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INTRAMOLECULAR HECK INSERTION OF A DIENE-ALLYLIC AMINATION CASCADE TO SYNTHESIZE A 2-ALKENYL-3,4-FUSED INDOLE STRUCTURE

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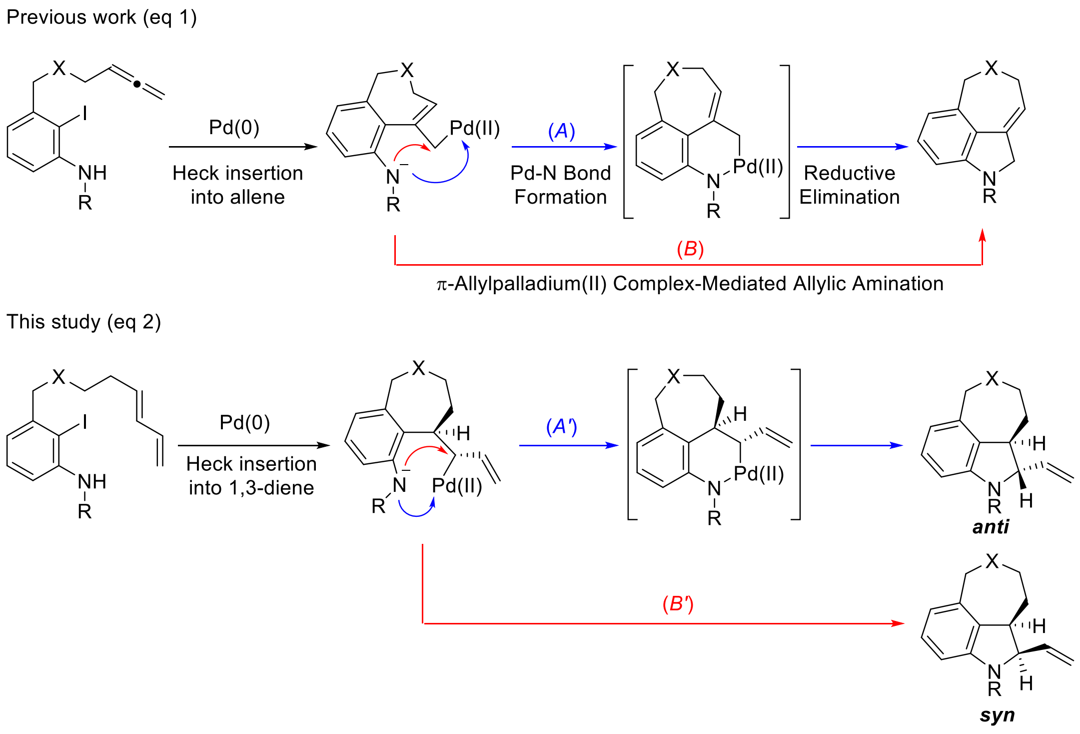
Dedicated with respect to Professor Kiyoshi Tomioka on his 70th birthday

Abstract – Iodoanilines bearing a diene side-chain at the 3-position were converted to tricyclic fused indole derivatives under palladium catalysis. This cascade reaction proceeds through an intramolecular Heck insertion of the diene, followed by an allylic amination reaction sequence. Experimental and computational studies indicated that η^3 π-allylpalladium complex-mediated substitution was operative for the latter cyclization.

Functionalized indole derivatives are an important class of heteroaromatic scaffolds present as the core structure in a wide variety of biologically active molecules.[1] Among them, synthetic organic chemists have focused considerable attention on 3,4-fused indole frameworks as a privileged molecular architecture due to their structural complexity as well as their ubiquity in natural products. Recent efforts have been directed toward constructing 3,4-fused tricyclic indole skeletons based on synthetic strategies using transition metal-catalyzed intramolecular formal (3+2) annulation reactions.[2] Our group also reported a palladium-catalyzed tandem cyclization through intramolecular Heck insertion of an allene−allylic amination cascade for the straightforward synthesis of a 3,4-fused indole skeleton (scheme 1, eq 1).[3] A detailed mechanistic analysis of the reaction, however, has not yet been performed, and whether the allylic amination step proceeds *via* η^3 π-allylpalladium complex-mediated substitution (path B) or reductive elimination from a palladacycle intermediate (path A) remains unknown. Given the paucity of studies of the reaction mechanism and the ubiquity of these tricyclic structures, our group has endeavored to design and develop a relevant reaction sequence[4] as well as synthetic application of these structures.[5]

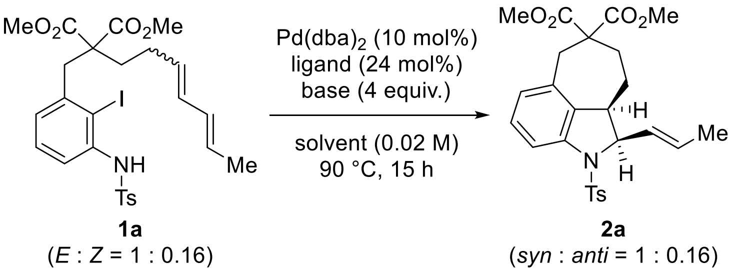
Palladium-catalyzed Heck insertion reaction of 1,3-dienes enables C-C bond formation accompanied by concomitant generation of π-allylpalladium species, enabling sequential functionalization with an external nucleophile.[6] We envisaged that an intramolecular Heck insertion-allylic amination cascade of 2-iodoaniline derivatives possessing a diene side-chain would be feasible for the synthesis of 3,4-fused indolines, which could be converted into indole derivatives under oxidative conditions (eq 2). In this reaction system, it would be possible to determine which reaction pathways are operative for the allylic amination step based on the relative configurations of the products (path A' or B'). Herein, we describe development of a palladium-catalyzed sequential reaction process to produce 2-substituted tricyclic indolines and its conversion into the corresponding 3,4-fused indole derivatives. Mechanistic studies on computational analysis were also performed to clarify the detailed mechanism.



Scheme 1. Synthesis of tricyclic indolines using Pd catalysis

We began our investigation with 2-iodo-aniline derivative **1a** possessing a diene side-chain at the 3-position as a model substrate (Table 1). Reaction of **1a** with Pd(dba)$_2$/TFP and K_2CO_3 in DMF solvent at 90 °C for 15 h afforded a functionalized tricyclic indoline **2a** in 35% yield (*syn* : *anti* = 1 : 0.16, entry 1).[7] The diastereomeric ratio of the product was identical to that of the substrate, supporting a stereospecificity of the reaction process. Solvent screening showed that toluene was a suitable reaction medium, improving the yield to 66% (entries 2-5). Subsequent survey of (bis)phosphine ligands showed no increase in the reaction efficiency (entries 6-9). After examining potentially applicable bases, the reaction conditions using potassium phosphate were determined to be optimal for this transformation (entry 15).

