Development of Novel Methods for Synthesis of Fused Indole-Type Compounds

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Contents

Preface

Nitrogen heterocycles are found in various biologically active compounds with high diversity. Among them, indole is one of the most important privileged scaffolds that form the structural core of many drugs and naturally occurring compounds.[1] For example, serotonin, tryptophan and indomethacin are representative bioactive compounds with the indole core (**Figure 1**). Indoline, dihydro-congener of indole, is also found in many biologically active natural products such as strychnine, strictamine, and vinblastine. Therefore, development of efficient methodologies for construction of these heterocyclic scaffolds is one of the most important subjects in modern organic chemistry.[2]

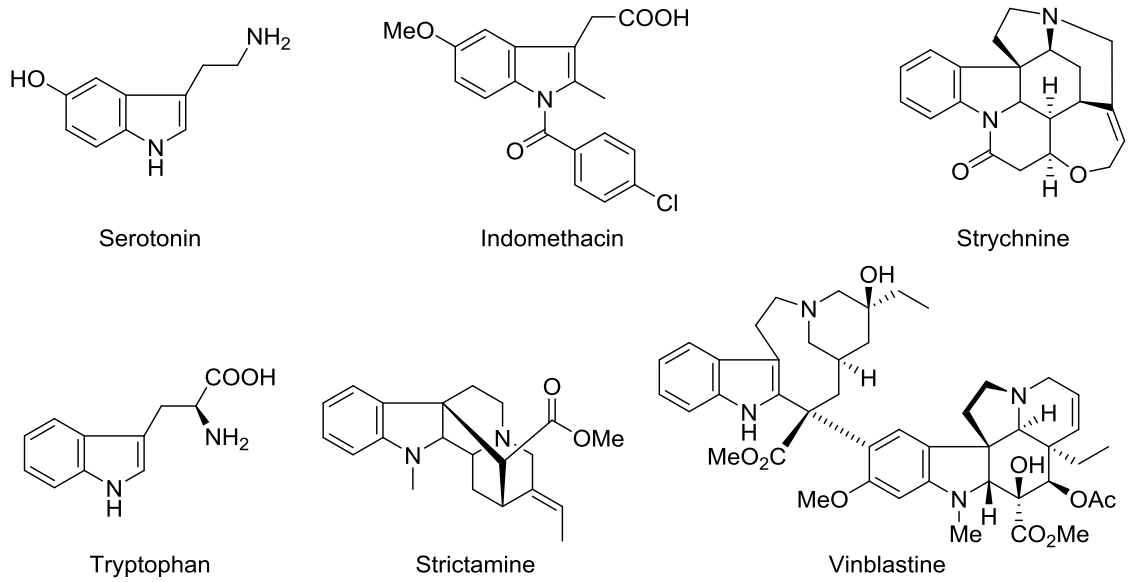
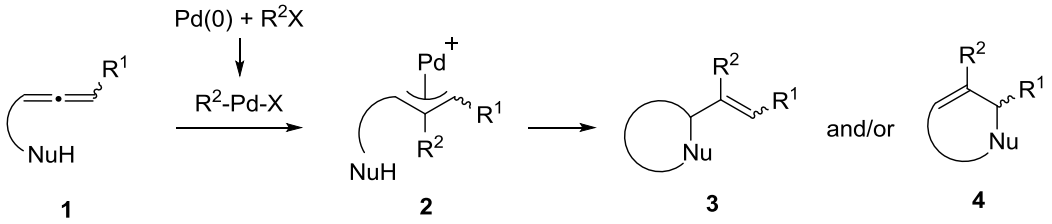


Figure 1. Representative Bioactive Compounds with an Indole or Indoline Core Structure

Development of efficient synthesis of valuable organic compounds is another important subject in both academic and industrial chemical communities. Besides selectivity and reactivity, organic chemists must take into account the atom efficiency, compatibility with the environment, and reduction in production cost.[3] Domino cyclizations, in which several new bonds are formed sequentially in a single operation with a rapid increase in the molecular complexity, are attractive for these purposes.[4] Compared to the traditional stepwise synthesis, these reactions can directly construct complex structures including fused nitrogen heterocycles from easily accessible starting materials, thus leading to improvement in synthetic efficiency and reduction in the separation processes and waste production.

Palladium is one of the most powerful transition metals in organic synthesis.[5] It is well known that palladium(0) complexes undergo oxidative addition with organic halides or their equivalents to form palladium(II) species. On the other hand, palladium(II) complexes activate unsaturated carbon–carbon bonds by π-coordination to facilitate various types of nucleophilic reactions. Furthermore, palladium catalysts can also promote other types of atom-economical elementary reactions such as C–H bond functionalization and insertion to carbon–carbon multiple bonds. Therefore, palladium complexes are highly useful to domino reactions for heterocycle syntheses.[6]

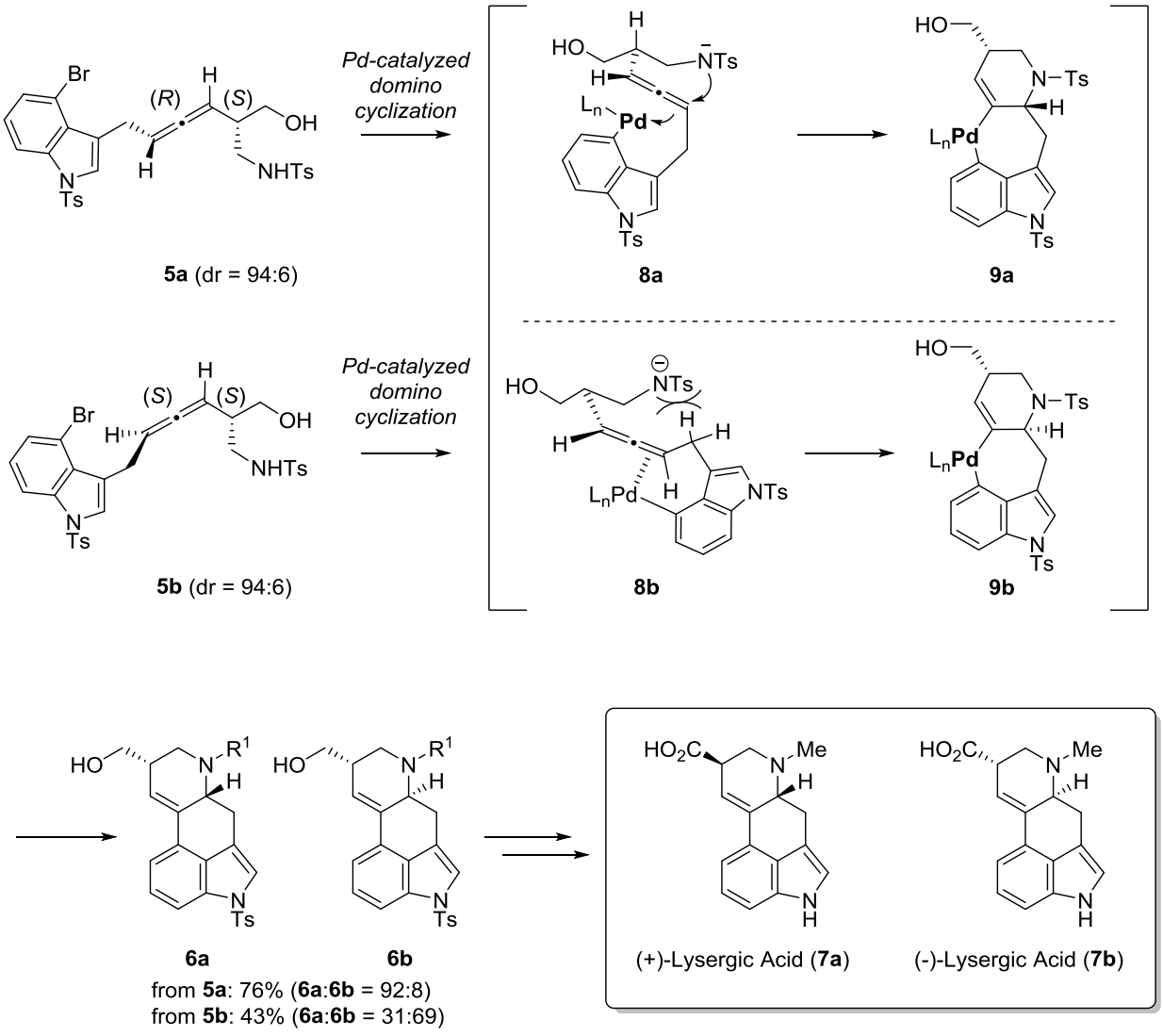
As the substrates in palladium-catalyzed domino reactions, allenes are useful and unique due to the presence of two π-orbitals orthogonal to each other. Many attractive reactions of allenic compounds on the basis of palladium catalysis have been developed.[7] Representative example of intermolecular electrophilic reaction of allene **1** with an organic halide (R^2X) followed by an intramolecular nucleophilic reaction is shown in **Scheme 1**. In most cases, the electrophilic reaction occurs at the central carbon of the allene and the nucleophilic reaction occurs at the one of the terminal positions. This selectivity can be readily understood by considering the mechanism of palladium-catalyzed reaction of allenes: carbopalladation of organopalladium(II) halide species (R^2–Pd–X; R^2 = aryl, alkenyl, or allyl) to allene proceeds in such a way to afford a η^3-allylpalladium intermediate **2**. Then, the cyclization product(s) **3** and/or **4** would be formed by intramolecular nucleophilic addition, where the regioselectivity depends on the substrate structure and reaction conditions.



Scheme 1. Reaction of Allenes in the Presence of a Palladium(0) Catalyst (Nu = nucleophile; R^1 = alkyl, aryl or alkenyl; R^2 = aryl, alkenyl or allyl; X = halogen)

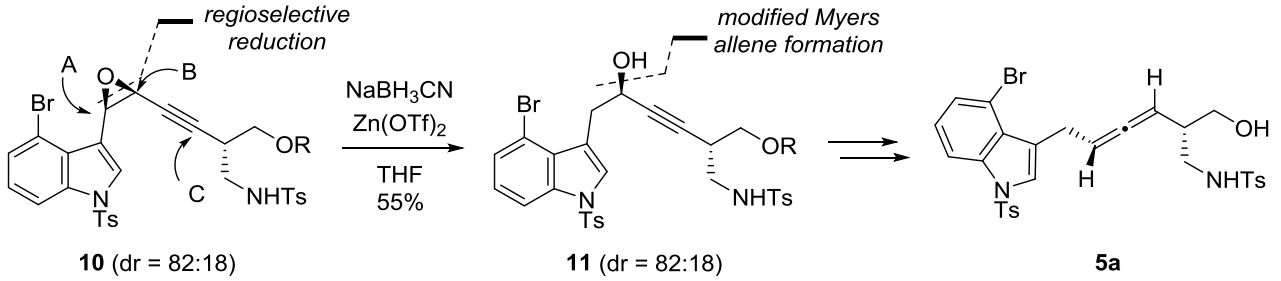
In light of this reactivity, the author's group developed a palladium-catalyzed domino cyclization of allene **5** containing an aryl halide group and a nucleophile at the appropriate positions (**Scheme 2**).[8] This domino reaction directly provides the tetracyclic indole intermediate **6** for ergot alkaloid synthesis. Reaction of **5a** (94:6) provided the desired product **6a** in good yield with good diastereoselectivity (92:8). In sharp contrast, when the reaction was conducted using diastereomeric allenic amides **5b** (94:6), the yield and stereoselectivity of the reaction were dramatically changed:

the undesired isomer **6b** was obtained as the major product in lower selectivity (**6a**:**6b** = 31:69). In this case, unfavorable steric interaction between the tosylamide group and the methylene protons would decrease reactivity of **5b** toward aminopalladation via **8b**. Because of the difference in reactivity and stereoselectivity between the diastereomeric substrates, efficient and diastereoselective synthesis of cyclization precursor **5** was crucial. With this domino reaction as the key step, the author's group reported the enantioselective total syntheses of (+)-lysergic acid (**7**) and related ergot alkaloids.[9]



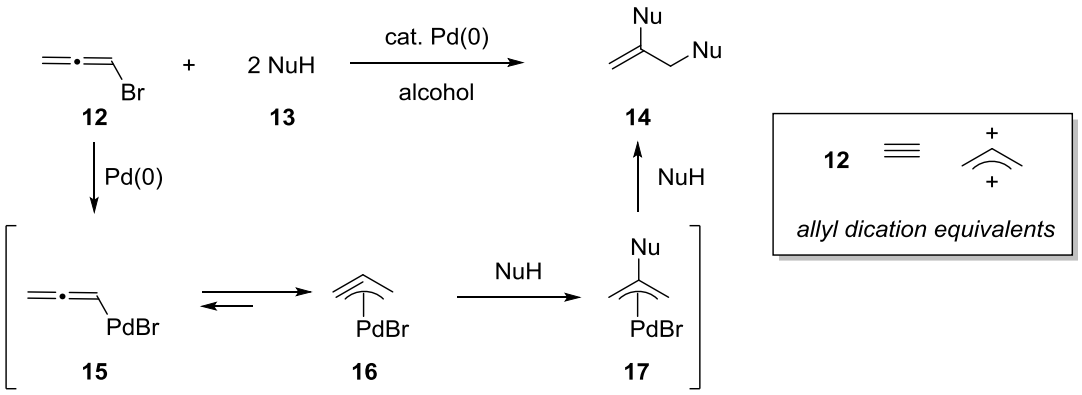
Scheme 2. Palladium(0)-Catalyzed Domino Cyclization of Allenic Tosylamide **5** Bearing a Bromoindolyl Group

Aiming at development of a more efficient enantioselective synthetic method of the allene **5** for the domino cyclization, the author designed and investigated a novel synthetic route based on a reductive ring-opening reaction of the chiral oxirane **10** (**Scheme 3**). The challenge of this strategy was to control the regioselectivity of the ring-opening reaction because of three reactive carbons of 2-alkynyloxirane **10**. In this study, the author found that $NaBH_3CN$ in the presence of $Zn(OTf)_2$ efficiently promoted the ring-opening reaction at the desired position to produce the propargyl alcohol **11** in 55% yield without promoting any epimerization at the propargylic position. Notably, propargyl alcohol could be stereospecifically transformed into the allene **5a** by use of the Myers method.



Scheme 3. This Study: New Synthetic Method of Allenic Tosylamide **5**

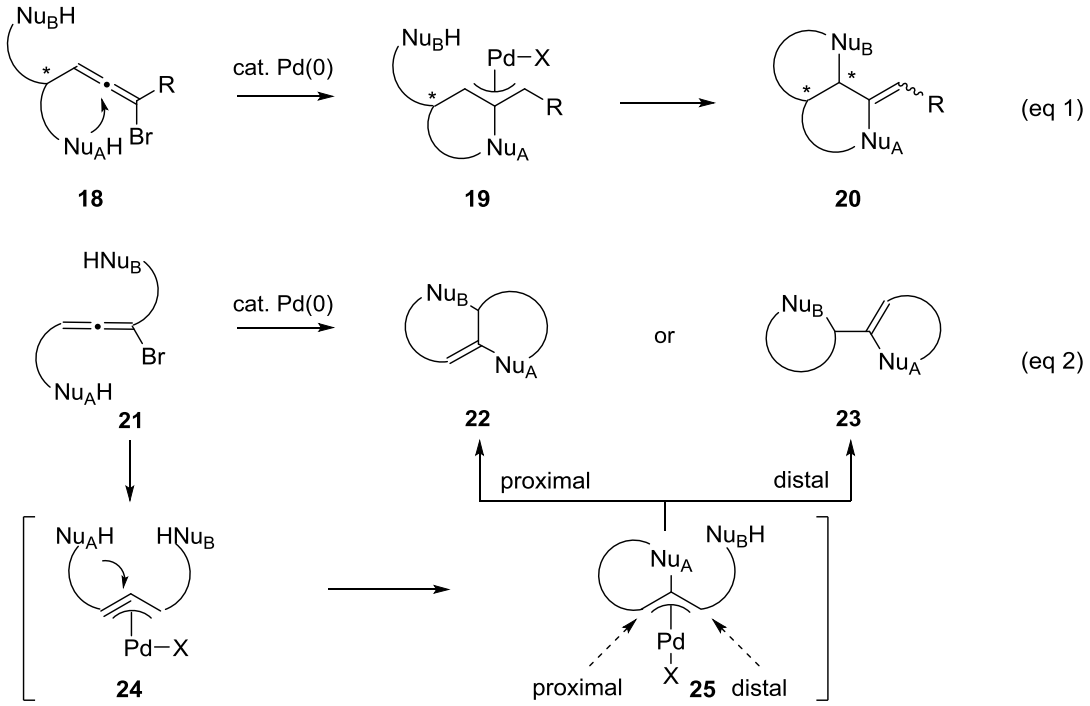
In 2003, the author's group reported that bromoallenes can act as synthetic equivalents of allyl dication in the presence of a palladium(0) catalyst.[10] This reactivity is extremely useful for the efficient introduction of two nucleophiles, such as hydroxy, amine or carbon nucleophiles to allenic compounds. The reaction mechanism can be explained as follows (**Scheme 4**): oxidative addition of bromoallenes **12** to palladium(0) would lead to formation of an allenyl palladium complex **15**, which undergoes transformation into η^3-propargylpalladium intermediate **16**. Subsequent nucleophilic attack at the central carbon of **16** would lead to a η^3-allylpalladium complex **17**, which can be converted to the adduct **14** by the second nucleophilic addition. It should be noted that the central carbon of the bromoallene reacts with a nucleophile, which is in sharp contrast with the reaction of simple allenes (**Scheme 1**).



