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Solution-Phase Parallel Synthesis of a Multisubstituted Cyclic Imidate Library

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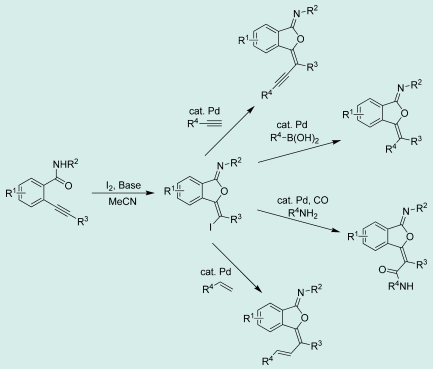
Supporting Information

ABSTRACT: The solution-phase parallel synthesis of a diverse 71-member library of multisubstituted cyclic imidates is described. The key intermediates, 3-iodomethylene-containing cyclic imidates, are readily prepared in good to excellent yields by the palladium/copper-catalyzed cross-coupling of various *o*-iodobenzamides and terminal alkynes, followed by electrophilic cyclization with I_2. These cyclic imidates were further functionalized by palladium-catalyzed Suzuki−Miyaura, Sonogashira, carbonylative amidation, and Heck chemistry using sublibraries of commercially available building blocks.

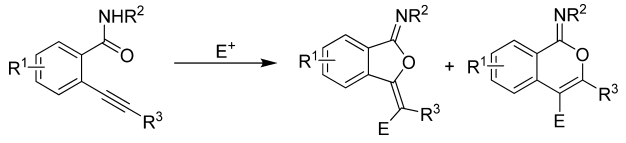


KEYWORDS: *solution-phase, parallel synthesis, iodocyclization, cyclic imidates, iminolactones, palladium coupling*

INTRODUCTION

Heterocyclic compounds are of great importance in a variety of areas, including medicinal chemistry, material science, etc. There has been an increasing demand for new and efficient strategies for the synthesis of important heterocyclic ring systems for the purpose of exploring their potential applications in the pharmaceutical industry and other relevant areas. We have previously reported the generation of various important heterocycles and carbocycles through very efficient electrophilic cyclization chemistry using halogen, sulfur and selenium electrophiles.[1] In particular, we and others have recently found that the iodocyclization of 2-(1-alkynyl)benzamides leads to the formation of the corresponding cyclic imidates, also known in the literature as iminolactones (Scheme 1), where electrophilic attack occurs on oxygen, rather than nitrogen.[2−4]

Scheme 1. Synthesis of Cyclic Imidates by Electrophilic Cyclization[2]



$E^+ = I_2$, ICl, NBS, *etc.*
R^1 = H, OMe; R^2 = Me, Bn, aryl; R^3 = alkyl, alkenyl, aryl, TMS

Several research groups have reported various synthetic routes for the synthesis of cyclic imidates.[5] Although the biological potential of this heterocyclic scaffold has not received much attention, there have been a few reports in the literature where interesting biological activities have been observed. Representative biologically active examples are shown in Figure 1.[6]

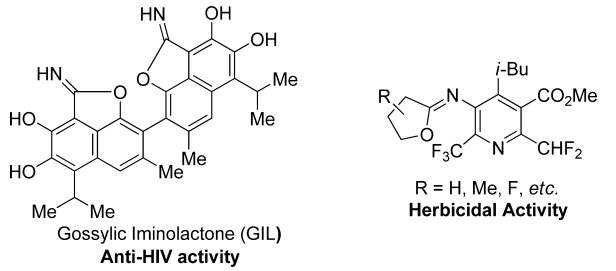


Figure 1. Biologically active cyclic imidates.

In our ongoing efforts to generate interesting libraries of potentially biologically active heterocyles,[7] we have used our iodocylization strategy described above and further diversified the resulting cyclic imidates to study the biological profile of

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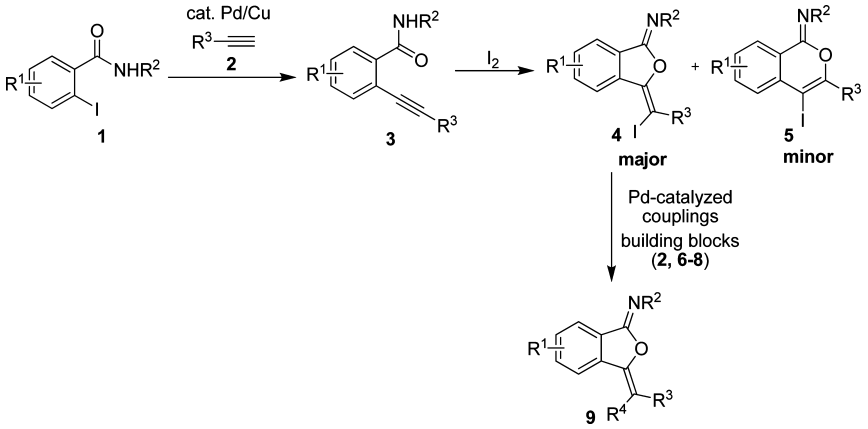
Scheme 2. Library Design for Tetrasubstituted Cyclic Imidates



