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Synthesis of Isoquinoline Derivatives Using ROM−RCM of Cyclobutene-yne

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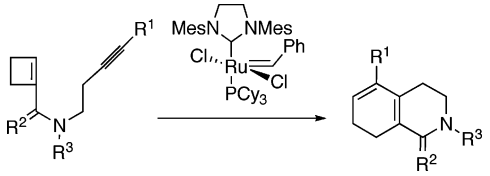
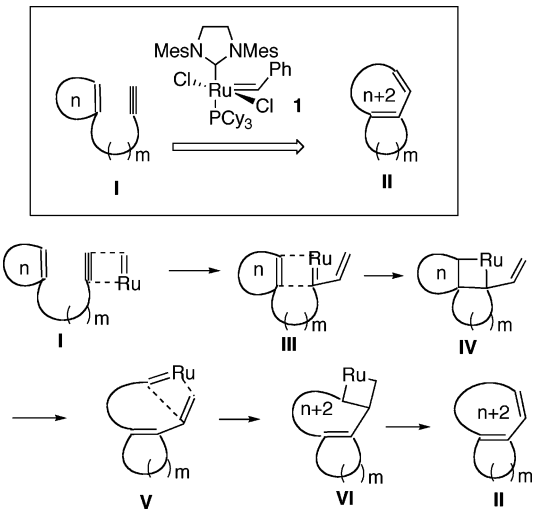


Isoquinoline derivatives were synthesized from cyclobutenylmethylamine derivatives having an alkyne moiety in a tether using a second-generation ruthenium carbene complex under ethylene gas in good yields.

Ring-opening metathesis (ROM)−ring-closing metathesis (RCM) is a very attractive reaction in synthetic organic chemistry.[1] We have already reported two types of ROM−RCM of cycloalkyne-yne.[2] During the course of our investigation of ROM−RCM of cycloalkene-yne **I**,[2b] we noticed that this reaction would be an attractive method for the synthesis of bicyclic compound **II**.

SCHEME 1. ROM−RCM of Cycloakene-yne



The possible reaction course for the formation of bicyclic compound **II** is shown in Scheme 1. The reaction of terminal alkyne and ruthenium methylidene carbene complex gives ruthenium carbene complex **III**, which reacts with cycloalkene to give highly strained ruthenacyclobutane **IV**. Ring opening of this complex **IV** gives ruthenium carbene complex **V**, which reacts with an alkene part of a diene moiety to give ruthenacyclobutane **VI**. Ring opening of this complex **VI** gives bicyclic compound **II**. In this reaction, the initial *n*-membered ring is converted into an $(n + 2)$-membered ring size. The other ring size is $(m + 2)$ and depends on the chain lengths between the double bond and the triple bond.

To examine the feasibility of this reaction course, when a CH_2Cl_2 solution of cyclopentenylmethylamine derivative **2** and 5 mol % second-generation ruthenium carbene complex **1**[3d] was refluxed for 3 h under ethylene gas,[4] 7−6 fused bicyclic compound **3** was obtained in 76% yield (Scheme 2). On the basis of this result, it was expected that isoquinoline derivative[5] **IIa** could be synthesized using this procedure. For that purpose, cyclobutenylmethylamine derivative **Ia** ($n = 4$, $m = 4$ in **I**) was required as a starting material.

When a CH_2Cl_2 solution of cyclobutenylmethylamine derivative **4a** and 5 mol % of second-generation ruthenium carbene complex **1** was refluxed in CH_2Cl_2 for 3 h

