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Novel synthesis of fused indoles and 2-substituted indoles by the palladium-catalyzed cyclization of *N*-cycloalkenyl-*o*-haloanilines

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ABSTRACT

A new palladium-catalyzed cyclization of *N*-alkenyl-*o*-haloanilines with selective isomerization of a double bond followed by formal 5-*endo*-*trig* cyclization was developed. A variety of fused and 2-substituted indoles were synthesized from enaminoesters prepared by condensation of β-ketoesters and *o*-iodoaniline.

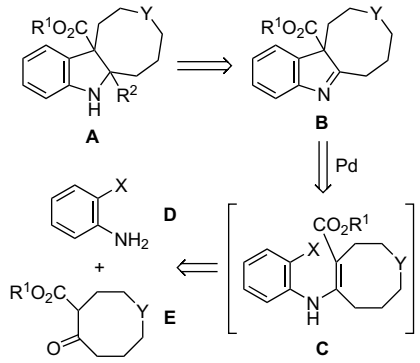
1. Introduction

The intramolecular Heck reaction[1] is an important and powerful method for the construction of carbo- and heterocyclic compounds. The synthesis of indoles using this reaction has also been widely studied.[2,3] However, the synthesis of fused indoles by palladium-catalyzed cyclization using *N*-cycloalkenyl-*o*-haloanilines, which are readily obtained from cyclic 1,3-diketones,[3q,r,t,u,w] has not been fully investigated, although the skeleton is involved in many important bioactive compounds. We have already reported the novel synthesis of fused indoles by the palladium-catalyzed cyclization of *N*-cycloalkenyl-*o*-iodoanilines with selective isomerization of a double bond.[4] In this article, we describe the details of this reaction.

2. Result and discussion

In connection with our recent work on the synthesis of indole alkaloids, we were interested in the synthesis of fused indolines **A**, which contain medium-sized rings and two quarternary centers, as shown in Scheme 1. For the synthesis of **A**, indolenines **B** is a possible intermediate, and may be prepared by the intramolecular Heck reaction of enaminoesters **C**. However, there has been no report on cyclization using enaminoesters **C**, obtained from cyclic-ketoesters **E** (Scheme 1). To realize this scheme, enaminoesters **C** were prepared by condensation of *o*-haloanilines **D** and β-ketoesters **E**.

Thus, *o*-bromo- or *o*-iodoaniline (**1a** or **1b**) was heated in benzene with 2-methoxycarbonylcyclooctanone (**2**) in the presence of 1.1–2.0 equiv of *p*-TsOH at reflux for 16–39 h to give bromo- or iodophenylenaminoester **3a** or **3b**, respectively (Scheme 2). The resulting bromophenylenaminoester **3a** was reacted with $Pd(PPh_3)_4$ in the presence of Et_3N in CH_3CN at 80 °C for 22 h.[5] The structure of the isolated product was determined by spectroscopy to be fused indole **4** (46%), and no indolenine **5**, which was expected from the formal 5-*endo* cyclization of intermediate **6**, was observed (Table 1, entry 1). Based on the structure of **4**, cyclization might



Scheme 1. A plan for the synthesis of fused indolines **A**.

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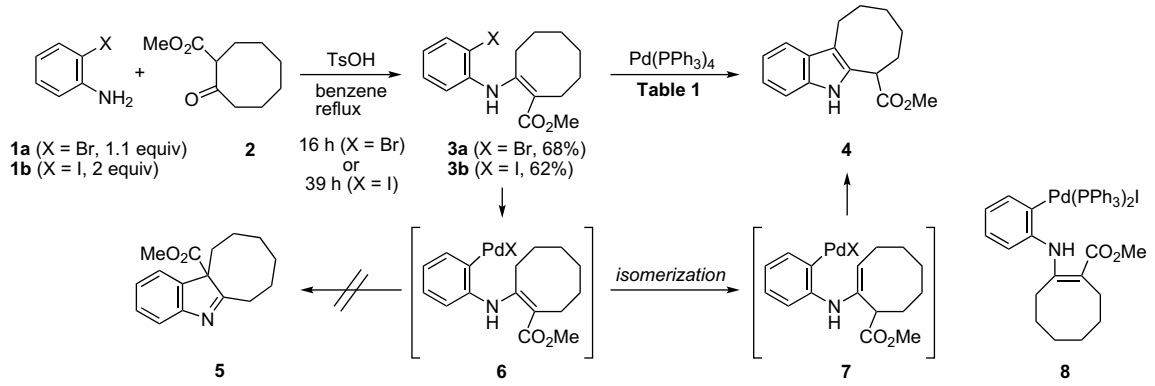


Scheme 2. Discovery of a new palladium-catalyzed cyclization with selective isomerization of a double bond.

proceed via intermediate **7**, which would be generated from **6** by selective isomerization of a double bond. Since **4** is also useful for indole alkaloid synthesis, we decided to study this reaction in detail.

A reduction in palladium(0) loading resulted in a low yield of **4** (entry 2). When iodophenylenaminoester **3b** was treated with 30 mol % of palladium(0), no desired **4** was obtained (entry 3). However, the reaction of **3b** with an equimolar amount of palladium(0) gave Pd complex **8** as a crystalline solid in 86% yield (entry 4). Its structure was unambiguously determined by X-ray crystallographic analysis[4,6] and showed that palladium metal is oxidatively inserted into the carbon–iodine bond without isomerization of a double bond. When the isolated palladium complex **8** was treated with Ag_3PO_4 (1 equiv)[7] in *N*,*N*-dimethylacetamide (DMA) at 100 °C for 35 h, cyclized **4** was obtained in 25% yield. Therefore, under the conditions using 10 mol % $Pd(PPh_3)_4$ in the presence of Ag_3PO_4 in CH_3CN at 80 °C, desired **4** was obtained in 94% yield (entry 5). It is interesting to note that arylbromide **3a** showed higher reactivity than aryliodide **3b**. This difference in reactivity may be explained by more electronegative character of bromine atom, which activates intermediate **6**.

To optimize the reaction conditions, we examined the effect of palladium catalysts, silver salts, and solvents on this Heck reaction. The results are summarized in Table 2. Although the cyclization in CH_3CN was very slow (Table 2, entry 1), a polar solvent such as DMF, DMA, and NMP gave **4** in short reaction times (entries 2–4).

The best result for cyclization was obtained when **3b** was treated with 10 mol % of $Pd(PPh_3)_4$ and 1 equiv of Ag_3PO_4 in DMSO to give **4** in quantitative yield (entry 5). Furthermore, **4** was obtained in high yield with 3 mol % of catalyst loading (entry 6). While other palladium catalysts and other silver salts, such as $AgNO_3$, and AgOTf, also promoted this reaction, they were less effective (entries 7–18). Other fused indoles **11** containing smaller rings were also prepared under optimized conditions described above (Scheme 3). When fused indole containing a six-membered ring was synthesized, oxidized product **12**[8] was obtained as a side product in low yield. Furthermore, we extended this methodology to produce fused indole containing a piperidine ring (Scheme 4). However, desired **14** and oxidized γ-carboline **15** were obtained in low yield.