Table 1. Optimization of the reaction conditions

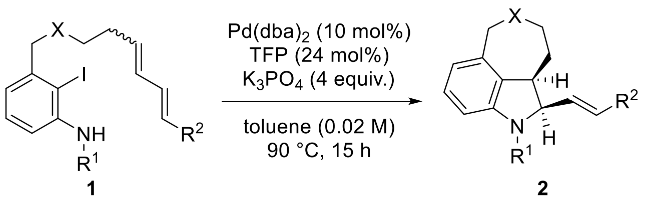


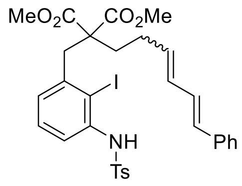
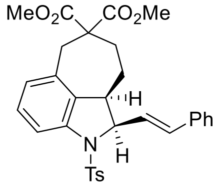
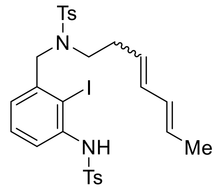
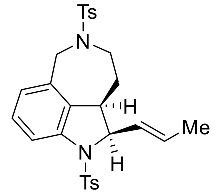
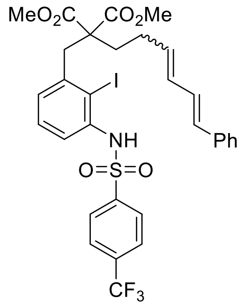
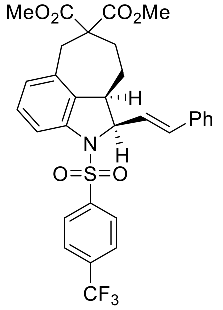
entry	solvent	ligand	base	yield of **2a**
1	DMF	TFP	K_2CO_3	35%
2	DMSO	TFP	K_2CO_3	36%
3	toluene	TFP	K_2CO_3	66%
4	dioxane	TFP	K_2CO_3	64%
5	$PhCF_3$	TFP	K_2CO_3	37%
6	toluene	PPh_3	K_2CO_3	46%
7	toluene	dppe	K_2CO_3	51%
8	toluene	dppf	K_2CO_3	43%
9	toluene	$AsPh_3$	K_2CO_3	40%
10	toluene	TFP	Li_2CO_3	trace
11	toluene	TFP	Cs_2CO_3	65%
12	toluene	TFP	KO*t*-Bu	43%
13	toluene	TFP	Et_3N	18%
14	toluene	TFP	$NaHCO_3$	19%
15	toluene	TFP	K_3PO_4	75%

TFP is tri-2-furylphosphine. dppf is 1,1'-bis(diphenylphosphino)ferrocene. dppe is 1,2-bis(diphenylphosphino)ethane.

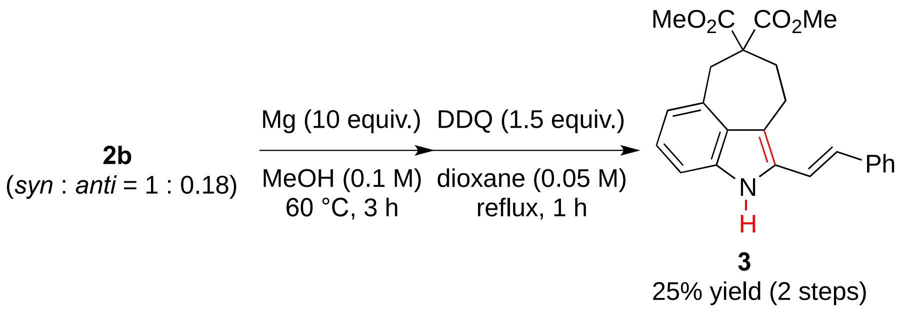
Having established the reaction conditions for the synthesis of indoline derivatives, we tested other substrates (table 2). Iodoaniline **1b** having a phenyl group on the diene moiety was converted into the corresponding indoline **2b** possessing a styryl group in excellent yield (96%, entry 1). The product **2c** containing an azepane ring was also accessible from sulfonamide-tethered diene **1c** under the optimum conditions (entry 2). Interestingly, an amino functionality with a highly electron-withdrawing group could be applied as the nucleophile on the allylic amination, furnishing **2d** in 75% yield (entry 3).

Table 2. Substrate scope



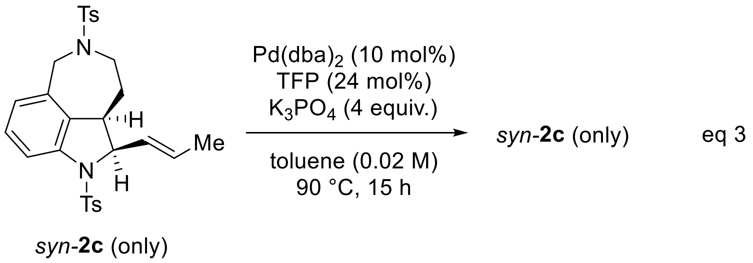
entry	1	2	yield
1	 **1b** (E : Z = 1 : 0.18)	 **2b** (*syn* : *anti* = 1 : 0.18)	96%
2	 **1c** (E : Z = 1 : 0.16)	 **2c** (*syn* : *anti* = 1 : 0.16)	89%
3	 **1d** (E : Z = 1 : 0.18)	 **2d** (*syn* : *anti* = 1 : 0.18)	75%

The synthesized indoline derivatives **2b** were transformed into 3,4-fused indole **3** through removal of the Ts group followed by DDQ oxidation (Scheme 2).



Scheme 2. Conversion from **2b** to indole derivatives. DDQ is 2,3-dichloro-5,6-dicyano-*p*-benzoquinone

Next, we initiated studies to gain mechanistic insight into the developed tandem cyclization. Treatment of *syn*-**2c** with Pd catalyst under the optimized conditions gave *syn*-**2c** as a sole isomer (eq 3), indicating that compound **2** obtained through the Heck insertion-allylic amination cascade was a kinetically controlled product.



To further elucidate the reaction mechanism, we performed density functional theory (DFT) calculations. The calculated potential energy profiles are summarized in Figure 1. Intramolecular migratory insertion of the (*E*, *E*)-diene **CP1** into the carbon-palladium bond proceeds with an activation energy of 27.5 kcal/mol, giving σ-allyl complex **INT1**. Two possible pathways exist for the latter allylic amination: reductive elimination from palladacycle intermediate **INT2** (depicted in blue) or η^3 π-allylpalladium complex-mediated substitution (depicted in red).

