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Asymmetric Heck Reaction of Alkenyl Iodides in the Presence of Silver Salts. Catalytic Asymmetric Synthesis of Decalin and Functionalized Indolizidine Derivatives

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Abstract: Decalin derivatives 3 (up to 80% ee) and indolizidine derivative 6 (up to 86% ee) have been synthesized by an asymmetric Heck reaction starting with prochiral alkenyl iodides 1 and 4, respectively. The important role of silver salts in the asymmetric Heck reaction is discussed, and the conversion of 6 to δ-coniceine (24) is also described.

In 1989, we reported the first example of an asymmetric Heck reaction,[1a] and while the enantioselectivity was only 46% for the cyclization of alkenyl iodide **1**, we later reported that **3** could be obtained in 92% ee when alkenyl triflate **2** was used as the substrate.[2] Other groups have also reported the advantage of alkenyl triflates as substrates in the asymmetric Heck reaction. However, in some cases, an efficient synthesis of alkenyl triflates is quite difficult, especially when complex molecules are involved. One such example involves alkenyl triflate **5**, which was desired as a substrate for asymmetric cyclization to indolizidine derivative **6**. Attempts to prepare triflate **5** from the corresponding aldehyde were unsuccessful presumably because of the reactivity of the enamide ring. In contrast, alkenyl iodide **4** is a readily available derivative (Figure 1),[3] but the efficient reaction of alkenyl iodides in the asymmetric Heck reaction is still a challenging problem for chemists. We have observed that silver salts strongly influences the enantiomeric excess of products obtained from the Heck reaction of alkenyl iodides, and here, we detail the effect of various silver salts on the catalytic asymmetric cyclization of iodides **1** (up to 80% ee)[1b] and **4** (up to 86% ee).[3,4]

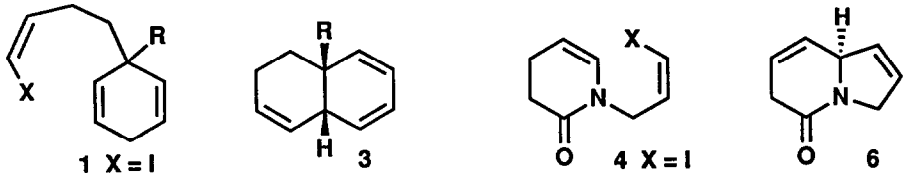
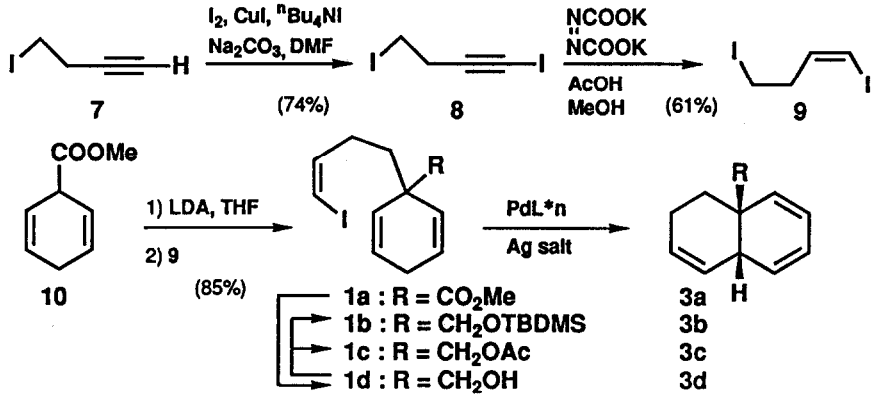


Figure 1

Catalytic Asymmetric Synthesis of Decalin Derivatives

Prochiral alkenyl iodide **1** was the first substrate we chose for the asymmetric Heck reaction, and its preparation is shown in Scheme 1. Cyclization of **1** was expected to create two chiral carbon centers, one quaternary and one tertiary carbon, and to give the optically active decalin derivative **3**. However

preliminary results using *N, N*-diisopropylethylamine or sodium acetate as the base and $Pd(OAc)_2$-DIPHOS as the achiral catalyst indicated that the cyclization of **1a** was slow, providing a mixture of regio- and/or stereoisomers in low yield. Since Hallberg *et al.*[5] and Overman *et al.*[6] have reported that silver salts enhance the rate of Heck arylation and alkenylation and suppress alkene isomerization, we decided to try Ag_2CO_3 as a base, and we were pleased to find that these conditions resulted in the formation of the cyclized product **3a** in 68% yield as a single isomer.



Scheme 1

Table 1. Ligand and Solvent Effects on the Asymmetric Synthesis of **3**[a]

Entry	Substrate	Ligand	Solvent	Temp (°C)	Time (hr)	Yield (%)	ee (%)
1	**1a**	(*S, R*)-BPPFA	DMF	60	22.5	38	3
2	**1a**	(*S, S*)-BPPM	DMF	60	19	66	1
3	**1a**	(*R*)-BINAP	DMF	60	8	69	19
4	**1a**	(*R*)-BINAP	CH_3CN	60	9.5	66	8
5	**1a**	(*R*)-BINAP	DMSO	60	16	99	1
6	**1a**	(*R*)-BINAP	THF	60	17	43	2
7	**1a**	(*R*)-BINAP	toluene	60	17	55	1
8	**1a**	(*R*)-BINAP	HMPA	60	16	58	20
9	**1a**	(*R*)-BINAP	TMU[b]	60	18	58	9
10	**1a**	(*R*)-BINAP	DMPU[c]	60	16.5	69	23
11	**1a**	(*R*)-BINAP	NMP[d]	60	12	54	33
12	**1b**	(*S*)-BINAP	NMP[d]	40	70	74	35
13	**1c**	(*S*)-BINAP	NMP[d]	40	27	69	20

[a] All reactions were carried out in the presence of 5 mol % of $Pd(OAc)_2$, 5.5 mol % of ligand, and 2.0 mol eq of Ag_2CO_3. [b] *N, N, N', N'*-tetramethylurea. [c] 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone. [d] 1-methyl-2-pyrrolidinone.

