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Synthesis of Polycyclic Isoindoline Derivatives via Tandem Pd-Catalyzed Coupling, Propargyl−Allenyl Isomerization, [4 + 2] Cycloaddition and Aromatization Reaction

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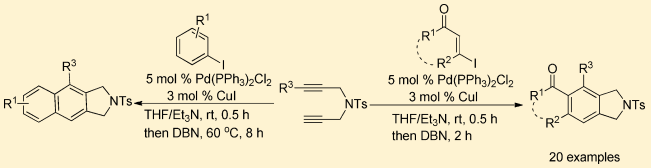
Supporting Information

ABSTRACT: We report in this paper an interesting sequential reaction involving sequential Sonogashira coupling, propargyl−allenyl isomerization, [4 + 2] cycloaddition and aromatization reaction, which provides a facile method for the synthesis of a variety of polycyclic isoindoline derivatives from easily accessible starting materials.



Isoindolines and their congeners display a remarkable variety of biological activities.[1] Some isoindolines act as selective serotonin uptake inhibitors, while others exhibit antitumor, diuretic, and herbicidal activity.[2] Hence, the study on isoindolines continues to be an active research area, and continuous efforts have been directed to the development of new and efficient synthetic methods toward isoindolines derivatives.[3]

The development of novel cascade reactions involving in situ generation of reactive functional groups such as allene intermediate is an intensively pursued goal in our group. Müller et al. pioneered the Sonogashira coupling/propargyl−allenyl isomerization reactions for the synthesis of a variety of useful compounds including chalcones, pyrazolines, pyrroles, fluorescent spirocycles, and some other pharmaceutically interesting heterocycles.[4] In this aspect, we previously established a series of sequential reactions wherein an allene intermediate, generated in situ, would undergo cycloaddition reaction under mild conditions, providing an efficient synthesis of structurally complex polycycles with 2,3-dihydrofuran units,[5] structurally diverse fused dihydroisobenzofuran derivatives,[6] and other structurally complex polycycles.[7] We anticipated that this protocol could be further extended to cyclic compounds in a broader dimension.

As a continuous exploration, herein we envisioned a sequence of palladium-catalyzed coupling, propargyl−allenyl isomerization, [4 + 2] cycloaddition and aromatization reaction: Oxidative addition of alkenyl iodide **1** with Pd(0) species would form intermediate **A**. Then it would react with alkynyl copper intermediate **B** via transmetalation to generate intermediate **C**. After reductive elimination regenerating Pd(0), enyne **D** was formed, which was expected to undergo propargyl−allenyl isomerization with a suitable base to afford the enyne−allene intermediate **E**, which may preferentially cyclize to produce intermediate **F** via [4 + 2] cycloaddition. In this paper, we wish to report our results on this Pd-catalyzed sequential reaction to access polycyclic isoindoline derivatives (Scheme 1).

We initiated this study by conducting the reaction of 3-iodo-5,5-dimethylcyclohex-2-enone **1a** and **2a** in THF using 5 mol % of $Pd(PPh_3)_2Cl_2$ and 3 mol % of CuI. The reaction with 2 equiv of DBU as base at room temperature for 2 h afforded the coupling product exclusively (Scheme 2).

We reasoned that 1 equiv of DBU was consumed in the Sonogashira coupling reaction, thus, the remaining DBU is not enough for further reaction. In fact, when 4 equiv of DBU were applied, the reaction afforded the expected product **3a** in 62% yield (Table 1, entries 1 and 2). *t*-BuOK was also investigated as the base; however, no product was detected. In the absence of an extra base or 1 mL of Et_3N was added, the reaction only afforded the coupling product (Table 1, entry 4), which means that triethylamine could not be sufficient to induce the isomerization step. When DBN was used as base, the yield was improved to 72% (Table 1, entry 5). Other solvents were also examined; however, no improvement was observed (Table 1, entries 6−10).

With the optimal conditions in hand, we next examined the reaction scope. Typical results are summarized in Table 2. As for substrate **2** wherein R^3 is an aromatic group such as phenyl, *p*-methylphenyl, *p*-methoxyphenyl and *p*-fluorophenyl group, the reactions proceeded smoothly under the established conditions, delivering the isoindoline derivatives **3** in good yields (Table 2, entries 1−4). Furthermore, when R^3 is an alkyl group, the reactions gave the expected product as well (Table 2, entries 5 and 6). The reaction was also applied to 3-iodocyclohex-2-enone **1b** and 3-iodocyclopent-2-enone **1c** (Table 2, entries 7−9). When (*E*)-ethyl 3-iodoacrylate **1d**

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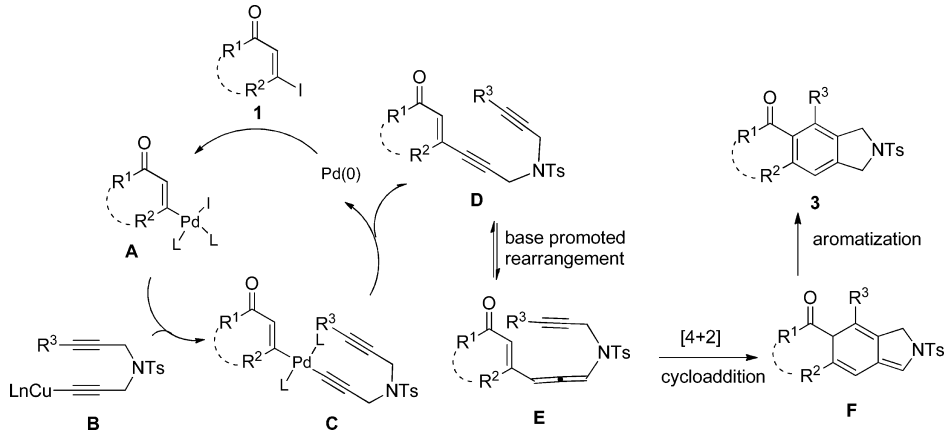
Scheme 1. Tandem Pd-Catalyzed Sequential Reaction



