Published in final edited form as:

ACS Comb Sci. 2013 May 13; 15(5): 247–254. doi:10.1021/co3001605.

Solution-Phase Parallel Synthesis of a Multi-substituted Cyclic Imidate Library

Saurabh Mehta^{†,‡}, Jesse P. Waldo[†], Benjamin Neuenswander[§], Gerald H. Lushington[§], and Richard C. Larock^{*,†}

[†]Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States

[‡]Department of Applied Chemistry, Delhi Technological University, Delhi, 110042 India

[§]The University of Kansas NIH Center of Excellence in Chemical Methodologies and Library Development, Lawrence, Kansas 66047, United States

Abstract

The solution-phase parallel synthesis of a diverse 71 member library of multi-substituted 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 I₂. 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

*Corresponding Author: Phone: (515) 294-4660. larock@iastate.edu.

The authors declare no competing financial interest.

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>.

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

Several research groups have reported various synthetic routes for the synthesis of cyclic imidates.⁵ Although the biological potential of this heterocyclic scaffold hasn't 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

In our ongoing efforts to generate interesting libraries of potentially biologically active heterocycles,⁷ we have used our iodocyclization strategy described above and further diversified the resulting cyclic imidates to study the biological profile of 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-coupling⁹ 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 I₂/NaHCO₃ 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 arylolefinyl 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

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.

(1)

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 amination¹³ (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.

Alkyne Sublibrary

Boronic Acid and Boronate Ester Sublibrary

Amine Sublibrary

Styrene Sublibrary

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 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 $\text{PdCl}_2(\text{PPh}_3)_2$ 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 imide 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 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, clog P, 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 imide 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, *i.e.* skin and muscle sheaths, was also calculated.¹⁷ The mean values, as well as the range of these parameters for this cyclic imide library, is provided in Table 4.

In conclusion, a highly substituted 71 member library of cyclic imides **9** with four points of diversity has been synthesized. 3-Iodomethylene-containing cyclic imides **4** are readily prepared by iodocyclization chemistry. We have demonstrated the diversification of these 3-iodomethylene-containing cyclic imides **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 imide 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 PdCl₂(PPh₃)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 NH₄Cl and water. The organic layer was dried over MgSO₄ 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**}**—¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₈H₁₇NO: 263.13101. Found: 263.13162.

General Iodocyclization Procedure Used for Preparation of the Cyclic Imides **4**{**1–6**}

To a solution of the starting alkyne **3** (4.0 mmol) in MeCN (20 mL) were added I₂ (3.0 equiv) and NaHCO₃ (3.0 equiv). The reaction mixture was allowed to stir at 25 °C and the reaction was monitored by TLC for completion. The excess I₂ was removed by washing with satd aq Na₂S₂O₃. The mixture was then extracted by EtOAc, and the combined organic layers were dried over anhydrous MgSO₄ 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 Imide **4{**1**}**—¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (100 MHz, CDCl₃) 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 C₁₈H₁₆INO: 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 $\text{PdCl}_2(\text{PPh}_3)_2$ (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 (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 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.

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), $\text{PdCl}_2(\text{PPh}_3)_2$ (5 mol %), DMF (1 mL) and the amine **7** (0.25 mL). The reaction mixture was stirred for 2 min at 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 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 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), $\text{Pd}(\text{OAc})_2$ (5 mol %), $n\text{-Bu}_4\text{NCl}$ (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 cooling, 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding Sources

We thank the National Institute of General Medical Sciences (GM070620 and GM079593) and the University of Kansas National Institutes of Health Center of Excellence in Chemical Methodologies and Library Development (GM069663) for support of this research.

We thank Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium catalysts, and Frontier Scientific and Synthoix for donations of boronic acids. We also thank Dr. Frank Schoenen (University of Kansas) for helpful discussions and Dr. Arkady Ellern and the Molecular Structure Laboratory of Iowa State University for providing X-ray crystallographic data for product **9** (**24**).

