

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

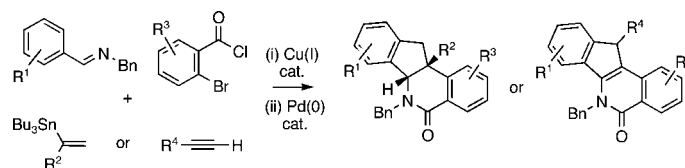
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ABSTRACT



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*-isoidolones (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.

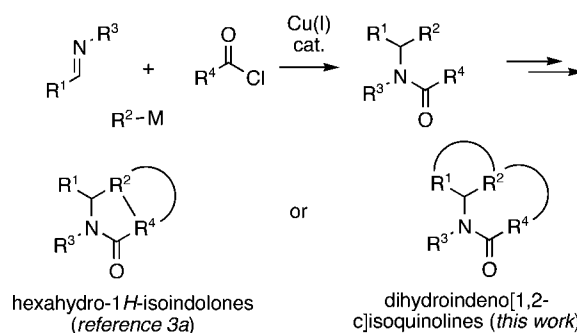


Figure 1. General strategy.

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

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(1) *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Trigg, D. J., Eds.; Elsevier: Amsterdam, Boston, 2007.

(2) Martin, S. F.; Sunderhause, J. D.; Dockendorff, C. *Org. Lett.* **2007**, 9, 4223.

(3) (a) Zhang, L.; Lushington, G. H.; Neuenswander, B.; Hershberger, J. C.; Malinakova, H. C. *J. Comb. Chem.* **2008**, 10, 285. (b) Zhang, L.; Malinakova, H. C. *J. Org. Chem.* **2007**, 72, 1484.

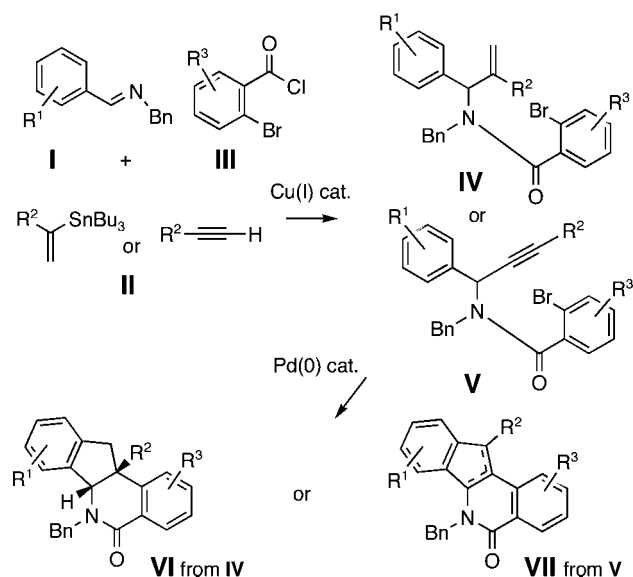
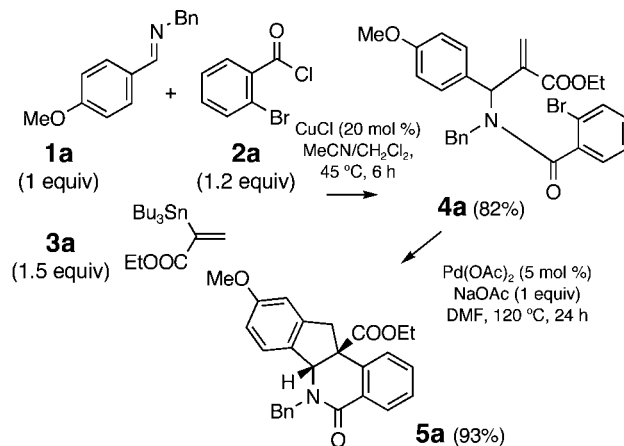


Figure 2. Strategy toward indenoisoquinolines.

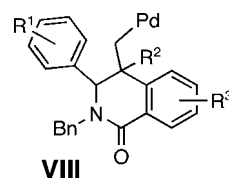
The method reported herein opens up a modular access to indenoisoquinolines and is well amenable to automation.