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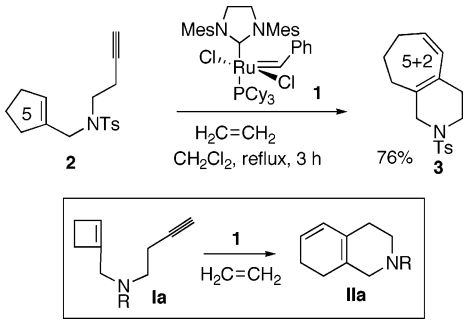
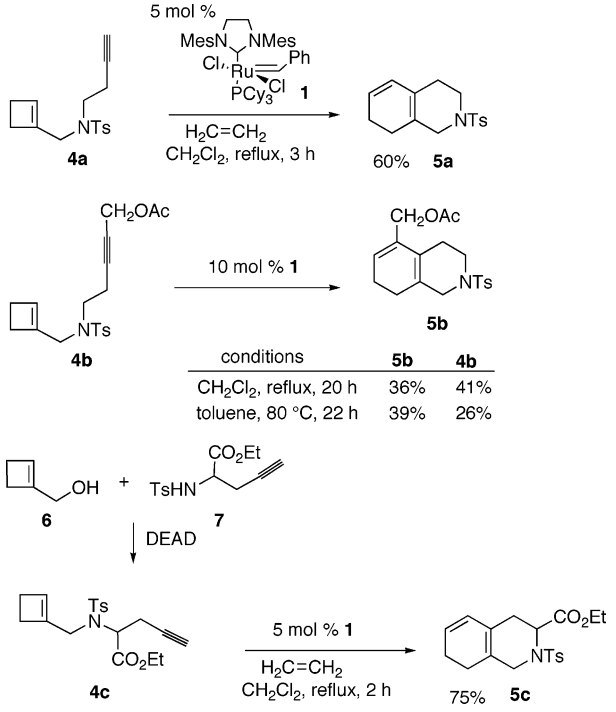
SCHEME 2. Synthesis of Fused 6,7-Membered Ring Compound



SCHEME 3. Synthesis of Isoquinoline Derivative

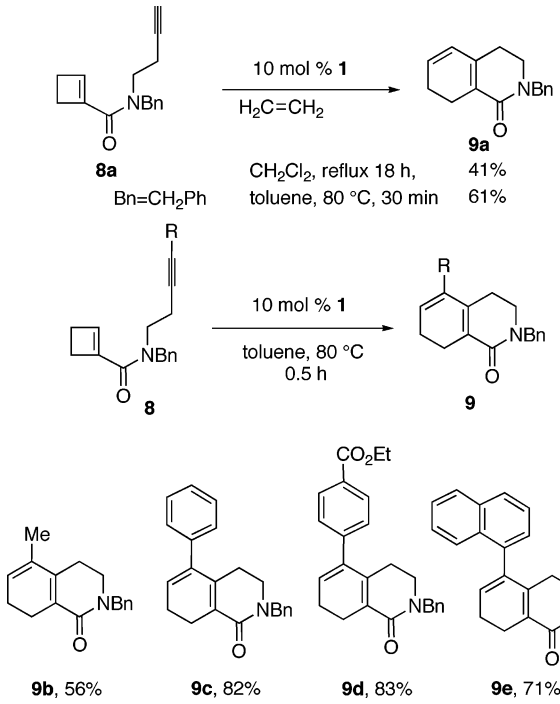


under ethylene gas (1 atm), we were very pleased to find that the desired isoquinoline derivative **5a** was obtained in 60% yield (Scheme 3). The reaction of cyclobutenylmethylamine derivative **4b** having disubstituted alkyne in a tether was treated in a similar manner under argon gas to give isoquinoline derivative **5b** having an acetoxymethyl group at the 5-position in 36% yield along with the starting material in 41% yield. Toluene can be used for this reaction, and the desired isoquinoline derivative **5b** was obtained in 39% yield.

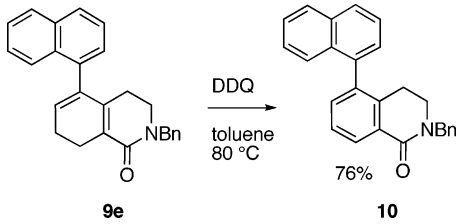
Next, synthesis of a cyclic amino acid using this method was investigated. Condensation of cyclobutenylmethyl alcohol **6** and amino acid derivative **7** using diethyl azodicarboxylate (DEAD) and PPh_3 gave cyclobutenylmethylamine derivative **4c**, which was treated with **1** in a similar manner to give cyclic amino acid **5c** in 75% yield.

Subsequently, an isoquinolone derivative was synthesized. The starting cyclobutenecarboxamide **8a** was synthesized and treated with 10 mol % **1** in CH_2Cl_2 under ethylene gas for 18 h to give the desired isoquinolone derivative **9a** in 41% yield (Scheme 4). The yield was improved to 61% when the reaction was carried out in

SCHEME 4. Synthesis of Isoquinoline Derivatives Using ROM−RCM of Cyclobutene-yne



SCHEME 5. Synthesis of Dihydroisoquinoline Derivatives



toluene. Furthermore, cyclobutene derivative **8b** (R = Me) having a methyl group on an alkyne part provided 5-methyl-2-tosyl-3,4,7,8-tetrahydroisoquinolone **9b** in 56% yield. Various cyclobutene derivatives **8c**−**e** were treated in a similar manner to afford the expected isoquinolone derivatives **9c**−**e** having substituents at the 5-position in good yields.

