Published in final edited form as:

ACS Comb Sci. 2011 May 9; 13(3): 265–271. doi:10.1021/co1000794.

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

Nataliya A. Markina[†], Raffaella Mancuso[‡], Benjamin Neuenswander[‡], Gerald H. Lushington[‡], and Richard C. Larock^{†,*}

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

[‡]Dipartimento di Chimica, Università della Calabria, 87036 Arcavacata di Rende (CS), Italy

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

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.

Introduction

Structures containing a 1,2-dihydroisoquinoline fragment are valuable intermediates for the synthesis of biologically active compounds, *e.g.* alkaloids and pharmaceuticals.¹ For example, cribrastatin 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 hypertension⁴.

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 nucleophiles⁵ 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 whom correspondence should be addressed. Phone: (515) 294-4660. larock@iastate.edu .

Supporting Information Available Synthetic methods, spectral assignments, and ¹H and ¹³C 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>.

In order to synthesize a library with greater chances for biological activity, the multi-substituted 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** (Figures 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.

The 2-(1-Alkynyl)benzaldehydes **3** are easily prepared by palladium/copper-catalyzed Sonogashira coupling¹¹ of the corresponding *o*-bromobenzaldehydes **4** (1.0 equiv of **4**, 1.05 equiv of terminal alkyne **5**, 2 mol % of $\text{PdCl}_2(\text{PPh}_3)_2$, 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 commercial 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, eq. 2). Since initiation 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 ¹³C 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 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-Miyaura¹³ and Sonogashira¹¹ couplings (Scheme 3).

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 Et₃N as the solvent under microwave irradiation for 40 min at 60 °C (Scheme 3). The Suzuki-Miyaura coupling of the 1,2-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 1M aqueous Cs₂CO₃ 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 due to 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 TLC, LC-MS, and HPLC. We have used Lipinski's rule of five¹⁰ 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 SYBYL¹⁵ 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 multi-substituted 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, multi-substituted 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institute of General Medical Sciences (GM070620 and GM079593) and the National Institutes of Health Kansas University Chemical Methodologies and Library Development Center of Excellence (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; and Dr. Akhilesh Verma for the preparation and characterization of 2-(1-alkynyl)benzaldehydes **3**{12}-**3**{15}.

References and Notes

- (1) a). Phillipson JD, Roberts MF, Zenk MH. The Chemistry and Biology of Isoquinoline Alkaloids. 1985Springer-VerlagNew York b)Bentley K. The Isoquinoline Alkaloids. 1998Harwood AcademicAustralia c) Ramesh P, Shrinivasa RN, Vencateswarlu Y. A New 1,2-Dihydroisoquinoline from the Sponge Petrosia Similis. J. Nat. Prod. 1999; 62:780–781. [PubMed: 10346970] d) Chrzanowska M, Rozwadowska MD. Asymmetric Synthesis of Isoquinoline Alkaloids. Chem. Rev. 2004; 104:3341–3370. [PubMed: 15250744] e) Su S, Porco JA Jr. 1,2-Dihydroisoquinolines as Templates for Cascade Reactions to Access Isoquinoline Alkaloid Frameworks. Org. Lett. 2007; 9:4983–4986. [PubMed: 17958365] for tetrahydroisoquinolines, see: f) Scott JD, Williams RM. Chemistry and Biology of the Tetrahydroisoquinoline Antitumor Antibiotics. Chem. Rev. 2002; 102:1669–1730. [PubMed: 11996547]
- (2). Gonzales JF, de la Cuesta E, Avendano C. Synthesis and Cytotoxic Activity of Pyrazino[1,2- β]-isoquinolines, 1-(3-Isoquinolyl)isoquinolines, and 6,15-Iminoisoquino[3,2- β]-3-benzazocines. Bioorg. Med. Chem. 2007; 15:112–118. [PubMed: 17070059]
- (3). Inoue K, Kulsum U, Chowdhury SA, Fujisawa S-I, Ishihara M, Yokoe I, Sakagami H. Tumor-Specific Cytotoxicity and Apoptosis-Inducing Activity of Berberines. Anticancer Res. 2005; 25:4053–4059. [PubMed: 16309199]
- (4). Larochelle P, Haynes B, Maron N, Dugas S. A Postmarketing Surveillance Evaluation of Quinapril in 3742 Canadian Hypertensive Patients: the ACCEPT Study. Accupril Canadian Clinical Evaluation and Patient Teaching. Clin. Therapeutics. 1994; 16:838–853.
- (5) a). Alexandre A, Amiot F. Enantioselective Addition of Organolithium Reagents on Isoquinoline. Tetrahedron: Asymmetry. 2002; 13:2117–2122.b) Diaz JL, Miguel M, Lavilla R. *N*-Acylazinium Salts: A New Source of Iminium Ions for Ugi-Type Processes. J. Org. Chem. 2004; 69:3550–3553. [PubMed: 15132569] c) Schmidt A, Gütlein J, Preuss A, Albrecht J, Reinke H, Langer P. Synthesis of 7,8-Benzo-3-hydroxy-9-azabicyclo[3.3.1]non-3-enes by Cyclocondensation of 1,3-Bis-silyl Enol Ethers with Isoquinolines. Synlett. 2005; 16:2489–2491.d) Shaabani A, Soleimani E, Khavasi HR. An Unexpected, Novel, Three-Component Reaction between Isoquinoline, an Isocyanide and Strong CH-Acids in Water. Tetrahedron Lett. 2007; 48:4743–4747.e) Alizadeh

