NOVEL SYNTHESIS OF HETEROCYCLES USING NICKEL(0)-CATALYZED [2+2+2] COCYCLIZATION: CATALYTIC ASYMMETRIC SYNTHESIS OF ISOINDOLINE AND ISOQUINOLINE DERIVATIVES

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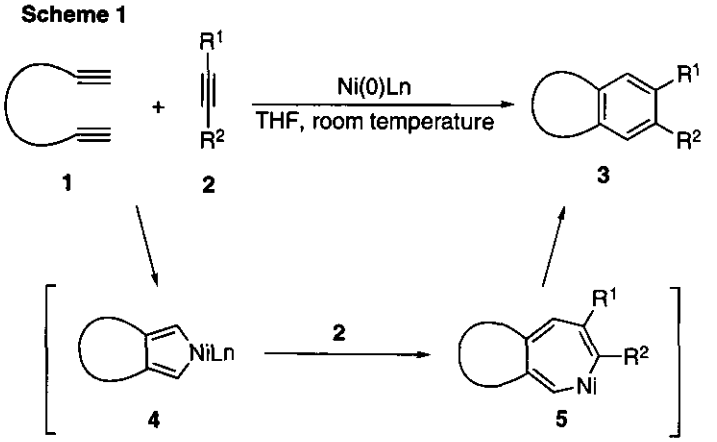
Abstract – A nickel(0)-catalyzed asymmetric [2+2+2] cocyclization has been realized for the first time. That involves conceptually new enantiotopic group selective formation of the nickelacyclopentadiene (**18**) and produces the isoindoline (**26a**) (73% ee, 78% conv. yield) and isoquinoline (**27b**) (54% ee, 62% yield) having benzylic chiral carbon centers.

A [2+2+2] cocyclization of α,ω-diynes and alkynes using a transition metal complex is important for the construction of aromatic ring in modern synthetic organic chemistry.[1,2] Recently, nickel(0)-promoted [2+2+2] cocyclization was reported.[3] The reaction mechanism was not clear, but it was speculated to involve the formation of a nickelacyclopentadiene (**4**) as an intermediate by oxidative cyclization of the two alkynes.[3,4] If the nickelacyclopentadiene (**4**) is truly an intermediate and then a seven-membered nickelacycle (**5**) is formed, the reaction should proceed using a catalytic amount of a low valent nickel complex analogous to a rhodium catalyzed cocyclization.[2]

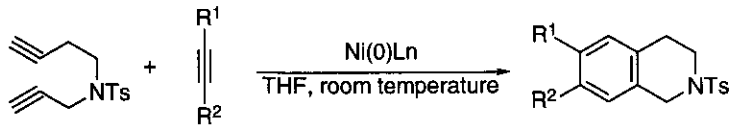
Scheme 1



Dedicated to Dr. Shigeru Oae (Prof. Emeritus of Tsukuba University) on the occasion of the 77th birthday.

Thus, we planned to synthesize the heterocycles by the nickel(0)-catalyzed [2+2+2] cocyclization of α,ω–diynes having nitrogen in a chain and alkynes.[5]

Scheme 2



6 **2** **7**

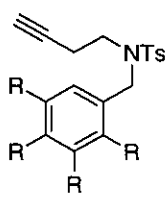
2a: R^1=CH_2OH, R^2=H
2b: R^1=R^2=TMS
2c: R^1=R^2=CH_2OH
2d: R^1=CH_2OH, R^2=TMS
2e: R^1=R^2=CO_2Me
2f: R^1=R^2=H (acetylene)

First of all, we examined the [2+2+2] cocyclization of diyne (**6**) and various alkynes. The nickel catalyzed [2+2+2] cocyclization of diyne (**6**) and monosubstituted alkyne (**2a**) in the presence of 10 mol % nickel(0) complex, generated from $Ni(acac)_2$ and DIBAH, smoothly proceeded to give an inseparable mixture of isoquinoline derivatives (**7a**) (2:1; the regio-isomers of the hydroxymethyl group on the aromatic ring) in 72% yield. However, disubstituted alkynes (**2b**, **2c** and **2d**) did not afford the cyclized products because of steric hindrance. When the reaction of **6** with dimethyl acetylenedicarboxylate (DMAD) (**2e**) was carried out in the presence of 10 mol % nickel(0) complex, only a small amount of the desired product (**7e**) (7% yield) was obtained in addition to **8** (27% yield) and **9**.

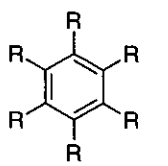
Table 1 [2+2+2] Cocyclization of 6 Affording the Isoindoline 7

alkyne[a]	Ni(0)Ln[b] (mol %)	ligand[c]	time (h)	yield (%)	SM recover (%)
2a	10	PPh_3	4.5	72[d]	—
2e	10	PPh_3	14	7	26
2e	10	PBu_3	22	35	30
2e	10	dppb	16	trace	89
2f	30	PPh_3	18	76	—

[a] 4 Eq of alkynes were used except for **2f**.
[b] Ni(0) complex was prepared from $Ni(acac)_2$ and DIBAH (2 eq to the Ni complex) in the presence of the ligand.
[c] Monodentate ligands (PPh_3 or PBu_3) were used in the ratio of 4 eq to the Ni complex, while bidentate ligand (dppb) was used in the ratio of 2 eq to the Ni complex.
[d] The ratio of the isomers (one of them: R^1=CH_2OH, R^2=H to the other: R^1=H, R^2=CH_2OH) was *ca.* 2 to 1.



8 (R=CO_2Me)

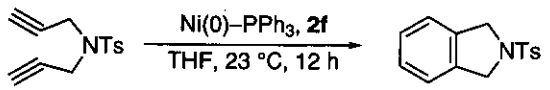


9 (R=CO_2Me)

Because it is considered that DMAD strongly coordinates to the low valent nickel complex owing to the back donation to the metal, we tried to examine the ligand effect. As expected, when PBu_3 was used as

the ligand, the yield of **7e** was improved (35% yield). Further, we found that it was possible to use gaseous acetylene as the alkyne. Treatment of **6** with 30 mol % nickel(0) complex in THF at room temperature under an atmosphere of acetylene (**2f**) gave the isoquinoline derivative (**7f**) in 76% yield. Subjection of **10** to the same conditions afforded the isoindoline derivative (**11**) in 91% yield.

