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Suzuki Cross-Coupling/Reductive Debenzyloxycarbonylation Sequence for the Syntheses of [*c*]Annulated Isoquinolines: Application for the Syntheses of Pancratistatin-like Isoquinolines

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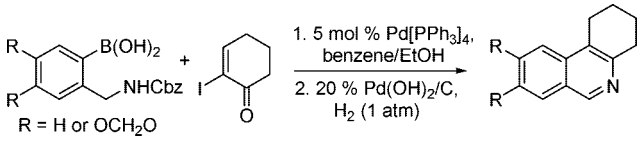
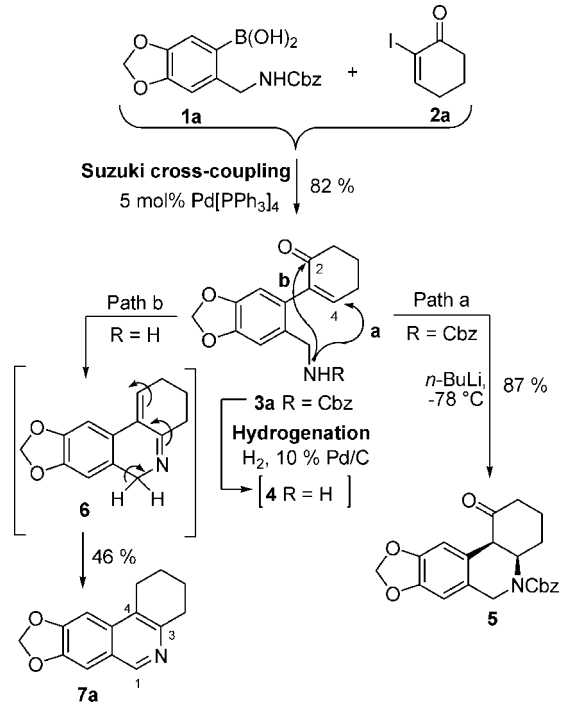


A two-step strategy involving Suzuki cross-coupling of boronic acids with a diverse array of α-iodoenones followed by hydrogenation is developed for the construction of [*c*]annulated isoquinolines. This mild and efficient procedure is also applied to the synthesis of highly oxygenated isoquinolines.

Isoquinolines and their dihydro and tetrahydro derivatives are the structural component of several biologically active natural alkaloids.[1] They are also known to serve as important molecular scaffolds for the syntheses of complex natural products.[2] Over the last two decades, there has been growing interest to develop mild and efficient syntheses of isoquinolines against tedious and conventional approaches.[3] Research toward this end has promoted the exploration of heteroannulation of aldimines with internal alkynes for the construction of 3,4-disubstituted isoquinolines employing stoichiometric amounts of palladacycles.[4] Although this approach was initially thought to be efficient but expensive, development of catalytic version[5a] subsequently, has produced diverse array of isoquinolines substituted with aryl,[5b−d] alkyl,[5b−d] aroyl,[5e] alkenyl,[5f] and fluoroalkyl[5g] at the 3,4-positions. Later, nickel-catalyzed annulations of the same starting materials were also developed which were claimed to make the process more efficient, mild, and highly regioselective.[6] The transition-metal chemistry focusing on isoquinoline syntheses has further been expanded by exploring other elements (Zr,[7] Rh,[8] and Cu[9]) of this series for their usefulness. Other important strategies in this regard concern the photochemical-mediated cascade iminyl radical addition/intramolecular cyclization with internal alkyne[10] and organolithium addition to 2-(2-methoxyethenyl)benzonitrile.[11]

SCHEME 1. Two Different Modes of Aza-Interactions



While exploring the strategy for the construction of alkaloid skeleton **5** through base-induced intramolecular aza-Michael reaction (*n*-BuLi, THF/HMPA, −78 °C) of **3a** (Scheme 1, path a), we also investigated the mode of interaction of the corresponding free amine of this substrate. Thus, reductive removal of benzyl carbamate (1 atm of H_2, 10% Pd/C) from **3a** produced an isoquinoline **7a** in 46% yield, possibly by involving intermediate **6** (path b).