- A, Zohreh N. A One-Pot Synthesis of 1,2-Dihydroisoquinoline Derivatives from Isoquinoline via a Four-Component Reaction. *Helv. Acta Chem.* 2008; 91:844–849.
- (6) a). Huang Q, Larock RC. Synthesis of 4-(1-Alkenyl)isoquinolines by Palladium(II)-Catalyzed Cyclization/Olefination. *J. Org. Chem.* 2003; 68:980–988. [PubMed: 12558424] b) Asao N, Yudha SS, Nogami T, Yamamoto Y. Direct Mannich and Nitro-Mannich Reactions with Non-activated Imines: AgOTf-Catalyzed Addition of Pronucleophiles to Ortho-Alkynylaryl Aldimines Leading to 1,2-Dihydroisoquinolines. *Angew. Chem., Int. Ed.* 2005; 44:5526–5528.c) Yanada R, Obika S, Kono H, Takemoto Y. In(OTf)₃-Catalyzed Tandem Nucleophilic Addition and Cyclization of Ortho-Alkynylarylaldimines to 1,2-Dihydroisoquinolines. *Angew. Chem., Int. Ed.* 2006; 45:3822–3825.d) Obika S, Kono H, Yasui Y, Yanada R, Takemoto Y. Concise Synthesis of 1,2-Dihydroisoquinolines and 1*H*-Isochromenes by Carbophilic Lewis Acid-Catalyzed Tandem Nucleophilic Addition and Cyclization of 2-(1-Alkynyl)arylaldimines and 2-(1-Alkynyl)arylaldehydes. *J. Org. Chem.* 2007; 72:4462–4468. [PubMed: 17503849] e) Guo Z, Cai M, Jiang J, Yang L, Hu W. Rh₂(OAc)₄-AgOTf Cooperative Catalysis in Cyclization/Three-Component Reactions for Concise Synthesis of 1,2-Dihydroisoquinolines. *Org. Lett.* 2010; 12:652–655. [PubMed: 20104897]
- (7) a). Ding Q, Wu J. Lewis Acid- and Organocatalyst-Cocatalyzed Multicomponent Reactions of 2-Alkynylbenzaldehydes, Amines, and Ketones. *Org. Lett.* 2007; 9:4959–4962. [PubMed: 17960938] b) Ding Q, Yu X, Wu J. AgOTf-Catalyzed One-Pot Reaction of 2-Alkynylbenzaldehyde, Amine, and Sodium Borohydride. *Tetrahedron Lett.* 2008; 49:2752–2755.c) Wu Y, Zhang Y, Jiang Y, Ma D. Synthesis of Polysubstituted 1,2-Dihydroisoquinolines via a CuI-Catalyzed Arylation/Condensation Cascade Process. *Tetrahedron Lett.* 2009; 50:3683–3685.
- (8) a). An HY, Cook PD. Methodologies for Generating Solution-Phase Combinatorial Libraries. *Chem. Rev.* 2000; 100:3311–3340. [PubMed: 11777426] b) Sun CM. Recent Advances in Liquid-Phase Combinatorial Chemistry. *Comb. Chem. High Throughput Screening.* 1999; 2:299–318.c) Merritt AT. Solution Phase Combinatorial Chemistry. *Comb. Chem. High Throughput Screening.* 1998; 1:57–72.d) Goodnow RA Jr. Guba W, Haap W. Library Design Practices for Success in Lead Generation with Small Molecule Libraries. *Comb. Chem. High Throughput Screening.* 2003; 6:649–660.e) Schuffenhauer A, Popov M, Schopfer U, Acklin P, Stanek J, Jacoby EC. Molecular Diversity Management Strategies for Building and Enhancement of Diverse and Focused Lead Discovery Compound Screening Collections. *Comb. Chem. High Throughput Screening.* 2004; 7:771–781.
- (9) a). Waldo JP, Mehta S, Neuenswander 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] b) Cho C-H, Neuenswander B, Lushington GH, Larock RC. Parallel Synthesis of a Multi-Substituted Benzo[*β*]furan Library. *J. Comb. Chem.* 2008; 10:941–947. [PubMed: 18937516] c) Roy S, Roy S, Neuenswander B, Hill D, Larock RC. Palladium- and Copper-Catalyzed Solution Phase Synthesis of a Diverse Library of Isoquinolines. *J. Comb. Chem.* 2009; 11:1061–1065. [PubMed: 19728736]
- (10) a). Lipinski CA, Lombardo F, Dominay 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, Dominay BW, Feeney PJ. Experimental and Computational Approaches to Estimate Solubility and Permeability in Drug Discovery and Development Settings. *Adv. Drug Delivery Rev.* 2001; 46:3–26.
- (11) a). Sonogashira K, Tohda Y, Hagihara N. Convenient Synthesis of Acetylenes. Catalytic Substitutions of Acetylenic Hydrogen with Bromoalkenes, Iodoarenes and Bromopyridines. *Tetrahedron Lett.* 1975; 16:4467–4470.b) Roesch K, Larock RC. Synthesis of Isoquinolines and Pyridines by the Palladium/Copper-Catalyzed Coupling and Cyclization of Terminal Acetylenes and Unsaturated Imines: the Total Synthesis of Decumbenine B. *J. Org. Chem.* 2002; 67:86–94. [PubMed: 11777443]
- (12) a). Asao N, Salprima YS, Nogami T, Yamamoto Y. Silver-Catalyzed Synthesis of 1,2-Dihydroisoquinolines through Direct Addition of Carbon Pronucleophiles to Ortho-Alkynylaryl Aldimines. *Heterocycles.* 2008; 76:471–483.b) Yu X, Wu J. Synthesis of 1-(1*H*-Indol-3-yl)-1,2-dihydroisoquinolines via AgOTf-Catalyzed Three-Component Reactions of 2-