this interesting little-studied heterocyclic scaffold. Since there is often a remarkable similarity in the reactivity pattern and biological activities of certain nitrogen heterocycles and their oxygen counterparts, these cyclic imidates might be expected to have biological activities similar to those of their structurally analogous isoindolin-1-one and isocoumarin counterparts. Furthermore, to the best of our knowledge, a library of this heterocyclic scaffold has not been reported previously in the literature. Herein, we report our studies on the solution-phase synthesis of a diverse 71-member library of cyclic imidates.

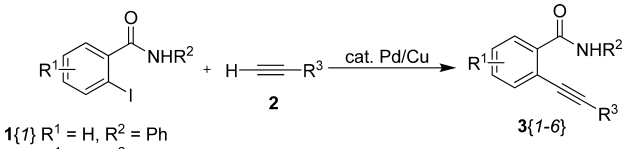
RESULTS AND DISCUSSION

Our strategy for library production is shown in Scheme 2. We anticipated that our previously described iodocyclization process should readily afford trisubstituted 3-iodomethylene-containing cyclic imidates (**4**) as key intermediates. Further functionalization can be achieved by taking advantage of the iodine handle present on the exocyclic double bond at the 3-position, through various coupling reactions to generate a library with four points of diversity.

The starting *o*-iodobenzamides (**1**) were conveniently prepared from the corresponding commercially available carboxylic acids by first refluxing the acid with thionyl chloride, followed in the same pot by reaction with the corresponding amine.[2,8] The alkynes **3** required for cyclization are readily prepared by the palladium/copper-catalyzed Sonogashira cross-coupling[9] of the *o*-iodobenzamides **1** with terminal alkynes **2** and the results are summarized in Table 1. As shown in the Table, the requisite alkynes **3**{*1*–*6*} are readily obtained in good to excellent yields by this straightforward approach.

As the key step in our library synthesis, variously substituted iodo cyclic imidates **4** have been efficiently prepared within 1–2 h by electrophilic cyclization of the corresponding *o*-(1-alkynyl)-benzamides **3**{*1*–*6*} using I_2/$NaHCO_3$ in MeCN at ambient temperature (Table 2). All of the cyclized products **4** have been purified by column chromatography. The reaction works well for all substrates containing alkyl, aryl, TMS or heteroaryl groups at the distal end of the carbon–carbon triple bond. It is noteworthy that in the presence of electron-donating methoxy groups on the amide phenyl ring **3**{*3*–*6*}, only 5-membered cyclic imidates were isolated exclusively. In fact, the electron-donating effect of the *para*-methoxy group (with respect to the alkyne) should increase the electron density on C-2 of the arylethynyl group, thus favoring intramolecular nucleophilic attack of the amide oxygen on C-1. The structure of the cyclized iodo imidates **4**{*2*} and **4**{*4*} has been confirmed by single crystal X-ray crystallography.[2]

Table 1. Library Data for the 2-(1-Alkynyl)benzamides 3{*1*–*6*}

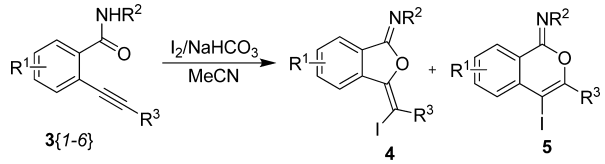


1{*1*} R^1 = H, R^2 = Ph
1{*2*} R^1 = H, R^2 = PMB
1{*3*} R^1 = 4,5-$(OMe)_2$, R^2 = Me

compd[a]	R^1	R^2	R^3	yield[b] (%)
3{*1*}	H	Ph	*n*-Pr	91
3{*2*}	H	Ph	TMS	76
3{*3*}	4,5-$(OMe)_2$	PMB	TMS	96
3{*4*}	4,5-$(OMe)_2$	Me	Ph	87
3{*5*}	4,5-$(OMe)_2$	Me	2-py	76
3{*6*}	4,5-$(OMe)_2$	Me	3-thienyl	83

[a]All reactions were carried out on a 5.0 mmol scale using 1.2 equiv of the alkyne, 2 mol % $PdCl_2(PPh_3)_2$, 1 mol % CuI, and DIPA (4 equiv) in DMF (25 mL) at 65 °C (see the Experimental section and Supporting Information for the detailed procedures). [b]Isolated yields after column chromatography.