REFERENCES AND NOTES

- (a) Larock, RC. Synthesis of Heterocycles and Carbocycles by Electrophilic Cyclization of Alkynes. In: Diederich, F.; Stang, P.J.; Tykwinski, R.R., editors. *Acetylene Chemistry. Chemistry, Biology, and Material Science*. Vol. 2. Wiley-VCH; New York, NY: 2005. p. 51-99. (b) Godoi B, Schumacher RF, Zeni G. Synthesis of Heterocycles via Electrophilic Cyclization of Alkynes Containing Heteroatom. *Chem Rev*. 2011; 111:2937–2980. [PubMed: 21425870]
- Mehta S, Yao T, Larock RC. Regio- and Stereoselective Synthesis of Cyclic Imidates *via* Electrophilic Cyclization of *o*-(1-Alkynyl)benzamides. A Correction. *J Org Chem*. 2012; 77:10938–10944. [PubMed: 23110553]
- Schlemmer C, Andernach L, Schollmeyer D, Straub BF, Opatz T. Iodocyclization of *o*-Alkynylbenzamides Revisited: Formation of Isobenzofuran-1(3*H*)-imines and 1*H*-Isochromen-1-imines Instead of Lactams. *J Org Chem*. 2012; 77:10118–10124. [PubMed: 23088716]
- Madaan C, Saraf S, Priyadarshani G, Reddy PP, Guchhait SK, Kunwar AC, Sridhar B. One-Pot, Three-Step Copper-Catalyzed Five-/Four-Component Reaction Constructs Polysubstituted Oxa(Thia)zolidin-2-imines. *Synlett*. 2012; 23:1955–1959.
- (a) Xiong T, Zhang Q, Zhang Z, Liu Q. A Divergent Synthesis of γ -Iminolactones, Dihydroquinolin-2-ones, and γ -Lactams from β -Hydroxymethylcyclopropanylamides. *J Org Chem*. 2007; 72:8005–8009. [PubMed: 17877406] (b) Tang Y, Li CZ. Facile 5-Endo Electrophilic Cyclization of Unsaturated Amides with t BuOCl/I₂. *Tetrahedron Lett*. 2006; 47:3823–3825. (c) Ma S, Gu Z, Yu Z. Pd(CH₃CN)₂Cl₂-Catalyzed Oxidative Heterodimerization Reaction of 2,3-Allenamides and 1,2-Allenyl Ketones: An Efficient Synthesis of 4-(Furan-3'-yl)-2(5*H*)-furanimines. *J Org Chem*. 2005; 70:6291–6294. [PubMed: 16050689] (d) Maghsoodlou MT, Hazeri N, Habibi-Khorasani SM, Heydari R, Marandi G, Nassiri M. Reaction of Alkyl and Aryl Isocyanides with Floren-9-ones in the Presence of Acetylenic Esters: Preparation of γ -Spiroiminolactones. *Synth Commun*. 2005; 35:2569–2574. (e) Esmaeili AA, Zendegani H. Three-component Reactions Involving Zwitterionic Intermediates for the Construction of Heterocyclic Systems: One Pot Synthesis of Highly Functionalized γ -Iminolactones. *Tetrahedron*. 2005; 61:4031–4034. (f) Nair V, Rajesh C, Vinod AU, Bindu S, Sreekanth AR, Mathen JS, Balagopal L. Strategies for Heterocyclic Construction via Novel Multicomponent Reactions Based on Isocyanides and Nucleophilic Carbenes. *Acc Chem Res*. 2003; 36:899–907. [PubMed: 14674781] (g) Ma S, Xie H. Steric Hindrance-Controlled Pd(0)-Catalyzed Coupling–Cyclization of 2,3-Allenamides and Organic Iodides. An Efficient Synthesis of Iminolactones and γ -Hydroxy- γ -lactams. *J Org Chem*. 2002; 67:6575–6578. [PubMed: 12201788]
- (a) Yu Y, Deck JA, Hunsaker LA, Deck LM, Royer RE, Goldberg E, Jagt DLV. Selective Active Site Inhibitors of Human Lactate Dehydrogenases A₄, B₄, and C₄. *Biochem Pharmacol*. 2001; 62:81–89. [PubMed: 11377399] (b) Royer RE, Deck LM, Jagt TJV, Martinez FJ, Mills RG, Young SA, Jagt DLV. Synthesis and Anti-HIV Activity of 1,1'-Dideoxygossypol and Related Compounds. *J Med Chem*. 1995; 38:2427–2432. [PubMed: 7608907] (c) Royer RE, Mills RG, Young SA, Jagt DLV. Comparison of the Antiviral Activities of 3'-Azido-3'-deoxythymidine (AZT) and Gossylic Iminolactone (GIL) Against Clinical Isolates of HIV-1. *Pharmacol Res*. 1995; 31:49–52. [PubMed: 7540302] (d) Hegde, SG.; Bryant, RD.; Lee, LF.; Parrish, SK.; Parker, WB. Synthesis and Chemistry of Agrochemicals IV; ACS Symposium Series 584. Vol. Chapter 6. American Chemical Society; Washington DC: 1995. Cyclic Imidate Derivatives of 5-Amino-2,6-bis(polyfluoroalkyl)pyridine-3-carboxylates, Synthesis and Herbicidal Activity; p. 60-69.
- (a) Cho CH, Shi F, Jung DI, Neuenswander B, Lushington GH, Larock RC. Solution-Phase Synthesis of a Highly Substituted Furan Library. *ACS Comb Sci*. 2012; 14:403–414. [PubMed: 22612549] (b) Cho CH, Jung DI, Neuenswander B, Larock RC. Parallel Synthesis of a Desketoralexifene Analogue Library via Iodocyclization/Palladium-Catalyzed Coupling. *ACS Comb Sci*. 2011; 13:501–510. [PubMed: 21721520] (c) Markina NA, Mancuso R, Neuenswander B, Lushington GH, Larock RC. Solution-Phase Parallel Synthesis of a Diverse Library of 1,2-Dihydroisoquinolines. *ACS Comb Sci*. 2011; 13:265–271. [PubMed: 21410207] (d) Cho CH,

