Highly Substituted Indole Library Synthesis by Palladium-Catalyzed Coupling Reactions in Solution and on a Solid Support

ARTICLE *in* JOURNAL OF COMBINATORIAL CHEMISTRY · SEPTEMBER 2009

Impact Factor: 4.93 · DOI: 10.1021/cc900057n · Source: PubMed

4 AUTHORS, INCLUDING:

Gerald Lushington
University of Kansas
185 PUBLICATIONS **2,479** CITATIONS

SEE PROFILE

Published in final edited form as:
J Comb Chem. 2009 ; 11(5): 875–879. doi:10.1021/cc900057n.

Highly Substituted Indole Library Synthesis by Palladium-Catalyzed Coupling Reactions in Solution and on a Solid Support

Shilpa A. Worlikar[†], **Benjamin Neuenswander**[‡], **Gerald H. Lushington**[‡], and **Richard C. Larock**[†,*]

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

[‡] University of Kansas NIH Center of Excellence in Chemical Methodologies and Library Development, Lawrence, Kansas 66047

Abstract

3-Iodoindoles have been synthesized by the iodocyclization of *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines, obtained by the Pd/Cu catalyzed coupling of terminal acetylenes with *N*,*N*-dialkyl-*o*-iodoanilines. These 3-iodoindoles undergo palladium-catalyzed Sonogashira and Suzuki coupling reactions to yield 1,2,3-trisubstituted indoles. These reactions have been applied to parallel library synthesis utilizing commercially available terminal acetylenes and boronic acids. The aforementioned chemistry has also been carried out on a chlorinated Wang resin as a solid support, affording 1,2,3,5-tetrasubstituted indoles after cleavage from the support. A diverse 42-member library of highly substituted indoles has been synthesized.

Introduction

Indoles are very important in medicinal chemistry and the indole moiety is prevalent in numerous naturally-occurring and synthetic biologically active compounds.[1] It is one of the most important nitrogen-containing pharmacophores,[2] and is present in various drugs.[1b,1g] Due to the importance of the indole nucleus, many synthetic approaches to this ring system have been developed in our research group and others and reported in the literature for the synthesis of substituted indoles.[3] Biologically active natural products are a good indicator of lead structures that might possess biological activity. Due to the biological importance of compounds containing the indole nuclei, it is quite likely that libraries of low molecular weight indoles will display similar activity and thus serve as valuable tools for drug development. Several methods are known for the synthesis of indoles in solution phase[4] and on a solid support[5] by combinatorial methods, but 3-iodoindoles have not previously been examined as key intermediates for indole library synthesis.

Yamanaka *et al*. have reported the coupling of 3-iodoindoles with terminal acetylenes, but satisfactory results were obtained only when the N atom of the indole was protected with an electron-withdrawing 1-methanesulfonyl group.[6] With an electron-donating group on the N atom of the 3-iodoindole, the C-I bond is electron-rich and this appears to limit further functionalization at the 3 position of the indole by palladium-catalyzed coupling reactions.

*Corresponding author: phone: (515) 294-4660. E-mail: larock@iastate.edu.
[†]Iowa State University.
[‡]University of Kansas.

Supporting Information Available. Experimental details and full characterization of previously unknown sublibrary members and a representative 20 library members, including ^{1}H and ^{13}C NMR spectra and HRMS data. This information is available free of charge via the internet at http://pubs.acs.org.

Previously, in our laboratory, we have synthesized *N*,*N*-dialkyl-*o*-(1-alkynyl)anilines (**1**) by coupling terminal acetylenes with *N*,*N*-dialkyl-*o*-iodoanilines in the presence of a Pd/Cu catalyst, which on iodocyclization yield 3-iodoindoles (**2**) in excellent yields (Scheme 1).[7] We have previously reported individual examples of Sonogashira[8] and Suzuki-Miyaura[9] cross-coupling reactions, which provide the corresponding 1,2,3-trisubstituted indoles in good yields (Scheme 2).[6b] We further optimized each of these processes in order to adapt them for library generation. We have previously also reported individual examples of these two coupling reactions on a solid support, followed by cleavage by base.[10] The development of a solid phase version of this chemistry allows the multistep synthesis of highly substituted indoles and eliminates cumbersome purification steps. We herein report the successful synthesis of 1,2,3,5-tetrasubstituted indoles on a solid support by slight modifications of our earlier procedure and alternative cleavage reactions (Scheme 3).

