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# Application of Sequential Cu(I)/Pd(0)-Catalysis to Solution-Phase Parallel Synthesis of Combinatorial Libraries of Dihydroindeno[1,2-*c*]isoquinolines

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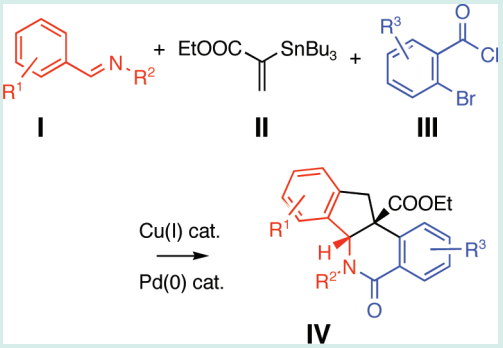
Supporting Information

**ABSTRACT:** Parallel solution-phase synthesis of combinatorial libraries of dihydroindenoisoquinolines employing a sequential Cu(I)/Pd(0)-catalyzed multicomponent coupling and annulation protocol was realized. The scope and limitations of the protocol with respect to the substitution pattern in the aryl ring of the indene core, as well as the *N*-substituent have been defined, revealing that the methodology is compatible with a wide-range of aliphatic linear, branched, and ester functionalized *N*-substituents. Unexpectedly, the formation of regioisomers featuring a 1,2,3-contiguous substitution pattern in the aromatic ring of the indene core was observed. Three distinct combinatorial libraries with a total of 111 of members were synthesized, and 80 highly substituted dihydroindenoisoquinolines structurally related to known medicinal agents including some consisting of mixtures of two regioisomers were made available for biological activity testing.




**KEYWORDS:** solution-phase parallel synthesis, combinatorial libraries of heterocycles, dihydroindenoisquinolines, multicomponent reactions, transition metal-catalyzed reactions

## INTRODUCTION

Solution-phase parallel synthesis serves as a powerful tool for the preparation of large libraries of compounds needed for drug discovery.[1] To deliver libraries featuring structurally complex and chemically diverse chemotypes, new technically challenging synthetic protocols must be adapted to the parallel synthesis format.[2] Multicomponent reactions, and particularly those catalyzed by transition metals,[3] are well suited for a rapid construction of diverse libraries. However, the application of transition metal-catalyzed reactions often utilizing sensitive organometallic reagents or reactive intermediates to parallel synthesis still presents a synthetic and technical challenge.[2]

Recently, we have reported a new methodology for the synthesis of indenoisoquinolines **IV** relying on a combination of Cu(I)-catalyzed three-component coupling followed by an intramolecular Pd(0)-catalyzed annulation, and demonstrated its utility by the preparation of a series of indenoisoquinolines in a classical synthetic format (Figure 1).[4] Mechanistically, the process involves an in situ formation of an acyliminium chloride from imines **I** and acyl chlorides **III**. The acylimminium intermediate is then attacked by an organocuprate generated from the vinyl stannane **II** and the Cu(I) catalyst yielding the amide product (Figure 1).[5] In the second step, Pd(0) catalyst initiates an intramolecular Heck reaction followed by an electrophilic palladation of the aromatic ring, and the entire sequence is terminated by a reductive elimination that closes the five-membered ring[4] (Figure 1).

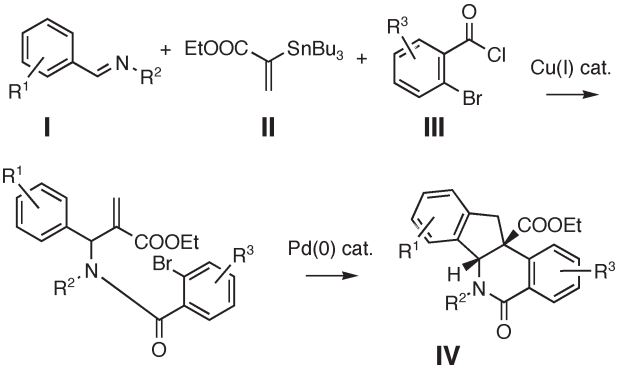



**Figure 1.** Synthetic strategy for the preparation of indenoisoquinolines.

Indenoisoquinolines **V** came into prominence in medicinal chemistry as prototypes of novel anticancer chemotherapeutic agents inspired by the structures of naturally occurring topoisomerase I inhibitors benzophenanthridine alkaloids, for example, fagaronine, and a natural product camptothecin believed to function as DNA intercalators (Figure 2).[6] Dihydroindenoisoquinolines **VI** have been shown to exhibit potent cytotoxicity

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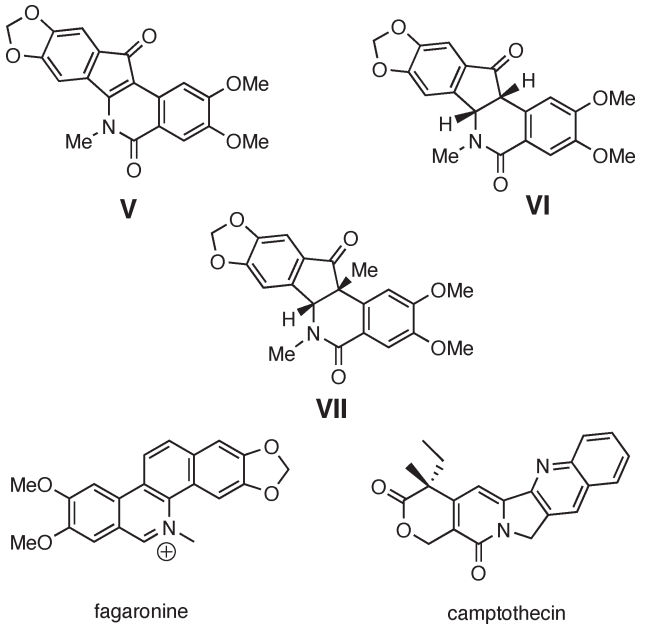


**Figure 2.** Naturally occurring and synthetic cytotoxic topoisomerase I inhibitors.

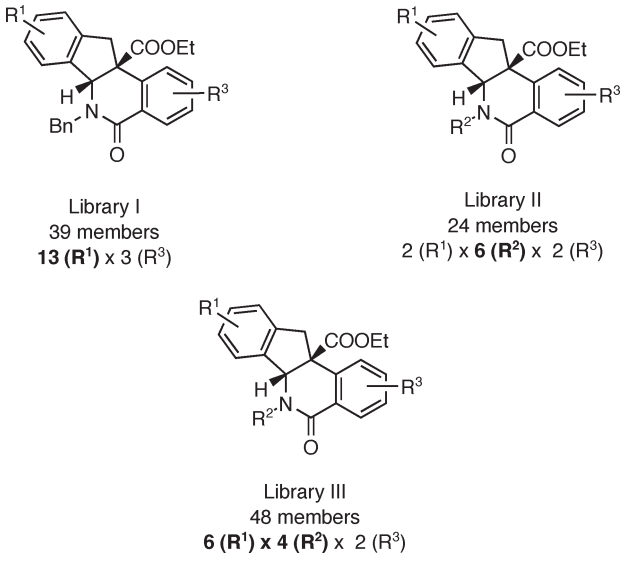


**Figure 3.** Libraries of indenoisoquinolines synthesized by our methodology.

serving as prodrugs of indenoisoquinolines in cancer cells.[7] In the context of those studies, the angularly substituted dihydroindenoisoquinoline **VII** was synthesized and found to be less cytotoxic but retained a moderate topoisomerise 1 inhibitory activity, apparently acting via a mechanism distinct from the DNA intercalation precluded by its nonplanar structure.[7a] This finding is a source of motivation for a broader survey of biological activities of angularly substituted indenoisoquinolines. Thus, the development of a viable solution-phase parallel synthetic methodology for the preparation of combinatorial libraries of novel indenoisoquinolines is essential to providing an efficient access to these valuable heterocyclic structures.

