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RESEARCH ARTICLE

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Solution-Phase Parallel Synthesis of a Diverse Library of 1,2-Dihydroisoquinolines

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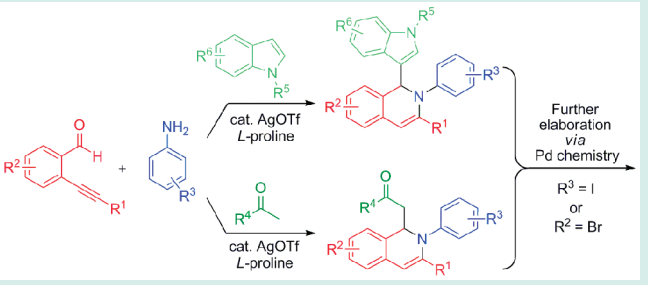
Supporting Information

ABSTRACT: Synthesis of a 105 membered library of 1,2-dihydroisoquinolines is described. The 1,2-dihydroisoquinoline compounds have been prepared in good yields using a Lewis acid and organocatalyst-cocatalyzed multicomponent reaction of 2-(1-alkynyl)benzaldehydes, amines, and ketones. Various indoles have also been employed as pronucleophiles, furnishing 1-(3-indolyl)-1,2-dihydroisoquinolines. The halogen functionality present in some of the synthesized compounds allows for further diversification by palladium-catalyzed Suzuki−Miyaura and Sonogashira cross-couplings to give more diversified 1,2-dihydroisoquinoline derivatives.



KEYWORDS: solution-phase, parallel synthesis, diverse library of 1,2-dihydroisoquinolines

INTRODUCTION

Structures containing a 1,2-dihydroisoquinoline fragment are valuable intermediates for the synthesis of biologically active compounds, for example, alkaloids and pharmaceuticals.[1] For example, cribrostatin 4 and acetoneberbine IK-2 have been shown to possess cytotoxicity against some human cancer cells (Figure 1).[2,3] The hydrochloride salt of the tetrahydroisoquinoline quinapril (sold under the brand name Accupril) is used for the treatment of congestive heart failure and hypertension.[4]

Among the numerous methods developed for synthesis of the 1,2-dihydroisoquinoline core, the most common strategies include functionalization of preformed isoquinoline units using various nucleophiles[5] or ring-forming reactions of 2-(1-alkynyl) arenecarboxaldehyde imines through transition metal-catalyzed processes.[6] The latter processes have also been extended to one-pot procedures that employ 2-(1-alkynyl)arenecarboxaldehydes and amines to preform the required imines in situ.[7]

The solution-phase parallel synthesis of libraries of low molecular weight compounds is increasingly important in modern medicinal chemistry.[8] This approach facilitates the high throughput screening of larger and more diverse sets of compounds with less time spent on optimization of the reaction conditions. In continuation of our work in adapting proven methods for the synthesis of heterocycles to a high throughput synthesis format,[9] we herein report the solution phase synthesis of a library of 1,2-dihydroisoquinolines.

To synthesize a library with greater chances for biological activity, the multisubstituted 1,2-dihydroisoquinoline template **1** has been evaluated computationally for its drug-like properties on the basis of Lipinski's "rule of five"[10] (Scheme 1).

Calculations have been performed based on the commercial availability of aldehydes **4** (Scheme 1), terminal alkynes **5** and **10**, ketones **6**, anilines **7**, indoles **9**, and boronic acids **11** (Figurezs 2 and 4). This data has been used to populate a virtual library of all theoretically possible products, giving 24,888 $[(8 \times 2 \times 6 \times 40) + (8 \times 50 \times 6 \times 3) + (8 \times 50 \times 6) + (8 \times 53 \times 9 \times 3)]$ unique potential compounds. A small subset of this virtual library, namely, 239 compounds, was shown to follow Lipinski's rules with ≤1 violation. The library synthesis of 1,2-dihydroisoquinolines described herein was primarily focused on the preparation of compounds that fall within these 239 examples.

RESULTS AND DISCUSSION

To study a wide variety of multisubstituted 1,2-dihydroisoquinolines, we developed the strategy described in Scheme 1. The 1,2-dihydroisoquinolines **1** can be prepared directly from the corresponding 2-(1-alkynyl)benzaldehydes **3** through reaction with anilines **7** and either ketones **6** or indoles **9**. More highly substituted 1,2-dihydroisoquinolines can be prepared via palladium-catalyzed couplings of the corresponding halogen-containing 1,2-dihydroisoquinolines **2**, prepared through the same three-component coupling reaction.

