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Solution-Phase Synthesis of a Highly Substituted Furan Library

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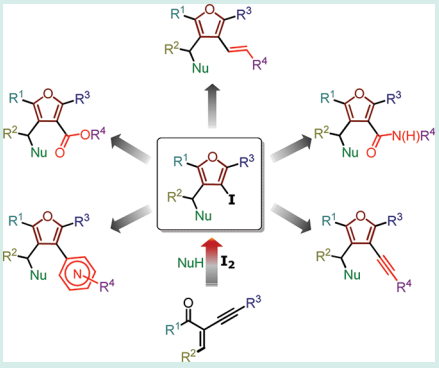
Supporting Information

ABSTRACT: A library of furans has been synthesized by iodocyclization and further diversified by palladium-catalyzed coupling processes. The key intermediate 3-iodofurans have been prepared by the electrophilic iodocyclization of 2-iodo-2-alken-1-ones in the presence of various nucleophiles in good to excellent yields under mild reaction conditions. These 3-iodofurans are the key components for library generation through subsequent elaboration by palladium-catalyzed processes, such as Suzuki−Miyaura, Sonagashira, Heck, aminocarbonylation, and carboalkoxylation chemistry to afford a diverse set of 2,3,4,5-tetrasubstituted furans.



KEYWORDS: *solution-phase parallel synthesis, multisubstituted furans, 3-iodofurans, iodocyclization, electrophiles, nucleophiles*

INTRODUCTION

Combinatorial chemistry and high-throughput screening (HTS) for drug discovery have made it possible to synthesize and screen large repositories of chemically diverse scaffolds in search of small molecules that disrupt or regulate macromolecular function.[1,2] Highly substituted furans are frequently found as subunits in many bioactive natural products and pharmaceutically important substances, and they are also important building blocks in organic synthesis.[3−11] Selected simple biologically active furan derivatives are shown in Figure 1. (+)-Furodysin (**I**) and (+)-furodysinin (**II**) are two sesquiterpenes isolated from pantropical marine sponges of the genus Dysidea.[12] Their absolute configurations has been established by the synthesis of their (−)-isomers from (+)-9-bromocamphor.[13] Interestingly, (−)-furodysinin was found in the Mediterranean *D. tupha*[14] and both (−)-furodysin (**III**) and (−)-furodysinin (**IV**) have been shown to occur in *D. herbacea*.[15] The pinguisane class have attracted interest because of their biological activity and rare carbon skeleton.[16] Two examples of pinguisanes are pinguisone (**V**) and norpinguisone (**VI**), which exhibit antifeedant and antifungal activity respectively.[17,18] The hugely successful drug molecule ranitidine (**VII**) (trade name Zantac),[19] is a histamine H_2-receptor antagonist that inhibits stomach acid production. It is commonly used in the treatment of peptic ulcer disease (PUD) and gastresophageal reflux disease (GERD). Ranitidine is also known to give false positives for methamphetamine on drug tests.[19−21]

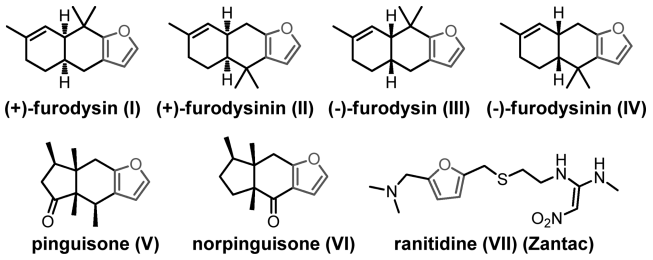
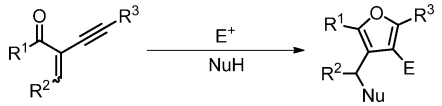


Figure 1. Examples of significant furan-containing natural products and pharmaceuticals.

Scheme 1. Efficient Synthesis of Multisubstituted Furans by Electrophilic Cyclization of 2-(1-Alkynyl)-2-alken-1-ones in the Presence of Various Nucleophiles



E = H (cat. $AuCl_3$); NuH = ROH, enol, ArH
E = I; NuH = ROH, RCO_2H, H_2O
E = PhSe; NuH = ROH

For these reasons, the efficient synthesis of multiply substituted furans continues to attract the interest of synthetic

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Scheme 2. Library Design for the Tetrasubstituted Furans 3

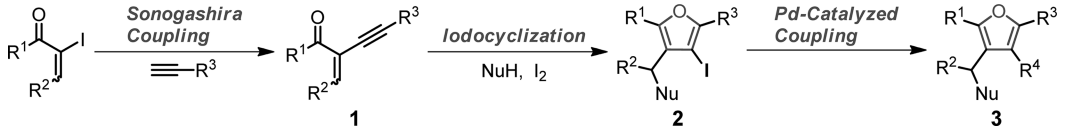
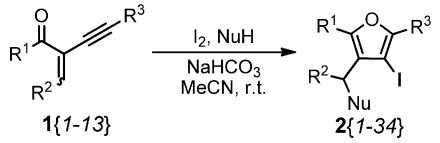


Table 1. Library Data for the 3-Iodofurans 2{*1*−*34*}[a]



entry	alkyne **1**	NuH	iodofuran **2**	yield (%)[b]	entry	alkyne **1**	NuH	iodofuran **2**	yield (%)[b]
1	**1**{*1*}	H_2O	**2**{*1*}	42	18	**1**{*3*}	n-C_3H_7OH	**2**{*18*}	49
2	**1**{*2*}	H_2O	**2**{*2*}	53[c]	19	**1**{*8*}	CH_3COOH	**2**{*19*}	85
3	**1**{*3*}	H_2O	**2**{*3*}	78	20	**1**{*1*}	CH_3COOH	**2**{*20*}	82
4	**1**{*4*}	H_2O	**2**{*4*}	89	21	**1**{*5*}	CH_3COOH	**2**{*21*}	77
5	**1**{*5*}	H_2O	**2**{*5*}	73	22	**1**{*7*}	CH_3COOH	**2**{*22*}	69
6	**1**{*6*}	H_2O	**2**{*6*}	47	23	**1**{*1*}	$HO(CH_2)_2OH$	**2**{*23*}	86
7	**1**{*7*}	H_2O	**2**{*7*}	68	24	**1**{*3*}	$HO(CH_2)_2OH$	**2**{*24*}	66
8	**1**{*3*}	CH_3OH	**2**{*8*}	53	25	**1**{*4*}	$HO(CH_2)_2OH$	**2**{*25*}	83
9	**1**{*8*}	CH_3OH	**2**{*9*}	73	26	**1**{*8*}	$HO(CH_2)_2OH$	**2**{*26*}	82
10	**1**{*6*}	CH_3OH	**2**{*10*}	59	27	**1**{*7*}	$HO(CH_2)_2OH$	**2**{*27*}	82
11	**1**{*7*}	CH_3OH	**2**{*11*}	77[c]	28	**1**{*9*}	$HO(CH_2)_2OH$	**2**{*28*}	87
12	**1**{*9*}	CH_3OH	**2**{*12*}	87	29	**1**{*10*}	$HO(CH_2)_2OH$	**2**{*29*}	89
13	**1**{*2*}	C_2H_5OH	**2**{*13*}	73	30	**1**{*11*}	$HO(CH_2)_2OH$	**2**{*30*}	82
14	**1**{*8*}	C_2H_5OH	**2**{*14*}	77	31	**1**{*12*}	$HO(CH_2)_2OH$	**2**{*31*}	81
15	**1**{*5*}	C_2H_5OH	**2**{*15*}	87	32	**1**{*13*}	$HO(CH_2)_2OH$	**2**{*32*}	84
16	**1**{*7*}	C_2H_5OH	**2**{*16*}	66	33	**1**{*4*}	$HO(CH_2)_4OH$	**2**{*33*}	77
17	**1**{*9*}	C_2H_5OH	**2**{*17*}	82	34	**1**{*4*}	$HO(CH_2)_5OH$	**2**{*34*}	65

[a]Unless otherwise noted, all of the reactions have been carried out using $NaHCO_3$ (2.0 equiv), the nucleophile (4.0 equiv), and I_2 (2.0 equiv) in MeCN (0.1 M conc.) at room temperature for 0.5 h. [b]Isolated yields after column chromatography. [c]An inseparable mixture was obtained. This material decomposes quickly in solution.

chemists. Numerous heteroannulation protocols, including transition metal-catalyzed reactions, leading to multisubstituted furans have been reported.[9,22−35] Among the variety of oxygen-containing compounds that can be subjected to cyclization, unsaturated alcohols or ketones are substrates of major interest.[25,36−41] Previously, we found that analogous 2-(1-alkynyl)-2-alken-1-ones, which are easily prepared from simple, readily available starting materials, can be very efficiently coupled with a wide variety of nucleophiles using either catalytic amounts of $AuCl_3$[38] or iodine[40,42,43] as an electrophile to afford functionally substituted furans (Scheme 1).