Results and Discussion

Our previous work on 3-iodoindole synthesis reported good yields of single cyclization products from the corresponding *N*,*N*-dimethyl- or *N*-methyl, *N*-phenyl-*o*-(1-alkynyl)anilines (**1**). After the iodocyclization step in the former case, the N-atom of the 3-iodoindole is protected by a methyl group, and, in the latter case, by a phenyl group. Our desire for a low molecular weight indole library led us to choose methyl as the preferred *N*-protecting group. Therefore, our choice of R^2 was a methyl group in our solution phase library synthesis. 3-Iodoindole **2**{1} was synthesized as our basic scaffold by using our previous cyclization method.[7] The 3-iodoindoles **2**{2} and **2**{3} were similarly synthesized from the corresponding *N*, *N*-dimethyl-*o*-(1-alkynyl)anilines **1**. Due to certain limitations in the types of R^1 and R^2 groups that can be employed in our iodocyclization methodology, we synthesized the 3-iodoindoles **2**{4}[11] and **2**{5}[12] by literature methods, while the 3-iodoindole **2**{6} was obtained by treatment of **2**{5} with $NaBH_4$. Thus, we choose a subset of 3-iodoindoles on the basis of the ease of synthesis from readily available starting materials and with different electron-donating and electron-withdrawing functionalities at the 2-position of the indoles (Figure 1).

The terminal alkyne sublibrary was chosen on the basis of commercially available acetylenes. Attempts were made to include heteroatoms in the acetylenes that could impart drug-like, hydrogen bond donor and/or acceptor properties to the indoles after Sonogashira coupling (Figure 2). For similar reasons, acetylenes **3**{5} and **3**{8} were chosen due to the increasing popularity of fluorine[13] and sulfur[14] atoms in drug molecules.

The boronic acids for the Suzuki-Miyaura reactions were also chosen on the basis of their commercial availability and their ability to provide the requisite diversity and drug-like properties to the indole scaffold after subsequent cross-coupling reactions (Figure 3). For instance, the methoxy-containing boronic acids **4**{1} and **4**{2} were chosen with a view towards increasing the polarity of the substituted indole. The *N*- heterocyclic boronic acids **4**{3}, **4**{4}, the *O*- heterocyclic boronic acids **4**{5}, **4**{6}, **4**{7}, the indolylboronic acid **4**{9}, and the benzamido boronic acid **4**{11} were chosen to include heteroatoms and increase the drug-like nature of the corresponding indoles. The fluorine-containing acids **4**{8} and **4**{10} were desirable due to the importance of fluorine in medicinal chemistry.

Having chosen these sublibraries, we proceeded to prepare a diverse library of 1,2,3-trisubstituted indoles via solution phase chemistry as outlined in Scheme 2 and 1,2,3,5-tetrasubstituted indoles using a chlorinated Wang resin as the solid support as depicted in Scheme 3. The crude products have been analyzed by LC/MS, followed by purification by preparative HPLC or flash chromatography.

A summary of the results of the library synthesis is provided in Tables 1–3. Most of the crude products were subjected to preparative HPLC. Purities in the range of 70–100% have been achieved after purification. Most of the Sonogashira coupling reactions proceeded well, except for those run with the terminal alkynes **3**{11} and **3**{12}. Suzuki-Miyaura reactions with the boronic acids **4**{10} and **4**{11} with electron-withdrawing groups failed to give the desired coupling products. The boronic acids **4**{3} and **4**{8} gave decent yields of the coupling products **5**{32} and **5**{33} and excellent purities when reacted with 3-iodoindole **2**{2}, but failed to give the corresponding trisubstituted indoles when coupled with 3-iodoindole **2**{3}. On the solid support, the cleavage by MeMgBr was successful, but EtMgBr failed to give the anticipated products. Out of a total of 51 palladium-catalyzed processes attempted, around 80% were successful.

Our goal in synthesizing these low molecular weight heterocycles is for use in high-throughput screening projects. Therefore, we carried out an *in silico* evaluation of these library members to determine their agreement with Lipinski's[15] "rule of five" and Veber's rules.[16] The SYBYL[17] program was used for the calculation of molecular weight, clog P, the number of hydrogen bond donors and acceptors, and the number of rotatable bonds for each library member (Table 4). According to these rules a potential drug molecule is more drug-like and more bioavailable if the clog P value is not more than 5, the molecular weight is less than 500, the hydrogen bond acceptors are not more than 10, the hydrogen bond donors are not more than 5, and the rotatable bonds in the molecule are not more than 12. One Lipinski violation is allowed for potential drug design. All of the indole library members are Lipinski compliant and no molecule has more than one Lipinski violation. The only violation that a molecule in the library had was clog P, which points towards potential solubility and delivery issues.

Conclusions

In conclusion, the synthesis of 4-iodoindoles and subsequent palladium-catalyzed Sonogashira and Suzuki-Miyaura cross-coupling reactions with various commercially available terminal alkynes and boronic acids have allowed the construction of a 42-member library of highly substituted indoles. The chemistry has been successfully transferred to a solid support and diversity has been achieved at the 5-position by different cleavage reactions. The average yield of the library was 46% and the average purity after purification was 94%.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We would like to thank Frank Schoenen for useful discussions and David Hill at the University of Kansas NIH Center of Excellence in Chemical Methodologies and Library Development for obtaining the NMR spectra of representative library compounds. We thank the National Institute of General Medical Sciences (R01 GM070620 and R01 GM079593) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (P50 GM069663) for support of this research; Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donations of palladium catalysts; and Frontier Scientific and Synthonix for donations of boronic acids.