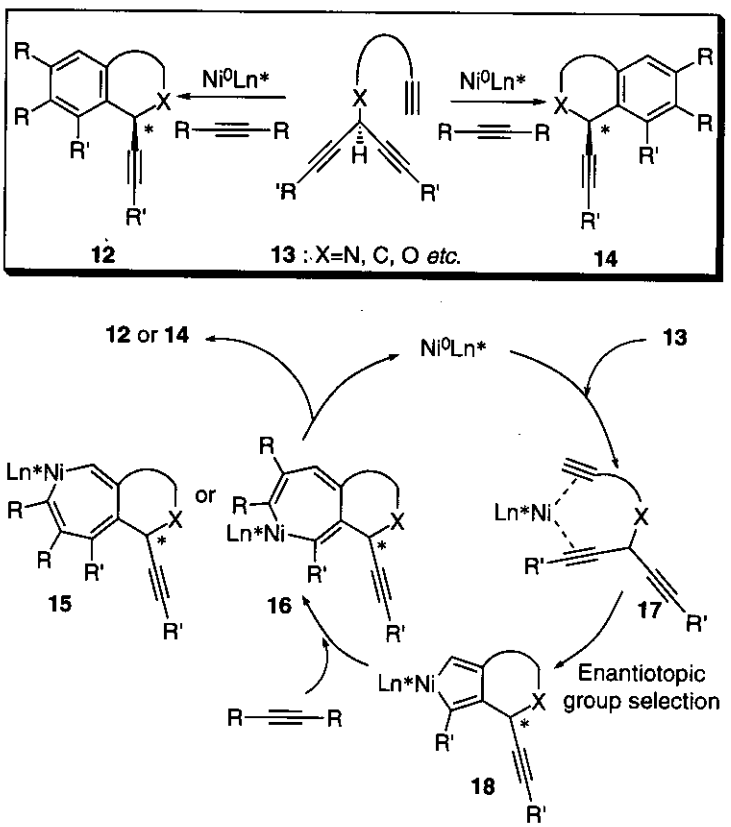
Scheme 3



10 **11** (91%)

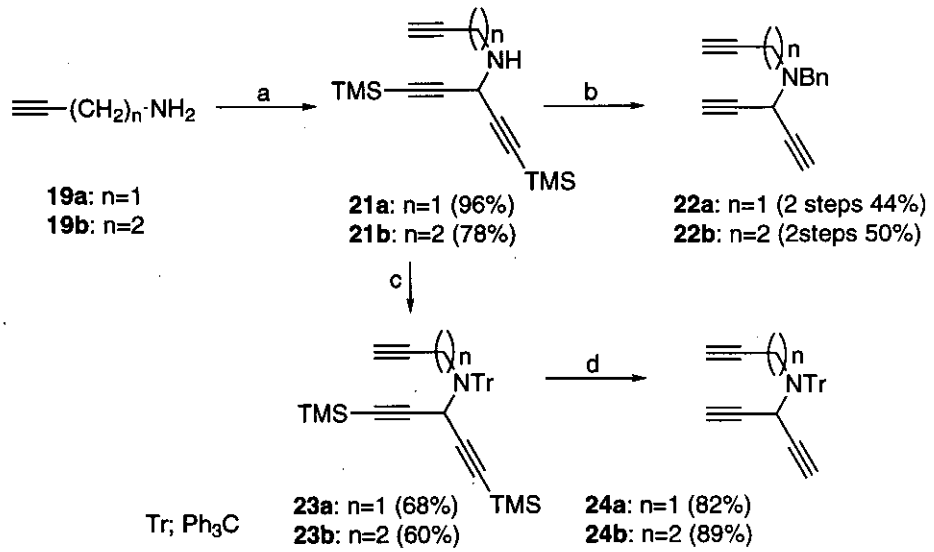
Having established a nickel(0)-catalyzed [2+2+2] cocyclization, we next turned our attention to the application of this cyclization to the catalytic asymmetric synthesis of isoindoline and isoquinoline derivatives having benzylic chiral carbon centers. Most analgesics such as morphine have chiral carbon centers at the benzylic position, and the construction of such centers is important for the synthesis of these compounds.[6,7] Our basic strategy is shown in Scheme 4, which involves conceptually new enantiotopic group selective formation of nickelacyclopentadiene.

Scheme 4



Two alkynes of the triyne (**13**) (one of them is a straight-chain alkyne, and the other is one of two branched alkynes) react with zerovalent nickel coordinated with a chiral ligand to give the nickelacyclopentadiene (**18**) in an optically active form *via* **17**. The insertion of alkyne into **18** would afford the nickelacycloheptatriene (**15**) or (**16**). Then reductive elimination would proceed, which provides the heterocycle (**12**) or (**14**) having the benzylic chiral carbon center. Thus, a catalytic asymmetric synthesis of isoindoline and isoquinoline would be realized. The staring materials (**23**~**28**) were synthesized as shown in Scheme 5.

Scheme 5[a]

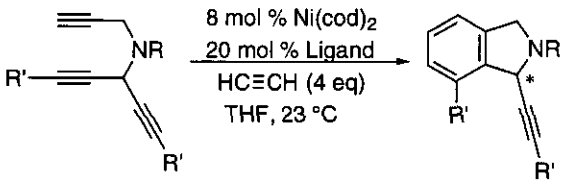


[a]Reaction conditions: (a) TMS—≡—CHO (**20**), $MgSO_4$, benzene, 23 °C; TMS—≡—H, BuLi, BF_3•Et_2O, THF, -78 °C; (b) BnBr, K_2CO_3, MeCN, 23 °C; Bu_4NF, THF, -78 °C; (c) Ph_3CCl, K_2CO_3, MeCN, 23 °C; (d) Bu_4NF, THF, 0 °C

The amine (**19a**) or (**19b**), having alkyne in a chain, was condensed with trimethylsilylpropynal (**20**) to give a corresponding imine, which was reacted with alkynylborane prepared from lithium acetylide and BF_3•Et_2O[8] producing triyne (**21a**) or (**21b**) in good yield, respectively. After protecting of amino group in **21a** or **21b** with benzyl group, resulting triyne was treated with Bu_4NF to afford triyne (**22a**) or (**22b**), having no substituents on the alkynes, respectively. On the other hand, protection of **21a** or **21b** with trityl group afforded **23a** or **23b**, which was also treated with Bu_4NF to give triyne (**24a**) or (**24b**) in good yield, respectively.

Initially, the [2+2+2] cocyclization of the triyne (**22a**) and gaseous acetylene in the presence of various chiral ligands was investigated. However, reproducible results for these reactions were not obtained because an excess amount of acetylene would act as an ligand to the nickel complex, which caused a partial dissociation of the chiral ligand from the metal. Thus, a THF solution of acetylene (*ca.* 0.5 M solution)

was prepared and the reaction of triyne (**22a**) and acetylene solution (4 equiv. to substrate) in the presence of 8 mol % $Ni(cod)_2$ and various chiral ligands (20 mol %) was investigated. Unfortunately, only a low enantiomeric excess of **25a** was obtained [e.g. (*R*)-BINAP[9a] → 4% ee, 22% yield; (–)-DIOP[9a] → 1% ee, 65% yield; (*S*,*S*)-BPPM[9a] → 2% ee, 52% yield; (*S*)-BINAPO[9b] → 7% ee, 34% yield]. However, it was found that the bulky substituents on the nitrogen atom affected the enantiomeric excess of the cyclized product (Table 2). Namely, the reaction of **24a** with acetylene in the presence of $Ni(cod)_2$ and (*S*,*S*)-BPPM as the chiral ligand afforded the isoindoline **27a** with 45% ee, 82% yield (run 3). The ee of isoindoline was improved in the reaction of **23a** having TMS groups on the alkynes. The reaction of **23a** with acetylene utilizing (*S*,*S*)-BPPM afforded the isoindoline (**26a**) in 60% ee, 92% yield (run 8), and we have found that the use of (*R*)-(*S*)-BPPFA[9c] gives **26a** in 73% ee (52% yield, 76% conversion yield).

