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

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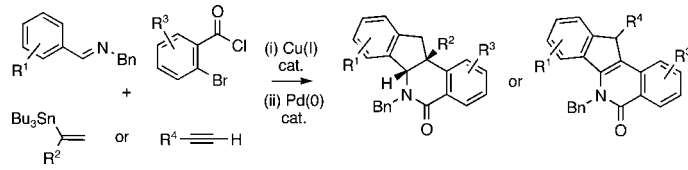
ABSTRACT



Copper-catalyzed coupling of imines, vinylstannanes, or alkynes and *o*-bromoaroyl 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 prevalance of *N*-heterocycles among established pharmaceutical agents[1] 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.

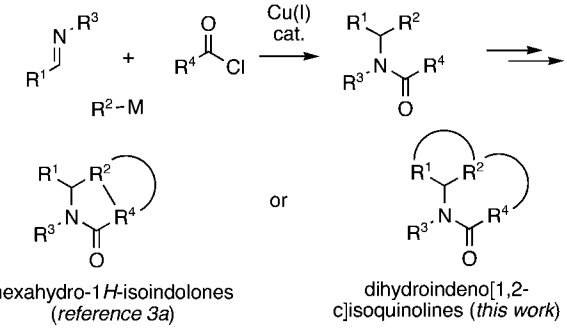


Figure 1. General strategy.

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]

† Undergraduate research participant (NSF-REU), Grinnell College.

(1) *Comprehensive Medicinal Chemistry II*; Taylor, J. B., Triggle, 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.

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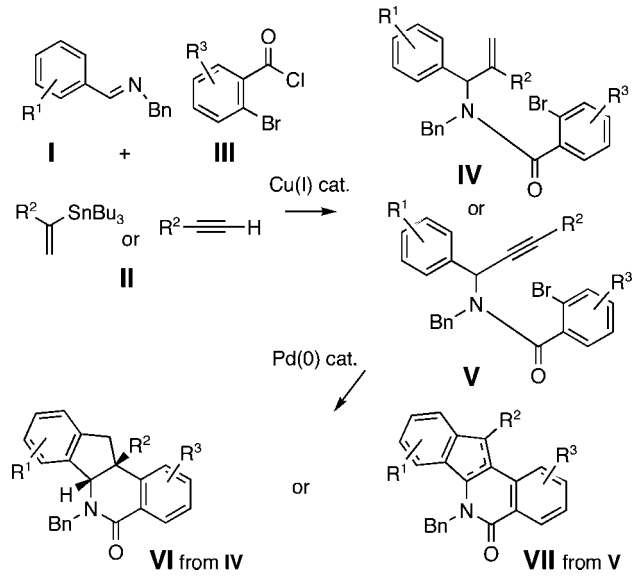
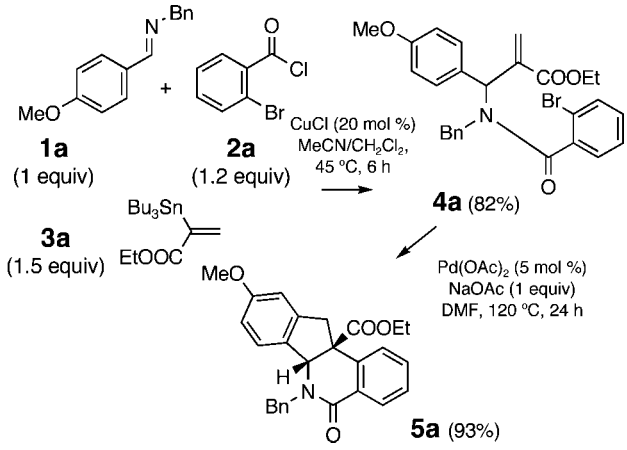


Figure 2. Strategy toward indenoisoquinolines.

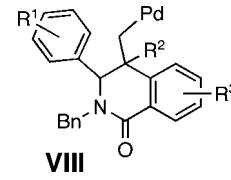
The method reported herein opens up a modular access to indenoisoquinolines and is well amenable to automation.

Initial studies were focused on extending the scope of the known Cu(I)-catalyzed coupling[6] to *o*-bromoaroyl 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 equiv[8] 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) 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 Na_2CO_3/*n*-Bu_4NCl applying modified Jeffery's conditions[12] (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** (R^2 = H) and **1d** (R^2 = 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.; Parmley, 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.; Kohlhagen, G.; Pommier, Y.; Cushman, M. *Bioorg. Med. Chem.* **2004**, *12*, 5147. (g) Fox, B. M.; Xiao, X.; Antony, S.; Kohlhagen, 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 hydrostannylation, 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.

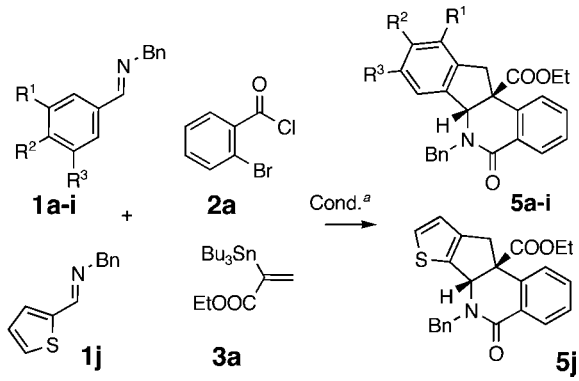
(9) Variations in the CuCl load and the excess of stannane **3a** in reactions under the conditions described in Scheme 1affected the yields of amide **4a**: (i) 20 mol % CuCl, 2.0 equiv **3a** gave **4a** in 80% yield; 20 mol % CuCl, 1.0 equiv **3a** gave **4a** in 62% yield; (iii) 10 mol % CuCl, 1.5 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) ^{1}H 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 asssigned 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