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 to 1.5 equiv⁸ and realize the coupling to imine **1a** and aryl 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) to 82% (with 20 mol % CuCl, Scheme 1).⁹ Next, the Pd-catalyzed cyclization of amide **4a** was explored, anticipating

Scheme 1. Protocol Utilizing an Isolated Amide



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

(4) Ryckebusch, A.; Garcin, D.; Lansiaux, A.; Goossens, J.-F.; Baldeyrou, B.; Houssin, R.; Bailly, C.; Henichart, J.-P. *J. Med. Chem.* **2008**, *51*, 3617. (b) Teicher, B. A. *Biochem. Pharmacol.* **2008**, *75*, 1262. (c) Antony, S.; Agama, K. K.; Miao, Z.-H.; Takagi, K.; Wright, M. H.; Robles, A. I.; Varticovski, L.; Nagarajan, M.; Morrell, A.; Cushman, M.; Pommier, Y. *Cancer Res.* **2007**, *67*, 10397.

(5) (a) D'Souza, D. M.; Kiel, A.; Herten, D.-P.; Rominger, F.; Müller, T. J. J. *Chem. Eur. J.* **2008**, *14*, 529. (b) Morrell, A.; Placzek, M.; Parnley, S.; Grella, B.; Antony, S.; Pommier, Y.; Cushman, M. *J. Med. Chem.* **2007**, *50*, 4388. (c) D'Souza, D. M.; Rominger, F.; Müller, T. J. J. *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. (e) Jagtap, P. G.; Baloglu, E.; Southan, G.; Williams, W.; Roy, A.; Nivorozhkin, A.; Landrau, N.; Desisto, K.; Saltzman, A. L.; Szabo, C. *Org. Lett.* **2005**, *7*, 1753. (f) Xiao, X.; Antony, S.; Kohlhaagen, G.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem.* **2004**, *12*, 5147. (g) Fox, B. M.; Xiao, X.; Antony, S.; Kohlhaagen, G.; Pommier, Y.; Staker, B.; Stewart, L.; Cushman, M. *J. Med. Chem.* **2003**, *46*, 3275. (h) Cho, W.-J.; Park, M.-J.; Imanishi, T.; Chung, B.-H. *Chem. Pharm. Bull.* **1999**, *47*, 900.

(6) Black, D. A.; Arndtsen, B. A. *J. Org. Chem.* **2005**, *70*, 5133.

(7) For the preparation of **3a** via hydrosilylation, see: Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. *Org. Lett.* **2008**, *10*, 861.

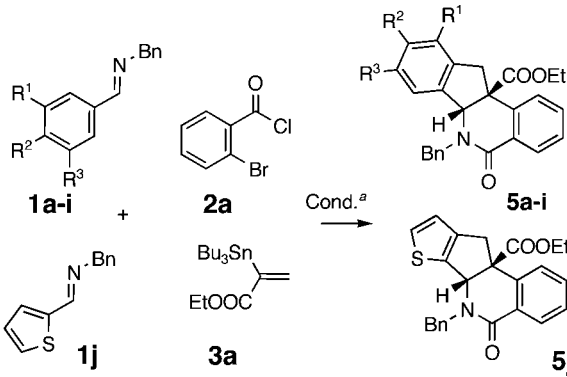
(8) Compare to our original method reported in ref 3a.

(9) 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.

(10) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2000**, *100*, 3009. (b) 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: (c) D'Souza, D. M.; Müller, T. J. J. *Chem. Soc. Rev.* **2007**, *36*, 1095.

(11) ¹H NMR analysis of the crude reaction mixtures indicated the presence of traces of a diastereomeric indenoisoquinoline. Isolation via chromatography followed by titration 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).

(12) (a) Jeffery, T. *Tetrahedron Lett.* **1985**, *26*, 2667. (b) Jeffery, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287.

Table 1. Angularly Substituted Indenoisoquinolines


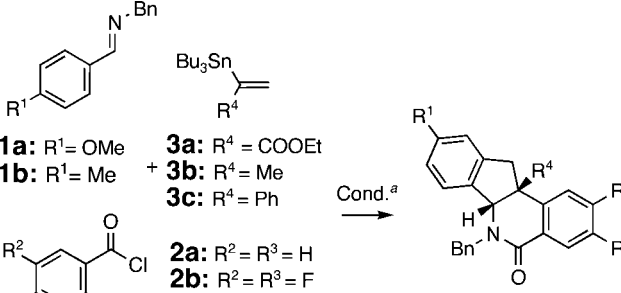
entry	R ¹	R ²	R ³	product ^b	yield ^c (%)
1	H	OMe	H	5a	75 (71) ^d
2	H	Me	H	5b	69
3	H	H	H	5c	67 (17) ^d
4	H	Cl	H	5d	49 (11) ^d
5	H	COOMe	H	5e	38
6	H	OMe	OMe	5f	77
7	H	-OCH ₂ CH ₂ O-	H	5g ^e	71
8	OMe	OMe	OMe	5h	64
9	H	NMe ₂	H	5i	59
10		thiophene-2-yl		5j	74

^a Method 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. ^b With one exception, a single diastereomer was isolated. ^c Isolated yield of heterocycles **5** obtained via Method A calculated per imine as the limiting reagent. ^d Yield 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. ^e Product was isolated as a 4:1 mixture of diastereomers (by ¹H NMR), the major diastereomer is shown.