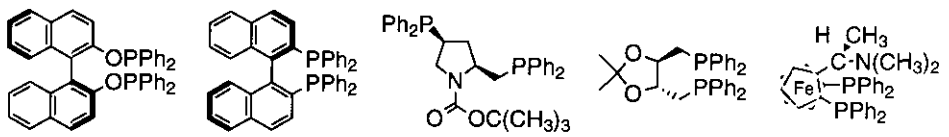


22a: R=Bn, R'=H
23a: R=Tr, R'=TMS
24a: R=Tr, R'=H

25a: R=Bn, R'=H
26a: R=Tr, R'=TMS
27a: R=Tr, R'=H

Table 2 Catalytic Asymmetric [2+2+2] Cocyclization of 23a and 24a

run	substrate	ligand	time (h)	yield (%)	ee (%)	SM recover (%)
1	**24a**	dppb	1.5	74	—	—
2		(*S*)-BINAPO	16	66	12	—
3		(*S*,*S*)-BPPM	2	82	45	—
4	**23a**	dppb	5	83	—	—
5		(*R*)-BINAP	140	57	22	18
6		(*S*)-BINAPO	115	52	18	14
7		(-)-DIOP	18	87	0	—
8		(*S*,*S*)-BPPM	18	92	60	—
9		(*R*)-(*S*)-BPPFA	150	52	73	33

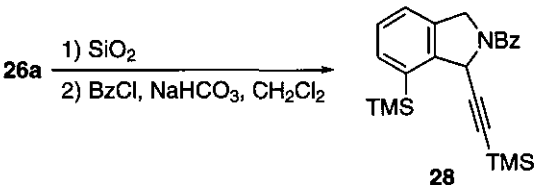


(*S*)-BINAPO (*R*)-BINAP (*S*,*S*)-BPPM (-)-DIOP (*R*)-(*S*)-BPPFA

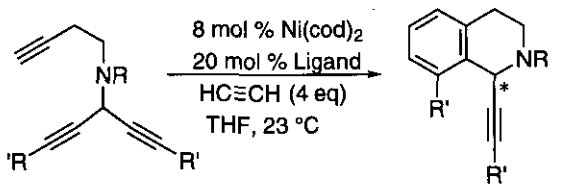
The ees of **25a** and **27a** were determined by hplc analysis with a chiral stationary phase column (**25a**: DAICEL CHIRALCEL OJ, hexane/2-propanol=9/1; **27a**: DAICEL CHIRALCEL OD, hexane/2-

propanol=9/1). In the case of **26a**, after converting to **28** by deprotection of the trityl group and successive protection with a benzoyl group, the ee of **28** was determined by hplc analysis (DAICEL CHIRALPAK AS, hexane/2-propanol=9/1). The absolute configurations of these isoindoline derivatives are still not determined.

Scheme 6



Subsequently, a [2+2+2] cocyclization of **22b**, **23b**, or **24b** affording the isoquinoline derivative was examined. In this case, the reaction of the triyne (**23b**), having TMS groups on the alkyne, with acetylene in the presence of 8 mol % $Ni(cod)_2$ and PPh_3 or dppb could not proceed. In the reaction of the triyne (**22b**) or (**24b**), having no substituents on the alkyne, with acetylene in the presence of 8 mol % $Ni(cod)_2$ and 20 mol % dppb, the isoquinoline (**25b**) or (**27b**) was obtained in 61% or 97% yield, respectively.

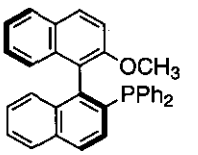


22b: R=Bn, R'=H
23b: R=Tr, R'=TMS
24b: R=Tr, R'=H

25b: R=Bn, R'=H
26b: R=Tr, R'=TMS
27b: R=Tr, R'=H

Table 3 Catalytic Asymmetric [2+2+2] Cocyclization of 24b

run	ligand	time (h)	yield of **27b** (%)	ee (%)	SM recover (%)
1	dppb	45	97	—	—
2	(*R*)-BINAP	137	—	—	82
3	(*S*,*S*)-BPPM	40	42	6	53
4	(*R*)-(*S*)-BPPFA	42	22	1	78
5	(*S*)-MeO-MOP[a]	1.5	36	58	—
6[b]	(*S*)-MeO-MOP[a]	1.5	62	54	—



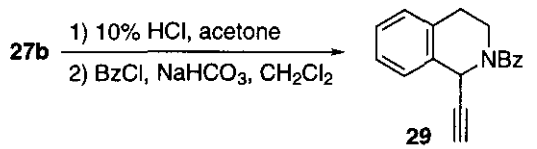
(*S*)-MeO-MOP

[a] The reaction was carried out using 40 mol % of (*S*)-MeO-MOP.
[b] Acetylene was used 10 eq to **24b**.

Next, a catalytic asymmetric [2+2+2] cocyclization of **22b** or **24b** utilizing either (*S*,*S*)-BPPM or (*R*)-(*S*)-BPPFA as a chiral bidentate ligand was investigated, giving the isoquinoline (**25b**) [(*S*,*S*)-BPPM; 1% ee, 16% yield] or (**27b**) (Table 3, runs 3 and 4) with only a low enantiomeric excess, respectively. On the other hand, the enantiomeric excess of **27b** increased to 58% in the reaction of **24b** using a chiral

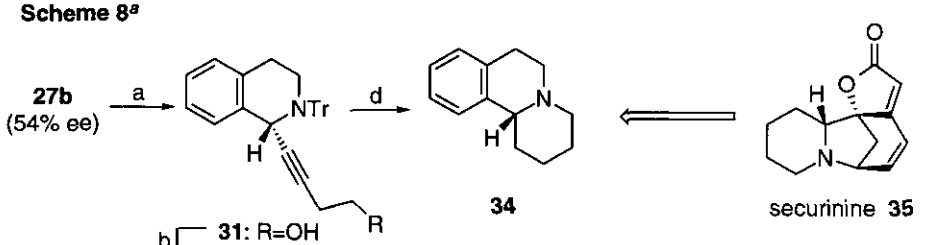
monodentate ligand, (*S*)-MeO-MOP.[10] It was very surprising to observe that, in the reaction of **23a** using (*S*)-MeO-MOP under the same conditions, **26a** was obtained in 0% ee, 43% yield. Though the reason was not clear, it was quite interesting that the cyclization of **24b** using a chiral monodentate ligand indicated a good result, although the isoindoline system (the cyclization of **23a**) was preferred for a chiral bidentate ligand. The ee of **25b** was determined by hplc analysis with a chiral stationary phase column (DAICEL CHIRALCEL OJ, hexane/ethanol=19/1). In the case of **27b**, the ee was determined by hplc analysis after converting to **29** (DAICEL CHIRALPAK AD, hexane/ethanol=19/1).

