

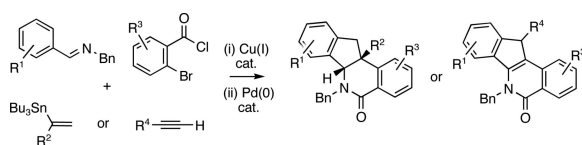
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Sequential Cu(I)/Pd(0)-Catalyzed Multicomponent Coupling and Annulation Protocol for the Synthesis of Indenoisoquinolines

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Abstract



Copper-catalyzed coupling of imines, vinylstannanes or alkynes and *o*-bromoaryl chlorides followed by Pd(0)-catalyzed annulations afforded indenoisoquinolines. Protocols requiring minimal purifications were developed, providing new methods for the construction of combinatorial libraries.

The prevalence of *N*-heterocycles among established pharmaceutical agents¹ continues to inspire the development of new synthetic methods. We have been exploring a protocol based on an assembly of α -*N*-substituted amides followed by various intramolecular cyclizations,² opening up access to combinatorial libraries of hexahydro-1*H*-isoindolones (Figure 1).³

Herein, we describe a powerful novel combination of the Cu(I)-catalyzed three-component coupling and an intramolecular Pd(0)-catalyzed 1,2-bisarylation of an olefin or an alkyne in amides **IV** and **V** to deliver substituted indenoisoquinolines **VI** and **VII** (Figures 1 and 2). The protocol allows a rapid increase in molecular complexity in only two steps.

Structurally related indenoisoquinolines have been shown to possess potent biological activities.⁴ Our protocol provides a more efficient alternative to the established preparations of indenoisoquinolines, particularly those substituted at the angular position or the benzylic carbon in the indene ring.⁵ The method reported herein opens up a modular access to indenoisoquinolines, and is well amenable to automation.

Initial studies were focused on extending the scope of the known Cu(I)-catalyzed coupling⁶ to *o*-bromoaryl chlorides **III** as well as to 1,1-disubstituted vinylstannanes **II** (Figure 2). We were able to decrease the molar excess of stannane **3a**,⁷ from 2.0 equiv to 1.5 equiv⁸ and realize the coupling to imine **1a** and aroyl chloride **2a** providing amide **4a** in good yields (Scheme 1). An increase in the CuCl catalyst load improved the yield of amide **4a** from 67% (with 10 mol % CuCl) and to 82% (with 20 mol % CuCl, Scheme 1).⁹ Next, the Pd-

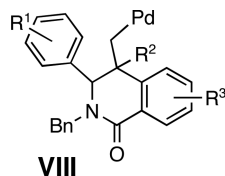
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Supporting Information Available Description of the synthesis and characterization of all new compounds, and X-ray crystallographic analyses on compounds **5j**, **5n** and **8c**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

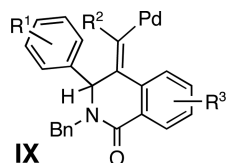
catalyzed cyclization of amide **4a** was explored, anticipating that an intramolecular Heck reaction would afford intermediate **VIII** poised for electrophilic arylation to yield dihydroindeno[1,2-c]isoquinolines **VI** (Figure 2).¹⁰ The treatment of amide **4a** with Pd(OAc)₂ (5 %) and NaOAc (1 equiv) afforded the indenoisoquinoline **5a** in a 93% yield as a single diastereomer (Scheme 1).¹¹