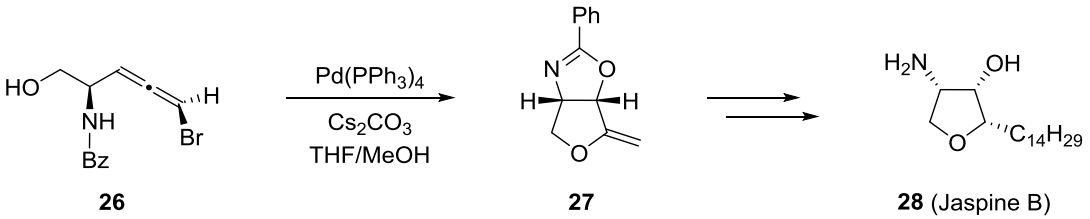
Scheme 4. Introduction of Two Nucleophiles into Bromoallenes in the Presence of a Palladium(0) Catalyst

This reactivity of bromoallenes provides direct access to bicyclic compounds. For example, palladium(0)-catalyzed domino cyclization of bromoallenes of types **18** or **21** bearing two nucleophilic moieties on the terminal carbon(s) affords the direct construction of fused and/or linked bicyclic compounds **20**, **22**, and/or **23** (**Scheme 5**). Recently, the author's group achieved total synthesis of jaspine B (**28**) through a palladium(0)-catalyzed bis-cyclization of bromoallene derivative **26** as a key step (**Scheme 6**).[11]

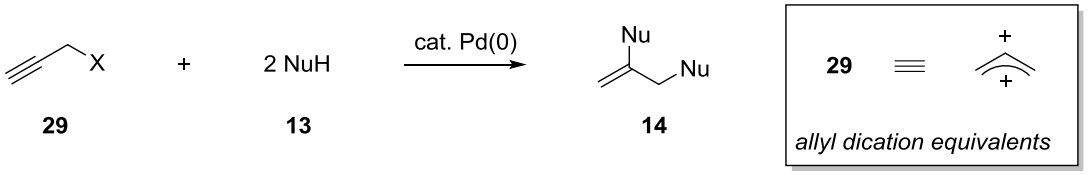
It is worth noting that efficient synthesis of 1,3-disubstituted bromoallenes of the type **21** via conventional bromination methods has proven to be difficult.[12] Thus, attention of the author's group turned to the reaction of propargyl compounds which is considered as a synthetic equivalent of bromoallenes in the palladium-catalyzed reaction. As shown in **Scheme 7**, the reaction of propargyl compounds with a palladium catalyst provides doubly substituted product **14** *via* η^3-propargylpalladium intermediates. Since the pioneering work reported by Tsuji in 1985,[13] a considerable number of reactions have been reported by the use of various bis-nucleophiles.[14,15] The author's group recently developed a palladium(0)-catalyzed domino cyclization of propargyl bromide **30** bearing two nucleophilic sites (**Scheme 8**).[16]



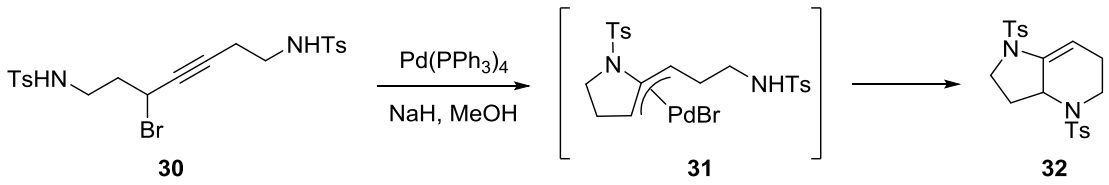
Scheme 5. Palladium(0)-Catalyzed Construction of Fused and Linked Bicyclic Structures by Using Bromoallenes as Allyl Dication Equivalents



Scheme 6. Synthesis of Jaspine B through a Palladium-Catalyzed Domino Cyclization of the Bromoallene



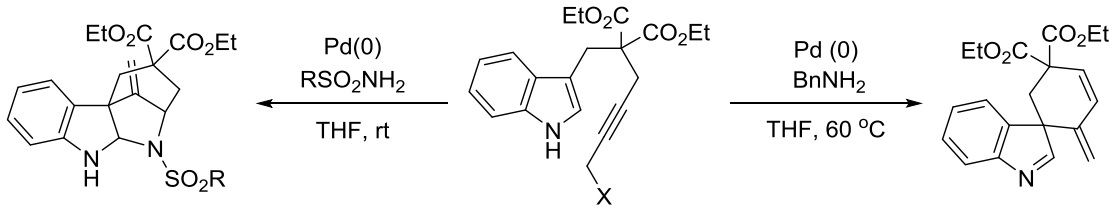
Scheme 7. Introduction of Two Nucleophiles into Propargyl Compounds in the Presence of a Palladium(0) Catalyst



30 **31** **32**

Scheme 8. Reaction of Propargyl Bromides Bearing Nitrogen Nucleophiles

Under these backgrounds, the author designed a novel palladium-catalyzed domino reaction on the basis of spirocyclization of indole **33** bearing a propargyl moiety (**Scheme 9**). It was envisaged the domino reaction between indoles **33** bearing a propargyl chloride side chain at the 3-position and various external nucleophiles could be accomplished by a palladium catalyst to provide fused tetracyclic indolines **34**. The author also expected that the reaction without using an external nucleophile would promote β-hydride elimination to produce spiroindoles **35** bearing a conjugated diene moiety.



34 **33** **35**

Scheme 9. Palladium-Catalyzed Spirocyclization of Indole-Based Propargyl Compounds

In this thesis, the author describes two novel synthetic methods for the direct construction of fused indole/indoline-type compounds based on palladium-catalyzed domino cyclization of allenic and propargylic compounds.

In Chapter 1, the author describes the regioselective reductive ring-opening reaction of alkynyloxiranes for asymmetric formal total synthesis of (+)-lysergic acid based on palladium-catalyzed domino cyclization of allenes bearing bromoindolyl group.

In Chapter 2, the author describes a palladium-catalyzed novel domino cyclization of indoles bearing a propargyl group at their 3-position. In the presence of external nucleophiles, fused tetracyclic indolines were obtained, whereas the same substrates afforded spiroindoles in the absence of an external nucleophile.

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Chapter 1. Formal Total Synthesis of (+)-Lysergic Acid via Zinc(II)-Mediated Regioselective Ring-Opening Reduction of 2-Alkynyl-3-Indolyloxirane

Summary

Enantioselective formal synthesis of (+)-lysergic acid was achieved with a reductive ring-opening reaction of chiral 2-alkynyl-3-indolyloxirane with $NaBH_3CN$ as the key step. With $Zn(OTf)_2$ as an additive, the ring-opening reaction proceeded regioselectively at the 3-position to give the corresponding propargyl alcohol, which was a precursor of the allenic amide for palladium-catalyzed cascade cyclization to construct the ergot alkaloid core structure.

The family of ergot alkaloids produced by the fungus *Claviceps purpurea* is one of the most intriguing classes of natural products because of their broad biological and pharmacological activities.[1,2] Furthermore, their synthetic derivatives, such as pergolide or bromocriptine, are used clinically as antiprolactin and anti-Parkinson's disease drugs. Ergot alkaloids, particularly lysergic acid, have a unique tetracyclic skeleton containing a [*cd*]-fused indole, $\Delta^{9,10}$-double bond and chiral centers at C5 and C8. The biological importance and structural features of ergot alkaloids have stimulated research in the synthetic community, and a number of total syntheses have been reported to date.[3] However, when the author started this work, the enantioselective syntheses of lysergic acid (**1**) have been reported by Szántay in 2004,[4] and Fukuyama in 2009.[5,6]

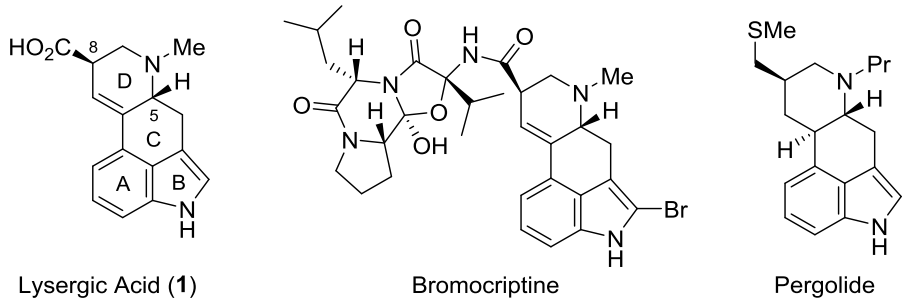
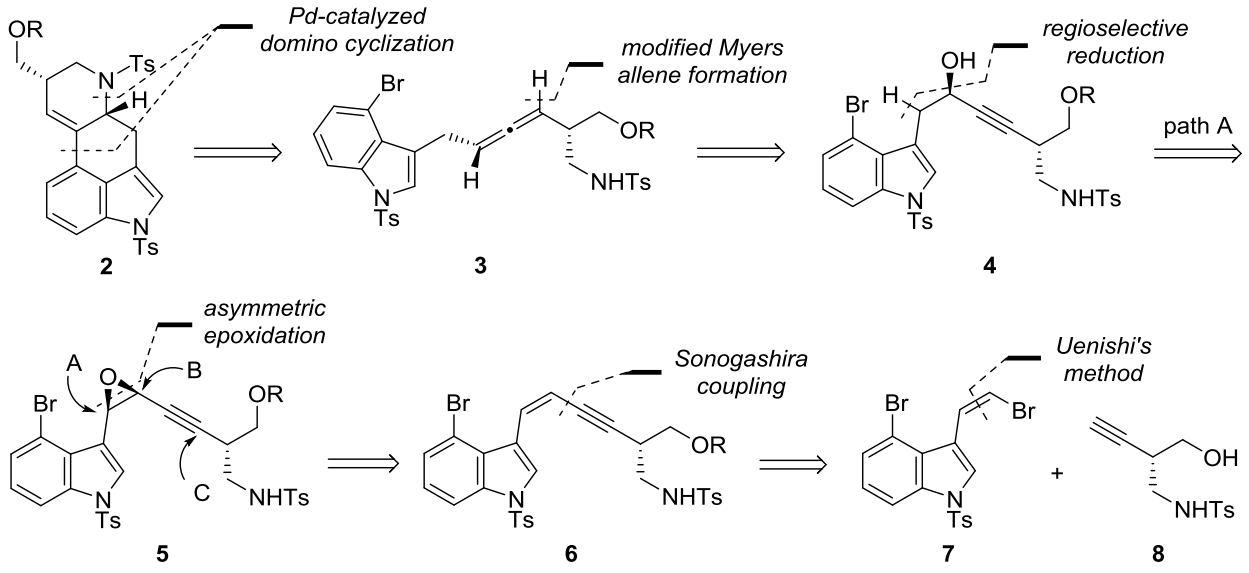


Figure 1. Indole Alkaloids of the Ergot Family and Synthetic Derivatives

As described in the Preface, the author's group reported the enantioselective total syntheses of (+)-lysergic acid (**1**) and related ergot alkaloids using a palladium-catalyzed domino cyclization of chiral allenic tosylamides **3** bearing a bromoindolyl group (**Scheme 1**).[7] In the previous synthetic route, the requisite allenic tosylamide **3** for the domino cyclization was prepared by method of Myers

from the propargyl alcohol **4**,[8] which in turn was obtained by the Nozaki-Hiyama-Kishi (NHK) reaction of an indolylacetaldehyde derivative with an iodoalkyne. The stereogenic center of **4** at the propargylic position, which was required for chiral allene formation, was created by a two-step Dess-Martin oxidation and (*R*)-Alpine-borane reduction.

The author planned an alternative route for novel synthesis of the allenic tosylamide **3** by a reductive ring-opening reaction of the chiral oxirane **5**. This new synthetic route omits the redundant oxidation–asymmetric reduction sequence of the previous synthesis. However, since the reductive ring-opening reaction of indolyl-substituted alkynyloxiranes is unprecedented, the author started his investigation for appropriate reaction conditions to control the regio- and stereoselectivities. In this Chapter, the author describes a regioselective reductive ring-opening reaction of alkynyloxirane **5** with $NaBH_3CN$ in the presence of $Zn(OTf)_2$ and the asymmetric formal total synthesis of lysergic acid. Mechanistic consideration of the reaction is also presented.

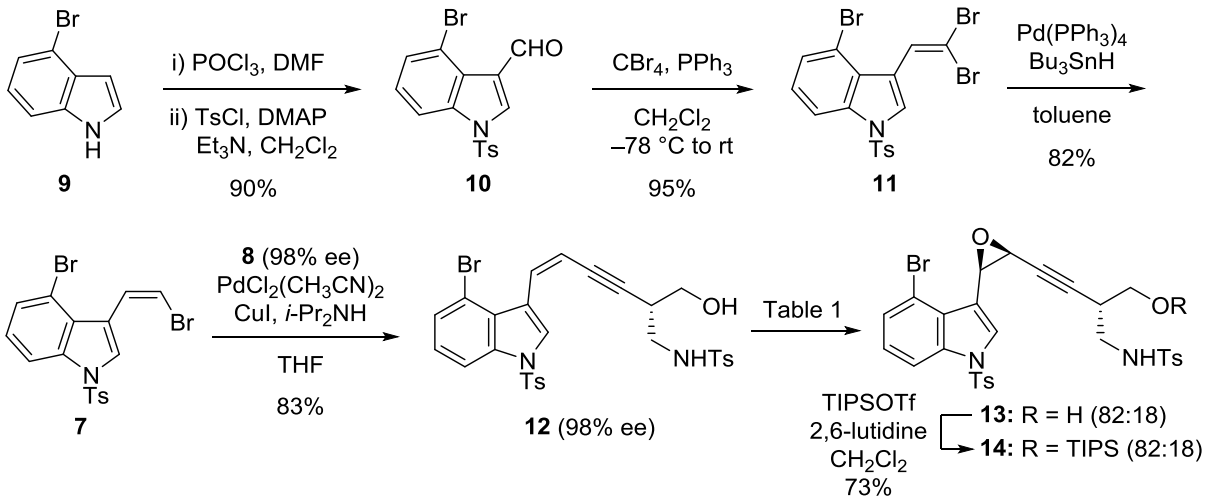


Scheme 1. Retrosynthetic Analysis of the Tetracyclic Indole **2**

Retrosynthetic analysis for the preparing the chiral propargyl alcohol **4**, which is the precursor of the allene amide **3** for stereoselective construction of **2**, is illustrated in **Scheme 1**. The alcohol **4** can be obtained by regioselective reduction of the oxirane **5** at the benzylic position. Oxirane **5** can be prepared by asymmetric/stereoselective epoxidation of enyne **6**. It is well known that (*E*)-enynes generally show sufficient asymmetric induction in Shi's asymmetric epoxidation.[9] However, the author's preliminary investigation showed that stereoselective preparation of the (*E*)-enyne was difficult in this case.[10] Therefore, the author planned to prepare enyne **6** with a (*Z*)-configuration by

a cross-coupling reaction between vinyl bromide **7** and the known enantiomer enriched alkyne **8**.[7] Stereoselective preparation of (*Z*)-vinyl bromide **7** would be achieved by Uenishi's method.[11]

The synthesis was started from commercially available 4-bromoindole **9** (**Scheme 2**). According to the literature procedure,[12] Vilsmeier–Haack reaction of **9** followed by protection of the indole nitrogen gave aldehyde **10**. Treatment of **10** with CBr_4 and PPh_3 followed by palladium-catalyzed selective hydrogenolysis of the bromo group at the trans position with Bu_3SnH (Uenishi's method)[11] gave the (*Z*)-vinyl bromide **7** in good yield. The existence of the bromo substituent at the indole 4-position was not problematic. Sonogashira coupling of **7** with the known alkyne **8** (98% ee),[7] prepared by the same five-step sequence from (*S*)-Garner's aldehyde via palladium/indium-mediated reductive coupling of an ethynylaziridine with formaldehyde,[13] afforded (*Z*)-enyne **12**, which is the precursor of the alkynyloxirane.

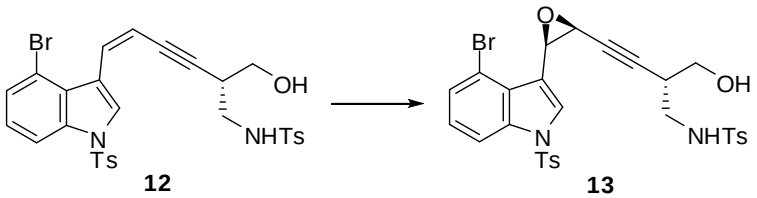


Scheme 2. Synthesis of 2-Alkynyl-3-indolyloxirane **14**

Next, asymmetric epoxidation of enyne **12** was investigated (**Table 1**). The reaction of **12** with Shi's catalyst **15** under the reported conditions[14] at 0 °C provided the desired chiral oxirane **13** in a low yield (35%, dr = 82:18, entry 1). Considering the poor solubility of enyne **12**, the volume of solvent in the reaction and the amount of the reagents (*n*-Bu_4NHSO_4 and Oxone) were increased to obtain **13** in 77% yield (dr = 82:18, entry 2). Decreasing the reaction temperature of the reaction (–10 °C) slightly decreased the yield (62%, dr = 82:18, entry 3). Unfortunately, Shi's ketone **16**,[15] which is widely used as a catalyst for asymmetric epoxidation of (*Z*)-alkenes, was not effective in this case (25% yield, dr = 50:50, entry 4). It should be noted that epoxidation using *m*CPBA was not successful and led to decomposition of the substrate **12** (entry 5). Using the 82:18 diastereomixture

13 obtained in entry 2 (the ratio determined by ^{1}H NMR and HPLC analysis), the oxirane **14** for the ring-opening reaction was prepared by silylation with TIPSOTf (**Scheme 2**).

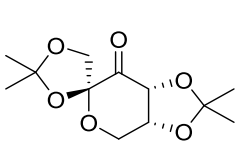
Table 1. Epoxidation of Enyne **12**[a]



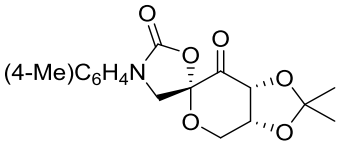
12 **13**

entry	oxidant: chiral cat.	oxidant: Oxone (equiv)	*n*-Bu_4NHSO_4 (equiv)	temp.	yield (%)[b]	recov. (%)	dr[c]
1	**15**	2	0.04	0 °C	35	48	82:18
2	**15**	3	0.4	0 °C	77	17	82:18
3	**15**	3	0.4	–10 °C	62	30	82:18
4	**16**	3	0.4	0 °C	25	34	50:50
5	*m*CPBA (3 equiv)		–	rt	ND[d]		–

[a] The reactions were carried out with a substrate concentration of 100 mM (entry 1) or 50 mM (entries 2–4), chiral catalyst **15** or **16** (50 mol%), Oxone in aqueous Na_2(EDTA) (4×10^{-4} M), 1.47 M aqueous KOH and *n*-Bu_4NHSO_4 in CH_3CN–DMM and K_2CO_3–AcOH buffer. [b] Isolated yield. [c] Determined by ^{1}H NMR analysis. [d] ND = Not detected. Oxone = $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$; DMM = dimethoxymethane.