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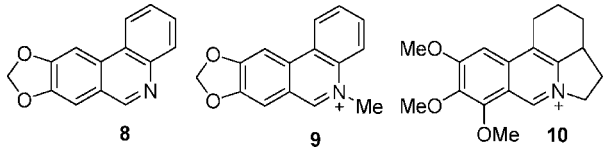
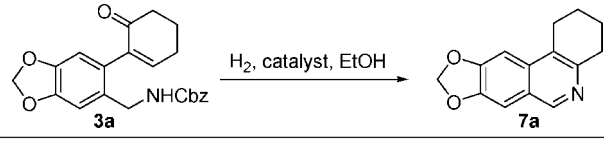


FIGURE 1. Few naturally occurring annulated isoquinolines.

TABLE 1. Optimization of Conditions for Reductive Debenzyloxycarbonylation



entry	catalyst[a]	pressure (atm)	time (h)	yield (%)
1	10% Pd/C	1	28	46[b]
2	10% Pd/C	4	12	52
3	W-2 Raney Ni	1	12	no reaction
4	W-2 Raney Ni	15[c]	12	39
5	20% $Pd(OH)_2/C$	1	8	96

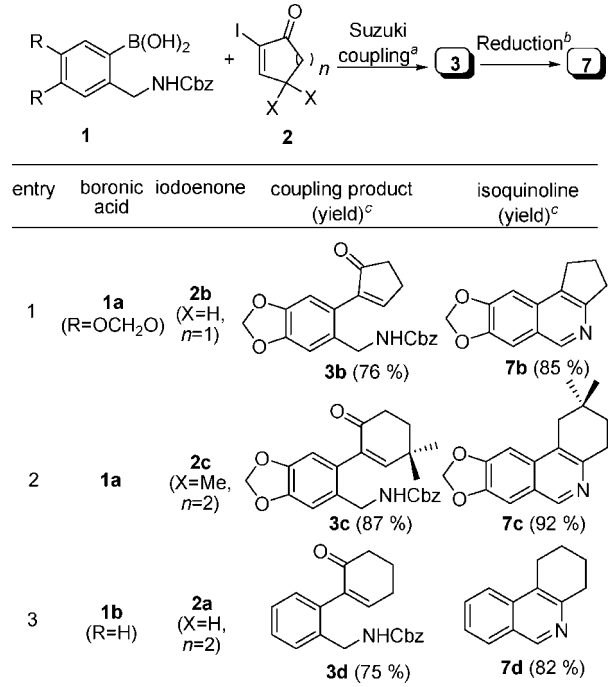
[a] All hydrogenations were performed with 20 mol % of the catalysts consistently. [b] **3a** was recovered in 48% yield. [c] Hydrogenation was conducted in a Parr reactor.

This unexpected observation, led us to explore the utility of this reaction for the syntheses of annulated isoquinilines as, to the best of our knowledge, there was no straightforward and easy approach to access annulated isoquinolines. We report herein a mild two-step synthesis of [*c*]annulated isoquinolines involving Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence (Scheme 1) between **1a** and iodoenone **2a**.

[*c*]Annulated isoquinolines of type **7a** are valuable synthetic precursor in the synthesis of trispheridine (**8**),[12] a naturally occurring phenanthridine alkaloid from the Amaryllidaceae plant family (Figure 1). Palladium catalyzed dehydrogenation of **7a** in refluxing xylene have been reported to produce **8**.[13] However, **7a** was synthesized via μ-wave assisted aza-6π-electrocyclization of 6-cyclohexenyl piperonal *O*-methyl oxime. Compound **7a** also shares close structural relationship with other alkaloids such as bicolorine (**9**)[14] and roserine (**10**).[15]

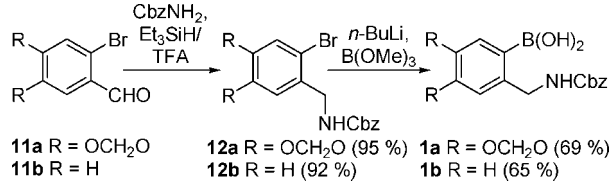
Driven by the easy access of annulated isoquinoline **7a** through the above route, we examined the in situ generation of free amine by the reductive removal of benzyloxycarbonyl moiety of **3a** to obtain the maximum yield of **7a**, and the results of the optimization studies are listed in Table 1. During the course of the hydrogenation, the conversion of **3a** was observed to be incomplete in the presence of catalytic 10% Pd/C under 1 atm of hydrogen and gave only 46% isolated yield of **7a** even after 28 h of the reaction. Therefore, we raised the hydrogen pressure to 4 atm, and although the reaction was complete in 12 h, the yield of **7a** did not improve significantly due to the formation of several undesired products. It was also noticed that **3a** remained inactive to Raney Ni mediated hydrogenation at 1 atm pressure of hydrogen but produced a complex reaction mixture along with required isoquinoline **7a** in small amounts (39%, entry 4) when the reaction was conducted at high pressure (15 atm). Pleasingly, the use of catalytic 20% $Pd(OH)_2/C$ cleanly effected complete conversion of **3a** at atmospheric pressure of the hydrogen and afforded **7a** in 96% yield (8 h, entry 5).