Having established that the *cis*-decalin derivative **3a** could be obtained in a stereo- and regiocontrolled manner, we turned our attention to the catalytic asymmetric synthesis of **3a** from alkenyl iodide **1a**. Using $Pd(OAc)_2$ and Ag_2CO_3 in DMF, a number of optically active bidentate ligands[7] were tested (Table 1). Only BINAP[7c] was found to promote the cyclization with moderate asymmetric induction (19% ee) and in good chemical yield (Table1, entry 3). Solvent effects were then examined for this ligand,

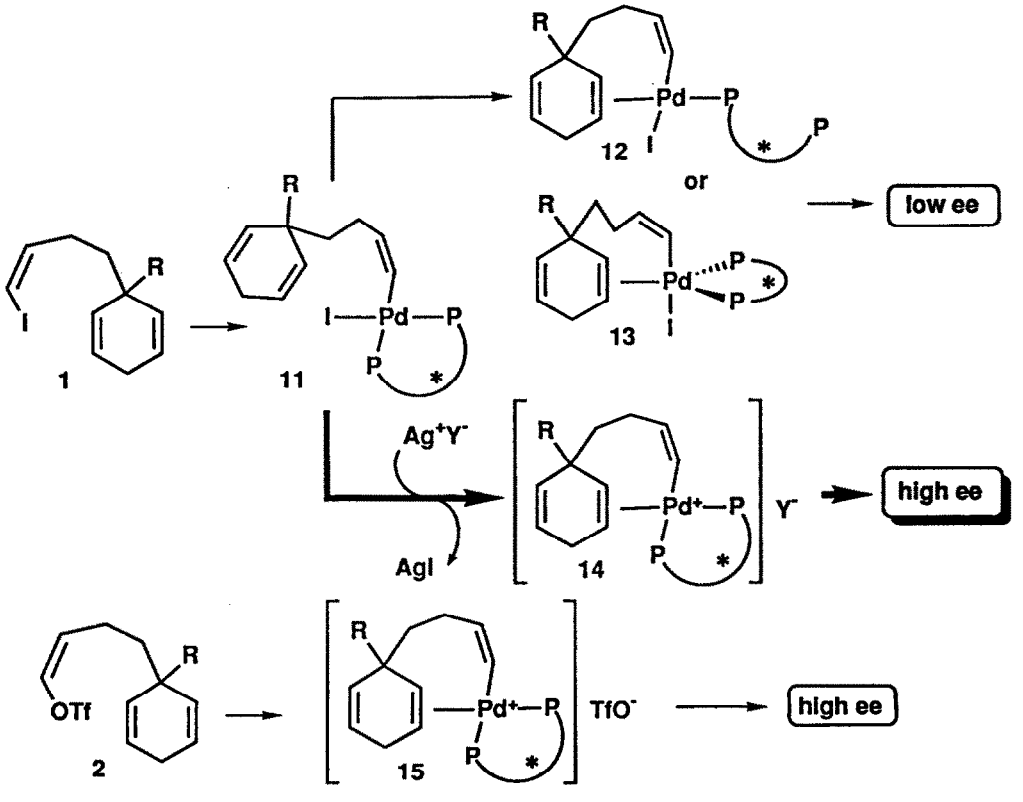
and it was generally observed that polar amide solvents such as DMPU and HMPA gave slightly higher enantiomeric excesses (20~23% ee) with NMP giving the highest (33% ee, entry 11). In contrast, solvents such as DMSO and THF, and non-polar solvents such as toluene were ineffective giving product of very low ee.

Table 2. The Effects of the Pd/BINAP Ratio on the Asymmetric Synthesis of **3a**[a]

Entry	Catalyst	(*R*)-BINAP	Time (hr)	Yield (%)	ee (%)
1	3 mol % $Pd(OAc)_2$	3.3 mol %	140	33	22
2	3 mol % $Pd(OAc)_2$	9 mol %	68	63	37
3	3 mol % $Pd(OAc)_2$	15 mol %	165	49	55
4	10 mol % Cl_2Pd[(*R*)-binap]	-	137	72	60

[a] The Pd^0 catalyst was generated *in situ* by reduction with cyclohexene.
All reactions were carried out in the presence of 2 mol eq of Ag_2CO_3 in NMP at 60 °C.

Hoping to improve the enantioselectivity of this reaction, we examined the conditions for catalyst preparation and observed the following: (1) Pre-reduction of $Pd(OAc)_2$ with cyclohexene in the presence of 3 or 5 equivalents of BINAP improves the ee of the product. (2) Product isolated after long reaction times



Scheme 2

has a higher ee than that isolated after short reaction times. (3) A high BINAP/Pd-ratio is required for high ee (Table 2). These facts imply that the low enantioselectivity observed is due to the participation of free or solvent-coordinated (non-BINAP coordinated) Pd(0) species in the cyclization. This problem can be alleviated by using the Cl_2Pd[*(R)*-binap] complex.[8] Despite the low BINAP/Pd ratio (=1), treatment of **1a** with Ag_2CO_3 and 10 mol % of the catalyst generated on prereduction of Cl_2Pd[*(R)*-binap] in NMP at 60 °C produced **3a** of 60% ee in 72% yield (Table 2, entry 4). Reaction using the Cl_2Pd[*(R)*-binap] complex without pre-reduction also gave **3a** of comparable ee (58% ee, Table 3, entry 1). These results clearly indicate that the efficient coordination of the chiral ligand to Pd(0) is essential for these asymmetric Heck-type reactions.

To clarify the effect of Ag_2CO_3 on the ee of the product, the cyclization was carried out with Et_3N as the base. It was found that the reaction was very slow and that the enantiomeric excess of the product was only 0.4% (low chemical yield), revealing that Ag_2CO_3 played a key role in the enantioselectivity of the reaction as well as the yield. These results are consistent with the hypothesis that the Heck reaction proceeds via the 16-electron Pd^+ intermediate **14** in the presence of Ag_2CO_3, but via the neutral palladium intermediate **12** and/or **13** in the absence of Ag_2CO_3 (Scheme 2).[9] The high enantioselectivity observed in the absence of Ag_2CO_3 when alkenyl triflate **2** is the cyclization substrate may also be explained by the ease with which the 16-electron Pd^+ intermediate **15** is generated.

Having observed that the addition of Ag_2CO_3 is essential for good enantioselectivity in the cyclization reaction, we examined the effect of a variety of other silver salts at 60 °C (Table 3). In general, silver cations with polyanions gave higher ee than those with monoanions.[10] AgOAc was a particularly poor salt giving the product in 6% ee. In this case, however, the reaction proceeded rather rapidly, suggesting that it was proceeding via the Pd^+ intermediate. It was found that the use of Ag_3PO_4 was most effective with the

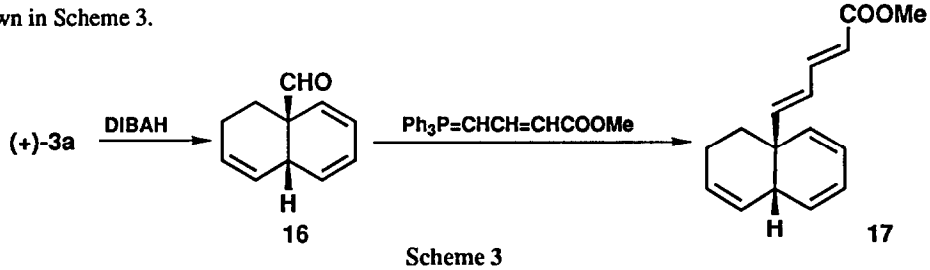
Table 3. On the Role of Silver Salts in the Asymmetric Heck Reaction (**1**→**3**)[a]