15

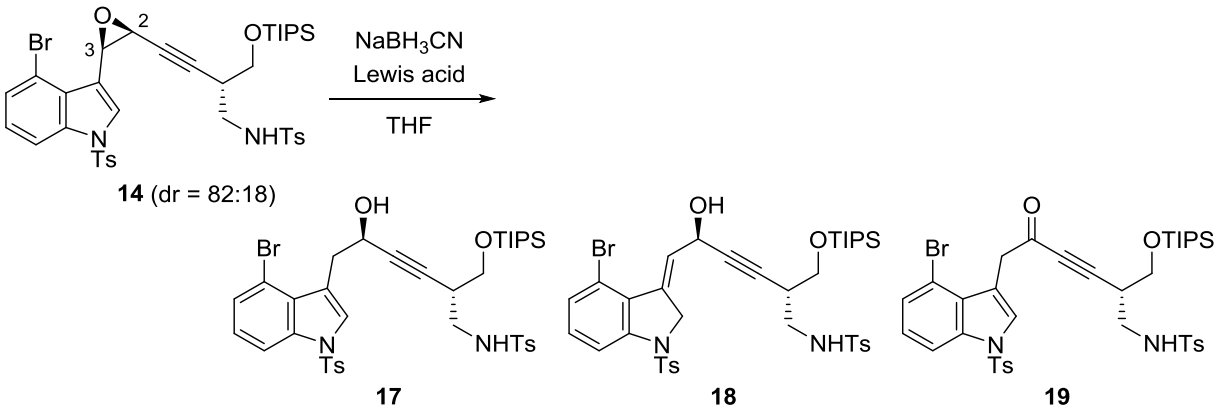


16

The reductive ring-opening reaction was then investigated using an 82:18 diastereomixture of **14** because of the difficulty in separating the diastereomers resulting from epoxidation. Reaction of oxirane **14** with various reducing agents such as $NaBH_4$ and DIBAL gave a complex mixture of unidentified products without producing the desired propargyl alcohol **17**. Oxirane **14** was inert to $NaBH_3CN$ reduction leading to 79% recovery of the starting material (**Table 2**, entry 1). The author then turned his attention to the Lewis acid-mediated reaction based on the known reductive ring-opening reaction of oxiranes[16] including 2,3-diaryl-substituted ones.[17] The author expected that an oxophilic Lewis acid would facilitate regioselective ring cleavage of the oxirane at the 3-position with the assistance of the electron-donating indole ring and produce the desired product **17** by hydride reduction of the resulting indolium intermediate. Among the several Lewis acids investigated, Me_2AlCl showed clean conversion to produce **17** regioselectively in 87% yield. However, the propargylic alcohol was almost completely epimerized (dr = 48:52, entry 4). Fortunately, use of

$ZnCl_2$ provided the desired alcohol **17** in 49% yield with only a slight decrease in the diastereomeric ratio (78:22, entry 5). Further screening of other zinc(II) salts (entries 6–9) revealed that $Zn(OTf)_2$ was the most effective and produced alcohol **17** in 55% yield without promoting any epimerization at the propargylic position (dr = 82:18, entry 8). In all the cases examined, neither the S_N2 product at the 2-position nor S_N2' product were isolated. By contrast, formation of the double bond isomer **18** and/or the ketone **19** occurred (entries 5–9). The stereochemistry at the propargylic position of **17** was confirmed by an alternative synthesis of **17** from the known propargyl alcohol obtained by reduction of the corresponding ketone with (*R*)-Alpine-Borane in the previous reported synthetic route.

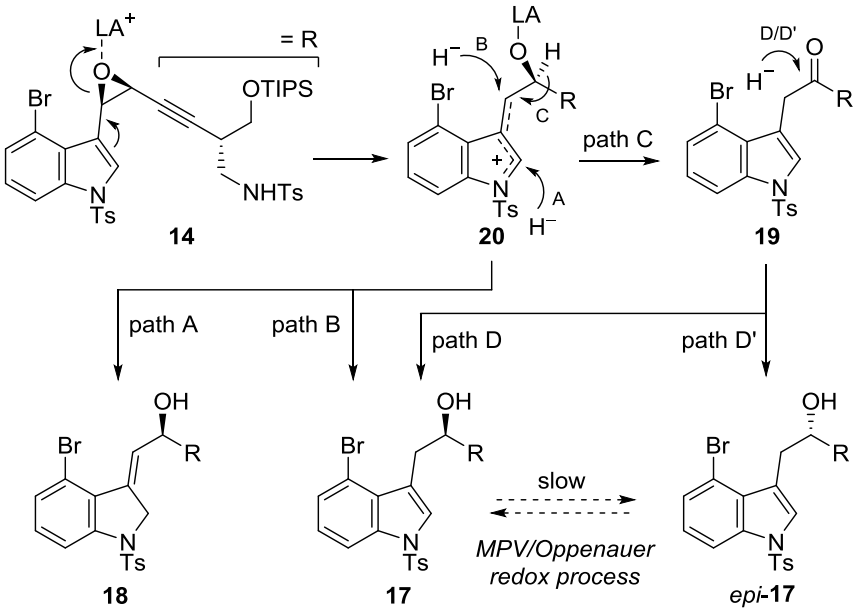
Table 2. Reductive Ring-Opening Reaction of 2-Alkynyl-3-indolyloxirane **14**[a]



entry	Lewis acid	temp (°C)	time (h)	yield (%)			recov. (%)
				17[b] (dr)[c]	**18**[b]	**19**[d]	
1	none	rt	2	–	–	–	79
2	$Sm(OTf)_3$	40	28	16 (57:43)	–	43	–
3	$In(OTf)_3$	60	0.5	13 (79:21)	2	34	–
4	Me_2AlCl	60	0.25	87 (48:52)	–	–	–
5	$ZnCl_2$	60	2.5	49 (78:22)	10	7	–
6	$ZnBr_2$	60	2	22 (80:20)	10	15	52
7	ZnI_2	60	2	22 (70:30)	–	47	–
8	$Zn(OTf)_2$	60	2	55 (82:18)	trace	20	–
9[e]	$Zn(OTf)_2$	100	0.5	45 (78:22)	–	52	–

[a] The reactions were carried out with substrate **14**, $NaBH_3CN$ (3 equiv) and Lewis acid (3 equiv) in THF. [b] Calculated from the combined isolated yields (**17** and **18**) and HPLC analysis (Chiralcel OD-H). [c] Determined by HPLC analysis (Chiralcel OD-H). [d] Isolated yields. [e] Reaction was carried out in dioxane.

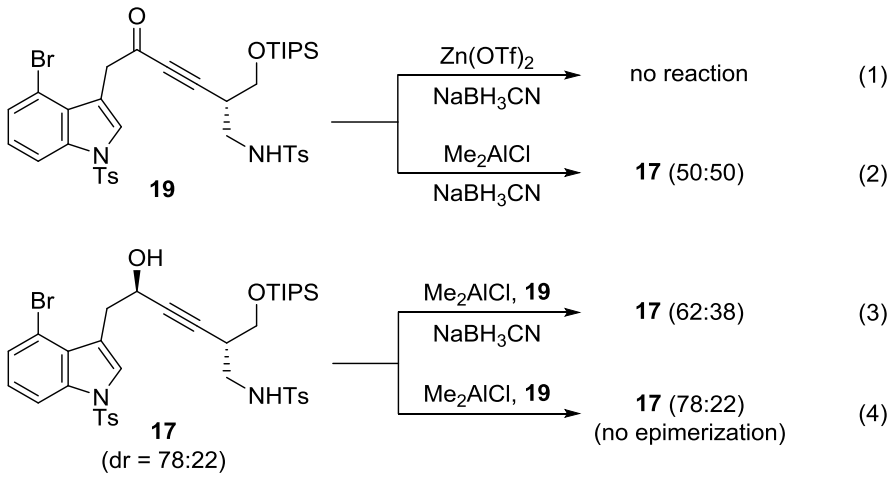
A rationale for the observed results of the reductive ring-opening reaction is depicted in **Scheme 3**. Lewis acid-activation of the oxirane **14** induces formation of the indolium intermediate **20**. Isolation of the double bond isomer **18**, which would be produced by hydride reduction of **20** at the indole 2-position (path A), partly supports the intermediacy of **20** in this reaction. The desired alcohol **17**, the major product in the $Zn(OTf)_2$-mediated reduction, results from hydride reduction at the indolyl position (path B). Alternatively, a 1,2-hydride shift from **20** (path C) followed by reduction of the resulting ketone **19** (path D and D') under the reductive conditions can explain the formation of **17** that accompanies complete epimerization when using Me_2AlCl (entry 4). As shown in entry 8 (**Table 2**), the $Zn(OTf)_2$-mediated reaction stereoselectively produced the desired product **17** and a considerable amount of the ketone **19**. This result suggests that the activation ability of $Zn(OTf)_2$ toward ketone reduction (path D and D') is relatively low compared to that of Me_2AlCl.



Scheme 3. Pathways for the Reductive Ring-Opening Reaction

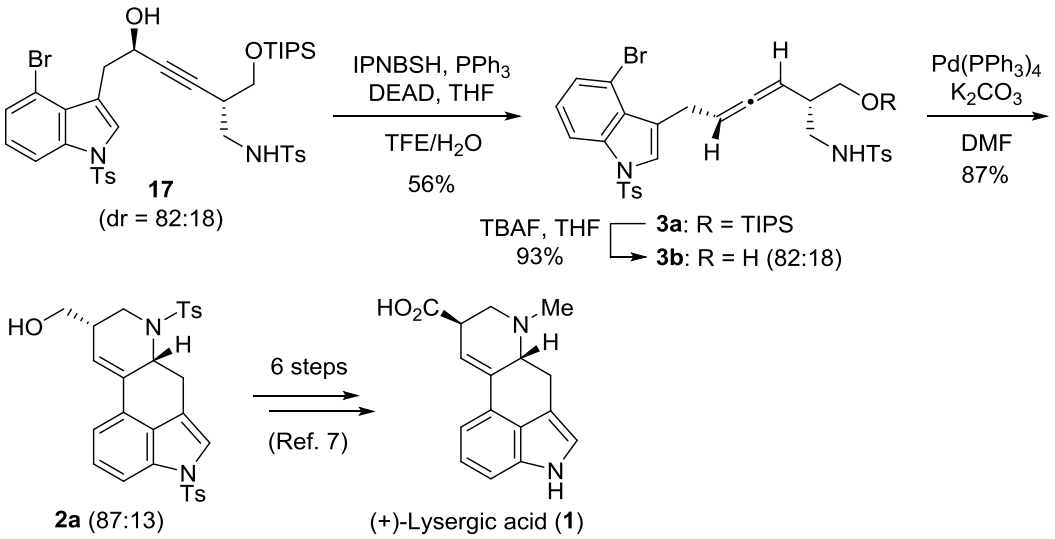
The above discussion was supported by the following experiments (**Scheme 4**). On treatment of ketone **19** under the $Zn(OTf)_2$-mediated reduction conditions [$NaBH_3CN$, $Zn(OTf)_2$ in THF at 60 °C], formation of the alcohols **17** and *epi*-**17** was not observed (Eq. 1). The reaction of ketone **19** under the Me_2AlCl-mediated reduction conditions afforded the alcohols **17** and *epi*-**17** in an almost 1:1 diastereomixture (Eq. 2). Furthermore, reaction of **17** (dr = 78:22) in the presence of **19** (1 equiv) with $NaBH_3CN$ and Me_2AlCl gave a 62:38 diastereomixture of **17** (eq 3), which was the predicted ratio considering the reduction of **19**. This confirmed that the Meerwein-Ponndorf-Verley

(MPV)/Oppenauer redox process[18] between **17** and **19** was not the major pathway for epimerization in the presence of Me_2AlCl (**Table 2**, entry 4). In the absence of $NaBH_3CN$, no epimerization of **17** was observed in the reaction after 2 h (Eq. 4).[19]



Scheme 4. Supporting Experiments for the Proposed Reaction Pathways

Finally, the asymmetric formal total synthesis of (+)-lysergic acid (**1**) was completed in two steps from the propargyl alcohol **17** (dr = 82:18) (**Scheme 5**). The alcohol **17** was stereoselectively transformed into the allene **3a** using the modified procedure for Myers allene formation.[20] Subsequent cleavage of the silyl group of **3a** gave the known allenic tosylamide **3b** (82:18).[7] As the author's group previously reported, the tetracyclic indole **2a** was obtained from **3b** in 87% yield with an 87:13 selectivity via the palladium-catalyzed domino cyclization of the allenic tosylamide **3b**. The reported six-step sequence of reactions, including separation of the diastereomers after oxidation and esterification, would provide (+)-lysergic acid (**1**).



Scheme 5. Formal Total Synthesis of Lysergic Acid

Abbreviations: IPNBSH = *N*-isopropylidene-*N*'-2-nitrobenzenesulfonyl hydrazine; TFE = trifluoroethanol.

In summary, a novel method for regio- and stereoselective construction of propargyl alcohol was developed based on a regioselective ring-opening reaction of 2-alkynyl-3-indolyloxirane at the 3-position. Addition of $Zn(OTf)_2$ was important for promotion of the epoxide cleavage at the 3-position and suppression of epimerization at the propargylic position. With this reduction as the key step, enantioselective formal total synthesis of (+)-lysergic acid was achieved in 14 steps (1.8% overall yield), which was one step shorter than the previous route (15 steps, 4.0% overall yield).

Experimental Section

General methods. All moisture-sensitive reactions were performed using syringe-septum cap techniques under an argon atmosphere and all glassware was dried in an oven at 80 °C for 2 h prior to use. Reactions at –78 °C employed a CO_2–MeOH bath. Melting points were measured by a hot stage melting point apparatus (uncorrected). Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^{1}H NMR) or the residual $CHCl_3$ signal (^{13}C NMR). ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). The compounds **8**[7] and **10**[21] were synthesized according to the reported procedures.

4-Bromo-3-(2,2-dibromovinyl)-1-tosyl-1*H*-indole (11). To a stirred mixture of PPh_3 (25.0 g, 95.4 mmol) in CH_2Cl_2 (100 mL) was added CBr_4 (15.8 g, 47.7 mmol) at –20 °C under argon. After stirring for 15 min at this temperature, a solution of aldehyde **10** (6.00 g, 15.9 mmol) in CH_2Cl_2 (40 mL) was added to the mixture at –78 °C. After stirring for 10 min at this temperature, the mixture was allowed to warm to room temperature and stirred for further 2.5 h at this temperature. Concentration under reduced pressure gave an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **11** as a pale yellow solid (7.66 g, 95% yield). Recrystallization from *n*-hexane–EtOAc gave pure **11** as colorless crystals: mp 152–153 °C; IR (neat): 1368 (NSO_2), 1163 (NSO_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 3H), 7.15 (dd, J = 8.0, 8.0 Hz, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 8.0 Hz, 2H), 7.96 (d, J = 8.0 Hz, 1H), 8.10 (d, J = 1.0 Hz, 1H), 8.11 (d, J = 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 90.5, 112.9, 114.2, 117.9, 125.9, 126.9, 127.0 (2C), 127.4, 128.3, 128.8, 130.1 (2C), 134.5, 135.4, 145.7. *Anal*. Calcd for $C_{17}H_{12}Br_3NO_2S$: C, 38.23; H, 2.26; N, 2.62. Found: C, 38.03; H, 2.17; N, 2.50.

(*Z*)-4-Bromo-3-(2-bromovinyl)-1-tosyl-1*H*-indole (7). To a stirred mixture of **11** (1.50 g, 2.81 mmol) in toluene (28 mL) were added $Pd(PPh_3)_4$ (130 mg, 0.110 mmol; 4 mol %) and Bu_3SnH (0.831 mL, 3.09 mmol) at room temperature under argon, and the mixture was stirred for 8.5 h at this temperature. The mixture was concentrated under reduced pressure to give a yellow oil, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (20:1) to give **7** as a white solid. Recrystallization from *n*-hexane–$CHCl_3$ gave pure **7** (1.05 g, 82%) as colorless crystals: mp 136–137 °C; IR (neat): 1373 (NSO_2), 1172 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.54

(d, *J* = 7.4 Hz, 1H), 7.14 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 8.35 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.6, 107.5, 112.8, 114.3, 116.9, 124.1, 125.6, 127.0 (2C), 127.2, 127.8, 128.3, 130.0 (2C), 134.6, 135.5, 145.5. *Anal*. Calcd for $C_{17}H_{13}Br_2NO_2S$: C, 44.86; H, 2.88; N, 3.08. Found: C, 44.73; H, 3.00; N, 2.98.

(*S*,*Z*)-*N*-[6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-(hydroxymethyl)hex-5-en-3-yn-1-yl]-4-methylbenzenesulfonamide (12). To a stirred mixture of **7** (800 mg, 1.76 mmol) in a mixed solvent of (*i*-Pr)$_2$NH (16 mL) and THF (16 mL) were added **8**[7] (608 mg, 2.40 mmol), $PdCl_2(CH_3CN)_2$ (22.9 mg, 0.0883 mmol) and CuI (33.6 mg, 0.176 mmol) at room temperature under argon and the mixture was stirred for 3 h at this temperature. The mixture was concentrated under reduced pressure to give a yellow amorphous solid, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to give **12** as a yellow amorphous solid (913 mg, 83% yield, 98% ee): $[\alpha]^{29}_{D}$ –41.7 (*c* 0.59, $CHCl_3$); IR (neat): 3323 (OH), 2248 (C≡C), 1415 (NSO_2), 1372 (NSO_2), 1173 (NSO_2), 1157 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.40 (s, 3H), 2.59 (dd, *J* = 6.3, 6.3 Hz, 1H), 3.03-3.09 (m, 1H), 3.25-3.36 (m, 2H), 3.85-3.96 (m, 2H), 5.20 (dd, *J* = 6.7, 6.7 Hz, 1H), 5.71 (dd, *J* = 11.7, 2.1 Hz, 1H), 7.14 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 11.7 Hz, 1H), 7.77-7.81 (m, 4H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 36.4, 43.4, 62.3, 83.2, 95.4, 106.3, 112.7, 114.5, 118.9, 125.5, 126.8, 127.0 (2C), 127.1 (2C), 127.5, 128.5, 129.3, 129.8 (2C), 130.2 (2C), 134.4, 135.5, 136.8, 143.6, 145.8. *Anal*. Calcd for $C_{29}H_{27}BrN_2O_5S_2$: C, 55.50; H, 4.34; N, 4.46. Found: C, 55.37; H, 4.46; N, 4.26.

