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A New Preparation of Homochiral *N*-Protected 5-Hydroxy-3-piperidenes, Promising Chiral Building Blocks, by Palladium-Catalyzed Deracemization of Their Alkyl Carbonates

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Dedicated to Professor Masakatsu Shibasaki on his 60th birthday.

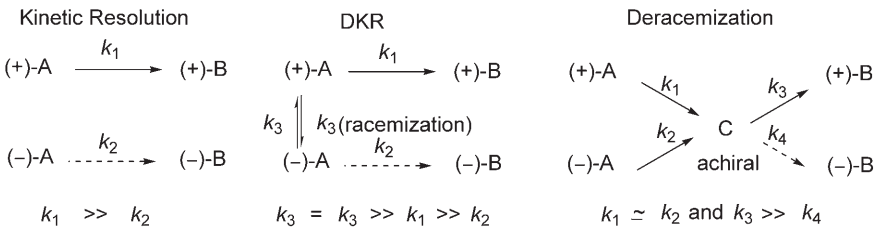
Abstract: The palladium-catalyzed deracemization of *N*-protected alkyl carbonates of 5-hydroxy-3-piperidenes by use of chiral phosphine ligands is described. A Trost ligand such as (*R*)-BPA was found to be a suitable chiral ligand for the deracemization, providing *N*-protected 5-hydroxy-3-piperidenes in good yields with good to high enantioselectivities. A plausible mechanism for the reaction is proposed.

Keywords: chiral building blocks; deracemization; *N*-protected alkyl carbonates of 5-hydroxy-3-piperidenes; *N*-protected 5-hydroxy-3-piperidenes

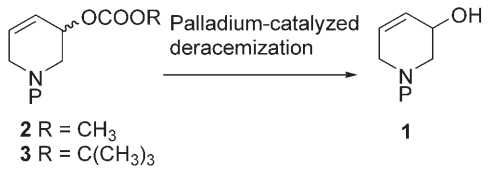
Introduction

N-Protected 5-hydroxy-3-piperidenes **1** containing an allyl alcohol unit, which has the potential for being transformed into a wide variety of functional groups, have been used as (chiral) building blocks for the construction of a variety of alkaloids,[1] in medicinal chemistry,[2] and other areas.[3] We have previously reported on an efficient synthesis of 1-azasugars using *N*-protected 5-hydroxy-3-piperidene.[4] Several procedures are available for their racemic synthesis from readily available starting materials (pyridine, 3-hydroxypyridine and butadiene monoxide). Enantiopure forms can be produced by enzyme-mediated kinetic resolution, providing greater than 99% *ee*. However, the selective kinetic discrimination between enantiomers in racemic mixtures has a fatal drawback in that the maximum theoretical yield of the desired enantiomer is 50%, and the other half may be waste material (Scheme 1). A solution offering the potential for a 100% yield is dynamic kinetic resolution (DKR).[5] This procedure combines enantioselective resolution and *in situ* racemization thus permitting the undesirable enantiomer to be recycled. A similar alternative is a deracemization process[6] in which, instead of separating the enantiomers, one is converted into the other. A simple deracemization process might arguably prove to be the most effective.

The palladium-catalyzed deracemization of cyclic allyl esters as described by Trost[6d] (Scheme 2) was performed to give cycloalkenols in high yields and enatioselectivites.[7] A similar deracemization of allylic carbonates using the hydrogen carbonate ion as a nucleophile has recently been reported by Gais et al.[8] In this paper we describe the preparation of homochiral *N*-protected 5-hydroxy-3-piperidenes **1**, which are



Scheme 1. Formation of chiral products from racemic substrates.

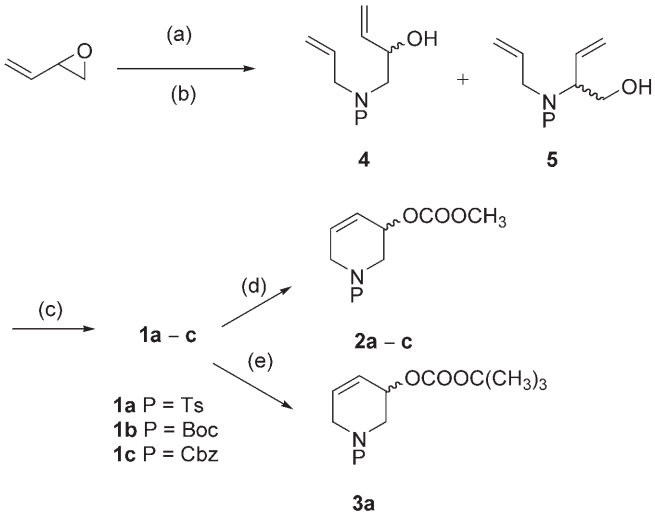


Scheme 2. Pd-catalyzed deracemization of *N*-protected alkyl carbonates of 5-hydroxy-3-piperidene.

useful building blocks for the preparation of biologically active nitrogen compounds by the Pd-catalyzed deracemization of their alkyl carbonates **2** and **3** using procedures similar to those reported by Trost[6d] and Gais.[8]

Results and Discussion

The preparation of racemic *N*-protected of 5-hydroxy-3-piperidenes **1** was carried out by a previously described procedure.[4] The regioselective opening of butadiene monoxide with allylamine, followed by protection ($TsCl/NaHCO_3$, $Boc_2O/NaOH$, $CbzCl/NaHCO_3$) of the secondary amine gave the metathesis precursors **4**, together with small amounts of regioisomers **5**. Grubbs' catalyst[9] could be used directly on **4** to afford the ring-closing metathesis products **1a–c** in high yields. The methoxycarbonylation of **1a–c** with methyl chloroformate in the presence of pyridine gave the methyl carbonates of 5-hydroxy-3-piperidenes **2a–c**. In a similar manner, **1a** was converted by reaction with Boc_2O using 1-methylimidazole as a base to *tert*-butyl carbonates **3a** (Scheme 3).