Table 2. Library Data for Compounds 4{*1*–*6*}



compd[a]	R^1	R^2	R^3	yield[b] (%) **4** + **5**
4{*1*}	H	Ph	*n*-Pr	92 + 6
4{*2*}	H	Ph	TMS	77 + 7
4{*3*}	5,6-$(OMe)_2$	PMB	TMS	80 + 0
4{*4*}	5,6-$(OMe)_2$	Me	Ph	79 + 0
4{*5*}	5,6-$(OMe)_2$	Me	2-py	91 + 0
4{*6*}	5,6-$(OMe)_2$	Me	3-thienyl	93 + 0

[a]All reactions were carried out on a 4.0 mmol scale using I_2 (3 equiv) and $NaHCO_3$ (3 equiv) in MeCN (20 mL) at 25 °C for 1–2 h. [b]Isolated yields after column chromatography.

Furthermore, the trimethylsilyl-containing cyclic imidates **4**{*2*} and **4**{*3*} were treated with fluoride to afford the corresponding deprotected cyclic imidates **4**{*7*} and **4**{*8*}, respectively, in good yields (eq 1). The sublibrary of 3-iodomethylene-containing cyclic Imidates **4**{*1*–*8*} is shown in Figure 2.

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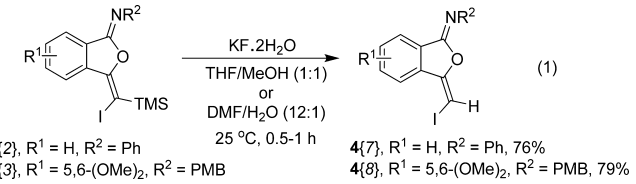


4{*2*}, R^1 = H, R^2 = Ph
4{*3*}, R^1 = 5,6-$(OMe)_2$, R^2 = PMB

4{*7*}, R^1 = H, R^2 = Ph, 76%
4{*8*}, R^1 = 5,6-$(OMe)_2$, R^2 = PMB, 79%

The 3-iodomethylene-containing cyclic imidates **4** can be further elaborated by using a variety of palladium-catalyzed processes, such as Sonogashira coupling,[9] Suzuki–Miyaura coupling,[10] carbonylative amidation,[11] Heck coupling,[12] and amination[13] (Scheme 3). The reagents used (e.g., terminal alkynes **2**, boronic acids **6**, styrenes **7**, and amines **8**) for substitution of the iodine-containing products **4** were chosen on the basis of their commercial availability, functional group diversity and potential drug-like properties (Figure 3). This could result in a library of ∼1300 theoretically possible products. This number was arrived at by determining all possible combinations of the R group and available starting materials. However, only a small subset of 71 compounds out of these 1300 virtual structures was actually prepared in the laboratory. The crude products **9** were analyzed by LC/MS, followed by purification by either column chromatography or preparative HPLC. The results of this parallel library synthesis are summarized in Table 3, which indicates that the products **9** can be obtained in modest to good yields with high purities.

Sonogashira coupling of the 3-iodomethylene-containing cyclic imidates **4** with various terminal acetylenes **2** affords the corresponding alkynyl products **9**{*1*–*17*} (method A). Suzuki–Miyaura coupling of the 3-iodomethylene-containing cyclic imidates **4** with various arylboronic acids **6** proceeded smoothly to give the desired products **9**{*18*–*62*} in modest yields. Most reactions were complete within 2 h at 80 °C in DMF (method B). The reaction was also examined using a boronate ester **6**{*21*}. However, the yield of the isolated compound **9**{*62*} was very low in this case. The structure of one of the products from the Suzuki–Miyaura coupling **9**{*24*} was confirmed using single crystal X-ray crystallography (see the Supporting Information for details). The stereochemistry around the C–C and C–N double bonds was found to be preserved during the Suzuki–Miyaura cross-coupling. Next, in an effort to synthesize amide-containing