Entry	Substrate	Silver salt (2 mol eq)	Time (hr)	Recov. of SM (%)	Yield (%)	ee (%)
1	**1a**	Ag_2CO_3	210	-	65	58
2	**1a**	Ag_2O	48	11	54	63
3[b]	**1a**	Ag_3PO_4	188	12	48	69
4[b]	**1a**	Ag_2SO_4	188	85	11	53
5[b]	**1a**	$AgNO_3$	134	-	39	27
6[b]	**1a**	$AgClO_4$	230	-	33	29
7[b]	**1a**	AgOTf	108	-	31	23
8[b]	**1a**	AgOAc	61	-	70	6
9[b]	**1a**	Ag-zeolite[c]	209	-	41	71
10	**1b**	Ag_2CO_3	156	-	58	68
11	**1b**	Ag_2O	66	-	59	77
12[b]	**1b**	Ag_3PO_4	84	-	67	80
13[b]	**1b**	Ag-zeolite[c]	23	-	63	73
14[b]	**1b**	Ag-zeolite[c]	205[d]	-	59	78

[a] All reactions were carried out in the presence of 10 mol % of Cl_2Pd[(*R*)-binap] in NMP at 60 °C. [b] $CaCO_3$ (2.2 mol eq) was added to the reaction mixture. [c] Ald 36,660-9 (corresponding to *ca.* 6 equiv of Ag). [d] Reaction temp: 40 °C.

prochiral substrate **1b** being converted to **3b** of 80% ee in 67% yield (entry 3 and 12). Silver-exchanged zeolite ($Ag_xNa_{y-x}[(AlO_2)_y(SiO_2)_z]\cdot nH_2O$),[11] which recently became commercially available from Aldrich, was also tested. Like Ag_3PO_4, silver-exchanged zeolite also promoted high asymmetric induction (entry 13 and 14), but the reaction rate was much faster. These facts indicate that the identity of the counter anion (Y^-) largely influences the asymmetric induction. For now, it is difficult to explain this drastic effect of silver salt; however, one hypothesis can be presented. Monovalent couterions such as AcO^- appear to make tight ion pairs with Pd^+, thus interfering with the ideal squareplaner geometry in the intermediate and giving product of low ee. In contrast, the interaction between Pd^+ and counterions such as $AgCO_3^-$, AgO^-, $Ag_2PO_4^-$, and $Ag_{x-1}Na_{y-x}[(AlO_2)_y(SiO_2)_z]\cdot nH_2O^-$ is expected to be weaker. Furthermore, when the silver salt is insoluble such as is silver-exchanged zeolite, the counterion should remain on the surface leaving the Pd^+ cation intermediate "anion-free". We believe that this "anion-free" squareplaner Pd^+ cation intermediate is responsible for the high asymmetric induction observed in this reaction.

For all reactions the enantiomeric excess (ee) was unequivocally determined by the HPLC analysis of **3d** obtained from either **3a** ~ **3c** by conventional methods, and the assignment of the absolute configuration of these products was achieved by application of the CD exciton chirality method to **17** prepared from **3a** as shown in Scheme 3.



Scheme 3

Catalytic Asymmetric Synthesis of a Functionalized Indolizidine Derivative

Indolizidine alkaloids such as castanospermine (**18**),[12] swainsonine (**19**)[13] and pumiliotoxin B (**20**)[14] have received much interest from the synthetic community because of their ability to inhibit glycosidase[15] and cardiotonic activity (Figure 2).[16] Moreover, the discovery of the anti-HIV activity of castanospermine and its derivatives[17] has stimulated both the search for superior therapeutic agents for AIDS treatment and the development of efficient synthetic approaches to such compounds and their analogs. To our knowledge

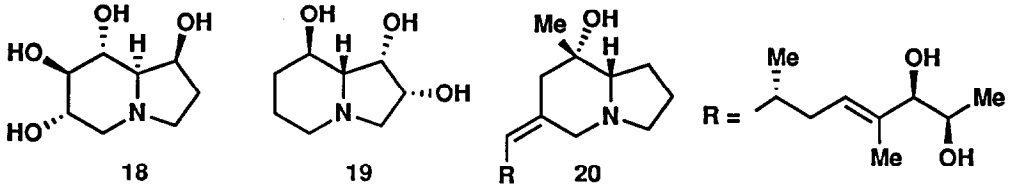
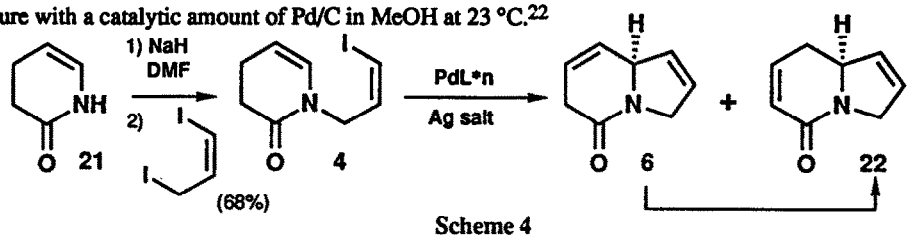


Figure 2

more than 60 syntheses of these compounds have been reported in this decade,[18] and with a few exceptions[19] most syntheses of these indolizidine derivatives have utilized natural chiral starting materials such as carbohydrates, amino acid derivatives and tartaric acid derivatives.

We planned to use a catalytic asymmetric intramolecular Heck reaction for the synthesis of the indolizidine skeleton (Scheme 4). Cyclization of iodide **4**, easily prepared from amide **21**,[20] was expected to

give the optically active indolizidine **6** when catalyzed with a chiral palladium(0) complex. First, however, we examined conditions for the cyclization of **4** using the $Pd_2(dba)_3$•$CHCl_3$ complex (5 mol % of Pd), diphenylphosphinobutane (dppb) (12 mol %) and silver phosphate (2 mol equiv) in various solvents.[21] It was found that **4** cyclized smoothly in DMF to give a mixture of the cyclized products **6** and **22** (4.7 : 1) in 67 % yield, and isomerization of **6** to **22** was readily achieved in quantitative yield by the treatment of this mixture with a catalytic amount of Pd/C in MeOH at 23 °C.[22]



Scheme 4

Next, we investigated the extent of asymmetric induction in DMF with a variety of commercially available chiral ligands (Table 4).[7] Cyclization using *(R)*-BINAP, the most commonly used ligand in the asymmetric Heck reaction, was quite slow even at 90 °C, and the enantiomeric excess of product **22** was only 34%. *(R)-(S)*-BPPFOH[7d] was found to be the best ligand for this cyclization, giving **22** as the only cyclized product in 74% enantiomeric excess and in 45% yield. Interestingly, although BPPFA and BPPFOAc are very similar in structure to BPPFOH, these ligands were less effective for this reaction.