***N*-{(*S*)-4-[(2*S*,3*R*)-(4-Bromo-1-tosyl-1*H*-indol-3-yl)oxiran-2-yl]-2-(hydroxymethyl)but-3-yn-1-yl}-4-methylbenzenesulfonamide (13).** All glassware used for the epoxidation reaction was carefully washed and coated with 0.1 M potassium hydroxide 2-propanolic solution. To a stirred mixture of **12** (50 mg, 0.080 mmol), the chiral ketone **15** (10.3 mg, 0.040 mmol), and *n*-Bu_4NHSO_4 (11 mg, 0.032 mmol) in CH_3CN/DMM (1.6 mL, 1:2) was added buffer solution (0.1 M K_2CO_3-AcOH in water; 800 μL) at room temperature under argon. After the mixture was cooled to 0 °C, solutions of Oxone (147.6 mg, 0.24 mmol) in 4 × 10^{-4} M aqueous EDTA (480 μL) and 1.47 M aqueous KOH (408 μL) were added dropwise to the reaction mixture separately and simultaneously over a period of 1.5 h. The mixture was stirred for 22 h at this temperature. The mixture was concentrated under reduced pressure to give a white residue, which was dissolved in EtOAc and

washed with water, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (2:1) to give **13** as a white amorphous solid (39.4 mg, 77% yield, dr = 82:18): $[\alpha]^{27}_D$ –17.7 [*c* 0.44, $CHCl_3$]; IR (neat): 3311 (OH), 2253 (C≡C), 1415 (NSO_2), 1373 (NSO_2), 1173 (NSO_2), 1158 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.16 (dd, *J* = 6.7, 6.7 Hz, 1H), 2.36 (s, 3H), 2.43 (s, 3H), 2.46-2.52 (m, 1H), 2.76-2.82 (m, 1H), 2.95-3.03 (m, 1H), 3.41-3.52 (m, 2H), 3.78 (d, *J* = 3.9 Hz, 1H), 4.63 (dd, *J* = 6.8, 6.8 Hz, 1H), 4.72 (d, *J* = 3.9 Hz, 1H), 7.17 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.66-7.70 (m, 3H), 7.78 (d, *J* = 8.4 Hz, 2H), 7.99 (d, *J* = 7.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 21.6, 34.9, 42.9, 48.6, 53.1, 61.8, 78.7, 83.7, 112.9, 113.7, 117.2, 125.8, 126.2, 127.0 (4C), 127.5, 128.6, 129.8 (2C), 130.1 (2C), 134.6, 135.9, 136.8, 143.6, 145.8; HRMS (FAB) calcd $C_{29}H_{26}BrN_2O_6S_2$: $[M–H]^–$, 641.0421; found: $[M–H]^–$, 641.0420.

***N*-{(*S*)-4-[(2*S*,3*R*)-3-(4-Bromo-1-tosyl-1*H*-indol-3-yl)oxiran-2-yl]-2-[(triisopropylsilyloxy)-methyl]but-3-yn-1-yl}-4-methylbenzenesulfonamide (14).** To a stirred mixture of **13** (50 mg, 0.078 mmol) in CH_2Cl_2 (218 μL) were added 2,6-lutidine (25.7 μL, 0.234 mmol) and TIPSOTf (31.4 μL, 0.117 mmol) at 0 °C. The mixture was stirred for 3.5 h at this temperature, and quenched by addition of saturated $NaHCO_3$. The whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **14** as a white amorphous solid (44.5 mg, 73% yield, dr = 82:18): $[\alpha]^{27}_D$ –32.6 [*c* 0.76, $CHCl_3$]; IR (neat): 3286 (OH), 1416 (NSO_2), 1377 (NSO_2), 1175 (NSO_2), 1162 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.92-1.02 (m, 21H), 2.35 (s, 3H), 2.41 (s, 3H), 2.43-2.48 (m, 1H), 2.86-2.92 (m, 1H), 2.99-3.04 (m, 1H), 3.35 (dd, *J* = 10.0, 10.0 Hz, 1H), 3.55 (dd, *J* = 10.0, 4.3 Hz, 1H), 3.76 (d, *J* = 3.9 Hz, 1H), 4.70 (d, *J* = 3.9 Hz, 1H), 4.94 (dd, *J* = 6.2, 6.2 Hz, 1H), 7.18 (dd, *J* = 8.4, 8.4 Hz, 1H), 7.25 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.62-7.68 (m, 3H), 7.76 (d, *J* = 8.4 Hz, 2H), 8.00 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7 (3C), 17.8 (6C), 21.5, 21.6, 34.7, 44.9, 48.6, 53.2, 64.6, 78.3, 83.6, 112.9, 113.6, 117.3, 125.7, 126.3, 126.9 (2C), 127.0 (2C), 127.4, 128.6, 129.7 (2C), 130.1 (2C), 134.7, 136.0, 136.9, 143.3, 145.6; HRMS (FAB) calcd $C_{38}H_{46}BrN_2O_6S_2Si$: $[M–H]^–$, 797.1755; found: $[M–H]^–$, 797.1757.

***N*-[(2*S*,5*R*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-5-hydroxy-2-{(triisopropylsilyloxy)methyl}hex-3-yn-1-yl]-4-methylbenzenesulfonamide (17), *N*-[(2*S*,5*R*,*Z*)-6-(4-Bromo-1-tosylindolin-3-ylidene)-**

5-hydroxy-2-{(triisopropylsilyloxy)methyl}hex-3-yn-1-yl]-4-methylbenzenesulfonamide (18), and (*S*)-*N*-{6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-5-oxo-2-[(triisopropylsilyloxy)methyl]hex-3-yn-1-yl}-4-methylbenzenesulfonamide (19) (Table 2). To a stirred mixture of $Zn(OTf)_2$ (27.3 mg, 0.075 mmol) and $NaBH_3CN$ (4.7 mg, 0.075 mmol) in THF (1.83 mL) was added **14** (20 mg, 0.025 mmol, dr = 82:18) at room temperature under argon. The mixture was allowed to warm to 60 °C and stirred for 2 h at this temperature, followed by quenching by addition of saturated $NaHCO_3$. The whole was extracted with EtOAc. The extract was washed with saturated $NaHCO_3$, water, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **17** (11 mg, 55% yield, dr = 82:18) and **19** (3.9 mg, 20% yield) (entry 8). When the reaction of **14** (20 mg, 0.025 mmol, dr = 82:18) was carried out with $ZnCl_2$ (1.00 M solution in Et_2O; 75 μL, 0.075 mmol) in place of $Zn(OTf)_2$, an isomeric mixture of **17** and **18** (11.8 mg, 49% yield, dr = 78:22) and **19** (1.5 mg, 7% yield) was obtained (entry 5). Compound **18** was isolated by HPLC [5C-18ARII column, 254 nm, MeCN:H_2O = 90:10, 10 mL/min; for analytical HPLC: 1 mL/min, *t* = 11.05 min].

Compound **17**: white amorphous solid; $[\alpha]^{29}_D$ –23.3 [*c* 0.64 (single isomer), $CHCl_3$]; IR (neat): 3310 (OH), 1413 (NSO_2), 1375 (NSO_2), 1173 (NSO_2), 1159 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00-1.08 (m, 21H), 1.91-2.00 (m, 1H), 2.35 (s, 3H), 2.41 (s, 3H), 2.69-2.75 (m, 1H), 3.11 (ddd, *J* = 12.0, 6.8, 5.7 Hz, 1H), 3.20 (ddd, *J* = 12.0, 5.7, 5.7 Hz, 1H), 3.30 (dd, *J* = 15.2, 6.9 Hz, 1H), 3.33 (dd, *J* = 15.2, 7.2 Hz, 1H), 3.58 (dd, *J* = 10.0, 8.6 Hz, 1H), 3.77 (dd, *J* = 10.0, 4.3 Hz, 1H), 4.65-4.70 (m, 1H), 5.15 (dd, *J* = 5.7, 5.7 Hz, 1H), 7.12 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (3C), 11.9 (6C), 21.5, 21.6, 34.6, 34.9, 45.1, 62.4, 64.8, 83.1, 84.4, 112.9, 114.3, 117.7, 125.4, 126.9 (3C), 127.1 (2C), 127.9, 128.6, 129.7 (2C), 130.0 (2C), 134.9, 136.4, 137.0, 143.4, 145.3; HRMS (FAB) calcd $C_{38}H_{48}BrN_2O_6S_2Si$: $[M–H]^–$, 799.1912; found: $[M–H]^–$, 799.1910.

Compound **18**: yellow amorphous solid; $[\alpha]^{27}_D$ –34.7 [*c* 0.44 (single isomer), $CHCl_3$]; IR (neat): 3297 (OH), 1416 (NSO_2), 1362 (NSO_2), 1163 (NSO_2), 1093 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99-1.08 (m, 21H), 1.57-1.72 (br m, 1H), 2.37 (s, 3H), 2.41 (s, 3H), 2.73-2.75 (m, 1H), 3.10-3.18 (m, 1H), 3.21-3.29 (m, 1H), 3.64 (dd, *J* = 9.9, 8.2 Hz, 1H), 3.80 (dd, *J* = 9.9, 4.4 Hz, 1H), 4.57-4.68 (m, 2H), 4.94 (d, *J* = 7.4 Hz, 1H), 5.32 (dd, *J* = 6.2, 6.2 Hz, 1H), 6.85-6.86 (m, 1H), 7.07 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.67-7.71 (m, 3H), 7.75 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.8 (3C), 17.9 (6C), 21.5 (2C), 34.9, 44.9, 52.7, 59.9, 64.6, 82.7, 83.3, 113.3, 118.4, 122.7, 126.5, 127.1 (2C), 127.2 (2C), 128.9, 129.7

(2C), 130.0 (2C), 130.4, 133.6, 134.0, 136.9, 143.5, 144.8, 146.4; HRMS (FAB) calcd $C_{38}H_{48}BrN_2O_6S_2Si$: $[M–H]^–$, 799.1912; found: $[M–H]^–$, 799.1910.

Compound **19**: yellow amorphous solid; $[\alpha]^{27}_D$ –7.68 (*c* 0.44, $CHCl_3$); IR (neat): 2216 (C≡O), 1681 (C=O), 1415 (NSO_2), 1377 (NSO_2), 1162 (NSO_2), 1095 (NSO_2); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99-1.08 (m, 21H), 2.36 (s, 3H), 2.42 (s, 3H), 2.73-2.80 (m, 1H), 3.05 (ddd, *J* = 12.7, 6.4, 6.4 Hz, 1H), 3.17 (ddd, *J* = 12.7, 6.4, 6.3 Hz, 1H), 3.57 (dd, *J* = 9.9, 7.9 Hz, 1H), 3.72 (dd, *J* = 9.9, 4.4 Hz, 1H), 4.13 (s, 2H), 4.97 (dd, *J* = 6.4, 6.4 Hz, 1H), 7.13 (dd, *J* = 8.3, 8.3 Hz, 1H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.55 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.96 (d, *J* = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 11.7 (3C), 17.9 (6C), 21.5, 21.6, 35.1, 42.3, 44.2, 63.8, 82.8, 91.7, 113.0, 114.3, 114.4, 125.7, 126.9 (2C), 127.1 (2C), 127.3, 127.8, 128.4, 129.8 (2C), 130.1 (2C), 134.8, 136.2, 136.8, 143.6, 145.5, 183.9; HRMS (FAB) calcd $C_{38}H_{46}BrN_2O_6S_2Si$: $[M–H]^–$, 797.1755; found: $[M–H]^–$, 797.1754.

***N*-{(2*S*,4*R*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-[(triisopropylsilyloxy)methyl]hexa-3,4-dienyl}-4-methylbenzenesulfonamide (3a).** To a stirred mixture of IPNBSH (39 mg, 0.150 mmol), PPh_3 (39 mg 0.150 mmol) and **17** (30 mg, 0.037 mmol, dr = 82:18) in THF (970 μL) was added diethyl azodicarboxylate (2.2 M solution in toluene; 68 μL, 0.150 mmol) at 0 °C under argon. The mixture was allowed to warm to room temperature and stirred for 2 h at this temperature. A mixture of TFE and water (1:1; 480 μL) was added to the reaction mixture to enable the formation of the propargylic diazene intermediate. After 16 h, the whole was extracted with Et_2O. The extract was washed with water, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (8:1) to give **3a** as a yellow amorphous solid (17 mg, 56% yield, dr = 82:18). Its purity was confirmed by ^{1}H NMR analysis. All the spectral data were in agreement with those reported by the author's group.[7]

***N*-[(2*S*,4*R*)-6-(4-Bromo-1-tosyl-1*H*-indol-3-yl)-2-(hydroxymethyl)hexa-3,4-dienyl]-4-methyl-benzenesulfonamide (3b).** To a stirred solution of **3a** (59 mg, 0.075 mmol, dr = 82:18) in THF (6.8 mL) was added TBAF (1.00 M solution in THF; 150 μL, 0.150 mmol) at 0 °C. The mixture was stirred for 20 min at room temperature and quenched by addition of saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with water, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:2) to give **3b** as a white amorphous (43.7

mg, 93% yield, dr = 82:18). Its purity was confirmed by ^{1}H NMR analysis. All the spectral data were in agreement with those reported by the author's group.[7]

[(6a*R*,9*S*)-4,7-Ditosyl-4,6,6a,7,8,9-hexahydroindolo[4,3-*fg*]quinolin-9-yl]methanol (2a). To a stirred mixture of **3b** (20 mg, 0.032 mmol, dr = 82:18) in DMF (0.87 mL) were added $Pd(PPh_3)_4$ (3.7 mg, 0.0032 mmol) and K_2CO_3 (13.3 mg, 0.096 mmol) at room temperature under argon, and the mixture was stirred for 2.5 h at 100 °C. The mixture was quenched by addition of saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with water, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (1:1) to give **2a** as a white amorphous solid (15.2 mg, 87% yield, dr = 87:13). Its purity was confirmed by ^{1}H NMR analysis. All the spectral data were in agreement with those reported by the author's group.[7]

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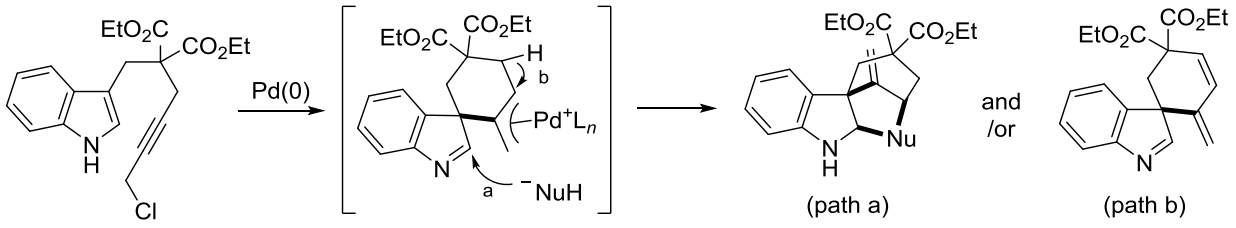
Chapter 2. Convenient Synthesis of Spiroindole Derivatives via Palladium-Catalyzed Cyclization of Propargyl Chlorides

Summary

Efficient palladium-catalyzed cyclization reactions of indoles bearing a propargyl chloride side chain at their 3-position is described. In the presence of an external nucleophile, such as a sulfonamides or malonate, indoles bearing a propargyl group at their 3-position gave fused tetracyclic indolines preferentially. However, in the absence of an external nucleophile, the same substrates afforded tricyclic spiroindoles bearing a conjugated diene moiety. *The attempts to develop a catalytic asymmetric spirocyclization onto a propargylpalladium species are also presented.*

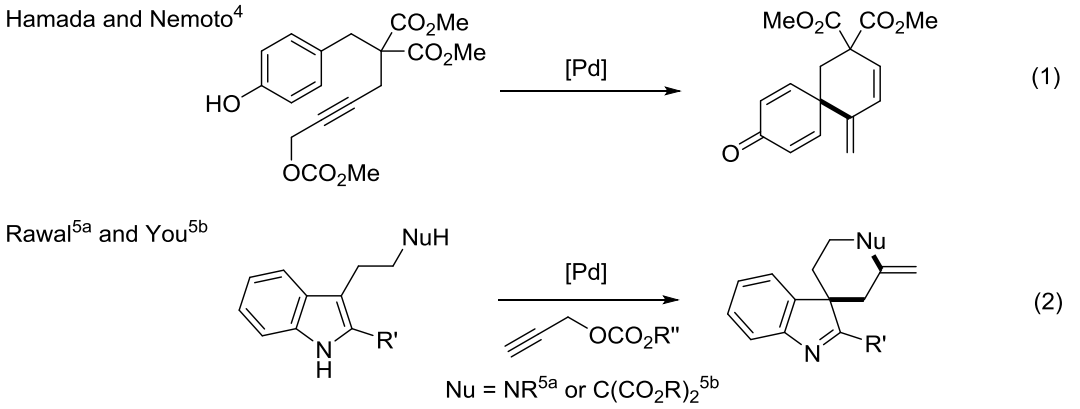
Spirocyclic compounds are currently attracting considerable interest in organic chemistry because of their unique molecular structure and diverse biological activities.[1] In particular, enantio-enriched spiroindoles and spiroindolines represent important structural motifs that can be found in a wide range of biologically active natural products and synthetic compounds.[2] As part of the author's ongoing efforts towards the construction of heterocyclic frameworks based on the palladium-catalyzed reactions of propargyl/allenic compounds, the author was interested in the intramolecular nucleophilic addition reactions of indoles as a strategy for the synthesis of spiroindoles.

As described in Preface, the author envisaged that the palladium-catalyzed intramolecular nucleophilic addition of indoles would provide facile access to tetracyclic indolines when it was used in combination with the intermolecular nucleophilic cyclization of an external nucleophile (**Scheme 1**, path a). The author also expected that running the same reaction without using an external nucleophile would promote β-hydride elimination (path b) to produce spiroindoles bearing a conjugated diene moiety.



Scheme 1. Palladium-Catalyzed Spirocyclization of Indole-Based Propargyl Compounds

Almost at the same time when the author reported this study as a communication,[3] Hamada and co-workers reported a palladium-catalyzed intramolecular spirocyclization of phenol-based propargylic carbonates (**Scheme 2**, eq. 1).[4] When tryptamine-derived carbonates were used, this reaction produced spiroindoles bearing an azepine moiety. Furthermore, the groups of Rawal[5a] and You[5b] independently reported the intermolecular reactions of indole-based dual nucleophiles and propargyl carbonates as general strategies for the synthesis of spiroindoles (eq. 2).