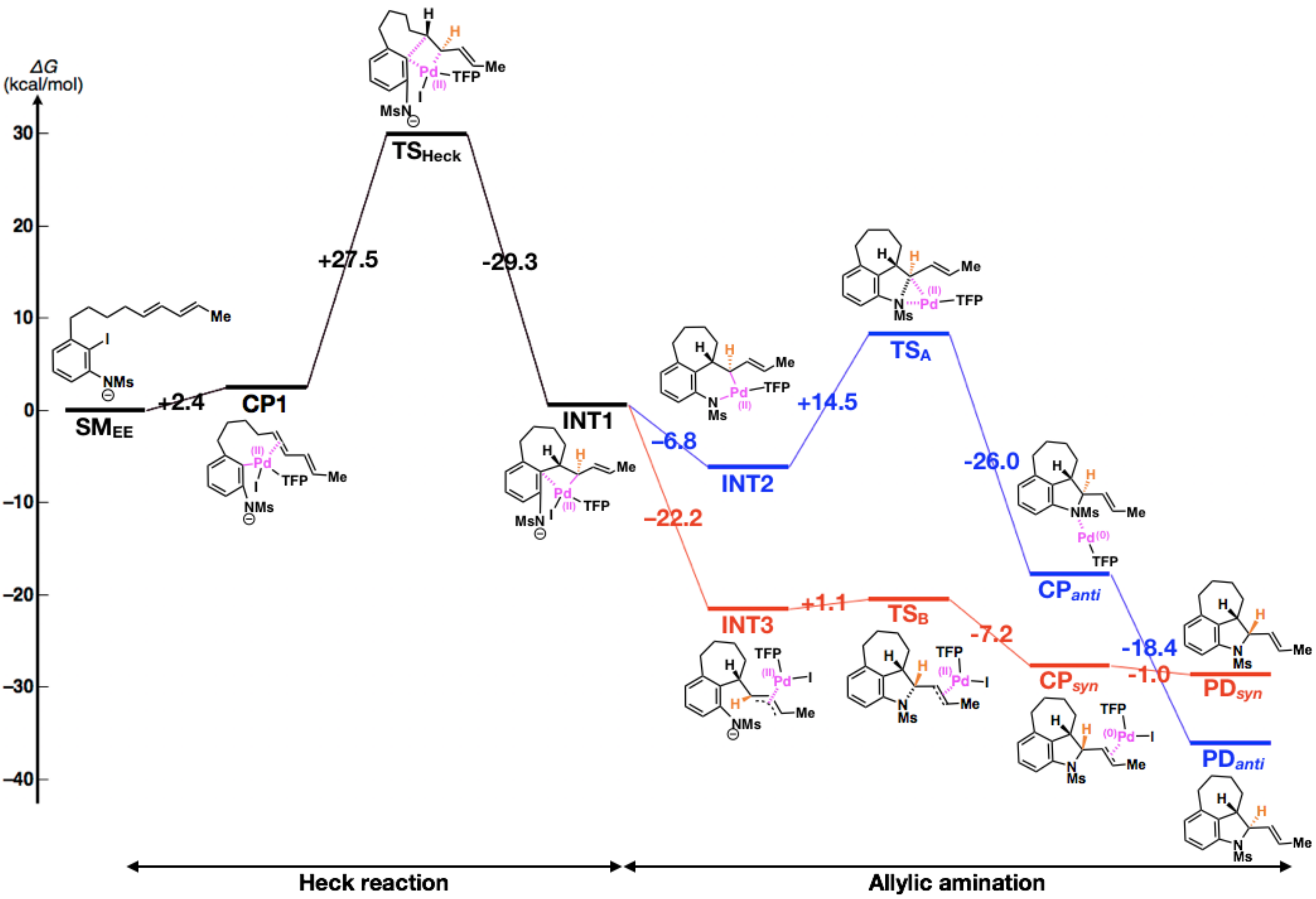


Figure 1. DFT-computed pathways for the Heck reaction and allylic amination. Optimization of geometries and frequencies are computed at the B3LYP/LanL2DZ (for Pd, I), 6-31+G* (others) levels, and single point energies are computed at the B3LYP/SDD (for Pd, I), 6-311++G** (others) levels.

Activation energy for the reductive elimination from **INT2** to **TS**$_{\mathbf{A}}$ was 14.5 kcal/mol, affording the *anti*-product **PD**$_{\boldsymbol{anti}}$ through metal dissociation from **CP**$_{\boldsymbol{anti}}$. On the other hand, η^3-π-allyl complex **INT3** is more thermodynamically stable than **INT2**. Furthermore, because the activation energy of the allylic amination *via* **TS**$_{\mathbf{B}}$ was 1.1 kcal/mol, this route, which gives *syn*-product **PD**$_{\boldsymbol{syn}}$, was considered an advantageous pathway. Both the DFT calculations and experimental analysis demonstrated that the reaction pathway through nucleophilic attack to the η^3 π-allylpalladium complex was kinetically favorable. As the *syn*-product was obtained as a major product from the cyclization precursor comprising (*E*, *E*)-diene as the main component, these computational data are consistent with the present experimental results.[8]

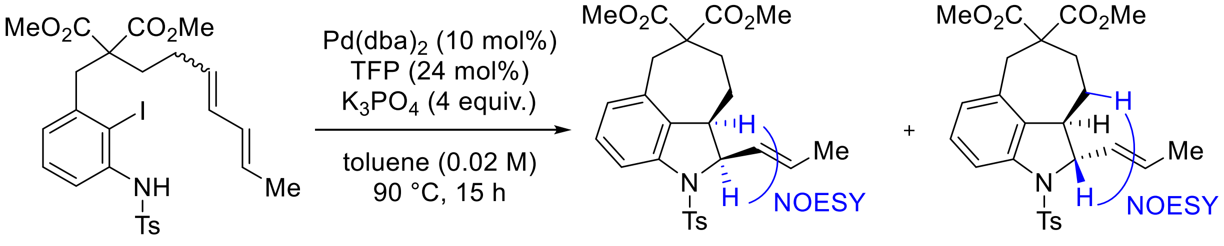
In summary, we developed a Pd-catalyzed cyclization cascade for the synthesis of tricyclic indolines that could be transformed into the corresponding 2-alkenyl-3,4-fused indole derivatives. DFT calculations to clarify the detailed reaction mechanism indicated that the tandem reaction proceeds *via* intramolecular Heck insertion of a diene, followed by nucleophilic attack to the η^3 π-allylpalladium species.

EXPERIMENTAL

1. General

Infrared (IR) spectra were recorded on a Fourier transform infrared spectrophotometer, equipped with ATR. NMR spectra were recorded with a 400 MHz or 600 MHz spectrometer. Chemical Shifts in $CDCl_3$ were reported downfield from TMS (= 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm)] as an internal reference. Positive-ion mass spectra were recorded by electrospray ionization (ESI-TOF). Column chromatography was performed with 63-230 mesh spherical neutral silica gel. Reactions were carried out in dry solvent. Other reagents were purified by the usual methods.

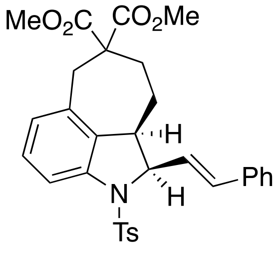
2. General Procedure for Pd-Catalyzed Cascade Cyclization



1a *syn*-**2a** *anti*-**2a**

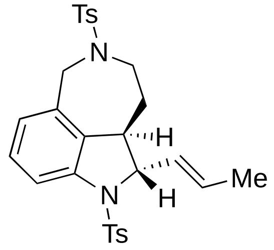
General Procedure: To a suspention of **1a** (29.4 mg, 0.0481 mmol), TFP (2.68 mg, 0.0115 mmol) and K_3PO_4 (40.8 mg, 0.192 mmol) in toluene (2.4 mL) was added $Pd(dba)_2$ (2.77 mg, 0.00481 mmol), and the mixture was stirred at 90 ºC for 15 h. The reaction was quenched with water at 0 ºC, followed by extraction with AcOEt (10 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo.* The residue was purified by flash column chromatography (hexane/AcOEt = 5/1) to give an inseparable mixture of *syn*- and *anti*-**2a** (17.5 mg, 75% yield) as colorless amorphous.