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The 2-(1-Alkynyl)benzaldehydes **3** are easily prepared by palladium/copper-catalyzed Sonogashira coupling[11] of the corresponding *o*-bromobenzaldehydes **4** (1.0 equiv of **4**, 1.05 equiv of terminal alkyne **5**, 2 mol % of $PdCl_2(PPh_3)_2$, 2 mol % of CuI, and Et_3N at 50 °C for 6 h) (Scheme 1). The yields of this process range from 65 to 100%, and this procedure readily accommodates various functional groups (Table 1).

For the synthesis of the 1,2-dihydroisoquinoline core, we utilized the procedure described by Ding et al.[7a] (Scheme 2, eq 1). The advantages of this three-component AgOTf and *L*-proline cocatalyzed process include the commercially availability of ketones **6** and amines **7**, three independent points of diversification, and formation of the desired products in one step.

Additionally, we are able to replace ketones with indoles in this process, which allows one to isolate 1-(3-indolyl)-1,2-dihydroisoquinolines in a single one-pot process (Scheme 2, eq 2). Since the start of this work, Yamamoto and Wu have independently reported the use of indoles in the same type of process under slightly modified reaction conditions.[12] By employing the reaction conditions optimized for ketones using a sublibrary of indoles **9**, we have been able to isolate 1-(3-indolyl)-1,2-dihydroisoquinolines in moderate to good yields in most cases, broadening the scope of the previously reported 1,2-dihydroisoquinoline synthesis.

The sublibraries of ketones, anilines, and indoles used for the synthesis of 1,2-dihydroisoquinolines **8** are presented in Figure 2.

The data for the 1,2-dihydroisoquinolines **8**{*1*−*30*} prepared, but not subjected to further diversification, is shown in Table 2.

1,2-Dihydroisoquinolines **8**{*31*−*51*}, containing halogen atoms that can be further subjected to palladium-catalyzed couplings, have been isolated and purified by column chromatography. All of the 1,2-dihydroisoquinolines **8**{*31*−*51*}, except **8**{*39*} and **8**{*45*}, which were used crude in the next step, were fully characterized using HRMS, as well as ^1H and ^{13}C NMR spectroscopy (see the Supporting Information for the experimental details). In most cases, moderate to good yields of the 1,2-dihydroisoquinolines **8**{*31*−*51*} have been obtained. The results are summarized in Figure 3.

As can be seen from both Table 2 and Figure 3, this process is generally functional group tolerant and allows one to obtain diversely substituted 1,2-dihydroisoquinolines in 9−98% yields. The major limitation of this procedure is that it does not tolerate

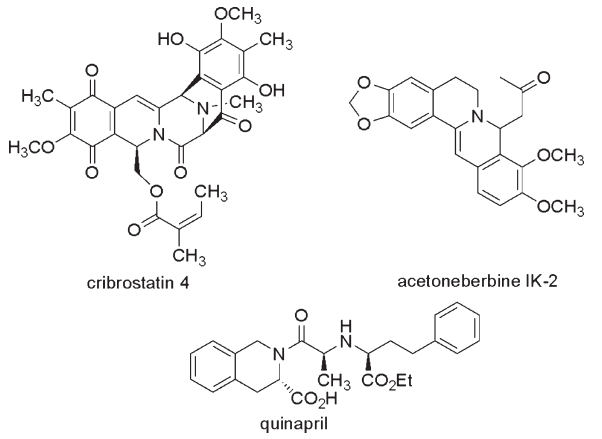


Figure 1. Examples of biologically active 1,2-dihydro- and tetrahydroisoquinolines.