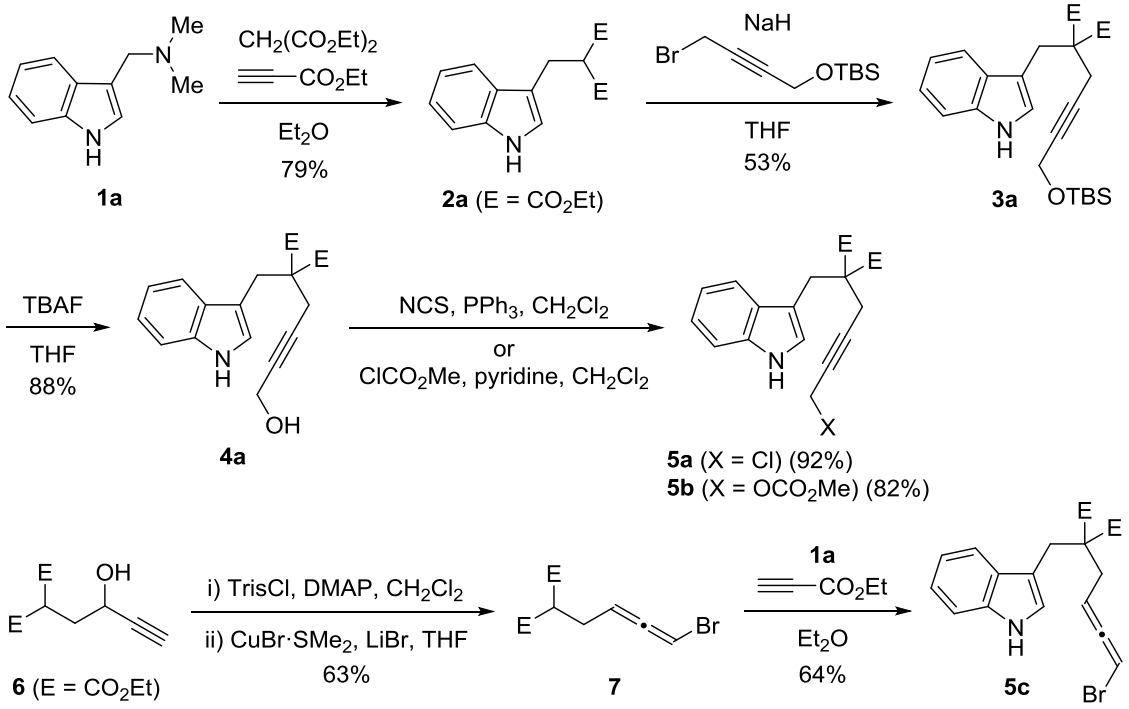


Scheme 2. Related Palladium-Catalyzed Spirocyclization Reaction Using Propargyl Compounds

In this Chapter, the author describes the construction of tetracyclic indolines and conjugated diene-type spiroindoles (**Scheme 1**) via the palladium-catalyzed cyclization of propargyl chlorides. The attempts at a catalytic asymmetric spirocyclization onto a propargyl palladium species are also presented.

Results and Discussion

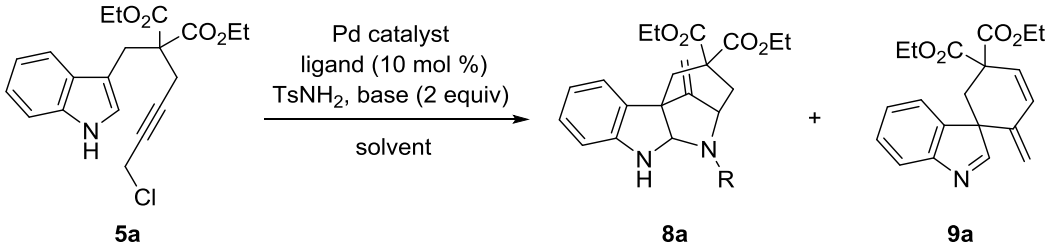
The route used for the preparation of substrates **5a**–**c** is shown in **Scheme 3**. In accordance with the reported procedure,[6] gramine (**1a**) was converted to the corresponding malonate **2a**. The subsequent alkylation of **2a** followed by a desilylation reaction afforded propargyl alcohol **4a**. Substrates **5a** and **5b** were obtained by the reaction of **4a** with NCS/PPh_3 or $ClCO_2Me$/pyridine, respectively. Bromoallene **5c** was prepared from propargyl alcohol **6** using an established procedure for the formation of bromoallenes.[7] The treatment of **6** with TrisCl (Tris = 2,4,6-triisopropylbenzenesulfonyl) and DMAP gave the corresponding sulfonate, which was converted to bromoallene **7** by treatment with $CuBr \cdot SMe_2$ in the presence of LiBr. Finally, the introduction of the indole unit to **7** was achieved by the reaction with gramine (**1a**) in the presence of ethyl propiolate to give bromoallene **5c**.



Scheme 3. Preparation of Substrates **5a**–**c**

Initially, the author investigated a series of screening experiments to identify the optimal reaction conditions using propargyl chloride **5a** as a model substrate (**Table 1**). The reaction of **5a** with 5 mol % $Pd(PPh_3)_4$, $TsNH_2$ and Cs_2CO_3 in THF gave spiroindole **9a**, the β-hydride elimination product, in only 20% yield (entry 1). When the reaction was conducted in the presence of 5 mol % $Pd(dba)_2$ and a bidentate ligand 1,1′-bis(diphenylphosphino)ferrocene (dppf), the reaction proceeded smoothly to afford the desired tetracyclic indoline **8a** in 47% yield (entry 2). A variety of different inorganic bases (entries 3–5), ligands (entries 6–10) and solvents (entries 11–13) were also screened, and the results revealed that the use of diphenylphosphinobutane (dppb) as the ligand with Cs_2CO_3 as the base in THF gave the best results, with compound **8a** being isolated in *ca*. 72% yield (entry 9). However, the main problem with these conditions was found to be poor reproducibility. Operating under the assumption that the poor reproducibility of these conditions was related to the purity of $Pd(dba)_2$, the author investigated the use of $Pd_2(dba)_3{\cdot}CHCl_3$ following its recrystallization from $CHCl_3$.[8] This change afforded the desired product **8a** in 72% yield reproducibly (entry 14).

Table 1. Optimization of the Reaction Conditions



5a **8a** **9a**

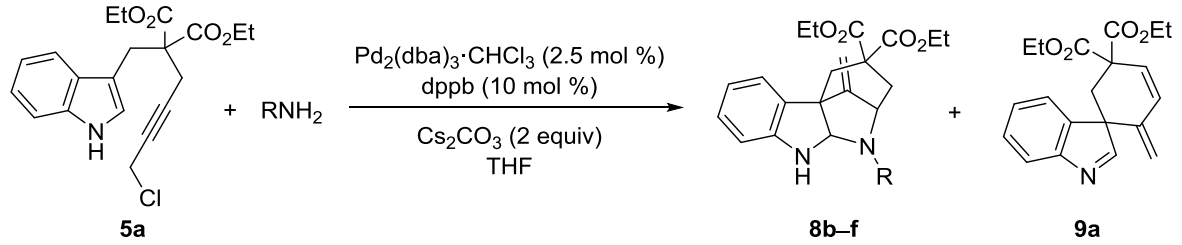
entry	Pd (mol %)	ligand[a]	base	solvent (M)	temp (°C)	time (h)	% yield[b]	
							8a	**9a**
1	$Pd(PPh_3)_4$ (5)	-	Cs_2CO_3	THF (0.1)	60	24	0	20
2	$Pd(dba)_2$ (5)	dppf	Cs_2CO_3	THF (0.1)	50	0.5	47	5
3	$Pd(dba)_2$ (5)	dppf	K_2CO_3	THF (0.1)	50	3	15	6
4	$Pd(dba)_2$ (5)	dppf	$CaCO_3$	THF (0.1)	60	24	0	0
5	$Pd(dba)_2$ (5)	dppf	$NaHCO_3$	THF (0.1)	60	24	0	0
6	$Pd(dba)_2$ (5)	dppm	Cs_2CO_3	THF (0.1)	60	24	0	17
7	$Pd(dba)_2$ (5)	dppe	Cs_2CO_3	THF (0.1)	60	7	22	62
8	$Pd(dba)_2$ (5)	dppp	Cs_2CO_3	THF (0.1)	50	1	29	6
9	$Pd(dba)_2$ (5)	dppb	Cs_2CO_3	THF (0.1)	rt	2.5	*ca.* 72	3
10	$Pd(dba)_2$ (5)	dpppe	Cs_2CO_3	THF (0.1)	50	5	37	2
11	$Pd(dba)_2$ (5)	dppb	Cs_2CO_3	dioxane (0.1)	70	20	*ca.* 13	3
12	$Pd(dba)_2$ (5)	dppb	Cs_2CO_3	DMF (0.1)	rt	2.5	*ca.* 59	1
13	$Pd(dba)_2$ (5)	dppb	Cs_2CO_3	CH_3CN (0.1)	40	2	*ca.* 54	1
14	$Pd_2(dba)_3 \cdot CHCl_3$ (2.5)	dppb	Cs_2CO_3	THF (0.067)	rt	3	72	5

[a] dppf = 1,1'-bis(diphenylphosphino)ferrocene; dppm = bis(diphenylphosphino)methane; dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dppb = 1,4-bis(diphenyl-phosphino)butane; dpppe = 1,5-bis(diphenylphosphino)pentane. [b] Isolated yields.

With the optimized conditions in hand, the author proceeded to examine the reaction in the presence of a variety of nucleophiles. The results are summarized in **Table 2** and **Scheme 4**. The reaction with sulfonamides (e.g., $PhSO_2NH_2$, $MtsNH_2$, $NsNH_2$, and $MsNH_2$) gave the corresponding tetracyclic indolines **8b**–**e** in moderate yields (entries 1–4). In contrast, benzylamine was found to be inert as the external nucleophile, with the β-hydride elimination product **9a** being isolated as the major product (entry 5). Interestingly, the use of dimethyl malonate as the nucleophile resulted in the formation of the regioisomeric indoline **10a** (17%) and spiroindole **9a** (15%) as shown in **Scheme 4**.

The use of acetylacetone, which is a more acidic carbon nucleophile than dimethyl malonate, led to an increase in the yield of indoline **10b** (50%), along with spiroindole **9a** (20%).

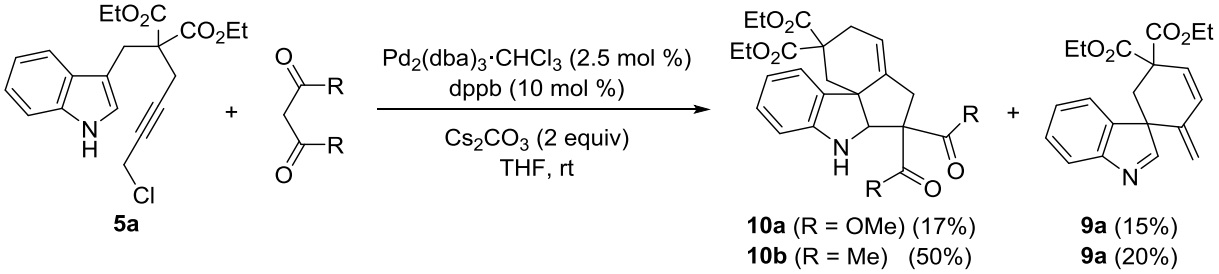
Table 2. Reaction with Various Nitrogen Nucleophiles



5a **8b–f** **9a**

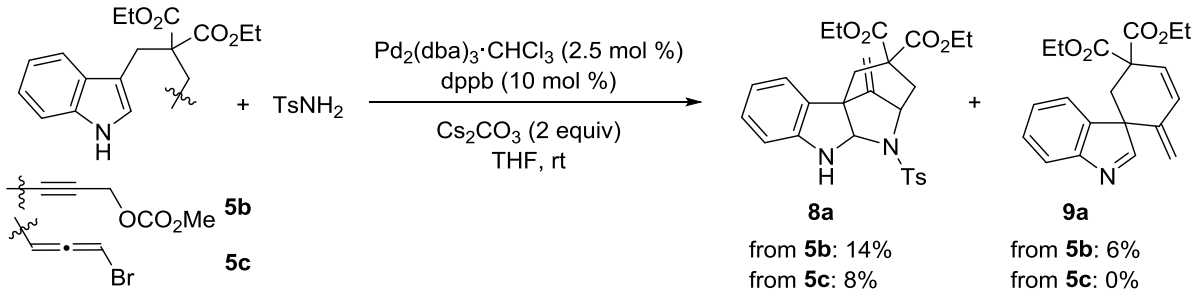
Entry	RNH_2	temp (°C)	time (h)	% yield[a] (product)	
				8	**9a**
1	$PhSO_2NH_2$ (1.5)	rt	5	64 (**8b**)	6
2	$MtsNH_2$[b] (1.5)	rt	3.5	55 (**8c**)	9
3	$NsNH_2$ (1.5)	60	2	43 (**8d**)	15
4	$MsNH_2$ (1.5)	60	24	68 (**8e**)	10
5	$BnNH_2$ (1.5)	60	7	0 (**8f**)	54

[a] Isolated yields. [b] Mts = 2,4,6-trimethylbenzenesulfonyl.



Scheme 4. Reaction with Carbon Nucleophiles

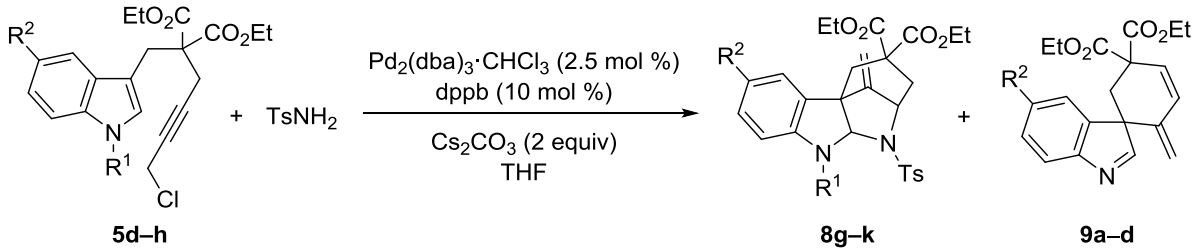
It is well known that bromoallenes are the synthetic equivalents of propargyl compounds including chlorides and carbonates in palladium-catalyzed transformations.[9] With this in mind, the author examined the reaction of propargyl carbonate **5b** and bromoallene **5c** (**Scheme 5**). Unfortunately, the reaction gave the desired indoline **8a** in only 8–14% yield. These results therefore demonstrated that substrates of these types are less effective for this reaction than propargyl chloride **5a**.



Scheme 5. Reaction of Carbonate **5b** and Bromoallene **5c**

The author next examined the scope and limitations of the reaction using a series of different indole substrates (**Table 3**). *N*-Substituted indoles **5d** and **5e** did not produce the spirocyclic products (entries 1 and 2). These results indicated that the nucleophilic attack by the indole 3-position would accompany deprotonation at the indole nitrogen. In contrast, indoles bearing an electron-withdrawing fluorine atom (**5f**) or electron-donating methoxy group (**5h**) at their 5-position reacted smoothly under the optimized conditions to give the desired products **8i** and **8k** in good yields (entries 3 and 5). However, when compound **5g** bearing a bromine atom at the 5-position of the indole was used as a substrate, a slightly lower yield (43%) of indoline **8j** was observed. The lower yield observed in this case was attributed to side reaction(s) involving the aryl bromide moiety of the substrate and the product **8j**.

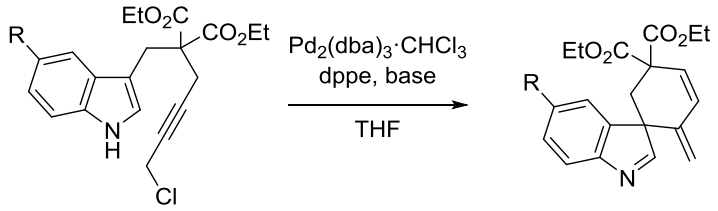
Table 3. Reaction of Various Indoles



entry	substrate	R^1	R^2	temp (°C)	time (h)	% yield (product)[a]	
						8	**9**
1	**5d**	Boc	H	60	24	0 (**8g**)	0 (**9a**)
2	**5e**	Me	H	60	24	0 (**8h**)	0 (**9a**)
3	**5f**	H	F	rt	3	71 (**8i**)	5 (**9b**)
4	**5g**	H	Br	60	3	43 (**8j**)	6 (**9c**)
5	**5h**	H	OMe	rt	2.5	71 (**8k**)	20 (**9d**)

[a] Isolated yields.

Table 4. Synthesis of Spiroindoles **9a–d**



5a (R = H), **5f** (R = F)
5g (R = Br), **5h** (R = OMe)

9a (R = H), **9b** (R = F)
9c (R = Br), **9d** (R = OMe)

entry	substrate	R	[Pd]/dppe (mol %)	base (equiv)	temp (°C)	time (h)	% yield [a] (product)
1	**5a**	H	5/10	Cs_2CO_3 (2)	70	4	7
2	**5a**	H	5/10	Et_3N (2)	55	24	3
3	**5a**	H	5/10	DIPEA (2)	55	24	4
4	**5a**	H	5/10	Et_3N (1.5)/Cs_2CO_3 (2)	55	24	11
5	**5a**	H	5/10	DIPEA (1.5)/Cs_2CO_3 (2)	55	20	21
6	**5a**	H	5/10	$BnNH_2$ (1.5)/Cs_2CO_3 (2)	55	24	33
7	**5a**	H	5/10	$BnNH_2$ (1.5)/Cs_2CO_3 (2)	60	3	68
8	**5a**	H	5/10	$BnNH_2$ (0.2)/Cs_2CO_3 (2)	60	4	45
9	**5a**	H	10/20	$BnNH_2$ (1.5)/Cs_2CO_3 (2)	60	3	64
10	**5a**	H	10/20	$BnNH_2$ (2)	60	24	trace
11	**5f**	F	5/10	$BnNH_2$ (1.5)/Cs_2CO_3 (2)	60	3	56 (**9b**)
12	**5g**	Br	5/10	$BnNH_2$ (1.5)/Cs_2CO_3 (2)	60	3	40 (**9c**)
13	**5h**	OMe	5/10	$BnNH_2$ (1.5)/Cs_2CO_3 (2)	60	3	74 (**9d**)

[a] Isolated yields.

The author then turned his attention to the selective synthesis of the β-elimination product **9** (**Table 4**). It was envisaged that **9** could be efficiently produced under the same reaction conditions in the absence of an external nucleophile. This assumption was based on the results shown in **Table 1**, where the use of dppe as a ligand afforded spiroindole **9a** as the major product in 62% yield (entry 7). Contrary to the author's expectation, the treatment of **5a** with $Pd_2(dba)_3{\cdot}CHCl_3$ (2.5 mol %) and dppe (10 mol %) in the presence of Cs_2CO_3 (2 equiv) at 70 °C afforded the desired product **9a** in only 7% yield (**Table 4**, entry 1). Based on this disappointing result, the author carefully examined the reaction parameters and screened a series of bases against the reaction (entries 2–6), including Cs_2CO_3, Et_3N, $(i\text{-Pr})_2NEt$ (DIPEA) and $BnNH_2$ at 50–55 °C. Among them, a combination of $BnNH_2$ and Cs_2CO_3 gave a better result (33%, entry 6) than the reaction using Cs_2CO_3 alone (entry 1).