Scheme 7



The cyclized product (**27b**), which has a chiral carbon center at the benzylic position, is useful for the synthesis of optically active isoquinoline derivatives. We tried to convert **27b** into the known tricyclic amine (**34**), derived from natural alkaloid securinine (**35**),[11] in order to determine the absolute configuration of **27b**. Treatment of lithium acetylide of **27b** with **30** followed by the deprotection of TBDMS group afforded **31** in 52% yield (2 steps). The alcohol (**31**) was converted into chloride (**33**) *via* mesylate (**32**). After catalytic hydrogenation of triple bond in **33**, resultant saturated chloride was treated with K_2CO_3 in MeOH to afforded desired tricyclic amine (**34**). The absolute configuration of **34** was determined by comparison of $[\alpha]_D$ sign of the hydrochloride salt of **34** with its literature specific rotation.[11]

Scheme 8[a]



[a] Reaction conditions: (a) BuLi, HMPA, Et_2O, $BrCH_2CH_2OTBS$ (**30**), -78 °C~reflux; TBAF, THF, 52%; (b) MsCl, Et_3N, CH_2Cl_2, 82%; (c) LiCl, DMF, 60 °C, 70%; (d) 10% Pd/C, H_2, HCl-MeOH; K_2CO_3, MeOH, 47%

In conclusion, a nickel(0)-catalyzed asymmetric [2+2+2] cocyclization has been realized for the first time. Although the enantioselectivity is still modest, we could develop a conceptually new methodology for the construction of benzylic chiral carbon centers, which are important for the synthesis of biologically active substances.

EXPERIMENTAL SECTION

All manipulations were performed under an argon atmosphere unless otherwise mentioned. Solvents were distilled under an argon atmosphere from sodium-benzophenone (THF, Et_2O, toluene, and benzene) or CaH_2 (CH_2Cl_2, CH_3CN, DMSO, and DMF). Gaseous acetylene was purified by passage through a dry-ice trap and a drying tube containing $CaCl_2$. All other reagents and solvents were purified when necessary using standard procedures. Column chromatography was performed on silica gel 60 (230~400 mesh) using the indicated solvent. Infrared (ir) spectra were measured on JASCO FT/IR-5300 or Perkin Elmer FT-IR 1605. ^{1}H-Nmr spectra were recorded with JEOL JNM-EX 270 (270 MHz), JNM-EX 400 (400 MHz) or Bruker ARX-500 (500 MHz). Mass spectra (ms) were obtained with JEOL JMS-DX 303 (EI-ms) or JMS-HX 110 (FAB-ms). Optical rotation was measured on a JASCO DIP-370.

***N*-(3-Butynyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide (6).** To a suspension of NaH (60% wt dispersion in mineral oil, 600 mg, 15 mmol) in THF (25 ml) was added a solution of *N*-propynyl-*p*-toluenesulfonamide (2.0 g, 9.6 mmol) in DMF (15 ml) at 0 ℃, and the mixture was stirred at room temperature for 10 min. 1-(1-Ethoxy)ethoxy-3-bromopropane (2.53 g, 12 mmol) was added to the mixture at 0 ℃, and the resultant mixture was stirred at 45 ℃ for 2 h. To the mixture was added 10% HCl (2 ml) at 0 ℃, and the mixture was stirred at room temperature for 1 h. The mixture was extracted with AcOEt, and the organic layer was washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel chromatography (hexane/AcOEt, 1:1) to afford *N*-(3-hydroxypropyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide (2.48 g, 97%) as a yellowish solid. ***N*-(3-Hydroxypropyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide.** Ir (KBr) 3410, 3287, 2120, 1597, 1344, 1161 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.78 (2H, tt, *J*=6.5, 6.5 Hz), 2.04 (1H, t, *J*=2.4 Hz), 2.40 (3H, s), 3.30 (2H, t, *J*=6.5 Hz), 3.72 (2H, t, *J*=6.5 Hz), 4.11 (2H, d, *J*=2.4 Hz), 7.30 (2H, d, *J*=8.0 Hz), 7.75 (2H, d, *J*=8.0 Hz); EIms m/z 267 (M^+), 222, 155, 112, 91. Anal. Calcd for $C_{13}H_{17}NO_3S$: C, 58.41; H, 6.41; N, 5.24. Found: C, 58.41; H, 6.51; N, 5.22. To a stirred solution of *N*-(3-hydroxypropyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide (500 mg, 1.87 mmol) and MS 4A (3.6 g) in CH_2Cl_2 (37 ml) was added PCC (1.21 g, 5.6 mmol) at 0 ℃, and the mixture was stirred at room temperature for 1 h. The mixture was filtered through Florisil, and the Florisil was washed with Et_2O. The filtrate was concentrated, and the residue was purified by silica gel chromatography (hexane/AcOEt, 2:1) to afford *N*-(2-formylethyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide (422 mg, 89%) as a colorless solid. ***N*-(2-Formylethyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide.** Ir (KBr) 3277, 2737, 1724, 1597, 1364, 1161 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.05 (1H, t, *J*=2.5 Hz), 2.40 (3H, s), 2.84 (2H, t, *J*=6.5 Hz), 3.49 (2H, t, *J*=6.5 Hz), 4.11 (2H, t, *J*=2.5 Hz), 7.30 (2H, d, *J*=8.0 Hz), 7.70 (2H, d, *J*=8.0 Hz), 9.80 (1H, br s); EIms m/z 265 (M^+), 237, 222, 155, 110, 91. Anal. Calcd for $C_{13}H_{15}NO_3S$: C, 58.85; H, 5.70; N, 5.28. Found: C, 58.87; H, 5.73; N, 5.26. To a stirred solution of carbon tetrabromide (1.12 g, 3.38 mmol) in CH_2Cl_2 (22 ml) was added PPh_3 (1.75 g, 6.67 mmol) at 0 ℃, and the mixture was stirred at the same temperature for 30 min. A solution of *N*-(2-formylethyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide (422 mg, 1.67 mmol) in CH_2Cl_2 (4.4 ml) was added to the mixture at 0 ℃, and the mixture was stirred for 5 min. The reaction mixture was quenched by addition of H_2O, and extracted with AcOEt. The organic layer was washed with

brine, and dried over $MgSO_4$. After removal of the solvent, and the residue was purified by silica gel chromatography (hexane/AcOEt, 4:1) to afford *N*-(4,4-dibromo-3-butenyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide (620 mg, 88%) as a yellowish solid. ***N*-(4,4-Dibromo-3-butenyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide**. Ir (KBr) 1622, 1597, 1348, 1161 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.08 (1H, t, *J*=2.4 Hz), 2,40 (2H, dt, *J*=7.1, 7.1 Hz), 2.43 (3H, s), 3.30 (2H, t, *J*=7.1 Hz), 4.14 (2H, t, *J*=2.4 Hz), 6.42 (1H, t, *J*=7.1 Hz), 7.30 (2H, d, *J*=8.0 Hz), 7.70 (2H, d, *J*=8.0 Hz); EIms m/z 421 (M^+), 302, 222, 155, 91. Anal. Calcd for $C_{14}H_{15}NO_2Br_2S$: C, 39.93; H, 3.59; N, 3.33; S, 7.61; Br, 37.94. Found: C, 39.80; H, 3.56; N, 3.42; S, 7.63; Br, 38.13. To a solution of *N*-(4,4-dibromo-3-butenyl)-*N*-(2-propynyl)-*p*-toluenesulfonamide (618 mg, 1.47 mmol) in THF (30 ml) was added BuLi (1.6 *M* in hexane, 3.6 ml, 5.9 mmol) at -78 ℃, and the mixture was stirred at the same temperature for 10 min. The reaction mixture was quenched by addition of saturated aq. NH_4Cl, and extracted with AcOEt. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent, and the residue was purified by silica gel chromatography (hexane/AcOEt, 5:1) to afford **6** (318 mg, 82%) as a colorless solid: Ir (KBr) 3260, 2118, 1597, 1448, 1342, 1160 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.01 (1H, t, *J*=2.6 Hz), 2.08 (1H, t, *J*=2.6 Hz), 2.38 (2H, dt, *J*=2.6, 7.3 Hz), 2.53 (3H, s),3.38 (2H, t, *J*=5.8 Hz), 4.21 (2H, d, *J*=2.6 Hz), 7.50 (2H, d, *J*=8.1 Hz), 7.74 (2H, d, *J*=8.1 Hz); EIms m/z 261 (M^+), 222, 155, 91. Anal. Calcd for $C_{14}H_{15}NO_2S$: C, 64.37; H, 5.75; N, 5.36. Found: C, 64.33; H, 5.80; N, 5.35.