Scheme 2

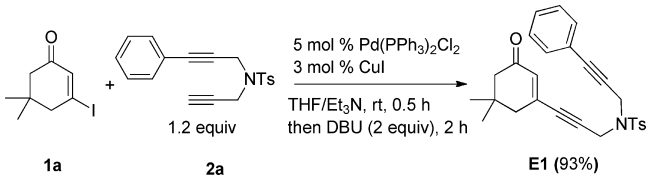
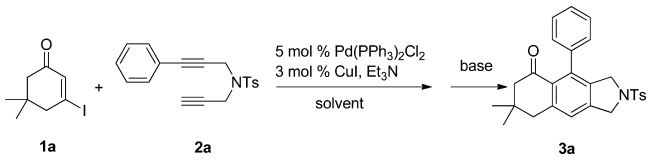


Table 1. Optimization of the Reaction Conditions for the Sequential Reaction of 1a and 2a[a]



entry	solvent	base/equiv	temp	time	yield of **3a** (%)[b]
1	THF	DBU/2	rt	2.5 h	0
2	THF	DBU/4	rt	2.5 h	62
3	THF	*t*-BuOK/4	rt	1 d	0
4	THF		rt	1 d	0[c]
5	THF	DBN/4	rt	2.5 h	72
6	toluene	DBN/4	rt	2.5 h	36
7	CH_3CN	DBN/4	rt	2.5 h	53
8	DMF	DBN/4	rt	2.5 h	45
9	CH_2Cl_2	DBN/4	rt	2.5 h	39
10	DCE	DBN/4	rt	2.5 h	46

[a]The reaction was carried out using **1** (0.25 mmol) and **2** (0.3 mmol) in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ and 3 mol % of CuI in 3 mL of solvent and 0.1 mL of Et_3N at rt for 30 min, and then 4 equiv of base was added. [b]Isolated yields. [c]1 mL of Et_3N was added; the reaction only afforded the coupling product as well.

was employed, the reactions occurred to give the expected products in good yields (Table 2, entries 10 and 11).

To further expand the scope of this reaction, we also investigated a range of electron-deficient aromatic halides. The reaction of **2** with methyl 4-iodobenzoate **4a** proceeded smoothly to afford the corresponding isoindoline derivatives **5** in 57−76% yields at 60 °C. For R^3, aromatic groups including *p*-Me, *p*-MeO, *p*-F, and *p*-Cl substituted phenyl groups and alkyl groups are all applicable (Table 3, entries 1−6). When methyl 2-iodobenzoate **4b** and 1-(4-iodophenyl)ethanone **4c** were employed under the established conditions, the expected product was obtained smoothly and in good yield as well (Table 3, entries 8 and 9).

As comparison, we also conducted the reaction of 1-iodobenzene (**4d**) or 1-iodo-4-methoxybenzene (**4e**) with **2a**, which exclusively gave the coupling products **E2** and **E3** in excellent yields, without further isomerization to form **5** (Scheme 3).

When 3-iodocyclohex-2-enone **1b** reacted with **2i** in 3 mL of THF and 1 mL of Et_3N using 5 mol % of $Pd(PPh_3)_2Cl_2$ and 3 mol % of CuI, the reaction afforded polycyclic isoindoline derivative **3l** in 35% yield (Scheme 4).

In summary, we have developed a convenient sequential Sonogashira coupling, propargyl−allenyl isomerization, [4 + 2] cycloaddition and aromatization reaction, leading to a facile and efficient synthesis of polycyclic isoindoline derivatives. In respect to the easy availability of the starting materials, simple manipulation, mild conditions and high efficiency, this reaction will be synthetically useful in organic chemistry.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under a N_2 atmosphere. Anhydrous solvents were distilled prior to use: THF was distilled from sodium-benzophenone; DMF was distilled from CaH_2. Petroleum ether refers to the fraction with the boiling point in the range 60−90 °C. All ^1H NMR and ^{13}C NMR spectra were measured in $CDCl_3$ with TMS as the internal standard. Chemical shifts are expressed in ppm, and *J* values are given in Hz.

1. Sequential Reactions Involving Coupling, Rearrangement, Intramolecular [4 + 2] Cycloaddtion, and Aromatizaiton for the Synthesis of Isoindoline Derivatives 3. *(1). 7,7-Dimethyl-4-phenyl-2-tosyl-2,3,7,8-tetrahydro-1H-benzo[f]isoindol-5(6H)-one (**3a**). Typical Procedure.* An oven-dried Schlenk tube containing a Teflon-coated stirring bar was charged with $PdCl_2(PPh_3)_2$ (9 mg, 5 mol %) and CuI (2 mg, 3 mol %). The Schlenk tube was sealed, evacuated and backfilled with N_2 (3 cycles). A solution of **1a** (63 mg, 0.25 mmol) and **2a** (97 mg, 0.3 mmol) in THF (3.0 mL) was subsequently injected to the Schlenk tube, and then 0.1 mL of Et_3N was injected. The reaction mixture was stirred at rt for 0.5 h, and then 4 equiv of DBN was added, and the resulting mixture was stirred for 2 h. When the reaction was complete as determined by TLC analysis, the resulting mixture was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with Et_2O. The combined organic extracts were washed sequentially with water and brine. The organic layers were dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 4/1) to afford 78 mg (72%) of **3a**. Pale solid: mp 180−184 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.4 Hz, 2H), 7.44−7.34 (m, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.06−6.98 (m, 3H), 4.66