Reagent and conditions: (a) allylamine/H_2O, 100 °C, 6 h;
(b) $TsCl/NaHCO_3$ or $Boc_2O/NaOH$ or $CbzCl/NaHCO_3$;
(c) Grubbs' catalyst, CH_2Cl_2; (d) CH_3OCOCl/pyridine, CH_2Cl_2;
(e) Boc_2O/1-methylimidazole, CH_2Cl_2

Scheme 3. Preparation of alkyl carbonates **2** and **3**.

With the *N*-protected 5-alkoxycarbonyloxy-3-piperidenes **2** and **3** in hand (Table 1), we investigated the palladium-catalyzed deracemization of **2a**. According to Gais's procedure, treatment of **2a** with $Pd_2(dba)_3$-$CHCl_3$ (2 mol%) using (*R*)-BPA[10] as a ligand in CH_2Cl_2/H_2O (9:1) gave (*R*)-**1a** with > 99% *ee* in 93% yield in 24 h. Screening experiments were conducted with **2a** using other chiral phosphine ligands [(*R*)-PhBPA,[10] (*R*)-naphthylBPA,[11] (*R*)-β-3,[12] and (*R*)-BINAP] (Figure 1) and the results are shown in

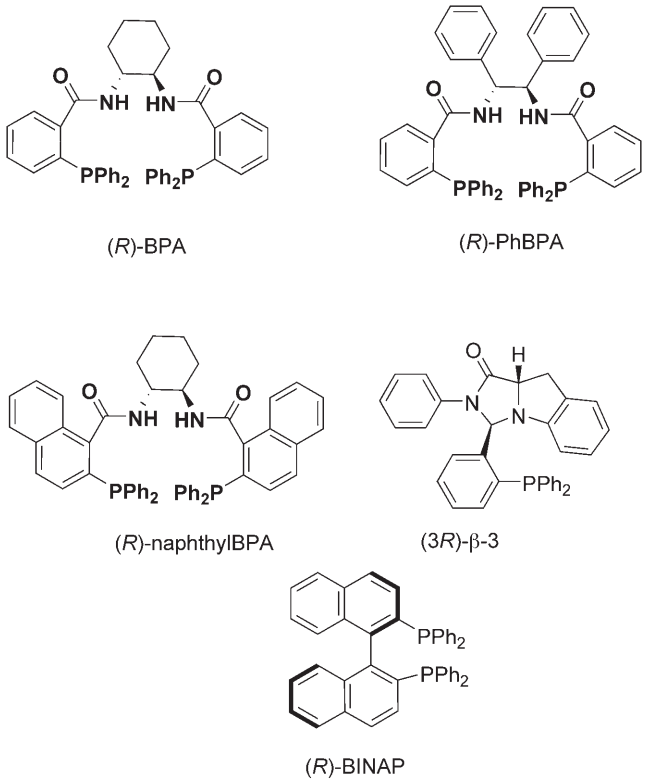


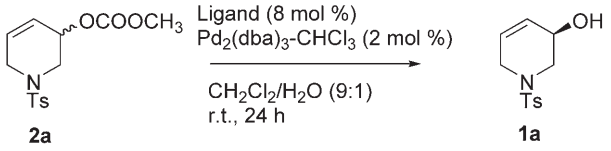
Figure 1. Chiral phosphine ligands.

Table 1. Preparation of *N*-protected 5-alkoxycarbonyloxy-3-piperidenes.

Entry	P	**4**	Yield [%][a]	**5**	Yield [%][a]	**1**	Yield [%][a]	**2**	Yield [%][a]	**3**	Yield [%][a]
1	Ts	**4a**	74	**5a**	6	**1a**	98	**2a**	99	**3a**	99
2	Boc	**4b**	66	**5b**	2	**1b**	98	**2b**	98	-	-
3	Cbz	**4c**	64	**5c**	12	**1c**	96	**2c**	92	-	-

[a] Isolated yield.

Table 2. Pd-Catalyzed deracemization of **2a** using different chiral phosphine ligands.



2a **1a**

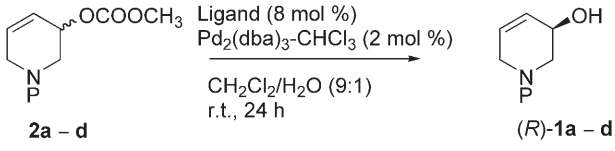
Entry	Ligand	(*R*)-**1a**, Yield [%][a]	(*R*)-**1a**, *ee* [%][b]
1	(*R*)-BPA	93	99
2	(*R*)-PhBPA	81	98
3	(*R*)-naphthylBPA	80	95
4	(3*R*)-β-3	57	94
5	(*R*)-BINAP	4[c]	30[d]
6	(*R*)-BPA[e]	85	99

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Compound **2a** was recovered in 88% yield.
[d] *ee* of (*S*)-**1a**.
[e] 4 mol% (*R*)-BPA and 1 mol% $Pd_2(dba)_3$-$CHCl_3$ were used.

Table 2. In terms of yield and *ee*, Trost's ligands were approximately the same as (*R*)-BPA, whereas (*R*)-β-3, and (*R*)-BINAP) were less than (*R*)-BPA.

The effect of solvents was next examined using (*R*)-BPA as a catalyst and the results are shown Table 3. The use of solvents which are less miscible with water, such as $(CH_2Cl)_2$ and toluene, gave good results (Table 3, entries 1 and 2). In addition, miscible solvents such as DMF and DMSO led to similar outcomes, although the *ee*s were slightly low (Table 3, entries 3 and 4). On the other hand, THF and acetonitrile were not useful. The use of CH_2Cl_2 gave the best *ee* (Table 2, entry 1).

Table 4. Influence of *N*-protected groups in the Pd-catalyzed deracemization of **2a–d** using (*R*)-BPA.