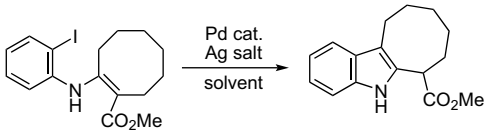
Next, the new palladium-catalyzed cyclization was applied to several acyclic enaminoesters (Table 3). In the reaction of trisubstituted enaminoesters **16a**[3u] and **16b**, indoles **18a** and **18b**[9] were obtained as major isomers and indoles **17a** and **17b**[10] were

Table 1
Synthesis of **4** from **3** by palladium-catalyzed cyclization[a]

Entry	X	Pd cat. (mol %)	Additive (equiv)	Time (h)	Product (%)
1	Br (**3a**)	100	Et_3N (2.4)	22	**4** (46)
2	Br (**3a**)	30	Et_3N (2.4)	64	**4** (25)
3	I (**3b**)	30	Et_3N (2.4)	24	**4** (0)[b]
4	I (**3b**)	100	Et_3N (2.4)	32	**8** (86)
5	I (**3b**)	10	Ag_3PO_4 (1)	29	**4** (94)

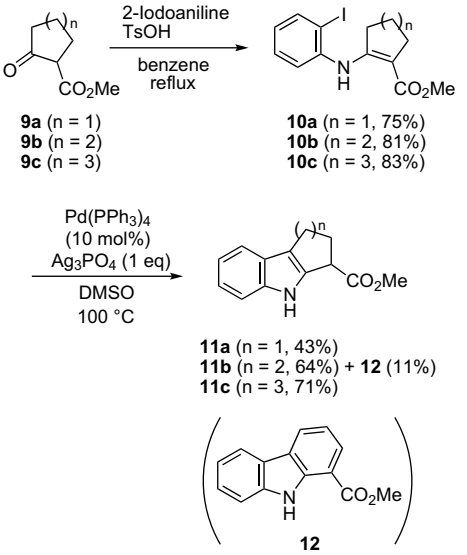
[a] These reactions were performed in the presence of $Pd(PPh_3)_4$ and additive in CH_3CN at 80 °C.
[b] A mixture of **3b** and **8** (2:1) was obtained.

Table 2
Optimization of reaction conditions[a]

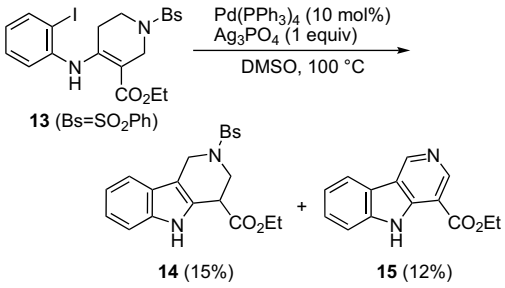


Entry	Pd cat.[b]	Ag salt[c]	Solvent	Time (h)	Yield (%)
1[d]	$Pd(PPh_3)_4$	Ag_3PO_4	CH_3CN	29	94
2	$Pd(PPh_3)_4$	Ag_3PO_4	DMF	1	83
3	$Pd(PPh_3)_4$	Ag_3PO_4	DMA	1	92
4	$Pd(PPh_3)_4$	Ag_3PO_4	NMP	1	90
5	$Pd(PPh_3)_4$	Ag_3PO_4	DMSO	1	Quant
6[e]	$Pd(PPh_3)_4$	Ag_3PO_4	DMSO	1	95
7	$PdCl_2(PPh_3)_2$	Ag_3PO_4	DMSO	1	20
8	$PdCl_2(PhCN)_2$	Ag_3PO_4	DMSO	1	63
9	$PdCl_2$	Ag_3PO_4	DMSO	1	80
10	$Pd(OAc)_2$	Ag_3PO_4	DMSO	1	75
11	$Pd(CN)_2$	Ag_3PO_4	DMSO	1	39
12[f]	$Pd(PPh_3)_4$	$AgNO_3$	DMSO	1	80
13[g]	$Pd(PPh_3)_4$	Ag_2SO_3	DMSO	2	71
14[f]	$Pd(PPh_3)_4$	AgOTf	DMSO	4	49
15[f]	$Pd(PPh_3)_4$	$AgOCOCF_3$	DMSO	5	18
16[f]	$Pd(PPh_3)_4$	AgOAc	DMSO	21	13
17[h]	$Pd(PPh_3)_4$	Ag_3PO_4	DMSO	1	72
18[i]	$Pd(PPh_3)_4$	Ag_3PO_4	DMSO	1	50

[a] These reactions were performed in the presence of 10 mol % of the palladium catalyst and 1 equiv of silver salt at 100 °C.
[b] The catalysts $Pd(dba)_2$ and Pd/C resulted in the production of unidentified products.
[c] Silver salts such as Ag_2O, Ag_2CO_3, $AgClO_4$, and AgCl resulted either in recovery of the starting material or the production of unidentified products.
[d] This reaction was performed at 80 °C.
[e] $Pd(PPh_3)_4$ (3 mol %).
[f] Silver salt (3 equiv).
[g] Silver salt (1.5 equiv).
[h] Silver salt (0.67 equiv).
[i] Silver salt (0.33 equiv).



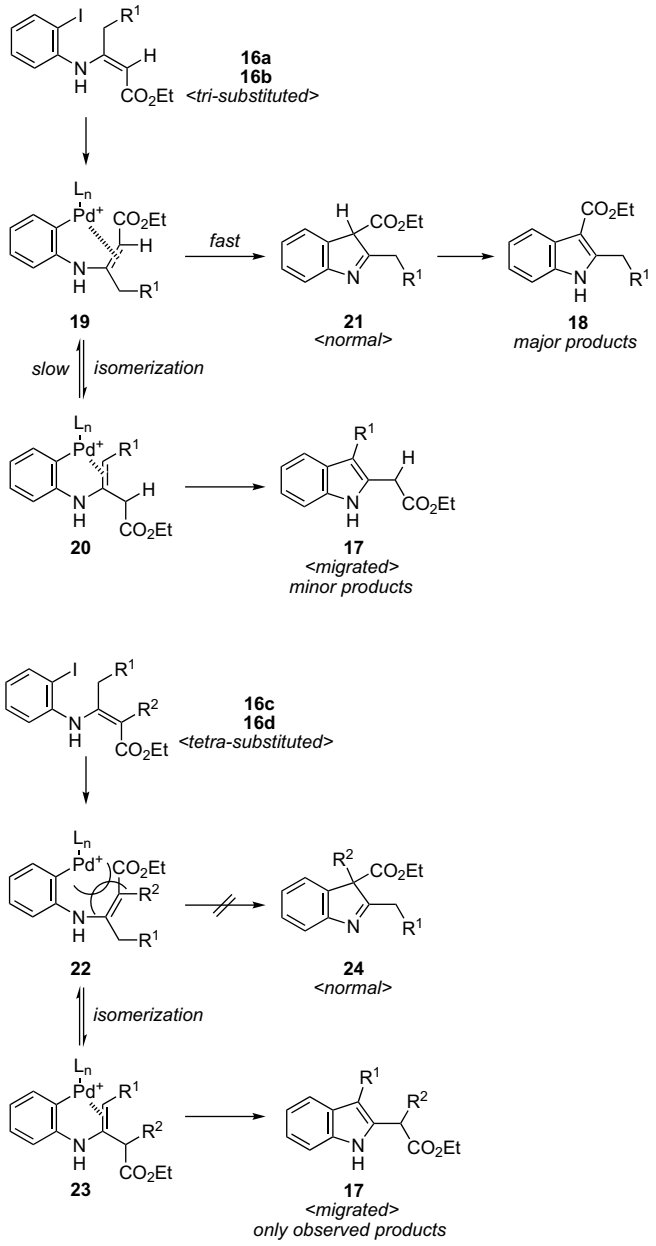
Scheme 3. Scope and limitations of fused indole synthesis.



Scheme 4. Synthesis of piperidine and pyridine fused indoles.

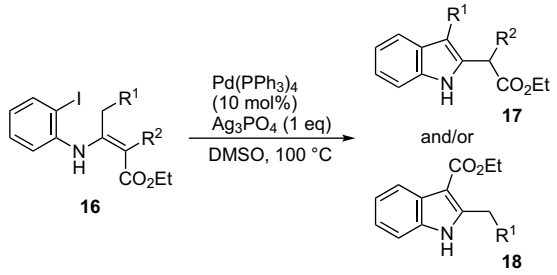
obtained in low yield (entries 1 and 2). In contrast, tetra-substituted enaminoesters **16c** and **16d** provided indoles **17c** and **17d** with complete regioselectivity (entries 3 and 4). These results provide the following mechanistic explanation (Scheme 5).