Typical Procedure for Cyclization of 6 with DMAD. To a stirred solution of $Ni(acac)_2$ (5.1 mg, 0.02 mmol) and Bu_3P (20 μl, 0.08 mmol) in THF (10 ml, degassed through freeze-pump-thaw cycles) was added DIBAH (1.0 *M* in hexane, 40 μl, 0.04 mmol) at 0 ℃, and the mixture was stirred at room temperature for 10 min. To the catalyst solution was added successively a solution of **6** (52 mg, 0.20 mmol) in degassed-THF (1.5 ml) and DMAD (98 μl, 0.80 mmol) at 0 ℃, and the mixture was stirred at room temperature for 22 h. Then, the solvent was evaporated and the residue was purified by silica gel chromatography (hexane/AcOEt, 4:1~2:1~1:1) to afford the desired product **7e** as a colorless oil (28 mg, 35%).

6,7-Bis(methoxycarbonyl)-2-*p*-toluenesulfonyl-1,2,3,4-tetrahydroisoquinoline (7e). Ir (neat) 2952, 1732, 1436, 1287, 1165 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.41 (3H, s), 2.95 (2H, t, *J*=5.8 Hz), 3.36 (2H, t, *J*=5.8 Hz), 3.85 (6H, s), 4.24 (2H, s), 7.25~7.37 (4H, m), 7.66 (2H, d, *J*=8.1 Hz); EIms m/z 403 (M^+), 371, 349, 248, 216, 91; HR-EIms calcd for $C_{20}H_{21}NO_6S$ 403.1090, found 403.1079.

Typical Procedure for Cyclization of 6 with Gaseous Acetylene. To a stirred solution of $Ni(acac)_2$ (15.4 mg, 0.06 mmol) and PPh_3 (63 mg, 0.24 mmol) in degassed-THF (10 ml) was added DIBAH (1.0 *M* in hexane, 0.12 ml, 0.12 mmol) at 0 ℃, and the mixture was stirred at room temperature for 10 min. To the catalyst solution was added a solution of **6** (52 mg, 0.20 mmol) in degassed-THF (1.5 ml), and the argon atmosphere in the reaction vessel was exchanged to acetylene. After the reaction mixture being stirred at room temperature for 18 hours, the solvent was evaporated, and the residue was purified by silica gel chromatography (hexane/AcOEt, 4:1) to afford **7f**[12] as a colorless solid (44 mg, 76%).

Typical Procedure for Cyclization of 10 with Gaseous Acetylene. To a stirred solution of $Ni(acac)_2$ (10.3 mg, 0.04 mmol) and PPh_3 (42 mg, 0.16 mmol) in degassed-THF (10 ml) was added DIBAH (1.0 *M* in hexane, 80 μl, 0.08 mmol) at 0 ℃, and the mixture was stirred at room temperature for

10 min. To the catalyst solution was added a solution of **10**[13] (50 mg, 0.20 mmol) in degassed-THF (1.5 ml), and the argon atmosphere in the reaction vessel was exchanged to acetylene. After the reaction mixture being stirred at room temperature for 12 h, the solvent was evaporated, and the residue was purified by silica gel chromatography (hexane/AcOEt, 4:1) to afford **11**[14] as a colorless solid (50 mg, 91%).

***N*-[Bis(trimethylsilylethynyl)methyl]-2-propynylamine (21a).** To a stirred solution of **20** (631 mg, 5.0 mmol) in benzene (5.0 ml) was added successively propargyl amine(**19a**)(0.34 ml, 5.0 mmol) and $MgSO_4$ (700 mg, 5.8 mmol) at 0 ℃, then the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to afford corresponding crude imine (987 mg) as a yellowish oil. To a stirred solution of trimethylsilylacetylene (1.4 ml, 10.0 mmol) in THF (10 ml) was added BuLi (1.6 *M* in hexane, 6.3 ml, 10.0 mmol) at -78 ℃, and the mixture was stirred at the same temperature for 30 min. Then, BF_3•Et_2O (1.6 ml, 10.0 mmol) was added to the resultant mixture at -78 ℃, and the mixture was stirred for 10 min. To the resultant alkynylborane solution was added a solution of crude imine (obtained above, 987 mg) in THF (5.0 ml) at -78 ℃, and the mixture was stirred at the same temperature for 10 min. The mixture was quenched by addition of saturated aq. NH_4Cl, and extracted with AcOEt. The organic layer was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel chromatography (hexane/AcOEt, 9:1) to give **21a** (1.26 g, 96%) as a yellowish oil: Ir (neat) 3310, 3270, 2955, 2170 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.18 (18H, s), 2.21 (1H, t, *J*=2.4 Hz), 3.54 (2H, d, *J*=2.4 Hz), 4.51 (1H, s); EIms m/z 261 (M^+), 246, 222, 188; HR-EIms calcd for $C_{14}H_{23}NSi_2$ 261.1369, found 261.1360. Anal. Calcd for $C_{14}H_{23}NSi_2$: C, 64.30; H, 8.86; N, 5.36. Found: C, 64.47; H, 8.74; N, 5.30.

***N*-[Bis(trimethylsilylethynyl)methyl]-3-butynylamine (21b).** Following the procedure for **21a**, **19b** (346 mg, 5.0 mmol) and **20** (631 mg, 5.0 mmol) were converted into crude imine, which was treated with alkynylborane generated from trimethylsilylacetylene (1.4 ml, 10 mmol), BuLi (1.6 M in hexane, 6.3 ml, 10 mmol), and BF_3•Et_2O. After workup, the residue was purified by silica gel chromatography (hexane/AcOEt, 9:1) to give **21b** (1.08 g, 78%) as a yellowish oil: Ir (neat) 3314, 3291, 2173 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.18 (18H, s), 1.69 (1H, brs), 2.01 (1H, t, *J*=2.6 Hz), 2.44 (2H, dt, *J*=2.6, 6.6 Hz), 2.90 (2H, t, *J*=6.6 Hz), 4.41 (1H, s); EIms m/z 274 (M^+-1), 260, 236, 207, 179. Anal. Calcd for $C_{15}H_{25}NSi_2$: C, 65.39; H, 9.15; N, 5.08. Found: C, 65.42; H, 9.06; N, 5.05.