2a – d (*R*)-**1a – d**

Entry	**2**	P	(*R*)-**1**, Yield[%][a]	(*R*)-**1**, *ee* [%][b]
1	**2a**	Ts	93	99
2	**2b**	Boc	94	94[c]
3	**2c**	Cbz	88	87
4	**2d**[d]	COOMe	90	99[e]

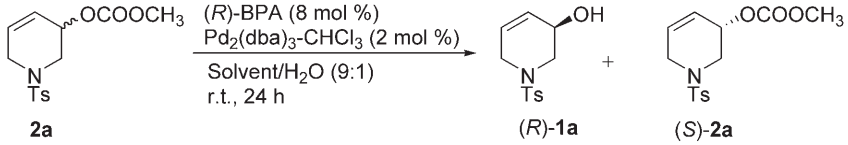
[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Determined by HPLC after conversion of **1b** to **1a**.
[d] Compound **2d** was prepared from **1b** in 5 steps (see Experimental Section).
[e] Determined by HPLC after conversion of **1d** to **1a**.

Third, influence of *N*-protected groups was observed using CH_2Cl_2/H_2O (9:1) as a solvent and the results are shown Table 4. The *ee*s for both *N*-Boc (*R*)-**1b** and *N*-Cbz (*R*)-**1c** were lower than those for *N*-Ts (*R*)-**1a** and *N*-COOMe (*R*)-**1d**. Fortunately, one recrystallization of (*R*)-**1b** gave > 99% *ee*. It thus appears that different *N*-protected groups have little effect on reactivity.

Fourth, reaction times were examined using **2a** and **2b** and the results are shown in Table 5. The reactions of both **2a** and **2b** were complete within 6 h.

Fifth, the effect of OR leaving groups was studied using **3a** and acetate **6** (Table 6) Although the deracemization of **3a** gave (*R*)-**1a** (81%) with 99% *ee*, unreacted (*S*)-**3a** was present in 18% yield with 99% *ee* even after an extended reaction time (24 h). Thus, the reaction rate of **3a** bearing a sterically bulky *O*-Boc is

Table 3. Solvent effect of Pd-catalyzed deracemization of **2a** using (*R*)-BPA.

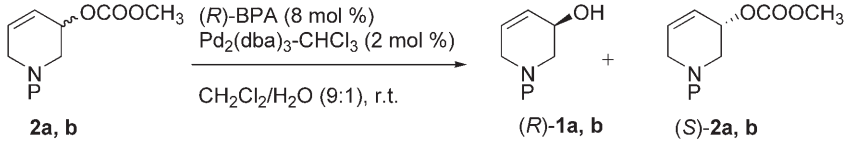


2a (*R*)-**1a** (*S*)-**2a**

Entry	Solvent	(*R*)-**1a**, Yield [%][a]	(*R*)-**1a**, *ee* [%][b]	(*S*)-**2a**, Yield [%][a]	(*S*)-**2a**, *ee* [%][b]
1	$(CH_2Cl)_2$	88	97	-	-
2	Toluene	78	97	-	-
3	DMF	99	95	-	-
4	DMSO	89	95	-	-
5	THF	72	94	27	98
6	CH_3CN	11	77	82	12

[a] Isolated yields.
[b] Determined by chiral HPLC.

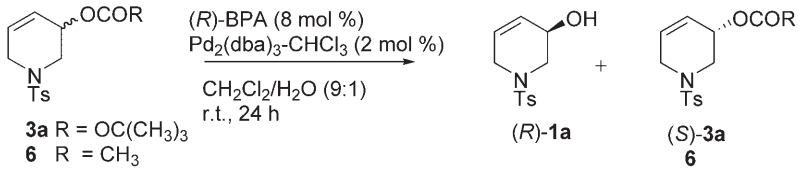
Table 5. Influence of reaction time in the Pd-catalyzed deracemization of **2a** and **b** using (*R*)-BPA.



Entry	**2**	Reaction time [h]	(*R*)-**1a**, Yield [%][a]	(*R*)-**1a**, *ee* [%][b]	(*S*)-**2a**, Yield [%][a]	(*S*)-**2a**, *ee* [%][b]
1	**2a**	1	42	99	49	86
2	**2a**	6	94	99	-	-
3	**2b**	1.5	30	99	55	58
4	**2b**	6	94	93	-	-

[a] Isolated yields.
[b] Determined by chiral HPLC.

Table 6. Effect of leaving group.



Entry	Substrate	(*R*)-**1a**, Yield [%][a]	(*R*)-**1a**, *ee* [%][b]	(*S*)-**3a** or **6** Yield [%][a]	(*S*)-**3a** or **6** *ee* [%][b]
1	**3a**	81	99	18 (**3a**)	99
2	**6**	0	-	99 (**6**)	1[c]

[a] Isolated yields.
[b] Determined by chiral HPLC.
[c] Absolute configuration remains undetermined.

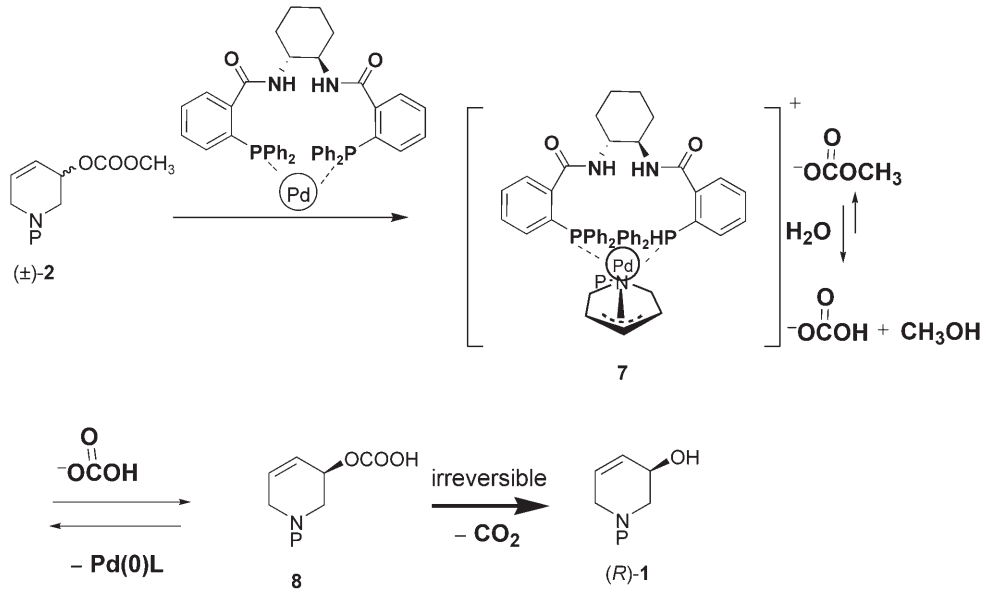
slow. In addition, the reaction of acetate **6** was very sluggish, resulting in **6** being recovered in 99% yield.