Since this procedure is very attractive for the synthesis of biaryl compounds, tetrahydroisoquinolone derivative **9e** was treated with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 5). As a result, dihydroisoquinolone derivative **10** was obtained in good yield.

In summary, ROM−RCM of cyclobutenylmethylamine having an alkyne moiety in a tether afforded isoquinoline derivatives in good yields in a one-step reaction.

Experimental Section

General Procedure for the Metathesis Reaction. A catalytic amount of **1** (5−10 mol %) and cycloalkene-yne **2**, **4**, or **8** were dissolved in dry CH_2Cl_2 (or dry toluene) (0.02−0.03 M). The solution was refluxed (or warmed at 80 °C) under ethylene gas (1 atm) or argon gas (1 atm). When cycloalkene-yne having a terminal alkyne was used as a substrate, the solution was degassed and ethylene gas was introduced into the reaction vessel. In the case of cycloalkene-yne having a disubstituted alkyne, the reaction was carried out under argon gas. After the

spot of the starting material had disappeared on TLC, a few drops of ethyl vinyl ether were added to this solution. The volatiles were removed in vacuo, and the residue was purified by column chromatography on silica gel to afford isoquinoline derivative **3**, **5**, or **9**.

2-(*p*-Toluenesulfonyl)-2,3,4,7,8,9-hexahydro-1*H*-cyclohepta[*c*]pyridine (3). A crude product, which was prepared from **2** (91.9 mg, 0.30 mmol) and **1** (13.2 mg, 15 μmol, 5 mol %) by refluxing in CH_2Cl_2 (10 mL) for 3 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 5:1) to give **3** (69.5 mg, 76%) as a colorless oil: IR (neat) 2924, 2856, 1597, 1346, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.81 (m, 2 H), 2.06 (m, 2 H), 2.25 (m, 4 H), 2.43 (s, 3 H), 3.11 (dd, J = 5.6, 6.0 Hz, 2 H), 3.51 (s, 2 H), 5.53 (d, J = 12.0 Hz, 1 H), 5.75 (dt, J = 12.0, 4.8 Hz, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 27.3 (CH_2), 30.8 (CH_2), 31.4 (CH_2), 32.7 (CH_2), 43.0 (CH_2), 49.1 (CH_2), 125.7 (C), 127.1 (C), 127.7 (CH x 2), 128.8 (CH), 129.5 (CH x 2), 131.3 (C), 132.5 (CH), 143.4 (C); LRMS *m/z* 303 (M^+), 288, 275, 262, 249, 236, 223, 155, 147, 91. Anal. Calcd for $C_{17}H_{21}NO_2S$: C, 67.29; H, 6.98; N, 4.62; S, 10.57. Found: C, 67.13; H, 6.97; N, 4.44; S, 10.41.

2-(*p*-Toluenesulfonyl)-1,2,3,4,7,8-hexahydroisoquinoline (5a). A crude product, which was prepared from **4a** (111.4 mg, 0.38 mmol) and **1** (16.3 mg, 19.25 μmol, 5 mol %) by refluxing in CH_2Cl_2 (15 mL) for 3 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 20:1) to give **5a** (66.3 mg, 60%) as an amorphous solid: IR (KBr) 1596 (w), 1346 (s), 1163 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94−2.02 (m, 2 H), 2.10−2.23 (m, 4 H), 2.43 (s, 3 H), 3.19 (t, J = 5.7 Hz, 2 H), 3.51 (s, 2 H), 5.64−5.73 (m, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (CH_3), 22.6 (CH_2), 24.9 (CH_2), 27.9 (CH_2), 43.2 (CH_2), 47.7 (CH_2), 124.3 (C), 124.8 (C), 124.9 (CH), 126.4 (CH), 127.6 (CH x 2), 129.5 (CH x 2), 133.0 (C), 143.4 (C); EI-LRMS *m/z* 289 (M^+), 133, 107, 91; EI-HRMS *m/z* calcd for $C_{16}H_{19}O_2NS$ (M^+) 289.1136, found 289.1138.