References

1. For reviews, see: (a)Sundberg RJ. Prog Heterocycl Chem 1989;1:111.(b)Sundberg RJ. Indoles. Academic PressNew York1996(c)Saxton JE. Nat Prod Rep 1986;3:357.1987;4:591.1989;6:1.(d) Ezquerra J, Pedregal C, Lamas C. J Org Chem 1996;61:5804.(e)Toyota M, Ihara M. Nat Prod Rep 1998;15:327.(f)Gribble GW. J Chem Soc, Perkin Trans 12000;:1045.(g)Mori H, Yoshimi N. Mutat Res 2001;480:201. [PubMed: 11506814](h)Tokuyama H, Fukuyama T. Kagaku Kogyo 2001;52:416.

(i)Xiong WN, Yang CG, Jiang B. Bioorg Med Chem 2001;9:1773. [PubMed: 11425579](j)Lobo AM, Prabhakar S. J Heterocycl Chem 2002;39:429.

2. (a) Balkenhohl F, von dem Bussche-Hünnefeld C, Lansky A, Zechel C. Angew Chem, Int Ed Engl 1996;35:2289. (b) Nefzi A, Ostresh JM, Houghten RA. Chem Rev 1997;97:449. [PubMed: 11848878] (c) Loughlin WA. Aust J Chem 1998;51:875.
3. (a) Hegedus LS. Angew Chem 1988;100:1147. (b) Larock RC, Yum EK. J Am Chem Soc 1991;113:6689. (c) Arcadi A, Cacchi S, Carnicelli V, Marinelli F. Tetrahedron 1994;50:437. (d) Larock RC, Yum EK, Refvik MD. J Org Chem 1998;63:7652. (e) Cacchi S, Fabrizi G, Pace P, Marinelli F. Synlett 1999:620. (f) Arcadi A, Cacchi S, Fabrizi G, Moro L. Eur J Org Chem 1999;64:1137. (g) Larock RC. J Organomet Chem 1999;576:111. (h) Rodriguez AL, Koradin C, Dohle W, Knochel P. Angew Chem, Int Ed Engl 2000;39:2488. [PubMed: 10941112] (i) Takeda A, Kamijo S, Yamamoto Y. J Am Chem Soc 2000;122:5662. (j) Pete B, Toke L. Tetrahedron Lett 2001;42:3373. (k) Kamijo S, Yamamoto Y. Angew Chem, Int Ed 2002;41:3230. (l) Kamijo S, Yamamoto Y. J Am Soc Chem 2002;124:11940. (m) Yasuhara A, Takeda Y, Suzuki N, Sakamoto T. Chem Pharm Bull 2002;50:235. [PubMed: 11848216] (n) Rossiter S. Tetrahedron Lett 2002;43:4671. (o) Zhou T, Chen ZC. Synth Commun 2002;32:903.Li, JJ.; Gribble, GW. Palladium in Heterocyclic Chemistry. Pergamon; Oxford, UK: 2000. p. 73-187.
4. (a) Gorohovsky S, Meir S, Shkoulev V, Byk G, Gellerman G. Synlett 2003:1411. (b) Jennings LD, Foreman KW, Rush TS III, Tsao DHH, Mosyak L, Kincaid SL, Sukhdeo MN, Sutherland AG, Ding W, Kenny CH, Sabus CL, Liu H, Dushin EG, Moghazeh SL, Labthavikul P, Petersen PJ, Tuckman M, Ruzin AV. Bioorg Med Chem 2004;12:5115. [PubMed: 15351395]
5. (a) Fagnola MC, Candiani I, Visentin G, Cabri W, Zarini F, Mongelli N, Bedeschi A. Tetrahedron Lett 1997;38:2307. (b) Smith AL, Stevenson GI, Swain CJ, Castro JL. Tetrahedron Lett 1998;39:8317. (c) Macleod C, Hartley RC, Hamprecht DW. Org Lett 2002;4:75. [PubMed: 11772094] (d) Yamazaki K, Kondo Y. J Comb Chem 2002;4:191. [PubMed: 12005476] (e) Wacker DA, Kasireddy P. Tetrahedron Lett 2002;43:5189. (f) Yamazaki K, Nakamura Y, Kondo Y. J Chem Soc, Perkin Trans 2002;119:2137. (g) Yamazaki K, Nakamura Y, Kondo Y. J Org Chem 2003;68:6011. [PubMed: 12868941] (h) Knepper K, Braese S. Org Lett 2003;5:2829. [PubMed: 12889885] (i) Tois J, Franzen R, Koskinen A. Tetrahedron 2003;59:5395. (j) Nicolaou KC, Roecker AJ, Hughes R, van Summeren R, Pfefferkorn JA, Winssinger N. Bioorg Med Chem 2003;11:465. [PubMed: 12517442] (k) Lee SH, Clapham B, Koch G, Zimmermann J, Janda KD. J Comb Chem 2003;5:188. [PubMed: 12625710] (l) Tanaka H, Ohno H, Kawamura K, Ohtake A, Nagase H, Takahashi T. Org Lett 2003;5:1159. [PubMed: 12688708] (m) Rosenbaum C, Katzka C, Marzinzik A, Waldmann H. Chem Commun 2003;15:1822. (n) Dai WM, Guo DS, Sun LP, Huang XH. Org Lett 2003;5:2919. [PubMed: 12889908] (o) Wu Z, Ede NJ. Org Lett 2003;5:2935. [PubMed: 12889912] (p) Rosenbaum C, Baumhof P, Mazitschek R, Mueller O, Giannis A, Waldmann H. Angew Chem, Int Ed 2004;43:224. (q) Ohno H, Tanaka H, Takahashi T. Synlett 2004;3:508. (r) Ohno H, Tanaka H, Takahashi T. Synlett 2005;7:1191. (s) Mun HS, Ham WH, Jeong JH. J Comb Chem 2005;7:130. [PubMed: 15638492] (t) Sun LP, Dai WM. Angew Chem, Int Ed 2006;45:7255. (u) Main CA, Petersson HM, Rahman SS, Hartley RC. Tetrahedron 2008;64:901.
6. Sakamoto T, Nagano T, Kondo Y, Yamanaka H. Chem Pharm Bull 1988;36:2248.
7. (a) Yue D, Larock RC. Org Lett 2004;6:1037. [PubMed: 15012094] (b) Yue D, Yao T, Larock RC. J Org Chem 2006;71:62. [PubMed: 16388618]
8. Sonogashira, K. In Metal-Catalyzed Cross-Coupling Reactions. Diederich, F.; Stang, PJ., editors. Vol. Chapter 5. Wiley-VCH; Weinheim, Germany: 1998. p. 203 (b) Sonogashira K, Tohda Y, Hagihara N. Tetrahedron Lett 1975:4467.
9. (a) Miyaura N, Suzuki A. Chem Rev 1995;95:2457. (b) Suzuki A. J Organomet Chem 1999;576:147.
10. Yao T, Yue D, Larock RC. J Comb Chem 2005;7:809. [PubMed: 16283788]
11. Zhang H, Larock RC. Org Lett 2001;3:3083. [PubMed: 11574000]
12. Choshi T, Sada T, Fujimoto H, Nagayama C, Sugino E, Hibino S. J Org Chem 1997;62:2535. [PubMed: 11671594]
13. Hudlicky, M.; Pavlath, AE., editors. A Critical Review. American Chemical Society; Washington, D. C: 1995. Chemistry of Organic Fluorine Compounds II. ACS Monograph 187Hiyama, T., editor. Chemistry and Applications. Springer-Verlag; New York: 2000. Organofluorine Compounds.
14. (a) Rajbhoj AS, Gaikwad ST, Chondhekar TK. J Ind Chem Soc 2007;84:987. (b) Walash MI, El-Brashy AM, Metwally MS, Abdelal AA. Bull Kor Chem Soc 2004;25:517. (c) Roopnarinesingh ES,