Aiming to establish a protocol amenable to automated synthesis, we sought to eliminate chromatographic purification of amide **4a**. The addition of solid KF and small quantities of water, followed by filtration was employed to remove tin residues from the reaction mixtures. The resulting crude amide **4a** was treated with Pd(OAc)₂ catalyst under conditions reported in Scheme 1 to afford indenoisoquinoline **5a** in 75% yield over two steps (entry 1, Table 1, Method A). A brief survey revealed that sodium acetate was the optimum base for the Pd-catalyzed cyclization.¹⁰ The replacement of NaOAc with Na₂CO₃/*n*-Bu₄NCl applying modified Jeffery's conditions¹² (compare Methods A and B, entries 1, 3 and 4, Table 1) resulted in a decrease in the reaction yields, particularly severe for the electronically deactivated imines **1c** (R² = H) and **1d** (R² = Cl) (entries 3 and 4, Method B, Table 1). Overall, the optimized sequential protocol afforded the corresponding indenoisoquinolines **5a-5e** in 38-75% yields over two steps (entries 1-5, Table 1, Method A). The lower yields of the electronically deactivated chloro and ester-substituted indenoisoquinolines **5d-e** are in agreement with the proposed involvement of electrophilic palladation in the key step, although the less facile iminolysis of the acyl chlorides may also be a contributing factor. The 3,4-disubstituted imines **1f** and **1g** afforded single regioisomers of heterocycles **5f** (77%) and **5g** (71%) arising from palladation at the least hindered position in the aromatic ring (entries 6 and 7, Table 1). A contiguous 1,2,3,4,5-substitution pattern was achieved in an activated imine yielding indenoisoquinoline **5h** in 64% yield (entry 8, Table 1). Efficient preparation of indenoisoquinolines **5i** and **5j** demonstrated the compatibility of the method with heteroatoms other than oxygen (entries 9 and 10, Table 1).

To expand the reaction scope, imines **1a** and **1b** were coupled to substituted aroyl chlorides **2b-c** and vinylstannanes **3a** and **3b-c**¹³ bearing aliphatic (Me) and aromatic (Ph) substituents. Indenoisoquinolines **5k-o** were obtained in good yields (59-76%) over two steps (Table 2). Heterocycles **5k-o** were isolated as single diastereomers following chromatography and trituration of the crude products. The relative stereochemistry in heterocycles **5** (R⁴ = COOEt and Ph, Tables 1 and 2) was assigned based on analogy with indenoisoquinolines **5j** and **5n**, the structure of which was elucidated via single crystal X-ray crystallographic analyses. The relative stereochemistry in products **5m** and **5o** (R⁴ = Me) was assigned via spectroscopic methods.¹⁴

To access a distinct substitution pattern in the indenoisoquinolines, propargyl amide **7a** was prepared from imine **1a**, aroyl chloride **2a** and alkyne **6a** in a good yield (54%) using conditions reported by Arndtsen¹⁵ (Scheme 2). We envisioned that Pd-catalyzed intramolecular bisfunctionalization of the alkyne¹⁶ would proceed via intermediate **IX** to afford indenoisoquinolines **VII** (Figure 2). Conceivably, a 1,3-shift of the allylic hydrogen in the intermediate **IX** would provide an organopalladium intermediate poised for the terminal electrophilic palladation.



Indeed, the treatment of amide **7a** with Pd(OAc)₂ catalyst and Na₂CO₃/*n*-Bu₄NCl additive mixture for a prolonged time period (36 h at 120 °C in DMF) afforded the corresponding indenoisoquinoline **8a** in an excellent yield (91%) (Scheme 2). Ultimately, the isolation of amide **7a** was avoided, limiting the purification of the crude reaction mixtures to the removal of excess alkyne via filtration through a short plug of silica. The resulting crude product was directly subjected to Pd-catalysis, affording indenoisoquinoline **8a** in a good yield (66%) over two steps (entry 1, Table 2). This protocol was then applied to the coupling of imines **1a**, **1b** and **1j** with aroyl chloride **2a** and aryl acetylenes **6a-6c** to provide indenoisoquinolines **8a-e** in good yields (51-68%) over two steps (Table 2). Single crystal X-ray crystallographic studies on heterocycle **8c** unequivocally established the structure, including the position of the double bond within the isoquinoline ring.¹⁷