When the substrates are tri-substituted enaminoesters **16a** and **16b**, since the rate of insertion (**19** to **21**) is faster than that of olefin isomerization of **19** to **20**, **18a** and **18b** are obtained as major products through a normal Heck reaction pathway. On the other hand, when the substrates are tetra-substituted enaminoesters **16c** and **16d**, the rate of insertion of **22** to give **24** is much slower than that of isomerization of **22** to **23** because the initial coordination of the double bond to palladium does not proceed due to steric effects in the reactive conformation.[5,11] Therefore, tetra-substituted enaminoesters **16c** and **16d** give only **17c** and **17d** through an olefin migratory Heck reaction pathway.



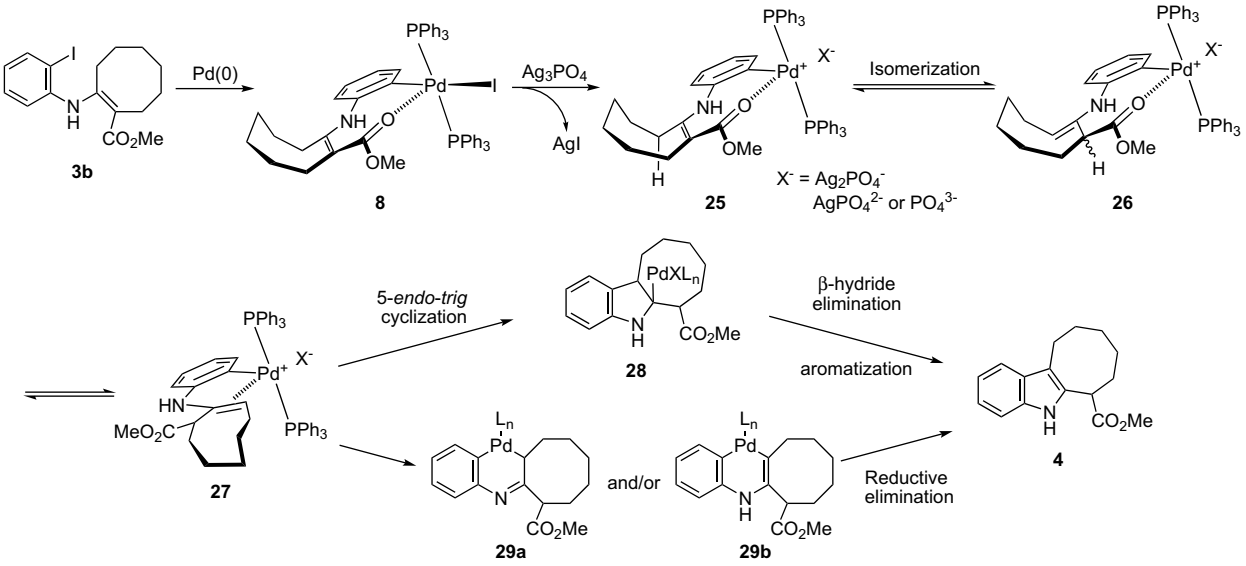
Scheme 5. Mechanistic analysis of acyclic enaminoesters.

Table 3
Palladium-catalyzed cyclization of acyclic enaminoesters



Entry	Enaminoester			Time (h)	Products (%)	
		R^1	R^2		**17**	**18**
1	**16a**	H	H	3.5	**17a** (17)	**18a** (79)
2	**16b**	Me	H	4.5	**17b** (6)	**18b** (86)
3	**16c**	H	*n*-Pr	3.0	**17c** (67)	—
4	**16d**	H	Bn	2.5	**17d** (82)	—

In the case of enaminoester **3b**, oxidative addition to Pd(0) gives Pd complex **8**. When **8** is treated with Ag_3PO_4, 16-electron Pd^+ intermediate **25** is generated. At this stage, tetra-substituted olefin is too bulky to coordinate cationic palladium, and intramolecular coordination of the carbonyl group to cationic palladium raises the acidity of γ-proton and causes isomerization of the double bond (**25** to **26**). The resulting tri-substituted enaminoester coordinates to cationic palladium (**26** to **27**). From **27**, carbopalladation via a 5-*endo* process affords **28**, and β-hydride elimination produces the indolenine that undergoes tautomerization to furnish the substituted fused indole **4**.[3c,f,o,v,w,12] However, we cannot rule out the another type of cyclization via palladacycle **29** by virtue of the



Scheme 6. Proposed reaction mechanism.

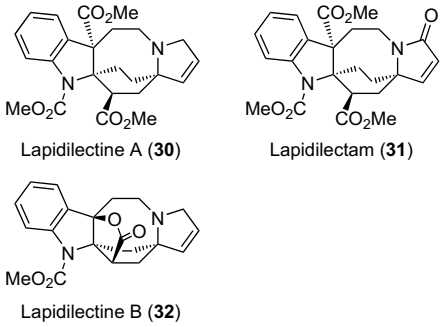
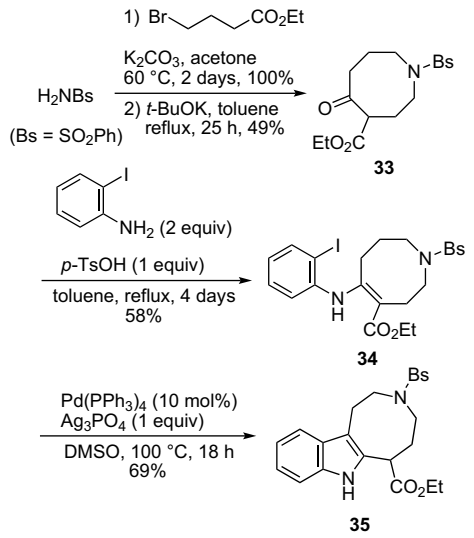


Figure 1. *K. lapidilecta* alkaloids.

nucleophilicity of the enaminoester unit. While both routes are possible, additional experiments are needed to clarify the reaction mechanism (Scheme 6).



Scheme 7. Application to synthesis of the azocinoindole **35**.

In connection with the total synthesis of *Kopsia lapidilecta* alkaloids[13] such as lapidilectine A (**30**), lapidilectam (**31**), and lapidilectine B (**32**)[14] (Fig. 1), we were also interested in applying our new cyclization to synthesize the azocinoindole **35** (Scheme 7). Thus, azocine derivative **33**,[15] which was prepared from benzenesulfonamide in two steps, was condensed with *o*-iodoaniline to give enaminoester **34** in 58% yield. Enaminoester **34** was converted to azocinoindole **35** in 69% yield under the optimized conditions described above.

3. Conclusion

In conclusion, we have developed a new type of palladium-catalyzed cyclization of *N*-cycloalkenyl-*o*-iodoanilines, which proceeds via the selective isomerization of a double bond in the enaminoester structure followed by formal 5-*endo-trig* cyclization. This reaction is useful for synthesizing fused and 2-substituted indoles.

4. Experimental

4.1. General methods

All reactions involving air- or moisture-sensitive reagents or intermediates were performed under an inert atmosphere of argon in glassware. Unless otherwise noted, solvents and reagents were reagent grade and used without purification. DMF, DMA, and NMP were distilled from anhydrous $MgSO_4$. DMSO, Et_3N, and pyridine were distilled from CaH_2. Benzene was freshly distilled from sodium/benzophenone prior to use. Toluene was used as received from Kanto, Chemical Co., Inc. Analytical and preparative TLC was carried on E. Merck 0.25 mm silica gel 60 GF_{254} plates. Flash column chromatography was performed using Kanto chemical silica gel 60N (40–50 μm spherical), E. Merck silica gel 60 (230–400 mesh ASTM), Fuji Silysia silica gel (PSQ 60B), or Kanto chemical silica gel 60 N (40–50 μm spherical, neutral). Celite® 545 was used for filtration. Melting points were determined on a Yanagimoto micro melting point apparatus or were uncorrected. ^1H NMR spectra were taken on 400 or 600 MHz and ^{13}C NMR spectra were taken on 100 or 150 MHz instrument (JEOL LNM-GSX 400α, JEOL JMN-ECP 400,

JEOL JMN-ECP 600) in the indicated solvent at room temperature unless otherwise stated and are reported. Chemical shifts are reported in parts per million (ppm) downfield from $(CH_3)_4Si$ (TMS). Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as follows: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared (IR) spectra were recorded on JASCO FT/IR-230 spectrometer. MS spectrometry and elemental analysis were carried out by the Chemical Analysis Center of Chiba University.