Steventon GB, Harris RM, Waring RH, Mitchell SC. Drug Metabolism and Drug Interactions 2005;21:75. [PubMed: 16355974] (d) Hiller KO, Hodd PL, Willson RL. Chem Biol Interact 1983;47:293. [PubMed: 6317211]

15. (a) Lipinski CA, Lombardo F, Dominay BW, Feeney PJ. Adv Drug Del Rev 1997;23:3. (b) Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Adv Drug Del Rev 2001;46:3.
16. Veber DF, Johnson SR, Cheng HY, Smith BR, Ward KW, Kopple KD. J Med Chem 2002;45:2615. [PubMed: 12036371]
17. *SYBYL*, version 8.0. The Tripos Associate; St. Louis, MO: 2007.

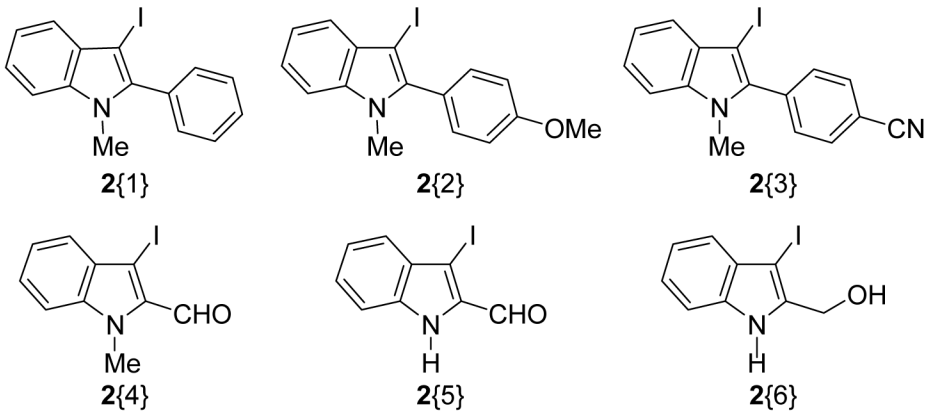


Figure 1.
3-Iodoindole sublibrary.