The new synthetic protocol described here rapidly and efficiently assembles indenoisoquinolines with distinct substitution patterns from three simple building blocks. The modular strategy is particularly well suited for the construction of combinatorial libraries of indenoisoquinolines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. Taylor, JB.; Triggle, DJ., editors. *Comprehensive Medicinal Chemistry II*. Elsevier; Amsterdam, Boston: 2007.
2. Martin SF, Sunderhause JD, Dockendorff C. *Org. Lett.* 2007; 9:4223. [PubMed: 17887692]
3. a Zhang L, Lushington GH, Neuenswander B, Hershberger JC, Malinakova HC. *J. Comb. Chem.* 2008; 10:285. [PubMed: 18237142] b Zhang L, Malinakova HC. *J. Org. Chem.* 2007; 72:1484. [PubMed: 17243720]
4. a Ryckebusch A, Garcin D, Lansiaux A, Goossens J-F, Baldeyrou B, Houssin R, Bailly C, Henichart J-P. *J. Med. Chem.* 2008; 51:3617. [PubMed: 18507368] b Teicher BA. *Biochem. Pharmacol.* 2008; 75:1262. [PubMed: 18061144] c Antony S, Agama KK, Miao Z-H, Takagi K, Wright MH, Robles AI, Varticovski L, Nagarajan M, Morrell A, Cushman M, Pommier Y. *Cancer. Res.* 2007; 67:10397. [PubMed: 17974983]
5. a D'Souza DM, Kiel A, Herten D-P, Rominger F, Müller TJJ. *Chem. Eur. J.* 2008; 14:529. [PubMed: 17933002] b Morrell A, Placzek M, Parmley S, Grella B, Antony S, Pommier Y, Cushman M. *J. Med. Chem.* 2007; 50:4388. [PubMed: 17676830] c D'Souza DM, Rominger F, Müller TJJ. *Angew. Chem. Int. Ed.* 2005; 44:153. d Xiao X, Miao Z-H, Antony S, Pommier Y, Cushman M. *Bioorg. Med. Chem. Lett.* 2005; 15:2795. [PubMed: 15911256] e Jagtap PG, Baloglu E, Southan G, Williams W, Roy A, Nivorozhkin A, Landrau N, Desisto K, Saltzman AL, Szabo C. *Org. Lett.* 2005; 7:1753. [PubMed: 15844898] f Xiao X, Antony S, Kohlhagen G, Pommier Y, Cushman M. *Bioorg. Med. Chem.* 2004; 12:5147. [PubMed: 15351398] g Fox BM, Xiao X, Antony S, Kohlhagen G, Pommier Y, Staker B, Stewart L, Cushman M. *J. Med. Chem.* 2003; 46:3275.

- [PubMed: 12852757] h Cho W-J, Park M-J, Imanishi T, Chung B-H. Chem. Pharm. Bull. 1999; 47:900. [PubMed: 10399841]
- Black DA, Arndtsen BA. J. Org. Chem. 2005; 70:5133. [PubMed: 15960515]
 - For the preparation of **3a** via hydrostannylation, see: Darwish A, Lang A, Kim T, Chong JM. Org. Lett. 2008; 10:861. [PubMed: 18237179]
 - Compare to our original method reported in reference 3a.
 - Variations in the CuCl load and the excess of stannane **3a** in reactions under the conditions described in Scheme 1 affected the yields of amide **4a**: (i) 20 mol % CuCl, 2.0 equiv **3a** gave **4a** in 80% yield; 20 mol % CuCl, 1.0 equiv **3a** gave **4a** in 62% yield; (iii) 10 mol % CuCl, 1.5 equiv **3a** gave **4a** in 67% yield.
 - Zeni G, Larock RC. Chem. Rev. 2000; 100:3009. [PubMed: 11749313] Brown D, Grigg R, Sridharan V, Tambyrajah V. Tetrahedron Lett. 1995:8137. For a review on the synthesis of heterocycles via transition metal catalysis, see: D'Souza DM, Müller TJ. J. Chem. Soc. Rev. 2007; 36:1095.
 - ¹H NMR analysis of the crude reaction mixtures indicated the presence of traces of a diastereomeric indenoisoquinoline. Isolation via chromatography followed by trituration from hexanes afforded a pure single diastereomer **5a**. The relative stereochemistry was assigned based on the comparison of the spectroscopic data with the spectroscopic data recorded for heterocycle **5j**, the structure of which was established by X-ray crystallography (vide infra).
 - a Jeffery T. Tetrahedron Lett. 1985; 26:2667. b Jeffery T. J. Chem. Soc. Chem. Commun. 1984:1287.
 - For the preparation of the stannanes, see: Darwish A, Chang JM. J. Org. Chem. 2007; 72:1507. [PubMed: 17253749]
 - The relative stereochemistry in heterocycle **5o** was established via ¹H NMR NOE study and the structure of **5m** was assigned accordingly. For details see the Supporting Information.
 - Black DA, Arndtsen BA. Org. Lett. 2004; 6:1107. [PubMed: 15040734]
 - Grigg R, Loganathan V, Sridharan V. Tetrahedron Lett. 1996; 37:3399.
 - Structures of all the remaining indenoisoquinolines were assigned accordingly. The structure assignment is also supported by 2D NMR and NOE ¹H NMR spectral studies performed on heterocycles **8c** and **8d** (see the Supporting Information).