Compound 2a (*syn+anti*): colorless amorphous. IR (ATR) ν 1731, 1455, 1354, 1245, 1165, 1091, 1062, 732, 707, 674 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.48-1.59 (m, 1H), 1.70-1.87 (m, 5H), 2.38 [s, 3H (*syn*)], 2.39 [s, 3H (*anti*)], 2.50-2.55 [m, 1H (*syn*)], 2.80 [m, 1H (*anti*)], 3.00 [d, *J* = 14.2 Hz, 1H (*syn*)], 3.10-3.26 [m, 2H (*syn*), 3H (*anti*)], 3.41 [s, 3H (*anti*)], 3.58 [s, 3H (*syn*)], 3.71 (m, 3H), 4.04-4.07 [m, 1H (*anti*)], 4.74 [dd, *J* = 9.4, 9.4 Hz, 1H (*syn*)], 5.39 [ddd, *J* = 1.8, 8.7, 15.2 Hz, 1H (*syn*)], 5.54 [ddd, *J* = 1.8, 7.3, 15.2 Hz, 1H (*anti*)], 5.71-5.86 (m, 1H), 6.80-6.82 (m, 1H), 7.07-7.27 (m, 3H), 7.45 [d, *J* = 8.2 Hz, 1H (*syn*)], 7.50 [d, *J* = 8.2 Hz, 2H (*anti*)], 7.54-7.58 [m, 2H (*syn*), 1H (*anti*)]; ^{13}C NMR ($CDCl_3$, *syn*): δ 17.7, 21.5, 25.2, 35.0, 39.7, 44.6, 52.2, 52.9, 56.0, 68.2, 114.6, 126.3, 127.2, 127.3, 127.8, 129.4, 129.5, 134.4, 135.4, 135.5, 140.6, 143.7, 170.1, 172.5; (+)-ESI-HRMS. Calcd for $C_{26}H_{29}NNaO_6S$ ($M+Na^+$): 506.1608, found: 506.1606.



2b

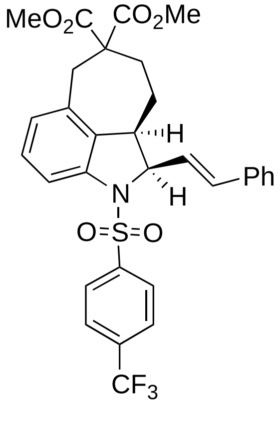
Compound 2b (*syn*+*anti*): colorless amorphous. IR (ATR) ν 1732, 1456, 1355, 1248, 1166, 1062, 734cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.58-1.64 (m, 1H), 1.77-1.90 (m, 2H), 2.34 [s, 3H (*syn*)], 2.38 [s, 3H (*anti*)], 2.40-2.47 [m, 1H (*anti*)], 2.49-2.54 [m, 1H (*syn*)], 2.94-2.98 [m, 1H (*anti*)], 3.01-3.05 [m, 1H (*syn*)], 3.11-3.14 [m, 1H (*anti*)], 3.22-3.28 (m, 1H), 3.32-3.38 [m, 1H (*syn*)], 3.43 [s, 3H (*anti*)], 3.57 [s, 3H (*syn*)], 3.70 (m, 3H), 4.29-4.32 [m, 1H (*anti*)], 4.97 [dd, *J* = 9.4, 9.4 Hz, 1H (*syn*)], 6.05 [dd, *J* = 9.2, 15.6 Hz, 1H (*syn*)], 6.22 [dd, *J* = 7.3, 16.0 Hz, 1H (*anti*)], 6.63 [d, *J* = 16.0 Hz, 1H (*syn*)], 6.69 [d, *J* = 15.6 Hz, 1H (*anti*)], 6.83-6.85 (m, 1H), 7.10-7.37 (m, 8H), 7.49 [d, *J* = 8.2 Hz, 1H (*syn*)], 7.54 [d, *J* = 8.2 Hz, 2H (*anti*)], 7.58-7.63 [m, 2H (syn), 1H (*anti*)]; ^{13}C NMR ($CDCl_3$, *syn*): δ 21.5, 25.4, 35.0, 39.7, 45.1, 52.2, 52.9, 56.0, 68.4, 114.3, 125.6, 126.3, 126.7, 127.3, 127.9, 128.0, 128.5, 129.5, 133.2, 134.5, 135.0, 135.7, 136.2, 140.6, 143.8, 170.1, 172.4; (+)-ESI-HRMS. Calcd for $C_{31}H_{31}NNaO_6S$ ($M+Na^+$): 568.1764, found: 568.1774.



2c

Compound 2c (*syn*): colorless amorphous. IR (ATR) ν 1334, 1154, 1089, 969, 813, 733, 705, 607, 652, 608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.41-1.51 (m, 1H), 1.61-1.77 (m, 4H), 2.37 (s, 6H), 3.05-3.18 (m, 2H), 3.84-3.88 (m, 1H), 4.08 (d, *J* = 16.0 Hz, 1H), 4.55 (d, *J* = 16.0 Hz, 1H), 4.73 (dd, *J* = 8.9, 8.9 Hz, 1H), 5.06 (ddd, *J* = 1.4, 9.2, 15.1 Hz, 1H), 5.71 (qd, *J* = 6.9, 15.1 Hz, 1H), 6.88 (d, *J* = 7.3 Hz, 1H), 7.14-7.20 (m, 5H), 7.48 (d, *J* = 8.2 Hz, 1H), 7.53 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 17.6, 21.4, 21.5, 28.6, 44.0, 49.8, 52.5, 68.2, 115.4, 123.3, 126.5, 127.00, 127.00, 128.2, 129.49, 129.49, 129.7, 133.7, 135.8, 136.0, 136.9, 141.4, 143.2, 143.8; (+)-ESI-HRMS. Calcd for $C_{28}H_{30}N_2NaO_4S_2$ (M+Na$^+$): 545.1539, found: 545.1526.

Compound 2c (*anti*): colorless amorphous. IR (ATR) ν 1354, 1334, 1155, 1090, 988, 813, 723, 704, 657 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.00-1.10 (m, 1H), 1.65-1.75 (m, 4 H), 2.40 (s, 6H), 2.87-2.99 (m, 2H), 3.89-3.97 (m, 3H), 4.57 (d, *J* = 15.1 Hz, 1H), 5.55 (ddd, 1.4, 7.8, 15.1 Hz, 1H), 5.73 (qd, *J* = 6.4, 15.1 Hz, 1H), 6.87 (d, 7.3 Hz, 1H), 7.16 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.23 (d, *J* = 7.8 Hz, 4H), 7.55-7.64 (m, 5H); ^{13}C NMR ($CDCl_3$): δ 17.6, 21.4, 21.5, 33.1, 48.3, 50.7, 53.2, 70.5, 115.0, 123.0, 126.9, 127.3 127.7, 128.4, 129.61, 129.61, 130.8, 132.4, 134.0, 135.6, 136.3, 141.7, 143.3, 144.3; (+)-ESI-HRMS. Calcd for $C_{28}H_{30}N_2NaO_4S_2$ (M+Na$^+$): 545.1539, found: 545.1532.