2-(*p*-Toluenesulfonyl)-1,2,3,4,7,8-hexahydroisoquinolin-5-ylmethyl Acetate (5b). A crude product, which was prepared from **4b** (44.7 mg, 0.12 mmol) and **1** (10.5 mg, 12.37 μmol, 10 mol %) in toluene (6 mL) by warming for 22 h under Ar, was purified by column chromatography on silica gel (hexane/ethyl acetate, 2:1) to give **5b** (17.6 mg, 39%) as a colorless liquid and recovered **4b** (11.7 mg, 26%): IR (neat) 1739 (s), 1599 (w), 1346 (m), 1245 (s), 1165 (s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.92−2.18 (m, 4 H), 2.04 (s, 3 H), 2.24−2.33 (m, 2 H), 2.42 (s, 3 H), 3.19 (t, J = 5.7 Hz, 2 H), 3.52 (s, 2 H), 4.52 (s, 2 H), 5.79 (t, J = 4.3 Hz, 1 H), 7.32 (d, J = 8.2 Hz, 2 H), 7.68 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 21.0 (CH_3), 21.5 (CH_3), 22.2 (CH_2), 24.8 (CH_2), 25.0 (CH_2), 43.2 (CH_2), 47.8 (CH_2), 64.8 (CH_2), 124.7 (C), 126.6 (CH), 126.9 (C), 127.7 (CH x 2), 129.6 (CH x 2), 131.4 (C), 133.0 (C), 143.6 (C), 170.7 (C); EI-LRMS *m/z* 361 (M^+), 301, 146, 91; EI-HRMS *m/z* calcd for $C_{19}H_{23}O_4NS$ (M^+) 361.1348, found 361.1328.

Ethyl 2-(*p*-Toluenesulfonyl)-1,2,3,4,7,8-hexahydroisoquinoline-3-carboxylate (5c). A crude product, which was prepared from **4c** (88.4 mg, 0.24 mmol) and **1** (10.4 mg, 12.23 μmol, 5 mol %) in CH_2Cl_2 (8 mL) by refluxing for 2 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 5:1) to afford **5c** (66.4 mg, 75%) as an amorphous solid: IR (KBr) 1728 (s), 1598 (m), 1346 (s), 1163 (s) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (t, J = 7.0 Hz, 3 H), 1.93−2.01 (m, 2 H), 2.04−2.19 (m, 2 H), 2.41 (s, 3 H), 2.47 (d, J = 10.6 Hz, 1 H), 2.62 (m, 1 H), 3.79 (d, J = 17.0 Hz, 1 H), 3.86 (m, 1 H), 3.95−4.04 (m, 2 H), 4.87 (dd, J = 1.6, 6.6 Hz, 1 H), 5.62−5.72 (m, 2 H), 7.28 (d, J = 8.2 Hz, 2 H), 7.69 (d, J = 8.2 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 21.5 (CH_3), 22.5 (CH_2), 24.6 (CH_2), 30.9 (CH_2), 45.0 (CH_2), 53.4 (CH), 61.1 (CH_2), 122.3 (C), 124.8 (C), 125.1 (CH), 126.3 (CH), 127.1 (CH x 2), 129.3 (CH x 2), 136.1 (C), 143.1 (C), 170.2 (C); EI-LRMS *m/z* 361 (M^+), 288, 206, 132, 91; EI-HRMS *m/z* calcd for $C_{19}H_{23}O_4NS$ (M^+) 361.1348, found 361.1352.

***N*-Benzyl-3,4,7,8-tetrahydro-1(2*H*)-isoquinolone (9a).** A crude product, which was prepared from **8a** (54.0 mg, 0.23 mmol) and **1** (19.2 mg, 22.56 μmol, 10 mol %) in toluene (8 mL) by warming at 80 °C for 0.5 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:2) to give **9a** (33.0 mg, 61%) as a pale yellow liquid: IR (neat) 1655 (s), 1621 (s), 1480 (m), 1441 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.22−2.35 (m, 4 H), 2.47−2.55 (m, 2 H), 3.31 (t, J = 7.1 Hz, 2 H), 4.64 (s, 2 H), 5.86 (d, J = 9.4 Hz, 1 H), 6.11 (dt, J = 9.4, 4.5 Hz, 1 H), 7.25−7.35 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.0 (CH_2), 23.2 (CH_2), 27.2 (CH_2), 44.3 (CH_2), 50.0 (CH_2), 123.8 (C), 126.2 (CH), 127.1 (CH), 127.8 (CH x 2), 128.4 (CH x 2), 132.7 (CH), 137.8 (C), 139.3 (C), 165.7 (C); EI-LRMS *m/z* 239 (M^+), 160, 91, 77; EI-HRMS *m/z* calcd for $C_{16}H_{17}ON$ (M^+) 239.1310, found 239.1295.