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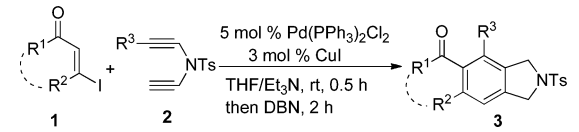
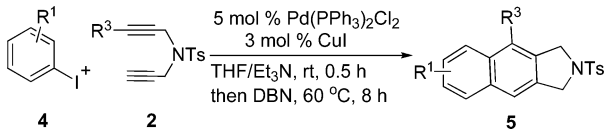
Table 2. Sequential Reactions Involving Coupling, Rearrangement, Intramolecular [4 + 2] Cycloadditon, and Aromatizaiton for the Synthesis of Isoindoline Derivatives 3[a]



entry	1	2	3	yield of 3 (%)[b]
1	1a	2a	3a	72
2	1a	2b	3b	75
3	1a	2c	3c	83
4	1a	2d	3d	65
5	1a	2e	3e	68
6	1a	2f	3f	61
7	1b	2a	3g	78
8	1b	2d	3h	64
9	1c	2a	3i	62
10	1d	2a	3j	76
11	1d	2c	3k	72

[a]The reaction was carried out using 1 (0.25 mmol) and 2 (0.3 mmol) in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ and 3 mol % of CuI in 3 mL of THF and 0.1 mL of Et_3N at rt for 30 min, and then 4 equiv of DBN was added, and the resulting mixture was stirred for 2 h. [b]Isolated yields.

Table 3. Sequential Reactions Involving Coupling, Rearrangement, Intramolecular [4 + 2] Cycloadditon, and Aromatizaiton for the Synthesis of Isoindoline Derivatives 5[a]



entry	4	2	5	yield of 5 (%)[b]
1	4a	2a	5a	62
2	4a	2b	5b	67
3	4a	2c	5c	72
4	4a	2d	5d	76
5	4a	2e	5e	57
6	4a	2g	5g	61
7	4a	2h	5h	35
8	4b	2a	5i	54
9	4c	2a	5j	57

[a]The reaction was carried out using 4 (0.5 mmol) and 2 (0.6 mmol) in the presence of 5 mol % of $Pd(PPh_3)_2Cl_2$ and 3 mol % of CuI in 6 mL of THF and 0.2 mL of Et_3N at rt for 30 min, and then 4 equiv of DBN was added, and the resulting mixture was stirred at 60 °C for 8 h. [b]Isolated yields.

(s, 2H), 4.24 (s, 2H), 2.86 (s, 2H), 2.40 (s, 3H), 2.38 (s, 2H), 1.04 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.7, 143.9, 143.7, 140.7, 139.8, 138.6, 135.5, 133.5, 129.8, 129.4, 128.4, 127.5, 127.0, 126.9, 122.7, 54.0, 53.8, 53.1, 44.7, 33.4, 28.0, 21.5 ppm; MS (EI, 70ev) m/z (%) 445 (M^+, 10.42), 290 (100); IR (neat) 2962, 1696, 1602, 1511, 1458, 1343, 1268, 1222, 1158, 1092, 1057 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{27}NO_3S$ (M^+) 445.1712, found 445.1715.

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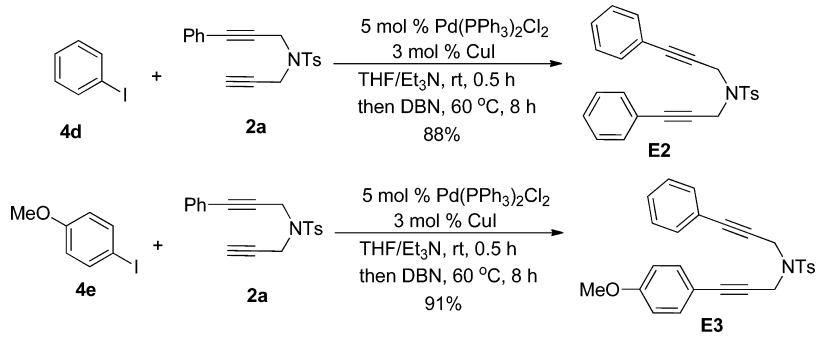
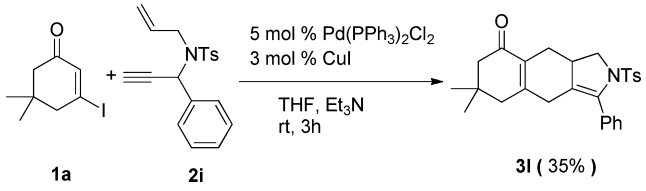
Scheme 3



Scheme 4



The following compounds were prepared according to this procedure.

*(2). 7,7-Dimethyl-4-p-tolyl-2-tosyl-2,3,7,8-tetrahydro-1H-benzo-[f]isoindol-5(6H)- one (**3b**).* Yield: 75% (86 mg). Pale solid: mp 188−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.0 Hz, 2H), 7.30 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 7.6 Hz, 2H), 7.00 (s, 1H), 6.91 (d, J = 7.6 Hz, 2H), 4.64 (s, 2H), 4.25 (s, 2H), 2.85 (s, 2H), 2.39 (s, 3H), 2.38 (s, 3H), 2.37 (s, 2H), 1.03 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 143.9, 143.7, 140.5, 138.6, 136.7, 136.4, 135.5, 133.4, 129.7, 129.5, 129.0, 127.4, 126.7, 122.5, 54.0, 53.8, 53.2, 44.6, 33.3, 27.9, 21.4, 21.2 ppm; MS (EI, 70ev) m/z (%) 459 (M^+, 13.45), 304 (100); IR (neat) 2957, 1690, 1602, 1512, 1438, 1345, 1287, 1224, 1161, 1094, 1055, 1017 cm^{-1}; HRMS (EI) calcd. for $C_{28}H_{29}NO_3S$ (M^+) 459.1868, found 459.1864.