Table 4. Ligand Effects on the Cyclization of **4**[a, b]

Entry	Ligand	Temp (°C)	Time	Ratio of **6** : **22**	Yield (%)	ee of **22** (%)	Configuration of **22**
1	*(R)*-BINAP	90	46 h	1 : 3.3	67	34	*R*
2	*(R, R)*-NORPHOS	90	3 d	1 : 2.2	11	11	*S*
3	*(S, S)*-DIOP	50	2.5 h	1 : 1.8	63	11	*R*
4	*(R, R)*-MOD-DIOP	50	21 h	1 : 1.1	32	42	*S*
5	*(S, S)*-BPPM	50	37 h	1.3 : 1	15	5	*R*
6	*(S, S)*-BCPM	50	46 h	1 : 5.9	6	60	*R*
7	*(R)-(S)*-BPPFA	50	8.5 h	1 : 5.5	79	45	*S*
8	*(R)-(S)*-BPPFOAc	50	14 h	1 : 12	62	52	*S*
9	*(R)-(S)*-BPPFOH	50	35 h	0 : 1	45	74	*S*

[a] The iodide **4** was treated with $Pd_2(dba)_3$•$CHCl_3$ (5 mol % of Pd), ligand (12 mol %), Ag_3PO_4 (2 mol equiv), and $CaCO_3$ (2.2 mol equiv) in DMF. The initial concentration of **4** was 0.05 *M*. [b] No reaction occurred after 3 days when *(S)-(R)*-PPFA, *(R, R)*-CHIRAPHOS, or *(R)*-PROPHOS was used as a ligand.

In all cases the enantiomeric excess was unequivocally determined by the HPLC analysis of **22** before and after isomerization of the mixture of **6** and **22**. Since no significant change in the ee of **22** was observed after isomerization, kinetic resolution in the double-bond migration catalyzed by PdL*n must not be occurring in this case.[23]

Table 5 summarizes our studies on the effect of solvent, temperature and silver salt on asymmetric induction. Contrary to the results described above for the decalin system, solvent did not significantly affect the ee of the product, and the reason is not yet clear. In DMSO, a solvent which was detrimental to the ee of the product in the decalin system the cyclization proceeded smoothly at 50 °C to afford the cyclized products with 73% ee and in 89% chemical yield. When the reaction was carried out at 23 °C, the ee of **22** was improved to 81% ee (chemical yield of 82%). The best result was obtained when silver-exchanged zeolite

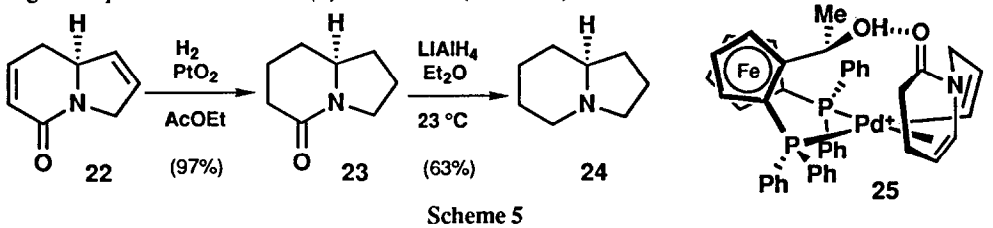
was used (Table 5, entry 12) with the reaction proceeding at 0 °C to give **22** of 86% ee in 94% yield. While no further improvement in the ee was observed, the reaction proceeded smoothly with silver-exchanged zeolite even at -13 °C. No reaction occurred with Ag_3PO_4 at 0 °C. Thus silver-exchanged zeolite has been found to be most effective for this asymmetric Heck reaction.

Table 5. Effects of Solvent, Silver Salt and Temperature on Cyclization of **4**[a]

Entry	Silver Salt	Solvent	Temp (°C)	Time	Ratio of **6** : **22**	Yield (%)	ee of **22**
1	Ag_3PO_4	DMF	50	21 h	1 : 3.3	69	74
2	Ag_3PO_4	NMP	50	14.5 h	0 : 1	21	71
3	Ag_3PO_4	DMA	50	65 h	1 : 2.9	73	71
4	Ag_3PO_4	TMU	50	13 h	0 : 1	49	69
5	Ag_3PO_4	DMSO	50	2 h	1 : 1.7	89	73
6	Ag_3PO_4	DMSO	23	7 h	1 : 2.5	82	81
7	Ag_2CO_3[b]	DMSO	50	17 h	1 : 2.2	98	71
8	$AgClO_4$	DMSO	50	7.5 h	1 : 2.8	12	25
9	Ag-zeolite[c]	DMSO	23	3.3 h	1 : 4.5	58	79
10	Ag-zeolite[d]	DMSO	23	41 h	1 : 13	42	76
11	Ag-zeolite[c]	DMSO-DMF (2.5:1)	0	5 d	1 : 1.6	78	84
12	Ag-zeolite[c]	DMSO-DMF (1:1)	0	5 d	1 : 1.4	94	86
13	Ag-zeolite[c]	DMSO-DMF (1:1)	-13	7 d	1 : 2	68	86

[a] The iodide **4** was treated with $Pd_2(dba)_3$•$CHCl_3$ (4 mol % of Pd), (*R*)-(*S*)-BPPFOH (9.6 mol %), Ag_3PO_4 (2 mol equiv) or silver-exchanged zeolite (corresponding to *ca.* 6 equiv of Ag), and $CaCO_3$ (2.2 mol equiv). The initial concentration of **4** was 0.05 *M*. [b] No $CaCO_3$ was used. [c] Ald 36,660-9. [d] Ald 38,228-0.

To elucidate the absolute configuration of chiral indolizidine derivative **22**, (-)-**22** obtained from the reaction using *(R)-(S)*-BPPFOH (86% ee): $[\alpha]_D^{24}$ -331 ° (*c* 1.18, CH_2Cl_2) was converted to known amide **23** then δ-coniceine (**24**) (Scheme 5). As the optical rotations of saturated amide intermediate **23** and δ-coniceine (**24**) are +3.0 ° (*c* 2.1, CH_2Cl_2) and +13.3 ° (*c* 0.94, EtOH) respectively, the absolute configuration of (-)-**22** must be *(S)*.[24] It is possible that the cyclization occurs via **25** with the interaction between the hydroxyl group of the ligand and the carbonyl group of the substrate stabilizing the intermediate shown and resulting in the predominance of the *(S)*-enantiomer (Scheme 5).



Scheme 5

In conclusion, decalin derivatives **3** and indolizidine derivative **22** have been efficiently synthesized in excellent enantioselectivity (~86% ee) by the asymmetric cyclization of the alkenyl iodides. The advantages of using silver-exchanged zeolite and silver phosphate in the asymmetric Heck-type cyclization of alkenyl iodides has been also demonstrated. These functionalized decalin and indolizidine derivatives (**3** and **22**) should be versatile intermediates for the synthesis of various biologically active compounds including indolizidine derivatives **18**, **19**, and **20**.

EXPERIMENTAL SECTION

General Methods Infrared (IR) spectra were measured on a JASCO A-300 diffraction grating infrared spectrophotometer. ^{1}H-NMR spectra were recorded with a JEOL JNM-FX 100 NMR spectrometer or a JEOL JNM-GX 270 NMR spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were obtained with a JEOL JMS-DX303, a JEOL JMS-D300, or a JEOL JMS HX-110 mass spectrometer. Optical rotation was measured on a JASCO DIP-140 polarimeter. In general, reactions were carried out in dry solvents under an argon atmosphere unless otherwise mentioned.