***N*-Benzyl-5-methyl-3,4,7,8-tetrahydro-1(2*H*)-isoquinolone (9b).** A crude product, which was prepared from **8b** (39.9 mg, 0.16 mmol) and **1** (13.4 mg, 15.75 μmol, 10 mol %) in toluene (8 mL) by warming at 80 °C for 0.5 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 2:1) to give **9b** (22.2 mg, 56%) as a pale yellow liquid: IR (neat) 1659 (s), 1622 (s), 1479 (m), 1442 (m), 1242 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.77 (dt, J = 1.8, 1.8 Hz, 3 H), 2.09−2.20 (m, 2 H), 2.28−2.50 (m, 4 H), 3.31 (t, J = 7.0 Hz, 2 H), 4.65 (s, 2 H), 5.86 (tq, J = 5.0, 1.8 Hz, 1 H), 7.25−7.35 (m, 5 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.5 (CH_3), 20.9 (CH_2), 22.9 (CH_2), 24.6 (CH_2), 44.1 (CH_2), 50.0 (CH_2), 125.4 (C), 127.2 (CH x 2), 128.0 (CH), 128.3 (CH), 128.5 (CH x 2), 131.8 (C), 138.0 (C), 141.7 (C), 166.1 (C); EI-LRMS *m/z* 252 (M^+ − 1), 174, 160, 91; EI-HRMS *m/z* calcd for $C_{17}H_{19}ON$ (M^+) 253.1467, found 253.1451.

***N*-Benzyl-5-phenyl-3,4,7,8-tetrahydro-1(2*H*)-isoquinolone (9c).** A crude product, which was prepared from **8c** (50.7 mg, 0.16 mmol) and **1** (13.6 mg, 16.07 μmol, 10 mol %) in toluene (8 mL) by warming at 80 °C for 0.5 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 2:1) to give **9c** (41.8 mg, 82%) as a pale yellow liquid: IR (neat) 1652 (s), 1620 (s), 1478 (m), 1443 (m), 1223 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.14−2.22 (m, 2 H), 2.29−2.39 (m, 2 H), 2.53−2.63 (m, 2 H), 3.24 (t, J = 7.0 Hz, 2 H), 4.66 (s, 2 H), 6.13 (t, J = 4.5 Hz, 1 H), 7.11−7.36 (m, 10 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.7 (CH_2), 23.3 (CH_2), 26.2 (CH_2), 44.5 (CH_2), 50.0 (CH_2), 126.5 (C), 127.2 (CH), 127.3 (CH), 128.0 (CH x 2), 128.2 (CH x 2), 128.2 (CH x 2), 128.2 (C), 128.6 (CH x 2), 131.2 (CH), 137.9 (C), 139.4 (C), 140.3 (C), 166.0 (C); EI-LRMS *m/z* 314 (M^+ − 1), 91; EI-HRMS *m/z* calcd for $C_{22}H_{21}ON$ (M^+) 315.1623, found 315.1642.

Ethyl 4-(2-Benzyl-1-oxo-1,2,3,4,7,8-hexahydroisoquinolin-5-yl)-benzoate (9d). A crude product, which was prepared from **8d** (25.5 mg, 0.07 mmol) and **1** (5.6 mg, 6.58 μmol, 10 mol %) in toluene (3.3 mL) by warming at 80 °C for 0.5 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:2) to give **9d** (21.2 mg, 83%) as a pale yellow liquid: IR (neat) 1716 (s), 1652 (s), 1622 (s), 1609 (s), 1274 (s), 755 (s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.39 (t, J = 7.1 Hz, 3 H), 2.12−2.20 (m, 2 H), 2.32−2.42 (m, 2 H), 2.55−2.64 (m, 2 H), 3.25 (t, J = 7.0 Hz, 2 H), 4.37 (q, J = 7.1 Hz, 2 H), 4.66 (s, 2 H), 6.19 (t, J = 4.6 Hz, 1 H), 7.21 (d, J = 8.3 Hz, 2 H), 7.24−7.35 (m, 5 H), 7.99 (d, J = 8.3 Hz, 2 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 14.3 (CH_3), 20.7 (CH_2), 23.3 (CH_2), 26.1 (CH_2), 44.5 (CH_2), 50.1 (CH_2), 61.0 (CH_2), 127.0 (C), 127.4 (CH), 128.1 (CH x 2), 128.2 (CH x 2), 128.6 (CH x 2), 129.4 (C), 129.5 (CH x 2), 132.3 (CH), 137.8 (C), 138.7 (C), 139.5 (C), 143.9 (C), 165.8 (C), 166.3 (C); EI-LRMS *m/z* 386 (M^+ − 1), 342, 91; EI-HRMS *m/z* calcd for $C_{25}H_{25}O_3N$ (M^+) 387.1834, found 387.1859.