*(3). 4-(4-Fluorophenyl)-7,7-dimethyl-2-tosyl-2,3,7,8-tetrahydro-1H- benzo[f]isoindol-5(6H)-one (**3c**).* Yield: 83% (96 mg). Pale solid: mp 217−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.2 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 7.16−7.07 (m, 3H), 6.99 (t, J = 6.0 Hz, 2H), 4.66 (s, 2H), 4.22 (s, 2H), 2.87 (s, 2H), 2.44−2.35 (m, 5H), 1.04 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.8, 161.8 (d, J = 244.1 Hz), 144.1, 143.8, 140.7, 137.5, 135.6, 133.3, 129.8, 129.4, 128.6 (d, J = 8.4 Hz), 127.4, 123.0, 115.5, 115.2, 53.9, 53.8, 53.0, 44.6, 33.3, 27.9, 21.4 ppm; MS (EI, 70ev) m/z (%) 463 (M^+, 12.32), 308 (100); IR (neat) 2958, 1690, 1604, 1508, 1451, 1344, 1267, 1225, 1157, 1092, 1052 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{26}NO_3SF$ (M^+) 463.1617, found 463.1620.

*(4). 4-(4-Methoxyphenyl)-7,7-dimethyl-2-tosyl-2,3,7,8-tetrahydro-1H- benzo[f]isoindol-5(6H)-one (**3d**).* Yield: 65% (77 mg). Pale solid: mp 190−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 7.6 Hz, 2H), 7.03 (s, 1H), 6.94 (t, J = 9.6 Hz, 4H), 4.65 (s, 2H), 4.26 (s, 2H), 3.86 (s, 3H), 2.86 (s, 2H), 2.44−2.35 (m, 5H), 1.04 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 158.5, 143.9, 143.7, 140.5, 138.4, 135.9, 133.4, 131.8, 129.8, 129.6, 128.1, 127.5, 122.5, 113.8, 55.2, 54.0, 53.9, 53.2, 44.7, 33.3, 28.0, 21.5 ppm; MS (EI, 70ev) m/z (%) 475 (M^+, 48.43), 320 (100); IR (neat) 2962, 1687, 1606, 1513, 1455, 1345, 1268, 1244, 1160, 1095, 1052, 1029 cm^{-1}; HRMS (EI) calcd. for $C_{28}H_{29}NO_4S$ (M^+) 475.1817, found 475.1813.

*(5). 4-Butyl-7,7-dimethyl-2-tosyl-2,3,7,8-tetrahydro-1H-benzo[f]-isoindol- 5(6H)-one (**3e**).* Yield: 68% (72 mg). Pale solid: mp 130−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.88 (s, 1H), 4.61 (s, 4H), 2.86 (t, J = 7.2 Hz, 2H), 2.79 (s, 2H), 2.45 (s, 2H), 2.41 (s, 3H), 1.42 (t, J = 3.6 Hz, 4H), 1.02 (s, 6H), 0.95 (t, J = 6.6 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.6, 144.5, 143.8, 140.9, 140.6, 135.1, 133.5, 129.8, 129.2, 127.5, 121.2, 54.6, 54.0, 52.8, 45.1, 33.0, 32.0, 31.6, 27.9, 23.3, 21.5, 13.9 ppm; MS (EI, 70ev) m/z (%) 425 (M^+, 18.75), 270 (100); IR (neat) 2957, 1685, 1605, 1513, 1453, 1343, 1245, 1159, 1096, 1057 cm^{-1}; HRMS (EI) calcd. for $C_{25}H_{31}NO_3S$ (M^+) 425.2025, found 425.2028.

*(6). 4-Cyclopropyl-7,7-dimethyl-2-tosyl-2,3,7,8-tetrahydro-1H-benzo[f]isoindol- 5(6H)-one (**3f**).* Yield: 61% (62 mg). Pale solid: mp 138−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.4 Hz, 2H), 6.89 (s, 1H), 4.68 (s, 2H), 4.57 (s, 2H), 2.77 (s, 2H), 2.48 (s, 2H), 2.41 (s, 3H), 2.15−2.06 (m, 1H), 1.04−0.95 (m, 8H), 0.26−0.18 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.7, 143.7, 143.6, 140.3, 139.7, 136.9, 133.4, 132.8, 129.8, 127.5, 121.3, 54.2, 53.5, 53.0, 44.6, 33.7, 28.1, 21.4, 13.8, 8.2 ppm; MS (EI, 70ev) m/z (%) 409 (M^+, 6.65), 254 (100); IR (neat) 2964, 1686, 1605, 1513, 1452, 1338, 1279, 1245, 1158, 1094, 1056, 1029 cm^{-1}; HRMS (EI) calcd. for $C_{24}H_{27}NO_3S$ (M^+) 409.1712, found 409.1715.