Finally, the reaction of **2a** was carried out in CH_2Cl_2 for 24 h under anhydrous conditions, producing (*R*)-**1a** in 9% yield (89% *ee*) accompanied by the recovery of (*S*)-**2a** in 69% yield (50% *ee*). This indicates that the presence of water is essential for promoting the reaction. On the other hand, the use of $KHCO_3$ instead of water gave (*R*)-**1a** in 61% yield (91% *ee*) and (*S*)-**2a** in 11% yield (36% *ee*). This suggests that the hydrogen carbonate ion plays a critical role in this deracemization.

Considering the above results, we considered a plausible mechanism for this deracemization according to the proposal of Trost[13] and Gais[8] (Scheme 4). The substrates **2** are converted to π-allyl palladium complex **7** *via* ionization by (*R*)-BPA. In the presence of water, a methyl carbonate ion is attacked by water, generating a hydrogen carbonate ion, which functions as a true nucleophile.[8] Evidence for this is the result of the reaction conducted in the presence of $KHCO_3$ (*vide supra*). Therefore, intermediate **7** would be transformed into the allylic hydrogen carbonate **8**. Apparently, the nucleophilic attack of a hydrogen carbonate ion is favored due to the less steric interaction between the right front wall and the incoming nucleophile, resulting in an *R* configuration. Finally, **8** undergoes irreversible decarboxylation, yielding the deracemization product (*R*)-**1**. The somewhat lower *ee* obtained using *N*-Boc **2b** and *N*-Cbz **2c** can be attributed to an unfavorable steric interaction between the larger *N*-protected substituents compared with *N*-Ts **2a** and *N*-$COOCH_3$ **2d** and the flap of the chiral pockets in intermediate **7**.

Conclusions

In summary, the Pd-catalyzed deracemization of alkyl carbonates of *N*-protected 5-hydroxy-3-piperidenes **2** using Trost's ligands is described. Among the ligands examined, (*R*)-BPA gave good results for substrates **2a–d**, furnishing the corresponding products **1**, which are promising chiral building blocks for the synthesis of biologically active nitrogen-compounds in good yields with good to high enantioselectivities.



Scheme 4. A plausible mechanism of Pd-catalyzed deracemization of **2** using (*R*)-BPA.

Experimental Section

Melting points were determined on a Mel-Temp melting point apparatus using an open capillary tube. All melting and boiling points are uncorrected. Infrared (IR) spectra were recorded on a Perkin–Elmer 1600 series FT-IR spectrometer. Mass spectra (MS) were recorded on a JEOL JMN-DX 303/JMA-DA 5000 spectrometer. Microanalyses were performed on a Perkin–Elmer CHN 2400 Elemental Analyzer. Enantiomeric excesses (*ee*s) were determined by chiral HPLC (Table 7). Optical rotations were measured with a JASCO DIP-360 or JASCO P-1020 digital polarimeter (Table 8). Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on JEOL JNM-EX 270 (270 MHz) or JEOL JNM-AL 400 (400 MHz) spectrometer, using tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Column chromatography was carried out on Merck silica gel 60 (230–400 mesh) or KANTO Silica Gel 60N (40–50 μm) for flash chromatography.

Table 8. Specific rotations of deracemization products.

Entry	Product	$[\alpha]_D^{25}$ ($CHCl_3$)	*c* [mg mL^{-1}]	ee [%[
1	(*R*)-**1a**	−98.5	1.20	>99
2	(*S*)-**2a**	+50.7	1.56	>99
3	(*R*)-**1b**	−22.2	1.22	98
4	(*S*)-**2b**	+46.7	1.78	58
5	(*R*)-**1c**	−57.3	2.26	87
6	(*R*)-**1d**	−109.0	1.18	99
7	(*S*)-**3a**	+42.2	1.55	99

1-(*N*-Allyl-*N*-*p*-toluenesulfonylamino)-2-hydroxy-3-butene (4a) and 2-(*N*-Allyl-*N*-*p*-toluenesulfonylamino)but-3-en-1-ol (5a)

To a solution of allylamine (8.5 mL, 114 mmol) and water (530 μL) was added butadiene monoxide (3.0 mL, 37.5 mmol) at 15 °C. The mixture was warmed to 100 °C and stirred for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethanol (150 mL) and $NaHCO_3$ (3.36 g, 40 mmol) and *p*-toluenesulfonyl chloride (7.63 g, 40 mmol) were added at −78 °C. The mixture was stirred at room temperature overnight and filtered off on Celite. The residue obtained after evaporation

Table 7. HPLC conditions.

Entry	Compound	Eluent *n*-hexane: AcOEt	Column CHIRAL-PAK	Flow rate (mL min^{-1})	Retention time (*R*)	Retention time (*S*)
1	**1a**	3:1	IA	0.9	19.6 min	21.9 min
2	**2a**	3:1	IA	0.9	11.7 min	13.6 min
3	**1c**	9:1[a]	OD	1.0	10.9 min	12.7 min
4	**3a**	3:1	IA	0.9	8.5 min	10.8 min
5	**6**	3:1	IA	0.9	13.6 min	14.7 min

[a] Eluent is a mixture of *n*-hexane and 2-propanol.

of the filtrate was taken up in AcOEt and washed with brine. The organic solution was dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 2:1) to give **4a** (yield: 7.8 g, 74%) as a colorless oil and **5a** (yield: 0.6 g, 6%) as a colorless oil.