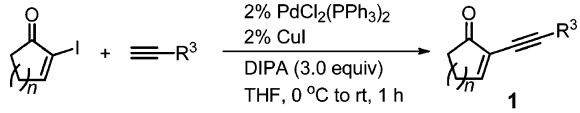
Electrophilic iodocyclization is one of the most powerful methods for the efficient synthesis of a variety of functionalized carbocycles and heterocycles under mild conditions.[4,39,42,44] Furthermore, we have demonstrated that the resulting iodine-containing products are very useful templates for further diversification by a variety of C−C, C−N, and C−O bond-forming processes and are thus valuable building blocks for combinatorial chemistry.[45−51]

Herein, in an extension of our previous studies,[40] we wish to report the synthesis of a solution phase furan library using this methodology and subsequent elaboration of the resulting multisubstituted 3-iodofurans **2** by various palladium-catalyzed couplings to generate 2,3,4,5-tetrasubstituted furans **3**. To synthesize a library with greater chances for biological activity, the multisubstituted furan template **3** has been evaluated computationally for its drug-like properties on the basis of Lipinski's "rule of five".[52]

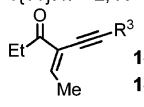
RESULTS AND DISCUSSION

We hypothesized that our previously described iodocyclization process[40] should readily afford 2,3,4,5-tetrasubstituted furans **3** as key intermediates to compounds of biological interest (Scheme 2). The alkynes **1**{*1*−*13*} were prepared by the palladium/copper-catalyzed

Scheme 3. Preparation of 2-(1-Alkynyl)-2-alken-1-ones 1{*1*−*13*}



1{*1*}: n = 1, R^3 = 4-$MeOC_6H_4$ (92%)
1{*2*}: n = 1, R^3 = 3-thiophenyl (87%)
1{*3*}: n = 1, R^3 = 4-$Me_2NC_6H_4$ (85%)
1{*4*}: n = 2, R^3 = C_6H_5 (74%)
1{*5*}: n = 2, R^3 = 3-$MeOC_6H_4$ (83%)
1{*6*}: n = 2, R^3 = 2,5-$(MeO)_2C_6H_3$ (58%)
1{*7*}: n = 2, R^3 = 3-thiophenyl (66%)
1{*8*}: n = 2, R^3 = 4-$MeOC_6H_4$ (91%)
1{*9*}: n = 2, R^3 = 4-$Me_2NC_6H_4$ (75%)
1{*10*}: n = 2, R^3 = 4-NCC_6H_4 (90%)
1{*11*}: n = 2, R^3 = 1-cyclohexenyl (87%)



1{*12*}: R^3 = C_6H_5 (66%)
1{*13*}: R^3 = 4-$MeOC_6H_4$ (81%)

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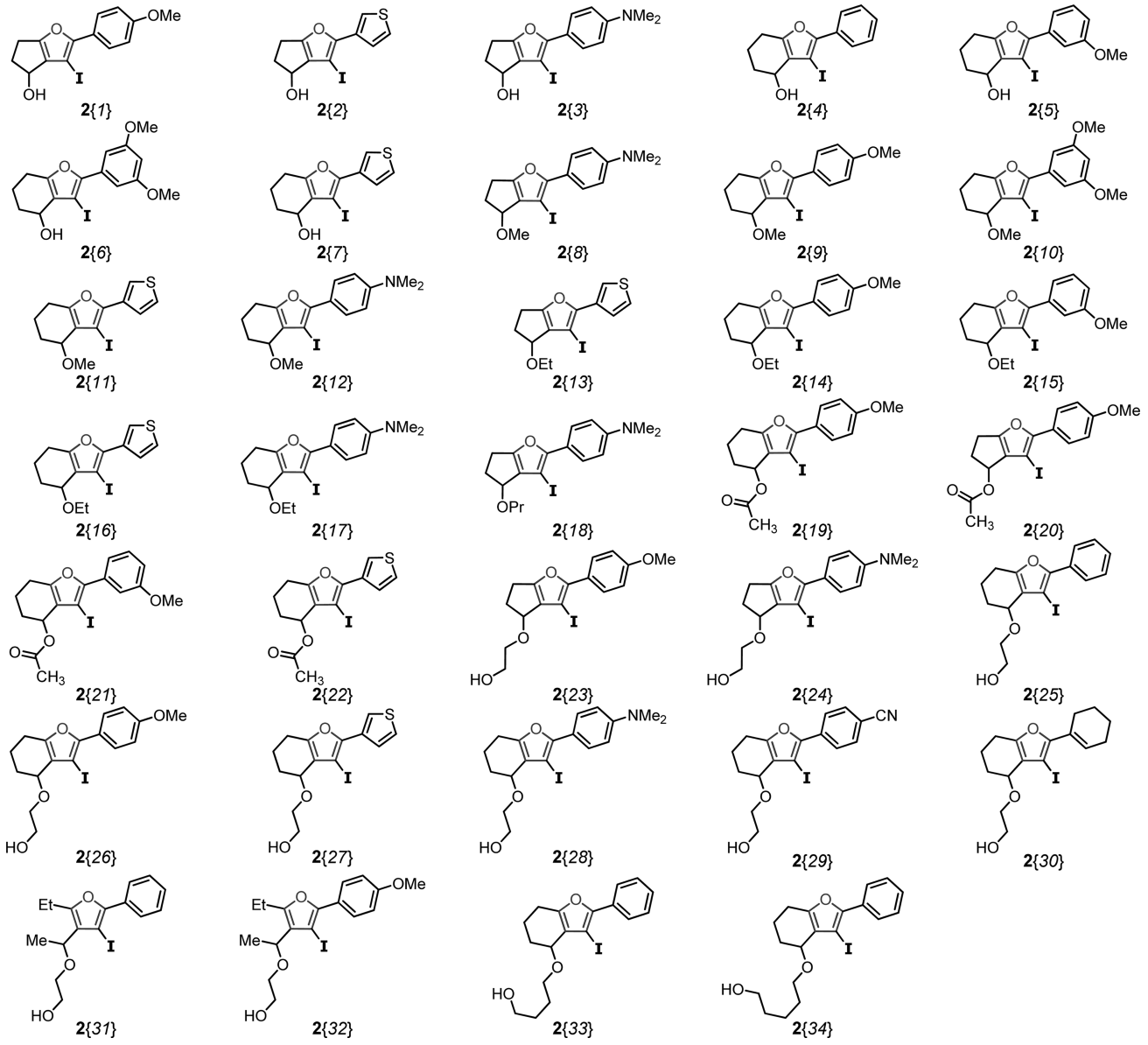

Figure 2. 3-Iodofuran Library 2{*1*−*34*}.

Sonogashira coupling of appropriate starting 2-iodo-2-alken-1-ones[53] with various terminal alkynes. Heteroatoms were included in the acetylenes to impart drug-like, hydrogen bond donor or acceptor properties to the 2,3,4,5-tetrasubstituted furans **3**. The results are summarized in Scheme 3.

Accordingly, a set of tetrasubstituted 3-iodofurans 2{*1*−*34*} were efficiently prepared by electrophilic cyclization of the corresponding alkynes **1** in the presence of various nucleophiles including water, primary alcohols, acetic acid, and various diols using I_2 for only 0.5 h under ambient conditions. The results of this iodocyclization process are summarized in Table 1 and Figure 2. All of the reactions were monitored by thin layer chromatography and the products purified by column chromatography. All compounds **2** were characterized by ^{1}H and ^{13}C NMR spectroscopy (see the Supporting Information for the experimental details).

These iodocyclization products **2** are the key components for library generation through subsequent elaboration by palladium-catalyzed processes, such as Suzuki−Miyaura, Sonagashira, Heck, aminocarbonylation, and carboalkoxylation reactions, affording a diverse set of 2,3,4,5-tetrasubstituted furans **3** (Scheme 4). Out of the numerous possible combinations, our efforts have been guided by using Lipinski's rule of five and the commercial availability of boronic acids **4**, terminal alkynes **5**, styrenes **6**, amines **7**, and alcohols **8** (Figure 3). The purity of the reaction mixtures has been analyzed by thin layer chromatography (TLC), liquid chromatography−mass spectrometry (LC-MS), and high performance liquid chromatography (HPLC). This data has been used to populate a virtual library of all theoretically possible products, giving roughly 8000 unique potential compounds in a combinatorial fashion.