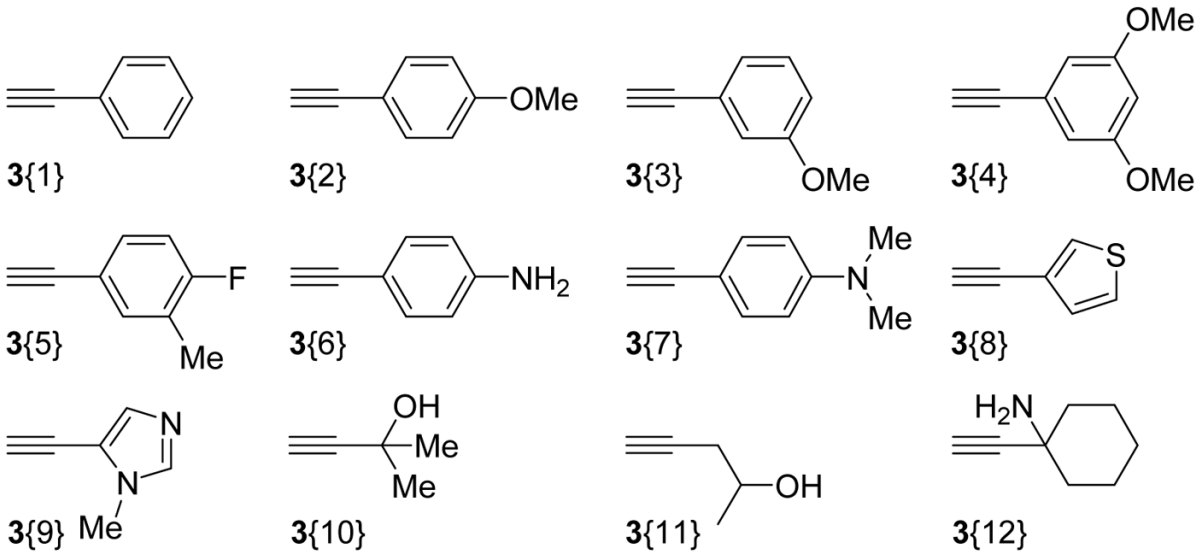


Figure 2.
Terminal acetylene sublibrary.

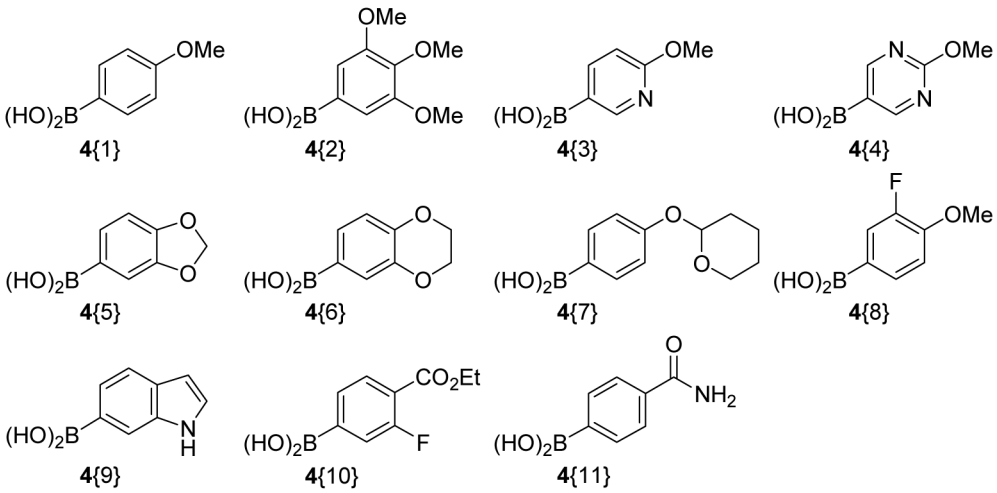
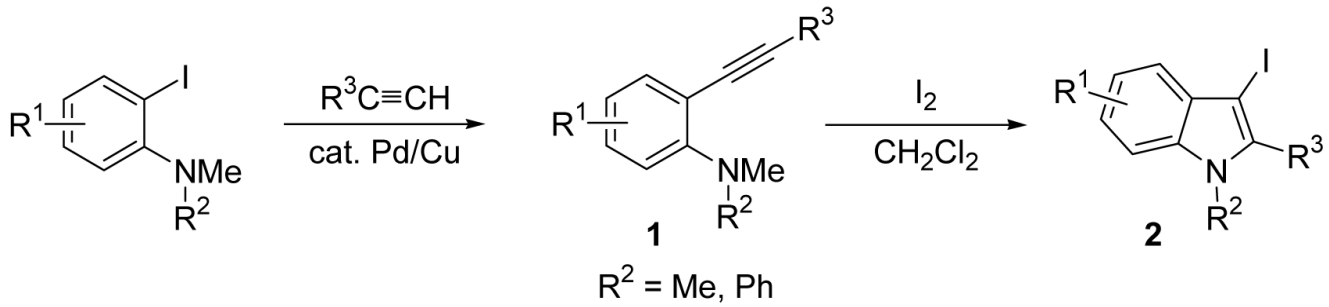
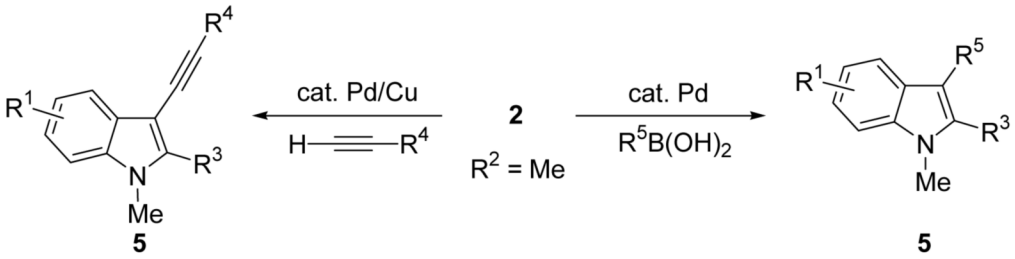