Alkynylbenzaldehydes, Amines, and Indoles. *J. Comb. Chem.* 2010; 12:238–244. [PubMed: 20058905]

- (13) a). Miyaura N, Suzuki A. Palladium-Catalyzed Cross-Coupling Reactions of Organoboron Compounds. *Chem. Rev.* 1995; 95:2457–2483. b) Suzuki A. Recent Advances in the Cross-Coupling Reactions of Organoboron Derivatives with Organic Electrophiles, 1995-1998. *J. Organomet. Chem.* 1999; 576:147–168.
- (14) a). Hudlicky, M.; Pavlath, AE. *Chemistry of Organic Fluorine Compounds II. A Critical Review.* American Chemical Society; Washington, DC: 1995. p. 1888-1912. ACS Monograph 187b) Hiyama, T., editor. *Organofluorine Compounds. Chemistry and Applications.* Springer-Verlag; New York: 2000.
- (15). SYBYL. version 8.0. The Tripos Associate; St. Louis, MO: 2007.

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

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

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

Scheme 1. Library outline and preparation of 2-(1-alkynyl)benzaldehydes **3**

Scheme 2.

Synthesis of 1,2-dihydroisoquinolines and 1-(3-indolyl)-1,2-dihydroisoquinolines **8**

Scheme 3.

Diversification of 1,2-dihydroisoquinolines **8**{31-51}

^aMethod **A** (Sonogashira coupling): 3 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, 3 mol % CuI , Et_3N , alkyne **10** (1.2 equiv.), 60 °C, 40 min under microwave irradiation. Method **B** (Suzuki-Miyaura coupling): 5 mol % $\text{Pd}(\text{PPh}_3)_4$, 1M Cs_2CO_3 (2 equiv.), boronic acid **11** (1.2 equiv), 1:1 EtOH/DMF, 120 °C, 20 min under microwave irradiation.

Table 1

Data for Compounds **3** {1-15}

3	R¹	R²	R³	X	yield (%)^a
3 {1}	4-(MeO)C ₆ H ₄	H	H	Br	99
3 {2}	3,5-(MeO) ₂ C ₆ H ₃	H	H	Br	96
3 {3}	3,5-(MeO) ₂ C ₆ H ₃	H	MeO	Br	85
3 {4}	3,5-(MeO) ₂ C ₆ H ₃	H	Br	I	68 ^b
3 {5}	3-(MeO)C ₆ H ₄	H	H	Br	78
3 {6}	3-(MeO)C ₆ H ₄	H	F	Br	100
3 {7}	4-(O ₂ N)C ₆ H 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 ₆ H ₄	H	H	Br	81
3 {13}	phenyl	H	NO ₂	Cl	89
3 {14}	4-(MeO)C ₆ H ₄	H	Br	I	56
3 {15}	Phenyl	H	F	Br	84

^a Isolated yields after column chromatography. All compounds **3** were characterized by ¹H NMR spectroscopy. Those not described in the literature were additionally characterized by ¹³C NMR and HRMS;

^b prepared from the corresponding methyl benzoate (1. LAH; 2. PCC);

c, this reaction used different reaction conditions: 3% PdCl₂(PPh₃)₂, 2% CuI, *i*-Pr₂NH (4 equiv.), DMF, 70 °C, 2 h.

Table 2

Library Data for Compounds **8**{1-30}

product	3	6 or 9	7	yield (%) ^d	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

product	3	6 or 9	7	yield (%) ^a	purity (%) ^c
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.

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

product	8	10 or 11	yield (%) ^a	purity (%) ^c	product	8	10 or 11	yield (%) ^a	Purity (%) ^c
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.