Furthermore, the reaction temperature had a significant impact on the yield of **9a**. For example, the reaction reached completion within 3 h at a slightly elevated temperature (60 °C) to afford the desired product in 68% yield (**Table 4**, entry 7). Lowering the loading of $BnNH_2$ (entry 8, 45%) or increasing the loading of the catalyst (entry 9, 64%) did not improve the yield of **9a**. It is noteworthy that the reaction involving the use of $BnNH_2$ as the only base afforded only a trace amount of **9a** (entry 10). Under the optimized conditions, substituted indoles **5f** and **5h** afforded spiroindoles **9b** and **9d**, respectively, in moderate to good yields (entries 11 and 13). Furthermore, the brominated substrate **5g** reacted under these conditions to **9c**, albeit in a lower yield (40%, entry 12).

A plausible mechanism for the cascade cyclization is shown in **Figure 1**. Briefly, propargyl chloride would initially react with a palladium catalyst to give the η^3-propargylpalladium complex **A**. Intramolecular nucleophilic addition of the indole to the central carbon atom of the η^3-propargylpalladium **A** would give η^3-allylpalladium complex **B**. Deprotonation at the indole nitrogen would be necessary for this step, considering that the *N*-substituted substrates **5d** and **5e** did not react under the optimized reaction conditions (**Table 3**, entries 1 and 2). The reaction *N*-substituted substrates would provide the iminium intermediates, which might cause undesired side reactions *e.g*. dimerization and skeletal rearrangement. The tetracyclic indolines **8** and/or **10** would then be formed by the intermolecular nucleophilic attack of the external nucleophile via path a and/or b. Path a represents the first intermolecular nucleophilic attack on the imine carbon, which would be followed by the allylic substitution reaction of intermediate **C**. Depending on which carbons of the allylic moiety in **C** participated in the cyclization (path d vs. e), the regioisomeric products **8** and **10** would be formed. Path b would occur to give intermediate **D** if the intermolecular allylic substitution reaction dominated over the addition of the nucleophile to the imine, with indoline **10** being formed as the major product. In this step, the occurrence of an intermolecular reaction at the more hindered carbon (path b') would be another possible pathway. In contrast, β-hydride elimination from **B** would produce diene **9a** (path c). When a sulfonamide was used as the external nucleophile, tetracyclic indoline **8** was obtained without producing any of the regioisomeric indoline **10**. This regioselectivity was most likely affected by steric hindrance during the reactions involved in path a, in that the product **10** as well as the transition state to **10** would be destabilized by unfavorable steric interactions between the indole proton at the 4-position (H_A) and the flagpole hydrogen (H_B) of the cyclohexene moiety. In contrast, the reaction using carbon nucleophile would favor the formation of regioisomer **10** (**Scheme 4**). This can be explained by considering both the sterically congested and soft characteristics of the carbon nucleophiles. Thus, the sterically hindered imine carbon (having a

quaternary carbon at the neighboring position) would induce the nucleophilic attack of the soft carbon nucleophiles at the η^3-allylpalladium moiety of **B** to form **10** via intermediate **D** (path b).[10]

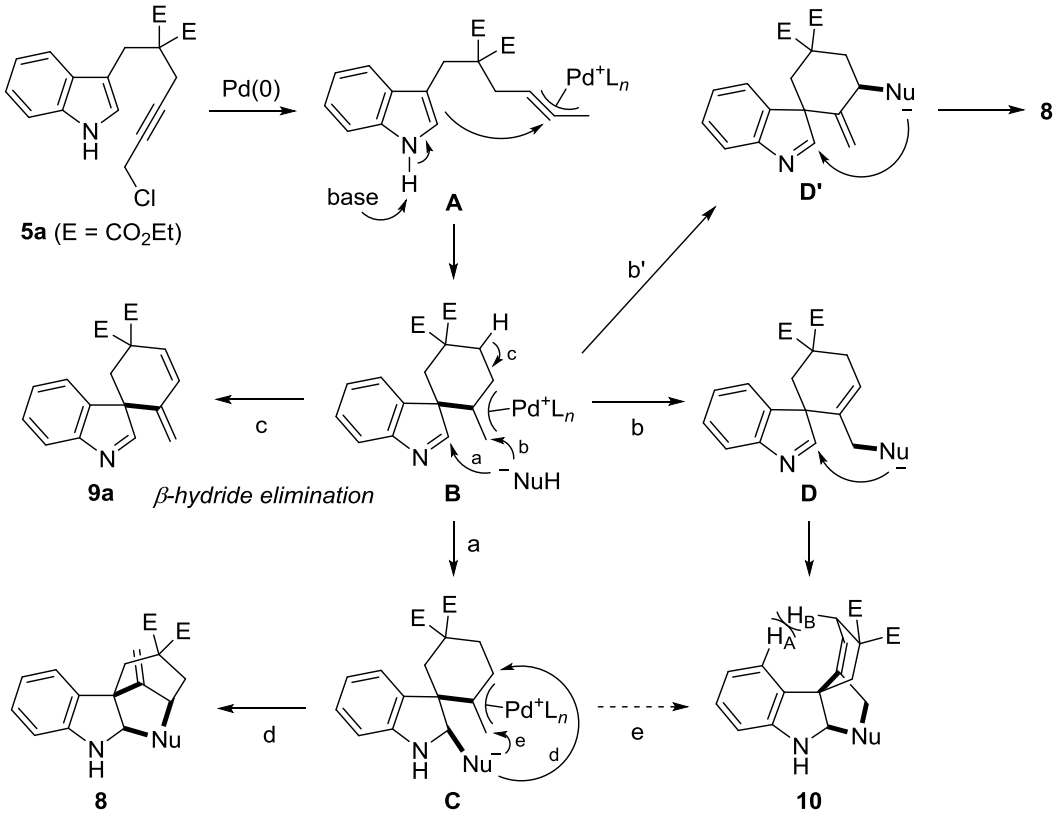
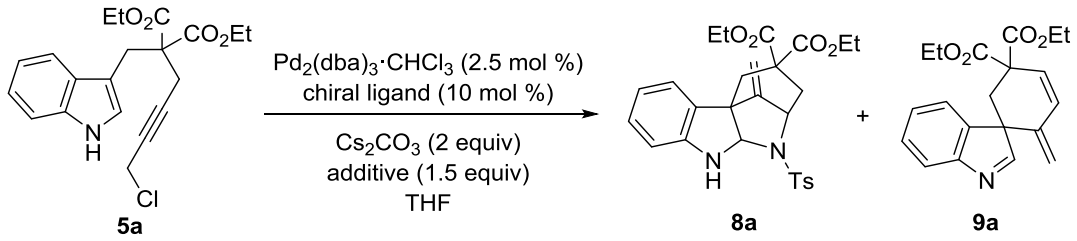


Figure 1. Proposed Mechanism for Palladium-Catalyzed Cascade Cyclization

Finally, the author attempted to carry out a catalytic asymmetric version of the current reaction. To the best of the author's knowledge, only two catalytic asymmetric reactions have been reported to date for the propargylpalladium chemistry. Rawal *et al.*[5a] reported an asymmetric version of the aforementioned intermolecular spirocyclization of a tryptamine-derived substrate (**Scheme 2**, eq 2) and obtained the spiroindole (Nu = NR) in 16% ee using (*R*)-BINAP. You *et al.*[5b] found that (*R*)-SEGPHOS showed more efficient asymmetric induction, affording the corresponding spiroindole [Nu = $C(CO_2Et)_2$] in 52% ee. The enantio-determining step in these reactions would be the allylic substitution step, where the chiral spirocenter would be formed by the nucleophilic reaction of the indole moiety. The author screened a series of chiral ligands against β-hydride elimination reaction to produce spiroindole **9a** (**Table 5**, entries 1–8). When (*R*)-SEGPHOS and (*R*)-DM-SEGPHOS were used, these reactions produced spiroindole **9a** with better enantioselectivities (51–53% ee, entries 6 and 7), although the yields of **9a** were unsatisfactory (12–24%). The author thus proceeded to examine the synthesis of tetracyclic indoline **8a** using (*R*)-SEGPHOS and (*R*)-DM-SEGPHOS.

Fortunately, the palladium-catalyzed reaction of **5a** with $TsNH_2$ in the presence of H_2O (1 equiv) using (*R*)-SEGPHOS gave the tetracyclic indoline **8a** (38% yield) and spiroindole **9a** (15% yield) with moderate enantioselectivities (65–71% ee, entry 10). The difference in enantioselectivity between **8a** and **9a** can be rationalized by considering the match/mismatch pairs between the indole spirocenter and the palladium species in the β-elimination step, which could increase the ee values of the elimination product **9a**. It should be noted that the addition of H_2O to the reaction was necessary for a high level of reproducibility. This result therefore highlights the great potential of a propargylpalladium complex in terms of its use in catalytic asymmetric reactions.

Table 5. Optimization of the Catalytic Asymmetric Reaction Conditions



entry	chiral ligand	additive	time (h)	% yield [a] (% ee) [b]	
				8a	**9a**
1	(*R*)-QUINAP	$BnNH_2$	5	-	trace
2	(*S*,*S*)-DIOP	$BnNH_2$	3.5	-	mixture
3	(*R*)-CHIRAPHOS	$BnNH_2$	7	-	13 (13)
4	(*R*)-BINAP	$BnNH_2$	4	-	22 (34)
5	(*S*)-SYNPHOS	$BnNH_2$	6	-	*ca.* 34 (40)
6	(*R*)-SEGPHOS	$BnNH_2$	6	-	12 (53)
7	(*R*)-DM-SEGPHOS	$BnNH_2$	4	-	24 (51)
8	(*R*)-DIFLUORPHOS	$BnNH_2$	24	-	5.5 (34)
9	(*R*)-SEGPHOS	$TsNH_2$	24	24 (56)	14 (73)
10	(*R*)-SEGPHOS	$TsNH_2$, H_2O [c]	14	38 (65)	15 (71)
11	(*R*)-DM-SEGPHOS	$TsNH_2$, H_2O [c]	20	16 (30)	4 (77)

[a] Isolated yields. [b] Determined by HPLC analysis (Chiralcel IC-3). [c] Reaction was carried out in addition to H_2O (1 equiv).

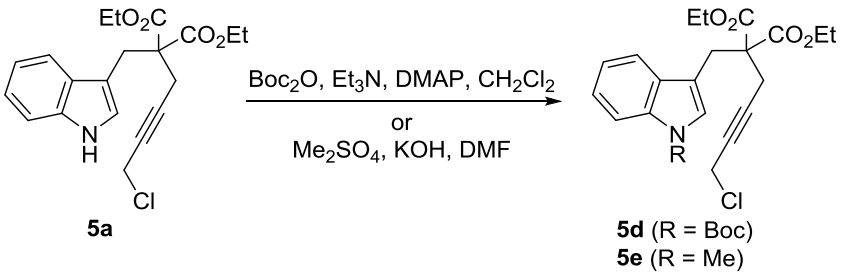
In conclusion, the author has developed a new reaction for the palladium-catalyzed spirocyclization of propargyl chlorides using an external nucleophile for the divergent synthesis of tetracyclic indolines. When this reaction was conducted in the absence of an external nucleophile, it gave the corresponding spiroindoles through β-hydride elimination. The regioselectivity of this reaction was found to be dependent on the external nucleophiles employed in the reaction. The author has also developed an asymmetric version of this reaction to produce tetracyclic indolines (65–71% ee). This methodology provides a novel approach to biologically active spiroindole derivatives.

Experimental Section

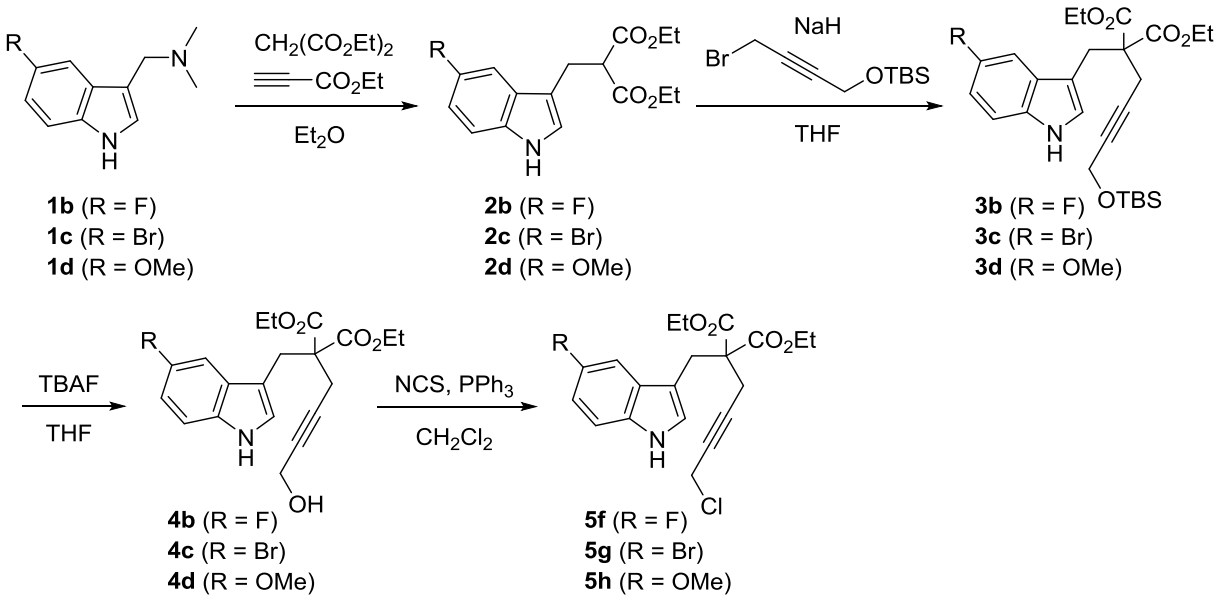
General Methods. All reactions under argon atmosphere were performed using syringe-septum cap techniques and all glassware was dried in an oven at 80 °C for 2 h prior to use. For flash chromatography, silica gel (Wakogel C-200E: Wako Pure Chemical Industries, Ltd) or NH_2 silica gel (Chromatorex NH-DM1020: Fuji Silysia Chemical Ltd.) was employed. Thin layer chromatography was performed on Merck TLC silica gel 60 F_{254} or Wako NH_2 silica gel 60 F_{254} plate (layer thickness 0.25 mm), which were developed using standard visualizing agents: UV fluorescence (254 nm) and anisaldehyde with heating. Melting points were measured by a hot stage melting point apparatus (uncorrected). ^{1}H NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer, and chemical shifts are reported in δ (ppm) relative to TMS as internal standard. ^{13}C NMR spectra were recorded using a JEOL AL-400 or JEOL ECA-500 spectrometer and referenced to the residual solvent signal. ^{1}H NMR spectra are tabulated as follows: chemical shift, multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), number of protons, and coupling constant(s). Exact mass (HRMS) spectra were recorded on a JMS-HX/HX 110A mass spectrometer. Infrared (IR) spectra were obtained on a JASCO FT/IR-4100 FT-IR spectrometer with JASCO ATR PRO410-S. The known compounds **2a**,[6] **2c**,[11] **2d**[6], **3a**,[12] **3c**,[12] **3d**,[12] **4a**,[12] **4c**,[12] **4d**[12] and **6**[13] were prepared according to the literature procedure.

Preparation of the Substrates

The chloride **5a**, carbonate **5b**, and bromoallene **5c** were prepared as shown in **Scheme 3**. The *N*-substituted chlorides **5d**,**e** and aryl-substituted chlorides **5f-h** were prepared according to the **Schemes** shown below.



Scheme 6. Preparation of *N*-Substituted Substrates **5d**,**e**



Scheme 7. Preparation of Aryl-Substituted Substrates **5f**–**h**

Diethyl 2-[(5-Fluoro-1*H*-indol-3-yl)methyl]malonate (2b). To a stirred mixture of **1b** (1.0 g, 5.20 mmol) and diethyl malonate (736 µL, 4.85 mmol) in Et_2O (2.6 mL) was added dropwise ethyl propiolate (529 µL, 5.20 mmol) at room temperature. The mixture was stirred for 45 min at this temperature, followed by quenching with H_2O. The whole was extracted with Et_2O. The extract was washed successively with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (8:1) to give the corresponding **2b** as a pale yellow needle (1.27 g, 77% yield): mp 60–61 °C; IR (neat): 3410 (NH), 1726 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.21 (t, J = 7.2 Hz, 6H), 3.33 (d, J = 7.7 Hz, 2H), 3.72 (t, J = 7.7 Hz, 1H), 4.12-4.20 (m, 4H), 6.93 (ddd, J = 9.2, 9.2, 2.5 Hz, 1H), 7.09 (d, J = 2.3 Hz, 1H), 7.23-7.26 (m, 2H), 8.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 24.4, 52.9, 61.4 (2C), 103.5 (d, J = 24.0 Hz), 110.4 (d, J = 26.4 Hz), 111.8 (d, J = 9.6 Hz), 112.3 (d, J = 4.8 Hz) 124.4, 127.5 (d, J = 9.6 Hz), 132.6, 157.8 (d, J = 235 Hz), 169.2 (2C). *Anal*. Calcd for $C_{16}H_{18}FNO_4$: C, 62.53; H, 5.90; N, 4.56. Found: C, 62.41; H, 5.93; N, 4.50.