TABLE 2. Syntheses of Isoquinolines Using Suzuki Cross-Coupling/Reductive Debenzyloxycarbonylation Sequence



[a] Suzuki cross-coupling reactions[16] were carried out by refluxing (80 °C) a mixture of **1a**,**b** (1.0 mmol) and **2a**−**c** (1.0 mmol) along with 5 mol % of $Pd[PPh_3]_4$ in benzene/ethanol (2:1, 15 mL) for 1−2 h. [b] Freshly purified **3b**−**d** were reduced in ethanol using optimized hydrogenation conditions defined in entry 5, Table 1. [c] Isolated yield. compound **7d** is previously known.[17]

SCHEME 2. Access of Requisite Boronic Acids (1)



The generality of the Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence was evaluated by synthesizing isoquinolines **7b**−**d**. The corresponding coupling partners (**1a**,**b** and **2a**−**c**), coupling products (**3b**−**d**), and respective yields of these reactions are summarized in Table 2.

The requisite starting materials of this reaction sequence were easily obtained through established procedures. While α-iodoenones (**2**) were readily obtained using Johnson's iodination protocol,[18] the other coupling partner (**1**) was easily synthesized from **12** using lithiation followed by boronation protocol (Scheme 2). The requisite bromide **12** were synthesized from the corresponding aldehyde **11** adopting Dubé's reductive N-alkylation of carbamate strategy.[19] It should be noticed that

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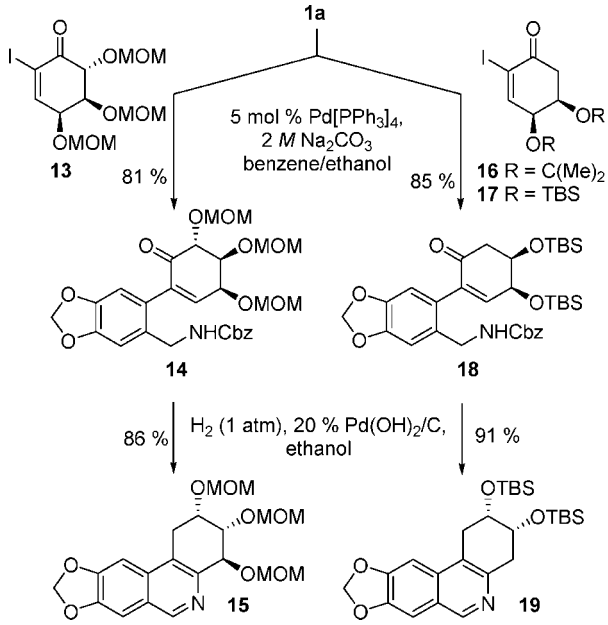
SCHEME 3. Syntheses of Oxygenated Isoquinolines



most of the *o*-bromo aldehydes **11** are commercially available for the syntheses of various aromatic substituted boronic acids.

Since the success of any methodology is defined by its application to the syntheses of complex molecule, we investigated the efficacy of this reaction sequence for the synthesis of **15**. Highly oxygenated α-iodoenone **13** was derived in 29% overall yield from the commercially available D-(−)-quinic acid.[20] The Suzuki cross-coupling of **13** with **1a** delivered **14** in 81% yield (Scheme 3), which upon hydrogenation afforded trialkoxycyclohexene annulated isoquinoline (**15**, 86%). It should be mentioned that oxygenated isoquinoline of this type has not been synthesized previously and would be difficult to obtain via classical approaches, as known approaches utilized normally strong acidic conditions. In order to demonstrate further the application of our methodology for the synthesis of isoquiniline of this series (e.g., **19**), we initially attempted the preparation of required hydrogenation precursor by coupling iodoenone **16**[21] with **1a**. However, it was disappointing to note that it did not produce the expected coupling product and gave some completely aromatized product, possibly by *β*-alkoxy elimination followed by aromatization under the basic reaction conditions. Therefore, we employed corresponding silyl protected iodoenone **17**[22] which was well suited to obtain **18** as well as isoquinoline **19** (77% combined yield).