1,4-Diiodo-1-butyne (8). To a suspension of sodium carbonate (18.45 g, 174.1 mmol), copper(I) iodide (1.66 g, 8.71 mmol) and tetra-*n*-butylammonium iodide (6.43 g, 17.4 mmol) in DMF (40 ml) was added a solution of 4-iodo-1-butyne (7)[25] (15.66 g, 87.0 mmol) in DMF (6 ml) at rt. To this mixture was slowly added iodine (22.10 g, 87.1 mmol) in DMF (50 ml) over 24 h, and the whole reaction mixture was stirred at rt for additional 24 h.[26] After dilution with ether and filtration, the filtrate was washed with 10% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and concentrated. The product was purified by silica gel chromatography (hexane) to give **8** as a colorless solid (19.74 g, 74%): ^{1}H-NMR ($CDCl_3$) δ 2.85-3.02 (m, 2H), 3.13-3.32 (m,.2H); IR (neat) 2940, 2870, 1460, 1370, 1240, 1170 cm^{-1}; MS *m/z* 306 (M^+), 179 (M^+-I), 127 (bp); Anal. Calcd for $C_4H_4I_2$: C, 15.71; H, 1.31; I, 82.98. Found: C, 15.67; H, 1.35; I, 82.79; mp 32-34 °C.

***(Z)*-1,4-Diiodo-1-butene (9).** To a suspension of potassium azodicarboxylate[27] (13.18 g, 67.0 mmol) in methanol (15 ml) was added 1,4-diiodo-1-butyne (**8**) (1.38 g, 4.52 mmol) in methanol (15 ml). The mixture was stirred while a solution of acetic acid (12.0 ml, 210 mmol) in methanol (30 ml) was added at such a rate as to cause gentle boiling. The reaction mixture was stirred for additional 2 h at rt, quenched by the addition of water at 0 °C, and extracted with ether. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel chromatography (hexane) to give **9** (849 mg, 61%) as an orange oil: ^{1}H-NMR ($CDCl_3$) δ 2.75 (ddt, J = 6.6, 1.3, 7.1 Hz, 2H), 3.20 (t, J = 7.1 Hz, 2H), 6.25 (dt, J = 7.5, 6.6 Hz, 1H), 6.43 (dt, J = 7.5, 1.3 Hz, 1H); IR (neat) 2940, 1610, 1420, 1280, 1160 cm^{-1}; MS *m/z* 308 (M^+), 181 (M^+-I, bp), 149, 127; HRMS (M^+) Calcd for $C_4H_6I_2$: 307.8560, Found 307.8589.

1-[*(Z)*-4-Iodo-3-butenyl]-1-methoxycarbonyl-2,5-cyclohexadiene (1a). To a solution of lithium diisopropylamide prepared from diisopropylamine (1.2 ml, 8.6 mmol), *n*-butyllithium (1.72 *M* in hexane, 4.7 ml, 8.1 mmol) and THF (12 ml) was added a solution of 1-methoxycarbonyl-2,5-cyclohexadiene (**10**)[28] (1.01 g, 7.30 mmol) in THF (15 ml) at 0 °C, and the mixture was stirred at 0 °C for 30 min. To the mixture was added a solution of the iodide **9** (2.48 g, 8.05 mmol) in THF (15 ml) at 0°C. After stirring at 0 °C for 1 h, the reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction of the mixture with ether. The combined organic layers were washed with 10% aqueous $Na_2S_2O_3$ and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel chromatography (hexane-CH_2Cl_2, 5:1) to give **1a** (1.98 g, 85%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.74-1.82 (m, 2H), 2.03-2.12 (m, 2H), 2.65-2.70 (m, 2H), 3.70 (s, 3H), 5.76 (ddd, J = 10.4, 1.8, 1.8 Hz, 2H), 5.95 (ddd, J = 10.4, 3.1, 3.1 Hz, 2H), 6.06-6.20 (m, 2H); IR (neat) 1730, 1605, 1430, 1230 cm^{-1}; MS *m/z* 318 (M^+), 259 (M^+-CO_2Me), 181, 131, 91 (bp); Anal. Calcd for $C_{12}H_{15}IO_2$: C, 45.30; H, 4.75; I, 39.89. Found: C, 45.49; H, 4.88; I, 39.72.

1-Hydroxymethyl-1-[*(Z)*-4-iodo-3-butenyl]-2,5-cyclohexadiene (1d). To a suspension of lithium borohydride (22.2 mg, 1.02 mmol) in ether (2 ml) was added the ester **1a** (104.2 mg, 0.328 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and at rt for 2.5 h. The reaction was quenched by the addition of acetone and then water. The mixture was stirred at rt for 30 min and extracted with ether. The organic layer was washed with brine, dried ($MgSO_4$) and concentrated. The product was purified by silica gel chromatography (hexane-ether, 2:1) to give the alcohol **1d** (65.7 mg, 69%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.20-1.60 (m, 3H), 1.95-2.25 (m, 2H), 2.60-2.80 (m, 2H), 3.40 (s, 2H), 5.40 (ddd, J = 10.4, 1.9, 1.9 Hz, 2H), 5.90-6.25 (m, 4H); IR (neat) 3400, 3030, 2940, 2880, 1610, 1420, 1300, 1030 cm^{-1}; MS *m/z* 259 (M^+-MeOH), 181, 163 (M^+-I), 145, 131, 91 (bp); HRMS (M^+-I) Calcd for $C_{11}H_{15}O$: 163.1105, Found 163.1125.

1-*tert*-Butyldimethylsilyloxymethyl-1-[*(Z)*-4-iodo-3-butenyl]-2,5-cyclohexadiene (1b). To a solution of the alcohol **1d** (24.2 mg, 0.083 mmol) in methylene chloride (0.5 ml) were added triethylamine (35 μl, 0.25 mmol), *t*-butyldimethylsilyl chloride (25.2 mg, 0.17 mmol), and a catalytic amount of *N, N*-dimethylaminopyridine at 0 °C, and the mixture was stirred at rt for 4 h. The reaction was quenched by the addition of water, and the mixture was extracted with ether. The organic layer was washed with brine, dried, and concentrated. The product was purified by silica gel chromatography (hexane) to give the silyl ether **1b**

(33.2 mg, 98%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ -0.03 (s, 6H), 0.84 (s, 9H), 1.30-1.56 (m, 2H), 1.85-2.16 (m, 2H), 2.52-2.72 (m, 2H), 3.36 (s, 2H), 5.46 (ddd, *J* = 10.4, 1.9, 1.9 Hz, 2H), 5.84 (ddd, *J* = 10.4, 3.8, 3.8 Hz, 2H), 6.06-6.30 (m, 2H); IR (neat) 1610, 1470, 1460, 1250, 1110, 1070, 840, 780 cm^{-1}; MS *m/z* 389 (M^+-Me), 347 (M^+-^{t}Bu), 145, 131, 115, 89 (bp); HRMS (M^+-^{t}Bu) Calcd for $C_{13}H_{20}OISi$: 347.0328, Found 347.0323.