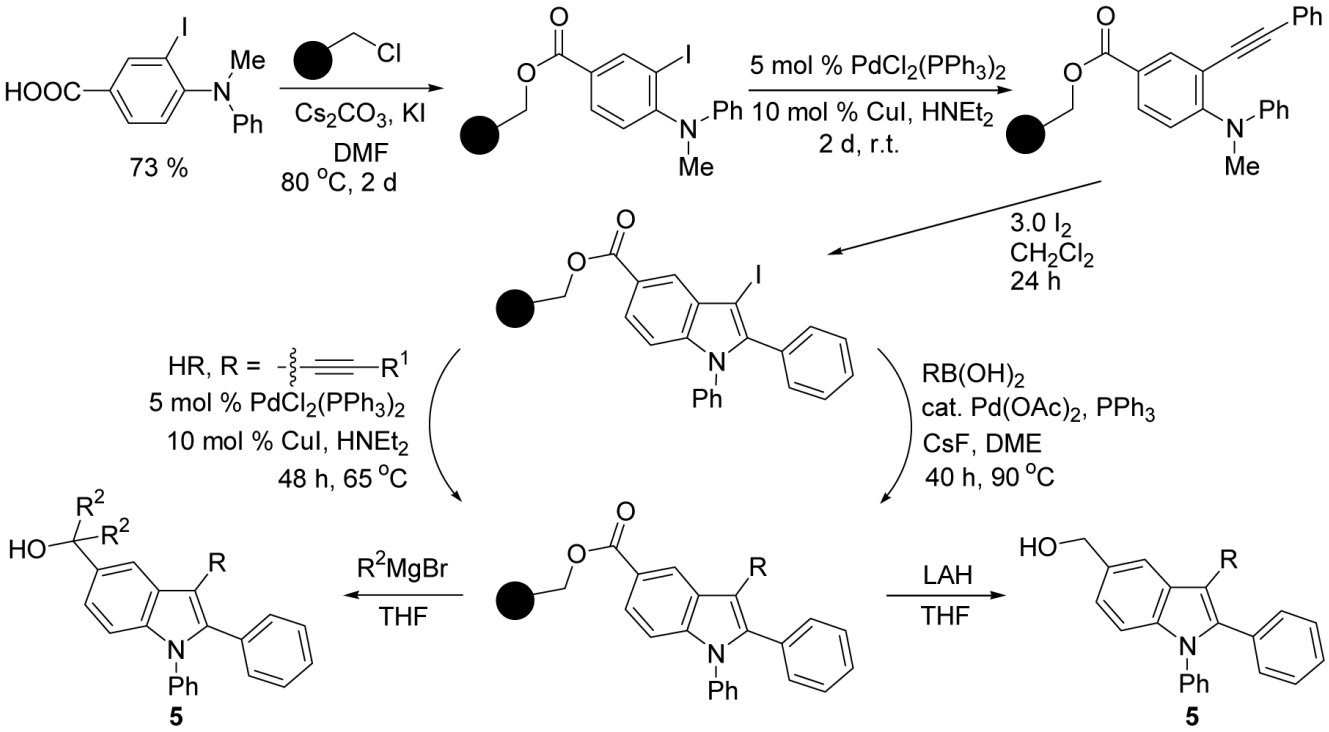
Figure 3.
Boronic acid sublibrary.



Scheme 1.



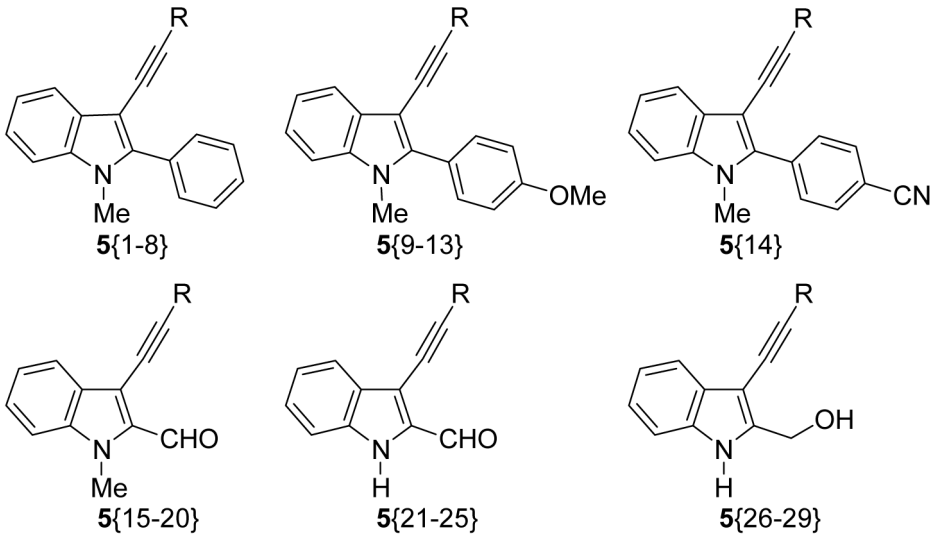
Scheme 2.