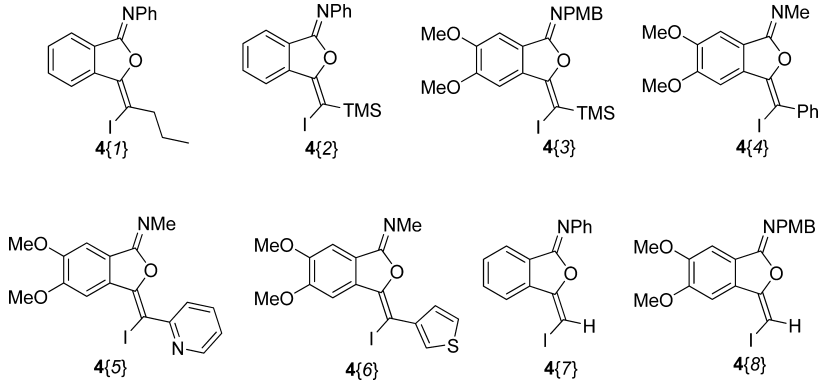
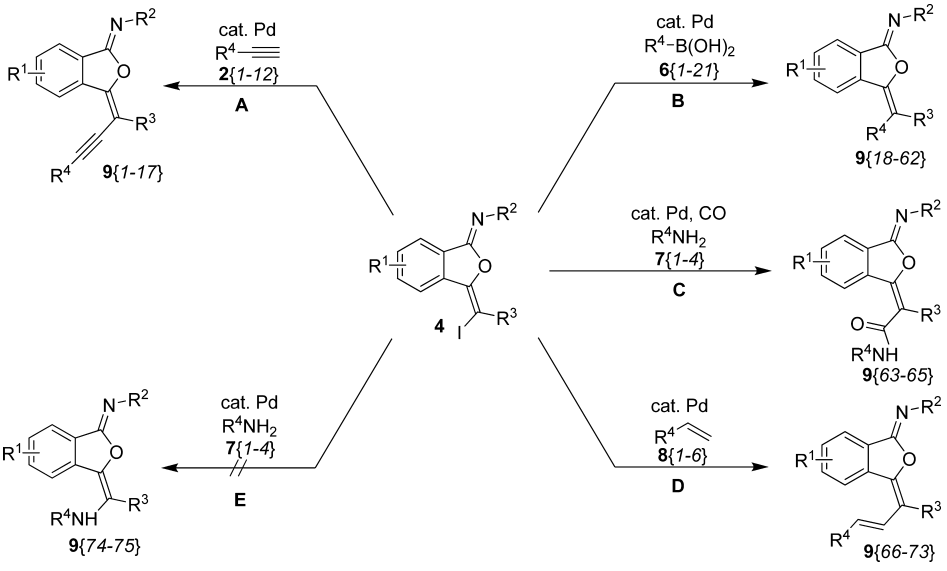


Figure 2. Sublibrary of 3-iodomethylene-containing cyclic imidates **4**{*1*–*8*}.

Scheme 3. Synthesis of Cyclic Imidates 9 Using Various Palladium-Catalyzed Reactions[a]



[a]Method A (Sonogashira coupling): 3 mol % $PdCl_2(PPh_3)_2$, 2 mol % CuI, DIPA (4 equiv), $R^4C{\equiv}CH$ (**2**, 1.2 equiv), DMF, 70 °C, 2 h. Method B (Suzuki–Miyaura coupling): 5 mol % $PdCl_2$, $KHCO_3$ (1.4 equiv), $R^4B(OH)_2$ (**6**, 1.2 equiv), 4:1 DMF/H_2O, 80 °C, 2 h. Method C (carbonylative amidation): CO (1 atm), 5 mol % $PdCl_2(PPh_3)_2$, R^4NH_2 (**7**, 0.25 mL), DMF, 65 °C, 3–6 h. Method D (Heck coupling): 5 mol % $Pd(OAc)_2$, *n*-Bu_4NCl (1.0 equiv), Na_2CO_3 (2.5 equiv), $R^4CH{=}CH_2$ (**8**, 4 equiv), DMF, 85 °C, 5–24 h. Method E (amination): 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$, 5 mol % BINAP, *t*-BuONa (1.4 equiv), R^4NH_2 (**7**, 1.2 equiv), DMF, 80 °C, 2.5 h.