*(7). 4-Phenyl-2-tosyl-2,3,7,8-tetrahydro-1H-benzo[f]isoindol-5(6H)-one (**3g**).* Yield: 78% (81 mg). Pale solid: mp 188−191 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 8.0 Hz, 2H), 7.44−7.33 (m, 3H), 7.30 (d, J = 8.0 Hz, 2H), 7.08 (s, 1H), 7.01 (d, J = 6.4 Hz, 2H), 4.65 (s, 2H), 4.23 (s, 2H), 2.96 (t, J = 5.8 Hz, 2H), 2.53 (t, J = 6.4 Hz, 2H), 2.40 (s, 3H), 2.11−2.02 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 145.7, 143.7, 140.3, 139.8, 138.9, 135.5, 133.4, 130.3, 129.8, 128.3, 127.4, 126.9, 126.8, 122.1, 54.0, 53.1, 40.3, 30.9, 22.8, 21.4 ppm; MS (EI, 70ev) m/z (%) 397 (M^+, 16.90), 242 (100); IR (neat) 2958, 1686, 1604, 1513, 1453, 1343, 1244, 1159, 1095, 1056, 1028 cm^{-1}; HRMS (EI) calcd. for $C_{25}H_{23}NO_3S$ (M^+) 417.1399, found 417.1394.

*(8). 4-Butyl-2-tosyl-2,3,7,8-tetrahydro-1H-benzo[f]isoindol-5(6H)-one (**3h**).* Yield: 64% (64 mg). Pale solid: mp 165−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.92 (s, 1H), 4.61 (s, 4H), 2.89 (t, J = 6.0 Hz, 2H), 2.84 (t, J = 6.8 Hz, 2H), 2.61 (t, J = 6.6 Hz, 2H), 2.41 (s, 3H), 2.06−1.96 (m, 2H), 1.43 (d, J = 1.8 Hz, 4H), 0.95 (t, J = 6.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 199.4, 146.2, 143.8, 141.0, 140.3, 135.1, 133.4, 130.1, 129.8, 127.4, 120.5, 54.0, 52.8, 41.0, 32.0, 31.7, 31.3, 23.2, 22.7, 21.4, 13.8 ppm; MS (EI, 70ev) m/z (%) 425 (M^+, 18.75), 270 (100); IR (neat) 2951, 1685, 1605, 1512, 1457, 1344, 1289, 1239, 1157, 1096, 1019 cm^{-1}; HRMS (EI) calcd. for $C_{23}H_{27}NO_3S$ (M^+) 397.1712, found 397.1714.

*(9). 4-Phenyl-2-tosyl-2,3,6,7-tetrahydrocyclopenta[f]isoindol-5(1H)-one (**3i**).* Yield: 62% (61 mg). Pale solid: mp 234−237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 7.42 (d, J = 4.8 Hz, 3H), 7.32 (d, J = 7.6 Hz, 2H), 7.24 (s, 1H), 7.17 (t, J = 3.6 Hz, 2H), 4.68 (s, 2H), 4.39 (s, 2H), 3.08 (t, J = 5.6 Hz, 2H), 2.64 (t, J = 5.8 Hz, 2H), 2.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.5, 156.5, 143.8, 143.0, 136.1, 135.4, 135.3, 133.32, 133.26, 129.9, 128.2, 128.1, 127.5, 119.8, 53.7, 52.4, 37.1, 25.0, 21.5 ppm; MS (EI, 70ev) m/z (%) 403 (M^+, 8.82), 248 (100); IR (neat) 1705, 1603, 1452, 1341, 1269, 1247, 1159, 1091, 1091, 1055 cm^{-1}; HRMS (EI) calcd. for $C_{24}H_{21}NO_3S$ (M^+) 403.1242, found 403.1247.

*(10). Ethyl 4-phenyl-2-tosylisoindoline-5-carboxylate (**3j**).* Yield: 76% (80 mg). Pale solid: mp 170−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.6 Hz, 1H), 7.70 (d, J = 8.0 Hz, 2H), 7.39 (d, J

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= 6.8 Hz, 3H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H),7.12 (t, *J* = 7.6 Hz, 2H), 4.69 (s, 2H), 4.37 (s, 2H), 3.99 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 143.7, 139.5, 138.5, 137.9, 136.3, 133.4, 130.6, 129.9, 129.8, 128.2, 127.6, 127.5, 127.4, 121.4, 60.8, 54.0, 53.3, 21.5, 13.5 ppm; MS (EI, 70ev) *m*/*z* (%) 421 (M^+, 9.85), 266 (100); IR (neat) 2955, 1701, 1603, 1512, 1459, 1344, 1286, 1224, 1159, 1127, 1095, 1061, 1017 cm^{-1}; HRMS (EI) calcd. for $C_{24}H_{23}NO_4S$ (M^+) 421.1348, found 421.1349.

(11). Ethyl 4-(4-fluorophenyl)-2-tosylisoindoline-5-carboxylate ***(3k)***. Yield: 72% (79 mg). Pale solid: mp 152−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.71 (d, *J* = 8.4 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 8.0 Hz, 1H), 7.10 (d, *J* = 7.2 Hz, 4H), 4.69 (s, 2H), 4.34 (s, 2H), 4.03 (q, *J* = 7.2 Hz, 2H), 2.40 (s, 3H), 0.98 (t, *J* = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 162.2 (d, *J* = 245.4 Hz), 143.8, 139.7, 136.9, 136.5, 134.4 (d, *J* = 3.6 Hz), 133.3, 130.5, 130.1, 129.8, 129.4 (d, *J* = 9.0 Hz), 127.4, 121.6, 115.3 (d, *J* = 21.2 Hz), 60.9, 54.0, 53.2, 21.4, 13.6 ppm; MS (EI, 70ev) *m*/*z* (%) 439 (M^+, 8.90), 284 (100); IR (neat) 2960, 1700, 1602, 1511, 1462, 1367, 1321, 1286, 1224, 1160, 1127, 1092, 1057, 1014 cm^{-1}; HRMS (EI) calcd. for $C_{24}H_{22}NO_4SF$ (M^+) 439.1254, found 439.1258.