4a: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.43$ (s, 3H), 2.66 (br s, 1H), 3.09 (dd, $J = 14.9$, 3.7 Hz, 1H), 3.19 (dd, $J = 14.9$, 8.5 Hz, 1H), 3.90 (ddd, $J = 33.8$, 15.6, 6.4 Hz,2H), 4.27–4.40 (m, 1H), 5.15–5.23 (m, 3H), 5.29–5.38 (m, 1H), 5.54–5.70 (m, 1H), 5.73–5.86 (m, 1H), 7.31 (d, $J = 8.5$ Hz, 2H), 7.72 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 52.4, 53.2, 71.1, 116.5, 119.4, 127.3, 129.8, 132.8, 137.4, 143.6; IR (KBr): $\nu = 1157$, 1340 (SO_2), 3526 cm^{-1} (OH); EI-MS: $m/z = 281$ (M^+); HR-MS: $m/z = 281.0989$, calcd. for $C_{14}H_{19}NO_5S$: 281.1086.

5a: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.26$ (br s, 1H), 2.42 (s, 3H), 3.65–3.79 (m, 3H), 3.90–4.01 (m, 1H), 4.40–4.47 (m, 1H), 5.01 (d, $J = 1.3$ Hz, 1H), 5.09–5.27 (m, 3H), 5.46–5.59 (m, 1H), 5.80–5.93 (m, 1H), 7.29 (d, $J = 8.1$ Hz, 2H), 7.73 (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.4$, 47.3, 61.7, 62.5, 117.8, 119.6, 127.2, 129.6, 132.4, 135.4, 137.5, 143.4; IR (KBr): $\nu = 1160$, 1332 (SO_2), 3527 cm^{-1} (OH); EI-MS: $m/z = 281$ (M^+); HR-MS: $m/z = 281.1110$, calcd. for $C_{14}H_{19}NO_5S$: 281.1086; anal. calcd. for $C_{14}H_{19}NO_3S$: C 59.76, H 6.81, N 4.98; found: C 59.66, H 6.78, N 5.00.

tert-Butyl *N*-Allyl-*N*-(2-hydroxy-3-butenyl)carbamate (4b) and Benzyl Allyl-1-hydroxybut-3-enylcarbamate (5b)

To a solution of allylamine (8.5 mL, 114 mmol) and water (530 μL) was added butadiene monoxide (3.0 mL, 37.5 mmol) at 15 °C. The mixture was warmed to 100 °C and stirred for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in dioxane (50 mL) and water (10 mL), then 1 mol/L NaOH (40 mL, 40 mmol) and $(Boc)_2O$ (8.37 g, 40 mmol) were added. The mixture was stirred at room temperature overnight. The residue obtained after evaporation was taken up in Et_2O, washed with water, 20% citric acid, and brine. The combined aqueous solutions were extracted with Et_2O. The combined organic solutions were dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 3:1–1:1) to give **4b** (yield: 5.6 g, 66%) as a colorless oil and **5b** (yield: 0.1 g, 2%) as a colorless oil.

4b: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.46$ (s, 9H), 1.80–2.44 (br m, 1H), 3.28 (br s, 2H), 3.86 (br s, 2H), 4.26–4.37 (m, 1H), 5.03–5.20 (m, 3H), 5.33 (d, $J = 17.1$ Hz, 1H), 5.67–5.90 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 28.3, 51.7, 53.4, 72.7, 80.4, 115.7, 116.4, 133.8, 138.4, 157.6; IR (KBr): $\nu = 1677$ (C=O), 3427 cm^{-1} (-OH); EI-MS: $m/z = 228$ ($M^+ + 1$); HR-MS: $m/z = 227.1538$, calcd. for $C_{12}H_{21}NO_3$: 227.1521; anal. calcd. for $C_{12}H_{21}NO_3$: C 63.41, H 9.31, N 6.16; found: C 63.10, H 9.52, N 6.28.

5b: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.46$ (s, 9H), 2.27–3.00 (br s, 1H), 3.77 (br d, $J = 7.1$ Hz, 4H), 4.38 (br d, $J = 5.6$ Hz, 1H), 5.06–5.26 (m, 4H), 5.74–5.96 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 28.4$, 48.3, 61.1, 63.6, 80.3, 117.5, 134.0, 135.3, 156.3; IR (KBr): $\nu = 1694$ (C=O), 3437 cm^{-1} (OH); EI-MS: $m/z = 228$ ($M^+ + 1$); HR-MS: $m/z = 227.1546$, calcd. for $C_{12}H_{21}NO_3$: 227.1521.

Benzyl *N*-Allyl-*N*-(2-hydroxy-3-butenyl)carbamate (4c) and 5c

To a solution of allylamine (8.5 mL, 114 mmol) and water (530 μL) was added butadiene monoxide (3.0 mL, 37.5 mmol) at 15 °C. The mixture was warmed to 100 °C and stirred for 6 h. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in ethanol (150 mL), then $NaHCO_3$ (3.36 g, 40 mmol) and benzyloxycarbonyl chloride (6.82 g, 40 mmol) were added at −78 °C. The mixture was stirred at room temperature overnight and filtered off on Celite. The residue obtained after evaporation of the filtrate was taken up in AcOEt and washed with brine. The organic solution was dried over $MgSO_4$, filtered, concentrated under vacuum, and purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 2:1 ~ 1:2) to give **4c** (yield: 6.2 g, 64%) as a colorless oil and **5c** (yield: 1.2 g, 12%) as a colorless oil.

4c: ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 3.17$–3.44 (m, 3H), 3.86–4.09 (m, 2H), 4.37 (br s, 1H), 5.15 (s, 5H), 5.31 (dd, $J =$ 56.8, 18.3 Hz, 1H), 5.71–5.90 (m, 2H), 7.27–7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 51.0$, 53.3, 67.4, 72.1, 115.7, 116.7, 127.7, 127.9, 128.3, 133.3, 136.3, 138.1, 157.5; IR (KBr): $\nu = 1685$ (C=O), 3692 cm^{-1} (OH); EI-MS: (m/z) = 261 (M^+); HR-MS: $m/z = 261.1337$, calcd. for $C_{15}H_{19}NO_3$: 261.1365.