***N*-Benzyl-*N*-(1-ethynyl-2-propynyl)-2-propynylamine (22a).** To a stirred solution of **21a** (126 mg, 0.48 mmol) in MeCN (5.0 ml) were added K_2CO_3 (0.30 g, 2.2 mmol) and benzyl bromide (0.24 ml, 2.0 mmol), and the mixture was stirred at room temperature for 16 h. The mixture was filtered, and the filtrate was evaporated to afford the crude benzylamine. To a stirred solution of crude benzylamine in THF (5.0 ml) was added tetrabutylammonium fluoride (1 *M* in THF, 2.0 ml, 2.0 mmol) at –78 ℃, and the mixture was stirred at the same temperature for 10 min. The reaction mixture was quenched by addition of H_2O, and extracted with AcOEt. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel chromatography (hexane/AcOEt, 9:1) to give **22a** (44 mg, 44% in 2 steps) as a yellowish oil: Ir (neat) 3292, 2818, 2120, 1456 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.24 (1H, t, *J*=2.3 Hz), 2.42 (2H, d, *J*=2.4 Hz), 3.41 (2H, d, *J*=2.3 Hz),

3.82 (2H, s), 4.63 (1H, t, *J*=2.4 Hz),. 7.21~7.40 (5H, m); EIms m/z 207 (M^+), 167, 149, 91; HR-EIms calcd for $C_{15}H_{13}N$ 207.1048, found 207.1039.

***N*-Benzyl-*N*-(1-ethynyl-2-propynyl)-3-butynylamine (22b).** Following the procedure for **22a**, **21b** (1.05 g, 3.81 mmol) was converted into crude benzylamine by treatment of K_2CO_3 (1.10 g, 8.0 mmol) and benzyl bromide (0.95 ml, 8.0 mmol), which was treated with tetrabutylammonium fluoride (1 *M* in THF, 15 ml, 15 mmol). After workup, the residue was purified by silica gel chromatography to give **22b** (422 mg, 50% in 2 steps) as a yellowish oil: Ir (neat) 3293, 2118 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.84 (1H, t, *J*=2.5 Hz), 2.24 (2H, d, *J*=2.6 Hz), 2.27 (2H, dt, *J*=2.5, 7.0 Hz), 2.74 (2H, t, *J*=7.0 Hz), 3.62 (2H, s), 4.27 (1H, t, *J*=2.6 Hz), 7.08~7.26 (5H, m); EIms m/z 221 (M^+), 182, 91, 43. Anal. Calcd for $C_{16}H_{15}N$: C, 86.84; H, 6.83; N, 6.33. Found: C, 86.80; H, 6.95; N, 6.28.

***N*-[Bis(trimethylsilylethynyl)methyl]-*N*-triphenylmethyl-2-propynylamine (23a).** A mixture of **21a** (427 mg, 1.64 mmol), triphenylmethyl chloride (1.3 g, 5 mmol), and K_2CO_3 (1.1 g, 8 mmol) in MeCN (5 ml) was stirred at room temperature for 4 h. The reaction mixture was filtered, and the filtrate was evaporated. The residue was purified by silica gel chromatography (hexane/AcOEt, 19:1) to give **23a** (565 mg, 68%) as a colorless solid: Ir (neat) 3312, 2174 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.09 (18H, s), 2.18 (1H, t, *J*=2.5 Hz), 3.53 (2H, d, *J*=2.5 Hz), 4.91 (1H, s), 7.14~7.29 (9H, m), 7.54~7.57 (6H, m); EIms m/z 503 (M^+), 488, 426, 260, 243, 165. Anal. Calcd for $C_{33}H_{37}NSi_2$: C, 78.67; H, 7.40; N, 2.78. Found: C, 78.76; H, 7.55; N, 2.58.

***N*-[Bis(trimethylsilylethynyl)methyl]-*N*-triphenylmethyl-3-butynylamine (23b).** Following the procedure for **23a**, **21b** (551 mg, 2.0 mmol) was converted into crude tritylamine by treatment of triphenylmethyl chloride (2.2 g, 8 mmol) and K_2CO_3 (1.1 g, 8 mmol), which was purified by silica gel chromatography to give **23b** (621 mg, 60%) as a colorless solid: Ir (Nujol) 3314, 2171 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.11 (18H, s), 1.99 (1H, t, *J*=2.5 Hz), 2.79 (2H, m), 2.91 (2H, t, *J*=6.8 Hz), 4.84 (1H, s), 7.14~7.29 (9H, m), 7.57 (6H, d, *J*=7.5 Hz); EIms m/z 517 (M^+), 464, 444, 243, 165. Anal. Calcd for $C_{34}H_{39}NSi_2$: C, 78.86; H, 7.59; N, 2.70. Found: C, 78.73; H, 7.52; N, 2.44.

***N*-(1-Ethynyl-2-propynyl)-*N*-triphenylmethyl-2-propynylamine (24a).** To a stirred solution of **23a** (290 mg, 0.58 mmol) in THF (10 ml) was added tetrabutylammonium fluoride (1 *M* in THF, 2.0 ml, 2.0 mmol) at 0 ℃, and the mixture was stirred for 15 min. The reaction mixture was quenched by addition of H_2O, and extracted with AcOEt. The organic layer was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by silica gel chromatography (hexane/AcOEt, 9:1) to give **24a** (170 mg, 82%) as a colorless solid: Ir (neat) 3295, 3288 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.20 (2H, d, *J*=2.5 Hz), 2.28 (1H, t, *J*=2.5 Hz), 2.57 (2H, d, *J*=2.5 Hz), 4.98 (1H, t, *J*=2.5 Hz), 7.16~7.38 (9H, m), 7.57 (6H, d, *J*=7.4 Hz); EIms m/z 359 (M^+), 296, 282, 243, 165. Anal. Calcd for $C_{27}H_{21}N$: C, 90.22; H, 5.89; N, 3.90. Found: C, 90.32; H, 6.01; N, 3.63.

***N*-(1-Ethynyl-2-propynyl)-*N*-triphenylmethyl-3-butynylamine (24b).** Following the procedure for **24a**, **23b** (250 mg, 0.48 mmol) was converted into crude tritylamine by treatment of tetrabutylammonium fluoride (1 *M* in THF, 1.5 ml, 1.5 mmol), which was purified by silica gel chromatography (hexane/CH_2Cl_2, 4:1~3:1) to give **24b** (159 mg, 89%) as a colorless solid: Ir (Nujol) 3310, 3294, 1597 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.01 (1H, t, *J*=2.5 Hz), 2.19 (2H, d, *J*=2.5 Hz), 2.86 (2H, m),

2.94 (2H, t, *J*=7.0 Hz), 4.92 (1H, t, *J*=2.5 Hz), 7.16~7,54 (9H, m), 7.57 (6H, d, *J*=7.4 Hz); EIms m/z 373 (M^+), 334, 243, 165. Anal. Calcd for $C_{28}H_{23}N$: C, 90.04; H, 6.21; N, 3.75. Found: C, 90.00; H, 6.34; N, 3.55.