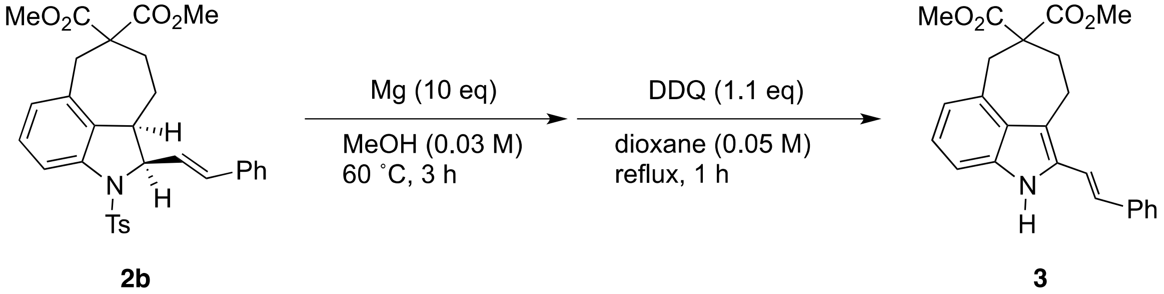
2d

Compound 2d (*syn*): colorless amorphous. IR (ATR) ν 1731, 1322, 1248, 1170, 1134, 1109, 1062, 714, 611 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.60-1.67 (m, 1H), 1.82-1.95 (m, 2H), 2.50-2.54 (m, 1H), 3.07 (d, *J* = 14.7 Hz, 1H), 3.30 (d, *J* = 14.7, 1H), 3.43-3.48 (m, 1H), 3.58 (s, 3H), 3.70 (s, 3H), 5.04 (dd, 9.6, 9.6 Hz, 1H), 5.93 (dd, *J* = 9.4, 16.0 Hz, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.87 (d, *J* = 7.3 Hz, 1H), 7.15 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.24-7.31 (m, 5H), 7.50 (d, *J* = 7.8 Hz, 1H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 25.3, 34.8, 39.6, 45.0, 52.2, 52.9, 56.0, 68.7, 113.5, 123.1 (q, *J* = 273 Hz), 124.8, 126.0 (q, *J* = 2.9 Hz), 126.6, 126.6, 127.7, 128.2, 128.2, 128.5, 133.9, 134.4 (q, *J* = 33 Hz), 134.5, 135.0, 135.7, 140.0, 142.6, 170.1, 172.3; (+)-ESI-HRMS. Calcd for $C_{31}H_{28}F_3NNaO_6S$ (M+Na$^+$): 622.1482, found: 622.1495.

Compound 2d (*anti*): colorless amorphous. IR (ATR) ν 1733, 1363, 1322, 1249, 1171, 1134, 1063, 714, 613 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.20-1.26 (m, 1H), 1.68-1.71 (m, 1H), 1.81-1.85 (m, 1H), 2.45-2.48 (m, 1H), 3.00-3.02 (m, 1H), 3.13 (d, *J* = 14.5 Hz, 1H), 3.27 (d, *J* = 14.5 Hz, 1H), 3.41 (s, 3H), 3.71 (s, 3H), 4.37-4.38 (m, 1H), 6.11-6.15 (m, 1H), 6.70 (d, *J* = 15.8 Hz, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 7.17 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.26-7.34 (m, 5H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.64 (d, *J* = 6.9 Hz, 2H), 7.82 (d, *J* = 7.6

Hz, 2H); ^{13}C NMR (CDCl$_3$): δ 29.5, 35.5, 39.4, 48.9, 51.7, 53.0, 55.6, 71.1, 114.2, 123.1 (q, *J* = 275 Hz), 126.0 (q, *J* = 2.9 Hz), 126.5, 126.6, 127.6, 128.0, 128.1, 128.3, 128.6, 131.7, 134.1, 134.7 (q, *J* = 33 Hz), 134.8, 135.9, 140.0, 141.4, 169.1, 172.4; (+)-ESI-HRMS. Calcd for $C_{31}H_{28}F_3NNaO_6S$ (M+Na$^+$): 622.1482, found: 622.1485.

3. Oxidation of Indoline to Indole

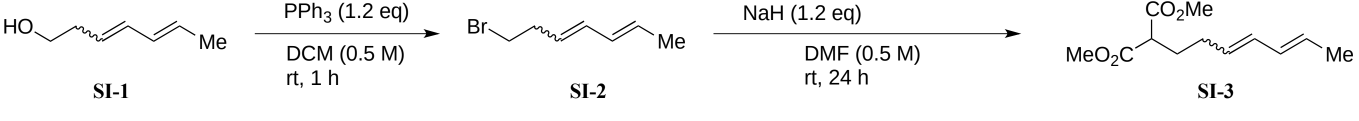


To a stirred solution of **2b** (18.1 mg, 0.0332 mmol) in MeOH (1.1 mL) was added Mg (8.07 mg, 0.332 mmol) and the mixture was heated at 60 ºC for 3 h. The reaction was quenched with sat. aq. NH$_4$Cl at room temperature, followed by the extraction with AcOEt (5 mL×3). The combined organic layer was washed with brine, dried over Na$_2$SO$_4$ and concentrated *in vacuo*. The obtained crude material was directly used in next step without further purification.

To a stirred solution of above crude material in dioxane (0.58 mL) was added DDQ (6.61 mg, 0.0291 mmol) and the mixture was stirred at reflux temperature. After 1 h, the reaction mixture was filtered through a short pad of celite, and filtrate was concentrated *in vacuo*. The residue was purified by PTLC (hexane/AcOEt = 10/1) to give **3** (3.2 mg, 25% yield) as pale yellow amorphous. IR (ATR) ν 1731, 1435, 1241, 1084, 753, 696, 608 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 2.56-2.58 (m, 2H), 3.10-3.13 (2H, m), 3.62 (s, 2H), 3.71 (s, 6H), 6.76 (d, *J* = 16.5 Hz, 1H), 6.86 (d, *J* = 6.9 Hz, 1H), 7.06 (dd, *J* = 6.9, 8.2 Hz, 1H), 7.13 (d, *J* = 16.5 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 1H), 7.26-7.28 (m, 1H), 7.36 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.50 (d, *J* = 7.3 Hz, 2H), 8.02 (s, 1H); ^{13}C NMR (CDCl$_3$): δ 21.4, 34.0, 38.6, 52.7, 58.8, 108.9, 116.8, 118.0, 120.2, 123.5, 125.7, 126.1, 127.5, 128.5, 128.8, 130.6, 130.7, 136.3, 137.1, 172.4; (+)-ESI-HRMS. Calcd for $C_{24}H_{23}NNaO_4$ (M+Na$^+$): 412.1519, found: 412.1513.

4. Substrate Synthesis

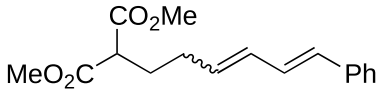
4-1. Experimental Procedure for the Synthesis of Side Chains



General Procedure: To a stirred solution of **SI-1** (790 mg, 7.04 mmol) and PPh_3 (2.22 g, 8.45 mmol) in CH_2Cl_2 (14.1 mL) was added CBr_4 (2.80 g, 8.45 mmol) slowly at 0 ºC, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water, followed by the extraction with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/AcOEt = 50/1) to give **SI-2** (1.23 g, quantitative yield) as colorless oil.