- Neuenschwander B, Lushington GH, Larock RC. Solution-Phase Parallel Synthesis of a Multi-substituted Benzo[b]thiophene Library. *J Comb Chem*. 2009; 11:900–906. [PubMed: 19569714] (e) Waldo JP, Mehta S, Neuenschwander B, Lushington GH, Larock RC. Solution Phase Synthesis of a Diverse Library of Highly Substituted Isoxazoles. *J Comb Chem*. 2008; 10:658–663. [PubMed: 18671435] (f) Yao T, Yue D, Larock RC. Solid-Phase Synthesis of 1,2,3-Trisubstituted Indoles and 2,3-Disubstituted Benzofurans via Iodocyclization. *J Comb Chem*. 2005; 7:809–812. [PubMed: 16283788]
8. Kundu NG, Khan MW. Palladium-Catalysed Heteroannulation with Terminal Alkynes: a Highly Regio- and Stereoselective Synthesis of (Z)-3-Aryl(alkyl)idene Isoindolin-1-ones. *Tetrahedron*. 2000; 56:4777–4792.
 9. Sonogashira K, Tohda Y, Hagihara N. A Convenient Synthesis of Acetylenes: Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes and Bromopyridines. *Tetrahedron Lett*. 1975; 16:4467–4470.
 10. Miyaura N, Suzuki A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem Rev*. 1995; 95:2457–2483.
 11. Schoenberg A, Heck RF. Palladium-Catalyzed Amidation of Aryl, Heterocyclic, and Vinylic Halides. *J Org Chem*. 1974; 39:3327–3331.
 12. Heck RF, Nolley JP Jr. Palladium-Catalyzed Vinylic Hydrogen Substitution Reactions with Aryl, Benzyl, and Styryl Halides. *J Org Chem*. 1972; 37:2320–2322.
 13. Ali MH, Buchwald SL. An Improved Method for the Palladium-Catalyzed Amination of Aryl Iodides. *J Org Chem*. 2001; 66:2560–2565. [PubMed: 11304171]
 14. (a) Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv Drug Delivery Rev*. 1997; 23:3–25. (b) Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv Drug Del Rev*. 2001; 46:3–26.
 15. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. Molecular Properties That Influence the Oral Bioavailability of Drug Candidates. *J Med Chem*. 2002; 45:2615–2623. [PubMed: 12036371]
 16. SYBYL, version 8.0. The Tripos Associate; St. Louis, MO: 2008.
 17. (a) Artursson P, Palm K, Luthman K. *Adv Drug Deliv Rev*. 2001; 46:27–43. [PubMed: 11259831] (b) Cruciani, G.; Meniconi, M.; Carosati, E.; Zamora, I.; Mannhold, R. VOLSURF: A Tool for Drug ADME-Properties Prediction. In: van de Waterbeemd, H.; Lennernäs, H.; Artursson, P., editors. *Methods and Principles in Medicinal Chemistry*. Wiley-VCH; Weinheim, Germany: 2003. p. 406-419.

