5*}	**6**{*9*}	C	81	98	**14**{*114*}	**9**{*8*}	**13**{*3*}	E	59	>99
14{*58*}	**9**{*5*}	**6**{*11*}	C	69	>99	**14**{*115*}	**9**{*13*}	**13**{*1*}	E	80[c]	99
14{*59*}	**9**{*5*}	**6**{*12*}	C	31	95	**14**{*116*}	**9**{*15*}	**13**{*1*}	E	53	>99
14{*60*}	**9**{*6*}	**6**{*5*}	C	69	>99	**14**{*117*}	**9**{*16*}	**13**{*1*}	E	58	98
14{*61*}	**9**{*6*}	**6**{*9*}	C	60	>99	**14**{*118*}	**9**{*17*}	**13**{*5*}	E	71[c]	>99
14{*62*}	**9**{*7*}	**6**{*2*}	C	79[c]	99	**14**{*119*}	**9**{*18*}	**13**{*1*}	E	74[c]	>99
14{*63*}	**9**{*7*}	**6**{*9*}	C	57	>99	**14**{*120*}	**9**{*20*}	**13**{*5*}	E	59	>99
14{*64*}	**9**{*8*}	**6**{*8*}	C	72	>99	**14**{*121*}	**9**{*21*}	**13**{*5*}	E	54[c]	99

[a] The THP ether-protected boronic acid **10**{*9*} was deprotected in situ using aq. HCl in THF at room temperature. [b] Isolated yield after preparative HPLC. [c] Isolated yield after column chromatography. [d] The number in parentheses is the yield of Suzuki-Miyaura direct coupling product. [e] UV purity determined at 214 nm after preparative HPLC.

tions. The 3-iodobenzofurans **9**{*1*−*24*} produced by this chemistry should be very useful for the synthesis of a wide variety of substituted benzo[*b*]furans **14**.

The 3-iodobenzofurans **9** can be further elaborated by using a variety of palladium-mediated processes, such as Suzuki−Miyaura coupling,[40,41] carbonylative Suzuki coupling,[42] Sonogashira coupling,[39] Heck coupling,[44] and carboalkoxylation[45] (Scheme 4). The crude products **14** were purified by either column chromatography or preparative HPLC. The results of this parallel library synthesis are summarized in Table 3, which indicates that the products **14** can be obtained in moderate to good yields with high purities. The reagents used for substitution of the iodine-containing products **9** were chosen on the basis of their commercial availability (e.g., boronic acids **10**, terminal alkynes **6**, styrenes **12**, and alcohols **13**) (Figure 3) and potential drug-like properties, resulting in a virtual library of all theoretically possible products of approximately 5000 potential compounds. This number was arrived at by determining all possible combinations of the R group variation with available starting materials. However, only a small subset of 121 compounds out of these 5000 virtual

