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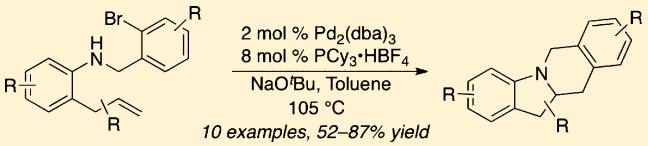
Synthesis of Substituted Tetrahydroindoloisoquinoline Derivatives via Intramolecular Pd-Catalyzed Alkene Carboamination Reactions

Jeremiah Alicea and John P. Wolfe*

Department of Chemistry, University of Michigan, 930 North University Avenue, Ann Arbor, Michigan 48109-1055, United States

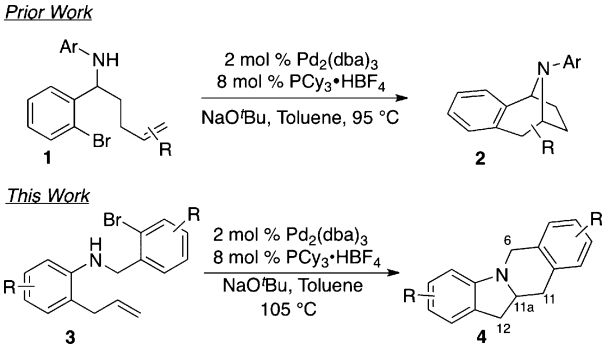
Supporting Information

ABSTRACT: Intramolecular Pd-catalyzed alkene carboamination reactions of substituted 2-allyl-*N*-(2-bromobenzyl)anilines are described. The substrates for these reactions are generated in two steps from readily available 2-allylanilines and 2-bromobenzaldehyde derivatives. The transformations afford substituted tetrahydroindoloisoquinolines, an uncommon class of fused bicyclic heterocycles, in good yield. The mechanism of these transformations is described, and a model that accounts for the observed product stereochemistry is proposed.



Many interesting biologically active molecules and natural products contain fused polycyclic heterocycles, and the development of methods for the generation of these compounds has been of longstanding interest.[1] In addition, new strategies that provide access to scaffolds that are uncommon or not easily obtained through existing routes have the potential to lead to interesting classes of compounds whose biological properties have yet to be explored.[2] For example, tetrahydroindoloisoquinoline derivatives **4** (Scheme 1) resemble scaffolds found in alkaloid natural products, but are a class of heterocycles that have rarely been prepared. Only one ring-forming method for the synthesis of tetrahydroindoloisoquinolines **4** has been described, which involved treatment of the HI salt of an *N*-methyl-3-benzylisoquinoline derivative with chloranil followed by subsequent *N*-demethylation.[3] A few transformations have been used to generate related compounds bearing carbonyl groups at C6, C11, or C12 including intramolecular aldol condensations, intramolecular Friedel–Crafts reactions, or Cu-mediated intramolecular C–H functionalization/alkene carboamination reactions of *N*-benzoyl-2-allylaniline derivatives. However, use of these strategies to access nonoxygenated derivatives such as **4** would require an additional reduction step.[4]

Scheme 1. Synthesis of Polycyclic Heterocycles via Pd-Catalyzed Alkene Carboamination



We have previously reported a method for the construction of benzo-fused tropane derivatives **2** via intramolecular Pd-catalyzed alkene carboamination reactions of 2-(2-bromophenyl)pent-4-enylamine derivatives **1** (Scheme 1).[5,6] These transformations generate both a C–N bond and a C–C bond during the ring-forming event and afford the desired products in good chemical yield with excellent stereocontrol. We reasoned that analogous transformations of related substrates in which the 2-bromoaryl unit was tethered to the N atom rather than attached to the α-carbon could provide access to fused bicyclic heterocycles. For example intramolecular alkene carboamination reactions of substrates such as **3** should directly afford tetrahydroindoloisoquinoline derivatives **4**,[7,8] and this route could allow for straightforward installation of substituents at C6, C11, C11a, or C12 through modification of the substrate.

To explore this hypothesis, the substrates **3** required for these experiments were prepared via two-step reductive amination between 2-bromobenzaldehyde derivatives **6** and 2-allylanilines **5** (Scheme 2). Most of the aldehydes were obtained from commercial sources, and the 2-allylanilines were typically generated via aza-Claisen rearrangement of the corresponding *N*-allylaniline.[9] Condensation of the aniline with the aldehyde followed by reduction with $LiAlH_4$ provided **3** in moderate to good yield. This concise and modular approach allowed for the facile generation of substrates bearing substituents on either aryl ring, on the alkene, at the benzylic position, or at the allylic position.

In initial studies we focused on the transformation of **3a** to **4a** (Table 1, entry 1), and the $Pd_2(dba)_3/PCy_3$ catalyst system that provided optimal results in tropane-forming reactions (Scheme 1) afforded the desired product **4a** in 85% yield. A

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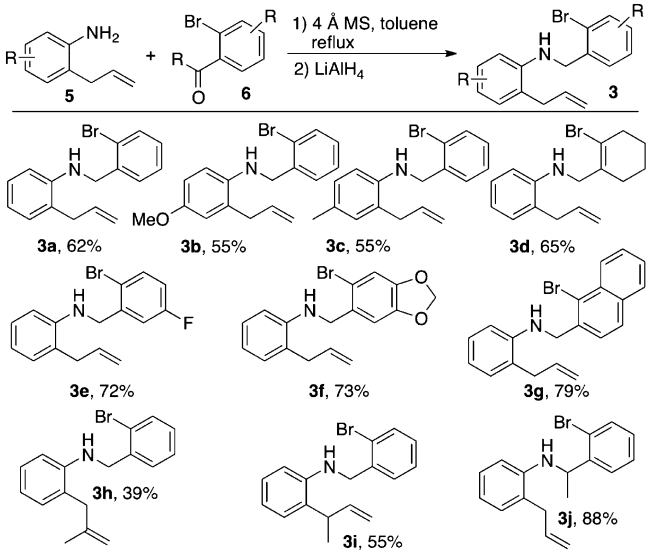
Scheme 2. Synthesis of Substrates



brief examination of other palladium sources and phosphine ligands did not lead to further improvement in the yield of this transformation, so we proceeded to explore the scope of these reactions. As shown in Table 1, the presence of fluorine atoms, alkoxy groups, or alkyl groups on either aromatic ring was tolerated. In addition, the sterically hindered 1-bromonaphthalene derived substrate **3g** was converted to **4g** in good yield (80%, entry 7). The conversion of an alkenyl bromide substrate (**3d**) to a polycyclic product (**4d**) was also successful, although the yield of this transformation was modest (55%, entry 4).