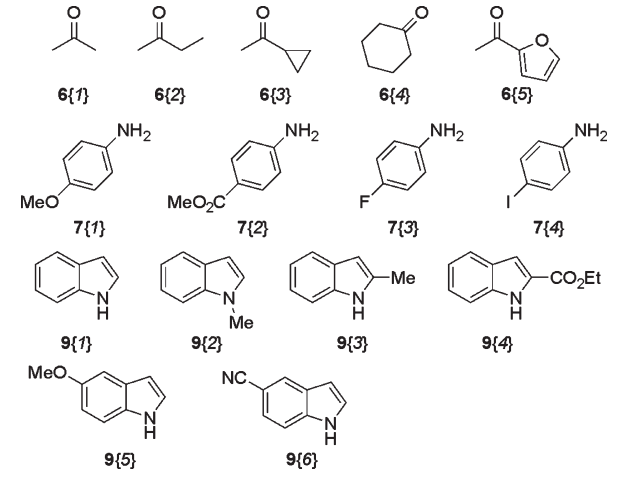
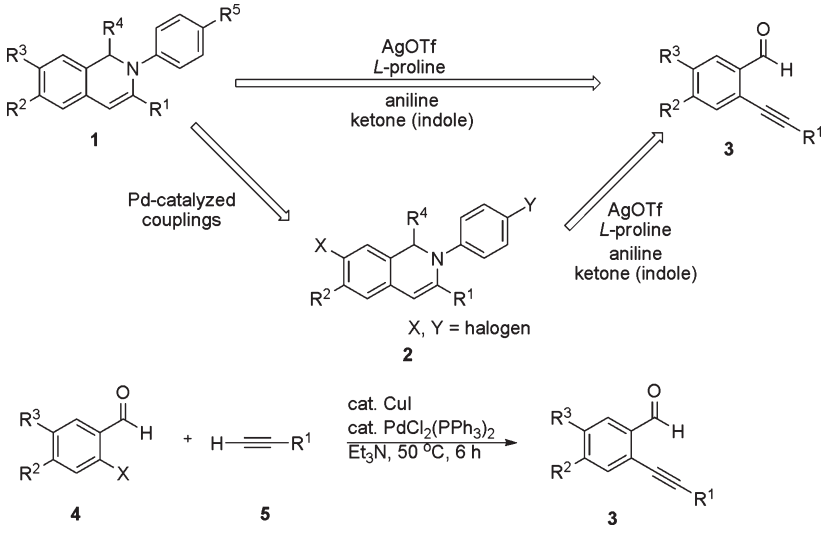


Figure 2. Ketone **6**{*1*−*5*}, aniline **7**{*1*−*4*}, and indole **9**{*1*−*6*} sublibraries.

Scheme 1. Library Outline and Preparation of 2-(1-Alkynyl)benzaldehydes 3



strong electron-withdrawing groups in the alkyne portion of the 2-(1-alkynyl)benzaldehydes **3**. For example, in the reactions of compound **3**{*7*}, bearing a nitro group, compounds **8**{*8*} and **8**{*9*} were not detected in the crude reaction mixtures, and compound **8**{*39*} was obtained in only an 11% yield. By employing indoles **9** instead of ketones **6** in this process, good yields from the unsubstituted indole **9**{*1*} have been obtained. This process exhibits good tolerance of various functional groups in positions 1 and 5 of the indole; thus, compounds **8**{*20*}, **8**{*50*}, and **8**{*51*} were obtained in 63, 46, and 75% yields, respectively. The presence of functional groups in position 2 of the indole significantly lowered the yields of the corresponding products; thus, compounds **8**{*4*} and **8**{*7*} were obtained in only 9 and 29% yields, respectively.

Finally, the 1,2-dihydroisoquinolines **8**{*31*−*51*} can be further elaborated using well-known palladium-mediated processes, such as Suzuki−Miyaura[13] and Sonogashira[11] couplings (Scheme 3).

Table 1. Data for Compounds 3{*1*−*15*}

3	R^1	R^2	R^3	X	yield (%)[a]
3{*1*}	4-(MeO)C_6H_4	H	H	Br	99
3{*2*}	3,5-$(MeO)_2C_6H_3$	H	H	Br	96
3{*3*}	3,5-$(MeO)_2C_6H_3$	H	MeO	Br	85
3{*4*}	3,5-$(MeO)_2C_6H_3$	H	Br	I	68[b]
3{*5*}	3-(MeO)C_6H_4	H	H	Br	78
3{*6*}	3-(MeO)C_6H_4	H	F	Br	100
3{*7*}	4-$(O_2N)C_6H_4$	H	H	Br	65[c]
3{*8*}	3-thiophenyl	H	H	Br	68
3{*9*}	3-thiophenyl	H	MeO	Br	87
3{*10*}	3-thiophenyl	H	F	Br	89
3{*11*}	3-thiophenyl			Br	90
3{*12*}	3-MeC_6H_4	H	H	Br	81
3{*13*}	phenyl	H	NO_2	Cl	89
3{*14*}	4-(MeO)C_6H_4	H	Br	I	56
3{*15*}	Phenyl	H	F	Br	84

[a] Isolated yields after column chromatography. All compounds **3** were characterized by ^{1}H NMR spectroscopy. Those not described in the literature were additionally characterized by ^{13}C NMR and HRMS. [b] Prepared from the corresponding methyl benzoate (1. LAH; 2. PCC). [c] This reaction used different reaction conditions: 3% $PdCl_2(PPh_3)_2$, 2% CuI, $^iPr_2NH$ (4 equiv.), DMF, 70 °C, 2 h.