4.2. Methyl 2-(2-bromophenylamino)cyclooct-1-enecarboxylate (3a)

To a solution of methyl 2-oxocyclooctanecarboxylate (5.0 g, 27 mmol) in benzene (27 mL) in a flask fitted with Dean–Stark apparatus were added 2-bromoaniline (5.1 g, 30 mmol) and *p*-TsOH·H_2O (2.6 g, 14 mmol) at room temperature. The mixture was heated for 14 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:80) to afford **3a** (6.25 g, 68%) as a colorless solid.

Spectral data of **3a**: mp 78–80 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.41–1.60 (m, 8H), 2.45–2.51 (m, 4H), 3.73 (s, 3H), 2.02–7.06 (m, 1H), 7.16–7.18 (m, 1H), 7.25–7.29 (m, 1H), 7.59–7.61 (m, 1H), 10.7 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.6, 26.2, 26.6, 27.1, 29.2, 30.3, 50.8, 97.1, 121.8, 126.5, 127.6, 128.2, 133.0, 139.1, 159.7, 171.0; IR (KBr) ν: 2935, 2857, 1604, 1483, 1431, 1246, 1156, 1101, 759 cm^{-1}; LRMS (FAB) *m*/*z* 337 $[M]^+$; HRMS (FAB) calcd for $C_{16}H_{20}BrNO_2$ $[M]^+$ 337.0677, found 337.0687.

4.3. Methyl 2-(2-iodophenylamino)cyclooct-1-enecarboxylate (3b)

To a solution of methyl 2-oxocyclooctanecarboxylate (3.4 g, 18.46 mmol) in benzene (37 mL) in a flask fitted with Dean–Stark apparatus were added 2-iodoaniline (8.08 g, 36.9 mmol) and *p*-TsOH (95 mg, 0.55 mmol) at room temperature. The mixture was heated for 43 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:80) to afford **3b** (4.42 g, 62%) as a colorless solid.

Spectral data of **3b**: mp 62–65 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.38–1.44 (m, 2H), 1.51–1.60 (m, 6H), 2.43 (t, *J*=6.1 Hz, 2H), 2.50 (t, *J*=6.1 Hz, 2H), 3.74 (s, 3H), 6.90 (td, *J*=1.5, 9.0 Hz, 1H), 7.14 (dd, *J*=1.2, 7.8 Hz, 1H), 7.30 (td, *J*=1.2, 7.8 Hz, 1H), 7.86 (dd, *J*=1.5, 7.8 Hz, 1H), 10.59 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 25.7, 26.1, 26.7, 27.1, 29.1, 30.3, 50.8, 96.9, 99.3, 127.0, 127.9, 128.6, 139.3, 142.3, 159.6, 171.0; IR (KBr) ν: 2924, 1648, 1598, 1436, 1245 cm^{-1}; LRMS (EI) *m*/*z* 385 $[M]^+$; HRMS (FAB) calcd for $C_{16}H_{20}INO_2$ $[M]^+$ 385.0539, found 385.0536.

4.4. Methyl 6,7,8,9,10,11-hexahydro-5*H*-cycloocta[*b*]indole-6-carboxylate (4) (Table 2, entry 6)

A suspension of **3b** (49.2 mg, 0.128 mmol), $Pd(PPh_3)_4$ (4.4 mg, 3.84 μmol), and Ag_3PO_4 (53.6 mg, 0.128 mmol) in DMSO (1.3 mL) was heated for 1 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:10) to afford **4** (31.2 mg, 95%) as a colorless oil.

Spectral data of **4**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.03–1.10 (m, 1H), 1.33–1.39 (m, 1H), 1.46–1.55 (m, 1H), 1.58–1.66 (m, 2H), 1.86–1.92 (m, 2H), 2.01–2.07 (m, 1H), 2.58 (ddd, *J*=3.0, 12.7, 14.7 Hz, 1H), 3.08 (dt, *J*=4.1, 14.7 Hz, 1H), 3.79 (s, 3H), 4.12 (dd, *J*=4.7, 12.4 Hz, 1H), 7.07–7.10 (m, 1H), 7.12–7.15 (m, 1H), 7.33 (dd, *J*=0.8, 8.0 Hz, 1H), 7.52 (d, *J*=8.0 Hz, 1H), 8.93 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.2, 25.1, 26.5, 31.1, 35.2, 41.1, 52.2, 110.9, 113.6, 117.9, 119.0, 121.3, 127.5, 130.5, 135.4, 175.5; IR (neat) ν: 3442, 2924, 2850, 1729, 1462, 1168, 742 cm^{-1}; LRMS (EI) *m*/*z* 257 $[M]^+$; HRMS (FAB) *m*/*z* calcd for $C_{16}H_{19}NO_2$ $[M]^+$ 257.1416, found 257.1406.

4.5. Methyl 2-(2-iodophenylamino)cyclopent-1-enecarboxylate (10a)

To a solution of methyl 2-oxocyclopentanecarboxylate **9a** (1.0 g, 7.0 mmol) and 2-iodoaniline (3.1 g, 14.1 mmol) in benzene (30 mL) in a flask fitted with a Dean–Stark apparatus was added *p*-TsOH (1.28 g, 7.0 mmol) at room temperature. The mixture was heated for 10 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:10 to 1:30) to afford **10a** (1.81 g, 75%) as a colorless solid.

Spectral data of **10a**: mp 58–60 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.88 (q, *J*=7.3 Hz, 2H), 2.59 (t, *J*=7.3 Hz, 2H), 2.71 (t, *J*=7.3 Hz, 2H), 3.77 (s, 3H), 6.77 (t, *J*=7.6 Hz, 1H), 7.13 (dd, *J*=1.2, 8.1 Hz, 1H), 7.26 (t, *J*=6.6 Hz, 1H), 7.82 (dd, *J*=1.2, 7.8 Hz, 1H), 9.48 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 21.8, 29.0, 33.5, 50.7, 92.9, 99.2, 121.7, 124.9, 128.8, 139.6, 141.9, 159.1, 168.4; IR (KBr) ν: 2941, 2856, 1656, 1609, 1441, 1276 cm^{-1}; LRMS (EI) *m*/*z* 343 $[M]^+$; HRMS (FAB) calcd for $C_{13}H_{14}INO_2$ $[M]^+$ 343.0069, found 343.0066.

4.6. Methyl 2-(2-iodophenylamino)cyclohex-1-enecarboxylate (10b)

To a solution of methyl 2-oxocyclohexanecarboxylate (**9b**, 0.1 mL, 0.7 mmol) and 2-iodoaniline (459.9 mg, 2.1 mmol) in benzene (10 mL) in a flask fitted with a Dean–Stark apparatus was added *p*-TsOH (60.2 mg, 0.35 mmol) at room temperature. The mixture was heated for 23 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:10 to 1:4) to afford **10b** (203.0 mg, 81%) as a colorless solid.

Spectral data of **10b**: mp 52–54 °C (*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.58–1.66 (m, 4H), 2.14 (t, *J*=5.1 Hz, 2H), 2.37 (t, *J*=6.1 Hz, 2H), 3.70 (s, 3H), 6.87 (td, *J*=1.7, 7.6 Hz, 1H), 7.13 (dd, *J*=1.5, 7.8 Hz, 1H), 7.28 (td, *J*=1.5, 7.8 Hz, 1H), 7.85 (dd, *J*=1.5, 8.1 Hz, 1H), 10.40 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 22.2, 22.6, 23.8, 28.0, 50.8, 94.2, 98.4, 126.7, 127.2, 128.5, 139.3, 141.8, 155.7, 171.0; IR (KBr) ν: 2941, 1654, 1594, 1478, 1437, 1244, 1184, 1091 cm^{-1}; LRMS (EI) *m*/*z* 357 $[M]^+$; HRMS (FAB) calcd for $C_{14}H_{16}INO_2$ $[M]^+$ 357.0226, found 357.0249.