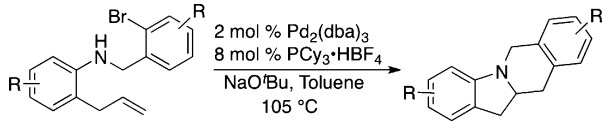
Substrate **3h**, which contains a methyl group on the internal alkene carbon atom was converted to **4h** in good yield (entry 8).[10] The reaction of substrate **3i** bearing an allylic methyl group provided **4i** in good yield and high diastereoselectivity (entry 9). In contrast, the transformation of substrate **3j** to **4j** provided a 2:1 mixture of diastereomers (entry 10), and competing intramolecular Heck arylation of this substrate was a significant problem.[11]

The mechanism of the tetrahydroindoloisoquinoline forming reactions is likely similar to that of other Pd-catalyzed alkene carboamination reactions of aryl halides (Scheme 3).[6] Oxidative addition of the aryl bromide to the Pd(0) complex generated in situ from $Pd_2(dba)_3$ and PCy_3 would provide **7**, which can react with NaO^{t}Bu to afford palladacyclic amido complex **8**. *Syn*-migratory insertion of the alkene into the Pd–N bond of **8** would provide **9**,[12] which upon reductive elimination would yield the observed product.

The competing Heck arylation[13] of substrate **3j**, which affords **12**, appears to be due to the presence of the methyl group at the benzylic position of the substrate. This substituent may slow the rate of Pd–N bond formation in the conversion of **7** to **8**, or the conversion of **7** to **8** may be reversible and the rate of alkene carbopalladation from Pd-alkene complex **10** (Scheme 4) could be close to the rate of conversion of **8** to **9** for this substrate.

The stereoselectivity or lack thereof in the reactions of **3i** and **3j** likely arises during the alkene aminopalladation step of the catalytic cycle, and in the conversion of **3i** to **4i** the alkene insertion step may proceed via transition state **13**, in which the allylic methyl group is in a pseudoequatorial position and A$^{(1,3)}$ strain between the alkene and the methyl group is minimized (Scheme 5). In contrast in the reaction of **3j** two possible transition states for aminopalladation (**14** and **15**) may be relatively close in energy, which leads to poor selectivity.

Table 1. Intramolecular Pd-Catalyzed Alkene Carboamination Reactions[a]



entry	substrate	product	yield (%)[b]
1	**3a**	**4a**	85
2	**3b**	**4b**	68
3	**3c**	**4c**	81
4	**3d**	**4d**	55
5	**3e**	**4e**	87
6	**3f**	**4f**	72
7	**3g**	**4g**	80
8	**3h**	**4h**	80
9	**3i**	**4i**	75 (18:1 dr)
10	**3j**	**4j**	52[c] (2:1 dr)

[a]Conditions: 1.0 equiv of substrate, 2.0 equiv of NaO^{t}Bu, 2 mol % $Pd_2(dba)_3$, 8 mol % PCy_3·HBF_4, toluene (0.1 M), 105 °C. [b]Isolated yields (average of two or more experiments). [c]This compound contained ca. 25% of an inseparable impurity tentatively assigned as 6-methyl-11-methylene-5,6,11,12-tetrahydrodibenzo[*b*,*f*]azocine, which results from competing intramolecular Heck arylation of the substrate.

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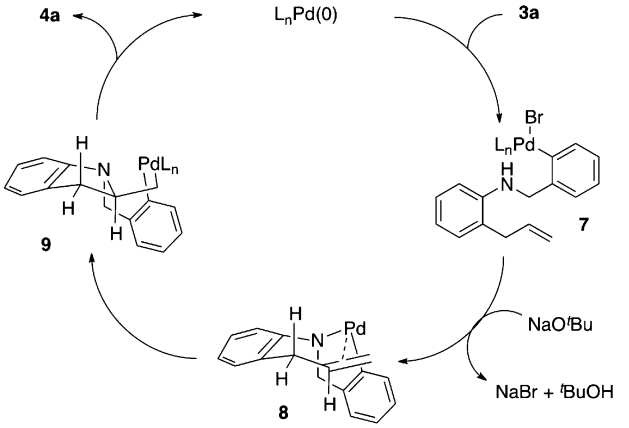
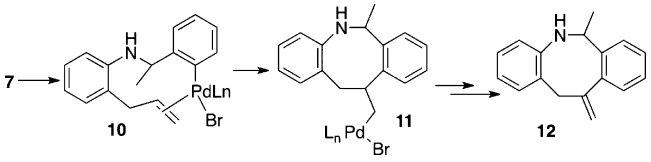
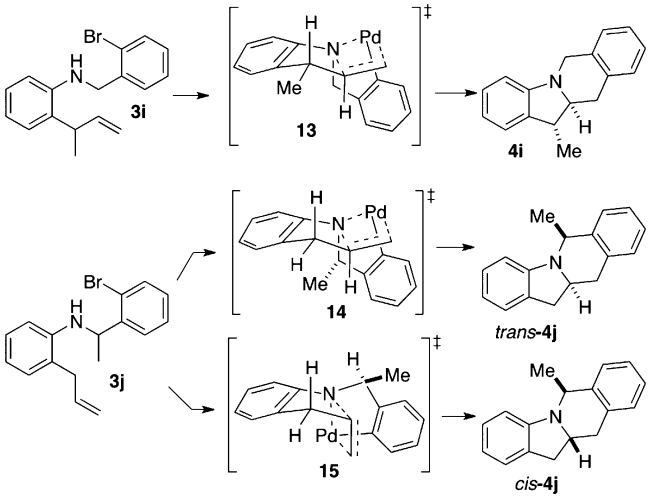
Scheme 3. Catalytic Cycle



Scheme 4. Formation of Heck Arylation Side Product



Scheme 5. Transition States for the Conversion of 3i to 4i and 3j to 4j



In conclusion, we have illustrated that the construction of tetrahydroindoloisoquinoline derivatives can be achieved using a concise strategy (four steps from commercially available materials) that employs an intramolecular Pd-catalyzed alkene carboamination reaction for generation of two rings, a C−C bond, and a C−N bond. This route allows for the construction of heterocyclic products bearing substituents on either aromatic ring, or at the 6, 11a, or 12 positions, and provides straightforward access to an uncommon class of heterocycles that have been generated by only a few other methods.