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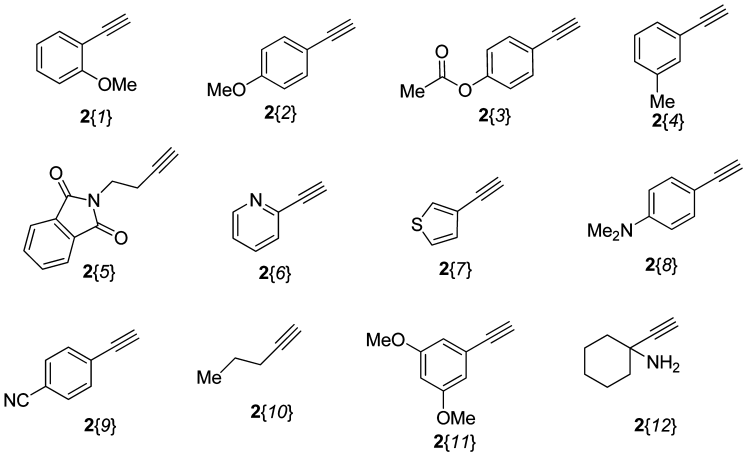
cyclic imidates, carbonylative amidation of the 3-iodomethylene-containing cyclic imidates **4** using one atmosphere of carbon monoxide and various amines **7** in the presence of catalytic amounts of $PdCl_2(PPh_3)_2$ was investigated (method C). However, the reaction product was isolated in only one case **9**{*64*} and only in a low yield. By allowing the compounds **4** to react under Heck reaction conditions in the presence of the styrenes **8**, we obtained the substituted olefin-containing cyclic imidate products **9**{*66*−*73*} (method D). Palladium-catalyzed amination reactions have also been attempted to introduce amino substituents into the library (method E). However, the reaction did not proceed well and the process resulted in complex reaction mixtures.

Because of our interest in the synthesis of potentially biologically active heterocycles for their use in high-throughput