4.7. Methyl 2-(2-iodophenylamino)cyclohept-1-enecarboxyate (10c)

To a solution of methyl 2-oxocycloheptanecarboxylate **9c** (0.1 mL, 0.64 mmol) and 2-iodoaniline (280.4 mg, 1.28 mmol) in benzene (6.4 mL) in a flask fitted with a Dean–Stark apparatus was

added *p*-TsOH (55.0 mg, 0.32 mmol) at room temperature. The mixture was heated for 4 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:10) to afford an inseparable mixture of **9c** (209.3 mg, 0.56 mmol determined by ^{1}H NMR) and 2-iodoaniline (63.0 mg, 0.29 mmol determined by ^{1}H NMR) as a yellow oil. To remove 2-iodoaniline, the mixture (272.3 mg) in benzene (10 mL) was reacted with succinic anhydride (115.1 mg, 1.15 mmol) in the presence of pyridine (0.09 mL, 1.15 mmol) and heated for 2 days at 70 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:10) to afford **10c** (237.6 mg, 83%) as a colorless crystal.

Spectral data of **10c**: mp 74–76 °C (EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.51–1.55 (m, 2H), 1.60–1.64 (m, 2H), 1.73–1.78 (m, 2H), 2.42–2.45 (m, 2H), 2.56–2.59 (m, 2H), 3.74 (s, 3H), 6.82 (td, *J*=1.5, 7.9 Hz, 1H), 6.95 (d, *J*=8.1 Hz, 1H), 7.28 (td, *J*=1.3, 7.7 Hz, 1H), 7.85 (dd, *J*=1.3, 7.9 Hz, 1H), 10.68 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 26.0, 26.3, 27.6, 30.2, 31.9, 51.0, 96.5, 100.6, 125.5, 125.9, 128.5, 139.4, 142.1, 162.2, 170.8; IR (KBr) ν: 2913, 2848, 1648, 1600, 1250, 1209 cm^{-1}; LRMS (EI) *m*/*z* 371 [M]$^+$; HRMS (FAB) calcd for $C_{15}H_{18}INO_2$ [M]$^+$ 371.0382, found 371.0370.

4.8. Methyl 1,2,3,4-tetrahydrocyclopenta[*b*]indole-3-carboxylate (11a)

A suspension of **10a** (276.2 mg, 0.8 mmol), $Pd(PPh_3)_4$ (92.4 mg, 0.08 mmol), and Ag_3PO_4 (334.9 mg, 0.8 mmol) in DMSO (8 mL) was heated for 5 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:4) to afford **11a** (74.4 mg, 43%) as a colorless oil.

Spectral data of **11a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.57–3.00 (m, 4H), 3.80 (s, 3H), 4.09–4.14 (m, 1H), 7.08 (td, *J*=1.0, 7.1 Hz, 1H), 7.14 (td, *J*=1.0, 7.1 Hz, 1H), 7.32 (d, *J*=7.8 Hz, 1H), 7.45 (d, *J*=7.8 Hz, 1H), 8.11 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.6, 32.3, 44.2, 52.2, 111.7, 119.0, 119.7, 120.8, 121.4, 124.3, 139.2, 141.1, 173.1; IR (neat) ν: 3019, 1732, 1449, 1216 cm^{-1}; LRMS (EI) *m*/*z* 215 [M]$^+$; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{13}NO_2$ [M]$^+$ 215.0946, found 215.0927.

4.9. Methyl 2,3,4,9-tetrahydro-1*H*-carbazole-1-carboxylate (11b) and methyl 9*H*-carbazole-1-carboxylate (12)

A suspension of **10b** (80.6 mg, 0.23 mmol), $Pd(PPh_3)_4$ (26.0 mg, 0.023 mmol), and Ag_3PO_4 (94.2 mg, 0.23 mmol) in DMSO (2.3 mL) was heated for 6 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:10 to 1:4) to afford **11b** (32.8 mg 64%) and **12** (5.6 mg, 11%) as a yellow solid, respectively.

Spectral data of **11b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.78–1.87 (m, 1H), 2.00–2.09 (m, 1H), 2.11–2.25 (m, 2H), 2.72 (td, *J*=1.7, 5.9 Hz, 2H), 3.77 (s, 3H), 3.85 (t, *J*=5.9 Hz, 1H), 7.08 (td, *J*=1.2, 8.1 Hz, 1H), 7.15 (td, *J*=1.2, 7.1 Hz, 1H), 7.31 (dd, *J*=0.7, 8.1 Hz, 1H), 7.47 (d, *J*=7.8 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 20.8, 21.9, 26.1, 40.0, 52.4, 110.9, 112.1, 118.4, 119.3, 121.9, 127.4, 129.4, 136.1, 173.1; IR (neat) ν: 2952, 1734, 1618, 1438, 1241 cm^{-1}; LRMS (EI) *m*/*z* 229 [M]$^+$; HRMS (FAB) *m*/*z* calcd for $C_{14}H_{15}NO_2$ [M]$^+$ 229.1103, found 229.1119.

Spectral data of **12**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.03 (s, 3H), 7.23–7.29 (m, 2H), 7.46–7.54 (m, 2H), 8.07–8.10 (m, 2H), 8.27 (d, *J*=7.6 Hz, 1H), 9.93 (br s, 1H); IR (neat) ν: 3406, 1676, 1601, 1260, 749 cm^{-1}; Reg# 51035-15-5.

4.10. Methyl 5,6,7,8,9,10-hexahydrocyclohepta[*b*]indole-6-carboxylate (11c)

A suspension of compound **10c** (198.0 mg, 0.53 mmol), $Pd(PPh_3)_4$ (61.3 mg, 0.053 mmol), and Ag_3PO_4 (223.3 mg, 0.53 mmol) in DMSO (5.3 mL) was heated for 2 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:4 to 1:2) to afford **11c** (91.0 mg, 71%) as a yellow oil.

Spectral data of **11c**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.75–1.79 (m, 2H), 1.85–1.93 (m, 1H), 2.05–2.13 (m, 3H), 2.76–2.92 (m, 2H), 3.76 (s, 3H), 3.95 (dd, 1H, *J*=3.4, 7.1 Hz), 7.07–7.15 (m, 2H), 7.29 (d, 1H, *J*=7.3 Hz), 7.50 (d, 1H, *J*=7.6 Hz), 8.44 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 23.9, 27.9, 29.1, 30.9, 45.1, 52.2, 110.6, 115.1, 118.0, 119.1, 121.3, 128.5, 132.6, 134.5, 173.8; IR (neat) ν: 3398, 2924, 1718, 1462, 1228, 1198 cm^{-1}; LRMS (EI) *m*/*z* 243 [M]$^+$; HRMS (FAB) calcd for $C_{15}H_{17}NO_2$ [M]$^+$ 243.1259, found 243.1257.

4.11. Ethyl 1-(4-benzenesulfonyl)-4-(2-iodophenylamino)-1,2,5,6-tetrahydropyridine-3-carboxylate (13)

To a solution of ethyl 1-(benzenesulfonyl)-4-oxopiperidine-3-carboxylate (254.7 mg, 0.82 mmol) and 2-iodoaniline (358.3 mg, 1.64 mmol) in benzene (10 mL) in a flask fitted with a Dean–Stark apparatus was added *p*-TsOH (70.3 mg, 0.41 mmol) at room temperature. The mixture was heated for 5 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:10 to 1:3) to afford **13** (419.1 mg, 81%) as a yellow solid. A colorless crystal was obtained by recystallization (EtOAc/*n*-hexane).