EXPERIMENTAL SECTION

General Considerations. All reactions were carried out under a nitrogen atmosphere in oven- or flame-dried glassware. All catalysts and reagents were obtained from commercial sources and were used without further purification with the exception of $BF_3{\cdot}OEt_2$, which was purified by distillation from CaH_2. *N*-Allyl-4-methylaniline,[11] 2-allyl-4-methylaniline,[14] 2-allylaniline,[9] 2-bromocyclohex-1-ene-1-carbaldehyde,[15] and 2-(but-3-en-2-yl)aniline[5] were prepared according to published procedures. Toluene and diethyl ether were purified using a GlassContour solvent system. Structural and stereochemical assignments were made on the basis of 2-D COSY, HSQC, and NOESY experiments. Ratios of diastereomers were determined by ^{1}H NMR analysis. High resolution ESI mass spectra were acquired using an instrument equipped with at TOF mass analyzer, and high resolution EI mass spectra were acquired using an instrument equipped with a magnetic sector mass analyzer. Yields refer to isolated yields of compounds estimated to be ≥95% pure as determined by ^{1}H NMR analysis unless otherwise noted. The yields reported in the Supporting Information describe the result of a single experiment, whereas the yields reported in Scheme 2 and Table 1 are average yields of two or more experiments. Thus, the yields reported in the Supporting Information may differ from those shown in Scheme 2 and Table 1.

2-Allyl-4-methoxyaniline. A thick-walled glass pressure tube equipped with a stir bar was sealed with a septum. The pressure tube was flame-dried and cooled under a vacuum and then purged with nitrogen. The flask was charged with *N*-allyl-4-methoxyaniline (2.5 g, 15.2 mmol) and xylenes (30.5 mL). The solution was cooled to 0 °C, $BF_3{\cdot}OEt_2$ was added dropwise, and the resulting solution was then allowed to warm to room temperature. The septum was removed, the pressure tube was replaced with a Teflon screw cap, the tube was immersed in a 170 °C oil bath, and the reaction mixture was allowed to stir for 2 h. The mixture was then cooled to room temperature, and 1 M NaOH (15 mL) was added. The resulting mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuo. The crude product was purified via flash chromatography on silica gel using 5% ethyl acetate:hexanes as the eluent to afford 870 mg (35%) of the title compound as an orange oil: ^{1}H NMR (700 MHz, $CDCl_3$) 6.66−6.62 (m, 3 H), 5.97−5.91 (m, 1 H), 5.13−5.08 (m, 2 H), 3.74 (s, 3 H), 3.40 (s, br, 2 H), 3.28 (d, J = 5.6 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) 152.9, 138.3, 135.7, 125.7, 116.9, 116.2, 116.0, 112.7, 55.7, 36.6; IR (film) 3357, 1500 cm^{-1}; MS (ESI+) 164.1071 (164.1070 calcd for $C_{10}H_{13}NO$, M + H$^+$).

2-(2-Methylallyl)aniline.[16] A flame-dried flask equipped a stir bar was cooled under a vacuum and then purged with nitrogen. This flask was charged with 2-iodonitrobenzene (3.6 g, 14.5 mmol) and THF (58 mL). The resulting solution was cooled to −40 °C in a MeCN/$CO_{2(s)}$ bath, and then a solution of PhMgBr (16 mL, 16.00 mmol, 1 M in THF) was added dropwise. The resulting mixture was stirred at −40 °C for 5 min, and then a solution of CuCN·2LiCl (29 mL, 29 mmol, 1 M in THF) was added dropwise. The reaction mixture was stirred at −40 °C for 10 min, and then 2-methylallyl bromide (2.4 g, 17.5 mmol) was added dropwise. The mixture was stirred at −40 °C for 1 h, and then the reaction was quenched with NH_4Cl (50 mL) and transferred to a separatory funnel. Water (50 mL) was added, the layers were separated, and the aqueous layer was extracted with EtOAc (2 × 50 mL). The organic layers were then combined, washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel using 5% ethyl acetate:hexanes as the eluent to yield slightly impure 2-(2-methylallyl)nitrobenzene (1.8 g, 70% yield), which was carried on to the next step without further purification.

A flame-dried flask equipped with a stir bar was cooled under a vacuum, purged with nitrogen, and charged with 2-(2-methylallyl)-nitrobenzene (1.8 g, 10 mmol) and EtOH (67 mL). The resulting mixture was stirred at rt until the 2-(2-methylallyl)nitrobenzene was completely dissolved, then powdered zinc (9.9 g, 151 mmol) and AcOH (8.6 mL, 151 mmol) were added. The resulting mixture solution was stirred at rt for 1 h and then was filtered through Celite, and the Celite was washed with Et_2O. The organic solutions were combined and concentrated in vacuo. The crude product was purified via flash chromatography on silica gel using 2−5% ethyl acetate:hexanes as the eluent to afford 1.16 g (54%) of the title compound as a yellow oil that contained ca. 10% of an unknown aromatic impurity. Data are for the major product: ^{1}H NMR (400 MHz, $CDCl_3$) 7.09−7.02 (m, 2 H), 6.74 (t, J = 7.6 Hz, 1 H), 6.67 (d, J = 7.6 Hz, 1 H), 4.87

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(s, 1 H), 4.74 (s, 1 H), 3.68 (s, br, 2 H), 3.28 (s, 2 H), 1.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) 145.2, 143.6, 131.0, 127.5, 123.9, 118.7, 115.9, 111.6, 41.1, 22.3; IR (film) 3394, 1480 cm^{-1}; MS (ESI+) 148.1125 (148.1121 calcd for $C_{10}H_{13}N$, M + H$^+$).

General Procedure A: Synthesis of Substrates. A flame-dried flask equipped with a stir bar and a reflux condenser was cooled under a vacuum and then was purged with nitrogen. The flask was charged with the appropriate 2-allylaniline derivative (1.25 equiv), the appropriate 2-bromobenzaldehyde derivative (1.0 equiv), 4 Å molecular sieves (1 g/mmol), and toluene (0.2 M). The resulting solution was heated to reflux with stirring overnight. The mixture was then cooled to rt and filtered, and the solids were washed with EtOAc. The combined organic solutions were then concentrated in vacuo, and the resulting crude imine was immediately used without further purification.