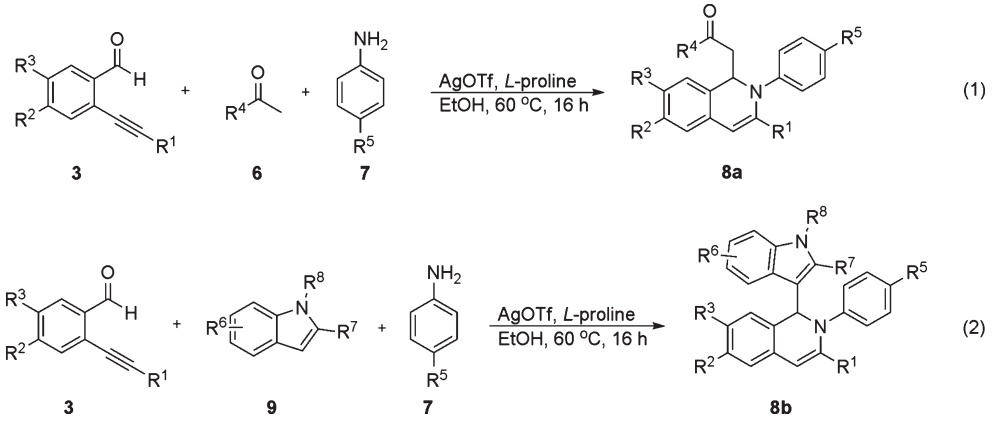
Sonogashira coupling of the 1,2-dihydroisoquinolines **8**{*31*−*51*} with various terminal alkynes **10** nicely provides the corresponding alkyne products **12a**{*1*−*22*} using Et_3N as the solvent under microwave irradiation for 40 min at 60 °C (Scheme 3). The Suzuki−Miyaura coupling of the 1,2-

Table 2. Library Data for Compounds 8{*1*−*30*}

product	3	6 or 9	7	yield (%)[a]	purity (%)[c]
8{*1*}	**3**{*1*}	**6**{*4*}	7{1}	33	96
8{*2*}	**3**{*1*}	**9**{*1*}	7{1}	69	98
8{*3*}	**3**{*2*}	**6**{*1*}	7{1}	43	99
8{*4*}	**3**{*2*}	**9**{4}	7{1}	9	88
8{*5*}	**3**{3}	**6**{*5*}	7{2}	15	100
8{*6*}	**3**{5}	**9**{*1*}	7{2}	76	95
8{*7*}	**3**{6}	**9**{3}	7{2}	29	100
8{8}	**3**{7}	**6**{3}	7{1}	0	
8{*9*}	**3**{7}	**9**{*5*}	7{2}	0	
8{*10*}	**3**{8}	**6**{*1*}	7{1}	56	96
8{*11*}	**3**{8}	**6**{*1*}	7{3}	56	99
8{*12*}	**3**{8}	**6**{2}	7{1}	56	93
8{*13*}	**3**{8}	**6**{4}	7{1}	72	42
8{*14*}	**3**{11}	**6**{*5*}	7{2}	15[b]	100
8{*15*}	**3**{11}	**9**{*1*}	7{1}	24	100
8{*16*}	**3**{12}	**6**{*1*}	7{1}	56	96
8{17}	**3**{12}	**6**{*1*}	7{3}	66	98
8{*18*}	**3**{12}	**6**{2}	7{1}	72	100
8{*19*}	**3**{12}	**6**{4}	7{1}	60	94
8{20}	**3**{12}	**9**{2}	7{1}	63	98
8{*21*}	**3**{12}	**9**{1}	7{1}	72	98
8{*22*}	**3**{13}	**6**{2}	7{1}	77	82
8{*23*}	**3**{14}	**6**{*1*}	7{1}	59	97
8{*24*}	**3**{14}	**6**{*1*}	7{3}	98	98
8{*25*}	**3**{14}	**6**{2}	7{1}	77	100
8{*26*}	**3**{14}	**6**{4}	7{1}	44	31
8{*27*}	**3**{15}	**6**{*1*}	7{1}	78	95
8{*28*}	**3**{15}	**6**{*1*}	7{3}	98	100
8{*29*}	**3**{15}	**6**{2}	7{1}	74	100
8{*30*}	**3**{15}	**6**{4}	7{1}	53	13

[a] Isolated yield after column chromatography. [b] Isolated yield after preparative HPLC. [c] UV purity determined at 214 nm after preparative HPLC.