Spectral data of **13**: mp 144–146 °C (EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (t, *J*=7.2 Hz, 3H), 2.30 (t, *J*=5.6 Hz, 2H), 3.19 (t, *J*=5.6 Hz, 2H), 3.92 (s, 2H), 4.21 (q, *J*=7.2 Hz, 2H), 6.91 (t, *J*=8.0 Hz, 1H), 7.04 (d, *J*=8.0 Hz, 1H), 7.31 (t, *J*=8.0 Hz, 1H), 7.55 (t, *J*=8.0 Hz, 2H), 7.62 (t, *J*=8.0 Hz, 1H), 7.84 (t, *J*=8.0 Hz, 3H), 10.33 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 27.6, 42.2, 43.4, 59.7, 90.6, 98.4, 127.3, 127.6, 127.6 (2C), 128.9, 129.1 (2C), 132.8, 136.6, 139.5, 140.7, 153.0, 168.2; IR (film) ν: 3055, 1666, 1613, 1257, 750 cm^{-1}; LRMS (EI) *m*/*z* 512 [M]$^+$; HRMS (FAB) calcd for $C_{20}H_{22}IN_2O_4S$ [M+H]$^+$ 513.0345, found 513.0319.

4.12. Ethyl 2-(benzenesulfonyl)-2,3,4,5-tetrahydro-1*H*-pyrido[4,3-*b*]indole-4-carboxylate (14) and ethyl 5*H*-pyrido[4,3-*b*]indole-4-carboxylate (15)

A suspension of **13** (285.8 mg, 0.56 mmol), $Pd(PPh_3)_4$ (64.7 mg, 0.056 mmol), and Ag_3PO_4 (234.4 mg, 0.56 mmol) in DMSO (6 mL) was heated for 24 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:5 to 1:2) to afford **14** (38.8 mg, 15%) as an orange amorphous solid and **15** (16.1 mg, 12%) as a colorless solid.

Spectral data of **14**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.33 (t, *J*=7.2 Hz, 3H), 3.42–3.47 (m, 1H), 4.02–4.05 (m, 1H), 4.11–4.19 (m, 2H), 4.27 (q, *J*=7.2 Hz, 2H), 4.67 (d, *J*=12.0 Hz, 1H), 7.10 (t, *J*=8.0 Hz,

1H), 7.19 (t, J=7.2 Hz, 1H), 7.34 (d, J=8.0 Hz, 1H), 7.41 (d, J=7.2 Hz, 1H), 7.52–7.62 (m, 3H), 7.89–7.91 (m, 2H), 8.63 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 40.0, 43.0, 44.9, 61.9, 107.1, 111.2, 117.8, 119.8, 122.4, 124.8, 127.3, 127.4 (2C), 129.2 (2C), 132.9, 135.9, 137.0, 169.6; IR (film) ν: 3450, 3054, 2985, 1731, 1446, 1265, 1169 cm^{-1}; LRMS (EI) m/z 384 $[M]^+$; HRMS (FAB) calcd for $C_{20}H_{21}IN_2O_4S$ $[M+H]^+$ 385.1222, found 385.1215.

Spectral data of **15**: mp 186–188 °C (EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.50 (t, J=7.2 Hz, 3H), 4.53 (q, J=7.2 Hz, 2H), 7.37 (t, J=7.6 Hz, 1H), 7.52–7.58 (m, 2H), 8.16 (d, J=7.6 Hz, 1H), 9.13 (s, 1H), 9.39 (s, 1H), 9.96 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.3, 61.3, 108.8, 111.5, 120.91, 120.93, 120.95, 121.5, 127.6, 139.5, 143.8, 145.5, 146.6, 166.7; IR (film) ν: 3749, 3434, 3051, 1699, 1604, 1265 cm^{-1}; LRMS (EI) m/z 240 $[M]^+$; HRMS (FAB) calcd for $C_{14}H_{13}N_2O_2$ $[M+H]^+$ 241.0977, found 241.0965.

4.13. (*Z*)-Ethyl 3-(2-iodophenylamino)-2-butenoate (16a)

To a solution of ethyl acetoacetate (90 μL, 0.68 mmol) and 2-iodoaniline (300 mg, 1.37 mmol) in benzene (7 mL) in a flask fitted with a Dean–Stark apparatus was added *p*-TsOH (58 mg, 0.34 mmol) at room temperature. The mixture was heated for 3 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:30) to afford **16a** (225.2 mg, quant) as a colorless oil.

Spectral data **16a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, J=7.2 Hz, 3H), 1.86 (s, 3H), 4.18 (q, J=7.2 Hz, 2H), 4.77 (s, 1H), 6.92 (dt, J=1.6, 8.0 Hz, 1H), 7.16 (dd, J=1.2, 7.2 Hz, 1H), 7.32 (dt, J=1.2, 7.2 Hz, 1H), 7.87 (dd, J=1.6, 8.0 Hz, 1H), 10.18 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.5, 20.1, 58.9, 87.0, 97.7, 126.8, 127.2, 128.7, 139.4, 141.2, 158.1, 170.2; LRMS (EI) m/z 331 $[M]^+$. Reg# 128942-81-4.

4.14. Ethyl 3-(2-iodophenylamino)pent-2-enoate (16b)

To a solution of ethyl 3-oxopentanoate (0.3 mL, 2.1 mmol) and 2-iodoaniline (559.1 mg, 2.52 mmol) in benzene (10 mL) in a flask fitted with a Dean–Stark apparatus was added *p*-TsOH (180.6 mg, 1.05 mmol) at room temperature. The mixture was heated for 50 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:10) to afford **16b** (275.8 mg, 38%) as a colorless oil.

Spectral data of **16b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.03 (t, J=7.6 Hz, 3H), 1.30 (t, J=7.2 Hz, 3H), 2.17 (q,J=7.6 Hz, 2H), 4.18 (q, J=7.2 Hz, 2H), 4.84 (s, 1H), 6.92 (t, J=8.0 Hz, 1H), 7.15 (d, J=8.0 Hz, 1H), 7.31 (t, J=8.0 Hz, 1H), 7.87 (d, J=8.0 Hz, 1H), 10.10 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 12.1, 14.5, 25.5, 58.9, 85.2, 98.4, 127.2, 127.4, 128.4, 139.4, 141.3, 163.8, 170.5; IR (neat) ν: 3428, 2979, 2936, 1653, 1614, 1580, 1457, 1262 cm^{-1}; LRMS (EI) m/z 345 $[M]^+$; HRMS (FAB) calcd for $C_{13}H_{17}INO_2$ $[M+H]^+$ 346.0304, found 346.0304.

4.15. Ethyl 2-benzyl-3-(2-iodophenylamino)-2-butenoate (16d)

To a solution of ethyl 2-benzyl-3-oxobutyrate (0.5 mL, 2.35 mmol) and 2-iodoaniline (617.7 mg, 2.82 mmol) in benzene (15 mL) in a flask fitted with a Dean–Stark apparatus was added *p*-TsOH (202.1 mg, 1.18 mmol) at room temperature. The mixture was heated for 3 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:30) to afford an inseparable mixture of **16d** (271.1 mg, 27% determined by ^{1}H NMR) and 2-iodoaniline (148.8 mg, determined by ^{1}H NMR) as a yellow oil. To remove 2-iodoaniline, the mixture (419.9 mg) was dissolved in benzene (12 mL) and heated with succinic anhydride (272.2 mg, 2.72 mmol) in presence of pyridine (0.23 mL, 2.72 mmol) for 3 h at 70 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:20) to afford **16d** (224.1 mg, 23%) as a colorless oil.