1-Acetoxymethyl-1-[(*Z*)-4-iodo-3-butenyl]-2,5-cyclohexadiene (1c). To a solution of the alcohol **1d** (103.3 mg, 0.356 mmol) in methylene chloride (2 ml) were added pyridine (0.3 ml, 3.7 mmol), acetic anhydride (0.2 ml, 1.8 mmol), and a catalytic amount of *N, N*-dimethylaminopyridine at 0 °C. The mixture was stirred at rt for 15 h, quenched by the addition of water (stirred for 30 min), and extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The product was purified by silica gel chromatography (hexane-ether, 2:1) to give the acetate **1c** (113.4 mg, 96%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.26-1.64 (m, 2H), 1.94-2.18 (m, 2H), 2.04 (s, 3H), 2.58-2.72 (m, 2H), 3.88 (s, 2H), 5.40 (ddd, *J* = 10.4, 1.9, 1.9 Hz, 2H), 5.90 (ddd, *J* = 10.4, 3.8, 3.8 Hz, 2H), 6.00-6.20 (m, 2H); IR (neat) 1745, 1605, 1380, 1300, 1230, 1030 cm^{-1}; MS *m/z* 205 (M^+-I), 181, 167, 91, 43 (bp); HRMS (M^+-I) Calcd for $C_{13}H_{17}O_2$: 205.1229, Found 205.1225.

Procedure for Asymmetric Cyclization of 1 (Table 1). $Pd(OAc)_2$ (5 mol %), ligand (5.5 mol %), and Ag_2CO_3 (2 mol equiv) were placed in a reaction flask. To this mixture was added a solution of the substrate **1** in solvent (0.1 *M*). The mixture was degassed by freeze-pump-thaw cycles, stirred at 60 °C (or 40 °C) until the starting material was consumed, diluted with ether at rt, and filtered through a celite pad. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated. The product was purified by silica gel chromatography (hexane-ether, 10:1 for **1a** and **1c**; hexane for **1b**) to give the cyclized product **3**.

Procedure for Asymmetric Cyclization of 1 (Table 2). To a suspension of $Pd(OAc)_2$, *(R)*-BINAP (or Cl_2Pd[*(R)*-binap]) and Ag_2CO_3 (0.4 mmol) in degassed NMP (1.0 ml) was added cyclohexene (2 equiv to Pd). The mixture was stirred at 60 °C for 3h. To this mixture was added a solution of the substrate **1a** (0.2 mmol) in degassed NMP (1.0 ml). The mixture was stirred at 60 °C until the starting material was consumed, diluted with ether at rt, and filtered through a celite pad. The filtrate was washed with brine, dried (Na_2SO_4), and concentrated. The product was purified by silica gel chromatography (hexane-ether, 10:1) to give the cyclized product **3a** as a colorless oil.

Procedure for Asymmetric Cyclization of 1 (Table 3). Cl_2Pd[*(R)*-binap] (10 mol %), silver salt (2 mol equiv) or silver-exchanged zeolite (Aldrich 36,660-9, Ag content = 20-25%, 100 mesh powder, 6 mol equiv of Ag), and $CaCO_3$ (2.2 mol equiv, if necessary) were placed in a reaction flask. To this mixture was added a solution of the substrate **1** in NMP (0.1 *M*). The mixture was degassed, stirred at 60 °C until the starting material was consumed, worked up, and purified in the same manner as described above. Spectral data of the product were as follows.

***(1S,6S)*-1-Methoxycarbonylbicyclo[4.4.0]deca-2,4,7-triene (3a):** ^{1}H-NMR ($CDCl_3$) δ 1.85-1.90 (m, 2H), 1.93-2.10 (m, 2H), 3.61 (m, 1H), 3.72 (s, 3H), 5.56 (bd, *J* = 9.5 Hz, 1H), 5.65-5.75 (m, 3H), 5.79 (dddd, *J* = 9.5, 5.1, 2.2, 0.7 Hz, 1H), 5.94 (ddd, *J* = 9.5, 5.1, 0.7 Hz, 1H); IR (neat) 1730, 1680, 1650, 1240 cm^{-1}; MS *m/z* 190 (M^+), 131 (bp), 115, 105, 91; HRMS (M^+) Calcd for $C_{12}H_{14}O_2$: 190.0994, found 190.0994; $[\alpha]_D^{20}$ +262 ° (*c* 0.84, $CHCl_3$) (69% ee).

***(1S,6S)*-1-*tert*-Butyldimethylsilyloxymethylbicyclo[4.4.0]deca-2,4,7-triene (3b):** ^{1}H-NMR ($CDCl_3$) δ 0.01 (s, 6H), 0.87 (s, 9H), 1.59 (dt, *J* = 13.2, 5.1 Hz, 1H), 1.77 (ddd, *J* = 13.2, 9.2, 5.5 Hz, 1H), 1.96 (m, 1H), 2.09 (m, 1H), 2.88 (m,.1H), 3.34 (d, *J* = 9.5 Hz, 1H), 3.50 (d, *J* = 9.5 Hz, 1H), 5.37 (d, *J* = 9.5 Hz, 1H), 5.45 (ddd, *J* = 9.9, 4.8, 2.2 Hz, 1H), 5.59 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.69-5.78 (m, 2H), 5.88 (dd, *J* = 9.9, 5.1 Hz, 1H); IR (neat) 2950, 1740, 1460, 1252, 1120, 835 cm^{-1}; MS *m/z* 276 (M^+), 219 (M^+-^{t}Bu), 144, 131, 115, 89, 73 (bp); HRMS (M^+) Calcd for $C_{17}H_{28}OSi$: 276.1910 Found 276.1901. $[\alpha]_D^{20}$ +242 ° (*c* 0.88, $CHCl_3$) (80% ee).

***(1S,6S)*-1-Acetoxymethylbicyclo[4.4.0]deca-2,4,7-triene (3c):** ^{1}H-NMR ($CDCl_3$) δ 1.62 (ddd, *J* = 13.2, 8.8, 5.9 Hz, 1H), 1.72 (dt, *J* = 13.2, 5.3 Hz, 1H), 1.90-2.20 (m, 2H), 2.07 (s, 3H), 2.80-2.90 (m,.1H), 3.98 (s, 2H), 5.35 (d, *J* = 9.5 Hz, 1H), 5.47 (ddd, *J* = 9.9, 5.5, 2.0 Hz, 1H), 5.63 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.72-5.83 (m, 2H), 5.94 (ddd, *J* = 9.5, 5.1, 0.7 Hz, 1H); IR (neat) 1740, 1440, 1380, 1240, 1030 cm^{-1}; MS *m/z* 204 (M^+), 145, 131, 43 (bp); HRMS (M^+) Calcd for $C_{13}H_{16}O_2$: 204.1150, Found 204.1167; $[\alpha]_D^{20}$ +89 ° (*c* 1.16, $CHCl_3$) (20% ee).