Scheme 2. Synthesis of 1,2-Dihydroisoquinolines and 1-(3-Indolyl)-1,2-dihydroisoquinolines 8



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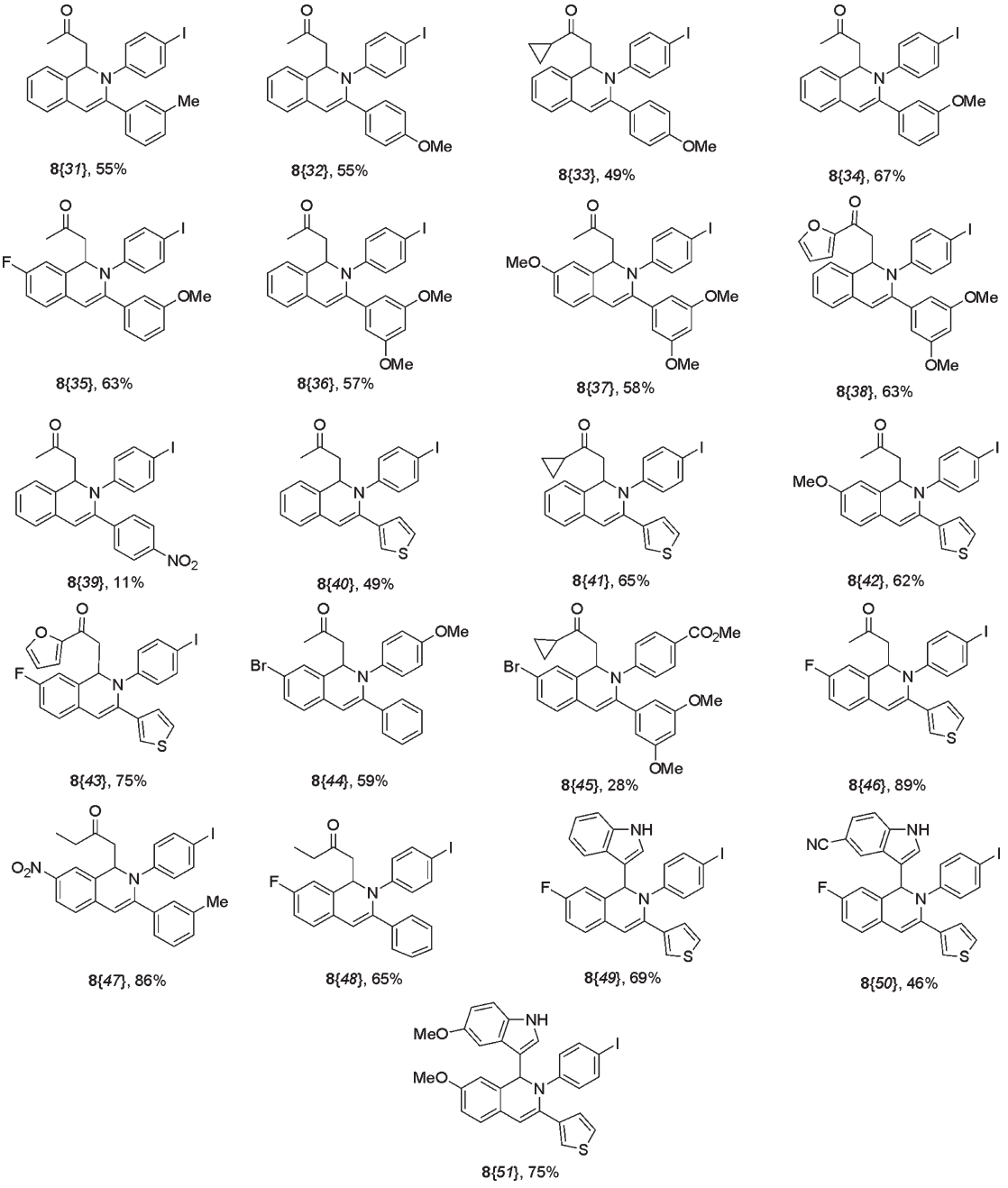

Figure 3. Halogen-containing 1,2-dihydroisoquinolines **8**{*31*−*51*}.

dihydroisoquinolines **8**{*31*−*51*} with various arylboronic acids **11** proceeded smoothly to give the desired products **12b**{*1*−*53*}. The reactions were carried out in a 1:1 ethanol/DMF mixture with the addition of 1 M aqueous Cs_2CO_3 solution at 120 °C under microwave irradiation for 20 min. The sublibraries of commercially available terminal alkynes **10** and boronic acids **11**, containing heterocycles and polar functionality to incorporate drug-like moieties into the resulting coupling products were chosen based on their commercial availability and the Lipinski compliance calculations mentioned above (Figure 4). Fluorine atom-containing 2-(1-alkynyl)benzaldehydes **3**{*6*}, **3**{*10*}, **3**{*15*}, aniline **7**{*3*}, and arylboronic acid **11**{*7*} have been chosen because the resulting fluorine-containing 1,2-dihydroisoquinolines and Suzuki−Miyaura coupling products are of considerable interest because of the many versatile applications of fluorine-containing compounds in industry and medicine.[14] The results for the Sonogashira and Suzuki−Miyaura couplings performed on the 1,2-dihydroisoquinolines **8**{*31*−*51*} are summarized in Table 3.