The results for the palladium-catalyzed coupling processes performed on the multisubstituted furans 3{*1*−*158*} are summarized in Tables 2−6. Various boronic acids **4** for the Suzuki−Miyaura coupling of the multisubstituted 3-iodofurans **2** were chosen on the basis of their commercial availability and their ability to give the desired products 3{*1*−*27,52*−*60,78*−*81,123*−*128*} (Method A, Scheme 4). Sonogashira coupling of the 3-iodofurans **2** with various terminal alkynes **5** provides the corresponding alkyne products 3{*28*−*40,61*−*71,82*−*93,104*−*110,129*−*139*} (Method B, Scheme 4). No reaction took place

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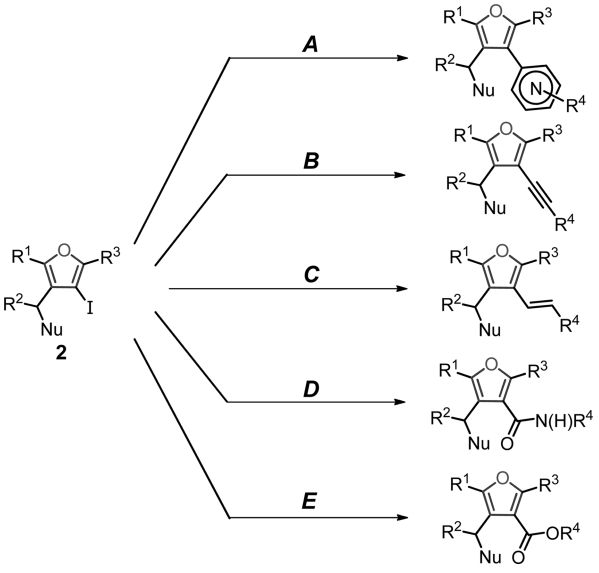
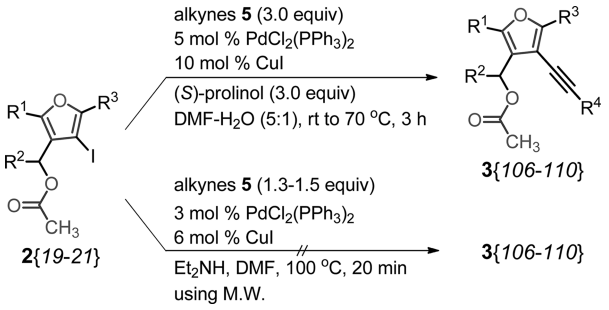
Scheme 4. Library Generation of Various Tetrasubstituted Furans 3 from the 3-Iodofurans 2[a]



[a]Method A (Suzuki–Miyaura coupling): 3{*1–27,52–60,78–81,123–128*} 10 mol % $Pd(PPh_3)_4$, K_2CO_3 (2.5 equiv), boronic acid **4** (1.5 equiv), toluene/EtOH/H_2O (20/5/1), 80 °C. Method B (Sonogashira coupling), 3{*28–40,61–71,82–93,104–105,129–139*} 3 mol % $PdCl_2(PPh_3)_2$, 6 mol % CuI, alkynes **5** (1.2 equiv), Et_2NH, DMF, 100 °C, 20 min, using microwave irradiation; 3{*106–110*} 5 mol % $PdCl_2(PPh_3)_2$, 10 mol % CuI, (*S*)-prolinol (3.0 equiv), alkynes **5** (1.2 equiv), DMF/H_2O (v/v, 5:1), 70 °C. Method C (Heck coupling): 3{*41–43*} 5 mol % $Pd(OAc)_2$, *n*-Bu_4NI (1.0 equiv), Na_2CO_3 (2.5 equiv), styrenes **6** (1.2 equiv), DMF, 80 °C. Method D (aminocarbonylation): 3{*72,94–96,140–141*} CO (1 atm), 10 mol % $PdCl_2(PPh_3)_2$, PPh_3 (0.2 equiv), amines **7** (1.5 equiv), DMF, Et_3N (2.0 equiv), 80 °C. Method E (carboalkoxylation): 3{*44–51,73–77,97–103,111–122,142–164*} CO (1 atm), 10 mol %

Scheme 5. Sonogashira Coupling Using the Acetoxy-Containing 3-Iodofurans 2{*19–21*} to Form Alkyne-Containing Furans 3{*106–110*}



when the acetoxy-containing iodofurans 2{*19–21*} were subjected to these reaction conditions. The combination of DMF/water as the solvent and (*S*)-prolinol as the base was more effective than the use of Et_2NH and organic solvents, such as DMF (Scheme 5).[54] Olefin-containing furan products 3{*41–43*} also have been prepared by the Heck coupling of 3-iodofurans **2** with a small styrene sublibrary **6** (Method C, Scheme 4). Amide-containing products 3{*72,94–96,140–141*} have been prepared by the palladium-catalyzed aminocarbonylation of 3-iodofurans **2** using one atmosphere of carbon monoxide and the amines **7** (Method D, Scheme 4). In addition, carboalkoxylation of the 3-iodofurans **2** using one atmosphere of carbon monoxide and various alcohols **8** in the presence of a palladium catalyst afforded the ester-containing furan products 3{*44–51,73–77,97–103,111–122,142–164*} (Method E, Scheme 4). These processes have been performed in parallel on approximately a 35–45 mg scale, starting from the 3-iodofurans **2**. All of the crude furan products **3** were isolated by either column chromatography or preparative HPLC.

We have used Lipinski's rule of five as a general guide for bioavailability, because compounds with poor bioavailability face more of a challenge in becoming successful clinical candidates. The distributions of molecular weight, clogP, hydrogen donors, hydrogen acceptors, and rotatable bonds for the synthesis library derived from 3{*1–164*} are shown in Figure 4. The molecular weight (less than 500), clogP (less than 5), number of hydrogen bond donors (less than 5 H) and acceptors (less than 10 H), and the number of rotatable bonds (less than 10) have been calculated for each of the library members using the SYBYL program.[20] As can be seen by viewing the data, most of the key parameters for members of the library within the range of those predicted for biologically active furan candidates.

CONCLUSIONS

In summary, we have designed a novel multisubstituted furan library, which has been rapidly constructed by solution-phase synthesis utilizing iodocyclization and palladium-catalyzed couplings. Various substituent 3-iodofurans **2** have been easily prepared through the iodocyclization of 2-(1-alkynyl)-2-alken-1-ones using I_2 as the electrophile in the presence of various nucleophiles. The multisubstituted furans **3** have been synthesized by palladium-catalyzed couplings, such as Suzuki–Miyaura, Sonogashira, Heck, aminocarbonylation, and carboalkoxylation chemistry, on a diverse set of 3-iodofuran **2** building blocks, which has provided about 20+ mg pure samples of each library compound. The elaborated multisubstituted furan **3** library members have been added to the collection of the Kansas University NIH Center for Chemical Methodologies and Library Development (KU CMLD) and will be submitted to the National Institutes of Health Molecular Library Screening Center Network (MLSCN) for evaluation by a broad range of assays. We expect this basic methodology to find extensive application in the fields of combinatorial chemistry, diversity-oriented synthesis and drug discovery.

EXPERIMENTAL PROCEDURES

General Procedure for Sonogashira Coupling to Form the 2-(1-Alkynyl)-2-alken-1-ones 1{*1–13*}. The desired products **1** were prepared by a literature procedure.[42] The appropriate 2-iodo-2-alken-1-one[53] (10.0 mmol), 2 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, and the terminal alkyne (15.0 mmol) were added to THF (50 mL) at 0 °C and then diisopropylamine (3.0 equiv) was added. The reaction mixture was stirred for 1 h at 0 °C and allowed to warm to room temperature to complete the reaction, which was monitored by TLC analysis. After the reaction was over, the resulting mixture was diluted with EtOAc (2 × 200 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes as the eluent to afford the corresponding 2-(1-alkynyl)-2-alken-1-ones **1**.