Diethyl 2-{4-[(*tert*-Butyldimethylsilyl)oxy]but-2-yn-1-yl}-2-[(5-fluoro-1*H*-indol-3-yl)methyl]-malonate (3b). To a solution of **2b** (1.14 g, 3.71 mmol) in THF was added NaH (60% suspension in mineral oil; 297 mg, 7.42 mmol) at 0 °C. The suspension was stirred for 30 min at 0 °C, then propargyl bromide (1.17 g, 4.45 mmol) in THF was added dropwise. The reaction was warmed up to room temperature and stirred for 2 h, followed by quenching with H_2O. The whole was extracted with EtOAc. The extract was washed successively with H_2O and brine, and dried over $MgSO_4$. The

filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (5:1) to give the corresponding **3b** as a colorless oil (682 mg, 38%): IR (neat): 3387 (NH), 2332 (C≡C), 1736 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.14 (s, 6H), 0.92 (s, 9H), 1.23 (t, *J* = 7.0 Hz, 6H), 2.81 (t, *J* = 2.1 Hz, 2H), 3.51 (s, 2H), 4.10-4.22 (m, 4H), 4.37 (t, *J* = 2.1 Hz, 2H), 6.90 (ddd, *J* = 9.0, 9.0, 2.5 Hz, 1H), 7.09 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.29 (dd, *J* = 9.9, 2.5 Hz, 1H), 8.12 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ –5.2 (2C), 13.9 (2C), 18.3, 23.1, 25.8 (3C), 27.3, 51.8, 58.0, 61.6 (2C), 80.2, 82.4, 103.8 (d, *J* = 24.0 Hz), 110.0 (d, *J* = 4.8 Hz), 110.4 (d, *J* = 26.4 Hz), 111.6 (d, *J* = 9.6 Hz), 125.3, 128.5 (d, *J* = 9.6 Hz), 132.3, 157.9 (d, *J* = 234 Hz), 170.1 (2C). HRMS (FAB) calcd $C_{26}H_{36}FNO_5Si$: [M^+], 489.2347; found: [M^+], 489.2350.

Diethyl 2-[(5-Fluoro-1*H*-indol-3-yl)methyl]-2-(4-hydroxybut-2-yn-1-yl)malonate (4b). To a stirred solution of **3b** (638 mg, 1.30 mmol) in THF was added TBAF (1.00 M solution in THF; 1.43 mL, 1.43 mmol) at 0 °C. The mixture was stirred for 1.5 h at this temperature and quenched by addition of saturated NH_4Cl. The whole was extracted with EtOAc. The extract was washed with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (3:1) to give the corresponding **4b** as a pale yellow oil (485 mg, 99% yield): IR (neat): 3410 (NH), 3403 (OH), 2254 (C≡C), 1720 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 6H), 1.97 (s, 1H), 2.80 (s, 2H), 3.51 (s, 2H), 4.11-4.25 (m, 4H), 4.31 (s, 2H), 6.90 (ddd, *J* = 8.9, 8.9, 2.5 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 7.22 (dd, *J* = 8.9, 4.4 Hz, 1H), 7.29 (dd, *J* = 10.0, 2.5 Hz, 1H), 8.19 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 23.1, 27.3, 51.2, 58.0, 61.7 (2C), 81.4, 82.2, 103.7 (d, *J* = 23.0 Hz), 109.7 (d, *J* = 4.8 Hz), 110.4 (d, *J* = 25.9 Hz), 111.7 (d, *J* = 10.5 Hz), 125.4, 128.5 (d, *J* = 11.5 Hz), 132.3, 157.9 (d, *J* = 235 Hz), 170.2 (2C). HRMS (FAB) calcd $C_{20}H_{22}FNO_5$: [M^+], 375.1482; found: [M^+], 375.1478.

General Procedure for the Synthesis of Propargyl Chloride (5a,f-h). To a stirred mixture of a propargyl alcohol **4** (1.0 equiv) and PPh_3 (1.5 equiv) in CH_2Cl_2 was added NCS (1.2 equiv) in CH_2Cl_2 at room temperature. The mixture was stirred for 1.5–3 h at this temperature and quenched by addition of H_2O. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel to give the corresponding propargyl chloride **5a,f-h**.

Diethyl 2-[(1*H*-Indol-3-yl)methyl]-2-(4-chlorobut-2-yn-1-yl)malonate (5a). Brown oil. Flash chromatography: *n*-hexane–EtOAc = 4:1. Yield = 90%: IR (neat): 3409 (NH), 2242 (C≡C), 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.3 Hz, 6H), 2.83 (t, *J* = 2.2 Hz, 2H), 3.57 (s, 2H), 4.10-4.25 (m, 6H), 7.03 (d, *J* = 2.4 Hz, 1H), 7.09 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H), 7.32 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.66 (dd, *J* = 8.0, 1.0 Hz, 1H), 8.08 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.3, 30.8, 58.2, 61.7 (2C), 78.3, 82.9, 109.6, 111.0, 118.9, 119.5, 122.0, 123.4, 128.1, 135.8, 170.1 (2C). HRMS (FAB) calcd $C_{20}H_{21}ClNO_4$: $[M - H]^-$, 374.1165; found: $[M - H]^-$, 374.1168.

Diethyl 2-(4-Chlorobut-2-yn-1-yl)-2-[(5-fluoro-1*H*-indol-3-yl)methyl]malonate (5f). Brown oil. Flash chromatography: *n*-hexane–EtOAc = 5:1. Yield = 87%: IR (neat): 3407 (NH), 2238 (C≡C), 1727 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.4 Hz, 6H), 2.82 (t, *J* = 2.3 Hz, 2H), 3.51 (s, 2H), 4.13-4.24 (m, 6H), 6.90 (ddd, *J* = 9.0, 9.0, 2.5 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 9.0, 4.3 Hz, 1H), 7.29 (dd, *J* = 9.0, 2.5 Hz, 1H), 8.17 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 23.1, 27.4, 30.7, 58.0, 61.8 (2C), 78.6, 82.7, 103.8 (d, *J* = 24.0 Hz), 109.7 (d, *J* = 4.8 Hz), 110.5 (d, *J* = 26.4 Hz), 111.7 (d, *J* = 9.6 Hz), 125.3, 128.5 (d, *J* = 9.6 Hz), 132.3, 157.9 (d, *J* = 235 Hz), 170.0 (2C). HRMS (FAB) calcd $C_{20}H_{21}ClFNO_4$: $[M^+]$, 393.1143; found: $[M^+]$, 393.1147.

Diethyl 2-[(5-Bromo-1*H*-indol-3-yl)methyl]-2-(4-chlorobut-2-yn-1-yl)malonate (5g). Brown oil. Flash chromatography: *n*-hexane–EtOAc = 4:1. Yield = 73%: IR (neat): 3384 (NH), 2238 (C≡C), 1727 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.27 (t, *J* = 7.2 Hz, 6H), 2.80 (t, *J* = 2.3 Hz, 2H), 3.52 (s, 2H), 4.15-4.25 (m, 6H), 7.06 (d, *J* = 2.4 Hz, 1H), 7.18 (d, *J* = 8.6 Hz, 1H), 7.23 (dd, *J* = 8.6, 1.9 Hz, 1H), 7.75 (d, *J* = 1.9 Hz, 1H), 8.17 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.2, 30.7, 57.8, 61.9 (2C), 78.7, 82.6, 109.3, 112.5, 112.9, 121.5, 124.8, 124.9, 129.7, 134.4, 169.9 (2C). HRMS (FAB) calcd $C_{20}H_{21}BrClNO_4$: $[M^+]$, 453.0342; found: $[M^+]$, 453.0345.

Diethyl 2-(4-Chlorobut-2-yn-1-yl)-2-[(5-methoxy-1*H*-indol-3-yl)methyl]malonate (5h). Brown oil. Flash chromatography: *n*-hexane–EtOAc = 4:1. Yield = 70%: IR (neat): 3417 (NH), 2239 (C≡C), 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23 (t, *J* = 7.0 Hz, 6H), 2.85 (t, *J* = 2.0 Hz, 2H), 3.53 (s, 2H), 3.86 (s, 3H), 4.14-4.24 (m, 6H), 6.83 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 7.15 (d, *J* = 2.5 Hz, 1H), 7.20 (d, *J* = 8.9 Hz, 1H), 8.00 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C),

23.1, 27.4, 30.7, 55.9, 58.5, 61.7 (2C), 78.3, 83.1, 100.5, 109.4, 111.8, 112.6, 124.1, 128.6, 131.0, 154.2, 170.0 (2C). HRMS (FAB) calcd $C_{21}H_{24}ClNO_5$: [M^+], 405.1343; found: [M^+], 405.1345.

Diethyl 2-[(1*H*-Indol-3-yl)methyl]-2-{4-[(methoxycarbonyl)oxy]but-2-yn-1-yl}malonate (5b). To a stirred mixture of **4a** (50 mg, 0.135 mmol), pyridine (33 μL, 0.41 mmol) in CH_2Cl_2 (675 μL) was added $ClCO_2Me$ (14 μL, 0.20 mmol) at 0 °C. The mixture was stirred for 30 min at this temperature and quenched by addition of saturated NH_4Cl. The whole was extracted with Et_2O. The extract was washed with H_2O, 1 N HCl, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (4:1) to give **5b** as a brown oil (47.5 mg, 82% yield): IR (neat): 3407 (NH), 2252 (C≡C), 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22 (t, *J* = 6.8 Hz, 6H), 2.82 (t, *J* = 2.3 Hz, 2H), 3.56 (s, 2H), 3.82 (s, 3H), 4.10-4.23 (m, 4H), 4.78 (t, *J* = 2.3 Hz, 2H), 7.01 (d, *J* = 2.3 Hz, 1H), 7.09 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.15 (ddd, *J* = 8.0, 8.0, 1.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 8.14 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 23.0, 27.3, 55.1, 55.9, 58.1, 61.6 (2C), 77.3, 83.7, 109.5, 110.0, 118.8, 119.4, 122.0, 123.5, 128.1, 135.8, 155.2, 170.0 (2C). HRMS (FAB) calcd $C_{22}H_{25}NO_7$: [M – H]$^-$, 414.1558; found: [M – H]$^-$, 414.1564.

Diethyl 2-(4-Bromobuta-2,3-dien-1-yl)malonate (7). To a stirred mixture of **6** (410 mg, 1.8 mmol) and TrisCl (1.36 g, 4.5 mmol) in CH_2Cl_2 (41 mL) was added DMAP (770 mg, 6.3 mmol) at room temperature. The mixture was stirred for 3 h at this temperature. Concentration of the mixture under reduced pressure followed by rapid filtration through a short pad of silica gel with Et_2O to give a crude sulfonate, which was used without further purification. $CuBr{\cdot}SMe_2$ (1.10 g, 5.4 mmol) and LiBr (465 mg, 0.373 mmol) were dissolved in THF (18 mL) at room temperature under argon, and the mixture was stirred for 30 min at this temperature. To this mixture was added a solution of the above crude sulfonate in THF (26 mL) at room temperature. The mixture was allowed to warm to 50 °C and stirred at this temperature for 1.5 h, which was quenched by addition of saturated NH_4Cl and 28% NH_4OH. The whole was extracted with EtOAc. The extract was washed with H_2O and brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (30:1) to give **7** as a colorless oil (330 mg, 63% yield): IR (neat): 1958 (C=C=C), 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26-1.31 (m, 6H), 2.73-2.78 (m, 2H), 3.52 (t, *J* = 7.4 Hz, 1H), 4.18-4.27 (m, 4H), 5.45 (dd, *J* = 12.6, 5.7 Hz, 1H), 6.00 (ddd, *J* = 5.7, 2.4, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C),

21.2, 50.8, 61.7 (2C), 73.7, 97.3, 168.4, 168.5, 202.3; HRMS (FAB) calcd $C_{11}H_{16}BrNO_4$: $[M + H]^+$, 291.0232; found: $[M + H]^+$, 291.0227.

Diethyl 2-(4-Bromobuta-2,3-dien-1-yl)-2-[(1*H*-indol-3-yl)methyl]malonate (5c). To a stirred mixture of **7** (286 mg, 1.13 mmol) and **1a** (306 mg, 1.05 mmol) in Et_2O (1.1 mL) was added dropwise ethyl propiolate (115 μL, 1.13 mmol) at room temperature. The mixture was stirred for 5 h at this temperature, followed by quenching with H_2O. The whole was extracted with EtOAc. The extract was washed successively with H_2O and brine, and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (8:1 to 5:1) to give **5c** as a brown oil (285 mg, 64% yield): IR (neat): 3393 (NH), 1957 (C=C=C), 1720 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.18-1.24 (m, 6H), 2.75-2.77 (m, 2H), 3.42-3.52 (m, 2H), 4.10-4.22 (m, 4H), 5.34-5.41 (m, 1H), 5.92-5.97 (m, 1H), 7.03 (d, *J* = 2.3 Hz, 1H), 7.10 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.17 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 8.05 (br s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 28.0, 31.9, 58.6, 61.5 (2C), 72.4, 95.7, 109.5, 111.1, 118.7, 119.4, 121.9, 123.4, 128.0, 135.7, 170.7 (2C), 203.6. HRMS (FAB) calcd $C_{20}H_{22}BrNO_4$: $[M^+]$, 419.0732; found: $[M^+]$, 419.0724.

Diethyl 2-{[1-(*tert*-Butoxycarbony)-1*H*-indol-3-yl]methyl}-2-(4-chlorobut-2-yn-1-yl)malonate (5d). To a stirred mixture of **5a** (100 mg, 0.27 mmol), DMAP (3.2 mg, 0.027 mmol) and Et_3N (46 μL, 0.32 mmol) in CH_2Cl_2 (2.6 mL) was added Boc_2O (70 mg, 0.32 mmol) at room temperature. The mixture was stirred for 30 min at this temperature and quenched by addition of H_2O. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (10:1) to give **5d** as a colorless oil (91.0 mg, 72% yield): IR (neat): 1733 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.26 (t, *J* = 7.3 Hz, 6H), 1.66 (s, 9H), 2.83 (t, *J* = 2.2 Hz, 2H), 3.49 (s, 2H), 4.14-4.25 (m, 6H), 7.22 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 7.29 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 7.41 (s, 1H), 7.63 (dd, *J* = 7.6, 1.0 Hz, 1H), 8.05-8.14 (br m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.2, 26.9, 28.2 (3C), 30.7, 57.9, 61.9 (2C), 78.7, 82.6, 83.7, 114.4, 115.2, 119.1, 122.5, 124.4, 124.9, 131.0, 135.1, 149.6, 169.7 (2C). HRMS (FAB) calcd $C_{25}H_{30}ClNO_6$: $[M^+]$, 475.1762; found: $[M^+]$, 475.1758.

Diethyl 2-(4-Chlorobut-2-yn-1-yl)-2-[(1-methyl-1*H*-indol-3-yl)methyl]malonate (5e). To a stirred mixture of **5a** (183 mg, 0.49 mmol) and KOH (64 mg, 0.97 mmol) in DMF (4.8 mL) was added

Me_2SO_4 (92 μL, 0.32 mmol) at room temperature. The mixture was stirred for 3.5 h at this temperature and quenched by addition of H_2O. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (6:1) to give **5e** as a pale yellow oil (100 mg, 53% yield): IR (neat): 2252 (C≡C), 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 6H), 2.83 (t, *J* = 2.3 Hz, 2H), 3.54 (s, 2H), 3.72 (s, 3H), 4.11-4.24 (m, 6H), 6.87 (s, 1H), 7.08 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.18 (ddd, *J* = 7.6, 7.6, 1.1 Hz, 1H), 7.23-7.26 (m, 1H), 7.63 (d, *J* = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 23.1, 27.3, 30.8, 32.7, 58.2, 61.6 (2C), 78.2, 83.0, 107.8, 109.1, 118.9 (2C), 121.5, 128.1, 128.6, 136.6, 169.7 (2C). HRMS (FAB) calcd $C_{21}H_{24}ClNO_4$: [M^+], 389.1394; found: [M^+], 389.1390.

General Procedure for the Synthesis of Tetracyclic indolines (8). To a stirred mixture of **5a** (30 mg, 0.080 mmol) and $TsNH_2$ (20.5 mg, 0.12 mmol) in THF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), dppb (3.4 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at room temperature under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (8:1) to give **8a** (29.3 mg, 72% yield) and **9a** (1.4 mg, 5.2% yield).

Diethyl 11-Methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8a). Colorless solid; mp 164–165 °C; IR (neat): 3361 (NH), 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 2.38 (s, 3H), 2.40 (d, *J* = 13.7 Hz, 1H), 2.48 (d, *J* = 13.7 Hz, 1H), 3.22 (d, *J* = 13.7 Hz, 2H), 4.09-4.10 (m, 1H), 4.13-4.39 (m, 4H), 4.44 (s, 1H), 4.66 (d, *J* = 4.1 Hz, 1H), 4.76 (s, 1H), 6.05 (d, *J* = 4.6 Hz, 1H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.82 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.07-7.15 (m, 2H), 7.25 (d, *J* = 8.2 Hz, 2H), 7.86 (d, *J* = 8.2 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 21.4, 37.7, 39.9, 52.3, 57.7, 61.3, 62.1, 62.6, 84.0, 103.4, 110.7, 119.3, 122.9, 127.4 (3C), 129.0, 129.6 (2C), 137.6, 143.2, 148.8, 151.7, 170.9, 171.3. HRMS (FAB) calcd $C_{27}H_{30}N_2O_6S$: [M^+], 510.1825; found: [M^+], 510.1832.

Diethyl 11-Methylene-1-(phenylsulfonyl)-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino [2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8b). IR (neat): 3355 (NH), 1727 (C=O); ^{1}H NMR (500 MHz,$CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 2.41 (d, *J* = 13.6 Hz, 1H), 2.49 (d, *J*

= 13.6 Hz, 1H), 3.21-3.27 (m, 2H), 4.10-4.12 (m, 1H), 4.13-4.40 (m, 4H), 4.46 (s, 1H), 4.67 (d, *J* = 4.0 Hz, 1H), 4.77 (s, 1H), 6.07 (d, *J* = 4.0 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 6.83 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 7.14 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.43-7.55 (m, 3H), 7.99 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 37.7, 39.9, 52.3, 57.7, 61.3, 62.1, 62.6, 84.0, 103.6, 110.8, 119.4, 122.9, 127.3 (2C), 127.4, 128.9 (2C), 129.0, 132.5, 140.5, 148.8, 151.6, 170.9, 171.2. HRMS (FAB) calcd $C_{26}H_{28}N_2O_6S$: [M^+], 496.1668; found: [M^+], 496.1668.

Diethyl 1-(Mesitylsulfonyl)-11-methylene-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino [2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8c). IR (neat): 3377 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.28 (m, 6H), 2.31 (s, 3H), 2.38 (d, *J* = 14.5 Hz, 1H), 2.64 (s, 6H), 2.73 (dd, *J* = 13.7, 2.9 Hz, 1H), 3.08 (dd, *J* = 14.5, 2.9 Hz, 1H), 3.21 (d, *J* = 13.7 Hz, 1H), 4.02 (d, *J* = 4.0 Hz, 1H), 4.10-4.33 (m, 4H), 4.37 (t, *J* = 2.9 Hz, 1H), 4.52 (s, 1H), 4.92 (s, 1H), 5.98 (d, *J* = 4.0 Hz, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 6.76 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.95 (s, 2H), 7.03-7.09 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7, 13.9, 21.0, 23.1 (2C), 38.6, 39.4, 51.5, 58.0, 62.0, 62.3, 62.4, 82.8, 103.7, 109.9, 118.6, 122.8, 126.8, 128.9, 132.0 (2C), 133.9, 140.2 (2C), 142.6, 148.9, 151.4, 170.9, 171.5. HRMS (FAB) calcd $C_{29}H_{34}N_2O_6S$: [M^+], 538.2138; found: [M^+], 538.2142.