Herein, we describe the application of our sequential Cu(I)/Pd(0)-catalyzed multicomponent coupling/annulation protocol

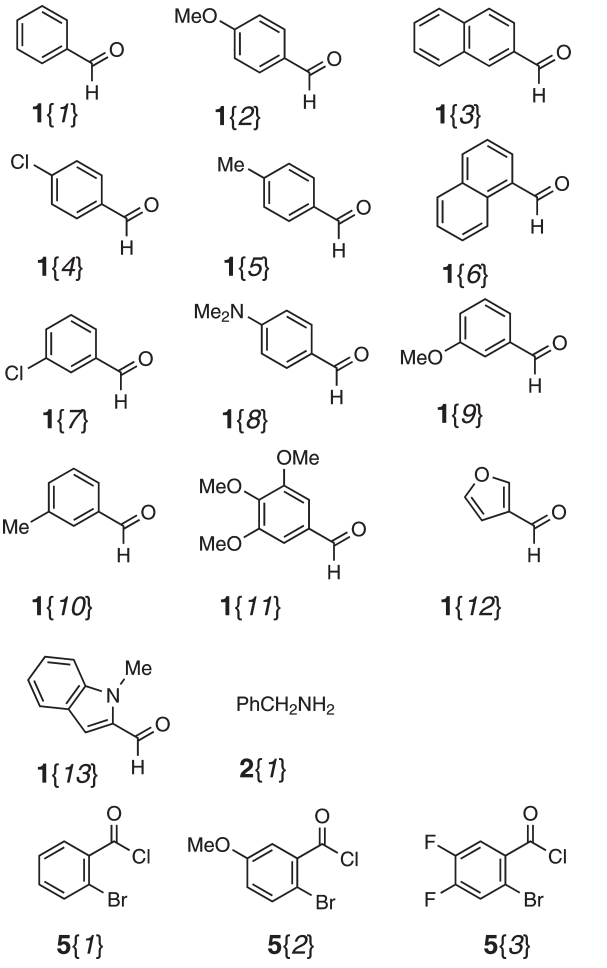


**Figure 4.** Building blocks for the validation library and Library I.

to solution-phase parallel synthesis of medium-size combinatorial libraries of indenoisoquinolines **IV** (Figure 3). The method was successfully adapted for the parallel synthesis format, and the scope and limitations in the substitution patterns on the indenoisoquinoline cores have been surveyed. The ability to achieve a broad variation in the *N*-substituent in the imine building block was demonstrated for the first time. Our methodology delivers a highly modular approach to substituted indenoisoquinolines and serves as a useful alternative to the traditionally employed routes.[8] Compounds prepared by this study have been made available for a broad array of biological screens.[9]

## RESULTS AND DISCUSSION

To asses the challenges of adapting our methodology to the solution-phase parallel library synthesis, we embarked on the preparation of a limited validation library of six indenoisoquinolines **6**{*1*–*3*, *1*, *1*–*2*}. The validation library featured two elements of diversity, including three aromatic aldehydes **1**{*1*–*3*} ($R^1$) and two aroyl chlorides **5**{*1*–*2*} ($R^3$) (Figure 4). In all cases *N*-benzylamine **2**{*1*} was used to prepare the corresponding imines **3**{*1*–*3*, *1*} (Scheme 1).

In the initial attempt at the validation library synthesis, the reactions were performed in SPE tubes at room temperature under argon atmosphere. No reaction was observed, presumably because of lower reactivity of the vinyl tin reagent at room


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temperature. Indeed reactions performed well at elevated temperatures (45 °C, 6 h) in glass tubes. Furthermore, higher quality of CuCl (>99% purity), improved drying of the imines building blocks produced in bulk quantities, and the addition of molecular sieves were employed. Thus, the protocol for the validation library synthesis was modified. The preparation was performed in the Miniblock XT synthesizer (24 membered) fitted with glass vials and reflux condensers, and the reactions were run at 45 °C for 6 h with magnetic stirring. Both the reagent addition and the reaction were carried out under closed dry argon atmosphere(for details see the Supporting Information).

Gratifyingly, this protocol afforded all six intended validation library members (Table 1) in good yields over the two synthetic steps and very respectable crude purities (38−78%). The final products reached the purity standard higher than 90% measured by HPLC (UV 214 nm) required for the samples to be acceptable for biological testing.[10] Identities of the products **6** were confirmed by $^1$H NMR analyses, and data for compounds **6**{*1,1,1*−*2*} were compared to data obtained for samples produced in the classical format.[4] The relative stereochemistry in products **6** reported in this study was assigned in accordance with the analytical data secured in our prior work.[4] As anticipated, both the C-1 and C-3 carbon in the 2-naphthyl substituted imine underwent the terminal carbon−carbon bond forming event, providing 1:1 mixtures of isomeric indenoisoquinolines **6**{*3,1,1*−*2*} as indicated by $^1$H NMR analyses, showing two sets of signals for the benzylic protons in the *N*-Bn group (signals at 5.61 ppm, and at 4.81 ppm in the spectra for **6**{*3,1,1*}) and for the methine CHN protons, signals at 5.54 ppm and at 5.46 ppm in the spectra for **6**{*3,1,1*}). However, HPLC analyses did not achieve separation of the peaks for the regioisomers, only giving rise to unsymmetrical peaks in the HPLC chromatograms.

Satisfied with the results of the validation library synthesis, we proceeded to explore the scope of the parallel synthesis protocol with respect to the range of structural diversity that could be tolerated in the aldehyde component. A series of imines **3**{*1*−*13,1*} all derived from *N*-benzyl amine component **2**{*1*} were prepared (Figure 4). Electronically distinct substituents (-Cl, -OMe, -Me, and −$NMe_2$) were placed at the *para* position (C-4) of the aldehydes, and components with a varied placement (*meta* and *para*) of electronically distinct substituents (-Cl, -OMe, -Me) were included. The substituents and substitution patterns in the aromatic rings were chosen based on the operational scheme for aromatic substitution suggested by Topliss in a study on the methods for designing the most potent medicinal agents in the series of compounds bearing aromatic rings.[11] Since electrophilic aromatic palladation reactions performed intermolecularly were shown to strongly favor the formation of the less sterically hindered regioisomers, failing to yield a contiguous 1,2,3-trisubstitution pattern,[12] we were reasoning that steric effects would disfavor the terminal palladation at the C-2 position of the *meta*-substituted aldehydes **1**{*7,9,10*}, and the formation

**Scheme 1. Synthetic Scheme for the Validation Library and Library I Synthesis**

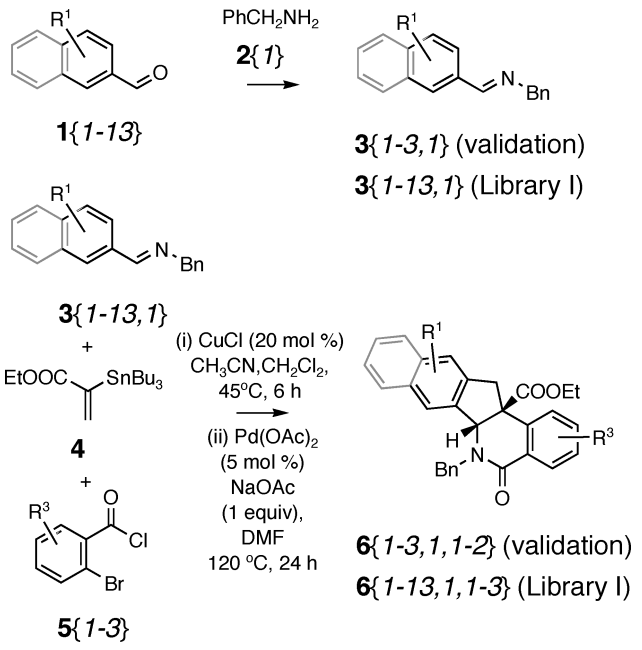
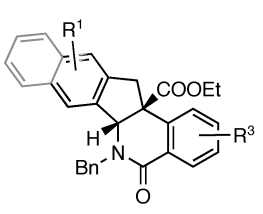
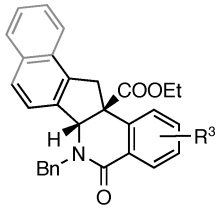



**Table 1. Results of the Validation Library Synthesis**



**6**{*1-3,1,1-2*}

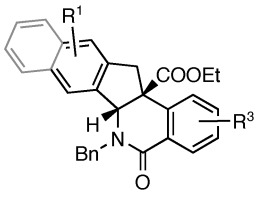


**6**{*3,1,1-2*}

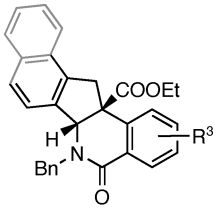
| entry | compd | $R^1$ | $R^3$ | yield[a] (%) | purity crude[b] (%) | purity final[b] (%) | HRMS[c] |
|---|---|---|---|---|---|---|---|
| 1 | **6**{*1,1,1*} | H | 5-H | 42 | 67 | 97 | 398.1755 (398.1756) |
| 2 | **6**{*1,1,2*} | H | 5-OMe | 48 | 68 | 100 | 428.1859 (428.1861) |
| 3 | **6**{*2,1,1*} | 4-MeO | 5-H | 50 | 64 | 100 | 428.1862 (428.1861) |
| 4 | **6**{*2,1,2*} | 4-MeO | 5-OMe | 42 | 38 | 100 | 458.1963 (458.1967) |
| 5 | **6**{*3,1,1*} | 2-naphthyl | 5-H | 71 | 78(1:1)[d] | 92(1:1)[d] | 448.1906 (448.1912) |
| 6 | **6**{*3,1,2*} | 2-naphthyl | 5-OMe | 57 | 70 (1:1)[d] | 92(1:1)[d] | 478.2009 (478.2018) |

[a] Isolated yield calculated for the entire two-step sequence. [b] UV purity determined at 214 nm. [c] The HRMS data for the M + 1 molecular ion of the compound **6** detected in the corresponding product. The calculated HRMS datafor the M + 1 molecular ion are given in parentheses. [d] Ratio of the regioisomers established by $^1$H NMR.