Alkyne Sublibrary



Boronic Acid and Boronate Ester Sublibrary

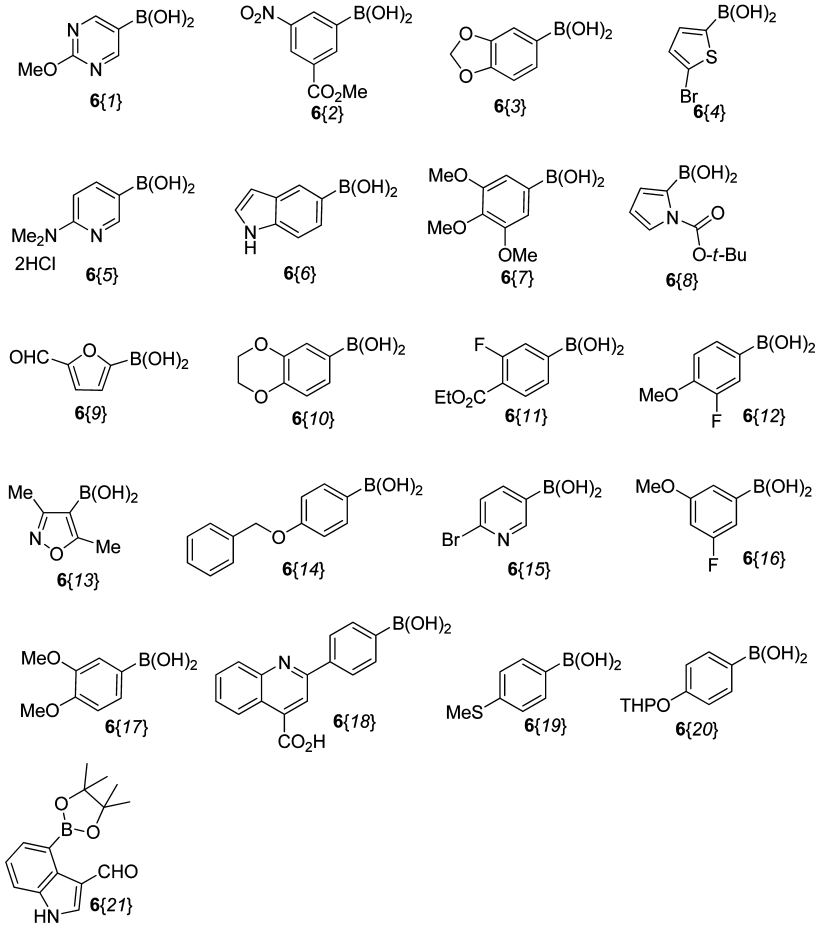


Figure 3. continued

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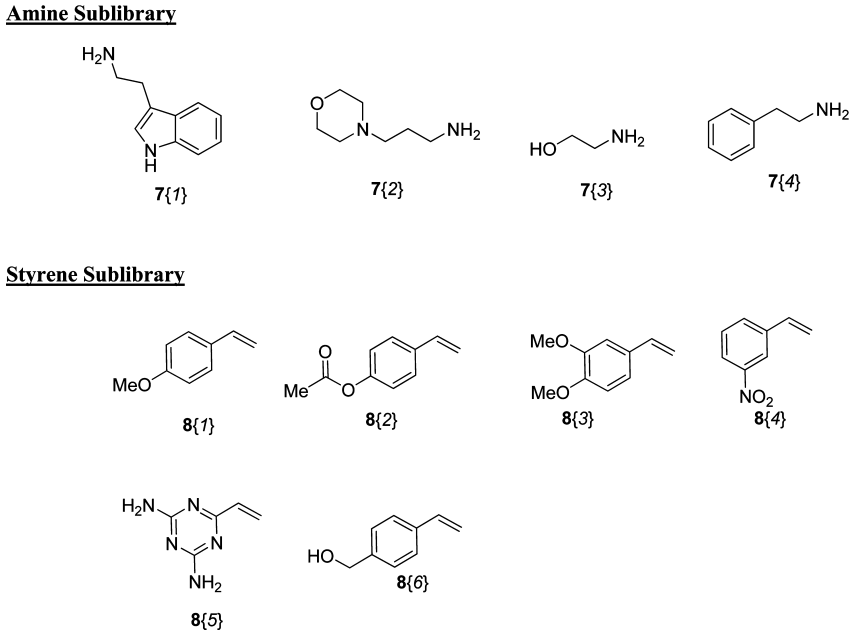

Figure 3. Diverse terminal alkynes **2**{*1*−*12*}, boronic acids **6**{*1*−*2*}, boronate ester **6**{*21*}, amines **7**{*1*−*4*}, and styrenes **8**{*1*−*6*} used for library synthesis.

screening, an in silico evaluation of the library members was carried out to check their conformity with Lipinski's "rule of five" and Veber's rules.[14,15] The molecular weight, clogP, number of hydrogen bond donors and acceptors, and the number of rotatable bonds were calculated for each of the library members using the SYBYL program.[16] Most of the 71 cyclic imidate library members were found to have either zero or one Lipinski violation. In addition, the cell monolayer absorption model Caco-2, a parameter indicating the ability of a compound to passively permeate epithelial cells, that is, skin and muscle sheaths, was also calculated.[17] The mean values, as well as the range of these parameters for this cyclic imidate library, is provided in Table 4.

In conclusion, a highly substituted 71-member library of cyclic imidates **9** with four points of diversity has been synthesized. 3-Iodomethylene-containing cyclic imidates **4** are readily prepared by iodocyclization chemistry. We have demonstrated the diversification of these 3-iodomethylene-containing cyclic imidates **4** with various building blocks, for example, terminal alkynes **2,** boronic acids **6**, carbon monoxide plus amines **7**, and styrenes **8**, to construct a diverse library through a variety of C−C bond forming reactions. The cyclic imidate library members **9** will be evaluated against various biological screens by the National Institutes of Health Molecular Library Screening Center Network.

EXPERIMENTAL PROCEDURES

General Sonogashira Coupling Procedure Used for Preparation of the 2-(1-Alkynyl)benzamides 3{*1*−*6*}. To a solution of the appropriate *o*-iodobenzamide **1** (5.0 mmol) in DMF (20 mL) were added $PdCl_2(PPh_3)_2$ (2 mol %) and CuI (1 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (4.0 equiv) was added by syringe. The reaction mixture was then heated to 65 °C. A solution of alkyne **2** (1.2 equiv) in DMF (5 mL) was added dropwise over 10 min, and the mixture was allowed to stir at 65 °C for 2 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was purified by column chromatography on silica gel using hexane−EtOAc as the eluent.

*Benzamide **3**{1}*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.96 (t, J = 7.6 Hz, 3H), 1.53−1.59 (m, 2H), 2.40 (t, J = 7.2 Hz, 2H), 7.09 (t, J = 7.6 Hz, 1H), 7.27−7.33 (m, 4H), 7.41−7.43 (m, 1H), 7.67 (d, J = 8.0 Hz, 2H), 7.95−7.97 (m, 1H), 9.43 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 21.5, 21.9, 79.2, 97.9, 119.8, 120.2, 124.1, 128.0, 128.8, 129.7, 130.5, 133.5, 135.5, 138.0, 164.4. HRMS Calcd for $C_{18}H_{17}NO$: 263.13101. Found: 263.13162.

General Iodocyclization Procedure Used for Preparation of the Cyclic Imidates 4{*1*−*6*}. To a solution of the starting alkyne **3** (4.0 mmol) in MeCN (20 mL) were added I_2 (3.0 equiv) and $NaHCO_3$ (3.0 equiv). The reaction mixture was allowed to stir at 25 °C and the reaction was monitored by TLC for completion. The excess I_2 was removed by washing with satd aq $Na_2S_2O_3$. The mixture was then extracted by EtOAc, and the combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under vacuum to yield the crude product, which was purified by flash chromatography on silica gel using hexane−EtOAc as the eluent.