Diethyl 11-Methylene-1-[(2-nitrophenyl)sulfonyl]-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8d). The reaction was performed for 2 h at 60 °C. IR (neat): 3372 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.31 (t, *J* = 7.2 Hz, 3H), 2.46-2.51 (m, 2H), 3.23-3.32 (m, 2H), 4.10-4.40 (m, 5H), 4.57 (s, 1H), 4.66 (d, *J* = 4.6 Hz, 1H), 4.95 (s, 1H), 6.07 (d, *J* = 4.6 Hz, 1H), 6.63 (d, *J* = 8.0 Hz, 1H), 6.86 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.12-7.17 (m, 2H), 7.59-7.71 (m, 3H), 8.18 (dd, *J* = 7.4, 1.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 37.8, 39.9, 52.3, 57.9, 62.3, 62.6, 62.8, 84.0, 104.3, 111.0, 119.8, 123.0, 124.4, 127.3, 129.1, 129.5, 132.1, 133.1, 134.6, 148.5, 148.9, 151.5, 170.8, 171.1. HRMS (FAB) calcd $C_{26}H_{27}N_3O_8S$: [M^+], 541.1519; found: [M^+], 541.1511.

Diethyl 11-Methylene-1-(methylsulfonyl)-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8e). The reaction was performed for 24 h at 60 °C. IR (neat): 3345 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.33 (t, *J* = 7.2 Hz, 3H), 2.43-2.48 (m, 2H), 2.98 (s, 3H), 3.20-3.26 (m, 2H), 4.11-4.33 (m, 4H), 4.35-4.37 (m, 1H), 4.50 (s, 1H), 4.55 (d, *J* = 4.6 Hz, 1H), 4.96 (s, 1H), 5.78 (d, *J* = 4.6 Hz, 1H), 6.67 (d, *J* = 7.4 Hz, 1H), 6.87 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.10-7.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 37.5, 40.5,

40.6, 52.6, 58.2, 61.8, 62.2, 62.6, 84.0, 103.4, 111.2, 119.8, 122.9, 127.8, 129.1, 148.6, 152.1, 170.7, 171.2. HRMS (FAB) calcd $C_{21}H_{26}N_2O_6S$: [M^+], 434.1512; found: [M^+], 434.1512.

Diethyl 7-Fluoro-11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8i). IR (neat): 3345 (NH), 1730 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.7 Hz, 3H), 1.35 (t, *J* = 7.7 Hz, 3H), 2.32 (d, *J* = 13.7 Hz, 1H), 2.39 (s, 3H), 2.48 (d, *J* = 14.9 Hz, 1H), 3.20-3.23 (m, 2H), 4.09-4.11 (m, 1H), 4.13-4.41 (m, 4H), 4.46 (s, 1H), 4.55 (d, *J* = 4.0 Hz, 1H), 4.79 (s, 1H), 6.07 (d, *J* = 4.6 Hz, 1H), 6.55 (dd, *J* = 8.0, 4.3 Hz, 1H), 6.80-6.86 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.85 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 21.5, 37.6, 39.9, 52.2, 57.7, 61.2, 62.2, 62.7, 84.4, 103.6, 110.6 (d, *J* = 22.8 Hz), 111.2 (d, *J* = 8.4 Hz), 115.1 (d, *J* = 25.2 Hz), 127.4 (2C), 128.9 (d, *J* = 10.8 Hz), 129.6 (2C), 137.5, 143.3, 144.7, 151.3, 157.1 (d, *J* = 243.5 Hz), 170.9, 171.11. HRMS (FAB) calcd $C_{27}H_{29}FN_2O_6S$: [M^+], 528.1730; found: [M^+], 528.1724.

Diethyl 7-Bromo-11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8j). The reaction was performed for 3 h at 60 °C. IR (neat): 3364 (NH), 1730 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.25 (t, *J* = 7.2 Hz, 3H), 1.34 (t, *J* = 7.2 Hz, 3H), 2.32 (d, *J* = 13.7 Hz, 1H), 2.39 (s, 3H), 2.48 (d, *J* = 12.6 Hz, 1H), 3.17-3.23 (m, 2H), 4.10 (s, 1H), 4.12-4.38 (m, 4H), 4.49 (s, 1H), 4.65 (d, *J* = 4.6 Hz, 1H), 4.79 (s, 1H), 6.06 (d, *J* = 4.6 Hz, 1H), 6.52 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 2.0 Hz, 1H), 7.23 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.26 (d, *J* = 8.0 Hz, 2H), 7.83 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 14.0, 21.5, 37.5, 39.8, 52.2, 57.6, 61.2, 62.2, 62.6, 84.1, 103.7, 111.0, 119.3, 126.0, 127.3 (2C), 129.0, 129.6 (2C), 129.7, 137.4, 143.3, 147.9, 151.1, 170.8, 171.0. HRMS (FAB) calcd $C_{27}H_{29}BrN_2O_6S$: [M^+], 588.0930; found: [M^+], 588.0926.

Diethyl 7-Methoxy-11-methylene-1-tosyl-2,3,10,10a-tetrahydro-1*H*-2,5a-methanoazepino[2,3-*b*]indole-4,4(5*H*)-dicarboxylate (8k). IR (neat): 3352 (NH), 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, *J* = 7.2 Hz, 3H), 1.35 (t, *J* = 7.2 Hz, 3H), 2.35 (d, *J* = 13.7 Hz, 1H), 2.38 (s, 3H), 2.46 (dd, *J* = 14.9, 1.7 Hz, 1H), 3.20-3.26 (m, 2H), 3.77 (s, 3H), 4.08-4.11 (m, 1H), 4.13-4.39 (m, 4H), 4.44 (d, *J* = 5.2 Hz, 1H), 4.47 (s, 1H), 4.77 (s, 1H), 6.03 (d, *J* = 5.2 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.67-6.71 (m, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 21.5, 37.7, 40.0, 52.3, 56.0, 57.9, 61.3, 62.1, 62.6, 84.3, 103.4, 110.1, 111.2, 113.6, 127.4 (2C), 128.8, 129.6 (2C), 137.6, 142.4, 143.1, 151.6, 153.7, 170.9, 171.3. HRMS (FAB) calcd $C_{28}H_{32}N_2O_7S$: [M^+], 540.1930; found: [M^+], 540.1935.

General Procedure for the Synthesis of Spiroindoles (9). To a stirred mixture of **5a** (30 mg, 0.080 mmol) and $BnNH_2$ (13 μl, 0.12 mmol) in THF were added $Pd_2(dba)_3 \cdot CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), dppe (3.2 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at 60 °C under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over silica gel with *n*-hexane–EtOAc (9:1 to 8:1) to give **9a** (18.5 mg, 68% yield).

Diethyl 2-Methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9a). Yellow oil: IR (neat): 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.28 (m, 6H), 2.37 (d, J = 14.3 Hz, 1H), 2.72 (d, J = 14.3 Hz, 1H), 4.16-4.30 (m, 4H), 4.56 (s, 1H), 4.87 (s, 1H), 6.18 (d, J = 10.3 Hz, 1H), 6.57 (d, J = 10.3 Hz, 1H), 7.27-7.35 (m, 2H), 7.37-7.43 (m, 1H), 7.66 (d, J = 8.0 Hz, 1H), 7.95 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 35.0, 55.5, 60.8, 62.3 (2C), 114.8, 121.5, 122.9, 125.4, 126.5, 128.5, 131.6, 137.6, 141.3, 155.4, 169.8, 170.1, 173.9. HRMS (FAB) calcd $C_{20}H_{22}NO_4$: $[M + H]^+$, 340.1549; found: $[M + H]^+$, 340.1555.

Diethyl 5'-Fluoro-2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9b). Yellow oil: IR (neat): 1731 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23-1.30 (m, 6H), 2.39 (d, J = 14.3 Hz, 1H), 2.66 (d, J = 14.3 Hz, 1H), 4.18-4.30 (m, 4H), 4.58 (s, 1H), 4.90 (s, 1H), 6.19 (d, J = 9.7 Hz, 1H), 6.56 (d, J = 9.7 Hz, 1H), 7.02 (dd, J = 8.0, 2.2 Hz, 1H), 7.08 (ddd, J = 8.6, 8.0, 2.2 Hz, 1H), 7.60 (dd, J = 8.6, 4.6 Hz, 1H), 7.91 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 34.8, 55.3, 61.3, 62.4 (2C), 110.7 (d, J = 25.2 Hz), 115.0, 115.3 (d, J = 2.5 Hz), 122.4 (d, J = 9.6 Hz), 125.4, 131.4, 137.1, 143.4, 151.4, 161.7 (d, J = 245.9 Hz), 170.0 (2C), 173.8. HRMS (FAB) calcd $C_{20}H_{21}FNO_4$: $[M + H]^+$, 358.1455; found: $[M + H]^+$, 358.1447.

Diethyl 5'-Bromo-2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9c). Yellow oil: IR (neat): 1729 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.23-1.30 (m, 6H), 2.40 (d, J = 14.3 Hz, 1H), 2.65 (d, J = 14.3 Hz, 1H), 4.19-4.28 (m, 4H), 4.59 (s, 1H), 4.91 (s, 1H), 6.19 (d, J = 10.3 Hz, 1H), 6.56 (d, J = 10.3 Hz, 1H), 7.43-7.45 (m, 1H), 7.51-7.53 (m, 2H), 7.92 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0 (2C), 34.7, 55.3, 61.1, 62.4, 62.5, 115.1, 120.4, 122.9, 125.5, 126.4, 131.3, 131.7, 136.8, 143.6, 154.4, 169.6, 169.9, 174.4. HRMS (FAB) calcd $C_{20}H_{21}BrNO_4$: $[M + H]^+$, 418.0654; found: $[M + H]^+$, 418.0650.

Diethyl 5'-methoxy-2-methylenespiro[cyclohexane-1,3'-indol]-3-ene-5,5-dicarboxylate (9d). Yellow oil: IR (neat): 1732 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.22-1.30 (m, 6H), 2.38 (d, J = 14.3 Hz, 1H), 2.68 (d, J = 14.3 Hz, 1H), 3.84 (s, 3H), 4.19-4.27 (m, 4H), 4.58 (s, 1H), 4.89 (s, 1H), 6.17 (d, J = 10.3 Hz, 1H), 6.56 (d, J = 10.3 Hz, 1H), 6.86 (d, J = 2.6 Hz, 1H), 6.90 (dd, J = 8.6, 2.6 Hz, 1H), 7.56 (d, J = 8.6 Hz, 1H), 7.82 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9 (2C), 25.8, 35.2, 55.5, 55.7, 60.9, 62.3, 109.1, 113.6, 114.9, 121.9, 125.3, 131.6, 137.8, 143.0, 149.0, 158.9, 169.8, 170.1, 171.9. HRMS (FAB) calcd $C_{21}H_{24}NO_5$: $[M + H]^+$, 370.1654; found: $[M + H]^+$, 370.1653.

Asymmetric Synthesis of the Spiroindoline (8a) and Spiroindole (9a). To a stirred mixture of **5a** (30 mg, 0.080 mmol), $TsNH_2$ (20.5 mg, 0.12 mmol) and H_2O (1.4μl, 0.080) in THF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), (*R*)-SEGPHOS (4.9 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at 60 °C under argon. The mixture was stirred for 14 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (10:1 to 8:1) to give **8a** (15.7 mg, 38% yield, 65% ee [HPLC, Chiralcel-IC-3 column eluting with 65:35 *n*-hexane/ *i*-PrOH at 0.75 mL/min, t_1 = 17.98 min (major isomer), t_2 = 26.74 min (minor isomer)]} and **9a** {4.1 mg, 15% yield and 71 % ee [HPLC, Chiralcel-IC-3 column eluting with 65:35 *n*-hexane/ *i*-PrOH at 0.75 mL/min, t_1 = 16.03 min (major isomer), t_2 = 39.26 min (minor isomer)]}.

2,2-Diethyl 6,6-Dimethyl 3,5,6a,7-Tetrahydro-1*H*-indeno[1,7a-*b*]indole-2,2,6,6-tetracarboxylate (10a). To a stirred mixture of **5a** (30 mg, 0.080 mmol) and dimethyl malonate (13.7 μl, 0.12 mmol) in THF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.1 mg, 3.9 μmol, 2.5 mol %), dppb (3.4 mg, 8.0 μmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at room temperature under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (6:1) to give **10a** as a yellow oil (6.5 mg, 17% yield): IR (neat): 1735 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.13 (t, J = 7.2 Hz, 3H), 1.23-1.28 (m, 3H), 2.53 (d, J = 14.9 Hz, 1H), 2.66-2.90 (m, 5H), 3.68 (s, 3H), 3.73 (s, 3H), 4.00-4.34 (m, 5H), 4.76 (s, 1H), 5.70-5.76 (m, 1H), 6.53 (d, J = 8.0 Hz, 1H), 6.67 (dd, J = 8.0, 8.0 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 6.99 (dd, J =

8.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 29.6, 29.7, 38.6, 39.9, 52.6, 52.9, 53.9, 54.7, 61.5, 65.6., 74.2, 109.4, 118.0, 119.4, 123.6, 128.2, 135.0, 140.9, 149.6, 169.3, 170.6, 171.0, 171.8. HRMS (FAB) calcd $C_{25}H_{29}NO_8$: [M^+], 471.1893; found: [M^+] , 471.1901.

Diethyl 6,6-Diacetyl 5,6,6a,7-Tetrahydro-1*H*-indeno[1,7a-*b*]indole-2,2(3*H*)-dicarboxylate (10b). To a stirred mixture of **5a** (30 mg, 0.080 mmol) and acetyl acetone (25 µl, 0.24 mmol) in THF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (2.1 mg, 3.9 µmol, 2.5 mol %), dppb (3.4 mg, 8.0 µmol, 10 mol %), and Cs_2CO_3 (52 mg, 0.16 mmol) at room temperature under argon. The mixture was stirred for 3 h at this temperature, and H_2O was added to the mixture. The whole was extracted with EtOAc. The extract was washed with H_2O, brine and dried over $MgSO_4$. The filtrate was concentrated under reduced pressure to give an oily residue, which was purified by flash chromatography over NH_2 silica gel with *n*-hexane–EtOAc (6:1) to give **10b** as a yellow oil (17.5 mg, 50% yield): Yellow oil; IR (neat): 3406 (NH), 1728 (C=O); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.15 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 2.01 (s, 3H), 2.18 (s, 3H), 2.37 (d, *J* = 14.7 Hz, 1H), 2.64-2.73 (m, 3H), 2.84-2.91 (m, 2H), 4.04-4.20 (m, 4H), 4.43 (br s, 1H), 4.83 (s, 1H), 5.70-5.75 (m, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.70 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.91 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.00 (ddd, *J* = 8.0, 8.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 26.3, 28.8, 29.5, 36.3, 40.4, 54.2, 55.0, 61.6 (2C), 73.3., 79.5, 110.2, 117.6, 119.8, 123.4, 128.3, 136.0, 141.1, 149.4, 170.8, 171.7, 203.1, 204.8. HRMS (FAB) calcd $C_{25}H_{29}NO_6$: [M^+], 439.1995; found: [M^+], 439.2000.

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8 It is well known that some commercially available palladium(0) sources contain up to 40% palladium nanoparticles, and $Pd_2(dba)_3 \cdot CHCl_3$ is the purest of all palladium(0) sources, see: Zalesskiy, S. S.; Ananikov, V. P. *Organometallics* **2012**, *31*, 2302.

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10 At present, formation of **10** through intermediate **C** (path E) cannot be completely excluded. The author performed an additional experiment with a separately prepared propargyl tosylamide (S_N2 adduct from **5a**) to confirm that this reaction does not proceed via the first S_N2 reaction. In addition, compound **8a** was not obtained from spiroindoles **9a** under the reaction conditions.

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12 Cera, G.; Crispino, P.; Monari, M.; Bandini, M. *Chem. Commun.* **2011**, *47*, 7803.

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Chapter 3. Conclusions

1. Regio- and stereoselective construction of propargyl alcohol was developed based on a regioselective ring-opening reaction of 2-alkynyl-3-indolyloxirane at the 3-position. With this reduction as the key step, enantioselective formal total synthesis of (+)-lysergic acid was achieved.

2. A novel reaction for the palladium-catalyzed spirocyclization of propargyl chlorides using an external nucleophile for the divergent synthesis of tetracyclic indolines was developed. The observed regioselectivity of this reaction was found to be dependent on the external nucleophiles employed. The asymmetric reaction using a chiral catalyst afforded the spiroindole derivatives in moderate enantioselectivities (65–71% ee). This reaction is the first attempt for the catalytic asymmetric construction of the spirocenter onto a propargyl palladium.

In summary, the author developed novel methods for the efficient synthesis of heterocyclic scaffolds. The efficient synthetic method for construction of Ergot alkaloids' core structure was accomplished with this ring opening reaction of indolyloxiranes. Furthermore, a novel strategy has been developed for the synthesis of the fused indole-type compounds by palladium-catalyzed domino cyclization of allenic and propargylic compounds. These reactions will contribute to the synthetic strategy for complex natural products and bioactive compounds bearing an indole/indoline core structure.

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List of Publications

This study was published in the following papers.

Chapter 1

1. Formal Total Synthesis of (+)-Lysergic Acid via Zinc(II)-Mediated Regioselective Ring-Opening Reduction of 2-Alkynyl-3-indolyloxirane.
   Akira Iwata, Shinsuke Inuki, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno.
   J. Org. Chem. **2011**, *76*, 5506–5512.

Chapter 2

2. Synthesis of Fused Tetracyclic Spiroindoles via Palladium-Catalysed Cascade Cyclisation.
   Akira Iwata, Shinsuke Inuki, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno.
   Chem. Commun. **2014**, *50*, 298–300.

3. Convenient Synthesis of Spiroindole Derivatives via Palladium-Catalyzed Cyclization of Propargyl Chlorides.
   Akira Iwata, Shinsuke Inuki, Shinya Oishi, Nobutaka Fujii, and Hiroaki Ohno.
   Tetrahedron **2015**, *71*, 6580–6585.