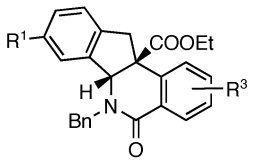
**Table 2. Results of Library I Synthesis**



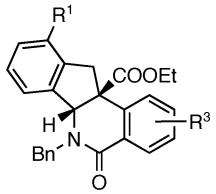

**6**{*1-13,1,1-3*}




**6**{*3,1,1-3*}




**6**{*7,1,1-3*}
**6**{*9-10,1,1-3*}




**6**{*7,1,1-3*}
**6**{*9-10,1,1-3*}

| entr | compd | $R^1$ | $R^3$ | yield[a] (%) run 1[f] | purity[b] (%) run 1[f] | yield[a] (%) run 2 | purity[b] (%) run 2 | amt (mg)[c] | pass/fail[d] | HRMS[e] |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **6**{*1,1,1*} | H | 5-H | 31 (42) | 97 (97) | 28 | 99 | 68 | + | 398.1752 (398.1756) |
| 2 | **6**{*1,1,2*} | H | 5-OMe | 2 (48) | 94 (100) | 31 | 98 | 59 | + | 428.1859 (428.1861) |
| 3 | **6**{*1,1,3*} | H | 4,5-$F_2$ | 16 | 92 | 14 | 86 | 12 | + | 434.1556 (434.1567) |
| 4 | **6**{*2,1,1*} | 4-MeO | 5-H | 42 (50) | 99 (100) | 25 | 95 | 85 | + | 428.1875 (428.1861) |
| 5 | **6**{*2,1,2*} | 4-MeO | 5-OMe | 4 (42) | 97 (100) | 30 | 99 | 60 | + | 458.1963 (458.1967) |
| 6 | **6**{*2,1,3*} | 4-MeO | 4,5-$F_2$ | 30 | 93 | 33 | 93 | 50 | + | 464.1671 (464.1673) |
| 7 | **6**{*3,1,1*} | 2-naphthyl | 5-H | × (71) | × (92) | 42 | 97 (1: 1)[g] | 86 | + | 448.1906 (448.1912) |
| 8 | **6**{*3,1,2*} | 2-naphthyl | 5-OMe | 6 (57) | 85 (92) | 57 | 97 (1: 1)[g] | 97 | + | 478.2009 (478.2018) |
| 9 | **6**{*3,1,3*} | 2-naphthyl | 4,5-$F_2$ | 32 | 85 | 33 | 73 (1: 1)[g] | 0 | − | 484.1700 (484.1724) |
| 10 | **6**{*4,1,1*} | 4-Cl | 5-H | 28 | 94 | 29 | 86 | 20 | + | 432.1356 (432.1366) |
| 11 | **6**{*4,1,2*} | 4-Cl | 5-OMe | 5 | 70 | 24 | 94 | 22 | + | 462.1464 (462.1472) |
| 12 | **6**{*4,1,3*} | 4-Cl | 4,5-$F_2$ | 7 | 88 | × | × | 0 | − | 468.1163 (468.1178) |
| 13 | **6**{*5,1,1*} | 4-Me | 5-H | 35 | 98 | 36 | 97 | 50 | + | 412.1895 (412.1912) |
| 14 | **6**{*5,1,2*} | 4-Me | 5-OMe | 4 | 94 | 38 | 96 | 32 | + | 442.2014 (442.2018) |
| 15 | **6**{*5,1,3*} | 4-Me | 4,5-$F_2$ | 35 | 98 | 22 | 93 | 43 | + | 448.1711 (448.1724) |
| 16 | **6**{*6,1,1*} | 1-naphthyl | 5-H | 13 | 95 | 7 | 95 | 15 | EX[h] | 448.1903 (448.1912) |
| 17 | **6**{*6,1,2*} | 1-naphthyl | 5-OMe | × | × | 15 | 88 | 0 | EX[h] | 478.2010 (478.2018) |
| 18 | **6**{*6,1,3*} | 1-naphthyl | 4,5-$F_2$ | 9 | 64 | × | × | 0 | EX[h] | 484.1716 (484.1724) |
| 19 | **6**{*7,1,1*} | 3-Cl | 5-H | 20 | 37[g] | 12 | 29[g] | 0 | − | 432.1359 (432.1366) |
| | | | | | 46 | | 59 | | | |
| 20 | **6**{*7,1,2*} | 3-Cl | 5-OMe | 19 | 61[g] | 15 | 46[g] | 15 | + | 462.1468 (462.1472) |
| | | | | | 30 | | 34 | | | |
| 21 | **6**{*7,1,3*} | 3-Cl | 4,5-$F_2$ | × | × | 10 | 13 | 0 | − | 468.1167 (468.1178) |
| 22 | **6**{*8,1,1*} | 4−$Me_2N$ | 5−H | 31 | 80 | 32 | 86 | 0 | − | 441.2177 (441.2178) |
| 23 | **6**{*8,1,2*} | 4−$Me_2N$ | 5−OMe | 14 | 80 | 26 | 84 | 0 | − | 471.2280 (471.2283) |
| 24 | **6**{*8,1,3*} | 4-$Me_2N$ | 4,5-$F_2$ | 14 | 76 | 17 | 85 | 0 | − | 477.1980 (477.1989) |
| 25 | **6**{*9,1,1*} | 3-OMe | 5-H | 29 | 72[g] | 34 | 63[g] | 50 | + | 428.1859 (428.1861) |
| | | | | | 27 | | 29 | | | |
| 26 | **6**{*9,1,2*} | 3-OMe | 5-OMe | 36 | 66 | 30 | 62[g] | 52 | + | 458.1963 (458.1967) |
| | | | | | 33[g] | | 31 | | | |
| 27 | **6**{*9,1,3*} | 3-OMe | 4,5-$F_2$ | 24 | 65[g] | 21 | 21[g] | 35 | + | 464.1665 (464.1673) |
| | | | | | 28 | | 66 | | | |
| 28 | **6**{*10,1,1*} | 3-Me | 5-H | 43 | 66[g] | 33 | 63[g] | 53 | + | 412.1916 (412.1912) |
| | | | | | 31 | | 32 | | | |
| 29 | **6**{*10,1,2*} | 3-Me | 5-OMe | 41 | 62[g] | 36 | 67[g] | 57 | + | 442.2019 (442.2018) |
| | | | | | 35 | | 27[g] | | | |
| 30 | **6**{*10,1,3*} | 3-Me | 4,5-$F_2$ | 28 | 63[g] | 31 | 74 | 45 | + | 448.1712 (448.1724) |
| | | | | | 34 | | | | | |
| 31 | **6**{*11,1,1*} | 3,4,5-$(OMe)_3$ | 5-H | 37 | 91 | 39 | 93 | 62 | + | 488.2066 (488.2073) |
| 32 | **6**{*11,1,2*} | 3,4,5-$(OMe)_3$ | 5-OMe | 41 | 93 | 34 | 92 | 66 | + | 518.2188 (518.2178) |
| 33 | **6**{*11,1,3*} | 3,4,5-$(OMe)_3$ | 4,5-$F_2$ | 45 | 97 | 9 | 82 | 40 | + | 524.1886 (524.1884) |
| 34 | **6**{*12,1,1*} | 3-furyl | 5-H | 24 | 74 | 19 | 69 | 0 | EX[h] | 388.1539 (388.1548) |
| 35 | **6**{*12,1,2*} | 3-furyl | 5-OMe | 15 | 75 | 17 | 75 | 0 | EX[h] | 418.1649 (418.1654) |
| 36 | **6**{*12,1,3*} | 3-furyl | 4,5-$F_2$ | 27 | 75 | 16 | 87 | 0 | EX[h] | 424.1354 (424.1360) |