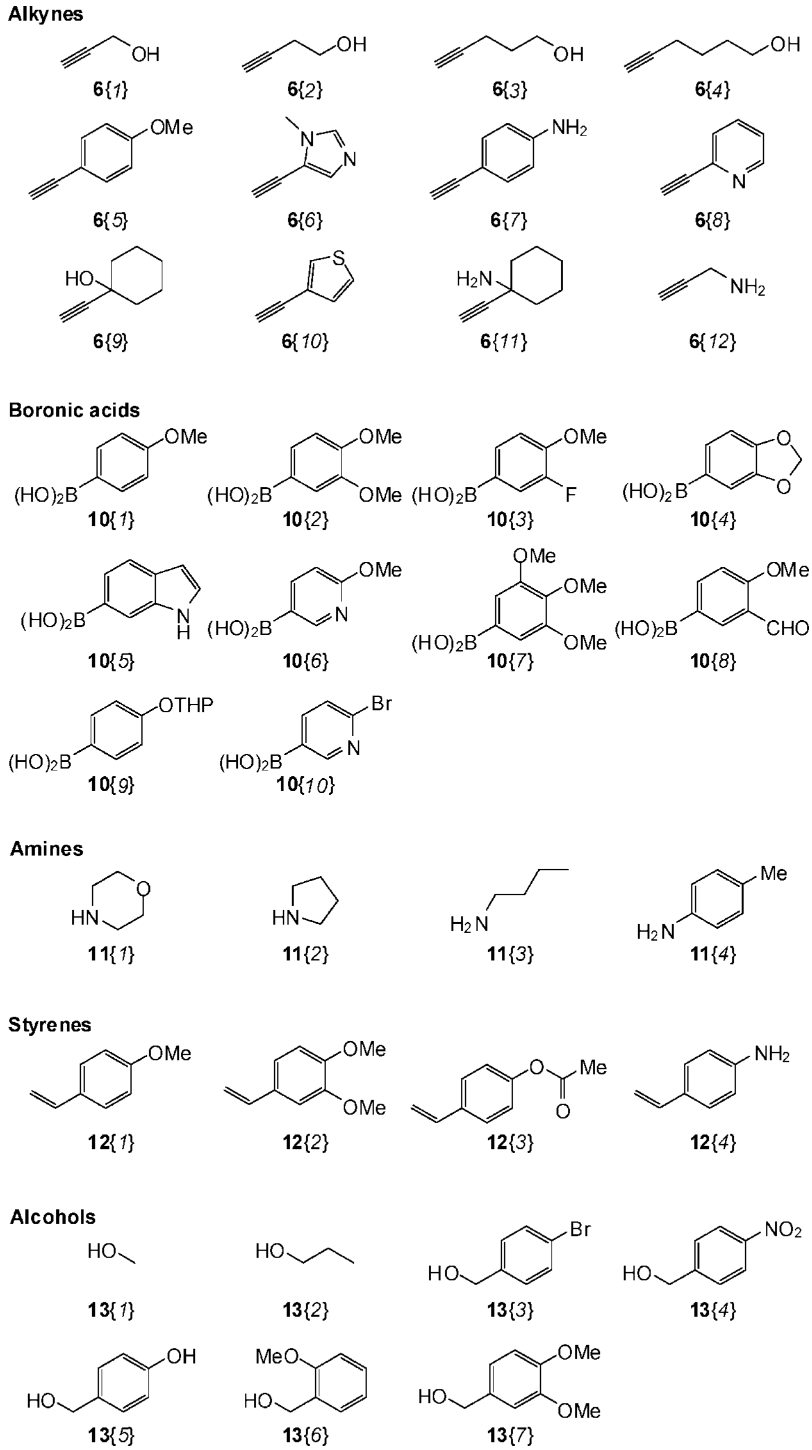
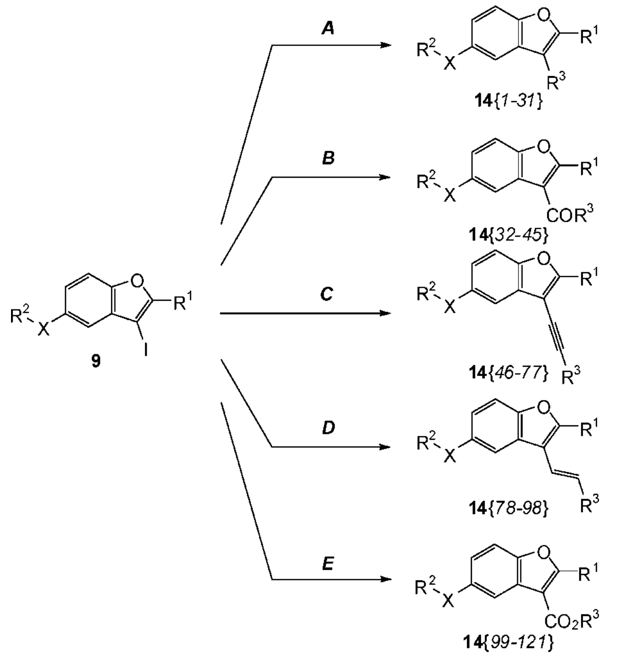


Figure 3. Diverse terminal alkynes **6**{*1*−*12*}, boronic acids **10**{*1*−*10*}, amines **11**{*1*−*4*}, styrenes **12**{*1*−*4*}, and alcohols **13**{*1*−*7*} used for library synthesis.

structures was actually made in the laboratory. Most of the selected 121 benzo[*b*]furan library members were Lipinski[46,47] compliant. The molecular weight, clogP, number of hydrogen bond donors and acceptors, and the number of rotatable bonds were either specified or calculated for each of the library members using the SYBYL[48] program.