A flame-dried flask with a stir bar was cooled under a vacuum and then purged with nitrogen. The flask was charged with the crude imine (1 equiv) and Et_2O (0.5 M) and was cooled to 0 °C. A solution of $LiAlH_4$ (2 equiv, 4 M in Et_2O) was added dropwise, and the resulting solution was allowed to warm to rt and stir overnight. The mixture was diluted with Et_2O, and then water (0.1 mL/mmol of LAH) was carefully added dropwise to the solution followed by dropwise addition of 1 M NaOH (0.1 mL/mmol of LAH). Additional water was then added dropwise until a white solid precipitated and clung to the walls of the flask. The solution was filtered, the flask was washed with Et_2O, and the resulting solution was also filtered. The combined organic solutions were then concentrated in vacuo, and the crude product was then purified via flash chromatography on silica gel using 2−5% ethyl acetate:hexanes as the eluent.

2-Allyl-*N*-(2-bromobenzyl)aniline (3a). The coupling of 2-allylaniline (894 mg, 6.72 mmol) with 2-bromobenzaldehyde (994 mg, 5.37 mmol) was accomplished according to General Procedure A. This procedure afforded 1.01 g (62%) of the title compound as a white solid: mp 42−44 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8 Hz, 1 H), 7.39 (d, J = 7.6 Hz, 1 H), 7.26−7.22 (m, 1 H), 7.14−7.06 (m, 3 H), 6.71 (t, J = 7.2 Hz, 1 H), 6.53 (d, J = 8 Hz, 1 H), 6.03−5.93 (m, 1 H), 5.16−5.09 (m, 2 H), 4.43 (s, 2 H), 4.27 (s, br, 1 H), 3.35 (d, J = 6 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) 145.7, 138.2, 136.0, 132.8, 129.9, 129.0, 128.6, 127.7, 127.5, 123.6, 123.2, 117.6, 116.4, 110.9, 48.2, 36.6; IR (film) 3440, 1512 cm^{-1}; MS (ESI+) 302.0544 (302.0539 calcd for $C_{16}H_{16}BrN$, M + H$^+$).

2-Allyl-*N*-(2-bromobenzyl)-4-methoxyaniline (3b). The coupling of 2-allyl-4-methoxyaniline (1.22 g, 7.47 mmol) with 2-bromobenzaldehyde (1.10 g, 5.97 mmol) was conducted according to General Procedure A. This procedure afforded 1.09 g (55%) of the title compound as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) 7.56 (d, J = 8 Hz, 1 H), 7.34 (d, J = 7.2 Hz, 1 H), 7.26−7.23 (m, 1 H), 7.12 (t, J = 8 Hz, 1 H), 6.72−6.63 (m, 2 H), 6.49 (d, J = 8.8 Hz, 1 H), 6.02−5.92 (m, 1 H), 5.15−5.09 (m, 2 H), 4.38 (s, 2 H), 3.97 (s, br, 1 H), 3.74 (s, 3 H), 3.33 (d, J = 6 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) 152.1, 139.8, 138.5, 135.7, 132.7, 129.1, 128.5, 127.5, 125.7, 123.3, 116.6, 116.6, 112.2, 112.1, 55.7, 49.0, 36.5; IR (film) 3428, 1508 cm^{-1}; MS (ESI+) 332.0645 (332.0645 calcd for $C_{17}H_{18}BrNO$, M + H$^+$).

2-Allyl-*N*-(2-bromobenzyl)-4-methylaniline (3c). The coupling of 2-allyl-4-methylaniline (2.20 g, 15.0 mmol) with 2-bromobenzaldehyde (2.21 g, 12.0 mmol) was conducted according to General Procedure A. This procedure afforded 2.07 g (55%) of the title compound as an orange oil: ^{1}H NMR (400 MHz, $CDCl_3$) 7.56 (d, J = 8 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.25−7.21 (m, 1 H), 7.11 (t, J = 7.2 Hz, 1 H), 6.91−6.89 (m, 2 H), 6.44 (d, J = 8.8 Hz, 1 H), 6.03−5.93 (m, 1 H), 5.14−5.09 (m, 2 H), 4.40 (s, 2 H), 4.14 (s, br, 1 H), 3.32 (d, J = 6.4 Hz, 2 H), 2.23 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) 143.4, 138.4, 136.1, 132.7, 130.7, 129.0, 128.5, 128.0, 127.5, 126.7, 123.8, 123.3, 116.3, 111.1, 48.5, 36.6, 20.4; IR (film) 3437, 1513 cm^{-1}; MS (ESI+) 316.0695 (316.0695 calcd for $C_{17}H_{18}BrN$, M + H$^+$).

2-Allyl-*N*-[(2-bromocyclohex-1-en-1-yl)methyl]aniline (3d). The coupling of 2-allylaniline (832 mg, 6.25 mmol) with 2-bromocyclohex-1-ene-1-carbaldehyde (945 mg, 5.00 mmol) was conducted according to General Procedure A. This procedure afforded 989 mg (65%) of the title compound as a yellow oil that contained ca. 10% of an unidentified impurity. Data are for the major product: ^{1}H NMR (400 MHz, $CDCl_3$) 7.15 (t, J = 8 Hz, 1 H), 7.04 (d, J = 6.8 Hz, 1 H), 6.70 (t, J = 8 Hz, 1 H), 6.64 (d, J = 8 Hz, 1 H), 6.00−5.90 (m, 1 H), 5.14−5.08 (m, 2 H), 4.12−3.91 (m, 3H), 3.29 (d, J = 6.4 Hz, 2 H), 2.60−2.50 (m, 2 H), 2.18−2.09 (m, 2 H), 1.71−1.60 (m, 4 H); ^{13}C NMR (175 MHz, $CDCl_3$) 146.2, 136.1, 133.9, 129.8, 127.8, 123.6, 121.3, 117.3, 116.3, 110.8, 49.4, 36.8, 36.6, 29.3, 24.7, 22.4; IR (film) 3438, 1508 cm^{-1}; MS (ESI+) 306.0852 (306.0852 calcd for $C_{16}H_{20}BrN$, M + H$^+$).