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**Table 2. Continued**

| entr | compd | $R^1$ | $R^3$ | yield[a] (%) run 1[f] | purity[b] (%) run 1[f] | yield[a] (%) run 2 | purity[b] (%) run 2 | amt (mg)[c] | pass/fail[d] | HRMS[e] |
|---|---|---|---|---|---|---|---|---|---|---|
| 37 | **6**{*13,1,1*} | 2-indolyl | 5-H | × | × | × | × | 0 | EX[h] | |
| 38 | **6**{*13,1,2*} | 2-indolyl | 5-OMe | × | × | × | × | 0 | EX[h] | |
| 39 | **6**{*13,1,3*} | 2-indolyl | 4,5-$F_2$ | × | × | × | × | 0 | EX[h] | |

[a] Isolated yield after HPLC purification calculated for the entire two-step sequence. [b] UV purity determined at 214 nm. [c] Amount of the sample that is available in UV purity >90% (in mg). [d] Pass rating signified as (+) denotes a library member that was produced in quantity of 5 mg or higher, and higher than 90% UV purity in at least one of the two runs. Fail rating signified by (−) denotes a library member that did not fulfill these criteria both in run 1 and run 2. [e] The HRMS data for the M + 1 molecular ion of the compound **6** detected in the corresponding product. The calculated HRMS datafor the M + 1 molecular ion are given in parentheses. [f] Results from the validation library run are indicated in parentheses for comparison. [g] Ratio of the regioisomeric products shown on the two lines (established from HPLC chromatograms) or in parentheses (established by $^1$H NMR). [h] EX = excluded, building blocks were found to be outside the scope of the methodology, data was not included into the final evaluation. × = failed to yield any product.

of single regioisomers of the corresponding indenoisoquinolines was anticipated. The selection of aldehydes **1**{*12, 13*} was driven by the desire to incorporate additional heteroatoms into the indenoisoquinolines **6**. The diversity of the aroyl chloride component was limited to three components **5**{*1*−*3*} representing electronically neutral, electron rich, and electron deficient substrates. Conceivably, electron deficient aroyl chlorides might favor the imminium salt formation, as well as the oxidative addition of the palladium(0) catalyst into the $Csp^2$-Br bond in the second step of the cascade event. Through the entire project, ethoxycarbonyl-substituted vinyl stannane **4** was employed, reasoning that the ester group in the indenoisoquinolines would allow for subsequent elaboration into any number of desirable appendages.

The protocol developed for the preparation of the validation library was applied to the synthesis of Library I (39 members) without modification. The crude reaction mixtures obtained in the final step were analyzed by HPLC to establish the crude purity (UV 214 nm), and were subsequently submitted to preparative HPLC with mass-directed fractionation to produce the final samples, the purity of which was established by HPLC (UV 214 nm) (run 1, Table 2). To evaluate reproducibility of the protocol, the preparation of the Library I was repeated under identical conditions for the synthesis (run 2, Table 2). A minor difference in the purification conditions involved the use of neutral mobile phase for the run one (1) analysis and purification, and an alkaline pH 9.8 mobile phase for analysis and purification of the run two (2). The yields, purities (HPLC, UV 214 nm) for both the runs one (1) and two (2) as well as final amount (mg) of material available in purity higher than 90% are given in Table 2. Furthermore, compound identities were confirmed by $^1$H NMR analyses that were performed on 21 out of the 39 members **6**. Selected library members (6 members) were fully characterized (see the Supporting Information).

Data in Table 2 indicate that imines derived from 1-naphthyl-, 3-furyl-, and 2-indolyl carbaldehydes **1**{*6*}, **1**{*12*} and**1**{*13*} did not prove to be competent substrates for this methodology, giving heterocycles **6** in low yields, and purities, or failing to deliver the products at all. Intrigued by the unexpectedly low purities initially reported for indenoisoquinolines **6** derived from the *meta*-substituted imines **3**{*7,1*}, **3**{*9,1*} and**3**{*10,1*} (3-Cl, 3-OMe and 3-Me), we carefully examined the HPLC chromatograms, MS data, and $^1$H NMR analyses of the corresponding indenoisoquinolines **6**. In fact, the analytical data revealed that purified samples of indenoisoquinolines **6** formed from imines **3**{*7,1*}, **3**{*9,1*}, and **3**{*10,1*} possessed both the regioisomeric indenoisoquinolines arising from substitution at either C-2 or C-6 carbons of the aromatic ring of the carbaldehydes in significant quantities (1:2−1:3).[13] Thus, an unexpected example of an intramolecular electrophilic palladation providing the contiguous 1,2,3-trisubstitution pattern was uncovered.[14,15] When integrations for both the partially resolved peaks of the regioisomeric indenoisoquinolines from the HPLC chromatograms were entered into the results in Table 2, the combined purities were found to be significantly higher than 90% for products **6**{*9*−*10,1,1*−*3*}, and 88% and 91% for products **6**{*7,1,1*} and **6**{*7,1,2*}, respectively, bearing an electron-withdrawing Cl substituent. As expected (vide infra) indenoisoquinolines **6**{*3,1,1*−*3*} derived from 2-naphthyl carbaldehyde were produced as 1:1 mixture of regioisomers that were not separated by HPLC.

Aldehydes bearing a hydrogen or an electron-donating substituent in the *para* position (15 entries) all afforded the corresponding indenoisoquinolines in good yields (20−40% over the two step sequence) and good purities (>90%), regardless of the choice of the acyl chloride component. Indenoisoquinolines **6**{*8, 1, 1*−*3*} derived from 4-$Me_2$N-substituted carbaldehyde **1**{*8*} proved to be an intriguing exception, being isolated in good yields but only 80−86% purity by HPLC (UV 214 nm). The samples of indenoisoquinolines **6**{*8,1,1*−*3*} were repurified by flash column chromatography. However, the purity by HPLC (UV 214 nm) had not improved. It is possible that the presence of the amine group and the choice of pH of the elution phase for HPLC leads to a retention of an impurity, the nature of which could not be elucidated from $^1$H and $^{13}$C NMR analyses. As anticipated based on our prior work,[5] electron deficient aldehydes **1**{*4*} and **1**{*7*} afforded the indenoisoquinoline products **6**{*4, 1, 1*−*3*} and **6**{*7, 1, 1*−*3*} in diminished yields lower than 30% (mostly 7−15%) and somewhat lower purities (88−94%).

The preparation of Library I allowed us to survey the scope of the aldehyde building block for the novel indenoisoquinoline synthesis in the parallel format, identifying three aldehydes (1-naphthyl, 3-furyl, and 2-indolyl, a total of 9 entries from 39, 23%) as unsuitable for the protocol. An unexpected formation of regioisomers via electrophilic aromatic palladation from *meta*-substituted aromatic carbaldehydes was observed. We confirmed that electron deficient carbaldehydes gave rise to lower yields, still providing useful product quantities. After subtracting the nine (9) entries that employed aldehydes outside the scope of this protocol and combining both the regioisomers of the indenoisoquinolines to signify a "combined final purity", the success rate within the remaining 30-membered suite of compounds, defined as obtaining more than 5 mg of the product with