Under our reaction conditions, microwave irradiation has been shown not only to dramatically reduce the reaction times, but to provide higher yields of both the desired alkyne products **12a**-{*1*−*22*} and the Suzuki−Miyaura coupling products **12b**{*1*−*53*} when compared to conventional heating methods. These processes have been performed in parallel on approximately a ∼35−60 mg scale, starting from 1,2-dihydroisoquinolines **8**{*31*−*51*}. All of the crude products **12a** and **12b** were isolated by either column chromatography or preparative HPLC. The purity of the reaction mixtures has been analyzed by thin layer

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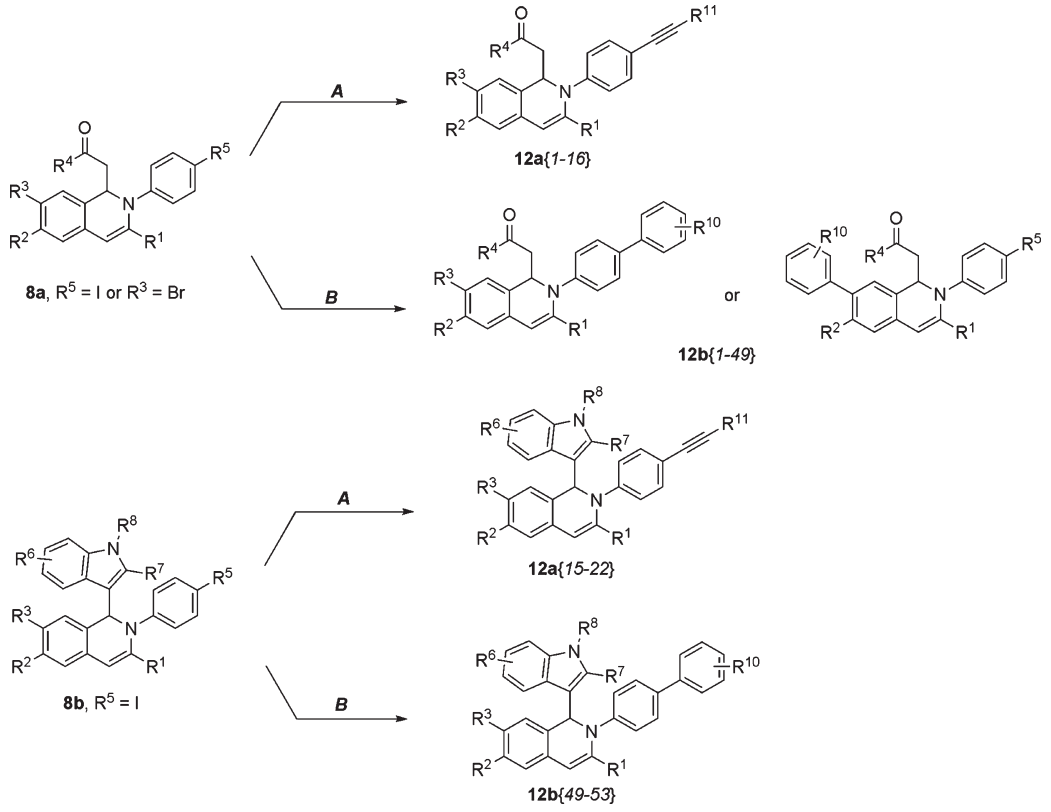
Scheme 3. Diversification of 1,2-Dihydroisoquinolines 8{*31−51*}[a]



[a] Method **A** (Sonogashira coupling): 3 mol % $PdCl_2(PPh_3)_2$, 3 mol % CuI, Et_3N, alkyne **10** (1.2 equiv.), 60 °C, 40 min under microwave irradiation. Method **B** (Suzuki−Miyaura coupling): 5 mol % $Pd(PPh_3)_4$, 1 M Cs_2CO_3 (2 equiv.), boronic acid **11** (1.2 equiv), 1:1 EtOH/DMF, 120 °C, 20 min under microwave irradiation.