Enantiomeric excess of the cyclized product (**3a-c**) was determined by the HPLC analysis of **3d**: DAICEL CHIRALCEL OJ, hexane-2-propanol, 9:1; retention time: 12.8 min (*1R, 6R*-enantiomer), 14.9 min (*1S, 6S*-enantiomer) (V_0 = 2.5 ml, 0.5 ml/min, 23 °C, UV monitor: 290 nm). Conversions of **3a-c** to **3d** were as

follows.

***(1S,6S)*-1-Hydroxymethylbicyclo[4.4.0]deca-2,4,7-triene (3d):** To a solution of **3a** (16.8 mg, 88 μmol) in ether (2 ml) was added lithium aluminum hydride (3.4 mg, 90 μmol) at 0 °C. The mixture was stirred at 0 °C for 1 h, quenched by the addition of $Na_2SO_4 \cdot 10H_2O$ and water, and extracted with ether. The ether layer was washed with brine, dried (Na_2SO_4), and concentrated. The product was purified by silica gel chromatography (hexane-ehter, 10:1) to give the alcohol **3d** (13.1 mg, 91%) as a colorless oil: ^{1}H-NMR ($CDCl_3$) δ 1.51-1.65 (m, 2H), 1.70 (dt, *J* = 12.8, 5.1 Hz, 1H), 1.90-2.20 (m, 2H), 2.87-2.93 (m, 1H), 3.47 (d, *J* = 10.6 Hz, 1H), 3.53 (d, *J* = 10.6 Hz, 1H), 5.35 (d, *J* = 9.5 Hz, 1H), 5.47 (ddd, *J* = 9.5, 5.1, 2.9 Hz, 1H), 5.65 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.72-5.82 (m, 2H), 5.99 (ddd, *J* = 9.5, 5.1, 1.1 Hz, 1H); IR (neat) 3330, 1640, 1580, 1090, 1020 cm^{-1}; MS *m/z* 162 (M^+), 144 (M^+-H_2O), 131 (bp), 116, 91; HRMS (M^+) Calcd for $C_{11}H_{14}O$: 162.1045, Found 162.1048. **From 3b:** To a solution of **3b** (11.3 mg, 41 μmol) in acetonitrile (2 ml) was added a mixture of 40% aqueous HF and acetonitrile (3:7, 250 μl) at -25 °C. The mixture was stirred at -25 °C for 20h, quenched with saturated $NaHCO_3$ (stirred at -25 °C for 30 min), and extracted with ether. The organic layer was washed with brine, dried (Na_2SO_4), and concentrated. The product was purified by silica gel chromatography (hexane-ehter, 2:1) to give the alcohol **3d** (7.9 mg, 100%) as a colorless oil. The acetate **3c** was converted to **3d** according to the same procedure as **3a** in quantitative yield.

***(1R, 6S)*-1-[*(E, E)*-4-methoxycarbonyl-1,3-butadienyl]bicyclo[4.4.0]deca-2,4,7-triene (17).** To a solution of (+)-**3a** (22 mg, 0.12 mmol) in hexane (0.6 ml) was added a solution of diisobutylaluminum hydride (1*M*, 250 μl, 0.25 mmol) at -80 °C. The mixture was stirred at -80 °C for 1 h, quenched with brine, and extracted with ether. The organic layer was dried (Na_2SO_4), and concentrated. The product was roughly purified by short silica gel column chromatography (hexane-CH_2Cl_2, 2:1) to give the crude aldehyde **16** (9.5 mg, *ca.* 52%). To a solution of the aldehyde in benzene (0.5 ml) was added methyl 4-(triphenylphosphoranylidene)-crotonate[29] (130 mg), and the mixture was refluxed for 15 h. After cooling to rt, the mixture was diluted with ether, passed through a short silica gel column, and concentrated. The product was purified by silica gel chromatography (hexane-CH_2Cl_2, 4:1) to give **17** (4.9 mg, 17% from **3a**): ^{1}H-NMR ($CDCl_3$) δ 1.50-1.66 (m, 1H), 1.78 (dt, *J* = 13.0, 5.0 Hz, 1H), 2.05-2.35 (m, 2H), 2.87 (m,.1H), 3.73 (s, 3H), 5.33 (d, *J* = 9.5 Hz, 1H), 5.48 (ddd, *J* = 9.9, 5.1, 2.2 Hz, 1H), 5.65 (dd, *J* = 9.5, 5.1 Hz, 1H), 5.72-5.85 (m, 2H), 5.83 (d, *J* = 15.4 Hz, 1H), 5.94 (ddd, *J* = 9.5, 5.1, 0.7 Hz, 1H), 6.12 (d, *J* = 15.4 Hz, 1H), 6.23 (dd, *J* = 15.4, 10.3 Hz, 1H), 7.28 (dd, *J* = 15.4, 10.3 Hz, 1H); IR (neat) 1720, 1640, 1430, 1260, 1240, 1140, 1000 cm^{-1}; MS *m/z* 242 (M^+), 210 (M^+-MeOH), 183 (M^+-CO_2Me), 155, 141, 130, 115, 91 (bp); HRMS (M^+) Calcd for $C_{16}H_{18}O_2$: 242.1307, Found 242.1310. CD spectrum of **17** showed a positive first Cotton ($\Delta\varepsilon_{max}$: 277 nm) and a negative second Cotton ($\Delta\varepsilon_{max}$: 248 nm).

***(Z)*-3-Iodo-2-propen-1-ol.** To a suspension of potassium azodicarboxylate[25] (69.0 g, 356 mmol) in methanol (200 ml) was added 3-Iodo-2-propyn-1-ol[30] (16.3 g, 86.7 mmol) in methanol (150 ml) at rt. The mixture was stirred while a solution of acetic acid (40.8 ml, 712 mmol) in methanol (100 ml) was added at such a rate as to cause gentle boiling. The reaction mixture was stirred for additional 2 h at rt, quenched by the addition of water at 0 °C, and extracted with ether. The organic layer was dried ($MgSO_4$), and concentrated to give a yellow oil. To this mixture was added *n*-propylamine for conversion of the overreduced product to the ammonium salt. The mixture was diluted with ether, washed with water and brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel chromatography (hexane-AcOEt, 3:1) to give *(Z)*-3-iodo-2-propen-1-ol (7.62 g, 49%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 1.92 (s, 1H), 4.12-4.48 (m, 2H), 6.30-6.48 (m, 1H), 6.51 (dt, *J* = 7.6, 5.1 Hz, 1H); IR (neat) 3350, 1610, 1280 cm^{-1}; MS *m/z* 184 (M^+), 57 (M^+-I, bp); HRMS (M^+) Calcd for C_3H_5OI: 183.9385, Found 183.9384.