5c: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 2.58$ (br s, 1H), 3.74 (br d, $J = 26$ Hz, 4H), 4.31–4.47 (m, 1H), 4.96–5.20 (m, 6H), 5.79 (br s, 2H), 7.16–7.31 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 48.0$, 63.1, 65.7, 67.3, 117.9, 127.7, 127.9, 128.4, 133.6, 134.8, 136.4, 156.6; IR (KBr): $\nu = 1683$ (C=O), 3447 cm^{-1} (OH); EI-MS: $m/z = 261$ (M^+); HR-MS: $m/z =$ 261.1330, calcd. for $C_{15}H_{19}NO_3$: 261.1365.

(±)-*N*-*p*-Toluenesulfonyl-5-hydroxy-3-piperidene [(±)-1a]

To a deoxygenated solution of **4a** (7.8 g, 27.5 mmol) in CH_2Cl_2 (450 mL) under an argon atomosphere was added bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (679 mg, 0.825 mmol, 3 mol%). The solution was stirred at room temperature overnight, then concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 1:1) to give (±)-**1a** as colorless prisms; yield: 5.7 g (81%); mp 99–105 °C (ether). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 1.94$ (br d, $J = 7.3$ Hz, 1H), 2.44 (s, 3H), 3.05 (dd, $J = 3.4$, 1.5 Hz, 1H), 3.31–3.40 (m, 2H), 3.77 (dt, $J = 16.8$, 1.9 Hz, 1H), 4.20 (br s, 1H), 5.77–5.83 (m, 1H), 5.87–5.94 (m, 1H), 7.34 (d, $J = 8.3$ Hz, 2H), 7.68 (dd, $J = 6.6$, 2.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 44.9, 50.1, 63.5, 77.2, 77.6, 125.9, 127.7, 128.1, 129.8, 133.1, 143.9; IR (KBr): $\nu =$ 1161, 1323 (SO_2), 3529 cm^{-1} (OH); EI-MS: $m/z = 253$ (M^+); HR-MS: $m/z = 253.0763$, calcd. for $C_{12}H_{15}NO_3S$: 253.0773; anal. calcd. for $C_{12}H_{15}NO_3S$: C 56.90, H 5.97, N, 5.53; found: C 56.98, H 5.84, N 5.37.

(±)-*N*-*tert*-Butoxycalbonyl-5-hydroxy-3-piperidene [(±)-1b]

To a deoxygenated solution of **4b** (5.0 g, 22.1 mmol) in CH_2Cl_2 (440 mL) under argon atomosphere was added bis(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (727.4 mg, 0.884 mmol, 4 mol%). The solution was stir-

red at room temperature overnight, then concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (*n*-hexane: AcOEt = 1:1) to give (±)-**1b** as colorless prisms; yield: 4.4 g (99%); mp 55–56 °C (*n*-hexane). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.44 (s, 9H), 2.46 (br s, 1H), 3.40 (br s, 1H), 3.63 (br s, 1H), 3.80 (dd, *J* = 2.20, 18.9 Hz, 1H), 3.89 (br s, 1H), 4.18 (br s, 1H), 5.78 (br s, 1H), 5.84–5.94 (m, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.3, 42.8, 46.9, 63.5, 80.0, 126.5, 128.3, 155.1; IR (KBr): ν = 1700 (C=O), 3421 cm^{-1} (OH); EI-MS: *m/z* = 199 (M^+); HR-MS: *m/z* = 199.1232, calcd. for $C_{10}H_{17}NO_3$: 199.1208; anal. calcd. for $C_{10}H_{17}NO_3$: C 60.28, H 8.60, N 7.03; found: C 60.37, H 8.57, N 6.87.

(±)-*N*-Benzyloxycarbonyl-5-hydroxy-3-piperidene [(±)-1c]

To a deoxygenated solution of **4c** (3.6 g, 13.6 mmol) in CH_2Cl_2 (300 mL) under argon atomosphere was added bis-(tricyclohexylphosphine)benzylidine ruthenium(IV) dichloride (447.7 mg, 0.544 mmol, 4 mol%). The solution was stirred at room temperature overnight, then concentrated under reduced pressure and the residue was purified by flash column chromatography on silica gel (*n*-hexane: AcOEt = 1:1) to give (±)-**1b** as an oil; yield: 3.0 g (96%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.38 (br s, 1H), 3.46–3.74 (m, 2H), 3.89 (br s, 1H), 4.03 (br t, *J* = 20.9 Hz, 1H), 4.21 (br d, *J* = 39.6 Hz, 1H), 5.15 (s, 2H), 5.81 (br d, *J* = 44.7 Hz, 1H), 5.91 (d, *J* = 10.3 Hz, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 43.3, 47.5, 47.9, 63.3, 67.3, 126.3, 127.2, 127.9, 128.0, 128.3, 128.4, 136.4, 155.6; IR (KBr): ν = 1702 (C=O), 3419 cm^{-1} (OH); EI-MS: *m/z* = 233 (M^+); HR-MS: m/z = 233.1055, calcd. for $C_{13}H_{15}NO_3$: 233.1052.

(±)-*N*-*p*-Toluenesulfonyl-5-methoxycarbonyloxy-3-piperidene [(±)-2a]

Methyl chloroformate (5.0 mL, 64.7 mmol) was dropwise added to a solution of **1a** (4.9 g, 19.4 mmol) and pyridine (6.4 mL, 73.7 mmol) in CH_2Cl_2 (100 mL) with ice cooling and then the mixture was stirred at room temperature for 3 h. Ether was added to the mixture. The whole layer was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) to give (±)-**2a** as colorless prisms; yield: 5.5 g (91%); mp 81–85 °C (ether). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.43 (s, 3H), 3.30 (dd, *J* = 12.5, 5.5 Hz, 1H), 3.42 (dd, *J* = 12.5, 4.4 Hz, 1H), 3.58 (dd, *J* = 16.9, 2.2 Hz, 1H), 3.68 (dd, *J* = 17.2, 1.8 Hz, 1H), 3.79 (s, 3H), 5.11–5.17 (m, 1H), 5.83–5.87 (m, 1H), 5.90–5.96 (m, 1H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.68 (d, *J* = 1.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.5, 44.6, 46.2, 54.9, 68.8, 123.7, 127.7, 128.3, 129.8, 133.4, 143.9, 155.1; IR (KBr): ν = 1168, 1349 (SO_2), 1745 cm^{-1} (C=O); EI-MS: *m/z* = 311 (M^+); HR-MS: *m/z* = 311.0793, calcd for $C_{14}H_{17}NO_5S$: 311.0828.