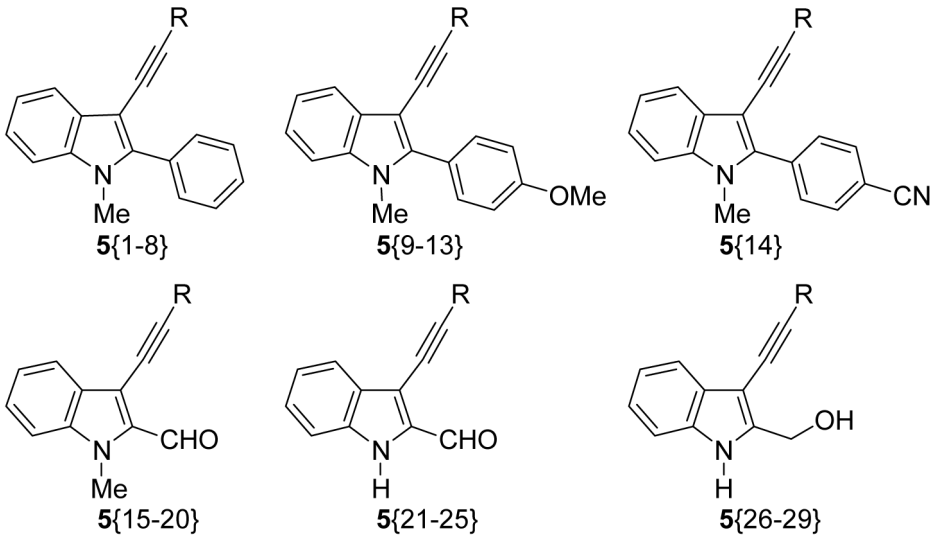
Scheme 3.

Table 1

Library Data for Compounds **5**{1–29}



compound	R	yield[a] (%)	purity[b] (%)
5{1}	4-MeOC$_6$H$_4$	12	97
5{2}	3,5-dimethoxyphenyl	38	94
5{3}	4-fluoro-3-methylphenyl	47	99
5{4}	4-H$_2$NC$_6$H$_4$	27	95
5{5}	4-Me$_2$NC$_6$H$_4$	30	79
5{6}	1-amino-1-cyclohexyl	-	-
5{7}	2-hydroxypropyl	-	-
5{8}	(1-hydroxy-1-methyl)ethyl	13	70
5{9}	C$_6$H$_5$	43	99
5{10}	3,5-dimethoxyphenyl	34	98
5{11}	4-Me$_2$NC$_6$H$_4$	59	97
5{12}	3-thiophenyl	20	93
5{13}	(1-hydroxy-1-methyl)ethyl	33	90
5{14}	C$_6$H$_5$	45	98
5{15}	C$_6$H$_5$	89	100
5{16}	4-MeOC$_6$H$_4$	90	97
5{17}	3-MeOC$_6$H$_4$	79	95
5{18}	3,5-dimethoxyphenyl	94	91
5{19}	1-methyl-1*H*-imidazol-5-yl	82	90
5{20}	(1-hydroxy-1-methyl)ethyl	77	95
5{21}	C$_6$H$_5$	52	100
5{22}	3,5-dimethoxyphenyl	52	90
5{23}	1-methyl-1*H*-imidazol-5-yl	36	98
5{24}	3-thiophenyl	76	93



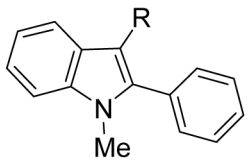
compound	R	yield[a] (%)	purity[b] (%)
5{25}	(1-hydroxy-1-methyl)ethyl	43	96
5{26}	4-$MeOC_6H_4$	21	86
5{27}	3-$MeOC_6H_4$	36	92
5{28}	3,5-dimethoxyphenyl	3	100
5{29}	(1-hydroxy-1-methyl)ethyl	13	95

[a] Isolated yield after preparative HPLC.

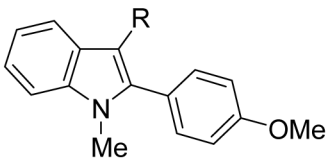
[b] UV purities determined at 214 nm after preparative HPLC.