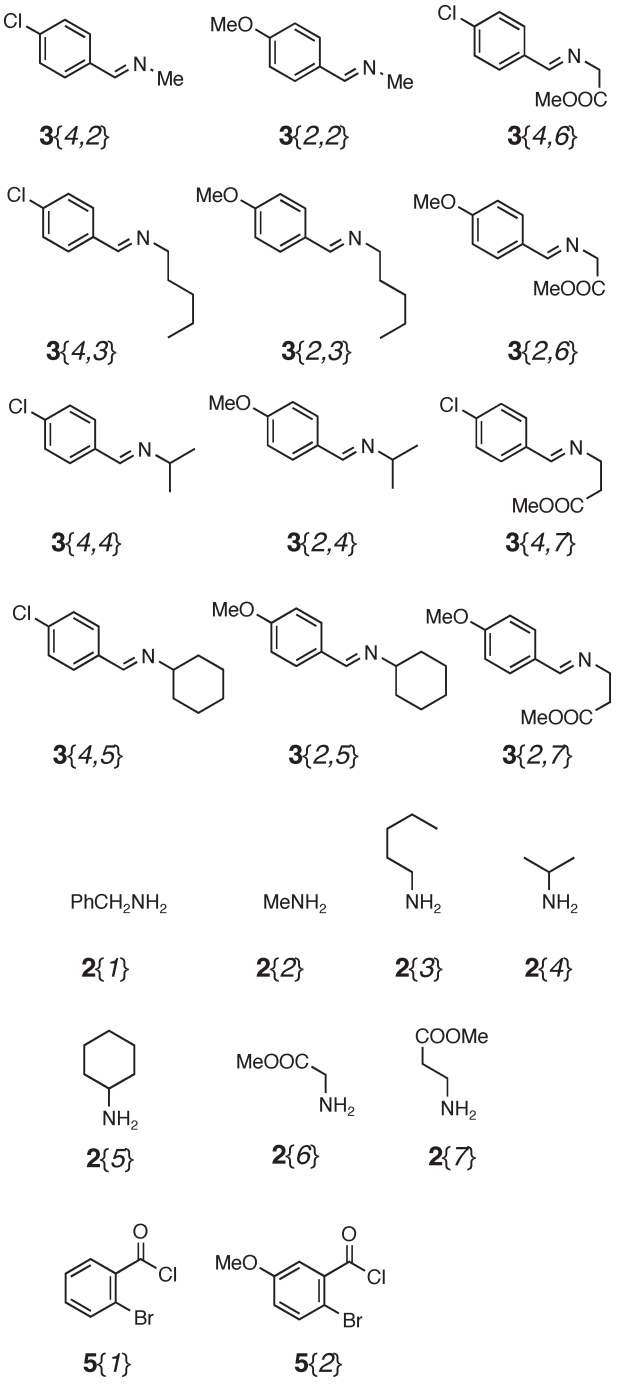
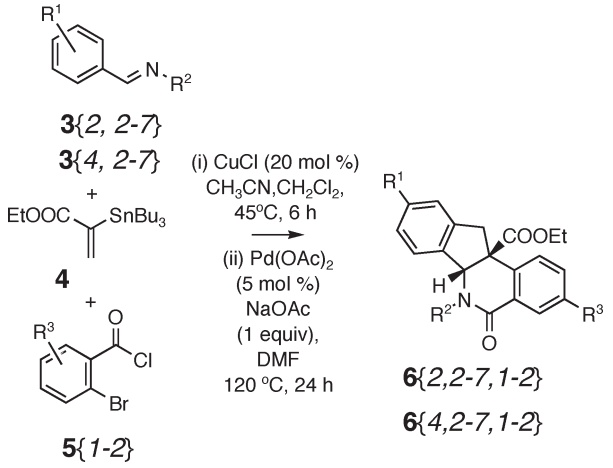



**Figure 5.** Building blocks for Library II.

HPLC (UV 214 nm) purity higher than 90% was 77%.[10] The seven (7) members considered as failed (from the 30-compound suite) include six compounds possessing relatively high purities (84−88% HPLC, UV 214 nm) and including the three 4-$Me_2N$-substituted products **6**{*8,1,1*−*3*} (84−86% HPLC purity) for which the contaminant could not be detected by $^1H$ and $^{13}C$ NMR spectroscopy.

Having defined the scope of the methodology with respect to the aldehyde building block **1**, we turned our attention to exploring for the first time the diversification of the amine building block **2**. Variations in the *N*-substituent present an opportunity to significantly modify the physical, chemical, and biological properties of the resulting heterocycles.[16] Thus we embarked on parallel synthesis of Library II (24 members). Previously, *N*-benzyl amine **2**{*1*} was employed exclusively in all our syntheses of indenoisoquinolines. For the construction of Library II, six amines **2**{*2*−*7*} including aliphatic amines with straight chains, branching in α-positions or an ester (−COOMe) group at either α- or in *β*-positions were combined with aldehydes **1**{*2*} and **1**{*4*} bearing an electron donating (OMe) or electron withdrawing (Cl) substituents in the *para* positions to afford imines substrates **3**{*2,2*−*7*} and **3**{*4,2*−*7*} (Figure 5). Aroyl chlorides **5**{*1*−*2*} were chosen to complete the building block set for Library II (Figure 5).

**Scheme 2. Synthesis of Library II**




The protocol for the synthesis and purification used in the preparation of Library I was applied to the preparation of Library II without modifications. The synthetic sequence is depicted in Scheme 2.

The purities of the final products were established by HPLC (UV 214 nm), and the identities of products **6** were confirmed by recording $^1H$ NMR spectra for 6 out of the total of 24 of library members (Table 3). Selected library members (5 members) were fully characterized (see the Supporting Information). Data in Table 3 confirm that a broad diversification in the *N*-substituent of indenoisoquinolines **6** can be realized. Indenoisoquinolines **6** were obtained in yields 29−45% over the two synthetic steps with three exceptions, predictably involving the electron deficient *para* chloro-substituted aldehyde **1**{*4*}. Imines **3**{*2,6*−*7*} and **3**{*4,6*−*7*} featuring the *N*-glycine and its homologue as the *N*-substituents proved to be the most challenging substrates, giving lower yields and purities of the corresponding indenoisoquinolines. Nevertheless, five (5) out of eight (8) total entries with these *N*-substituents afforded acceptable quantities and purities of the indenoisoquinolines **6** with the glycine or homoglycine *N*-substituents (entries 9−12 and 21−24 Table 3). Twenty library members were obtained in quantities higher than 5 mg (10−38 mg) and purities higher than 90% (HPLC, UV 214 nm) corresponding to 83% success rate for Library II preparation. A single diastereomer of each product was obtained.The relative stereochemistry at the C-5/C-6 ring juncture in the heterocycles **6**{*2,2*−*7,1*−*2*} and **6**{*4,2*−*7,1*−*2*} was assigned in analogy to the structures of indenoisoquinolines **6** bearing the *N*-benzyl substituent, and an NOE study on product **6**{*2,3,1*} was also attempted.[17]


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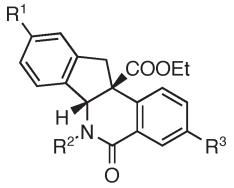
**Table 3. Results from Library II Synthesis**




**6**{*2,2-7,1-2*}

**6**{*4,2-7,1-2*}

| entry | compd | $R^1$ | $R^2$ | $R^3$ | yield[a] (%) | purity[b] (%) | amt (mg)[c] | pass/fail[d] | HRMS[e] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **6**{*4,2,1*} | 4-Cl | Me | H | 37 | 94 | 22 | + | 356.1049 (356.1053) |
| 2 | **6**{*2,2,1*} | 4-OMe | Me | H | 33 | 100 | 20 | + | 352.1577 (352.1548) |
| 3 | **6**{*4,3,1*} | 4-Cl | *n*-$C_5H_{11}$ | H | 17 | 100 | 12 | + | 412.1666 (412.1679) |
| 4 | **6**{*2,3,1*} | 4-OMe | *n*-$C_5H_{11}$ | H | 45 | 97 | 31 | + | 408.2171 (408.2174) |
| 5 | **6**{*4,4,1*} | 4-Cl | *i*-$C_3H_7$ | H | 20 | 100 | 13 | + | 384.1375 (384.1366) |
| 6 | **6**{*2,4,1*} | 4-OMe | *i*-$C_3H_7$ | H | 31 | 97 | 20 | + | 380.1885 (380.1861) |
| 7 | **6**{*4,5,1*} | 4-Cl | $C_6H_{11}$ cyclohexyl | H | 20 | 100 | 14 | + | 424.1671 (424.1679) |
| 8 | **6**{*2,5,1*} | 4-OMe | $C_6H_{11}$ cyclohexyl | H | 39 | 93 | 28 | + | 420.2175 (420.2174) |
| 9 | **6**{*4,6,1*} | 4-Cl | $CH_2COOMe$ | H | 10 | 98 | 7 | + | 414.1122 (414.1108) |
| 10 | **6**{*2,6,1*} | 4-OMe | $CH_2COOMe$ | H | 17 | 98 | 12 | + | 410.1606 (410.1603) |
| 11 | **6**{*4,7,1*} | 4-Cl | $(CH_2)_2COOMe$ | H | 20 | 76 | 14 | − | 428.1270 (428.1264) |
| 12 | **6**{*2,7,1*} | 4-OMe | $(CH_2)_2COOMe$ | H | 41 | 95 | 30 | + | 424.1781 (424.1760) |
| 13 | **6**{*4,2,2*} | 4-Cl | Me | OMe | 41 | 98 | 27 | + | 386.1188 (386.1159) |
| 14 | **6**{*2,2,2*} | 4-OMe | Me | OMe | 29 | 100 | 19 | + | 382.1664 (382.1654) |
| 15 | **6**{*4,3,2*} | 4-Cl | *n*-$C_5H_{11}$ | OMe | 37 | 96 | 28 | + | 442.1798 (442.1785) |
| 16 | **6**{*2,3,2*} | 4-OMe | *n*-$C_5H_{11}$ | OMe | 29 | 94 | 21 | + | 438.2293 (438.2280) |
| 17 | **6**{*4,4,2*} | 4-Cl | *i*-$C_3H_7$ | OMe | × | × | × | − | |
| 18 | **6**{*2,4,2*} | 4-OMe | *i*-$C_3H_7$ | OMe | 35 | 99 | 25 | + | 410.1978 (410.1967) |
| 19 | **6**{*4,5,2*} | 4-Cl | $C_6H_{11}$ cyclohexyl | OMe | 27 | 96 | 21 | + | 454.1773 (454.1785) |
| 20 | **6**{*2,5,2*} | 4-OMe | $C_6H_{11}$ cyclohexyl | OMe | 31 | 92 | 24 | + | 450.2276 (450.2280) |
| 21 | **6**{*4,6,2*} | 4-Cl | $CH_2COOMe$ | OMe | 6 | 17 | 4 | − | 444.1211 (444.1213) |
| 22 | **6**{*2,6,2*} | 4-OMe | $CH_2COOMe$ | OMe | 16 | 98 | 12 | + | 440.1694 (440.1709) |
| 23 | **6**{*4,7,2*} | 4-Cl | $(CH_2)_2COOMe$ | OMe | 20 | 84 | 15 | − | 458.1363 (458.1370) |
| 24 | **6**{*2,7,2*} | 4-OMe | $(CH_2)_2COOMe$ | OMe | 45 | 94 | 38 | + | 454.1848 (454.1865) |