Removal of the protecting groups from **15** as well as **19** using 6 N HCl in MeOH afforded isoquinolines **20** [87%, mp 239−241 °C, $[\alpha]^{27}_D$ +48.5 (*c* 0.5, DMF)] and **21** [91%, mp 286−291 °C, $[\alpha]^{27}_D$ −43.1 (*c* 0.5, DMF)], respectively (Figure 2). These isoquinolines (**20** as well as **21**) bear considerable structural similarity with 7-deoxypancratistatin (**22**),[23] a naturally occurring and promising anticancer agent from plants of the Amaryllidaceae family. Therefore, we also screened both these

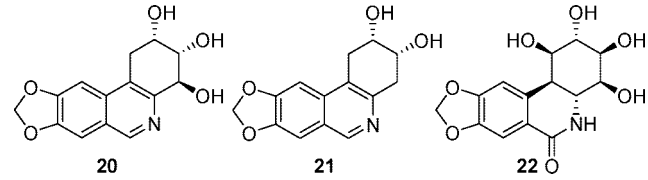


FIGURE 2. Pancratistatin-like isoquinolines.

compounds (**20** and **21**) for their anticancer activity against murine P388 lymphocytic leukemia and two other human cancerous cell lines—MCF-7 (breast adenocarcinoma) and THP-1 (promonocytic leukemia). However, they exhibited >100-fold less activity (IC_{50} values in the order of >40 μg/mL) in these cell lines in comparison to natural **22**.

In summary, we have developed a mild, two-step strategy to synthesize [*c*]annulated isoquinolines involving Suzuki cross-coupling/reductive debenzyloxycarbonylation sequence. The practical viability of the strategy for isoquinoline synthesis is appropriately acknowledged by the catalytic nature and operational simplicity of both the steps involved and also by the easy accessibility of starting materials. The method was successfully applied to the syntheses of range of both substituted and unsubstituted cycloalkene-fused isoquinolines.

Experimental Section

General Procedure for Suzuki Cross-Coupling Reactions. To a solution of iodoenone (**2/13/17**, 2 mmol) in benzene (20 mL) was added a predissolved solution of boronic acid (**1**, 2 mmol) in ethanol (10 mL), aqueous 2 M Na_2CO_3 (5 mL), and a catalytic amount of $Pd[PPh_3]_4$ (0.1 mmol). The vigorously stirring yellow solution was heated in an oil bath set at 65−80 °C for 20 min−2 h under an atmosphere of argon. The dark reddish mixture produced was cooled, diluted with water (15 mL), and extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue obtained was purified by column chromatography to afford **3/14/18**.

Benzyl (6-(6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (3a): yield 82%, colorless solid; mp 123−124 °C; IR ($CHCl_3$) 2947, 1712, 1694, 1504, 1230, 1040 cm^{-1}; ^1H NMR (benzene-d_6, 500 MHz) δ 7.32 (s, 1H), 7.31 (s, 1H), 7.21−7.11 (m, 3H), 7.00 (s, 1H), 6.52 (s, 1H), 6.40 (t, *J* = 4.1 Hz, 1H), 5.54 (bs, 1H), 5.43 (s, 2H), 5.16 (s, 2H), 4.21 (bs, 2H), 2.24 (t, *J* = 6.4 Hz, 2H), 1.83 (m, 2H), 1.54 (quintet, *J* = 6.4 Hz, 2H); ^{13}C NMR (benzene-d_6, 125 MHz) δ 197.6, 156.5, 149.4, 148.0, 147.2, 140.6, 137.6, 131.7, 130.3, 128.5, 128.3, 127.9, 110.4, 109.4, 101.1, 66.5, 43.3, 38.6, 26.1, 22.8; MS (ESI) 402 (M + Na^+, 55), 272 (55), 258 (52), 244 (100). Anal. Calcd for $C_{22}H_{21}NO_5$: C, 69.64; H, 5.58; N, 3.69. Found: C, 69.48; H, 5.51; N, 3.79.