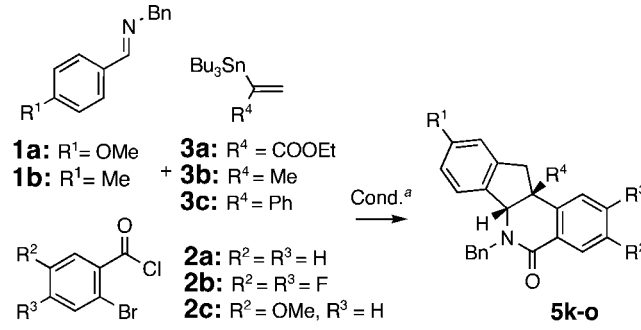
entry	R^1	R^2	R^3	product[b]	yield[c] (%)
1	H	OMe	H	**5a**	75 (71)[d]
2	H	Me	H	**5b**	69
3	H	H	H	**5c**	67 (17)[d]
4	H	Cl	H	**5d**	49 (11)[d]
5	H	COOMe	H	**5e**	38
6	H	OMe	OMe	**5f**	77
7	H	-OCH_2CH_2O-		**5g**[e]	71
8	OMe	OMe	OMe	**5h**	64
9	H	NMe_2	H	**5i**	59
10	thiophene-2-yl			**5j**	74

[a] Method A was used for all the entries: (i) CuCl (20%), MeCN/CH_2Cl_2, 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 Na_2CO_3 (1.0 equiv)/*n*-Bu_4NCl (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 aroyl 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

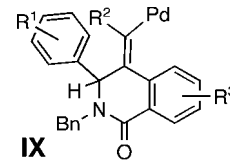


entry	R^1	R^2	R^3	R^4	product[b]	yield[c] (%)
1	Me	OMe	H	COOEt	**5k**	62
2	OMe	F	F	COOEt	**5l**	76
3	OMe	H	H	Me	**5m**	68
4	OMe	H	H	Ph	**5n**	59
5	Me	H	H	Me	**5o**	54

[a] Reaction conditions: (i) CuCl (20%), MeCN/ CH_2Cl_2, 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** (R^4 = 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** (R^4 = 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 Arndtsen[15] (Scheme 2). We envisioned that Pd-catalyzed intramolecular bisfunctionalization of the alkyne[16] 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.



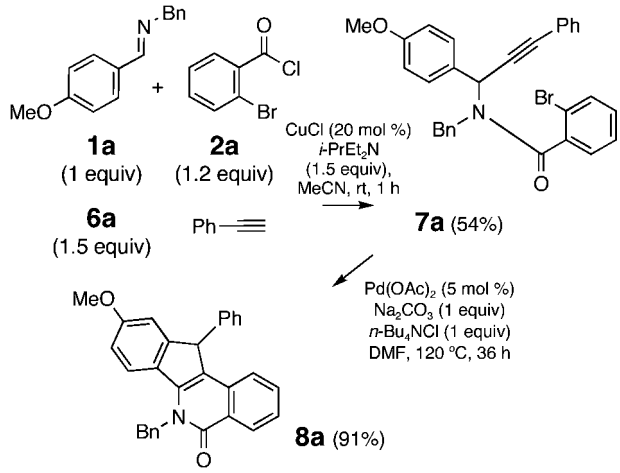
Indeed, the treatment of amide **7a** with $Pd(OAc)_2$ catalyst and Na_2CO_3/*n*-Bu_4NCl additive mixture for a prolonged time period (36 h at 120 °C in DMF) afforded the corresponding indenoisoquinoline **8a** in an excellent yield (91%) (Scheme

(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



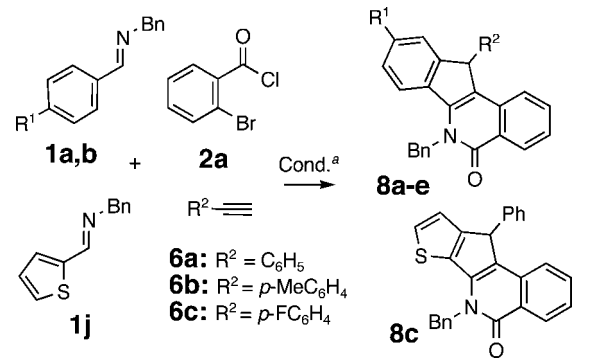
2). Ultimately, the isolation of amide **7a** was avoided, limiting the purification of the crude reaction mixtures to the removal of excess alkyne via filtration through a short plug of silica. The resulting crude product was directly subjected to Pd-catalysis, affording indenoisoquinoline **8a** in 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 aroyl 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 modular strategy is particularly well suited for the construction of combinatorial libraries of indenoisoquinolines.

(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 ^{1}H 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_6H_5-	**8a**	66
2	Me	C_6H_5-	**8b**	51
3	thiophene-2-yl	C_6H_5-	**8c**	68
4	OMe	p-$CH_3C_6H_4$-	**8d**	63
5	OMe	p-FC_6H_4-	**8e**	57

[a] Reaction conditions: (i) CuCl (20%), *i*-$PrEt_2N$ (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%), Na_2CO_3 (1.0 equiv), *n*-Bu_4NCl (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.

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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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