***(Z)*-1-Iodo-3-methanesulfonyloxy-1-propene.** To a solution of *(Z)*-3-iodo-2-propen-1-ol (4.90g, 26.9 mmol) in methylene chloride (90 ml) was added triethylamine (7.50 ml, 53.8 mmol) and then methanesulfonyl chloride (3.20 ml, 41.4 mmol) at -30 °C. The mixture was stirred at -30 °C for 1 h, diluted with ether, washed with brine, dried ($MgSO_4$), and concentrated. The product was purified by silica gel chromatography (hexane-AcOEt, 1:1) to give *(Z)*-1-iodo-3-methanesulfonyloxy-1-propene (6.53 g, 93%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 3.15 (s, 3H), 4.81 (dd, *J* = 5.8, 1.5 Hz, 2H), 6.56 (dt, *J* = 8.0, 5.8 Hz, 1H), 6.68 (dt, *J* = 8.0, 1.5 Hz, 1H); IR (neat) 1353, 1171, 945, 817 cm^{-1}; MS *m/z* 262 (M^+), 183 (M^+-CH_3SO_2), 167 (M^+-CH_3SO_3, bp), 135 (M^+-I); HRMS (M^+) Calcd for $C_4H_7O_3IS$: 261.9161, Found 261.9152.

3,4-Dihydro-1-[*(Z)*-3-iodo-2-propenyl]-2(1*H*)-pyridone (4). To a solution of *(Z)*-1-iodo-3-methanesulfonyloxy-1-propene (3.40 g, 13.0 mmol) in acetone (18.6 ml) was added sodium iodide (1.94 g, 13.0 mmol) at 0 °C. The mixture was stirred at rt for 2h, diluted with ether, and filtered. The filtrate was washed with 10% aqueous $Na_2S_2O_3$ and brine, dried (Na_2SO_4), and concentrated. The product was purified

by silica gel chromatography (hexane) to give *(Z)*-1,3-diiodo-1-propene (3.19 g, 83%) as a dark red oil. This unstable iodide was immediately used for next step. To a solution of the iodide in DMF (6.7 ml) was added sodium salt of 3,4-dihydro-2(1*H*)-pyridone prepared from 3,4-dihydro-2(1*H*)-pyridone[20] (810 mg, 8.34 mmol) and sodium hydride (60%, 367 mg, 9.17 mmol) in DMF (10.0 ml) (0 °C-rt, 1.3 h). The mixture was stirred at rt for 1.5 h, and directly purified by silica gel chromatography (hexane-AcOEt, 2:1) to give 4 (1.49 g, 68%) as a yellow oil: ^{1}H-NMR ($CDCl_3$) δ 2.26-2.37 (m, 2H), 2.53 (t, *J* = 8.0 Hz, 2H), 4.21 (dd, *J* = 6.8, 1.5 Hz, 2 H), 5.17 (dt, *J* = 8.0, 4.0 Hz, 1 H), 6.03 (dt, *J* = 8.0, 1.8 Hz, 1 H), 6.25 (dt, *J* = 8.0, 6.8 Hz, 1H), 6.46 (dt, *J* = 8.0, 1.5 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 169.3, 136.5, 129.3, 106.6, 84.9, 49.6, 31.2, 20.3; IR (neat) 2926, 1664 cm^{-1}; MS *m/z* 263 (M^+), 167, 137, 136 (bp), 96; HRMS (M^+) Calcd for $C_8H_{10}ONI$: 262.9808, Found 262.9796.

(*S*)-3,5,8,8a-Tetrahydro-5-oxo-indolizine (22). Representative procedure for the asymmetric cyclization reaction of 4 is as follows. To a mixture of $Pd_2(dba)_3$•$CHCl_3$ (3.3 mg, 3.14 μmol), silver-exchanged zeolite (Aldrich 36,660-9, Ag content = 20-25%, 100 mesh powder, 508 mg, *ca.* 0.942 mmol of Ag), $CaCO_3$ (34.6 mg, 0.345mmol), *(R)-(S)*-BPPFOH (9.0 mg, 15.1 μmol) and DMF (0.5 ml) was added a solution of 4 (41.2 mg, 0.157 mmol) in DMF (1.0 ml) and DMSO (1.5 ml) at rt. The mixture was degassed by freeze-pump-thaw cycles, stirred at 0 °C for 5 d, diluted with AcOEt-methanol (10:1) at 0 °C, and filtered through a short silica gel column. The filtrate was concentrated at 100 °C under reduced pressure (40 mmHg). Under this condition almost all DMF but not DMSO was removed without loosing the desired products. The resulting residue was purified by silica gel column chromatography (hexane-acetone, 5:4) to give a mixture of 6 and 22 as a colorless oil (19.9 mg, 94%, 6:22, 1:1.4). This mixture of cyclized products was dissolved in methanol (4.6 ml), and 10% Pd/C (2.7 mg) was added. The mixture was stirred at rt for 2 d, filtered through a celite pad, and concentrated to afford 22 (19.9 mg, 100%) as a colorless oil: ^{1}H NMR (C_6D_6) δ 1.53-1.62 (m, 2 H), 3.91-4.16 (m, 2 H), 4.33-4.45 (m, 1 H), 5.06-5.13 (m, 1 H), 5.20-5.31 (m, 1 H), 5.81 (ddd, *J* = 10.0, 5.5, 3.6 Hz, 1 H), 6.06 (dt, *J* = 10.0, 2.0 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ 162.7, 138.3, 129.3, 127.7, 126.6, 62.6, 52.0, 30.0; IR (neat) 2922, 1658 cm^{-1}; MS *m/z* 135 (M^+, bp); HRMS (M^+) Calcd for C_8H_9ON: 135.0684, Found 135.0684.

Enantiomeric excess of the cyclized product (22) was determined by the HPLC analysis: DAICEL CHIRALPAK AS, hexane-2-propanol, 4:1; retention time: 25 min (*S*-enantiomer), 18 min (*R*-enantiomer) (V_0 = 2.5 ml, 1.0 ml/min, 23 °C, UV monitor: 254 nm).

5-Oxoindolizidine (23). To a solution of 22 (41.7 mg, 309 μmol) in ethyl acetate (2.0 ml) was added platinum(IV) oxide (12.6 mmol). The mixture was stirred under hydrogen atmosphere at rt for 13 h, filtered through a celite pad, and concentrated to give 23 (43.8 mg, 97%). The spectral data of 23 were identical with those reported.[31] The amide 23 was converted to 24 according to the reported procedure.[31]

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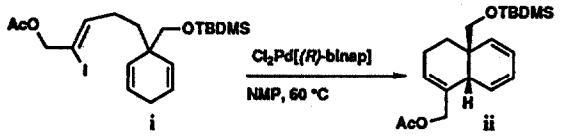

i ii

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22. The isomerization was also achieved under the following conditions: silica gel in acetone; catalytic amount of *t*-BuOK or K_2CO_3 in *t*-BuOH at 23 °C; DBU in toluene at 100 °C. In all cases no change in ee was observed after the isomerization.
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