***N*-Benzyl-5-naphthalen-1-yl-3,4,7,8-tetrahydro-1(2*H*)-isoquinolone (9e).** A crude product, which was prepared from **8e** (61.6 mg, 0.17 mmol) and **1** (14.3 mg, 16.86 μmol, 10 mol %) in toluene (8.5 mL) by warming at 80 °C for 1 h under ethylene, was purified by column chromatography on silica gel (hexane/ethyl acetate, 3:1) **9e** (43.9 mg, 71%) as a pale yellow liquid: IR (neat) 1653 (s), 1620 (s), 1478 (s), 1226 (m), 756 (s) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.88 (t, J = 7.1 Hz, 2 H), 2.32−2.69 (m, 3 H), 2.86 (m, 1 H), 3.02−3.22 (m, 2 H), 4.58 (d, J = 14.8 Hz, 1 H), 4.66 (d, J = 14.8 Hz, 1 H), 6.18 (dd, J = 4.0, 4.9 Hz, 1 H), 7.18−7.32 (m, 6 H), 7.40−7.50 (m, 3 H), 7.70−7.85 (m, 3 H);

^{13}C NMR (67.8 MHz, $CDCl_3$) δ 20.6 (CH_2), 23.3 (CH_2), 25.1 (CH_2), 44.4 (CH_2), 50.1 (CH_2), 125.3 (C), 125.3 (CH), 125.4 (CH), 125.9 (CH), 126.2 (CH), 126.6 (CH), 127.2 (CH), 127.8 (CH), 128.0 (CH x 2), 128.3 (CH), 128.4 (CH x 2), 132.0 (C), 132.3 (CH), 133.3 (C), 137.3 (C), 137.6 (C x 2), 141.4 (C), 166.0 (C); EI-LRMS *m/z* 364 ($M^+ - 1$), 215, 91; EI-HRMS *m/z* calcd for $C_{26}H_{23}ON$ (M^+) 365.1779, found 365.1769.

***N*-Benzyl-5-naphthalen-1-yl-3,4-dihydro-1(2*H*)-isoquinolone (10).** To a solution of **9e** (42.6 mg, 0.12 mmol) in toluene (2 mL) was added DDQ (79.4 mg, 0.35 mmol) at room temperature, and the solution was stirred at 80 °C for 3 h. The solution was filtered, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 2:1) to afford **10** (32.1 mg, 76%) as an amorphous solid: IR (KBr) 1650 (s), 782 (m), 755 (m) cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.44 (t, J = 6.6 Hz, 2 H), 3.21 (t, J = 6.6 Hz, 2 H), 4.69 (s, 2 H), 7.14−7.45 (m, 12 H), 7.80 (t, J = 7.5 Hz, 2 H), 8.20 (dd, J = 2.0, 7.1 Hz, 1 H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.9 (CH_2), 45.1 (CH_2), 50.5 (CH_2), 125.3 (CH), 125.6 (CH), 125.9 (CH), 126.3 (CH), 126.7 (CH), 126.9 (CH), 127.4 (CH), 128.0 (CH), 128.0 (CH x 2), 128.3 (CH), 128.3 (CH), 128.6 (CH x 2), 129.7 (C), 131.9 (C), 133.5 (C), 133.7 (CH), 137.0 (C), 137.3 (C), 137.7 (C), 138.4 (C), 164.7 (C); EI-LRMS *m/z* 363 (M^+), 272, 259, 243, 229, 215, 91; EI-HRMS *m/z* calcd for $C_{26}H_{21}ON$ (M^+) 363.1623, found 363.1642.

Supporting Information Available: Information on experimental procedures and spectral data of **2**, **4a**−**c**, **8a**−**e**, **14**, and **15**. This material is available free of charge via the Internet at http://pubs.acs.org.

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