2. Sequential Reactions Involving Coupling, Rearrangement, Intramolecular [4 + 2] Cycloaddtion, and Aromatizaiton for the Synthesis of Isoindoline Derivatives 5. *(1). Methyl 4-phenyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-6-carboxylate* ***(5a)***. *Typical Procedure.* An oven-dried Schlenk tube containing a Teflon-coated stirring bar was charged with $PdCl_2(PPh_3)_2$ (18 mg, 5 mol %) and CuI (3 mg, 3 mol %). The Schlenk tube was sealed, evacuated and backfilled with N_2 (3 cycles). A solution of **4a** (131 mg, 0.5 mmol) and **2a** (194 mg, 0.6 mmol) in THF (6.0 mL) was subsequently injected to the Schlenk tube, and then 0.2 mL of Et_3N was injected. The reaction mixture was stirred at rt for 0.5 h, and then 4 equiv of DBN (248 mg, 2 mmol) were added, and the resulting mixture was stirred at 60 °C for 8 h. When the reaction was complete as determined by TLC analysis, the resulting mixture was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with Et_2O. The combined organic extracts were washed sequentially with water and brine. The organic layers were dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 4/1) to afford 142 mg (62%) of **5a**. Pale solid: mp 195−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1H), 8.02 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.67 (s, 1H), 7.57−7.47 (m, 3H), 7.34−7.23 (m, 4H), 4.80 (s, 2H), 4.49 (s, 2H), 3.85 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.8, 136.8, 136.6, 135.8, 135.5, 134.4, 133.1, 130.9, 129.8, 129.2, 128.9, 128.7, 128.2, 128.1, 127.6, 125.3, 120.5, 53.5, 53.0, 52.2, 21.4 ppm; MS (EI, 70ev) *m*/*z* (%) 457 (M^+, 4.41), 301 (100); IR (neat) 2954, 1717, 1599, 1508, 1443, 1342, 1284, 1259, 1226, 1161, 1058, 1000 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{23}NO_4S$ (M^+) 457.1348, found 457.1342.

(2). Methyl 4-p-tolyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-6-carboxylate ***(5b)***. Yield: 67% (158 mg). Pale solid: mp 233−237 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.00 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.63 (s, 1H), 7.34−7.25 (m, 4H), 7.13 (d, *J* = 7.6 Hz, 2H), 4.78 (s, 2H), 4.49 (s, 2H), 3.85 (s, 3H), 2.47 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 143.7, 137.8, 136.8, 135.8, 135.5, 134.4, 133.5, 133.1, 131.0, 129.7, 129.5, 129.0, 128.7, 128.1, 127.5, 127.4, 125.2, 120.3, 53.5, 53.0, 52.1, 21.4, 21.2 ppm; MS (EI, 70ev) *m*/*z* (%) 471 (M^+, 15.81), 315 (100); IR (neat) 2953, 1714, 1597, 1447, 1338, 1314, 1285, 1262, 1226, 1161, 1095, 1059 cm^{-1}; HRMS (EI) calcd. for $C_{28}H_{25}NO_4S$ (M^+) 471.1504, found 471.1508.

(3). Methyl 4-(4-fluorophenyl)-2-tosyl-2,3-dihydro-1H-benzo[f]-isoindole-6- carboxylate ***(5c)***. Yield: 72% (171 mg). Pale solid: mp 196−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.68 (s, 1H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.24 (d, *J* = 6.0 Hz, 4H), 4.80 (s, 2H), 4.47 (s, 2H), 3.87 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 162.5 (d, *J* = 245.8 Hz), 143.9, 136.8, 135.5, 134.6 (d, *J* = 11.9 Hz), 133.1, 132.5 (d, *J* = 3.0 Hz), 131.0, 130.9, 129.8, 128.4, 128.2, 127.7, 127.6, 125.4, 120.8, 116.2, 116.0, 53.5, 52.9, 52.2, 21.5 ppm; MS (EI, 70ev) *m*/*z* (%) 475 (M^+, 11.54), 319 (100); 2953, 1711, 1602, 1513, 1446, 1339, 1286, 1261, 1222, 1150, 1119, 1096, 1067, 1001 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{22}NO_4SF$ (M^+) 475.1254, found 475.1257.

(4). Methyl 4-(4-methoxyphenyl)-2-tosyl-2,3-dihydro-1H-benzo-[f]isoindole-6- carboxylate ***(5d)***. Yield: 76% (185 mg). Pale solid: mp 217−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.00 (d, *J* = 8.8 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.63 (s, 1H), 7.29 (d, *J* = 7.6 Hz, 2H), 7.17 (d, *J* = 8.0 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 4.78 (s, 2H), 4.50 (s, 2H), 3.91 (s, 3H), 3.86 (s, 3H), 2.37 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.0, 159.4, 143.7, 136.8, 135.6, 134.6, 133.3, 131.2, 130.4, 129.7, 128.7, 128.1, 127.53, 127.46, 125.2, 120.2, 114.3, 55.3, 53.5, 53.0, 52.1, 21.4 ppm; MS (EI, 70ev) *m*/*z* (%) 487 (M^+, 7.56), 331 (100); IR (neat) 2951, 1714, 1608, 1513, 1442, 1338, 1285, 1253, 1226, 1155, 1098, 1025 cm^{-1}; HRMS (EI) calcd. for $C_{28}H_{25}NO_5S$ (M^+) 487.1453, found 487.1453.