Benzyl (6-((3*S*,4*S*,5*R*)-3,4,5-tris(methoxymethoxy)-6-oxocyclohex-1-enyl)benzo[*d*][1,3]dioxol-5-yl)methylcarbamate (14): yield 81%; $[\alpha]^{27}_D$ +69.5 (*c* 1.16, $CHCl_3$); IR (neat) 2895, 1730, 1713, 1693, 1504, 1485, 1371, 1240, 1042 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 7.32 (s, 5H), 6.90 (s, 1H), 6.81 (d, *J* = 3.7 Hz, 1H), 6.51 (s, 1H), 5.93 (s, 2H), 5.39 (bs, 1H), 5.07 (s, 2H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.81−4.70 (m, 6H), 4.50 (d, *J* = 7.6 Hz, 1H), 4.27 (dd, *J* = 7.5, 2.9 Hz, 1H), 4.02 (bs, 2H), 3.41 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.8, 156.2, 147.9, 146.8, 145.1, 139.3, 136.6, 131.1, 128.2, 127.8, 127.5, 109.6, 109.3, 101.2, 96.9, 96.8, 96.4, 77.2, 76.9, 71.4, 66.5, 55.9, 55.6, 55.5, 42.7; MS (ESI) 583 (MH + Na^+, 29), 582 (M + Na^+, 100), 577 (M + NH_4^+, 12), 560 (13). Anal. Calcd for $C_{28}H_{33}NO_{11}$: C, 60.10; H, 5.94; N, 2.50. Found: C, 60.24; H, 5.76: N, 2.43.

General Procedure for the Syntheses of Isoquinolines. A solution of Suzuki cross-coupling product (**3/14/18**, 0.5 mmol) in ethanol (25 mL) was hydrogenated at atmospheric pressure in the

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(22) (a) Iodoenone **23** has been synthesized from the corresponding enone utilizing Johnson's iodination protocol[18] in quantitative yield. For enone synthesis, see: (b) Pandey, G.; Murugan, A.; Balakrishnan, M *Chem Commun.* **2002**, *624* (23), 22.

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presence of 20% $Pd(OH)_2$ on charcoal (50 mg). The reaction was monitored for its starting material consumption (TLC analysis, 9−14 h). After complete disappearance of starting material, the reaction mixture was passed through a short pad of Celite. The solvent was removed by rotary evaporation and the residue was purified by column chromatography to produce **7/15/19**.

1,2,3,4-Tetrahydro[1,3]dioxolo[4,5-*j*]phenanthridine (7a): yield 96%, colorless solid; mp 89−91 °C; IR ($CHCl_3$) 3053, 2306, 1460, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.73 (s, 1H), 7.07 (s, 2H), 6.02 (s, 2H), 2.98 (s, 2H), 2.87 (s, 2H), 1.88 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 150.8, 149.2, 147.7, 147.0, 133.6, 124.2, 123.8, 103.5, 01.3, 98.5, 32.5, 25.1, 23.0, 22.7; MS (ESI) 250 ($M + Na^+$, 100). Anal. Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.92; H, 5.68; N, 6.26.

(2*S*,3*S*,4*S*)-2,3,4-Tris(methoxymethoxy)-1,2,3,4-tetrahydro[1,3]dioxolo[4,5-*j*]phenanthridine (15): yield 86%; $[\alpha]^{27}_D$ +118.1 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$) 3433, 2360, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.88 (s, 1H), 7.21 (s, 1H), 7.15 (s, 1H), 6.08 (d, J = 2.3 Hz, 2H), 5.12 (d, J = 6.8 Hz, 1H), 4.92 (d, J = 3.5 Hz, 1H), 4.90−4.78 (m 4H), 4.73 (d, J = 6.8 Hz, 1H), 4.50−4.40 (m, 2H), 3.47 (s, 3H), 3.46 (s, 3H), 3.32 (dd, J = 16.0, 6.3 Hz, 1H), 3.30 (s, 3H), 3.15 (dd, J = 16.0, 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.3, 149.4, 148.2, 144.7, 133.1, 125.1, 123.9, 103.7, 101.7, 99.3, 97.2, 96.6, 95.4, 78.8, 75.4, 71.3, 55.9, 55.5, 55.54, 27.6; MS (ESI) 408 (MH^+, 100), 228 (68), 214 (66). Anal. Calcd for $C_{20}H_{25}NO_8$: C, 58.96; H, 6.18; N, 3.44. Found: C, 58.92; H, 6.24; N, 3.32.

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Supporting Information Available: Experimental procedures, characterization details, and copies of ^1H NMR and ^{13}C NMR spectra of compounds **1**−**3**, **5**, **7**, **12**−**15**, and **17**−**21**. This material is available free of charge via the Internet at http://pubs.acs.org.

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