Figure 1.
Biologically Active Cyclic Imidates.

Figure 2.
Sublibrary of 3-Iodomethylene-containing Cyclic Imidates 4{1–8}.

Figure 3.

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

$E^+ = I_2, ICl, NBS, \text{ etc.}$

$R^1 = H, OMe; R^2 = Me, Bn, \text{ aryl}; R^3 = \text{ alkyl, alkenyl, aryl, TMS}$

Scheme 1.

Synthesis of Cyclic Imidates by Electrophilic Cyclization²

Scheme 2.
Library Design for Tetrasubstituted Cyclic Imidates

Scheme 3.**Synthesis of Cyclic Imidates **9** Using Various Palladium-catalyzed Reactions^a**

^aMethod A (Sonogashira coupling): 3 mol % PdCl₂(PPh₃)₂, 2 mol % CuI, DIPA (4 equiv), R⁴C≡CH (**2**, 1.2 equiv), DMF, 70 °C, 2 h. Method B (Suzuki-Miyaura coupling): 5 mol % PdCl₂, KHCO₃ (1.4 equiv), R⁴B(OH)₂ (**6**, 1.2 equiv), 4:1 DMF/H₂O, 80 °C, 2 h. Method C (carbonylative amidation): CO (1 atm), 5 mol % PdCl₂(PPh₃)₂, R⁴NH₂ (**7**, 0.25 mL), DMF, 65 °C, 3–6 h. Method D (Heck coupling): 5 mol % Pd(OAc)₂, *n*-Bu₄NCl (1.0 equiv), Na₂CO₃ (2.5 equiv), R⁴CH=CH₂ (**8**, 4 equiv), DMF, 85 °C, 5–24 h. Method E (amination): 5 mol % Pd₂(dba)₃·CHCl₃, 5 mol % BINAP, *t*-BuONa (1.4 equiv), R⁴NH₂ (**7**, 1.2 equiv), DMF, 80 °C, 2.5 h.

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

compd ^a	R ¹	R ²	R ³	yield ^b (%)
3 {1}	H	Ph	<i>n</i> -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 % PdCl₂(PPh₃)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	<i>n</i> -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 I₂ (3 equiv) and NaHCO₃ (3 equiv) in MeCN (20 mL) at 25 °C for 1–2 h.

^b Isolated yields after column chromatography.

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

compd	4	building block	method ^a	yield ^b (%)	purity ^c (%)
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

compd	4	building block	method ^a	yield ^b (%)	purity ^c (%)
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	

^aMethod A, Sonogashira coupling; B, Suzuki-Miyaura coupling; C, carbonylative amidation; D Heck coupling; E, amination.

^bIsolated yield after preparative HPLC.

^cUV purity determined at 214 nm after 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
$C \log P$	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