Typical Experimental Procedure for the Catalytic Asymmetric [2+2+2] Cocyclization of 23a with Acetylene (Table 2, run 9). To a solution of $Ni(cod)_2$ (8 mol % to **23a**) and (*R*)-(*S*)-BPPFA (20 mol % to **23a**) in degassed-THF was added a solution of **23a** in degassed-THF and then a solution of acetylene (0.50 M solution in degassed-THF, 4 equiv. to **23a**) at 0 ℃. After being stirred for 150 h at room temperature, the reaction mixture was concentrated. The residue was purified by silica gel column chromatography to afford **26a** (52%, 73% ee) as a colorless solid, and to recover **23a** (33%).

***N*-Benzyl-1-ethynylisoindoline (25a).** Ir (neat) 3280 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.46 (1H, d, *J*=2.3 Hz), 3.75 (1H, dd, *J*=1.8, 12.8 Hz), 3.83 (1H, d, *J*=12.8 Hz), 3.97 (1H, br d, *J*=12.8 Hz), 4.27 (1H, d, *J*=12.8 Hz), 4.76 (1H, br s), 7.13~7.45 (9H, m); EIms m/z 233 (M^+), 206, 142, 91; HR-EIms calcd for $C_{17}H_{15}N$ 233.1204, found 233.1177.

1-Trimethylsilylethynyl-7-trimethylsilyl-*N*-triphenylmethylisoindoline (26a). Ir (neat) 2957, 2166, 1741, 1489, 1448, 1248 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 0.19 (18H, s), 4.13 (1H, d, *J*=16.1 Hz), 4.60 (1H, d, *J*=16.1 Hz), 5.13 (1H, s), 6.74 (1H, d, *J*=7.4 Hz), 6.89 (1H, t, *J*=7.4 Hz), 7.01~7.18 (10H, m), 7.55~7.60 (6H, m); EIms m/z 529 (M^+), 452, 286, 243, 165, 73. Anal. Calcd for $C_{35}H_{39}NSi_2$: C, 79.34; H, 7.42; N, 2.64. Found: C, 79.45; H, 7.57; N, 2.55.

1-Ethynyl-*N*-triphenylmethylisoindoline (27a). Ir (neat) 3297, 3056, 1595, 1488, 1448 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.41 (1H, d, *J*=2.3 Hz), 4.13 (1H, d, *J*=15.9 Hz), 4.63 (1H, d, *J*=15.9 Hz), 5.09 (1H, d, *J*=2.3 Hz), 6.73~6.76 (1H, m), 6.86~6.93 (2H, m), 7.04~7.25 (10H, m), 7.58~7.61 (6H, m); EIms m/z 385 (M^+), 308, 243, 165; HR-EIms calcd for $C_{29}H_{23}N$ 385.1831, found 385.1854.

***N*-Benzoyl-1-trimethylsilylethynyl-7-trimethylsilylisoindoline (28).** After deprotection of the trityl group in **26a**, the crude resultant amine (4.0 mg, 0.014 mmol) was treated with $NaHCO_3$ (6.0 mg, 0.070 mmol) and benzoyl chloride (4 μl, 0.03 mmol) in CH_2Cl_2 (1.0 ml) at 0 ℃ for 10 min. The reaction mixture was diluted with AcOEt, and the mixture was washed with saturated aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by preparative tlc (hexane/AcOEt, 9:1) to afford **28** (9.5 mg, 71%) as a yellowish oil: Ir (neat) 2170, 1645 cm^{-1}; ^{1}H-nmr ($CDCl_3$, at 23 ℃) δ 0.05 and 0.14 (total 9H, two s), 0.26 and 0.44 (total 9H, two s), 4.55 (1/2H, d, *J*=14.0 Hz), 4.88 (1/2H, d, *J*=15.6 Hz), 4.97 (1/2H, d, *J*=14.0 Hz), 5.11 (1/2H, d, *J*=15.6 Hz), 5.73 & 6.35 (total 1H, two s), 7.14~7.29 (2H, m), 7.46 (4H, m), 7.63 (2H, m); EIms m/z 391 (M^+), 376, 318, 286, 105; HR-EIms calcd for $C_{23}H_{29}NOSi_2$ 391.1788, found 391.1766. Anal. Calcd for $C_{23}H_{29}NOSi_2$: C, 70.53; H, 7.46; N, 3.58. Found: C, 70.16; H, 7.56; N, 3.58.

Typical Experimental Procedure for the Catalytic Asymmetric [2+2+2] Cocyclization of 24b with Acetylene (Table 3, run 6). To a solution of $Ni(cod)_2$ (8 mol % to **24b**) and (*S*)-MeO-MOP (40 mol % to **24b**) in degassed-THF was added a solution of **24b** in degassed-THF and then a solution of acetylene (0.50 M solution in degassed-THF, 10 equiv. to **24b**) at 0 ℃. After being stirred for 1.5 h at room temperature, the reaction mixture was concentrated. The residue was purified by silica gel column chromatography to afford **27b** (62%, 54% ee).

***N*-Benzyl-1-ethynyl-1,2,3,4-tetrahydroisoquinoline (25b).** Ir (neat) 3287, 2920, 2826, 1495, 1453 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.47 (1H, d, *J*=2.2 Hz), 2.74~2.87 (2H, m), 2.87~2.95 (2H, m), 3.85 (1H, d, *J*=13.2 Hz), 3.88 (1H, d, *J*=13.2 Hz), 4.60 (1H, br s), 7.11~7.46 (9H, m); EIms m/z 247 (M^+), 220, 156, 128, 91; HR-EIms calcd for $C_{18}H_{17}N$ 247.1361, found 247.1335.

(*S*)-1-Ethynyl-*N*-triphenylmethyl-1,2,3,4-tetrahydroisoquinoline (27b). Ir (neat) 3298, 1595 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.72 (1H, d, *J*=2.6 Hz), 2.77 (1H, dd, *J*=4.5, 16.5 Hz), 3.06 (1H, dt, *J*=4.5, 11.6 Hz), 3.19~3.28 (1H, m), 3.32~3.41 (1H, m), 5.03 (1H, br s), 7.02 (1H, d, *J*=7.5 Hz), 7.12~7.25 (12H, m), 7.51 (6H, d, *J*=7.8 Hz); EIms m/z 399 (M^+), 322, 279, 243, 165; HR-EIms calcd for $C_{30}H_{25}N$ 399.1987, found 399.2968. Anal. Calcd for $C_{30}H_{25}N$: C, 90.19; H, 6.31; N, 3.51. Found: C, 90.11; H, 6.38; N, 3.53. $[\alpha]_D^{21}$ -3.48°(*c* 0.69, $CHCl_3$) (58% ee).