The Suzuki−Miyaura coupling of the 3-iodobenzofurans **9** with various arylboronic acids **10** proceeded smoothly to give the desired products **14**{*1*−*31*} in modest yields. Most reactions were complete within 6 h in refluxing toluene (method A).[40,41] Product **14**{*24*}, containing a tetrahydropyranyl (THP) ether protecting group, was deprotected in situ in 69% yield using aqueous hydrochloric acid in THF at room temperature for a few minutes.[49] The carbonylative Suzuki coupling of 3-iodobenzofurans **9** with arylboronic acids **10** has been carried out in anisole in the presence of $PdCl_2(PPh_3)_2$ under carbon monoxide at atmospheric pressure (method B).[42] These reactions produced both the corresponding CO inserted carbonyl products and the direct Suzuki−Miyaura coupling products. The products were separated by column chromatography to give **14**{*32,34,36,38,40,42*} and **14**{*33,35,37,39,41,43*}, respectively. Sonogashira coupling

Scheme 4. Synthesis of Benzo[*b*]furans **14** using Various Palladium-Catalyzed Reactions[a]



[a] Method A (Suzuki-Miyaura coupling): 10% $Pd(PPh_3)_4$, KOH (3.0 equiv), **10** (1.5 equiv), toluene/EtOH/H_2O (20/5/1), reflux. Method B (carbonylative Suzuki coupling): CO (1 atm), 3 mol % $PdCl_2(PPh_3)_2$, K_2CO_3 (3.0 equiv), NaI (3.0 equiv), **10** (1.1 equiv), anisole, 80 °C. Method C (Sonogashira coupling): 3% $PdCl_2(PPh_3)_2$, 3% CuI, Et_2NH, **6** (1.2 equiv), DMF, 50 °C. Method D (Heck coupling): 5 mol % $Pd(OAc)_2$, n-Bu_4NI (1.0 equiv), Na_2CO_3 (2.5 equiv), $R^3CH{=}CH_2$ **12** (1.2 equiv), DMF, 80 °C. Method E (carboalkoxylation): CO (1 atm), 3 mol % $Pd(OAc)_2$, 5 mol % dppf, TEA (2.0 equiv), R^3OH **13** (1.5 equiv), DMF, 70 °C.

of the 3-iodobenzofurans **9** with various terminal acetylenes **6** nicely provides the corresponding alkynyl products **14**{*46*−*77*} (method C).[39] In addition, we have been able to perform Heck coupling on the 3-iodobenzofurans **9**. By allowing the compound to react under Heck reaction conditions in the presence of the styrenes **12**, we obtained the substituted olefin-containing benzo[*b*]furan products **14**{*78*−*98*} (method D).[44] Carboalkoxylation of the 3-iodobenzofurans **9** using one atmosphere of carbon monoxide and various alcohols **13** in the presence of catalytic amounts of $Pd(OAc)_2$ and dppf ligand afforded the ester-containing benzo[*b*]furans **14**{*99*−*121*} (method E).[45]

In conclusion, the 3-iodobenzofurans **9** have proven to be very useful templates for further diversification by a variety of C−C, C−N, and C−O bond forming reactions,[50−53] and are thus valuable building blocks for combinatorial chemistry.[54,55] We have demonstrated that 3-iodobenzofurans **9** readily react with various building blocks, for example, boronic acids **10**, terminal alkynes **6**, styrenes **12**, and carbon monoxide plus alcohols **13**, to efficiently construct a 121-member library of highly substituted benzo[*b*]furans **14**. The desired 3-iodobenzofurans **9** are readily prepared by our previously published electrophilic cyclization chemistry. Of the 121 compounds produced, 74 compounds were obtained in >99% purity. The benzo[*b*]furan library members **14** will be evaluated against various biological screens by the National Institutes of Health Molecular Library Screening Center Network.

Acknowledgment. We thank the National Institute of General Medical Sciences (GM070620 and GM079593) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (GM069663) for support of this research, Johnson Matthey, Inc., and Kawaken Fine Chemicals Co., Ltd., for donations of palladium catalysts, and Frontier Scientific and Synthonix for donations of boronic acids.

Supporting Information Available. Synthetic methods, spectral assignments, and copies of ^1H and ^{13}C NMR spectra for all previously unreported starting materials and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC800120Y