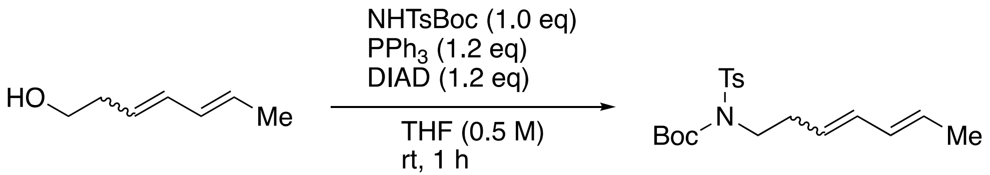
To a stirred solution of dimethyl malonate (0.97mL, 8.45 mmol) in DMF (12.1 mL) was added NaH (60% oil, 338mg, 8.45 mmol) at 0 ºC, and the mixture was stirred for 15 min. Then **SI-2** (1.23 g, 7.04 mmol) in DMF (2.0 mL) was added to the reaction, and the mixture was stirred for 24 h at room temperature. The reaction was quenched with water, followed by the extraction with AcOEt (10 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/AcOEt = 50/1) to give **SI-3** (675 mg, 42% yield) as colorless oil. IR (ATR) ν 2953, 1733, 1435, 1198, 1152, 988, 635, 620, 608 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.73 [d, *J* = 6.4 Hz, 3H (E,E)], 1.77 [d, H = 6.9 Hz, 3H (Z,E)], 1.97-2.03 (m, 2H), 2.10 [dt, *J* = 7.3, 7.3 Hz, 2H (E,E)], 2.22 [dt, *J* = 7.3, 7.3 Hz, 2H (Z,E)], 3.37-3.43 (m, 1H), 3.73 [s, 6H (E,E)], 3.74 [s, 6H (Z,E)], 5.23 [dt, *J* = 7.8, 10.5 Hz, 1H (Z,E)], 5.43-5.51 [m, 1H (E,E)], 5.56-5.65 [m, 1H (E,E)], 5.70 [dq, *J* = 7.3, 7.3 Hz, 1H (Z,E)], 5.97-6.04 [m, 2H (E,E), 1H (Z,E)], 6.20-6.27 [m, 1H (Z,E)]; ^{13}C NMR ($CDCl_3$, (E,E)): δ 17.9, 28.3, 30.0, 50.7, 52.4, 127.8, 129.1, 131.2, 131.8, 169.7; (+)-ESI-HRMS. Calcd for $C_{12}H_{18}NaO_4$ (M+Na$^+$): 249.1097, found: 249.1087.

Reference for compound **SI-1**: J. Wu, X. Jiang, J. Xu, W.-M. Dai, *Tetrahedron*, 2011, **67**, 179-192



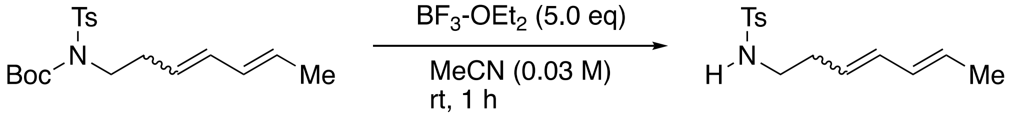
SI-4

Compound SI-4: colorless oil. IR (ATR) ν 1731, 1434, 1153, 990, 748, 692 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.03-2.08 (m, 2H), 2.20 [dt, *J* = 6.9, 6.9 Hz, 2H (E,E)], 2.35 [dt, *J* = 7.6, 7.6 Hz, 2H (Z,E)], 3.40-3.45 (m, 1H), 3.73-3.75 (m, 6H), 5.46 [dt, *J* = 7.6, 10.3 Hz, 1H (Z,E)], 5.74 [dt, *J* = 6.9, 14.4 Hz, 1H (E,E)], 6.21 (m, 1H), 6.45 [d, *J* = 15.1 Hz, 1H (E,E)], 6.54 [d, *J* = 15.1 Hz, 1H (Z,E)], 6.73 [dd, *J* = 10.7, 15.5 Hz, 1H (E,E)], 6.99 [dd, *J* = 11.0, 14.4 Hz, 1H (Z,E)], 7.18-7.23 (m, 1H), 7.28-7.32 (m, 2H), 7.37 [d, *J* = 7.6 Hz, 2H (E,E)], 7.41 [d, *J* = 7.6 Hz, 2H (Z,E)]; ^{13}C NMR ($CDCl_3$, (E,E)): δ 28.3, 30.4, 50.8, 52.5, 126.2, 127.3, 128.5, 128.8, 130.9, 132.0, 132.9, 137.3, 169.7; (+)-ESI-HRMS. Calcd for $C_{17}H_{20}NaO_4$ (M+Na$^+$): 311.1254, found: 311.1257.



SI-1 **SI-5**

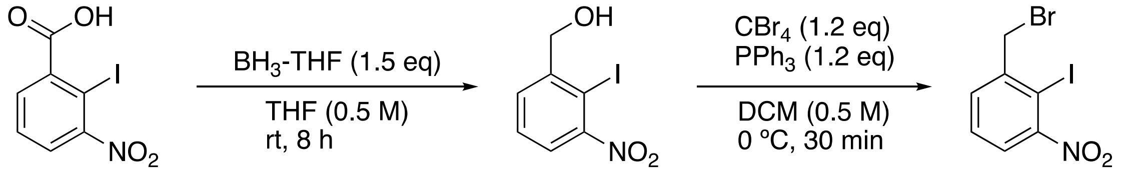
To a stirred solution of **SI-1** (249 mg, 2.22 mmol), NHTsBoc (602 mg, 2.22 mmol) and PPh$_3$ (699 mg, 2.66 mmol) in THF (4.4 mL) was added diisopropyl azodicarboxylate (DIAD, 0.52 mL, 2.66 mmol) at 0 ºC, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with water followed by the extraction with AcOEt (10 mL×3). The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/AcOEt = 6/1) to give **SI-5** (718 mg, 88% yield) as colorless oil. IR (ATR) ν 1725, 1354, 1287, 1153, 1089, 988, 721, 673 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.34 [s, 9H (E,E)], 1.35 [s, 9H (Z,E)], 1.74 [d, J = 6.4 Hz, 3H (E,E)], 1.79 [d, J = 6.0 Hz, 3H (Z,E)], 2.44 (s, 3H), 2.50 [dt, J = 7.3, 7.3 Hz, 2H (E,E)], 2.63 [dt, J = 7.8, 7.8 Hz, 2H (Z,E)], 3.82-3.87 (m, 2H), 5.30 [dt, J = 8.0, 10.5 Hz, 1H (Z,E)], 5.50 [dt, J = 7.3, 14.2 Hz, 1H (E,E)], 5.62 [dt, J = 7.3, 14.2 Hz, 1H (E,E)], 5.73 [dt, J = 6.9, 15.1 Hz, 1H (Z,E)], 5.98-6.11 [m, 2H (E,E), 1H (Z,E)], 6.35-6.42 [m, 1H (Z,E)]; ^{13}C NMR (CDCl$_3$, (E,E)): δ 18.0, 21.6, 27.8, 33.4, 46.6, 84.1, 126.6, 127.9, 128.3, 129.2, 131.2, 133.1, 137.4, 144.0, 150.9; (+)-ESI-HRMS. Calcd for $C_{19}H_{27}NNaO_4S$ (M+Na$^+$): 388.1553, found: 388.1561.