Table 2

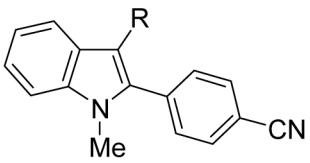
Library Data for Compounds **5**{30–45}



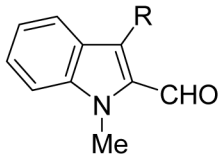
5{30}



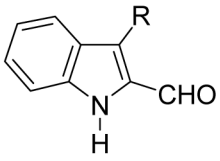
5{31-37}



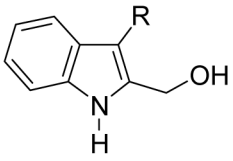
5{38-39}



5{40-42}



5{43-44}



5{45}

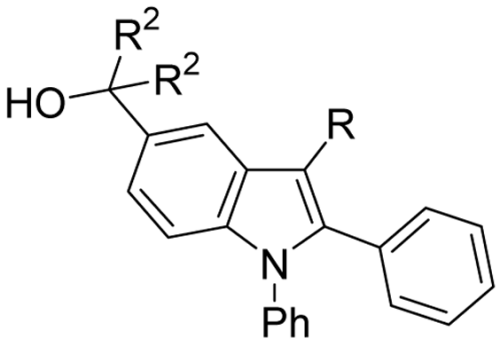
compound	Ar	yield[a] (%)	purity[b] (%)
5{30}	4-$MeOC_6H_4$	23	100
5{31}	3,4,5-trimethoxyphenyl	79	83
5{32}	3-fluoro-4-methoxyphenyl	42	100
5{33}	2-methoxy-5-pyridinyl	50	98
5{34}	benzo[1,3]dioxol-5-yl	39	99
5{35}	2-methoxy-5-pyrimidinyl	59	99
5{36}	4-$H_2NC(O)C_6H_4$	-	-
5{37}	4-EtO_2C-3-FC_6H_3	-	-
5{38}	3-fluoro-4-methoxyphenyl	-	-
5{39}	2-methoxy-5-pyridinyl	-	-
5{40}	2,3-dihydrobenzo[1,4]dioxin-6-yl	84	89
5{41}	2-methoxy-5-pyrimidinyl	2	100
5{42}	6-indolyl	25	94
5{43}	benzo[1,3]dioxol-5-yl	9	100
5{44}	6-indolyl	-	-
5{45}	4-(tetrahydropyran-2-yloxy)phenyl	9	91

[a] Isolated yield after preparative HPLC.

[b] UV purities determined at 214 nm after preparative HPLC.

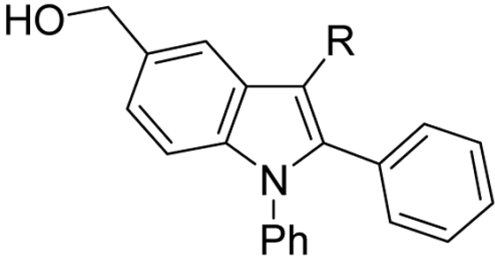
Table 3

Library Data for Compounds **5**{46–51} Synthesized on a Solid Support

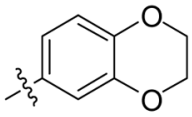
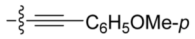
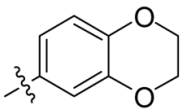
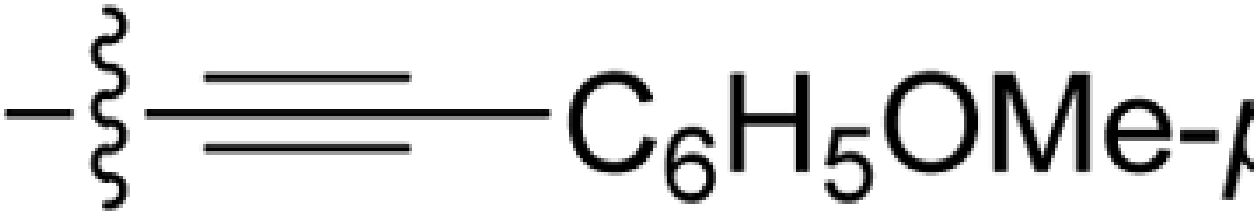


5{46} : R^2 = Me

5{47-48} : R^2 = Et



5{49-51}

compound	R
5{46}	C_6H_5
5{47}	
5{48}	 C_6H_5OMe-*p*
5{49}	C_6H_5
5{50}	
5{51}	 C_6H_5OMe-*p*

[a] Isolated yield after preparative HPLC.

[b] UV purities determined at 214 nm after preparative HPLC.

[c] Isolated yield after flash chromatography.

[d] Purities determined by H^1 NMR spectroscopy after flash chromatography.

Table 4

In silico parameters for gauging oral availability/drug-likeness

	Mean	St. Dev.	Range
Clog P	5.1	1.9	0.6 – 8.0
Mol. Weight	317	53	227–433
H-Bond Acceptors	2.0	0.9	0 – 4
H-Bond Donors	0.8	0.8	0 – 3
Rotatable Bonds	4.1	1.1	2 – 6