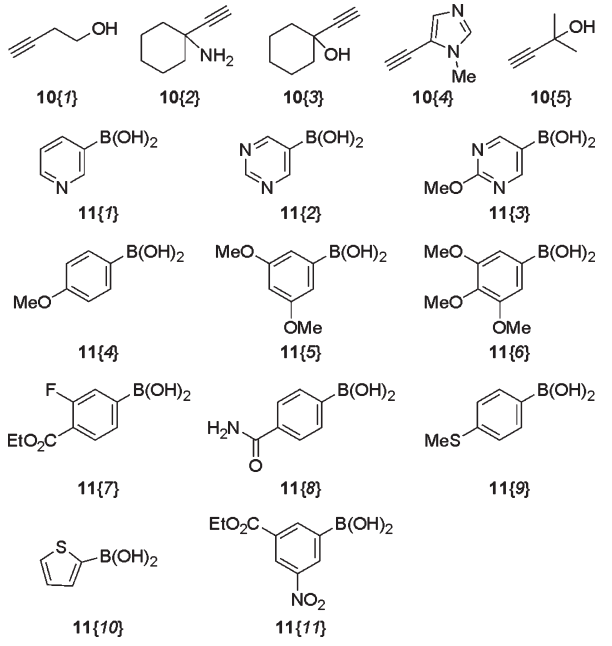


Figure 4. Terminal alkyne **10**{*1−5*} and boronic acid **11**{*1−11*} sublibraries.

chromatography (TLC), liquid chromatography-mass spectrometry (LC-MS), and high performance liquid chromatography (HPLC). We have used Lipinski's rule of five[10] as a general guide for bioavailability, because compounds with poor bioavailability face more of a challenge in becoming successful clinical candidates. According to Lipinski's rules, the favorable drug candidates should have a molecular weight less than 500, clogP less than 5, the number of hydrogen bond donors less than 5 and acceptors less than 10, and the number of rotatable bonds less than 10. These parameters were calculated for each of the library members using the SYBYL[15] program. The majority of the 105 1,2-dihydroisoquinolines **8**{*1−30*}, **12a**{*1−22*} and **12b**{*1−53*} synthesized satisfy these requirements.

In summary, a simple and efficient method for the parallel synthesis of multisubstituted 1,2-dihydroisoquinolines **8** and **12** has been developed employing a one-pot, three-component AgOTf and *L*-proline-cocatalyzed reaction of 2-(1-alkynyl)benzaldehydes, amines, and ketones or indoles. Palladium-catalyzed couplings, such as Suzuki−Miyaura and Sonogashira cross-couplings have been used to further diversify the 1,2-dihydroisoquinolines **8**, providing pure 5+ mg samples of each library compound. The average purity of the 105 members of this library is 94.1%, and the average yield is 55.7%. The elaborated, multisubstituted 1,2-dihydroisoquinolines **8**{*1−30*}, **12a**{*1−22*} and **12b**{*1−53*} 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.

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Table 3. Library Data for Compounds 12a{*1*−*22*}and 12b{*1*−*53*}