(*S*)-*N*-Benzoyl-1-ethynyl-1,2,3,4-tetrahydroisoquinoline (29). To a stirred solution of **27b** (29 mg, 0.073 mmol) in acetone (2.0 ml) was added 2*M* HCl (0.1 ml) at 0 ℃, then the mixture was stirred at 0 ℃ for 1 h. The reaction mixture was diluted with CH_2Cl_2, and extracted with H_2O. The combined aqueous layer was made alkaline by addition of saturated aq. $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with brine, and dried over $MgSO_4$. After removal of the solvent, the crude isoquinoline (9 mg) was obtained. To a stirred solution of the crude isoquinoline (9 mg) in CH_2Cl_2 (2 ml) was added $NaHCO_3$ (25 mg, 0.3 mmol) and benzoyl chloride (14 μl, 0.12 mmol) at 0 ℃, and the mixture was stirred at the same temperature for 15 min. The reaction mixture was diluted with AcOEt, and the solution was washed with saturated aq. $NaHCO_3$ and brine, and dried over $MgSO_4$. After removal of the solvent, the residue was purified by preparative tlc (hexane/AcOEt, 4:1) to afford **29** (9.1 mg, 48% in 2 steps) as a colorless oil: Ir (neat) 3284, 2111, 1635, 1418 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.44 (1H, br s), 2.85 (1H, br s), 3.64 (1H, br s), 3.90 (1/2H, br s), 4.77 (1/2H, br s), 5.54 (1/2H, br s), 6.45 (1/2H, br s), 7.11 (9H, m); EIms m/z 261 (M^+), 232, 217, 156, 105, 77; HR-EIms calcd for $C_{18}H_{15}NO$ 261.1154, found 261.1127. $[\alpha]_D^{20}$ -83.2°(*c* 0.54, $CHCl_3$) (58% ee).

(*S*)-1-(4-Hydroxy-1-butynyl)-*N*-triphenylmethyl-1,2,3,4-tetrahydroisoquinoline (31). To a stirred solution of **27b** (25.7 mg, 0.064 mmol) in Et_2O (1 ml) was added BuLi (1.6 *M* in hexane, 0.05 ml, 0.08 mmol) and HMPA (0.014 ml, 0.08 mmol) at -78 ℃, and the mixture was stirred at 0 ℃ for 10 min. To the resultant solution was added 2-*tert*-butyldimethylsilyloxy-1-bromoethane (**30**) (0.017 ml, 0.084 mmol) at -78 ℃, and the mixture was refluxed for 3 h. To the reaction mixture was added saturated aq. NH_4Cl, and the solution was extracted with AcOEt. The organic layer was washed with brine, and dried over $MgSO_4$. After removal of the solvent, the residue was dissolved in THF (1 ml), and tetrabutylammonium fluoride (1 *M* in THF, 1 ml, 1 mmol) was added to the mixture at room temperature. After being stirred for 1 h, the reaction mixture was diluted with AcOEt, and the solution was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent , the residue was purified by silica gel column chromatography (hexane/AcOEt, 2:1) to afford **31** (15 mg, 52% in 2 steps) as a colorless oil: Ir (neat) 3384, 1595, 1490, 1448 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 1.94 (2H, dt, *J*=1.8, 6.2 Hz), 2.75~2.85 (1H, m), 2.99~3.07 (1H, m), 3.24~3.39 (4H, m), 5.06 (1H, br d, *J*=1.8 Hz), 7.01 (1H, d, *J*=7.4 Hz), 7.11~7.29 (12H, m), 7.52 (6H, d, *J*=7.4 Hz); EIms m/z 443 (M^+), 412, 366, 243, 165; HR-EIms calcd for $C_{32}H_{29}NO$ 443.2249, found 443.2249. $[\alpha]_D^{19}$ -7.5°(*c* 1.19, $CHCl_3$) (54% ee).

(*S*)-1-(4-Methanesulfonyloxy-1-butynyl)-*N*-triphenylmethyl-1,2,3,4-tetrahydroisoquinoline (32). A solution of **31** (12 mg, 0.0264 mmol), triethylamine (11 µl, 0.08 mmol), and methanesulfonyl chloride (4 µl, 0.05 mmol) in CH_2Cl_2 (0.5 ml) was stirred at 0 ℃ for 20 min. To the reaction mixture was added saturated aq. $NaHCO_3$, and the mixture was extracted with AcOEt. The organic layer was washed with H_2O, brine, and dried over $MgSO_4$. After removal of the solvent , the residue was purified by silica gel column chromatography (hexane/AcOEt, 1:1) to afford **32** (11 mg, 82%) as a colorless oil: Ir (neat) 1490, 1448, 1359, 1175 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.09 (2H, dt, *J*=1.9, 7.0 Hz), 2.69 (3H, s), 2.72~2.79 (1H, m), 2.95~3.03 (1H, m), 3.12~3.34 (2H, m), 3.82 (2H, t, *J*=7.0 Hz), 5.01 (1H, br d, *J*=1.9 Hz), 6.98 (1H, d, *J*=7.5 Hz), 7.09~7.27 (12H, m), 7.51 (6H, br d, *J*=7.4 Hz); EIms m/z 521 (M^+), 444, 426, 278, 243, 165; HR-EIms calcd for $C_{33}H_{31}NO_3S$ 521.2025, found 521.2025. $[\alpha]_D^{17}$ -10.8°(*c* 1.13, $CHCl_3$) (54% ee).

(*S*)-1-(4-Chloro-1-butynyl)-*N*-triphenylmethyl-1,2,3,4-tetrahydroisoquinoline (33). A solution of **32** (9 mg, 0.017 mmol) and LiCl (100 mg) in DMF (1 ml) was stirred at 60 ℃ for 1 h. The reaction mixture was diluted with AcOEt, and the solution was washed with H_2O and brine, and dried over $MgSO_4$. After removal of the solvent , the residue was purified by silica gel column chromatography (hexane/AcOEt, 9:1) to afford **33** (6 mg, 70%) as a colorless oil: Ir (neat) 1490, 1448 cm^{-1}; ^{1}H-nmr ($CDCl_3$) δ 2.03 (2H, dt, *J*=1.7, 7.8 Hz), 2.73~2.82 (1H, m), 2.92~3.02 (1H, m), 3.09 (2H, t, *J*=7.8 Hz), 3.14~3.36 (2H, m), 5.02 (1H, br d, *J*=1.7 Hz), 6.99 (1H, d, *J*=7.5 Hz), 7.12~7.27 (12H, m), 7.50 (6H, br d, *J*=7.5 Hz); EIms m/z 463 and 461 (M^+), 426 (M^+-Cl), 384, 243, 165; HR-EIms calcd for $C_{32}H_{28}NCl$ 461.1910, found 461.1933. $[\alpha]_D^{20}$ -12.3°(*c* 0.55, $CHCl_3$) (54% ee).

(*R*)-1,3,4,6,7,11b-Hexahydro-2H-benzo[*a*]quinolizine (34). To a solution of **33** (12 mg, 0.025 mmol) in MeOH (1 ml) was added 2 *M* HCl (0.1 ml) at 0 ℃, and the mixture was stirred for 30 min. To the resultant mixture was added 10% Pd/C (0.5 mg), and the mixture was stirred under an atmosphere of hydrogen (1 atm) at room temperature for 5 h. The reaction mixture was diluted with AcOEt, and the solution was washed with saturated aq. $NaHCO_3$ and brine, and dried over Na_2SO_4. After removal of the solvent, the residue was dissolved in MeOH (1 ml), and K_2CO_3 (10 mg) was added to the solution. After being stirred at room temperature for 3 h, the reaction mixture was diluted with AcOEt. The mixture was washed with brine, and dried over Na_2SO_4. After removal of the solvent, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH, 29/1) to afford **34** (2 mg, 47% in 2 steps) as a colorless oil. Spectral characteristics of **34** were completely identical to those reported.[11]

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