Spectral data of **16d**: ^{1}H NMR and ^{13}C NMR spectrum of **16d** showed that **16d** exists as a mixture of imine–enamine tautomeric isomers in a ratio of 24:76 at room temperature in $CDCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.22 (t, J=7.2 Hz, 0.76×3H), 1.24 (t, J=7.2 Hz, 0.24×3H), 1.77 (s, 0.24×3H), 1.88 (s, 0.76×3H), 3.30 (q, J=7.6 Hz, 0.24×1H), 3.38 (q, J=7.6 Hz, 0.24×1H), 3.74 (s, 0.76×2H), 3.85 (t, J=7.6 Hz, 0.24×1H), 4.14–4.22 (m, 0.76×2H+0.24×2H), 6.46 (d, J=8.0 Hz, 0.24×1H), 6.75 (t, J=8.0 Hz, 0.24×1H), 6.87 (t, J=8.0 Hz, 0.76×1H), 7.05 (d, J=8.0 Hz, 0.76×1H), 7.14–7.30 (m, 0.76×6H+0.24×6H), 7.78 (d, J=8.0 Hz, 0.24×1H), 7.85 (d, J=8.0 Hz, 0.76×1H), 11.0 (br s, 0.76×1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2, 14.4, 17.1, 19.7, 32.9, 35.3, 57.9, 59.4, 61.1, 88.4, 96.5, 97.4, 118.9, 124.9, 125.5, 126.46, 126.49, 126.6, 127.8, 128.1, 128.4, 128.6, 128.8, 129.0, 138.6, 139.0, 139.3, 141.9, 142.0, 151.8, 156.4, 169.5, 170.7, 170.8; IR (neat) ν: 2979, 1733, 1649, 1598, 1479, 1365, 1253, 1205, 1075, 1015 cm^{-1}; LRMS (EI) m/z 421 $[M]^+$; HRMS (FAB) calcd for $C_{19}H_{21}INO_2$ $[M+H]^+$ 422.0617, found 422.0620.

4.16. Ethyl (1*H*-indol-2-yl)acetate (17a) and ethyl 2-methyl-1*H*-indole-3-carboxylate (18a)

A suspension of **16a** (229.3 mg, 0.69 mmol), $Pd(PPh_3)_4$ (79.7 mg, 0.069 mmol), and Ag_3PO_4 (288.8 mg, 0.69 mmol) in DMSO (6.8 mL) was heated for 3.5 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:10 to 1:3) to afford **17a** (23.1 mg, 17%) and **18a** (126.6 mg, 79%) as a colorless solid, respectively.

Spectral data of **17a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.30 (t, J=7.2 Hz, 3H), 3.83 (s, 2H), 4.21 (q, J=7.2 Hz, 2H), 6.35 (s, 1H), 7.09 (dt, J=1.2, 7.2 Hz, 1H), 7.15 (dt, J=1.2, 7.2 Hz, 1H), 7.35 (dd, J=1.2, 7.2 Hz, 1H), 7.54 (dd, J=1.2, 7.2 Hz, 1H), 8.68 (br s, 1H). Reg# 33588-64-6.

Spectral data of **18a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.45 (t, J=7.2 Hz, 3H), 2.75 (s, 3H), 4.40 (q, J=7.2 Hz, 2H), 7.19 (dt, J=1.6, 7.1 Hz, 1H), 7.22 (dt, J=1.6, 7.1 Hz, 1H), 7.31 (dd, J=1.6, 7.1 Hz, 1H), 8.10 (dd, J=1.6, 7.1 Hz, 1H), 8.27 (br s, 1H). Reg# 53855-47-3.

4.17. Ethyl (3-methyl-1*H*-indol-2-yl)acetate (17b) and ethyl 2-ethyl-1*H*-indole-3-carboxylate (18b)

A suspension of **16b** (212.6 mg, 0.616 mmol), $Pd(PPh_3)_4$ (71.1 mg, 0.062 mmol), and Ag_3PO_4 (257.8 mg, 0.62 mmol) in DMSO (6 mL) was heated for 4.5 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with $CHCl_3$ to afford **17b** (8.0 mg, 6%) as a brown solid and **18b** (114.6 mg, 86%) as a colorless solid.

Spectral data of **17b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.29 (t, J=7.6 Hz, 3H), 2.56 (s, 3H), 3.76 (s, 2H), 4.20 (q, J=7.2 Hz, 2H), 7.09 (t, J=8.0 Hz, 1H), 7.16 (t, J=8.0 Hz, 1H), 7.31 (d, J=8.0 Hz, 1H), 7.50 (d, J=8.0 Hz, 1H), 8.49 (br s, 1H). Reg# 14190-78-4.

Spectral data of **18b**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31 (t, J=7.6 Hz, 3H), 1.44 (t, J=7.2 Hz, 3H), 3.17 (q, J=7.6 Hz, 2H), 4.40 (q,

J=7.2 Hz, 2H), 7.18 (dt, J=1.6, 7.2 Hz, 1H), 7.22 (dt, J=1.6, 7.2 Hz, 1H), 7.30 (dd, J=1.6, 7.0 Hz, 1H), 8.14 (dd, J=1.6, 7.2 Hz, 1H), 8.79 (br s, 1H). Reg# 94445-86-0.

4.18. Ethyl 3-(1*H*-indol-2-yl)-pentanate (17c)

To a solution of ethyl 2-propyl-3-oxobutyrate (381.7 mg, 2.22 mmol) and 2-iodoaniline (972.5 mg, 4.44 mmol) in benzene (22 mL) in a flask fitted with a Dean–Stark apparatus was added *p*-TsOH (190.9 mg, 1.11 mmol) at room temperature. The mixture was heated for 19 h under reflux. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with *n*-hexane to afford an inseparable mixture of **16c** (705.8 mg, 1.89 mmol, 85%, determined by ^{1}H NMR) and 2-iodoaniline (128.3 mg, determined by ^{1}H NMR). This impure **16c** was employed in the next step without further purification because **16c** was unstable.

A suspension of **16c** (273.9 mg, 0.73 mmol), $Pd(PPh_3)_4$ (84.4 mg, 0.073 mmol), and Ag_3PO_4 (305.6 mg, 0.73 mmol) in DMSO (7.3 mL) was heated for 3 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:10) to afford **17c** (120 mg, 67%) as a colorless solid.

Spectral data of **17c**: mp 46–47 °C (EtOAc/*n*-hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ: 0.92 (t, J=7.2 Hz, 3H), 1.26 (t, J=7.2 Hz, 3H), 1.29–1.40 (m, 2H), 1.81–1.91 (m, 1H), 1.98–2.07 (m, 1H), 3.80 (t, J=7.6 Hz, 1H), 4.11–4.24 (m, 2H), 6.34 (s, 1H), 7.07 (t, J=7.2 Hz, 1H), 7.14 (t, J=7.2 Hz, 1H), 7.32 (d, J=7.2 Hz, 1H), 7.54 (d, J=7.2 Hz, 1H), 8.60 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.6, 14.1, 20.5, 35.6, 45.1, 61.2, 101.1, 110.8, 119.7, 120.1, 121.6, 128.0, 135.5, 136.1, 173.8; IR (neat) ν: 3373, 1715, 1178, 746 cm^{-1}; LRMS (EI) m/z 245 $[M]^+$; HRMS (EI) calcd for $C_{15}H_{19}NO_2$ $[M]^+$ 245.1416, found 245.1406.

4.19. Ethyl 2-(1*H*-indol-2-yl)-3-phenylpropionate (17d)

A suspension of **16d** (202.0 mg, 0.48 mmol), $Pd(PPh_3)_4$ (55.5 mg, 0.048 mmol), and Ag_3PO_4 (200.9 mg, 0.48 mmol) in DMSO (5 mL) was heated for 2.5 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:10) to afford **17d** (114.9 mg, 82%) as a colorless solid.

Spectral data of **17d**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.13 (t, J=7.2 Hz, 3H), 3.17 (dd, J=6.8, 13.6 Hz, 1H), 3.36 (dd, J=8.8, 13.6 Hz, 1H), 4.02–4.15 (m, 3H), 6.32 (s, 1H), 7.06–7.37 (m, 8H), 7.53 (d, J=7.6 Hz, 1H), 8.59 (br s, 1H). Reg# 332365-87-4.

4.20. Ethyl 1-phenylsulfonyl-5-oxoazocane-4-carboxylate (33)

To a solution of benzenesulfonamide (5.0 g, 31.8 mmol) in acetone (100 mL) were added K_2CO_3 (24 g, 0.17 mmol) and ethyl 4-bromobutyrate (12 mL, 83.9 mmol) at room temperature. After the mixture was stirred for 2 days at 60 °C, the reaction was quenched by addition of water at 0 °C. The mixture was concentrated under reduced pressure and was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:4) to afford ethyl 4-[phenylsulfonyl-(3-ethoxycarbonylpropyl)amino]butyrate (13.8 mg, quant) as a pale yellow oil.