(5). Methyl 4-butyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-6-carboxylate ***(5e)***. Yield: 57% (125 mg). Pale solid: mp 182−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (s, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.86−7.74 (m, 3H), 7.51 (s, 1H), 7.33 (d, *J* = 7.6 Hz, 2H), 4.76 (s, 2H), 4.74 (s, 2H), 3.98 (s, 3H), 2.95 (t, *J* = 7.8 Hz, 2H), 2.39 (s, 3H), 1.68−1.56 (m, 2H), 1.52−1.41 (m, 2H), 0.98 (t, *J* = 7.4 Hz, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 143.8, 136.9, 135.9, 134.9, 133.9, 133.3, 130.4, 129.8, 128.7, 127.6, 127.2, 126.7, 124.9, 119.2, 53.5, 52.6, 52.3, 32.5, 29.6, 23.0, 21.5, 13.9 ppm; MS (EI, 70ev) *m*/*z* (%) (M^+, 10.84), 281 (100); IR (neat) 2952, 1713, 1612, 1447, 1402, 1346, 1284, 1259, 1226, 1162, 1096, 1063 cm^{-1}; HRMS (EI) calcd. for $C_{25}H_{27}NO_4S$ (M^+) 437.1661, found 437.1666.

(6). Methyl 4-(4-chlorophenyl)-2-tosyl-2,3-dihydro-1H-benzo[f]-isoindole-6-carboxylate ***(5g)***. Yield: 61% (150 mg). Pale solid: mp 238−241 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (s, 1H), 8.04 (d, *J* = 8.0 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.69 (s, 1H), 7.52 (d, *J* = 7.6 Hz, 2H), 7.32 (d, *J* = 7.6 Hz, 2H), 7.21 (d, *J* = 7.2 Hz, 2H), 4.80 (s, 2H), 4.46 (s, 2H), 3.88 (s, 3H), 2.40 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.9, 143.9, 140.2, 136.9, 135.6, 135.0, 134.53, 134.49, 134.35, 133.1, 130.8, 130.6, 129.9, 129.3, 128.3, 127.8, 127.6, 125.5, 120.9, 53.5, 52.9, 52.3, 21.5 ppm; MS (EI, 70ev) *m*/*z* (%) 493 (M^+(^{37}Cl), 2.38), 491 (M^+(^{35}Cl), 6.27), 335 (100); IR (neat) 3090, 1713, 1614, 1496, 1445, 1339, 1286, 1260, 1227, 1201, 1151, 1093, 1066, 1004 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{22}NO_4S^{35}Cl$ (M^+) 491.0958, found 491.0952.

(7). Methyl 4-(4-(methoxycarbonyl)phenyl)-2-tosyl-2,3-dihydro-1H- benzo[f]isoindole-6-carboxylate ***(5h)***. Yield: 35% (90 mg). Pale solid: mp 172−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 3H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 1H), 7.73 (t, *J* = 8.2 Hz, 3H), 7.36 (d, *J* = 7.6 Hz, 2H), 7.31 (d, *J* = 7.6 Hz, 2H), 4.80 (s, 2H), 4.45 (s, 2H), 4.01 (s, 3H), 3.86 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 166.6, 143.9, 141.4, 136.9, 135.5, 134.6, 134. 3, 133.0, 130.5, 130.2, 130.0, 129.8, 129.4, 128.3, 128.1, 127.8, 127.5, 125.5, 121.1, 53.4, 52.7, 52.3, 52.2, 21.4 ppm; MS (EI, 70ev) *m*/*z* (%) 515 (M^+, 6.05), 359 (100); IR (neat) 2954, 1713, 1610, 1440, 1401, 1347, 1284, 1259, 1163, 1095, 1063 cm^{-1}; HRMS (EI) calcd. for $C_{29}H_{25}NO_6S$ (M^+) 515.1403, found 515.1408.

(8). Methyl 9-phenyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-5-carboxylate ***(5i)***. Yield: 54% (123 mg). Pale solid: mp 196−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (s, 1H), 8.12 (d, *J* = 6.8 Hz, 1H), 7.74 (t, *J* = 7.6 Hz, 3H), 7.56−7.44 (m, 3H), 7.36−7.26 (m, 3H), 7.22 (d, *J* = 6.8 Hz, 2H), 4.82 (s, 2H), 4.48 (s, 2H), 3.98 (s, 3H), 2.36 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 143.7, 137.2, 136.1, 134.6, 133.6, 133.1, 132.1, 131.3, 130.9, 130.0, 129.7, 129.2, 128.7, 127.9, 127.5, 126.7, 124.4, 118.6, 53.8, 53.0, 52.2, 21.4 ppm; MS (EI, 70ev) *m*/*z* (%) 457 (M^+, 7.61), 301 (100); IR (neat) 2952, 1712, 1597, 1509, 1426, 1343, 1315, 1257, 1184, 1157, 1094, 1065, 1013 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{23}NO_4S$ (M^+) 457.1348, found 457.1346.

*(9). Methyl 9-phenyl-2-tosyl-2,3-dihydro-1H-benzo[f]isoindole-5-carboxylate (**5j**).* Yield: 57% (126 mg). Pale solid: mp 190−193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 8.8 Hz, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.67 (s, 1H), 7.58−7.46 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 7.2 Hz, 2H), 4.80 (s, 2H), 4.50 (s, 2H), 2.49 (s, 3H), 2.39 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 143.8, 137.1, 136.5, 136.0, 135.6, 134. 53, 134.46, 133.1, 131.0, 129.8, 129.2, 128.9, 128.4, 128.3, 127.9, 127.6, 123.9, 120.5, 53.5, 52.9, 26.5, 21.5 ppm; MS (EI, 70ev) m/z (%) 441 (M^+, 12.20), 285 (100); IR (neat) 3058, 1715, 1686, 1602, 1494, 1344, 1339, 1310, 1285, 1254, 1223, 1157, 1091, 1056 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{23}NO_3S$ (M^+) 441.1399, found 441.1394.