product	8	10 or 11	yield (%)[a]	purity (%)[c]	product	8	10 or 11	yield (%)[a]	purity (%)[c]
12a{*1*}	**8**{*33*}	**10**{*1*}	65	100	**12b**{*17*}	**8**{*38*}	**11**{*1*}	15[b]	100
12a{*2*}	**8**{*34*}	**10**{*1*}	99	100	**12b**{*18*}	**8**{*38*}	**11**{2}	38[b]	100
12a{*3*}	**8**{*35*}	**10**{*2*}	69		**12b**{19}	**8**{*38*}	**11**{*3*}	34[b]	100
12a{*4*}	**8**{*35*}	**10**{*3*}	96	100	**12b**{*20*}	**8**{*38*}	**11**{*8*}	66	100
12a{*5*}	**8**{*35*}	**10**{*1*}	84	100	**12b**{21}	**8**{*39*}	**11**{*3*}	45	98
12a{*6*}	**8**{*36*}	**10**{*1*}	89	100	**12b**{22}	**8**{*40*}	**11**{*2*}	86	96
12a{7}	**8**{*36*}	**10**{2}	54	100	**12b**{*23*}	**8**{*40*}	**11**{*3*}	68	100
12a{8}	**8**{*36*}	**10**{3}	75	99	**12b**{*24*}	**8**{*40*}	**11**{*4*}	76	97
12a{*9*}	**8**{*37*}	**10**{*3*}	31[b]	100	**12b**{25}	**8**{*40*}	**11**{*6*}	75	100
12a{*10*}	**8**{*37*}	**10**{*1*}	62	100	**12b**{*26*}	**8**{*40*}	**11**{10}	52	98
12a{*11*}	**8**{*37*}	**10**{2}	58	100	**12b**{27}	**8**{*40*}	**11**{*11*}	20	100
12a{*12*}	**8**{*40*}	**10**{*1*}	84	98	**12b**{28}	**8**{*41*}	**11**{*1*}	41	99
12a{*13*}	**8**{*42*}	**10**{*1*}	69	98	**12b**{29}	**8**{*41*}	**11**{2}	84	94
12a{*14*}	**8**{*43*}	**10**{*1*}	75	100	**12b**{*30*}	**8**{*42*}	**11**{1}	26[b]	100
12a{*15*}	**8**{*46*}	**10**{*3*}	94	100	**12b**{*31*}	**8**{*42*}	**11**{3}	64	98
12a{*16*}	**8**{*46*}	**10**{*4*}	77	100	**12b**{32}	**8**{*42*}	**11**{*10*}	48[b]	100
12a{*17*}	**8**{49}	**10**{5}	100	98	**12b**{33}	**8**{*43*}	**11**{3}	58	100
12a{*18*}	**8**{49}	**10**{*1*}	12[b]	100	**12b**{*34*}	**8**{*43*}	**11**{*8*}	42[b]	100
12a{*19*}	**8**{49}	**10**{*4*}	25	93	**12b**{*35*}	**8**{*43*}	**11**{11}	0	-
12a{*20*}	**8**{*50*}	**10**{1}	21[b]	100	**12b**{*36*}	**8**{*44*}	**11**{*2*}	36[b]	92
12a{*21*}	**8**{*50*}	**10**{5}	100	100	**12b**{37}	**8**{*44*}	**11**{*4*}	69	98
12a{22}	**8**{51}	**10**{*1*}	11[b]	100	**12b**{38}	**8**{*44*}	**11**{*5*}	71	98
12b{*1*}	**8**{*31*}	**11**{5}	70	95	**12b**{*39*}	**8**{*44*}	**11**{7}	13[b]	99
12b{2}	**8**{32}	**11**{10}	28[b]	98	**12b**{*40*}	**8**{*44*}	**11**{9}	16[b]	95
12b{3}	**8**{32}	**11**{7}	16[b]	93	**12b**{*41*}	**8**{*44*}	**11**{*10*}	27[b]	92
12b{*4*}	**8**{32}	**11**{*5*}	91	99	**12b**{*42*}	**8**{*45*}	**11**{*1*}	21[b]	100
12b{*5*}	**8**{33}	**11**{2}	100	100	**12b**{*43*}	**8**{*45*}	**11**{3}	43[b]	100
12b{*6*}	**8**{33}	**11**{*6*}	63	100	**12b**{*44*}	**8**{*45*}	**11**{*8*}	16[b]	>99
12b{7}	**8**{*34*}	**11**{2}	49[b]	97	**12b**{*45*}	**8**{*46*}	**11**{*1*}	63	100
12b{8}	**8**{35}	**11**{2}	89	100	**12b**{*46*}	**8**{*46*}	**11**{3}	75	100
12b{*9*}	**8**{35}	**11**{*6*}	91	100	**12b**{47}	**8**{*46*}	**11**{*8*}	58[b]	100
12b{10}	**8**{35}	**11**{7}	48	100	**12b**{*48*}	**8**{*47*}	**11**{*4*}	50	96
12b{11}	**8**{*36*}	**11**{2}	77	100	**12b**{*49*}	**8**{*48*}	**11**{*4*}	77	94
12b{*12*}	**8**{*36*}	**11**{*6*}	100	99	**12b**{*50*}	**8**{*49*}	**11**{4}	93	100
12b{*13*}	**8**{*36*}	**11**{*10*}	100	99	**12b**{*51*}	**8**{*50*}	**11**{*6*}	36[b]	100
12b{*14*}	**8**{*37*}	**11**{2}	42[b]	100	**12b**{*52*}	**8**{*50*}	**11**{7}	18[b]	100
12b{*15*}	**8**{*37*}	**11**{*4*}	55	100	**12b**{*53*}	**8**{*51*}	**11**{10}	40	85
12b{16}	**8**{37}	**11**{*10*}	22[b]	100					

[a] Isolated yield after column chromatography. [b] Isolated yield after preparative HPLC. [c] UV purity determined at 214 nm after preparative HPLC.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Synthetic methods, spectral assignments, and ^{1}H and ^{13}C NMR spectra for all previously unreported starting materials, intermediate compounds, and 21 representative library members. This material is available free of charge via the Internet at http://pubs.acs.org.

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