(±)-*N*-*tert*-Butoxycarbonyl-5-methoxycarbonyloxy-3-piperidene [(±)-2b]

Methyl chloroformate (0.5 mL, 6.6 mmol) was dropwise added to a solution of **1b** (399 mg, 2.0 mmol) and pyridine (0.64 mL, 7.49 mmol) in CH_2Cl_2 (10 mL) with ice cooling and then the mixture was stirred at room temperature for 3 h. Ether was added to the mixture. The whole layer was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) to give (±)-**2b** as an oil; yield: 480 mg (94%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.46 (s, 9H), 3.56 (br d, *J* = 37.7 Hz, 1H), 3.79 (s, 5H), 4.08 (br dd, *J* = 85.0, 16.5 Hz, 1H), 5.08 (br d, *J* = 57.5 Hz, 1H), 5.95 (br d, *J* = 67.0 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 28.3, 42.7, 44.8, 54.8, 69.2, 80.1, 123.1, 131.1, 154.7, 155.2; IR (KBr): ν = 1702, 1749 cm^{-1} (C=O); EI-MS: *m/z* = 256 (M^+−1); HR-MS: *m/z* = 257.1281, calcd. for $C_{12}H_{19}NO_5$: 257.1263; anal. calcd. for $C_{12}H_{19}NO_5$: C 56.02, H 7.44, N 5.44; found: C 56.18, H 7.38, N 5.43.

(±)-*N*-Benzyloxycarbonyl-5-methoxycarbonyloxy-3-piperidene [(±)-2c]

Methyl chloroformate (0.39, 5 mmol) was dropwise added to a solution of **1c** (460 mg, 1.9 mmol) and pyridine (0.5 mL, 5.7 mmol) in CH_2Cl_2 (8 mL) with ice cooling and then the mixture was stirred at room temperature for 3 h. Ether was added to the mixture. The whole layer was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane: AcOEt = 3:1) to give (±)-**2c** as an oil; yield: 509 mg (92%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.63 (t, *J* = 13.9 Hz, 1H), 3.72(s, 2H), 3.79 (s, 1H), 3.82–3.98 (m, 2H), 4.18 (dd, *J* = 49.8, 18.7 Hz, 1H), 5.03–5.23 (m, 3H), 5.81 (br d, *J* = 44.7 Hz, 1H), 5.91 (d, *J* = 10.3 Hz, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 43.2, 44.6, 54.8, 60.4, 67.2, 68.8, 123.1, 127.7, 128.5, 129.6, 130.6, 136.5, 155.1; IR (KBr): ν = 1707, 1748 cm^{-1} (C=O); EI-MS: *m/z* = 291 (M^+); HR-MS: *m/z* = 291.1095, calcd for $C_{15}H_{17}NO_5$: 291.1107.

(±)-*N*-*p*-Toluenesulfonyl-5-*tert*-butoxycarbonyloxy-3-piperidene [(±)-3a]

A mixture of **1a** (507 mg, 2.0 mmol), 1-methylimidazole (41 μL, 0.5 mmol), and $(Boc)_2O$ (1.1 g, 4.9 mmol) in CH_2Cl_2 (20 mL) was stirred at room temperature overnight. The mixture was concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) to give (±)-**3a** as colorless prisms; yield: 738 mg (99%); mp 119–120 °C (ether). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.49 (s, 9H), 2.43 (s, 3H), 3.25 (dd, *J* = 12.5, 5.5 Hz, 1H), 3.44 (dd, *J* = 12.1, 4.4 Hz, 1H), 3.61 (ddd, *J* = 33.5, 17.0, 2,6 Hz, 2H), 5.07–5.13 (m, 1H), 5.80–5.86 (m, 1H), 5.86–5.91 (m, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.64–7.71 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 21.5, 27.7, 44.4, 46.3, 67.8, 82.7, 124.2, 127.7, 129.7, 133.4, 143.8, 152.7. IR (KBr): ν = 1167, 1278 (SO_2), 1731 cm^{-1} (C=O); EI-MS: *m/z* = 353 (M^+); HR-MS: *m/z* = 353.1208, calcd. for $C_{17}H_{23}NO_5S$: 353.1259; anal. calcd. for $C_{17}H_{23}NO_5S$: C 57.77, H 6.56, N 3.96; found: C 57.50, H 6.34, N 3.87.

(±)-*N*-Methoxycarbonyl-5-hydroxy-3-piperidene [(±)-1d]

A mixture of **(±)-1a**, **(**996 mg, 5 mmol), imidazole (510 mg, 7.5 mmol), DMAP (122 mg, 1 mmol), and *tert*-butyldiphenylsilyl chloride (1.5 g, 5.5 mmol) in CH_2Cl_2 (17 mL) was stirred at room temperature overnight. The reaction mixture was filtered on celite and the filtrate was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 12:1) to give (±)-*N*-*tert*-Butoxycarbonyl-5-(*tert*-butyldiphenylsilyloxy)-3-piperidene as an oil; yield: 2.2 g (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (s, 9H), 1.40 (s, 9H), 3.20 (br s, 1H), 3.57–3.80 (m, 2H), 3.89 (d, J = 17.6 Hz, 1H), 4.24 (br s, 1H), 5.67 (br s, 2H), 7.31–7.50 (m, 6H), 7.60–7.73 (m, 4H); ^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 19.2, 26.9, 28.4, 42.7, 48.0, 65.2, 79.6, 127.6, 127.7, 129.7, 129.7, 135.7, 135.8, 154.7; IR (KBr): ν = 1702, 1749 cm^{-1} (C=O); EI-MS: m/z = 437 (M^+); HR-MS; m/z = 437.2369, calcd. for $C_{26}H_{35}NO_3Si$: 437.2386.