3. Reactions Affording the Direct Coupling Products E1, E2, and E3. *(1). N-(3-(5,5-Dimethyl-3-oxocyclohex-1-en-1-yl)prop-2-yn-1-yl)-4-methyl-N-(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**E1**).* Yield: 93% (103 mg). Oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.0 Hz, 2H), 7.33−7.18 (m, 7H), 5.95 (s, 1H), 4.44 (s, 2H), 4.39 (s, 2H), 2.38 (s, 3H), 2.20 (s, 2H), 2.11 (s, 2H), 0.99 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.6, 144.0, 139.9, 135.2, 131.9, 131.5, 129.6, 128.6, 128.1, 127.9, 127.8, 121.9, 92.0, 89.0, 84.8, 81.2, 50.8, 43.7, 37.7, 37.5, 33.4, 27.9, 21.4 ppm; MS (EI, 70ev) m/z (%) 445 (M^+, 6.43), 91(100); IR (neat) 2958, 1663, 1596, 1491, 1440, 1351, 1305, 1277, 1243, 1161, 1093 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{27}NO_3S$ (M^+) 445.1712, found 445.1717.

*(2). 4-Methyl-N,N-bis(3-phenylprop-2-yn-1-yl)benzenesulfonamide (**E2**).* Yield: 88% (176 mg). Oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 2H), 7.29−7.16 (m, 12H), 4.44 (s, 4H), 2.28 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 135.2, 131.5, 129.5, 128.4, 128.1, 127.8, 122.0, 85.7, 81.5, 37.4, 21.3 ppm; MS (EI, 70ev) m/z (%) 399 (M^+, 2.23), 243 (100); IR (neat) 3058, 1597, 1490, 1440, 1350, 1256, 1160, 1093, 1070, 1026 cm^{-1}; HRMS (EI) calcd. for $C_{25}H_{21}NO_2S$ (M^+) 399.1293, found 399.1296.

*(3). N-(3-(4-Methoxyphenyl)prop-2-yn-1-yl)-4-methyl-N-(3-phenylprop-2-yn-1-yl) benzenesulfonamide (**E3**).* Yield: 91% (195 mg). Oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 2H), 7.32−7.12 (m, 9H), 6.77 (d, J = 8.8 Hz, 2H), 4.44 (s, 2H), 4.42 (s, 2H), 3.77 (s, 3H), 2.31 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 143.7, 135.3, 133.1, 131.6, 129.5, 128.4, 128.1, 127.8, 122.1, 114.2, 113.7, 85.7, 81.6, 80.1, 55.2, 37.5, 37.4, 21.4 ppm; MS (EI, 70ev) m/z (%) 429 (M^+, 16.12), 273 (100); IR (neat) 2926, 1603, 1509, 1440, 1349, 1291, 1247, 1160, 1093 cm^{-1}; HRMS (EI) calcd. for $C_{26}H_{23}NO_3S$ (M^+) 429.1399, found 429.1394.

Synthesis of 6,6-Dimethyl-3-phenyl-2-tosyl-4,5,6,7,9,9a-hexahydro-1*H*-benzo-[*f*]isoindol-8(2*H*)-one (3l). An oven-dried Schlenk tube containing a Teflon-coated stirring bar were charged with $PdCl_2(PPh_3)_2$ (9 mg, 5 mol %) and CuI (2 mg, 3 mol %). The Schlenk tube was sealed, evacuated and backfilled with N_2 (3 cycles). A solution of **1a** (63 mg, 0.25 mmol) and **2i** (97 mg, 0.3 mmol) in THF (3.0 mL) was subsequently injected to the Schlenk tube, and then 1 mL of Et_3N was injected. The reaction mixture was stirred at rt for 3 h. When the reaction was complete as determined by TLC analysis, the resulting mixture was quenched with a saturated aqueous solution of ammonium chloride, and the mixture was extracted with Et_2O. The combined organic extracts were washed sequentially with water and brine. The organic layers were dried over Na_2SO_4 and filtered. Solvents were evaporated under reduced pressure. The residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 6/1) to afford 39 mg (35%) of **3l**. Oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 8.8 Hz, 2H), 7.46−7.33 (m, 5H), 7.27−7.24 (m, 2H), 4.24 (dd, J_1 = 8.8 Hz, J_2 = 12.8 Hz, 1H), 3.57 (dd, J_1 = 9.2 Hz, J_2 = 12.4 Hz, 1H), 3.01−2.84 (m, 3H), 2.52−2.39 (m, 4H), 2.21 (s, 2H), 2.17−1.99 (m, 2H), 1.64−1.55 (m, 1H), 0.95 (s, 3H), 0.93 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 198.2, 151.4, 143.7, 135.5, 133.7, 132.5, 129.4, 129.1, 128.9, 128.3, 127.9, 127.8, 126.2, 56.8, 51.2, 44.8, 38.5, 33.0, 32.0, 28.7, 28.3, 28.1, 21.6. ppm; MS (EI, 70ev) m/z (%) 447 (M^+, 4.08), 292 (100); IR (neat) 2961, 1670, 1443, 1301, 1243, 1162, 1093 cm^{-1}; HRMS (EI) calcd. for $C_{27}H_{29}NO_3S$ (M^+) 447.1868, found 447.1865.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^{1}H and ^{13}C NMR spectra for **3**, **5**, **E**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

†Prof. Xian Huang passed away on March 6, 2010. He had been fully in charge of this project. At this moment, Prof. Luling Wu is helping him to finish all the projects with the help from Prof. Shengming Ma.

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