[a] Isolated yield after HPLC purification calculated for the entire two-step sequence. [b] UV purity determined at 214 nm. [c] Amount of the sample that is available in UV purity >90% (in mg). [d] Pass rating signified as (+) denotes a library member that was produced in quantity of 5 mg or higher, and higher than 90% UV purity. Fail rating signified by (−) denotes a library member that did not fulfill these criteria. [e] The HRMS data for the M + 1 molecular ion of the compound **6** detected in the corresponding product.The calculated HRMS datafor the M + 1 molecular ion are given in parentheses. × = failed to yield any product.

After evaluating the results from the Library I and Library II syntheses, building blocks for the preparation of Library III were selected, aiming to assess the performance of the parallel synthetic methodology in systems diversifying both the amine and the aldehyde components. Building blocks that performed successfully in syntheses of Libraries I and II were chosen. Thus, electron neutral, electron rich, and electron deficient as well as one *meta*-substituted aldehyde **1**{*1,2,4,5,10 and 11*} (Figure 4) were combined with four (4) amines **2**{*2,4,5, and 7*} (Figure 5) to deliver the corresponding imines **3** (Figure 6). Utilizing the imines **3** shown in Figure 6 and two (2) aroyl chlorides **5**{*1*−*2*} a 48-membered Library III of indenoisoquinoliens **6** was synthesized proceeding according to the synthetic sequence outlined in Scheme 3 and employing the previously established method for the synthesis and purification (Table 4).

To confirm the identities of the library members, $^1$H NMR was recorded on 15 out of the total of 48 library members, and seven (7) indenoisoquionolines were fully characterized (see the Supporting Information). Representative structures of indenoisoquinolines **6** prepared in Library III are shown in Figure 7.

In agreement with our prior observations, the inspection of HPLC and $^1$H NMR data for indenoisoquinolines arising from the *meta*-Me substituted aldehyde **1**{*10*} indicated the formation of significant quantities (2:3 to 1:2 ratios) of both the regioisomers featuring two distinct substitution patterns in the aromatic ring of the indene substructure (Figure 7).[18]

When the final purities of these library members were adjusted for considering the "combined" content of both the regioisomers, 37 out of a total of 48 samples were obtained in purities higher than 90% (HPLC, UV 214 nm) and sufficient quantities. Out of the 11 members that failed to fulfill these criteria, 6 library members were obtained in good quantities and purities 81−89%. These results translate into a success rate of 77% for compounds with HPLC purities >90%, and a success rate 89% for

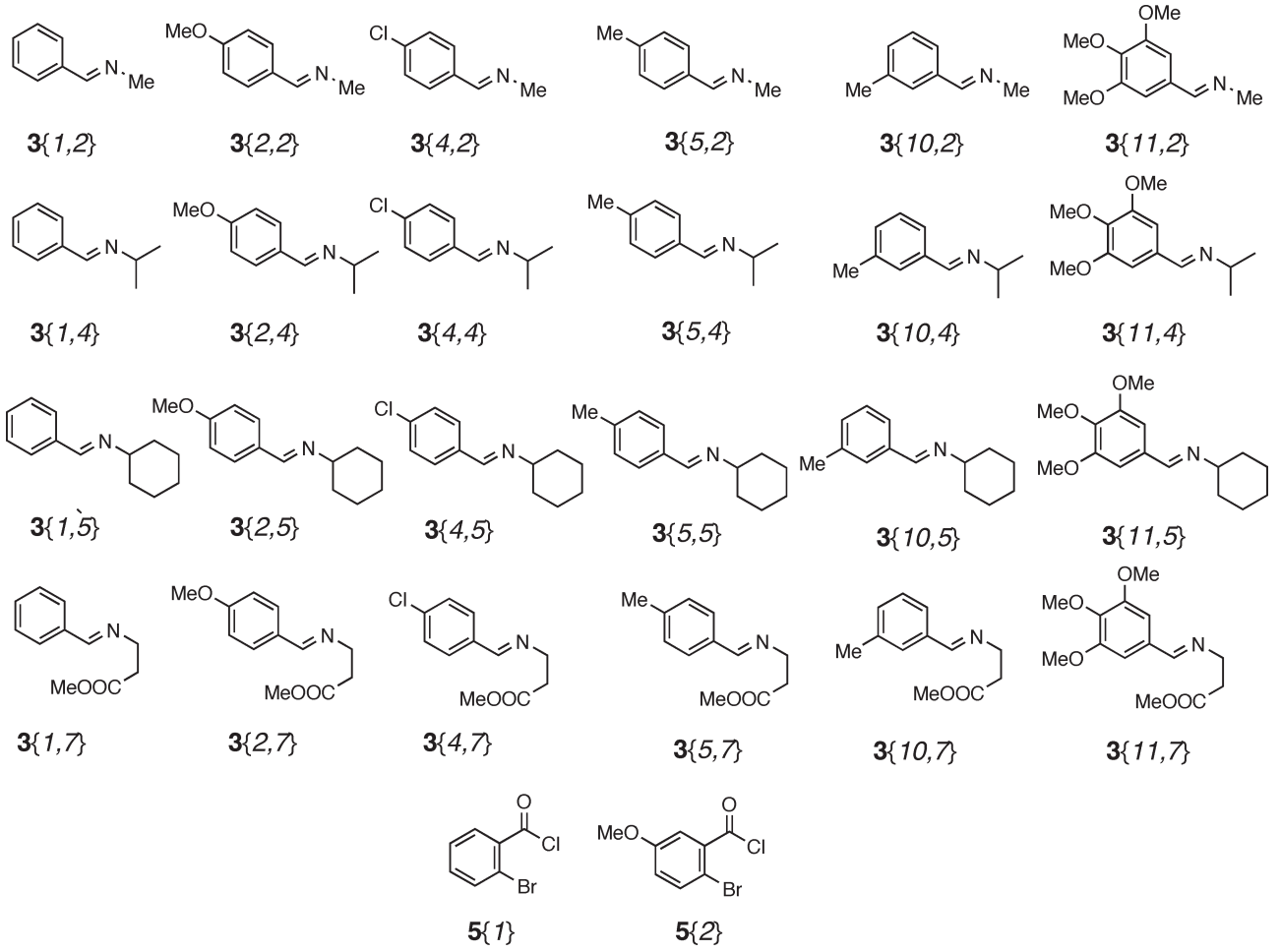
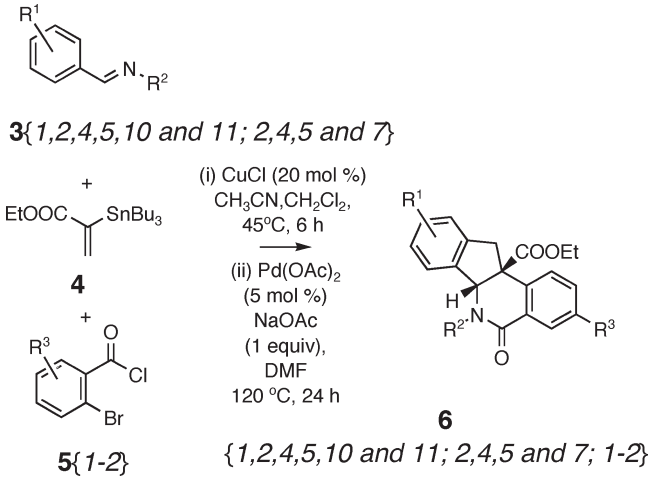



**Figure 6.** Building blocks for Library III.

**Scheme 3. Synthesis of Library III**




compounds with HPLC purities (>80%). As anticipated, lower yields (10−15%) in comparison to the yields of other members (20−30%) were achieved with the electron deficient *para*-chloro substituted aldehyde, and 4 out of the 11 library members that failed the 90% purity criteria employed the aldehyde **1**{*4*}. Furthermore, the two library members utilizing the challenging *N*-homoglycine substituent and the electron deficient aldehyde were among the members that failed the purity criteria giving products with only 72% and 84% purity by HPLC (UV 214 nm).