SI-5 **SI-6**

To a stirred solution of **SI-5** (718 mg, 1.96 mmol) in MeCN (65 mL) was added BF$_3$·OEt$_2$ (1.2 mL, 9.82 mmol) at 0 ºC, and the mixture was stirred at room temperature for 1 h. The reaction was quenched with sat. aq. NaHCO$_3$ followed by the extraction with AcOEt (50 mL×3). The combined organic layer was washed with brine, dried over Na$_2$SO$_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (hexane/AcOEt = 6/1) to give **SI-6** (477 mg, 92% yield) as colorless amorphous. IR (ATR) ν 1597, 1433, 1321, 1153, 1092, 986, 812, 658, 610 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 1.72 [d, J = 6.9 Hz, 3H (E,E)], 1.76 [d, J = 6.9 Hz, 3H (Z,E)], 2.19 [dt, J = 6.9, 6.9 Hz, 2H (E,E)], 2.30 [dt, J = 6.9, 6.9 Hz, 2H (Z,E)], 2.43 (s, 3H), 2.96-3.01 (m, 2H), 4.74 (br-s, 1H), 5.08 [dt, J = 7.8, 10.5 Hz, 1H (Z,E)], 5.30 [dt, J = 7.3, 13.3 Hz, 1H (E,E)], 5.59 [dq, J = 6.9, 6.9 Hz, 1H (E,E)], 5.70 [dq, J = 6.9, 6.9 Hz, 1H (Z,E)], 5.90-6.04 [m, 2H (E,E), 1H (Z,E)], 6.15 [dd, J = 4.6, 11.0 Hz, 1H (Z,E)], 7.30-7.32 (m, 2H), 7.73-7.76 (m, 2H); ^{13}C NMR (CDCl$_3$, (E,E)): δ 18.0, 21.5, 32.4, 42.5, 126.2, 127.1, 128.8, 129.6, 130.8, 133.5, 136.8, 143.3; (+)-ESI-HRMS. Calcd for $C_{14}H_{19}NNaO_2S$ (M+Na$^+$): 288.1029, found: 288.1017.

4-2. Experimental Procedure for the Synthesis of Benzyl Bromide



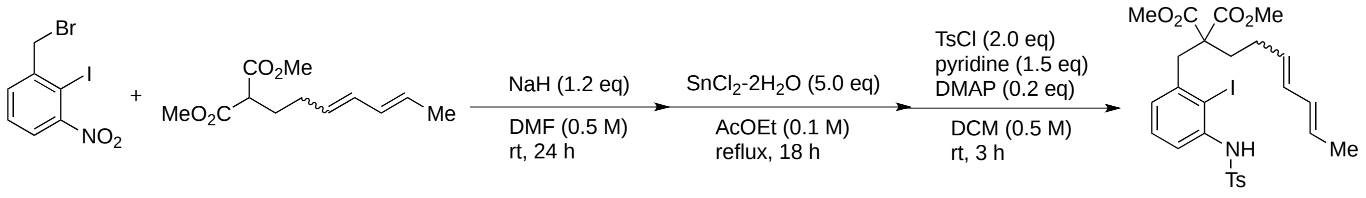
SI-7 **SI-8** **SI-9**

To a stirred solution of **SI-7** (6.10 g, 20.8 mmol) in THF (41.6 mL) was added BH_3-THF (24.9 mL, 0.92 M solution in THF, 31.2 mmol) at 0 ºC. After being stirred for 8 h at room temperature, the reaction was quenched with 1N aq. HCl followed by the extraction with AcOEt (50 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt = 5/1) to give **SI-8** (5.102 g, 88% yield) as yellow solid.

To a stirred solution of **SI-8** (889 mg, 3.18 mmol) and PPh_3 (1.00 g, 3.82 mmol) in CH_2Cl_2 (6.4 mL) was added CBr_4 (1.27 g, 3.82 mmol) at 0 ºC and kept stirring at the same temperature for 30 min. The reaction was quenched with water followed by extraction with CH_2Cl_2 (10 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt = 20/1) to give **SI-9** (991 mg, 91% yield) as yellow solid.

Reference for compound **SI-7**: E. C. Y. Woon, A. Dhami, M. F. Mahon, and M. D. Threadgill, *Tetrahedron*, 2006, **62**, 4829.

4-3. Experimental Procedure for the Synthesis of Aniline Derivatives

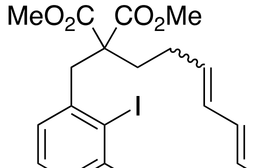


SI-9 **SI-3** **1a**

To a stirred solution of **SI-3** (525 mg, 2.32 mmol) in DMF (4.6 mL) was added NaH (60% oil, 111.4 mg, 2.78 mmol) at 0 ºC, and the mixture stirred for 15 min. Then, **SI-9** (793 mg, 2.32 mmol) in DMF (1.0 mL) was added to the above mixture, and the mixture was stirred for 24 h at room temperature. The reaction was quenched with water followed by extraction with AcOEt (10 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was filtered through a short pad of silica gel and the obtained residue was used for the next reaction without further purification.

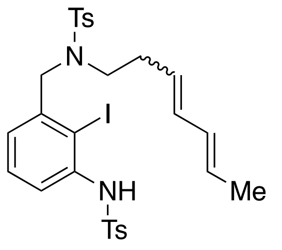
To a stirred solution of the above crude material (924 mg) in AcOEt (19.0 mL) was added $SnCl_2$-$2H_2O$ (2.14g, 9.50 mmol). The mixture was heated at reflux temperature for 18 h. The reaction was quenched with sat. aq. $NaHCO_3$ followed by extraction with AcOEt (30 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The obtained crude material was used for the next reaction without further purification.