2-Allyl-*N*-(2-bromo-5-fluorobenzyl)aniline (3e). The coupling of 2-allylaniline (1.66 g, 12.5 mmol) with 2-bromo-5-fluorobenzaldehyde (2.02 g, 10.0 mmol) was conducted according to General Procedure A. This procedure afforded 2.28 g (72%) of the title compound as a pale yellow solid: mp 46−47 °C; ^{1}H NMR (700 MHz, $CDCl_3$) 7.49 (dd, J = 4.9, 8.4 Hz, 1 H), 7.10−7.06 (m, 3 H), 6.83 (t, J = 7.7 Hz, 1 H), 6.72 (t, J = 7 Hz, 1 H), 6.43 (d, J = 7.7 Hz, 1 H), 6.02−5.96 (m, 1 H), 5.17−5.12 (m, 2 H), 4.38 (s, 2 H), 4.30 (s, br, 1 H), 3.37 (d, J = 4.9, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) 162.4 (d, J = 245.3 Hz), 145.3, 140.8 (d, J = 6.8 Hz), 136.0, 133.9 (d, J = 7.3 Hz), 130.1, 127.8, 123.7, 117.9, 116.8 (d, J = 2.6 Hz), 116.5, 115.9 (d, J = 23.8 Hz), 115.6 (d, J = 22.9 Hz), 110.8, 48.1, 36.6; IR (film) 3440, 1463 cm^{-1}; MS (ESI+) 320.0450 (320.0445 calcd for $C_{16}H_{15}BrFN$, M + H$^+$).

2-Allyl-*N*-[(6-bromobenzo[*d*][1,3]dioxol-5-yl)methyl]aniline (3f). The coupling of 2-allylaniline (1.66 g, 12.5 mmol) with 6-bromo-1,3-benzodioxole-5-carboxaldehyde (2.29 g, 10.0 mmol) was conducted according to General Procedure A. This procedure afforded 2.51 g (73%) of the title compound as a white solid: mp 53−55 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.13−7.06 (m, 2 H), 7.02 (s, 1 H), 6.85 (s, 1 H), 6.71 (t, J = 7.6 Hz, 1 H), 6.51 (d, J = 8.4 Hz, 1 H), 6.03−5.94 (m, 3 H), 5.16−5.09 (m, 2 H), 4.31 (d, J = 5.6 Hz, 2 H), 4.22 (s, br, 1 H), 3.34 (d, J = 6 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) 147.6, 147.4, 145.6, 136.0, 131.6, 129.9, 127.7, 123.7, 117.6, 116.4, 113.3, 112.8, 110.9, 109.0, 101.6, 48.1, 36.5; IR (film) 3439, 1478 cm^{-1}; MS (ESI+) 346.0440 (346.0437 calcd for $C_{17}H_{16}BrNO_2$, M + H$^+$).

2-Allyl-*N*-[(1-bromonaphthalen-2-yl)methyl]aniline (3g). The coupling of 2-allylaniline (1.7 g, 12.5 mmol) with 1-bromo-2-naphthaldehyde (2.35 g, 10.00 mmol) was conducted according to General Procedure A except after addition of $LiAlH_4$ the reaction mixture was heated to reflux overnight. This procedure afforded 2.77 g (79%) of the title compound as an orange solid: mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 8.34 (d, J = 8.4 Hz, 1 H), 7.80 (d, J = 8 Hz, 1 H), 7.74 (d, J = 8.8 Hz, 1 H), 7.60 (t, J = 7.2 Hz, 1 H), 7.52−7.48 (m, 2 H), 7.10−7.06 (m, 2 H), 6.71 (t, J = 7.2 Hz, 1 H), 6.55 (d, J = 8.8 Hz, 1 H), 6.05−5.95 (m, 1 H), 5.16−5.11 (m, 2 H), 4.66 (s, 2 H), 4.39 (s, br, 1 H), 3.37 (d, J = 6.0 Hz, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) 145.8, 136.6, 136.0, 133.9, 132.4, 130.0, 128.1, 127.8, 127.8, 127.4, 126.9, 126.3, 126.1, 123.7, 123.0, 117.6, 116.5, 111.0, 49.2, 36.6; IR (film) 3442, 1541 cm^{-1}; MS (ESI+) 352.0700 (352.0695 calcd for $C_{20}H_{18}BrN$, M + H$^+$).

***N*-(2-Bromobenzyl)-2-(2-methylallyl)aniline (3h).** The coupling of 2-(2-methylallyl)aniline (1.16 g, 7.84 mmol) with 2-bromobenzaldehyde (1.16 g, 6.28 mmol) was conducted according to General Procedure A. This procedure afforded 767 mg (39%) of the title compound as a white solid: mp 43−46 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.56 (d, J = 8 Hz, 1 H), 7.32 (d, J = 6 Hz, 1 H), 7.25−7.21 (m, 1 H), 7.14−7.04 (m, 3 H), 6.70 (t, J = 7.2 Hz, 1 H), 6.51 (d, J = 8 Hz, 1 H), 4.88 (s, 1 H), 4.76 (s, 1 H), 4.42−4.39 (m, 3 H), 3.33 (s, 2 H), 1.73 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) 146.1, 143.7, 138.3, 132.7, 130.8, 128.8, 128.5, 127.7, 127.5, 123.5, 123.2, 117.4, 112.0, 110.9, 48.1, 41.4, 22.3; IR (film) 3430, 1510 cm^{-1}; MS (ESI+) 316.0692 (316.0695 calcd for $C_{17}H_{18}BrN$, M + H$^+$).

***N*-(2-Bromobenzyl)-2-(but-3-en-2-yl)aniline (3i).** The coupling of 2-(but-3-en-2-yl)aniline (298 mg, 2.02 mmol) with 2-bromobenzaldehyde (300 mg, 1.62 mmol) was conducted according to General Procedure A. This reaction afforded 451 mg (88%) of the title compound as a yellow oil that contained ca. 6% of the analogous crotyl regioisomer. Data are for the major product: ^{1}H NMR (400 MHz, $CDCl_3$) 7.57 (d, J = 8 Hz, 1 H), 7.34 (d, J = 7.6 Hz, 1 H), 7.24−7.22 (m, 1 H), 7.15−7.07 (m, 3 H), 6.75 (t, J = 8 Hz, 1 H), 6.54 (d, J = 8

Hz, 1 H), 6.03−5.94 (m, 1 H), 5.12−5.07 (m, 2 H), 4.42−4.37 (m, 3 H), 3.52 (quint, J = 6.4 Hz, 1 H), 1.43 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) 145.2, 142.3, 138.3, 132.8, 129.0, 128.6, 128.5, 127.5, 127.4, 126.9, 123.3, 117.7, 114.2, 111.1, 48.3, 38.1, 18.9; IR (film) 3434, 1506 cm^{-1}; MS (ESI+) 316.0693 (316.0695 calcd for $C_{17}H_{18}BrN$, M + H$^+$).