Alkyne [1{1}]. The product was obtained as a pale red solid (92% yield): mp =99–100 °C (uncorrected); ^1H NMR (400 MHz, $CDCl_3$) δ 2.41–2.47 (m, 2H), 2.66–2.73 (m, 2H), 3.77

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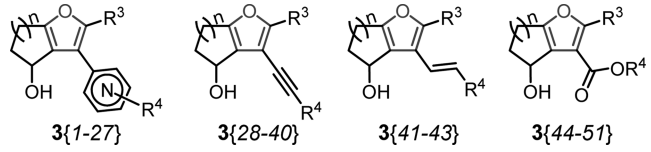
Table 2. Library Data for Compounds 3{*1*−*51*}



3{*1-27*} 3{*28-40*} 3{*41-43*} 3{*44-51*}

product **3**	*n*	R^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity (%)[a]	yield (%)[b]
3{*1*}	1	4-$MeOC_6H_4$	4{*2*}	A	$[M + H]^+$	350.1518	351.1530	97	74[f]
3{*2*}	1	4-$MeOC_6H_4$	4{*5*}	A	$[M + H]^+$	396.1373	397.1388	99	66[f]
3{*3*}	1	4-$MeOC_6H_4$	4{*17*}	A	$[M + H]^+$	338.1267	339.1351	>99	62
3{*4*}	1	3-thiophenyl	4{*9*}	A	$[M + H]^+$	372.1031	373.1043	99	58[f]
3{*5*}	1	3-thiophenyl	4{*10*}	A	$[M + H]^+$	372.0832	373.0903	97	19
3{*6*}	1	3-thiophenyl	4{*16*}	A	$[M + H]^+$	326.1089	327.1175	82	41
3{*7*}	1	4-$Me_2NC_6H_4$	4{*4*}	A	$[M + H]^+$	367.1584	368.1592	99	52
3{*8*}	2	C_6H_5	4{*1*}	A		348.1362			67[f]
3{*9*}	2	C_6H_5	4{*9*}	A	$[2M + H]^+$	380.1623	761.3345	>99	72
3{*10*}	2	C_6H_5	4{*11*}	A	$[M]^+$	348.1362	348.1372		81[f]
3{*11*}	2	C_6H_5	4{*18*}	A	$[M + Na]^+$	308.1049	331.0943	98	61
3{*12*}	2	3-$MeOC_6H_4$	4{*4*}	A	$[M + H]^+[-H_2O]$[c]	368.1424	385.1464	99	77
3{*13*}	2	3-$MeOC_6H_4$	4{*6*}	A	$[M + H]^+[-H_2O]$	378.1467	361.1430	>99	39
3{*14*}	2	3-$MeOC_6H_4$	4{*7*}	A	$[M + H]^+[-H_2O]$	378.1467	361.1431	84	26
3{*15*}	2	3-$MeOC_6H_4$	4{*11*}	A	$[M + H]^+$	362.1519	363.1598	98	75[f]
3{*16*}	2	3-$MeOC_6H_4$	4{*13*}	A	$[M + H]^+$	378.1467	379.1553	99	61
3{*17*}	2	3-$MeOC_6H_4$	4{*14*}	A	$[M + H]^+$	399.0470	400.0532	>99	13
3{*18*}	2	3-$MeOC_6H_4$	4{*15*}	A	$[M + H]^+$	351.1471	352.1545	>99	88[f]
3{*19*}	2	3-$MeOC_6H_4$	4{*17*}	A	$[M + H]^+$	352.1423	353.1506	78	41
3{*20*}	2	3-$MeOC_6H_4$	4{*18*}	A	$[M + H]^+$	338.1143	339.1222	62	24
3{*21*}	2	3,5-$(MeO)_2C_6H_3$	4{*8*}	A	$[M + H]^+$	386.1330	387.1343	97	56
3{*22*}	2	3-thiophenyl	4{*3*}	A	$[M + H]^+$	354.0926	355.0939	98	61
3{*23*}	2	3-thiophenyl	4{*4*}	A	$[M + H]^+$	344.0882	345.0891	97	53
3{*24*}	2	3-thiophenyl	4{*6*}	A	$[M + H]^+[-H_2O]$	354.0926	337.0890	>99	26
3{*25*}	2	3-thiophenyl	4{*14*}	A	$[M + H]^{+}$[d]	374.9929	377.9978	88	23
3{*26*}	2	3-thiophenyl	4{*15*}	A	$[M + H]^+$	327.0929	328.0996	92	36
3{*27*}	2	3-thiophenyl	4{*18*}	A	$[M + Na]^+$	314.0613	337.0500	83	12
3{*28*}	1	4-$MeOC_6H_4$	5{*2*}	B	$[M + H]^+$	298.1205	299.1275	>99	26
3{*29*}	1	3-thiophenyl	5{*2*}	B	$[M + H]^+$	274.0664	275.0742	27	3
3{*30*}	1	3-thiophenyl	5{*9*}	B	$[M]^+$	321.0823	321.0831	91	67[f]
3{*31*}	2	3-$MeOC_6H_4$	5{*1*}	B	$[M + H]^+$	298.1205	299.1340	>99	78[f]
3{*32*}	2	3-$MeOC_6H_4$	5{*2*}	B	$[M + H]^+$	312.1362	313.1434	97	17
3{*33*}	2	3-$MeOC_6H_4$	5{*5*}	B	$[M + H]^+$	326.1518	327.1650	>99	81[f]
3{*34*}	2	3-$MeOC_6H_4$	5{*6*}	B	$[M + H]^+[-H_2O]$	366.1831	349.1793	>99	62
3{*35*}	2	3-$MeOC_6H_4$	5{*7*}	B	$[M + H]^+$	365.1991	366.2099	>99	23
3{*36*}	2	3-$MeOC_6H_4$	5{*8*}	B	$[M + H]^+$	359.1521	360.1620	79	38
3{*37*}	2	3-$MeOC_6H_4$	5{*10*}	B	$[M + H]^+$	387.1834	388.1902	84	14
3{*38*}	2	3-$MeOC_6H_4$	5{*11*}	B	$[M + H]^+$	345.1365	346.1444	94	12
3{*39*}	2	3,5-$(MeO)_2C_6H_4$	5{*6*}	B	$[M + H]^+[-H_2O]$	396.1937	379.1900	86	51
3{*40*}	2	3-thiophenyl	5{*5*}	B	$[M + H]^+[-H_2O]$	302.0977	285.0938	>99	3
3{*41*}	1	4-$MeOC_6H_4$	6{*3*}	C	$[M + H]^+$	390.1467	391.1480	72	43[f]
3{*42*}	2	3-$MeOC_6H_4$	6{*1*}	C	$[M + H]^+$	406.1780	407.1876	>99	56
3{*43*}	2	3-thiophenyl	6{*1*}	C	$[M + H]^+$	323.0980	324.0988	78	28
3{*44*}	1	3-thiophenyl	8{*3*}	E	$[M + NH_4]^+$	320.1082	338.1432	>99	15
3{*45*}	1	3-thiophenyl	8{*5*}	E	$[M + H]^+[-H_2O]$	320.1092	303.1043	>99	29[f]
3{*46*}	1	4-$Me_2NC_6H_4$	8{*4*}	E	$[M + H]^+$	358.1893	359.2002	98	47
3{*47*}	2	C_6H_5	8{*11*}	E	$[M]^+$	302.1154	302.1160	99	73[f]
3{*48*}	2	3-$MeOC_6H_4$	8{*2*}	E	$[M + H]^+[-CH_4O]$[e]	316.1311	285.1115	>99	48[f]
3{*49*}	2	3-$MeOC_6H_4$	8{*4*}	E	$[M + H]^+$	359.1733	360.1814	>99	53[f]
3{*50*}	2	3-$MeOC_6H_4$	8{*6*}	E	$[M + H]^+$	399.2046	400.2121	99	71
3{*51*}	2	3-$MeOC_6H_4$	8{*10*}	E	$[M + H]^+$	368.1260	369.1418	>99	55[f]

[a]UV purity determined at 214 nm after preparative HPLC. [b]Isolated yield after preparative HPLC. [c]Isotope: [A+(−17)]. [d]Isotope: [A+2]. [e]Isotope: $[A^+(-31)]$ [f]Isolated yield after column chromatography. Isolated desired products **3** were characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information).