A solution of the above silyl ether (1.75 g, 4 mmol) and CF_3COOH (14 mL) in CH_2Cl_2 (70 mL) was stirred at room temperature for 2 h. The mixture was concentrated under reduced pressure. To a solution of the residue in 1,4-dioxane (50 mL) were added H_2O (50 mL), $NaHCO_3$ (3.36 g, 40 mmol), and methyl chloroformate (0.454 g, 4.8 mmol). The mixture was stirred at room temperature for 3 h and extracted with AcOEt. The extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to leave an oil. To a solution of the oil in THF (5 mL) was added 1 M tetra-*n*-butylammoniumu fluoride in THF (5 mL, 5 mmol). The mixture was stirred at room temperature for 2 h and then concentrated under reduced pressure. To the residue were $CHCl_3$ and saturated $NaHCO_3$ and the whole mixture was separated. The organic layer was dried and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 1:2) to give **1d** as a colorless oil; yield: 0.57 g (91%). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.84 (br s, 1H), 3.34–3.60 (m, 2H), 3.68 (s, 3H), 3.79–3.87 (m, 1H), 3.87–4.06 (m, 1H), 4.17 (d, J = 32.8 Hz, 1H), 5.76 (d, J = 33.2 Hz, 1H), 5.88 (dd, J = 10.3, 3.5 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 43.2, 47.4, 52.7, 63.2, 126.1, 128.6, 156.4; IR (KBr): ν = 1705 (C=O), 3415 cm^{-1} (OH); EI-MS: m/z = 157 (M^+); HR-MS: m/z = 157.0719, calcd for $C_7H_{11}NO_3$: 157.0739.

(±)-*N*-Methoxycarbonyl-5-methoxycarbonyloxy-3-piperidene [(±)-2d]

Methyl chloroformate (0.51 mL, 6.7 mmol) was dropwise added to a solution of **1d** (314 mg, 2.0 mmol) and pyridine (0.65 mL, 7.6 mmol) in CH_2Cl_2 (10 mL) with ice cooling and then the mixture was stirred at room temperature for 3 h. Ether was added to the mixture. The whole layer was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) to give (±)-**2d** as an oil; yield: 333 mg (78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.57–3.69 (m, 1H), 3.72 (s, 3H), 3.74–3.93 (m, 5H), 4.11 (br d, J = 17.3 Hz, 1H), 5.10 (br d, J = 15.4 Hz, 1H), 5.87–6.04 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 43.1, 44.5, 52.8, 54.8, 68.9, 123.3, 130.3, 138.4, 155.2; IR (KBr): ν = 1707, 1748 cm^{-1} (C=O); EI-MS: m/z = 215 (M^+); HR-MS: m/z = 215.0770, calcd for $C_9H_{13}NO_5$: 215.0794.

(±)-*N*-*p*-Toluenesulfonyl-5-acetoxy-3-piperidene [(±)-6]

Acetyl chloride (0.7 mL, 9.9 mmol) was dropwise added to a solution of **1a** (760 mg, 3.0 mmol) and pyridine (0.96 mL, 11.2 mmol) in CH_2Cl_2 (15 mL) with ice cooling and then the mixture was stirred at room temperature for 3 h. Ether was added to the mixture. The whole layer was washed with saturated NH_4Cl and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 3:1) to give (±)-**6** as a yellow oil; yield: 888 mg (99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3H), 2.43 (s, 3H), 3.19 (ddd, J = 12.6, 4.0, 0.7 Hz, 1H), 3.37–3.51 (m, 2H), 3.81 (dt, J = 17.1, 1.8 Hz, 1H), 5.20–5.27 (m, 1H), 5.77–5.84 (m, 1H), 5.89–5.97 (m, 1H), 7.30–7.37 (m, 2H), 7.64–7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 21.5, 44.4, 46.6, 65.3, 124.0, 127.7, 128.2, 129.8, 133.5, 143.8, 170.5; IR (KBr): ν = 1167, 1352 (SO_2), 1738 cm^{-1} (C=O); EI-MS: m/z = 295 (M^+); HR-MS: m/z = 295.0910, calcd. for $C_{14}H_{17}NO_4S$: 295.0878; anal.calcd. for $C_{14}H_{17}NO_4S$: C 56.93, H 5.80, N 4.74; found: C 56.55, H 5.40, N 4.58.

General Procedure for Pd-Catalyzed Deracemization in Tables 2–6

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (10.4 mg, 0.01 mmol) and (*R*)-BPA (27.6 mg, 0.04 mmol) or other ligands in solvent (1.8 mL) was stirred for 15 min under argon and then H_2O (0.2 mL) and (±)-**2a–d**, **3a**, or **6** (0.5 mmol) were added to the mixture. The mixture was stirred at room temperature for 24 h under argon and then diluted with $CHCl_3$. The whole mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 5:4) to give (*R*)-**1a–d** (yields and *ee*s are shown in Tables 2–6).

Deracemization of 2a under Anhydrous Conditions

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (10.4 mg, 0.01 mmol) and (*R*)-BPA (27.6 mg, 0.04 mmol) in dry CH_2Cl_2 (2 mL) was stirred for 15 min under argon and then (±)-**2a** (0.5 mmol) was added to the mixture. The mixture was stirred at room temperature for 24 h under argon and then diluted with $CHCl_3$. The whole mixture was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 2:1–1:1) to give (*S*)-**2a** (yield: 100 mg, 64%, 50% *ee*) and (*R*)-**1a** (yield: 25 mg, 9%, 89% *ee*).

Deracemization of 2a using $KHCO_3$

A mixture of $Pd_2(dba)_3{\cdot}CHCl_3$ (10.4 mg, 0.01 mmol) and (*R*)-BPA (27.6 mg, 0.04 mmol) in CH_2Cl_2 (2 mL) was stirred for 15 min under argon and then $KHCO_3$ (70 mg, 0.7 mmol) and (±)-**2a** (0.5 mmol) were added to the mixture. The mixture was stirred at room temperature for 24 h under argon and then diluted with $CHCl_3$. The whole mixture was dried

over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (*n*-hexane:AcOEt = 2:1–1:1) to give (*S*)-**2a** (yield: 18 mg, 11 %, 36 % *ee*) and (*R*)-**1a** (78 mg, 61 %, 91 % *ee*).

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