## CONCLUSION

In conclusion, a new and efficient method for solution phase parallel synthesis of combinatorial libraries of dihydroindeno-[1,2-*c*]isoquinolines relying on a sequence of Cu(I)-catalyzed three-component coupling and Pd(0)-catalyzed intramolecular annulation[4] was developed. The scope and limitations of the protocol with respect to the substitution pattern in the aryl ring of the indene core, as well as the *N*-substituent have been defined, revealing that the methodology is compatible with a wide-range of aliphatic linear, branched, and ester functionalized *N*-substituents. Unexpectedly, the formation of regioisomers possessing a 1,2,3-contiguous substitution pattern in the aromatic ring of the indene core via an intramolecular electrophilic palladation was observed. Since preparative HPLC purification methods that have not been specifically optimized for the separation of the regioisomers already achieved a partial separation, we conclude that preparation of pure individual regioisomers is feasible, and work toward this goal is ongoing. To date, three distinct combinatorial libraries were synthesized and delivered 80 compounds with novel highly substituted indenoisoquinoline structures (some consisting of mixtures of regioisomers) that are


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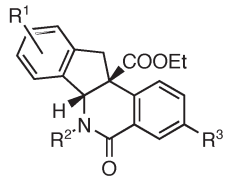
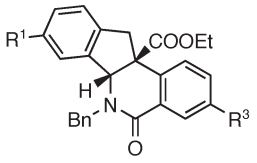
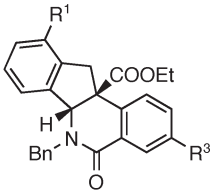
**Table 4. Results from Library III Synthesis**




**6**

*{1,2,4,5,10 and 11; 2,4,5 and 7; 1-2}*




**6**{*10; 2,4,5 and 7; 1-2*}

| entry | compd | $R^1$ | $R^2$ | $R^3$ | yield[a] (%) | purity[b] (%) | amt (mg)[c] | pass/fail[d] | HRMS[e] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **6**{*1,2,1*} | H | Me | H | × | × | 0 | – | – |
| 2 | **6**{*1,2,2*} | H | Me | OMe | 32 | 100 | 19 | + | 352.1553 (3521548) |
| 3 | **6**{*2,2,1*} | 4-OMe | Me | H | 27 | 100 | 16 | + | 352.1550 (352.1548) |
| 4 | **6**{*2,2,2*} | 4-OMe | Me | OMe | × | 13 | 1 | – | 382.1650 (382.1654) |
| 5 | **6**{*4,2,1*} | 4-Cl | Me | H | 26 | 99 | 16 | + | 356.1058 (356.1053) |
| 6 | **6**{*4,2,2*} | 4-Cl | Me | OMe | 31 | 87 | 21 | – | 386.1170 (386.1159) |
| 7 | **6**{*5,2,1*} | 4-Me | Me | H | 27 | 100 | 16 | + | 336.1605 (336.1599) |
| 8 | **6**{*5,2,2*} | 4-Me | Me | OMe | 31 | 99 | 19 | + | 366.1724 (366.1705) |
| 9 | **6**{*10,2,1*} | 3-Me | Me | H | 40 | 58[f] 42 | 17 | + | 336.1607 (336.1599) |
| 10 | **6**{*10,2,2*} | 3-Me | Me | OMe | 30 | 56[f] 43 | 19 | + | 366.1711 (366.1705) |
| 11 | **6**{*11,2,1*} | 3,4,5-$(OMe)_3$ | Me | H | 27 | 95 | 19 | + | 412.1763 (412.1760) |
| 12 | **6**{*11,2,2*} | 3,4,5-$(OMe)_3$ | Me | OMe | 33 | 97 | 25 | + | 442.1859 (442.1865) |
| 13 | **6**{*1,4,1*} | H | *i*-Pr | H | 16 | 94 | 9 | + | 350.1754 (350.1756) |
| 14 | **6**{*1,4,2*} | H | *i*-Pr | OMe | 22 | 98 | 14 | + | 380.1859 (380.1861) |
| 15 | **6**{*2,4,1*} | 4-OMe | *i*-Pr | H | 16 | 99 | 10 | + | 380.1867 (380.1861) |
| 16 | **6**{*2,4,2*} | 4-OMe | *i*-Pr | OMe | 23 | 96 | 16 | + | 410.1967 (410.1967) |
| 17 | **6**{*4,4,1*} | 4-Cl | *i*-Pr | H | 10 | 100 | 7 | + | 384.1349 (384.1366) |
| 18 | **6**{*4,4,2*} | 4-Cl | *i*-Pr | OMe | 15 | 89 | 11 | – | 414.1475 (414.1472) |
| 19 | **6**{*5,4,1*} | 4-Me | *i*-Pr | H | 14 | 99 | 8 | + | 364.1920 (364.1912) |
| 20 | **6**{*5,4,2*} | 4-Me | *i*-Pr | OMe | 27 | 78 | 18 | – | 394.2017 (394.2018) |
| 21 | **6**{*10,4,1*} | 3-Me | *i*-Pr | H | 11 | 38[f] 58 | 7 | + | 364.1914 (364.1912) |
| 22 | **6**{*10,4,2*} | 3-Me | *i*-Pr | OMe | 26 | 61[f] 33 | 17 | + | 394.2023 (394.2018) |
| 23 | **6**{*11,4,1*} | 3,4,5-$(OMe)_3$ | *i*-Pr | H | 23 | 95 | 17 | + | 440.2079 (440.2073) |
| 24 | **6**{*11,4,2*} | 3,4,5-$(OMe)_3$ | *i*-Pr | OMe | 21 | 96 | 17 | + | 470.2180 (470.2178) |
| 25 | **6**{*1,5,1*} | H | cyclohexyl | H | 23 | 89 | 15 | + | 390.2076 (390.2069) |
| 26 | **6**{*1,5,2*} | H | cyclohexyl | OMe | 24 | 94 | 17 | + | 420.2174 (420.2174) |
| 27 | **6**{*2,5,1*} | 4-OMe | cyclohexyl | H | 25 | 81 | 18 | – | 420.2183 (420.2174) |
| 28 | **6**{*2,5,2*} | 4-OMe | cyclohexyl | OMe | 23 | 86 | 18 | – | 450.2276 (450.2280) |
| 29 | **6**{*4,5,1*} | 4-Cl | cyclohexyl | H | 15 | 96 | 11 | + | 424.1680 (424.1679) |
| 30 | **6**{*4,5,2*} | 4-Cl | cyclohexyl | OMe | 7 | 98 | 5 | + | 454.1777 (454.1785) |
| 31 | **6**{*5,5,1*} | 4-Me | cyclohexyl | H | 17 | 97 | 12 | + | 404.2233 (404.2225) |
| 32 | **6**{*5,5,2*} | 4-Me | cyclohexyl | OMe | 28 | 91 | 20 | + | 434.2333 (434.2331) |
| 33 | **6**{*10,5,1*} | 3-Me | cyclohexyl | H | 21 | 95[g] | 15 | + | 404.2238 (404.2225) |
| 34 | **6**{*10,5,2*} | 3-Me | cyclohexyl | OMe | 26 | 91[g] | 19 | + | 434.2337 (434.2331) |
| 35 | **6**{*11,5,1*} | 3,4,5-$(OMe)_3$ | cyclohexyl | H | 14 | 89 | 12 | – | 480.2370 (480.2386) |
| 36 | **6**{*11,5,2*} | 3,4,5-$(OMe)_3$ | cyclohexyl | OMe | 29 | 97 | 25 | + | 510.2476 (510.2491) |
| 37 | **6**{*1,7,1*} | H | $(CH_2)_2$ COOMe | H | 14 | 96 | 9 | + | 394.1669 (394.1654) |
| 38 | **6**{*1,7,2*} | H | $(CH_2)_2$ COOMe | OMe | 20 | 94 | 15 | + | 424.1760 (424.1760) |
| 39 | **6**{*2,7,1*} | 4-OMe | $(CH_2)_2$ COOMe | H | 22 | 97 | 16 | + | 424.1776 (424.1760) |
| 40 | **6**{*2,7,2*} | 4-OMe | $(CH_2)_2$ COOMe | OMe | × | × | 0 | – | – |