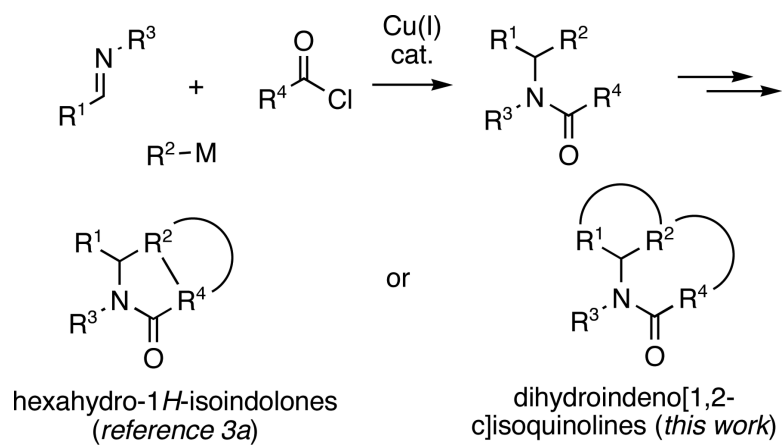


Figure 1.
The general strategy

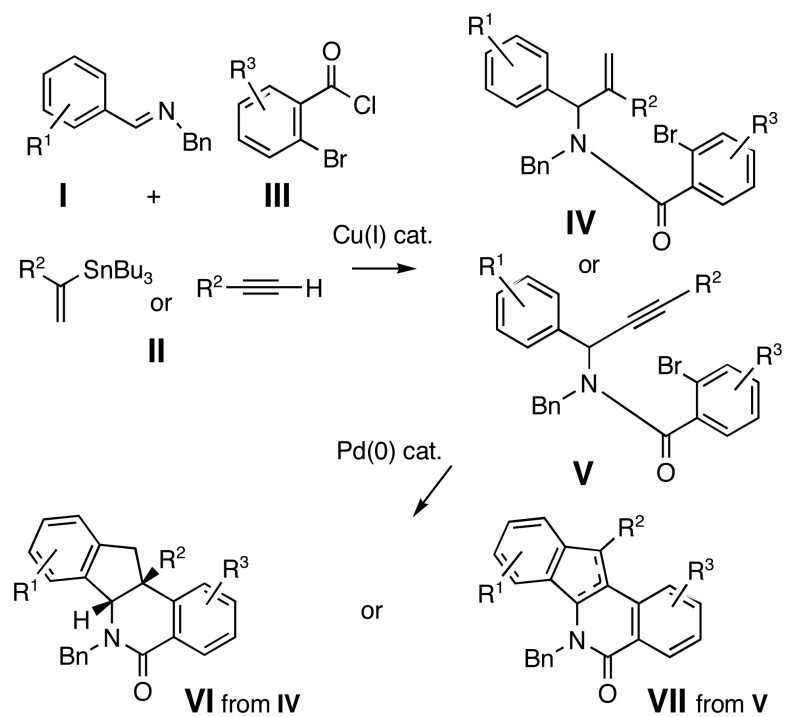
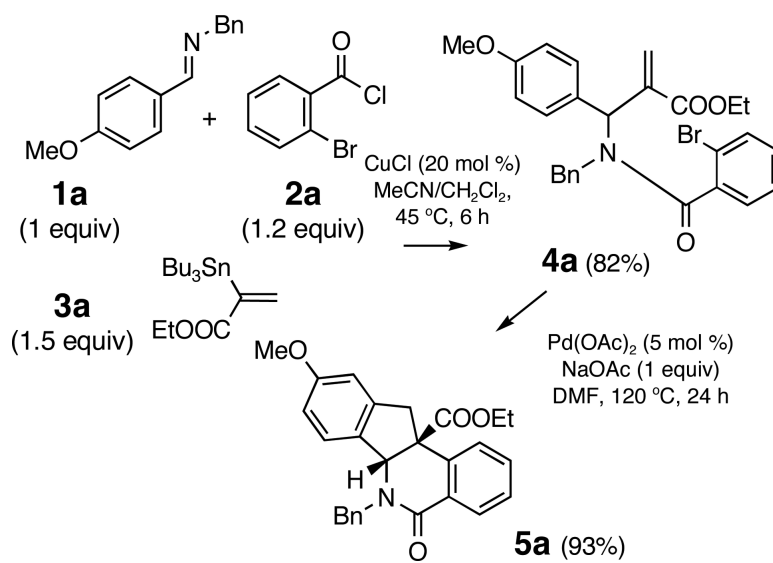
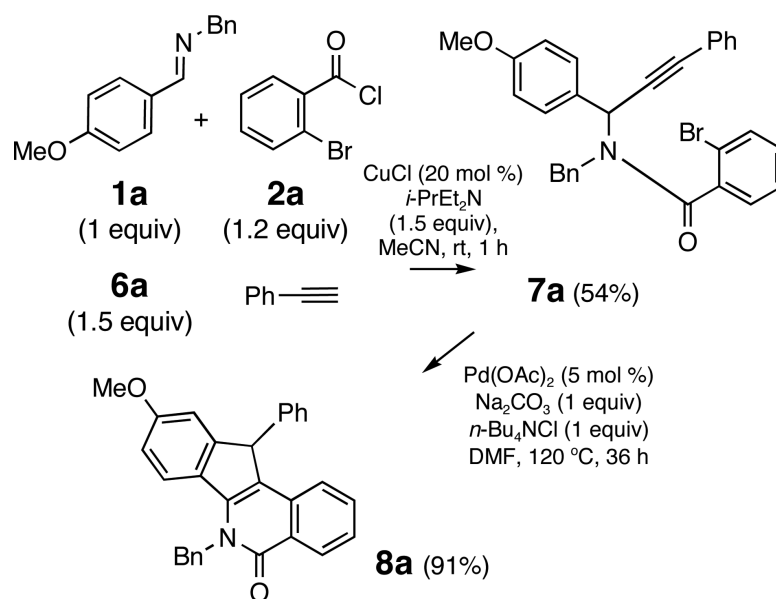


Figure 2.
Strategy toward indenoisoquinolines



Scheme 1.
Protocol utilizing an isolated amide



Scheme 2.
Protocol utilizing an isolated propargyl amide

Table 1

Angularly Substituted Indenoisoquinolines

entry	R ¹	R ²	R ³	prdt ^b	yield ^c (%)
1	H	OMe	H	5a	75 (71) ^d
2	H	Me	H	5b	69
3	H	H	H	5c	67 (17) ^d
4	H	Cl	H	5d	49 (11) ^d
5	H	COOMe	H	5e	38
6	H	OMe	OMe	5f	77
7	H	-OCH ₂ CH ₂ O-		5g ^e	71
8	OMe	OMe	OMe	5h	64
9	H	NMe ₂	H	5i	59
10		thiophene-2-yl		5j	74