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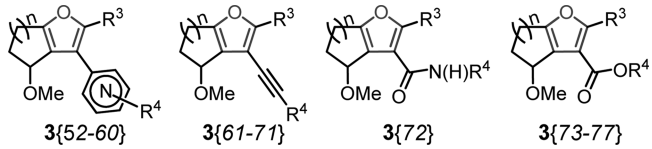
Table 3. Library Data for Compounds 3{*52*−*77*}

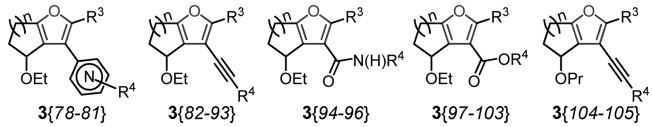


3{*52-60*} 3{*61-71*} 3{*72*} 3{*73-77*}

product **3**	*n*	R^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity (%)[a]	yield (%)[b]
3{*52*}	2	4-$MeOC_6H_4$	**4**{*2*}	A	$[M + H]^+[-CH_4O]$	378.1831	347.1636	95	66[c]
3{*53*}	2	4-$MeOC_6H_4$	**4**{*3*}	A	$[M + H]^+$	392.1624	393.1683	>99	58
3{*54*}	2	4-$MeOC_6H_4$	**4**{*4*}	A	$[M + H]^+$	382.1580	383.1592	99	52
3{*55*}	2	4-$MeOC_6H_4$	**4**{*6*}	A	$[M + H]^+$	392.1624	393.1695	84	20
3{*56*}	2	4-$MeOC_6H_4$	**4**{*8*}	A	$[M + H]^+$	370.1380	371.1390	99	61
3{*57*}	2	4-$MeOC_6H_4$	**4**{*13*}	A	$[M + H]^+$	392.1624	393.1713	95	17
3{*58*}	2	3,5-$(MeO)_2C_6H_4$	**4**{*15*}	A	$[M + H]^+$	395.1733	396.1745	96	38
3{*59*}	2	4-$Me_2NC_6H_4$	**4**{*2*}	A	$[M + H]^+[-CH_4O]$	391.2147	360.1955	69	52
3{*60*}	2	4-$Me_2NC_6H_4$	**4**{*18*}	A	$[M + Na]^+$	365.1627	388.1609	92	12
3{*61*}	1	4-$Me_2NC_6H_4$	**5**{*2*}	B	$[M + H]^+$	325.1678	376.1744	66	28
3{*62*}	1	4-$Me_2NC_6H_4$	**5**{*4*}	B	$[M + H]^+$	353.1991	354.2057	81	55[c]
3{*63*}	1	4-$Me_2NC_6H_4$	**5**{*5*}	B	$[M + H]^+$	339.1834	340.1904	76	61
3{*64*}	2	4-$MeOC_6H_4$	**5**{*1*}	B	$[M + H]^+$	312.1362	313.1434	>99	12
3{*65*}	2	4-$MeOC_6H_4$	**5**{*4*}	B	$[M + H]^+$	354.1831	355.1899	>99	16
3{*66*}	2	4-$MeOC_6H_4$	**5**{*5*}	B	$[M + H]^+$	340.1675	341.1763	99	27
3{*67*}	2	4-$MeOC_6H_4$	**5**{*6*}	B	$[M + H]^+$	380.1988	381.2058	99	22
3{*68*}	2	3,5-$(MeO)_2C_6H_4$	**5**{*2*}	B	$[M + H]^+$	392.1736	393.1749	99	58
3{*69*}	2	3-thiophenyl	**5**{*1*}	B	$[M + H]^+$	288.0820	289.0907	99	77[c]
3{*70*}	2	4-$Me_2NC_6H_4$	**5**{*2*}	B	$[M + H]^+$	339.1834	340.1902	97	51
3{*71*}	2	4-$Me_2NC_6H_4$	**5**{*4*}	B	$[M + H]^+[-CH_4O]$	367.2147	336.1952	67	43
3{*72*}	2	4-$MeOC_6H_4$	**7**{*2*}	D	$[M + H]^+$	399.2158	400.2166	93	36
3{*73*}	1	4-$Me_2NC_6H_4$	**8**{*1*}	E	$[M + H]^+$	315.1471	316.1541	34	11
3{*74*}	1	4-$Me_2NC_6H_4$	**8**{*2*}	E	$[M + H]^+$	329.1627	330.1693	>99	61[c]
3{*75*}	2	4-$MeOC_6H_4$	**8**{*2*}	E	$[M + H]^+$	330.1467	331.1529	99	20
3{*76*}	2	4-$Me_2NC_6H_4$	**8**{*1*}	E	$[M + H]^+$	329.1627	330.1694	89	25
3{*77*}	2	4-$Me_2NC_6H_4$	**8**{*2*}	E	$[M + H]^+[-CH_4O]$	343.1784	312.1588	69	14

[a]UV purity determined at 214 nm after preparative HPLC. [b]Isolated yield after preparative HPLC. [c]Isolated yield after column chromatography. Isolated desired products **3** were characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information).

Table 4. Library Data for Compounds 3{*78*−*105*}



3{*78-81*} 3{*82-93*} 3{*94-96*} 3{*97-103*} 3{*104-105*}

product **3**	*n*	R^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity (%)[a]	yield (%)[b]
3{*78*}	1	3-thiophenyl	**4**{*2*}	A	$[M + H]^+$	354.1290	355.1298	95	63[d]
3{*79*}	1	3-thiophenyl	**4**{*6*}	A	$[M + H]^+$	368.1082	369.1141	86	21[d]
3{*80*}	1	3-thiophenyl	**4**{*18*}	A	$[M + H]^+$	328.0769	329.0850	97	6
3{*81*}	2	3-thiophenyl	**4**{*17*}	A	$[M + H]^+$	356.1195	357.1254	99	68[d]
3{*82*}	1	3-thiophenyl	**5**{*1*}	B	$[M + H]^+$	288.0820	289.0828	96	48
3{*83*}	1	3-thiophenyl	**5**{*4*}	B	$[M + H]^+[-C_2H_6O]$[c]	330.1290	285.0941	>99	67
3{*84*}	1	3-thiophenyl	**5**{*5*}	B	$[M + H]^+$	316.1133	317.1202	99	55
3{*85*}	2	4-$MeOC_6H_4$	**5**{*2*}	B	$[M + H]^+$	340.1675	341.1734	>99	53[d]
3{*86*}	2	4-$MeOC_6H_4$	**5**{*5*}	B	$[M + H]^+$	354.1831	355.1901	>99	39
3{*87*}	2	4-$MeOC_6H_4$	**5**{*11*}	B	$[M + Na]^+$	373.1678	396.1560	97	26
3{*88*}	2	4-$Me_2NC_6H_4$	**5**{*4*}	B	$[M + H]^+$	381.2304	382.2365	72	30
3{*89*}	2	4-$Me_2NC_6H_4$	**5**{*7*}	B	$[M + H]^+$	406.2620	407.2629	83	22
3{*90*}	2	3-$MeOC_6H_4$	**5**{*1*}	B	$[M + H]^+$	326.1518	327.1603	68	14
3{*91*}	2	3-$MeOC_6H_4$	**5**{*4*}	B	$[M + H]^+$	368.1988	369.2079	97	17
3{*92*}	2	3-$MeOC_6H_4$	**5**{*7*}	B	$[M + H]^+$	393.2304	394.2380	96	28
3{*93*}	2	3-thiophenyl	**5**{*5*}	B	$[M + H]^+$	330.1290	331.1366	86	25
3{*94*}	2	4-$MeOC_6H_4$	**7**{*1*}	D	$[M + H]^+$	400.1998	401.2061	85	6
3{*95*}	2	4-$MeOC_6H_4$	**7**{*2*}	D	$[M + H]^+$	413.2315	414.2388	>99	56
3{*96*}	2	4-$MeOC_6H_4$	**7**{*3*}	D	$[M + H]^+$	387.2046	388.2115	96	31

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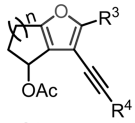
Table 4. continued

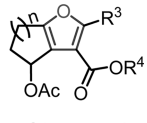
product **3**	*n*	R^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity (%)[a]	yield (%)[b]
3{*97*}	1	3-thiophenyl	**8**{*1*}	E	$[M + H]^+[-C_2H_6O]$	292.0769	247.0418	>99	62
3{*98*}	1	3-thiophenyl	**8**{*8*}	E	$[M + H]^+$	428.1294	429.1366	98	12
3{*99*}	1	3-thiophenyl	**8**{*9*}	E	$[M + H]^+[-C_2H_6O]$	412.1344	367.0993	92	8
3{*100*}	2	4-$MeOC_6H_4$	**8**{*1*}	E	$[M + H]^+[-C_2H_6O]$	330.1467	285.1119	>99	78
3{*101*}	2	4-$MeOC_6H_4$	**8**{*2*}	E	$[M + Na]^+$	344.1624	367.1498	97	62[d]
3{*102*}	2	4-$Me_2NC_6H_4$	**8**{*1*}	E	$[M + H]^+[-CH_4O]$	343.1784	312.1580	92	39
3{*103*}	2	4-$Me_2NC_6H_4$	**8**{*2*}	E	$[M + H]^+$	357.1940	358.1995	87	66
3{*104*}	1	4-$Me_2NC_6H_4$	**5**{*4*}	B	$[M + H]^+$	381.2303	382.2389	74	8
3{*105*}	1	4-$Me_2NC_6H_4$	**5**{*12*}	B	$[M + H]^+$	389.2103	390.2172	76	63[d]

[a]UV purity determined at 214 nm after preparative HPLC. [b]Isolated yield after preparative HPLC. [c]Isotope: $[A^+(-45)]$ [d]Isolated yield after column chromatography. Isolated desired products **3** were characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information).