Spectral data of ethyl 4-[phenylsulfonyl-(3-ethoxycarbonylpropyl)amino]butyrate: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (t, J=7.1 Hz, 6H), 1.87 (quintet, J=7.3 Hz, 4H), 2.34 (t, J=7.3 Hz, 4H), 4.12 (q, J=7.1 Hz, 4H), 7.49–7.79 (m, 3H), 7.80 (d, J=7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.2 (2C), 23.9 (2C), 31.0 (2C), 47.8 (2C), 60.5 (2C), 127.1 (2C), 129.1 (2C), 132.5, 139.5, 172.8 (2C); IR (neat) ν: 2982, 1732, 1447, 1374, 1338, 1163 cm^{-1}; LRMS (FAB) m/z 386 $[M+H]^+$; HRMS (FAB) m/z calcd for $C_{18}H_{28}NO_6S$ $[M+H]^+$ 386.1637, found 386.1624.

To a solution of *t*-BuOK (1.0 M solution in THF, 16 mL, 16 mmol) in toluene (400 mL) was added ethyl 4-[phenylsulfonyl-(3-ethoxycarbonylpropyl)amino]butyrate (2.0 g, 5.2 mmol) in toluene (120 mL) dropwisely over 19 h at 120 °C. After the reaction was quenched by addition of 1 N HCl and water at 0 °C, the mixture was extracted with EtOAc. The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation under reduced pressure, the residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (from 1:2 to 1:1) to afford **33** (0.87 g, 49%) as brown oil.

Spectral data of **33**: ^{1}H NMR and ^{13}C NMR spectrum of **33** showed that **33** existed as a mixture of keto–enol tautomeric isomers in a ratio of 50:50 at room temperature in $CDCl_3$; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.24 (t, J=7.1 Hz, 1.5H), 1.26 (t, J=7.1 Hz, 1.5H), 1.94–2.04 (m, 1.5H), 2.20 (ddd, J=3.7, 7.1, 14.8 Hz, 1H), 2.24–2.33 (m, 1H), 2.44–2.56 (m, 2.5H), 2.63 (ddd, J=3.5, 12.4, 13.7 Hz, 0.5H), 3.00 (ddd, J=3.5, 11.7, 13.7 Hz, 0.5H), 3.17–3.27 (m, 3H), 3.57 (dd, J=3.5, 11.7 Hz, 0.5H), 4.14 (q, J=7.1 Hz, 1H), 4.16 (q, J=7.1 Hz, 1H), 7.48–7.62 (m, 3H), 7.76–7.79 (m, 2H), 12.6 (s, 0.5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 13.9, 14.2, 26.2, 27.0, 28.9, 30.2, 30.4, 39.4, 46.8, 47.9, 48.5, 50.8, 55.7, 60.5, 61.3, 97.9, 126.8, 127.4, 129.0, 129.1, 132.3, 132.8, 137.4, 139.3, 169.4, 172.0, 176.2, 206.9; IR (neat) ν: 2939, 1739, 1706, 1447, 1333, 1164 cm^{-1}; LRMS (EI) m/z 339 $[M]^+$; HRMS (FAB) m/z calcd for $C_{16}H_{22}NO_5S$ $[M+H]^+$ 340.1219, found 340.1209.

4.21. Ethyl 1-benzenesulfonyl-5-(2-iodophenylamino)-1,2,3,6,7,8-hexahydroazocine-4-carboxylate (34)

To a solution of **33** (120 mg, 0.35 mmol) in benzene (5 mL) in a flask fitted with Dean–Stark apparatus were added *p*-TsOH·H_2O (67 mg, 0.35 mmol) and 2-iodoaniline (150 mg, 0.71 mmol). The mixture was heated for 4 days under reflux. After the reaction mixture was filtrated through a Celite pad, the filtrate was concentrated under reduced pressure to give a residue, which was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:15) to afford **34** (110 mg, 58%) as a colorless amorphous solid.

Spectral data of **34**: ^{1}H NMR (400 MHz, $CDCl_3$, 55 °C) δ: 1.25 (t, J=7.1 Hz, 3H), 1.64 (br s, 2H), 2.51 (t, J=6.4 Hz, 2H), 2.71 (t, J=5.1 Hz, 2H), 3.21 (t, J=5.6 Hz, 2H), 3.25 (br s, 2H), 4.14 (q, J=7.1 Hz, 2H), 6.92 (td, J=1.2, 7.6 Hz, 1H), 7.15 (dd, J=1.2, 7.8 Hz, 1H), 7.32 (td, J=1.2, 7.6 Hz, 1H), 7.46–7.55 (m, 3H), 7.77–7.80 (m, 2H), 7.86 (dd, J=1.2, 7.8 Hz, 1H), 10.6 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 55 °C) δ: 14.5, 25.6, 28.3, 29.3, 47.5, 51.5, 59.5, 95.2, 99.5, 127.0 (2C), 127.7, 128.4, 128.9, 129.0 (2C), 132.2, 139.5, 140.0, 142.0, 159.5, 169.8; IR (film) ν: 2970, 1653, 1596, 1333, 1258, 1230 cm^{-1}; LRMS (EI) m/z 541 $[M+H]^+$; HRMS (FAB) m/z calcd for $C_{22}H_{26}IN_2O_4S$ $[M+H]^+$ 541.0658, found 541.0644.

4.22. Ethyl 3-phenylsulfonyl-2,3,4,5,6,7-hexahydro-1*H*-azocino[5,4-*b*]indole-6-carboxylate (35)

A suspension of compound **34** (150 mg, 0.28 mmol), $Pd(PPh_3)_4$ (32 mg, 0.028 mmol), and Ag_3PO_4 (120 mg, 0.28 mmol) in DMSO (1.0 mL) was heated for 18 h at 100 °C. After filtration of the reaction mixture through a Celite pad, the filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography on silica gel eluted with EtOAc/*n*-hexane (1:5) to afford **35** (78.5 mg, 69%) as a colorless amorphous solid.

Spectral data of **35**: ^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.35 (t, J=7.1 Hz, 3H), 1.87 (td, J=2.8, 12.9 Hz, 1H), 2.18 (ddd, J=3.9, 12.6, 14.8 Hz, 1H), 2.56 (t, J=12.1 Hz, 1H), 2.66 (tt, J=5.0, 12.9 Hz, 1H), 2.94 (ddd, J=3.0, 12.1, 15.1 Hz, 1H), 3.13 (ddd, J=1.4, 3.6, 15.1 Hz, 1H), 3.48 (dd, J=4.1, 15.1 Hz, 1H), 4.12 (dt, J=3.9, 13.2 Hz, 1H), 4.24–4.32 (m, 2H), 4.37 (dd, J=5.2, 12.7 Hz, 1H), 7.06 (td, J=1.1, 7.1 Hz, 1H), 7.13 (td, J=1.1, 8.0 Hz, 1H), 7.33 (d, J=8.0, Hz, 1H), 7.42 (d, J=8.0 Hz, 1H), 7.47 (td, J=1.4, 7.7 Hz, 2H), 7.54 (tt, J=1.4, 7.2 Hz, 1H), 7.78–7.80 (m, 2H), 9.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ: 14.3, 25.8, 36.5, 39.4, 48.5, 53.7, 61.6, 111.2, 111.3, 117.6, 119.5, 121.9, 126.9 (2C), 127.0, 129.2 (2C), 130.9, 132.7, 135.5, 139.1, 174.8; IR (KBr) ν: 3424, 1710, 1338, 1159 cm^{-1}; LRMS (EI) m/z 413 $[M+H]^+$; HRMS (FAB) calcd for $C_{22}H_{24}N_2O_4S$ $[M]^+$ 412.1457, found 412.1462.

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