2-Allyl-*N*-[1-(2-bromophenyl)ethyl]aniline (3j). The coupling of 2-allylaniline (1.66 g, 12.5 mmol) with 2′-bromoacetophenone (2.00 g, 10.0 mmol) was conducted according to General Procedure A except after addition of $LiAlH_4$ the reaction mixture was heated to reflux overnight. This procedure afforded 1.75 g (55%) of the title compound as a yellow oil that contained ca. 6% of an unknown impurity: ^{1}H NMR (400 MHz, $CDCl_3$) 7.54 (d, J = 8 Hz, 1 H), 7.37 (d, J = 7.6 Hz, 1 H), 7.19 (t, J = 7.2 Hz, 1 H), 7.08−7.02 (m, 2 H), 6.97 (t, J = 8 Hz, 1 H), 6.63 (t, J = 7.6 Hz, 1 H), 6.18 (d, J = 8 Hz, 1 H), 6.07−5.97 (m, 1 H), 5.23−5.18 (m, 2 H), 4.84 (quint, J = 6.4 Hz, 1 H), 4.25 (s, br, 1 H), 3.40 (d, J = 6 Hz, 2 H), 1.48 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) 144.7, 143.6, 136.3, 132.9, 129.7, 128.3, 128.0, 127.6, 126.7, 122.9, 122.6, 117.2, 116.3, 111.6, 52.4, 36.9, 23.1; IR (film) 3746, 1506 cm^{-1}; MS (ESI+) 316.0692 (316.0695 calcd for $C_{17}H_{18}BrN$, M + H$^+$).

General Procedure B: Intramolecular Pd-Catalyzed Alkene Carboamination Reactions. A flame-dried Schlenk tube equipped with a stir bar was cooled under a vacuum and then purged with nitrogen. The tube was charged with NaO^{t}Bu (96 mg, 1 mmol), $Pd_2(dba)_3$ (9 mg, 0.01 mmol), and $PCy_3{\cdot}HBF_4$ (15 mg, 0.040 mmol). The substrate (0.5 mmol) was dissolved in toluene (5 mL) and added to the flask. The resulting solution was heated 105 °C with stirring for 18 h, at which time the substrate was judged to be completely consumed by GC, TLC, or ^{1}H NMR analysis of an aliquot removed from the reaction mixture. The mixture was then cooled to rt, and saturated aqueous NH_4Cl (10 mL) was added. The mixture was transferred to a separatory funnel, the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was then purified via flash chromatography on silica gel using 2% ethyl acetate:hexanes as the eluent to afford a product that still contained small amounts of impurities. The product was then dissolved in 30% Et_2O/hexanes (5 mL, 0.1 M) and 2 M HCl in Et_2O (1.5 mL, 3 equiv) was added dropwise. The resulting solution was stirred at rt for 1 min, and a white solid (the product HCl salt) precipitated from the solution. The salt was then filtered and washed with hexanes. The salt was then dissolved in dicholoromethane (10 mL) and transferred to a separatory funnel. A solution of 4 M NaOH was added, and the mixture was shaken vigorously for 1 min. The layers were then separated, and the aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford the desired product.

6,11,11a,12-Tetrahydroindolo[1,2-*b*]isoquinoline (4a). The cyclization of **3a** (151 mg, 0.500 mmol) was conducted according to General Procedure B to afford 94 mg (85%) of the title compound as a yellow solid: mp 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.20−7.10 (m, 6 H), 6.72 (t, J = 7.2 Hz, 1 H), 6.55 (d, J = 8 Hz, 1 H), 4.58 (d, J = 15.6 Hz, 1 H), 4.02 (d, J = 15.2 Hz, 1 H), 3.58−3.50 (m, 1 H), 3.15 (dd, J = 7.6, 15.2 Hz, 1 H), 3.05−3.00 (m, 2 H), 2.75 (dd, J = 11.2, 15.0 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) 151.8, 134.7, 133.5, 129.5, 129.3, 127.5, 126.9, 126.3, 126.1, 124.4, 118.5, 107.0, 61.6, 48.5, 35.7, 35.6; IR (film) 2778, 1456 cm^{-1}; MS (EI) 221.1201 (221.1204 calcd for $C_{16}H_{15}N$, M$^+$).

2-Methoxy-6,11,11a,12-tetrahydroindolo[1,2-*b*]isoquinoline (4b). The cyclization of **3b** (166 mg, 0.500 mmol) was conducted according to General Procedure B except only 1 equiv of 2 M HCl in Et_2O was used. This procedure afforded 86 mg (68%) of the title compound as a yellow solid: mp 134 °C (dec); ^{1}H NMR (700 MHz, $CDCl_3$) 7.19−7.14 (m, 4 H), 6.80 (s, 1 H), 6.68 (d, J = 7 Hz, 1 H), 6.50 (d, J = 7 Hz, 1 H), 4.54 (d, J = 14.7 Hz, 1 H), 3.93 (d, J = 14.7 Hz, 1 H), 3.74 (s, 3 H), 3.45−3.40 (m, 1 H), 3.11 (dd, J = 7.7, 14.7 Hz, 1 H), 3.05−3.02 (m, 2 H), 2.73 (dd. J = 11.9, 14.7 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) 153.4, 146.2, 134.6, 133.6, 131.2, 129.3, 126.9, 126.3, 126.0, 112.2, 111.6, 107.3, 62.6, 56.0, 49.6, 36.0, 35.4; IR (film) 2781, 1486 cm^{-1}; MS (EI) 251.1314 (251.1310 calcd for $C_{17}H_{17}NO$, M$^+$).