Table 5. Library Data for Compounds 3{*106−122*}



3{*106-110*}



3{*111-122*}

product **3**	*n*	R^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity (%)[a]	yield (%)[b]
3{*106*}	1	4-$MeOC_6H_4$	**5**{*2*}	B	$[M + H]^+$	340.1311	341.1320	>99	23
3{*107*}	1	4-$MeOC_6H_4$	**5**{*6*}	B	$[M + H]^+[-C_2H_4O_2]$	394.1780	335.1642	99	34
3{*108*}	1	4-$MeOC_6H_4$	**5**{*7*}	B	$[2M + H]^+$	393.1940	787.3894	98	16
3{*109*}	2	4-$MeOC_6H_4$	**5**{*6*}	B	$[M + H]^+[-C_2H_4O_2]$	408.1937	349.1797	98	43
3{*110*}	2	3-$MeOC_6H_4$	**5**{*9*}	B	$[2M + H]^+$	401.1627	803.3313	>99	31
3{*111*}	2	4-$MeOC_6H_4$	**8**{*1*}	E	$[M + H]^+[-C_2H_4O_2]$	344.1260	285.1116	98	53[c]
3{*112*}	2	4-$MeOC_6H_4$	**8**{*2*}	E	$[M + Na]^+$	358.1416	381.1305	98	38
3{*113*}	2	4-$MeOC_6H_4$	**8**{*5*}	E	$[M + Na]^+$	400.1886	423.1766	>99	46[c]
3{*114*}	2	4-$MeOC_6H_4$	**8**{*9*}	E	$[M + NH_4]^+$	464.1835	482.2159	95	11
3{*115*}	2	4-$MeOC_6H_4$	**8**{*7*}	E	$[M + Na]^+$	443.1944	466.1744	96	44
3{*116*}	2	3-$MeOC_6H_4$	**8**{*1*}	E	$[M + H]^+[-C_2H_4O_2]$	344.1260	285.1116	98	26
3{*117*}	2	3-$MeOC_6H_4$	**8**{*2*}	E	$[M + Na]^+$	358.1416	381.1312	69	47
3{*118*}	2	3-thiophenyl	**8**{*1*}	E	$[M + H]^+[-C_2H_4O_2]$	320.0718	261.0576	98	41
3{*119*}	2	3-thiophenyl	**8**{*2*}	E	$[M + H]^+[-C_2H_4O_2]$	334.0875	275.0731	>99	34
3{*120*}	2	3-thiophenyl	**8**{*3*}	E	$[M + Na]^+$	376.1344	399.1223	>99	28
3{*121*}	2	3-thiophenyl	**8**{*7*}	E	$[M + Na]^+$	419.1403	442.1203	97	33
3{*122*}	2	3-thiophenyl	**8**{*9*}	E	$[M + NH_4]^+$	440.1294	458.1622	98	28[c]

[a]UV purity determined at 214 nm after preparative HPLC. [b]Isolated yield after preparative HPLC. [c]Isolated yield after column chromatography. Isolated desired products **3** were characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information).

(s, 3H), 6.84 (d, J = 8.4 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.77 (t, J = 2.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.3, 34.0, 55.2, 78.8, 95.6, 113.9 (×2), 114.4, 129.9, 133.2 (×2), 159.9, 164.6, 205.6.

General Procedure for I_2-Induced Cyclization to the 3-Iodofurans 2{*1−34*}. The iodofurans **2** were prepared by a modified literature procedure.[40,42] To a mixture of the 2-(1-alkynyl)-2-alken-1-one **1** (2.0 mmol), I_2 (4.0 mmol), and $NaHCO_3$ (4.0 mmol) was added a solution of the appropriate diol (8.0 mmol) in MeCN (20 mL). The resulting mixture was stirred at room temperature for 0.5 h, unless otherwise specified. The reaction was monitored by TLC to establish completion. The mixture was diluted with EtOAc (250 mL). The excess I_2 was removed by washing with saturated aq $Na_2S_2O_3$. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under a vacuum to yield the crude product, which was purified by flash chromatography on silica gel using EtOAc/hexanes as the eluent to afford the 3-iodofurans **2**.

*3-Iodofuran [**2**{1}].* The product was obtained as a pale yellow oil (42% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 1.87 (d, J = 5.5 Hz, 1H), 2.28−2.35 (m, 1H), 2.66−2.73 (m, 1H), 2.85−2.94 (m, 1H), 2.98−3.05 (m, 1H), 3.84 (s, 3H), 5.08 (br s, 1H), 6.95 (d, J = 8.9 Hz, 2H), 7.83 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.0, 38.7, 55.5, 57.1, 69.8, 114.0 (×2), 123.8, 127.8 (×2), 134.1, 156.0, 159.6, 160.5; HRMS calcd for $C_{14}H_{13}IO_3$ $[M]^+$, 355.9909, found 355.9919.

General Procedure for Suzuki−Miyaura Coupling to Prepare Furans 3{*1−27,52−60,78−81,123−128*}. To a 4 dram vial was added the 3-iodofuran **2** (0.2 mmol), boronic acid (0.3 mmol), K_2CO_3 (0.5 mmol), and 10 mol % $Pd(PPh_3)_4$ in 20:5:1 toluene/ethanol/H_2O (20 mL). The solution was vigorously stirred for 5 min at room temperature, flushed with argon, and then heated to 80 °C for 12 h. Upon cooling to room temperature, the resulting reaction mixture was extracted with EtOAc. The crude product was purified by column chromatography on silica gel using EtOAc/hexanes as the eluent to afford the heteroatom ring-containing furans **3**.

*Heteroatom Ring-Containing Furan [**3**{1}].* The product was obtained as slightly yellow solid (74% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 2.33−2.38 (m, 1H), 2.65−2.71 (m, 1H), 2.86−3.04

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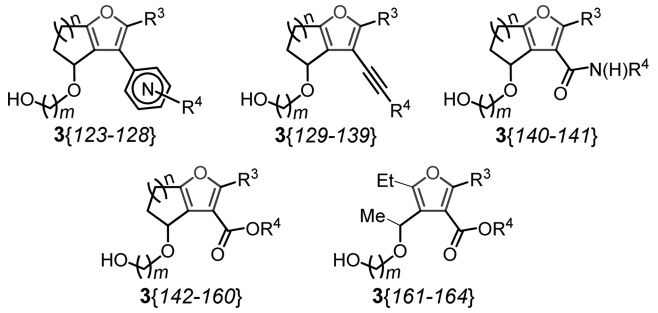
Table 6. Library Data for Compounds 3{*123*−*164*}