1, Method A). The lower yields of the electronically deactivated chloro- and ester-substituted indenoisoquinolines **5d** and **5e** 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 aryl chlorides **2b,c** and vinylstannanes **3a** and **3b,c**¹³ bearing aliphatic (Me) and aromatic (Ph)

substituents. Indenoisoquinolines **5k–5o** were obtained in good yields (59–76%) over two steps (Table 2). Hetero-

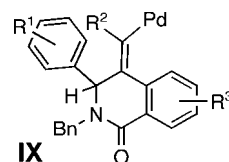
Table 2. Diversification of Additional Building Blocks


entry	R ¹	R ²	R ³	R ⁴	product ^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

^a Reaction conditions: (i) CuCl (20%), MeCN/CH₂Cl₂, 45 °C, 6 h, imine/acyl chloride/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. ^b Single diastereomer was isolated. ^c Isolated yield of heterocycles **5** calculated per imine as the limiting reagent.

cycles **5k–5o** 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**, aryl 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.

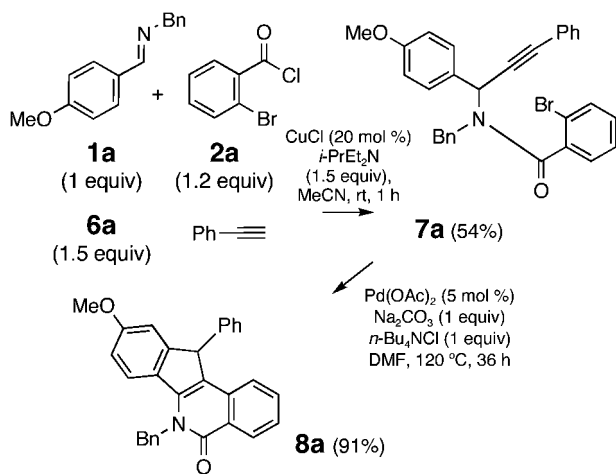


Indeed, the treatment of amide **7a** with Pd(OAc)₂ catalyst and Na₂CO₃/*n*-Bu₄NCl additive mixture for a prolonged time period (36 h at 120 °C in DMF) afforded the corresponding indenoisoquinoline **8a** in an excellent yield (91%) (Scheme

(13) For the preparation of the stannanes, see: Darwish, A.; Chang, J. M. *J. Org. Chem.* **2007**, *72*, 1507.

(14) The relative stereochemistry in heterocycle **5o** was established via ¹H NMR NOE study, and the structure of **5m** was assigned accordingly. For details see Supporting Information.

(15) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.

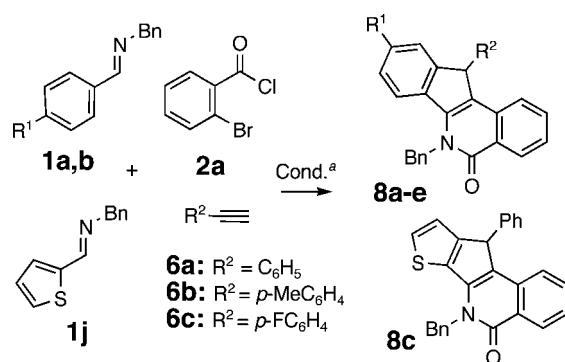
Scheme 2. Protocol Utilizing an Isolated Propargyl Amide

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 aryl chloride **2a** and aryl acetylenes **6a–6c** to provide indenoisoquinolines **8a–8e** 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

(16) Grigg, R.; Loganathan, V.; Sridharan, V. *Tetrahedron Lett.* **1996**, 37, 3399.

(17) 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 Supporting Information).

Table 3. Indenoisoquinolines with a Benzylic Substituent

entry	R ¹	R ² (aryl)	product ^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

^a Reaction conditions: (i) CuCl (20%), *i*-PrEt₃N (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. ^b Single diastereomer was isolated. ^c Isolated yield of heterocycles **8** calculated per imine as the limiting reagent.

modular strategy is particularly well suited for the construction of combinatorial libraries of indenoisoquinolines.

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

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