2-Methyl-6,11,11a,12-tetrahydroindolo[1,2-*b*]isoquinoline (4c). The cyclization of **3c** (162 mg, 0.512 mmol) was conducted according to General Procedure B to afford 98 mg (81%) of the title compound as a brown solid: mp 68−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.21−7.15 (m, 4 H), 6.97−6.92 (m, 2 H), 6.49 (d, J = 8 Hz, 1 H), 4.58 (d, J = 15.2 Hz, 1 H), 3.98 (d, J = 15.2 Hz, 1 H), 3.52−3.44 (m, 1 H), 3.11 (dd, J = 14.8, 7.6 Hz, 1 H), 3.04−3.02 (d, J = 6.8 Hz, 2 H), 2.74 (dd, J = 14.8, 11.2 Hz, 1 H), 2.27 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) 149.8, 134.8, 133.7, 129.9, 129.3, 128.0, 127.6, 127.0, 126.4, 126.1, 125.4, 107.0, 62.2, 49.2, 35.7, 35.6, 20.9; IR (film) 2918, 1491 cm^{-1}; MS (EI) 235.1358 (235.1361 calcd for $C_{17}H_{17}N$, M$^+$).

6,7,8,9,10,11,11a,12-Octahydroindolo[1,2-*b*]isoquinoline (4d). The cyclization of **3d** (153 mg, 0.500 mmol) was conducted according to General Procedure B. In order to remove a small amount of unreacted starting material from the product, the crude product was dissolved in dichloromethane (2.5 mL), and DMAP (6.1 mg, 0.050 mmol) and Et_3N (104 μL, 0.750 mmol) were added to the solution. Acetic anhydride (61 μL, 0.650 mmol) was added, and the solution was allowed to stir at rt for 3 h and was then concentrated in vacuo. The crude product was purified via flash chromatography to afford 62 mg (55%) of the title compound as a brown solid: mp 88−90 °C; ^{1}H NMR (700 MHz, $CDCl_3$) 7.09−7.06 (m, 2 H), 6.67 (t, J = 7.0 Hz, 1 H), 6.45 (d, J = 7.7 Hz, 1 H), 3.68 (d, J = 15.4 Hz, 1 H), 3.34−3.29 (m, 1 H), 3.18 (d, J = 15.4 Hz, 1 H), 3.03 (dd, J = 7.0, 14.7 Hz, 1 H), 2.61 (t, J = 12.6 Hz, 1 H), 2.21 (t, J = 14.7 Hz, 1 H), 2.12 (d, J = 16.1 Hz, 1 H), 2.02−1.91 (m, 4 H), 1.77−1.71 (m, 2 H), 1.57−1.52 (m, 2 H); ^{13}C NMR (175 MHz, $CDCl_3$) 151.9, 129.6, 127.5, 127.3, 125.7, 124.2, 118.1, 106.8, 61.5, 49.6, 36.5, 35.8, 30.2, 27.7, 22.9, 22.8; IR (film) 2916, 1607 cm^{-1}; MS (EI) 225.1518 (225.1518 calcd for $C_{16}H_{19}N$, M$^+$).

8-Fluoro-6,11,11a,12-tetrahydroindolo[1,2-*b*]isoquinoline (4e). The cyclization of **3e** (161 mg, 0.505 mmol) was conducted according to General Procedure B to afford 105 mg (87%) of the title compound as a yellow solid: mp 92−93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.13−7.07 (m, 3 H), 6.89−6.85 (m, 2 H), 6.73 (t, J = 7.2 Hz, 1 H), 6.54 (d, J = 8 Hz, 1 H), 4.54 (d, J = 15.6 Hz, 1 H), 3.98 (d, J = 15.6 Hz, 1 H), 3.55−3.47 (m, 1 H), 3.15 (dd, J = 4.6, 14.8 Hz, 1 H), 3.02−2.90 (m, 2 H), 2.74 (dd, J = 11.2, 14.8 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) 161.3 (d, J = 242.6 Hz), 151.6, 135.4 (d, J = 7 Hz), 130.7 (d, J = 7.5 Hz), 130.3 (d, J = 2.6 Hz), 129.5, 127.6, 124.5, 118.8, 113.6 (d, J = 21 Hz), 113.3 (d, J = 21.7 Hz), 107.1, 61.8, 48.6 (d, J = 1.9 Hz), 35.6, 34.9; IR (film) 2789, 1480 cm^{-1}; MS (EI) 239.1116 (239.1110 calcd for $C_{16}H_{14}FN$, M$^+$).

5,11,11a,12-Tetrahydro-[1,3]dioxolo[4,5-*g*]indolo[1,2-*b*]isoquinoline (4f). The cyclization of **3f** (173 mg, 0.500 mmol) was conducted according to General Procedure B to afford 95 mg (72%) of the title compound as a white solid: mp 90−92 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.12−7.09 (m, 2 H), 6.72 (t, J = 7.2 Hz, 1 H), 6.60 (d, J = 6.8 Hz, 2 H), 6.53 (d, J = 8 Hz, 1 H), 5.88 (s, 2 H), 4.46 (d, J = 14.8 Hz, 1 H), 3.92 (d, J = 14.8 Hz, 1 H), 3.52−3.43 (m, 1 H), 3.13 (dd, J = 7.6, 15.0 Hz, 1 H), 2.90 (d, J = 7.2 Hz, 2 H), 2.74 (dd, J = 10.8, 15.0 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) 151.6, 146.1, 146.1, 129.4, 127.6, 127.4, 126.2, 124.3, 118.5, 108.8, 106.9, 106.5, 100.8, 61.5, 48.5, 35.5, 35.5; IR (film) 2891, 1484 cm^{-1}; MS (EI) 265.1103 (265.1103 calcd for $C_{17}H_{15}NO_2$, M$^+$).

7,13,13a,14-Tetrahydrobenzo[*f*]indolo[1,2-*b*]isoquinoline (4g). The cyclization of **3g** (173 mg, 0.491 mmol) was conducted according to General Procedure B to afford 106 mg (80%) of the title compound as a red solid: mp 95−97 °C; ^{1}H NMR (400 MHz, $CDCl_3$) 7.94 (d, J = 8.4 Hz, 1 H), 7.79 (d, J = 8 Hz, 1 H), 7.66 (d, J = 8.4 Hz, 1 H), 7.50 (t, J = 7.2 Hz, 1 H), 7.44 (t, J = 6.8 Hz, 1 H), 7.22 (d, J = 8.4 Hz, 1 H), 7.16−7.12 (m, 2 H), 6.75 (t, J = 7.2 Hz, 1 H), 6.60 (d, J = 8 Hz, 1 H), 4.64 (d, J = 15.6 Hz, 1 H), 4.12 (d, J = 15.6 Hz, 1 H), 3.60−3.51 (m, 2 H), 3.22 (dd, J = 7.2, 14.8 Hz, 1 H), 3.09 (t, J = 12.8 Hz, 1 H), 2.85 (dd, J = 11.6, 14.2 Hz, 1 H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 151.9, 132.5, 132.4, 130.9, 129.9, 129.8, 128.6, 127.6, 126.6, 126.3, 125.4, 125.4, 124.6, 122.9, 118.8, 107.3, 61.8, 49.3, 36.1, 32.0; IR (film)

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2924, 1482 cm^{-1}; MS (EI) 271.1351 (271.1361 calcd for $C_{20}H_{17}N$, M^+).