product **3**	*n*	*m*	R^3	building blocks	method	ion HRMS	calcd for HRMS	found HRMS	purity (%)[a]	yield (%)[b]
3{*123*}	1	2	4-$MeOC_6H_4$	**4**{*6*}	A	$[M + H]^+$	408.1573	409.1588	98	23
3{*124*}	1	2	4-$MeOC_6H_4$	**4**{*17*}	A	$[M + H]^+$	382.1529	383.1538	92	41
3{*125*}	2	5	C_6H_5	**4**{*11*}	A	$[M]^+$	418.2144	418.2156	99	46[c]
3{*126*}	2	4	C_6H_5	**4**{*18*}	A	$[M + Na]^+$	380.1624	403.1515	99	29
3{*127*}	2	2	4-$Me_2NC_6H_4$	**4**{*12*}	A	$[M + H]^+$	420.2049	421.2125	95	53
3{*128*}	2	2	4-$Me_2NC_6H_4$	**4**{*17*}	A	$[M + H]^+$	409.2001	410.2076	65	47
3{*129*}	1	2	4-$MeOC_6H_4$	**5**{*4*}	B	$[M + H]^+$	370.1780	371.1851	97	46
3{*130*}	1	2	4-$MeOC_6H_4$	**5**{*5*}	B	$[M + H]^+$	356.1634	357.1693	99	41
3{*131*}	1	2	4-$MeOC_6H_4$	**5**{*6*}	B	$[M + H]^+$	396.1937	397.1997	98	7
3{*132*}	1	2	4-$Me_2NC_6H_4$	**5**{*2*}	B	$[M + H]^+$	355.1784	356.1801	>99	23
3{*133*}	2	2	C_6H_5	**5**{*2*}	B	$[M + H]^+$	326.1518	327.1530	99	76[c]
3{*134*}	2	2	C_6H_5	**5**{*6*}	B	$[M + NH_4]^+$	380.1988	398.2320	>99	58
3{*135*}	2	2	4-$MeOC_6H_4$	**5**{*2*}	B	$[M + H]^+$	356.1624	357.1683	>99	8
3{*136*}	2	2	4-$MeOC_6H_4$	**5**{*5*}	B	$[M + H]^+$	370.1780	371.1842	91	31
3{*137*}	2	2	4-$Me_2NC_6H_4$	**5**{*5*}	B	$[M + H]^+$	383.2097	384.2105	98	46
3{*138*}	2	2	4-$Me_2NC_6H_4$	**5**{*12*}	B	$[M + H]^+$	405.2052	406.2061	65	12
3{*139*}	2	2	4-$Me_2NC_6H_4$	**5**{*7*}	B	$[M + H]^+$	422.2569	423.2581	96	23
3{*140*}	2	5	C_6H_5	**7**{*3*}	D	$[M]^+$	415.2359	415.2370	99	47[c]
3{*141*}	2	5	C_6H_5	**7**{*4*}	D	$[M]^+$	470.2781	470.2793	>99	53[c]
3{*142*}	1	2	4-$MeOC_6H_4$	**8**{*11*}	E	$[M]^+$	362.1366	362.1354	99	67[c]
3{*143*}	1	2	4-$Me_2NC_6H_4$	**8**{*1*}	E	$[M]^+$	345.1576	345.1583	99	73[c]
3{*144*}	1	2	4-$Me_2NC_6H_4$	**8**{*6*}	E	$[M]^+$	442.2468	442.2470	97	35
3{*145*}	1	2	4-$Me_2NC_6H_4$	**8**{*11*}	E	$[M]^+$	375.1682	375.1691	>99	85[c]
3{*146*}	2	2	4-$Me_2NC_6H_4$	**8**{*1*}	E	$[M]^+$	359.1733	359.1737	>99	76[c]
3{*147*}	2	2	4-$Me_2NC_6H_4$	**8**{*11*}	E	$[M]^+$	389.1838	389.1841	>99	81[c]
3{*148*}	2	2	4-$Me_2NC_6H_4$	**8**{*12*}	E	$[M]^+$	403.1995	403.2002	97	77[c]
3{*149*}	2	2	3-$MeOC_6H_4$	**8**{*1*}	E	$[M]^+$	346.1416	346.1423	>99	72[c]
3{*150*}	2	2	4-$MeOC_6H_4$	**8**{*1*}	E	$[M]^+$	346.1416	346.1423	99	81[c]
3{*151*}	2	2	4-$MeOC_6H_4$	**8**{*11*}	E	$[M]^+$	376.1522	376.1534	>99	76[c]
3{*152*}	2	2	4-$MeOC_6H_4$	**8**{*12*}	E	$[M]^+$	390.1679	390.1688	>99	74[c]
3{*153*}	2	2	4-$MeOC_6H_4$	**8**{*13*}	E	$[M]^+$	404.1835	404.1838	>99	68[c]
3{*154*}	2	2	4-$MeOC_6H_4$	**8**{*14*}	E	$[M]^+$	418.1992	418.2005	99	72[c]
3{*155*}	2	2	3-thiophenyl	**8**{*1*}	E	$[M]^+$	308.0718	308.0725	99	71[c]
3{*156*}	2	2	3-thiophenyl	**8**{*1*}	E	$[M]^+$	322.0875	322.0880	99	68[c]
3{*157*}	2	2	3-thiophenyl	**8**{*11*}	E	$[M]^+$	352.0981	352.0985	>99	78
3{*158*}	2	2	4-NCC_6H_4	**8**{*12*}	E	$[M]^+$	385.1525	385.1534	98	66[c]
3{*159*}	2	2	1-cyclohexenyl	**8**{*1*}	E	$[M]^+$	320.1624	320.1632		71[c]
3{*160*}	2	2	1-cyclohexenyl	**8**{*11*}	E	$[M]^+$	350.1729	350.1737		82[c]
3{*161*}		2	C_6H_5	**8**{*11*}	E	$[M]^+$	348.1573	348.1580		37[c]
3{*162*}		2	4-$MeOC_6H_4$	**8**{*1*}	E	$[M]^+$	348.1573	348.1580	99	82[c]
3{*163*}		2	4-$MeOC_6H_4$	**8**{*11*}	E	$[M]^+$	378.1679	378.1686	99	82[c]
3{*164*}		2	4-$MeOC_6H_4$	**8**{*14*}	E	$[M]^+$	420.2148	420.2158	>99	82[c]

[a]UV purity determined at 214 nm after preparative HPLC. [b]Isolated yield after preparative HPLC. [c]Isolated yield after column chromatography. Isolated desired products **3** were characterized by ^1H and ^{13}C NMR spectroscopy (see the Supporting Information).

(m, 2H), 3.43 (s, 3H), 3.80 (s, 3H), 4.44 (s, 2H), 5.17 (d, J = 6.6 Hz, 1H), 6.82 (d, J = 8.8 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 8.8 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.6, 39.6, 55.4, 58.6, 69.6, 74.8, 114.1 (×2), 118.7, 124.7, 128.2 (×2), 128.3 (×2), 128.9 (×2), 130.6, 133.1, 136.9, 153.4, 159.2, 160.3; HRMS calcd for $C_{22}H_{22}O_4$ $[M + H]^+$, 350.1518, found 351.1530.

General Procedure for Sonogashira Coupling to Prepare Furans 3. *Method A (Using Et_2NH and DMF).* The

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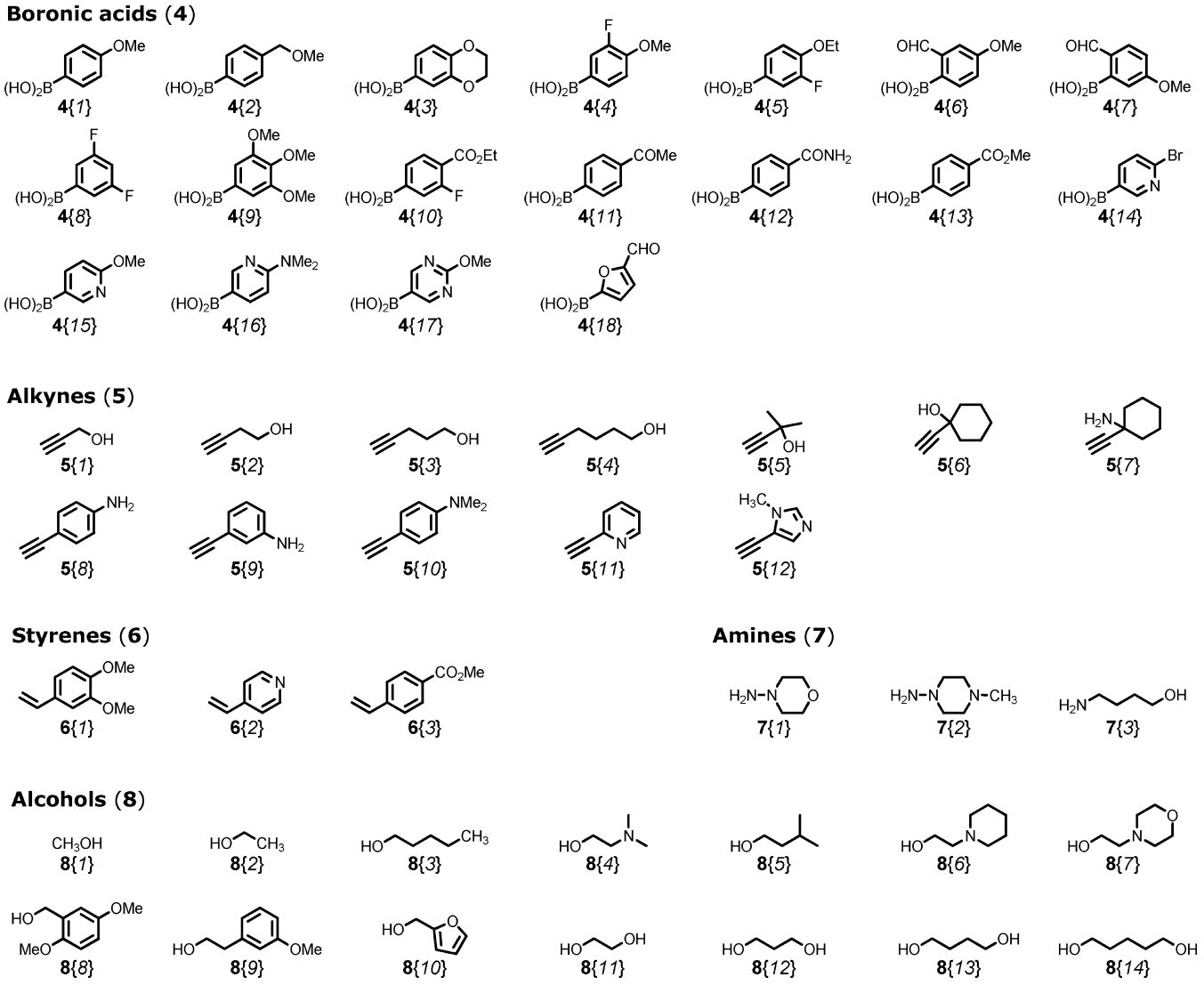

Figure 3. Sublibraries of boronic acids **4**, terminal alkynes **5**, styrenes **6**, amines **7**, and alcohols **8**.