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**Table 4. Continued**

| entry | compd | $R^1$ | $R^2$ | $R^3$ | yield[a] (%) | purity[b] (%) | amt (mg)[c] | pass/fail[d] | HRMS[e] |
|---|---|---|---|---|---|---|---|---|---|
| 41 | **6**{*4,7,1*} | 4-Cl | $(CH_2)_2$ COOMe | H | 13 | 72 | 10 | − | 428.1279 (428.1264) |
| 42 | **6**{*4,7,2*} | 4-Cl | $(CH_2)_2$ COOMe | OMe | 21 | 84 | 17 | − | 458.1358 (458.1370) |
| 43 | **6**{*5,7,1*} | 4-Me | $(CH_2)_2$ COOMe | H | 28 | 93 | 20 | + | 408.1812 (408.1810) |
| 44 | **6**{*5,7,2*} | 4-Me | $(CH_2)_2$ COOMe | OMe | 26 | 98 | 19 | + | 438.1903 (438.1916) |
| 45 | **6**{*10,7,1*} | 3-Me | $(CH_2)_2$ COOMe | H | 25 | 53[f] | 18 | + | 408.1820 (408.1810) |
| | | | | | | 37 | | | |
| 46 | **6**{*10,7,2*} | 3-Me | $(CH_2)_2$ COOMe | OMe | 22 | 58 | 16 | + | 438.1907 (438.1916) |
| | | | | | | 37[f] | | | |
| 47 | **6**{*11,7,1*} | 3,4,5-$(OMe)_3$ | $(CH_2)_2$ COOMe | H | 28 | 96 | 23 | + | 484.1965 (484.1971) |
| 48 | **6**{*11,7,2*} | 3,4,5-$(OMe)_3$ | $(CH_2)_2$ COOMe | OMe | 32 | 95 | 28 | + | 514.2053 (514.2077) |

[a] Isolated yield after HPLC purification calculated for the entire two-step sequence. [b] UV purity determined at 214 nm. [c] Amount of the sample that is available in UV purity >90% (in mg). [d] Pass rating signified as (+) denotes a library member that was produced in quantity of 5 mg or higher, and higher than 90% UV purity. Fail rating signified by (−) denotes a library member that did not fulfill these criteria. [e] The HRMS data for the M + 1 molecular ion of the compound **6** detected in the corresponding product.The calculated HRMS datafor the M + 1 molecular ion are given in parentheses. [f] Ratio of the regioisomeric products established from the HPLC chromatogram is shown on the two lines. [g] The peaks for the regioisomers were not resolved by HPLC, the presence of regioisomers was detected by $^1$H NMR. × = failed to yield any product.

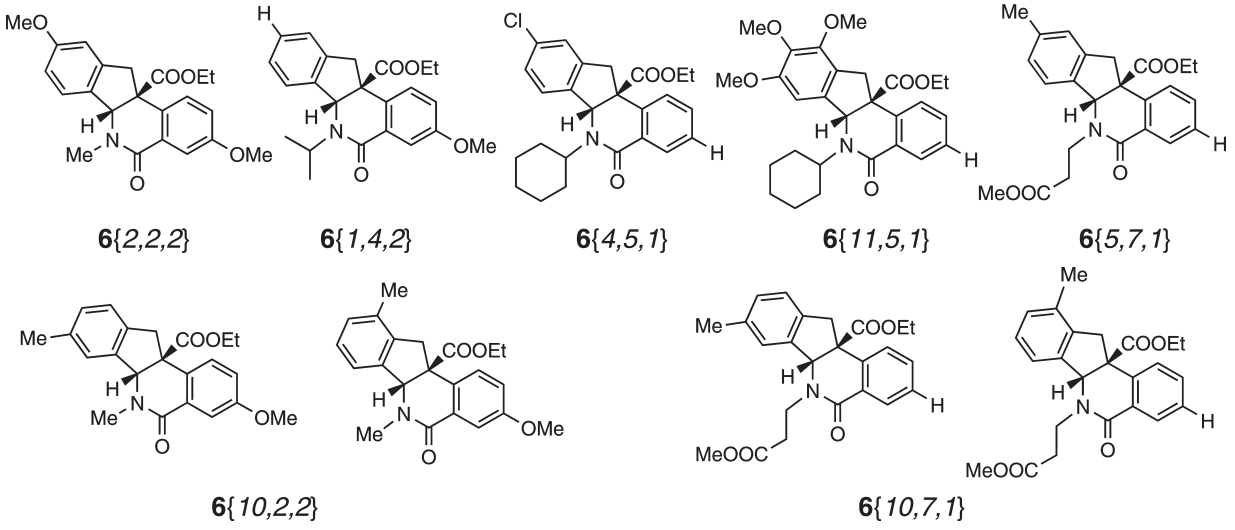


**Figure 7.** Examples of indenoisoquinolines prepared in Library III.

currently being evaluated in high-throughput screens for a wide range of biological activities.[9]

## EXPERIMENTAL PROCEDURES

**General Procedure for the Parallel Synthesis of the Libraries.** 24-Member MiniBlock XT synthesizer vials (17 × 100 mm) were charged with activated 3 Å MS (2.0 g) and CuCl (≥99.0% purity, 3.4 mg, 0.034 mmol, 0.2 equiv) utilizing a solid dispenser. Reaction vials were flushed with dry argon for 5 min. The stock solutions of imines **3** (0.17 mmol, 1.5 mL, 1.0 equiv) and aroyl chlorides **5** (0.22 mmol, 1.5 mL, 1.3 equiv) in acetonitrile were injected via a syringe into the reaction vials. The reaction mixtures were stirred at room temperature for 5 min under dry argon atmosphere followed by the addition of the stock solution of the vinylstannane **4** (0.34 mmol, 1.5 mL, 2.0 equiv) in dichloromethane. The reaction vials were stirred at 45 °C for 6 h under argon atmosphere on IKA stirring plates with a thermocouple inserted into the metal block. The reaction mixtures were cooled to room temperature and diluted with ethyl acetate (1.0 mL) and saturated aqueous KF solution (1.0 mL) and stirred further at room temperature for 16 h. The reaction mixtures were filtered into reaction vials (17 × 100 mm) through PrepSep silica gel tubes (SPE) under air pressure, and each tube was rinsed with ethyl acetate (2 × 3 mL) and the rinsed portions were eluted through SPE tubes. The eluents were evaporated using a GeneVac EZ-2 evaporator.

Anhydrous sodium acetate (13.9 mg, 0.17 mmol, 1.0 equiv) and palladium acetate (1.9 mg, 0.0085 mmol, 0.05 equiv) were added by solid dispensers to reaction vials (17 × 100 mm) containing the crude products from the first step, the reaction vials were flushed with dry argon for 5 min at room temperature, and anhydrous DMF (1.8 mL) was added via a syringe. Reaction mixtures were heated under argon atmosphere at 120 °C for 24 h on IKA plates with the thermocouple inserted into the metal block. The reaction mixtures were cooled to room temperature and diluted with ethyl acetate (2.0 mL) and filtered into barcoded CCT tubes through PrepSep silica gel columns (SPE) under air pressure. The reaction tubes were washed with ethyl acetate


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(2 × 2 mL) and filtered through SPE tubes as well. The solvents were removed on GeneVac HT4 evaporator. Crude products were subjected to HPLC (UV 214 nm) analysis followed by preparative HPLC purification with mass directed fractionation.

## ■ ASSOCIATED CONTENT

**Supporting Information.** General experimental procedures, full characterization data for 18 compounds and copies of $^{1}H$ and $^{13}C$ NMR spectra and HPLC traces for fully characterized compounds (18) and additional selected products. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

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(10) The KU-CMLD is required, under the terms of its grant, to adhere to these standards (HPLC assay >90% (UV 214 nm), 5 mg minimum mass) for submission of compounds to the Molecular Libraries and Small Molecule Repository (MLSMR). KU biological collaborators obtain the identical compounds directly from CMLD.

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(17) The NOE data recorded for the indenoisoquinoline **6**{*2,3,1*} were consistent with the proposed structure, but were inconclusive in terms of assigning the relative stereochemistry. Efforts to obtain single crystals of several indenoisoquinolines **6** with diverse *N*-groups are in progress, but so far did not afford satisfactory results.

(18) $^{1}$H NMR spectra recorded for compound **6**{*10,5,2*} (no resolution of regioisomers was indicated by HPLC chromatogram) indicated the presence of two regioisomers in approximately 1:1 ratio, revealed by the signals at 6.94 ppm (s, 0.5 H); 5.33 (s, 0.5 H), 5.32 (s, 0.5 H).