*Cyclic Imidate **4**{1}*. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, J = 7.6 Hz, 3H), 1.56−1.62 (m, 2H), 2.81 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 7.2 Hz, 1H), 7.35 (t, J = 7.6 Hz, 2H), 7.42−7.51 (m, 4H), 7.94 (d, J = 7.2 Hz, 1H), 8.56 (d, J = 7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.2, 22.5, 41.6, 82.2, 123.7, 123.9, 124.2, 124.8, 128.7, 129.9, 131.6, 132.2, 135.3, 145.5, 147.3, 152.1. HRMS Calcd for $C_{18}H_{16}INO$: 389.02766. Found: 389.02853.

General Sonogashira Coupling Procedure Used for the Preparation of Alkynes 9{*1*−*17*}. To a solution of the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol) in DMF (4 mL) were added $PdCl_2(PPh_3)_2$ (3 mol %) and CuI (2 mol %). The reaction vial was flushed with Ar and the reaction mixture was stirred for 5 min at room temperature. DIPA (4.0 equiv) was added by syringe. The reaction mixture was heated to 70 °C. A solution of alkyne **2** (1.2 equiv) in DMF

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Table 3. Library Data for Compounds 9{*1*−*75*}

compd	4	building block	method[a]	yield[b] (%)	purity[c] (%)
9{*1*}	4{*1*}	2{*1*}	A	34	89
9{*2*}	4{*1*}	2{*5*}	A	26	98
9{*3*}	4{*1*}	2{*7*}	A	30	98
9{*4*}	4{*1*}	2{*8*}	A	34	100
9{*5*}	4{*1*}	2{*9*}	A	27	97
9{*6*}	4{*1*}	2{*10*}	A	21	99
9{*7*}	4{*1*}	2{*11*}	A	14	100
9{*8*}	4{*1*}	2{*12*}	A	8	91
9{*9*}	4{*6*}	2{*4*}	A	51	87
9{*10*}	4{*6*}	2{*6*}	A	19	89
9{*11*}	4{*7*}	2{*1*}	A	55	97
9{*12*}	4{*7*}	2{*2*}	A	59	100
9{*13*}	4{*7*}	2{*3*}	A	38	91
9{*14*}	4{*7*}	2{*4*}	A	63	80
9{*15*}	4{*7*}	2{*5*}	A	16	97
9{*16*}	4{*7*}	2{*6*}	A	69	100
9{*17*}	4{*7*}	2{*7*}	A	8	98
9{*18*}	4{*1*}	6{*1*}	B	43	100
9{*19*}	4{*1*}	6{*2*}	B	28	100
9{*20*}	4{*1*}	6{*3*}	B	62	99
9{*21*}	4{*1*}	6{*4*}	B	7	94
9{*22*}	4{*1*}	6{*5*}	B	52	100
9{*23*}	4{*1*}	6{*6*}	B	73	100
9{*24*}	4{*1*}	6{*7*}	B	67	100
9{*25*}	4{*1*}	6{*9*}	B	25	98
9{*26*}	4{*1*}	6{*10*}	B	59	99
9{*27*}	4{*1*}	6{*11*}	B	62	100
9{*28*}	4{*1*}	6{*12*}	B	78	100
9{*29*}	4{*1*}	6{*13*}	B	16	100
9{*30*}	4{*1*}	6{*14*}	B	64	61
9{*31*}	4{*1*}	6{*15*}	B	13	98
9{*32*}	4{*1*}	6{*17*}	B	52	95
9{*33*}	4{*1*}	6{*18*}	B	7	100
9{*34*}	4{*1*}	6{*20*}	B	49	99
9{*35*}	4{*4*}	6{*1*}	B	30	100
9{*36*}	4{*4*}	6{*10*}	B	28	97
9{*37*}	4{*4*}	6{*16*}	B	92	58
9{*38*}	4{*5*}	6{*6*}	B	15	84
9{*39*}	4{*5*}	6{*10*}	B	32	64
9{*40*}	4{*5*}	6{*14*}	B	26	54
9{*41*}	4{*5*}	6{*16*}	B	36	60
9{*42*}	4{*6*}	6{*1*}	B	22	94
9{*43*}	4{*6*}	6{*6*}	B	30	84
9{*44*}	4{*6*}	6{10}	B	39	93
9{*45*}	4{*6*}	6{*19*}	B	32	81
9{*46*}	4{7}	6{*1*}	B	27	100
9{*47*}	4{7}	6{2}	B	33	96
9{*48*}	4{7}	6{3}	B	57	88
9{*49*}	4{7}	6{*4*}	B	18	95
9{*50*}	4{7}	6 {*5*}	B	43	98
9{*51*}	4{7}	6{*6*}	B	29	93
9{*52*}	4{7}	6{7}	B	14	71
9{*53*}	4{7}	6{*8*}	B	25	98
9{*54*}	4{7}	6{*9*}	B	52	98
9{*55*}	4{7}	6{*10*}	B	32	87
9{*56*}	4{7}	6{*11*}	B	48	100
9{*57*}	4{7}	6{*12*}	B	38	82
9{*58*}	4{7}	6{*13*}	B	7	75
9{*59*}	4{7}	6{*14*}	B	34	85
9{*60*}	4{7}	6{*15*}	B	43	91
9{*61*}	4{7}	6{*20*}	B	36	99
9{*62*}	4{7}	6{*21*}	B	4	81
9{*63*}	4{*1*}	7{2}	C	0	
9{*64*}	4{*1*}	7{3}	C	14	90
9{*65*}	4{*1*}	7{*4*}	C	0	
9{*66*}	4{*1*}	8{*1*}	D	41	85
9{*67*}	4{*1*}	8{2}	D	50	95
9{*68*}	4{*1*}	8{3}	D	46	86
9{*69*}	4{*1*}	8{*4*}	D	20	92
9{*70*}	4{*1*}	8{*5*}	D	10	96
9{*71*}	4{7}	8{2}	D	50	80
9{*72*}	4{7}	8{*5*}	D	14	100
9{*73*}	4{7}	8{*6*}	D	31	78
9{*74*}	4{7}	7{*1*}	E	0	
9{*75*}	4{7}	7{2}	E	0	