3-iodofurans **2** (0.2 mmol), the alkynes **5** (0.24 mmol), 3 mol % $PdCl_2(PPh_3)_2$, 6 mol % CuI, DMF (1.5 mL), and Et_2NH (1.5 mL) were mixed in a 0.5−2.0 mL Biotage microwave vial equipped with a magnetic stirrer. The vessel was placed in the microwave reactor and irradiated to ramp the temperature from room temperature to 100 °C and then held at that temperature for 20 min. The mixture was then cooled down and diluted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by either column chromatography or preparative HPLC to afford the corresponding furans **3**{*28*−*40*,*61*−*71*,*82*−*93*,*104*−*105*,*129*−*139*}.

*Method **B** (Using (S)-Prolinol and DMF/H_2O).* To a 4 dram vial was added the 3-iodofurans **2**{*19*−*21*} (0.2 mmol), alkynes **5** (0.24 mmol), 5 mol % $PdCl_2(PPh_3)_2$, 10 mol % CuI, (*S*)-prolinol (0.6 mmol), and DMF-H_2O (v/v, 5:1, 1.2 mL). The solution was stirred at room temperature, flushed with argon, and then heated to 70 °C for 3 h. Upon cooling to room temperature, the reaction mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by preparative HPLC to afford the corresponding furans **3**{*106*−*110*}.

*Alkyne-Containing Furan [**3**{105}].* The product was obtained as a pale yellow oil that solidified upon standing to an ivory solid (63% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (t, J = 7.3 Hz, 3H), 1.57−1.66 (m, 2H), 2.35−2.46 (m, 1H), 2.59−2.69 (m, 1H), 2.75−2.98 (m, 3H), 3.00 (s, 6H), 3.46−3.57 (m, 1H), 3.71 (s, 3H), 4.86 (d, J = 6.9 Hz, 1H), 6.72 (d, J = 8.9 Hz, 2H), 7.41−7.56 (m, 2H), 7.90 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.0, 23.5, 23.8, 32.4, 36.2, 40.5 (×2), 70.9, 76.1, 90.8, 97.4, 112.1 (×2), 119.6, 126.2 (×2), 128.6, 128.7, 129.6, 132.3, 132.4, 150.3, 159.7, 161.0; HRMS calcd for $C_{24}H_{27}N_3O_2$ $[M + H]^+$, 389.2103, found 390.2172.

General Procedure for Heck Coupling to Prepare the Furans 3{*41*−*43*}. To a 4 dram vial was added the appropriate 3-iodofuran **2** (1.0 mmol), the styrene **6** (1.2 mmol), 5 mol % $Pd(OAc)_2$, *n*-Bu_4NI (1.0 mmol), Na_2CO_3 (2.5 mmol), and DMF (1.5 mL). The solution was stirred at room temperature and flushed with argon, and then heated to 80 °C until TLC revealed complete conversion of the starting material. The solution was allowed to cool and diluted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by either column chromatography or preparative HPLC to afford the olefin-containing furans **3**.

*Olefin-Containing Furan [**3**{41}].* The product was obtained as a pale yellow oil that solidified upon standing to an ivory solid (43% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (d, J = 5.5 Hz,

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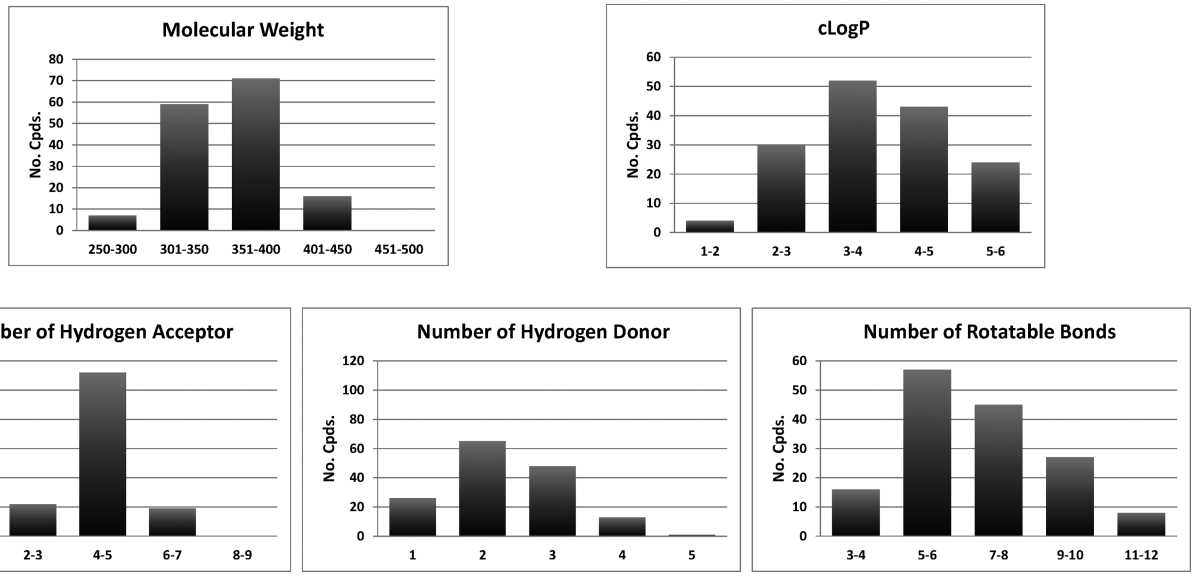

Figure 4. Distribution of physicochemical and structural properties across the library entries.

1H), 2.30 (s, 3H), 2.34−2.45 (m, 1H), 2.62−2.74 (m, 1H), 2.91−3.05 (m, 2H), 3.86 (s, 3H), 5.32 (br s, 1H), 6.99 (d, J = 8.8 Hz, 2H), 7.05 (d, J = 8.4 Hz, 2H), 7.07−7.18 (m, 2H), 7.46 (d, J = 8.4 Hz, 2H), 7.53 (d, J = 8.8 Hz, 2H); HRMS calcd for $C_{24}H_{22}O_5$ $[M + H]^+$, 390.1467, found 391.1480.

General Procedure for Aminocarbonylation to Prepare Furans 3{*72,94−96,140−141*}. A mixture of the appropriate 3-iodofurans **2** (0.8−1.2 mmol), 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3, TEA (2.0 equiv), and the amine (1.5 equiv) in DMF (1.0 mL) was flushed with an atmosphere of carbon monoxide for 2 min. The solution was stirred at room temperature and then heated to 80 °C until TLC revealed complete conversion of the starting material. Then, the solution was allowed to cool and diluted with EtOAc. The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by either column chromatography or preparative HPLC to afford the corresponding amide-containing furans **3**.

General Procedure for Carboalkoxylation to Prepare Furans 3{*44−51,73−77,97−103,111−122,142−164*}. A stirred mixture of the appropriate 3-iodofuran **2** (0.10 mmol), 10 mol % $Pd(OAc)_2$, 20 mol % PCy_3, TEA (0.40 mmol), and excess R^4OH (0.50−1.0 mmol) in DMF (2.0 mL) was charged in a 50 mL long flask at room temperature. The mixture was flushed with CO gas for 2 min, and the flask was fitted with a balloon of CO gas. The reaction mixture was heated at 110 °C with vigorous stirring. Upon cooling to room temperature, the resulting reaction mixture was extracted with EtOAc (2 × 20 mL). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford the ester-containing furans **3**.

*Ester-Containing Furan [**3**{111}].* The product was obtained as a pale yellow oil that solidified upon standing to an ivory solid (53% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.77−2.02 (m, 3H), 2.03−2.11 (m, 1H), 2.04 (s, 3H), 2.54−2.63 (m, 1H), 2.73−2.81 (m, 1H), 3.75 (s, 3H), 3.85 (s, 3H), 6.17 (br s, 1H), 6.94 (d, J = 8.9 Hz, 2H), 7.85 (d, J = 8.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3, 21.5, 23.1, 29.3, 51.6, 55.5, 65.5, 111.3, 113.7 (×2), 117.2, 122.7, 130.2 (×2), 154.0, 157.7, 160.6, 164.3, 170.5; HRMS calcd for $C_{19}H_{20}O_6$ $[M + H]^+[-C_2H_4O_2]$, 344.1260, found 285.1116.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic methods, spectral assignments, and copies of ^{1}H 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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Notes

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