^aMethod A: was used for all the entries; (i) CuCl (20%), MeCN/CH₂Cl₂, 45 °C, 6 h, imine : acyl chloride : stannane = 1.0 : 1.2 : 1.5 (mol); (ii) aqueous KF, filtration, evaporation; (iii) Pd(OAc)₂ (5%), NaOAc (1.0 equiv), DMF, 120 °C, 24 h.

^bWith one exception, a single diastereomer was isolated.

^cIsolated yield of heterocycles **5** obtained via Method A calculated per imine as the limiting reagent.

^dYield of heterocycle **5** obtained by Method B is given in parentheses. Method B: same as Method A, but substituting Na₂CO₃ (1.0 equiv)/*n*-Bu₄NCl (1.0 equiv) for NaOAc.

Product was isolated as a 4 : 1 mixture of diastereomers (by $^1\text{H NMR}$), the major diastereomer is shown.

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Table 2

Diversification of Additional Building Blocks

entry	R ¹	R ²	R ³	R ⁴	prdt ^b	yield ^c (%)
1	Me	OMe	H	COOEt	5k	62
2	OMe	F	F	COOEt	5l	76
3	OMe	H	H	Me	5m	68
4	OMe	H	H	Ph	5n	59
5	Me	H	H	Me	5o	54

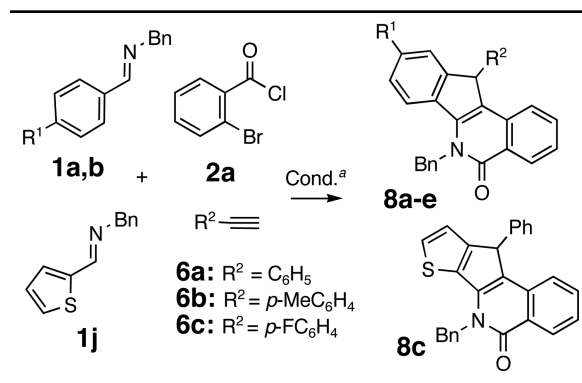
^aReaction conditions: (i) CuCl (20%), MeCN/CH₂Cl₂, 45 °C, 6 h, imine : stannane = 1.0 : 1.2 : 1.5 (mol); (ii) treatment with aqueous KF, filtration, evaporation; (iii) Pd(OAc)₂ (5%), NaOAc (1.0 equiv), DMF, 120 °C, 24 h.

^bSingle diastereomer was isolated.

^cIsolated yield of heterocycles **5** calculated per imine as the limiting reagent.

Table 3

Indenoisoquinolines with a benzylic substituent



entry	R ¹	R ² (aryl)	prdt ^b	yield ^c (%)
1	OMe	C ₆ H ₅ -	8a	66
2	Me	C ₆ H ₅ -	8b	51
3	thiophene-2-yl	C ₆ H ₅ -	8c	68
4	OMe	<i>p</i> -CH ₃ C ₆ H ₄ -	8d	63
5	OMe	<i>p</i> -FC ₆ H ₄ -	8e	57

^aReaction conditions: (i) CuCl (20%), *i*-PrEt₂N (1.5 equiv) MeCN, rt, 1 h, imine : acyl chloride : alkyne = 1.0 : 1.2 : 1.5 (mol); (ii) treatment with aqueous KF, filtration, evaporation; (iii) Pd(OAc)₂ (5%), Na₂CO₃(1.0 equiv), *n*-Bu₄NCl (1.0 equiv), DMF, 120 °C, 36 h.

^bSingle diastereomer was isolated.

^cIsolated yield of heterocycles **8** calculated per imine as the limiting reagent.