[a]Method A, Sonogashira coupling; B, Suzuki−Miyaura coupling; C, carbonylative amidation; D, Heck coupling; E, amination. [b]Isolated yield after preparative HPLC. [c]UV purity determined at 214 nm after preparative HPLC.

(1 mL) was added dropwise over 10 min, and the mixture was allowed to stir at 70 °C for 2 h. After cooling, the reaction mixture was diluted with EtOAc, and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was either purified by column chromatography on silica gel using hexane-EtOAc as the eluent, or was flushed through a short silica gel plug and purified by preparative HPLC.

General Suzuki−Miyaura Coupling Procedure Used for the Preparation of Imidates 9{*18*−*62*}. To a 4-dram vial were added the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol), the boronic acid **6** (0.30 mmol), $KHCO_3$ (0.35 mmol), and $PdCl_2$ (0.0125 mmol) in 4:1 DMF/H_2O (2.5 mL). The reaction mixture was stirred for 5 min at room temperature and flushed with Ar and then heated to 80 °C for 2 h. After it was cooled, the reaction mixture was diluted with EtOAc and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was either purified by column chromatography on silica gel using hexane−EtOAc as the eluent or was flushed through a short silica gel plug and purified by preparative HPLC.

Table 4. In Silico Data for Lipinski and Cell Permeability Parameters

parameter	mean	range	optimum value
mol. weight	391.3	315.3−510.6	≤500
H-bond acceptors	3.9	2−7	≤10
H-bond donors	1.5	1−3	≤5
ClogP	5.7	2.9−9.2	≤5.0
rotatable bonds	4.8	2−7	≤10
Caco-2	1.2	0.2−2.1	≥0.4

Carbonylative Amidation Procedure Used for the Preparation of Amide 9{*64*}. To a 4-dram vial were added the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), DMF (1 mL), and the amine **7** (0.25 mL). The reaction mixture was stirred for 2 min at

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room temperature and flushed with carbon monoxide. A balloon of carbon monoxide was placed on the vial, which was heated to 65 °C for 3 h. After it was cooled, the reaction mixture was diluted with EtOAc and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was flushed through a short silica gel plug and purified by preparative HPLC.

General Heck Coupling Procedure Used for the Preparation of Alkenes 9{*66*−*73*}. To a 4-dram vial were added the appropriate 3-iodomethylene-containing cyclic imidate **4** (0.25 mmol), the styrene **8** (1.0 mmol), $Pd(OAc)_2$ (5 mol %), *n*-Bu_4NCl (0.25 mmol), Na_2CO_3 (0.625 mmol), and DMF (2 mL). The reaction mixture was then heated to 85 °C for 5−24 h. After it was cooled, the reaction mixture was diluted with EtOAc (20 mL) and washed with satd aq NH_4Cl and water. The organic layer was dried over $MgSO_4$ and concentrated under vacuum to give the crude product, which was flushed through a short silica gel plug and purified by preparative HPLC.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details, conditions for the high throughput liquid chromatography purification, X-ray crystallographic data for compound **9**{*24*}, and the characterization data for all previously unreported starting materials, intermediate compounds, and a representative 20 library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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