11a-Methyl-6,11,11a,12-tetrahydroindolo[1,2-*b*]isoquinoline (4h). The cyclization of **3h** (163 mg, 0.517 mmol) was conducted according to General Procedure B to afford 97 mg (80%) of the title compound as a yellow solid: mp 47−50 °C; ^{1}H NMR (700 MHz, $CDCl_3$) 7.19−7.14 (m, 3 H), 7.06 (m, 3 H), 6.63 (t, J = 7.0 Hz, 1 H), 6.41 (d, J = 7.7 Hz, 1 H), 4.50 (d, J = 16.1 Hz, 1 H), 4.25 (d, J = 16.1 Hz, 1 H), 3.10 (d, J = 15.4 Hz, 1 H), 2.94 (s, 2 H), 2.70 (d, J = 15.4 Hz, 1 H), 1.15 (s, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) 150.5, 134.6, 132.9, 129.8, 128.3, 127.6, 126.5, 126.4, 126.0, 124.8, 117.2, 106.2, 62.3, 43.7, 43.7, 40.0, 20.9; IR (film) 2924, 1482 cm^{-1}; MS (EI) 235.1364 (235.1361 calcd for $C_{17}H_{17}N$, M^+).

(±)-(11a*S*,12*R*)-12-Methyl-6,11,11a,12-tetrahydroindolo[1,2-*b*]isoquinoline (4i). The cyclization of **3i** (64 mg, 0.202 mmol) was conducted according to General Procedure B to afford 36 mg (75%) of the title compound as a yellow oil. This product was judged to have been formed with 18:1 dr by ^{1}H NMR analysis. Data are for the major isomer: ^{1}H NMR (700 MHz, CD_3OD) 7.19−7.15 (m, 4 H), 7.09−7.06 (m, 2 H), 6.76 (t, J = 7.7 Hz, 1 H), 6.62 (d, J = 7.7 Hz, 1 H), 4.58 (d, J = 15.4 Hz, 1 H), 3.83 (d, J = 14.7 Hz, 1 H), 3.06 (d, J = 14.7 Hz, 1 H), 2.92−2.84 (m, 3 H), 1.37 (d, J = 6.3 Hz, 3 H); ^{13}C NMR (175 MHz, CD_3OD) 152.7, 136.1, 135.6, 134.6, 130.3, 128.4, 127.9, 127.4, 127.1, 123.5, 120.3, 108.7, 71.5, 50.3, 43.3, 35.0, 16.1; IR (film) 3676, 1506 cm^{-1}; MS (EI) 235.1363 (235.1361 calcd for $C_{17}H_{17}N$, M^+).

6-Methyl-6,11,11a,12-tetrahydroindolo[1,2-*b*]isoquinoline (4j). The cyclization of **3j** (165 mg, 0.500 mmol) was conducted according to the General Procedure B to afford 64 mg (52%) of the title compound as a yellow oil. This material was judged to be an inseparable ca. 2:1:1 mixture of the two possible diastereomers and a side product tentatively assigned as 6-methyl-11-methylene-5,6,11,12-tetrahydrodibenzo[*b*,*f*]azocine, which results from competing intramolecular Heck reaction.[11] Data are for the mixture: ^{1}H NMR (700 MHz, $CDCl_3$) 7.26−7.24 (m, 1 H), 7.22−7.20 (m, 1.5 H), 7.19−7.16 (m, 2.5 H), 7.16−7.14 (m, 2.5 H), 7.12−7.07 (m, 4.5 H), 7.02 (d, J = 7.7 Hz, 1 H), 6.97 (t, J = 10.5 Hz, 1 H), 6.68−6.63 (m, 2 H), 6.60 (d, J = 7.7 Hz, 0.5 H), 6.48 (d, J = 8.4 Hz, 1 H), 6.45 (d, J = 7.7 Hz, 0.5 Hz), 6.29 (ddd, J = 3.5, 10.5, 17.3 Hz, 0.5 H), 5.23−5.13 (m, 1 H), 4.84−4.78 (m, 1.5 H), 4.53−4.50 (m, 1 H), 3.97−3.92 (m, 1 H), 3.76−3.60 (m, 1 H), 3.23 (dd, J = 8.4, 14.7 Hz, 1 H), 3.06−2.92 (m, 4 H), 2.77−2.72 (m, 1.5 H), 1.55 (d, J = 6.3 Hz, 1.5 H), 1.53 (d, J = 7.0 Hz, 1.5 H), 1.36 (d, J = 7.0 Hz, 3 H); ^{13}C NMR (175 MHz, $CDCl_3$) 151.3, 149.8, 146.0, 143.5, 140.9, 140.4, 139.8, 139.2, 134.5, 134.0, 132.6, 130.2, 129.6, 129.3, 129.0, 128.8, 127.7, 127.7, 127.5, 127.4, 127.4, 127.2, 127.1, 127.0, 126.5, 126.3, 126.0, 124.5, 124.2, 123.5, 122.3, 117.9, 117.8, 117.5, 117.3, 115.3, 106.9, 106.3, 62.7, 56.4, 54.6, 53.9, 50.6, 48.0, 36.3, 36.1, 35.8, 35.3, 24.9, 19.2, 17.2; IR (film) 3362, 1617 cm^{-1}; MS (ESI+) 236.1442 (236.1434 calcd for $C_{17}H_{17}N$, M + H^+).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Assignment of relative stereochemistry of **4i** and copies of ^{1}H and ^{13}C NMR spectra for all substrates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jpwolfe@umich.edu.

Notes

The authors declare no competing financial interest.

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