To a stirred mixture of above crude material, pyridine (0.21 mL, 2.9 mmol) and DMAP (41.5 mg, 0.38 mmol) in CH_2Cl_2 (3.8 mL) was added TsCl (648 mg, 3.8 mmol) at 0 ºC, and the reaction mixture was stirred for 3 h at room temperature. The reaction was quenched with 1N aq. HCl followed by extraction with CH_2Cl_2 (5 mL×3). The combined organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography (hexane/AcOEt = 6/1) to give **1a** (615 mg, 48% yield, 3steps) as colorless amorphous. IR (ATR) ν 1728, 1437, 1382, 1328, 1162, 1090, 988, 911, 849, 813 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.72-1.77 (m, 3H), 1.80-1.86 (m, 2H), 1.96-2.02 [m, 2H (E,E)], 2.05-2.11 [m, 2H (Z,E)], 2.36 [s, 3H (E,E)], 2.39 [s, 3H (Z,E)], 3.45 [s, 2H (E,E)], 3.47 [s, 2H (Z,E)], 3.61 [s, 3H (E,E)], 3.62 [s, 3H (E,E)], 3.64 [s, 3H (Z,E)], 3.65 [s, 3H (Z,E)], 5.10 [dt, *J* = 7.3, 10.5 Hz, 1H (Z,E)], 5.39 [dt, *J* = 6.4, 13.3 Hz, 1H (E,E)], 5.59 [dq, *J* = 6.4, 13.7 Hz, 1H (E,E)], 5.68 [dq, *J* = 7.3, 14.6 Hz, 1H (Z,E)], 5.90-6.04 [m, 2H (E,E), 1H (Z,E)], 6.18 [dd, *J* = 11.9, 14.2 Hz, 1H (Z,E)], 6.89-6.92 (m, 1H), 7.02-7.04 (m, 1H), 7.16-7.23 (m, 3H), 7.53-7.55 (m, 1H), 7.60-7.61 (m, 2H); ^{13}C NMR ($CDCl_3$, (E,E)): δ 18.0, 21.5, 27.8, 32.6, 43.7, 52.4, 58.6, 102.0, 121.2, 126.7, 127.4, 127.8, 128.7, 129.5, 129.6, 131.1, 131.2, 135.8, 137.9, 141.3, 144.1, 171.1; (+)-ESI-HRMS. Calcd for $C_{26}H_{30}INNaO_6S$ ($M+Na^+$): 634.0731, found: 634.0751



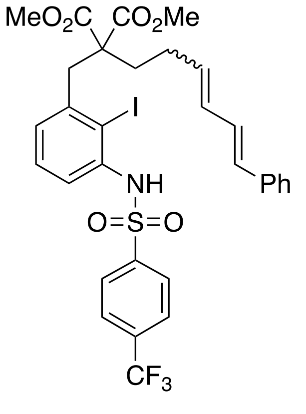
1b

Compound 1b: colorless amorphous. IR (ATR) ν 1727, 1530, 1434, 1363, 1200, 989, 910, 804, 731, 693 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.86-1.92 (m, 2H), 2.07-2.12 [m, 2H (E,E)], 2.19-2.25 [m, 2H (Z,E)], 2.35 (m, 3H), 3.47 [s, 2H (E,E)], 3.50 [s, 2H (Z,E)], 3.63 [s, 6H (E,E)], 3.66 [s, 6H (Z,E)], 5.35 [dt, *J* = 7.3, 10.5 Hz, 1H (Z,E)], 5.67 [dt, *J* = 7.3, 14.9 Hz, 1H (E,E)], 6.12-6.21 (m, 1H), 6.45 [d, *J* = 15.6 Hz, 1H (E,E)], 6.53 [d, *J* = 15.6 Hz, 1H (Z,E)], 6.71 [dd, *J* = 10.5, 15.6 Hz, 1H (E,E)], 6.83-6.94 [m, 1H (E,E), 2H (Z,E)], 7.03-7.05 (m, 1H), 7.17-7.23 (m, 4H), 7.28-7.34 (m, 2H), 7.36-7.40 (m, 2H), 7.54-7.58 (m, 1H), 7.60-7.62 (m, 2H); ^{13}C NMR ($CDCl_3$, (E,E)): δ 21.5, 28.1, 32.5, 43.8, 52.5, 58.6, 102.0, 121.2, 126.1, 126.7, 127.3, 127.4, 128.5, 128.6, 128.7, 128.7, 129.6, 130.9, 131.3, 133.2, 137.3, 138.0, 141.3, 144.1, 171.1; (+)-ESI-HRMS. Calcd for $C_{31}H_{33}INO_6S$ (M+H$^+$): 674.1068, found: 674.1051.



1c

Compound 1c: colorless amorphous. IR (ATR) ν 1448, 1385, 1322, 1157, 1089, 988, 908, 849, 812 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.68-1.74 (m, 3H), 1.93 [dt, *J* = 7.3, 7.3 Hz, 2H (E,E)], 2.02 [dt, *J* = 7.8, 7.8 Hz, 2H (Z,E)], 2.35 (m, 3H), 2.44 (m, 3H), 3.02-3.10 (m, 2H), 4.26 [s, 2H (E,E)], 4.29 [s, 2H (Z,E)], 4.92 [dt, *J* = 8.4, 8.4 Hz, 1H (Z,E)], 5.13 [dt, *J* = 7.3, 14.8 Hz, 1H (E,E)], 5.53 [dq, *J* = 6.9, 14.9 Hz, 1H (E,E)], 5.64 [dq, *J* = 6.9, 14.2 Hz, 1H (Z,E)], 5.74 [dd, *J* = 10.5, 15.1 Hz, 1H (E,E)], 5.82-5.95 [m, 1H (E,E), 2H (Z,E)], 7.02 (m, 1H), 7.18-7.33 (m, 6H), 7.56-7.59 (m, 1H), 7.62-7.64(m, 2H), 7.68-7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, (E,E)): δ 18.0, 21.5, 21.5, 31.4, 48.6, 57.8, 96.9, 121.5, 126.2, 126.4, 127.1, 127.4, 128.4, 129.1, 129.6, 129.8, 130.9, 132.8, 135.7, 136.3, 137.6, 140.1, 143.5, 144.2; (+)-ESI-HRMS. Calcd for $C_{28}H_{31}IN_2NaO_4S_2$ (M+Na$^+$): 673.0662, found: 673.0667.



1d

Compound 1d: colorless amorphous. IR (ATR) ν 1731, 1322, 1169, 1133, 1063, 713, 607 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.89-1.93 (m, 2H), 2.27-2.13 [m, 2H (E,E)], 2.19-2.25 [m, 2H (Z,E)], 3.46 [s, 2H (E,E)], 3.50 [s, 2H (Z,E)], 3.62 [s, 6H (E,E)], 3.65 [s, 6H (Z,E)], 5.35 [dt, *J* = 7.3, 10.5 Hz, 1H (Z,E)], 5.67 [dt, *J* = 6.6, 14.2 Hz, 1H (E,E)], 6.12-6.21 (m, 1H), 6.45 [d, *J* = 15.6 Hz, 1H (E,E)], 6.53 [d, *J* = 15.6 Hz, 1H (Z,E)], 6.71 [dd, *J* = 10.3, 15.8 Hz, 1H (E,E)], 6.94 [dd, *J* = 11.4, 16.4 Hz, 1H (Z,E)], 6.98-7.00 (m, 1H), 7.04 [s, 1H (Z,E)], 7.06 [s, 1H (E,E)], 7.19-7.26 (m, 2H), 7.28-7.34 (m, 2H), 7.36-7.40 (m, 2H), 7.56-7.59

(m, 1H), 7.69-7.71 (m, 2H), 7.82-7.85 (m, 2H); (+)-ESI-HRMS. Calcd for $C_{31}H_{29}F_3INNaO_6S$ (M+Na$^+$): 750.0605, found: 750.0608.

ACKNOWLEDGEMENTS

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7. The relative configuration of each isomer was determined by NOESY experiments.
8. See the Supporting Information for computational details including the calculation of the (*Z*, *E*)-diene.